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# TOPIC: POSSIBILITIES AND RESULTS OF SECOND-LOOK TUR FOR NON-MUSCLE INVASIVE BLADDER CANCER

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## Introduction

The incidence rate of bladder cancer per 100,000 population of the Republic of Uzbekistan was 7.0 (data from the State Statistics Committee of the Republic of Uzbekistan on the average annual population by region for 2021 were used to calculate all indicators), which is 1.5% higher than in 2017 and 2.7% higher than in 2021 (M.N. Tillyashaikhov, MD Ibragimova Sh.N., Dzhanklich S.M.).

Non-muscle invasive bladder cancer (NMIBC) accounts for 75% of the total number of patients with bladder cancer, but is characterized by a pronounced tendency to relapse in 50-70%, with 10-30% of them progressing to invasive and metastatic forms [Siergal R.L., Miller K.D. Cancer J Clin 2017:67(1)7-30].

The occurrence of relapses is due to the multicentricity of tumor seeds, the presence of undiagnosed areas of carcinoma in situ, the possibility of implantation of tumor cells during surgery, and non-radical removal of the tumor itself [2,4]. The leading surgical intervention in the diagnosis and treatment of NMIBC is transurethral resection (TUR). It is used alone or in combination with intravesical adjuvant immuno- and chemotherapy (CT). The correctness of the staging, the frequency of recurrence and progression of the disease depends on the adequacy of the performed primary TUR. In order to control the quality of the performed primary TUR, it was proposed to conduct a second (secondlook - SL) TUR [5,6]. SL TUR is a refinement of the stage by obtaining additional morphological material that provides information about the lamina propria, the muscle layer and the presence of a residual tumor. SL TUR performed 2-6 weeks later, after the first operation; it allows reducing staging misses and removing the residual tumor, which is detected in 20-78% of patients during repeated resection.

The frequency of stage underestimation varies from 4 to 30% [7]. The most important risk factor and

source of error is the absence of the underlying muscle layer in the resected tumor. A number of studies have demonstrated a positive effect of SL TUR on the incidence of BC relapses and on the survival of patients with NMI BC. It is known that the timely correct determination of the stage of the disease is fundamental in the choice of adequate tactics for the treatment of patients with NMI BC.

**Materials and methods**

The work is based on the retrospective data analysis of patients with NMI BC, who underwent TUR of the urine bladder (UB) in the period from 2015 to 2022 in RSNPMCOR and Tashkent city branch of the RSNPMCOR. In all patients, transitional cell bladder cancer was histologically confirmed. The mean follow-up time was 49.0±2.9 months. The age of patients is from 36 to 80 years.

The object of the study was 155 patients with NMI BC in T1 stage. According to the inclusion criteria of patients, 2 groups were formed:

Group 1 is the main group, patients who underwent TUR and SL - 80 patients.

Group 2 is control group, patients who underwent only TUR - 75 patients.

In both groups, after TUR if available, intravesical CT was administered with doxorubicin or mitomycin C and with the domestic drug thiotepa.

Overall survival (OS) and specific survival (SS) were assessed by the Kaplan-Meier method, survival differences were determined using the log - rank test. To identify prognostic significant factors, single- and multivariate Cox regression analysis was used.

Group 1 included 80 patients with primary morphologically verified NMIBC Ta - T1N0M0 and Grade 2-3, who underwent SL TUR after primary TUR. Indications for SL TUR were: absence of muscular layer in resected specimen, poor differentiation of tumor (G-3), the large size of the tumor, the uncertainty of the surgeon in the completeness of the performed surgery. When performing SL TUR, tissues were resected in the area of the bed of the previously removed tumor, as well as all suspicious areas localized in the area of the previous TUR. The interval between operations in our study ranged from 2 to 8 weeks.

The 2nd (control) group included 75 patients with primary morphologically verified NMIBC Ta - T1N0M0 and Grade 2-3, without SL TUR.

