Feasibility of Transurethral Resection of Bladder Lesion Performed Entirely by Means of Narrow-Band Imaging

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Abstract

Purpose: To assess the feasibility of transurethral resection (TUR) of bladder lesions performed entirely by means of a narrowband imaging (NBI) modality.

Patients and Methods: Data from an ongoing prospective randomized trial (NCT01004211) were extracted. Quality outcomes of standard TUR and NBI TUR were compared. Complications were graded according to the Clavien-Dindo system.

Results: To date, 33 and 29 subjects were randomized to standard and NBI TUR. No significant differences regarding age, sex, American Society of Anesthesiologists score, rate of multiple lesions, or lesions larger than 3 cm in the two groups were found, whereas rate of TUR for recurrent bladder cancer was greater in the NBI group. All procedures ended with complete clearance of the suspected or overt bladder tumor in the modality assigned. No death or major surgical or medical complications were registered. Overall grade I to II complications rate in the NBI and standard groups was, respectively, 8/29 (27%) and 11/33 (33%) (P = 0.831). Median surgery time was, respectively, 20 and 30 minutes in the NBI and standard group (P = 0.381). Median time to catheter removal was, respectively, 2 and 3 days in the NBI and standard groups (P = 0.288). Median time to discharge was 2 and 3 days (P = 0.173). No patient was readmitted after discharge. Muscle tissue was absent in the specimen of one patient who underwent standard TUR.

Conclusion: NBI TUR appears to be feasible. The results of the ongoing randomized trial will show whether NBI TUR is able to reduce significantly the 1-year recurrence rate of bladder tumors.

Introduction

An experimental study showed that by narrowing the wave band of white light to 415 ± 30 nm, it was possible to enhance the contrast of the capillary pattern in the superficial layer of the tongue mucosa. Narrowband light did not reach lower layers of tissue and was absorbed well by the blood vessels. As a result, the areas with light reflection, mucous membrane, and the areas with no reflection, blood vessel, could be distinguished from one another and displayed with higher contrast. Subsequent clinical trials in gastroenterologic endoscopy demonstrated that the technology, denominated narrowband imaging (NBI), is superior to standard broadband white light for the endoscopic diagnosis of early cancer.

Recently, NBI has been used in the endoscopic management of nonmuscle-invasive bladder cancer. Regarding NBI cystoscopy, the bandwidth of the light output from the endoscopy system is limited to 415 nm and 540 nm. At this range, the aspect of a bladder lesion is dark—black against almost white normal mucos—whereas the lesion appears red against a pink normal mucosa at white-light examination. As a result, the color contrast of a lesion is enhanced.

NBI is able to increase the detection of urothelial lesions with respect to standard white-light imaging. In particular, it improves the diagnosis of recurrent nonmuscle-invasive bladder cancer, including carcinoma in situ (CIS), and in those who have undergone a bacille Calmette-Guérin (BCG) induction cycle. To date, NBI always has been tested sequentially after a white-light inspection or transurethral resection (TUR) of the bladder. One of the major criticisms to this approach is that the observer is allowed to take a “second look” with the alternative light and a “third look” with the white light, generating a bias. Moreover, the study design, within patient comparison, is prone to the statistical phenomenon of the regression to the mean.

To disclose the objective advantages of NBI technology on bladder cancer management, a prospective trial that compares TUR of bladder lesions, carried out entirely with NBI (including introduction of the resectoscope, preliminary...
cystoscopy, tumor resection, coagulation), vs TUR of bladder lesions, carried out entirely with standard white light, is ongoing. Our previous study showed feasibility of the use of the resectoscope in the NBI modality. The procedure, however, was performed after an accurate coagulation of any source of bleeding.

Given the strong absorption of light under NBI by hemoglobin, we were concerned about visibility and eventual consequent impaired outcomes of NBI TUR. Here, we extracted data from the ongoing trial to assess feasibility of NBI TUR of bladder lesions.

Patients and Methods

Data from an ongoing randomized trial (registered at ClinicalTrials.gov – identifier: NCT01004211) that compares the 1-year recurrence rate of standard TUR vs NBI TUR of overt or suspected bladder cancer were extracted. All patients were adult; women who were pregnant, breast-feeding, or not with adequate contraceptive measures were excluded. All patients provided a written informed consent before the study.

The study is being conducted in accordance with Good Clinical Practice and the Declaration of Helsinki 1964, including the most recent amendment (Edinburgh, Scotland, 2000) and after written approval of the local medical ethical committee. Consecutive patients from two centers in Liguria (IST – Genova and Centro Urologico di Eccellenza ASL 1 - Imperia) with overt or suspected bladder cancer, including CIS detected by random biopsies or a positive urinary cytology, are being included in the study and randomized to two treatments arms—respectively, standard TUR and NBI TUR.

