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NEW IMAGING TECHNIQUES (A RASTINEHAD AND S RAIS-BAHRAMI, SECTION EDITORS)

Preoperative Imaging for Staging Bladder Cancer

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Abstract Accurate preoperative staging of bladder cancer is essential in determining the extent of disease and optimal treatment. The current gold standard of transurethral resection of bladder tumor (TURBT) followed by computed tomography (CT) imaging provides excellent staging specificity, but often understages the disease, leading to pathologic upstaging and adverse outcomes in patients undergoing radical cystectomy. Newer imaging modalities, such as multiparametric magnetic resonance (MR) imaging and positron emission tomography (PET) combined with CT or MR provides promising imaging alternatives which may improve accuracy of staging both local and distant disease.

Keywords Bladder cancer · Cancer staging · Computed tomography · Magnetic resonance imaging · PET · Understaging

Abbreviations

MIBC	Muscle-invasive bladder cancer
NMIBC	Non-muscle-invasive bladder cancer
MR	Magnetic resonance
DCE-MR	Dynamic contrast-enhanced MR
DWI-MR	Diffusion-weighted image MR
CT	Computed tomography
PET	Positron emission tomography
NSF	Nephrogenic systemic fibrosis
TURBT	Transurethral resection of bladder tumor
2D US	Two-dimensional ultrasound
3D US	Three-dimensional ultrasound
CE-US	Contrast-enhanced ultrasound
USPIO	Ultra-small super-paramagnetic particles of iron oxide
ADC	Apparent diffusion coefficient
FDG	^{18}F-fluorodeoxyglucose
GFR	Glomerular filtration rate
ROC	Receiver operating characteristic

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Introduction

Bladder cancer is the sixth most commonly diagnosed malignancy in the USA, with an incidence of about 75,000 new cases and 16,000 deaths annually [1]. Diagnosis is generally made via transurethral resection of a bladder mass found on evaluation for hematuria. Approximately 20–25 % of patients initially present with muscle-invasive bladder cancer (MIBC), the gold-standard treatment for which is radical cystectomy (RC) with pelvic lymphadenectomy. Prior to surgery, these patients must be evaluated with cross-sectional imaging to assess for local tumor invasion and to detect metastatic spread. Should the patient prove to have extravesical or distant disease, the optimal treatment may vary significantly. Herein, we will review the currently recommended imaging protocols and explore recent data for alternative or investigational imaging modalities that may improve diagnostic and prognostic accuracy for bladder cancer patients.

Currently Recommended Bladder Cancer Staging

For non-muscle-invasive bladder cancer (NMIBC), the American Urologic Association (AUA) and National Comprehensive Cancer Network (NCCN) guidelines recommend upper tract imaging with ultrasound, computed tomography (CT),

magnetic resonance (MR), or intravenous pyelogram, and pelvic imaging if the tumor is sessile or high grade [2]. For staging of newly diagnosed MIBC, AUA and NCCN guidelines recommend contrasted CT urography or MR urography of the abdomen and pelvis, and either plain film x-ray or non-contrast CT of the chest, and bone scan for patients with symptoms and/or an elevated alkaline phosphatase [2, 3]. Contrast-enhanced CT is the current standard of care for the assessment of nodal or distant disease, but CT is poor in its evaluation of depth of bladder invasion. MR excels in assessing bladder invasion due to better tissue differentiation when compared to CT, and limited data regarding assessment of nodal disease indicate that MR is comparable to CT. Multiple studies of CT and MR have demonstrated modest sensitivity in detection of pelvic lymph node involvement, varying with size cutoffs [4, 5].

Despite advances in radiological imaging over the last several decades, current modalities are plagued by clinical understaging of MIBC in a significant number of patients, as high as 42 % in a sizable recent series [6, 7] (Table 1). Large, well-designed trials of newer imaging modalities are essential to advance the field and improve the care of bladder cancer patients.

