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## The use of probiotics in the complex treatment of bladder cancer

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### Резюме

**Цель исследования:** Повышение эффективности диагностики и лечения больных с поверхностным раком мочевого пузыря.

**Материал исследования:** В 2014-2016 гг. в отделении онкоурологии Республиканского онкологического научного центра обследовано 142 больных с с поверхностным раком мочевого пузыря.

**Результаты исследования:** гистологическом исследовании переходноклеточный рак мочевого пузыря был верифицирован у 65 пациентов основной группы (94,2%), у 4 (5,8%) - плоскоклеточный рак мочевого пузыря, в контрольной группе - 69 (94,5%) и у 4 (94,51%).

**Ключевые слова:** рак мочевого пузыря, пробиотики, трансуретральная резекция, микрофлора, рецидив.

### Хулоса

**Тадқиқотнинг мақсади:** Юзаки қовуқ саратонига чалинган беморларни ташхислаш ва даволаш самарадорлигини ошириш.

**Тадқиқот материали:** 2014-2016 йилларда қовуқ саратонига чалинган 142 нафар бемор Республика онкологик илмий марказининг Онкоурология бўлимида текширувдан ўтказилди.

**Тадқиқот натижалари:** қовуқ саратон юзаки саратони бидан огриган беморларда куйидагича гистологик хулосалар олинди назорат гуруҳида - - 65 (94,2%) ва 4 (5,8%) асосий гуруҳ (54,5%) 4 (94,5%) ва 4 (94,51%) беморларнинг гистологик текшириш текширувларида утувчи хужайрали саратон аникланди.

**Калит сўзлар:** қовуқ саратони, пробиотиклер, трансуретрал резекция, микрофлора, рецидив.

### Summary

**The purpose of the study:** Improving the effectiveness of diagnosis and treatment of patients with superficial bladder cancer.

**Research material:** Improving the effectiveness of diagnosis and treatment of patients with superficial bladder cancer in 2014-2016. 142 patients with superficial bladder cancer were examined in the Oncourology department of the Republican Oncological Research Center

**Research results:** histological examination of transitional cell bladder cancer was verified in 65 patients of the main group (94.2%), in 4 (5.8%) - squamous cell bladder cancer, in the control group - 69 (94.5%) and in 4 (94.51%)..

**Key words:** *bladder cancer, probiotics, transurethral resection, microflora, relapse.*

**Introduction.** Bladder cancer is the most common malignant tumor of the urinary tract and ranks 7th place in the structure of oncopathology among men and 17th place among women in terms of prevalence [4]. Depending on the geographic location, the incidence of bladder cancer in different countries differs by about ten times. Thus, in Western Europe and the United States, the incidence is higher than in Eastern Europe and Asia. In the European Union, the age-standardized incidence rate is 19.1 for men and 4.0 for women [3]. Globally, the age-standardized mortality rate (per 100,000 population) is 3.2 for men and 0.9 for women [6]. In the structure of oncological morbidity in the population of Russia, bladder cancer ranks 9th among men and 16th among women. The incidence rate per 100 thousand population was 13.2 for men and 2.3 for women. The increase in morbidity for both sexes over the past 10 years was 28.3%. The standardized mortality rate for men and women was 4.7 and 0.5, respectively [5]. According to the age structure, patients over 60 years of age prevail, in Russia they account for 78.4%. The average age of cases in Russia for men is 66.6 years, for women - 69.6 [5]. Bladder cancer occurs among men more often than among women (ratio 3: 1), which is associated with a greater prevalence of smoking among men and occupations associated with carcinogens that increase the risk of developing the disease [2]. There are racial differences in the incidence of bladder cancer. Thus, in the United States, among black men and American Indians, it is, respectively, 2 and 8 times lower, and in Asian settlements - 60% lower than among white Americans [7].

In the structure of oncological morbidity in the Republic of Uzbekistan, bladder cancer takes the 15th place, its frequency is 1.32 cases per 100,000 people per year. Besides, over the past 3 years, the increase in the number of patients with bladder cancer in the Republic of Uzbekistan was 12.6% (Cancer Reg 2020 Uzbekistan).

