Update on Multiparametric MRI of Urinary Bladder Cancer

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While many institutions perform MRI during the work-up of urinary bladder cancer, others use MRI rarely if at all, possibly due to a variation in the reported staging accuracy and unfamiliarity with the potential benefits of performing MRI. Through increased application of functional imaging techniques including diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging, there has been a resurgence of interest regarding evaluation of bladder cancer with MRI. Several recent meta-analyses have shown that MRI is accurate at differentiating between ≤T1 and T2 disease (with pooled sensitivity/specificity of ~90/80%) and differentiating between T2 and ≥T3 disease. DWI and DCE, in combination with high-resolution T2-weighted images, improves detection and possibly local staging accuracy of bladder cancer. High b value echo-planar DWI is particularly valuable for tumor detection. Zoomed field of view and segmented readout DWI techniques improve image quality by reducing susceptibility artifact, while methods to extract calculated high b value images save time and improve the contrast-to-noise ratio. DCE traditionally required imaging of the pelvis with high temporal but lower spatial resolution; however, advances in parallel and keyhole imaging techniques can preserve spatial resolution. The use of compressed sensing reconstruction may improve utilization of DCE of the bladder, especially when imaging the abdomen simultaneously, as in MR urography. Quantitative imaging analysis of bladder cancer using pharmacokinetic modeling of DCE, apparent diffusion coefficient values, and texture analysis may enable radiomic assessment of bladder cancer grade and stage.

Level of Evidence: 3
Technical Efficacy: Stage 2

The American Cancer Society estimates that there will be 81,190 new cases of urinary bladder cancer, and 17,240 deaths from bladder cancer, in the United States in 2018.1 Bladder cancer is the sixth most common type of cancer.1 The management of bladder cancer is determined predominantly by stage and grade of disease at diagnosis. Local staging is traditionally dependent on findings at cystoscopy and transurethral resection of bladder tumor (TURBT). Abdomen pelvis computed tomography (CT) is commonly used to assess for nodal disease or metastases, along with either a preoperative chest x-ray or chest CT.2 Fluorodeoxyglucose positron emission tomography CT (FDG PET/CT) can improve sensitivity for detection of nodal and metastatic disease and may be appropriate in some settings.3,4 A key distinction for the local staging of bladder cancer is the presence or absence of muscle invasion, which has a significant impact on the management strategy as outlined in multiple guidelines including those issued by the National Comprehensive Cancer Network (NCCN), the American Urological Association/Society of Urologic Oncology (AUA/SUO), and the European Association of Urology (EAU).5–7 Muscle-invasive bladder cancer (MIBC) is treated with radical cystectomy and increasingly neoadjuvant therapy. Non-MIBC is often treated with bladder-sparing techniques. TURBT is the current standard for determining the presence or absence of muscle invasion, and also provides an estimate of histologic subtype and grade, and in some instances can be

completely curative if the entire tumor is resected.\textsuperscript{8} However, TURBT has been found to under estimate T stage in up to 40\% of patients, is inaccurate at determining tumor grade in up to 15\% of patients, and frequently needs to be repeated.\textsuperscript{9,10} Furthermore, adherence to guidelines recommending repeat TURBT varies widely between urologists.\textsuperscript{11}

Multiparametric magnetic resonance imaging (mp-MRI) of the bladder has reemerged as a noninvasive tool that can help assess the local stage and grade of bladder cancer with relatively high accuracy.\textsuperscript{12–17} mp-MRI consists of high-resolution $T_2$-weighted ($T_2$W) images, diffusion-weighted imaging (DWI), and dynamic contrast-enhanced (DCE) imaging.\textsuperscript{16} mp-MRI can demonstrate tumor growth into the bladder detrusor muscle, peri-vesical extension, and can also assess regional nodes and pelvic metastases. mp-MRI remains relatively accurate at bladder cancer local staging even after TURBT.\textsuperscript{18} It is anticipated that utilization of mp-MRI for bladder cancer local staging will increase as awareness of its accuracy in the urology community improves. Several recent meta-analyses assessing the topic of local staging of bladder cancer with mp-MRI confirm an increased interest in the genitourinary community.\textsuperscript{19–21}

This article reviews urinary bladder anatomy and histology with MRI correlations, MRI techniques including updates on DWI, DCE, and MR urography (MRU), MRI staging and accuracy, bladder cancer variants, and finally discusses the applications of radiomic analysis and machine learning to bladder cancer.

**Bladder Anatomy**

The luminal surface of the bladder is lined by the urothelium, an epithelial layer which is intermediate between nonkeratinizing squamous and pseudostratified columnar epithelium and 3–7 cells thick depending on the degree of bladder distention. The urothelium is the most superficial layer of the bladder wall mucosa, which is composed of the urothelium, the loose connective tissue of the lamina propria (containing blood vessels, lymphatics, and fat), and an incomplete and poorly-developed muscle layer known as the muscularis mucosa.\textsuperscript{22} Deep to the mucosa lies the muscularis propria, also known as the detrusor muscle, which is composed of layers of smooth muscle (inner longitudinal, middle circular, and outer longitudinal) as well as interspersed paraganglia.\textsuperscript{23} The detrusor muscle provides the primary contractile function for the bladder. A loose connective tissue layer of adventitia surrounds the muscularis propria.