In both groups, immediately after TUR, in the absence of contraindications, single intravesical chemotherapy was performed with doxorubicin 50mg or mitomycin C 40mg. Intravesical adjuvant chemotherapy or immunotherapy with BCG vaccine was started at 4-6 weeks after TUR (Table 1).

***Table 1.*** *Clinical-morphological features of included patients*

| Index | | 1st group (with SL TUR), n=80 | 2nd group (without SL TUR), n=75 | Total number n=155 | *p* |
|---|---|---|---|---|---|
| Age (average), years | | 66.0±10.7 | 69.0 ± 11.8 | 66.7 ± 10.9 | 0.124 |
| Average surveillance time, months | | 46.4 ± 18.1 _ | 51.4 ± 24.4 | 50.1 ± 22.9 | 0.090 |
| Sex | Men, n (%) | 67 (83.8) | 59 (78) | 123 (79.2) | 0.246 |
| | Women, n (%) | 13 (16.2) | 16 (22) | 23 (20.8) | 0.246 |
| Tumor size | < 3 sm, n (%) | 27 (33.8) | 34 (45*) | 67 (43.2) | 0.047 |
| | > 3 sm, n (%) | 53 (66.2) | 41 (55*) | 88 (56.8) | 0.047 |
| Tumor amount | Single, n (%) | 55 (68.8) | 60 (79) | 118 (76) | 0.079 |
| | Multiple, n (%) | 25 (31.2) | 20 (21.5) | 37 (24) | 0.079 |
| T stage | Ta, n (%) | 3 (3.7) | 7 (10) | 13 (8.7) | 0.065 |
| | T1, n (%) | 77 (96.3) | 68 (90) | 142 (91.3) | 0.065 |
| Degree of differentiation G | G2, n (%) | 17 (21.2) | 48 (64) | 82 (52.6) | 0.0001 |
| | G3, n (%) | 63 (78.8) | 27 (36) | 73 (47.4) | 0.0001 |
| Risk of recurrence according to the EORTC scale | Intermediate risk, n (%) | 64 (80) | 65 (87) | 132 (85.4) | 0.113 |
| | High risk, n (%) | 16 (20) | 10 (12) | 23 (14.6) | 0.113 |
| Risk of progression according to the EORTC scale | Intermediate risk, n (%) | 13 (16.2) | 22 (29.8) | 41 (26.3) | eleven |
| | High risk, n (%) | 67 (83.8) | 55 (70.2) | 114 (73.7) | 0.018 |
| ** Significant differences between groups, p<0.05* | | | | | |

As can be seen from Table 1, patients of the 1st and 2nd groups had no significant differences in gender, age and surveillance time. In the 1st group, tumors larger than 3 cm were found in 2/3 of patients, which was significantly more common (p=0.04) than in the 2nd group, where majority of patients were with T1 G-3 (p=0,0001), this is because high-risk NMIBC is an indication for SL TUR.

The number of patients with poorly differentiated bladder cancer (G 2-3) in groups significantly differed (p=0.00001): in the 1st group, urothelial cancer G 2 was detected in 21.2%, G 3 – in 78.7%, in 2nd

group with moderate and high degree of malignancy - respectively in 63.6 and 36.4%.

Based on the obtained clinical and morphological data (number of tumors, tumor size, category T, tumor cell differentiation (G), concomitant CIS), groups were identified according to the risk of recurrence and progression according to the EORTC recommendations. As can be seen from Table 1, all patients belonged to the groups of intermediate and high risk of recurrence and progression. When assessed on the EORTC scale, patients of the 1st group were distributed as follows: 80% with an intermediate and 20% with a high risk of recurrence; in the 2nd group with an intermediate risk – 87.3%, with a high risk – 12.7%, which did not differ significantly from the 1st group. Significantly different indicators for the risk of progression in the 1st and 2nd groups with an intermediate risk of progression of 16.2 and 83.8%, with a high risk of 29.8 and 70.2%, respectively (p=0.01). in the presence of residual tumors detected after SL TUR, the risk of recurrence was reassessed and the patient was transferred to the appropriate risk group.

