

The Clinical Research Office of the Endourological Society (CROES) multicentre randomised trial of narrow band imaging–assisted transurethral resection of bladder tumour (TURBT) versus conventional white light imaging–assisted TURBT in primary non–muscle-invasive bladder cancer patients

CROES Narrow Band Imaging Global Study Group

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1 **The Clinical Research Office of the Endourology Society (CROES) multicentre**
2 **randomised trial of narrow band imaging-assisted transurethral resection**
3 **(TURBT) versus conventional white light-assisted TURBT in primary non-**
4 **muscle-invasive bladder cancer patients: trial protocol and 1-year results**

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3 transurethral resection of bladder tumour; non-muscle invasive bladder cancer

4

1 **Abstract**

2 **Background:** White light (WL) is the established imaging modality for transurethral
3 resection of bladder tumour (TURBT). Narrow band imaging (NBI) is a promising
4 addition.

5 **Objectives:** To compare 12-mo recurrence rates following TURBT using NBI versus
6 WL guidance.

7 **Design, setting, and participants:** The Clinical Research Office of the Endourology
8 Society (CROES) conducted a prospective, randomised, single-blind, multicentre
9 study. Patients with primary non-muscle-invasive bladder cancer (NMIBC) were
10 randomly assigned 1:1 to TURBT guided by NBI or by WL.

11 Intervention: TURBT for NMBIC using NBI or WL.

12 **Outcome measurements and statistical analysis:** 12-mo recurrence rates were
13 compared by chi-square tests and survival analyses.

14 **Results and limitations:** Of the 965 patients enrolled in the study, 481 patients
15 underwent WL-assisted TURBT and 484 patients received NBI-assisted TURBT. Of
16 these, 294 and 303 patients, respectively, completed 12-mo follow-up, with
17 recurrence rates of 27.1% and 25.4%, respectively ($p = 0.585$, Intention-to-treat
18 (ITT) analysis). In patients at low risk for disease recurrence, recurrence rates at 12-
19 mo were significantly higher in the WL group compared with the NBI group: 27.3% vs
20 5.6% ($p = 0.002$, ITT analysis). Although TURBT took longer on average with NBI
21 plus WL compared with WL alone (38.1 min vs 35.0 min; $p = 0.039$, ITT; 39.1 vs 35.7
22 min; $p = 0.047$, Per protocol (PP) analysis), lesions were significantly more often
23 visible with NBI than with WL ($p = 0.033$). The frequency and severity of adverse
24 events were similar in both treatment groups. Possible limitations were: lack of

1 uniformity of surgical resection, data on smoking status, central pathology review,
2 and specific date regarding adjuvant intravesical instillation therapy.

3 **Conclusions:** NBI and WL guidance achieved similar overall recurrence rates 12-mo
4 after TURBT in patients with NMIBC. NBI-assisted TURBT significantly reduced the
5 likelihood of disease recurrence in low-risk patients.

6

7 **Patient summary:** Using a narrow band imaging technique might provide greater
8 detection of bladder tumours and subsequent treatment, leading to reduced
9 recurrence in low-risk patients

10

11

12

1 **1. Introduction**

2 The standard intervention following initial diagnosis of non-muscle invasive bladder
3 cancer (NMIBC) is transurethral resection of bladder tumour (TURBT) with white light
4 (WL) imaging guidance [1]. However, small bladder tumours, such as flat malignant
5 lesions (carcinoma *in situ*; CIS) or small papillary tumours, can be missed [2,3].

6 These undetected or incompletely resected tumours with diffuse borders can recur,
7 with some becoming invasive, which emphasises the need for improved techniques
8 to detect NMIBC. Moreover, some authors consider the majority of early recurrences
9 to result from initial surgical failure [4].

10 Research has focused on improved methods of detection, including narrow band
11 imaging (NBI), a high-resolution endoscopic optical technique. Filtering white light
12 into two bandwidths of 415 and 540 nm, which are absorbed by haemoglobin,
13 enhances the contrast between normal urothelium and hypervascular cancer tissue.
14 NBI enhances the submucosal capillaries and, because bladder tumours are well
15 vascularised with densely arranged irregular vessels, the contrast between tumours
16 and normal mucosa is improved.

