American College of Radiology
ACR Appropriateness Criteria®

Clinical Condition: **Pretreatment Staging of Invasive Bladder Cancer**

Radiologic Procedure	Rating	Comments	RRL*
X-ray chest	9	Preoperative screen.	☢
CT abdomen and pelvis without and with IV contrast	8	Perform as CT urogram (CTU) to include excretory phase for locoregional staging and upper-tract screening. Noncontrast images helpful for assessing enhancement of abnormalities.	☢ ☢ ☢ ☢
MRI pelvis without and with IV contrast	8	Best test for determining T-stage. Can be complementary to CTU (CTU better for upper-tract assessment).	O
CT abdomen and pelvis with IV contrast	7		☢ ☢ ☢ ☢
FDG-PET/CT whole body	6	Emerging role.	☢ ☢ ☢ ☢
CT chest without IV contrast	5		☢ ☢ ☢
MRI abdomen without and with IV contrast	5	If performed in conjunction with MR pelvis as MR urography and if iodinated contrast is contraindicated.	O
MRI pelvis without IV contrast	5	For local staging if intravenous contrast is contraindicated.	O
CT chest with IV contrast	5		☢ ☢ ☢
CT abdomen and pelvis without IV contrast	3	Could be considered in settings when patients cannot get iodinated contrast or unenhanced MRI.	☢ ☢ ☢ ☢
CT chest without and with IV contrast	3		☢ ☢ ☢
CT pelvis with IV contrast	3	For local staging if patient is not a candidate for MRI with contrast.	☢ ☢ ☢
CT pelvis without and with IV contrast	3		☢ ☢ ☢ ☢
MRI abdomen without IV contrast	3		O
US pelvis (bladder)	3		O
Tc-99m bone scan whole body	3		☢ ☢ ☢
X-ray intravenous urography	2		☢ ☢ ☢
CT pelvis without IV contrast	2		☢ ☢ ☢
MRI head without IV contrast	2		O
MRI head without and with IV contrast	2		O
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			***Relative Radiation Level**

PRETREATMENT STAGING OF INVASIVE BLADDER CANCER

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Summary of Literature Review

Introduction/Background

The National Cancer Institute estimates that in 2012 there will be 73,510 new cases of bladder cancer and 14,880 deaths from the disease in the U.S. [1]. Bladder cancer has a high tendency toward multifocality at presentation and recurrence after treatment [2]. Transitional cell carcinoma of the bladder (TCCB) is the most common form of bladder cancer in industrialized nations, accounting for more than 90% of all cases [3]. The average age of patients with TCCB in the U.S. is 65 at diagnosis. Almost 85% of patients with TCCB present with hematuria, which is either gross or microscopic and is usually painless and intermittent [4].

TCCB spreads by local extension through the basement membrane into the muscular layer, then to the perivesical fat. Progressive extension into the muscular layer allows vascular and lymphatic invasion and more distant spread. The most common metastatic sites for muscle invasive bladder cancer include lymph nodes, bone, lung, liver, and peritoneum [5]. Superficial lesions do not metastasize until they become deeply invasive but may remain indolent for many years. It has been estimated that 70%-85% of TCCB is superficial at presentation, confined to the mucosa or submucosa, without muscle invasion [3]. However, a population-based study from the northeastern U.S. reported that only 7.6% of bladder tumors identified through the New Hampshire state cancer registry were stage T2 or higher [6]. As far as muscle invasive bladder cancer is concerned (pT2-4), higher T category tumors metastasize earlier. Similarly, this is true of tumors with an atypical histology, which also demonstrate a greater frequency of peritoneal disease [5]. Only invasive tumors will be considered here. The imaging workup begins after the bladder tumor has been identified or confirmed cystoscopically and has been proven by biopsy.

Staging

TCCB is staged by its extension at presentation and graded according to microscopic (pathologic) criteria of aggressiveness [4]. The standard staging system for bladder cancer is now the Tumor, Node, Metastasis (TNM) system [4,7]. It encompasses the status of the primary tumor (T), the lymph nodes (N), and any metastases (M) (Appendix 1).

Tumor grade relates directly to depth of invasion, but inversely to curability. In a multi-institutional study from Japan, patients with pT1 (p = pathologic) or lower stage pT2, pT3, and pT4 disease without lymph node metastases had 5-year overall survival rates of 81%, 74%, 47%, and 38%, respectively [8]. Another study of 507 patients who underwent radical cystectomy without neoadjuvant therapy had 5-year recurrence-free and overall survival rates of 73% and 62% for organ-confined, node-negative tumors and 56% and 49% for non-organ-confined, node-negative tumors [9]. In a study of 300 cystectomy patients, there was a clear dichotomy in disease-specific survival rates between organ-confined disease (67%) and non-organ-confined disease (31%) [10]. Differentiating between microscopic (pT3a) and gross (pT3b) extravesical TCCB does not have prognostic significance for patients undergoing radical cystectomy [11]. In such patients, recurrence-free and overall survival is significantly better in patients with lymph-node-negative disease irrespective of the extent (microscopic or gross) of extravesical involvement [8,9,11].

