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Development of Diagnostic and Treatment Tactics for Non-Muscle-Invasive Bladder Cancer Using Minimally Invasive Technologies

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Abstract: Non-muscle invasive bladder cancer 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. Problems, early diagnosis and new methods of treating non-invasive cancer are discussed. stage 1 bladder cancer.

Keywords: non-invasive bladder cancer, transurethral resection of the bladder, photodynamic therapy + TUR diagnostics and treatment of bladder cancer.

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. Tillyashaykhova, MD Ibragimova Sh.N., Dzhanklich S.M).

Non-muscle invasive bladder cancer accounts for 75% of the total number of patients with bladder cancer, but is characterized by a pronounced tendency to recurrence 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 caused by the multicentricity of tumor rudiments, the presence of undiagnosed areas of carcinoma in situ, the possibility of tumor cell implantation 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 both independently and in combination with intravesical adjuvant immuno- and chemotherapy (CT). The correctness of staging, the frequency of relapse and disease progression depend on the adequacy of the performed primary TUR. In order to control the quality of the performed primary TUR, it was proposed to perform a repeated (secondlook - SL) TUR [5,6]. SL TUR is a clarification of the stage due to obtaining additional morphological material that provides information about the proper plate, muscle layer and the presence of residual tumor. SL TUR, performed after 2-6 weeks. after the first operation, it allows to reduce staging errors and remove residual tumor, which is detected in 20-78% of patients during repeated resection.

The frequency of underestimation of the stage varies from 4 to 30% [7]. The most important risk factor and source of errors is the absence of the underlying muscular layer in the resected tumor. A number of studies have demonstrated the positive effect of SLTURP on the frequency of relapses of BC and on the survival of patients with NMI BC. It is known that timely correct determination of the stage of the disease is fundamental in choosing adequate treatment tactics for patients with NMI BC.

Materials and methods

The study included 227 patients with clinically verified MNCBC, treated in the urology departments of the RSSPMCOiR and its Tashkent city branch. The study design is presented in Figure 1.

Depending on the treatment method, the patients were divided into 3 study groups, which differed in the tactics of treatment measures:

Group 1 of the study consisted of 84 patients with bladder cancer MNCBC, who underwent standard transurethral resection of the bladder and Second look TUR, followed by intravesical chemotherapy;

The 2nd study group consisted of 53 patients with MNSCC who underwent PDT of the bladder along with TUR; the 3rd group – control, consists of 90 patients with MNSCC who underwent TUR of the bladder tumor as a radical intervention.

