



LONG-TERM RESULTS OF THREE-MODULE TREATMENT OF MUSCLE-INVASIVE BLADDER CANCER.

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Article history:	Abstract:
Received: April 4 th 2023 Accepted: May 6 th 2023 Published: June 6 th 2023	Objective: to study the long-term results of three-modal therapy (TMT) of muscle-invasive bladder cancer (MIRMP) in a comparative aspect.
Keywords: three-modal therapy	

INTRODUCTION

Bladder cancer is the eighth most common cancer in Uzbekistan in 2021. The tumor can spread to the perivesical tissue or beyond (stage T3 or T4). MIRMP accounts for approximately 25% of all localized cases of bladder and (compared to other lower stages), which portends a worse prognosis with higher rates of metastasis and cancer mortality after 6 months in the absence of treatment. The "gold standard" of treatment is radical cystectomy (RC) or organ-preserving three-modal treatment (TMT), consisting of maximum transurethral resection of a bladder tumor (TURMP), radiation therapy (LT) and chemotherapy. When the average age of patients is more than 70 years, when treating MIRMP, ideally, a balance should be sought between adequate therapeutic therapy and taking into account the patient's concomitant diseases, functional state and quality of life. There is no randomized data that adequately compares RC with TMT to make a decision. We present a retrospective analysis of the TMT experience in the conditions of RSNPMTSOIR.

MATERIALS AND METHODS In the conditions of RSNPMTSOIR, from 2017-2020, three-week therapy (tour + chemotherapy + radiation therapy) was performed in 32 patients with MIRMP. The primary documentation of the disease and treatment was studied retrospectively. Overall survival(s) and relapse-free survival (BRV) with preserved bladder were evaluated using the Kaplan-Meyer method. Prognostic factors were evaluated using a regression of proportional Cox risks. The follow-up period of patients is 36 months.

THE RESULTS OBTAINED

In 32 patients receiving TMT with an average dose of 64 Gy for T2 (78%), T3 (19%) and T4 (3%), an average of 19 months were observed, 31% had associated carcinoma in situ; 12.5% had concomitant hydronephrosis. Gemcitabine and isplatin (GC scema) were taken. Overall survival rates were 84% after 1

year and 61% after 3 years. The frequency of BRV was 84% and 61%, and the frequency of BRV with preserved bladder was 84% and 60% after 1 year and 3 years, respectively. The rates of rescue cystectomy after 1 year and 3 years were 4% and 9%, respectively. 4 patients had locally invasive relapses 8, 11, 34 and 37 months after the initial diagnosis of MIRMP, 2 of whom underwent radical cystectomy. 10 (31%) patients in the long-term period developed a relapse on average 13 months after the start of treatment. In contrast to local relapse, long-term relapses were associated with worse OV and the risk coefficient was 3.4 (P = 0.039). during the period from 2017 to 2020, 32 patients who received therapeutic therapy with preservation of the bladder by the TMT method were treated in the conditions of RSNPMTSOIR. Evaluation after completion of treatment included cytological examination of urine and regular cystoscopy with ultrasound (as necessary) at 3-month intervals during the first year with less frequent follow-up. At the time of this analysis, 3 patients were out of observation, without any information about the continuation of oncological/palliative treatment or death. Overall survival(s) were determined from the date of histological confirmation of MIRMP. Relapse-free survival (BRV) was determined by the date of invasive local relapse or distant metastasis. Kaplan-Meyer survival analysis was used to calculate the indicators of OV, BRV; statistical comparisons between groups were carried out using logarithmic rank analysis. One - dimensional regression was performed using Cox proportional hazards regression . The value of P <0.05 was considered statistically significant.

CONCLUSIONS

ОВ и БРВ были сопоставимы с опубликованными ранее данными. Наши результаты подтверждают, что ТМТ является эффективным вариантом для тщательно отобранных пациентов с МИРМП.



RESULTS

The average age of patients was 74 years (Table 1). The median follow-up for all patients was 19 months

(36 on average; range 6-213). For 15 surviving patients with ongoing cancer treatment, the median follow-up was 30 months

Table 1. Characteristics of the patient, tumor and treatment

Characteristic	№ (%) / median and IQR
Age at the time of diagnosis (years)	median 73,5; DI 64,5-80
Paul	
Male	25 (78,1)
Female	7 (21,9)
Клиническая стадия	
T2	25 (78,1)
T3+	7 (21,9)
Tumor size (sm)	median 3,5; DI 2-5
Histology of the urothelial tumor	32
Hydronephrosis	12.5
Positive	4 (12,5)
negative	28 (77,5)
Neoadjuvant chemotherapy	
yes	12 (37,5)
no	20 (62,5)
TUR	
Radically	17 (53,1)
Conditionally radical	9 (28,1)
Palliative	6 (18,8)