Treatment ranges from cystoscopic local excision or segmental bladder resection with pelvic lymphadenectomy for early tumors to irradiation, chemotherapy, and/or radical extirpation for deep invasion [3,12]. Radical

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cystectomy with pelvic lymphadenectomy remains the standard treatment for muscle-invasive urothelial tumors of the bladder [13].

Since clinical staging by cystoscopy and bimanual examination under anesthesia is inaccurate in more than 50% of patients, imaging is vital to the proper treatment of these patients [14]. The principal task is to identify muscle invasion, extravesical spread, and nodal metastases [14]. Bladder lymph node mapping has recently demonstrated the complexity and extent of bladder drainage. Single-photon emission computerized tomography (SPECT) with intraoperative gamma probe verification found primary lymphatic landing sites for the bladder much larger than initially thought [15]. Drainage extends well beyond the external iliac vessels and obturator fossa, included in a limited pelvic nodal dissection, to also involve the internal iliacs and common iliac vessels up to the uretero-iliac crossing and occasionally extending to the inferior mesenteric artery [15]. Traditionally, lymph nodes have been considered suspicious based on increased size or altered, rounded morphology; however positron emission tomography/computed tomography (PET/CT) has an emerging role to potentially detect malignancy in subcentimeter-sized nodes [16,17]. Otherwise, none of the imaging modalities can identify microscopic spread to muscle layer, perivesical fat, lymph nodes, or other organs.

Emerging research is investigating genetic markers and biologic properties of primary tumors, including p53, E-cadherin, Bcl-2, insulin-like growth factor binding protein 2 gene, and VEGF-C, that may portend a greater propensity for them to metastasize [5,18]. For example, bladder tumors expressing VEGF-C significantly correlate with pelvic lymph node metastasis, and associating VEGF-C expression with CT imaging can improve sensitivity, specificity, and accuracy in diagnosing lymph node metastasis [18].

Cystography, pelvic angiography, lymphangiography (LAG) with or without percutaneous fine-needle aspiration (FNA) biopsy, and radiographic whole-lung laminography are no longer routinely used in staging TCCB since the advent of contemporary cross-sectional imaging.

Intravenous Urography

Intravenous urography (IVU) was once the best screening examination for upper-tract disease and was the most sensitive test in detecting small urothelial lesions [19]. The widespread use of CT urography and emerging use of magnetic resonance (MR) urography have essentially replaced IVU for evaluating the renal collecting systems and ureters [20,21]. Although only 60% of known bladder tumors are visualized by IVU, historically, obstruction of a ureteral orifice at the level of the ureterovesical junction is usually due to invasive bladder tumor, if urolithiasis is excluded [22,23]. Any degree of ureteric obstruction is significantly associated with both decreased overall survival rates and decreased tumor-free interval [24]. Preoperative hydronephrosis is also associated with higher tumor stage and grade as well as more adverse pathologic features for upper-tract urothelial carcinoma [25]. However, ureteral obstruction from bladder carcinoma or a more proximal urothelial carcinoma can be clearly demonstrated by CT urography or MR urography.

Yousem et al [19] found synchronous TCC above the bladder in 14 of 597 (2.3%) patients with TCCB; 8 (1.3%) with ureteral TCC, and 6 (1.0%) with renal TCC. They reported a range of incidence of synchronous upper-urinary-tract lesions between 0% and 6.4% and stated that IVU "must be performed" when TCCB is first diagnosed. It is important to note that this recommendation predates the widespread availability of CT urography and that the importance of this historical study is primarily to emphasize the multiplicity, which is a hallmark of TCC. An estimated 2%-4% of patients with TCC of the bladder will also develop upper-tract disease, thus requiring evaluation and surveillance of the entire urothelium [26]. Sensitivity of excretory urography to detect upper urinary tract lesions is reportedly 50%-70% [21]. However, a recent study comparing the accuracy of detection and localization of upper urinary tract urothelial carcinoma with CT urography versus excretory urography favored CT urography with per-patient sensitivity, specificity, and overall accuracy rates of 93.5%, 94.8%, and 94.2%, respectively, compared to 80.4%, 81.0%, and 80.8%, respectively, for excretory urography [21]. Advantages of a cross-sectional technique, such as CT urography, include the ability to directly visualize small masses, which may be obscured by contrast material or overlying bowel gas on excretory urography, to identify focal wall thickening, and to distinguish otherwise nonspecific filling defects as enhancing tumor versus nonenhancing calculi or blood clots [21,27]. CT or MR urography also offers limited assessment of a nonfunctioning/obstructed kidney that would not excrete the contrast medium required for excretory urography [21,27]. These strengths compelled Jinzaki et al [21] to conclude that "CT urography should be considered as the initial examination for the evaluation of patients at high risk for upper urinary tract urothelial carcinoma." Furthermore, Cohan et al [28] in their review, concluded that "the consensus is that CT urography can detect many more bladder cancers than excretory urography."

