

# A Comparison of the Progression and Recurrence Risk Index in Non-Muscle-Invasive Bladder Tumors Detected by Narrow-Band Imaging Versus White Light Cystoscopy, Based on the EORTC Scoring System

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## Abstract

**Background:** Transitional cell carcinoma of the bladder, the second most common urologic malignancy, is amenable to early diagnosis. This study presents the potential prognostic benefit for a less invasive modification to the standard endoscopic approach.

**Objectives:** To evaluate the risk index for the progression and recurrence of additional tumors detected with narrow-band imaging (NBI) cystoscopy compared to standard white light imaging (WLI) cystoscopy in non-muscle-invasive bladder cancer (NMIBC), based on the European organization for research and treatment of cancer (EORTC) scoring system.

**Patients and Methods:** Patients with NMIBC, who were scheduled for resection between May 2012 and May 2013, were studied and mapped under NBI and WLI cystoscopy by independent surgeons prior to resection. Detection rates and tumor characteristics, including EORTC progression and the recurrence risk index, were compared.

**Results:** Fifty patients, aged  $63.86 \pm 10.05$  years, were enrolled. The overall detection rate was 98.9% for NBI vs. 89.4% for WLI ( $P = 0.001$ ), and the false-positive rates were 9.6% and 5.8%, respectively ( $P = 0.051$ ). Ten tumors were detected by NBI alone, including four grade I tumors, four grade III tumors, and two carcinomas in situ. The tumor progression index was not significantly reduced with NBI compared to WLI ( $P > 0.05$ ); however, the recurrence index was significantly lower in the NBI group ( $P < 0.05$ ).

**Conclusions:** NBI cystoscopy improved the detection rate. Although false positives were more common with NBI, this was not statistically significant. NBI found additional aggressive tumors, which underscores the impact of detection in EORTC recurrence risk scoring.

**Keywords:** Narrowband Imaging, EORTC Score, Urothelial Carcinoma, Bladder Cancer, Transitional Cell Carcinoma, Cystoscopy, Recurrence

## 1. Background

Bladder cancer is the fourth most common cancer among males in Iran (1). More than 60000 new cases are recorded each year, leading to approximately 13000 deaths (2). More than 70% of bladder cancers present as moderate-to-well-differentiated non-muscle-invasive papillary bladder cancer (NMIBC), and are treated with endoscopic transurethral resection (TUR). Fifty percent of these patients suffer a recurrence, and 5% - 25% progress to muscle-invasive cancer after repeated recurrences. The progression rate increases to 53% in high-grade bladder cancer (3).

The high rate of recurrence is a major challenge in NMIBC. These recurrences are categorized as either 'true' recurrence due to aggressive tumor biology or implantation of floating cancer cells, or as residual tumors that are likely overlooked on the initial TUR, including carcinoma in situ (CIS) and small or flat urothelial malignancies. The latter underlines the impact of TUR quality (2, 4). Therefore, improved TUR techniques can help prevent recurrences.

TUR with white-light imaging (WLI) is the current standard diagnostic and therapeutic procedure for NMIBC. However,

WLI is not without drawbacks, most notably the possibility of missing small papillary tumors or CIS (4, 5). This emphasizes the need for better techniques to detect NMIBC and to improve TUR quality. For this purpose, several new optical detection methods have been developed, including photodynamic diagnosis (PDD) and narrow-band imaging (NBI).

NBI is an image-processing modality based on filtering white light down to two narrow bandwidths of 415 and 540 nm, which correspond to the visible blue and green light spectra, respectively. These wavelengths are preferentially absorbed by hemoglobin, enhancing the perceptible contrast between normal urothelium and tumor. In contrast to PDD, NBI does not require fluorescent agents to improve the visualization of vascularized mucosal lesions, such as NMIBC (6).

## 2. Objectives

NBI has recently been applied for the cystoscopic diagnosis of NMIBC (6). However, whether utilizing this method can actually impact the risk of recurrence and progression, based on tables (7) proposed by the Euro-

pean organization for research and treatment of cancer (EORTC), has not been addressed to date, and is what this study was devised to answer.

### 3. Patients and Methods

We performed a prospective study to compare NBI versus WLI cystoscopy leading up to the resection of bladder tumors. Consecutive consenting patients with bladder cancer who were scheduled for restaging TUR (re-TUR) at our center between May 2012 and May 2013 were enrolled. The study was approved by the institutional medical ethics committee.

