

PET/CT in renal and bladder cancers

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SUMMARY

FDG is the most frequently used positron emission tomography probe but it has certain limitations when used in urological cancers due to its urinary elimination, which prevents the proper visualization of the bladder and kidneys. The introduction of co-registered PET and computed tomography (PET/CT) represents a major advance in technology and now become the new standard for many cancers. For the staging and surveillance of renal cell cancer, FDG PET/CT had results that were at least as good as conventional methods, which are potentially harmful for the remained renal function. FDG-PET/CT is able to evaluate early response to sunitinib or sorafenib treatment in metastatic renal cell cancer. An early decrease in the mean glucose uptake was found in both soft and skeletal lesions after treatment, thus PET seems to be more advantageous compared with RECIST evaluation. In addition, the survival of patients with advanced renal cell cancer can be predicted by evaluating their SUVmax using FDG-PET/CT. Although urinary bladder cancer demonstrates sufficiently increased FDG uptake, primary tumors are difficult to identify due to the renal excretion of FDG. The accuracy of FDG-PET/CT in metabolically active metastases is generally higher when compared to conventional CT except for identifying small lung deposits. PET/CT with delayed images after a diuretic and oral hydration may improve detection of locally recurrent or residual UBC and could replace standard CT and bone scintigraphy in the presurgical staging and monitoring of patients with urinary bladder cancer. 18F-choline PET may be useful for staging of urinary bladder cancer in addition to FDG PET.

Key words: Kidney Neoplasms; Urinary Bladder Neoplasms; Diagnostic Imaging; Positron-Emission Tomography; Positron-Emission Tomography and Computed Tomography; Fluorodeoxyglucose F18

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2% to 3% of all adult cancers (1). This type of cancer is the most lethal of all urological cancers, since approximately 25% of patients with RCC will die from it. RCC is highly angio-invasive and results in widespread haematogenous and lymphatic metastases, typically spreading to the lung, liver, lymph nodes, bone, and brain (2). Urinary bladder cancer (UBC) is the fourth most common cancer in males, with incidence rate of 7%. It is three times more common in men than in women for whom it is not even among ten leading cancer types (1). Approximately 75% to 85% of all new bladder cancers are superficial tumor in situ (Tis), or T1. About 20% of new UBC show evidence of muscle invasion at the time of diagnosis and muscle invasion develops in additional 40% of patients initially presented with superficial disease. About 25% of patients have multifocal disease at the time of presentation, which causes many local recurrences after successful transurethral resection (TUR) performed at primary detected site (3).

GENERAL MANAGEMENT OF RCC AND UBC PATIENTS

The standard therapy for nonmetastatic RCC is radical nephrectomy in which the malignant tumor is removed along with the kidney, the adrenal gland, and the perinephritic fat. Less aggressive operations may be considered in patients who have early stage tumors, especially in those with poor renal reserve or absence of a normal functioning contralateral kidney (3, 4). Chemotherapy has not produced significant results in RCC patients. However, agents that target relevant biological pathway (multiple tyrosine kinase inhibitors such as sunitinib, sorafenib, and pazopanib, and inhibitors of the mammalian Target of Rapamycin, such as temsirolimus and everolimus) have been introduced and they revolutionized the treat-

ment of RCC (5, 6). They were recently recommended in the National Comprehensive Cancer Network guideline (NCCN) (3).

In UBC patients, besides the differences in histology, which affect patient management, the clinical spectrum of UBC affects prognosis, management, and therapeutic aims (7). The first category of patients consists of non-muscle invasive tumors, the second group includes the muscle invasive lesions, and the third group is patients having metastatic disease. Transurethral resection of the bladder tumor (TUR) is the initial treatment for all UBC, but in muscle invasive disease intravesical therapy may be recommended and is used as prophylactic or adjuvant chemotherapy. Different chemotherapeutic protocols are under investigation for effectiveness, and the most frequently applied are methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), cisplatin, metotrexate, vinblastine (CMV) and gemcitabine, cisplatin (GC). Since UBC patients are usually elderly people with compromised liver or renal status lower toxicity profiles should be used (7, 8).

