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ORIGINAL ARTICLE

MICROBIOCENOSIS OF ADENOCARCINOMA TISSUE IN COLON CANCER PATIENTS WITH DIFFERENT PREOPERATIVE PREPARATION

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ABSTRACT

Purpose of the study. To assess the effect of inclusion of lactoglobulin in complex preoperative preparation of colon cancer patients on their tumor and resection line tissue microbiota.
Materials and methods. 40 patients with colon cancer stages II–III, in whom the operation was the first stage of treatment, during standard preoperative preparation, were injected with a preparation of antibodies against opportunistic intestinal microorganisms obtained from colostrum of immunized cows, 2 g twice a day orally before surgery for 3 days (total dose of 12 g) (main group); 40 patients received standard antibiotic prophylaxis (control group). The quantitative composition of the microbiota was determined in the samples of the removed tumor and tissue of the resection line.
Results. The total microbial contamination of the tumor was 9.2 times lower in the main group relative to the control group; the frequency of E.coli and Clostridiae excretion was also statistically significantly lower (p = 0.004 and 0.03, respectively). In the tumors of patients of the main group out of twelve studied representatives of microorganisms, the number of six was statistically significantly lower than in control group, and three of those found in the control group were not detected. Since they were potentially pathogenic (Pseudomonas aeruginosa, Staphylococcus aureus, fungi of the Candida spp.), the microbial composition of the tumor of patients in the main group can be considered more favorable than the control group. Similar differences were noted in non-t umor intestinal tissue, in which the content of Enterobacter spp, Streptococcus, Clostridiae, Peptostreptococci was statistically significantly lower than in the control group.
Conclusion. Thus oral administration of colostrum antibodies caused positive changes in tumor and colon tissue microbiota. We suggest the application of lactoglobulin to be useful for surgical treatment of such patients taking into account the possible impact of microbiota in patients' response to chemo- and immunotherapy.

Keywords: colon cancer, tissue microbiota, tumor and intact colon tissue, lactoglobulin

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Compliance with ethical standards: the research was carried out according to the ethical principles, set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Biomedical Ethics Committee at the National Medical Research Center for Oncology (extract from the protocol of the meeting No. 2 dated 01/22/2021. Informed consent was obtained from all participants of the study.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

МИКРОБИОЦЕНОЗ ТКАНИ АДЕНОКАРЦИНОМЫ ОБОДОЧНОЙ КИШКИ В ЗАВИСИМОСТИ ОТ ВАРИАНТА ПРЕДОПЕРАЦИОННОЙ ПОДГОТОВКИ БОЛЬНЫХ

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РЕЗЮМЕ

Цель исследования. Оценка влияния включения препарата лактоглобулина в комплекс предоперационной подготовки больных раком ободочной кишки на состав микробиоты опухоли и ткани, взятой по линии резекции.
Материалы и методы. 40 больным раком ободочной кишки II–III стадий, у которых операция была первым этапом лечения, в курсе стандартной предоперационной подготовки вводили препарат антител против условно-патогенных микроорганизмов кишечника, полученный из молозива иммунизированных коров, по 2 г 2 раза в день перорально перед операцией в течение 3-х дней (суммарная доза 12 г) (основная группа); 40 больных получали стандартную антибиотикопрофилактику (контрольная группа). В образцах удаленной опухоли и ткани линии резекции определяли количественный состав микробиоты.
Результаты. У больных основной группы общая микробная обсемененность опухоли была в 9,2 раза ниже контрольной; частота выделения E.coli и Clostridiae была также статистически значимо ниже (p = 0,004 и 0,03 соответственно). В опухолях больных основной группы из двенадцати исследованных представителей микроорганизмов количество шести было статистически значимо ниже контроля, а три из обнаруженных в контрольной группе не выявлялись. Поскольку они относились к потенциально патогенным (Pseudomonas aeruginosa, Staphylococcus aureus, грибы рода Candida), микробный состав опухоли больных основной группы можно считать более благоприятным, чем контрольной. Подобные различия отмечены и в неопухолевой ткани кишки, в которой содержание Enterobacter spp, Streptcocci, Clostridiae, Peptostreptococci было статистически значимо ниже, чем в контроле.
Заключение. Итак, пероральное применение антительного препарата лактоглобулина вызывает положительные изменения микробиоты опухоли и неопухолевой ткани кишки. Учитывая возможное влияние состава микробиоты на ответ больного на дальнейшую химио- и иммунотерапию, считаем целесообразным использование препарата для подготовки к адъювантному лечению.

