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Updates for the radiologist in non-muscle-invasive, muscle-invasive, and metastatic bladder cancer

Jooae Choe,[1] Marta Braschi-Amirfarzan,[2,3] Sree Harsha Tirumani,[3] Atul B. Shinagare,[2,3] Kyung Won Kim,[1] Nikhil H. Ramaiya,[2,3] Katherine M. Krajewski[2,3]

[1]Department of Radiology and Research Institute of Radiology, Asan Medical Center, University of Ulsan College of Medicine, 86 Asanbyeongwon-gil, Songpa-gu, Seoul 138-736, Republic of Korea
[2]Department of Imaging, Dana Farber Cancer Institute, Harvard Medical School, 450 Brookline Avenue, Boston, MA 02215, USA
[3]Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA

Abstract

Urothelial bladder cancer is a common malignancy requiring a multidisciplinary approach to treatment. Significant recent advances have been made in terms of the genetic and molecular characterization of bladder cancer subtypes, and novel treatment approaches are being investigated and approved. Given the important role of imaging in the diagnosis, staging, and follow-up of this disease, it is necessary for radiologists to remain up-to-date in terms of nomenclature and standards of care. In this review, recent developments in bladder cancer characterization and treatment will be discussed, with reference to the contributions of imaging in non-muscle-invasive, muscle-invasive, and metastatic settings.

Key words: Bladder cancer—Urothelial carcinoma—Diagnosis—Management—Oncologic imaging

Bladder cancer is one of the most common malignancies of the urinary tract, which is predominantly a disease of older men (M:F = 4:1). The American Cancer Society's estimates for bladder cancer in the United States for 2016 are about 76,960 new cases per year (about 58,950 in men and 18,010 in women) and about 16,390 cancer-related deaths from bladder cancer (about 11,820 in men and 4570 in women) [1]. Imaging plays an important role in bladder cancer staging and follow-up, and accurate interpretation is necessary for optimized disease management and survival outcomes. It is therefore important for radiologists who interpret imaging studies of bladder cancer patients to be familiar with current standards of care as well as advances on the horizon, including efforts to genetically and molecularly characterize disease subtypes and novel treatment approaches. Recently, the U.S. Food and Drug administration approved an immune checkpoint inhibitor for patients with locally advanced or metastatic urothelial cancer, representing the first new treatment approved for bladder cancer in over thirty years. In this article, we provide a practical review of current bladder cancer diagnosis, relevant genomics, imaging, and management in non-muscle-invasive, muscle-invasive, and metastatic disease.

Clinical, pathologic, and molecular features of urothelial bladder cancer

Patients with suspected bladder cancer most commonly present with painless hematuria [2, 3]. Some may also have irritative symptoms such as dysuria, frequency, or urgency. According to the 2012 revised guidelines from American Urological Association (AUA) [2], assessment of a patient with asymptomatic hematuria begins with medical history, physical examination, and laboratory examination, to assess for potential benign causes as well as risk factors for malignancy. In adults over age 35, asymptomatic hematuria often prompts a thorough urologic evaluation including urine cytology, cystoscopy, and imaging of the upper urinary tracts (commonly using multiphasic CT urography). If intravenous contrast use is contraindicated in a patient, an MR urogram or retrograde pyelogram in combination with non-contrast, cross-sectional imaging is an alternative diagnostic tool [4].

In various reports, the incidence of urologic cancers in adults with asymptomatic gross or microscopic

Correspondence to: Jooae Choe; *email:* jooae23@gmail.com

hematuria is on the order of 5%–10% [5–7]. Most of these are urothelial carcinomas (UC), greater than 90% of which arise from the urinary bladder, 8% arise from the renal pelvis, and 2% from ureter or urethra. While greater than 90% of bladder cancers are pure UC, other non-urothelial cancers include pure squamous cell carcinoma (3% of bladder tumors in the U.S.), pure adenocarcinomas (often urachal, 1.4%), and small cell tumors (1%) (Table 1). Variant morphologies of UC have also been described, containing variable amounts of typical UC with elements of "divergent differentiation" including squamous and glandular variants, as well as UC micropapillary, plasmacytoid, or sarcomatoid features [8, 9]. Variant subtypes of UC are generally associated with aggressive disease and worse prognosis [8, 10].

Urothelial tumor staging and grading remain paramount in guiding management decisions. The latest WHO criteria (2016) divide urothelial neoplasms into non-invasive lesions (papillary lesions [Ta] and carcinoma in situ [Tis]) and infiltrating urothelial carcinoma, which invades beyond the basement membrane [10]. Urothelial carcinoma is staged according to the TNM system (Table 2).

Papillary lesions include papilloma, papillary urothelial neoplasm of uncertain or low malignant potential, and papillary urothelial carcinoma of low or high grade (Fig. 1). Activating mutations in the fibroblast growth factor receptor 3 (FGFR3) gene, which encodes a receptor tyrosine kinase involved in cell growth and survival pathways, occur more frequently in non-invasive papillary tumors than in flat or invasive tumors and selectively identify patients with favorable disease features [14–16]. Additionally, alterations/mutations in the catalytic subunit of phosphoinositide 3-kinase (PIK3CA) have been significantly associated with reduced recurrence of non-muscle-invasive bladder cancer [17] (Table 3).

Pathology literature emphasizes the distinct nature of papillary and flat tumor growth patterns, reflecting different underlying genetic/molecular alterations and differing biologic behavior of such lesions [18]. Flat lesions include urothelial proliferation of uncertain malignant potential (hyperplasia [19]), dysplasia, and carcinoma in situ. In contrast to papillary lesions, high-grade flat and invasive lesions have been associated with inactivating mutations in tumor suppressor genes such as TP53 and RB1. One report examining 144 biopsy specimens from urothelial carcinoma patients identified two major molecular subtypes (MS1 and MS2) with differing genomic, gene mutation and gene expression features [20]. MS1 tumors demonstrated more activating FGFR3/PIK3CA mutations, whereas MS2 tumors were characterized by greater genomic instability, TP53/MDM2 alterations, and RB1 losses. Lindgren et al. defined gene signatures differentiating low- from high-grade tumors, as well as non-muscle-invasive from muscle-invasive tumors with high precision and sensitivity. Molecular characterization of muscle-invasive urothelial bladder carcinoma has been undertaken by the Cancer Genome Atlas project as well, with analysis of 131 tumors [21]. This study identified a large number of DNA alterations in general, third in number behind lung cancer and melanoma, among all cancers study by the Cancer Genome Atlas project. Statistically significant recurrent mutations in 32 genes involving the aforementioned pathways, and potential therapeutic targets were identified in 69% of the tumors evaluated.

The genetic milieu of bladder cancer and its treatment implications are just starting to be understood. While the distinction between non-invasive and invasive disease is

Table 1. Histological classification of bladder cancer

Infiltrating urothelial carcinoma
Squamous differentiation
Glandular differentiation
Trophoblastic differentiation
Nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Lymphoma-like
Plasmacytoid
Sarcomatoid
Giant cell
Undifferentiated
Squamous cell carcinoma
Adenocarcinoma (enteric, mucinous, signet-ring cell, and clear cell)
Small cell carcinoma

Table 2. TNM staging for bladder cancer

T—primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumour
Ta	Non-invasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopically
T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the prostate, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate, uterus, or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N—regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node 2 cm or less in greatest dimension
N2	Metastasis in a single lymph node more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
N3	Metastasis in a lymph node more than 5 cm in greatest dimension
M—distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

