Chapter 10

Recent Technological Advances in Cystoscopy for the Detection of Bladder Cancer

Byong Chang Jeong
Sungkyunkwan University, Seoul, South Korea

Chapter Outline

INTRODUCTION

Bladder cancer is the most common type of malignancy in the urinary tract showcasing a high recurrence rate and aggressive feature [1]. Most patients with bladder cancer are pathologically diagnosed with urothelial carcinoma [2,3]. Approximately 70% of patients with urothelial carcinoma in the urinary bladder have a superficial or non-muscle invasive tumor confined to mucosa or submucosa layers of the wall [2,3].

Since the 1930s, cystoscopy has been regarded as a fundamental diagnostic tool for detecting bladder cancer [4]. However, conventional cystoscopy such as the white light imaging system has a critical drawback when detecting small papillary tumors or carcinoma *in situ* (CIS) [5]. Actually, white light cystoscopy shows the 10%−20% of missing rates of these ill-defined lesions of bladder tumors. In this regard, non-muscle-invasive bladder cancers (NMIBC) show an early and high recurrence rate [3].

To overcome this limitation, technological advancements in endoscopic visualization of bladder cancers, such as narrow band imaging (NBI), fluorescence

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cystoscopy, and optical coherence, have been achieved [6]. Here, the clinical evidence supporting the use of these specific technologies are reviewed.

VARIOUS CYSTOSCOPIC FINDINGS OF BLADDER TUMOR

Various cystoscopic findings of bladder tumor are illustrated in Figs. 10.1–10.5.

NARROW BAND IMAGING

NBI, developed in 2005, is a high-resolution endoscopic optical image enhancement technology [7]. This novel tool can improve the visibility of microvasculatures or capillary networks [8]. NBI utilizes the light of two

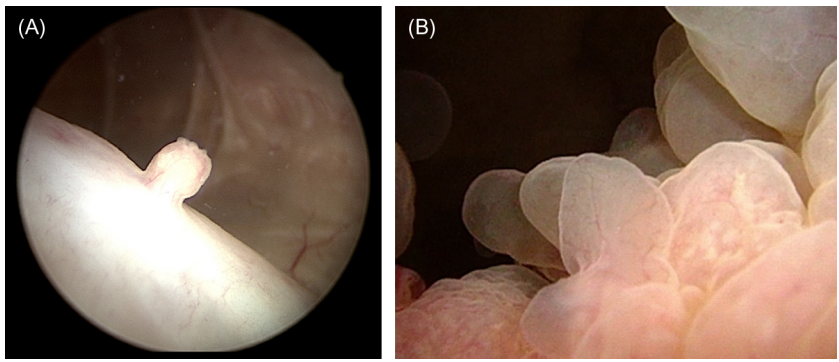

FIGURE 10.1 Benign tumors of the bladder. (A). Inverted papilloma. This benign tumor is typically a pedunculated or sessile polypoid lesion usually <30 mm in size, with a smooth or nodular mucosal surface. (B). Cystitis glandularis. It is a common finding in normal bladder and most often found in the trigone area. These benign tumors are usually present as cystic nests.

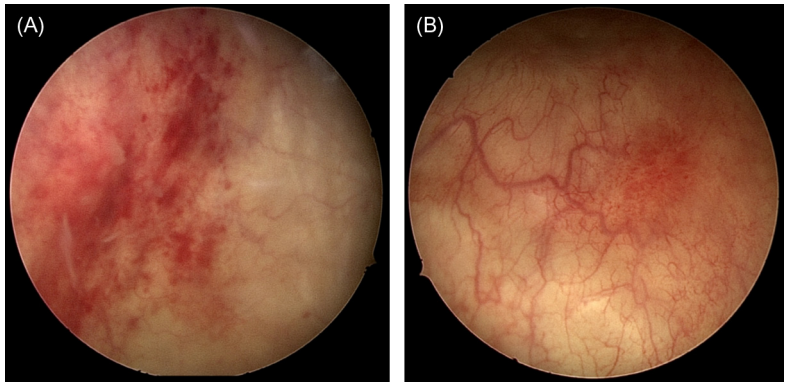

FIGURE 10.2 Non-muscle invasive bladder cancer. (A) Flat tumor appearance. (B) Carcinoma in situ. Carcinoma in situ is a high-grade, flat (velvety patch or moss-like growth) malignancy confined to the urothelium.