Ключевые слова: рак ободочной кишки, микробиота опухоли и интактной ткани кишечника, лактоглобулин

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено Комитетом по биомедицинской этике при ФГБУ «НМИЦ онкологии» (выписка из протокола заседания № 2 от 22.01.2021 г.). Информированное согласие получено от всех участников исследования.

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INTRODUCTION

In recent years, the attention of researchers around the world has been attracted to the definition of the role of microbiota involved in oncological processes. More and more scientific arguments are accumulating that the imbalance of the intestinal microbiota contributes to carcinogenesis and tumor growth; primarily this applies to colorectal cancer [1–3]. The effect of the microbiota composition on the sensitivity of colorectal cancer to the action of a new generation of antitumor immunopreparations – checkpoint inhibitors [4], as well as cytostatics [5; 6].

In this regard, microbiota correction in cancer patients is the current agenda [7]. With the development of a tumor in the colon, excessive growth of opportunistic bacteria is detected, the accumulating metabolites of which can cause the suppression of normal microflora, which is accompanied by a change in the trophic, protective, metabolic and immunological functions of autochthonous microorganisms of the large intestine [8]. As a result, there is an increase in the biochemical activity of microflora, a change in pH, which creates a favorable environment for the reproduction of opportunistic bacterial species, increased putrefactive processes and inflammation in the colon, i. e., a vicious circle arises. The formation of dysbiosis leads to a decrease in the immune reactivity of the body and contributes to the progression of the tumor process [9; 10]. Even though many papers have been published describing the composition of the microbiota of the colon in various pathologies, including oncological, there are significantly fewer publications on the study of the microbiota of the tumor itself [11; 12].

Modern standard therapeutic technologies for the preparation of patients with colon cancer do not aim to eliminate microecological disorders. On the contrary, due to the appointment of a preventive course of antibiotic therapy, they can contribute to the aggravation of dysbiosis. Meanwhile, the presence of an increased number of opportunistic microorganisms in the colon of patients is an unfavorable background for the postoperative course of the disease. This disadvantage can be leveled by prescribing probiotics in the preoperative period [13].

Lactoglobulin, not being a probiotic in the strict sense, is intended for the correction of the microbiota. It has such an effect due to the presence in its composition of colostrum antibodies to conditionally pathogenic microorganisms (Proteus vulgaris, Proteus mirabilis, Pseudomonas aeruginosa, Klebsiella pneumoniae, Salmonella thyphimurium, Salmonella enteritidis, Salmonella dublin), as well as lactoferrin, bifidogenic factors, as a result of which it contributes to the suppression of conditionally pathogenic and stimulation symbiont microorganisms [14].

Purpose of the study was to evaluate the effect of the inclusion of lactoglobulin in the complex of preoperative preparation of patients with colon cancer on the composition of the tumor microbiota and mucosal tissue taken along the resection line.

MATERIALS AND METHODS

The subject for the study were samples of a tumor and tissue taken by resection during surgery for colon cancer in 80 patients who were treated at the National Medical Research Centre for Oncology. All patients signed an informed consent to participate in the study. The age of the patients ranged from 40 to 80 years, the average age corresponded to 65.6 ± 4.5 years, among them there were 32 men and 48 women (40 and 60 %, respectively). All were diagnosed with stage II–III colon cancer, the operation was the first stage of treatment. In all cases, the histological structure of the tumor was adenocarcinoma. 40 patients were included in the main and 40 in the control group; the groups were comparable in gender, age, and stage of the disease. The control group of patients underwent standard preoperative preparation, including antibiotic prophylaxis of postoperative complications (ceftriaxone 1 g 2 times a day, metrogil 500 mg 2 times a day); the main group of patients, in addition, received 12 g of lactoglobulin before surgery for 3 days (2 g 2 times a day orally). All 80 patients underwent standard antibiotic therapy in the postoperative period. In the future, all patients received adjuvant chemotherapy according to the FOLFOX scheme. During the operation, a fragment from the tumor tissue and mucosa from the intact intestine taken along the resection line were excised in patients for microbiological examination, microbiocenosis in the tissues was studied and its comparative analysis was carried out between two groups of patients.

