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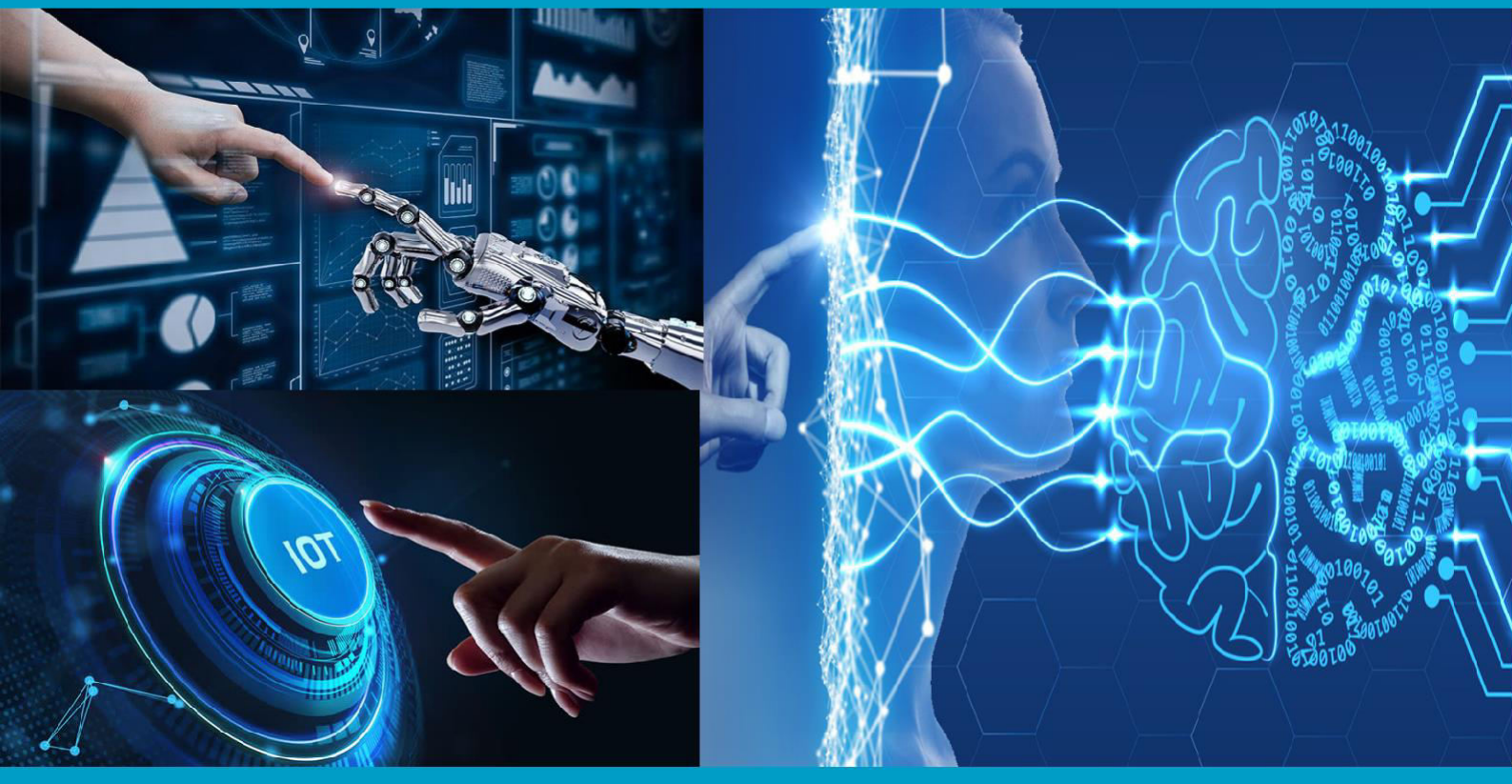

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Organ-Preserving Treatment for Bladder Cancer Using Intravesical Ronleukin Immunotherapy

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Annotation: The main method of treatment of invasive RMP is radical cystectomy (RCE).Despite a significant amount of surgical intervention within 2 years after RCE for invasive RMP, 50% of patients have distant metastases, and 13-25% have local recurrence of the tumor in the pelvic cavity. Cystectomy is a traumatic surgical intervention. A significant part of patients have postoperative complications. Therefore, there is currently a growing number of supporters of an organ-preserving approach in the treatment of invasive bladder cancer using chemoradiotherapy. Based on the results of studies on this problem in 2018, a new scheme of complex organ-preserving treatment of patients with invasive bladder cancer using neoadjuvant PCT according to the GP scheme against the background of intravesical immunotherapy with roncoleukin (interleukin-2-IL-2) was developed and a prospective randomized study of the effectiveness of the proposed treatment method was conducted.