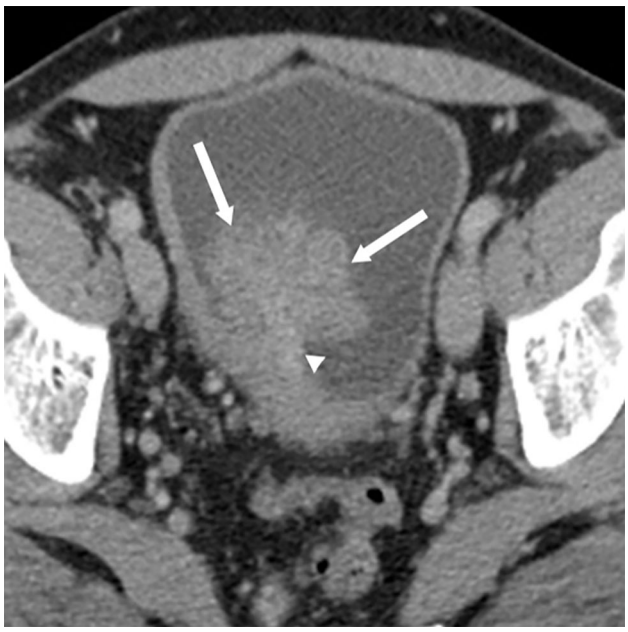


Fig. 1. 54-year-old man with high-grade, invasive papillary urothelial cancer of bladder. **A** Axial CT image at diagnosis shows a large polypoid enhancing mass (*white arrows* **A**), originating from a thickened right posterolateral bladder wall (*white arrowhead* **A**). Subsequent cystectomy revealed T3a disease.

important, there are three clinically relevant categories of bladder cancer patients: namely patients with non-muscle-invasive bladder cancer (Ta, Tis and T1 UC), non-metastatic muscle-invasive bladder cancer (T2 and above), and metastatic disease. Patients are commonly managed according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, last updated in 2016 [22]. Since imaging contributes to staging and follow-up/surveillance of bladder cancer patients with these categories of disease, the role of the radiologist will be discussed in each setting.

Non-muscle-invasive bladder cancer

Non-muscle-invasive bladder cancer (NMIBC) is the most common form of bladder cancer, representing three quarters of patients with bladder cancer, typically low grade [12]. These can be multifocal and can arise from hyperplastic epithelium. Goals of care for NMIBC patients include accurate staging, cure, and identification of risk factors [including high-grade papillary (Ta), T1 urothelial carcinoma and carcinoma in situ] which may increase the risk of recurrence or progression. Five-year recurrence rates depend upon risk factors, however range from 31% to 78% [23], and thus these patients require long-term monitoring.

In NMIBC, diagnosis primarily relies upon cystoscopy and tissue sampling. If the cystoscopic appearance of a bladder tumor is solid (sessile), or if high-grade features or muscle invasion is suspected, imaging with abdominopelvic CT or MRI is recommended before transurethreal resection of bladder tumor (TURBT) according to the NCCN guidelines [22]. However, if the tumor is papillary in appearance or if only mucosal abnormality is suspected, imaging can be performed after TURBT, as findings will rarely change management in these situations. The role of imaging in NMIBC includes concomitant assessment of the bladder and upper urinary tracts, for potential synchronous tumors. Upper tract tumors occur in less than 5% of patients but may be more likely in patients with tumor at the trigone, carcinoma in situ, and/or high-risk disease [24].

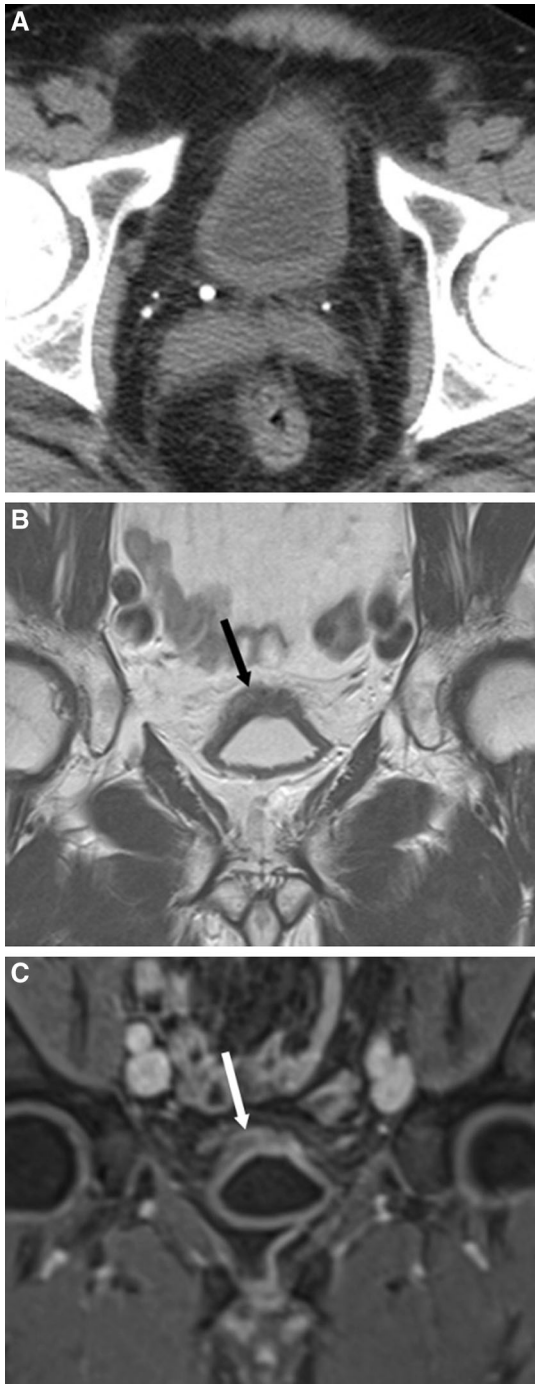
Imaging

General imaging findings in urothelial bladder cancer have been well described in the literature. Urothelial carcinoma manifests as either single or multiple nodular, sessile, or infiltrating lesion (s) with blood flow or early enhancement [11]. Specific MR imaging features of papillary lesions have been described, including the presence

Table 3. Genetic mutations in bladder cancer

Affected gene	Function
Fibroblast growth factor receptor 3 (FGFR3)	Modulating RTK/RAS signaling pathway Associated with low-grade superficial papillary urothelial carcinoma, NMIBC
HRAS	Favorable disease feature
Phosphoinositide 3-kinase (PIK3CA)	More activated in MS1 tumor, associated with reduced recurrence of NMIBC
TP53	Tumor suppressor gene
MDM2	Associated with high-grade dysplasia and MIBC
RB1	Tend to metastasize
PTEN (phosphatase and tensin homology)	More frequent deletion in MIBC, associated with high-grade stage and grade (opposite pattern compared to activating PIK3CA mutations) Dephosphorylates PI3P, which prevents it from activating downstream proliferation and survival signals (PTEN-PI3K-AKT pathway)

RTK, receptor tyrosine kinase; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; PI3P, phosphoinositol (3,4,5)-trisphosphate



◀**Fig. 2.** 59-year-old man with history of non-muscle-invasive (T1) bladder cancer treated with multiple TURBT, perioperative mitomycin C, and instillations of Bacillus Calmette–Guérin (BCG). **A** Axial non-contrast CT image after initial TURBT shows a diffusely thickened though underdistended urinary bladder. Mild stranding is seen in the adjacent perivesical fat. **B** Follow-up coronal T2-weighted MR image was obtained 5 months after intravesical BCG, repeat TUR and perioperative mitomycin C demonstrates irregular asymmetric thickening of the superior bladder wall (*black arrow* **B**). **C** Fat-suppressed gadolinium chelate-enhanced T1-weighted image at the same level shows significant enhancement with extension to perivesical fat (*white arrow* **C**). Imaging features were worrisome for recurrent bladder cancer. However, benign urothelial mucosa was pathologically confirmed; imaging findings were then attributed to post-treatment change after intravesical BCG.

of a stalk of lower T2 signal intensity to tumor, with less enhancement on dynamic contrast-enhanced images and stronger enhancement on delayed images [13].