#### 3.1. Study Procedure

All surgeries were carried out under general or spinal anesthesia. We used a 24 Ch rigid endoscope (Olympus medical systems, Tokyo, Japan) connected to an Olympus Evis Exera II xenon light source. Switching from WLI to NBI was effectuated by pushing a button on the light source. Each patient was randomly assigned to one of two surgeons, who examined the bladder under WLI cystoscopy and mapped the targets onto a diagram to represent the number and estimate the size. The other surgeon subsequently repeated the task, using NBI cystoscopy. The procedures (WLI or NBI) were randomly assigned to the two surgeons, who were each unaware of the other's findings at this stage. The surgeons independently indicated the number and location of tumors or suspicious areas on separate bladder diagrams. Next, one of the two surgeons would proceed to thoroughly resect the tumors based on these templates, first under WLI, followed by NBI. Specimens obtained from areas topographically agreed upon by both imaging methods were collected as one sample, and those uniquely found by one or the other technique were numbered separately. All samples were examined by our institution's pathology department. Stage and grade were defined according to the tumor node metastasis 2002 (8) classifications and the world health organization 1973 (9) classifications, respectively. Both the 1973 and the 2002 WHO grading systems were used in our study because the calculator itself was originally based on a study by Sylvester et al. (7) that utilized both grading systems. The risk of tumor progression and recurrence was then defined by the EORTC risk score for progression and recurrence (7).

#### 3.2. Outcome Measures and Statistics

The primary outcome was the mean number of urothelial carcinomas detected per patient by WLI and NBI. Counting was based on the diagrams. In addition, the detection rates (i.e. the number of tumors detected by one technique divided by the total number of tumors detected), as well as the false-positive rates (the number of pathologically benign lesions detected by one technique divided by the total number of lesions detected by that technique), were compared. The risk of progression and recurrence according to EORTC risk score was evaluated in both groups. Sta-

tistical analysis was performed using the statistical package for social sciences, version 18.0 (SPSS, Chicago, IL, USA).

#### 3.3. Ethical Issues

None of the authors has any commercial financial incentive associated with publishing this manuscript, and the study was not supported by any extra-institutional funding, specifically that provided by commercial companies. This study was reviewed and approved by our institutional ethics committee.

### 4. Results

During the study period, 50 patients (16 women and 34 men, with a mean age of  $63.86 \pm 10.05$  years) consented to participate in the research and were enrolled. The patient characteristics are listed in Table 1.

#### 4.1. Tumor Number and Size

NBI rendered a mean of 1.88 tumors per patient, compared to 1.7 by WLI (CI:  $-0.03$  to  $-0.05$ ). The mean size of lesions per patient as identified by WLI and NBI were 3.77 cm and 3.94 cm, respectively (CI:  $-0.28$  to  $-0.05$ ).

#### 4.2. Tumor Level

Among all of the tumors, 10.52% ( $n = 10$ ) were found only with NBI, and 1.05% ( $n = 1$ ) were found only with WLI cystoscopy. The detection rate for NBI was 98.9%, compared to 89.4% for WLI ( $P = 0.001$ ). The overall false-positive rate for NBI was 9.6% ( $n = 10$ ), compared to 5.88% ( $n = 5$ ) for WLI ( $P = 0.051$ ). The pathologic features of the lesions detected by each method are listed in Table 2.

#### 4.3. EORTC Risk Score for Progression and Recurrence

The risk of tumor progression and recurrence, as defined by the EORTC risk score for progression and recurrence, was measured in the NBI and WLI groups. The comparison is shown in Table 3.

**Table 1.** Patient Characteristics<sup>a</sup>

Characteristics	Values
<b>Gender</b>	
Male	34 (68)
Female	16 (32)
<b>Prior intravesical instillations</b>	
Yes	3 (6)
No	47 (94)
<b>Prior interventions</b>	
None	42 (84)
TUR	8 (16)
<b>Total number of patients</b>	50
<b>Age, y</b>	$63.86 \pm 10.05$

Abbreviation: TUR, transurethral resection.

<sup>a</sup>Values are presented as mean  $\pm$  SD or No. (%).

**Table 2.** Pathological Results for Lesions Uniquely Identified by WLI or NBI<sup>a</sup>

	WLI(+) NBI( -) (n =1)	WLI( -) NBI(+) (n =10)
<b>Stage</b>		
Ta	1	6
T1	0	4
Tis	0	2
<b>Grade</b>		
G1	1	5
G2	0	1
G3	0	4

Abbreviations: NBI, narrow-band imaging; WLI, white light imaging.

<sup>a</sup>CIS coexisted with other forms of cancer in both cases.

**Table 3.** EORTC Risk Score for Progression and Recurrence for NBI and WLI<sup>a</sup>

	EORTC Score for Recurrence			EORTC Score for Progression		
	WLI	NBI	P Value	WLI	NBI	P Value
<b>1-year</b>	32.44	33.92	.051	4.45	4.93	.159
<b>2-year</b>	42.4	43.8	.045	7.17	7.89	.159
<b>3-year</b>	47.1	48.5	.045	9.3	10.06	.159
<b>4-year</b>	50.1	51.5	.045	12.3	13.26	.159
<b>5-year</b>	52.6	53.9	.045	14.06	15.18	.159

Abbreviations: EORTC, European organization for research and treatment of cancer; NBI, narrow-band imaging; WLI, white light imaging.