Several bladder anatomic structures can be identified and assessed on both MRI and cystoscopy, and may serve as useful landmarks when describing pathology. This includes the ureteric orifices and the interureteric ridge, which extends between the ureteric orifices. Together with the internal urinary meatus, these structures define the bladder trigone.

At MRI, the bladder wall typically demonstrates uniformly low $T_2$W signal intensity, corresponding to the detrusor muscle, which is the only layer of the bladder wall that is readily depicted on noncontrast MRI.\textsuperscript{24} Occasionally, an inner low $T_2$W signal intensity stripe and outer intermediate $T_2$W signal intensity stripe can be distinguished, corresponding to compact inner and loose outer smooth muscle layers, respectively.\textsuperscript{25} At DCE imaging, the mucosa enhances early, with the detrusor muscle enhancing later. On delayed phase postcontrast $T_1$-weighted ($T_1$W) images, the bladder wall demonstrates homogeneous enhancement.\textsuperscript{24}

**MRI Technique**

The cornerstone for an MRI protocol that assesses the bladder is multiplanar high-resolution $T_2$W images. $T_2$W-MRI provides the best method to directly assess for depth of involvement of malignancies (which are typically of intermediate $T_2$W signal intensity) with respect to the low $T_2$W signal intensity detrusor muscle,\textsuperscript{24,26} which is a critical determinant of patient care in bladder malignancy (Fig. 1). $T_2$W imaging is generally performed using 2D fast or turbo spin-echo (FSE/TSE), which provide a robust signal-to-noise ratio (SNR) that is utilized to improve spatial resolution. Imaging can be performed at 1.5 or 3T, with improvements in SNR at 3T used to enhance spatial resolution. 3D FSE/TSE sequences (CUBE, General Electric

**FIGURE 1: Multifocal urothelial carcinoma.** a,b: Axial $T_2$W images at different levels reveal multiple intraluminal filling defects extending along the bladder wall with intermediate $T_2$W signal, without disruption of the underlying $T_2$ hypointense detrusor muscle, consistent with superficial spread of tumor (arrows). Axial $b = 1000$ sec/mm$^2$ DWI (c) and corresponding ADC map (d) in the same patient show flat tumor that restricts diffusion. These findings are consistent with stage T1 disease.
FSE/TSE, although at the cost of lower contrast. We consider the choice of using conventional FSE/TSE versus periodically rotating overlapping parallel lines (PROPELLER, GE Healthcare; BLADE, Siemens Healthcare; MultiVane, Philips Healthcare), which has been shown to potentially improve image sharpness, overall image quality, and reduce artifact compared to conventional rectilinear filling of k-space in FSE/TSE, although at the cost of lower contrast. We consider the choice of using conventional FSE/TSE versus periodically rotating overlapping parallel lines sequences an institutional preference; however, in cases of severe motion artifact on FSE/TSE, periodically rotating overlapping parallel lines sequences an improvement of the bladder compared to conventional 2D FSE/TSE, which in our own experience radiologists generally still prefer. Moreover, susceptibility to motion artifact during the 3D acquisition, which impacts the entire dataset, is a major limitation when imaging the bladder, which may be more impacted by the abdominal wall and bowel peristalsis than other deep pelvic structures such as the prostate and cervix. Patients should be instructed to partially void the bladder prior to pelvic MRI if overly full, as patients should be as comfortable as possible during the examination to prevent motion artifacts; however, a completely collapsed urinary bladder is not ideal, as a moderate amount of urine generally improves visualization of tumors and their relationship to the bladder wall. A bowel relaxant (hyoscine butylbromide [Buscopan] or glucagon) can be used to reduce artifacts related to bowel peristalsis in pelvic MRI; however, in our opinion it is generally not needed for high-quality bladder MRI, and at our institutions is not performed. Bowel and abdominal wall motion can be mitigated wholly or in part by setting the phase-encoding direction to direct motion away from the bladder (eg, on an axial T2W image, the phase-encoding direction should be set left-to-right rather than anterior-to-posterior) and by increasing the number of excitations (NEX). T2W imaging can be acquired using periodically rotating overlapping parallel lines (PROPELLER, GE Healthcare; HASTE, Siemens Healthcare; SSH-TSE/UFSE, Philips Healthcare), which is ideal for imaging the kidneys and ureters, as high signal intensity lesions that differ from the low signal intensity of the detrusor muscle and urine. Tumors on ADC maps are generally depicted as being of low signal (generally iso- or hypointense to the low ADC signal intensity detrusor muscle) in contrast to the high signal intensity of urine. For this reason, in our experience, the trace high b value EPI images often depict tumors as high signal intensity lesions that differ from the low signal intensity of the detrusor muscle and urine. Tumors on ADC images often depict tumors better than ADC maps, as there is more contrast between the tumor and surrounding structures. The use of very high b values (>1000 sec/mm2) to improve contrast between tumor and adjacent tissues has been shown to be valuable in other pelvic tumors and is also valuable for delineating bladder tumors. Acquiring very high b value DWI is time-consuming, as a proportional increase in NEX is generally required to offset the loss of signal that occurs with higher diffusion weighting; however, vendors now provide commercially available software to calculate or derive the very high b value data by extrapolation from the lower b value acquisitions. Studies have shown comparable image quality in calculated high b value compared to acquired high b value DWI in the pelvis, with generally higher contrast on calculated compared to acquired images and substantial reductions in acquisition time. Diffusion kurtosis imaging, which models non-Gaussian diffusion effects at high b values, is likely useful for discriminating a posttreatment change from recurrent or residual bladder tumor, and may improve bladder MRI in other ways that have yet to be explored.

