Urothelial Carcinoma: Epidemiology and Imaging-Based Review

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ABSTRACT

Bladder cancer is the 6th most common malignancy in the United States, with urothelial carcinomas comprising over 95% of cases of bladder cancer, and commands a significant disease burden in Rhode Island. Imaging studies can provide valuable diagnostic information for urothelial carcinomas at initial presentation and are routinely used for noninvasive staging, treatment response monitoring, and post-treatment surveillance. This review aims to discuss and highlight three imaging modalities: ultrasonography, computed tomography, and magnetic resonance imaging, with particular focus on the notable features and appearance of urothelial carcinoma on each modality and their relative utility throughout the disease course. A general overview of disease epidemiology and treatment practices is also provided.

KEYWORDS: Bladder cancer, urothelial carcinoma, imaging, MRI, CT

INTRODUCTION

Bladder cancer remains a significant contributor to morbidity and mortality, representing the 6th most common malignancy in the United States.[1] An estimated 82,290 new cases of bladder cancer will be diagnosed in 2023 in the United States with an estimated 16,710 deaths resulting from bladder cancer over this period.[2]

Urothelial carcinoma is the predominant histological subtype, comprising upwards of 95% of cases in the United States, and tends to be less aggressive than non-urothelial bladder carcinomas which are more commonly found in regions where Schistosoma is endemic.[3] The presence of histologic variants in urothelial carcinoma is associated with increased risk of progression.[4]

The strongest risk factor for bladder cancer development is advanced age, with a median age at diagnosis of 73 years.[2,5] Male sex is another important risk factor, with men being diagnosed with bladder cancer about four times as frequently as women, which may be explained by differences in exposures and lifestyle as well as urinary retention due to prostate enlargement and resulting stasis of urine-containing carcinogens.[6] Females typically present with more advanced disease and inferior outcomes, including increased rates of recurrence and reduced overall survival, which is commonly attributed to delays in diagnosis from lack of recognition and appropriate imaging at the time of first presenting symptoms.[7,8] Non-Hispanic White persons have the highest age-adjusted incidence of bladder cancer while Black persons have worse disease-specific outcomes which may be explained by differences in access to treatment and care.[7]

Cigarette smoking is the principal modifiable risk factor, accounting for approximately 50% of cases.[9] One meta-analysis of 89 observational studies found that smokers had over three times the risk of bladder cancer compared to never smokers and nearly two times the risk compared to former smokers.[10] While smoking exposures may be complex, it appears that the higher the cumulative smoking exposure, the higher the risk of developing bladder cancer.[11] Occupational and environmental exposures, particularly to aromatic amines and benzenes, account for approximately 10% of bladder cancer cases.[9] Chronic bladder inflammation, either through recurrent UTIs or chronic bladder catheterization, may also increase the risk of developing bladder cancer.[12,13] It has been established that diabetes mellitus is associated with an increased risk of bladder cancer, particularly in men, and recent analyses have also found an association between metabolic syndrome and bladder cancer as well.[14,15]

Genetic syndromes, most notably Lynch syndrome, may also confer increased risk of developing bladder cancer due to mutations in DNA damage repair genes, with up to 21% of patients found to have pathogenic germline variants.[9] The most common pathogenic germline variants in targeted sequencing studies are *MSH2*, *MLH1*, *BRCA1*, *BRCA2*, and *ATM*, with 18.6% of patients in the largest study harboring an actionable variant with preventive or therapeutic utility.[16]

According to statewide data obtained from the Rhode Island Cancer Registry, in Rhode Island, males were about three times as likely as females to be diagnosed with urothelial carcinoma from the period of 1995 to 2019 compared to male predominance, at a rate of about four times as likely nationally (**Table 1**). Rhode Islanders who were diagnosed with urothelial carcinoma over this period were also more likely to identify as White compared with national rates (perhaps reflecting overall racial and ethnic distributions or cancer disparities), though the overall incidence of urothelial carcinoma has decreased in Rhode Island in line with national trends.[1,2]

Table 1. Demographics and age-adjusted incidence rate of urothelial carcinoma (ICD-O-3 8120/2-3) in RI (1995–2019)

