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Comparative analysis of some immunological parameters depending on the tumor location on the right and left sides of colon

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Abstract

Background: Colorectal cancer is now an urgent problem in oncology. Recently, specialists have been interested in a comparative analysis of differences in the clinical course of malignant tumors in the proximal and distal colon. The sections differ not only in their embryogenesis and sources of blood supply, but also in the clinical course and population and epidemiological characteristics. The issue of distinctive immunological characteristics of tumors of the colon depending on the location remains open.

Objective: A comparative analysis of local subpopulations of immunocompetent cells and an assessment of number of cells with the CD45+/- phenotype expressing toll-like receptors (TLRs) depending on the tumor location on the right or left sides of the colon.

Material and methods: The study included 50 patients with verified colon cancer. The majority of patients were females – 26 (52%), aged 67 ± 0.4 years, and 50% of patients with stage II disease. Depending on the tumor location (the right or left sides of the colon), the patients were divided into 2 groups of 25 people each. All patients underwent standard surgery at the initial stage. The obtained material was used for subsequent studies: a cell suspension was obtained from a tumor tissue fragment, the perifocal zone (1–3 cm from the tumor) which was processed using an antibody panel (Becton Dickinson, USA) to identify the main subpopulations of leukocytes and lymphocytes. Expression of TLRs (2, 3, 4, 8, 9) on CD45+, CD45- cell populations was also determined using the BD FACSCanto flow cytometer (Becton Dickinson, USA). Statistical processing of the results was performed using the STATISTICA 13.3 package (StatSoft Inc., USA).

Results: A comparative analysis of immunological parameters, depending on the tumor location on the right or left sides of the colon, showed:

1. Tissues of the right-sided tumors had a higher T-lymphocytic infiltration, compared to the left-sided tumors, while the latter showed a higher B-lymphocytic infiltration ($p = 0.025$).
2. Peritumoral zone tissues of left-sided tumors demonstrated a decrease of lymphocytes levels ($p = 0.027$), NKT – ($p = 0.035$), NK – ($p = 0.041$) and B lymphocytes ($p = 0.038$), and a significant increase in CD8+- ($p = 0.02$) and DP cells ($p = 0.0018$).
3. Left-sided tumors showed a percentage decrease of CD45- cells expressing TLR4 and TLR8, compared to right-sided tumors, by 38% ($p = 0.038$) and 25% ($p = 0.043$).
4. There was a decrease in the number of CD45+ cells expressing TLR2 and TLR4 in left-sided tumors by 54% ($p = 0.035$) and 33% ($p = 0.04$) respectively, than in right-sided tumors.
5. The percent of CD45- cells expressing TLR4 in the perifocal tissues of left-sided tumors decreased by 61% ($p = 0.031$) in comparison to the corresponding tissues in right-sided tumors.
6. The numbers of CD45+ cells expressing TLR2 and TLR4 were 81% ($p = 0.02$) and 87% ($p = 0.018$) lower respectively in the peritumoral tissues of left-sided tumors, compared to the corresponding tissues in right-sided tumors.

Conclusion: The revealed characteristics of the local subpopulations of immunocompetent cells and the numbers of CD45+/- cells expressing TLRs depending on the tumor location on the right or left sides of the colon can serve as a prognosis of the disease clinical course and the choice of further treatment tactics.

Keywords: colon cancer, local cellular immunity, toll-like receptors

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Сравнительный анализ некоторых иммунологических параметров в зависимости от локализации опухоли в правой и левой половинах ободочной кишки

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Резюме

Актуальность: На сегодняшний день колоректальный рак – актуальная проблема в онкологии. В последнее время интерес специалистов прикован к сравнительному анализу различий клинического течения заболеваний злокачественными опухолями ободочной кишки, в частности, ее проксимального и дистального отделов. Как известно, данные отделы имеют не только различные эмбриогенезы, источники кровоснабжения, но и несходные клиническое течение и популяционно-эпидемиологические характеристики. Вопрос о наличии отличительных иммунологических особенностей между опухолями ободочной кишки, в зависимости от локализации, остается открытым.

Цель исследования: Сравнительный анализ локального субпопуляционного состава иммунокомпетентных клеток, а также оценка количества клеток с фенотипом CD45+/-, которые экспрессируют толл-подобные рецепторы (Toll-like receptors (TLRs) в зависимости от локализации опухоли в правой и левой половинах ободочной кишки.

