Imaging Recommendations for Diagnosis, Staging, and Management of Bladder and Urethral Malignancies

Jinita Majithia[1]   Gagan Prakash[2]   MH Thakur[1]   Palak Popat[1]   Nilesh Sable[1]   Aparna Katdare[1]
Suyash Kulkarni[3]   Daksh Chandra[4]

[1] Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra, India
[2] Department of Uro-Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[3] Department of Radiology, Tata Memorial Hospital, Mumbai, Maharashtra, India
[4] Intervention Radiology, Tata Memorial Hospital, Mumbai, Maharashtra, India

Address for correspondence Jinita Majithia, MBBS, DNB, Consultant, Department of Radiodiagnosis, Tata Memorial Hospital, Mumbai, Maharashtra 400012, India (e-mail: jinita_10@hotmail.com).

Abstract

Bladder cancer (BCa) is a leading cause of cancer worldwide with high incidence and mortality across all ages. Early diagnosis and treatment can lead to significantly improved survival rate and overall prognosis. Smoking is the biggest contributing factor for the development of BCa. Urothelial carcinoma is the most common histological subtype. Commonly implemented imaging techniques include computed tomography urography (CTU) and multiparametric magnetic resonance imaging (mpMRI). CTU is the investigation of choice for muscle invasive bladder cancer (MIBC) and is best utilized for local assessment and staging of larger and higher staged tumors, that is, T3b and T4. mpMRI encompasses T2-weighted imaging, diffusion-weighted imaging, and dynamic contrast-enhanced imaging. It can differentiate $\leq$T1 and $\geq$T2 tumors based on the Vesicle Imaging-Reporting and Data System (VI-RADS) assessment as well as differentiate Ta from T1 tumors, and is useful in post-therapy response assessment of BCa. Positron emission tomography/computed tomography is used in selected patients of MIBC for metastatic evaluation, particularly those with deranged renal function. A synoptic reporting template should be used to have standardization of data. Primary urethral cancer (UCa) is a rare and aggressive malignancy, accounting for less than 1% of all malignancies. MRI is the investigation of choice for UCa.

Keywords
► bladder cancer
► radiology
► staging
► urethral cancer
► urology

Introduction and Epidemiology

As per GLOBOCAN 2020, there were 573,278 new cases with a total of 212,536 number of deaths associated with bladder cancer (BCa) across all ages and both sexes in the year 2020.[1] BCa was ranked 10th in incidence and 13th in mortality among all cancers, and is estimated to be the 6th most commonly diagnosed cancer in men worldwide.[1] In India, it is ranked 17th in incidence and 19th in mortality, having varying incidence rates across different regions and populations.[2]

As per the SEER statistics (Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, US), the 5-year survival rate is as high as 90% for carcinoma in situ and 70% for localized disease, with a significant drop to 36% for regional and 5% for metastatic disease.[3] This

indirectly reflects the success of early diagnosis and poor prognosis of metastatic disease. Improved understanding of the disease, superior imaging techniques for diagnosis, and advances in treatment have contributed to a significant decrease in the BCa-related mortality rates worldwide.[4]

A four times higher incidence rate has been observed in men than women.[5] The worldwide age-standardized incidence rate (per 100,000 person/years) is 9.5 for men and 2.4 for women.[5] Almost 90% of the newly diagnosed cases of BCa are seen in individuals of age 55 years or older with an average age of diagnosis of 73 years.[6] BCa is not typically hereditary; however, some cancer syndromes can predispose an individual to BCa, like Cowden syndrome and Lynch syndrome.[7,8]

Risk Factors and Etiopathogenesis

Active and passive tobacco smoking has a strong relationship with BCa and is one of the greatest risk factors that is quantity and duration dependent. The relative risk for cancer-mortality from smoking is second only to lung cancer.[9] The attributable risk to smoking is similar between men and women.[5,9] Exposure to aromatic amines, polycyclic aromatic hydrocarbons, and chlorinated hydrocarbons from dyes, paint, metal, rubber, or petroleum industries is another common preventable risk factor for BCa. Occupational exposures are responsible for approximately 18% of all BCa cases.[10] An environmental factor most commonly implicated in BCa is arsenic consumption, typically through ingestion of contaminated water.[11] Increased rates of secondary BCa have also been reported following use of external-beam radiotherapy (EBRT) for gynecological malignancies; however, lower rates have been observed with use of intensity-modulated radiotherapy for prostate cancer.[12,13] A tropical protozoan schistosomiasis, through generation of N-nitroso carcinogenic compound,[14] and chronic bladder irritation from indwelling catheters or vesicle stones are responsible for squamous cell carcinoma (SCC) of the bladder.