Demographics	Mean Age (years)	Male (%)	White (%)		
Urothelial carcinoma in situ (8120/2)	71.80 ± 11.05	75.44	97.81		
Urothelial carcinoma (8120/3)	72.81 ± 11.60	73.18	97.16		
Incidence (Age-adjusted incidence rate, per 100,000 individuals)	**1995–1999**	**2000–2004**	**2005–2009**	**2010–2014**	**2015–2019**
Urothelial carcinoma in situ (8120/2)	1.47	1.31	1.52	1.69	1.30
Urothelial carcinoma (8120/3)	5.94	5.35	5.60	4.92	4.08

Source: Rhode Island Cancer Registry

The most common presentation of bladder cancer is gross or microscopic hematuria. The risk of bladder cancer in a patient with gross hematuria is greater than in one with microscopic hematuria, found in one study to be 18.9% with gross hematuria compared to 4.8% with microscopic hematuria.[17] Other presentations include irritation while voiding, reduced bladder capacity, or incidental discovery on imaging. Less common presentations include urinary tract infection or upper-tract obstruction or pain with more advanced lesions.

According to the 2023 National Comprehensive Cancer Network (NCCN) guidelines on bladder cancer, there are three categories that bladder cancer can be divided into clinically based on differences in prognosis, management, and therapeutic aims: non-muscle invasive bladder cancer (NMIBC), muscle invasive bladder cancer (MIBC), and metastatic disease.[18] Visualization of the bladder is critical to the staging (using the TNM system) and management of bladder cancer, and is often done directly with cystoscopy as the gold standard for detection of bladder cancer.[18] Imaging studies are often performed at the time of initial presentation – radiologic evaluation can provide key diagnostic information and can be useful for noninvasive staging and post-treatment surveillance, particularly in higher risk patients. Here we discuss the relative utility of three imaging modalities (ultrasonography, computed tomography, and MRI) in the assessment and management of bladder cancer as well as the associated imaging features of bladder cancer in each modality.

IMAGING FEATURES

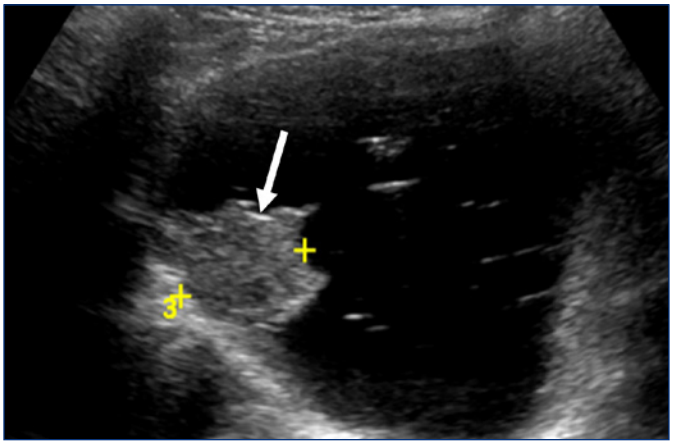
Ultrasonography

Ultrasound can be a useful imaging modality because it is non-invasive, low cost, and it does not expose patients to ionizing radiation. In the United States, the Centers for Medicare & Medicaid Services (CMS) determines the fee for services for patients with Medicare on a national scale; the CMS non-facility price, the rate set for services performed in office, for a bladder ultrasound study is relatively inexpensive at $48.46.[19] However, the role of ultrasound in the evaluation of urothelial carcinoma is currently limited. On initial presentation of a patient with gross hematuria, ultrasound is not a first-line imaging modality due to its relatively low sensitivity. The most recent American College of Radiology (ACR) Appropriateness Criteria places ultrasound in the "May Be Appropriate" category for this use as several studies have shown that ultrasound has relatively poor sensitivity compared to both CT and the gold standard of cystoscopy in the diagnosis of bladder cancer.[20,21] Ultrasound is also in the "May Be Appropriate" category for the initial evaluation of patients with microhematuria with risk factors or without a known benign cause. It is usually not appropriate in patients without known risk factors or with hematuria that is attributable to a non-malignant cause.[20] The ACR has also put out Appropriateness Criteria for the pre-treatment staging of MIBC and the post-treatment surveillance of both NMIBC and MIBC. Ultrasound is deemed to be usually not appropriate for these uses due to its limited ability in visualization beyond the bladder wall which prevents reliable detection of nodal enlargement and identification of MIBC. Whereas for NMIBC, it cannot replace the need for cystoscopic surveillance.[22,23] However, techniques such as 3-D ultrasound rendering and contrast-enhanced sonography have improved the sensitivity of ultrasound to detect bladder cancer at first presentation and discriminate between NMIBC and MIBC, which may lead to increased usage in the future.[24,25]