17

18 NBI has proved more effective than conventional WL cystoscopy [5,6]. Currently,
19 there is limited experience with NBI in detecting bladder cancer but early results are
20 encouraging [7–9]. The aim of the present study was to compare the efficacy and
21 safety of TURBT using NBI or WL cystoscopy in NMIBC. We hypothesize that use of
22 NBI at the time of TURBT will decrease recurrence rates at one year, compared to
23 WL cystoscopy alone.

24

25 **2. Methods**

1 **2.1. Study design and participants**

2 The CROES NBI Study was a prospective, randomised, single-blind, multicentre trial,
3 which was conducted at 26 specialist urological centres in 16 countries from August
4 2010 to October 2014. The study included patients aged 18 yr or older scheduled for
5 treatment of a primary (initially diagnosed) NMIBC; those eligible for inclusion were
6 patients scheduled for TURBT with papillary bladder tumour(s) detected by imaging
7 or cystoscopy or those scheduled for random biopsies and/or TURBT because of
8 bladder lavage fluid or voided urine cytology with malignant (G3) cells. Exclusion
9 criteria included: the presence of tumours in the upper urinary tract; muscle invasive
10 bladder tumour; previous irradiation of the pelvis; gross haematuria (defined as heavy
11 bladder bleeding resulting in marked amounts of blood in the urine) which might
12 interfere with cystoscopy at the time of TURBT; participation in other clinical studies
13 with investigational drugs either concurrently or within the last 30 d; pregnancy; and
14 any condition associated with a risk of poor protocol compliance (for example
15 patients with severe comorbidity interfering with thorough follow-up).

16

17 Patients eligible for the study were contacted through medical staff and provided with
18 verbal and written information. All participants were required to sign informed consent
19 forms. The study was approved by the Institutional Review Board of each
20 participating centre and carried out according to the guidelines of good clinical
21 practice [1]. The trial was registered in The Netherlands Trial Register (NTR3645). All
22 data were collected through an on-line electronic data management system
23 (<https://www.croes-dms.org>). Access to this secure system was restricted to each
24 centre investigator and CROES data managers and enabled by individual passwords.

25

1 **2.2. Randomisation**

2 After enrolment, patients were randomly allocated in a 1:1 ratio to parallel control
3 (WL) and intervention (NBI) arms. Randomisation was conducted by means of a
4 concealed computer-generated random sequence of numbers using permuted blocks
5 and stratified for: multiplicity (single or multiple tumours), macroscopic findings
6 (papillary or solid/flat tumour) and age (either \geq or $<$ 40 yr). The process was
7 implemented through the on-line data management system. Patients were blinded for
8 the treatment arm they were randomised to.

9

10 **2.3. Procedures and follow-up**

11 In the out patients clinic, patients diagnosed as bladder tumour using WL cystoscopy
12 were evaluated for inclusion and exclusion criteria, and preoperative data were
13 collected, including age, gender, weight, height, ethnicity, anticoagulation therapy,
14 co-morbidity, symptoms, urinalysis, urine culture and cytology, and upper urinary
15 tract imaging results.

16

17 In the operating room, eligible patients in both arms of the study underwent
18 cystoscopy evaluation of the bladder and indication of all tumours using WL
19 cystoscopy. Registration of lesions on the bladder chart included presence of lesion,
20 type (papillary, or flat), number of lesions and location (bladder neck anterior, trigone,
21 around ureteric orifice right, around ureteric orifice left, posterior floor, right lateral
22 wall, cranial wall, left lateral wall, dome, anterior bladder wall and bladder neck
23 posterior). Patients in the WL arm were then treated according to the normal hospital
24 routines, i.e. complete resection of all papillary lesions, and biopsy and subsequent
25 complete fulguration of all flat lesions including suspicious areas with WL. In patients

1 of the NBI arm, following documentation of tumours visualized under WL and prior to
2 resection, the bladder tumours were remapped on the bladder diagram under NBI.
3 Then, complete resection of all papillary lesions, and biopsies and subsequent
4 complete fulguration of all flat lesions including suspicious areas were conducted with
5 NBI. Operative factors recorded for all patients included the date and duration of
6 surgery, antibiotic prophylaxis, type of resection, visibility of lesion, performance of
7 routinely random biopsies, tumour location and intraoperative complications.
8 Postoperatively, the duration of catheterization and hospital stay, antibiotics use,
9 pathological characteristics and complications were noted. Surveillance WL
10 cystoscopy was planned to be done in all patients at the 3- and 12-mo follow-up
11 visits, with histological confirmation to assess recurrence. If recurrent CIS was
12 suspected by urine cytology, biopsy was performed to confirm CIS histologically

