

IMAGING OF BLADDER CANCER: UPDATE ON CURRENT APPROACHES FOR DIAGNOSIS

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Imaging plays a mainstay role in evaluation of patients with bladder cancer, especially for diagnosis, local and distant staging and treatment follow up. In this article, we aim to review and to update conventional and functional imaging methods used in clinical management of bladder cancer.

Key-word: Bladder neoplasms, diagnosis.

Bladder cancer is the fourth most common cancer among men in the United States (1). It has a propensity to be multifocal with a high rate of recurrence. Therefore, it requires reliable diagnostic work-up. Despite new emerging imaging technologies, the diagnosis of bladder cancer is based on cystoscopic visualization and tissue sampling by means of biopsy and excision. The majority of newly diagnosed bladder cancers are low grade and noninvasive. But high grade disease, which manifests as local invasion, adjacent organ extension, and distant metastases, can also occur. As pretreatment staging highly affects the treatment approach and survival, accurate imaging work-up is almost always needed. Herein, we will review the imaging modalities used in the detection of bladder cancer and local staging.

Ultrasonography

Ultrasonography (US) is a widely used, inexpensive, easily performed, and repeatable non-invasive imaging modality. US is the first line imaging method for bladder pathologies (2). US examination of the bladder requires adequate distension of the bladder, which can be accomplished by ingesting water or other fluids. In the majority of cases, a transabdominal approach is enough for accurate evaluation of bladder walls if adequate distention is present. Occasionally, a transrectal or a transvaginal approach can be used if the bladder neck or trigone needs to be evaluated. On US, bladder cancer lesions can appear as papillary, infiltrating, invasive or mixed. Papillary lesions appear as small echogenic masses projecting from the bladder wall which can

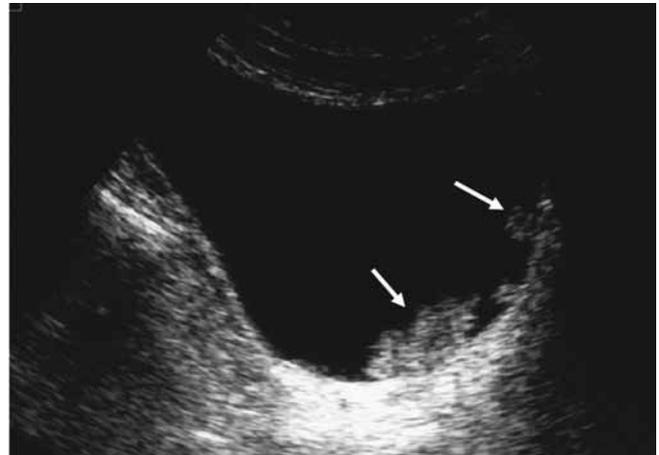


Fig. 1. — Transabdominal ultrasound image of a male with bladder cancer demonstrates mixed type (papillary and infiltrating) tumor lesions at posterior wall of bladder (arrows).

usually be detected when they reach a diameter of 2-3 mm. Infiltrating lesions appear as hypo-echogenic masses with bladder wall disruption, they can bear papillary component and can be detected soon after they reach a diameter of 5 mm (Fig. 1, 2). Infiltrating lesions can be associated with wall rigidity and asymmetric bladder distension. Color and/or power Doppler mode can be used to ascertain the pattern of flow within the lesion, moreover can be helpful to distinct a focal mass from a clot (3). Despite its operator experience dependency; US allows visualization of all bladder cancers greater than 5mm in diameter, provided that it is optimally distended (2).

Computed tomography (CT)

Multidetector computed tomography (MDCT) is the method of choice for the assessment of gross hematuria and suspected urothelial tumor.

It is also important for the detection of local pelvic wall invasion and for accurate evaluation of distant metastasis in patients with invasive bladder carcinoma.