Retrograde ureteropyelography, often performed at the time of cystoscopy, is also excellent for detailed study of the urothelium, especially when intravenous contrast is contraindicated. Alternatively, MR urography can be used when iodinated contrast is contraindicated, for instance in those patients with an allergy to iodinated contrast [29].

Chest Radiograph and Computed Tomography of the Chest

All patients with invasive TCCB need pulmonary evaluation. The chest radiograph is an effective, inexpensive, low-morbidity screen [30]. Patients with findings on chest radiograph and those thought to be at high risk should have chest CT.

Radionuclide Bone Scan

The incidence of metastases in TCCB patients increases with tumor stage at time of diagnosis [30]. A 4.6% positive rate was found in 458 bone scan studies, with only a 2.8% true-positive rate [31]. Since therapy was affected in only 0.9%, the conclusion was that scintigraphy has "no place in the routine preoperative staging of bladder carcinoma" [31]. Another study of 91 patients with precystectomy bone scan concluded that "the findings of a routine preoperative bone scan are usually unable to identify patients with bladder cancer of stage ≥T2 who will not be cured by total cystectomy" [32]. Nonetheless, when one parcels out only those patients with muscle invasive disease, the likely positivity of bone scanning increases, as does its importance in guiding proper management and avoiding unnecessary radical surgery and expense. One study looking at 179 consecutive patients with bladder cancer found that 14.5% had bone metastasis at presentation; however, 61.5% of those with metastatic disease had deep muscle invasion, compared with 19.2% demonstrating superficial muscle invasion, and 7.7% demonstrating no muscle invasion, leading the authors to advocate the routine use of bone scan in patients with muscle-invasive bladder cancer [33]. The cumulative 3-year incidence for developing bone metastasis after treatment in patients without evidence of metastases on initial evaluation was 19.4%, and it increased with higher clinical stage and among those with more than one risk factor, including grade >3, p ≥4a, and positive lymphadenopathy at surgery [33]. Otherwise, bone scanning may be limited to patients with bone pain and/or elevated levels of serum alkaline phosphatase. Further evaluation with radiographs and/or magnetic resonance imaging (MRI) can be helpful, and, if necessary, guided needle biopsy can be definitive.

MRI of the Head

Neurologic complications directly related to TCCB are rare and usually the result of local extension rather than brain metastases. One study of the metastatic pattern of muscle-invasive bladder cancer found the brain to be the ninth most common site of metastatic disease, occurring in 5% of patients [5]. Therefore, MRI of the head is not recommended for asymptomatic patients [34].

Ultrasound: Transabdominal, Transrectal, and Transurethral

The distended bladder is a superb acoustic window, although size and location of the tumor affect detectability with ultrasound (US) [35]. Lesions <0.5 cm that are flat and/or near the bladder neck can be easily missed [35]. A study by Ozden et al [36] of 214 bladder tumors in 85 patients showed the lowest detection rate for US for tumors located at the inferior region of the anterior wall (47%). In this same study, detection rates were significantly lower for tumors <5 mm. US is limited in visualization beyond the bladder wall and cannot reliably detect nodal enlargement [37]. Some investigators have correlated sonographically determined contact length and height-to-length ratio with depth of tumor invasion [38]. Color Doppler with transrectal US (TRUS) adds nothing to evaluation of stage or grade [39].

TRUS is excellent for evaluating the prostate and seminal vesicles. Transurethral US (TUUS) is more sensitive than transabdominal US (TAUS) and TRUS and is more accurate in staging depth of wall involvement, but it is not widely available [39]. TRUS provides local staging information with 62%-100% accuracy, highest for superficial tumors [37,40]. TRUS staging is unreliable for tumors ≥3 cm and tumors with calcifications, largely because of acoustic shadowing [37]. It is poor (70%) for evaluating extravesical spread [40].

Three-dimensional US rendering is yet another newer diagnostic tool with potential to aid in discriminating superficial from muscle-invasive tumors [41]. The use of transabdominal 3D US to detect bladder tumors was recently assessed. The combination of gray-scale US, multiplanar reconstruction, and 3D virtual US had a sensitivity of 96.4%, specificity of 88.8%, positive predictive value (PPV) of 97.6%, and negative predictive value (NPV) of 84.2% for bladder tumor detection [42]. This technique is most helpful for small tumors, as 3D volumetric reconstructed US significantly improved sensitivity for detecting bladder tumors <1 cm when compared with traditional 2D US [43]. Contrast-enhanced sonography, not currently available in the U.S., has also been shown to better differentiate muscle infiltrating from superficial bladder neoplasms [35].

