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Effect of Repeat Transurethral Resection to Bacillus Calmette-Guerin Therapy in High-Grade T1 Non-Muscle Invasive Bladder Cancer

Tasnim Alam Manzer[1#≡*], Nahid Rahman Zico[2#ϖ], K. M. Arifur Rahman[3#†], Fahim Hossain[4#‡], Sayeef Ullah Sujan[5#¥], A. S. M. Badruddoza[6#‡] and Md. Ashraful Islam[2#]

[1]Department of Urology, East West Medical College, Dhaka, Bangladesh.
[2]Department of Urology, Dhaka Medical College Hospital, Dhaka, Bangladesh.
[3]Mugda Medical College Hospital, Dhaka, Bangladesh.
[4]Department of Urology, National Institute of Kidney Disease and Urology, Dhaka, Bangladesh.
[5]Department of Urology, Sir Salimullah Medical College, Dhaka, Bangladesh.
[6]Department of Urology, Mugda Medical College and Hospital, Dhaka, Bangladesh.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Standard treatment of high-risk non-muscle-invasive bladder cancer (NMIBC) consists of transurethral resection of bladder tumor (TURBT) with the addition of intravesical Bacillus Calmette-Guerin (BCG). Despite this standard treatment, patients with NMIBC are experiencing recurrence and progression. To reduce the failure rate of BCG therapy, repeat

Dr.;
≡ *Assistant Professor;*
ϖ *Indoor Medical Officer;*
† *Assistant Registrar;*
‡ *Medical Officer;*
¥ *Resident;*
**Corresponding author: Email: thetaibmc@gmail.com;*

transurethral resection (TUR) has emerged as a new standard of care for high-risk NMIBC approved by different guidelines.

Aim of the Study: The study aimed to compare the findings of repeat and no-repeat transurethral resection to Bacillus Calmette-Guerin therapy in high grade T1 non**-**muscle-invasive bladder cancer. **Methods:** This comparative study was conducted in the Department of Urology, Dhaka Medical College Hospital Dhaka, Bangladesh, from August 2018 to January 2020**.** A total of 40 patients with T1 bladder cancer fulfilled the selection criteria**.** Patients were divided into two groups**.** In the repeat TUR group (Group A), there were 20 patients, and in the no-repeat TUR group (Group B), there were other 20 patients**.** All the patients of both groups received induction of intravesical BCG therapy All the patients were followed up with predefined schedule.

Results: Among 20 patients of Group A, the residual tumor was found in 35% of patients at 6 weeks, and there was no upstaging at 6 weeks. Recurrence between two groups was statistically significant at 3, 6, 9, and 12 months follow up ($p < 0.05$). Total recurrence was detected in 20% of the patients in Group A and 70% in Group B at 12 months of follow-up**.** The most frequent recurrence was seen at 3 months in patients with Group B, which was 5 times higher than Group A. In Group A and Group B, disease progression seen at 12 months follow-up was 5% and 20%, respectively, $p<0.001$.

Conclusion: Repeat-transurethral resection improves the initial response to BCG therapy by significantly decreasing the recurrence rate and progression in patients with high-grade T1 TCC of the urinary bladder.

Keywords: Repeat transurethral resection; Bacillus Calmette-Guerin therapy; Non-muscle; Invasive bladder cancer.

1. INTRODUCTION

Urothelial cancer of the bladder affects more than 430,000 people worldwide each year [1] and is the most common urologic malignancy [2]. It is the 7th most common cancer in the male population worldwide and 11th when both genders are considered [3]. About 20-27% of all urothelial cancer is associated with industrial exposure to some chemicals. Smoking is the most common causative agent with a 2-6 times greater chance of developing urothelial carcinoma [4]. As Bangladesh is an industrialized country and a large number of the population of Bangladesh are smokers, the incidence of urothelial cancer is rising in Bangladesh. The majority of urothelial cancers present as non-muscle-invasive bladder cancer, of which about 74% are confined to the epithelium or submucosa, 18% locally advanced, and 8% are metastatic diseases [5]. Among non-muscle invasive bladder cancer, 25% are papillary urothelial carcinoma of low malignant potential, 50% are low grade, 25% are high-grade including CIS [4]. Transurethral resection of bladder tumor (TURBT) is the cornerstone of diagnosis and gold standard treatment for the patient with a non-muscle-invasive bladder cancer [6].

