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Platinum Priority – Urothelial Cancer

A Randomized Prospective Trial to Assess the Impact of Transurethral Resection in Narrow Band Imaging Modality on Non–Muscle-Invasive Bladder Cancer Recurrence

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Abstract

Background: Narrow band imaging (NBI) is an optical enhancement technology that filters white light into two bandwidths of illumination centered on 415 nm (blue) and 540 nm (green). NBI cystoscopy can increase bladder cancer (BCa) visualization and detection at the time of transurethral resection (TUR). NBI may therefore reduce subsequent relapse following TUR.
Objective: Assess the impact of NBI modality on 1-yr non–muscle-invasive BCa (NMIBC) recurrence risk.
Design, setting, and participants: Consecutive patients with overt or suspected BCa were included in a prospective study powered to test a 10% difference in 1-yr recurrence risk in favor of cases submitted to NBI TUR. Excluding patients with muscle-invasive BCa, negative pathologic examination, or without follow-up, the study population was composed of 148 subjects randomized from August 2009 to September 2010 to NBI TUR (76 cases) or white light (WL) TUR (72 cases).
Intervention: TUR was performed in NBI or standard WL modality.
Measurements: The 1-yr recurrence risks in NBI or WL TUR groups were compared using odds ratio (OR) point and interval estimates derived from logistic regression modeling.
Results and limitations: The 1-yr recurrence-risk was 25 of 76 patients (32.9%) in the NBI and 37 of 72 patients (51.4%) in the WL group (OR = 0.62; $p = 0.0141$). Simple and multiple logistic regression analyses provided similar OR points and interval estimates.
Conclusions: TUR performed in the NBI modality reduces the recurrence risk of NMIBC by at least 10% at 1 yr.

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1. Introduction

Narrow band imaging (NBI) is an optical enhancement technology that increases the contrast between vasculature and superficial tissue structures of the mucosa [1]. It consists of two bandwidths of illumination centered on 415 nm, blue, and 540 nm, green. In the NBI mode, light is absorbed strongly by hemoglobin and penetrates only the

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superficial layers of the tissue increasing the visibility of capillaries and superficial tissue structures. Since its introduction in the endoscopic systems, the use of NBI has spread rapidly. Regarding bladder cancer (BCa), NBI is known to increase the detection rate in prospective within-subject studies in which the bladder is examined sequentially in standard and NBI modality [2–4] even by different observers [5]. Most importantly, nonrandomized studies evidenced an impact of the examination of the bladder in NBI modality while performing transurethral resection (TUR) or follow-up cystoscopy on recurrence probability of non–muscle-invasive BCa (NMIBC) [6,7]. We performed a prospective randomized trial to assess the impact of TUR performed in NBI modality on NMIBC recurrence risk.

2. Patient and methods

All patients were adults; women who were pregnant, breastfeeding, or not on adequate contraceptive measures were excluded. All patients provided a written informed consent prior to the study. The study was conducted in accordance with good clinical practice and the 1964 Declaration of Helsinki, including the most recent amendments (Edinburgh, Scotland, 2000), and after written approval of the local medical ethical committee. The trial was registered and the identifier NCT01004211 assigned.

2.1. Patient selection

Consecutive patients from two centers in Liguria (IST, Genova, and Centro Urologico di Eccellenza ASL 1, Imperia) with overt or suspected BCa were included in the study and randomized to two treatments arms, standard white light (WL) TUR and NBI TUR, respectively.

TUR was carried out entirely in the WL or in the NBI mode (introduction of the resectoscope, preliminary cystoscopy, tumor resection, coagulation). A switch from standard to NBI mode or vice versa during the procedure was not allowed.

Indication for TUR or adjuvant intravesical therapy was given on the basis of the AURO.it Guideline Committee on BCa 2008 [8]. Accordingly, no patient was submitted to immediate postoperative intravesical bladder instillation of any chemotherapeutic agent.

Randomization was centralized and performed by means of a random table. All surgeons involved in the study were trained to use the NBI modality. Patients were submitted to WL or NBI TUR and/or cold cup biopsies of all visible lesions known or suspected to be BCa. A second TUR was performed in the same modality (WL or NBI) in case of newly diagnosed high-grade NMIBC or of grossly incomplete resection or of absence of muscle in the specimen and was considered part of the same endoscopic procedure in regard to the trial.