A standard CT scan in conjunction with CT urography can be used to evaluate the entire urinary system in one step. The standard CT scan consists of unenhanced and post-contrast nephrographic phase images. CT urography includes excretory phase images.

Precontrast images, which include the kidneys, ureters and bladder, are helpful to exclude the presence of urinary stones, which accounts for the most common etiology of hematuria. Postcontrast nephrographic phase images, covering the entire abdomen and pelvis, are obtained 70-90 seconds after the intravenous administration of iodinated contrast material (1.5-2 cc/kg at a rate of 3-4 ml/sec). On these images, bladder cancer can be seen as a papillary, sessile, infiltrating, mixed or flat lesion with contrast enhancement. Urothelial carcinomas enhance early and more intensely than normal bladder wall because of their increased vascularity; prior studies

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Fig. 2. — Trans-abdominal ultrasound image of a male with bladder cancer shows a large infiltrating tumor lesion at posterior wall of bladder (arrows).

has shown that peak enhancement occurs approximately 60-80 seconds after contrast injection at a standardized dose and injection rate (dose: 2 ml/kg-maximum 160 ml-; injection rate: 4 ml/sec) (4). Urothelial carcinoma can be differentiated from blood clot, tissue debris and non-specific wall edema according to its contrast enhancement characteristics. Nephrographic phase images can also demonstrate abdominal and pelvic lymphadenopathy, hepatic metastases, as well as incidental renal cortical masses. Tumor extension to periureteral and extravascular area can be differentiated depending on the high contrast interphase between the bladder and perivesical fat. The overall accuracy of MDCT and CT urography in detecting bladder cancer ranges from 89% to 97% in different studies (4-6). However, it is also known that the diagnostic value of parenchymal phase CT is limited for detecting lesions smaller than 1 cm with a reported sensitivity of 80%-83% (5). To avoid false positive diagnosis and pitfalls, the bladder must be optimally distended prior to the scan. Under-distension of the bladder increases the trabeculation of the wall, on the other hand over-distension may cause the underestimation of wall thickness and effacement of fat planes; both of these conditions can reduce the accuracy of CT.

Excretory phase images are acquired when contrast material is excreted to the collecting tubules and the bladder is opacified with a delay time of approximately 7-10 minutes. Bladder tumors can be detected as a mass or plaque-like filling defects in an optimally distended

and homogeneously opacified bladder. Instructing patient to take alternate prone and supine positions on the table or applying abdominal compression for optimum distention prior to scan are helpful maneuvers for obtaining a homogeneous contrast density in the bladder. In addition to conventional axial slices, multi-planar reformatted images facilitate the presentation of findings and may improve the performance of CT, specifically for tumors at the base and dome of the bladder. A single coronal image showing contrast filled collecting system and the bladder similar to intravenous urography technique can be achieved from axial excretory phase images using a maximum intensity projection algorithm. Excretory phase CT urography has been found to be comparable with IV urography for the evaluation of the urinary tract in patients with painless hematuria (7) (Fig. 3, 4). Additionally, early arterial phase images were reported to be useful in detection of renal pelvis and bladder malignancies (8).

For local staging, CT cannot identify the depth of bladder wall invasion, but it can distinguish the perivesical fat infiltration, which indirectly depicts transmural tumor extension or stage T3b tumor and it should be remembered that transurethral tumor resection can lead to over-staging due to resultant focal wall thickening and perivesical fat stranding (9). Kim et al. reported an overall sensitivity and specificity of 89% and 95%, respectively, for the diagnosis of perivesical invasion on MDCT (4). If a time interval of 7 or more days between CT imaging and transurethral resection is provided,

the sensitivity and specificity can improve to 92% and 98%, respectively.

Currently, the diagnosis of nodal metastasis is based on CT morphologic and size criteria. Pelvic lymph nodes with a diameter greater than 10 mm in short axis and internal iliac and obturator lymph nodes greater than 8 mm are generally considered as metastatic (10). However, lymph nodes can enlarge secondary to a benign process and non-enlarged normal looking lymph nodes can contain microscopic metastases. Liver, bones and lungs are frequently involved in late stage metastatic disease (11).

