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Narrow Band Imaging reduces persistence of cancer in patients with pT1 high grade bladder cancer

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ABSTRACT

Purpose: To evaluate persistence rate on repeated transurethral resection of the bladder (re-TURB) 6 weeks after the first TURB in patients with pT1HG disease undergoing resection of the margins and bed on Narrow Band Imaging.

Materials and methods: A consecutive series of patients undergoing TURB and a diagnosis of pT1 high grade disease were prospectively enrolled. On initial TURB patients underwent classic white light resection of the tumour followed by narrow band image (NBI) resection of margins and bed. After 6 weeks from the initial TURB, patients underwent a re-TURB under white light. Persistence rates on re-TURB were recorded.

Results: Overall 797 patients underwent TURB, out of them 126 patients with pT1 high grade disease were included in the study. The total number of lesions was 226 meaning 1.79 lesions per patient. On re-TURB 24/126 (19%) of the patients presented residual disease with a total of 28/226 (12%) lesions identified. All these patients presented a pTa residual disease. Out of them 8/21 (38%) presented bladder cancer on the resection bed and 13/21 (62%) presented bladder cancer on margins.

Conclusion: Narrow Band Imaging trans-urethral resection of the bladder is an oncological effective procedure in the treatment of pT1HG disease. The procedure has a 19% of persistence rate which is inferior when compared to the available evidence on white light TURB. Further multicenter studies are needed in order to validate our results.

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Introduction

Non-muscle invasive bladder cancers (NMIBC) represent approximately 70% of all newly diagnosed bladder tumours, including stage Ta, stage T1 and carcinoma in situ (CIS) [1]. T1 bladder cancer represents 5%–20% of NMIBC and is defined as an invasion of the lamina propria without invasion of the muscularis

propria [2]. In patients with high-risk tumours, intravesical bacillus Calmette-Guérin (BCG) immunotherapy after transurethral resection of the bladder (TURB) reduces the risk of tumour recurrence; however failure may result in poor prognosis [3].

NMIBC exist on a continuum of risk in which patients with T1 high-grade (T1HG) bladder cancer are at the aggressive end of the spectrum. Following classic transurethral resection of the bladder (TURB) alone, T1HG bladder cancer has a 69%–80% recurrence rate and a 33%–48% chance of progression to muscle-invasive disease [4].

In order to achieve an accurate staging and improve prognosis in patients with pT1HG bladder cancer a second resection (re-TURB) 2–6 weeks after the initial TURB (iTURB) is recommended by the latest EAU guidelines [5]. At time of re-resection, 45%–76% of patients present residual bladder cancer and 29%–40% are upstaged to muscle-invasive disease [6]. However, re-TURB remains poorly performed ranging from 7 to 49% across different tertiary centers highlighting a poor adherence to guidelines worldwide [7–10].

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Notwithstanding the importance of re-TURB, the main goal of the surgeon should be improvement in quality of the initial resection (iTURB). re-TURB can be considered a quality control of the iTURB [5]. Narrow-band imaging (NBI) has been recently introduced to enhance the contrast between normal urothelium and hyper-vascular cancer tissue. According to the latest systematic review and meta-analysis, the use of NBI showed a reduction in the 3 months, 12 months and 24 months recurrence risk when compared to white light (WL) [11,12]. NBI improves tumour visibility by enhancing the contrast between vascularized lesions and normal mucosal [13–15], therefore the use of NBI when resecting margins and bed of the resection should guarantee a more accurate and complete iTURB.

With this knowledge in mind the aim of our study was to evaluate persistent rates on re-TURB (performed 6 weeks after iTURB), in patients with pT1HG disease undergoing resection of the margins and bed using Narrow Band Imaging during iTURB.

Materials and methods

After an internal review board approval, all patients with a pT1HG diagnosis on TURB between March 2013 and April 2014 were prospectively enrolled. All patients signed an informed consent and all the procedures were performed in accordance to the Declaration of Helsinki. All patients underwent clinical history and physical examination before TURB. Patients with no detrusor muscle in the specimens were excluded from the analysis.

Surgical procedure

All patients were submitted to WL iTURB plus NBI classic resections of the margins and bed in the same surgery session. Focality, number of lesions and dimensions were recorded.

