# American College of Radiology ACR Appropriateness Criteria® Pretreatment Staging of Muscle-Invasive Bladder Cancer

# **Variant 1:** Pretreatment staging of muscle-invasive bladder cancer.

Procedure	Appropriateness Category	Relative Radiation Level
CT abdomen and pelvis without and with IV contrast	Usually Appropriate	❖❖❖❖
X-ray chest	Usually Appropriate	<b>②</b>
MRI abdomen and pelvis without and with IV contrast	Usually Appropriate	0
CT abdomen and pelvis with IV contrast	Usually Appropriate	❖❖❖
MRI pelvis without and with IV contrast	Usually Appropriate	0
FDG-PET/CT skull base to mid-thigh	May Be Appropriate	<b>⊕⊕⊕</b>
CT chest with IV contrast	May Be Appropriate	❖❖❖
CT chest without IV contrast	May Be Appropriate	❖❖❖
MRI pelvis without IV contrast	May Be Appropriate	0
CT abdomen and pelvis without IV contrast	May Be Appropriate	<b>♦</b>
CT abdomen with IV contrast	Usually Not Appropriate	<b>♦</b>
CT abdomen without and with IV contrast	Usually Not Appropriate	❖❖❖❖
CT abdomen without IV contrast	Usually Not Appropriate	**
CT chest without and with IV contrast	Usually Not Appropriate	**
CT pelvis with IV contrast	Usually Not Appropriate	<b>♦</b>
CT pelvis without and with IV contrast	Usually Not Appropriate	***
CT pelvis without IV contrast	Usually Not Appropriate	**
MRI abdomen and pelvis without IV contrast	Usually Not Appropriate	0
MRI abdomen without IV contrast	Usually Not Appropriate	0
MRI abdomen without and with IV contrast	Usually Not Appropriate	0
MRI head without and with IV contrast	Usually Not Appropriate	0
Bone scan whole body	Usually Not Appropriate	<b>♦</b> ♦
US pelvis (bladder)	Usually Not Appropriate	0
MRI head without IV contrast	Usually Not Appropriate	0
Radiography intravenous urography	Usually Not Appropriate	<b>♦</b> ♦

#### PRETREATMENT STAGING OF MUSCLE-INVASIVE BLADDER CANCER

Expert Panel on Urologic Imaging: Christian B. van der Pol, MD<sup>a</sup>; V. Anik Sahni, MD<sup>b</sup>; Steven C. Eberhardt, MDc; Aytekin Oto, MDd; Oguz Akin, MDe; Lauren F. Alexander, MDf; Brian C. Allen, MD<sup>g</sup>; Fergus V. Coakley, MD<sup>h</sup>; Adam T. Froemming, MD<sup>i</sup>; Pat F. Fulgham, MD<sup>j</sup>; Keyanoosh Hosseinzadeh, MDk; Jodi K. Maranchie, MDl; Rekha N. Mody, MDm; Nicola Schieda, MDn; MD°: Aradhana Venkatesan.  $MD^p$ : David M. Schuster. M. Carolvn L.  $MD^q$ : Mark E. Lockhart, MD, MPH.<sup>r</sup>

### **Summary of Literature Review**

# Introduction/Background

The American Cancer Society estimates that in 2017 there will be 79,030 new cases of bladder cancer and 16,870 deaths from the disease in the United States [1]. Bladder cancer has a high tendency toward multifocality at presentation and recurrence after treatment [2]. Urothelial carcinoma (previously known as transitional cell carcinoma) of the bladder is overwhelmingly the most common histologic type of bladder cancer in industrialized nations, accounting for more than 90% of all cases [3]. The median age of patients at diagnosis with bladder cancer in the United States is 73 years. Almost 85% of patients with bladder cancer present with hematuria, which is either gross or microscopic and is usually painless and intermittent [4].

Bladder urothelial carcinoma spreads by local extension from the urothelium, through the lamina propria, into the muscularis propria or detrusor muscle layer, then to the perivesical fat. It has been estimated that 70% to 85% of bladder urothelial carcinoma is non-muscle-invasive at presentation [3]. Invasion of the muscularis propria and beyond, termed muscle-invasive bladder cancer (MIBC), increases the risk for more distant spread. The most common metastatic sites for MIBC include lymph nodes, bone, lung, liver, and peritoneum [5].

Bladder lymph node mapping has demonstrated the complexity and extent of bladder lymphatic drainage. Drainage extends 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 [6]. Traditionally, lymph nodes have been considered suspicious based on increased size; however, newer magnetic resonance imaging (MRI) techniques and fluorine-18-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG-PET/CT) can improve malignancy detection in subcentimeter-sized nodes [7-9].

Bladder urothelial carcinoma is staged by its extent at presentation and graded as either low grade or high grade. The standard staging system for bladder cancer is the Tumor, Node, Metastasis (TNM) system, which encompasses the status of the primary tumor (T), lymph nodes (N), and metastases (M). Since the last edition of this document, the 8<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) Staging Manual was published, which reclassified bladder cancer N staging based on the number of metastatic regional lymph nodes and reclassified common iliac nodes as regional lymph nodes (N3) rather than metastatic disease [10].