Endoluminal US (ELUS), also known as intravesical US (IVUS), uses a miniature, high-frequency transducer introduced by a rigid cystoscope for intravesical evaluation [44,45]. ELUS is both sensitive and specific in detecting muscle invasion in bladder cancer, with rates comparable to those of TUUS, and it provides greater bladder wall detail. Limitations include difficulty in depicting the tumor base in certain locations and in depicting the depth of invasion in tumors >2 cm with broad bases [44,46].

With progression from TAUS to TRUS to TUUS and ELUS, the diagnostic accuracy of US has improved. In 214 new cases of TCCB with pathological correlation, Fang et al [47] reported overall accuracy of 78.6% in local staging with TAUS. They had 9.8% overstaging and 11.7% understaging. Their accuracy was 87% for stage A, 60.5% for stage B, 41.2% for stage C, and 83.3% for stage D. Akdas et al [48] reported an overall accuracy of 96.5% in diagnosing and staging bladder tumors with TUUS in 104 patients: 96.2% for stage Ta-T1 lesions, 100.0% for T2 lesions, 91.7% for T3 lesions, and 100.0% for T4 lesions. There was no discussion of N or M staging.

Studies have shown ELUS to be 100% sensitive, 75% specific, and 84% accurate in detecting muscle invasion in bladder cancer, with reported PPV and NPV of 100% [44,45]. 3D rendering had a 66% staging accuracy for pTa tumors, 83% for pT1 tumors, and 100% for >pT1 or muscle-invasive tumors [41].

Computed Tomography of the Pelvis and Abdomen

In general, reported sensitivities for CT in detecting bladder cancer range from 79%-89.7%, with specificities in the range of 91%-94.7% [26]. The primary contribution of conventional CT is distinguishing tumors that are organ-confined from those with extravesical extension [2]. It demonstrates bulky thickening of the bladder wall, perivesical extension, lymph node enlargement, and distant metastases very well [49]. As with US, tumor location affects detection rates by CT. Identification of the primary lesion can be difficult in the areas of the anterior wall, bladder neck, and dome [28,36]. CT cannot distinguish inflammatory postoperative or postradiation edema or fibrosis from tumor and cannot assess depth of invasion of the bladder wall [28]. CT is also unable to detect microscopic or small-volume extravesical tumor extension and metastases in nonenlarged lymph nodes [26].

Voges et al [50] found an accuracy of 50% in CT staging of pT2(B1) and pT3a(B2) lesions, understaging of 29.5% of cases, and overstaging of 20.5% of cases. Staging of pT3b(C) lesions was 46.2% accurate, with 53.8% understaged. Of 16 pT4 lesions, one (6.3%) was correctly diagnosed and 15 were understaged. All had infiltration into prostate or seminal vesicle. However, this study was completed more than 20 years ago, and improved results might be expected with contemporary equipment and protocols.

Barentsz et al [37] reviewed 437 cases in the literature using CT to stage TCCB. Overall accuracy ranged from 40%-85%, with correct staging of nodes and metastases ranging from 82%-97%. For extravesical extension, accuracy ranged from 40%-92% with a mean of 74%. Paik et al found overall accuracy of 54.9%, with 39% understaging and 20.7% false negative for extravesical spread. Preoperative CT staging altered planned surgical management in only 3.7% of cases [51]. Multi-detector CT (MDCT) with intravenous (IV) contrast and 60-second delayed images is a highly sensitive and specific method for detecting bladder cancer and associated perivesical invasion, particularly when the CT scan follows transurethral resection by more than 7 days. Its sensitivity and specificity are up to 92% and 98%, respectively, in this setting [52].

Various methods for bladder distension have been studied to increase the accuracy of detecting muscle invasion in bladder cancer on CT imaging. These include evaluating the bladder filled with urine, urine opacified with iodinated contrast material, and gas [53-55]. These methods have accuracies of approximately 84%, 89% and 93%, respectively, with overstaging and understaging percentages comparable, ranging from 4%-7% for overstaging and 2%-4% for understaging [53,54]. Combining CT cystography with virtual cystoscopy increases the sensitivity and specificity of lesion detection, and also decreases the lower dimension threshold for lesion detection to 1.4 mm [56].