CT urography (CTU) is most commonly employed for upper and lower urinary tract imaging. A multiphasic scan protocol is used, including unenhanced imaging of the abdomen and pelvis, a nephrographic phase scan of the kidneys, and an excretory phase scan of the abdomen and pelvis, with desired homogeneous opacification of urine to improve bladder cancer detection [25, 26]. Sometimes, the nephrographic and excretory phases can be combined following a split-bolus of intravenous contrast medium in an attempt to reduce the radiation dose [27]. Patients are asked to void immediately prior to the CT, and intravenous diuretics may be administered to increase bladder filling. Another alternative method for homogeneous bladder opacification is to actively mix bladder contents by rolling the patients on the CT table or making patients walk around the CT room before the excretory phase image acquisition [28, 29]. CTU has a reported sensitivity of 79% and specificity of over 95% for the diagnosis of bladder cancer in patients with hematuria [30].

Importantly, CT urography is complimentary to (not a replacement for) diagnostic cystoscopy in most patients. A limitation of CT is that it does not allow the confident diagnosis of flat lesions or lesions at the bladder base adjacent to the prostate gland, particularly in patients with benign prostatic hypertrophy. Additionally, the diagnostic accuracy of CT is considerably lower in patients with previous urothelial cancer, because it may be difficult to differentiate tumor recurrence from inflammatory wall thickening or postoperative/post-treatment changes after transurethral resection of bladder tumor (TURBT).

Management and follow-up

Complete TURBT is the primary means of diagnosis and treatment of NMIBC. A second or repeat TURBT is recommended in case of incomplete first TURBT, no muscle in the biopsy specimen, or high-risk non-muscle-invasive bladder cancer (cT1 or high grade). Cystectomy may be considered in patients with high-grade T1 cancer. Intravesical therapy using BCG or mitomycin C is used as prophylactic or adjuvant therapy after a complete endoscopic resection in a high-risk patients (high-grade papillary, T1 UC or carcinoma in situ) or rarely, as a therapy eradicating residual disease which could not be resected completely. Close follow up for all patients is

needed according to risk group, and upper tract imaging should be repeated every one to two years in a high-risk patient. It is important for radiologists to have an awareness of prior TURBT, with or without intravesical therapy, to best interpret follow-up studies of affected patients (Fig. 2). Intravesical BCG-related complications, such as granulomatous disease, may mimic primary or metastatic tumors in patients, including cystitis, granulomatous prostatitis, renal abscesses, pneumonitis, and hepatitis, among other entities [31]. Radiologists should consider this possibility when imaging abnormalities are encountered, especially in patients treated with intravesical treatment, and biopsy of the relevant abnormalities may be necessary to provide a diagnosis in difficult cases.

Non-metastatic muscle-invasive bladder cancer

A minority of patients present with non-metastatic muscle-invasive bladder cancer (MIBC). Treatment in this group includes removal of the tumor with curative intent and systemic therapy to optimize the chances of cure. Accurate staging is pivotal to appropriate management. When MIBC is detected, the workup includes cross-sectional imaging of the abdomen and pelvis (including upper tract imaging), chest radiographs, and examination under anesthesia. If alkaline phosphatase is elevated, a bone scan can also be obtained for staging.

Imaging

In MIBC, multiparametric MRI is often employed due to its high soft-tissue contrast resolution which allows differentiation between bladder wall layers and intramural tumor invasion [32, 33] Protocols often include T2-weighted images (three standard orthogonal planes), axial T1-weighted images, dynamic contrast-enhanced images, and diffusion-weighted images [33, 34] (Table 4). Compared to bladder wall which shows low signal intensity (SI) on T2-weighted images, tumor shows increased SI, therefore, in patients with muscle-invasive tumor, the low SI muscle layer is interrupted by tumor. In patients with extravesical disease spread, a clear extravesical mass can be seen in stage T3b disease, and adjacent organ invasion can also be visualized in T4 disease. However, the T2 SI of tumor can be variable, sometimes similar to detrusor muscle [32]. Additionally, inflammatory change or fibrosis adjacent to tumor can cause overstaging. Axial spin-echo (SE) T1-weighted images with a large FOV are useful for evaluating the perivesical fat planes for extravesical tumor infiltration, pelvic lymphadenopathy, and bone metastases (Fig. 3). The usefulness of dynamic contrast-enhanced T1-weighted images is still debatable, and overall accuracy of staging using dynamic contrast-enhanced MRI is reportedly 52%–85% [32, 34–36]. Three-dimensional fat-suppressed fast spoiled GRE T1-weighted images demonstrate early enhancement of tumor, mucosa, and submucosa, and later enhancement of the muscle layer.

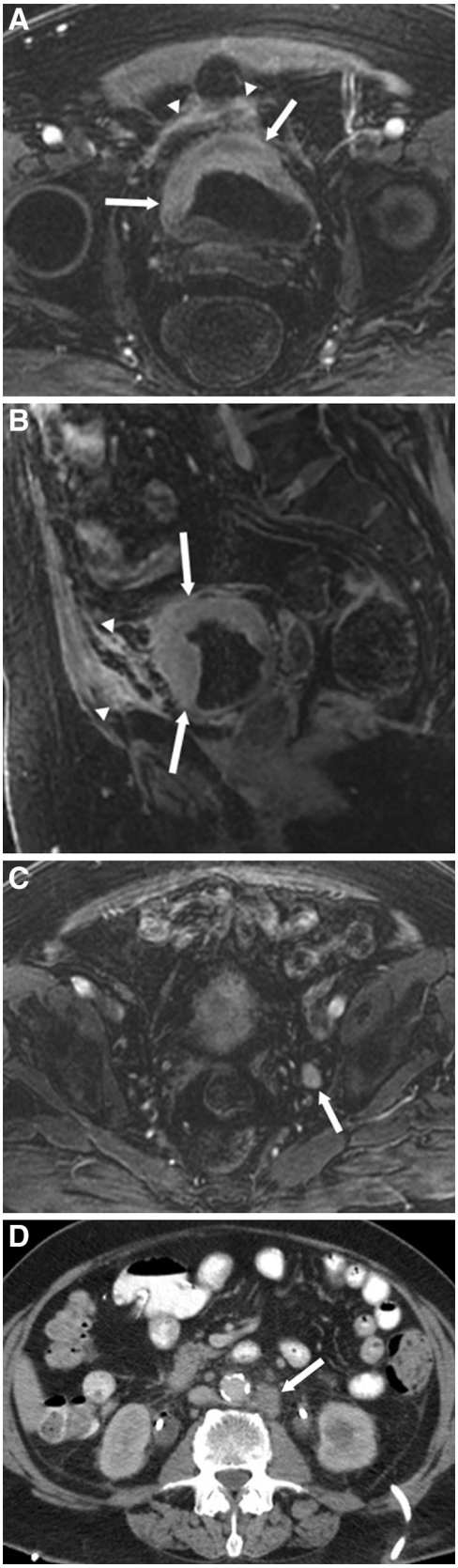
Diffusion-weighted imaging (DWI) contributes to bladder cancer staging. On DWI, the SI of background tissue is suppressed while bladder cancer is of high SI. Literature supports the role of DWI in differentiating muscle-invasive from non-muscle-invasive tumors (Fig. 4), and ADC has been found to be predictive of histologic grade [35]. Furthermore, DWI of the entire pelvis and lower abdomen has the potential to improve accurate pelvic lymph node assessment [37–39], which could improve upon the known limitations of anatomic assessment of nodes by CT/MRI. While pelvic lymph node dissection is increasingly being performed for muscle-invasive bladder cancer, it is important to identify nodes in the common iliac chain or in the retroperitoneum, which may not be included in the usual operative field. In the recent reports, DWI could be the promising tool for differentiating benign from early malignant lymph nodes [38, 40] but further validation studies are needed.

