

Comparison of 3-Month Recurrence Rates after White-Light versus Narrow-Band Imaging Transurethral Resection for Non-Muscle Invasive Bladder Cancer: A Prospective, Randomized Control Trial

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Background: Narrow-band imaging [NBI] is a new imaging modality that filters white light into short bandwidths of blue light (415 nm) and green light (540 nm). This technology was developed to enhance the detection and visualization of bladder cancer. For this reason, a transurethral resection of a bladder tumor [TUR-BT] with NBI may reduce the 3-month recurrence rate when compared to a TUR-BT with standard white light imaging [WLI].

Objective: To evaluate the 3-month recurrence rate of NBI TUR-BT versus WLI TUR-BT for the treatment of non-muscle invasive bladder cancer [NMIBC] in the Thai population.

Materials and Methods: A randomized, controlled trial of 123 patients suspected to have NMIBC was conducted between January 2015 and August 2016. The patients were randomized into standard WLI TUR-BT and NBI TUR-BT groups. Surveillance cystoscopy and urine cytology were evaluated at the 3-month follow-up period. The patients' baseline characteristics, cancer-free rates, and complications were recorded.

Results: Eighty-three TUR-BT were excluded due to the following, a synchronous upper urinary tract tumor, post-operative intravesical therapy before surveillance, a tumor too large to complete resection, a tumor was a benign lesion, muscle invasive disease, and lost follow-up patients. One hundred fifty eight TUR-BTs were performed during the study period. After exclusion, there were 44 NBI TUR-BTs and 31 WLI TUR-BTs, respectively. The mean age at enrollment was 75 years in the NBI TUR-BT group and 66 years in the WLI TUR-BT group. Tumor characteristics and complication rates were similar in both groups ($p = 0.15$ and 0.692 , respectively). After the 3-month follow-up period, the recurrence rate was 31.8% (11 of 44 patients) in the NBI TUR-BT group and 61.3% (19 of 31 patients) in the WLI TUR-BT group ($p = 0.011$).

Conclusion: This is the first study of NBI TUR-BT in the Thai population. The results demonstrated that using an NBI TUR-BT had significantly reduced recurrence rates three months after a TUR-BT for NMIBC and had comparable post-operative complications when compared to WLI TUR-BT.

Keywords: Bladder cancer, Narrow band imaging, TUR-BT

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Bladder cancer is the eighth most common cancer in Thailand with the prevalence of 4.5/100,000 in males and 1.2/100,000 in females. The mortality rate is 2.2/100,000 in males and 0.6/100,000 in females⁽¹⁾. The major challenges for the treatment of non-muscle invasive bladder cancer [NMIBC] are the high

recurrence rates and chances of disease progression. The standard management of NMIBC is a transurethral resection of the bladder tumor [TUR-BT] under white light imaging [WLI]⁽²⁾. For a low grade Ta lesion, the recurrence and progression rates are 50% to 70% and 5%, respectively⁽³⁾. In contrast, a high grade T1 lesion has a recurrence and progression rates of more than 80% and 50%, respectively⁽⁴⁾.

Narrow-band imaging [NBI] is a new technology designed to enhance the visualization of bladder cancer by filtering white light into short bandwidths of blue

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light (415 nm) and green light (540 nm) that penetrate the superficial bladder tissue and are strongly absorbed by hemoglobin in the capillary vessels^(5,6).

From the literature, cystoscopy with NBI has a higher detection rate of bladder tumor and carcinoma in situ when compared to cystoscopy with standard WLI⁽⁷⁻¹¹⁾. Furthermore, TUR-BT with NBI reduces bladder cancer recurrence rates and improves the treatment outcomes of TUR-BT⁽¹²⁾.

However, most NBI studies have been conducted in western countries, especially in Europe and the United States, and there are very limited data in Asian populations. Therefore, the authors hypothesized that TUR-BT with NBI can improve the treatment outcomes of NMIBC by increasing the chances of tumor detection and complete resection. The objective of the present study was to evaluate the recurrence rates of NMIBC three months after a TUR-BT was performed.