Optimal ultrasound evaluation of the bladder involves the use of a 3.5–6 MHz transducer to assess the bladder transabdominally in both transverse and longitudinal orientations while the bladder is under moderate distension.[26] Doppler can be useful to identify vascularity within any focal masses present. Spectral Doppler is used to demonstrate arterial or venous blood flow which would be suggestive of bladder cancer (**Figure 1**).[25] Because upwards of 30% of bladder cancers are multifocal, identification of one lesion should lead to the search of other lesions locally.[27]

The most common presentation of visible urothelial carcinoma on ultrasound is a polypoid mass with heterogeneous echotexture arising from the bladder wall, typically located along the posterior wall at the base of the bladder. The mass is immobile, without changes in patient position.[26,27] In MIBC and higher-grade urothelial carcinoma, the mass can invade the musculature and extend into the abdominal wall, prostate, or uterus. Additionally, tumors that arise in bladder

Figure 1. Transverse ultrasound image of a confirmed urothelial carcinoma appearing as a mass arising from the right lateral bladder wall.



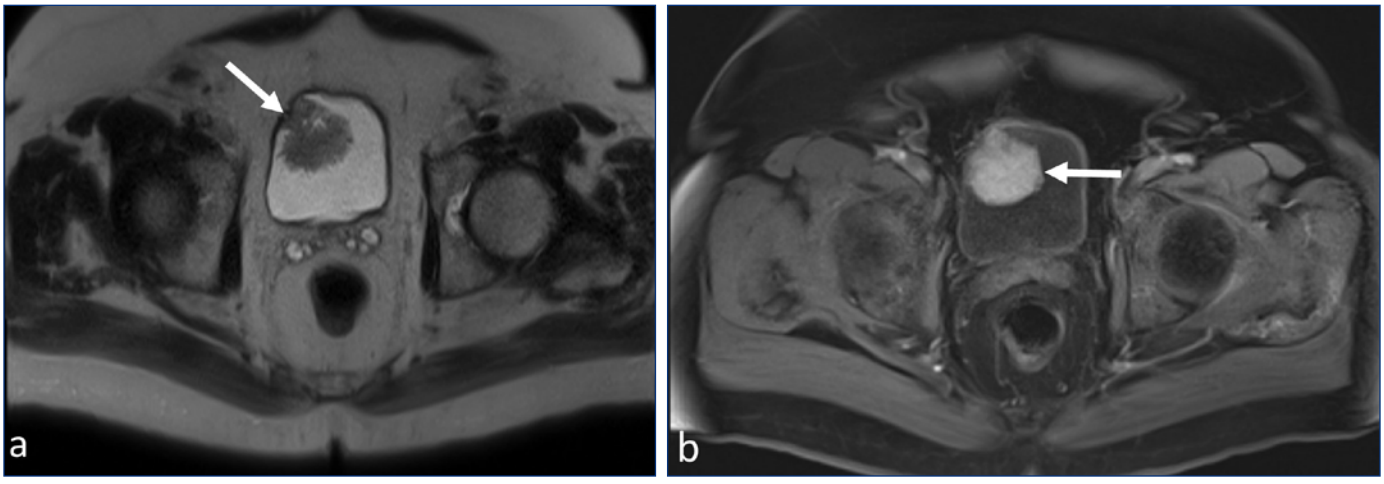
diverticula can have early transmural extension, a sign of poor prognosis.[26] Tumors located at the vesicoureteric junction may cause ureteral obstruction and hydronephrosis, while tumors at the urinary orifice may cause bladder outlet obstruction and urinary retention. In some cases, bladder cancer may appear only as focal wall thickening with or without extension into the lumen. Wall thickening > 3 mm in a well-distended bladder or > 5 mm in a poorly distended bladder is indicative of pathology.[26] Focal calcifications may also be seen in 5% of urothelial carcinomas, with idiopathic focal wall calcifications raising suspicion for an underlying tumor; these can be appreciated on ultrasound as echogenic foci with or without shadowing.[26,27] Important mimics of urothelial carcinoma on ultrasound include other neoplasms such as urachal carcinoma, lymphoma, paraganglioma, metastases, or benign conditions such as cystitis, thrombus, or calculi. Careful sonographic interrogation and thoughtful history or histopathologic correlation are helpful in distinguishing between the aforementioned entities.[26]