Recently, several novel acquisition techniques for pelvic DWI have become commercially available and have been shown to improve image quality compared to single-shot EPI. Inhomogeneities which result in cumulative dephasing...
of off-resonance spins during the EPI readout leading to mis-mapping causes spurious areas of artifactual signal increase or dropout and geometric warping and distortion on the final images.\textsuperscript{37} The sensitivity of EPI to off-resonance is dependent on the rate at which $k$-space is sampled along the phase-encoding direction\textsuperscript{37}; therefore, reducing the imaging FOV along the phase-encoding direction should reduce sensitivity of EPI to susceptibility artifacts. Studies evaluating reduced FOV EPI in the pelvis (FOCUS, GE Healthcare, and Z-EPI, Siemens Healthcare) have shown improved image quality and reduced artifact compared with conventional single-shot EPI of the whole pelvis.\textsuperscript{37,45,46} In a case series by Rosenkrantz and Taneja, reduced FOV EPI provided diagnostic quality images in patients undergoing prostate MRI with hip prosthesis, which is otherwise generally not possible due to severe artifact encountered with conventional single-shot EPI.\textsuperscript{47} In segmented readout EPI, the same diffusion preparation is used as in single-shot EPI; however, the $k$-space trajectory is divided into multiple segments in the readout direction with 2D Navigator echoes to reduce sensitivity to motion (RESOLVE, Siemens Healthcare).\textsuperscript{48} This sampling scheme has been shown to reduce artifact and improve image quality compared to conventional $k$-space sampling in single-shot EPI in the pelvis.\textsuperscript{45} Another advantage of reduced FOV DWI is higher spatial resolution compared to whole-pelvis single-shot EPI; however, smaller FOV and higher matrix sizes result in lower SNR compared to whole pelvis EPI, which requires a period of adjustment for the user and radiologists should be aware that the use of reduced FOV DWI for imaging of an organ (in this case, the bladder) results in an inability to assess the remainder of the pelvis, for example, to detect lymph node metastases.

DCE MRI is also an important component of bladder MRI.\textsuperscript{24} DCE imaging is generally performed before and after gadolinium injection using fat-suppressed 3D $T_1$W spoiled GRE images. Imaging planes vary; in our experience, axial or sagittal imaging is adequate in most cases. Dynamic imaging following contrast administration is essential; bladder cancers typically demonstrate enhancement on the earlier phase images (45–120 seconds after intravenous injection), along with the bladder wall mucosa, whereas the detrusor muscle appears dark on the earlier phase images and demonstrates enhancement on the more delayed images. We perform dynamic imaging every 10 seconds for 5 minutes and initiate the acquisition of images timed with the injection of gadolinium intravenously through the use of a power injector. An alternative is to perform lower temporal resolution imaging (for example, every 30 seconds) and, to our knowledge, these techniques have not been objectively compared. Lower temporal resolution would result in an ability to improve spatial resolution and coverage; however, an advantage of higher temporal resolution is the ability to extract pharmacokinetic semiquantitative and quantitative analyses (discussed below), which may be useful as future radiomic markers of bladder cancer grade and stage. The use of parallel imaging should be considered fundamental for DCE as a method to improve temporal resolution with decreases in SNR offset through the use of increased signal from gadolinium. Parallel imaging combined with keyhole imaging techniques (DISCO, GE Healthcare; TWIST, Siemens Healthcare; 4D-TRAK, Philips Healthcare) can further be implemented in the pelvis to achieve higher temporal resolution.\textsuperscript{49,50} More recently, the use of compressed sensing (which exploits spatial and spatio-temporal correlations) with parallel imaging has been described to accelerate acquisition times and achieve high temporal and spatial resolution.\textsuperscript{51} With compressed sensing, $k$-space is undersampled randomly, preferably in a radial trajectory, enabling acquisition as a free-breathing technique with robust correction of motion artifacts.\textsuperscript{52} In a study by Parikh et al, this technique, which employed free-breathing