ORGAN-PRESERVING TREATMENT FOR BLADDER CANCER USING INTRAVESICAL RONLEUKIN IMMUNOTHERAPY.

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Cystectomy is a traumatic surgical intervention. A significant part of patients have postoperative complications. Perioperative mortality is 2,3-26,9% [3,4, 6-9]. Complications of the early postoperative period occur in 11-70% of patients [2,3,10-13]. Therefore, the number of supporters of an organ-preserving approach in the treatment of invasive RMP using chemoradiotherapy is currently growing [14-15]. At the same time, the five-year survival rate varies from 42 to 62% [15]. With the local prevalence of the T2 tumor, the survival rate is even higher and is 64-68%. These data are fully comparable with the results of total cystectomy in patients with the same stage of the disease and the appropriate age [14-15].

However, the effect when using standard schemes of polychemotherapy (PCT) with invasive RMP is usually achieved only after 3-4 cycles of treatment, and this is not always possible due to the pronounced toxicity of the GP scheme used in such cases, which is noted by almost all researchers. Therefore, today the issue of increasing the effectiveness of

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chemotherapy for RMP is quite acute, which allows you to reduce the number of courses of treatment, and consequently, the toxicity.

The main progress in the treatment of RMP is associated with immunotherapy. Based on the results of studies on this problem [16] in 2018, a new scheme of complex organ-preserving treatment of patients with invasive RMP using neoadjuvant PCT according to the GP scheme against the background of intravesical immunotherapy with roncoleukin (interleukin-2-IL-2) was developed and a prospective randomized study of the effectiveness of the proposed treatment method was conducted. This article analyzes the immediate and long-term results of treatment.

Materials and methods

The study included 60 patients with newly diagnosed invasive RMP without remote and regional metastases with T2a -4 N0 M0 stages II-III. The age of the patients ranged from 39 to 80 years (average age 60.2 years). The characteristics of patients are presented in Table 1

Indicator	Control group(n=30)		Main group (n=30)		Total (n=60)	
	Absolutely	**%**	**Absolutely**	**%**	**Absolutely**	**%**
men	27	90,0	26	86,7	53	88,3
women	3	10,0	4	13,3	7	11,7
MLocal prevalence of the process:естная распространенность процесса:						
pT2	20	66,7	24	80,0	44	73,3
pT3	2	6,7	1	3,3	3	5,0
pT4a	8	26,6	5	16,7	13	21,7
The degree of differentiation of the tumor:						
G1	4	13,3	4	13,3	8	13,3
G2	15	50,0	16	53,4	31	51,7
G3	11	36,7	10	33,4	21	35,0

Table 1.
Characteristics of patients

At the first stage, all patients underwent cytoreductive transurethral resection (TUR) of the bladder, which provided for the maximum possible removal of the exophytic part of the bladder tumor with a part of the muscle layer in order to verify the diagnosis, determine the depth of invasion of the bladder wall by the tumor and reduce the volume of the tumor mass. The presence of tumor invasion of the muscles was subsequently confirmed histologically. The study included patients with muscle-invasive transitional cell RMP without distant regional metastases.

After randomization using the Statistica 2020 program (StatSoft,Inc.) using the random number method, patients were divided into two groups (30 patients each). In the 1st control group, 2 courses of neoadjuvant PCT were conducted according to the GP scheme (cisplatin, gemcitabine). In the 2nd group-2 courses of neoadjuvant PCT according to the cisplatin, gemcitabine – GP scheme on the background of intravesical immunotherapy. The PCT courses according to the scheme included the introduction of cisplatin and gemcitabine. Conducted according to the standard methodology. On day 1, cisplatin was administered intravenously at a dose of 50 mg/ m2. Before the introduction of cisplatin, intravenous hyperhydration and alkalinization (about 2000 ml of liquid and sodium bicarbonate) were performed, and cisplatin was not administered until the pH of urine was 7.0 or higher. On days 1 and 8, gemcitabine was administered intravenously at a dose of 1 g / m2 in 400 ml of isotonic solution in the form of a 1-hour infusion. Cisplatin was started to be administered when the diuresis reached 100-150 ml / h. Mannitol (30g of mannitol) was used to force diuresis

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For intravesical immunotherapy, the drug roncoleukin was used - an injectable dosage form of recombinant human IL - 2. The drug was injected into the bladder for 20 ml of saline solution at a dose of 1 million units 2 times a day. The exposure time after each injection was 3 hours. The second injection was performed 3 hours after the first. In total, 10 instillations were carried out for one patient per course. The drug was administered for 5 consecutive days.

