New Imaging Techniques for Non-Muscle Invasive Bladder Cancer: Ready for Primetime

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KEYWORDS

• Non-muscle invasive bladder cancer • Transurethral resection • White light cystoscopy
• Fluorescence cystoscopy • Narrow band imaging • Optical coherence tomography
• Confocal laser endomicroscopy

KEY POINTS

- Non-muscle invasive bladder cancer (NMIBC) is confined to the epithelium and lamina propria.
- Complete eradication and bladder preservation is the goal of transurethral resection (TUR).
- Technological limitations contribute to failure of TUR.
- Failure results in recurrence and progression.
- New imaging modalities that increase the urologist's ability to detect, stage, and treat NMIBC at TUR can have a significant impact in the treatment of NMIBC.

FLUORESCENCE CYSTOSCOPY

- Enhances tumor detection at initial resection for all stages and grades.
- Detection of carcinoma in situ is particularly enhanced with fluorescence cystoscopy (FC).
- Decreases rates of recurrence.

NARROW BAND IMAGING

- Shows similar efficacy in detection of tumors as FC.
- Does not require instillation of fluorophore in bladder before usage.

OPTICAL COHERENCE TOMOGRAPHY

- Provides real-time tumor grading during TUR.

CONFOCAL LASER ENDOMICROSCOPY

- Allows microscopic examination of urothelium in real-time for histopathologic analysis.

Bladder cancer remains one of the most difficult clinical conundrums for the practicing urologist. On the extremities of the disease, management of bladder cancer is simplified. The progressive nature of muscle-invasive disease dictates definitive management and the gold standard remains radical cystectomy. At the other extreme, the likelihood of a single, subcentimeter, superficial (Ta) low-grade tumor progressing to muscle invasion is less than 1%.[1] Adequate management

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of such a lesion is eradication by transurethral resection (TUR) and a single instillation of intravesical chemotherapy at the time of resection. Recurrence and progression are monitored by quarterly cystoscopy for 1 year, decreasing in frequency thereafter if the patient remains free of tumor. Most patients, however, lie in between these 2 extremes. For these patients with non-muscle invasive bladder cancer (NMIBC), tumor recurrence and progression to muscle-invasive disease are a lifelong risk despite the multimodal application of chemotherapeutics, immune therapies, and repeated surgical resections.

Non-muscle invasive disease is confined to the epithelium (Ta) or the lamina propria (T1). A patient suspected of having bladder cancer undergoes evaluation with upper tract imaging, urine cytology, and cystoscopy.[2] The standard for evaluation of the lower urinary tract is white light cystoscopy (WLC), followed by TUR of any tumor that is discovered. Accurate assessment of histopathologic grade and depth of tumor invasion is required for the implementation of proper treatment. This implementation is accomplished by complete and accurate endoscopic resection at the time of TUR. For TUR to be successful, the tumor must be removed in its entirety, along with a sufficient margin of surrounding mucosae and the muscle directly beneath the tumor.[2]

WLC is, however, a technology fraught with deficiencies. Complete resection of papillary tumors is problematic and, as Brausi and colleagues[3] demonstrated, often leads to early recurrence. As a result, a single TUR is often insufficient for the task. A repeat TUR, performed within 2 to 6 weeks of the initial TUR, shows residual disease a significant portion of the time depending on stage, grade, and tumor multiplicity. For pathologically confirmed disease confined to the epithelium (pTa), residual tumor is seen between 6% and 37% of the time.[4,5] The rate is higher for disease that has been pathologically confirmed to invade into, but not through, the lamina propria (pT1) (33%–78%) and carcinoma in situ (CIS) (70%–80%)[5,6] and incomplete resection is not the only limitation. High-grade Ta or T1 tumors are understaged 10% of the time even when muscle is present in the original resection specimen and will be found to be muscle invasive at re-resection. To what degree deficiencies of surgical technique contribute to this phenomenon is unknown. It is doubtless a factor, but there are also significant technological limitations that contribute to a surgeon's inability to eradicate a bladder tumor completely at the time of resection.

Further evidence supporting this comes from the difficulty of finding and eradicating CIS as reported from trials that have recently explored the utility of random bladder biopsies. Despite the relative ease with which CIS is detected by bladder wash—fully 90% of patients with CIS are thought to have a positive cytology[2]—standard WLC fails to detect a lesion 50% of the time.[7] CIS is a flat, high-grade noninvasive lesion that, unlike Ta and T1 disease, has a high potential for progression when left untreated.[8] Classically described as a red "velvety" lesion, CIS is often multifocal and may be macroscopically invisible. Occult CIS is common when high-grade pTa or pT1 lesions have been identified and is present upward of 40% of the time.[8]

Of prognostic significance, CIS is, after tumor histopathologic grade, the second most important factor predicting progression to muscle invasive disease.[8] Its detection is therefore paramount for accurate risk stratification and the implementation of treatment. Random bladder biopsies are often performed for just such a reason, as a random survey of the bladder mucosae for occult CIS. One recent study demonstrated random biopsies to be positive for CIS 8% of the time.[9] Of clinical significance was the fact that, in a different study of random biopsying, random biopsies changed the indicated therapy 4.6% of the time.[10]

Finally, the economic impact of bladder cancer is immense. From diagnosis to death, bladder cancer is the most expensive cancer in the United States.[11] The inefficacy of cystoscopy for diagnosis and surveillance, in conjunction with the recurrent nature of the disease, is responsible for much of its financial burden. Technological advancements that can decrease recurrence have the potential to have a significant financial impact on health care costs if implemented properly.

FLUORESCENCE CYSTOSCOPY

The topical application of the protoporphyrin 5-aminolevulinic acid (5-ALA) was first performed in the early 1990s by a group of Munich urologists.[12] Before this, it had been shown that the intravenous injection of heme derivatives preferentially accrued in urothelial carcinomas.[13] Heme derivatives are photoactive substances that absorb light at one wavelength and emit at another. Initially, the practical implementation of photodynamic tumor detection using heme derivatives, in particular porphyrin II, was attempted, but ultimately abandoned because of the systemic effects of skin photosensitization due to the porphyrins. Of practical importance, however, was the exposition that a photosensitizer could be used to enhance cystoscopy and tumor detection.