MRI

MRI is of increasing interest in bladder cancer due to its high soft-tissue contrast and spatial resolution. MRI is the most expensive imaging modality with a CMS non-facility price totaling $681.73 for assessment of bladder cancer.[19] It is useful for assessing the depth of bladder wall invasion and involvement of adjacent anatomic structures. This makes it a good tool for local staging of bladder cancer. The Vesical Imaging Reporting and Data System (VI-RADS) scoring system was developed in 2018 and has since been consistently validated as a way to standardize the MRI acquisition and interpretation of urothelial cancer using a multiparametric protocol.[28] A 1.5- or 3-T coil should be used and the acquisition protocol should include multiplanar T2-weighted MRI, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) MRI to identify tumor extent. Non-fat-saturated T1-weighted sequences are useful for identifying clot or hemorrhage in the bladder and metastases to bone.[28] The field-of-view (FOV) should be large enough to include the entirety of the bladder, proximal urethra, pelvic nodes, prostate, uterus, ovaries, fallopian tubes, and vagina, in accordance with sex.[29] A VI-RADS score is assigned to each of the sequences on a scale from 1 to 5. Scores of 1 and 2 represent tumors unlikely to invade the muscularis propria, while scores of 4 and 5 are likely to invade the detrusor muscle. A score of 3 is equivocal, serving as the cutoff to define MIBC.[30]

A typical suspicious lesion on MRI appears as an intravesical lesion with T2 signal hyperintensity, high DWI signal intensity, low signal intensity at the apparent diffusion coefficient (ADC) map, and early enhancement at DCE-MRI (**Figure 2 a,b**).[28] Furthermore, analyses using ADC values as a biomarker have been demonstrated to correlate with tumor aggressiveness in bladder cancer, with lower ADC values corresponding to more aggressive disease.[28] The layers of the bladder wall that are recognized here from a radiologic perspective are the inner mucosal and submucosal layer, the

Figure 2. MR imaging of muscle invasive urothelial carcinoma. **a**) Axial T2-weighted image showing hypointense anterior mass with detrusor invasion and **b**) axial T1 image demonstrating post-contrast gadolinium enhancement of the mass.



muscularis propria, and the perivesical fat; distinguishing between these layers across different sequences allows for differentiation between NMIBC and MIBC, or higher grade tumors.[28] A tumor may appear as an intramurally growing endophytic mass, an endoluminally growing exophytic mass, a flat lesion, or as a mixed lesion. Of the exophytic masses, these can be sessile or pedunculated papillary masses, and masses with a stalk tend to have more favorable prognoses than those without despite the tumor usually being larger.[28,31] Using DWI, the "inchworm sign" which appears as an archlike shape of high signal intensity with a low signal intensity submucosal stalk, has been proposed to predict aggressiveness. Specifically, its absence can be indicative of lower-stage cancer.[32]

MR urography (MRU) is a special MRI study that is tailored for the evaluation of the urinary system and improves visualization of the upper and lower urinary tracts. MRU makes use of heavily T2-weighted (or static fluid) sequences, utilizing the high signal intensity from urine to image the urinary tract which can be done without contrast enhancement.[33] MRU studies may also include dynamic T1-weighted images acquired after contrast administration to obtain images in three phases. The first is the corticomedullary phase, which is acquired first between 40 and 70 seconds after contrast injection to evaluate the enhanced outer renal cortex and medulla. The next is the nephrographic phase which is acquired 80 to 120 seconds after contrast injection to evaluate the enhanced renal parenchyma. The final phase is the excretory phase, which is acquired 10 to 15 minutes after contrast injection to evaluate the enhanced collecting system.[34] Urothelial tumors may appear as filling defects on the static fluid or excretory phase images, enhance quickly after contrast administration, and tend to have irregular contours at the margins compared to benign entities such as calculi.[34] Comparisons between images obtained immediately after contrast administration and unenhanced T1-weighted images are helpful in detecting enhancement of malignant lesions in the bladder wall.[34]

