ORIGINAL PAPER

Prognostic impact of ReTURB in high grade T1 primary bladder cancer

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Summary
Purpose: To evaluate whether pathological outcomes of ReTURB have a prognostic impact on recurrence and progression of primitive T1HG bladder cancer.

Material and methods: Patients affected by primitive T1HG TCC of bladder underwent restaging TURB (ReTURB). Patients with muscle invasive disease at ReTURB underwent radical cystectomy; those with non-muscle invasive residual (NMI-R) and those with no residual tumour (NRT) received an intravesical BCG therapy. We compared recurrence and progression in NMRT patients and NRT patients at restaging TURB. Patients were followed every 3-6 months with cystoscopy and urine cytology.

Results: 212 patients were enrolled in the study. At ReTURB, residual cancer was detected in 92 of 196 (46.9%) valuable patients: 14.3% of these were upstaged to T2. At follow up of 26.3 ± 22.8 months, there were differences in recurrence and progression rates between NRT and NMRT patients: 26.9% and 45.3% (p < 0.001), 10.6% and 23.4% (p 0.03), respectively. Recurrence-free and progression-free survivals were significantly higher in NRT compared to NMRT patients: 73.1% and 54.7% (p < 0.001), 89.4% and 76.6 (p 0.03), respectively.

Conclusions: ReTURB allows to identify a considerable number of residual and understaged cancer. Patients with NMRT on ReTURB have worse prognosis than those with NRT in terms of recurrence and progression free survival. These outcomes seem to suggest a prognostic impact of findings on ReTURB that could be a valid tool in management of high grade T1 TCC.

Key words: Bladder cancer; ReTURB; Prognosis.

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INTRODUCTION
Bladder cancer includes tumours of extremely heterogeneous biological behaviour. Approximately 75-85% of all patients present with non muscle invasive (NMI) bladder cancer (1). Transurethral resection of the bladder (TURB) is the cornerstone approach in the diagnosis, initial staging and therapy of transitional cell carcinoma (TCC). However the rate of residual tumour after TURB of neoplasms invading the lamina propria (T1 TCC) ranges from 28% to 76% at any site (2-11) and from 22 to 74% at the same site of first TURB (12-15). Moreover 9 to 49% of tumours after TURB are understaged; particularly, up to 28% of T1 TCC are upstaged to T2 at the second resection (16). High grade T1 TCC present a high risk of progression and represent a controversial therapeutic issue. It has been demonstrated that restaging TURB (ReTURB) is a valid tool to improve recurrence-free and progression-free survival, and, improving staging accuracy, to identify understaged T2 cancer that could benefit from an early radical treatment (17). However, it is not clear whether or not patients with no residual cancer at ReTURB have a better prognosis than those with residual cancer. We have evaluated the usefulness of second TURB and whether pathological outcomes of ReTURB have a prognostic impact on recurrence and progression of primitive T1G3 bladder cancer.

MATERIALS AND METHODS
Patients affected by primitive T1G3 transitional cell carcinoma of bladder were enrolled in this study and underwent second look TURB 4-6 weeks following the initial TURB. Informed consent was obtained from each patient. Patients who refused ReTURB and those who have undergone incomplete resection were excluded from the study. Restaging TURB consisted of fractioned resection of all visible lesions, depth resection of base and borders of previous resection area, biopsy of any abnormal mucosal area, it was performed by the same urologist who performed the first TURB. Pathological evaluation was carried out according to the TNM system of UICC and to the WHO grading classification. Patients with muscle invasive disease underwent radical cystectomy; those with non-muscle invasive residual (NMI-R) and those with no residual tumour (NRT) received an induction 6 weeks course of intravesical BCG followed by maintenance SWOG schedule (Table 1). All patients were followed with cystoscopy and voiding urine cytology every 3-4 months for the first and second year, every 6 months for the third and fourth year, and annually thereafter. Diagnostic imaging of the upper tract and chest X ray were performed at least annually or when clinically indicated. In order to evaluate the prognostic significance of ReTURB outcomes, we compared recurrence and progression rate, and recurrence and progression free survival in NMI-R and NRT patients at restaging TURB. Recurrence was defined as first evidence of any tumour at follow up, progression was defined as

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muscle invasive tumour or evidence of metastasis. Categorical variables are presented as numbers and frequency values and compared by chi-square and Fisher exact test as appropriate. Continuous variables are expressed as mean ± standard deviation and compared by T Student test. A cumulative survival curve for recurrence-free and progression-free survival was drawn using the Kaplan-Meier method, log-rank test was used to compare differences between NMIRT and NRT patients. A p value ≤ 0.05 with the 2-tailed test was considered to be statistically significant. Statistical analysis was carried out by Statistical Package for Social Sciences software package version 16.0 (SPSS, Chicago, Ill. USA).