Urothelial carcinoma (UC), also known as transitional cell carcinoma, is the most common subtype of BCa, seen in 90% of cases.[15] At presentation, approximately 2% cases with urothelial BCa will have a synchronous upper urinary tract tumor and approximately 6% will develop a metachronous lesion.[16] SCC is the second most common subtype of BCa, representing 6 to 8% of all cases. The incidence rate of SCC is disproportionately higher, up to 50%, in endemic areas of schistosomiasis.[14] Adenocarcinomas are rare, accounting for less than 2% cases. They may be urachal (one-third) or nonurachal (two-third). Other histologic types of BCa, such as lymphoma, carcinosarcoma, small cell carcinoma, pheochromocytoma and sarcoma, are also extremely rare.[17] The presence of some of these variant histology subtypes increases the chances of distant metastases even in nonmuscle invasive bladder cancer (NMIBC), suggesting the need for cross sectional imaging.

Clinical Features

The most common presentation of BCa is painless hematuria, either gross or microscopic. Other symptoms like urgency, dysuria, increased frequency, pelvic pain, and symptoms related to urinary tract obstruction may also be observed. Urinary tract infection is a less common presenting symptom. Urine cytology for voided exfoliated cancer cells has good sensitivity and is a useful indicator of high-grade malignancy; however, it lacks specificity as it is unable to localize the origin of the UC in the entire urinary tract. A negative cytology does not exclude malignancy. Urine cytology is not routinely performed for initial evaluation of hematuria but can be considered when there is suspicion of BCa, as per NCCN (National Comprehensive Cancer Network) guidelines.[18] The United States Food and Drug Administration (FDA) has currently approved six urinary assays to use alongside cystoscopy for diagnosis and surveillance; these include nuclear matrix proteins 22 and bladder tumor antigen assays.

Role of Imaging

Imaging plays a key role in the diagnosis, locoregional, and distant staging, for deciding management protocols and for follow-up. Various techniques are available for imaging the urinary tract, commonly used are computed tomography urography (CTU), magnetic resonance imaging (MRI) pelvis, and whole body [^{18}F]Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) and historically intravenous urography. According to NCCN, no single follow-up plan is suitable or appropriate for all patients and the follow-up intervals should be individualized. Routine screening for BCa beyond the high-risk population is currently not recommended.[19] The gold standard for confirmation of BCa is direct visualization of the tumor on cystoscopy (flexible or rigid) and transurethral resection of bladder tumor (TURBT). TURBT is performed for pathological confirmation with the goal to resect all of the visible tumor up to muscle depth.

Ultrasonography

According to the American College of Radiology "Appropriateness Criteria," ultrasound is recommended as the initial diagnostic evaluation for microscopic hematuria.[20] The specificities of ultrasonography and CTU are found to be similar; however, CTU has a higher sensitivity.

Computed Tomography

CTU is the most common and preferred imaging modality for patients in whom intravenous iodinated contrast can be safely injected without contraindications and has successfully replaced the historical fluoroscopy-guided intravenous pyelography. It has high diagnostic accuracy (91%), sensitivity (79–93%), and specificity (83–99%).[21,22] The high specificity of CTU allows the treating physician to eliminate the use of a diagnostic flexible cystoscopy in the outpatient department and directly do a rigid cystoscopy, often at the same time as TURBT. CTU can be performed by the "single-bolus technique" with administration of a full bolus and acquisition of three phases, that is, noncontrast, urothelial, and delayed excretory or by the "split-bolus technique" with a

noncontrast phase and a single urothelial and excretory phase following administration of a partial bolus. Split-bolus technique has the advantage of reduced radiation exposure but comes at the potential cost of missing smaller lesions.

According to the NCCN guidelines, CTU is the investigation of choice for patients with high suspicion for BCa, for primary evaluation of diagnosed cases, for staging and restaging, and for surgical planning.[18] It is also the investigation of choice for metastatic assessment in MIBC.[23] It allows macroscopic characterization (site, size, and number) and extent of lesion; **T** Stage, evaluation of spread to primary/regional (perivesicle, internal iliac, external iliac, obturator, and presacral) and secondary/distant (common iliac, para-aortic, aortocaval, and paracaval) lymph nodes; **N** Stage, aides in assessing the involvement of upper urinary tract and distant organs; **M** Stage, involvement of lymph nodes above the iliac chain is considered metastatic disease. Metastasis to the lung and liver is common and to the bone and brain is rare.