13

14

15 **2.4. Outcomes**

16 The primary outcome measure was recurrence rate at 1 yr. A recurrence was
17 defined as the new occurrence of a bladder cancer at the same or different site to the
18 index cancer. Secondary outcomes were tumour recurrence at first follow-up (3-mo
19 post-TURBT) or presence of recurrent/residual tumour at previously resected
20 locations (within 60 d of initial TURBT). Basically, re-resection was performed within
21 60 d of initial TURBT with WL in both groups for patients with pT1 tumour, whose
22 initial resected specimen did not contain sufficient muscle layer and those who were
23 suspected of incomplete resection regardless of tumour stage. The local pathologist
24 conducted histological assessment of both biopsied tissue and samples from

1 resected lesions. The study also assessed perioperative morbidity (within the first 30
2 d of TURBT) using the Clavien-Dindo score [10].

3
4 Adverse events (AEs) were assessed and recorded for 7 d after the initial TURBT
5 procedure or until resolution. They were also recorded at the 3- and 12-mo follow-up.
6 AE severity was graded on a 5-point scale according to the US National Cancer
7 Institute Common Terminology Criteria for Adverse Events v3.0 [11].

8

9 **2.5. Statistical analyses**

10 The expected recurrence rate in the WL-assisted TURBT group was 35% [12]. To
11 detect a clinically relevant difference in recurrence detection rates of $\geq 10\%$ at a 5%
12 significance level and a power of 80%, the required sample size per treatment was
13 calculated to be 329 patients (658 patients in total). To allow for a non-compliance
14 rate of 25% and a 15% loss of patients who could be diagnosed with a pT0 or \geq pT2
15 tumour later in the process, and assuming no crossover and no differential loss to
16 follow-up between arms, the calculated sample size was increased proportionately
17 resulting in a target recruitment of 946 patients.

18

19 The primary efficacy analysis was performed on the intention-to-treat (ITT)
20 population, which included those participants who were correctly randomised and
21 were willing to participate in the study. A per protocol (PP) analysis was also
22 performed on the study population who were correctly randomised, were willing to
23 participate in the study and had no protocol violations. Pearson's chi-square analysis
24 was used for dichotomous or categorical variables. When the Pearson's chi-square
25 assumptions were not met, the Fisher's exact test was used. Analysis of variance

1 (ANOVA) was used for continuous variables to compare characteristics and
2 outcomes between the two groups. Survival analysis was performed using the log-
3 rank test, and shown in Kaplan Meier curves; both analyses used patient information
4 up to the point at which censoring occurred. As all data were not available for every
5 patient, last observation carried forward (LOCF) was also applied. The level of
6 statistical significance was set at $p < 0.05$. Percentages were calculated and
7 analyses performed on available data. A sub-analysis was conducted according to
8 disease status, including low, intermediate and high-risk European Organisation for
9 Research and Treatment of Cancer risk classification [12].

10

11 **3. Results**

12 Between August 2010 and October 2014, 981 patients at 28 centres in 14 countries
13 (Appendix 1) were assigned to the two study groups. The trial profile is shown as a
14 CONSORT flow diagram in Figure 1. Sixteen patients at two centres were
15 subsequently excluded because the quality of the data could not be assured; shortly
16 after the start of the study these centres changed to using equipment other than NBI.
17 The ITT population thus comprised 481 patients randomised to the WL group and
18 484 patients randomised to the NBI group. Following histopathological examination,
19 66 patients had no available pT, or pT could not be assessed (pTx). 78 patients were
20 excluded for muscle-invasive disease (category pT2 or higher) and absence of
21 disease (pT0) was found in 77 patients who were then also excluded. One further
22 patient received no intervention (surgery), leaving 365 patients in the WL group and
23 379 patients in the NBI group available for the PP analysis.

24

1 The baseline characteristics of the patients included in this study are shown in Table
2 1. There were no significant differences in terms of tumour location, tumour number
3 and tumour size between the patients in the WL and the NBI groups for the ITT and
4 PP populations.

