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Bladder Cancer

Repeat Transurethral Resection (TUR) + Bacillus Calmette-Guérin (BCG) Versus Upfront Induction BCG After TUR in High-risk Non–muscle-invasive Bladder Cancer: Feasibility Phase of a Randomized Controlled Study

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Abstract

Background: High-level evidence supporting the role of repeat transurethral resection (reTUR) in non–muscle-invasive bladder cancer (NMIBC) is lacking. A randomized controlled trial (RCT) assessing whether immediate reTUR has an impact on patient prognosis is essential. However, since such a RCT will require enrollment of a high number of patients, a preliminary feasibility study is appropriate.

Objective: To assess the feasibility of an RCT investigating the impact of immediate reTUR + adjuvant bacillus Calmette-Guérin (BCG) versus upfront induction BCG after initial TUR in NMIBC.

Design, setting, and participants: Eligible patients were randomly assigned to receive either reTUR + adjuvant BCG or upfront induction BCG after TUR. Patients with macroscopically completely resected high-grade T1 NMIBC, with or without concomitant carcinoma in situ, and with detrusor muscle (DM) present in the initial TUR specimen were considered eligible for inclusion. Exclusion criteria included lymphovascular invasion (LVI), histological subtypes, hydronephrosis, concomitant upper tract urothelial carcinoma (UTUC), or urothelial carcinoma within the prostatic urethra. The aim was to enroll 30 patients in this feasibility study.

Outcome measurements and statistical analysis: The patient recruitment rate was the primary outcome. Oncological outcomes (recurrence-free and progression-free survival) were secondary endpoints.

Results and limitations: Overall, 30 patients (15 per arm) were randomized over a period of 14 mo (August 2020–October 2021). Two eligible patients refused the randomization, resulting in a patient compliance rate of 93.3% for the study protocol. We excluded 49 ineligible patients before randomization because of histological subtypes (n = 16, 33%),

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LVI (n = 9, 18%), DM absence in the TUR specimen (n = 12, 24%), metastatic disease (n = 5, 10%), concomitant UTUC (n = 3, 6%), or hydronephrosis (n = 4, 8%). At reTUR, persistent disease was found in four patients (29%) and upstaging to muscle-invasive disease in one (7%). Over median follow-up of 17 mo, disease recurrence was detected in three patients (23%) in the reTUR arm and six patients (40%) in the upfront BCG arm. Progression to muscle-invasive disease was observed in one patient treated with upfront BCG.

Conclusions: The feasibility of conducting an RCT comparing upfront BCG versus reTUR + BCG in high-grade T1 NMIBC has been demonstrated. Our results underline the need to screen a large number of patients owing to characteristics meeting the exclusion criteria in a high percentage of cases.

Patient summary: We found that a clinical trial of the role of a repeat surgical procedure to remove bladder tumors through the urethra would be feasible among patients with high-grade non–muscle-invasive bladder cancer. These preliminary results may help in refining the role of this repeat procedure for patients in this category.

1. Introduction

There is still only weak clinical evidence regarding the role of repeat transurethral resection (reTUR) of the bladder in non–muscle-invasive bladder cancer (NMIBC). International guidelines recommend a second resection within 2–6 wk after the first TUR after an incomplete initial TUR, if there is no detrusor muscle (DM) in the specimen after initial TUR, except in cases of low-grade (LG)/G1 Ta tumors and primary carcinoma in situ (CIS), and for all T1 tumors [1]. The rationale for performing reTUR is the high risk of residual disease following the initial resection, which ranges from 17% to 71%, depending on the series [2], and the risk of understaging (up to 50% in historical series of patients with G3 T1 disease treated with upfront radical cystectomy [RC]) [3].

Not all studies agree on the role of reTUR. A recent large retrospective study in patients with G3 T1 disease treated with BCG found no advantage for reTUR when DM was present in the primary TUR specimen [4]. Hence, there is controversy regarding whether patients with DM in the TUR specimen (considered a proxy for good TUR quality and accurate staging) can be spared a second TUR [5]. Moreover, with the aim of sparing selected patients from reTUR, efforts have been made to investigate predictors of residual disease and/or upstaging, mostly with unsatisfactory results [6,7]. To date, only one randomized controlled trial (RCT) comparing reTUR to no reTUR in patients receiving intravesical instillations of mitomycin C has been published; however, the results have high risk of bias owing to selective exclusion of patients from the analysis and inadequate adjuvant treatment with mitomycin C [8]. It should also be underlined that reTUR represents an invasive and morbid procedure for patients who have just undergone an endoscopic resection and maybe still be suffering from related symptoms. Moreover, reTUR is not devoid of complications and requires general or locoregional anesthesia. Finally, reTUR has a non-negligible impact on health care costs, waiting lists, and patients' quality of life.