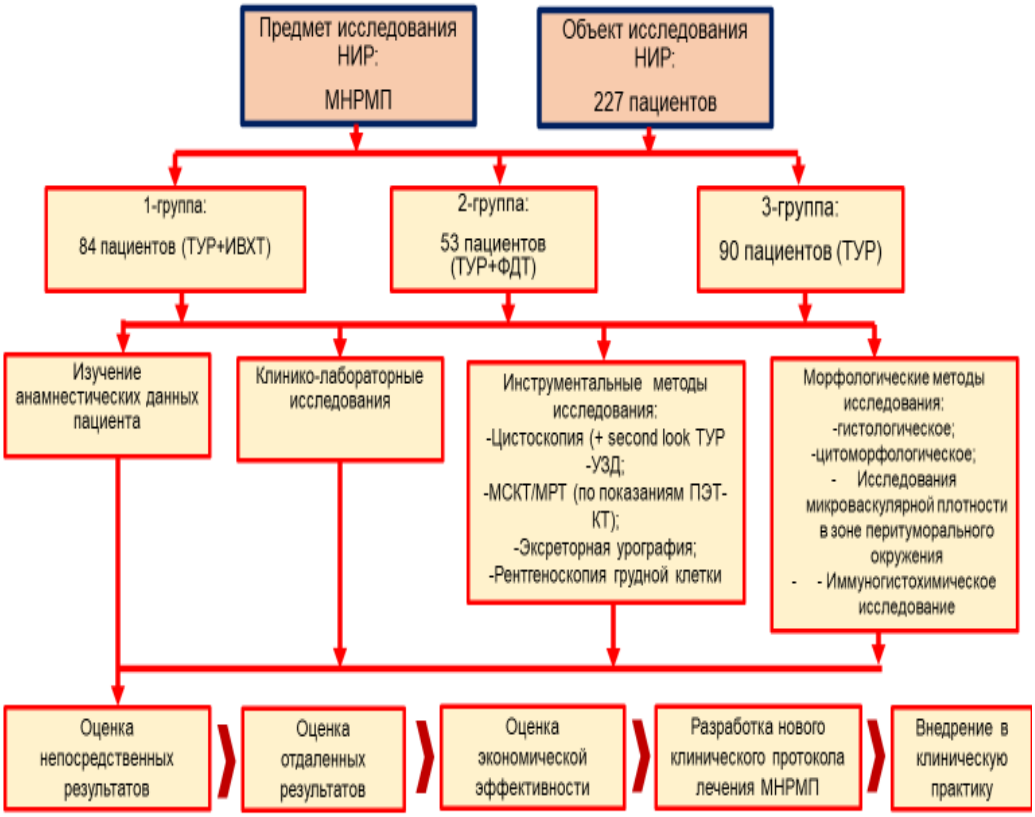

Fig. 2.1. Design of research work.

The dissertation is devoted to the development and implementation of effective methods of combined treatment of MNSCC with the inclusion of photodynamic therapy in the arsenal.

Clinical characteristics of patients with MNSCC depending on gender and age indicators, localization and spread of the pathological process, histological type and degree of differentiation of the tumor, concomitant diseases are presented in Table 2.7.

Gradations	All patients n=227	1-group n=84 (TUR+IVHT)	2-group n=53 (TUR+PDT)	3-group n=90 (TUR)	p
Age years (M ± m)	61,4+0,7 лет	59,3+0,9	63,4+0,8	61,7+0,5	0,394
Gender:					
Male	156 (68,7%)	59 (70,2%)	42 (79,2%)	55 (61,1%)	0,161
Female	71 (31,3%)	25 (29,7%)	11 (20,8%)	35 (43,2%)	
Tumor localization:					
Anterior	43 (29,0%)	18 (21,4%)	11 (20,7%)	14 (15,5%)	0,302
Posterior	65 (28,6%)	26 (30,9%)	14 (26,4%)	25 (27,7%)	
Floor	23 (10,1%)	7 (8,3%)	4 (7,5%)	12 (13,3%)	
Multicentric	17 (7,5%)	6 (7,1%)	3 (5,7,8%)	8 (8,9%)	
Right wall	40 (17,6%)	15 (17,8%)	9 (16,9%)	16 (17,7%)	
Left wall	39 (17,1%)	12 (14,3%)	12 (22,6%)	15 (16,6%)	
Tumor size, cm					

Mean (M ± m) Median	2,3±0,3 1,5	1,9±0,2 2,2	2,1±0,2 2,3	2,5±0,4 2,7	0,608
Risk of recurrence according to the EORTC scale: Low risk Intermediate risk High risk	 62 (27,3%) 104 (45,8%) 61 (26,8%)	 23 (27,4%) 37 (44,0%) 24 (28,6%)	 12 (22,6%) 26 (49,0%) 15 (28,3%)	 27 (30,0%) 41 (45,6%) 22 (24,4%)	0,0001
Degree of differentiation of urothelial cancer:G1 G2 G3	 75 (33,0%) 53 (23,4%) 99 (43,6%)	 25 (29,7%) 18 (21,4%) 41 (48,8%)	 19 (35,8%) 11 (20,7%) 23 (43,4%)	 31 (34,4%) 24 (26,7%) 35 (38,9%)	0,082
Category rT: pTa pT1	 55 (24,2%) 172 (75,8%)	 21 (25,0%) 63 (75,0%)	 8 (15,1%) 45 (84,9%)	 26 (28,8%) 64 (71,1%)	0,014

The average age of patients was 61.5 years; in all three groups, the disease was mainly observed in males (68.7%).