Radical cystectomy with pelvic lymphadenectomy remains the reference standard treatment for MIBC [11]. Neoadjuvant cisplatin-based combination chemotherapy is increasingly being used in these patients, and has been shown to improve disease-specific and overall survival compared with surgery alone [12,13]. Moving forward, immune-checkpoint inhibitors and molecular-profiling technologies hold potential to fundamentally change management of bladder cancer [14].

Reprint requests to: <u>publications@acr.org</u>

<sup>&</sup>lt;sup>a</sup>Research Author, Brigham & Women's Hospital, Boston, Massachusetts. <sup>b</sup>Principal Author, Brigham & Women's Hospital, Boston, Massachusetts. <sup>c</sup>Panel Chair, University of New Mexico, Albuquerque, New Mexico. <sup>d</sup>Panel Vice-chair, University of Chicago, Chicago, Illinois. <sup>c</sup>Memorial Sloan Kettering Cancer Center, New York, New York. <sup>f</sup>Emory University Hospital, Atlanta, Georgia. <sup>g</sup>Duke University Medical Center, Durham, North Carolina. <sup>h</sup>Oregon Health & Science University, Portland, Oregon. <sup>i</sup>Mayo Clinic, Rochester, Minnesota. <sup>j</sup>Urology Clinics of North Texas, Dallas, Texas; American Urological Association. <sup>k</sup>Veterans Administration, Durham, North Carolina. <sup>i</sup>UPMC, Pittsburgh, Pennsylvania; American Urological Association. <sup>m</sup>Cleveland Clinic, Cleveland, Ohio. <sup>n</sup>Ottawa Hospital Research Institute and the Department of Radiology, The University of Ottawa, Ottawa, Ontario, Canada. <sup>o</sup>Emory University Hospital, Atlanta, Georgia. <sup>p</sup>University of Texas MD Anderson Cancer Center, Houston, Texas. <sup>q</sup>University of Washington, Seattle Cancer Care Alliance, Seattle, Washington. <sup>i</sup>Specialty Chair, University of Alabama at Birmingham, Birmingham, Alabama.

The American College of Radiology seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply individual or society endorsement of the final document.

The principal task of imaging is to identify MIBC, extravesical spread, and nodal and distant metastases [15]. The imaging workup begins after the bladder tumor has been identified or confirmed cystoscopically and has been proven by biopsy.

# **Discussion of Procedures by Variant**

# Variant 1: Pretreatment staging of muscle-invasive bladder cancer.

#### **CT Pelvis**

In many centers, abdominal imaging, usually with contrast, will be obtained in conjunction with pelvis/bladder imaging as part of complete staging. For details regarding bladder cancer detection, refer to the ACR Appropriateness Criteria® on "Hematuria" [16] and the ACR Appropriateness Criteria® on "Post-Treatment Surveillance of Bladder Cancer" [17].

The contribution of CT for bladder cancer staging includes identification of multifocal disease, extravesical extension, adenopathy, and metastases [2]. CT demonstrates bulky thickening of the bladder wall, perivesical extension, lymph node enlargement, and distant metastases very well [18]. CT cannot distinguish inflammatory post-treatment edema or fibrosis from tumor and cannot assess depth of invasion of the bladder wall [19]. CT is also unable to detect microscopic or small-volume extravesical tumor extension and metastases in nonenlarged lymph nodes [20].

Barentsz et al [21] reviewed 437 cases in the literature using CT to stage bladder urothelial carcinoma. Overall accuracy ranged from 40% to 85%, with correct staging of nodes and metastases ranging from 82% to 97%. For extravesical extension, accuracy ranged from 40% to 92% with a mean of 74%. Paik et al [22] found overall accuracy of 55%, with 39% understaging and 21% false negative for extravesical spread. Tritschler et al [23] in a retrospective review of 276 patients found that CT accuracy for predicting pathological tumor stage was 49% and accuracy for predicting lymph node metastases was 54%, and concluded that multidetector CT had little impact on decision making for local treatment of MIBC during radical cystectomy. Another study by the same group found that there was significant interobserver variability in CT findings that might contribute to the limited accuracy of CT in the detection of extravesical tumor spread, infiltration of extravesical organs, and lymph node involvement [24].

Yuan et al [25], in a prospective study of 63 patients, showed that CT T-stage could help surgeons determine the extent of pelvic lymph node dissection required, with lower-stage tumors requiring less extensive nodal dissection, reducing the risk of complications. A study by Horn et al [26] found that the sensitivity of CT imaging for the detection of lymph node metastases was low, while high values for specificity were achieved.

In addition to multidetector CT, the use of multiplanar reformation, 3-D reconstruction, and creation of images mimicking traditional cystoscopy (a technique often referred to as virtual cystoscopy) have been assessed in the literature. Using multiplanar reformation, Wang et al [27] found an overall accuracy of 88% in CT staging of all stages of bladder cancer and, more specifically, 77% for Ta-T2 lesions and 95% 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.