![Figure 2](image-url)
continuous acquisition without a predetermined temporal resolution (which can be later reconstructed at various temporal resolutions from source data) using compressed sensing with radial acquisition (GRASP, Siemens Healthcare) achieved high-quality imaging at varying temporal resolutions during simultaneous MRU. The added value of DCE in addition to DWI and $T_2^*$W sequences for the local staging of bladder cancer is unclear; however, optimized MRU can provide an alternative for patients receiving repeated MRI exams, since the clinical effects of cumulative doses of gadolinium are unknown.

A summary of an mp-MRI technique used for imaging of the bladder is provided (Table 1). Combined imaging of the bladder and upper tracts through an MRU technique is now technologically feasible on most commercial systems. Comprehensive evaluation of the upper tracts is critical in the context of bladder cancer due to the risk of synchronous or metachronous upper tract disease. CT urography (CTU) remains the preferred imaging modality, with a sensitivity of 88–100% for upper tract disease versus 69% for MRU; however, optimized MRU can provide an alternative for patients in which CT may be contraindicated. The sensitivity of MRU increases in the context of urinary obstruction, where CTU may be limited by poor contrast excretion into the collecting system. Additionally, MRU is superior to CTU in diagnosing noncalcaeous causes of urinary obstruction.

MRU can be performed using static-fluid sensitive and excretory techniques. Static-fluid sensitive MRU utilizes $T_2^*$W images to evaluate the collecting system and ureters (Fig. 6). This relies on adequate distention of the urinary tract and adequate hydration is critical in nonobstructed patients. Intravenous hydration, use of a diuretic (eg, furosemide), or extrinsic compression devices may be used prior to scanning to augment ureteric filling. Rapid acquisition sequential images can help distinguish fixed obstruction from ureteric peristalsis. Excretory MRU, on the other hand, relies on excretion of gadolinium into the collecting system where ureteric abnormalities appear as filling defects akin to CTU. The concentration of excreted gadolinium is an important consideration, as the $T_2^*$ effects of gadolinium may overwhelm the desired $T_1$ shortening effect if too concentrated. This shortcoming can be overcome by utilizing diluted gadolinium (eg, reducing dose, hydrating the patient, and using a diuretic) or hepatocyte-specific gadolinium agents.

MRI Staging and Accuracy

Bladder cancer T stage is defined in the eighth edition of the American Joint Committee on Cancer (AJCC) Staging Manual. Ta refers to noninvasive papillary carcinoma and Tis refers to noninvasive carcinoma in situ or “flat tumor.” T1 bladder cancer invades the lamina propria without muscle invasion. T2 is indicated by the presence of bladder cancer muscle invasion, and can be divided into tumor limited to the inner half of the muscle (T2a) or involving the outer half of the muscle (T2b). T3 tumor invades the peri-vesical fat either microscopically (T3a) or macroscopically (T3b). T4 tumor invades the prostate, seminal vesicles, uterus, or vagina (T4a) or the pelvic or abdominal wall (T4b). Unlike prior editions, the eighth edition provides clarity on intraurethral prostatic stromal invasion, which is considered T2 disease, similar to urethral cancer staging. Tumors arising in bladder diverticula, which usually do not have a muscularis propria, can no longer be classified as T2. The eighth edition also recommends that attempts be made to subcategorize T1 disease on TURBT.

The soft-tissue contrast resolution of MRI makes it the optimal imaging exam for determining bladder cancer T stage. The manifestation of each T stage depends on the MRI sequence, with different features for $T_2^*$W images, DCE images, and DWI (Table 2). Multiple studies suggest that the accuracy of MRI for determining bladder cancer T stage is optimized when using all three of these sequences together (mp-MRI), however, a recent meta-analysis found that there was no significant difference in accuracy of discrimination between non-MIBC and MIBC, and between the absence and presence of peri-vesical invasion, using different MRI techniques.

On $T_2^*$W images, the normal detrusor muscle appears as a $T_2$ hypointense band outlining the bladder lumen. An intact $T_2$ hypointense band suggests stage Ta, Tis, or T1 bladder cancer. An irregular inner margin at the junction of the bladder tumor and the $T_2$ hypointense band is considered T2a disease, while disruption of the $T_2$ hypointense band, without invasion of the adjacent peri-vesical fat, is considered T2b. Tumor signal extending into the fat is considered T3b, and extension into the adjacent organs or the pelvic wall is T4 disease.