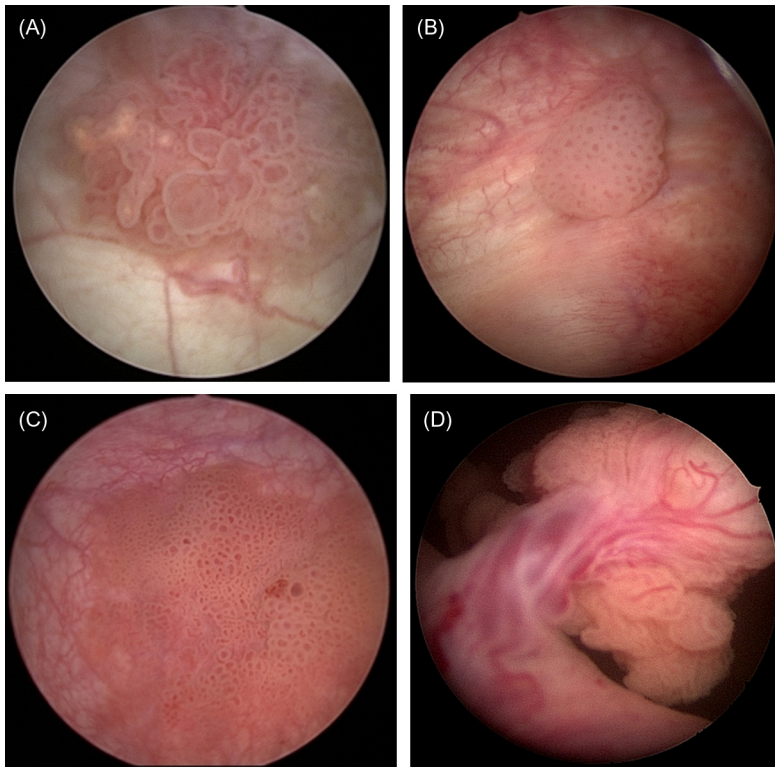

FIGURE 10.3 Papillary tumor appearance. Superficial papillary bladder tumors usually appear as small mushrooms growing out of the bladder wall (Ta low-grade tumor) (A, B). Flat (sessile) papillary bladder tumors (Ta high-grade tumor) (C). Small papillary tumor on a stalk (Ta low grade tumor) (D).

distinct wavelengths, blue (415 nm) and green (540 nm), both of which are well absorbed by hemoglobin [8]. The blue and green lights focus the capillary networks and subepithelial blood vessels, respectively [9]. Thus, blood vessels are shown in brown or green colors compared to the surrounding mucosa in NBI system, enhancing its visibility. Therefore, it is very useful in differentiating normal tissue from a more vascularized malignant tissue [9].

Since the first utilization of the NBI system in 2007 [10], several reports have shown the advantage of this system in detecting bladder cancer compared to standard white light cystoscopy. Li et al. [11] conducted a meta-analysis from seven prospective studies encompassing 1040 patients with NMIBC. Here, NBI showed an additional 24% and 28% detection rate of papillary tumors and CIS, respectively, when compared to white light cystoscopy. Xiong and colleagues recently published a meta-analysis of 25 studies and revealed that NBI had higher detection rates in NMIBC than white light