TURs are therefore performed entirely in the standard modality or in the NBI mode (including introduction of the resectoscope, preliminary cystoscopy, tumor resection, coagulation). A switch from standard to NBI mode or vice versa during the procedure is not allowed. Indication for TUR or adjuvant intravesical therapy is based on the AURO.it during the procedure is not allowed. Indication for TUR or adjuvant intravesical therapy is based on the AURO.it guideline on bladder cancer 2008 and, accordingly, no patient undergoes immediate postoperative intravesical bladder instillation of any chemotherapeutic agent. Randomization is centralized and performed by means of a random table. All surgeons involved in the study were trained to use the NBI modality.

Patients undergo standard or NBI TUR and/or cold-cup biopsies of all visible lesions known or suspected to be bladder cancer; six random cold-cup biopsies from healthy mucosa of bladder trigone, anterior, posterior, and lateral walls are taken (bladder mapping) in case of a second TUR of newly diagnosed/recurrent high grade nonmuscle-invasive bladder cancer or in case of positive urinary cytology and negative standard office cystoscopy.

The specimen of each lesion is analyzed individually by a pathologist who is blinded to the mode of identification of the single lesion (by white-light imaging or NBI) and reviewed centrally. Staging is performed in accordance to the Tumor-Node-Metastasis classification (2002 International Union Against Cancer) and grading by the World Health Organization 2004 classification. The primary end point of this trial is the 1-year intravesical recurrence-free survival rate. This preliminary analysis of the first 62 cases has been performed to assess the feasibility of NBI TUR with respect to standard TUR. Quality outcomes of standard TUR and NBI TUR were compared by means of the median t or chi-square test. Complications were graded according to the Clavien-Dindo system.

Results

To date, 29 patients were randomized to NBI TUR and 33 to standard TUR in the National Institute for Cancer Research, Genoa, Italy. Each procedure was performed entirely in the assigned modality and ended with complete clearance of the suspected or overt bladder tumor. Results are summarized in Tables 1 and 2. Median age in the NBI and the standard group was, respectively, 72 years (range 44–87 y), and 69 years (range 19–89 y) (P = 0.439). In the NBI group, 3/29 (10%) were women, and in the standard group, 9/33 (27%) were women (P = 0.174). The median ASA score was 2 and ranged 1 to 3 in the groups.

Lesions were multiple in 13/29 (45%) patients in the NBI group and in 11/33 (33%) in the standard group (P = 0.505). At least one lesion was larger than 3 cm in 7/29 (24%) of the NBI group and 13/33 (39%) of the standard group (P = 0.313). In the NBI group, 20/29 (68%) were recurrent lesions, as were 11/33 (33%) in the standard group (P = 0.011). Regarding patients with recurrent lesions, 14/20 had a history of high-grade bladder cancer in the NBI group and 9/11 in the standard group (P = 0.771); 10/20 had a history of multifocal bladder cancer in the NBI group, 6/11 in the standard group (P = 1). 15/20 had a history of chemotherapy and/or immunophylaxis in the NBI group (in particular, 5 had chemophylaxis, 6 immunophylaxis, 4 chemotherapy and immunophylaxis) and 4/11 (in particular, 2 had chemotherapy and immunophylaxis) in the standard group (P = 0.084).

No death or major surgical or medical complications were registered in the study population. Overall, the grade I to II complications rate in the NBI and standard groups was, respectively, 8/29 (27%) and 11/33 (33%) (P = 0.831). Of patients with postoperative hematuria, 2/29 (7%) and 3/33 (9%) (P = 1) needed bladder irrigation during hospitalization for at least 12 hours; no one needed blood transfusion. Ultrasonography of the abdomen was performed in 3/29 (10%) and 4/33 (12%) (P = 1) patients with a bladder perforation; no fluid extravasation was found. Three patients in each group (P = 1) needed to be recatheterized for acute urinary retention because of prostate enlargement.

The median surgery time was 20 minutes in the NBI group (range 10–60 min) and 30 minutes in the standard group (range 10–50 min) (P = 0.381). The median time to catheter removal was 2 days in the NBI group (range 1–7 d) and 3 days in the standard group (range 1–7 d) (P = 0.288).

The median time to discharge was 2 days in the NBI group (range 2–8 d) and 3 days in the standard group (range 2–7 d) (P = 0.173). No patient was readmitted after discharge.