On DCE imaging, early phase contrast-enhanced images reveal bladder tumors, the bladder mucosa, and lamina propria to enhance, whereas the underlying detrusor muscle remains hypointense; for example, between 45–120 seconds after intravenous injection. For Ta, Tis, and
<table>
<thead>
<tr>
<th>Sequence</th>
<th>Imaging plane</th>
<th>Field of view (mm)</th>
<th>Matrix size</th>
<th>Slice thickness/gap (mm)</th>
<th>TR/TE (msec)</th>
<th>Echo train length</th>
<th>Flip angle</th>
<th>Acceleration factor</th>
<th>Receiver bandwidth (Hz/voxel)</th>
<th>Acquisition time (min)</th>
<th>Number of signals averaged</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1 TSE</strong></td>
<td>Axial</td>
<td>350 x 350</td>
<td>320 x 320</td>
<td>5.0/1.0</td>
<td>720/ 8–14</td>
<td>3</td>
<td>111</td>
<td>N/A</td>
<td>244</td>
<td>4 min</td>
<td>2</td>
</tr>
<tr>
<td><strong>T1 3D dual echo GRE</strong></td>
<td>Axial</td>
<td>240 x 240</td>
<td>292 x 224</td>
<td>4.0/1.0</td>
<td>4.8/1.1–1.3; TE12.2–2.5; TE2</td>
<td>N/A</td>
<td>12</td>
<td>2</td>
<td>558</td>
<td>Breath Hold</td>
<td>1</td>
</tr>
<tr>
<td><strong>T2 TSE</strong></td>
<td>Coronal</td>
<td>220 x 220</td>
<td>320 x 256</td>
<td>4.0/0 3.0/0 3.0/0</td>
<td>3890–5250/105–125</td>
<td>27-35</td>
<td>111</td>
<td>N/A</td>
<td>122</td>
<td>4 min</td>
<td>1–2</td>
</tr>
<tr>
<td><strong>DWI</strong></td>
<td>Axial</td>
<td>280 x 280</td>
<td>128 x 80</td>
<td>3-5.0/0</td>
<td>4200/ 90</td>
<td>1</td>
<td>90</td>
<td>2</td>
<td>1950</td>
<td>5 min</td>
<td>4–10</td>
</tr>
<tr>
<td><strong>T1 GRE</strong></td>
<td>Axial</td>
<td>220 x 220</td>
<td>128 x 128</td>
<td>4.0/0</td>
<td>4.3/1.3</td>
<td>N/A</td>
<td>12</td>
<td>2</td>
<td>488</td>
<td>6 min</td>
<td>1</td>
</tr>
</tbody>
</table>

$a$Integrated pelvic surface coils (4–16 channels) with activated spine coils (8–12 channels).
$b$Clinical 3T systems: TRIO TIM (Siemens Medical, Malvern, PA) and Discovery 750W (General Electric, Milwaukee, WI).
$c$Turbo/Fast Spin Echo.
$d$Gradient Recalled Echo.
$e$DWI = Diffusion weighted imaging performed with spectral fat suppression echo planar imaging with tridirectional motion probing gradients and b values of 0, 500, 1000 with automatic apparent diffusion coefficient map generation.
$f$Dynamic fast spoiled 2D GRE performed with a temporal resolution of 10 seconds after injection of 0.1 mmol/kg of gadobutrol (Gadovist, Bayer, Toronto, ON) at a rate of 3 mL/sec.
T1 disease, on the early postcontrast images, the muscle underlying the tumor remains hypointense. The presence of intact submucosal linear enhancement beneath the tumor on early phase images is also indicative of Ta, Tis, or T1 disease. An irregular inner margin at the junction of the bladder tumor and muscle on the early postcontrast images suggests stage T2a disease, whereas disruption of the hypointense muscle wall, without early enhancing tissue extending into the peri-vesical fat, suggests stage T2b disease (Fig. 3). T3 and T4 tumors demonstrate abnormal early enhancement extending into the peri-vesical fat and surrounding structures, respectively.

Takeuchi et al described and validated bladder cancer T stage on DWI. They found that flat-appearing bladder tumors, and those with either an underlying thickened submucosa or a submucosal stalk that does not restrict diffusion,......
MRI to differentiate <T1 from >T2 stage before and/or after initial TURBT identifying <T1 tumor. This is critical to determine the necessity of cystectomy. Given sufficient accuracy, MRI could replace re-resection prior to intravesical therapy, lead to usage of neoadjuvant chemotherapy prior to cystectomy if muscle-invasion is confirmed, or help guide the usage of bladder-preserving therapy with concurrent chemoradiotherapy.

2. MRI to determine T-any vs. T0 stage before and/or after initial TURBT.

3. MRI to differentiate <T2 vs. >T3 stage before and/or after initial TURBT or repeat TURBT. This can be used to help guide patients on the benefit/harm balance of neoadjuvant chemotherapy.

