

# The Clinical Value of Immediate Second Transurethral Resection in Patients with High Grade Non-Muscle Invasive Bladder Cancer (HG-NMIBC)

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## ABSTRACT

**Objectives:** This study was designed to estimate the value of a second transurethral resection of bladder tumor in patients with initially diagnosed T1 High-grade bladder cancer. **Material & Methods:** Between October 2008 and November 2015, a total of 350 patients were diagnosed with T1 high grade non-muscle invasive bladder cancer. These patients were divided into two groups. Group A: 150 patients who underwent an early re-resection. Group B: 200 patients who did not undergo early re-resection. Data were collected retrospectively which included patient's history, physical examination, and investigation, histological parameters including presence of detrusor muscle at initial TUR and at second TUR, recurrences and progression rates. **Results:** The detrusor muscle was present in 90

patients out of 150 patients (60%) in Group A and in 158 patients out of 200 patients (79%) in Group B, at initial TUR. At early re-resection, detrusor muscles were present in 76.67% of patients. The residual tumor was present in 55% of re-resected patients. The overall incidence of tumor recurrence was 34.66% and 42% in Groups A and B, respectively. There was a significantly higher rate of tumor progression in patients who did not undergo early re-resection during follow up. (Group 14.28% v. s. Group 3.85%  $P < 0.05$ ). **Conclusion:** A second TUR should be routinely advised in all patients with T1 high grade bladder cancer, to achieve a complete resection and to identify patients who may need to undergo radical cystectomy.

**Key words:** Urinary bladder neoplasm Second transurethral resection, Non-muscle-invasive bladder cancer.

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## INTRODUCTION

Carcinoma of the bladder is the most common malignancy of the urinary tract. The peak incidence is in persons from 50 to 70 years old with a male to female predominance of all most 3:1. It is the 7<sup>th</sup> most common malignancy in men and 17<sup>th</sup> in women.<sup>1</sup>

Approximately 70% to 85% of patients with bladder cancer are diagnosed with non-muscle-

invasive bladder cancer (NMIBC). 20% to 30% of these NMIBC invade lamina propria and are staged as T1.<sup>2</sup> Recurrence is common with this group ranging from 0 to 80%. Disease progression has been demonstrated to correlate with the tumor size, multifocality, tumor stage, grade and early recurrence.<sup>2,3</sup>

Transurethral resection of bladder tumor (TURBT) is the cornerstone of diagnosis and gold standard treatment for patients with NMIBC.<sup>4</sup> Initial TUR may be insufficient at completely removing and staging tumor, increasing the likelihood of tumor recurrence and progression. If transurethral resection is not complete, NMIBC could progress to muscle invasive disease. Sometimes muscle

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invasive lesion might be over looked and disease course would be aggressive. European Association of urology (EUA) guidelines suggests the early resection may improve recurrence-free survival.<sup>4,5,6</sup>

### Aims & Objectives

This study was designed to estimate the value of early re-resection on the incidence of tumor recurrence and progression of patients with PT1 high- grade non-muscle invasive bladder tumor.

### MATERIALS & METHODS

This study was conducted at the department of Urology, Jinnah Hospital/ Allama Iqbal Medical College, Lahore. Between October 2009 and November 2015, a total of 350 patients were diagnosed with PT1 high grade bladder cancers. The patients who were diagnosed with Ta tumors and those patients with T2 tumors were excluded from the study. The initial transurethral resections in all these patients were performed by two experienced surgeons. The urinary bladder was through by examined with 30° lens. After the first resection, the surgeon documented the location, size and number of the tumors on a designed bladder map. The 350 patients were randomized to two groups:-

Group 1: 150 patients were included in group A who underwent an early resection within six weeks from initial TUR.

Group 2: 200 patients were included in Group B who did not undergo early resection.

The medical records of all these 350 patients were reviewed retrospectively. Data collected included the baseline patient characteristics, clinical and histological characteristic at initial TUR, and re-resection as well as the histological grade and stage of subsequent recurrence. The incidence of the presence or absence of detrusor muscle at initial TUR and at 2<sup>nd</sup> TUR as recorded respectively.

All patients (group 1 and 2) received a single instillation of 40mg mitomycin (MMC) following their initial TUR. Follow up parameter collected recurrence rate, the time to recurrence and the rate of stage progression at recurrence. The primary objective of our study was to analyze the potential impact of second TUR in detecting residual tumor and restaging disease following initial TUR. The second objective was to evaluate the potential impact of tumor recurrence and stage progression. Tumors were classified according to TNM system of the union international centre le cancer and were graded according to the word Health Organization Classification.<sup>7</sup>

Informed consent for the treatment strategy was obtained from each patient, and local ethical committee approval was obtained.

