Advances in Imaging Technologies in the Evaluation of High-Grade Bladder Cancer

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KEYWORDS

• Bladder cancer • Confocal laser endomicroscopy • Fluorescence cystoscopy • Molecular imaging • Narrow band imaging • Optical coherence tomography • Photodynamic diagnosis

KEY POINTS

- Improved optical imaging of the bladder can lead to more effective use of bladder-sparing management for low-grade cancer and more aggressive treatment for high-grade cancer.
- Photodynamic diagnosis and narrow band imaging are macroscopic imaging modalities and provide contrast enhancement of suspicious lesions that improve detection rates.
- Confocal laser endomicroscopy is an example of a microscopic optical biopsy technology that provides high-resolution and subsurface tissue characterization similar to histology.
- Confocal laser endomicroscopy is the only clinical technology capable of differentiating high-grade and low-grade bladder cancer.
- The highest image resolution is inferred by molecular specificity. The development of molecular markers and binding agents for molecular imaging can serve to differentiate low-grade and high-grade disease.

INTRODUCTION

Bladder cancer is the sixth most common cancer in the United States with 74,690 new cases and 15,580 deaths expected in 2014.[1] The natural history of bladder cancer is heterogeneous, ranging from low-grade variant that does not recur after local resection to a high-grade subtype that recurs and progresses to metastatic, lethal disease.[2] Although 80% of patients present at a non–muscle-invasive stage (Ta, T1, TIS) that may be managed endoscopically, recurrence rate reaches 61% at 1 year and 78% at 5 years.[3,4] As a result of its high recurrence rate and associated need for lifelong surveillance and repeat resections, the health care costs for bladder cancer are among the highest of all malignancies.[3,5]

White light cystoscopy (WLC) is the standard for evaluation of bladder urothelium. In the office setting, flexible cystoscopes are used for initial

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identification of suspected lesions and subsequent surveillance for recurrence. In the operating room, complete transurethral resection (TUR) with larger rigid cystoscopes is performed for tissue diagnosis and local staging. Despite its central role, WLC has well-recognized limitations.[6,7] Although sufficient for the identification of papillary lesions, visual appearance under white light is unreliable for the determination of low- and high-grade cancer and cannot assess level of invasion.[8] Additionally, nonpapillary and flat malignant lesions such as carcinoma in situ (CIS) can be difficult to differentiate from inflammation,[6] with detection rates of CIS only 58% to 68% by WLC.[9–11] Smaller or satellite tumors can be missed, which contributes to the up to 40% rate of residual bladder cancer found at the time of 'second-look' TUR.[12,13] Finally, indistinct borders and difficult visualization of submucosal tumor margins during TUR can lead to incomplete tumor resection and understaging of bladder cancer.[14,15] These limitations of WLC contribute to the increased risk of cancer persistence, recurrence, and in the case of high-grade bladder cancer, progression to metastatic lethal disease.[2,16,17]

To address the shortcomings of WLC, several adjunctive optical imaging technologies have emerged with the goal to improve bladder cancer detection and resection (**Table 1**). The imaging technologies can be broadly categorized based on their field of view. Photodynamic diagnosis (PDD) and narrow band imaging (NBI) are examples of macroscopic imaging modalities that survey a large area of mucosa, similar to WLC, but provide additional contrast enhancement to distinguish suspicious lesions from noncancerous mucosa. Microscopic modalities including optical coherence tomography (OCT) and confocal laser endomicroscopy (CLE) provide high-resolution, subsurface tissue characterization similar to histology and thus offer the potential for 'optical biopsy' of bladder cancer. Molecular imaging, through coupling of optical imaging technologies with fluorescently labeled binding agents (eg, antibodies), may enable real-time cancer imaging with molecular specificity. These technological advances have the potential to improve optical diagnosis and endoscopic management of bladder cancer. The most recent literature on adjunctive optical imaging technologies is reviewed, with consideration for the evaluation of high-grade bladder cancer highlighted.

PHOTODYNAMIC DIAGNOSIS

PDD, also known as fluorescence cystoscopy or blue light cystoscopy, provides wide-field fluorescence imaging of the bladder with a field of view comparable to WLC. PDD requires preoperative intravesical administration of a photosensitive

Table 1
Characteristics and properties of adjunct optical imaging technologies for bladder cancer

Name	Mechanism	Contrast Agent	Resolution	Depth	Scope or Probe (Diameter)	Status
PDD	Fluorescence	HAL	mm – cm	Surface	Standard rigid cystoscope	Clinical
NBI	Absorption	None	mm – cm	Surface	Flexible cystoscope (5.5 mm) or standard rigid cystoscope	Clinical
CLE	Fluorescence	Fluorescein	1–3.5 μm	120 μm	Probe (0.85–2.6 mm)	Clinical/ investigational (in vivo)
OCT	Scattering	None	10–20 μm	~2.5 mm	Probe (2.7 mm)	Clinical/ investigational (in vivo)
Raman	Scattering	Optional (SERS)	—	2 mm	Probe (2.1 mm)	Investigational (in vivo)
UV	Fluorescence	None	mm – cm	Surface	Probe (3 mm)	Investigational (in vivo)
SFE	Reflectance + fluorescence	None	mm – cm	Surface	Scope/Probe (1.2 mm)	Investigational (ex vivo)

Abbreviations: CLE, confocal laser endomicroscopy; HAL, hexaminolevulinate; NBI, narrow band imaging; OCT, optical coherence tomography; PDD, photodynamic diagnosis; SERS, surface-enhanced Raman scattering; SFE, scanning fiber endoscopy; UV, ultraviolet.