In addition to conventional CT, helical and MDCT with multiplanar reformation, 3D reconstruction, and creation of images mimicking traditional cystoscopy (a technique often referred to as virtual cystoscopy or CTVC) have been described in the literature. Using helical CT and multiplanar reformation, Wang et al [57] found an overall accuracy of 87.7% in CT staging of all stages of bladder cancer and, more specifically, 76.9% for Ta-T2 lesions and 94.7% for T3-T4 lesions. Pathologic lymph nodes were confirmed in six of seven cases. Multiplanar reformation was shown to be useful in evaluating the origin and extent of extravesical invasion, as well as the tumor's relationship to the ureter. A study by Browne et al [58] found that the sensitivity of 3D reconstruction in detecting bladder carcinomas of all stages was 76.9%. CT traditional cystography and CTVC may find use in

patients unable to tolerate traditional cystoscopy, in those for whom traditional cystoscopy failed, in patients with contraindications to traditional cystoscopy, or in those with narrow-necked bladder diverticula that may contain lesions [58,59]. Tsampoulas et al [59] detected 96% of bladder tumors found at conventional cystoscopy with MDCT using multiplanar reformation and CTVC, including 18 of 20 tumors ≤5 mm in size. Kishore et al [60] detected all but two of 14 bladder tumors in 11 patients using CTVC performed by instilling dilute contrast medium into the bladder. Both tumors missed in this study were 7 mm. CTVC provides comparable views to traditional cystoscopy but may not add additional diagnostic data in patients able to tolerate traditional cystoscopy [58,61].

Multidetector CT urography (which includes thin-section imaging of the collecting systems, ureters, and bladder during the excretory phase) provides collecting system opacification comparable to that of IVU [21]. As upper tracts are increasingly evaluated by CT for hematuria, the addition of lower-tract evaluation adds negligible cost and avoids the discomfort that may be associated with traditional cystoscopy, thereby streamlining the evaluation of patients with hematuria [62]. In a study by Tsili et al [63] MDCT urography detected 20 urinary bladder tumors in 75 patients being evaluated for hematuria. In this study, there were two false-positive cases of bladder tumor and a false-negative case of a small (<5 mm) bladder tumor obscured by blood clot.

A 200-patient study conducted at a fast-track hematuria clinic demonstrated 93% sensitivity and 99% specificity for bladder cancer detection by CT urography, rates similar to those of traditional cystoscopy [62]. More recently, Sadow et al [64] found an overall sensitivity and specificity of 79% and 94%, respectively, for bladder cancer detection with CT urography in a group of 779 patients. Absolute degree of contrast enhancement of tumor may correlate with histologic grade in TCCB, as demonstrated in a study of 65 patients. Although interesting, this finding may find greater application in research on tumor angiogenesis and regression after antiangiogenesis therapy [65].

CT imaging not only can be used to assess the primary bladder tumor, but also to look for distant metastatic disease. Rajesh et al [66] looked at 201 patients with biopsy-proven bladder TCC and a whole-body staging CT at time of diagnosis for evaluation of distant metastatic disease. Of these patients 5.5% had distant metastatic spread, most commonly retroperitoneal lymph nodes. While case reports have described pulmonary and bone metastases in superficial bladder cancer, none of the patients with superficial bladder cancer in this study had metastases, leading the authors to conclude that staging CT for distant metastatic disease can be restricted to those patients with muscle invasion [66]. Two histologic specimens from patients with distant metastatic disease did not include muscle and were classified as T1X; however, initial staging MR or CT in both cases suggested T2 disease or greater; therefore these cases where included in the muscle invasive group [66]. The detection of peritoneal metastases from bladder cancer with CT has also been described [5,67]. In one study, CT findings of peritoneal metastases were found in 8 of 105 patients and were indicative of a poor prognosis [67]. A more recent study found peritoneal metastasis in 24 of 150 patients, occurring more frequently in those with atypical histology [5].

Magnetic Resonance Imaging

MRI is superior to CT in demonstrating the lower pelvic anatomy. There is striking inherent contrast between the bright perivesical fat and the intermediate-signal-intensity bladder wall on T1-weighted images. Superior contrast resolution gives MRI an advantage over CT in detecting adjacent organ involvement [26]. Enhancement with gadolinium-based contrast agent improves visualization of tumors on T1-weighted images and improves staging [2]. Fat suppression techniques can help identify perivesical extension after this enhancement [2]. Deep-muscle invasion presents as disruption of the low-signal-intensity bladder wall by tumor, which usually is initially of higher signal intensity on T2-weighted images [26,68]. After intravenous gadolinium-based contrast agent is administered, TCCB shows earlier and greater enhancement than normal bladder or nonmalignant tissue [69]. Parameters, including peak time enhancement in the first minute, and steepest slope from dynamic contrast-enhanced MRI have been correlated with microvessel density and histologic grade of bladder tumors [69].