### **CT Abdomen**

Abdominal CT can be acquired at the same time as a pelvic CT in one continuous scan and can be useful for the detection of abdominal adenopathy and metastases. Rajesh et al [28] looked at 201 patients with biopsy-proven bladder urothelial carcinoma and a CT whole-body staging at time of diagnosis for evaluation of distant metastatic disease. Of these patients, 6% had distant metastatic spread, most commonly retroperitoneal lymph nodes. None of the patients with non-muscle-invasive bladder cancer had metastases. The detection of peritoneal metastases from bladder cancer with CT has also been described [5,29]. In one study, CT findings of peritoneal metastases were found in 8 of 105 patients and were indicative of a poor prognosis [29]. Another study found peritoneal metastasis in 24 of 150 patients, occurring more frequently in those with atypical histology including squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and undifferentiated tumors [5].

An estimated 2% to 4% of patients with urothelial carcinoma of the bladder will also develop upper-tract disease, thus requiring evaluation of the entire urothelium [20]. An abdomen-pelvis CT urogram protocol can aid in the detection of upper tract disease. The widespread use of CT urography and emerging use of MR urography have essentially replaced intravenous urography (IVU) for evaluating the renal collecting systems and ureters [30,31]. Advantages of a cross-sectional technique, such as CT urography, includes 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 [31,32]. CT and MR urography offer the ability to potentially assess a nonfunctioning/obstructed kidney that would not excrete the contrast medium required for excretory urography [31,32]. These strengths compelled Jinzaki et al [31] to conclude "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 [19] concluded "the consensus is that CT urography can detect many more bladder cancers than excretory urography."

### **MRI Pelvis**

MRI is the best imaging modality for locally staging bladder cancer. The soft tissue contrast resolution of MRI makes it more optimal than CT for detecting bladder cancer invasion of the detrusor muscle, perivesical tissues, and adjacent organs [20,33,34]. The addition of newer sequences has been shown to further improve local staging accuracy and detection of malignant regional lymph nodes [9,35-38]. El-Assmy et al [35] compared the staging accuracy of diffusion-weighted imaging (DWI) to T2-weighted sequences, finding DWI superior in staging organ-confined tumors ≤T2 disease. Likewise, Takeuchi et al [36] found that DWI 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. In a study by Thoeny et al that included both bladder and prostate cancer, a combination of DWI signal intensity relative to groin lymph nodes, as well as morphologic criteria at T2-weighted imaging, was used to identify malignant nodes [9]. They reported sensitivity of 61% to 94%, specificity of 90% to 99%, and accuracy of 83% to 96% for malignant node detection on a per-patient basis and a sensitivity of 55% to 87%, specificity of 94% to 100%, and accuracy of 88% to 96% for malignant node detection on a per-pelvic side basis.

The addition of gadolinium-based contrast has been shown to further improve the local staging accuracy of bladder cancer on MRI. Daneshmand et al [39] conducted a prospective study on 122 patients using gadolinium-enhanced MRI. They found that MRI had 88% sensitivity, 48% specificity, and 74% accuracy in differentiating organ-confined from non–organ-confined bladder cancer, as well as 41% sensitivity, 92% specificity, and 80% accuracy for the detection of positive nodal disease. Interobserver agreement for T and N staging was moderate, similar to other studies which showed moderate-to-good agreement [40,41]. Multiple other publications report the sensitivity and specificity of MRI for differentiating non-muscle-invasive from muscle invasive tumors at 78% to 98% and 82% to 100% and the sensitivity and specificity for differentiating organ-confined from non–organ-confined tumors at 90% to 94% and 60% to 94% [40-43]. The combination of dynamic contrast-enhanced imaging with DWI and T2-weighted imaging is referred to as multiparametric MRI, which is likely the most optimal MRI technique for the local staging of bladder cancer [2,34,44].

MRI has been shown to have a tendency towards overestimation of T-stage, with anywhere from 32% to 55% of patients having a reduced T-stage at resection [33,42,45]. This could, in part, be due to comparison to transurethral resection of bladder tumor specimens as the reference standard in some studies, which has been shown to underestimate local staging in up to 40% of cases [46].

Noting that MRI has better sensitivity and specificity than CT for local staging, Klein and Pollack [47] 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. Barentsz et al [21] 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." A review by Beyersdorff et al [15] contends "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 DWI to standard pelvic MRI may help differentiate treatment response and residual/recurrent disease [48].

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 to 5 mm [8,9]. Lymph node metastases in patients with tumors <T3 are rare, but if deep muscle layers are involved (T2b) or if extravesical invasion is seen, the incidence of lymph node metastases rises to 20% to 30% and 50% to 60%,

respectively. If a lymph node is considered to contain metastasis, a fine-needle aspiration biopsy should be considered.

As with CT, there has also been interest in 3-D 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. These techniques are mostly experimental at present.

### **MRI Abdomen**

Abdomen MRI and, in particular, MR urography may be performed for nodal, upper-tract, and metastatic staging in conjunction with dedicated pelvic imaging for local bladder staging. Non-contrast enhanced MR urography can be used to assess the renal collecting systems and ureters using a heavily T2-weighted sequence when iodinated contrast is contraindicated, such as in those with a severe allergy to iodinated contrast, in pregnancy, and in pediatric patients [49].