Материал и методы: В работу включены 50 пациентов с верифицированным раком ободочной кишки. Бóльшую часть составили больные женского пола – 26 (52%), средний возраст 67 ± 0,4 лет. 50% выборки – пациенты, у которых выявлена II стадия. Больные были разделены на 2 равные группы, в зависимости от локализации опухоли (правая или левая половина ободочной кишки). Всем пациентам на начальном этапе выполнено стандартное оперативное вмешательство. Полученный материал был использован для последующих исследований: из фрагмента ткани опухолей, перифокальной зоны (1–3 см от опухоли) была получена клеточная суспензия, которую обрабатывали при помощи панели антител (Becton Dickinson, USA) для выявления основных субпопуляций лейкоцитов и лимфоцитов. Также была определена экспрессия TLRs (2, 3, 4, 8, 9) на клетках с фенотипом CD45+, CD45- с использованием проточного цитометра BD FACSCanto (Becton Dickinson, USA). Статистическая обработка данных проводилась с использованием пакета STATISTICA 13.3 (StatSoft Inc., США).

Результаты: При проведении сравнительного анализ ряда иммунологических параметров, в зависимости от локализации опухоли в правой и левой половинах ободочной кишки, были получены следующие данные:

1. В тканях опухолей ободочной кишки правосторонней локализации определялась более выраженная Т-лимфоцитарная инфильтрация по сравнению с тканями опухолей левой половины, характерной особенностью которых являлась повышенная В-лимфоцитарная инфильтрация ($p = 0,025$).
2. Во фрагментах тканей перитуморальной зоны при локализации опухолей в левой половине ободочной кишки отмечалось снижение содержания количества лимфоцитов ($p = 0,027$), NKT ($p = 0,035$), NK ($p = 0,041$) и В-лимфоцитов ($p = 0,038$), а также значимое повышение содержания CD8+- ($p = 0,02$) и ДП клеток ($p = 0,0018$).
3. При сравнении данных фрагментов тканей опухолей левой и правой половины ободочной кишки отмечено снижение процентного содержания клеток с фенотипом CD45-, которые экспрессируют TLR4: 8 на 38% ($p = 0,038$) и 25% ($p = 0,043$).
4. При оценке количества клеток с фенотипом CD45+, которые экспрессируют TLR2, TLR4, отмечено снижение количества этих клеток на 54% ($p = 0,035$) и 33% ($p = 0,04$) по сравнению с тканями опухолей правой половины ободочной кишки.
5. Анализ полученных данных перитуморальной зоны опухолей левосторонней локализации, по сравнению с правосторонней, продемонстрировал снижение процентного содержания клеток с фенотипом CD45, которые экспрессируют TLR4, на 61% ($p = 0,031$).
6. Оценка количественного состава клеток с фенотипом CD45+, которые экспрессируют TLR2, TLR4, выявила снижение количества клеток на 81% ($p = 0,02$) и 87% (p = 0,018) соответственно, по сравнению с перитуморальной зоной опухолей правой половины ободочной кишки.

Заключение: Выявленные особенности локального субпопуляционного состава иммунокомпетентных клеток при раке ободочной кишки, в зависимости от локализации опухоли, а также данные о количественном клеточном составе клеток с фенотипом CD45+/-, экспрессирующих TLRs, могут быть использованы в прогнозе течения заболевания, а также при выборе тактики лечения.

Ключевые слова: рак ободочной кишки, локальный клеточный иммунитет, Toll-подобные рецепторы

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Background

Colorectal cancer (CRC) is an urgent problem in oncology today, more than 60% of which is colon cancer, which occupies the 4th place of the total oncological incidence in Russian Federation [1–5].

In recent decades, the attention of specialists has been drawn to a comparative analysis of the differences in the clinical course of malignant tumors of the colon, which come from its proximal and distal parts [6].

First of all, these parts have a difference in embryogenesis, which defines the border between them at the level of the distal and middle 1/3 of the transverse colon. Thus, the right part of colon includes: the cecum, the ascending colon, and the proximal part of the transverse colon. The left part includes: the splenic flexure of the transverse colon, the descending colon, the sigmoid colon, and the rectum. The right half develops from the midgut and the left half – from the hindgut, which also determines the characteristics of the blood supply, which in the right half comes from the superior mesenteric artery, and the in left half – from the inferior mesenteric artery [7].

There are also differences in the population and epidemiological terms: tumors of the right half of the colon often develop in older women [5].