**Results**

Residual tumor was detected in intervals from 2 to 8 weeks in the SL TUR group in 42 (53%) out of 80 cases of NMI BC Ta-T1 G2 – G3. Respectively, in 38 (47%) patients primary TUR was performed radically.

According to the results of SL TUR, a change in the T category was revealed: 7 patients had invasion into the lamina propria, and therefore they were transferred from Ta to the T1 G2 category. An increase in the stage and a change in treatment tactics as a result of repeated intervention was noted in 7 (8.7%) patients.

In the SL TUR group, the transition of NMI BC to muscle-invasive cancer and, consequently, the transition of the stage from T1 G 2-3 to the stage above T2 (T2 G3) occurred in 5 (6.25%) patients. Patients re-staged into category T2 were recommended surgical intervention in the amount of radical cystectomy.

The overall recurrence rate during follow-up among all patients with NMI BC with and without SL TUR was 4.6% (125 out of 308) with a median time to recurrence of 19 (3-83) months. Early relapses before 1 year were noted in 12.3% of cases. When comparing the frequency of early relapses in groups with primary and SL TUR in patients T1 G 2-3, statistically significant differences were revealed (Table 2).

**Table 2** . *The frequency of relapses and progression in the study groups*

| Index | | 1st group (with SL TUR), n=80 | 2nd group (without SL TUR), n=75 | Total number n=155 | *P* |
|---|---|---|---|---|---|
| Early relapses before 1 year, n (%) | | 2 (2.5%) | 36 (48%) | 38 (14%) | 0.001 |
| General relapses up to 5 years, n (%) | | 24 (30%) | 33 (44%) | 57(36.7%) | 0.02 |
| Frequency of progression T > T1, n (%) | | 10(12.5%) | 39(17.1%) | 49 (15) | 0.33 |
| Intermediate risk, n (%) | Total number | 64 (80%) | 64 (85%) | 128 (83%) | - |
| | Relapses up to 1 year | 1 (1.6) | 6 (10) | 36 (9.1) | 0.02 |
| | Relapses in 5 years | 11 (17.2) | 25 (39) | 85 (32.3) | 0.003 |
| High risk, n (%) | Total number | 16 (20%) | 11 (15%) | 27 (17%) | - |
| | Relapses up to 1 year | 1 (6.3) | 5 (45) | 6 (3.9%) | 0.008 |
| | Relapses in 5 years | 13 (81.3) | 10 (90) | 23 (88.9) | 0.23 |

** Significant differences between groups, p<0.05.*

In the SL TUR group, early relapses were observed significantly less frequently - in 2 (2.5%) patients, the frequency of total relapses was significantly lower, in 24 (30%) patients (p=0.02). As can be seen from Table 2, most patients of 2nd group had relapses occurred in first year of follow-up (16%), which is statistically significantly more frequent (p=0.001) than in main group (2.5%). Median time to first relapse was 29 and 17 months respectively, however, the difference did not reach a significant value.

In the group of intermediate risk of recurrence during 5 years of observation in the 1st and 2nd groups, relapses were recorded in 11 (17.2%) and 25 (39%) of 80 and 75 patients, which is significantly less in the 1st group (p=0.003) (Table 2). The mean time to relapse in the groups did not differ significantly: in the 1st and 2nd groups - 27.3 and 22.7 months, respectively. Statistically significant differences were observed up to 1 year: the frequency of early relapses in patients with an intermediate risk of 1st and 2nd group was 1.6 and 10.0%, respectively (p=0.02).

When analyzing the high-risk group T1 G 2-3, it was found that the frequency of relapses over 5 years of observation in the groups did not statistically differ 44.8% (p=0.008) (Table 2).

The progression rate for groups 1 and 2 was 12.5 and 17.1%, respectively (p=0.33). The mean time to progression was 19.4 months compared with the SL TUR group - 24.9 months.