Tekes et al [70] demonstrated staging accuracies of 85% and 82% in differentiating superficial from muscle invasive tumors and organ-confined from non-organ-confined tumors, respectively. Additionally, the accuracy of pathologic lymph node detection was 96%. Overstaging occurred in 32% of cases. The length of time between transurethral resection and MRI did not affect staging accuracy [70]. Barentsz et al [37] reviewed 340 cases using MRI. The T staging of tumor was accurate in 73%-96% of cases, and the staging of nodes and metastases was accurate in 73%-98% of cases. The best staging results were with gadolinium-enhanced T1-weighted fast spin-echo sequences 14 seconds after injection. These authors suggest that following cystoscopic identification of tumor, MRI should be used as the initial imaging modality to stage the tumor. Hayashi et al [71] reviewed 71

patients using gadolinium enhancement and endorectal coil and reported an 83% overall staging accuracy. Muscle invasion was diagnosed with 87% accuracy, 91% sensitivity, and 87% specificity. More recently, Roe et al [72] demonstrated that the normalized area between tumor and muscle contrast uptake curves generated with dynamic gadolinium-enhanced MRI correlates with T stage for bladder cancer.

As with CT, there has also been interest in 3D rendering techniques with MR data sets (including multiplanar reconstructions and creation of cystoscopic-like images) as a replacement for traditional cystoscopy and to assist in staging. High diagnostic accuracy has been demonstrated, with sensitivity of 90.7% and specificity of 94.0% using combined cystoscopic-like views created from MR data sets and multiplanar reconstructions. These results are comparable to those of CT, and MR cystography is especially promising in special cases where traditional cystoscopy may be contraindicated (urethral stricture), or suboptimal (narrow-necked bladder diverticula) [73]. Similar conclusions were previously drawn by Lammle et al [74].

Investigators have demonstrated that diffusion-weighted MRI (DWI) can differentiate between bladder carcinoma and surrounding structures and that bladder carcinoma has a lower apparent diffusion coefficient (ADC) value than surrounding, nonneoplastic structures [75,76]. El-Assmy et al [77] recently compared the staging accuracy of DWI to T2-weighted sequences, finding DWI superior in staging organ-confined tumors less than or equal to T2 disease. Likewise, Takeuchi et al [68] found that diffusion-weighted images added information to T2-weighted images alone when evaluating the T stage of bladder cancer, significantly improving accuracy, specificity, and area under the receiver operating curves, with best results from combining T2-weighted images, contrast-enhanced images, and diffusion-weighted images. ADC values were also useful in predicting histologic grade of tumor [68]. Infiltrative inflammatory and fibrous changes most often seen in patients undergoing neoadjuvant chemotherapy and radiation complicate staging with MRI [78]. However, DWI has also been suggested to improve specificity and accuracy in assessing therapeutic response to induction chemoradiotherapy in patients with muscle-invasive bladder cancer, predicting complete response, and optimizing patient selection for bladder-sparing protocols as well as to monitor recurrence [79].

The role of MRI for assessing bladder cancer has recently been summarized by Verma et al [80].

Computed Tomography versus Magnetic Resonance Imaging

CT urography offers the potential for a one-stop-shop examination to assess local disease, lymph nodes, distant metastases, and the upper urinary tracts, while MRI may offer advantages over CT for local staging [2]. Noting that MRI appears to have slightly better sensitivity and specificity than CT for local staging, Klein and Pollack [81] stated that MRI and CT have similar accuracy for detecting perivesical fat invasion and that the most notable advantage of MRI is its apparent ability to differentiate between superficial and deep invasion of the bladder wall. Barentz et al [37] concluded that MRI is the best technique for staging invasive tumors, as it was slightly better than or equal to CT at differentiating T3a from T3b lesions and superior to CT for detecting tumors at the bladder dome or base. In deeply infiltrating tumors (stages T3b-T4b), they asserted that MRI "is generally agreed to be the most accurate staging technique," and "when MRI is available, CT is no longer needed." MacVicar [49] in a review article stated that MRI is the investigation of choice for local staging and is the preferred technique in postcystectomy and radiation therapy follow-up. A more recent review by Beyersdorff et al [14] contends that "MRI is superior [to CT] for evaluation of the depth of invasion in the bladder wall." These authors go on to say that "both modalities continue to have difficulties in determining whether perivesical changes are related to tumor or inflammation from the previous transurethral biopsy." However, emerging data regarding the addition of diffusion-weighted imaging to standard pelvic MRI may help differentiate treatment response and residual/recurrent disease [79]. MRI has been reported to be more precise in the identification and localization of lymph nodes in the setting of pelvic malignancy when compared to CT, in particular for smaller nodes ranging in size from 1-5 mm [17]. However, both CT and MRI rely on enlargement of lymph nodes as a criterion for metastasis and are limited in detecting metastases to normal-sized nodes. This may change if further studies corroborate the early results of using lymphotropic nanoparticle-enhanced MRI for detecting micrometastasis in nonenlarged lymph nodes [82]. Deserno et al [83] found that MRI performed with ferumoxtran-10 (ultrasmall superparamagnetic iron oxide) contrast demonstrated an accuracy in pathologic lymph node detection of up to 92% and a sensitivity of up to 96%. Alternatively using fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT has the potential to detect metastatic disease in an otherwise normal-size node [84,85]. Lymph node metastasis in patients with superficial tumors (less than T3) is rare, but if deep muscle layers are involved (T2b) or if extravesical invasion is seen, the incidence of lymph node metastasis rises to 20%-30% and 50%-60%, respectively. If a lymph node is considered to contain metastasis, an FNA biopsy should be considered.