Materials and Methods

Study design and participants

The prospective, randomized, single-blind control study at Ramathibodi Hospital, Mahidol University. The authors estimated the sample size of 200 randomized patients to give 80% power at the 5% significant level (two-side) based on the recurrence rates of 39.7% in the NBI TUR-BT group and 21.1% in the WLI TUR-BT group (alpha 0.05, beta 0.9)⁽¹³⁾. Between January 2015 and August 2016, 158 patients suspected of having bladder cancer based on cystoscopy or bladder imaging were enrolled in the present study. After enrollment, patients were randomly allocated with a computerized random permute block to TUR-BT with NBI or TUR-BT with WLI. Both surgeons and patients were blinded from randomization before the procedure. NBI TUR-BT was done using an EVIS EXERA II CLV-180 (Olympus). All TUR-BTs were done by experienced urology staff or by third-year urology residents under supervision.

The inclusion criteria were histopathology-visualized NMIBC and complete resection of the visualized tumor. The exclusion criteria were muscle invasive bladder cancer, incomplete tumor resection, histopathology-visualized non-cancerous lesion, synchronous upper urinary tract cancer, and post-operative intravesical therapy before surveillance cystoscopy. Patient demographic data, tumor characteristics, cystoscopic findings at three months, and complications were recorded.

After exclusion, the authors analyzed 37 patients that underwent 44 operations in the NBI TUR-BT arm,

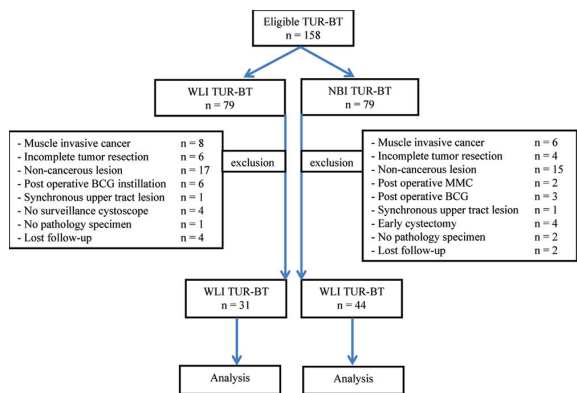


Figure 1. Flow chart and criteria for selection. TUR-BT: transurethral resection of bladder tumor; WLI: white light imaging; NBI: narrow band imaging; BCG: Bacillus Calmette-Guerin; MMC: Mitomycin C.

and 25 patients that underwent 31 operations in the WLI TUR-BT arm (Figure 1). All eligible patients in the present study signed the informed consent before randomization. The present study was approved by the Mahidol University Institutional Review Board for Ethics in Human Research.

Pathological examination

The specimens were sent to pathologists to be individually analyzed, and the pathologists were blinded to the TUR-BT procedure (WLI or NBI). The pathological staging was classified based on the 2009 TMN staging classification (AJCC cancer staging manual seventh edition), and the grading system was set forth by the World Health Organization's 2004 classification^(14,15).

Primary and secondary end points

The primary end point of the present study was to evaluate the 3-month recurrence rates after NBI TUR-BT versus those after WLI TUR-BT. The recurrence rate was defined by all visual abnormalities in the bladder mucosa at the time of the surveillance cystoscopy or by a positive urine cytology in those cases where carcinoma in situ of the bladder was suspected.

The secondary end point of the present study was to evaluate the complication rates after NBI TUR-BT compared to those after WLI TUR-BT. The complications included bladder perforations (both extraperitoneal or intraperitoneal perforation), clot retentions that required endoscopic treatment, intra-operative or post-operative bleeding that required a blood transfusion, and urinary tract infections.

Follow-up scheme

Three months after their TUR-BT, all patients underwent an outpatient surveillance cystoscopy, and urine was collected for a cytology analysis to detect bladder tumor recurrence.

Statistical analysis

Statistical analysis was performed using independent t-test, Chi-square, Fisher's exact test, and the Mann-Whitney test to analyze patient demographic data, tumor characteristics, and complication rates. The recurrence rates at three months was analyzed with Chi-square and Fisher's exact test. Univariate and multivariate analyses were used to identify factors associated with a 3-month recurrence. All statistical analyses were performed with Stata v.14 (StataCorp LP). A *p*-value smaller than 0.05 was considered to be a statistically significant difference.