DIAGNOSTIC WORKUP AND STAGING OF RCC AND UBC PATIENTS

If renal neoplasm is suspected the imaging algorithm includes intravenous urography, ultrasonography (USG), and contrast-enhanced computed tomography (CECT). The role of magnetic resonance imaging (MRI) in renal imaging is still mainly in differentiating benign lesions from malignant lesions in patients with non-diagnostic CT results as a problem solving modality. A metastatic workup should include a chest x-ray and CT or MRI of the abdomen and pelvis and bone scan (3).

In UBC patients, staging with direct visualization throughout cystoscopy is best suited for non-muscle-invasive tumors. Since urothelial cancer

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is panurothelial disease, extensive diagnostic workup is required for the evaluation of the primary tumor and the identification of possible extra lesions in addition to the primary site (9). TUR of the bladder tumor is usually performed in order to assess the tumor stage and grade from biopsy specimen. Additional workup should include urine cytology and intravenous urography (IVU) or newer imaging modalities, such as CT, computed tomography urography (CTU), MRI and USG for the evaluation of upper urinary tracts (10).

Hybrid imaging with PET/CT performed with fluorine-18-fluoro-2-deoxy-D-glucose (FDG), an analogue of glucose, is used in the assessment of malignant diseases in patients suspected of a RCC and UBC as well (11-13). The use of FDG PET/CT is limited in the evaluation of genitourinary lesions due to the significant uptake and excretion of FDG through the kidneys, which results in intense activity in the renal collecting system and the urinary bladder (14). Despite the fact that FDG in urinary tract mimics the disease and interferes with the image interpretation, the role of this imaging method for patients suspected of renal or bladder cancer has increased over the last several years (14). FDG PET/CT can help for staging and for postoperative surveillance of advanced RCC and UBC (14-16).

FDG PET/CT IN EVALUATION AND STAGING OF RCC PATIENTS

The most widely used metabolic tracer in urological oncology is FDG, although it is well known that, due to its urinary elimination, FDG is not an ideal radiotracer. To minimize this limitation, FDG PET/CT studies in renal and bladder cancer patients are partly modified by performing bladder catheterization or by introducing diuretics. Other segments of PET/CT imaging procedure are the same as in other cancer patients.

RCC typically presents as visually detectable area of focally increased FDG uptake, although uptake can be inconsistent which partly depends on the subtype and the size of the cancer.

One must keep in mind that normal, physiological increased FDG uptake seen within the renal regions is usually focal. Focal accumulation can be observed along the ureters, especially in the pelvic part of ureters. In addition, false positive finding can occur in benign conditions such as adrenal adenomas or infectious lesions in the renal region, which is not so rare. The maximum SUV value (SUVmax) within the region of interest represents the highest radioactivity concentration in one voxel within the tumor and it is often used for comparison between PET studies. SUV provides highly reproducible parameters of tumor glucose utilization but unfortunately, there is no cut-off value that would be specific for RCC. Values can diverge from undetectable (below 1.5) to levels over 24.0 (17, 18). Regarding the cell subtype of RCC, no correlation in SUV values was found (19). Concerning the relation to tumor size significant difference was observed, but only if lesions were larger than 5 cm (20). This is due to the existence of physiologic activity in the renal collecting system, which mimics activity in smaller lesions nearby.

Patients with RCC tumors presenting with high SUVmax index have poor prognosis and survival rate of the patients with SUVmax value higher than 8.8 was the lowest (17, 18).

FDG was proved to be highly sensitive for metastatic lesions of RCC. FDG accumulation is positive in over 95% lesions diagnosed by CT (17, 21).

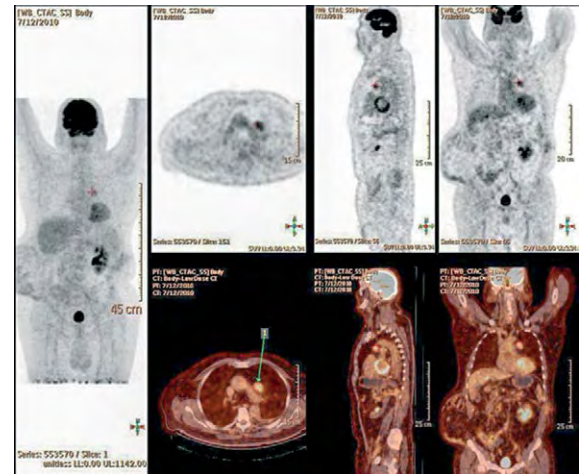


Figure 1. 55 year old male with right nephrectomy for adenocarcinoma: PET images performed for staging after metastatic disease in left adrenal gland was operated, showing intensive focal FDG activity corresponding to the single mediastinal lymph node (arrow labeled 1), SUVmax 3.4.