On CT, BCa appears as intraluminal papillary masses with frond-like appearance or as nodular masses or as focal or diffuse wall thickening. Early enhancement is observed. Calcification can be seen in approximately 5% cases, typically encrusting the surface of the tumor and may be nodular or arched.[24] CTU is suboptimal, as compared with MRI, in the differentiation of NMIBC from muscle invasive bladder cancer (MIBC) and in the local staging of smaller tumors and cancers less than T3a stage. However, it is best utilized for local assessment and staging of larger and higher staged tumors, that is, T3b and T4.[25] CT is also used for restaging high-risk NMIBC and MIBC following treatment. CT is useful for nodal staging of BCa, as it identifies regional and distant nodal metastasis. Morphological abnormalities, such as enlarged size, round shape, irregular borders, central necrosis, and loss of fatty hilum, are the major criteria for categorizing lymph nodes. The accepted measurement cutoff for suspicious lymph nodes is 10 mm for abdominal adenopathy and 8 mm for pelvic adenopathy in the short axis[26] however, the accuracy varies widely based on the cutoff used.

Magnetic Resonance Imaging

Growing interest in the application of multiparametric MRI (mpMRI) for imaging in BCa is a result of its superior soft tissue resolution. mpMRI has proven to be successful in differentiating MIBC from NMIBC with a high diagnostic accuracy; thus, it is the investigation of choice for T-Staging of BCa. Recent systemic reviews and meta-analysis have shown a better sensitivity and specificity of mpMRI for differentiating ≤T1 and ≥T2 tumors.[27,28]

MRI should be performed before endoscopic management or at least 2 weeks after cystoscopic procedures and intravesicle treatments and a gap of 2 days should be maintained after removal of indwelling catheters to minimize artifacts from intravesicle air. Optimal bladder distention and administration of antispasmodic agents are methods to reduce motion artifacts from peristalsis. mpMRI consists of anatomical T2-weighted images (T2WI), functional diffusion-weighted images (DWI), and dynamic contrast-enhanced (DCE). Ideally, large field-of-view (FOV) T1W spin echo

sequence, from the aortic bifurcation to the pubic symphysis, should also be performed before contrast administration for the evaluation of metastatic retroperitoneal adenopathy. mpMRI has limitations in assessment of metastatic disease because of the smaller FOV; however, there is a paradigm shift to MRI for metastatic evaluation with the introduction of PET/MR and whole-body MRI.[23]

T2WI without fat saturation performed in at least two planes (axial, coronal and / or sagittal) is primarily used for anatomic characterization of the tumor, like lesion size, growth pattern, morphology, location, and the degree of interruption of muscle, all of which are essential for local staging.[22,29] Isotropic three-dimensional T2W images can serve as an adjunct.[29] DWI provides qualitative and quantitative data regarding cellularity of the tumor. High cellularity tumors reveal bright signal intensity on DWI. The apparent-diffusion coefficient (ADC) map is a quantitative representation of restricted diffusion showing decreased signal intensity corresponding to the high cellularity and aggressiveness of the tumor, thus identifying the possible histological grade of the tumor. The muscularis propria layer of the bladder wall is identified on T2WI and DWI, showing low-signal intensity on T2WI and intermediate signal on DWI. The tumor can be easily distinguished by its intermediate signal intensity on T2WI and high-signal intensity on DWI. Muscle invasion can be inferred if interruption in the low signal intensity is seen on T2WI and intermediate signal intensity on DWI can be demonstrated, thus making these two sequences the most useful sequences for identifying MIBC and consequently for local staging of BCa.[29] The infiltration of extravesicle tissue is also best demonstrated on T2WI as hypo- to intermediate intensity infiltrative streaks in contrast to the hyperintense extravesicle fat. Higher b-value sequences improve the detection of nodal disease and marginally improve the sensitivity and specificity[30]; thus, DWI should be generated with at least two b-value sequences.