Results

Between January 2015 and August 2016, 158 TUR-BTs were performed, and 31 WLI TUR-BT and 44 NBI TUR-BT cases met the inclusion criteria. The reasons for exclusion are shown in Figure 1. Most patients were discharged from the hospital two days after surgery, and the average duration of catheterization was one day. The baseline of the patients' characteristics included in the present study is shown in Table 1. There was no significant difference in patient comorbidities and bladder cancer risk factors between the two groups except the patients' ages; patients in the NBI TUR-BT group were older than those in the WLI TUR-BT group (the median age was 75 versus 66, *p* = 0.005). The operative findings and histopathological characteristics between the two groups are shown in Table 2. There were no significant differences in the pathological staging and grading of bladder tumors between the two groups (*p* = 0.14 and 0.15, respectively).

There was no significant difference in the complication rates between the groups (6.45% versus 11.36%, *p* = 0.692). There were two extraperitoneal bladder perforations in the WLI TUR-BT group, neither of which required further treatment except for prolonged period of catheterization. In the NBI TUR-BT group, there were four extraperitoneal bladder perforations that did not require further treatment. Additionally, there was one urethral injury that was also treated with prolonged catheterization.

The recurrence rates at three months were significantly higher in the WLI TUR-BT group when

Table 1. Baseline patient characteristics

Demographic data	WLI (n = 31)	NBI (n = 44)	<i>p</i> -value
Age, median (IQR)	66 (59 to 74)	75 (67.5 to 81.5)	0.005
Height (cm), mean (SD)	159.23 (9.11)	161.91 (7.81)	0.175
Weight (kg), median (IQR)	61 (46 to 74)	60 (53.5 to 73.5)	0.474
Sex, n (%)			0.090
Male	20 (64.52)	36 (81.82)	
Female	11 (35.48)	8 (18.18)	
Underlying, n (%)			
DM	7 (22.58)	18 (40.91)	0.097
HT	14 (45.16)	33 (75.00)	0.009
DLP	13 (41.94)	22 (50.00)	0.491
CVD	3 (9.68)	11 (25.00)	0.134
Respiratory disease	3 (9.68)	6 (13.64)	0.728
Neurological disease	6 (19.35)	7 (15.91)	0.698
CKD & ESRD	8 (25.81)	9 (20.45)	0.586
Clinical of patient, n (%)			
No family history of bladder cancer	31 (100)	44 (100)	-
Smoke	15 (48.39)	30 (68.18)	0.085
Drink	16 (51.61)	30 (68.18)	0.147
Radiation	0 (0.00)	0 (0.00)	-
History of UTI	1 (3.23)	1 (2.27)	0.999
History of CMT	2 (6.45)	2 (4.55)	0.999
ASA class, n (%)			0.240
Class 1	4 (12.90)	1 (2.27)	
Class 2	10 (32.26)	11 (25.00)	
Class 3	13 (41.94)	26 (59.09)	
Class 4	4 (12.90)	6 (13.64)	

WLI = white light imaging; NBI = narrow-band imaging; DM = diabetes mellitus; HT = hypertension; DLP = dyslipidemia; CVD = cardiovascular disease; CKD = chronic kidney disease; ESRD = end-stage renal disease; UTI = urinary tract infection; CMT = Charcot-Marie-Tooth disease; ASA = American Society of Anesthesiologists

Table 2. Operative findings and histopathological reports of bladder tumor

Demographic data	WLI (n = 31)	NBI (n = 44)	<i>p</i> -value
Foci of tumor, n (%)			0.999
One	14 (45.16)	19 (43.18)	
More than one	17 (54.84)	25 (56.82)	
Operative finding, n (%)			0.183
Sessile	5 (16.13)	5 (11.36)	
Papillary	24 (77.42)	39 (88.64)	
Velvety lesion	2 (6.45)	0 (0.00)	
Size of tumor, n (%)			0.224
<1 cm	6 (19.35)	16 (36.36)	
1 cm	13 (41.94)	12 (27.27)	
>1 cm	12 (38.71)	16 (36.36)	
Pathologic stage, n (%)			0.171
Tis	2 (6.45)	0 (0.00)	
Ta	22 (70.97)	37 (84.09)	
T1	7 (22.58)	7 (15.91)	
Pathological grade, n (%)			0.091
Low grade TCC	15 (48.39)	30 (68.18)	
High grade TCC	14 (45.16)	14 (31.82)	
CIS	2 (6.45)	0 (0.00)	

WLI = white light imaging; NBI = narrow-band imaging; TCC = transitional cell carcinoma; CIS = carcinoma in situ