Microbiological methods of quantitative analysis for dysbiosis were used to assess the composition

of the microbiota (OST 91500.11.0004-2003). The tissue suspension was washed from the lumen microflora, dissected and its internal parts were used for further research. Sample preparation was carried out on a Medimachine device. Serial dilutions were prepared from the obtained suspension of biological material, which were seeded with 0.1 ml per petri dish with differential diagnostic media. Chromogenic Uriselect agar (Bio-Rad, France), blood agar (Columbia blood agar base with the addition of 5 % defibrinated horse blood, yolk-salt agar (salt agar with mannitol/Mannitol Salt Agar, with the addition of egg yolk emulsion/Egg Yolk Emulsion), medium were used for sowing Saburo (Saburo Agar with glucose and chloramphenicol/ Sabouraud Chloramphenicol), as well as a medium for the isolation of lactobacilli lactobacilli, Wilson-Blair agar for clostridium; all media, except chromogenic Uriselectagar, were manufactured by HiMedia Laboratories Pvt. Limited (India). Incubation in a thermostat at 37 °C was carried out for aerobic microflora for 24–48 hours, for anaerobic under anaerostat conditions for 6–7 days, except for clostridium, which were grown for 24 hours. Next, the grown colonies were counted, if necessary, screening was carried out to isolate a pure culture and subsequent identification of microorganisms, which was carried out on an automatic bacteriological analyzer Vitek 2 (BioMerieux, France).

Microorganisms related to opportunistic pathogens were identified to the following strains: E.soli, S. aureus, P. aeruginosa, K. pneumoniae, Enterobacter, Proteus. The results were expressed in lg/g of tissue, and the total microbial contamination was expressed in colony-forming units (CFU/g of tissue).

Statistica 12 (Stat Soft, USA) and MedCalc 19.3.0 (MedCalc Software bv, USA) programs were used for statistical processing of the results. The estimation of the distribution of values and the normality of the distribution were analyzed according to the Shapiro-Wilk criterion (Statistica 12 frequency analysis module). When calculating variational statistics, the Statistica 12 descriptive statistics module was used with the calculation of the average value (M), its error (m), median (Me) and interquartile range [Q25; Q75]. In the presence of a normal distribution of indicators, the Student-Fisher criterion was used to assess the statistical significance of differences, in the absence of a normal distribution, the Mann–Whitney criterion was used. When comparing the average values of independent samples, the criterion for the significance of differences was the value $p \leq 0.05$.

STUDY RESULTS AND DISCUSSION

Several quantitative and qualitative differences were observed after preoperative preparation with and without the inclusion of lactoglobulin in the studied tissues of patients of the main and control groups. Representatives of the microflora of the gastrointestinal tract were found in the tumor tissue of patients of both groups, however, the degree of microbial contamination differed. Thus, in the tumor

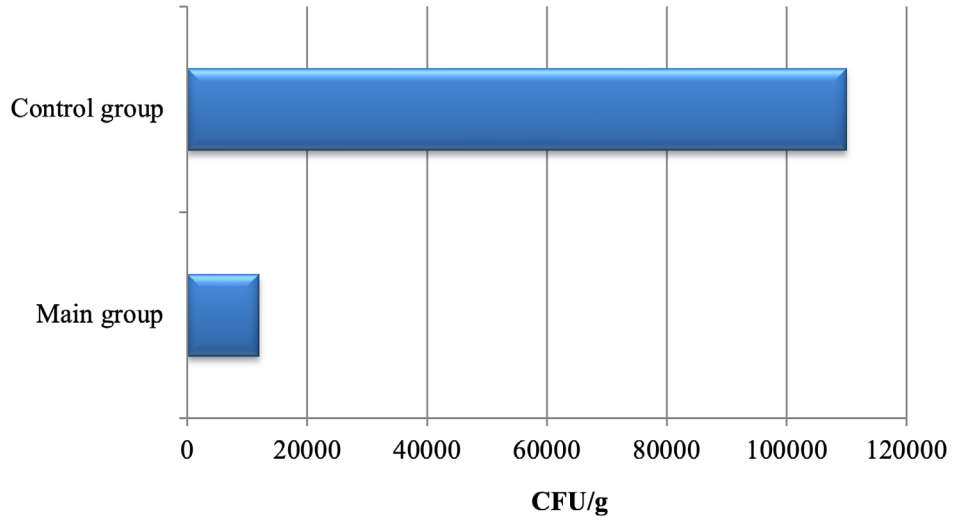

Fig. 1. Microbial contamination of colonic tumor tissue (CFU/g) in the main and control groups.