DCE images are multiple, rapidly acquired fat suppressed gradient echo sequence T1WIs obtained before, during and after intravenous administration of gadolinium contrast. The highly vascular inner layer, that is, the urothelium and lamina propria, which is not well visualized on T2WI and DWI, can be very well demonstrated on early sequences of DCE images as an avidly enhancing inner most layer. The muscularis layer enhances later, slowly, and progressively. Thus, DCE imaging is best suited for demonstration of the early enhancing BCa. There is a statistically significant improvement in the specificity and accuracy of mpMRI in differentiating T1 stage BCa from lower-grade tumors T2 stage BCa when DCE imaging supplements DWI and T2WI.[31]

Patients in whom TURBT reveals muscle invasion, surgery becomes only of diagnostic value. There is concern that this could delay the definitive management of MIBC, which entails chemotherapy and cystectomy or radiation therapy. Further, there are also concerns of micro-perforations during TURBT of large tumors which might potentially upstage the disease. Based on this apprehension, the BladderPath trial was designed which is trying to assess if MRI could obviate the need for TURBT in patients who are likely to be harboring a muscle invasive disease.[32]

Differentiation of Ta from T1 tumors is also possible with mpMRI. These tumors present as sessile or pedunculated masses and the imaging features of the center or stalk of the tumor can correspond to the stage of the lesion. The phase of enhancement of the submucosal tissue is usually earlier than that of the cancer component in Ta cancer; however, the cancer component usually enhances as strongly as the submucosal tissue in T1 cancer on DCE imaging.[33] Additionally, difference in the Ta to T1 tumors can also be related to the size of the tumor in contact with the bladder wall.[33]

T2WI has limited application in post-therapy evaluation of BCa due to presence of inflammation and fibrosis. DWI has higher specificity and sensitivity compared with T2WI and DCE for accurately predicting histopathological response.[29] Changes in the ADC value after administration of neoadjuvant chemotherapy or following chemoradiation is an early indicator of pathologic response.[34] A recent study (PURE-01) evaluated the potential use of mpMRI as a tool for assessing complete tumor response to pembrolizumab, which is an FDA approved immune checkpoint inhibitor (programmed cell death protein 1 [PD-1] inhibitor).[34,35]

Positron Emission Tomography

As per the American College of Radiology (ACR) Appropriateness Criteria for pre-treatment staging of MIBC, the use of PET/CT in BCa is considered as "may be appropriate."[36] European Association of Urology and the European Society for Medical Oncology recently issued a consensus statement, stating that FDG-PET/CT should be used for staging of oligometastatic BCa when radical treatment is considered to minimize the risk of overtreatment.[37] The NCCN guidelines suggest that PET/CT may be useful for selected patients $\geq$T2 tumors of MIBC and can significantly alter the treatment approach in $\geq$T3 tumors. PET/CT has a pooled sensitivity and specificity for detection of lymph node metastases of 57 and 95%, respectively.[38] PET/CT is most often utilized in MIBC where the incidence of metastasis is much higher compared with NMIBC, where routine use of PET/CT is not justified.

PET/CT can be utilized for metastatic staging of BCa (not local staging) and for response assessment and restaging after neoadjuvant chemotherapy. The greatest strength of PET/CT is its ability to detect metastasis in lymph nodes that are not pathologically enlarged. An integrated approach, with information on the standardized uptake values and the size criterion of lymph nodes, can improve the accuracy of PET/CT.[39] FDG-PET/CT also serves as a noninvasive indicator of PD-1/PD-L1 expression that is extremely beneficial especially with introduction of newer targeted immunotherapy, like pembrolizumab.[40] FDG-PET/CT is accurate in distinguishing primary tumor downstaging from nonresponse in BCa.[41] For the detection of recurrent BCa, the sensitivity and specificity of PET/CT are 94 and 76%, respectively.[42]

PET/MR is a novel hybrid imaging modality that combines the advantage of superior soft tissue resolution of mpMRI with the metabolic and functional information of PET, providing greater accuracy for detecting tumors, pelvic lymph node metastasis, and nonnodal pelvic malignancy.[43] It is also useful for evaluating response to neoadjuvant chemotherapy.

Two new, alternative, experimental radiotracer agents being evaluated for use in imaging of BCa are $[^{11}C]$ choline and $[^{11}C]$ acetate. Their diagnostic accuracy for lymph node staging showed a pooled sensitivity and specificity of 66 and 89%, respectively.[44]

A significant proportion of patients with MIBC present with obstructive uropathy and deranged parameters. While some of them may be eligible for contrast studies following urinary diversion, an early assessment of the disease burden in these patients can best be done using FDG-PET-CT.