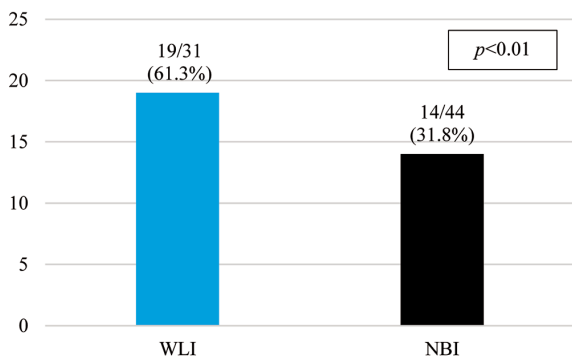


Figure 2. Recurrent tumors at 3-month surveillance.

compared with those of the NBI TUR-BT group ($p = 0.011$) as shown in Figure 2. A bladder tumor was found in 19 of the 31 (61.3%) patients treated by WLI TUR-BT versus 11 of 44 (31.8%) patients treated by NBI TUR-BT. The positive urine cytology for urothelial cancer did not show a significant difference between

the two groups ($p = 0.69$). However, at the time of surveillance, the urine cytology was not collected in 20 patients of the WLI TUR-BT group, and in 29 patients of the NBI TUR-BT.

Univariate and multivariate analyses were evaluated to identify the factors associated with the 3-month recurrence rates after TUR-BT (Table 3). The NBI TUR-BT group had better treatment outcomes in both univariate and multivariate analyses when compared to the WLI TUR-BT group with regard to 3-month recurrence rates (adjusted OR 0.117, 95% CI 0.041 to 0.334, $p < 0.001$). The other factors, including diabetes mellitus and dyslipidemia, were statistically significant in the univariate analysis. However, only dyslipidemia showed a statistically significant difference in the multivariate analysis (adjusted OR 9.019, 95% CI 2.753 to 29.555, $p < 0.001$).

Discussion

The standard treatment for NMIBC is TUR-BT.

Table 3. Univariate analysis and multivariate analysis for factors associated with 3-month recurrence

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>p</i> -value	Adjusted OR	95% CI	<i>p</i> -value
Age	1.019	0.978 to 1.062	0.365	1.030	0.973 to 1.091	0.298
DM	2.597	0.956 to 7.053	0.061	2.061	0.622 to 6.827	0.236
HT	1.237	0.470 to 3.256	0.666	0.886	0.240 to 3.264	0.856
DLP	4.168	1.554 to 11.175	0.005	9.019	2.753 to 29.555	<0.001
CKD & ESRD	0.497	0.166 to 1.490	0.212	0.396	0.104 to 1.509	0.175
Foci of tumor						
One	1.000	-	-	1.000	-	-
More than one	1.618	0.662 to 3.955	0.291	2.437	0.775 to 7.665	0.128
Operative finding						
Sessile	1.000	-	-	1.000	-	-
Papillary	0.539	0.163 to 1.786	0.313	0.405	0.089 to 2.056	0.275
Valvety lesion	-	-	-	-	-	-
Size of tumor						
<1 cm	1.000	-	-	1.000	-	-
1 cm	2.218	0.752 to 6.542	0.149	3.100	0.841 to 11.424	0.089
>1 cm	1.028	0.346 to 3.061	0.959	1.535	0.405 to 5.8140	0.528
Pathologic stage						
Tis	1.000	-	-	1.000	-	-
Ta	0.989	0.082 to 11.937	0.993	1.026	0.079 to 13.296	0.984
T1	1.267	0.087 to 18.291	0.862	1.349	0.076 to 23.955	0.838
Pathological grade						
Low grade TCC	1.000	-	-	1.000	-	-
High grade TCC	1.038	0.414 to 2.604	0.936	0.489	0.126 to 1.905	0.303
CIS	1.012	0.078 to 13.005	0.993	0.593	0.222 to 1.579	0.296
Method						
WLI	1.000	-	-	1.000	-	-
NBI	0.266	0.118 to 0.601	<0.010	0.117	0.041 to 0.334	<0.001

CI = confidence interval; OR = odd ratio; WLI = white light imaging; NBI = narrow-band imaging; DM = diabetes mellitus; HT = hypertension; DLP = dyslipidemia; CKD = chronic kidney disease; ESRD = end-stage renal disease; TCC = transitional cell carcinoma; CIS = carcinoma in situ