4. MRI to determine <T4b vs. pT4b stage, which can help determine feasibility of resection vs. palliative radiation.

The results from this meta-analysis are highlighted (Table 3). It was concluded from this study that MRI staging for <T1 vs. >T2, <T2 vs. >T3, and <T4b vs. pT4b is potentially superior to the current standard for clinical staging. However, MR accuracy for T-any vs. T0 may not be superior to clinical staging. In addition, no difference in accuracy was identified for different MR techniques (mp-MRI including DWI and DCE) for thresholds 1 and 3; there was insufficient data to evaluate technical parameters for thresholds 2 and 4. Despite the lack of difference in accuracy when comparing the addition of these individual MRI sequences to T2W imaging, the higher accuracy of MRI than originally estimated could be due to a combination of functional imaging along with improved base resolution and higher field strength. Generalizability and clinical applicability of these results should be somewhat guarded, since there were concerns about the risk of bias of included studies (for all thresholds) and sample size (for two of the thresholds). Future prospective trials comparing clinical staging strategies vs. MR are needed.

Woo et al performed a recent meta-analysis, with a pooled sensitivity and specificity of 0.92 and 0.87, respectively, for differentiating <T1 vs. >T2 disease. Huang et al also published a recent meta-analysis obtaining a pooled sensitivity and specificity of 0.90 and 0.88, respectively, for differentiating <T1 vs. >T2 disease.

Bladder cancer N stage criteria were modified in the more recent 7th and 8th editions of the AJCC Staging.
Manual. N stage is now determined by the number of pathologic lymph nodes, and includes common iliac nodes as regional nodal disease. N0 indicates no pathologic nodes. N1 is defined as a single regional nodal metastasis in the true pelvis, which includes the peri-vesical, obturator, internal iliac (hypogastric), external iliac, and presacral nodal stations. N2 refers to more than one nodal metastasis in the true pelvis. N3 is defined by the presence of one or more pathologic common iliac lymph nodes. Retroperitoneal lymph nodes are considered M1a disease.

Determination of pathologic lymph nodes on cross-sectional imaging is limited. This may be due to the lack of research directly correlating individual node features on imaging with node histopathology. Most studies assessing nodal disease from pelvic malignancies are on a per-patient, per-pelvic side or per-nodal station basis rather than a per-node basis. Traditionally, pathologic lymph nodes were determined on cross-sectional imaging based solely on node short axis size greater than 10 mm; however, in 2014, Thoeny et al demonstrated that MRI could be used to detect normal-sized pathologic lymph nodes when DWI was incorporated into the staging protocol. Their approach involved first identifying lymph nodes with higher signal than inguinal nodes on DWI (b = 1000 sec/mm²). Node morphologic features were then assessed on the other sequences, with the following features considered suspicious for malignancy: round shape (equal diameter in three planes), irregular or ill-defined border, and/or lower T2 signal than muscle or inguinal lymph nodes (Fig. 5). Nodes with eccentric fat, and symmetric pelvic nodes, were considered benign.

Node short axis size greater than 10 mm, and the approach applied by Thoeny et al above, can be used to help distinguish benign and malignant lymph nodes when staging bladder cancer. Unfortunately, accuracy for determining nodal metastases on cross-sectional imaging remains limited. Despite incorporating morphologic criteria when analyzing normal size lymph nodes, Thoeny et al found that sensitivity for determining nodal metastases on a per-pelvic side basis remained limited (71% and 73%).

**Bladder Cancer Variants**

Several more aggressive histological variants of urothelial carcinoma have been described, including: plasmacytoid,

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**TABLE 3. Accuracy of Bladder MRI for Assessing Bladder Cancer T Stage**

<table>
<thead>
<tr>
<th>Study Question</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1: Differentiate ≤T1 from ≥T2 stage before and/or after initial TURBT identifying &lt;T1 tumor</td>
<td>87 (82–91)</td>
<td>79 (72–85)</td>
</tr>
<tr>
<td>Q2: Differentiate T-any vs. T0 stage before and/or after initial TURBT</td>
<td>65 (23–92)</td>
<td>90 (83–94)</td>
</tr>
<tr>
<td>Q3: Differentiate ≤T2 vs. ≥T3 stage before and/or after initial TURBT or repeat TURBT</td>
<td>83 (75–88)</td>
<td>87 (78–93)</td>
</tr>
<tr>
<td>Q4: Differentiate &lt;T4b vs. pT4b stage</td>
<td>85 (63–95)</td>
<td>98 (95–99)</td>
</tr>
</tbody>
</table>

Source: Gandhi et al. TURBT = transurethral resection of bladder tumor.