Radiation therapy dose (GR) MEDIAN 64,; di 64

Of the 32 patients, 25 (78%) had the disease stage as T2, 6 (19%) as T3, and 1 (3%) had the disease stage T4. The regimens included gemcitabine, cisplatin in 30 patients. 2 patients did not receive chemotherapy. Radiation therapy was performed at an average dose of 64 Gy using radiation therapy with modulated IMRT (including volume-modulated VMAT) in 47% of cases. 4 patients had local invasive relapses 8, 11, 34 and 36 months after the initial diagnosis of MIRMP. 2 patients with local relapse underwent life-saving radical cystectomy 8 and 15 months after diagnosis; 1 patient was treated conservatively, and 1 patient showed signs of distant disease 4 months after local relapse. Initial long-term relapses were more common: 10 (31%) patients developed a long-term disease on

average 13 months after diagnosis. The frequency of life-saving cystectomy after 1 year and 3 years was 4% and 9%, respectively. There were no cystectomies or long-term interventions for late high-grade (i.e. 3 or 4) radiation-induced toxicity or bleeding; unfortunately, the degree of toxicity was not recorded uniformly throughout the study period.

Overall survival rates were 84% and 61% after 1 year and 3 years, respectively. The indicators of BRV were 84% and 60% after 1 year and 3 years, respectively (Table 2). Any relapse (local or remote) was marginally associated with lower overall survival with a risk factor of 2.7 (95% confidence interval [CI], 0.8–9; P = 0.098). Compared with local relapses, long-term relapses were significantly associated with OS with a



risk factor of 3.4 (95% CI, 1.1-11; P = 0.039) shows numerically better results with complete TUR and stage T2 (compared with T3/T4); however, this was

not statistically significant (P = 0.16, 0.34, respectively).

Table 2 . Indicators of survival and preservation of the bladder

Characteristic	1 year	3 year
Overall survival	84%	61%
DFS	84%	61%
The bladder is preserved by BRV	84%	60%
RS	4%	9%

Abbreviations: BRV = relapse-free survival;

RC = radical cystectomy.

DISCUSSION

In our retrospective study, we summarized the experience of TMT in our institution. To date, the method of choice for MRMJ is RC with a 5-year relapse-free period and a survival rate of 68% and 66%, respectively. 4 These results are consistent and comparable with the results of a large multidisciplinary combined analysis of 6 studies of the radiation therapy group in oncology with 5-year relapse-free survival and overall survival of 71% and 57%. Our experience of bladder preservation gives similar indicators of cancer control with 3-year relapse-free survival and overall survival of 61% (95% CI, 37%-77%) and 61% (95% CI, 38%-77%), respectively. In our cohort, 22% of patients had stage T3 or higher disease, 53% had visible complete radical transurethral resection of the bladder. Other data from individual institutions show that TMT can give indicators of BRV approaching 85% after 3 years, when examining a more carefully selected cohort (with full TURBT, etc.). 6 Although long-term relapses were associated with poorer overall survival, local relapses were not; Locally recurrent disease occurred in 4 patients, none of them died. This highlights the importance of careful clinical monitoring after TMT.

Our approach (especially in recent years) is to use radiation therapy with intensity modulation; patients are modeled and treated using the geometry of an empty bladder, which is confirmed by daily visual monitoring. Of those who underwent radiation therapy (LT), more than 80% received a cisplatin-based chemotherapy regimen, and 42% received MVAC. These factors were not statistically significant predictors of survival in our analysis. Data from randomized trials show that LT improves survival rates before RC, but these results have not been replicated

with TMT. 7 An earlier study, Radiation Therapy Oncology Group 8903, found no benefit from adding 2 cycles of MVAC before TMT with a dose of 64 Gy. 8 However, more recently this strategy has been further studied: a large series of patients receiving LT followed by chemotherapy demonstrated that 2 to 4 cycles of gemcitabine and cisplatin were well tolerated and resulted in a 2-year survival rate of 74%. 9

Our study is limited by the fact that no uniform selection criteria for TMT in patients were used as a retrospective analysis. TMT in this cohort was offered to patients who were not ideal candidates and had other factors such as T3+ disease, the presence of hydronephrosis, in situ carcinoma and the absence of a clearly completed TUR, all of which were shown to be predictors of poorer disease control. 6 Although these variables were associated with poorer outcomes in this cohort, the results were not statistically significant, in part due to the limited number of patients in this series. Despite the heterogeneity of patients, the results of this cohort are comparable with similar series. This means that for better selected patients, TMT can give even better results and thus represents a very viable treatment method for certain patients.

Conclusion: To date, although attempts have been made, no randomized controlled trial has been able to adequately compare the results between RC and TMT. 10, 11 When trying to randomize patients for these very different treatments, many problems arise, including strong preferences expressed by patients and providers. 12 For these reasons, the decision to conduct RC or TMT requires an interdisciplinary approach and the clarification of careful selection criteria for the preservation of the bladder.



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