To assess the effect, a bladder tour was performed 4-5 weeks after the end of PCT. In the case of complete clinical regression, a tour of the tumor location was performed in order to histologically confirm the effect obtained.

In case of detection of tumor tissue in the biopsy of the cut-off edges or the bottom of the resection wound after organ-preserving surgery, as well as in case of stabilization or progression after two courses of PCT, RCE was performed. In total, RCE was performed in 19 patients. Preference was given to iliocystoplasty as a method of urine removal (11 patients), while the Studer method was used in 3 patients (U.Studer). In the presence of contraindications to iliocystoplasty, the following operations were performed: E.Bricker surgery - 3 patients, urethrosigmoanastomosis according to the standard Le Duc procedure (LeDuk) and urethrocutaneostomy - 2 patients each.

The immediate effect of treatment was assessed by the degree of tumor regression. The Statistica. 2020 program (StatSoft,Inc.) was used for statistical processing of the results. Long-term results were evaluated once a year by constructing survival tables using the interval method from the date of the start of treatment (cytoreductive surgery). The overall and relapse-free survival was studied. The survival rate was calculated using the Kaplan-Mayer method. A nonparametric log-rank test was used to compare survival rates in the groups. Statistically significant differences were considered at $p<0.05$.

Results and their discussion

The groups of patients were comparable by sex, age, local prevalence of the process and the degree of tumor differentiation (see Table 1). There were no significant differences in the above indicators in the groups ($p> 0.05$)

In general, the toxicity of the treatment regimens used was moderate and practically did not differ in the main and control groups (Table 2). Nephro-, cardio- and hepatotoxicity were insignificant. The most frequent toxic effects were alopecia, leukopenia and vomiting. At the same time, no toxic effects of the IV degree were noted, and the toxicity of the III degree was relatively rare. In 3 (10%) patients of the control group and in 2 (6.7%) of the main group, grade III leukopenia was observed, in 6 (20%) and 5 (16.7%) patients, respectively, grade III alopecia and in one patient in each group (3.3%)-grade III vomiting. Differences in the toxicity of treatment between the groups are unreliable ($p>0.05$). Local reactions with intravesical administration of roncoleukin were not noted.

The immediate effect of therapy was significantly higher in the main group (Table 3). Complete regression of the tumor was obtained in 16 (53.3 ±9.1%) patients of the main group and in 8 (26.7 ±8.1%) patients of the control group, and the progression of the process was noted in 2 (6.7±4.6%) and 7 (23.3±7.7%) of patients, respectively. The differences are significant ($p=0.049$, U is the Mann–Whitney criterion). Organ-preserving surgery was performed in 24 (80%) patients of the main and 16 (53.3±9.1%) of the control group (differences were significant, $p=0.03, \chi 2$). In other cases, the RCE was performed. At the same time, in the main group, the operation was performed radically in all six cases (R0), and in the control group, 2 (15.4%) patients out of 13 had tumor growth at the edges of the cut-off after cystectomy during morphological examination (R1). Two patients in each group (6.6%) categorically refused to perform RCE.

Tab 2.

The immediate effect of treatment

Effect	Control group (n=30)		Main group (n=30)	
	Absolutely	%	Absolutely	%
Full regression	8	26,7±8,1	16	53,3±9,1
Partial regression	9	30,0±8,3	8	26,7±8,1
Stabilization	6	20,0±7,3	4	13,3±6,2
Progression	7	23,3±7,7	2	6,7±4,6