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**FIGURE 5: Contrast-enhanced axial CT image (a) demonstrates a left common iliac lymph node not meeting size criterion for a pathologic node (short axis >10 mm) (arrow). b: Axial T2W image of the urinary bladder depicts a large mass involving predominantly the right bladder wall with extension into the peri-vesical fat (arrow). c: Coronal T2W image again shows tumor extension into the peri-vesical fat (thick arrows). The normal size lymph nodes on CT were found to have abnormal morphology on MRI, namely irregular borders (thin arrows), suggestive of pathologic nodes as has been described by Thoeny et al.**
micropapillary, and sarcomatoid urothelial carcinoma. Intraoperative and histopathological descriptions of plasmacytoid urothelial carcinoma (PUC) have a characteristic pattern of local invasion, with sheet-like spread of malignant cells along pelvic fascial planes. This is hypothesized to be related to the loss of E-cadherin expression. Recently, imaging findings of PUC have been described resembling histological spread of tumor with invasive T2W hypointense sheets of soft tissue extending from the primary tumor and spreading along fascial planes with restricted diffusion (Fig. 7). A propensity for locally recurrent disease and peritoneal metastases has also been described in PUC. Imaging features of micropapillary and sarcomatoid variants have not, to our knowledge, been described in the imaging literature.

Other epithelial neoplasms of the bladder include squamous cell and adenocarcinoma, far less common than urothelial carcinoma. Squamous cell carcinoma represents 3–7% of bladder malignancies in the United States, typically presenting in older patients. Common risk factors in developed nations include: neurogenic bladder and chronic bladder irritation or infection; however, schistosomiasis is a specific etiological organism associated with bladder squamous cell carcinoma, resulting in much higher rates in endemic nations. Squamous cell carcinoma demonstrates no specific imaging features, typically appearing as a focal mass or wall thickening; the exception being in the case of prior infection with schistosomiasis, where diffuse curvilinear bladder wall calcification with concomitant bladder mass should suggest a squamous cell histology. Adenocarcinoma represents only 2% of bladder malignancies, with a third of adenocarcinomas being urachal in origin. Urachal adenocarcinomas are characterized by a typical location at the midline bladder dome at

![Figure 6](image1.png)  
**Figure 6:** A 77-year-old female with multifocal urothelial carcinoma. a: Coronal T2W image from an MR urogram demonstrates moderate left hydroureteronephrosis with a polypoid filling defect at the level of the left mid-ureter (arrow). b: Coronal fat-suppressed contrast-enhanced T1-weighted MR image in the urothelial phase demonstrates enhancement of the ureteric mass (arrow). Surgical pathology confirmed papillary urothelial carcinoma of the left ureter.

![Figure 7](image2.png)  
**Figure 7:** An 83-year-old male with rectal pain and biopsy-proven plasmacytoid urothelial carcinoma of the urinary bladder. Axial T2W image (a) demonstrates marked bladder wall thickening (dotted arrows) and thick T2 hypointense soft tissue extending along the mesorectal fascia (arrowhead). This soft tissue demonstrates enhancement on DCE imaging (b) with diffusion restriction confirmed by high signal on high b-value DWI (c) and low signal on the ADC map (d). More confluent mass-like perirectal soft tissue is noted more inferiorly (solid white arrows), which again demonstrates low signal intensity on T2W imaging (e), with contrast enhancement (f) and diffusion restriction (g,h). Soft tissue is again noted extending along the mesorectal fascia (arrowheads).
the insertion of the median umbilical ligament (Fig. 8). Ura-
chal adenocarcinoma mural invasion is from external to lumi-
nal, potentially resulting in a submucosal mass on imaging
and at cystoscopy. Mucinous differentiation may be seen in
adenocarcinomas, resulting in markedly $T_2W$ hyperintense
signal within the primary mass or nodal metastases, which
may distinguish adenocarcinomas from other epithelial
malignancies.85

Malignant bladder masses may also be secondary to
involvement by a nonbladder primary malignancy, either by
direct invasion (eg, colonic, rectal, prostatic, or cervical carci-
nomas) or metastatic disease (eg, lymphoma/leukemia, gastric,
melanoma, lung, or breast).86 The remainder of bladder neo-
plasms are predominantly accounted for by mesenchymal
tumors. These lesions are typically benign and will again pre-
serve a smooth inner urothelial contour at imaging, suggest-
ing their origin from the sub-urothelial layers of the bladder
wall.87

**Radiomic Analysis**

Radiomic analysis of mp-MRI imaging features shows prom-
ise at both predicting local tumor stage and histological grade
of bladder cancer.88–90 $T_2W$ images can be used to evaluate
tumor heterogeneity, which is a marker for various
histological features (including cellular proliferation, necrosis,
tumor angiogenesis) and can be evaluated quantitatively using
texture analysis.88,91 Radiomic features can be extracted from
functional MRI images providing information on tumor biol-
ogy at the cellular level. For example, ADC analysis provides
information regarding the diffusivity of water, which is influ-
enced by tumor cellularity, cell membrane integrity, and
structural changes.90,92 Diffusion kurtosis imaging may have
a relationship with the complexity of microstructures in tis-
sues.44 DCE analysis can further provide information regard-
ting tumor microvasculature and surrounding cellular
environment.93