Depending on the localization, the clinical course of the process differs: as a rule, tumors of the right half are characterized by large sizes and frequent association with toxic-anemic syndrome, while in tumors of the left half, obturation syndrome and intestinal obstruction predominate [8].

There is also a difference in the microflora of the colon. An increase in the bacteria amount from the proximal colon sections to the distal ones was noted [9].

Due to the fact that the right and left parts of the colon have embryonic differences, the gene expression profile of the colonocytes of the right and left parts also have differences [10].

In recent decades, it has been important to study the role of various parts of the immune system in the beginning, development, and progression of the oncological process [11].

Local immunity of the gastrointestinal tract plays an important role in protective mechanisms, and local and systemic inflammatory reactions play an important role in carcinogenesis, affect the clinical course, as well as the outcome of the disease. Tumors of the colon and rectum are infiltrated by various inflammatory and immune cells, the most important of which is the number of T-lymphocytes infiltrating the tumor [12].

According to some authors, macrophage infiltration of tumor tissues and the peritumoral zone can be considered as a prognostic factor: low infiltration density correlates with more pronounced invasive properties of tumors [13, 14].

Currently the functions and expression of Toll-like receptors (TLRs), which are the most important representatives of pattern recognition receptors (PRRs), are also being actively studied [15].

It has been proven that TLRs are expressed not only on immune cells, but also on various somatic cells, tumor cells, including colorectal tumors [16].

Expression of TLRs on tumor cells plays a dual role in carcinogenesis, but the biological and clinical significance of this fact remains rather controversial [17].

The issue of the presence of distinctive immunological features between tumors of the colon, depending on the localization, remains open. It is due to the lack of works and evidence base on this issue, which determines the relevance of our study.

Objective

Analysis of the local subpopulation composition of immunocompetent cells, and assessment of the number of cells with the CD45+/- phenotype that express TLRs depending on the location of the tumor in the right and left parts of the colon.

Material and methods

The study included 50 patients diagnosed with colon cancer. Most of the subjects were female patients – 26 (52%), with a mean age of 67 ± 0.4 years (mean age of men – 66 ± 0.3 years). Patients with II stage of the disease predominated – 25 (50%). Depending on the tumor location (the right or left sides of the colon), the patients were divided into 2 equal groups.

All patients underwent standard surgery at the initial stage. The obtained material was used for subsequent studies: a cell suspension was obtained from a tumor tissue fragment, the perifocal zone (1–3 cm from the tumor) which was processed using an antibody panel (Becton Dickinson, USA) to identify the main subpopulations of leukocytes and lymphocytes. Expression of TLRs (2, 3, 4, 8, 9) on CD45+, CD45- phenotype cells was also determined using the BD FACSCanto flow cytometer (Becton Dickinson, USA). Statistical processing of the results was carried out using the STATISTICA 13.3 package (StatSoft Inc., USA). The significance of differences was assessed using the nonparametric Mann–Whitney U test ($p < 0.05$).

Results

A decrease by 47% ($p = 0.034$) in lymphocytic infiltration in tissue fragments of left-sided tumors was determined in comparison to the other group.

In the tissues of the left-sided colon tumors, tissue infiltration with NK-cells is 28% higher than in tumors of the right side. Left-side tumors are characterized by an increase in the content of CD19+ by 107% ($p = 0.025$), in comparison with the tissues of the tumors of the right side (figure 1).

Peritumoral zone tissues of left-sided tumors demonstrated a decrease of relative lymphocytes levels by 59% ($p = 0.027$), NKT by 34% ($p = 0.035$), NK by 26%

