



REVIEW

Narrow band imaging for bladder cancer



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Abstract Narrow band imaging (NBI) is a newly developed technology aiming to provide additional endoscopic information for patients with bladder cancer. This review focuses on the diagnostic accuracy and treatment outcome using NBI cystoscopy for the treatment of non-muscle invasive bladder cancer. Current results showed improved sensitivity of NBI cystoscopy compared to conventional white light cystoscopy, although lower specificity and increased false-positive results were reported using NBI cystoscopy. The treatment outcome using NBI technology in transurethral resection of bladder tumor had a positive impact while decreased number of residual tumors and tumor recurrence at follow-up were reported. In the future, the application of NBI technology might refine the treatment and follow-up protocol in patients with non-muscle invasive bladder cancer. However, this large scale prospective studies are required to confirm the real cost-effectiveness of this new technology.

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1. Introduction

Bladder cancer is the second most common genitourinary cancer and the fifth most common cancer in the United States with an estimated 74,690 new cases in 2014, while the median age at diagnosis was 73 years old [1]. The incidence of bladder cancer is 4 times higher in men than in women. Approximately 80% of bladder cancer was initially

diagnosed to be non-muscle invasive bladder cancer [2]. The standard care for non-muscle invasive bladder cancer (pTa, pT1, carcinoma *in situ*) is endoscopic evaluation and complete tumor resection [2]. However, the high recurrence rate and possibility for stage and grade progression in non-muscle invasive bladder cancer warrant a life-long surveillance. Surveillance includes screening for urine cytology and endoscopic examination on a regular basis [3]. Since the follow-up of non-muscle invasive bladder cancer depends mainly on accurate endoscopic evaluation, urologists are looking forward to have an ideal cystoscopy for the surveillance of non-muscle invasive bladder cancer. The ideal endoscopic image should be highly sensitive for cancer detection, clear identification between benign

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and malignant lesions and can identify stage and grade characteristically. Traditionally, white light cystoscopy is the cornerstone for evaluation of the lower urinary tract for more than a century and serves as the most cost-effective method to diagnose and detect the recurrence of bladder cancer [2]. However, it is difficult to detect small bladder cancer, such as small papillary tumors or carcinoma *in situ* using white light cystoscopy, which might be related to high recurrence rate after endoscopic resection (approximately 50%–90%) [4,5]. It is reported that up to half of patients with high grade pTa or pT1 disease might be under staged at first transurethral resection of bladder tumor [6], requiring a second look transurethral resection to evaluate the resected area during previous operation and trying to resect all suspected lesions to allow more accurate diagnosis and treatment protocol selection [7]. In order to facilitate the limitation of white light cystoscopy, some novel imaging techniques are developed to improve the detection of bladder cancer, such as narrow band imaging (NBI), photodynamic diagnosis and Storz Professional Imaging Enhancement System [8]. NBI is an optic enhancement technique which filters the white light into two different bandwidths, including blue (415 nm) and green (540 nm) spectrum. In the NBI mode, the light is strongly absorbed by hemoglobin and only penetrates the tissue superficially, which increases the identification of small capillaries and superficial tissue structures [9–11]. Since bladder tumors are vascular abundant structures, the tumors could appear in brown or green color against a white background under NBI scenario [12]. NBI technique has become a hot topic in recent years [13–17]. The aim of this review is to describe the outcome of diagnosis and treatment using NBI technology for the management of non-muscle invasive bladder cancer.

2. Diagnosis of bladder cancer

Traditionally, white light cystoscopy is the gold standard for the diagnosis of bladder cancer. However, the limitation of white light cystoscopy to detect small bladder tumors and carcinoma *in situ* resulted in the continuous investigation of novel imaging techniques in the past decade [8,12]. In 2008, the first published study suggested that improved detection rate of recurrent bladder cancer in NBI cystoscopy [12]. A total of 29 patients with recurrent non-muscle invasive bladder cancer were enrolled in this study. An additional 41% detection rate was found in NBI cystoscopy as compared to conventional white light cystoscopy. The authors concluded that NBI cystoscopy is highly valuable in the detection of both new and recurrent non-muscle invasive bladder cancer and a further investigation is warranted in more patients. In the same year, Herr and Donat [18] reported the outcome of NBI technology for the diagnosis of non-muscle invasive bladder cancer. A total of 427 patients were enrolled into this study while 103 patients had tumor recurrence. The overall recurrence rate was 24.1%. The detection rate of recurrent bladder tumor was 87.4% in white light cystoscopy and 100% in NBI cystoscopy. The additional detection rate was 12.6% found only in NBI cystoscopy. The average number of recurrent tumors detected by white light cystoscopy was 2.3 while 3.4 were