Positron Emission Tomography and Radioimmunoscintigraphy

Bouchelouche and Oehr [86] reviewed the use of PET and PET/CT for imaging of urothelial malignancies, concluding that despite advances in these techniques, larger clinical trials are needed to establish their role for imaging urological malignancies. Conventional FDG-PET is limited for imaging bladder tumors because of its high urinary excretion, although it may have a role in detecting recurrent or metastatic disease [87]. Subsequent studies have shown that images obtained after intravenous administration of diuretic and oral hydration can improve results of FDG-PET/CT for detecting locally recurrent or residual bladder tumors [88,89]. FDG-PET is 67% sensitive, 86% specific, and 80% accurate in detecting pathologic lymph nodes in patients with bladder cancer, which exceeds both CT and MRI [90]. A study correlating FDG-PET and CT results in the same patients reported sensitivity, specificity, and accuracy of 60%, 88%, and 78%, respectively, in nodal and metastasis staging, suggesting improved distant metastatic and locoregional node staging [91]. PET imaging with FDG may be more limited in detecting metastatic disease once a patient has received chemotherapy, with sensitivity for proven metastases of only 50% in one small series [92].

FDG-PET/CT results do affect clinical decisions in patients with bladder cancer. Apolo et al [84] prospectively looked at patients with bladder cancer through the national oncology PET registry and conducted a clinical impact analysis. Physicians surveyed noted that PET/CT found more disease in 40% of patients and less disease in 18% of patients. Overall, PET/CT results changed the treatment plan in 68% of patients. Even after applying an imaging-adjusted impact for patients in whom a different imaging test such as CT or MR may have led to the same management strategy, PET/CT still changed the treatment plan in 47% of patients [84]. Physicians surveyed also noted that additional testing was avoided in 70% of patients based on PET/CT results, including eliminating the need for biopsy in 21% of patients. Systemic chemotherapy was added in 19% of patients who were found to have metastatic disease on PET/CT but who initially were only intended to receive treatment of organ-confined muscle-invasive disease [84].

Patients with muscle-invasive disease and normal presurgical CT imaging have an estimated 25% chance of lymph node metastasis prior to cystectomy, generally microscopic disease [84]. Therefore, PET/CT has greater use in evaluating patients with invasive disease, as nodal involvement and metastatic disease are rare with superficial bladder cancer. Kibel et al [85] prospectively evaluated FDG-PET/CT for staging of muscle-invasive bladder carcinoma in patients with no evidence of metastatic disease by conventional staging methods, reporting a sensitivity of 70%, and specificity of 94%, a PPV of 78%, and a NPV of 91% for PET/CT among this population. Of note, FDG-PET/CT detected occult metastatic disease in 7 of 42 patients with negative conventional preoperative evaluations, including CT and bone scan. In this study, treatment approach was altered in two patients, one receiving neoadjuvant chemotherapy and a second with widespread metastatic disease receiving palliative chemotherapy [85].

Looking at muscle-invasive urothelial carcinoma before radical cystectomy, after radical cystectomy, and after systemic chemotherapy, Lodde et al [16] found FDG-PET/CT to be more sensitive than CT in detecting the primary urothelial bladder cancer, although less specific. While CT and FDG-PET/CT had similar specificity for lymph node metastasis, FDG-PET/CT demonstrated almost twice the sensitivity of CT. FDG-PET/CT was also useful in detecting metastatic disease outside of the pelvis and was in agreement with bone scans for all patients with bone metastasis, except in one patient in whom two additional lesions were detected by FDG-PET/CT. These results led Lodde et [16] all to conclude that "FDG-PET/CT could replace standard CT and bone scintigraphy in the presurgical staging and monitoring of patients with urothelial carcinoma after surgery or chemotherapy" as a cost-effective single method of staging and surveillance. Despite promising early results with FDG-PET/CT for detecting metastatic disease in patients with bladder cancer, two small studies found no advantage of FDG-PET/CT for lymph node staging over MR or CT alone. However, neither study was sufficiently powered to substantiate a statistically significant difference in N staging between these modalities [93,94].

^{11}C-choline PET when compared with CT promises slightly increased accuracy of lymph node staging (63.0% vs 88.9%, $P<0.01$) and may avoid false-positive results for lymph nodes due to reactive hyperplasia when compared with CT, although further evaluation with this agent is needed to confirm these findings [95]. Gofrit et al [96] studied ^{11}C-choline PET for preoperative staging of transitional cell carcinomas in 18 patients (17 bladder tumors), finding that uptake was present in all primary TCCs and that ^{11}C-choline PET was "highly positive for primary and metastatic bladder cancer."