Six random cold cup biopsies from healthy mucosa of bladder trigone, anterior, posterior, and lateral walls were taken in case of a second TUR of newly diagnosed/recurrent high-grade NMIBC or in case of positive urinary cytology and negative standard office cystoscopy.

2.2. Exclusion criteria

Patients with invasive BCa or absence of urothelial cancer after pathologic examination or without follow-up were excluded.

2.3. Pathologic examination

The specimen of each lesion was analyzed individually by a pathologist blinded to the mode of identification of the single lesion (WL or NBI). Staging was given in accordance with the TNM classification (2002 Union Internationale Contre le Cancer) and grading by the World Health Organization 2004 classification. Patients with pure carcinoma in situ (CIS) were grouped as having high-grade cancer.

2.4. End points

The primary end point was the 1-yr intravesical recurrence risk. Recurrence was defined as positive findings on cystoscopy or on urine cytology that had to be confirmed histologically. Only patients diagnosed with pure CIS were considered at risk of a recurrence in case of consecutive positive findings on cytology even in the absence of histologic confirmation. The secondary end points were 3-mo recurrence risk and the detection rate.

2.5. Follow-up scheme

Follow-up was conducted in the standard WL mode to assess uniformly the main end point of the study. Three months after the endoscopic treatment, a urinary cytology (in cases of high-grade BCa) and a cystoscopy were performed given their great prognostic impact [9]. Thereafter patients with high-grade cancer were monitored with urinary cytology and cystoscopy every 3 mo and computed tomography (CT) scan urography every year. Patients with low-grade cancer at high risk of recurrence (namely newly diagnosed multiple or newly diagnosed single low-grade NMIBC >3 cm or any recurrent low-grade NMIBC) were monitored with cystoscopy every 6 mo and with CT scan urography yearly (only if highly recurrent). Patients with low-grade cancer at low risk of recurrence (newly diagnosed single low-grade NMIBC <3 cm) were monitored with a urinary cytology and cystoscopy after 9 mo and yearly thereafter [8]. Thus recurrence status of all patients included was available at 3 and 12 mo.

2.6. Study design and statistical analysis

It is estimated that the proportion of lesions detected is increased by approximately 20% using NBI compared with WL cystoscopy [2,3,10]. We hypothesized that such a rise in detection rate could be translated into a reduction of the relapse probability. Therefore, we assumed a 1-yr recurrence risk of 50% in the WL TUR group and of 40% in the NBI TUR group. To appreciate statistically such a difference ($\Delta = -10\%$), considering a power of 80%, a two-tailed significance level of 5%, and a lost to follow-up proportion of 10%, we calculated a sample size of 85 patients per study group, 170 total, by using the Cohen formula [11].

Potential imbalances by TUR techniques in patients' background factors (ie, age and year of enrollment, gender, clinical status, multifocal tumor, grading, staging, and adjuvant therapy regimen) were statistically evaluated using the chi-square test or, whenever useful, the Fisher exact test. The chi-square test was also applied to evaluate the difference between the two 1-yr recurrence risks (primary end point). Finally, logistic regression analysis [12] was applied to model the recurrence probabilities, and, accordingly, the odds ratio (OR) was used as an index of relative risk (RR) of recurrence (NBI vs WL). Simple and multiple regression analyses were performed to evaluate the effect of patients' background characteristics on the study relationships [13]. For each OR, 95% confidence limits (95% CIs) were also computed.

All tests were two tailed, and statistical significance was considered achieved if p value < 0.05. Data were analyzed using Stata software v.11.2 (StataCorp, College Station, TX, USA).