Clinical–pathologic stage discrepancies in bladder cancer remain problematic. The accuracy of contrast-enhanced CT for local staging of bladder cancer is only

Table 4. 3T-MR protocol for evaluating bladder cancer

Sequence	Plane	TR/TE (ms)	Flip angle	Bandwidth	FOV (cm)	Slice thickness (mm)	Matrix	Echo train length
T2W TSE	Axial (P), sagittal (P), coronal (P)	7080/65	160	200	28	4	512 × 512	15
T1W TSE	Axial (P)	600/12	160	170	28	4	512 × 512	3
T1W FS TSE	Axial (P)	730/9	160	170	28	4	512 × 512	3
Gd-enhanced T1W TSE	Axial (P), sagittal (P), coronal (P)	890/12	160	170	28	4	512 × 512	3
DWI	Axial (P)	7500/75	90	2220	36	4	128 × 128	63
DWIBS	Coronal (AP)	10500/76	90	2055	40	4	128 × 128	47
T2 SSH TSE	Axial (AP)	1300/92	160	710	36	4	320 × 320	90

T2W, T2 weighted; TSE, turbo spin echo; FS, fat suppressed; GRE, gradient echo sequences; DWI, diffusion-weighted image; DWIBS, diffusion-weighted whole-body imaging with background body signal suppression; SSH, single-shot turbo spin echo; P, pelvis (scan range); AP, abdomen and pelvis (scan range)



◀**Fig. 3.** 69-year-old man with muscle-invasive urothelial carcinoma (cT4b stage). **A** Axial and **B** sagittal fat-suppressed gadolinium chelate-enhanced T1-weighted MRI shows marked thickening of anterior and right lateral bladder wall (*white arrow* **A**), ill-defined enhancement in the space of Retzius and along the posterior aspect of the inferior rectus abdominis muscle (*white arrowheads* **B**). **C** Axial T1 post-contrast image shows an enlarged left obturator lymph node, representing a lymph node metastasis. **D** Axial contrast-enhanced CT images obtained after radical cystectomy and 8 months of adjuvant treatment shows left paraortic adenopathy (*white arrow* **D**).

40%–60% [41, 42]. Although the overall accuracy of staging using MRI is reportedly moderate according to previous studies (52%–93%) [32, 43], it better demonstrates the extent of bladder wall invasion and perivesical disease for differentiating superficial (≤T1) vs invasive (≥T2) disease and organ-confined (≤T2) vs non-organ-confined (≥T3) disease with good reproducibility compared to CT. Microscopic perivesical spread (stage T3a disease) cannot be identified with either CT or MRI. Improved detection of perivesical fat stranding on MRI, which could represent reactive/inflammatory change or extravesical spread of tumor, could lead to increased sensitivity but decreased specificity, with overestimation of tumor extent. For the differentiation of T2 and T1 disease, non-malignant changes associated with recent transurethral resection could also result in overstaging of cancer. For these reasons, the overall staging accuracy of MR remains lower than desired.

In terms of lymph node staging, CT has an accuracy of 70%–90%, with false-negative rates of 25%–40%, whereas MR imaging has an accuracy of 64%–92% [44, 45]. 18F-FDG PET/CT is of limited utility in bladder cancer, mainly because the urinary excretion of 18F-FDG interferes with the ability to distinguish wall activity from luminal activity [46]. Other tracers like 11C-choline, 11C-acetate, and 11C-methionine, all of which have minimal urinary excretion, have been used for PET/CT in bladder cancer in some cases. In previous preliminary studies, 11C-acetate and 11C-choline showed equivalent results in preoperative evaluation of bladder cancer and seemed to be promising tracers which could contribute to select patients who would benefit from neoadjuvant chemotherapy due to their high specificity and negative predictive value for lymph node involvement [47]. However, in a subsequent study of 11-C-choline PET/CT, there was limited depiction of local disease (high rate of false-negative results) [48]. The high rate of true-positive and true-negative results in lymph node disease in this report led the authors to suggest that this technique was most useful in patients with a high risk of nodal metastasis.