Muscle tissue was absent only in the specimen of one patient who underwent standard TUR. Final pathologic examination revealed T2 bladder cancer in 2/29 (7%) and 2/33 (6%) patients (P = 1); T1 in 3/29 (10%) and 7/33 (21%) (P = 0.415); high-grade nonmuscle-invasive bladder cancer in 8/29 (27%) and 12/33 (37%) (P = 0.641); 5/29 (17%) and 2/33 (6%) were found with CIS (P = 0.325).
NBI is an optical enhancement technology that narrows the bandwidth of the light output from the endoscopy system to 415 nm and 540 nm. At this range, the light is strongly absorbed by hemoglobin, and the visibility of surface capillaries and blood vessels in the submucosa is enhanced.

NBI flexible cystoscopy is a relatively young application that allows the detection of urothelial lesions that are missed with standard white-light imaging in patients with known bladder cancer.4–7 A feasibility report showed that NBI flexible cystoscopy is able to increase the detection of urothelial carcinomas, finding 15 additional lesions in 12 of the 29 subjects examined.4 In a series of 427 patients who underwent follow-up cystoscopy, 109 were found with recurrence. Ninety were identified by both standard and NBI cystoscopy, 13 only by NBI. In particular, NBI detected extra papillary tumors or more extensive CIS in 58 (56%) patients who were found to have recurrences.5 In another series, 61 patients were examined 3 months after starting induction BCG therapy. Twenty-two had residual cancer. Interestingly, only 1 of 30 patients who had negative NBI cystoscopy findings had tumor. NBI cystoscopy outperformed urine cytology in detecting residual tumor after BCG therapy.6

In a previous experience, we used NBI for the first time during TUR. We performed cold-cup biopsies of lesions that were suspected to be bladder cancer under NBI at the end of an extensive protocol of transurethral restaging of newly diagnosed high-grade nonmuscle-invasive bladder cancer performed under standard white-light imaging.7 Areas with increased vasculature, characterized by a more intense dark green to black aspect, were found in 40 of 47 patients and were biopsied. Of 72 NBI biopsies, 11 were positive. Thanks to the 11 positive biopsies, nine patients were identified by NBI with microscopic high-grade cancer. Of this nine, six had a high-grade cancer that was not detected by means of white light.7

To date,4–7 NBI always has been tested sequentially after white-light inspection or resection of the bladder. As a matter of fact, up to date, only within patients prospective studies have been performed, leading to a bias that precludes understanding its real impact. After white-light inspection, the bladder mucosa is inspected by NBI. Thereafter, the TUR is performed with white light, including overt or suspected lesions that were identified by NBI inspection.

One of the major criticisms to the approach is that the observer is allowed to take a "second look" with the alternative light and a "third look" with the white light, generating a bias. Moreover, the study design, a within patient comparison, is

### Table 1. Characteristics of Patients Who Underwent Standard or Narrow-Band Imaging Transurethral Resection

<table>
<thead>
<tr>
<th></th>
<th>NBI group</th>
<th>Standard group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, range</td>
<td>72, 44–87</td>
<td>69, 19–89</td>
<td>0.439</td>
</tr>
<tr>
<td>Median ASA, range</td>
<td>2, 1–3</td>
<td>2, 1–3</td>
<td>1</td>
</tr>
<tr>
<td>Number of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males–females</td>
<td>26–3</td>
<td>24–9</td>
<td>0.174</td>
</tr>
<tr>
<td>Single–multiple lesions</td>
<td>16–13</td>
<td>22–11</td>
<td>0.505</td>
</tr>
<tr>
<td>At least one lesion larger than 3 cm–no lesion larger than 3 cm</td>
<td>7–22</td>
<td>13–20</td>
<td>0.313</td>
</tr>
<tr>
<td>Newly diagnosed–recurrent lesions</td>
<td>9–20</td>
<td>22–11</td>
<td>0.011</td>
</tr>
<tr>
<td>Recurrent lesions with previous history of high-grade bladder cancer–of low-grade bladder cancer</td>
<td>14–6</td>
<td>9–2</td>
<td>0.771</td>
</tr>
<tr>
<td>Recurrent lesions with previous history of multifocal bladder cancer–of single-site bladder cancer</td>
<td>10–10</td>
<td>6–5</td>
<td>1</td>
</tr>
<tr>
<td>Recurrent lesions with previous history of intravesical instillation of chemotherapeutic agent</td>
<td>9–11</td>
<td>4–7</td>
<td>0.932</td>
</tr>
<tr>
<td>Recurrent lesions with previous history of intravesical instillation of BCG</td>
<td>10–10</td>
<td>2–9</td>
<td>0.176</td>
</tr>
</tbody>
</table>

NBI = narrow-band imaging; BCG = bacille Calmette-Guérin.