5

6 Surgery time including resection time and time for mapping out the bladder tumour
7 was significantly longer if NBI guidance was used compared with WL ($p = 0.039$,
8 ITT); this difference was also significant in the PP analysis ($p = 0.047$) (Table 2). A
9 lesion was significantly more often visible in NBI compared with WL ($p = 0.033$, ITT).
10 Tumour location in the dome region was significantly more frequent in the NBI group
11 (13.9%) compared with the WL group (9.6%) for the ITT populations ($p = 0.041$).
12 There were no other significant differences between the two groups in regard to
13 tumour characteristics, operative factors or peri-operative complications (Table 2).

14

15 LOCF data on the frequency of re-resection (re-TURBT) and recurrence at re-TURBT
16 are shown in Table 3 and indicate a similar frequency in the two treatment groups. A
17 significantly lower rate of recurrence was found in low-risk patients (pTa, Grade 1, <
18 30 mm, and no CIS) [1] in the NBI group compared with the WL group, which was
19 evident after 3-mo (0 vs 15.1%; $p = 0.006$) and 12-mo (5.6% vs 27.3%; $p = 0.002$) of
20 follow-up. Similar proportions of patients completed 12-mo follow-up ($n = 294$ [62.6%]
21 WL group; $n = 303$ [61.1%] NBI group, ITT analysis). Recurrence rates reported were
22 27.1% ($n = 109$) and 25.4% ($n = 104$) in the WL and NBI groups, respectively ($p =$
23 0.585; ITT analysis).

24 Analysis of recurrence vs time showed diverging recurrence-free survival rates for
25 low-risk patients in the two treatment groups from 60–70 d follow-up (Fig. 2B), in

1 contrast to the similar rates found throughout follow-up in intermediate-risk, high-risk
2 and all-patient groups (Fig. 2C, 2D and 2A, respectively).

3

4 There were no significant differences between treatment groups in the number and
5 severity of AEs (Appendix Table 1).

6

7 **4. Discussion**

8 Overall, this study found no difference in tumour recurrence between NBI-assisted
9 TURBT and WL-assisted TURBT at 12-mo follow-up, but did find a significantly lower
10 rate of recurrence in low-risk patients. Most of the recurrence in these patients may
11 be due to small tumours, which are often overlooked during the TUR. We
12 hypothesise that NBI provided greater visualisation of such overlooked lesions,
13 therefore reducing the recurrence rate in low-risk patients. The better 3-mo
14 recurrence-free rate in the NBI group for low risk patients may be reflective of a more
15 complete superficial (but not deep) resection by using NBI. In contrast, the
16 recurrence in intermediate or high-risk patients may be caused by not only
17 development of overlooked small tumours but also regrowth of high-grade tumour
18 cells disseminated during TUR [13]. NBI, through more precise detection and
19 resection of small tumours, may be able to decrease recurrence rate, but it is unlikely
20 to influence regrowth of disseminated high-grade tumour cells. Consequently, the
21 benefit of NBI was clear in the low-risk group but not in intermediate- or high-risk
22 groups.

23

24 Compared with published studies, the present study has a fundamental difference in
25 its design. The inclusion of only those patients with primary tumours enables the

1 evaluation of a specific test in a given population. In addition, previous studies have
2 primarily included patients with (highly) recurrent papillary tumours that are
3 overrepresented by low risk disease. In contrast, in the present study, there was a
4 larger patient population with intermediate- and high-risk disease (equally distributed
5 in the WL and NBI groups). In line with this, in the present work the overall
6 recurrence rate was significantly lower than was initially expected.

7

8 The CROES Council approved all centres participating in this study and the principal
9 investigator at each study site was a member of the Endourological Society. This
10 high standard of uro-oncological engagement and expertise within the study is likely
11 to have ensured efficient tumour identification and thorough resection (particularly of
12 larger tumours) with either imaging modality. Surgeon experience and technical
13 ability both affect the clinical outcome (including recurrence) after TURBT of new
14 NMIBC [14], although the reliability of bladder tumour evaluation by NBI cystoscopy
15 has been reported to be unaffected by urologists' prior experience [15]. Furthermore,
16 it is considered within the field that familiarity with image-enhancement modalities
17 (such as NBI) improves a surgeon's ability to detect small lesions with WL alone. We
18 interpret the emergence of a difference in recurrence rate between NBI-assisted
19 TURBT and WL-assisted TURBT only in low-risk patients as indicative of the higher
20 efficacy of NBI in visualising smaller tumours, but we accept the possibility of
21 observer bias e.g. double mapping favouring NBI as a limitation of this single-blind
22 study. Furthermore, in recent years, the quality of WL imaging equipment has also
23 improved considerably.