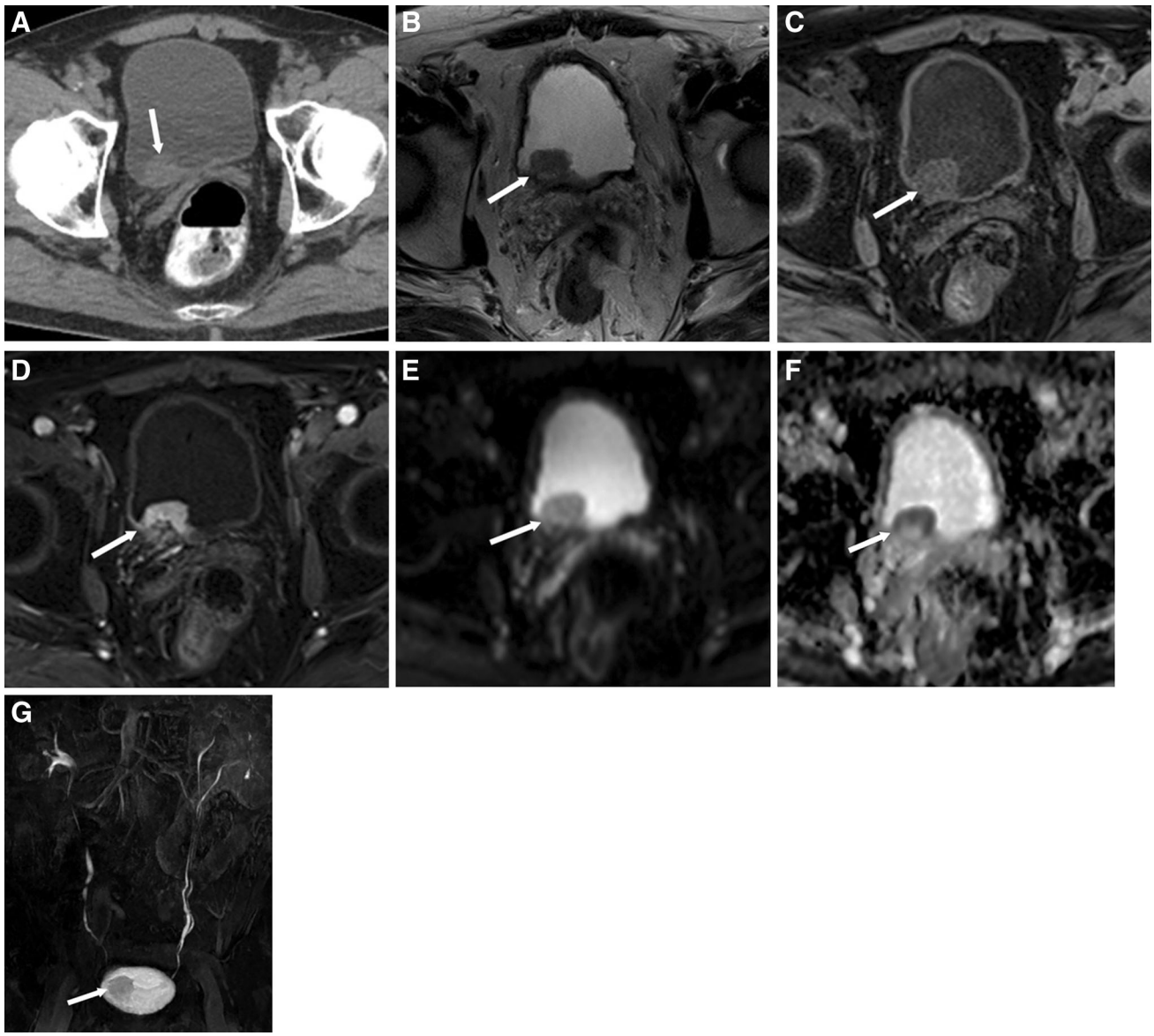


Fig. 4. 75-year-old man with staging work up for bladder cancer (pT1 stage). **A** Axial non-contrast CT image shows an irregular mass in right posterior bladder wall, concerning for bladder cancer. There was no evidence of distant metastatic disease. **B** Axial T2-weighted MR image shows an intermediate signal intensity mass corresponding to the right posterior bladder wall CT finding, in close proximity to right ureterovesical junction. High signal intensity along the posterior detrusor muscle of bladder raised concern for muscle invasion (*white arrow* **B**). **C**, **D** Axial fat-suppressed T1-weighted images pre and post intravenous injection of gadolinium show avid enhancement of the tumor and subtle enhancement of the adjacent detrusor muscle. **E**, **F** However, the axial diffusion-weighted image and ADC map show diffusion restriction confined to the intraluminal portion, in keeping with non-muscle-invasive disease. **G** MIP image of delayed MR urogram shows no hydronephrosis in the right urinary tract to indicate right UVJ obstruction or synchronous urothelial cancers. Incidental duplication of the left collecting system was noted. Patient underwent TURBT; pathology confirmed non-muscle-invasive papillary urothelial carcinoma.

Management and follow-up

Treatment for non-metastatic MIBC most often includes radical cystectomy with extended lymphadenectomy, though partial cystectomy and bladder preservation options (with TURBT, chemoradiotherapy, and/or external beam radiation) exist in certain cases. The general management of non-metastatic MIBC does not differ among the T2, T3 and T4 stages. Evidence supports the use of neoadjuvant chemotherapy prior to cystectomy in patients with T2, T3, or T4a disease, often with methotrexate, vinblastine, adriamycin, cisplatin (MVAC), or gemcitabine/cisplatin (GC)-based regimens

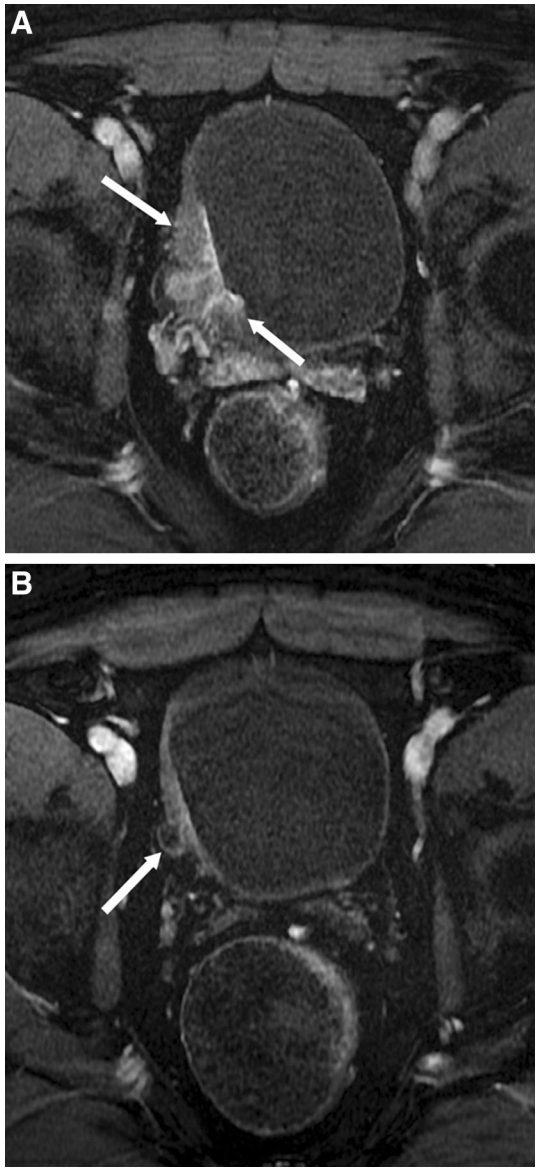


Fig. 5. 45-year-old man with high-grade muscle-invasive urothelial carcinoma of the bladder with response to neoadjuvant chemotherapy (cT3b stage). **A** Axial fat-suppressed gadolinium chelate-enhanced T1-weighted MRI at diagnosis shows infiltrative irregularly enhancing right bladder wall thickening (*white arrows* **A**). **B** Follow-up axial fat-suppressed gadolinium chelate-enhanced T1-weighted MRI after 6 months of neodjuvant therapy shows significant interval decrease of the right bladder wall mass and a small bladder diverticulum, representing response to neoadjuvant treatment.

[49]. The rationale for the use of neoadjuvant treatment includes treatment of microscopic metastases, in vivo assessment of chemosensitivity, downstaging to facilitate surgery, preserved renal function to facilitate the use of cisplatin, and a precise treatment endpoint that can be assessed with imaging and pathology [50]. Adjuvant chemotherapy is not as strongly supported as neoadjuvant therapy, but it seems to have benefit/delays recurrence in a patients with high risk of relapse (pT3-4, positive nodes, positive margin, or high grade) [51].

MRI is useful for post-treatment bladder and pelvis assessment after neoadjuvant chemotherapy (Fig. 5). Care needs to be taken when re-assessing invasive bladder tumors treated with neoadjuvant chemoradiation therapy, because inflammatory and/or fibrous changes caused by the chemotherapy or chemoradiotherapy can complicate interpretation [52], though MRI changes in response to therapy have been well described. Responders to MVAC therapy have been identified after two, four, and six cycles using conventional and dynamic contrast-enhanced MRI techniques [53, 54]. Responders were identified by 50% size reduction in tumor in two dimensions or 50% decrease in the summed products of the longest perpendicular diameters of all lesions, without a new or increased lesion on anatomic imaging, and a shift of tumoral enhancement from early (<10 s after arterial enhancement) to late (>10 s after arterial enhancement). In one recent phase II study of dose-dense MVAC in muscle-invasive urothelial cancer, 62% of patients achieved radiologic response evidenced by the aforementioned imaging changes, while 30% did not achieve response by these measures [55]. Response to treatment on imaging and in pathologic specimens has been shown to correlate with disease-free survival outcomes [55, 56].

In patients post cystectomy, radiologists should also be aware of various postoperative complications. These range from ureteric injury leading to urinary leak, obstruction, or fistula in the early postoperative period. Later on, anastomotic stenosis, hydronephrosis, parastomal hernias, and urinary tract calculi may develop [57].

According to the NCCN guidelines, surveillance imaging of chest, upper urinary tracts, abdomen, and pelvis is recommended every 3–6 months for 2 years, based on the risk of recurrence, then as clinically indicated (Fig. 6) [22]. Additionally, urine cytology and laboratory studies are performed at similar intervals. If the bladder is preserved in selected patients, cystoscopy and urine cytology with or without selected mapping biopsy are recommended every 3–6 months for 2 years, and subsequent follow-up is performed at increasing intervals as appropriate.

Metastatic bladder cancer

Bladder cancer is the ninth leading cause of cancer death in the United States [58]. Only 4% of bladder cancer patients present with distant metastatic disease [59]; however, about a third of the patients relapse after cystectomy [60]. The risk of recurrence depends on many factors including pathologic stage of the tumor, presence of positive surgical margins, and nodal status. Most post-cystectomy recurrences develop within 2–3 years [61].