A new prospective RCT investigating whether reTUR has an impact on patient prognosis (and may thus be an unnecessary procedure) is thus essential to fill the current evidence gap in this field. However, since such an RCT will require enrollment of a very high number of patients, a feasibility study is mandatory. Moreover, since international guidelines make a strong case for immediate reTUR in any T1 disease in spite of the low level of scientific evidence, patient awareness may reduce compliance with study participation.

The objective of the present study was to evaluate the feasibility of conducting an RCT investigating clinical outcomes of immediate reTUR followed by standard conservative therapy (BCG) versus upfront induction BCG after TUR without reTUR in selected cases of high-grade (HG) T1 NMIBC. Secondary endpoints were the NMIBC persistence and recurrence rates at reTUR, and recurrence and progression rates after BCG treatment.

2. Patients and methods

2.1. Patients and randomization

This was a single-center feasibility RCT. Patients aged ≥18 yr with a new diagnosis of completely resected HG T1 NMIBC, with or without concomitant CIS, were considered eligible for the study. DM presence in the specimen from the initial TUR was also required. The presence of hydronephrosis, lymphovascular invasion (LVI), histological subtypes, cN+/M+ disease on computed tomography, concomitant upper tract urothelial carcinoma, or involvement of the prostatic urethra were considered exclusion criteria. The study received ethical approval (00125/2020). Before randomization, all patients underwent a staging computed tomography scan of the thorax, abdomen, and pelvis.

2.2. Treatment and follow-up

After providing consent, participants were randomly assigned (1:1) to either reTUR plus induction BCG, or to upfront induction BCG after initial TUR, without stratification. Patients randomized to the reTUR group underwent reTUR within 2–6 wk after their first TUR. reTUR was defined as loop resection of the scar of the first TUR with or without cold biopsies of suspicious areas. After reTUR, patients were treated with induction BCG (6 weekly instillations). In cases with upstaging (defined as the occurrence of muscle-invasive bladder cancer [MIBC]) at reTUR, patients were treated with RC, eventually preceded by neoadjuvant chemotherapy. Patients randomized to the upfront BCG group were treated

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immediately with induction BCG (6 weekly instillations). Maintenance BCG was given at 3 and 6 mo and every 6 mo thereafter for up to 3 yr in both groups.

Follow-up was performed according to international guidelines and usually consisted of urine cytology, ultrasound of the abdomen/pelvis, and flexible cystourethroscopy every 3 mo for the first 2 yr, and every 6 mo thereafter. Cold biopsy/TUR of suspected areas was performed when appropriate. Imaging of the upper tract was usually carried out at diagnosis and yearly thereafter. In cases with positive urine cytology and negative cystoscopy, random bladder biopsies, prostatic urethra resection, and upper urinary tract evaluation were performed.

2.3. Statistical analysis

Results are reported as the absolute number and percentage for categorical variables, and the median and interquartile range (IQR) for continuous variables. The main study outcome was the number of patients screened and identified as eligible during the study period, with assessment of the recruitment rate. Secondary outcomes were acceptance of the allocated treatment and exploratory analysis of preliminary oncological outcomes (recurrence-free survival [RFS] and progression-free survival [PFS]) in the two groups. RFS and PFS were defined as the time from initial HG T1 diagnosis on initial TUR and the occurrence of NMIBC recurrence or progression to MIBC, respectively, during follow-up. The Kaplan-Meier method was used to estimate RFS and PFS according to treatment allocation. The log-rank test was used to compare differences in RFS and PFS between the two groups. For RFS and PFS, patients without an event were censored at the time of the last negative disease recurrence/progression assessment or last negative cystoscopy. Statistical analyses were performed using Stata version 16 (Stata Corp., College Station, TX, USA). All tests were two-sided and $p < 0.05$ was considered statistically significant.