### Statistical Analysis

Statistical analysis was performed using SPSS version 18.0 statistical analysis software.

### RESULTS

A total of 350 patients with newly diagnosed pT1 high grade non-muscle-invasive bladder cancer following initial TUR of bladder tumor entered the study between October 2009 and November 2015. In order to evaluate the impact of early re-resection, we conducted a retrospective analysis comparing those patients who underwent an early re-resection (Group 1, n=150) and those who did not (Group2, n=200).

The mean age was 70.34± 7.62 years in Group 1 patients. The age range in these 105 Group 1 patients was 42.8± 88.32 years. The means age in Group 2 patients was 71.24± 8.42 years (age range 38.89-99.38). Although there was a statistical significant difference in the age presentation of both groups, this has no bearing on offering patients an early re-resection (Table1

**Table 1: The baseline patient characteristics of Group 1 and Group 2**

		All patients N=350	Re-resection N=150	No Re-Resection N=200	P- Value
Age	Mean± SD	72.33± 7.2	70.34± 7.62	71.24± 8.42	0.0085
	Range	38.89± 99.2	42.8± 88.32	38.89± 99.33	
Gender	Male	270(77.14%)	120(80%)	150(75%)	NS
	female	80(22.86%)	30 (20%)	50 (25%)	

The sex distribution was comparable among the two groups with 80% men and 20% women in Group 1 and 75% men and 25% women Group 2 (Table1)

The median follow up in Group 1 and Group 2 patients were 53.40 months (range 3-140.5months) and 48.78 months ( range 3-150.0) respectively ( P=0.2, Not significant).

**Table 2: Follow up in Group 1 and Group 2 patients**

	All Patients N= 350	Group 1 N= 150	Group 2 N= 200	P
Follow/up				
Mean $\pm$ S.D	52.68 $\pm$ 32.81	53.40 $\pm$ 35.20	51.40 $\pm$ 31.34	NS
Median Range	49.65 3.1-150.5	49.90 3.1-140.5	48.78 3.1-150.0	

Histological examination of resection specimens at initial TUR demonstrated the presence of detrusor muscle in 90/150 (60%) vs. 158/200 (79%) of patients in Group 1 and group 2 patients.

**Table 3: The histopathological finds at initial TUR among the Group 1 and Group 2 patients**

	All Patients N=35	Group 1 N=150	Group 2 N200
Detrusor muscle presence at initial TUR			
Yes	248(70.86%)	90 (60%)	158 (79%)
No	102 (29.14%)	60 (40%)	42 (21%)
Histology at initial TUR			
T1G2 High grade	106	40	66
T1 G3	100	47	53
Tis	02	01	01
T1 G2+ Tis	00	00	00
T1 G3+ Tis	00	00	00
T1 G2 + G3	84	41	43

150 patients in group 1 were subjected to an early re-resection with 6 weeks of initial TUR. The histological examination of the resected tissue demonstrated the presence of detrusor muscle in 115 out of 150 patients (76.67%). The residual tumor was identified at second TUR in 82 out of 150 patients (54.66%). Among these residual tumors, 16 patients out of these 82 patients were found to be upgraded compared to original histology at initial TUR. This represents a rate of upgrading of 19.51%. As a result, of this upgrading, 12 patients in this group were advised immediate cystectomy.

41 patients out of 82 patients (50%) in group 1 and 58.3% (117/200) in Group 2 received intravesical BCG. The recurrence rate of tumors within patients who received BCG was 48.78% (20/41) in Group 1 and 58.84% (63/117%) in group 2 patients (p=ns).

With a mean follow up period of 50.80 $\pm$  30.78 months, 34,66% (52/150) of patients in Group 1 and 42% (84/200) of patients I Group 2 developed tumor recurrences. This recurrence rate in those patients who underwent an early re-resection was lower than those who did not undergo second TUR but this difference was not statistical difference in recurrence free survival between the two groups (Group 1 = 12.20 $\pm$  13.78 months vs. Group 2 : 12.38 $\pm$  16.28 months) (P=NS) (Table 3)

**Table 3: Histology of bladder tumors at second TUR in Group 1 patients**

Tumour stage	No. Of Patients
Tx	03
To	75
Tis	02
Ta	28
T1	40
T2	12
Total	150

Histological assessment of those recurrences demonstrated statistically significant difference in tumor upstaging between two groups. Of 52 cases, only two progressed in Group 1 compared to 12 of 84 recurrences in Group 2. This represents a stage progression rate at a recurrence of 3.85 % vs.