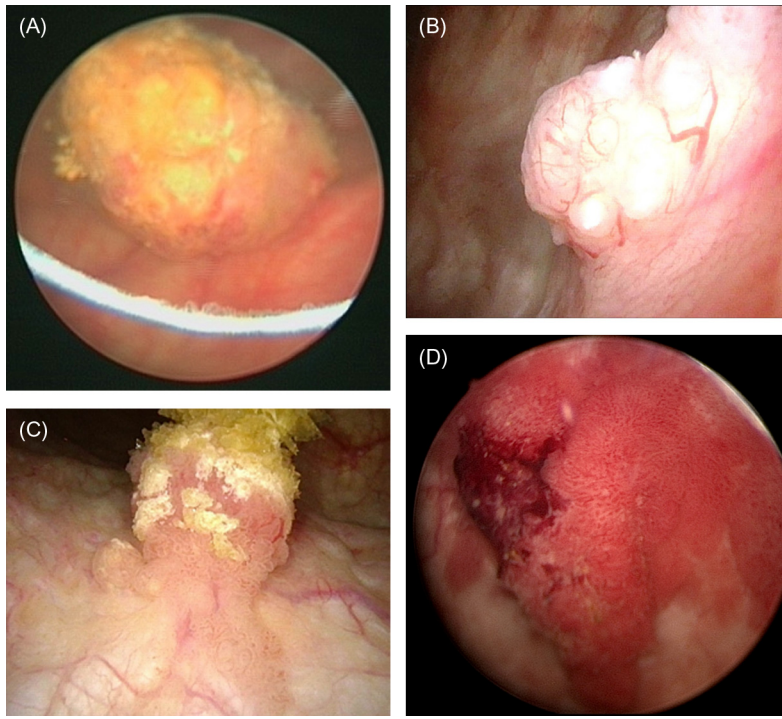

FIGURE 10.4 Solid tumor appearance. (A) Solid looking, small round shape tumors (T1 high-grade tumor). (B) Papillo-nodular tumors (T1 low-grade tumor). Papillary and sessile mixed, round tumors partly covered with calcification (C) and blood clot (D) (T1 high-grade tumor).

cystoscopy, and an additional 18.6% and 31.1% for superficial tumors and CIS lesion, respectively [12]. Furthermore, NBI significantly decreased the risk of the disease recurrence at 3 months [hazard ratio (HR) = 0.43, 95% confidence interval (CI) = 0.23−0.79] and 12 months (HR = 0.81, 95% CI = 0.69−0.95) after initial treatment.

However, the current limitation of NBI is the high frequency of false positives and subsequent negative biopsies [13]. In addition, the effects of NBI on oncological outcomes such as the progression and cancer-specific survival are still ill-defined [13]. Thus, further research is required to determine the routine use of the NBI system for endoscopic examination of bladder cancers (Fig. 10.6).

FLUORESCENCE CYSTOSCOPY

Fluorescent cystoscopy is a novel diagnostic tool using topical photosensitizers, 5-aminolevulinic acid (5-ALA), or hexyl-aminolevulinate (HAL), improving the ability in detecting bladder cancers, particularly small