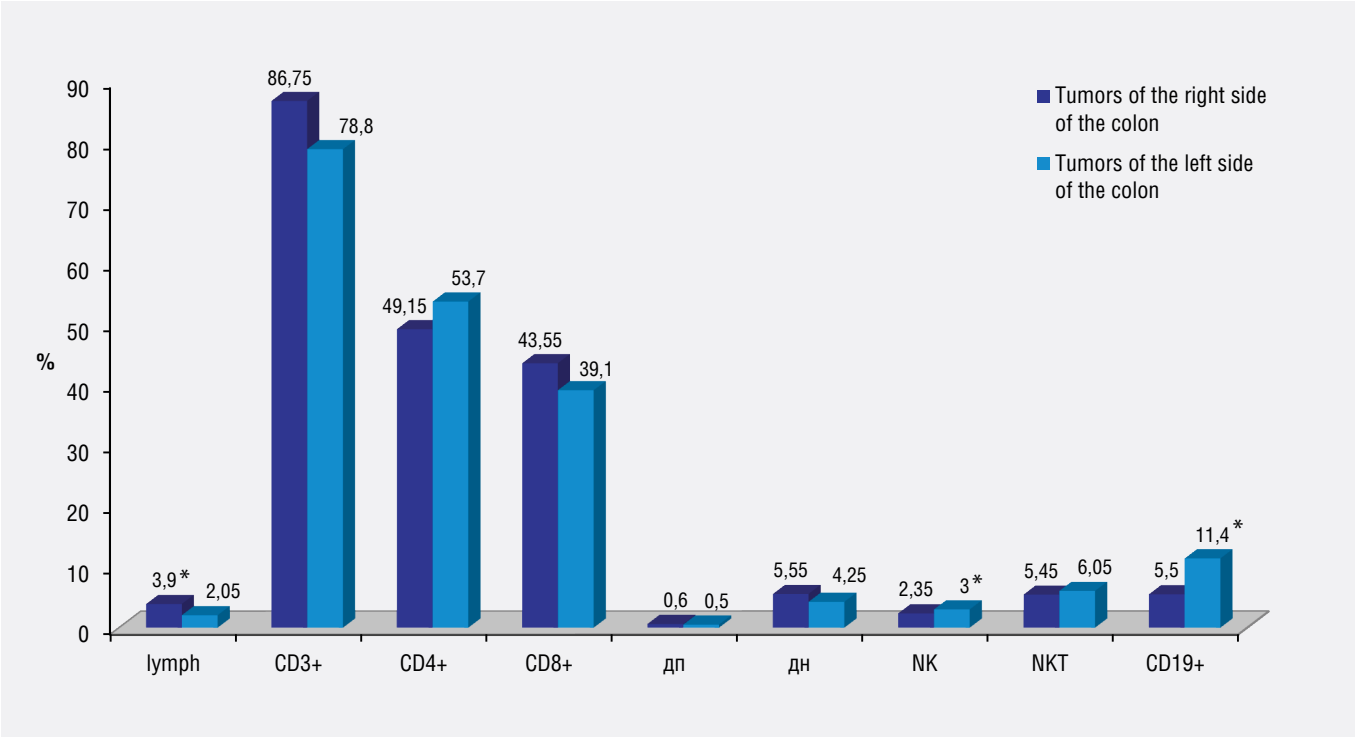

Figure 1. Subpopulation composition in the tumor tissue of patients with colon tumors
Note: * – statistically significant differences
Рисунок 1. Субпопуляционный состав в опухолевой ткани пациентов с опухолями ободочной кишки
Прим.: * – статистически значимые различия