Imaging Modalities

Computed Tomography

Though the technology is aging, computed tomography (CT) remains the gold standard in radiologic staging of MIBC. Advantages include rapid image acquisition, relatively low cost, wide availability, and reasonable accuracy in assessing for nodal or distant disease. Disadvantages include exposure to ionizing radiation, poor assessment of the primary tumor, and intolerability of IV contrast in patients with chronic kidney disease (CKD). Because CT is an anatomic rather than a functional study, detection of extravesical disease is limited to lesions above certain size thresholds, which leads to understaging patients with small nodal metastases. Current recommendations suggest that pelvic nodes ≥8 mm and abdominal nodes ≥1 cm measured on the short axis be considered pathologic [9]. While sensitive to detection of enlarged loco-regional and distant lymph nodes, CT provides no data regarding metabolic activity or function of the lymph node, and thus is unable to discriminate between nodes harboring metastatic disease versus those that are inflammatory or of other benign etiology [5, 10]. CT provides poor discrimination between non-muscle-invasive versus muscle-invasive bladder tumors, as tissue differentiation is inadequate. Though CT has a lower sensitivity than MR for detecting perivesical invasion, it has a higher specificity, as a T2 tumor may cause extravesical inflammation that is detected by MR and is mistaken for perivesical invasion, leading to overstaging with MR [11]. Studies have demonstrated that CT is able to successfully differentiate T3b and T4 disease from non-muscle-invasive, but overall is inaccurate for local tumor staging [12].

Table 1 Summary of imaging modalities for staging bladder cancer

	Overall accuracy	Understaging	Overstaging	Sensitivity	Specificity
Primary tumor					
CT	35–55	10–39	6–34	93–95	28–71
MR	62–85	13[a]–26	7–49[a]	80–100	78–91
PET/CT	–	–	–	–	–
Pelvic lymph nodes (distant disease)					
CT	54[c]–97	8–29[b,c]	8–24[c]	85	67–91[c]
MR	73–98	2–8[d]	11–33[d]	76[e]–83	89[e]–98
PET/CT	82–92[f]	9–16	0–29	46–70 (82)[f]	91[g]–100 (89)[f]

Adopted from Bostrom 2010 unless otherwise indicated.

[a] Liedberg et al. 2013 [8]

[b] Paik 2000

[c] Tritschler 2012

[d] MR-USPIO

[e] Papilia 2012

[f] Adapted from Lu 2012

[g] Maurer 2012

Magnetic Resonance Imaging

MR imaging (MRI) has emerged as an exciting and possibly more versatile option for MIBC staging when compared to CT. MR has no ionizing radiation and soft tissue contrast is excellent, providing more anatomic data than CT, especially in assessing the primary tumor. Newer MR protocols also add functional data which may assist in more accurate staging in these patients.

T1-weighted MRI is useful for identifying extravesical fat infiltration, pelvic lymphadenopathy, and bone metastases [13••]. However, normal detrusor and bladder tumor both have similar, intermediate signal intensity, making the depth of bladder wall invasion difficult to discern. T2-weighted imaging excels in demonstrating tumor depth (NMIBC versus MIBC), and extravesical extension. On T2 imaging, the normal detrusor muscle appears as a hypointense line; thus, interruption in the line is indicative of muscle-invasive disease [13••, 14]. While these standard MR modalities show some advantages over CT in assessing the primary tumor, functional MR imaging protocols are where potential substantive advancements lie in improving overall staging accuracy.

Dynamic contrast-enhanced MR (DCE-MR) utilizes paramagnetic contrast agents and can be used to detect differences in blood flow within a tumor, including areas of ischemia and necrosis [15]. Several studies investigating DCE-MR have

demonstrated an accuracy of 85 % in distinguishing non-muscle-invasive bladder cancer (NMIBC) from MIBC, 82 % accuracy in determining organ-confined from non-organ-confined disease, and 80 % accuracy in detecting nodal disease [16••, 17]. Using DCE-MR as a marker of angiogenesis may predict disease recurrence; a 24-patient pilot study suggested that patients with stronger, faster enhancement were more likely to recur [18]. DCE-MR has proven useful in predicting complete response to chemotherapy in breast and rectal cancer [19, 20], and in a 30-patient pilot study of patients undergoing neoadjuvant chemotherapy prior to radical cystectomy, certain pharmacokinetic parameters can characterize the microcirculatory changes within the tumor, providing information regarding the early chemotherapeutic response [21•]. Gadolinium must be used with caution in patients with severe renal insufficiency, as there is increased risk of nephrogenic systemic fibrosis (NSF). The American College of Radiologists suggests discussing NSF risks with those with a glomerular filtration rate (GFR) <40 mL/min/1.73 m^2, though it is exceedingly rare in patients with GFR >15 mL/min/1.73 m^2 [22].