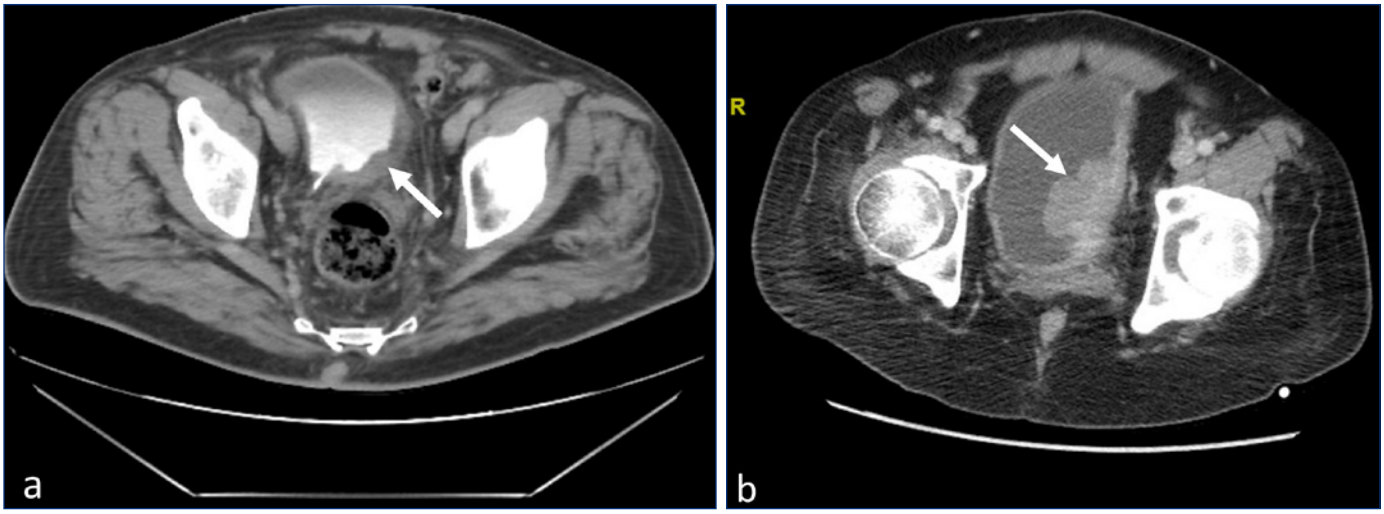
The ACR appropriateness criteria deems MRI abdomen and pelvis (distinguished from MRU) to be usually not appropriate for the evaluation of patients with microhematuria, but notes that MRU may be appropriate for evaluation of pregnant patients or patients with risk factors and no known benign cause of microhematuria.[20] For patients with gross hematuria, MRU is usually appropriate for initial imaging while MRI abdomen pelvis may also be appropriate, noting one study which showed a 98.5% sensitivity in determining the cause of gross hematuria using MRI.[20,35] For locally staging bladder cancer, MRI is noted to be the best imaging modality by the ACR, offering superior soft tissue contrast resolution, sensitivity, and specificity when compared with CT.[22] Additionally, the NCCN guidelines recommend MRI of the abdomen and pelvis if logistically feasible as an option to characterize lesions and evaluate the depth of invasion prior to resection. They recommend MRU as a viable option to evaluate the upper tracts.[18] For post-treatment surveillance, MRU also provides comprehensive evaluation of the genitourinary tract and is usually appropriate to use in NMIBC, and with risk factors or MIBC. MRI abdomen and pelvis without and with IV contrast is usually an appropriate equivalent procedure according to the ACR although there may currently be insufficient evidence for its use in MIBC surveillance compared with MRU. [24]

CT

CT is among the most commonly ordered imaging modalities, and because of its frequent use and impressive spatial resolution, bladder malignancies can often be discovered incidentally on CT. Current NCCN guidelines recommend a CT abdomen and pelvis study prior to transurethral resection if able as an alternative to MRI, and CT urography (CTU) is the preferred study in the evaluation of the upper tract in patients with bladder cancer who can receive IV contrast.[18] The CMS non-facility price of a CTU study is $343.16.[19] CTU differs from a traditional CT pelvis scan in that the protocol includes a precontrast, nephrographic, and excretory phase which is tailored for evaluation of the upper and lower tracts. There are three common protocols used for CTU: the single-bolus technique which involves administering one bolus of contrast with separate arterial, venous, and excretory phase images; the split-bolus technique which involves two administrations of contrast with acquisition in a combined excretory and nephrographic phase; and the triple-bolus technique which involves administration of three small boluses of contrast with acquisition in a combined corticomedullary-nephrographic-excretory phase.[36] The single-bolus technique is the most sensitive for identification of subtle filling defects but the latter techniques reduce the radiation dose significantly.[37]