There is no relationship between the SUV values in primary tumor and metastatic lesions or between the different metastatic organs in the same patient. Although lungs are the most frequent metastatic region, some regions, which are rarely affected by RCC metastatic disease (uterus, pancreas, muscle metastasis), can present with the most intensive pathologic FDG accumulation (17).

The importance of viewing the CT component to identify the well-known morphological features of renal region cannot be over-emphasized as the CT component significantly contributes to lesion characterization. The CT component of fused PET/CT is often an unenhanced low-dose CT, which is sometimes not sufficient for morphology description. Although, due to the variability in uptake and insufficiency in morphologic characterization, FDG PET/low-dose CT has a limited role in the characterization of renal masses, it can be used as a problem solving modality which can help prevent unnecessary biopsies and ensure optimal management of suspicious renal lesions.

Timing of PET scan should be carefully planned in concordance with the other procedures that could affect metabolism in the affected region (recent surgery, radiotherapy, or chemotherapy). Increased FDG uptake can be seen in tissue after radiation therapy and it is therefore recommended to wait at least 8 weeks after external beam radiation before evaluating the irradiated area for the residual disease. For patients treated with chemotherapy, the FDG PET/CT should be acquired at least 4 weeks after the last cycle to avoid false negative PET results due to the metabolic stunning of tumor tissue. In addition, there are some other PET radiopharmaceuticals beyond FDG, which can be applied for RCC patients, so in future this modality can potentially have a more important role in the imaging of renal tumors (22-24).

FDG PET/CT IN POSTOPERATIVE SURVEILLANCE AND ASSESSMENT OF TREATMENT RESPONSE OF ADVANCED RCC

According to the ESMO recommendation and NCCN guidelines the radiological and other examinations should be symptom driven and dependent on the individual clinical situation (3, 25). Therefore, there can be no firm

recommendations on the specific use of FDG/PET/CT in surveillance of RCC patients. However, recent studies confirm that the imaging methods used for follow-up can help with the earlier detection of the disease and the appropriate administration of salvage therapy. Generally, there is a wide disparity in the accuracy of FDG PET imaging for RCC. Reports of sensitivity range from 31% (20) to 95% (17). FDG PET/CT was found to be better for evaluating distant metastases. The conventional methods were of higher sensitivity and lower specificity compared to FDG PET (94.7% vs. 89.5% and 80.0% vs. 83.3%, respectively), but the accuracy of both methods was the same (85.7%). The potential role of whole-body PET in the postoperative surveillance of RCC comes from its ability to image entire body for additional sites of metastatic disease. This role is particularly important in confirming the presence of only one solitary metastasis in patients who, if treated aggressively, might have significant palliation of symptoms and prolonged survival.

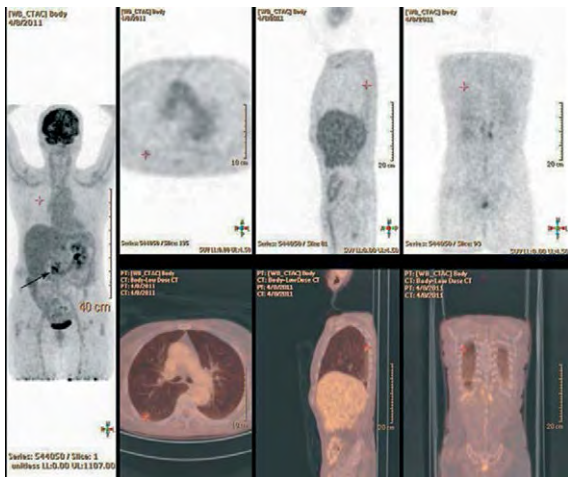


Figure 2. 62 year old female with right nephrectomy for adenocarcinoma: PET/CT study performed for follow-up of previously detected small right pulmonary lesion; PET/CT detected progression of the lung lesion (labeled with +) with increased FDG uptake and additionally enlarged retroperitoneal lymph nodes and node in the right renal region, not previously recorded (arrow), SUVmax 1.8 to 5.3.