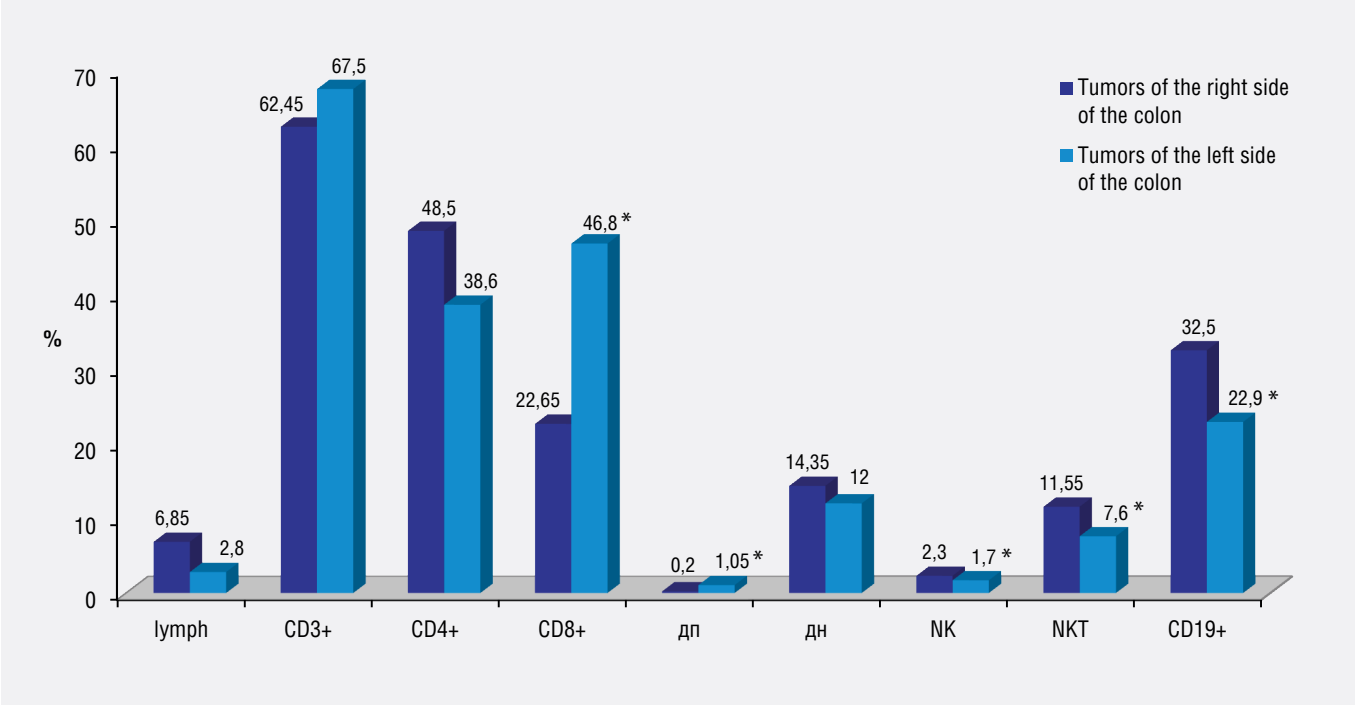

Figure 2. Subpopulation composition in the peritumoral zone tissue of patients with colon tumors
Note: * – statistically significant differences
Рисунок 2. Субпопуляционный состав в ткани перитуморальной зоны пациентов с опухолями ободочной кишки
Прим.: * – статистически значимые различия

(p = 0.041) and CD19+ by 30% (p = 0.038) in comparison with the tissue of the peritumoral zone of tumors in the right half. An increase of the CD8+ by 107% (p = 0.02) and DP cells by 425% (p = 0.0018) was revealed in tumors of the left side (figure 2).

The analysis of the left side tumors tissue showed a decrease in the percentage of cells with the CD45- phenotype expressing TLR4 by 38% (p = 0.038) and TLR8 by 25%, respectively (p = 0.043), in comparison with tumors of the right side (figure 3)

The analysis of left-side colon tumor data revealed a decrease in the relative number of cells with the CD45+ phenotype expressing TLR2 by 54% (p = 0.035) and TLR4 by 33% (p = 0.04) (figure 4).