However, the tumor-free rate following a TUR-BT varies between 50% to 70%⁽³⁾. To improve the efficacy of TUR-BT, a complete tumor resection is one of the most important key factors. Nonetheless, small papillary lesions or a carcinoma in situ (high grade flat lesion) could be missed by WLI during a TUR-BT. NBI is a new technology that improves visualization, and it increases the chances of tumor detection and eventual, complete tumor resection. Our study is the first NBI study in the Thai population that aimed to evaluate the efficacy of NBI in improving tumor-free rates following a TUR-BT. The strength of our study is its prospective, randomized study that will minimize other confounding factors. The authors found that there was a significant decrease in tumor recurrence rates at the 3-month cystoscopy and no increase in complication rates in the NBI TUR-BT group. Our findings support the beneficial effects of a TUR-BT with NBI as well as the hypothesis that the procedure enhances detection of small abnormal bladder lesions that may be overlooked during a TUR-BT with WLI. Therefore, an NBI TUR-BT can decrease early tumor recurrence and possibly increase long-term survival of NMIBC.

In addition, the authors also excluded other confounding factors that usually affect the recurrence rates of bladder tumor such as concomitant upper urinary tract urothelial cancer or receiving intravesical therapy such as mitomycin C and BCG. In the present study, the difference in the recurrence rates after a TUR-BT was due to the differences in imaging modalities.

Many studies have been documented that fluorescence-assisted cystoscopy and TUR-BT also enhances the visualization of abnormal lesions from the normal lining of the bladder mucosa. This technique significantly improves detection rates and decreases recurrence rates when compared with standard WLI⁽¹⁶⁻²⁰⁾. However, the major disadvantage of fluorescent cystoscopy is that physicians need to instill a photosensitizing agent into the patient's bladder one hour before the cystoscopy or the TUR-BT. This technique is not practical in Thailand, especially in high volume patient hospitals as it takes longer to complete than the procedure itself. Additionally, the patients must pay for the extra cost of the instillation agent. On the contrary, NBI imaging can be used during a routine cystoscopy or a TUR-BT without any prior instillation.

The present study confirmed that TUR-BT with NBI showed significant decreases in 3-month recurrence rates on both univariate and multivariate analyses. There is a potential benefit to bladder cancer patients with the routine use of NBI for surveillance

cystoscopy or for TUR-BT. However, the present study had several limitations. First, the data for the urine cytology at the 3-month follow-ups were lost in some patients, so the effect of an NBI TUR-BT on the treatment of a carcinoma in situ could not be analyzed. Second, the duration for the follow-up was three months, so the patients' long-term survival and the progression rates could not be compared between the two groups. Because of this limitation, the cost effectiveness between an NBI TUR-BT and a WLI TUR-BT could not be directly compared. Further long-term studies are needed to draw these conclusions.

In the future, large scale, prospective, multicenter, randomized control trials with long-term follow-up are necessary to further confirm the advantages of NBI. The authors hope that this technology will increase recurrence-free survival rates, improve the quality of life due to decreased frequency of surveillance cystoscopy and surgery, offer cost effectiveness, and postpone or avoid intravesical therapy due to a complete tumor resection.

Conclusion

This is the first study of TUR-BT with NBI in the Thai population. The results demonstrated that NBI TUR-BT showed significant decrease in recurrence rates and comparable post-operative complications for NMIBC three months after the TUR-BT when compared with those of WLI TUR-BT.

What is already known on this topic?

Bladder cancer is a common type of cancer in the Thai population. The major challenges for the treatment of NMIBC are the high rates of recurrence and the chance of disease progression. NBI is a new technology that enhances the visualization of bladder cancer that can improve treatment outcome. From previous studies, it has been shown that NBI TUR-BT significantly reduces recurrence rates and improves recurrence-free survival compared with standard WLI TUR-BT^(13,21-23). Most NBI studies are conducted in western countries, especially in Europe and the United States, but there are very limited data in Asian and Thai populations regarding this imaging modality.

What this study adds?

This is the first study of its kind in Thailand. The study showed that TUR-BT with NBI significantly reduced recurrence rates when compared to the standard TUR-BT with WLI. The authors hope that performing NBI TUR-BT may reduce treatment costs

and improve the survival rates of bladder cancer patients. However, studies with large, multi-center, randomized control trials with long-term follow-up schemes are needed in the future to support the impacts and outcomes of NBI TUR-BT.

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Potential conflicts of interest

The authors declare no conflict of interest.

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