Urothelial carcinoma has propensity to be multicentric with multiple lesions in the bladder or with synchronous and metachronous lesions in the upper urinary system (9). CT urography is a good choice to scan the entire urinary system for the presence of multicentric lesions. Additionally, superficial bladder cancers, especially multifocal and high grade tumors, have a high propensity to recur and progress in grade and stage after treatment by transurethral resection (12). The standard follow-up procedure of these patients includes repeated conventional cystoscopy with biopsy to detect recurrence. Since the survival of the patient can be life-long, a minimal or non-invasive screening method would be a better choice. Virtual CT cystoscopy has become a promising method that can be used as a screening tool in the follow-up of these patients to reduce the number of repeated conventional cystoscopies. Up to date, it is mainly used for patients with contraindications for conventional method.

CT cystography and virtual cystoscopy is performed by axial scanning of bladder after drainage of urine and distension of bladder with room air or carbon dioxide. The axial source data is reconstructed using surface rendering or volume rendering algorithm to obtain virtual cystoscopic images which allows real time three dimensional fly through examination of the bladder. The accuracy of CT cystoscopy for identifying masses greater than 5 mm in diameter was shown to be 100% and the accuracy for detecting neoplasm in these lesions was 95% (13). However, the reliability of virtual cystoscopy in detection and characterization of lesions smaller than 10 mm is inadequate. Recently, MDCT scanners promise better results in detection of small lesions due to improved spatial resolution.



Fig. 3. — Contrast enhanced computed tomography images at nephrographic (A) and urographic (B) phases demonstrate a papillary bladder cancer lesion at posterior wall of the bladder (arrows). Same lesion is also visualized at virtual CT cystography (C) (arrow).

Kim et al. reported a detection rate of 85% in lesions smaller than 10 mm using a 4-detector CT scanner (4). Tsampoulas et al., showed an overall sensitivity of 96% in detection of bladder cancer using a 16-detector CT (14). Virtual cystoscopy can also be performed by filling the bladder with contrast agent instead of air.

Magnetic resonance imaging

Magnetic resonance imaging has advantages over CT for staging

bladder neoplasm with its high soft tissue resolution, and direct multi-planar imaging capabilities. It has comparable results for detection of bladder carcinoma. A standard MRI protocol should include T1-weighted spin echo images of the entire pelvis, T2-weighted fast spin echo images of the bladder with a small field of view in at least two different planes, pre and post contrast dynamic T1-weighted images with fat suppression. For dynamic imaging, arterial and later phase images are



Fig. 4. — Contrast enhanced computed tomography of male admitted with hematuria demonstrates a tumor lesion localized at the left sided bladder diverticula (arrow).

obtained with fast spoiled gradient echo sequences. Optimal distention of the bladder is crucial for diagnostic accuracy and this can be achieved by instructing the patient to not void for at least 2 hours before the examination.

T1-weighted images are helpful in detecting extravescical infiltration of bladder cancer, adjacent organ invasion (except prostate), pelvic lymphadenopathies and bone metastasis. Bladder wall and tumor demonstrate a low to intermediate signal intensity that is significantly different from high signal intensity of the perivesical fat and low signal intensity urine. T2-weighted images are mainly used to determine the depth of bladder wall invasion, presence of adjacent organ and pelvic side wall involvement. On T2-weighted images, bladder tumors show intermediate signal intensity whereas; bladder wall and urine are characterized with low and high signal intensities, respectively. Dynamic contrast-enhanced images also delineate the presence and extent of muscle invasion and may differentiate tumor from fibrosis or edema. However, this distinction is still difficult to make shortly after transurethral resection. Bladder cancer enhances strongly and earlier than bladder wall on dynamic enhanced images. In staging, both T1- and T2-weighted images are helpful. Muscular layer invasion manifests as an interruption of the normal bladder wall signal intensity by the tumor signal. Presence of perivesical fat extension on T1- and T2-weighted images is consistent with a stage 3 disease (Fig. 5).