3. Results

Baseline patient characteristics are listed in Table 1. Overall, 30 patients (15 per arm) were randomized over a period of 14 mo (August 2020–October 2021). Two eligible patients refused their randomization, resulting in a patient compliance rate of 93.3% for the study protocol. We excluded 49 patients before randomization because of histological subtypes (n = 16, 33%), LVI (n = 9, 18%), DM absence in the initial TUR specimen (n = 12, 24%), metastatic disease (n = 5, 10%), concomitant UTUC (n = 3, 6%), or hydronephrosis (n = 4, 8%; Table 2).

One patient randomized to the reTUR arm did not undergo reTUR because of an acute cardiovascular event. At reTUR, nine patients (64%) were disease-free, while persistent Ta disease was found in two patients (14%) and persistent T1 disease in a further two (14%). One patient (7%) was upstaged to MIBC at reTUR and was subsequently treated with neoadjuvant chemotherapy and RC. Therefore, 13 of the 15 patients in the reTUR group were treated with induction BCG as planned. All of the patients randomized to the upfront BCG arm received and completed induction BCG.

Table 1 – Descriptive characteristics for the cohort of 30 patients with high-grade T1 non–muscle-invasive bladder cancer randomized in the trial between August 2020 and October 2021

Parameter	Overall	Randomization arm	
		Repeat TUR	Upfront BCG
Patients, *n* (%)	30	15 (50)	15 (50)
Median age, yr (IQR)	74 (66–80)	73 (64–83)	74 (66–78)
Sex, *n* (%)			
Female	5 (17)	1 (7)	4 (27)
Male	25 (83)	14 (93)	11 (73)
Smoking status, *n* (%)			
Smoker	25 (83)	1 (7)	4 (27)
Never smoker	5 (17)	14 (93)	11 (73)
Occupational exposure, *n* (%)	7 (23)	5 (33)	2 (13)
Median tumor size, cm (IQR)	3 (2–3)	3 (2–4)	3 (2–3)
Concomitant carcinoma in situ, *n* (%)	4 (13)	3 (20)	1 (7)
Multifocal tumor, *n* (%)	13 (43)	6 (40)	7 (47)

TUR = transurethral resection; BCG = bacillus Calmette-Guérin; IQR = interquartile range.

3.1. Exploratory oncological outcomes

Over median follow-up of 17 mo (IQR 15–19), disease recurrence was detected in three patients (23%) in the reTUR arm and six patients (40%) in the upfront BCG arm (Fig. 1; p = 0.3). Disease progression to MIBC has been observed in one patient treated with upfront BCG (Fig. 2; p = 0.4). During follow-up, two patients (both in the upfront BCG group) underwent early RC for BCG-unresponsive disease.

4. Discussion

We demonstrated the feasibility of conducting an RCT in a selected population with HG T1 NMIBC to compare the standard of care, represented by reTUR followed by intravesical BCG, with upfront BCG after initial TUR. Our results highlight the need to screen a large number of patients owing to characteristics meeting the exclusion criteria in a high percentage of cases.

High-quality evidence on the oncological role of reTUR is urgently needed. Although reTUR is recommended for all T1 tumors and for patients without DM in their initial TUR specimen (with the exception of LG Ta disease) [1], its routine use has been questioned for several reasons. First, in a retrospective series of 2451 patients with G3 T1 NMIBC treated with BCG, a positive impact of reTUR on oncological outcomes such as RFS, PFS, cancer-specific survival, and overall survival was found only for patients with no DM

Table 2 – Reasons for screening failure among 49 patients diagnosed with high-grade T1 non–muscle-invasive bladder cancer between August 2020 and October 2021

Reason for screening failure	Patients, *n* (%)
Histological subtypes	16 (27)
DM absence in TUR specimen	12 (20)
Lymphovascular invasion	9 (15)
cN+/M+ disease	5 (8)
Hydronephrosis	4 (7)
Upper tract urothelial carcinoma	3 (5)
Enrollment refused	2 (3)
Incomplete resection	2 (3)
Prostatic urethra involvement	1 (2)

DM = detrusor muscle; TUR = transurethral resection.