Based on the obtained clinical and morphological data (number of tumors, tumor size, T category, tumor cell differentiation (G), concomitant CIS), groups were identified according to the degrees of risk of relapse 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 relapse and progression. When assessed according to the EORTC scale, patients in group 1 were distributed as follows: 44% with intermediate and 28.6% with high risk of relapse; in group 1 28.6%, group 2 28.3%, in group 3 24.4%.

According to the histological structure, urothelial cancer was morphologically confirmed in all patients (100%), according to the gradation: low grade (Gl) - 75 (33.0%), intermediate grade (G2) - 53 (23.4%) and high grade (G3) - 99 (43.6%). In 17 patients (7.5%), 2 or more tumor formations in the bladder were detected during examination. PDT was used in the treatment of patients with an intravesical visual component of the tumor greater than 1.0 cm and creeping tumors of no more than 3 cm in area. Taking into account the above, the 2nd group of patients was formed, who underwent PDT - 53 (23.3%). In general, the study in all groups included patients with low, intermediate and high risk of relapse of the disease, for whom organ-preserving treatment is planned. The proposed method of combined endoscopic surgical treatment - TUR of the tumor with PDT and IVHT is an original and priority development of the State Budgetary Institution "RSNPMC of Oncology and Radiology".

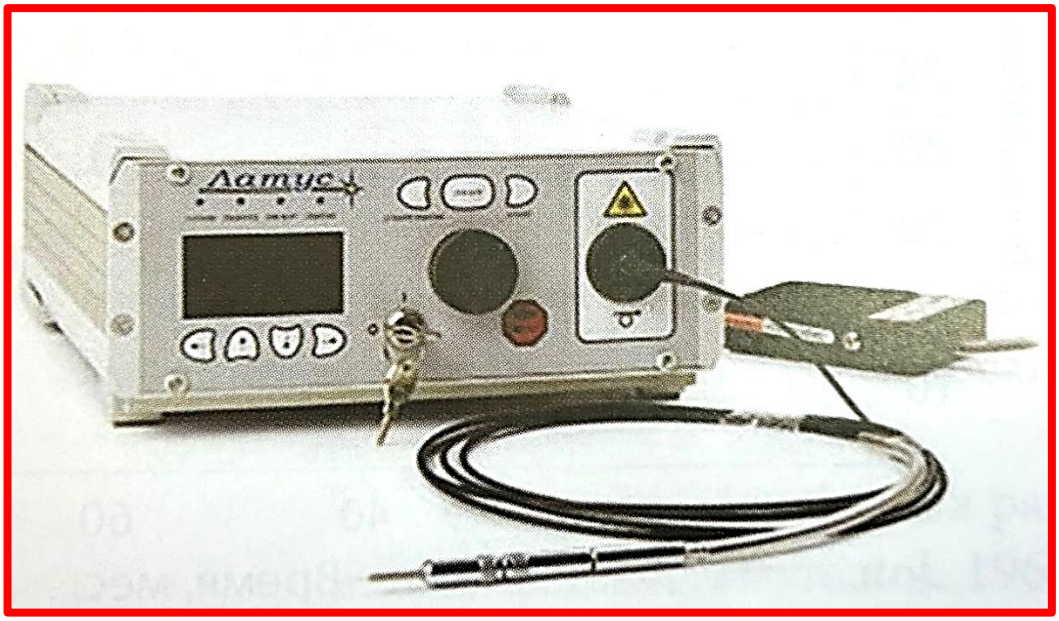

Fig. 2.1. Apparatus for photodynamic therapy of bladder cancer

Results.

In the course of the research work, the results of measures for the diagnosis and treatment of recurrent MNCBC in patients after TUR and combination therapy in 68 (29.9%) patients were studied.

Relapses occurred in 47 (69.1%) men and 21 (30.9%) women, with an age variation of 27 to 79 years (median - 52.5 years) (Table 2.8).