The accuracy of MRI in the staging of bladder cancer and in detecting deep muscle invasion ranges from 62% to 85% and 82% to

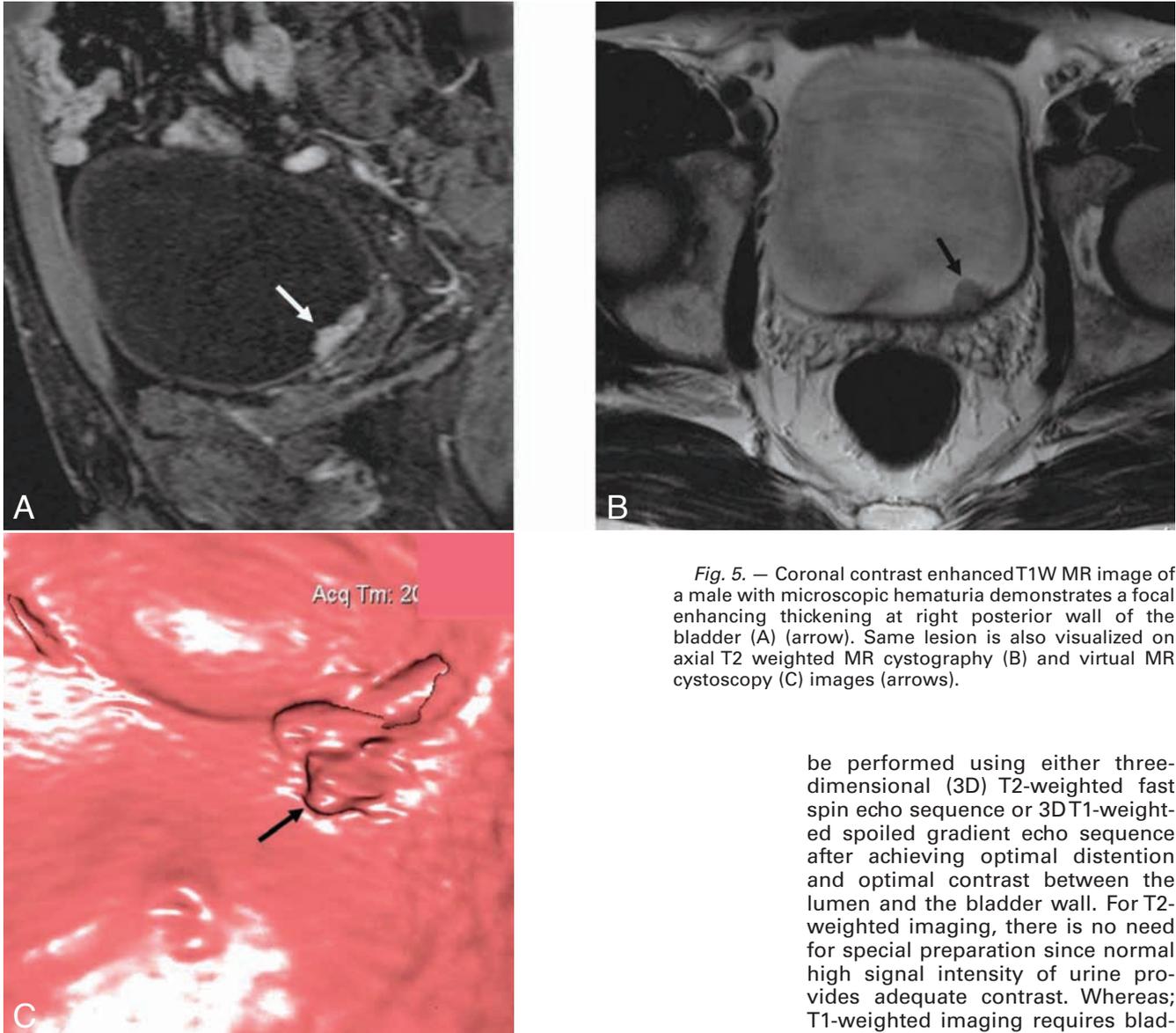


Fig. 5. — Coronal contrast enhanced T1W MR image of a male with microscopic hematuria demonstrates a focal enhancing thickening at right posterior wall of the bladder (A) (arrow). Same lesion is also visualized on axial T2 weighted MR cystography (B) and virtual MR cystoscopy (C) images (arrows).

96%, respectively (15-20). Overstaging has shown to be the most common error, which may be due to the presence of post-biopsy inflammation and edema. However, Tekes et al. concluded that the time interval was not affecting the accuracy of MRI in differentiating superficial and muscle invasive tumor (15).

Metastatic lymph nodes have no specific signal intensity characteristics on both T1 and T2 weighted images; staging for nodal metastases relies on anatomic size and morphology criteria, similar to CT. With these criteria, microscopic metastasis in normal sized lymph nodes can easily be missed. Recently, IV administration of Ferumoxtran-10, which consists of ultra-small iron particles, has enabled better results in depicting nodal metastases even in normal sized lymph nodes. Deposition of

Ferumoxtran-10 in macrophages of normal lymph nodes causes signal loss on T2* weighted images. On the other hand, metastatic lymph nodes are characterized by high signal intensity since normal macrophages are replaced by tumor cells. Deserno et al. reported a significant improvement in nodal staging due to better depiction of metastases with the use of Ferumoxtran-10 in patients with bladder cancer (21). Distant metastasis can be screened by either MRI or CT, but MRI is superior for the evaluation of bone marrow metastasis.