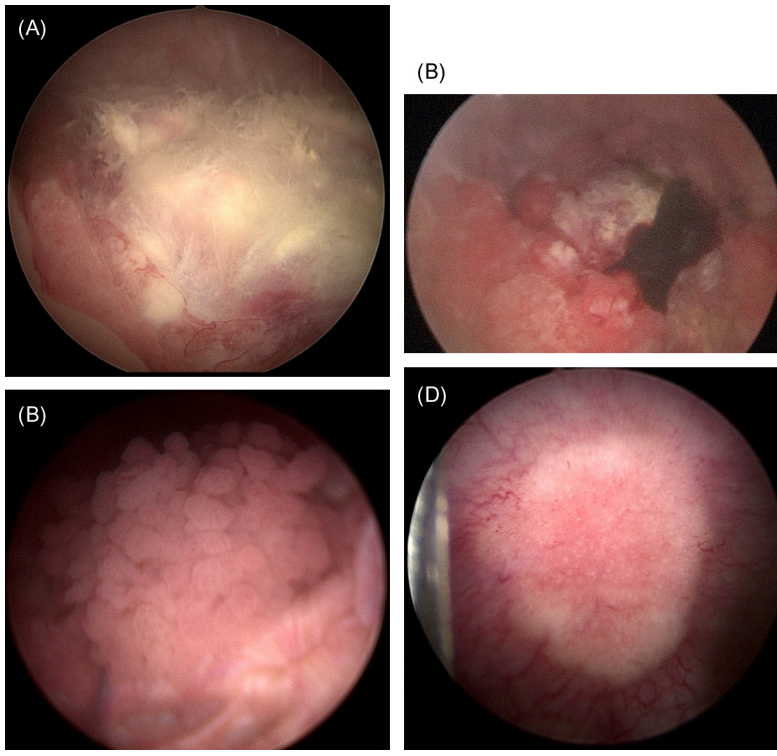

FIGURE 10.5 Invasive and metastatic bladder cancer. Muscle-invasive bladder cancer. Solid, infiltrating bladder tumor. (A) Its surface is wholly necrotic. (B) The normal vessel architecture has completely disappeared. (C) Large papillary bladder tumors. (D) Metastatic bladder tumor form gastric cancer.

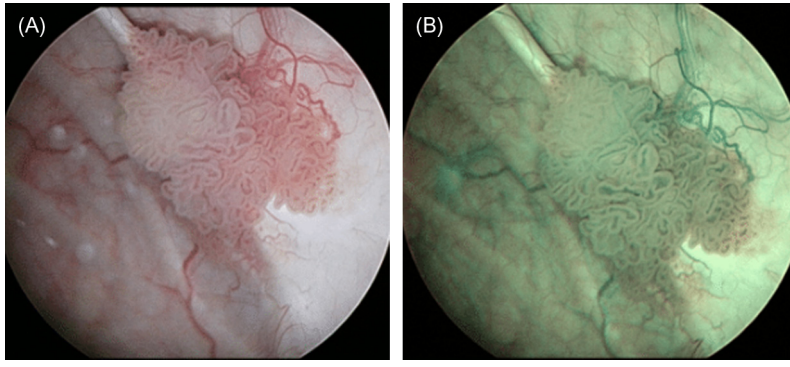

FIGURE 10.6 (A) White light cystoscopy image. (B) NBI image with enhanced contrast of vasculature.

papillary and CIS lesions [14]. After intravesical instillation of 5-ALA or HAL, there is a preferential uptake of these agents by precancerous and cancerous cells and they convert into photoactive porphyrin (protoporphyrin IX) [15]. When fluorescent blue light is illuminated on the urothelium of the urinary bladder, only red fluorescence is emitted from the abnormal urothelium [15]. This distinct feature allows the differentiation between normal and malignant tissue.

Many studies confirmed that fluorescent cystoscopy showed higher detection rates of bladder cancers when compared to the standard resulting in lower recurrence rates. Burger et al. [16] conducted a meta-analysis to clinically assess the ability of fluorescent cystoscopy to detect NMIBC and tumor recurrence. They showed that fluorescent cystoscopy significantly increased the detection rates and reduced the risk of recurrence at 9−12 months. More importantly, Chou et al. [17] investigated the comparative effectiveness of fluorescent cystoscopy and white light cystoscopy on oncological outcomes in patients with NMIBC. Notably, the authors reported that fluorescent cystoscopy was significantly associated with a risk reduction of disease recurrence at short-term [relative risk (RR) = 0.59], intermediate-term (RR = 0.70), and long-term follow-up periods (RR = 0.81). However, there were no significant differences of the disease progression rates and survival estimates between the two techniques.