detected by NBI cystoscopy. In 2010, Tatsugami et al. [14] reported a prospective controlled study evaluating the efficacy of NBI cystoscopy for the detection of non-muscle invasive bladder cancer. A total of 104 patients were enrolled into this study. A total of 313 biopsies were taken for pathological examination. The incidence of malignancy identified only by NBI cystoscopy was 55.7%. In 26.9% of patients, bladder tumors were only identified by NBI cystoscopy. The authors concluded that NBI cystoscopy is a simple and effective method for identification of non-muscle invasive bladder tumors. In 2012, Zheng et al. [19] reported the clinical effective of NBI cystoscopy compared to white light cystoscopy in patients with bladder cancer. A total of 1022 patients were enrolled in this meta-analysis. The pooled sensitivity and specificity of NBI cystoscopy was 0.94 and 0.85 compared to 0.85 and 0.87 for white light cystoscopy, respectively. The pooled sensitivity and specificity for the diagnosis of carcinoma *in situ* was 0.93 and 0.77 for NBI cystoscopy. The odds ratio was 4.55 of NBI cystoscopy compared to white light cystoscopy. The authors concluded that NBI cystoscopy can provide higher diagnostic precision of non-muscle invasive bladder cancer than white light cystoscopy. In 2013, Li et al. [20] reported a systemic review and meta-analysis on the diagnostic rate using NBI technology in the diagnosis of non-muscle invasive bladder cancer. A total of seven studies including 1040 patients were reviewed while 601 patients with 1476 tumors were enrolled in this meta-analysis. The overall recurrence rate was 58.8%. An additional 17% of patients and 24% of tumors were detected using NBI cystoscopy. An additional 28% of carcinoma *in situ* was detected using NBI cystoscopy. The false-positive rate of cystoscopic biopsy revealed comparable results using either white light cystoscopy or NBI cystoscopy. The authors concluded that NBI cystoscopy might serve as an alternative diagnostic technique for non-muscle invasive bladder cancer. In 2015, Ye et al. [21] reported a prospective randomized and multi-center study evaluating the role of NBI and white light cystoscopy in detecting non-muscle invasive bladder cancer. A total of 384 patients were enrolled into this study and the incidence of non-muscle invasive bladder cancer was 20.3%. The sensitivity of NBI cystoscopy was 97.7% and 66.7% of white light cystoscopy. The authors concluded that NBI cystoscopy has a high sensitivity to detect and superior detection rate for the diagnosis of non-muscle invasive bladder cancer than white light cystoscopy. Although NBI cystoscopy has a higher detection rate for non-muscle invasive bladder cancer, it is also reported that the false positive findings are common following intravesical instillation of chemotherapeutic agents or other inflammatory condition, with the rates ranging from 32% to 36% [18,22]. In 2010, Herr [22] reported the preliminary results using NBI cystoscopy to evaluate the response following bacillie Calmette–Guerin therapy. A total of 61 patients were evaluated in this study while the overall recurrence rate was 36% (22/61). NBI cystoscopy could correctly detect tumors in 21 patients and only one patient with tumors had negative findings under NBI cystoscopy. The author concluded that NBI cystoscopy could provide better results in patients who had suspected residual tumors following bacillie Calmette–Guerin therapy. In 2016, Song et al. [23] reported the results of NBI cystoscopy early after

intravesical instillation of chemotherapeutic agents. The data revealed that similar sensitivity between NBI cystoscopy and white light cystoscopy (100% vs. 94.1%), but a significant lower specificity was found in NBI cystoscopy compared to white light cystoscopy (50% vs. 86.9%). The author concluded that NBI cystoscopy might result in unnecessary biopsies for the evaluation of recurrence early after intravesical instillation of chemotherapeutic agents. Although the sensitivity of NBI cystoscopy shows better results compared to white light cystoscopy, the low specificity (0.5–0.85) deserves further investigation regarding the accuracy rate of NBI cystoscopy in the diagnosis of bladder cancer [18–24].