### **IVU**

The widespread use of CT urography and emerging use of MR urography have essentially replaced IVU for evaluation of the urothelium in the renal collecting systems and ureters. Sensitivity of excretory urography to detect upper urinary tract lesions is reportedly 50% to 70% [31]. However, a 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 with 80.4%, 81.0%, and 80.8%, respectively, for excretory urography [31].

Retrograde ureteropyelography, often performed at the time of cystoscopy, is also excellent for detailed study of the urothelium.

#### FDG-PET/CT

Conventional PET is limited for the local staging of bladder tumors because of high FDG activity in excreted urine. The current body of literature regarding the ability of FDG-PET to stage bladder cancer suggests it improves sensitivity for diagnosing nodal and metastatic disease, particularly when combined with CT (FDG-PET/CT).

A study of 233 patients by Goodfellow et al [50] found the sensitivity and specificity of CT for pelvic lymph node involvement was 45% and 98%, respectively. Using PET/CT, the sensitivity for pelvic lymph node involvement increased to 69% with a 3% reduction in specificity to 95%. In a prospective study of 25 patients by Nayak et al [51], in nine patients who had positive lymph nodes for metastases on histopathology, CT and PET/CT scans had a sensitivity of 44% and 78%, respectively. Other authors have found FDG-PET/CT sensitivity for detection of nodal metastases to range between 47% and 56% and specificity to range between 93% and 98%, with specificity often slightly lower than CT [52].

Pichler et al [53] retrospectively analyzed 70 bladder cancer patients staged with FDG-PET/CT before radical cystectomy and found that sensitivity, specificity, and accuracy were 55%, 90%, and 84% for FDG-PET alone; 46%, 92%, and 84% for CT using an 8-mm cutoff; and 27%, 97%, and 86% for CT using a 10-mm cutoff. Combined FDG-PET/CT resulted in a nonsignificant increase of diagnostic accuracy using a cutoff >8 mm for lymph node evaluation (64%, 86%, and 83%, respectively).

Goodfellow et al [50] found that FDG-PET detected metastatic disease outside of the pelvis with a sensitivity of 54% compared with 41% for CT, while both PET/CT and CT had similar specificities of 97% and 98%, respectively. Kibel et al [54] prospectively evaluated FDG-PET/CT for staging of MIBC in patients with no evidence of metastatic disease by conventional staging methods, reporting a sensitivity of 70%, specificity of 94%, PPV of 78%, and a NPV of 91% for PET/CT among this population. In this study, treatment approach was altered in two patients, one receiving neoadjuvant chemotherapy and a second with widespread metastatic disease receiving palliative chemotherapy.

FDG-PET/CT results can affect clinical decisions in patients with bladder cancer. Apolo et al [55] 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 MRI may have led to the same management strategy, PET/CT still changed the treatment plan in 47% of patients [55]. In another study,

Kollberg et al [56] prospectively assessed 103 patients with high-risk MIBC who underwent FDG-PET/CT in addition to CT, and found that FDG-PET/CT findings led to an altered provisional treatment plan in 27% of patients. A study by Mertens et al of 96 consecutive patients with bladder cancer found that FDG-PET/CT provided additional staging information that influenced the treatment of MIBC in almost 20% of cases [57].

<sup>11</sup>C-choline PET is mostly experimental at present. When compared with CT, <sup>11</sup>C-choline PET promises increased accuracy of lymph node staging and may avoid false-positive results for lymph nodes due to reactive hyperplasia when compared with CT [58]. The current literature suggests that <sup>11</sup>C-choline PET/CT has a sensitivity of 42% to 59% and specificity of 84% to 90% for detecting nodal disease [59,60]. Golan et al [61] compared <sup>11</sup>C-choline PET/CT with FDG-PET/CT for a total of 51 lesions in 20 consecutive patients with bladder cancer. The PPV for all detected lesions was 85% for <sup>11</sup>C-choline PET/CT and 91% for FDG-PET/CT. The corresponding PPVs for extravesical lesions were 79% and 88%, respectively. FDG-PET/CT correctly identified four extravesical metastases missed by <sup>11</sup>C-choline PET/CT. The authors concluded that <sup>11</sup>C-choline PET/CT had no advantage compared to FDG-PET/CT in the detection of metastatic bladder cancer.

# Radiography

All patients with MIBC need pulmonary evaluation [28]. The chest radiograph is an effective and low-morbidity screen [62].

### CT Chest

Patients with findings on chest radiographs and those thought to be at high risk should have chest CT, as is recommended in other guidelines [63,64]. Original research comparing the usefulness of chest radiographs to chest CT in this patient population is lacking.

#### **Bone Scan**

The incidence of metastases in bladder cancer patients increases with tumor stage at time of diagnosis [62]. A 4.6% positive rate was found in 458 bone scan studies, with only a 2.8% true-positive rate [65]. Because therapy was affected in only 0.9%, the conclusion was that scintigraphy has "no place in the routine preoperative staging of bladder carcinoma" [65]. Another study of 91 patients with precystectomy bone scan concluded that, in the absence of additional investigations such as MRI, "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" [66]. Nonetheless, when one considers only those patients with MIBC, 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 MIBC [67]. 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 MRI can be helpful, and, if necessary, guided-needle biopsy can be definitive.

