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Contemporary role of advanced imaging for bladder cancer staging

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Abstract

Optimized pretreatment staging of bladder urothelial carcinoma is essential in guiding appropriate treatment. This staging process relies heavily on tissue pathology from transurethral resection of bladder tumor as well as imaging for diagnosis of local, regional, nodal, or distant visceral spread. Accurate preoperative staging is critical for appropriate treatment decision making and patient counseling as these are based on the extent of disease involvement, largely classifying the cancer as having local, regional, or distant spread. Currently, the gold standard of transurethral resection of bladder tumor followed by computed tomography imaging with intravenous contrast provides excellent staging specificity in cases of more advanced bladder cancers with suspicion of spread; however, this often under stages patients that can lead to adverse oncologic outcomes in these patients undergoing radical cystectomy. Incorporation of novel imaging modalities including multiparametric magnetic resonance imaging and positron emission tomography imaging have shown promise in improving accuracy of staging for both local and distant disease in patients with bladder urothelial carcinoma.

Keywords: Urothelial carcinoma; Transitional cell carcinoma; MRI; PET

Introduction

Cancer of the urinary bladder is the sixth most commonly diagnosed malignancy in the United States with an annual incidence of approximately 74,000 new cases and is responsible for 16,000 deaths annually [1]. It is one of the most expensive cancers to treat in a public health setting in the United States despite several cancers affecting several fold more patients [2]. Diagnosis of bladder cancer via cystoscopic evaluation and tissue sampling via cystoscopic bladder biopsy or transurethral resection of bladder tumor (TURBT) is most commonly prompted by a finding of hematuria or irritative voiding symptoms in patients with recognized risk factors.

The standard cystoscopic examination for detection of mucosal abnormalities leading to bladder biopsy or TURBT uses white light, but advances in cystoscopic technologies have allowed for (1) tissue fluorescence or photodynamic diagnosis (PDD) cystoscopy, (2) narrow-band imaging, (3) real-time optical coherence tomography, (4) concurrent confocal laser endomicroscopy, and (5) confocal Raman spectroscopy, all of which have shown potential promise in improved detection or evaluation of local extent of bladder cancer involvement [3–11].

Most patients with bladder cancer diagnoses are found to have non–muscle-invasive bladder cancer (NMIBC), which is commonly managed with local resection of the gross disease, intravesical therapies, and close surveillance as many recur and a significant proportion are at risk for progression to higher-stage disease over time. However, approximately 1 quarter of patients initially present with MIBC at the time of diagnosis. The gold-standard treatment for patients diagnosed with MIBC is radical cystectomy, pelvic lymph node dissection and urinary diversion with or without neoadjuvant systemic chemotherapy. Classically, before undergoing radical cystectomy, patients undergo cross-sectional anatomic imaging with contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) to assess for local/regional extravesical tumor invasion and to evaluate for distant metastatic spread. In cases where extravesical, nodal, or visceral metastatic disease spread is suspected, the operative plan may be

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aborted or altered, with preference toward recommending another management approach.

With major recent advances in functional imaging technology, newer imaging modalities have been developed and investigated as alternatives or adjuncts to the classical imaging for preoperative staging of bladder urothelial carcinoma. Herein, we present some of these advanced imaging technologies and their current state of usage for the staging of bladder cancer.

Established standard imaging for localized staging of bladder cancer

Non–muscle-invasive bladder cancer

For NMIBC, either carcinoma in situ, cTa or cT1 urothelial carcinoma of the bladder, well-recognized guidelines rendered by the American Urologic Association and National Comprehensive Cancer Network recommend some forms of upper tract imaging. This can be with ultrasound, CT, MR, or intravenous pyelography to rule out extent of disease into the urothelial lining of the ureters and renal collecting systems given the field effect theory of urothelial cancers. In addition to upper tract imaging, repeat TURBT and axial pelvic imaging is recommended for NMIBC when tumors are sessile, multifocal, or high grade on resection pathology [2]. This provides for evaluation of occult intramural/transmural extension or measurable pelvic lymphadenopathy suggestive of local spread. This is based on a 25% to 40% rate of upstaging to MIBC in series where repeat TURBT was performed in cases of NMIBC on initial TURBT pathology [12,13]. Advances in imaging from basic white light cystoscopy (i.e., narrow-band imaging and fluorescence cystoscopy) have helped with local disease diagnosis and preventing residual disease after resection, which of course improves our local staging of a patient's disease. Narrow-band imaging uses optical enhancement by using different wavelengths of light to enhance the contrast between mucosal surfaces and microvascular structures. Herr and Donat [14] has shown promising results in decreasing recurrence in using this technology. PDD through the use of hexaminolevulinate fluorescence cystoscopy has improved on white light standard cystoscopy. It has been shown to detect more tumors than conventional white light cystoscopy and leave behind less residual tumor after PDD based TURBT [15].

Muscle-invasive bladder cancer

Staging of MIBC following a new diagnosis of $\geq$cT2 disease on TURBT pathology typically involves more imaging and laboratory evaluation than is recommended for NMIBC. Based on the American Urologic Association and National Comprehensive Cancer Network guidelines for MIBC, a contrast-enhanced CT of the abdomen and pelvis with excretory phase known as CT urography or MR urography are recommended in addition to chest x-ray or noncontrast CT of the chest. A nuclear medicine bone scan is also recommended as a part of staging for patients with MIBC with an elevated serum alkaline phosphatase level or symptoms that could be attributed to bony metastases [2,3].

CT and MRI of the abdomen and pelvis are recommended in cases of high-grade NMIBC and MIBC and have relatively high sensitivity and specificity for cancer detection and staging differentiation between patients with transmural spread to the extravesical space vs. those with tumor confined to the bladder wall [16–18]. Advantages of conventional contrast-enhanced CT and MRI include that these are readily available, relatively low in cost, and have validated value in assessing overall nodal and distant metastatic stage. Tumor staging between non–muscle-invasive disease and muscle-invasive disease still remains better achieved with TURBT than any non-invasive imaging technique investigated despite the exquisite soft-tissue resolution provided by MRI. However, MRI has been shown to be very useful in detecting T3 and T4 disease where TURBT has been reported to under stage in approximately 40% of these cases [19,20]. Nodal involvement is predicted with these anatomic imaging studies largely based on size of visible nodes. Recommendations suggest that pelvic lymph nodes greater than or equal to 8 mm and abdominal/retroperitoneal lymph nodes $\geq$1 cm as measured in short axis are suspicious for metastatic involvement [21]. It is well-recognized that using size the sole threshold for deeming a lymph node suspicious for metastatic involvement is fraught with potential error; metabolic and other functional activity is not being assessed and false-negative assessment can result from micrometastatic disease and false-positive assessment can results from the inability to differentiate between cancer and inflammatory enlargement [22,23].

Advanced imaging for local staging and detection of nodal spread

The current conventional approach to cross-sectional imaging with CT and standard anatomic MRI for bladder cancer patients harbors a critical shortcoming in accurate determination of local stage and lymph node involvement. Up to 25% of patients with lymph node metastases found on final pathology were not visualized on imaging characterization before undergoing radical cystectomy. This realized nodal understaging with conventional imaging, is a result of simply using size parameters as an indirect surrogate for predicting metastatic involvement with reported sensitivity of detecting lymph node positivity in cases of bladder cancer taken to radical cystectomy ranging between 31% and approximately 50% [22,24–26]. Specificity of CT imaging based on size criteria has been reported