The experimental modality of radioimmunoscintigraphy using anti-MUC1 mucin monoclonal antibody C595 labeled with various radiotracers has been shown to be up to 90% sensitive in detecting invasive cancer and 88% sensitive in detecting distant metastases in sites such as lymph node, bone, and lung. [97,98].

Optical Coherence Tomography

Optical coherence tomography (OCT) is a new method of imaging biological tissues *in vivo* with exceptional spatial resolution (10-15 μm) [99]. OCT uses light generated by a superluminescent diode to image tissue in a manner analogous to B-mode US. OCT has been used to evaluate superficial bladder carcinoma as well as to identify muscle-invasive bladder carcinoma with encouraging but very preliminary results [99,100]. One study found adding OCT as an adjunct to fluorescence cystoscopy can reduce false-positive biopsies by increasing specificity [101]. However, another study looking at the quantitative measurement of attenuation coefficients using OCT *ex vivo* was unable to detect morphological urothelial carcinoma changes [102]. At this time, the depth and width of the scanning field are severely limited, and OCT remains experimental.

Summary

- With the increasingly widespread use of CT urography, the role of IVU has been replaced. CT urography not only is effective for local staging but also provides information regarding the upper urinary tracts, the liver, and the nodal status.
- Chest CT can be limited to high-risk patients or those with chest radiograph findings.
- Although there exists some evidence that the yield of radionuclide bone scan increases with tumor stage, radionuclide bone scan is typically not indicated without bone pain and/or elevated serum alkaline phosphatase levels.
- Radiographs can be limited to sites of increased uptake and/or bone pain.
- MRI of the head is needed only if neurological symptoms are present.
- US is useful for local tumor (T) staging; TUUS and ELUS appear to be equally effective in this regard.
- Contrast-enhanced MRI is preferred over CT for local staging and is equivalent to it in assessing regional lymph nodes. Preliminary results suggest that the addition of diffusion-weighted sequences to MRI can improve results.
- CT or MRI supplemented with 3D rendering techniques may be used in specific cases such as evaluation of narrow-necked bladder diverticula, which may be poorly evaluated by traditional cystoscopy, but 3D rendering techniques are not necessary in the majority of patients.
- CT and MRI supplemented with 3D rendering techniques may also be of use in patients unable to tolerate traditional cystoscopy and may be considered to streamline evaluation of hematuria, combining staging and screening.
- There is an emerging role for FDG-PET/CT in staging of muscle-invasive bladder cancer, as some studies suggest this modality has greater sensitivity for detecting lymph node metastases in particular and has been shown to detect metastases occult by conventional preoperative CT and bone scan. Recent evidence suggests that FDG-PET/CT can affect clinical decision making in patients with bladder cancer.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared to those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document.

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢ ☢	0.1-1 mSv	0.03-0.3 mSv
☢ ☢ ☢	1-10 mSv	0.3-3 mSv
☢ ☢ ☢ ☢	10-30 mSv	3-10 mSv
☢ ☢ ☢ ☢ ☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies".		

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Appendix 1. Staging of Bladder Cancer [103]

Primary tumor (T)

Stage	Sub-Stage	Definition
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary carcinoma
Tis		Carcinoma in situ (ie, flat tumor)
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscle
	pT2a	Tumor invades superficial muscle (inner half)
	pT2b	Tumor invades deep muscle (outer half)
T3		Tumor invades perivesical tissue
	pT3a	Microscopically
	pT3b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall
	T4a	Tumor invades the prostate, uterus, vagina
	T4b	Tumor invades the pelvic wall, abdominal wall

[*Note: The suffix "m" should be added to the appropriate T category to indicate multiple lesions. The suffix "is" may be added to any T to indicate the presence of associated carcinoma in situ.*]

Regional lymph nodes (N)

Stage	Sub-Stage	Definition
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single lymph node, ≤2 cm in greatest dimension
N2		Metastasis in a single lymph node, >2 cm but ≤5 cm in greatest dimension; or multiple lymph nodes, ≤5 cm in greatest dimension
N3		Metastasis in a lymph node, >5 cm in greatest dimension

Distant metastasis (M)

Stage	Sub-Stage	Definition
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Appendix 2. Stage Grouping [104]

Stage 0a	Ta, N0, M0
Stage 0is	Tis, N0, M0
Stage I	T1, N0, M0
Stage II	T2a, N0, M0
	T2b, N0, M0
Stage III	T3a, N0, M0
	T3b, N0, M0
	T4a, N0, M0
Stage IV	T4b, N0, M0
	Any T, N1, M0
	Any T, N2, M0
	Any T, N3, M0
	Any T, Any N, M1