#### US

The distended bladder is a superb acoustic window. In 214 new cases of bladder urothelial carcinoma with pathological correlation, Fang et al [68] reported overall accuracy of 79% in local staging with transabdominal ultrasound (TAUS). They had 10% overstaging and 12% understaging. However, TAUS is limited in visualization beyond the bladder wall and cannot reliably detect nodal enlargement [21]. TAUS is also less accurate for detecting stage T3 and T4 disease compared to T1 and T2 disease [69]. Some investigators have correlated sonographically determined contact length and height-to-length ratio with depth of tumor invasion at TAUS [70]. A contact length of >41.5 mm and a height-to-length ratio of <0.605 were calculated as cutoff values for differentiating non-muscle-invasive and invasive tumors.

Three-dimensional US rendering is yet another newer diagnostic tool with potential to aid in discriminating non-muscle-invasive from muscle-invasive tumors [71]. Contrast-enhanced sonography has also been shown to better differentiate MIBC from non-muscle-invasive bladder neoplasms [72].

Aside from TAUS, other approaches include transurethral US and endoluminal US, also known as intravesical US. Akdas et al [73] reported an overall accuracy of 97% in diagnosing and staging bladder tumors with transurethral US in 104 patients: 96% for stage Ta-T1 lesions, 100% for T2 lesions, 92% for T3 lesions, and 100% for T4 lesions. Endoluminal US uses a miniature, high-frequency transducer introduced by a rigid cystoscope for intravesical evaluation [74,75].

#### MRI Head

Neurologic complications directly related to bladder cancer are rare and are usually the result of local extension, for example to the lumbosacral plexus, rather than brain metastases. One study of the metastatic pattern of MIBC 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 [76].

# **Summary of Recommendations**

• The most appropriate imaging studies for pretreatment staging of muscle-invasive bladder cancer are; (1) CT abdomen and pelvis without and with contrast (CT urography), (2) CT abdomen and pelvis with IV contrast, (3) MRI abdomen and pelvis without and with IV contrast (MR urography), (4) MRI pelvis without and with IV contrast, and (5) chest radiographs. The imaging studies listed above are complementary; meaning more than one can be performed.

# **Summary of Evidence**

Of the 77 references cited in the ACR Appropriateness Criteria® Pretreatment Staging of Muscle-Invasive Bladder Cancer document, 8 are categorized as therapeutic references including 1 well-designed study, 1 good-quality study, and 1 quality study that may have design limitations. Additionally, 69 references are categorized as diagnostic references including 2 well-designed studies, 22 good-quality studies, and 19 quality studies that may have design limitations. There are 31 references that may not be useful as primary evidence.

The 77 references cited in the ACR Appropriateness Criteria® Pretreatment Staging of Muscle-Invasive Bladder Cancer document were published from 1988 to 2017.

Although there are references that report on studies with design limitations, 26 well-designed or good-quality studies provide good evidence.

### **Appropriateness Category Names and Definitions**

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk- benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

# **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<sup>®</sup> Radiation Dose Assessment Introduction document [77].

Relative Radiation Level Designations			
Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range	
0	0 mSv	0 mSv	
<b>⊕</b>	<0.1 mSv	<0.03 mSv	
<b>⊕⊕</b>	0.1-1 mSv	0.03-0.3 mSv	
<b>♦</b>	1-10 mSv	0.3-3 mSv	
❖❖❖❖	10-30 mSv	3-10 mSv	
❖❖❖❖❖	30-100 mSv	10-30 mSv	

<sup>\*</sup>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 <a href="https://www.acr.org/ac">www.acr.org/ac</a>.

#### References

- 1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
- 2. Zhang J, Gerst S, Lefkowitz RA, Bach A. Imaging of bladder cancer. *Radiol Clin North Am.* 2007;45(1):183-205.
- 3. Amling CL. Diagnosis and management of superficial bladder cancer. *Curr Probl Cancer*. 2001;25(4):219-278.
- 4. Kirkali Z, Chan T, Manoharan M, et al. Bladder cancer: epidemiology, staging and grading, and diagnosis. *Urology*. 2005;66(6 Suppl 1):4-34.
- 5. Shinagare AB, Ramaiya NH, Jagannathan JP, Fennessy FM, Taplin ME, Van den Abbeele AD. Metastatic pattern of bladder cancer: correlation with the characteristics of the primary tumor. *AJR Am J Roentgenol*. 2011;196(1):117-122.
- 6. Roth B, Wissmeyer MP, Zehnder P, et al. A new multimodality technique accurately maps the primary lymphatic landing sites of the bladder. *Eur Urol.* 2010;57(2):205-211.
- 7. Lodde M, Lacombe L, Friede J, Morin F, Saourine A, Fradet Y. Evaluation of fluorodeoxyglucose positronemission tomography with computed tomography for staging of urothelial carcinoma. *BJU Int.* 2010;106(5):658-663.
- 8. Saokar A, Islam T, Jantsch M, Saksena MA, Hahn PF, Harisinghani MG. Detection of lymph nodes in pelvic malignancies with Computed Tomography and Magnetic Resonance Imaging. *Clin Imaging*. 2010;34(5):361-366.
- 9. Thoeny HC, Froehlich JM, Triantafyllou M, et al. Metastases in normal-sized pelvic lymph nodes: detection with diffusion-weighted MR imaging. *Radiology*. 2014;273(1):125-135.
- 10. Amin MB, Edge S, Greene F, et al. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.
- 11. Malkowicz SB, van Poppel H, Mickisch G, et al. Muscle-invasive urothelial carcinoma of the bladder. *Urology*. 2007;69(1 Suppl):3-16.
- 12. Zaid HB, Patel SG, Stimson CJ, et al. Trends in the utilization of neoadjuvant chemotherapy in muscle-invasive bladder cancer: results from the National Cancer Database. *Urology*. 2014;83(1):75-80.
- 13. Griffiths G, Hall R, Sylvester R, Raghavan D, Parmar MK. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. *J Clin Oncol.* 2011;29(16):2171-2177.
- 14. Funt SA, Rosenberg JE. Systemic, perioperative management of muscle-invasive bladder cancer and future horizons. *Nat Rev Clin Oncol*. 2016.