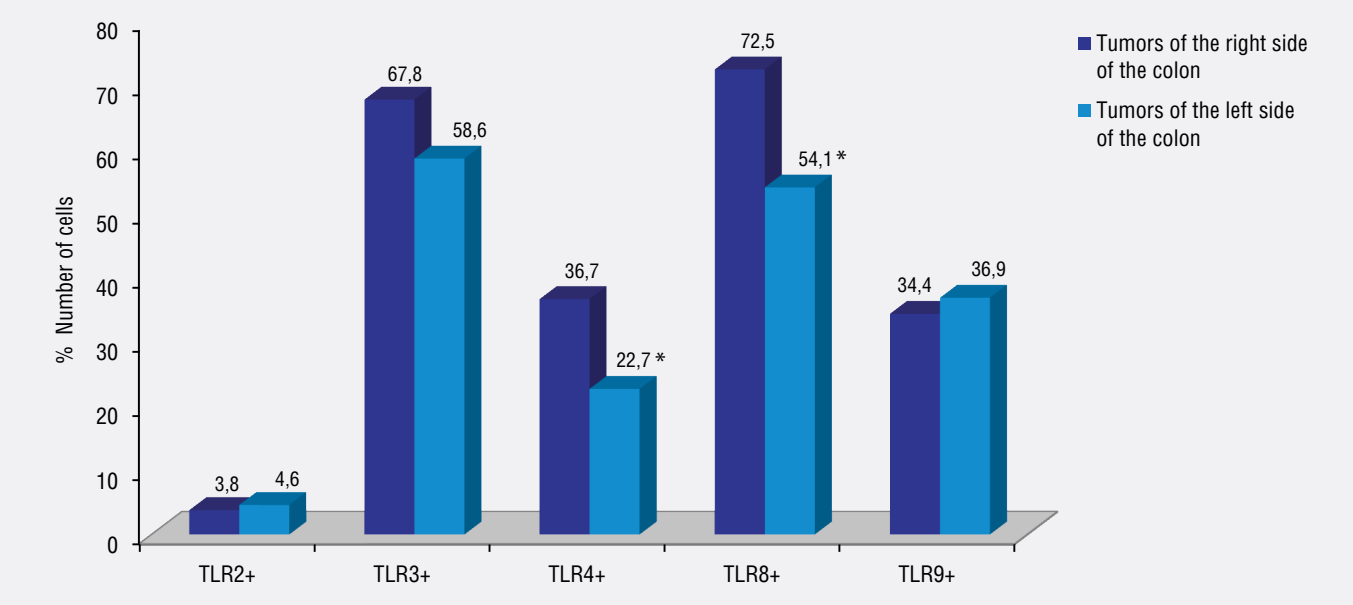

Figure 3. Relative number of cells with CD45- phenotype expressing TLRs in tumor tissues of patients with colon tumors
Note: * – statistically significant differences
Рисунок 3. Относительное содержание клеток с фенотипом CD45-, экспрессирующих TLRs, в тканях опухоли пациентов с опухолями ободочной кишки
Прим.: * – статистически значимые различия

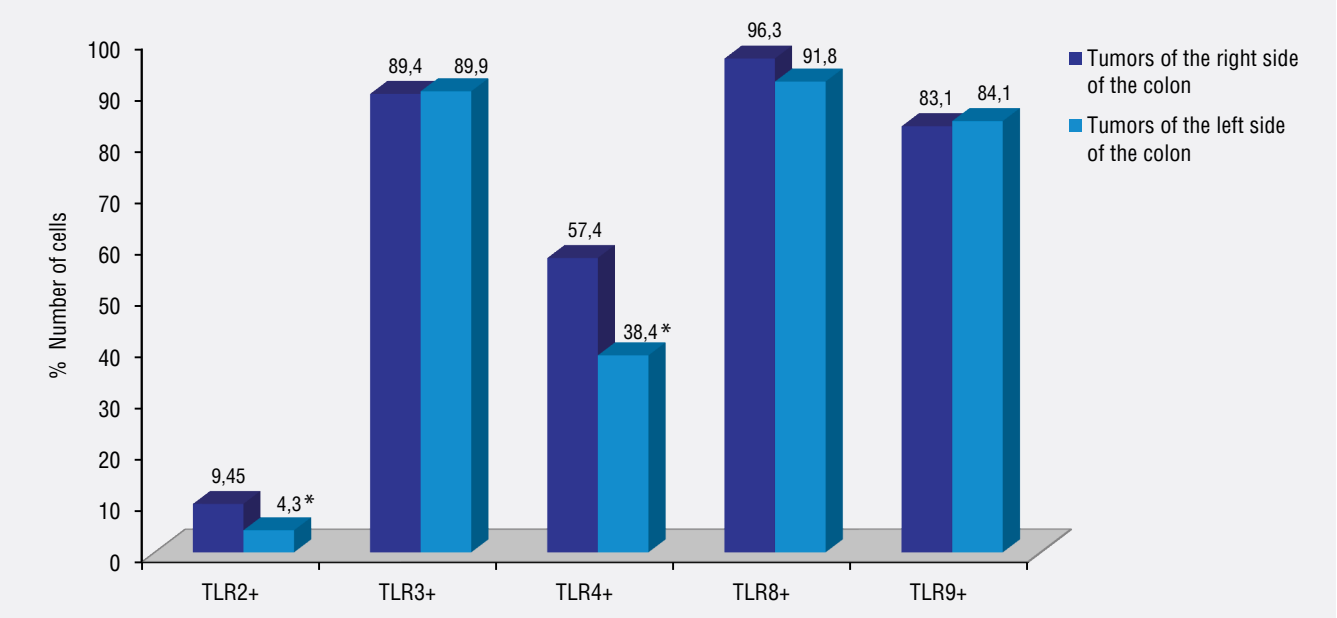

Figure 4. Relative number of cells with CD45+ phenotype expressing TLRs in tumor tissues of patients with colon tumors
Note: * – statistically significant differences
Рисунок 4. Относительное содержание клеток с фенотипом CD45+, экспрессирующих TLRs, в тканях опухоли пациентов с опухолями ободочной кишки
Прим.: * – статистически значимые различия