**Survival**

Overall survival (OS) did not differ significantly between groups (p=0.26) with a median follow-up of 49.9 months. (Table 2). A trend towards significance (p=0.09) was observed in cancer-specific survival (CSS). Progression-free survival was not statistically significant (p=0.36).

When analyzing the long-term results of NMI BC treatment in the group with an intermediate risk of recurrence according to the EORTC scale, there were no significant differences in OS, CSS, and progression-free survival.

In the group of intermediate risk of recurrence, a significant advantage of DFS was revealed in the SL TUR group (p=0.003) (Fig. 2). Median DFS in both groups was not achieved.

In both groups, overall survival and progression -free survival were practically the same, but the CSS value in the SL TUR group was 90.4%. In the group TUR – 84.5%. It should be noted, that DFS in the group with SL TURP was 63.3%, which is 13% higher compared to the group TUR.

The recurrence rate, depending on the characteristics of the tumor, differed between the control group and the SL TUR group in patients with single tumors > 3 cm in diameter, regardless of the degree of differentiation (G 2-3), in the absence of muscle tissue in the surgical material, cancer emboli in the vessels and lymphovascular invasion in patients of the intermediate prognosis group (Table 4).

In multivariate regression analysis (COX), the most significant factors influencing OS, CSS, and progression-free survival (Tables 5 and 6) were: SL surgery and degree of differentiation. The number of tumors had a significant prognostic value along with the above factors for DFS.

**Table 3**. *Five-year survival of patients with NMI BC depending on the performance of SL TUR and the risk of recurrence*

| Index | Group 1 (with SL TUR), n=80, % | group 2 (without SL TUR), n=75, % | Total number n=155, % | *P* |
|---|---|---|---|---|
| OS | 86.8 | 82.6 | 84.2 | 0.26 |
| CSS | 90.4 | 84.5 | 86.6 | 0.09 |
| Survival without progression | 84.1 | 83.2 | 83.9 | 0.36 |
| DFS | 63.3 | 50 | 57.9 | 0.018 |
| intermediate risk | n=64 | n=64 | n=128 | - |
| OS | 88.6 | 84.9 | 86.5 | 0.29 |
| CSS | 91.6 | 87.1 | 88.9 | 0.15 |
| Survival without progression | 87.1 | 85.4 | 86.3 | 0.34 |
| DFS | 77.6 | 57.6 | 62.7 | 0.003 |
| high risk | n=16 | n=11 | n= 27 | - |
| OS | 61.0 | 63.9 | 68.5 | 0.41 |
| CSS | 66.4 | 63.9 | 70.7 | 0.23 |
| Survival without progression | 54.8 | 63.4 | 65.9 | 0.47 |
| DFS | - | 3.0 | 2.9 | 0.11 |

**Table 4**. *Recurrence rate depending on the characteristics of the tumor*

| Index | | group 1 (with SL TUR), n=80, % | group 2 (without SL TUR), n=75, % | *p* |
|---|---|---|---|---|
| Tumor size | < 3 cm | 33.3 | 44.3 | 0.30 |
| | > 3 cm | 28.3 | 44.3 | 0.04 |
| Number of tumors | Single | 21.8 | 38.0 | 0.03 |
| | Multiple | 48.0* | 67.4* | 0.11 |
| Degree of differentiation G | G2 | 11.8 | 39.3 | 0.02 |
| | G3 | 34.9 | 53.0 | 0.02 |
| Presence of muscle | No | 20.8 | 56.8 | 0.002 |
| | Yes | 33.9 | 38.3 | 0.34 |

| | | | | |
|---|---|---|---|---|
| Cancer emboli in blood vessels | No | 24.1 | 43.8 | 0.01 |
| | Yes | 50.0 | 55.6 | 0.59 |
| Lymphovascular invasion | No | 30.6 | 45.1 | 0.03* |
| | Yes | 25.0 | 30.8 | 0.59 |
| Risk of relapse according to the EORTC scale | Intermediate | 17.2 | 37.2 | 0.002* |
| | High | 81.3 | 93.1 | 0.23 |