Another issue, also affecting treatment decisions in RCC patients, is the registration of incidentalomas - second primary cancers. Overall, 5% - 10% of patients on whom FDG-PET/CT is performed are confirmed as having second primary tumor and FDG is proved to be highly sensitive method with reported sensitivity of over 90% (26).

Increasing knowledge of the underlying biology of RCC has identified interesting signaling pathways for targeted therapy, implying an increasing need for surrogate markers to assess tumor response early. It has been observed that new drugs (sunitinib, sorafenib, temsirolimus, etc.) cause disease stabilization, rather than substantial tumor regression. Treatment with those drugs is associated with a low response rate, but also with the improvement of overall survival (OS). Therefore, in early evaluation, patients with stable disease (SD) according to the RECIST criteria cannot be discriminated from patients who will have progressive disease (PD) or partial response (PR). Currently the most commonly applied system is Response Evaluation Criteria in Solid Tumors (RECIST) are not sufficient (27). The Choi criteria, the modified Choi criteria, the Size

and Attenuation CT criteria (SACT) and Morphology, Attenuation, Size, and Structure (MASS) criteria are also under evaluation but those criteria have specific other limitations which resulted in the introduction of new criteria based on functional imaging methods, such as PET. A significant decrease of FDG uptake has been observed in treated patients after only one treatment cycle with sorafenib or sunitinib. The most interesting finding is that the patients with decrease in SUV values can, at the same time, have an increase in tumor size and better overall survival. Therefore, the change in size was explained as probably due to the necrosis (28). Patient whose SUVmax decreased less than 20% after therapy (cut-of for response) had worse prognosis. PET scanning is still not incorporated in commonly used response evaluation criteria; however it is accepted as an adjunct to the determination of the progression of disease (27). The PET Criteria in Solid Tumors (PERCIST) has been proposed for metabolic tumor response and as a starting point for PET-based responses, but only in clinical trials (29).

FDG PET/CT IN DETECTING RESIDUAL OR RECURRENT UBC

As has already been said, due to its urinary elimination and the consequent difficulty in visualizing bladder and renal pelvis cancer, FDG is not an ideal radiotracer in urological oncology, but is still the most widely used and explored metabolic tracer in bladder cancer patients (11-13). Washing out the excreted FDG by forced diuresis with furosemide and acquiring post-voiding images is considered to be crucial for overcoming the above-mentioned disadvantage. First attempts to empty bladder were made by Kosuda et al. who used retrograde saline irrigation of urinary bladder, but they were unable to reduce tracer activity to background levels and they reported a 40% false negative rate for detection of recurrent or residual tumor in the bladder (30). In fact, continuous bladder irrigation and immediate post-voiding images are not effective in reducing intravesical activity because the kidneys keep filling the bladder with the urine, which is highly concentrated with FDG. Besides, bladder catheterization and retrograde filling of the bladder are invasive procedures that increase the risk of urinary infection for the patient and, in addition, increase radiation exposure for the staff.

After those attempts, a dual-phase protocol was introduced, with oral hydration, forced diuresis and post-voiding imaging at two to three hours after the FDG injection (31, 32). In dual protocol, after the initial scanning diuretic furosemide is injected (usually 60-90 min after FDG injection) and one hour after the diuretic injection delayed imaging is acquired. Dual protocol enabled excellent urinary radiotracer washout in bladder-preserved patients, reducing bladder activity to background levels. It is important to note that this effect could not be obtained in patients with cystectomy and urinary diversions due to the higher residual urine volumes and FDG activities in those patients. Anyway, the overall assessment of cystectomized patients for recurrent local disease, nodal metastases, or metachronous upper urinary tract lesions was not affected by that fact (31, 32). Several studies analyzed the accuracy of FDG PET/CT in assessing residual or recurrent local disease by using furosemide dual phase protocol and all of them showed high potential of the method and reached high sensitivity (over 85%) and high specificity (54% to 100%).