There are several CT imaging features considered suspicious for malignancy which would warrant further workup with cystoscopy. Focal or multifocal bladder wall thickening in a well-distended bladder is a common imaging finding in urothelial carcinoma, while diffuse wall thickening is rarely representative of malignancy (**Figure 3 a,b**).[37] Although not specific for malignancy, the presence of calcifications in the bladder wall along with wall thickening should also raise concern for malignancy. Discrete bladder nodules or masses, particularly those that are avidly enhancing and are often best appreciated on early phase images, or which result in discrete filling defects in delayed phase images, are also common presentations of malignant lesions.[37] Urothelial carcinomas may also present as abnormal urothelial enhancement with focal areas of hyperenhancement in the absence of a discrete mass, most readily appreciated on early phase images before contrast has been excreted into the bladder.[37] A "stipple sign" has been described on CTU

Figure 3. Contrast-enhanced CT imaging of noninvasive and invasive urothelial carcinoma. **a**) Axial image of noninvasive papillary urothelial carcinoma of the left bladder wall appearing as asymmetric wall thickening. **b**) Axial image of infiltrating high grade papillary urothelial carcinoma in a predominantly left-sided mass.



in urothelial carcinoma with a papillary architecture. It appears as dappled contrast filling in between the papillary projections, though this appearance may sometimes be seen in other entities such as fungus balls and blood clots.[38]

The ACR designates that the standard CT abdomen and pelvis with and without contrast may be appropriate for use in patients with microhematuria and gross hematuria. CTU is usually appropriate for patients with microhematuria with risk factors (and without known benign cause) and for patients with gross hematuria.[20] For pretreatment staging of MIBC, CTU and CT chest abdomen and pelvis with IV contrast are both usually appropriate and complementary.[22] CTU is also usually appropriate in NMIBC with symptoms or risk factors, and MIBC for post-treatment surveillance, with CT abdomen and pelvis with contrast an equivalent alternative for MIBC.[23]

TREATMENT & OUTCOMES

Treatment differs between NMIBC and MIBC, with overall outcomes being much more favorable in NMIBC. In NMIBC, tumors are further stratified into low, intermediate, and high risk based on clinical presentation and presence of risk factors. In low risk NMIBC, transurethral resection of bladder tumor (TURBT) is the first-line treatment with a five-year progression-free survival rate of 93%. With routine cystoscopy surveillance there is no need for upper-tract imaging.[7,18] In intermediate risk NMIBC, TURBT remains the first-line treatment followed by the option of six weeks of induction intravesical therapy, typically with Bacille Calmette-Guérin (BCG) immunotherapy. This results in a five-year progression-free survival rate of 74%, with recommendation for routine cystoscopy and upper tract imaging every one to two years.[7,18] For high risk NMIBC, TURBT with BCG induction and maintenance therapy is the mainstay of treatment, with an option for radical cystectomy if treatment resistant. The five-year progression-free survival rate is 54%, with recommendations for routine cystoscopy and upper tract imaging every one to two years.[7,18]

In MIBC, first-line therapy is neoadjuvant cisplatin chemotherapy followed by radical cystectomy (which confers a survival benefit over bladder sparing options) with a five-year survival rate between 36% and 48%, and recommendations for routine surveillance with CTU or MRU as well as CT or MRI of the chest.[7,18] In metastatic disease, first-line therapy is cisplatin-based chemotherapy or checkpoint inhibitor therapy with agents such as pembrolizumab if ineligible for cisplatin with a five-year survival rate of 5% to 36% depending on how distant the metastases are.[7,18] Recent advances in molecular profiling and pharmacology have led to the approval of targeted therapies by the FDA for some somatic mutations in bladder cancer such as erdafitinib for FGFR-alteration positive cancer with several other clinical trials underway.[40,41]

CONCLUSION

Advances in imaging techniques across multiple modalities in recent years have improved their utility and changed the way that localized and advanced bladder cancer is worked up and managed, though cystoscopy remains the gold standard for characterization today. The therapeutic landscape has also continued to expand, with immunotherapy and targeted therapies seeing more use.

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