3. Results

A total of 223 patients scheduled for TUR from August 2009 to September 2010 were assessed for eligibility. Of these, 9

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declined participation and 26 consented to another study. Thus 188 were randomized to standard (93 patients) or NBI (95 patients) TUR. After obtaining histologic examination, 24 were excluded for invasive disease (T2 or more), 8 for absence of disease, and 1 for the diagnosis of endometriosis, leaving 76 patients in the standard group and 79 in the NBI group. Four patients in the standard group and three patients in the NBI group did not relapse and did not reach 1-yr follow-up, and therefore they were excluded from the analysis. Finally, 72 and 76 patients in the standard and NBI group remained for the final analysis as reported in the Consolidated Standards of Reporting Trials diagram (Fig. 1). Clinical and pathologic characteristics were balanced among the two groups (Table 1). A second TUR was performed in 39 cases (26%): 36 cases had a newly diagnosed Ta/T1 high-grade cancer, one case had a grossly incomplete resection of a voluminous tumor, and one case was found without muscle tissue in the specimen. Overall the BCa detection rate (a secondary end point) was 1.36 lesions per person in the WL group and 1.55 per person in the NBI group ($p = 0.07$). The incidence of false-positive findings was 46 of 164 (28%) and 26 of 124 (21%) in the NBI and in the standard group, respectively (RR: 1.34; 95% CI, 0.86–2.11; $p = 0.217$). Median follow-up was 11 mo (range: 2–19 mo). Follow-up ended due to recurrence in 61 cases (41.2%). Recurrences were histologically confirmed in all cases, but two had a pure CIS and positive consecutive findings on urinary cytology. The 3-mo and 1-yr recurrence risks were 15 of 148 (10.1%) and 61 of 148 (41.2%), respectively. The respective figures were 12 of 72 (16.7%) and 37 of 72 (51.4%) in the WL group and 3 of 76 (3.9%) and 24 of 76 (31.6%) in the NBI group. Accordingly, 1-yr risk difference (primary end point) results were approximately 20% in favor of the NBI group ($\Delta = -19.8$; 95% CI, −34.4 to −4.2; $p = 0.0141$). A discernable risk reduction was also observed after 3 mo of follow-up (secondary end point). However, in this case the NBI group showed an appreciably lower absolute advantage of almost 13% ($\Delta = -12.8$; 95% CI, −22.4 to −3.1; $p = 0.0084$) (Table 2). Comparison between simple and multiple logistic regression results did not show any substantial difference in OR point and interval estimates (Table 2). Ultimately, NBI technique reduced the 1-yr and 3-mo relapse probability of almost 40% (OR: 0.62; 95% CI, 0.4–0.92) and 75% (OR: 0.24; 95% CI, 0.07–0.81), respectively (Table 1).

4. Discussion

Evidence shows that NBI increases the detection of BCa [2–5]. We hypothesized this would reduce subsequent recurrence by removing cancers overlooked by WL cystoscopy. To date, two reports have looked at the impact of NBI on recurrence risk [6,7]. In the first, 126 patients with recurrent BCa were followed from 2003 to 2006 with standard cystoscopy and from 2006 to 2009 with NBI cystoscopy. The median (95% CI) recurrence-free survival time on standard surveillance was 13 mo (range: 11.6–14) compared with 29 mo (range: 26–32) on NBI cystoscopy ($p = 0.001$) [6]. This study had several limitations. For example, the cohorts were not randomized, and the same surgeon performed WLC and NBI, allowing a potential "second-look" bias [6]. In the second study, 118 patients