All transurethral resections were performed using a 26 Ch resectoscope (Olympus, Tokyo, Japan), using a 30° optics with an ESG 400 scalpel, bipolar generator (Olympus, Tokyo, Japan). Saline solution was used as irrigation fluid. Resection of each lesion was carried out with classic technique resection [16]. After WL resection, the NBI light was used and TURB was performed on the margins and on the bed. More specifically, the four margins (up, down, left and right) of the lesion were resected with a median width of 2 mm however if NBI showed suspicious tissue the resection was extended. Resection of the bed was carried out to include detrusor muscle in the specimen. Six weeks after the initial re-TURB was performed under WL. All the material removed from the margins and/or from the bottom, was sent separately for histological examination. All procedures were carried out under regional anaesthesia by a single experienced surgeon (RG).

Histological analysis

Each single lesion was analysed by a single dedicated uropathologist blinded of all clinical data. Staging was given in accordance with the TNM classification (TNM 2009, Union International Contre le Cancer) [2] and graded according to the World Health Organization 2004 [17].

Statistical evaluation

Statistical analysis was performed using SPSS 24.0 software (SPSS Inc, Chicago, IL, USA). Evaluation of data distribution confirmed a not normal distribution of the study dataset. Differences between groups of patients in medians for quantitative variables and differences in distributions for categorical variables were tested with the Kruskal Wallis one-way analysis of variance and

Chi-square test, respectively. An alpha value of 5% was considered as the threshold for significance.

Results

Overall 797 patients underwent TURB, out of them 126 patients with pT1HG disease were included in the study. Out of the 126 patients enrolled 71 (56%) were males. Characteristics of the cohort are described in Table 1.

The total number of lesions was 226 meaning 1.79 lesions per patient. At the initial TURB using NBI the presence of tumour on the bed, on the margins and in both sites was detected in 6%, 37% and 35% of the cases respectively.

On re-TURB 24/126 (19%) of the patients presented residual disease with a total of 28/226 lesions identified (12%). All the lesions were pTa on histological examination. Out of them 8/28 (28%) presented bladder cancer on the resection bed, 13/28 (46%) presented bladder cancer on margins and 7/28 (25%) on both. When comparing patients with and without residual disease on re-TURBT, no statistically significant differences in terms of status, focality, dimension, positivity of bed resection and positivity of margins were recorded (Table 2).

Discussion

The present study evaluates the risk of persistence on re-TURB (performed 6 weeks after initial TURB), in pT1HG patients undergoing TURB of margins and bed using NBI technology. Standing to our results persistence rate at 6 weeks is 19% which is lower than the available series using WL TURB. Moreover, we observed on iTURB residual tumour in 78% of the lesions when resecting margins and bed on NBI. The latter result highlights the importance of resecting the margins and bed using NBI to achieve a complete resection. Lastly, the lack of pT2 and pT1 disease on re-TURB suggest NBI is an adequate tool to improve tumour staging on iTURB. To our knowledge, this is the first study available describing persistence rates on re-TURB in patients with pT1HG undergoing an accurate resection of margins and bed using NBI technology.

TURB is the essential surgical procedure used to diagnose, stage and treat primary and recurrent non-muscle invasive bladder tumours. Although ideally the iTURB should complete, many factors may jeopardize the quality of resection. These include the multiplicity, extent and location of tumours, surgical skills of the urological surgeon, quality of specimens provided and pathological analysis [18]. The available literature often concentrates on persistent rates in terms of number of patients with persistent disease. However, when evaluating the accuracy of the resection we strongly believe that persistency rates should be evaluated in terms of lesions. Therefore, in our study we carefully recorded the number

Table 1
Characteristics of the cohort population.

Sex (M/F)	71/55
Age	69 ± 4.2
Status	
Primitive	72/126 (57%)
Recurrent	54/126 (43%)
Focality	
Unifocal	57/126 (45%)
Multifocal	69/126 (55%)
Dimensions	
<3 cm	58/126 (46%)
>3 cm	68/126 (54%)
Positive Bed Resection	99/126 (79%)
Positive Margins	81/126 (64%)

Table 2

Characteristics of the cohort population according to re-TURBT resection outcomes.