Without adequate resection with good quality of underlying detrusor muscle, the pathologist will not fully differentiate between Ta, T1, and T2 bladder cancers [7]. Complete resection of bladder tumor is the essential part of the management of these early-stage cancers. The procedure is mandatory for adequate staging and crucial in delaying and preventing tumor recurrence and progression [8]. In the case of newly diagnosed high-risk nonmuscle invasive bladder cancer, standard treatment consists of transurethral resection of bladder tumors (TURBT), with the addition of intravesical bacillus Calmette-Guerin [9]. American Urological Association (AUA), the European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) guidelines also strongly recommend this treatment option. Despite this treatment protocol, tumor recurrence is 16% to 40%, and disease progression is 4.4% to 40% [10]. There is a 9-49% chance of persistence of urinary bladder cancer in the first resection [11]. There is a 40-50% chance of upstaging T1 lesions when the muscle was absent compared with 15-20% when the muscle was present [9]. If there is the persistence of tumors, 82% of cases intravesical BCG therapy is not responding [12]. Lack of response to BCG therapy due to incomplete transurethral resection raises the question of whether repeat transurethral resection after the first resection can improve BCG response rate, reduce the frequency of recurrent tumor and delay or prevent tumor progression [9]. Repeat transurethral resection

for a patient with high-risk NMIBC has diagnostic, prognostic, and therapeutic benefits. It improves staging accuracy, resects residual tumor, and potentially improves response to intravesical therapy, thus decreasing the risk of recurrence and progression of the disease [13]. According to AUA, EUA, NCCN guidelines, repeat TUR for newly diagnosed high- risk NMIBC before intravesical BCG therapy has become the standard of care. Very few studies are conducted on this topic in Bangladesh.

2. METHODOLOGY AND MATERIALS

This comparative study was conducted in the Department of Urology, Dhaka Medical College Hospital Dhaka, Bangladesh, from August 2018 to January 2020. A total of 40 patients with T1 bladder cancer fulfilled the selection criteria. Patients were divided into two groups. In the repeat TUR group (Group A), there were 20 patients, and in the no-repeat TUR group (Group B), there were other 20 patients. All the patients of both groups received induction of intravesical BCG therapy. The patients were followed up by a predefined schedule. According to the study's inclusion criteria, patients with newly diagnosed non-muscle-invasive high-grade T1 TCC of urinary bladder undergoing complete resection of the primary lesion were included. This study was approved by Ethical Review Committee of Dhaka Medical College Hospital.

On the other hand, according to the exclusion criteria of this study, patients with concomitant CIS, with recurrent urinary bladder cancer, cases with urinary bladder cancer with variant histology, patients of multiple tumors >4 or tumor size >3cm, and cases of cancer with lympho-vascular invasion were excluded. One group of patients underwent repeat TUR at 2 to 6 weeks of initial TURBT. On the other hand, no-repeat TURBT was done following initial TURBT. Age of patients, sex, number of the tumors, and size of tumor were the independent variables of this study. Recurrence and progression rates were the outcome variables of this study. Following counseling, informed consent, optimization of the comorbidities, all patients underwent urethrocystoscopy and completed TURBT under spinal anesthesia. Tissues were sent for histopathology examination to the Department of Pathology of Dhaka Medical College or other reliable centers to see the type, grade, stage, and lympho-vascular invasion. Macroscopic features of the tumor site, size, number, morphology were noted in a bladder diagram (Fig. 4). Post-operative intravesical Mitomycin-C (40 mg) was given to every patient within 24 hours, preferably within 6 hours if no hematuria is present. Histopathology reports were analyzed, and those who fulfilled the selection criteria that was non-muscle-invasive high-grade pT1 TCC of urinary bladder ≤ 4 in number and less than 3 cm were enrolled in this study.