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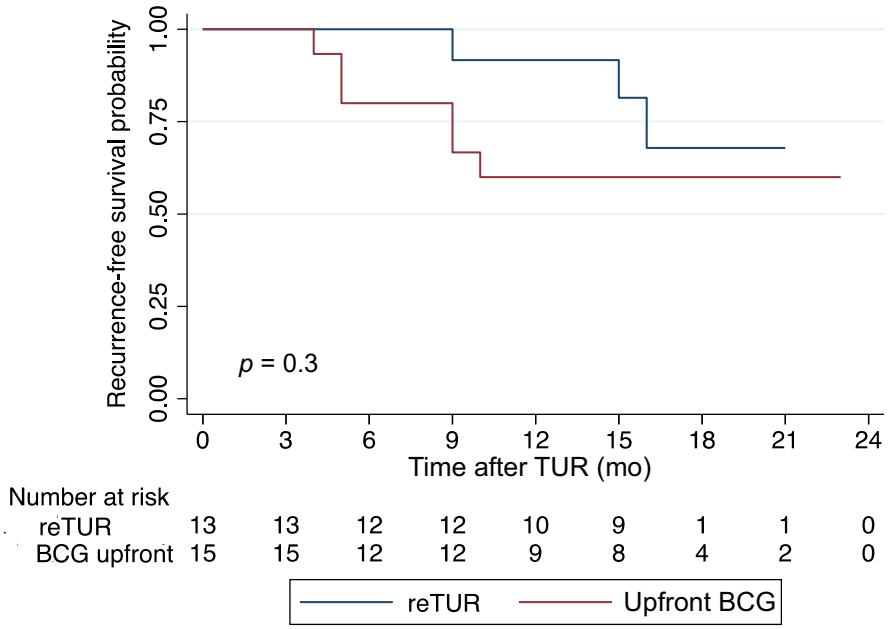

Fig. 1 – Recurrence-free survival for the cohort of 30 patients with high-grade T1 non–muscle-invasive bladder cancer randomized in the trial between August 2020 and October 2021. BCG = bacillus Calmette-Guérin; reTUR = repeat transurethral resection.

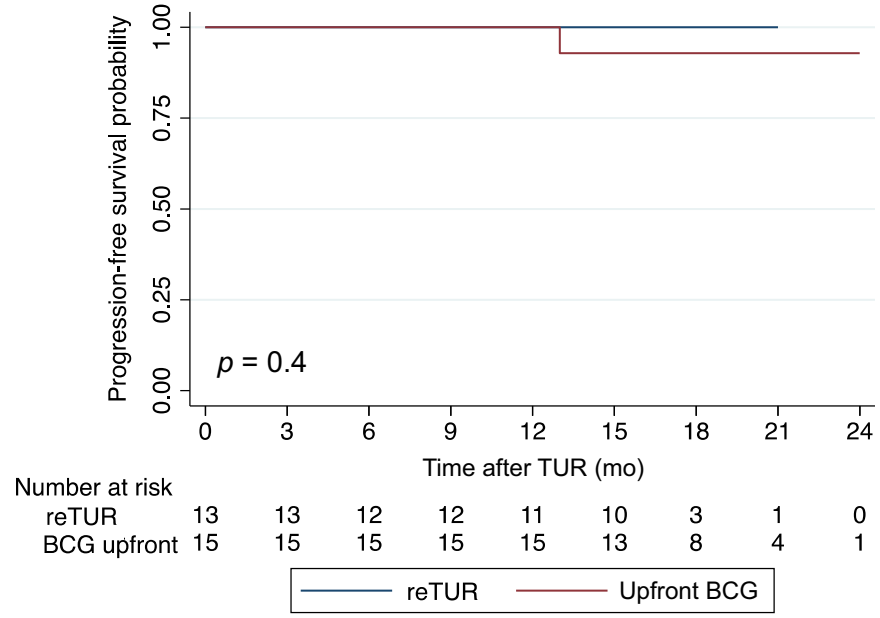

Fig. 2 – Progression-free survival for the cohort of 30 patients with high-grade T1 non–muscle-invasive bladder cancer randomized in the trial between August 2020 and October 2021. BCG = bacillus Calmette-Guérin; reTUR = repeat transurethral resection.