Diffusion-weighted MR (DW-MR) measures water diffusion across the cell membrane, which varies between normal tissues and tumor, as tumor tissues tend to have greater cellularity, reducing water diffusion [23, 24]. While primarily used in assessing local tumor spread, recent studies have demonstrated DW-MRs utility in predicting histologic grade and aggressiveness. In a prospective study of 51 patients with suspected bladder cancer, the area under the receiver operating characteristic (ROC) curve for predicting MIBC and high-grade disease using DW-MR apparent diffusion coefficient (ADC) thresholds was 0.884 and 0.906, respectively [25]. Another study of 132 patients undergoing transurethral resection of bladder tumor (TURBT) demonstrated strong correlation between lower ADC and high-grade, high-stage, sessile tumors [26•]. DW-MR is also more accurate than T2-MR in staging organ-confined (≤T2) disease, with staging accuracy of 69.7 versus 15.1 %, respectively [11].

In addition to providing functional information about the primary tumor, DW-MR may have utility in monitoring response to treatment. With good response, ADC will often decrease, indicating decreased cellularity. In hepatocellular carcinoma, cervical cancer, and several metastatic disease states, response to chemotherapy and radiation is accurately monitored with DW-MR [27–30]. In patients with MIBC undergoing neoadjuvant chemotherapy, monitoring for change in ADC may provide additive information that could guide treatment decisions toward early cystectomy or continued chemotherapy based on radiologic tumor response [19].

Lymphotropic nanoparticle-enhanced MR (Ultra-small super-paramagnetic particles of iron oxide (USPIO)-MR) is a functional study that allows for differentiation of benign and malignant enlarged lymph nodes. USPIO are administered intravenously and are phagocytosed by macrophages within the lymph nodes. Given the higher density of functioning macrophages in benign lymph nodes, benign nodes have higher signal intensity than malignant nodes on T2 imaging. Early studies have demonstrated excellent sensitivity (96 %), specificity (95 %), and accuracy (95 %) [31]. Recently, USPIO-MR combined with DW-MR has demonstrated improved detection of lymph node metastases compared to USPIO-MR imaging alone, and it shortened interpretation times, which is important for potential widespread implementation [32•]. Data remain preliminary, but USPIO-MR imaging is a promising modality that may improve accuracy of lymph node staging compared to conventional techniques.

Positron Emission Tomography

Positron emission tomography (PET) imaging, especially when combined with CT (PET/CT) for anatomic localization, has a myriad of applications within oncology due to its ability to locate metabolically active tissues that may represent foci of cancer that cannot be visualized on standard cross-sectional imaging due to small size. In bladder cancer, its role is not well defined. Previous meta-analysis of the diagnostic accuracy of PET/CT demonstrate a global accuracy of 0.92, but the studies were small and heterogeneous in nature [33–38]. In a larger, more recent study of 233 patients undergoing cystectomy for bladder cancer, PET/CT was evaluated against CT in staging MIBC and high-risk NMIBC. PET/CTs accuracy in detection of pelvic lymph nodes was 0.87 compared to 0.83 for CT, and in detection of distant disease, the accuracy was 0.86 versus 0.83, respectively. In this study, only 3 % of patients were found to have metastatic disease on PET/CT that was missed on CT, possibly changing their treatment course [39••]. The role of PET/CT after chemotherapy for bladder cancer appears limited, as sensitivity in detecting LN metastases decreases to ~50 % [40]. One of the biggest hurdles in PET/CT for bladder cancer is that the most commonly used radiotracer, ^{18}F-fluorodeoxyglucose (FDG), is excreted in the urine, masking FDG uptake by the primary bladder tumor and hindering visualization of perivesical lymph nodes. To counteract the inherent limitations of FDG imaging of the bladder, various protocols use increased hydration, catheterization, delayed images, and forced diuresis with some improvement in accuracy [35, 41].

Novel PET radiotracers are also under investigation to enhance staging accuracy in bladder cancer [12].C-acetate PET/CT has demonstrated promise in a small number of patients, but has demonstrated modest overall accuracy (~0.65–0.75) [42]. ^{11}C-choline and ^{11}C-methionine are alternative options as they are not excreted in the urine. In a study of 27 patients, ^{11}C-choline PET has demonstrated efficacy in detecting residual disease after TURBT that is comparable to CT, and was superior in detecting pathologic pelvic lymph nodes [43].

However, a 44 patient study of ^{11}C-choline PET/CT in patients with MIBC scheduled for cystectomy demonstrated no improvement in staging accuracy compared to CT alone [44]. A disadvantage of ^{11}C-choline is a very short half-life, limiting its use to facilities with an on-site cyclotron. Data is limited for ^{11}C-methionine in bladder cancer staging, and small studies suggest non-superiority to conventional imaging [45]. In patients with suspected bony lesions from metastatic bladder cancer, ^{18}F-flouride PET has demonstrated superior accuracy in detection of lytic lesions compared to (99 m)Tc-MDP bone scan. Most data regarding ^{18}F-flouride PET is from non-bladder solid malignancies [46, 47], but a recent 48-patient study in patients with bladder cancer with suspected bony metastases found that ^{18}F-flouride PET was more sensitive, specific, and accurate than (99 m)Tc-MDP bone scan [48].