Informed written consent was taken from all patients. Then patients were recorded in a predesigned data entry form. The purposive sampling technique was followed. The patients with muscle-invasive high-grade T1 TCC > 3 cm, multiple >4 in number, lympho-vascular invasion, and concomitant CIS were excluded from the study. In group A, patients were selected for repeat TUR within 2-6 weeks, and in group B patients, repeat TUR was not done before induction of intravesical BCG therapy. At first, the bladder was evaluated by cystoscopy for any visible residual tumor at the previous site or only scar mark at the previous site. Then biopsy was taken from the previous scar mark and/or from the tumor if present. All the patients of both groups got induction of intravesical BCG therapy. All patients were advised to visit urology outdoor for follow-up at 3, 6, 9, and 12 months from the initial TURBT or earlier if develops any urological symptoms. During follow up visits, detailed history was taken and physical examination, investigations like urine routine examination, urine culture and sensitivity, urine cytology, serum creatinine, ultrasonography of KUB (kidney, ureter, bladder) with MCC (maximum cystometric capacity) and PVR (post-void residue) were performed. Check cystoscopy under local anaesthesia was done to detect any tumor recurrence and if any recurrence occurs, macroscopic features of cancer including site, size, number, and morphology were noted in a bladder diagram (Figs. 5-6). Then patients were advised for admission in DMCH for restage TURBT.

2.1 Statistical Analysis

Appropriate statistical analysis was done using SPSS (Statistical Program for scientific study) version 25 statistical package. Data were analyzed using unpaired Student's t-test*, Fisher's exact test**, Chi-square$(x2)$ test***, Z - test of proportion and level of significance was < 0.05.