Transurethral resection (TUR) is a radical intervention in patients with superficial Ta-T1 tumors. After surgery, relapses are observed in 60-80% of cases, in most cases -

within the first year after primary treatment. In order to prevent relapses, the European Association of Urologists in the first 6-8 hours after TUR recommended additional drug therapy: intravesical administration of chemotherapeutic drugs (doxorubicin, mitomycin C, etc.) or BCG vaccine. Many authors perform TUR also at T2. This is possible in small tumors, as well as among patients with absolute contraindications for cystectomy (James A.C. et al., 2014). According to E.N. Sitdykova and A.Yu. Zubkova (2013), TUR of the bladder should be performed on patients with disease stages T1 and T2, and in later stages - T3 for palliative purposes. A relatively new electrosurgical method for treating superficial forms of bladder cancer is electrovaporization, which consists of 13 rapid evaporation of tissue with instant coagulation of large areas of the surface. Until now, the place of this method in the treatment of malignant neoplasms of the bladder has not yet been fully determined. Transurethral electrovaporization of a bladder tumor shortens the operation time, allows you to quickly control bleeding, and shortens the hospital stay. A relative disadvantage is the absence of histological material, in connection with which an intraoperative biopsy with a standard loop was proposed as an obligatory component of the operation. TUR is superior to open resection in both efficiency and safety of the intervention.

Over the past few years, a large number of studies have been conducted demonstrating that certain living microorganisms (probiotics), introduced into the human body from the outside in adequate amounts, can have a beneficial effect on health. Based on the above definition, a probiotic must meet at least three criteria: first, the microorganisms must be alive during ingestion; secondly, microorganisms must enter the body in an amount sufficient to cause a beneficial effect (as a rule, at least 10<sup>8</sup>-10<sup>9</sup> CFU per day); thirdly, microorganisms must benefit the macroorganism. The vast majority of probiotics are bifidobacterium and lactobacilli, which are the most typical representatives of normal human microflora. It should be noted that the genus of lactobacilli is

quite numerous and includes 56 species, and the genus of bifidobacterium includes 32 species. The main positive effects of probiotics are: an increase in the anti-infectious defense of the body due to antagonism with pathogenic bacteria and the formation of a protective film on the surface of the intestinal mucosa; immunomodulation; improvement of metabolic and synthetic processes (for example, the synthesis of vitamins of group B, K and C, as well as essential amino acids is enhanced); improvement of the barrier properties of the intestinal mucosa and detoxification effects (neutralization of exogenous and endogenous toxins). It should be emphasized that probiotics, even those belonging to the same genus, have different effects on the human body. In this regard, it is impossible to transfer the beneficial properties of any strain to other representatives of this kind of microorganisms, that is, the beneficial effects of probiotics are strain-specific. [1]

In this regard, the main goal of our study was to study the effect of the probiotic - lactobacterium, as an accompanying therapy in combination with TUR in cases of superficial tumors of bladder cancer.

**Material and methods.** The study is based on a comparative analysis of the results of the new proposed diagnostic methods and the optimal treatment method for patients with superficial bladder cancer, who

underwent various options for combination therapy, including TUR in combination with intravesical administration of drugs. The study was carried out in patients who received inpatient treatment in the conditions of the Department of Oncurology of the Republican Cancer Research Center of the Ministry of Health of the Republic of Uzbekistan for the period 2011-2018.

There were 142 patients under our supervision (19 women (13.3%) and 123 (86.7%) men) aged from 42 to 71 years.

All patients were divided into 2 groups depending on the type of treatment. The first main group consisted of 69 (48.6%) patients with bladder cancer who underwent transurethral tumor resection in combination with the probiotic lactobacterium. The second control group (73-51.4%) included patients who underwent a standard TUR operation in combination with intravesical administration of a chemotherapy drug, doxorubicin.