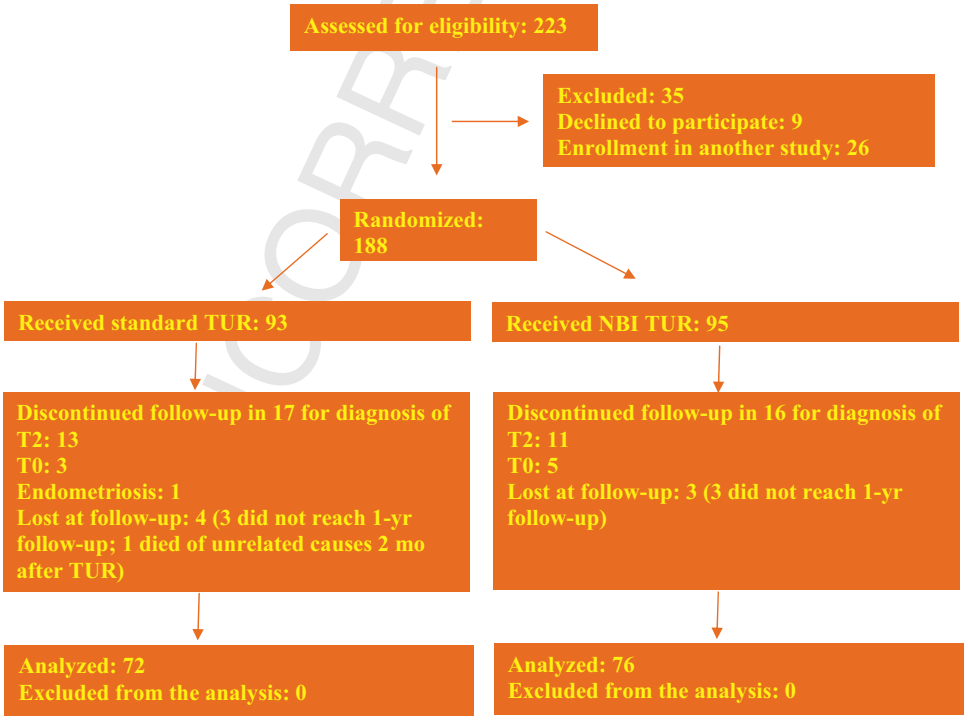

Fig. 1 – Consolidated Standards of Reporting Trials diagram.
NBI = narrow band imaging; TUR = transurethral resection.

Table 1 – Population characteristics (white light group vs narrow band imaging group)

Variables	TUR		*p* value
	WL	NBI	
Age			0.694
Mean ± SD	71.6 ± 12.4	70.8 ± 10.3	
Gender			0.231
Female	55	64	
Male	17	12	
Year of enrollment			0.814
2009	25	25	
2010	47	51	
Collaborative center			0.343
Hospital 1	10	15	
Hospital 2	62	61	
Clinical status			0.230
Recurrent	28	37	
Newly diagnosed	44	39	
Multifocal tumor			0.505
No	39	37	
Yes	33	39	
Grade			0.492
Low	41	39	
High*	31	37	
Stage			0.569
Ta**	52	58	
T1	20	18	
CIS			0.599
Pure	4	8	
Associated	6	6	
Tumor size			0.865
≤3 cm	53	55	
>3 cm	19	21	
Adjuvant topical therapy			0.166
No therapy	49	42	
BCG	19	24	
Mitomycin	4	10	
Whole sample (%)	72 (48.7)	76 (51.3)	–

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; NBI = narrow band imaging; *p* value: significance level of chi-square or Fisher exact test; SD = standard deviation; TUR = transurethral resection; WL = white light.
* Includes patients with pure or associated CIS.
** Includes patients with pure CIS.

submitted to standard TUR/bladder biopsies were retrospectively selected and a group of 40 patients were prospectively enrolled in a NBI TUR/bladder biopsies program [7]. The end point was patient status at 3 mo. Residual tumor was detected in 36 of 118 patients (30.5%) treated by standard TUR and 6 of 40 patients (15.0%) treated by NBI TUR, thus an absolute difference in 3-mo residual/recurrent cancer risk of 15.5% in favor of NBI TUR ($p = 0.04$). The result was confirmed in a logistic regression model showing that the probability of finding residual/recurrence tumor at 3 mo was significantly higher in patients previously submitted to standard TUR (OR: 2.7; 95% CI, 1.2–6.1; one-sided p value = 0.03) [7].

Fluorescence cystoscopy is a well-established procedure that increases BCa detection rate similarly to NBI [14–17]. The impact of fluorescence TUR on the recurrence rate of NMIBC in well-designed prospective randomized studies is not yet clear [14–17].

A study including 416 patients, randomly assigned to WL TUR, fluorescence TUR with 5-aminolevulinic acid, and fluorescence TUR with hexaminolevulinate showed a benefit of about 10% in terms of lower 3-yr recurrence risk for the fluorescence TUR [14]. In a cohort of 115 patients randomly submitted to WL or fluorescence TUR, fluorescence TUR improved the recurrence-free risk of about 20% within the first year of follow-up [15]. Two subsequent randomized studies failed to confirm the ability of fluorescence cystoscopy to decrease the recurrence risk [16,17].