Image-Guided Interventions

Intractable hematuria in patients with lower urinary tract malignancies has been successfully treated with selected transcatheter arterial embolization. Cross-sectional imaging may depict intravesicle clots; however, CTU and DCE MRI both can be unsuccessful in accurately locating the site of bleed. When radical surgery is not feasible or contraindicated, angiography with embolization, as a palliative approach, provides a minimally invasive means to control bladder hemorrhage.[45]

Percutaneous cryoablation is being explored as a minimally-invasive technique, which can be used as an adjuvant therapy with TURBT to eliminate the possibility of residual tumor in MIBC and high-risk NMIBC to the maximum possible extent.[46] It is also considered in few cases to eliminate the of systemic chemotherapy and decrease the degree of complications.[47] Very few studies have used CT guidance for cryoablation; transurethral approach is generally preferred. Although still under exploration, it shows a promise in the future as an alternative to the current first-line of treatment, that is, TURBT.

VI-RADS

Vesicle Imaging-Reporting and Data System (VI-RADS), developed in 2018, is a standardized mpMRI-based scoring system, incorporating tumor appearances on T2WI, DWI, and DCE imaging for assessing the overall risk of muscle invasion. It provides a systemic reporting template for preoperative staging of BCa. It also provides information on the management approach, assessment of therapeutic response, and prognosis. Multiple retrospective and prospective studies have investigated the validity and reproducibility of VI-RADS upon confirmation with TURBT, and demonstrated good diagnostic accuracy and reliability.[48–50]

VI-RADS score incorporates three categories; structural category (SC) that is assessed on T2WI, contrast-enhanced category (CE) assessed on DCE imaging and the diffusion-weighted category (DW) assessed on DWI which have been tabulated in Tables 1, 2 and 3, in an attempt to simplify the different assessment categories.[29]

The final score is firstly based on T2WI based on morphology, because of its high spatial resolution in evaluating the integrity of muscularis propria. However, the presence of definitive muscle invasion is decided by DWI and DCE imaging, which are the dominant sequences for risk assessment. In case of discordance between T2WI and DCE images,

DWI improves the accuracy.[51,52] An algorithm for approach to final VI-RADS category of BCa is provided in Table 4. A schematic diagram of mpMRI appearances of VI-RADS categories has been presented in Figure 1.

Approach to Reporting

The American Joint Committee on Cancer (AJCC) Staging Manual, 8th edition, provides structured guidelines for the staging of BCa (Table 5.1 and 5.2). A TNM Stage; **T** (tumor), **N** (node) and **M** (metastasis); of the tumor is provided which stratifies patients into different stages of cancer allowing prognostication and guiding patient management.

A synoptic template for reporting is also proposed, elaborating primary tumor characteristics and nodal and metastatic disease, making it simpler for a radiologist and the treating physician and surgeon to follow a checklist which includes all relevant clinical and radiological information that can potentially influence patient management (Figure 2).

Urethral Cancer

Primary urethral cancer (UCa) is a rare and aggressive malignancy. Secondary UCa is a recurrent carcinoma, following a treated primary in the urinary tract, usually reported after radical cystectomy in a case of BCa.[53] Primary UCa accounts for less than 1% of all malignancies[54] and as per the SEER analysis, the incidence is highest above the age of 75 years (0.76/lakh) and almost negligible in less than 55 years (0.02/lakh),[55] with a male preponderance. The common predisposing risk factors for UCa include urethral strictures, chronic irritation after intermittent catheterization/urethroplasty, external-beam radiation therapy (EBRT) to the pelvis, radioactive seed implantation, and chronic urethral inflammation or urethritis following sexually transmitted diseases (like HPV16) in men and urethral diverticula and recurrent urinary tract infections in women. UC is the predominant histologic subtype, followed by SCC and adenocarcinoma. Clear cell adenocarcinoma has a congenital cause.

The most common location for UCa in men is the bulbo-membranous urethra, whereas in women the anterior urethra, comprising of the distal one-third, is the most common location. Conventional imaging techniques, like voiding cystourethrography and retrograde urethrography, are helpful for urethral imaging in men, however, and are invasive and unable to evaluate extraluminal spread or periurethral conditions.[56] High-resolution, transvaginal, transperineal, and transurethral ultrasound have also been explored; however, MRI is the mainstay for urethral imaging in both sexes.