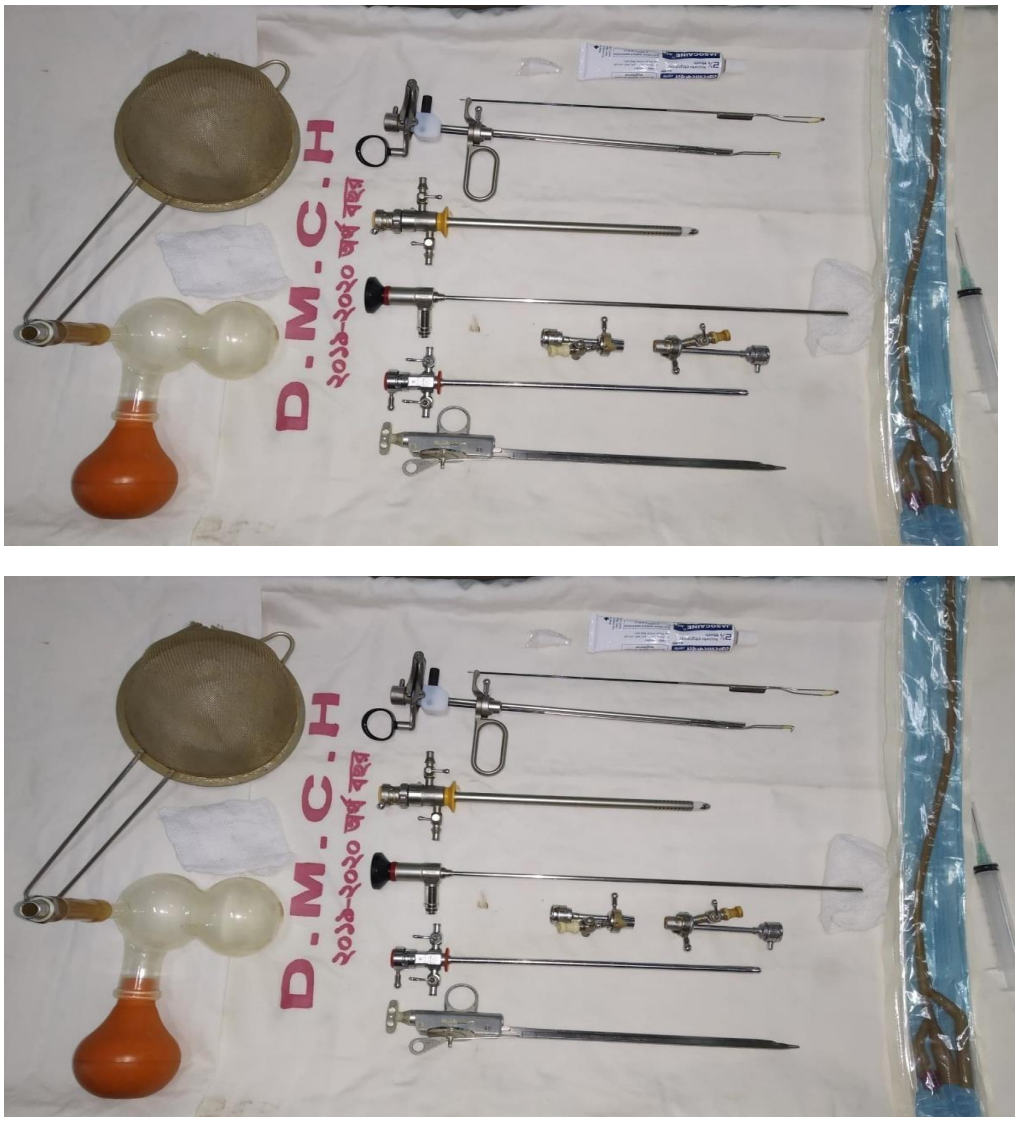

Fig. 1. Arrangement of instruments for TURBT

3. RESULTS

In this study, the mean age of group A was 60.7 (±10.12) years, and in the group, B was 62.95 (±11.39) years, p=0.48. 17 (85%) cases in group A and 16 (80%) cases in group B were males. On the other hand, 3 (15%) cases in group A and 4 (20%) of group B were females, p=0.17. The mean tumor size was 2.6 (± 0.48) cm in group A and 2.7 (± 0.1) cm in group B (p= 0.496), which was not significant. In Group A, 12 (60%) patients had a single tumor, and 8 (40%) patients had more than one tumor**;** in Group B, 15 (75%) patients had a single tumor, and 5 (25%) patients had more than one tumor (p=1.025). The difference between two groups was not significant. In Group A and Group B, the papillary tumor was present in 14 (70%) patients and 15 (75%) patients, respectively**;** sessile tumors in Group A and Group B were in 6 (30%) and 5 (25%) patients respectively (p=0.125). All the patients of both groups had T1 high-grade disease. In this study, the recurrence detected during follow up at 3, 6, 9, 12 months in Group A was 5%, 5%, 5%, 5%, respectively and in Group B was 25%, 15, 15%, 15% respectively (Fig. 2). The most frequent recurrence was seen at 3 months in patients of Group B (no-repeat TUR group), which was 5 times higher than Group A (repeat TUR group). Total recurrence was detected at 12 months in Group A in 4 (20%) patients and Group B in 14 (70%) patients. At 3-, 6-, 9- and 12-months recurrence rate between two groups was statistically significant (p=<0.05). In this study, if we exclude the patient with recurrence at 3 months, the recurrence rate at 6-,

9- and the 12-months rate was in 5%, 10%, 15% in Group A and 15%, 30%, 45% of patients in Group B respectively, 3 times higher recurrence rate in Group B. The overall recurrence rate was decreased from 5 times to 3 times in Group B. Progression of non-muscle invasive bladder cancer to muscle-invasive bladder cancer after the development of recurrence during follow up period was detected in 1 (5%) of the patient in the Group A (repeat TUR group), and 4 (20%) of the patients in Group B (no-repeat TUR group) and this difference was statistically significant (p = <0.00001) (Fig. 3).

Table 1. Comparison of tumor characteristics between two groups (N=40)

Characteristics	Group A (Repeat TUR) (n=20)	Group B (No repeat TUR) (n=20)	p-Value
Tumor size (cm)	2.6±0.48	2.7± 0.1	0.496*
Number, n (%)			0.227**
Single	12 (60.0)	15 (75.0)	
2	5 (25.0)	1 (5.0)	
3	3 (15.0)	4 (20.0)	
Morphology, n (%)			0.125***
Papillary	14 (70.0)	15 (75.0)	
Non papillary	6 (30.0)	5 (25.0)	
Stage, pT1, n (%)	20 (100.0)	20(100.0)	
Grade, High, n (%)	20 (100.0)	20(100.0)	