- 15. Beyersdorff D, Zhang J, Schoder H, Bochner B, Hricak H. Bladder cancer: can imaging change patient management? *Curr Opin Urol.* 2008;18(1):98-104.
- 16. American College of Radiology. ACR Appropriateness Criteria<sup>®</sup>: Hematuria. Available at: https://acsearch.acr.org/docs/69490/Narrative/. Accessed December 4, 2017.
- 17. American College of Radiology. ACR Appropriateness Criteria<sup>®</sup>: Post-Treatment Surveillance of Bladder Cancer. Available at: https://acsearch.acr.org/docs/69364/Narrative/. Accessed December 4, 2017.
- 18. MacVicar AD. Bladder cancer staging. BJU Int. 2000;86 Suppl 1:111-122.
- 19. Cohan RH, Caoili EM, Cowan NC, Weizer AZ, Ellis JH. MDCT Urography: Exploring a new paradigm for imaging of bladder cancer. *AJR Am J Roentgenol*. 2009;192(6):1501-1508.
- 20. Vikram R, Sandler CM, Ng CS. Imaging and staging of transitional cell carcinoma: part 1, lower urinary tract. *AJR Am J Roentgenol*. 2009;192(6):1481-1487.
- 21. Barentsz JO, Ruijs SH, Strijk SP. The role of MR imaging in carcinoma of the urinary bladder. *AJR Am J Roentgenol*. 1993;160(5):937-947.
- 22. Paik ML, Scolieri MJ, Brown SL, Spirnak JP, Resnick MI. Limitations of computerized tomography in staging invasive bladder cancer before radical cystectomy. *J Urol.* 2000;163(6):1693-1696.
- 23. Tritschler S, Mosler C, Straub J, et al. Staging of muscle-invasive bladder cancer: can computerized tomography help us to decide on local treatment? *World J Urol.* 2012;30(6):827-831.
- 24. Tritschler S, Mosler C, Tilki D, Buchner A, Stief C, Graser A. Interobserver variability limits exact preoperative staging by computed tomography in bladder cancer. *Urology*. 2012;79(6):1317-1321.
- 25. Yuan JB, Zu XB, Miao JG, Wang J, Chen MF, Qi L. Laparoscopic pelvic lymph node dissection system based on preoperative primary tumour stage (T stage) by computed tomography in urothelial bladder cancer: results of a single-institution prospective study. *BJU Int.* 2013;112(2):E87-91.
- 26. Horn T, Zahel T, Adt N, et al. Evaluation of Computed Tomography for Lymph Node Staging in Bladder Cancer Prior to Radical Cystectomy. *Urol Int.* 2016;96(1):51-56.
- 27. Wang D, Zhang WS, Xiong MH, Yu M, Xu JX. Bladder tumors: dynamic contrast-enhanced axial imaging, multiplanar reformation, three-dimensional reconstruction and virtual cystoscopy using helical CT. *Chin Med J (Engl)*. 2004;117(1):62-66.
- 28. Rajesh A, Sokhi H, Fung R, Mulcahy KA, Bankart MJ. Role of whole-body staging computed tomographic scans for detecting distant metastases in patients with bladder cancer. *J Comput Assist Tomogr.* 2011;35(3):402-405.
- 29. Turkbey B, Basaran C, Karcaaltincaba M, et al. Peritoneal carcinomatosis in urinary bladder cancer. *Clin Imaging*. 2008;32(3):192-195.
- 30. Kawashima A, Vrtiska TJ, LeRoy AJ, Hartman RP, McCollough CH, King BF, Jr. CT urography. *Radiographics*. 2004;24 Suppl 1:S35-54; discussion S55-38.
- 31. Jinzaki M, Matsumoto K, Kikuchi E, et al. Comparison of CT urography and excretory urography in the detection and localization of urothelial carcinoma of the upper urinary tract. *AJR Am J Roentgenol*. 2011;196(5):1102-1109.
- 32. Vikram R, Sandler CM, Ng CS. Imaging and staging of transitional cell carcinoma: part 2, upper urinary tract. *AJR Am J Roentgenol*. 2009;192(6):1488-1493.
- 33. Tekes A, Kamel I, Imam K, et al. Dynamic MRI of bladder cancer: evaluation of staging accuracy. *AJR Am J Roentgenol*. 2005;184(1):121-127.
- 34. Wang HJ, Pui MH, Guo Y, et al. Multiparametric 3-T MRI for differentiating low-versus high-grade and category T1 versus T2 bladder urothelial carcinoma. *AJR Am J Roentgenol*. 2015;204(2):330-334.
- 35. El-Assmy A, Abou-El-Ghar ME, Mosbah A, et al. Bladder tumour staging: comparison of diffusion- and T2-weighted MR imaging. *Eur Radiol.* 2009;19(7):1575-1581.
- 36. 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(1):112-121.
- 37. Wu LM, Chen XX, Xu JR, et al. Clinical value of T2-weighted imaging combined with diffusion-weighted imaging in preoperative T staging of urinary bladder cancer: a large-scale, multiobserver prospective study on 3.0-T MRI. *Acad Radiol.* 2013;20(8):939-946.
- 38. Kobayashi S, Koga F, Yoshida S, et al. Diagnostic performance of diffusion-weighted magnetic resonance imaging in bladder cancer: potential utility of apparent diffusion coefficient values as a biomarker to predict clinical aggressiveness. *Eur Radiol.* 2011;21(10):2178-2186.