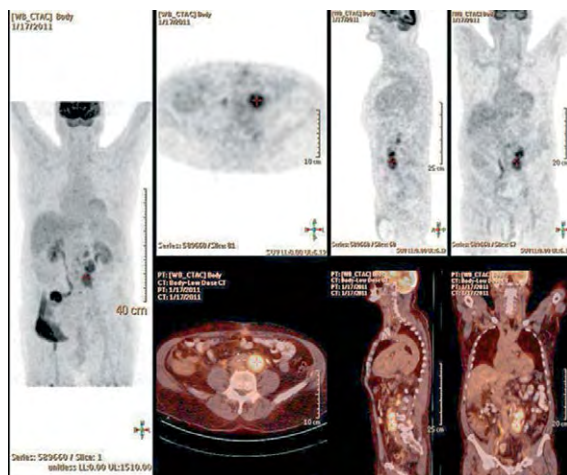


Figure 3. 74 year old male after cystectomy for invasive UBC: PET/CT confirmed progressive metastatic disease in multiple retroperitoneal lymph nodes (left paraaortic and bilateral iliac)

Regarding the SUVmax index, there is no official cutoff value for UBC and PET/CT interpretation primarily depends on the visual assessment of the findings. In addition, SUV values are mostly recorded for the future follow-up studies. In a study by Apolo et al, for the purpose of retrospective analysis an arbitrary SUV cutoff of 4.0 was used to define malignancy (33). According to the range of SUVmax values referred in other publications, SUV of 4.0 would achieve high sensitivity (31, 32).

The combined PET and CT scan may provide additional information to ascertain the nature of FDG accumulation in the urinary bladder in patients with bladder thickening. CT images may not be useful in patients with distorted anatomy or postsurgical inflammation, and also unfilled bladders may cause difficulties in the evaluation of the bladder wall on CT scans. However, there are some recently published data on FDG PET/CT studies with good accuracy for local and distant staging of UBC patients, even if dual diuretic protocol was not applied (33,34). Those good PET results were consequence of a carefully explored “low-dose” CT images and watchful comparison of CT and PET images. PET/CT improved the accurate staging of local region in UBC patients and affected the clinical management in 17% patients (34). Finally, there is a recently published study with an interesting adaptation of dual protocol, which achieved the sensitivity, specificity, and accuracy of PET/CT of 92%, 87%, and 89% respectively (35). All invasive interventions were avoided, patients first received oral hydration, and then it was required of them to void frequently before initial scanning. After the initial scanning patients were requested to hold back the urine, so that the additional pelvic images could be obtained.

FDG PET/CT IN THE SURVEILLANCE OF PATIENTS WITH UBC

The presence of lymph node involvement (N) and distant metastases (M) in patients with invasive bladder cancer is a major determinant of survival and it is essential in the therapeutic management. Many FDG PET/CT studies conducted on UBC patients (although some retrospectively, some prospectively and on a relatively small number of patients) showed moderate to high sensitivity (53% to 100%) and specificity (72% to 100%) of the method regarding the staging and the assessment of the metastatic

disease. One of the early prospective studies conducted on 70 patients assessed moderate sensitivity regarding lymph node staging (57%), but even this was much better than CT sensitivity (33%) in the same patient group (36). All patients with a single node metastatic disease were assessed as such by PET and missed by CT, with overall sensitivity of 60%, specificity of 88% and accuracy of 78%. Patients with a single node metastatic disease have median survival of less than 2 years, so this FDG PET/CT advantage of having the sensitivity that enables it to detect early metastatic disease can have great implication on the future patient management.

Another potentially important finding in a study by Lodde et al, relates to the pattern of UBC metastases. Among the patients with FDG positive retroperitoneal and mediastinal nodes there was a further progression to the systemic metastases in 90% and 60% died during the follow up period (37). Among the patients with a single distant metastatic lesion (mostly lung), but without any linked lymph node affected by the disease, only 20% had progression. The results of the study suggested that UBC progresses primarily through the lymph nodes.

Regarding the specific regions of the metastatic disease, FDG PET showed better sensitivity and specificity for bone lesions than did the bone scan (37). Study by Apolo et al, performed prospectively on 57 patients resulted in the sensitivity of 81% and the specificity of 94% for metastatic disease (33). PET/CT survey revealed better accuracy than MRI or CT in 40% patients, which was confirmed on post-PET follow-up of those patients. FDG PET/CT changed clinicians planned management in even 68% of patients. Almost 20% of patients planned for treatment of organ-confined muscle-invasive UBC were found to have metastatic disease, thus requiring systemic chemotherapy (33).