Table 2.8 Distribution of patients with recurrent MNCBC, n=68

Indicator	Group I (n=84)		Group II (n=53)		Group III (n=90)		P
	Number of patients	%	Number of patients	%	Number of patients	%	
Gender							
women	5	5.9	2	3.8	11	12.2	0,5
men	15	17.8	8	15.1	27	30.0	
Median age	55,6	-	51,7	-	53,2	-	0,81
Tumor size							
from > 1,5 cm to < 4 cm	20	100	10	100	38	100	0,57
Number of tumors							
1	7	35	4	40	14	36,8	0,6
2 and more	13	65	6	60	24	63,2	
Category T							
pTa	5	25	2	20	17	44,7	0,41
PT1	14	70	8	80	19	50	
Tx	1	5	0	0	2	5,3	
Tumor grading							
Low grade (G3)	11	55	7	70	19	50	0,47
Intermediate grade (G2)	5	25	1	10	13	34,2	
High grade (G1)	4	20	2	20	6	15,8	

According to the data presented in the table, in the first and second study groups, male patients with primary T1 stage and Low grade (G1) differentiation of BC predominated. At the same time, statistically significant differences between the primary measures were revealed in the comparison groups.

Results of transurethral resection in the treatment of MNSCC.

In this case, TUR as the main and only method of treatment was performed in 90 patients with MNCBC. The treatment was assessed during the first control cystoscopy 3 weeks after TUR. Then, control cystoscopy was performed every 3 months during the first year of observation. The duration of observation of patients was up to 60 months (median observation 32 + 0.7 months).

When performing TUR, out of 90 patients, postoperative complications were observed in 11 (12%) patients: bleeding - in 7 (7.8%) patients, urinary tract infection (cystitis) - in 3 (3.3%) and perforation with bleeding - in 1 (1.1%) patient (Table 3.1).

Table 3.1. Complications in patients with TUR of the tumor

Studied complication indicators	Group -3 (n=90)	
	Absolute number	IN %
Bleeding	7	7,8
Cystitis	3	3,3

Perforation	1	1,1

According to the data in Table 3.3, after TUR, disease progression at various observation periods was detected in 38 (42.2%) patients. In 52 (57.8%) patients, no relapse of the disease was detected during the 60-month monitoring period. If relapse was detected in 10% of patients with tumors up to 2 cm in size, then with an increase in size, the relapse rate increases up to 3 times, reaching 32.2% ($p \leq 0.04$). At the same time, a single relapse was noted in 26.7% of patients after TUR. In 15.5% of patients, relapses occurred 2 or more times.

Table 3.3 Results of TUR in patients with MNCBC

Indicators	Group 1, n=90		P
	Number of patients	IN %	
Relapse:			
No	52	57,8	
Yes	38	42,2	0,04
Recurrence rate:			
Single	24	26,7	
2 or more	14	15,5	0,8
Gender:			
Women	11	12,2	
Men	27	30,0	0,4
Median age	53,2	-	
Tumor size:			
from 2 to 4 cm	29	32,2	
up to 2 cm	9	10,0	
up to 1 cm	2	3	0,04
Category T:			
pTa	17	44,7	
pT1	21	55,3	0,21
Degree of histological differentiation:			
G1 (high grade)	6	15,8	
G2(intermade grade)	13	34,2	
G3 (low grade)	19	50,0	0,47
Timing of first relapse:			
up to 1 year	5	5,5	
up to 2 years	11	12,2	
up to 4 years	18	20,0	
more than 5 years	4	4,5	0,03

The degree of histological differentiation of the tumor directly affected the development of progression. Thus, after TUR, only 15.8% of patients had a relapse of bladder cancer. In contrast, 50% with a relapse had a low grade G3 differentiation degree.

Results of combined treatment - TUR followed by intravesical chemotherapy in the treatment of non-muscle invasive bladder cancer.

In this study, we studied the effectiveness of TUR with IVCT in 84 patients with MNCBC. The antitumor antibiotic MMC was administered into the bladder in 50 ml of diluted saline. A positive response to intravesical application of MMC was observed in 64 (76.2%) patients. The median monitoring in these patients was 27.3+0.5 months, which indicates a fairly high effectiveness of MMC (Table 3.4).