** Significant differences between groups, p<0.05*

**Discussion**

According to many authors, the detection rate of a residual tumor after TUR reaches 74%, while restaging into muscle-invasive cancer after histological examination of the material after SL TUR is 30% [7,8-13]. In our study, in the SL TUR group, a residual tumor was detected in 53% of 80 cases, the transition of NMI BC to muscle-invasive cancer and, consequently, a change in stage from T1 G 2-3 to T2 occurred in 5 patients - T2 G3, from Ta G3 to T1 G3 - in 3 patients. Thus, an increase in the stage and a change in treatment tactics as a result of repeated intervention were noted in 7 (8.7%) patients. As is known, muscle invasion after TUR is established based on the examination of the muscle tissue under the tumor. Data on the underestimation of the muscle layer in tumor samples in the literature are presented by the works of G. Dalbagni et al. [9]. Morphological analysis of the specimen in 155 patients after primary TUR revealed that the muscle layer was absent in 53% of patients, which did not allow establishing the T category. Similar data was obtained in the works of H. W. Herr [7]: the prevalence of tumor lesion of the bladder and category T could not be established in 65 out of 155 patients.

**Table 5** . *Multivariate regression analysis (Cox) of OS and CSS for patients in SL TUR group*

| **Index** | OS | | CSS | |
|---|---|---|---|---|
| | OR | *p* | OR | *p* |
| SL TUR | 0.779 | 0.049 | 1.283 | 0.010 |
| Number of nodes | 0.398 | 0.209 | 0.548 | 0.103 |
| Size | 0.162 | 0.125 | 0.183 | 0.114 |
| G | 0.740 | 0.019 | 1.109 | 0.002 |

**Table 6** . *Multivariate regression analysis (Cox) DFS and progression-free survival for patients in SL TUR group*

| Index | OS | | PFS | |
|---|---|---|---|---|
| | OR | *p* | OR | *p* |
| SL TUR | 0.869 | 0.0003 | 0.793 | 0.034 |
| Number of nodes | 0.825 | 0.000002 | 0.492 | 0.107 |
| Size | -0.04 | 0.465 | 0.117 | 0.247 |
| G | 0.540 | 0.005 | -1.071 | 0.0008 |

It should be noted that the assessment of the true depth of invasion is sometimes accompanied by a number of difficulties for objective and subjective reasons, such as bleeding, deep resection with the threat of perforation or the presence of artifacts in histological preparations - a tangential section of the block, thermal damage to the material during TUR, inflammatory tissue reaction [14].

One of the standards in the treatment of NMI BC is TUR of UB followed by (adjuvant) intravesical chemotherapy or immunotherapy, subsequent therapy will depend on histological findings after TUR performed [15].

H.W. Herr [16] reports a recurrence rate of 45% (n=67) after SL TUR before BCG therapy and 80% (n=30) of patients who received BCG without SL TUR. In this study, all patients had multiple poorly differentiated tumors pT1 G3 and the majority also had CIS. The authors concluded that SL TUR improves the response to BCG therapy and reduces the incidence of tumor recurrence.

In our results, the overall recurrence rate during follow-up among all patients with NMI BC with and without SL TUR was 51.6% (80 out of 155) with a median time to recurrence of 19 (3-83) months. In some studies, the recurrence rate in the SL TUR group was 33% compared with 57.75% and 88.0% in the presence of residual tumor after primary TUR with stages Ta, Tis and T1, respectively, during a mean follow-up of 60 months in patients with NMI BC [17].

We found significant differences between the groups in the frequency and timing of early and general relapses. Among 155 patients, early relapses (up to 1 year) were observed in 14.0% of cases. In the SL T1 G2-3 group, early relapses up to 1 year were observed significantly less frequently (p=0.001) - in 2 (2.5%) vs. 36 (15.8%) patients in the control group. Given the high recurrence rate in the control group, the question arises whether the so-called relapses of NMI BC are residual tumors missed during primary TUR. Similar data were obtained by H.W. Herr et al. [16] in a non-randomized phase II study based on the results of treatment of 340 patients with NMI BC. In groups with TUR and SL TUR for 12 months the recurrence rate was 59% and 16%, respectively.