- 39. Daneshmand S, Ahmadi H, Huynh LN, Dobos N. Preoperative staging of invasive bladder cancer with dynamic gadolinium-enhanced magnetic resonance imaging: results from a prospective study. *Urology*. 2012;80(6):1313-1318.
- 40. Rajesh A, Sokhi HK, Fung R, Mulcahy KA, Bankart MJ. Bladder cancer: evaluation of staging accuracy using dynamic MRI. *Clin Radiol*. 2011;66(12):1140-1145.
- 41. Rabie E, Faeghi F, Izadpanahi MH, Dayani MA. Role of Dynamic Contrast-Enhanced Magnetic Resonance Imaging in Staging of Bladder Cancer. *J Clin Diagn Res.* 2016;10(4):TC01-05.
- 42. Ghafoori M, Shakiba M, Ghiasi A, Asvadi N, Hosseini K, Alavi M. Value of MRI in local staging of bladder cancer. *Urol J.* 2013;10(2):866-872.
- 43. Gupta N, Sureka B, Kumar MM, Malik A, Bhushan TB, Mohanty NK. Comparison of dynamic contrast-enhanced and diffusion weighted magnetic resonance image in staging and grading of carcinoma bladder with histopathological correlation. *Urol Ann.* 2015;7(2):199-204.
- 44. Nguyen HT, Pohar KS, Jia G, et al. Improving bladder cancer imaging using 3-T functional dynamic contrast-enhanced magnetic resonance imaging. *Invest Radiol.* 2014;49(6):390-395.
- 45. Liedberg F, Bendahl PO, Davidsson T, et al. Preoperative staging of locally advanced bladder cancer before radical cystectomy using 3 tesla magnetic resonance imaging with a standardized protocol. *Scand J Urol.* 2013;47(2):108-112.
- 46. Shariat SF, Palapattu GS, Karakiewicz PI, et al. Discrepancy between clinical and pathologic stage: impact on prognosis after radical cystectomy. *Eur Urol.* 2007;51(1):137-149; discussion 149-151.
- 47. Klein L, Pollack HM. Computed tomography and magnetic resonance imaging of the female lower urinary tract. *Radiol Clin North Am.* 1992;30(4):843-860.
- 48. Yoshida S, Koga F, Kawakami S, et al. Initial experience of diffusion-weighted magnetic resonance imaging to assess therapeutic response to induction chemoradiotherapy against muscle-invasive bladder cancer. *Urology*. 2010;75(2):387-391.
- 49. Takahashi N, Kawashima A, Glockner JF, et al. Small (<2-cm) upper-tract urothelial carcinoma: evaluation with gadolinium-enhanced three-dimensional spoiled gradient-recalled echo MR urography. *Radiology*. 2008;247(2):451-457.
- 50. Goodfellow H, Viney Z, Hughes P, et al. Role of fluorodeoxyglucose positron emission tomography (FDG PET)-computed tomography (CT) in the staging of bladder cancer. *BJU Int.* 2014;114(3):389-395.
- 51. Nayak B, Dogra PN, Naswa N, Kumar R. Diuretic 18F-FDG PET/CT imaging for detection and locoregional staging of urinary bladder cancer: prospective evaluation of a novel technique. *Eur J Nucl Med Mol Imaging*. 2013;40(3):386-393.
- 52. 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(9):1229-1237.
- 53. Pichler R, De Zordo T, Fritz J, et al. Pelvic Lymph Node Staging by Combined 18F-FDG-PET/CT Imaging in Bladder Cancer Prior to Radical Cystectomy. *Clin Genitourin Cancer*. 2016.
- 54. Kibel AS, Dehdashti F, Katz MD, et al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography/computed tomography for staging of muscle-invasive bladder carcinoma. *J Clin Oncol*. 2009;27(26):4314-4320.
- 55. Apolo AB, Riches J, Schoder H, et al. Clinical value of fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography in bladder cancer. *J Clin Oncol.* 2010;28(25):3973-3978.
- 56. Kollberg P, Almquist H, Blackberg M, et al. [(18)F]Fluorodeoxyglucose positron emission tomography/computed tomography improves staging in patients with high-risk muscle-invasive bladder cancer scheduled for radical cystectomy. *Scand J Urol.* 2015;49(4):296-301.
- 57. Mertens LS, Fioole-Bruining A, Vegt E, Vogel WV, van Rhijn BW, Horenblas S. Impact of (18) F-fluorodeoxyglucose (FDG)-positron-emission tomography/computed tomography (PET/CT) on management of patients with carcinoma invading bladder muscle. *BJU Int.* 2013;112(6):729-734.
- 58. Picchio M, Treiber U, Beer AJ, et al. Value of 11C-choline PET and contrast-enhanced CT for staging of bladder cancer: correlation with histopathologic findings. *J Nucl Med*. 2006;47(6):938-944.
- 59. Brunocilla E, Ceci F, Schiavina R, et al. Diagnostic accuracy of (11)C-choline PET/CT in preoperative lymph node staging of bladder cancer: a systematic comparison with contrast-enhanced CT and histologic findings. *Clin Nucl Med.* 2014;39(5):e308-312.
- 60. Ceci F, Bianchi L, Graziani T, et al. 11C-choline PET/CT and bladder cancer: lymph node metastasis assessment with pathological specimens as reference standard. *Clin Nucl Med.* 2015;40(2):e124-128.