RESULTS
From January 2002 to September 2013, 212 eligible patients were enrolled in the study. Were excluded from the study, 11 patients who refused restaging TURB and 5 who underwent incomplete resection. The average age of 196 valuable patients (173 males and 23 females) was 69.5 ± 9.5 years. Of the entire cohort of 196 patients, 146 (74.5%) had a solitary tumour and 50 (25.5%) had multiple lesions, at first TURB, 6 patients showed concomitant Carcinoma in Situ (CIS). In 19 patients (9.7%) pathological analysis revealed absence of muscle in specimen. The TURB was performed by 6 experienced urologists and pathological evaluation was carried out by 1 dedicated uropathologist. At Restaging TURB residual cancer was histologically detected in 92 patients (46.9%). In 5 cases (2.3%) was observed prolonged bleeding (> 24 hours), but not requiring any blood transfusion. There was no significant statistical association between primitive tumour locale and evidence of residual cancer at ReTURB: 35.3% (44/124) of patients with solitary tumour had residual cancer compared to 45.4% (20/44) of patients with multiple lesions (p 0.28). Among the 92 patients with residual cancer at ReTURB, 41 (20.9%) presented identical stage and grade, while 28 (14.3%) were upstaged to T2. Histological outcomes of the remaining patients with residual cancer are listed in Table 2.

Patients with muscle invasive cancer underwent radical cystectomy. Of the remaining 168 patients with no residual tumour (NRT) and those with non muscle invasive residual tumour (NMIRT), 57 (33.9%) had recurrence and 26 (15.5%) progressed to muscle invasive disease after a mean follow up of 26.3 ± 22.8 months. There was statistically significant difference in recurrence rate between NRT and NMIRT patients: 26.9% vs 45.3% respectively (p < 0.001) (Table 3). Estimated actuarial recurrence-free survival rate was significantly higher in NRT group (73.1%) compared to NMIRT patients (54.7%) (log-rank 10.64; p < 0.001) (Figure 1). Progression of the disease occurred in 10.6% of NRT patients and in 23.4% of NMIRT patients (p = 0.03), estimated actuarial progression-free survival rate was higher in NRT group (89.4%) compared to NMIRT patients (76.6%) (log-rank 4.58; p = 0.03) (Figure 2). Follow up of NRT patients was significantly longer than that of NMI-RT patients (34.8 ± 24.0) vs 22.8 ± 15.6 months, p = 0.005).

DISCUSSION
T1HG TCC are high risk tumours and they represent a great challenge for the urologists; they can present with various biological behaviour, so it is not easy to identify those with worse prognosis that could benefit by early radical cystectomy. Recurrence within 3 months of TURB is one of the most important prognostic factors for time to progression and progression free survival of NMI bladder cancer (18, 19). This rate depends on several factors such as stage, tumour size, number of lesions, use of adjuvant therapy, surgeon's experience (20). However it is essential to distinguish between patients with true early recurrence and those with residual tumour due to an incomplete resection. It has been demonstrated that residual cancer after TURB of T1 bladder cancer ranges from 28 to 76% at any site (2-11) and from 22 to 74% at the same site of first TURB (12-15), depending on stage, grade, multiplicity, appearance of tumour, surgeon's experience and modality of resection (2, 3, 10, 11, 21). Moreover several studies, assessing the staging value of ReTURB, proved that 9-49% of NMI bladder cancer had been underestimated at first TURB (3, 4, 7, 8), and, par-

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**Table 1.** Groups of patients.

|               | NRT (pts) | NMIRT (pts) | p value |
|---------------|-----------|-------------|---------|
| Total (196 pts) | 104       | 64          |         |
| Residual tumour (92 pts; 46.9%) | 51 (28 pts; 14.3%) | 23 (33.3%) | 0.0005 |
| Non muscle invasive residual tumour [NMIRT] (64 pts; 32.7%) | 31 (20 pts; 12.5%) | 31 (48.4%) | 0.0005 |

**Table 2.** Histological outcomes of ReTURB.

| Stage and grade | Pts (n) |
|----------------|---------|
| T0             | 104     |
| TaG1 (+CIS)    | 6 (1)   |
| TaG1           | 4       |
| TaG2 (+CIS)    | 1 (2)   |
| TaG3           | 1       |
| TaG3 (+CIS)    | 39 (2)  |
| CIS            | 8       |
| T2             | 28      |

**Table 3.** Outcomes of NRT and NMIRT patients.

|                      | NRT (pts) | NMIRT (pts) | p value |
|----------------------|-----------|-------------|---------|
| Pts (n)              | 104       | 64          |         |
| Age (years)          | 69.3 ± 9.9| 70.6 ± 9.0  | 0.38    |
| Mean follow up (months) | 34.8 ± 24.0 | 22.8 ± 15.6 | 0.005   |
| Multilocality at first TURB (%) | 23.1 | 31.2 | 0.28 |
| Recurrence rate % (n) | 26.9 (28/104) | 45.3% (29/64) | < 0.001 |
| Progression rate % (n) | 10.6 (11/104) | 23.4 (15/64) | 0.03 |

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TURB for T1G3 TCC, the specimens were suitable for complete pathological assessment (26). In the study of Bernardini et al. muscularis propria was absent in 55 of 149 (36%) patients (27), likewise Cheng et al. reported absence of muscle in TURB samples in 66% of patients with T1 TCC (28). Herr et al. demonstrated understaging in 49% of T1 patients without and in 14% of those with muscularis propria in the specimens of first TURB. In this study 8% of Ta/Cis tumours and 27.6% of T1 were upstaged to muscle invasive cancer by ReTURB (29).