<sup>a</sup>P values less than 0.05 are considered significant.

## 5. Discussion

Our study showed that the detection rate of urothelial cancer was enhanced by applying NBI (98.9% with NBI vs. 89.4% with WLI). This was in accordance with previous studies showing that NBI increases the detection rate of bladder cancer (6, 10-13). Herr et al. have demonstrated detection rates of 100% with NBI compared to 87% with WLI (12). In addition, a significantly greater tumor detection rate was described with NBI cystoscopy than with WLI in a study by Geavlete et al. (94.9% vs. 84.3%, respectively) (14).

Cauberg et al. reported that NBI cystoscopy revealed additional tumors in 35.9% of patients. In some other reports, these numbers are even higher, reaching 51.7% and even 56% (11). A new diagnostic technique is expected to bring superior sensitivity, but not at the expense of diminishing specificity. Therefore, a high false-positive rate is an important challenge, as it can result in unnecessarily resected bladder tissue. In our study, the false-positive detection rate for NBI was not statistically different from that of WLI (9.6% with NBI compared to 5.8% with WLI), which is within the acceptable range. In one other study (12), comparable false-positive rates were reported for NBI (36%) and WLI (33%). Conversely, the false-positive rate with NBI in Cauberg et al.'s series was higher than that of WLI (31.6% vs. 24.5%, respectively) (10).

It is important to assess the type of additional tumors identified by the NBI diagnostic technique (15), and the value of detecting only low-grade, noninvasive urothelial cancers can be questioned. In our study, ten tumors were detected only with NBI, including four T1 tumors, four G3 tumors, and two CIS lesions. Meanwhile, the only tumor uniquely detected by WLI was a Ta G1 tumor. Cauberg et al. (10) reported that tumors additionally detected by NBI were mainly grade 3. Therefore, early detection is definitely of clinical importance. In our study, 40% of tumors detected only by NBI were grade 3 and 40% were stage T1, which underscores the importance of an accurate detection method.

EORTC scoring has been used to evaluate the risk of recurrence and progression in NMIBC (16). However, our study is the first to use EORTC scoring to compare the risk of recurrence and progression between tumors detected by NBI cystoscopy versus WLI in NMIBC. The progression risk score was modestly reduced by applying NBI compared to using WLI alone, but this fell short of statistical significance. Hence, the statistical analysis for significance only supported clear improvement in the recurrence risk score by including NBI. Recent reports have looked at the impact of NBI on actual recurrence rates in a limited number of patients. Herr et al. (17) compared

the recurrence rate of bladder tumors resected using WLI and NBI in patients who were followed for three years, and this rate showed a 32% decrease in the NBI group. In a recent randomized trial, Herr (18) showed that the recurrence rate after two years of follow-up for re-TUR decreased from 33% in the WLI-TUR group to 22% in the NBI-TUR group. Naselli et al. (19) studied the three-month recurrence rate, reporting 3.9% and 16.7% for NBI and WLI, respectively. They also showed that TUR performed with the NBI modality reduced the recurrence of NMIBC by at least 10%. Cauberg et al. (11) further showed that NBI-TUR decreased the residual tumor rate by approximately 15.5% during three months of follow-up. Unlike these case series, our study looked at the calculated recurrence risk based on the EORTC scoring tools. Overall, although NBI cystoscopy showed an improvement in the detection of bladder tumors, it has some limitations, such as a higher false-positive rate, observer bias, and a limited number of high-quality randomized clinical trials (20), which indicates the necessity for further studies.

An additional important factor that should be mentioned is cost (21). In comparison to other techniques for augmented cystoscopic examination, such as PDD, which requires a fluorescent agent such as 5-aminolevulinic acid (5-ALA), as well as hexyl ester hexaminolevulinic acid (HAL), hypericin-induced fluorescence, and optical coherence tomography (OCT) (22), NBI has the advantage of being much more readily available as an option on existing imaging units, and it does not require additional medications or interventions (23). This translates to lower initiation and operational costs, and greater accessibility.

Our study confirms that NBI cystoscopy improves the overall detection rate for urothelial cancer, with false-positive detection statistically within the same range as standard light. Furthermore, NBI contributes to the detection of additional tumors that show a more aggressive histology. When tested according to the EORTC recurrence-risk scoring system, the augmented diagnosis afforded by NBI translates into a significantly lower recurrence risk in patients undergoing TUR for bladder cancer.

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## Footnote

**Authors' Contribution:** Pejman Shadpour contributed to the study concept, design, management of patients, data analysis and preparation of the manuscript. Maryam Emami contributed to the study design, management of patients and preparation of the manuscript. And Saeid Haghdani has contributed to the study design, management of patients statistical analysis and preparation of the manuscript.

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