Similar to CT, virtual MR cystoscopy is also a potential alternative to conventional cystoscopy. However, one advantage of MR over CT is that it does not require radiation exposure and therefore, can be repeated more frequently as a screening tool. MR cystography can

be performed using either three-dimensional (3D) T2-weighted fast spin echo sequence or 3DT1-weighted spoiled gradient echo sequence after achieving optimal distention and optimal contrast between the lumen and the bladder wall. For T2-weighted imaging, there is no need for special preparation since normal high signal intensity of urine provides adequate contrast. Whereas, T1-weighted imaging requires bladder filling with gadolinium based contrast agent via a catheter or intravenous application to obtain adequate contrast. Alternatively, for obtaining non-contrast T1-weighted images, bladder can be distended by air similar to CT application. Virtual cystoscopy images are reconstructed from these volumetric dataset using same post-processing techniques with CT. The tumor detection rate of MR cystography and virtual MR cystoscopy ranges between 70% and 100% depending on the size of the tumor (22, 23). All studies agree that the accuracy of this technique is limited for tumors smaller than 5 mm in diameter, on the other hand, anterior bladder wall and intradiverticular lesions, which are challenging to detect via cystoscopy, can be more easily detected and better depicted on MR cystoscopy (24).

Recently, El-Assmy and Matsuki examined the feasibility of diffusion

weighted (DW) MRI in detection of bladder cancer. Initial results showed that bladder carcinomas had significantly lower apparent diffusion coefficient (ADC) values compared to surrounding tissues. Sensitivity and positive predictive values were 100% in both of those studies. These preliminary results promise the use of DW MRI in detection of bladder cancer. However, further studies are required to better understand the reliability of this technique (25, 26).