24

1 Assuming recurrence was caused by a tumour undetected during the first resection
2 [13], the difference in rate of recurrence in low-risk patients between treatments
3 evident at 3-mo post-intervention was unexpected. By including patients with primary
4 NMIBC, we anticipated that many tumours undetected initially would still be too small
5 to detect 3-mo after initial TURBT and that recurrences in this patient group would be
6 detectable only after longer term follow-up.

7

8 The reduction in recurrence rate in low-risk patients has obvious clinical benefits and
9 is likely to be accompanied by favourable economic effects; lower recurrence rates
10 with NBI compared with WL would reduce the need for further TURBTs and the
11 frequency of surveillance [16]. Furthermore, lesions initially overlooked by WL that
12 subsequently become visible at the 3-mo check cystoscopy would be incorrectly
13 classed as recurrence. Management of patients with recurrence includes closer
14 surveillance and further TURBT, resulting in increasing cost compared with
15 identification during the preliminary examination with NBI. While the cost of the
16 TURBT procedure is likely to be similar for NBI and WL, longer operating room use
17 with NBI procedures in certain patients would add to resource use costs. The
18 additional time needed is only an average of 3 min per procedure, which can be
19 balanced against the lack of a significant difference in the frequency and the severity
20 of grades of peri-operative complications and AEs in the two treatment groups.

21

22 Several previous studies have reported improved detection of bladder tumours with
23 NBI cystoscopy compared with standard WL cystoscopy [8,17–21]. Recent meta-
24 analyses of clinical trials in bladder cancer show that NBI provides comparable or
25 higher diagnostic precision than WL [9,22]. Li et al calculated that an additional 17%

1 of patients (95% CI 10–25%) and an additional 24% of tumours (95% CI 17–31%)
2 were detected by NBI [22]. The small number of clinical trials that have reported
3 disease recurrence show that the use of NBI vs WL improves recurrence rates by
4 15–32%, with time to recurrence of 29 and 13-mo, respectively [13,23–25]. The
5 present study addresses the relative lack of prospective recurrence data for NBI.
6 Further support for the benefits of improved visualisation of bladder tumours can be
7 found in some studies of photodynamic diagnosis (PDD), which show recurrence-free
8 rates at 12-mo 11–27% higher with PDD than with WL and the difference in outcome
9 between the two techniques extended over several years [16,26]. In other studies,
10 however, higher tumour detection rates with PDD did not translate into lower rates of
11 NMIBC recurrence [27].

12

13 In addition to earlier mentioned limitations, other possible limitations of the present
14 study include: 1. the lack of documentation of smoking status/ongoing environmental
15 exposures that may increase the risk of urothelial carcinoma; 2. the lack of central
16 review pathology; 3. Lack of documentation in the use of adjuvant intravesical
17 instillation therapy. Furthermore, we are aware of the substantial number of patients
18 who did not receive the 3 or 12-mo follow-up cystoscopies and loss to follow-up in
19 this study. However, this was taken into account in the sample size calculation.

20

21 In summary, this large, prospective, multicentre, randomised clinical trial in patients
22 with primary NMIBC showed that, while NBI and WL guidance achieved similar
23 overall recurrence rates after TURBT at 12-mo follow-up, NBI-assisted TURBT
24 significantly reduced disease recurrence in low-risk patients (pTa, Grade 1, <30 mm,

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1 and no CIS). This finding supports the use of NBI guidance as an alternative to the
2 current standard approach involving WL.

3

4

1 **Figure legends**

2 **Fig. 1** – Study flow chart. ITT = intention-to-treat. PP = per protocol. No cystoscopy:
3 follow-up performed without cystoscopy. Not performed: follow-up at certain moment
4 not performed. Lost to follow-up: Patient received no further follow-up at all. Not
5 available: no data available.

6 **Fig. 2** – Survival curves for no recurrence over a 12-mo follow-up period for the
7 intention-to-treat population and risk subgroups following white-light- (WLI) or narrow
8 band imaging- (NBI) assisted transurethral resection of bladder tumour. (A) all
9 patients; (B) low-risk patients; (C) intermediate-risk patients; and (D) high-risk
10 patients. Patients were stratified into risk groups using tumour characteristics
11 according to European Association of Urology Guidelines [1]. CI = confidence
12 interval.

13

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17

18

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