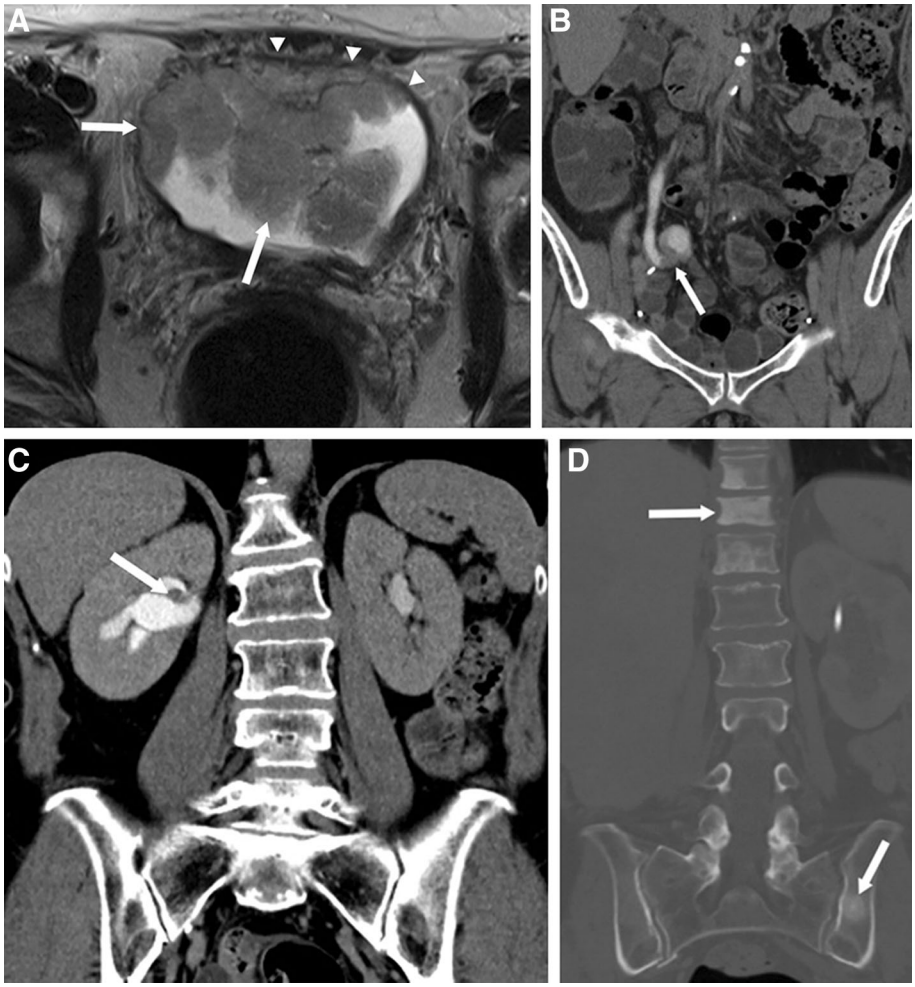


Fig. 6. 65-year-old woman with history of recurrent, high-grade papillary urothelial cancer (pT1a stage). **A** Axial T2-weighted MR image shows a large multi-lobular mass originating from the anterior bladder wall, almost completely replacing the bladder cavity (*white arrows* **A**). The outer contour of the detrusor muscle is intact (*white arrowheads* **A**). Cystectomy revealed high-grade pT1a disease. **B** Follow-up coronal CT urogram image in excretory phase obtained 31 months after radical cystectomy shows a partially obstructing solid mass at the right ureteral–ileal anastomosis (*white arrow* **B**) and a small similar filling defect at the origin of superior right renal calyx (*white arrow* **C**) suggestive of recurrent multifocal metachronous urothelial carcinoma. **D** Coronal CT image in bone window demonstrates mutiple ill-defined sclerotic lesions involving the lower thoracic spine and left iliac bone, consistent with osseous metastatic disease.

According to one recent report of 1110 patients who underwent radical cystectomy for bladder cancer, 324 patients experienced recurrence [60]. In patients with recurrent disease, 61.7% were at a single site and 38.3 were at multiple sites; 22% were local (cystectomy bed (Fig. 7) or pelvic lymph node dissection "template"), 69% were distant (bone, lung, liver, other), and 9.5% developed second metachronous urothelial carcinomas [60]. Metachronous urothelial carcinomas often occur at median interval of 3–3.3 years after cystectomy, but may occur up to nine years after the initial diagnosis [62, 63]. In general, distant recurrence occurs more commonly than local recurrence.

Imaging

To best interpret staging and/or surveillance scans of bladder cancer patients, radiologists should be familiar with the common metastatic patterns. Most common sites of distant metastasis are lymph nodes followed by liver, bone, and lung [64, 65]; other metastatic sites include the adrenal glands, kidneys, and the peritoneum in the form of carcinomatosis (Fig. 8). Lymphadenopathy usually occurs in the pelvic or retroperitoneal stations and less commonly in the mediastinum and supraclavicular areas. However, enlarged thoracic or supraclavicular lymph nodes in the absence of pelvic or abdominal

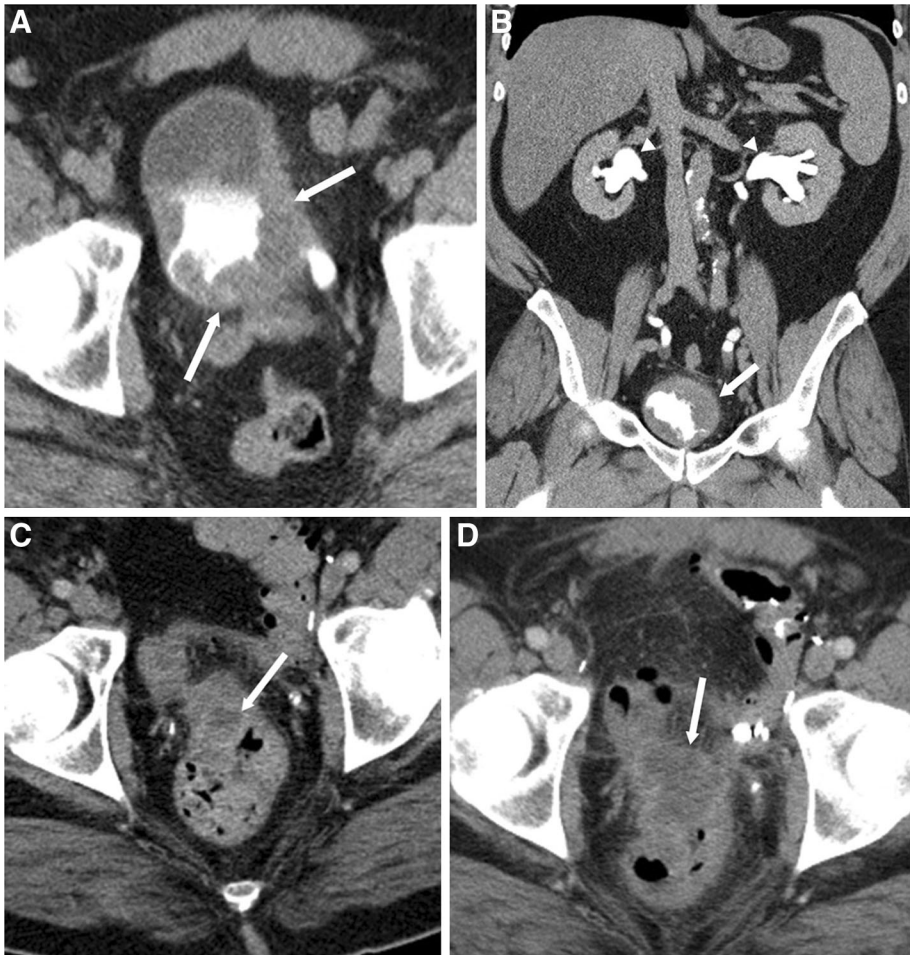


Fig. 7. 54-year-old man with 6-month history of gross hematuria and diagnosis of high-grade invasive papillary urothelial carcinoma, and subsequent local recurrence after surgery. **A**, **B** Axial and coronal CT urogram images in the excretory phase at diagnosis show irregular thickening of the posterior and lateral bladder wall with bilateral ureterovesical junction obstruction (*white arrows* **A**) causing hydroureteronephosis (*arrowheads* **B**). **C** First postoperative axial CT image 3 months after radical cystectomy revealed a small deep pelvic low-density collection with peripheral enhancement inseparable from the rectal wall (*white arrow* **C**); this raised concern for fluid collection/infection vs recurrence. **D** 12-week follow-up axial contrast-enhanced CT demonstrates increased size of the deep pelvic mass with peripheral enhancement which remained inseparable from the anterior rectal wall (*white arrow* **D**). CT-guided biopsy confirmed recurrent urothelial carcinoma.

adenopathy are less likely to represent metastatic disease, unless lung metastases are also present [45]. Compared with UC, patients with tumors of variant or atypical histologic features are significantly more likely to experience a shorter metastasis-free interval and a higher incidence of peritoneal metastasis [44]. In patients with any small cell component or neuroendocrine features, disease is known to be aggressive with clinical behavior similar to small cell carcinoma of the lung (Fig. 9).