in their first TUR specimen (hazard ratio for disease progression 0.31; $p = 0.07$). Conversely, reTUR in patients whose first TUR specimen contained DM did not improve outcomes for any of the endpoints [4]. These findings highlight the importance of performing a high-quality first TUR, for which DM presence plays a crucial role and should be considered a proxy for TUR quality [9]. Second, a recent systematic review revealed that the mean probability of upstaging to MIBC at the time of reTUR was approximately 8% [2]; however, the probability was ≤3% in 11 series and 0% in two studies, highlighting high variability between centers and emphasizing the importance of experienced and dedicated surgeons and the quality of the first TUR. Third, the prognostic role of histology at reTUR remains a matter of debate. Although the presence of pT1 disease at reTUR has been considered a strong predictor of adverse long-term oncological outcomes, with 25–70% of patients experiencing progression within 5 yr, depending on the series [10,11], these results should be interpreted with caution, taking into account the ablative effect of BCG

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(as demonstrated by marker lesion studies) [12], recent technological advances (such as enhanced tumor visualization techniques), and the adoption of new surgical techniques (such as en bloc resection) yielding a higher rate of DM presence at first TUR [13]. Finally, it is important to consider that reTUR is a morbid and invasive procedure not devoid of complications and with a detrimental impact on patients' quality of life, health care costs, and waiting lists [6].

A few retrospective studies have investigated the possibility of predicting final pathology at reTUR, with the aim of safely avoiding reTUR in selected patient groups. In a retrospective multicenter series of 321 cases of HG T1 NMIBC, we found that DM presence in the first TUR specimen, the absence of concomitant CIS, and resection performed using the en bloc technique independently predict pT0 stage at reTUR (accuracy of the model 74%) [6,7]. To date, only one RCT comparing reTUR versus no reTUR in T1 NMIBC has been published [8]. Overall, 142 patients with T1 NMIBC with a macroscopically complete first TUR and the absence of concomitant CIS were randomized to receive either reTUR followed by adjuvant mitomycin C, or upfront adjuvant mitomycin C. The recurrence rate was significantly higher in the group that did not undergo reTUR (63% vs 26%; $p < 0.001$), with no difference in disease progression. However, several drawbacks limit the reproducibility of these findings. First, both LG and HG cases were enrolled, leading to high population heterogeneity; second, despite having their disease classified as high-risk NMIBC, patients were treated with intravesical chemotherapy instead of the BCG recommended by international guidelines.

We therefore decided to conduct a new prospective RCT to clarify the role of reTUR in HG T1 NMIBC. However, since such an RCT would require enrollment of a very large sample, with tremendous efforts in terms of costs and resources, we designed an RCT to test the feasibility of enrolling a high number of patients within a relatively short timeframe. On the basis of previous evidence of a higher rate of upstaging among cases with histological subtypes, hydronephrosis, or LVI, and in order to preserve patient safety, we decided to include only patients with HG T1 NMIBC with DM present in their initial TUR specimen and without additional risk factors. We demonstrated the feasibility of such an RCT, with enrolment of 30 patients over a period of 14 mo at one referral center. The study was not powered to provide evidence regarding the impact of reTUR on disease recurrence and progression; however, exploratory analyses highlight possibly worse oncological outcomes for patients not receiving reTUR, which is worrying. To confirm these preliminary results, we are planning a second phase of the trial; an interim safety analysis is planned after enrollment of the first 100 patients to identify any differences in disease recurrence and progression between the groups. Results from a meta-analysis by Cumberbatch et al [2] revealed that the upstaging rate varied between 0% and 32% (median 4%), depending on the series, so we have decided to use a threshold of 4% as safety cutoff for evaluation on interim analysis.

Our study is not devoid of limitations, mainly inherent to its feasibility nature. First, we were not able to provide data regarding the role of reTUR and, as already pointed out, the oncological results should be considered exploratory and taken with caution. Second, despite being based on clinical evidence, the choice of the inclusion and exclusion criteria may be a matter of discussion and may limit translation of the results into clinical practice.

5. Conclusions

The feasibility of an RCT comparing upfront BCG after TUR versus reTUR + BCG in high-grade T1 NMIBC has been demonstrated. Our results underline the need to screen a large number of patients, as a high percentage of cases had characteristics meeting the exclusion criteria. There is a plan to start a second phase of the trial in 2023, with the aim of increasing the sample size to 100 patients.

Author contributions: Matteo Rosazza 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: Soria, Rosazza.
Acquisition of data: Rosazza, Livoti, Dutto, Colucci.
Analysis and interpretation of data: Soria, Rosazza.
Drafting of the manuscript: Soria, Rosazza.
Critical revision of the manuscript for important intellectual content: Sylvester, Shariat, Babjuk, Palou.
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