Table 2. Comparison of tumor characteristics between two groups (N=40)

Recurrence	Group A (Repeat TUR) (n=20)		Group B (No Repeat TUR) (n=20)		p-Value
	n	%	n	%	
At 3 months, n (%)	1	5.0	5	25.0	<0.00001
At 6 months, n (%)	1	5.0	3	15.0	0.00079
At 9 months, n (%)	1	5.0	3	15.0	0.00079
At 12 months, n (%)	1	5.0	3	15.0	0.00079
Total number of cases Recurrences (Total)	4	20	14	70	<0.00001

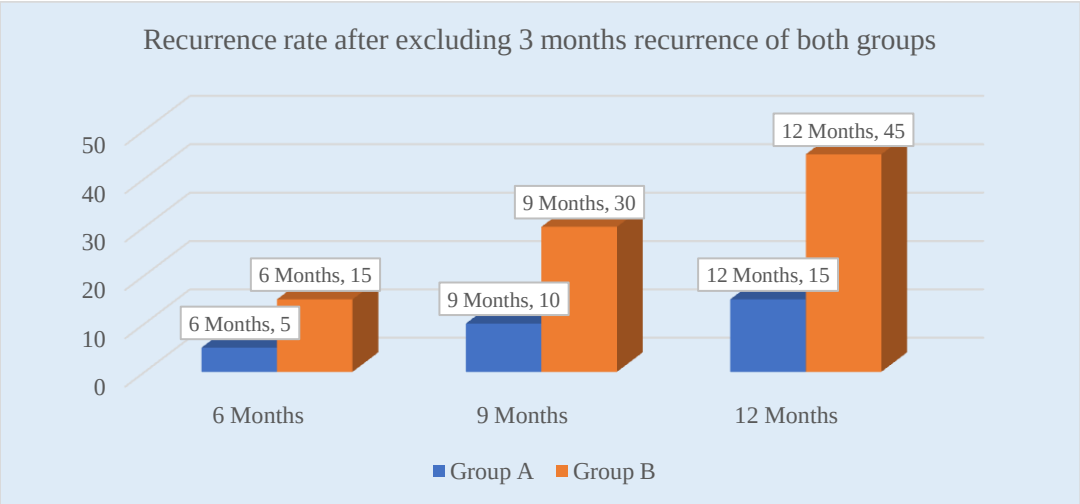

Fig. 2. Recurrence rate after excluding 3 months recurrence in both groups (N=40). Here, the x-axes show the specific month intervals (6, 9, 12 months), and y-axes show the percentage of recurrence rate