Management

According to the NCCN guidelines, patients with suspected positive or involved lymph nodes on imaging should be considered for biopsy to confirm nodal spread if it is technically feasible. These patients are treated with chemotherapy, with or without radiation, and the extent of primary disease in the bladder should be assessed [22]. For disseminated metastatic disease, systemic chemotherapy has been employed, often using a combination, cisplatin-based regimen for medically fit patients. The goal of management is to prolong the quantity of life as well as maintain the quality of life. While patients with metastatic disease may respond initially to systemic chemotherapy, median overall survival in patients treated with traditional GC or MVAC has been 14–15 months [66].

Immune checkpoint blocker agents have become an attractive and effective option in the treatment arma-

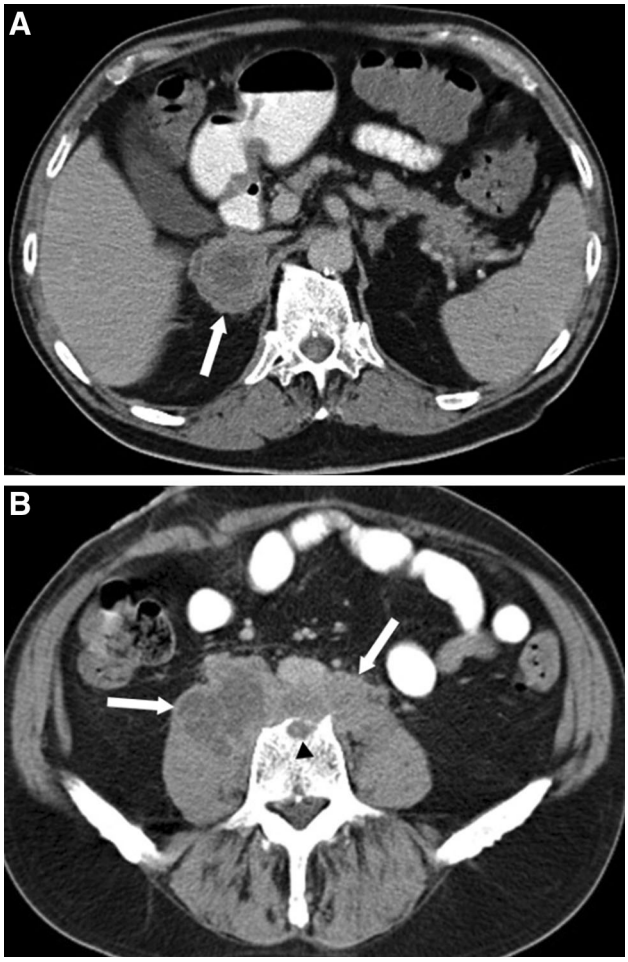


Fig. 8. 71-year-old man with history of urothelial carcinoma of the bladder with typical sites of metastatic disease. **A** Axial contrast-enhanced CT image show a heterogeneously enhancing right adrenal gland mass (*white arrow* **A**), consistent with metastasis. **B** Axial contrast-enhanced CT image shows a large retroperitoneal nodal conglomerate (*white arrows* **B**) with focal bone destruction in the anterior aspect of the vertebral body (*black arrowhead* **B**), representing nodal metastases.

mentarium for bladder cancer. In May 2016, atezolizumab (Tecentriq®, Genentech, San Francisco, CA) became the first immune checkpoint blocker and second-line therapy approved by the United States Food and Drug Administration in patients with locally advanced or metastatic UC, who have progressed during or after a platinum-based regimen, or within 12 months of platinum-containing neoadjuvant or adjuvant chemotherapy. Atezolizumab is a monoclonal antibody which binds to PD-L1, a molecule expressed by cancer cells involved in inhibiting T cell function and immune response. Atezolizumab thus removes an inhibitory signal on the immune system, enhancing the ability of the im-

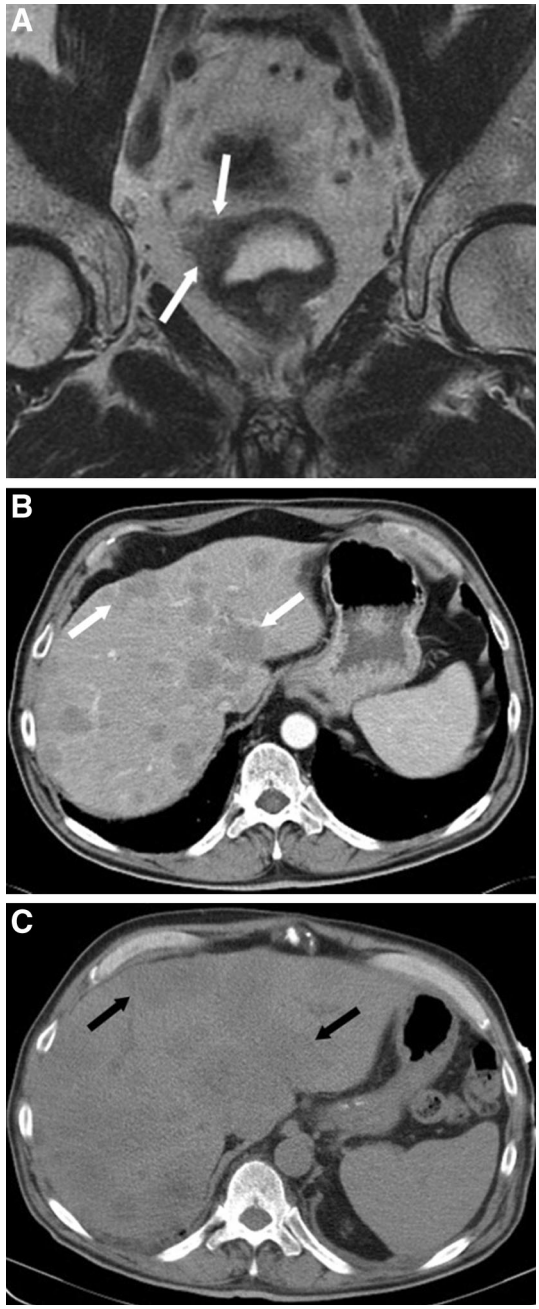


Fig. 9. 72-year-old male with small cell carcinoma of the bladder, aggressively metastatic to the liver (cT3b stage). **A** Coronal T2-weighted MRI at diagnosis shows irregular right lateral bladder wall thickening (*white arrows* **A**) with ill-defined extension into the perivesical fat, in keeping with muscle-invasive bladder cancer. No nodal or distant metastatic disease was found at diagnosis. **B** 3-month follow-up axial contrast-enhanced CT shows innumerable low attenuating hepatic lesions (*white arrows* **B**), consistent with metastases. **C** Restaging axial non-contrast CT obtained 2 months later due to increasing abdominal pain shows increased size of the entire liver and increased size of the hepatic lesions, indicating worsening of disease.