Unfortunately, to date no comparison study between NBI and fluorescence cystoscopy has been performed, and, apart from ours, there is only one other ongoing prospective study from the Clinical Research Office of the Endourological Society [18] to assess the impact of NBI on recurrence risk.

In a previous paper we showed that TUR in the NBI modality is feasible [19]. The study was designed to disclose a 10% absolute risk difference in favor of the group treated with the NBI modality. The actual 1-yr difference was about 20%, and, most importantly, the objective was reached with the use of NBI, a minimal technical modification to the

Table 2 – Results of logistic regression analyses of 1-yr and 3-mo recurrence risks

Time to recurrence	TUR		Simple		Multiple
	WL No. (%)	NBI No. (%)	Δ (Δ%) (95% CI) *p* value	OR (95% CL)	OR (95% CI) *p* value
1 yr	37 (51.4)	24 (31.6)	−19.8 (−38.5) (−4.2 to −35.4) 0.0141	0.62 (0.41–0.92)	0.57 (0.38–0.85) 0.0053
3 mo	12 (16.7)	3 (3.9)	−12.8 (−76.7) (−22.4 to −3.1) 0.0084	0.24 (0.07–0.81)	0.26 (0.07–0.75) 0.0090
Whole sample	72 (100.0)	76 (100.0)			

TUR = transurethral resection; Δ = absolute difference in recurrence risks; Δ% = relative difference in recurrence risks; OR = odds ratio, relative risk of recurrence; WL = white light; NBI = narrow band imaging; 95% CI = 95% confidence limits for Δ or OR; *p* value = significance level.
Note: Simple/Multiple: OR point and interval estimates unadjusted/adjusted for background patients' characteristics (ie, age and year of enrollment, gender, clinical status, multifocal tumor, grading, staging, and adjuvant therapy regimen).

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standard TUR. The main limitation of our study was that surgeons could not be blinded to the modality used.

The 3-mo recurrence risk, a secondary end point, was 3.9% and 16.7% in the NBI and WL group, respectively. The early recurrence risk is lower than usual [9] and, to our knowledge, it can only be explained by the increased detection that avoids recurrences due to overlooked tumors.

Accordingly, the detection rate, another secondary end point of the study, was increased in the NBI group (1.36 lesions per person in the WL group, 1.55 in the NBI group; $p = 0.07$). However, it corresponds to a slight increase in the incidence of false-positive findings that was 46 of 164 (28%) and 26 of 124 (21%) in the NBI and in the standard group, respectively (RR: 1.34; 95% CI, 0.86–2.11; $p = 0.217$). However, it does not seem clinically relevant inasmuch as it translates as less than one additional biopsy/resection for a suspected lesion for every 10 performed in a patient who should undergo TUR anyway.

It should be noted that although the recurrence probability increased in the NBI group during the study from 4% at 3 mo to 32% at 1 yr, it increased from 12% to 51% in the standard group. A possible explanation for the higher tendency toward increment of recurrence frequency may be that some recurrences are explained by causes other than missed tumors such as the "field cancerization" effect [20] or the "clonality" origin of urothelial cancer [21] that are not yet completely understood.

5. Conclusions

TUR performed in NBI modality reduces the 1-yr recurrence risk of NMIBC by at least 10%.

Author contributions: Angelo Naselli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Naselli, Puppo.
Acquisition of data: Naselli, Bertolotto, Introini, Timossi, Germinale, Spina.
Analysis and interpretation of data: Naselli, Puppo, Fontana, Pezzi.
Drafting of the manuscript: Naselli, Puppo.
Critical revision of the manuscript for important intellectual content: Naselli, Puppo.
Statistical analysis: Naselli, Puppo, Fontana, Pezzi.
Obtaining funding: Naselli, Puppo.
Administrative, technical, or material support: Naselli, Puppo, Bertolotto, Introini, Timossi.
Supervision: Naselli, Puppo, Fontana.
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