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The recurrence rate was studied in patients with preserved bladder with follow-up periods from 6 to 75 months (on average 24.5±20.0 months). Relapse-free survival was slightly higher in the main group, although the differences were unreliable (p=0.67, log-rank test). Distant metastases appeared in 3 (10.0%) percent of patients in the main group and in 5 (16.7%) of the control group. 5 (16.7%) and 12 died from the progression of the disease.
(40.0%) of patients, respectively. Survival before progression (before the appearance of invasive relapse or metastases) was unreliable (p=0.35, log-rank test).
The overall 5-year survival rate for all patients included in the study was 60.1±8.7%. When studying the dependence of overall survival on the treatment method, significant differences between the groups were revealed. The cumulative survival rate of patients in the main group was significantly higher than the corresponding indicator in the control group (p=0.02, log-rank test). At the same time, the overall 5-year survival rate was 81.4±7.6 and 46.5±12.5%, respectively. The median life time in the control group was 40.1 months, and in the main group it is currently not reached.
When comparing the results obtained with the data of other authors, attention is drawn to approximately the same frequency of aggression after chemotherapy (Table. 3), however, in our study, a significantly smaller number of PCT courses were conducted. This can explain the good tolerability of treatment. When using standard PCTs according to the M-VAC scheme, 3-4 courses of treatment are usually carried out, when severe toxic reactions are noted.

Tab3.

The frequency of achieving complete tumor regression in the T2 – T4 stage after chemotherapy

Author	Treatment regimen	Full regression, %
H. Scheru соавт. [22]	TYuR + GP 2-5 courses	48
W. Lynchи соавт. [23]	TYuR+ CMV 2 courses	47
R. Farahи соавт. [24]	M-VAC 4courses	32
R. Sheareru соавт. [25]	GP2-4 courses	32
R. Halli соавт. [26]	CM±VE 2-4 courses	37
НИИО и МР им. Н.Н. Александрова	TYuRGP2 courses + interleukin-2	53,3
Note. M – methotrexate, V– vinblastine, A– adriamycin, C– cisplatin, E–epirubicin, G-gemcitabine		

It should be noted that the survival of patients directly depends on the effect of treatment. The best results were observed in patients with complete regression of the tumor, and differences in the survival rate of patients with different effects of chemotherapy were significant (p=0.028).
The greatest chance of preserving the bladder are those patients who have complete regression of the tumor after a TOUR and several courses of chemotherapy, which was confirmed by studies in various clinics [2, 22]. This can also explain the significantly higher survival rate of patients with preserved bladder compared to patients who underwent RCE (Fig. 5). The overall survival rate of patients after organ-preserving treatment was significantly higher than after RCE (p=0.01, log-rank test).
Table 4 compares the results of this study with the results of organ-preserving treatment (TUR + chemoradiotherapy) of patients with invasive RMP in similar studies by other authors. As can be seen from the data presented, the survival rate of patients and the time to cystectomy (Fig. 6) in our study is slightly higher than according to the literature.

Table 5.

Results of organ-preserving treatment (TUR + chemoradiotherapy)
of patients with invasive RMP

Author	Number of patients	5-year survival rate, %	
		observed	with the preservation of the bladder
D. Kaufman и соавт. [27]	106	52	43
R. Sauer соавт. [28]	79	52	41
W. Tester соавт. [15]	42	52	42
W. Tester соавт. [16]	91	62	44
M. Orsatticoавт. [17]	76	42	-

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RSS and PMC of O and R, RSS and PMC of O and RTCb TYuR + XT + IL-2	30	81,4±7,6	70,0±8,4

Conclusions

The proposed scheme of complex treatment of invasive RMP using neoadjuvant PCT and intravesical immunotherapy is well tolerated by patients. Additional intravesical administration of roncoleukin (IL-2) did not affect the frequency and severity of the toxic effects of PCTs. Local reactions with intravesical administration of roncoleukin were not noted.

The immediate effect of the proposed treatment regimen is higher than the standard PCT according to the GP scheme. The number of complete regressions was 53.3±9.1 and 26.7±8.1%, respectively (p=0.049, Mann-Whitney U-test).

Increasing the effectiveness of PCT allowed to maintain a satisfactory functioning bladder in a much larger number of patients. Organ–preserving surgery was performed in 24 (80.0%) patients of the main and 16 (53.3%) patients of the control group, the differences were significant (p=0.03, $\chi 2$).

The cumulative survival rate of patients in the main group was significantly higher than in the control group (p=0.02, log-rank test). The overall 5-year survival rate in the groups was 81.4±7.6 and 46.5±12.5%, respectively.Increased survival was achieved due to an increase in the number of patients with complete tumor regression after chemotherapy, characterized by a more favorable prognosis for life expectancy.

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