Receptor-specific radiolabeled biomarkers for PET/CT provide the attractive possibility of targeting tumor markers specific to a bladder tumor, theoretically increasing the specificity of PET/CT. In some bladder cancers, EGFR and HER2 are overexpressed, thus radiolabeled trastuzumab could allow for in vivo monitoring of tumor HER2 expression [49].

Magnetic Resonance/Positron Emission Tomography

In an effort to capitalize on the excellent soft tissue contrast seen in MR imaging and the imaging of metabolically active tissues suspicious for malignancy with PET, the hybrid magnetic resonance/positron emission tomography (MR/PET) was developed and first introduced clinically in 2006 (Fig. 1). Protocols for different tumor types are still in development, but initial experiences suggest that image quality is at least comparable to PET/CT [50, 51]. Currently, at our center, we are investigating the sensitivity and specificity of preoperative MR/PET using surgical pathology as the gold standard in patients undergoing radical cystectomy (NCT01655745). We hypothesize that MR/PET, with the combination of improved spatial resolution of soft tissue and functional imaging provided by PET, will improve staging relative to CT.

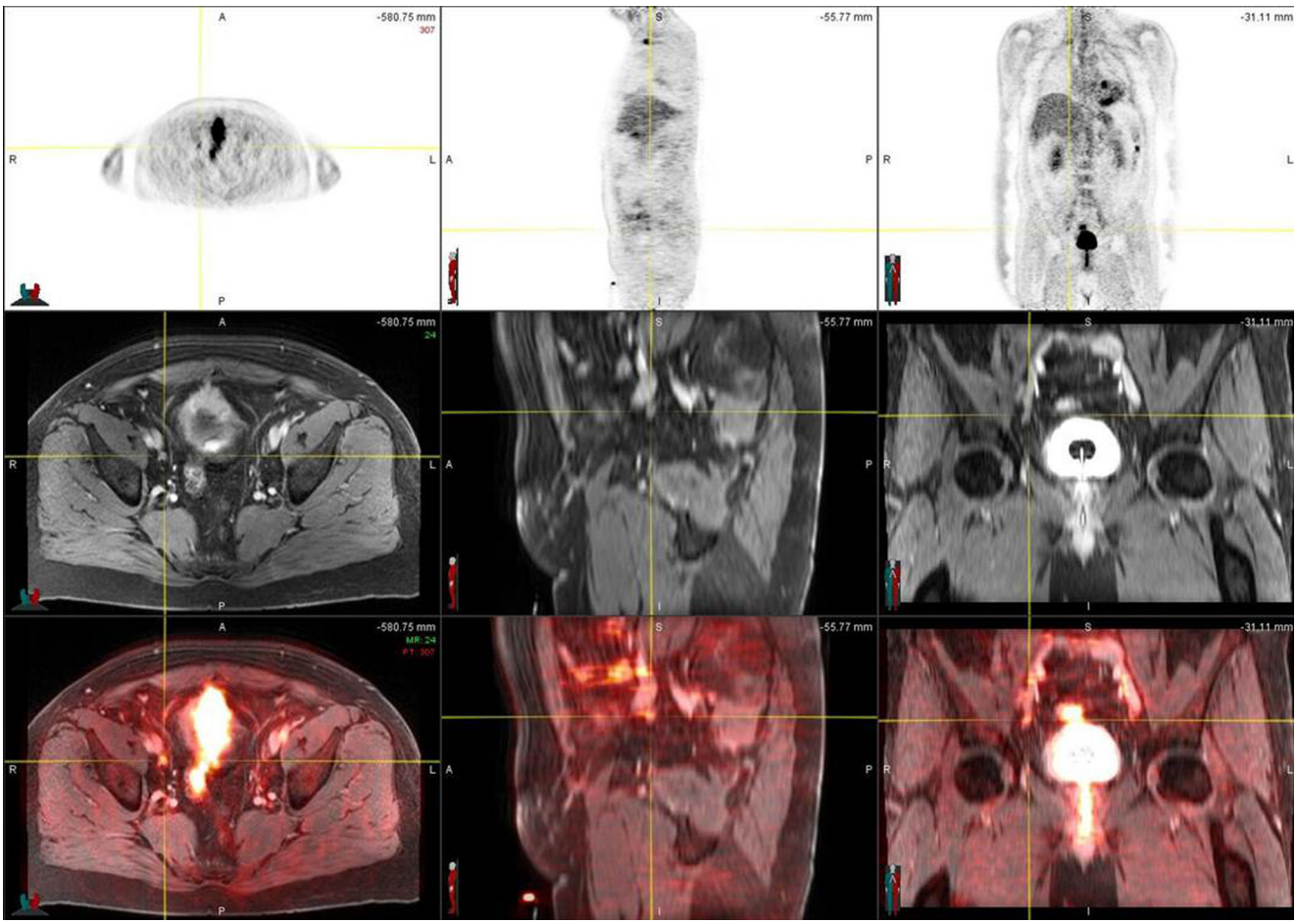

Fig. 1 Fused MR/PET in a 72-year-old male with bladder cancer. The cross hairs are placed on a right external iliac metastatic lymph node. *Row 1* shows PET scan, there is no increased uptake to suggest metastatic disease. *Row 2* shows contrast-enhanced MRI with enhancement of the bladder and vessels. Again, the lymph node shows minimal enhancement. *Row 3* shows fused MR and PET images with bright enhancement of the lymph node indicating tumor involvement. (Image courtesy of Julia Fielding, MD. Department of Radiology, The University of North Carolina at Chapel Hill)

Ultrasound

While not presently used in bladder cancer staging algorithms, ultrasound is widely used to assist in diagnosis though evaluation of gross hematuria. Conventional 2D transabdominal ultrasound technology (two-dimensional ultrasound (2D US)) is limited by subjectivity and expertise of the examiner, and in its ability to assess local depth of invasion. Three-dimensional ultrasound (3D US) allows for more systematic visualization of the tumor in multiple planes, increasing accuracy [52•]. In a pilot study of 14 patients with bladder tumors visualized on cystoscopy, 3D ultrasound was significantly more sensitive in detection of the tumor (78.6 versus 67.9 %), and was 100 % accurate in detecting serosal invasion of the tumor (≥T3b), compared to 88.9 % accuracy with 2D US [53].