Table 3.4. Results of TUR + IVHT for MNCRP, n=84.

Indicator	Group II, , n=84.		p
	Abs.	In the proc.	
Relapse: No Yes	 64 20	 76,2 23,8	0,05
Recurrence rate: Single 2 or more	 2 18	 2,4 21,4	0,6
Gender: Female Male	 5 15	 5,9 17,9	0,5
Median age	55,6	-	0,91
Tumor size: from 2 to 4 cm up to 2 cm up to 1 cm	 17 3	 20,3 3,5	0,02
Category T: pTa pT1	 17 3	 8,3 15,5	0,033
Degree of histological differentiation: G1 (hight grade) G2(Intermade grade) G3 (Low grade)	 1 3 16	 1,3 3,5 19,0	0,06

According to the obtained results of TUR with IVCT, locoregional progression of the tumor process was noted in 20 patients (23.8%). Men with a relapse of the process accounted for 17.9%, women 5.9%. At the same time, relapse in the pT1 category is observed almost 2 times more often than in pTa - 15.5 and 8.3%, respectively, even after IVCT, multicentric relapses were most often observed - 21.4% (18 patients). Only 2 patients (2.4%) had a single relapse in the TUR zone of the bladder mucosa, relapses more often occurred with tumors up to 4 cm - 20.3% (p = 0.06). A direct relationship between the frequency of progression and the degree of histological differentiation was observed in this group (p = 0.06), i.e. with G-1, relapse occurred in 1.3%, then with G3- in 19%.

In general, after combination treatment with intravesical chemotherapy, relapses were observed in 9 (10.7%) patients for 1 year. The highest number of relapses was also observed in the period from 1 to 5 years - 10 (11.9%). The average duration of the relapse-free period in these patients was 27.1+-0.8 months, and the median of the progression-free period was 33.5+-0.9 months (p≥0.05.).

Results of TUR in combination with photodynamic therapy.

In our work, photodynamic therapy in the adjuvant mode was used in 53 patients with urothelial cancer and the indications for PDT were:

a) primary urothelial cancer Ta and T1 stages, regardless of the histological differentiation of urothelial cancer.

b) predominantly exophytic tumor growth with localization of the pathological process in the area of the bottom and lateral walls, from 2 to 4 cm in size.

c) multicentric location of the tumor, there was involvement of the ureteral orifice and detrisor.

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c) multicentric location of the tumor, with involvement of the ureteral orifice and detrisor.

Table 3.7 Results of TUR and PDT for MNCRP, n=53.

Indicators	Group III n=53		P
	Abs	IN %	
Relapse: No Yes	 43 10	 81,1 18,9	 0,03
Recurrence rate: Single 2 or more	 1 9	 1,9 17	 0,04
Gender: Female Male	 2 8	 3,8 15,1	 0,09
Medina age	52,2	-	0,91
Tumor size: from 2 to 4 cm up to 2 cm	 10 -	 18,9	 0,07
Category T: pTa pT1	 3 7	 5,7 13,2	 0,43
Degree of histological differentiation: G1 (high grade) G2 (intermate grade) G3 (low grade)	 - 2 8	 3,8 15,1	 0,31

The study of the recurrence periods showed that after PDT no progression was noted in the period up to 6 months. During the first year of observation, relapse occurred in 1 (1.9%) patient. The greatest number of relapses is observed in the period up to 24 months in 7 (13.2%). When assessing the development of relapse depending on the histological differentiation of the tumor, it was revealed that in patients with high grade (G1) no progression was noted in the observation period after PDT. In contrast, with G- 2 and G- 3, the proportional relationship between the degree of differentiation and this group of patients was 31.2+-1.1 months.

Remote results of treatment of MNRC.