tissue in patients of the main group, it varied from 10^3 to 10^5 (M ± m 1.2 ± 0.3 × 10^4/g), and in the control group – in the range of 10^4 to 10^7 (M ± m 1.1 ± 0.2 × 10^5/g), that is, it was 9.2 times higher (Fig. 1).

The contamination of the mucosa of the intact intestine did not exceed 103 and mainly ranged from 10^1–10^2.

The frequency of isolation of individual microorganisms in the samples of the studied tissues is reflected in Table 1, which presents a comparative characteristic of tumors of patients of both groups, as well as tumors and intact intestine in each of them.

In the tumor tissue of patients of both groups, E.coli aerobes were most often found, and Bacteroides spp and Clostridiae anaerobes. Statistically significant differences between the groups were noted only in the content of E.coli and Clostridiae in the tumor, which were less frequently represented in the tumor tissue of patients of the main group. The frequency of detection of the remaining studied representatives of the microbiota was also lower in the main group, although these differences were not statistically significant. Of the 12 identified microorganisms, 9 were found in the tumors of the patients of the main group, 6 in the tissue of the intact intestine.

In the colon mucosa taken by resection in patients of the main group, bacteroids were detected in almost half of the observations (47.5 %), in 10 % – E.coli, in a small percentage of observations – Clostridiae, Peptostreptococci, Klebsiella pneumoniae, Proteus spp. In the main group, Bacteroides spp. were statistically significantly more often detected in the tumor tissue compared to the intact intestine, whereas E.coli and Clostridiae were statistically significantly more often detected in the tumors of patients in the control group, in addition to bacteroids.

In the control group, the spectrum of microorganisms in the tumor tissue was wider than in the intact

Table 1. Frequency of detection of microorganisms obtained from tumor tissues and mucosa of the intact intestine in patients of the main and control groups

Indicator	Tissue samples									
	Main group				*p*	Control group				*p*
	Tumor tissue		Intact intestines			Tumor sample		Intact intestines		
	abs.	%	abs	%		abs	%	abs	%	
E.coli	6	15	4	10	> 0.05	19	47.5	7	17.5	0.04*
Klebsiella pneumoniae	4	10	2	5	> 0.05	8	20	3	7.5	> 0.05
Proteus spp.	3	7.5	2	5	> 0.05	6	15	3	7.5	> 0.05
Enterobacter spp.	2	5	0	0	-	5	12.5	2	5.0	> 0.05
Streptcocci	2	5	0	0	-	5	12.5	2	5.0	> 0.05
Bacteroides spp	33	82.5	19	47.5	0.002*	36	90	15	37.5	0.03*
Clostridiae	8	20	3	7.5	> 0.05	18	45	8	20.0	0.04*
Peptostreptococci	3	7.5	2	5	> 0.05	7	17.5	2	5.0	> 0.05
Peptococci	1	2.5	0	0	-	2	5	1	2.5	> 0.05
Pseudomonas aeruginosa	0	0	0	0	-	3	7.5	0	0	-
Staphylococcus aureus	0	0	0	0	-	3	7.5	0	0	-
Candida spp. fungi	0	0	0	0	-	1	2.5	0	0	-

Note: * – statistically significant differences between the parameters of the tumor tissue and the resection line in each of the compared groups ($p < 0.05$); "-" – p cannot be determined due to the actual absence of representatives of the microbiota in the tissue samples

intestine: 12 pathogens were identified in the tumor tissue, and 9 in the intact intestine (Table 1). The frequency of detection of microorganisms in the tumor tissue was statistically significantly higher compared with the intact intestine for E.coli, Bacteroides spp., Clostridiae. Noteworthy is the presence of Pseudomonas aeruginosa, Staphylococcus aureus and Candida fungi in the tumor tissue and the absence of their intact intestinal mucosa, which did not allow us to assess the reliability of the differences. In the