Positron emission tomography (PET)

Positron emission tomography (PET) has been increasingly utilized in Oncology. While the routine clinical spatial resolution of PET imaging is limited (~4-6 mm), the ability to interrogate specific physiological processes, such as the rate of glucose and/or fatty acid metabolism, provides information which cannot be obtained with other anatomical imaging techniques. The most common tracer for PET imaging, ^{18}F -fluoro-2-deoxy-2-D-glucose (^{18}F -FDG) has been proved helpful in initial staging re-staging, and monitoring response to treatment in a wide variety of tumors. However, the main obstacle in the evaluation of bladder cancer is that the urinary excretion of ^{18}F -FDG interferes with the visualization of primary tumors and regional lymph nodes (Fig. 6) (27). In order to help overcome this limitation, Kamel et al. employed a method of diuretics and parenteral physiologic saline infusion in order to better evaluate abdominopelvic malignancies (28). In a study by Anjos et al., diuretics and oral hydration were used to remove excreted tracer in 17 patients, 11 of whom had not undergone cystectomy. ^{18}F -FDG PET was able to detect bladder lesions in 6 of these 11 patients and 41% of patients were upstaged based on diuretic mediated ^{18}F -FDG PET scans (29). There have been few reports on the utility of ^{18}F -FDG PET in detection of distant metastases in bladder cancer (Fig. 7, 8). Kosuda et al. assessed the feasibility of ^{18}F -FDG PET imaging in 12 patients with histologically proven bladder cancer. They were able to demonstrate all sites of distant metastases and 2 of 3 nodal metastases (30). Heicappell et al. demonstrated the utility of ^{18}F -FDG PET in pretreatment evaluation of distant metastases in bladder cancer in a limited patient population of 8, 3 of whom had nodal

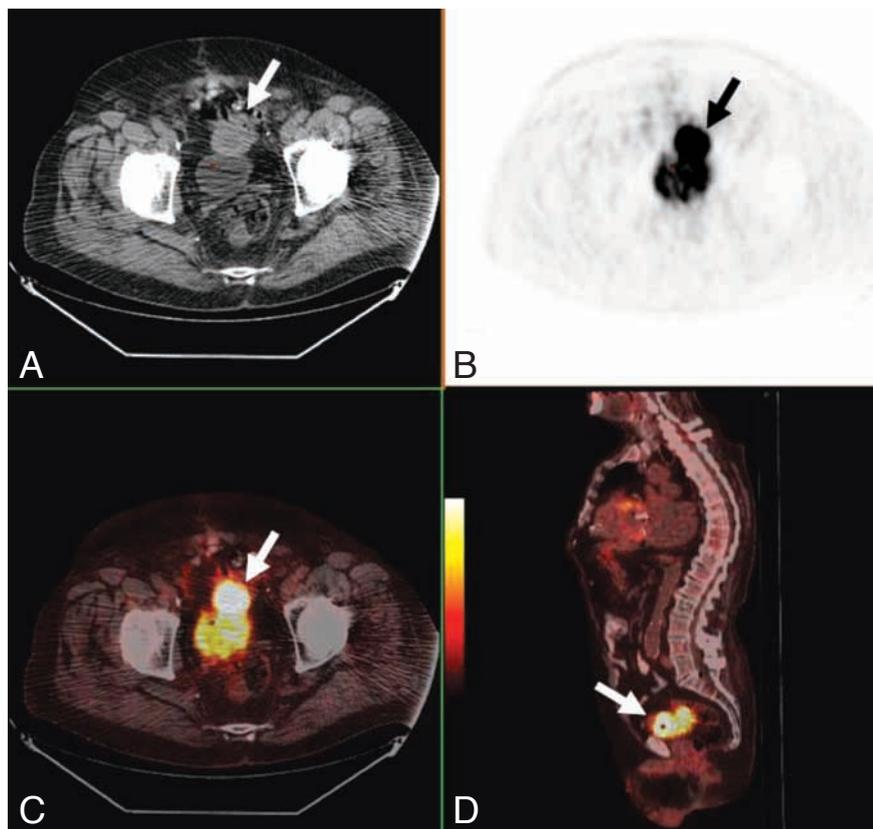


Fig. 6. — Axial CT (A), PET (B), axial (C) and coronal (D) fused ^{18}F -FDG PET-CT images of a male demonstrate a focus of increased radiotracer uptake at the anterior wall of the bladder consistent with bladder cancer (arrows).