Current evidence indicates that fluorescent cystoscopy can improve the detection rate of bladder cancer and reduce the recurrence compared to white light cystoscopy. However, further clinical trials are required to confirm its effects on the disease progression and survival outcome among bladder cancer patients (Fig. 10.7).

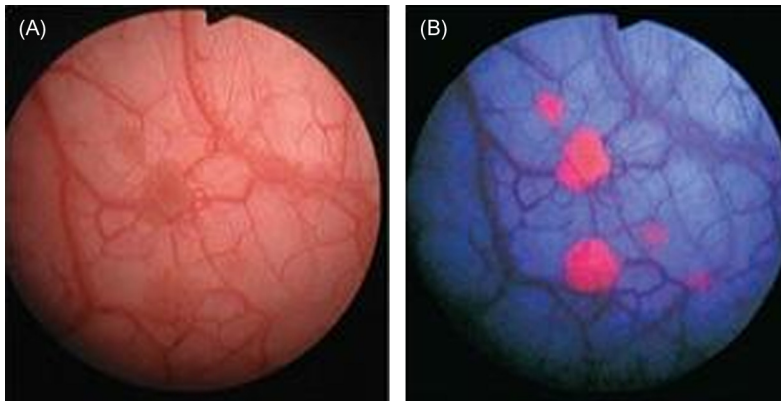

FIGURE 10.7 (A) White light cystoscopy alone. (B) Blue light cystoscopy as an adjunct to white light.

OPTICAL COHERENCE TOMOGRAPHY

Optical coherence tomography (OCT) is an emerging minimally invasive imaging technology using a near-infrared light to obtain cross-sectional images of the tissue [18]. In contrast to the low spatial resolution (70−1000 μm) of conventional noninvasive imaging tools such as ultrasonography or computed tomography, OCT produces higher resolution images using 10−20 μm of spatial resolution and 2−3 mm of imaging depths by calculating the magnitude and echo time delay of the unique backscattered light. [19]. Interestingly, OCT has been widely used in ophthalmology to examine the retina and has recently gained interest in the field of urology [19,20]. By inserting the probe via the working channel of a cystoscope, this attractive real-time imaging method can significantly differentiate the cancerous mucosa from normal urothelium of the urinary bladder by performing functional and structural analysis of the images [21].

Several reports have shown the ability of OCT to distinguish cancerous lesions from normal mucosa of the urinary bladder. The prospective single-center study by Schmidbauer et al. [22] investigated whether targeted OCT for the suspicious lesions on the standard cystoscopy or fluorescent cystoscopy potentiated the diagnostic accuracy for bladder cancer. The authors studied 66 patients with 232 lesions of NMIBC and discovered that the targeted OCT showed an additional 15%−20% detection rate of tumors compared to the white light or fluorescent cystoscopy alone. The sensitivity and specificity of targeted OCT were significantly higher than those without the combination of OCT (100% vs 87.9% and 87.5% vs 62.5%, respectively). Moreover, Goh and colleagues revealed that OCT had the ability to discriminate the clinical stage of bladder tumor in a real-time manner [23]. The authors evaluated 32 patients who underwent cystoscopic biopsy or transurethral resection of the bladder tumor and showed that the use of OCT in addition to the standard cystoscopy correctly distinguished Ta, T1, and T2 tumors with a sensitivity of 90%, 75%, and 100%, and a specificity of 89%, 97%, and 90%, respectively.

However, there are still unresolved limitations of this novel imaging tool in terms of bladder cancer detection including the risk of false-positive readings of bladder inflammatory lesions, the inability to take accurate images on large tumors with broadened involvement, and the equipped limited probe size with limited endoscopic view for whole urinary bladder wall [4]. Again, additional clinical evidence are required before applying this technology into the real-world clinical practice (Figs. 10.8 and 10.9).