Contrast-enhanced ultrasound (CE-US) uses intravenous microbubble contrast to help delineate vasculature on ultrasound and has been shown in small studies to compare favorably to conventional ultrasound in bladder cancer staging. A 34-patient study of CE-US versus 2D US demonstrated the ROC area under the curve of 0.996 for CE-US, compared to 0.613 for 2D US in detection of muscle-invasive disease [54]. Combining 3D and CE-US appears to have additive benefits as well. In a trial comparing 60 patients with the diagnosis of bladder cancer, CE-US, 3D US, and CE+3D US were used and compared to final pathology after TURBT. Combined CE+3D US was 100 % sensitive and 93 % specific in diagnosing MIBC versus NMIBC, and there was better intra-reader agreement when compared to CE-US and 3D US alone [52•].

Cystoscopic ultrasound is an investigational technique utilizing a flexible ultrasound bronchoscope as a cystoscope, allowing for local ultrasound of the primary bladder tumor. In a small pilot study, this technique was 95.7 % accurate in detection of MIBC, and sensitivity of MIBC detection was significantly higher with cystoscopic ultrasound compared to initial TURBT [55].

Despite technologic advances that have overcome some of the limitations of 2D ultrasound, the role of ultrasound in the staging of bladder cancer has not been well-defined, which has limited widespread clinical utility.

Conclusion

The management of bladder cancer varies depending upon clinical staging of the disease, and the mainstay imaging modality for preoperative staging is CT, though MR imaging has shown promise. CT remains the gold standard as a fast, relatively inexpensive study that provides a good deal of anatomic information and can easily identify enlarged lymph nodes, but is limited in its ability to accurately evaluate local tumor burden and invasion, and provides no functional information about suspicious lymph nodes. Multiparametric MR complements some weaknesses of CT, providing excellent soft tissue discrimination and accurate assessment of the primary tumor, and some protocols such as DCE-MR and DW-MR provide functional data, possibly increasing staging accuracy. However, the exact role of MR in staging bladder cancer is unclear, given a current paucity of large, well-powered studies. PET imaging, when combined with CT and MR, allows for assessment of metabolic activity of tissue, and may help with restaging and assessing response to chemotherapy. The urinary excretion of FDG makes bladder cancer staging with PET difficult due to interference in visualizing the bladder and surrounding tissues, but novel protocols and radiotracers may minimize that hurdle in the future, possibly expanding the indication and utility of PET in this population.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Maxim J. McKibben and Dr. Michael E. Woods each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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