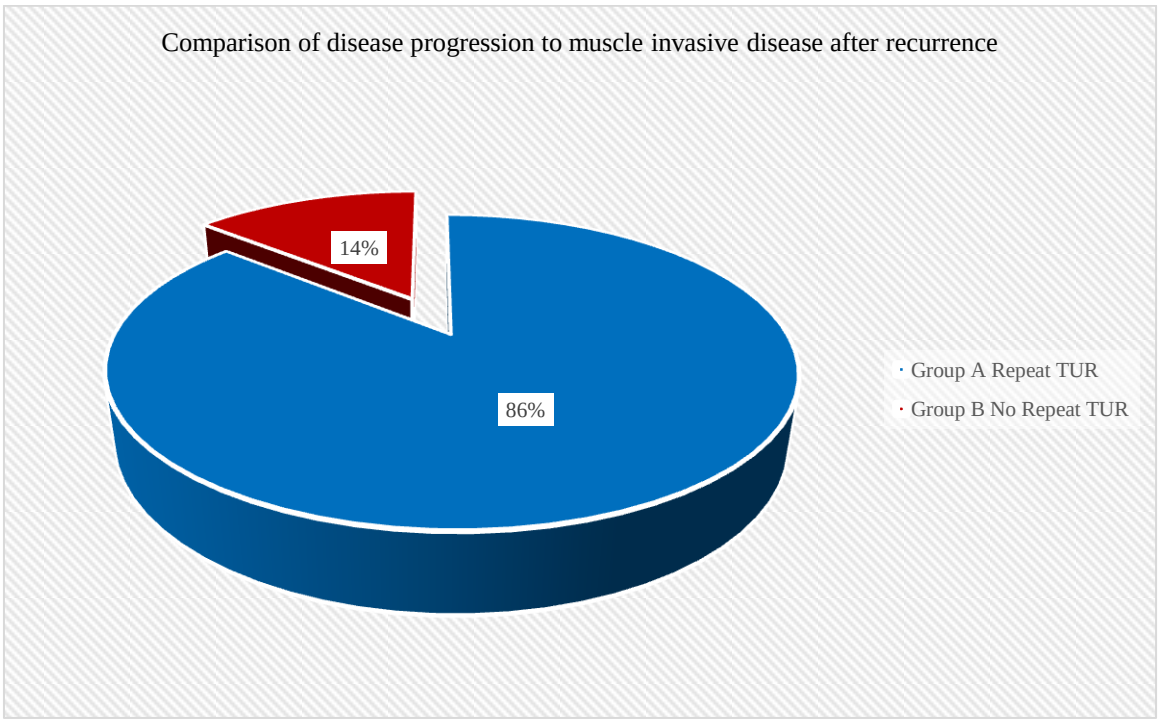

Fig. 3. Comparison of disease progression to muscle-invasive disease after recurrence (N=40)