MRI is useful for diagnosis and characterization of tumor and local staging of UCa. The commonly performed sequences include T1WI, T2WI, and post-contrast T1WI in small FOV. Larger FOV is used for imaging the pelvic and inguinal lymph nodes that constitute the route for metastatic spread of UCa. Relative to the normal corporal tissue, Uca appears hypointense on T1WI, hypointense on T2WI, and progressively enhances on post-contrast T1WI. In men, invasion of the corpus spongiosum, prostate and periurethral muscle,

upstages UCa with further upstaging following invasion of corpus cavernosa. Anterior urethral lesions can metastasize to the inguinal group of lymph nodes and eventually external iliac group, whereas posterior UCa extends to the deep pelvic lymph nodes.

The differential diagnosis for UCa includes complex cystic periurethral lesions like inflamed urethral diverticulum, amyloidosis, and rarely hematogenous metastasis to corpus spongiosum in men with melanoma, prostate, bladder, colon, testicular, and renal cancers.[57]

The extent of surgical clearance of disease may vary from only urethrectomy to total penectomy to cysto-prostato-urethrectomy and MRI is the cornerstone imaging for surgical planning.

References

1 Accessed December 12, 2022, at: https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf

2 Three-Year Report of Population Based Cancer Registries 2012–2014. 2016. Incidence, Distribution, Trends in Incidence Rates and Projections of Burden of Cancer (Report of 27 PBCRs in India). Accessed December 12, 2022, at: http://www.ncdirindia.org/NCRP/all_ncrp_reports/pbcr_report_2012_2014/all_content/pdf_printed_version/preliminary_pages_printed.pdf

3 SEER*Explorer. [(accessed on 13 January 2020)]; Accessed December 12, 2022, at: https://seer.cancer.gov/explorer/

4 Al-Husseini MJ, Kunbaz A, Saad AM, et al. Trends in the incidence and mortality of transitional cell carcinoma of the bladder for the last four decades in the USA: a SEER-based analysis. BMC Cancer 2019;19(01):46

5 Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of bladder cancer. Med Sci (Basel) 2020;8(01):15

6 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(01):7–34

7 Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract 2010;8(01):6. Doi: 10.1186/1897-4287-8-6

8 van der Post RS, Kiemeney LA, Ligtenberg MJL, et al. Risk of urothelial bladder cancer in Lynch syndrome is increased, in particular among MSH2 mutation carriers. J Med Genet 2010;47(07):464–470

9 Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA 2011;306(07):737–745

10 Chen HI, Liou SH, Loh CH, Uang SN, Yu YC, Shih TS. Bladder cancer screening and monitoring of 4,4′-methylenebis(2-chloroaniline) exposure among workers in Taiwan. Urology 2005;66(02):305–310

11 Marshall G, Ferreccio C, Yuan Y, et al. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. J Natl Cancer Inst 2007;99(12):920–928

12 Chrouser K, Leibovich B, Bergstralh E, Zincke H, Blute M. Bladder cancer risk following primary and adjuvant external beam radiation for prostate cancer. J Urol 2005;174(01):107–110, discussion 110–111

13 Zelefsky MJ, Housman DM, Pei X, et al. Incidence of secondary cancer development after high-dose intensity-modulated radiotherapy and image-guided brachytherapy for the treatment of localized prostate cancer. Int J Radiat Oncol Biol Phys 2012;83 (03):953–959

14 Verma S, Rajesh A, Prasad SR, et al. Urinary bladder cancer: role of MR imaging. Radiographics 2012;32(02):371–387

15 Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of tumors of the urinary system and

male genital organs-part B. Prostate and Bladder Tumors. Eur. Urol. 2016;70:106–119

16 Lee CH, Tan CH, Faria SC, Kundra V. Role of imaging in the local staging of urothelial carcinoma of the bladder. AJR Am J Roentgenol 2017;208(06):1193–1205

17 Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J 2009;3(6, Suppl 4):S193–S198

18 Flaig TW, Spiess PE, Agarwal N, et al. Bladder cancer, Version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2020;18(03):329–354

19 Sun M, Trinh Q-D. Diagnosis and staging of bladder cancer. Hematol Oncol Clin North Am 2015;29(02):205–218, vii

20 Wolfman DJ, Marko J, Nikolaidis P, et al. Expert panel on urological imaging. ACR Appropriateness Criteria® Hematuria. J Am Coll Radiol 2020;17(5S):S138–S147