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14.28% for group 1 and group 2, respectively (P= 0.0241).

## DISCUSSION

Transurethral resection of the bladder (TURB) is the initial and critical step in the management of bladder tumors. The aim of the procedure is to establish the histological diagnosis, to determine tumor stage and grade, and to achieve complete removal of non-muscle-invasive bladder tumors.<sup>8</sup> However the results of TUR are far from optimum, and the diagnosis and therapeutic purposes are not always achieved.<sup>9</sup> Tumors are frequently overlooked and left behind during initial resection, or more dangerously, their depth of invasion can be underestimated.<sup>9,10</sup>

European Association of Urology (EAU) guidelines recommends a second TUR if there is suspicion that the initial resection was incomplete.<sup>10,11</sup> In high grade non-muscle invasive bladder tumor, second TUR plays a vital role. It is meant to defect and clear residual tumor and in case of upstaging it helps to plan an appropriate treatment.<sup>12</sup>

In the present study, we evaluate the clinical value of early-resection in 350 consecutive patients with newly diagnosed high T1 carcinoma of the urinary bladder.

The primary objective of our study was to evaluate the value of second TUR on cancer detection rates and accurate restaging. The rate of residual tumor after initial TUR varies widely in the published literature, ranging from 4% to 78%.<sup>13, 14</sup>

In our present study, we identified residual tumor at resection in 55% of patients. This is in agreement with most of the recent published reports.<sup>15,16,17</sup> twelve cases in our study were upgraded to muscle-invasive disease ( $\geq$ , T2). These twelve patients were advised immediate radical cystectomy and urinary diversion. There results are highlighting the importance of accurate staging in the management of high grade non-muscle-invasive bladder cancer. Overall, 19.5% of cases were upgraded on second TUR which is in agreement with the most published reports.<sup>17,18,19</sup>

In our study, the detrusor muscle was present in 60% (90/150 Group1, re-resection) versus 79% (158/200 Group 2, no resection) respectively. At

second TUR, histological examination of the specimen demonstrated the presence of detrusor muscles in 77% (115/150) of cases. The absence of muscle in some resections is explained by different level of experience among surgeons performing TUR.

Although many studies showed that a second TUR improves patients outcome, appropriate timing for performing such an effective and important procedure is not well established. Review of the literature concerning the timing of a second TUR reveals a large variation ranging an immediate TUR to 3 months after the initial TUR.<sup>20,21</sup> Second TUR is mostly recommend within 14-42 days after initial TUR.<sup>21</sup> Many studies have advocated a delay of two to six weeks. This delay allows post-resection inflammatory change to settle facilitating better visualization and demarcation of tissues.<sup>20,21</sup> In our study, all patients in Groups (n=150) underwent an early resection within six weeks from initial TUR, demonstrating the presence of residual tumor in 55% of the cases. This rate of residual tumor emphasizes the importance of re-resection. Our rate of residual tumor is similar to 52% rate reported by Engethardt and his associates. Moreover, this is comparable to the other published series. All these studies confirmed that there should be shorter re-resection time interval from four to six weeks.<sup>20,21,22</sup>

The second objective of our study was to assess the value of early re-resection on the long term outcome of new diagnosed HG-NMIBC. This objective was measured as reduction in recurrence rates, increase in time to recurrence and impact on tumor stage progression of subsequent recurrences. No doubt, that our study is a retrospective study. However, there was a reduction in overall recurrence rate in Group 1 compared to Group 2 (42% vs 34.66% respectively). But this difference was of no statistical significance. However, the results of our study recommends early re-resection for all patients with HG-NMIBC within six weeks of initial TURBT to prevent progression.

## CONCLUSION

The results of our study confirms that early re-resection facilitates accurate staging and clearance of residual tumor. The rates of tumor stage

progression are significantly improved when compared to those who did not undergo second TUR. We therefore recommend early re-resection for all patients with high grade non-muscle-invasive bladder cancer to achieve a complete tumor resection and to identify cystectomy.

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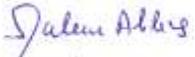
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