	Negative reTURBT 102/126: 81%	Positive reTURBT 24/126: 19%	p
Age	68 ± 3.2	70 ± 4.2	0.545
Status			
Primitive	58/102 (57%)	14/24 (58%)	0.896
Recurrent	44/102 (43%)	10/24 (42%)	
Focality			
Unifocal	46/102 (45%)	11/24 (46%)	0.948
Multifocal	56/102 (55%)	13/24 (54%)	
Dimensions			
<3 cm	45/102 (44%)	13/24 (54%)	0.374
>3 cm	57/102 (56%)	11/24 (46%)	
Positive Bed Resection on iTURB	79/102 (81%)	20/24 (62%)	0.527
Positive Margins on iTURB	65/102 (67%)	16/24 (52%)	0.787

of lesions and their location and then evaluated the persistence of disease for each lesion. The persistence rate on re-TURB when using NBI during iTURB is then 12% which is an excellent result specially when considering that the main goal of TURB is to remove all possible sites of tumours.

The latest EAU guidelines underline the importance of the quality of TURB to achieve a good prognosis [5]. In our series all the operations were performed by a single experienced surgeon and all the specimens included detrusor muscle. The accurate resection of bed and margins on NBI during first TURB revealed bladder cancer in 78% of the lesions and in 17 cases (patients excluded from the analysis) revealed muscle invasive bladder cancer. Given the high percentage of lesions observed in the margins and bed on first TURB and the low persistence rate on re-TURB, the use of NBI technology seems essential to guarantee a complete resection and staging of the disease. As stated by the latest EAU guidelines re-TURB should be performed to evaluate the quality of the initial resection.

Since the initial resection of the bladder is often incomplete, re-TURB is considered essential specially in patients with high risk disease to improve staging and recurrence rates. In 2002 Schips and colleagues, evaluated the value of re-TURB in patients with newly diagnosed bladder cancer [19]. According to their results, up to 36.4% of the patients presented residual disease and approximately 10% were under-staged [19]. They concluded reTURB is justified specially in patients with HG bladder cancer. Similar results were reported by Angulo and Grimm confirming the poor quality of initial resections [20,21]. The latest meta-analysis [22] including 29 studies found a pooled persistence rate of 61% and a pooled risk of under-staging of 15% in pT1HG patients.

Although reTURB is an effective procedure to improve staging and management of NMIBC, as much as 40% of patients will be overtreated. Ideally if the surgeon could improve the quality of the initial resection, reTURB would not be necessary. NBI and photodynamic diagnosis have been recently introduced to improve tumour visualization and quality of resection.

The role of NBI technology in reducing recurrence rate after TURB has been recently analysed in a meta-analysis by Kang and colleagues [11]. According to their results, NBI-TUR in NMIBC was associated with a significant benefit in the 3-mo (RR: 0.39; 95% CI, 0.26–0.60; $p < 0.0001$), 1-yr (RR: 0.52; 95% CI, 0.40–0.67; $p < 0.00001$) and 2-yr (RR: 0.60; 95% CI, 0.42–0.85; $p = 0.004$) recurrence risks compared with WLI-TUR [11]. As well, the role of NBI in NMIBC staging has been evaluated by Kim and colleagues in their prospective randomized trial to investigate the value of immediate second resection of the tumour bed [23]. The study authors stated that immediate second resection of the tumour bed after complete TURB improved the effectiveness of the resection by immediately confirming the presence of MP in the specimen and

accurately differentiating muscle-invasive diseases. The main advantages of the immediate second resection were precise prediction on final pathology results and reduced early recurrence. Moreover, NBI technology improves persistent lesions not visible in WL in 12–20% of the cases [24]. The risk of under-staging after TURB has been reported in up to 50% of the patients, however according to our results this risk is minimized when applying NBI technology considering that no pT1 or pT2 disease was found on reTURB. Specially, we strongly believe that the use of NBI technology when resecting the base and the margins of the lesions enables a better staging of the disease.