In our study, we have evaluated the usefulness and the prognostic significance of second TURB in patients affected by primitive high grade T1 TCC. The second TURB was safe and only 5 self-limiting bleeding occurred. However, though resection of bladder was performed by experienced surgeons, residual cancer occurred in 46.9% of patients. Histological evaluation revealed muscle invasive disease in 28 (14.3%) patients and CIS in 13 (6.6%). Particularly, 6 of 19 (31.6%) patients without muscularis propria in samples of first TURB were classified as T2 TCC on second TURB; these data underline relevance of adequate samples containing muscularis propria, as yet demonstrated in other series.

The prognostic value of second look TURB on natural history of bladder cancer has not enough been elucidated; in fact, only few studies have investigated impact of pathological outcomes of ReTURB on recurrence and progression of primitive T1 bladder cancer. In a study on 42 patients affected by primitive T1G2-3 TCC, restaging TURB revealed 64% of residual tumours, 48% of muscle invasive cancers and 19% of CIS. At mean follow up of 60 months the recurrence rate of no residual tumour (NRT) patients was 33% compared to 57%, 75% and 87.5% of Ta, Cis and T1 residual cancer (Tr) patients, respectively; moreover, organ preservation rate was 100% for NRT patients and 64% for Tr patients (8). In a prospective randomized trial, Divrik et al. compared outcomes of ReTURB plus intravesical MMC (Group 1) with TURB plus intravesical MMC (Group 2) in 210 patients affected by T1 TCC of bladder; at mean follow up of 66.1 months, recurrence rate was 37/93 % in group 1 and 70/98 2% in group 2. Median recurrence free survival (RFS) was 47 months for group 1 compared to 12 months for group 2. Progression was
observed in 6.5% of patients for group 1 and in 23.5% of patients for group 2 (p = 0.001). Median progression-free survival (PFS) was 73 months for group 1 compared to 53.5 months for group 2. Overall survival of both groups was 67.7% and 61.3% (log rank 0.363), respectively. This study demonstrated that the differences in terms of recurrence between two groups were due to the presence of residual tumour in group 2 rather than true recurrence and that intravesical chemotherapy did not compensate for inadequate resection (17).

In a recent study on 352 T1 TCC patients with a 7.5 years of median follow up, those with T1 residual cancer on ReTURB presented higher BCG failure rate (53%), recurrence rate (88%) and progression rate (82%) than patients with no residual cancer (3%, 48% and 8%, respectively). The authors suggest that early cystectomy may be advised for patients with T1 residual cancer on Restaging TURB (30).

Our data revealed a statistical significant difference in recurrence rate, recurrence free survival, progression rate and progression free survival between patients with and without residual cancer on ReTURB. Patients with no muscle invasive residual tumour on ReTURB have higher recurrence (45.3% vs 26.9%), progression rates (23.4% vs 10.6%) and worse recurrence and progression free survival than those with no residual tumour, though they presented significant shorter follow up (22.8 vs 34.8 months).

These outcomes seem to suggest a prognostic impact of findings on ReTURB that could be a valid tool in identifying patients at high risk of progression that could be ideal candidates for an early radical cystectomy. However, evidences of our study are limited by retrospective data evaluation and relatively short follow up.

**Conclusions**

Complete tumour eradication and correct staging are of paramount importance in primary diagnosis and treatment of bladder cancer. It has been clearly shown that persistence of tumour can negatively affect recurrence and even progression free survival. Understaging with delay of appropriate treatment can affect overall patient survival after radical cystectomy.

TURB still remains the cornerstone modality for staging and primary treatment of bladder cancer. However, even in experienced hands, it is far from being perfect, with a consistent percentage of residual disease or tumour understaging left behind. Second look TURB in a short delay appears to be very useful in case of T1 and/or high grade tumours and mandatory whenever the tissue specimen does not allow a correct evaluation of the muscular layer. In our study patients with non muscle invasive residual tumour on ReTURB show worse prognosis than those with no residual tumour in terms of recurrence and progression of disease.

A longer follow up and a larger series of patients are essential to confirm the prognostic value of findings on ReTURB and to demonstrate whether ReTURB outcomes can identify patients at high risk of progression that could benefit from early cystectomy.

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