- 61. Golan S, Sopov V, Baniel J, Groshar D. Comparison of 11C-choline with 18F-FDG in positron emission tomography/computerized tomography for staging urothelial carcinoma: a prospective study. *J Urol.* 2011;186(2):436-441.
- 62. Kuroda M, Meguro N, Maeda O, et al. Stage specific follow-up strategy after cystectomy for carcinoma of the bladder. *Int J Urol.* 2002;9(3):129-133.
- 63. Alfred Witjes J, Lebret T, Comperat EM, et al. Updated 2016 EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. *Eur Urol.* 2017;71(3):462-475.
- 64. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2014;25 Suppl 3:iii40-48.
- 65. Brismar J, Gustafson T. Bone scintigraphy in staging of bladder carcinoma. Acta Radiol. 1988;29(2):251-252.
- 66. Braendengen M, Winderen M, Fossa SD. Clinical significance of routine pre-cystectomy bone scans in patients with muscle-invasive bladder cancer. *Br J Urol*. 1996;77(1):36-40.
- 67. Taher AN, Kotb MH. Bone metastases in muscle-invasive bladder cancer. *J Egypt Natl Canc Inst.* 2006;18(3):203-208.
- 68. Fang YC, Chou YH, Hsu CC, Chang T. Staging of bladder cancer by transabdominal real-time ultrasound. *Zhonghua Yi Xue Za Zhi (Taipei)*. 1993;52(1):21-25.
- 69. Tadin T, Sotosek S, Rahelic D, Fuckar Z. Diagnostic accuracy of ultrasound T-staging of the urinary bladder cancer in comparison with histology in elderly patients. *Coll Antropol.* 2014;38(4):1123-1126.
- 70. Ozden E, Turgut AT, Yesil M, Gogus C, Gogus O. A new parameter for staging bladder carcinoma: ultrasonographic contact length and height-to-length ratio. *J Ultrasound Med.* 2007;26(9):1137-1142.
- 71. Wagner B, Nesslauer T, Bartsch G, Jr., Hautmann RE, Gottfried HW. Staging bladder carcinoma by three-dimensional ultrasound rendering. *Ultrasound Med Biol.* 2005;31(3):301-305.
- 72. Caruso G, Salvaggio G, Campisi A, et al. Bladder tumor staging: comparison of contrast-enhanced and gray-scale ultrasound. *AJR Am J Roentgenol*. 2010;194(1):151-156.
- 73. Akdas A, Turkeri L, Ersev D, Ersev A, Kullu S. Transurethral ultrasonography, fiberoptic cystoscopy and bladder washout cytology in the evaluation of bladder tumours. *Int Urol Nephrol*. 1992;24(5):503-508.
- 74. Saga Y, Numata A, Tokumitsu M, et al. Comparative study of novel endoluminal ultrasonography and conventional transurethral ultrasonography in staging of bladder cancer. *Int J Urol.* 2004;11(8):597-601.
- 75. Tomita Y, Kobayashi K, Saito T, Tanikawa T, Kimura M, Takahashi K. Use of miniature ultrasonic probe system for intravesical ultrasonography for transitional cell cancer of the urinary tract. *Scand J Urol Nephrol*. 2000;34(5):313-316.
- 76. Anderson TS, Regine WF, Kryscio R, Patchell RA. Neurologic complications of bladder carcinoma: a review of 359 cases. *Cancer*. 2003;97(9):2267-2272.
- 77. American College of Radiology. ACR Appropriateness Criteria® Radiation Dose Assessment Introduction. Available at: http://www.acr.org/~/media/ACR/Documents/AppCriteria/RadiationDoseAssessmentIntro.pdf. Accessed December 4, 2017.

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.