Several quantitative features may be useful for predict-
ing tumor stage prior to surgery in addition to qualitative
visual assessment of the primary tumor, bladder wall, and sur-
rounding fat on $T_2W$, DWI, and DCE imaging.88,89 A few
$T_2W$ textural features can help differentiate normal bladder
wall from cancer,93,94 and certain radiomic textural features
may be associated with MIBC.88 Whether texture analysis is
useful for diagnosis of $>T2$ disease remains unknown and
requires further study. In addition to tumor stage, radiomic
features have been found to provide information on tumor
grade and disease aggressiveness, factors that impact both
medical and surgical management.93,95–97 DCE-derived
tumor washout may be associated with higher-grade cancer.93

**FIGURE 8:** A 44-year-old male undergoing workup for gross hematuria and found to have a bladder mass on ultrasound. a: Sagittal
$T_2W$ image shows a mass associated with the bladder dome, at the expected location of the urachal remnant, between the dome and
umbilicus (arrows). This mass restricts diffusion (b) and demonstrates early enhancement on DCE imaging (c). Pathology revealed this
mass to be a urachal adenocarcinoma.

**FIGURE 9:** A 63-year-old male with high-grade T3 bladder urothelial carcinoma. Lobulated urothelial carcinoma (solid white arrows)
arising from the left bladder wall with intermediate signal on the axial $T_2W$ image (a), marked restricted diffusion with high signal on the
$b = 1000$ sec/mm$^2$ (b) and corresponding low signal on the ADC map (c). Intermediate $T_2$ signal intensity and corresponding
restricted diffusion (open arrows) extends from the tumor, through the bladder wall (arrowheads), and into the peri-vesical fat, consistent
with T3b disease. The tumor was contoured using commercially available texture analysis software and the corresponding entropy texture
map (d) visually demonstrates the textural data. Preliminary data shows promise in certain textural features being able to predict stage
and grade of tumor. Further work is needed prior to widespread clinical use.
and quantitative ADC values have been shown to inversely correlate with tumor grade.\(^9^2\) Combining ADC values with different texture features (including entropy and kurtosis) shows promise for predicting higher-grade bladder cancer, although further work is needed to verify the results from these preliminary studies.\(^9^0,^9^3\) Examples illustrating radiomic texture analysis of urinary bladder tumors are depicted for both relatively more heterogeneous (Fig. 9) and homogeneous (Fig. 10) tumors.

There are several common genetic mutations associated with bladder cancer, including those affecting cell-cycle regulation, chromatin regulation, and kinase signaling pathways.\(^9^8\) Known distinct genetic pathways between MIBC and non-MIBC may often account for the differences in clinical outcomes and patient prognosis.\(^2^6,^9^9\) Non-MIBC are associated with mutations involving fibroblastic growth factors, which affects the kinase signaling pathways, while MIBC can be associated with defects in p53 and retinoblastoma tumor suppressor pathways, which affect cell cycle control.\(^9^9,^1^0^0\) Knowledge of these pathways may be helpful for the discovery of useful radiomic features associated with different genetic mutations.\(^3^8,^1^0^0\) A study by Sevcenco et al showed an association between ADC values and cell cycle regulators including p53 and p21.\(^1^0^0\) Also Ki-67, which is a known marker for cellular proliferation, has been shown to inversely correlate with ADC values.\(^1^0^1\) These findings suggest that features on ADC may be useful biomarkers in the radiomic analysis of bladder cancer. As knowledge of the genetic basis of bladder tumors evolves and the application of radiomic features derived from MRI improves, the potential for MRI biomarkers to become a noninvasive diagnostic test useful for assessing the genetic makeup of tumors, providing more accurate grading and staging of disease, may be realized.

A recent and rapidly expanding area of study in medical imaging is the application of deep learning (ie, artificial intelligence) to imaging data. This includes algorithms that have incorporated radiomic features for bladder cancer staging and assessment of treatment response.\(^1^0^2,^1^0^3\) Work on machine-learning models that can automatically detect and segment organs and disease processes in the abdomen and pelvis is under way. Future research directions may include automated detection of bladder tumors, bladder tumor subtype differentiation, and the development of prediction models for bladder tumors likely to respond to treatment.

Conclusion

The future contribution of MRI to the management of bladder cancer will likely increase as the accuracy of MRI compared to current staging techniques is more widely recognized, particularly with regard to identification of muscle invasion. The application of radiomic features, and incorporation of machine-learning algorithms to enhance interpretation of bladder MRI, may further improve staging accuracy and may also provide other useful information such as assessment of treatment response. Current bladder cancer management guidelines may benefit from further integration of MRI into their staging strategies. Moving forward, studies are needed to assess the added value of mp-MRI for the preoperative grading and staging of urinary bladder cancer using traditional and emerging MRI techniques, and to further explore bladder cancer radiomic analysis and the application of machine learning to bladder cancer MRI.

References