In the preoperative period, all patients underwent a comprehensive examination, which included: ultrasonography of the bladder, uroflowmetry, cystoscopy, radiography, computed and nuclear magnetic resonance imaging of the pelvic organs. Patients were surveyed in accordance with the International IPSS scale and quality of life according to QoL criteria.

**Table 1.**

**Distribution of patients with bladder cancer depending on the size, stage and localization of the tumor lesion**

Dimensions and stage of the process	Main group (69 patients)		Control group (73 patients)	
	Studied	%	Studied	%
<b>Tumor size</b>				
<b>Up to 1 cm</b>	28	40,5	31	42,4
<b>Up to 2 cm</b>	41	59,5	42	57,5
<b>Stage of the tumor T<sub>1</sub>N<sub>0</sub>M<sub>0</sub></b>	32	46,4	34	46,6
<b>T<sub>2</sub>N<sub>0</sub>M<sub>0</sub></b>	37	53,6	39	53,4

<b>Localization of the tumor</b>				
Apex	11	30,4	22	30,7
Bladder wall	32	46,4	33	45,2
Bottom	16	23,2	18	24,6

The study took into account the size, number of tumors, stage of lesion and localization of the process (Table 1).

As can be seen from Table 1, in the main group, the tumor size among 28 patients was up to 1 cm (40.5%), among 41 - up to 2 cm (59.5%). In the control group, among 31 patients (42.4%) up to 1 cm, among 42 (57.5%) - up to 2 cm. In the main group, the stage of the tumor process in the bladder was assessed as T1N0M0 among 32 patients, which was 46.4 %; in the control group among 34 patients (46.6%). In the main group, T2N0M0 among 37 patients was 53.6%, in the control group among 39 (53.4%).

The predominant localization of the tumor was the lateral walls of the bladder, which were affected in 32 (46.4%) in the main group, and in 33 (45.2%) in the control group. In the area of the bladder apex, tumors in the main group were found among 21 (30.4%), and in the control group - among 22 (30.7%) patients, in the area of the bottom, respectively, among 16 (23.2%) and 18 (24, 6%).

In the main observation group, lactobacterium solution was injected into the bladder cavity for 5 days before and after the operation. This type of treatment was carried out according to the protocol and patent of the invention №IAP 05549 [8].

After the completion of the clinical examination, operations were performed under spinal anesthesia at the L2-L3 level using 5% lidocaine solution and potentiated intravenous anesthesia using calypsol. Operations were performed with Storz resectoscopes with a tube size of 18 Ch.

Distilled water was used as a washing liquid, which underwent a two-stage mechanical and bactericidal sterilization.

After removal of the bladder tumor, hemostasis of the wound was performed, the bladder was drained with a 3-way Foley 18 Ch catheter. During the next 5 days, the patients were administered a probiotic - lactobacterium - into the bladder cavity.

In the second group, TUR tumors were combined with the injection of doxorubicin solution (No. 6) into the bladder cavity in a single dose of 50 mg and in a total dose of 300 mg with an interval of 7 days.

**Results.** During histological examination, transitional cell bladder cancer was verified among 65 patients of the main group (94.2%), among 4 (5.8%) - squamous cell bladder cancer, in controls - 69 (94.5%), and among 4 (94.51 %). At the same time, highly differentiated bladder cancer (G1) was found among 33 (47.8%) patients, moderately differentiated (G2) - among 36 (52.2%) patients of the second group, respectively, G1 occurred among 39 (53.4%) and G2 among 34 (46.6%).

As shown by the results of observation of the disease in the first days after surgery, in the control group, 4 (5.7%) had slight bleeding from the postoperative wound, which was eliminated by hemostatic therapy, and 6 (8.2%) patients had dysuric phenomena that liquidated in the next day. In the main group, these complications were not observed.