21 Trinh TW, Glazer DI, Sadow CA, Sahni VA, Geller NL, Silverman SG. Bladder cancer diagnosis with CT urography: test characteristics and reasons for false-positive and false-negative results. Abdom Radiol (NY) 2018;43(03):663–671

22 Mirmomen SM, Shinagare AB, Williams KE, Silverman SG, Malayeri AA. Preoperative imaging for locoregional staging of bladder cancer. Abdom Radiol (NY) 2019;44(12): 3843–3857

23 Galgano SJ, Porter KK, Burgan C, Rais-Bahrami S. The role of imaging in bladder cancer diagnosis and staging. Diagnostics (Basel) 2020;10(09):703

24 Moon WK, Kim SH, Cho JM, Han MC. Calcified bladder tumors. CT features. Acta Radiol 1992;33(05):440–443

25 Mossanen M, Chang SL, Kimm S, Sonpavde GP, Kibel AS. Current staging strategies for muscle-invasive bladder cancer and upper tract urothelial cell carcinoma. Urol Clin North Am 2018;45(02): 143–154

26 Pichler R, De Zordo T, Fritz J, et al. Pelvic lymph node staging by combined ^{18}F-FDG-PET/CT imaging in bladder cancer prior to radical cystectomy. Clin Genitourin Cancer 2017;15(03): e387–e395

27 Cornelissen SWE, Veenboer PW, Wessels FJ, Meijer RP. Diagnostic accuracy of multiparametric MRI for local staging of bladder cancer: a systematic review and meta-analysis. Urology 2020; 145:22–29

28 Gandhi N, Krishna S, Booth CM, et al. Diagnostic accuracy of magnetic resonance imaging for tumour staging of bladder cancer: systematic review and meta-analysis. BJU Int 2018;122 (05):744–753

29 Panebianco V, Narumi Y, Altun E, et al. Multiparametric magnetic resonance imaging for bladder cancer: development of VI-RADS (vesical imaging-reporting and data system). Eur Urol 2018;74 (03):294–306

30 Caglic I, Panebianco V, Vargas HA, et al. MRI of bladder cancer: local and nodal staging. J Magn Reson Imaging 2020;52(03): 649–667

31 Takeuchi M, Sasaki S, Ito M, et al. Urinary bladder cancer: diffusion-weighted MR imaging–accuracy for diagnosing T stage and estimating histologic grade. Radiology 2009;251(01): 112–121

32 Bryan RT, Liu W, Pirrie SJ, et al. Comparing an imaging-guided pathway with the standard pathway for staging muscle-invasive bladder cancer: preliminary data from the BladderPath Study. Eur Urol 2021;80(01):12–15

33 Yuan L, Li D, Mu D, et al. Combined T2 SPAIR, dynamic enhancement and DW imaging reliably detect T staging and grading of bladder cancer with 3.0T MRI. Front Oncol 2020;10:582532

34 Necchi A, Bandini M, Calareso G, et al. Multiparametric magnetic resonance imaging as a noninvasive assessment of tumor response to neoadjuvant pembrolizumab in muscle-invasive bladder cancer: preliminary findings from the PURE-01 study. Eur Urol 2020;77(05):636–643

35 Bidnur S, Savdie R, Black PC. Inhibiting immune checkpoints for the treatment of bladder cancer. Bladder Cancer 2016;2(01): 15–25

36 van der Pol CB, Sahni VA, Eberhardt SC, et al; Expert Panel on Urologic Imaging. ACR appropriateness criteria® pretreatment staging of muscle-invasive bladder cancer. J Am Coll Radiol 2018; 15(5S):S150–S159

37 Witjes JA, Babjuk M, Bellmunt J, et al. EAU-ESMO consensus statements on the management of advanced and variant bladder cancer-An International Collaborative Multistakeholder Effort[†]: Under the Auspices of the EAU-ESMO Guidelines Committees. Eur Urol 2020;77(02):223–250

38 Soubra A, Hayward D, Dahm P, et al. The diagnostic accuracy of 18F-fluorodeoxyglucose positron emission tomography and computed tomography in staging bladder cancer: a single-institution study and a systematic review with meta-analysis. World J Urol 2016;34(09):1229–1237