3. Treatment of bladder cancer

The cornerstone management of non-muscle invasive bladder cancer is the transurethral resection of bladder tumor (TUR-BT) [4,5]. Since NBI cystoscopy could improve the detection rate of bladder tumors in patients with newly diagnosed or recurrent bladder cancer, it is reasonable to evaluate the therapeutic outcomes in NBI assisted TUR-BT [25–31]. In 2010, Naselli et al. [25] reported the treatment outcome in patients received white light TUR-BT followed by NBI TUR-BT. A total of 47 patients were enrolled into this study. The detection rate of tumor recurrence using white light TUR-BT was 21.3% (10/47) while 34.0% (16/47) in those received NBI TUR-BT. The authors concluded that NBI biopsies at the end of white light TUR-BT might enhance the identification of missed high grade residual or recurrent urothelial carcinoma of urinary bladder. In 2011, Cauberg et al. [26] reported the treatment outcome comparing white light TUR-BT and NBI TUR-BT in a matched cohort study. A total of 160 patients were retrospectively collected while 40 patients received NBI TUR-BT and 120 patients received white light TUR-BT. The data revealed the recurrence rate at first follow-up cystoscopy (3 months after transurethral resection) was 30.5% following white light TUR-BT and 15.0% following NBI TURBT. The odd ratio was 2.7 in patients received white light TUR-BT. In 2012, a randomized controlled trial was conducted by Naselli et al. [27] to assess the recurrence rate of non-muscle invasive bladder cancer after NBI TUR-BT. A total of 148 patients were randomized into received either white light TUR-BT (72 cases) and NBI TUR-BT (76 cases). The overall detection rate of non-muscle invasive bladder cancer was 1.36 per person in white light TUR-BT group and 1.55 per person in the NBI TUR-BT group, respectively. The incidence of false-positive findings was 28% in the NBI TUR-BT group and 21% in the white light TUR-BT group, respectively. The 1-year recurrence risk was 32.9% in the NBI TUR-BT group and 51.4% in the white light TUR-BT group. The authors concluded that TUR-BT performed under NBI technology could reduce the recurrence risk by at least 10% at the first year. In 2015, Kobatake et al. [28] reported the advantage of NBI TUR-BT for the management of non-muscle invasive bladder cancer. A total of 135 patients with non-muscle invasive bladder cancer were enrolled into this study. All patients did not receive additional postoperative treatment and were followed up for more than 1 year. The sensitivity is 95% in

the NBI TUR-BT group compared to 70% in the white light TUR-BT group. The specificity was 77.2% in the NBI TURBT group compared to 89.7% in the white light TUR-BT group. The 3-month recurrence rate was 3.5% in the NBI TUR-BT group compared to 3.8% in the white light TUR-BT group. The 1-year recurrence rate was 21.1% in the NBI TUR-BT group compared to 39.7% in the white light TUR-BT group. The authors concluded that NBI TUR-BT was more advantageous than white light TUR-BT for patients with non-muscle invasive bladder cancer. Although treatment outcomes are more favorable in patients with non-muscle invasive bladder cancer received NBI TUR-BT, the variability between different urologists and lack of standardized consensus for tumor discrimination under NBI might limit the future perspectives in NBI TUR-BT [15,25].

4. Cost-effectiveness of NBI technology

The application of NBI technology in the diagnosis and treatment of non-muscle invasive bladder cancer in the past decade shows a promising result compared to conventional white light technology. However, the cost-effectiveness of this novel technology should be concerned during daily clinical practice although limited data are available from world literature. NBI technology is marketed by Olympus™ as an additional function of the current endoscopic facilities. The cost of one complete set of Olympus™ endoscopic tower is around 60,000–90,000 USD including the light source, video processor and one flexible cystoscopy. It is reported that about 230–500 USD will be saved per year based on the decreased disease recurrence, although the cost of pathological analysis, additional operative time and possible patient factors do not include in total health care utilization [8]. The real cost-effectiveness of NBI technology compared to conventional white light technology in the diagnosis and treatment of non-muscle invasive bladder cancer deserves further investigation in the near future.

5. Conclusion

NBI technology facilitates the diagnosis and treatment of non-muscle invasive bladder cancer. More large-scale, randomized trials are needed to evaluate the diagnostic and treatment accuracy of NBI technology and the possibility to redefine the follow-up protocol in patients with non-muscle invasive bladder cancer.

Conflicts of interest

The authors declare no conflict of interest.

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