metastases (31). More recently, in a study involving 47 evaluable patients, ^{18}F -FDG PET/CT detected more malignant disease than conventional CT/MRI in 40% of patients and demonstrated overall sensitivity and specificity of 87% and 88% respectively. Moreover, the use of ^{18}F -FDG PET/CT changed management in 68% of patients (32). The limitations associated with urinary excretion of ^{18}F -FDG have led to attempts in investigation of different tracers that are not excreted in urine. Carbon-11 labeled choline (^{11}C -choline), which is not excreted by the kidneys, has been reported as a new PET agent for tumor detection and staging. Choline is an important component of the phospholipids in the cell membranes and elevated levels of choline and choline kinase can be found in malignant cells with high proliferation and increased cell membrane metabolism, all of which can result in increased ^{11}C -choline uptake on PET. De Jong et al. evaluated 5 healthy volunteers and 18 patients with bladder cancer with ^{11}C -choline PET. The tracer uptake of bladder wall was low in 5 healthy subjects and tumor foci were

demonstrated in 10 patients and lymph node metastases in 2 patients. Moreover, urinary tract radioactivity was absent in 27 of 28 subjects (33). Gofrit et al. used ^{11}C -choline PET in preoperative staging of 18 patients with 19 tumor regions and ^{11}C -choline uptake was found to be increased in all cancer lesions. In 6 patients, uptake of ^{11}C -choline in lymph nodes as small as 5 mm was visualized. Of these patients, 4 underwent surgery and histopathology confirmed malignancy in 3 of 4 (34). Picchio et al. compared diagnostic accuracies of contrast enhanced CT and ^{11}C -choline PET in 27 patients with urothelial bladder cancer, and concluded that ^{11}C -choline PET is comparable to CT in residual disease detection, but superior to CT in lymph node metastases visualization (35). Recently, Yoshida et al. reported ^{11}C -choline PET findings in 4 cases of bladder cancer. In one patient, a tumor focus was detected within the bladder with accompanying bone metastases, which was negative on bone scan. In the remaining 3 cases, intense accumulation of the tracer within the bladder hampered the ^{11}C -choline