Table 2. The content of microorganisms in the tumor tissue and mucosa of the intact intestine in patients of the main and control groups (lgCFU/g, M ± m)

Indicator	Tissue samples					
	Main group		Control group			
	Tumor tissue	Intact intestine	Tumor tissue	Intact intestine	*p* 1–3	*p* 2–4
	1	2	3	4		
E.coli	3.5 ± 0.3*	2.3 ± 0.2	6.3 ± 0.7	2.4 ± 0.02	0.015	> 0.05
	p = 0.027		*p* < 0.001			
Klebsiella pneumoniae	1.7 ± 0.2*	0.7 ± 0.08	4.6 ± 0.5	0.5 ± 0.02	0.002	> 0.05
	p = 0.023		*p* < 0.001		>0.05	> 0.05
Proteus spp.	3.1 ± 0.4	2.2 ± 0.3	4.5 ± 0.8	2.0 ± 0.07	>0.05	> 0.05
	p = 0.046		*p* = 0.004			
Enterobacter spp.	1.3 ± 0.1*	0.9 ± 0.05**	2.7 ± 0.4	1.3 ± 0.02	0.03	0.04
	p = 0.048		*p* = 0.005			
Streptcocci	0.6 ± 0.1*	0.3 ± 0.09**	2.6 ± 0.3	0.7 ± 0.03	0.008	0.035
	p = 0.067		*p* < 0.001			
Bacteroides spp.	4.2 ± 0.7	2.5 ± 0.1	5.2 ± 0.4	2.4 ± 0.2	> 0.05	> 0.05
	p = 0.02		*p* < 0.001			
Clostridiae	2.9 ± 0.3*	1.5 ± 0.06**	5.5 ± 0.5	2.0 ± 0.1	0.04	0.045
	p = 0.01		*p* < 0.001			
Peptostreptococci	0.3 ± 0.07*	0.2 ± 0.03**	1.7 ± 0.3	0.5 ± 0.08	0.009	0.04
	p = 0.26		*p* < 0.01			
Peptococci	1.0	0.1 ± 0.02	1.5 ± 0.2	1.0	-	-
	p = 0.57					
Pseudomonas aeruginosa	0	0	0.4 ± 0.03	0.1 ± 0.03	-	-
			p < 0.01			
Staphylococcus aureus	0	0	1.1 ± 0.02	0.2 ± 0.001	-	-
			p < 0.001			
Candida spp. fungi	0	0	2.5 ± 0.2	0.5 ± 0.01	-	-
			p < 0.001			

Note: * – statistically significant differences between the parameters of the tumor tissue; ** – statistically significant differences between the parameters of the intact intestine tissue ($p < 0.05$); "-" – *p* cannot be determined due to the actual absence of representatives of the microbiota in the samples of the main group of patients

intact intestine, Bacteroides spp. (37.5 %), Clostridiae (20 %), E.coli (17.5 %) were more common than others, and in isolated cases, coccoid microflora (Peptococci – 2.5 %, Peptostreptococci – 5 %, Streptcocci – 5 %) (Table 1).

Quantitative indicators of the content of various microorganisms in the studied tissue samples of patients of the main and control groups are shown in Table 2.

As seen from Table 2, in the tumor tissue, the quantitative content of almost all the studied microorganisms in patients of the main group was statistically significantly lower ($p < 0.05$) than in the control group (Fig.3). Similar contamination of tumor tissue in the main and control groups was noted only for bacteroids.

Worth noting, that after preoperative use of lactoglobulin from the tumor tissue of patients, it was not possible to isolate such representatives of opportunistic microflora as Enterococcus faecalis, Pseudomonas aeruginosa, Staphylococcus aureus, Candida fungi, and the number of other species, in particular, coccoid microflora, was significantly lower compared to the control group (Peptococci 1.5 times, Peptostreptococci by 82 %, Streptcocci by 77 %) (Tables 1, 2, Fig. 2).