39 Girard A, Rouanne M, Taconet S, et al. Integrated analysis of ^{18}F-FDG PET/CT improves preoperative lymph node staging for patients with invasive bladder cancer. Eur Radiol 2019;29(08): 4286–4293

40 Chen R, Zhou X, Liu J, Huang G. Relationship between the expression of PD-1/PD-L1 and ^{18}F-FDG uptake in bladder cancer. Eur J Nucl Med Mol Imaging 2019;46(04):848–854

41 van de Putte EEF, Vegt E, Mertens LS, et al. FDG-PET/CT for response evaluation of invasive bladder cancer following neo-adjuvant chemotherapy. Int Urol Nephrol 2017;49(09): 1585–1591

42 Zattoni F, Incerti E, Colicchia M, et al. Comparison between the diagnostic accuracies of 18F-fluorodeoxyglucose positron emission tomography/computed tomography and conventional imaging in recurrent urothelial carcinomas: a retrospective, multicenter study. Abdom Radiol (NY) 2018;43(09):2391–2399

43 Rosenkrantz AB, Friedman KP, Ponzo F, et al. Prospective pilot study to evaluate the incremental value of PET information in patients with bladder cancer undergoing 18F-FDG simultaneous PET/MRI. Clin Nucl Med 2017;42(01):e8–e15

44 Kim S-J, Koo PJ, Pak K, Kim I-J, Kim K. Diagnostic accuracy of C-11 choline and C-11 acetate for lymph node staging in patients with bladder cancer: a systematic review and meta-analysis. World J Urol 2018;36(03):331–340

45 Loffroy R, Pottecher P, Cherblanc V, et al. Current role of trans-catheter arterial embolization for bladder and prostate hemorrhage. Diagn Interv Imaging 2014;95(11):1027–1034

46 Liu S, Zhang L, Zou L, Wen H, Ding Q, Jiang H. The feasibility and safety of cryoablation as an adjuvant therapy with transurethral resection of bladder tumor: a pilot study. Cryobiology 2016;73 (02):257–260

47 Liang Z, Fei Y, Lizhi N, et al. Percutaneous cryotherapy for metastatic bladder cancer: experience with 23 patients. Cryobiology 2014;68(01):79–83

48 Barchetti G, Simone G, Ceravolo I, et al. Multiparametric MRI of the bladder: inter-observer agreement and accuracy with the Vesical Imaging-Reporting and Data System (VI-RADS) at a single reference center. Eur Radiol 2019;29(10):5498–5506

49 Ueno Y, Takeuchi M, Tamada T, et al. Diagnostic accuracy and interobserver agreement for the Vesical Imaging-Reporting and Data System for muscle-invasive bladder cancer: a multireader validation study. Eur Urol 2019;76(01):54–56

50 Del Giudice F, Barchetti G, De Berardinis E, et al. Prospective Assessment of Vesical Imaging Reporting and Data System (VI-RADS) and Its Clinical Impact on the Management of High-risk Non-muscle-invasive Bladder Cancer Patients Candidate for Repeated Transurethral Resection. Eur Urol 2020;77(01):101–109

51 Panebianco V, De Berardinis E, Barchetti G, et al. An evaluation of morphological and functional multi-parametric MRI sequences in classifying non-muscle and muscle invasive bladder cancer. Eur Radiol 2017;27(09):3759–3766

52 Woo S, Suh CH, Kim SY, Cho JY, Kim SH. Diagnostic performance of MRI for prediction of muscle-invasiveness of bladder cancer: a systematic review and meta-analysis. Eur J Radiol 2017;95:46–55

53 Boorjian SA, Kim SP, Weight CJ, Cheville JC, Thapa P, Frank I. Risk factors and outcomes of urethral recurrence following radical cystectomy. Eur Urol 2011;60(06):1266–1272

54 Gatta G, van der Zwan JM, Casali PG, et al; RARECARE working group. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer 2011;47(17):2493–2511

55 Swartz MA, Porter MP, Lin DW, Weiss NS. Incidence of primary urethral carcinoma in the United States. Urology 2006;68(06):1164–1168

56 Chaudhari VV, Patel MK, Douek M, Raman SS. MR imaging and US of female urethral and periurethral disease. Radiographics 2010;30(07):1857–1874

57 Kawashima A, Sandler CM, Wasserman NF, LeRoy AJ, King BF Jr, Goldman SM. Imaging of urethral disease: a pictorial review. Radiographics 2004;24(Suppl 1):S195–S216