Standing to the available evidence NBI technology improves cancer detection, staging and recurrence rates however photodynamic diagnosis (PDD) and SPIES technology (Karl Storz, Tuttlingen, Germany) have been proposed as an alternative to this technology. Photodynamic diagnosis (PDD) is performed using violet light after intravesical instillation of 5-aminolaevulinic acid (ALA) or hexamino-laevulinic acid (HAL). Chou and colleagues in their recent meta-analysis have successfully confirmed the role of PDD in reducing recurrence rates when compared to WL (RR 0.59, 95% CI 0.40 to 0.88, $I^2 = 69%$) [25]. Moreover, PDD may be associated with a decreased risk of progression, but more studies with long-term follow up are needed to better understand the effects of the photosensitizer used on progression [25]. Although many trials have assessed NBI and PDD vs WLC, head to head RCT between NBI and PDD are lacking [26]. Lee et al. addressed this issue in their network meta-analysis comparing these visualization technologies [27]. According to their results the recurrence rate of cancers resected using PDD versus NBI did not significantly differ. They concluded that the recurrence rate of some bladder cancers can be decreased by the implementation of either PDD- and NBI-assisted TURB [27]. Certainly, a well-designed comparative study between both visualization systems (NBI vs PDD) is needed to understand which method is the most accurate. Moreover, to our knowledge no studies using PDD have looked at persistence rates on re-TURB. PDD technology is not available in our center, otherwise the inclusion of a comparative arm would have certainly enhanced the scientific quality of our paper. The absence of this data can be acknowledged as a limitation of this study. SPIES technology is based on the modular IMAGE1 S camera platform that incorporates four different visualization modes [28]. The first pilot study evaluated the variability in interpretation of the same bladder mucosa image using the four different modalities and WLI. The technology improved interobserver agreement when compared to WL [29]. A RCT endorsed by the CROES in 2015 comparing the recurrence rate in patients treated with SPIES-assisted vs. WLI TURB is still ongoing and therefore SPIES is to be considered an experimental technology [30].

The present study has other limitations. The study is a single center study, therefore our results apply to the enrolled population

and may be not representative of other cohorts. The lack of a control group may be a limitation, however for ethical reasons we didn't want to perform TURB without NBI technology in any patient given the well-known results in terms of recurrence rates. As well the number of patients may be a possible bias, however we selected only pT1HG tumours from a larger cohort and to our knowledge this is the largest and only cohort evaluating the persistence of disease on re-TURB using NBI technology during the iTURB. Moreover, the lack of data on increase in surgical time by the use of NBI may be considered a possible limitation of our study. However, in our experience, the activation of NBI light takes just few seconds and we don't think surgical time is increased significantly when compared to classic WL TURB. Further studies addressing this issue should be performed. Lastly, the lack of follow up is a possible limitation of our study. However, the study was designed prospectively to investigate the possible role of NBI in improving the quality of the initial resection and therefore the lack of follow up do not alter the primary objective of the study neither our conclusions.

Conclusions

The use of NBI technology in the resection of margins and base improves persistence rates on re TURB in patients with pT1HG disease. Moreover, we didn't observed any pT2 disease in reTURB. If our results should be confirmed in further large multicentre cohort studies, NBI technology may have a role in improving the initial staging of the disease.

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Authorship

Authors have made a substantial contribution to the following:

Roberto Giulianelli: research design, acquisition, analysis and interpretation of data; draft the paper, approved the submitted and final versions.

Barbara Cristina Gentile: research design, acquisition of data; revised the paper critically; approved the submitted and final versions.

Gabriella Mirabile: research design, analysis of data; revised the paper critically; approved the submitted and final versions.

Luca Albanesi: research design, interpretation of data; revised the paper critically; approved the submitted and final versions.

Luca Mavilla: research design, interpretation of data; revised the paper critically; approved the submitted and final versions.

Paola Tariciotti: research design, acquisition, analysis and interpretation of data; drafted the paper or; approved the submitted and final versions.

Giorgio Rizzo: research design, acquisition of data; revised the paper critically; approved the submitted and final versions.

Francesco Fabi: research design, interpretation of data; revised the paper critically; approved the submitted and final versions.

Cristina Falavolti: research design, acquisition of data; revised the paper critically; approved the submitted and final versions.

Pietro Aloisi: research design, analysis and interpretation of data; drafted the paper; approved the submitted and final versions.

Giorgio Vincenti: research design, analysis and interpretation of data; drafted the paper; approved the submitted and final versions.

Giorgia Tema: research design, acquisition of data; revised the paper critically; approved the submitted and final versions.

Riccardo Lombardo: research design, acquisition, analysis and interpretation of data; drafted the paper or; approved the submitted and final versions.

Competing interests

The authors have no competing interests.

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