In patients of the control group, the microflora contamination of tumor tissue was significantly higher compared to the mucosa of the intact intestine for all pathogens. The main differences were formed for Klebsiella rheimopiae (9.2 times higher compared to the intact intestine), Pseudomonas aeruginosa (4 times), Candida spp. fungi (5 times) (Table 2).

Figure 2 shows the excess of the titer of microorganisms (in %) in the tumor tissue compared with the intact intestine along the resection line in patients of the main and control groups. In patients of the control group, these differences were significantly higher compared to the main group; they were mainly characteristic of Klebsiella rheimopiae, Streptcocci, Peptococci (Fig. 2).

CONCLUSIONS

Preoperative administration of lactoglobulin preparation against conditionally pathogenic microorganisms contributes to the formation of a more favorable microbial landscape of the tumor and tissue taken along the resection line in patients with colon cancer, which manifests itself in a decrease in the total microbial contamination of the studied tissue samples, as well as in a decrease in the frequency

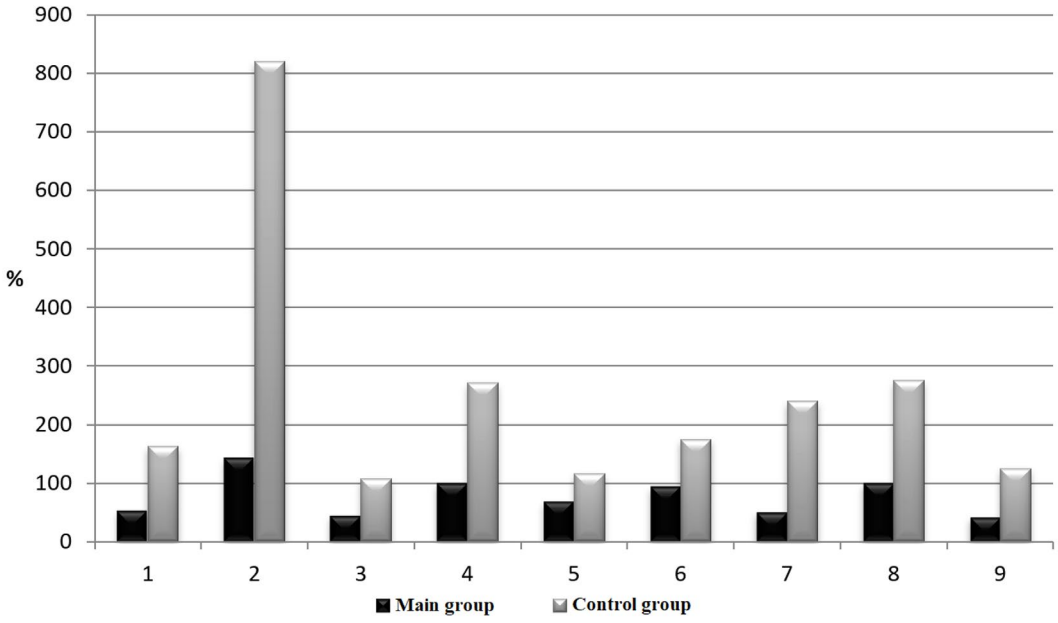

Fig. 2. Comparative characteristics of the content of microorganisms in the tumor tissue in patients of the main and control groups (% in the tumor tissue compared with the tissue of the intact intestine).
Note: 1 – E.coli, 2 – Klebsiella pneumoniae, 3 – Enterobacter spp., 4 – Streptcocci, 5 – Bacteroides spp., 6 – Clostridiae, 7 – Peptostreptococci, 8 – Peptococci, 9 – Proteus spp.

of detection and the number of several conditionally pathogenic microorganisms. We found a high number of studied microbiota representatives in the tumor tissue of patients, which corresponds to the literature data on their potentially pro-oncogenic effect, which is described in Klebsiella pneumonia [15], streptococci [16], peptostreptococci [17], clostridium [18; 19]. Since among the mechanisms of the growth-stimulating effect of these microorganisms, attention is paid to the production of toxins, the maintenance of local inflammation, and the imbalance of the immune microenvironment, it seems important to correct the microbiota with the help of an immune drug, which especially applies to the tissue of the resection line, since it remains in the patient's body after surgery, and the composition of its microbiota can contribute not only to postoperative tissue regeneration, but also affect the further course of the disease.

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