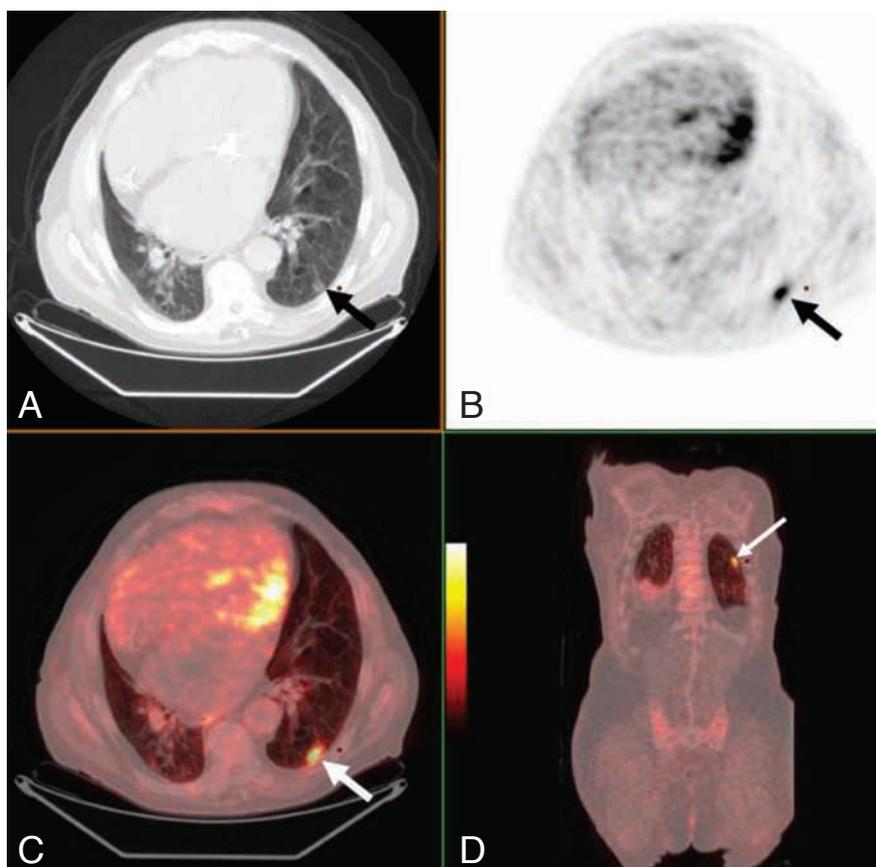


Fig. 7. — Axial CT (A), PET (B), axial (C) and coronal (D) fused ^{18}F -FDG PET-CT images of a male with bladder cancer (same patient in fig. 6) demonstrate a focus of increased radiotracer uptake at lower lobe of left lung consistent with metastases from bladder cancer (arrows).

PET evaluation and this accumulation was attributed to inflammatory and proliferative changes secondary to previous catheterizations (36).

Amino acid transport and mechanism can be increased in cancer cells resulting in increased uptake of ^{11}C -methionine. Similar to ^{11}C -choline, ^{11}C -methionine is not excreted in urine and can be used in detection of urinary tract malignancies by PET. Letocha et al. investigated the utility of ^{11}C -methionine PET for diagnosis and treatment evaluation in 29 patients. In this study, the diagnostic accuracy of ^{11}C -methionine PET was poor and the technique did not monitor the therapeutic effect of neoadjuvant chemotherapy (37). The same group evaluated the utility of ^{11}C -methionine PET in the diagnosis and staging of urinary bladder carcinoma in a cohort of 23 patients. Eighteen of 23 primary tumors were detected on ^{11}C -methionine PET; moreover, tracer uptake levels were shown to be positively correlating with tumor stage (38).

In regards to PET imaging of bladder cancer, ^{18}F -FDG PET is useful for

detection of distant metastases, whereas its value is limited for detection of primary tumors or local recurrence. Though PET experience is limited with novel tracers such as ^{11}C -choline and ^{11}C -methionine, may play a role in the detection of tumor lesions confined the bladder.

Conclusion

Bladder cancer is a common cancer type among men with propensity of multifocality and high recurrence rates. Imaging plays an important role in the early diagnosis and the staging of bladder cancer. Among current imaging modalities, ultrasound is used as a screening method for patients with hematuria, whereas CT and MR cystogram (with virtual applications) appear to be more accurate for lesion detection as well as for local staging. PET-CT with ^{18}F -FDG has limited role in diagnosis and local staging due to urinary excretion of the tracer, but it can be utilized for the depiction of distant metastases. Finally, early results of PET-CT applications with ^{11}C -choline



Fig. 8. — 62-year-old female with bladder cancer, status post cystectomy with ileal conduit. ^{18}F -FDG PET-CT image shows hypermetabolic adenopathies in the paraaortic and bilateral common iliac regions (arrowheads), as well as in the left external iliac region (short arrows). There is an additional small node in the left supraclavicular region, which is suspicious for metastasis (arrow) (Image courtesy of Dr. Mark P. Dunphy from Memorial Sloan-Kettering Cancer Center, New York, NY, USA).

and ^{11}C -methionine, which are not excreted through urine, can be more helpful for early diagnosis and local staging, but further research is required in this field.

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