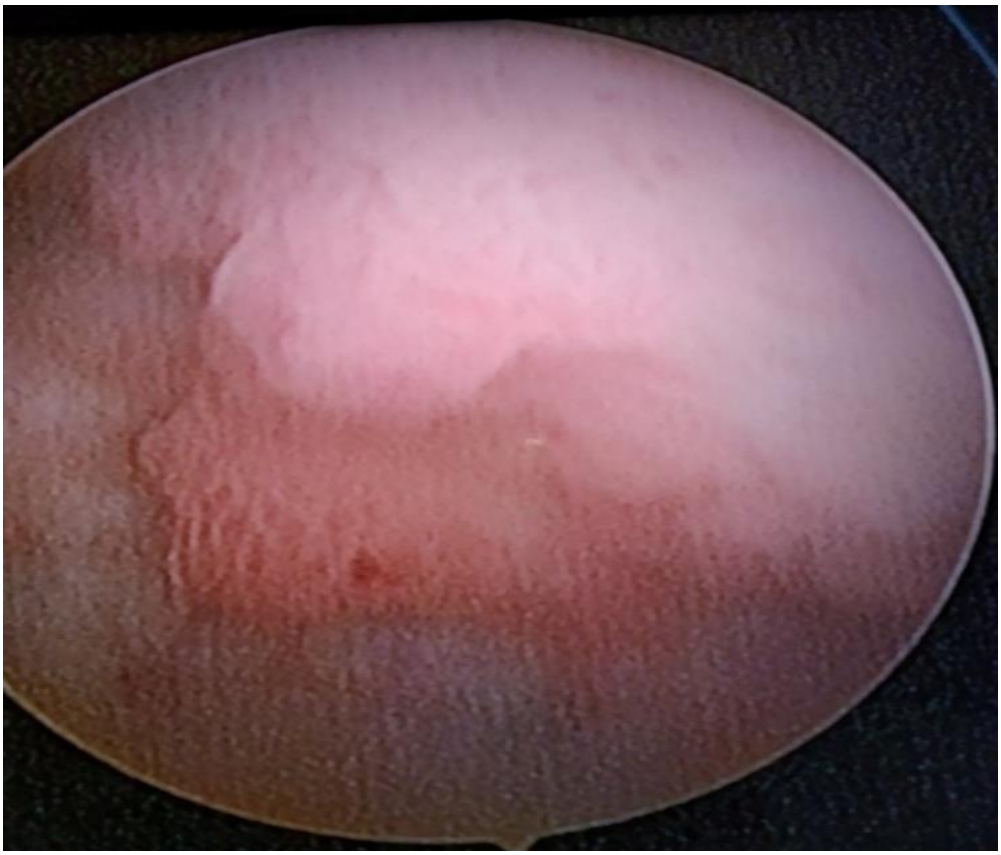

Fig. 4. Picture of primary bladder cancer

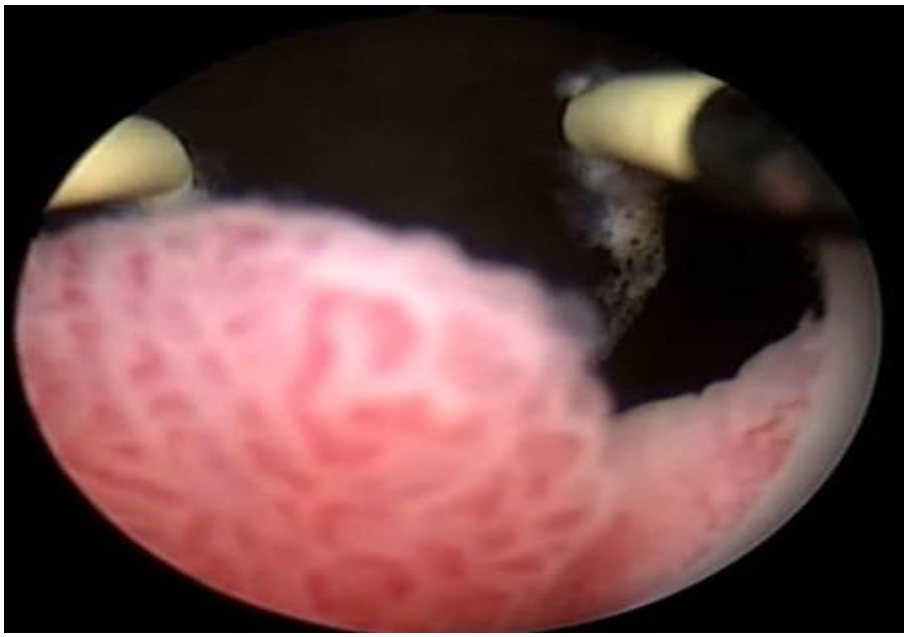

Fig. 5. During TURBT for primary bladder cancer

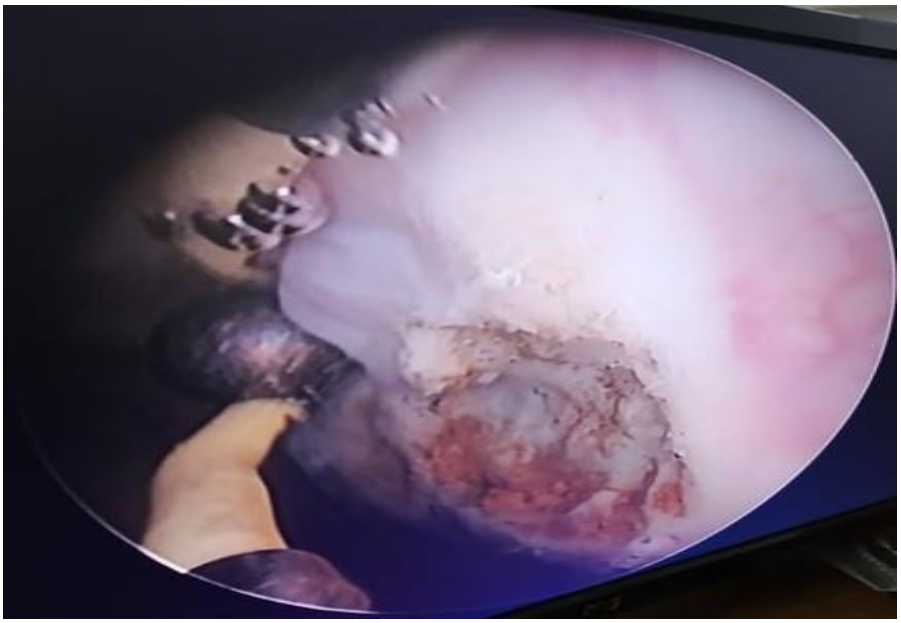

Fig. 6. Repeat TUR from the previous scar at 5 week

4. DISCUSSION

The study aimed to compare the findings of repeat and no-repeat transurethral resection to Bacillus Calmette-Guerin therapy in high-risk non-muscle-invasive bladder cancer. Repeat transurethral resection is strongly recommended for high-grade T1 bladder cancer. It plays an important role in resecting residual tumors, detecting staging error, and improving BCG function, decreasing early recurrence and progression. In this study, different prognostic factors were compared between Group A and Group B. Morphology of tumor in Group A and Group B were papillary 70%, 75%, and sessile 30%, 25%, respectively. There was no statistically significant difference seen in the two groups. Similar results were found in a study by Sfakianos et al. [14]. In this present study, repeat TUR was routinely done in Group A patients within 6 weeks of initial TURBT for bladder cancer where complete resection was possible.

Among 20 patients of Group A, residual tumors were found in 7 (35%) patients. Residual tumor found in the present study was comparable to the study conducted by Schips et al., [15] where the residual tumor was found in 36.4%, 33.3%, and 33% cases. In the present study, no upstaging to muscle-invasive bladder cancer was seen. But theoretically, for high-grade T1 cancer, there is an increased chance of upstaging bladder cancer to muscle-invasive disease in 15-20% cases if the muscle is present at initial TURBT. Our finding was compatible with Lida et al. [16], where no upstaging of bladder cancer was not found at repeat TUR at 6 weeks and also compatible with Adenet et al. [1] where upstaging to T2 bladder cancer was found 4.5% and 2%, respectively. In this study, all the patients underwent 1 year follow up from initial resection and follow up was done according to AUA recommended follow up protocol for non-muscle invasive bladder cancer. In our study, recurrence rate of repeat TUR was significantly reduced after initial TUR with $p < 0.00001$ at 12 months. Recurrence rate found at 3, 6, 9, 12 months in Group A was 5%, 10%, 15% and 20% respectively and in Group B was 25%, 40%, 55% and 70% respectively. The recurrence rate of the present study was compatible with the study conducted by Sfakianos et al. [14], were at 6 months and 12 months, recurrence in restage TUR Group was 16.6%, 28.2%, and in single TUR Group was 44.8% and 44.8% respectively. At 3 