### Table 2. Quality Outcome Indicators and Pathologic Examination of the Lesions Removed Either by Narrow-Band Imaging or Standard Transurethral Resection

<table>
<thead>
<tr>
<th></th>
<th>NBI group</th>
<th>Standard group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications rate (only grade I and II)</td>
<td>8/29 (27%)</td>
<td>11/33 (33%)</td>
<td>0.831</td>
</tr>
<tr>
<td>Median surgery time, range</td>
<td>20, 10–60</td>
<td>30, 10–50</td>
<td>0.381</td>
</tr>
<tr>
<td>Median time to catheter removal (days), range</td>
<td>2, 1–7</td>
<td>3, 1–7</td>
<td>0.288</td>
</tr>
<tr>
<td>Median time to discharge (days)</td>
<td>2, 2–8</td>
<td>3, 2–7</td>
<td>0.173</td>
</tr>
<tr>
<td>Rate of absence of muscle tissue in the specimen</td>
<td>0/29</td>
<td>1/33</td>
<td>–</td>
</tr>
<tr>
<td>Rate of T2 bladder cancer in the specimen</td>
<td>2/29 (7%)</td>
<td>2/33 (6%)</td>
<td>1</td>
</tr>
<tr>
<td>Rate of T1 bladder cancer in the specimen</td>
<td>3/29 (10%)</td>
<td>7/33 (21%)</td>
<td>0.415</td>
</tr>
<tr>
<td>Rate of high-grade nonmuscle-invasive bladder cancer</td>
<td>8/29 (27%)</td>
<td>12/33 (37%)</td>
<td>0.641</td>
</tr>
<tr>
<td>Rate of CIS</td>
<td>5/29 (17%)</td>
<td>2/33 (6%)</td>
<td>0.325</td>
</tr>
</tbody>
</table>

NBI = narrow-band imaging; CIS = carcinoma in situ.
prone to the statistical phenomenon of the regression to the mean.

To disclose the objective advantages of NBI technology on bladder cancer management, a prospective trial that compares TUR of bladder lesions, performed entirely with NBI, vs TUR of bladder lesions, performed entirely with standard white light is ongoing (registered at ClinicalTrials.gov - identifier: NCT01004211). The primary end point is to assess the recurrence rate of bladder cancer with each treatment modality. The study is designed to disclose an inferior recurrence rate (estimated at about 10%) in the group treated by NBI TUR with respect to the control group, treated by standard TUR.

Our previous study showed feasibility of the use of the resectoscope in the NBI modality. The procedure, however, was performed after an accurate coagulation of any source of bleeding. NBI light is strongly adsorbed by hemoglobin, and bleeding could interfere with visibility during NBI TUR. Therefore, we decided to extract data of the patients who were randomized from September to December 2008 in our center to assess whether any substantial differences in terms of surgery time, intraoperative and postoperative complications, or hospital stay could be detected between the two treatments groups.

Notably, the two treatment groups are homogenous with regard to age, sex, American Society of Anesthesiologists score, and multiplicity and dimension of the lesions resected. Indeed, the NBI group is characterized by a greater proportion of patients who underwent TUR of recurrent lesions: 20/29 (68%) in the NBI group vs 11/33 (33%) in the standard group \( P = 0.011 \). Theoretically, complications are likely to occur more frequently during TUR performed in a bladder in which there were previous procedures or intravesical instillations. Thus, the greater incidence of NBI TUR of recurrent lesions does not represent an argument against feasibility of the NBI TUR.

No death or grade III to IV complication was registered in the two groups. No significant difference was found regarding surgery time or time to catheter removal or discharge. Surprisingly, even if the difference does not reach statistical significance, the median surgery time and median time to catheter removal were fairly lower in the NBI group, although the baseline morphologic and pathologic characteristics of the lesions removed were similar.

Conclusion

NBI TUR appears feasible. The results of the ongoing randomized trial will show whether NBI TUR may reduce significantly the 1-year recurrence rate of bladder tumors.

Acknowledgments

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Disclosure Statement

No competing financial interests exist.

References


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Abbreviations Used

AURO.it = Associazione Urologi Italiani (Italian Association of Urologists)
NBI = narrow-band imaging
NBI TUR = transurethral resection performed in the NBI modality
TUR = transurethral resection