Although pathologic confirmation of suspected metastatic disease remains the gold standard, biopsy is not always possible because of the risk involved with lesions deep in the body, near vascular structures and due to the other medical contraindication. FDG PET/CT may serve as an acceptable substitute to assess the extent of the disease, to direct treatment and for follow-up of treatment response.

OTHER PET RADIOTRACERS USED IN RCC AND UBC

The most widely used metabolic tracer in renal cancer patients is, as already mentioned, FDG. Other radiotracers, which use different metabolic pathways and are not excreted in the urine, are being investigated in RCC patients as well (38). Many factors are under evaluation regarding the use of different radiotracers in PET/CT studies, to assess cell proliferation and tumor hypoxia, which are well-known factors of poor prognosis, radioresistance, and chemoresistance. Fluorine-18- 3-deoxy-3-fluorothymidine (FLT) is a tracer used for imaging tumor proliferation by PET (23). Tumor hypoxia can be noninvasively assessed in vivo by fluorine-18-fluoromisonidazole (FMISO) PET/CT (22). Monoclonal antibody (MAb) G250 was shown to be a very strong biomarker for ccRCC due to its absence in normal kidney tissue and a chimeric form of G250 (cG250) labeled with iodine-124 (124I) has of recent been used for molecular imaging in RCC (24). Human clinical trials using iodine-124-cG250 have demonstrated excellent sensitivity, specificity, positive and negative predictive values in visualization of primary tumor, as well as known metastatic lesions. Thus

the utilization of PET/CT with chimeric MAb G250 has been given the name “imaging histology.”

Early studies on 11C- and 18F-choline PET/CT in bladder cancer patients were quite optimistic, indicating a significantly higher accuracy of PET compared to CT for local disease (96% vs. 85%) as well as for lymph node staging (62% vs. 50%) (39). However, in a study recently conducted on 44 UBC patients referred to PET/CT prior to radical cystectomy, compared to conventional CT choline PET could not improve diagnostic efficacy. Sensitivity, specificity, and accuracy were 58%, 66% and 81%, respectively, for 11C-choline PET/CT and 75%, 56% and 86%, respectively, for CT (40). The use of 11C-acetate PET/CT in tumor imaging has been suggested in various malignancies, mostly in brain, nasopharyngeal, liver, prostate, and bladder tumors (38). Studies on using acetate in bladder cancer patients are infrequent and majority are only recently published (41). A prospective study on 14 patients was recently conducted in order to evaluate accuracy of 11C-choline and 11C-acetate in each patient and so far it is the first intraindividual comparison of those tracers in patients with bladder urothelial carcinoma (42). Study confirmed previously reported high negative predictive value of both methods for lymph node involvement. However, further studies are necessary to accurately analyze usefulness of those methods, so due to the low availability of the 11C- labeled radiotracers it will probably take additional effort in time and expenses to assess that.

CONCLUSION

Implementation of more sensitive methods into clinical practice is to be expected, as it is a key to successful management of cancer patients. Since primary therapy is very often the only curative treatment option for RCC patients, accurate staging is very important for optimization of treatment plan. On the other hand, highly sensitive methods always include potential hazard of reporting more false positive findings, which could result in obstructing the applicable treatment options due to the overstaging of patient. PET/CT methods are currently under evaluation to validate their usefulness in cancer patients during early stages of targeted therapy. However, the feasibility, accuracy, and reproducibility of the new method should be determined before these new imaging tools are implemented and before the response evaluation criteria to determine the therapy efficacy are changed.

To achieve the near perfect accuracy of the method, a wide knowledge of oncology, nuclear medicine, radiology, urology, and molecular biology, as well as the exchanged of it between the involved physicians (oncologist, urologist, nuclear medicine specialist, and radiologist) is required. In PET/CT studies in particular, since different radiotracers and equipment are applying, it is necessary to standardize protocols, including timing of response evaluation and timing of the acquisition of imaging data, in order to compare the results in individual patient as well as among different institutions.

Currently, FDG PET/CT in RCC and UBC patients should be used and recommended on the individual basis. Whenever an oncologist or an urologist is in a dilemma regarding the staging of the disease or regarding the proposed therapy protocol, there is a place for this sensitive imaging method.

Conflict of interest

We declare no conflicts of interest.

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