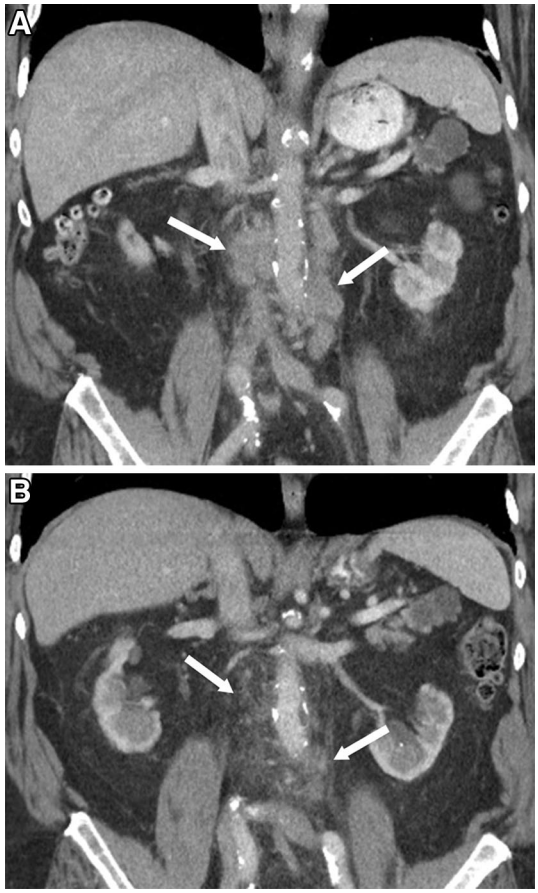


Fig. 10. 91-year-old man with urothelial carcinoma of bladder, with retroperitoneal nodal spread of disease, responding to adjuvant treatment with PD-1 inhibitor. **A** Coronal contrast-enhanced CT image demonstrates multiple enlarged retroperitoneal lymph node metastases (*white arrows* **A**). Follow-up coronal contrast-enhanced CT image at the same level after 12 weeks of treatment with PD-1 inhibitor demonstrates significant interval decrease in retroperitoneal lymph nodes representing response to treatment (*white arrows* **B**).

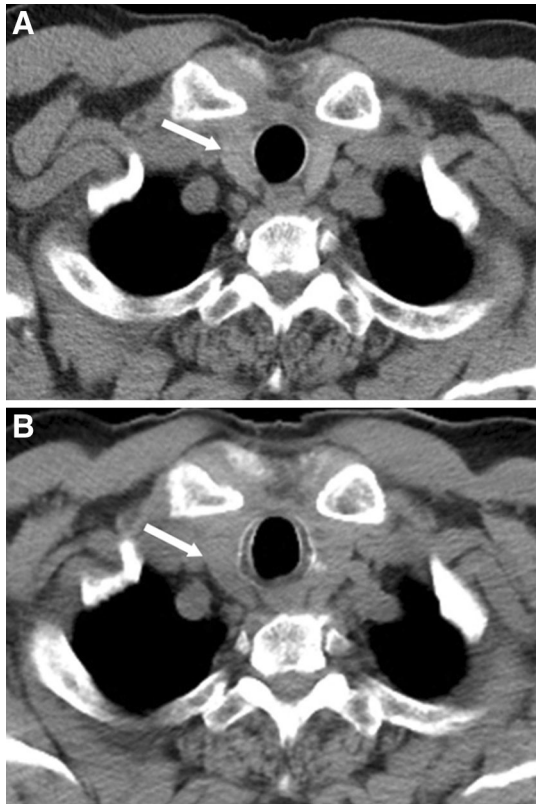


Fig. 11. 72-year-old man with history of poorly differentiated urothelial carcinoma of the bladder with pelvic nodal metastases, status post radical cystectomy. **A** Non-contrast axial CT image of the upper mediastinum shows normal size and density of the thyroid. **B** Follow-up CT after 12 weeks of treatment with PD-1 inhibitor shows diffuse interval enlargement of the thyroid and decreased density, which, in the context of altered thyroid function tests, suggested thyroiditis.

mune system to attack cancer cells. In one cohort of 310 phase II study patients treated with second-line atezolizumab, the overall objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) was 15% [67]. Complete responses were seen in 5% of all patients in the cohort (Fig. 10). With median follow-up of nearly 1 year, responses were ongoing in 84% of responders.

Response assessment and toxicities

This phase II clinical trial also included imaging assessment of response according to immune-modified RECIST, to capture potential atypical response patterns associated with immunotherapy [67]. Treatment response after immunotherapeutic agents has been categorized into four distinct response patterns: (a) shrinkage in baseline lesions, without new lesions; (b) durable stable disease (in some patients followed by a slow, steady decline in total tumor burden); (c) response after an increase in total tumor burden; and (d) response in the presence of new lesions which are all associated with favorable survival [68, 69]. In this phase II study, immune-modified response rates were similar to RECIST 1.1 results [67]. Importantly, however, to account for potential "pseudoprogression," patients in this study were allowed to continue atezolizumab treatment beyond RECIST progression, and 17% of the patients treated beyond RECIST progression subsequently achieved partial response. These data highlight the importance of imaging study interpretation in this treatment-specific setting and emphasize the role of the radiologist in suggesting two consecutive follow-up imaging studies performed at least 4 weeks apart to confirm the presence or absence of disease progression, in keeping with immune-related response criteria guidelines [68, 70].

While appropriate response assessment is necessary in this new treatment setting, it is also important for radi-

ologists to be familiar with immune-related adverse events (irAE) which can manifest on follow-up imaging studies. Adverse events associated with immunotherapy include pneumonitis, hepatitis, colitis, thyroiditis, pancreatitis, and sarcoid-like reaction, amongst others (Fig. 11) [70–72]. In the phase II trial of atezolizumab discussed, grade 3/4 adverse events occurred in 5% of treated patients, especially pneumonitis and hepatitis/increased LFTs [67]. Specific imaging features of irAE in the bladder cancer population have not been separately reported. However, organ-specific patterns of irAE have been described in advanced cancer patients in general. For example, patterns of pneumonitis in patients treated with PD-1 inhibitors have been recently described; this most commonly occurs in a cryptogenic organizing pneumonia pattern, but also in non-specific interstitial pneumonia, hypersensitivity pneumonitis, and acute interstitial pneumonia patterns [73].

The identification of immune targets, mutated genes, and gene products expressed in invasive and metastatic bladder tumors has enlivened the design, development, and study of new targeted therapies in bladder cancer, a setting in which relatively few treatment lines and options have existed in the recent past. Clinical trials of pembrolizumab in advanced UC are ongoing [74]. Alterations in TP53 and RB1 common in muscle-invasive disease are also attractive targets for potential treatment. Additionally, human epidermal growth factor receptors (HER) 1 and 2 have been theorized to be involved in bladder cancer progression; a recent phase III study evaluated the utility of maintenance lapatinib, a HER1, and HER2-tyrosine kinase inhibitor, in HER1/2-positive advanced/metastatic urothelial bladder cancer. Lapatinib did not improve progression-free survival in selected patients, indicating complexity of the molecular milieu in this disease [75]. The study of rational, directed cancer therapies will undoubtedly increase in the coming years, and imaging will continue to play an important role in response assessment and patient management.

Conclusion

Urothelial bladder cancer is an important cause of morbidity and mortality in the United States and worldwide. Given the substantial role of imaging in the staging, follow-up, and treatment response assessment in affected patients, it is important for radiologists to be cognizant of the pathologic subtypes of disease, associated underlying genetic features, rationale approaches to therapy, and expected response patterns, to best contribute to optimized outcomes.

Compliance with ethical standards

Conflict of interest Atul B. Shinagare: Consultant, Arog Pharmaceuticals (not directly related to the contents of this manuscript). No disclosures for the other authors.

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