OTHER EMERGING IMAGING TECHNOLOGIES

There are other advanced imaging technologies in the developing stage to improve the accuracy in detecting bladder cancer. Confocal laser

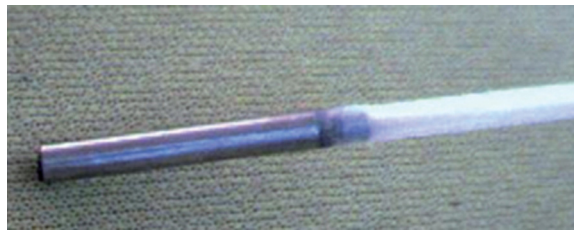

FIGURE 10.8 OCT probe inserted into the bladder via the working channel of the cystoscope sheath.

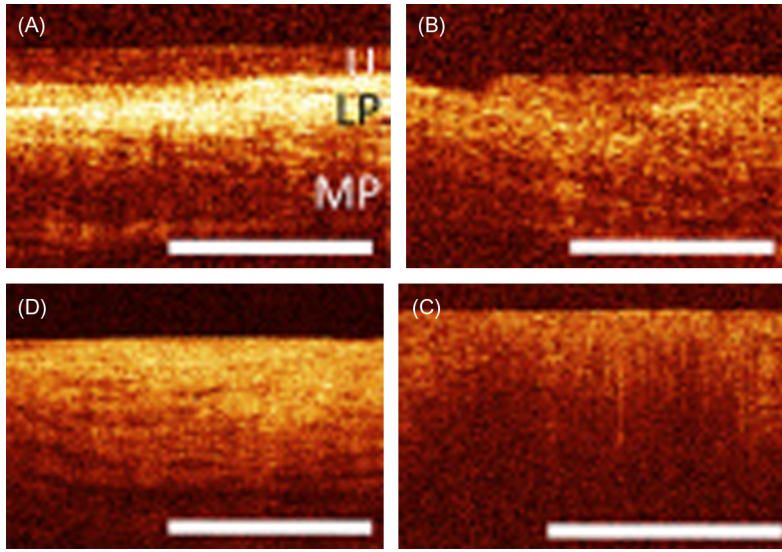

FIGURE 10.9 Layer of a healthy urinary bladder as generated by OCT. CIS: U + LP appear as single bright layer and MP is intact. T1: U + LP appear as single layer without clear demarcation with MP. T2: no evidence of horizontal structure. *CIS*, carcinoma in situ; *U*, urothelium; *LP*, lamina propria; *MP*, muscularis propria.

endomicroscopy (CLE) is the combined imaging tool with confocal microscopy and fiber optics with the highest resolution, up to 2−5 μm. [24]. CLE can obtain the microscopic, real-time, and histopathologic imaging data that provide optical biopsy in the suspicious lesions in vivo [25]. Two-photon laser microscopy is one of the fluorescence imaging techniques displaying the ability to detect autofluorescence of both cells as well as the extracellular matrix in the ultraviolet range and visualize the three-dimensional localization of target molecules in the living cells [26]. The ratio of distinct fluorescence of normal and malignant cells is used to differentiate them [27]. High-frequency endoluminal ultrasound shows a high resolution with significantly greater depth of penetration (up to 20 mm) improving the diagnostic

accuracy for the larger and invasive tumors [28]. Specific molecular imaging agents conjugated with fluorophores, such as fluorescently labeled CD47 antibody, improve the visualization of tumorous lesions, and also reduce the false-positive readings by the inflammatory changes in the urinary bladder. Further studies are required to determine the suitability of these emerging technologies for accurately detecting bladder cancer [29].

CONCLUSIONS

In this chapter, several novel endoscopic imaging modalities for diagnosing and surveilling bladder cancer are reviewed. These include NBI, fluorescence cystoscopy, optical coherence, and other emerging technologies. Though the new imaging tools still do not replace the pathological confirmation of specimens where additional trials are desirable for their clinical use, they hold great potential to accurately detect cancer and estimate the oncological outcomes among patients with bladder cancer in the near future.

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