According to the literature, studies of R.T. Divirik et al. the recurrence rate after SL TUR reached 40% of cases, while in the group with a single TUR it was up to 71% (p=0.0001) [10]. H.W. Herr et al. showed the important role of SL TUR and its prognostic significance [18]. During 5 years of follow-up, 490 patients out of 710 (69%) had recurrent BC and 149 (21%) had progression. When comparing histological material between TUR, it was found that SL TUR significantly better predicts the progression of NMI BC than the results of the morphological study of the removed material during the initial TUR.

In our study, the frequency of recurrence of BC T G2-3 for 5 years was significantly lower in the SL group – 12.5% versus 17.1% in the control group (see Table 2).

Numerous works also emphasize that performing SL TUR increases the DFS [10,19]. According to research by R.T. Divirik et al. DFS with a single TUR after 1, 3, and 5 years of follow-up reached 57, 37, and 32%, respectively, and 82, 65, 59% in patients with SL TUR (p=0.0001) [10]. In the data of M.O. Grimm et al., the group after a single TUR 1-, 2-, and 3-year DFS was 79%, 42%, and 59%, respectively,

while similar indicators in patients after SLTUR were 82, 71, and 68% (p=0.03) [19]. Similarly, our results indicate a significant advantage of DFS after SL TUR in the groups of patients with BC T1 G2-3 (see Fig. 1). Indicators of 1-, 3- and 5-year DFS in the group with SL TUR were 97.4; 72.9 and 63.3%, respectively, in the control group - 84.1; 62.7 and 50.5% with a median follow-up of 58.8 months.

When distributing patients with NMI BC G2-3 according to the EORTC scale into risk groups for recurrence, we found significant differences in DFS in patients with intermediate risk (p=0.003) (see Fig. 2), while with a high risk of recurrence, SL and a single TUR had no significant effect on DFS scores (p = 0.11).

In the works of M.O. Grimm et al., progression to muscle-invasive disease was detected in only 2 (3%) patients in the TUR group [19]. According to R.T. Divirik et al. progression was detected in 23.5% of patients in the single TUR group compared with 6.5% in the SL TUR group (p=0.001) [10]. According to some reports, progression rates in NMI BC may vary between 5-49% of cases [20]. In studies conducted by H.W. Herr et al., out of 340 patients with IUI of bladder cancer in the single and SL TUR groups, progression was observed in 32% in the single and 7% in the SL TUR group during 5 years of follow-up [16].

The overall rate of progression in our cohort of 155 patients with BC T1 G2-3 who received intravesical chemotherapy and immunotherapy was 75% of cases with a mean time to progression of 20.5±11.6 months. Progression was noted in 10 (12,5%) and 39 (17.1%) patients in the 1st and 2nd groups, respectively. The mean time to progression was less in the control group: 19.4±12.6 months, while in the SL group it was 24.9±10.2 months.

In a study by R.T. Divirik et al. [10,20,21] factors influencing DFS and progression-free survival in multivariate analysis were number, grade of tumor differentiation, and SL TUR (p=0.001).

In our study, the most significant parameters influencing DFS were SL TUR (p=0.0003), the number of tumors and their degree of differentiation G (p=0.000002 and p=0.005, respectively). Performing SL TUR (p=0.034) and grade of tumor differentiation (p=0.0008) also significantly correlated with progression-free survival.

The most significant factors influencing OS were SL performance (p =0.049) and degree of differentiation (p=0.019). These factors also influenced CSS (p =0.01).

**Conclusion**

The use of SL TUR makes it possible to assess the true depth of tumor invasion and identify residual tumors, thereby leading to a decrease in the frequency of recurrence and progression.

NMI BC patients with high and intermediate risk of recurrence who undergoing primary SL TUR will have statistically significant differences in 5-year DFS. Patients undergoing SL TUR have considerably high level of DFS.

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