A multigrade study of remote results showed the development of relapses of the disease in 42.2% after TUR and 30 (29.9%) - after combined treatment was 2:1. This trend was characteristic of the recurrence of the process more than 1 time. The frequency of multiple relapses after combined treatment was 12.7% versus 15.5% after TUR in monotherapy. The lowest number of single and multiple relapses was noted in the group of patients with TUR and PDT - 5.6 and 13.2%, respectively. These indicators in group 1 were also significantly lower compared to the indicators only after TUR.

Statistically, the average terms of relapse development differed significantly depending on the treatment method used. The shortest average relapse period was typical for TUR – 149+1.1 months. After TUR with IVHT, the average manifestation of recurrent disease development was 16.3+0.9 months, which after TUR with PDT increased to 21.8+1.5 months. Considering the typicality of the average term of recurrent disease manifestation only for patients with verified relapse, it was

considered appropriate to separately study relapse-free survival in relation to the study groups. In particular, 2 gradations of relapse-free survival were distinguished: the average relapse-free period and the median relapse-free period. Consequently, the SPBRP was the shortest after TUR with IVHT, amounting to 20.3+2.1 months. In contrast to the indicators of groups 1 and 2, in patients with only minimally invasive resection of the bladder, a statistically significant duration of the MPRP of up to 27.4+2.1 months was observed. Similar indicators were observed in the assessment of the median MPRP. However, the MPRP was short in patients of group 2. The MPRP indicators in groups 1 and 3 had almost identical values - 29.7+1.7 and 31.3+2.1 months, respectively.

Table 7.1 Comparative results of multimodal treatment of MNCs

Key indicators	Comparison groups						p=
	I		*II*		*III*		
	abs	%	abs	%	abs	%	
Survival:							
3 years	79	94,0	50	94,3	83	92,2	0,002
5 years	64	76,2	46	86,8	62	68,9	
Bezrets survived.							
SPBRP	20,0+2,4	-	22,8+1,9	-	27,4+2,3		0,03
MBRP	29,7+2,1	-	25,9+2,2		31,3+2,1		
Complications:							
Bleeding	7	8,3	-	-	7	7,8	
Cystitis	6	7,1	2	3,8	3	3,3	
Perforation	-	-	-	-	1	1,1	0,004
Pain syndrome	11	13,1	1	1,9	2	2,2	
Resi	18	21,4	3	5,7	-	-	
Hematuria	3	3,6	-	-	4	4,4	
Relapse:							
Average relapse period	16,3+0,9	-	21,8+1,5	-	14,9+1,1	-	
Relapse frequency.	20	-	10	-	38	-	0,06
Single	14	16,7	7	13,2	24	26,7	
Multiple	6	7,1	3	5,6	14	15,5	
3-year cancer-specific mortality	4	4,7	2	3,8	6	6,7	0,01
Quality of life EGOC							
At discharge:							
1-2 points	57	67,9	38	71,7	63	70,0	
3 points	27	32,1	15	28,3	27	30,0	
After 6 months:							
1-2 points	69	82,1	47	88,7	81	90,0	0,06
3 points	15	17,9	6	11,3	9	10,0	

Despite the above indicators, the results of the assessment of 3- and 5-year survival showed adequate efficiency of various treatment models in the comparative aspect. At the same time, the 3-year survival rates in all groups were quite high, amounting to more than 90% (p = 0.002). Against this background, 3-year cancer-specific mortality was 3.8% (in group 2) to 6.7% (in group 3). During the further observation period, a significant decrease in the survival rate was noted in groups 1 and 3 of the study. In our opinion, this is due to the high CR and the transition of some patients from the non-invasive cohort to the invasive one.

Conclusion

1. The use of SLTURP + IVCT and TURP + photodynamic therapy allows us to assess the true depth of tumor invasion and identify residual tumors, thereby reducing the incidence of recurrence and progression.

2. Patients who underwent primary TURP + photodynamic therapy have statistically significant differences in 5-year RFS. Patients with TURP + photodynamic therapy and SLTURP + IVCT have a significantly higher RFS rate.
3. Intravesical adjuvant immunotherapy and chemotherapy are the main method for preventing recurrence of non-invasive bladder cancer.

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