months, the recurrence rate of Sfakianos et al. [14] was compatible with the present study in the repeat TUR group, where the recurrence rate in the restaging TUR group was 9.6%, but not compatible with the no-repeat TUR group where recurrence was 43.3%. The difference of the present study in Group B with Sfakianos study was due to multiple tumors and high-volume tumors in their study, and these two variables independently responsible for frequent disease recurrence. Normally high-grade nonmuscle invasive bladder cancer progresses to muscle-invasive bladder cancer in 27-61% of cases [4]. In this present study, stage progression to muscle-invasive bladder cancer was present as recurrence in 5% of Group A patients and 20% in Group B within 12 months of follow-up. The difference in progression between Group A and Group B was statistically significant. The progression rate was compatible with restaging TUR group of Herr [9] study, where the progression rate was 8%, but not compatible with no restage TUR group, where the progression rate was 43% at 12 months. Higher progression rate in no restage TUR group of Herr [9] study was due to the persistence of more residual tumor in initial cystoscopy. This result was not compatible with a study conducted by Divrik [8] where progression was 6.5% in second TUR group and 23% in no second TUR group at 3 years. Higher progression rate in the present study might be due to the study being done in all patients with high grade T1 disease and the small sample size also might be a cause of increased progression rate.

5. CONCLUSION AND RECOMMENDATION

Repeat transurethral resection improves the initial response to BCG therapy by significantly decreasing the rate of recurrence as well as progression to muscle invasive bladder cancer in patients with high-grade T1 TCC of urinary bladder. Repeat TUR should be performed in all patients of high-grade T1 bladder cancer after initial TURBT before initiating BCG therapy, which improves BCG efficacy, thus delay recurrence of bladder cancer and progression to muscle invasive bladder cancer within 12 months. A large multicenter comparative study with a long term follow-up is needed for further comment about patient's long term recurrence free survivals and progression free survival.

6. LIMITATION OF THE STUDY

It was a single centered non-randomized study with small sample size and short duration follow-up period.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval was taken from the Ethical Review Committee of Dhaka Medical College Hospital, Bangladesh.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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