The most demonstrative was the study of the dynamics of the healing of the postoperative tumor bed and the restoration of urine microflora (Table 2)

Table 2

### Time of tumor bed healing and restoration of urine microflora

	Recovery time in days
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Process type and treatment method	Up to 10 days		Up to 20 days		Up to 30 days and more	
	studied	%	studied	%	studied	%
<b>TUR + probiotic</b> Time of healing of the postoperative tumor bed	64	92,7	5	7,3	-	-
Terms of normalization of urine microflora	44	63,7	25	36,3	-	-
<b>TUR + monochemotherapy</b> Time of healing of the postoperative tumor bed	-	-	4	5,5	69	94,5
Terms of normalization of urine microflora	-	-	2	2,7	71	97,3

According to the data obtained, in the main observation group, where TUR was combined with intravesical administration of lactobacterium, postoperative wound healing was noted within 10 days among 64 (92.7%) patients, and up to 20 days among 5 (7.3%) patients. In the control group of patients who received TUR followed by a course intravesical administration of doxorubicin, signs of healing of the postoperative tumor bed by day 20 were observed only among 4 (5.5%) patients, and among the remaining 69 (94.5%) patients, healing was found after 30 days of observation. ( $P < 0.05$ ).

The process of repairing the epithelium damaged as a result of surgery is reflected in the terms of normalization of the urine microflora. At the same time, in the

main group, this was noted among 44 (63.7%) patients during the first 10 days, and among 25 (36.3%) patients by 20 days of observation. In the control group, a tendency towards normalization of microflora by day 10 was noted only among 2 (2.7%), and among the remaining 71 (97.3%), infectious inflammations were noted.

All patients were followed up for up to 1 year. Among the patients we observed, a relapse of bladder cancer after surgery was detected among 32 (22.5%) patients; of them in the first group among 3 (4.3%) and in the second - among 29 (39.7%). A more detailed study of this criterion for the effectiveness of treatment is presented in Table 3.

Table 3.

### The timing of the onset of recurrent bladder cancer, depending on the type of treatment

Type of treatment	The timing of the occurrence of relapses					
	Up to 3 months		Up to 6 months		Up to 12 months	
	studied	%	studied	%	studied	%
<b>TUR + probiotic</b>					3	2,1
T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	-	-	-	-	1	1,4
T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	-	-	-	-	2	2,8
<b>TUR + monochemotherapy</b>					6	8,2
T <sub>1</sub> N <sub>0</sub> M <sub>0</sub>	-	-	5	6,8	10	13,6
T <sub>2</sub> N <sub>0</sub> M <sub>0</sub>	-	-	8	9,6		

The data obtained showed that in the main observation group, where TUR of the tumor was carried out together with the use of intravesical administration of lactobacterium, single relapses (3-4.2% of patients) were found only by the 12th month of observation.

In the control group of patients, the appearance of relapses was noted already by the 6th month of observation among 13 (17.8%), and by the 12th month among 16 (21.9%) patients, mainly with more pronounced manifestations of the tumor process.

Comparison of treatment results in the two compared groups revealed a significant difference in the studied criteria ( $P < 0.05$ ).

**Discussions.** Comparative analysis of the results of observations of bladder cancer in two groups of 142 patients, representative of the stage of the tumor process, showed a distinct difference in the therapeutic effect, depending on the type of treatment. The introduction of the probiotic lactobacterium into the antitumor therapy regimen reliably reduces the degree of trauma to the urinary bladder epithelium in the postoperative period and shortens the

healing time of the postoperative wound compared to the control ( $P < 0.05$ ). The use of lactobacterium also contributes to a clear improvement in the general condition of patients and significantly increases the relapse period ( $P < 0.05$ ). The study of the microflora of urine during treatment has proven to be a valuable monitoring method to reduce the incidence of infection during endoscopic procedures.

**Conclusions.** The results of the study lead to the following conclusions:

1. A method for the treatment of superficial neoplasms of bladder cancer with the use of TUR and the probiotic lactobacterium has been developed.
2. Performing TUR in combination with the introduction of lactobacterium will reliably reduce the frequency of recurrence of bladder tumors and increase the duration of the recurrence-free period ( $P < 0.05$ ).
3. The use of lactobacterium in the course of treatment significantly reduces the level of infectious and inflammatory complications in the postoperative period, and also contributes to the restoration of normal microflora of urine ( $P < 0.05$ ).

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