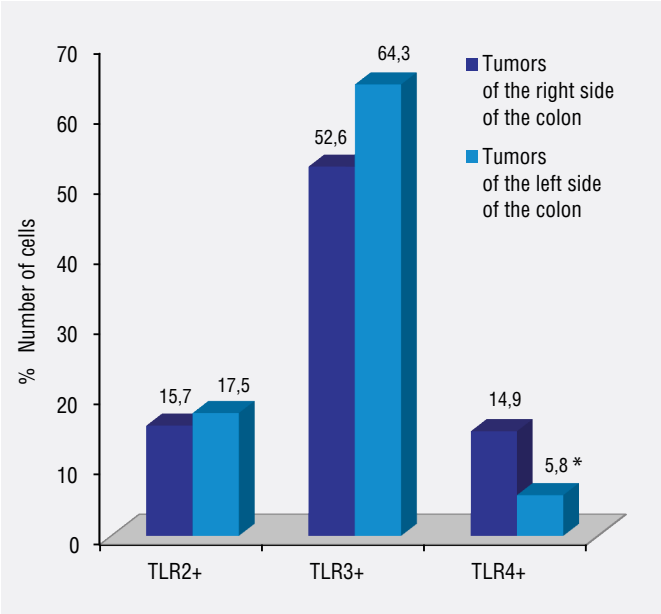

Figure 5. Relative number of cells with CD45- phenotype expressing TLR 2, 3, 4 in the perifocal tissues of colon tumors
Note: * – statistically significant differences
Рисунок 5. Относительное содержание клеток с фенотипом CD45-, экспрессирующих TLR 2, 3, 4, в тканях перифокальной зоны опухолей ободочной кишки
Прим.: * – статистически значимые различия

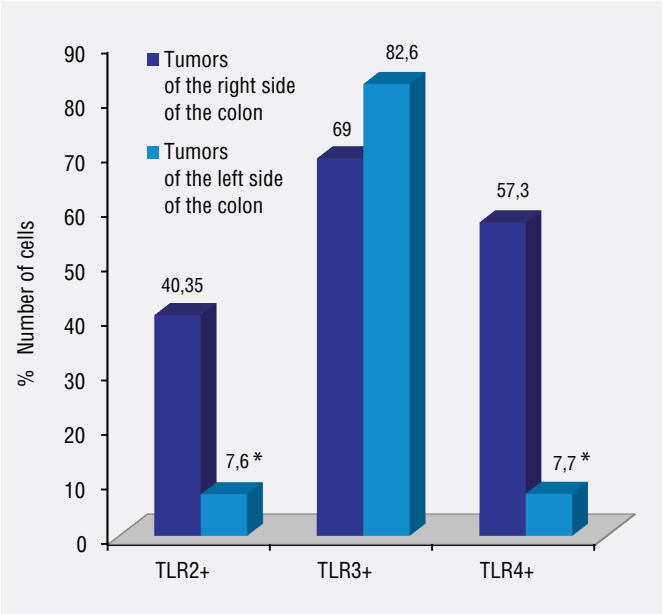

Figure 6. Relative number of cells with CD45+ phenotype expressing TLR 2, 3, 4 in the perifocal tissues of colon tumors
Note: * – statistically significant differences
Рисунок 6. Относительное содержание клеток с фенотипом CD45+, экспрессирующих TLR 2, 3, 4, в тканях перифокальной зоны опухолей ободочной кишки
Прим.: * – статистически значимые различия

During the analysis of the data obtained in cell suspensions from the tissues of the left-side perifocal zone tumors and from the right side, a decrease by 61% ($p = 0.031$) in the number of cells with the CD45- phenotype expressing TLR4 was detected (figure 5).

During the assessment of the number of cells with the CD45+ phenotype expressing TLR2, a decrease in the percentage of cells by 81% ($p = 0.02$) and TLR4 by 87% ($p = 0.018$) was revealed, in comparison with the right side (figure 6).

Discussion

The literature describes the results indicating that the tumor tissue in CRC is infiltrated by T-lymphocytes. F. Pages et al. demonstrated that severe lymphocytic infiltration of the peritumoral zone is a prognostic factor for good patient survival rate [18–20].

However, not only the quantitative, but also the qualitative composition of immunocompetent cells present in tumor tissues is important: the accumulation of CD8+ T-cells in the tumor significantly correlates with longer survival rate of patients [21, 22].

TLRs have currently been proven to have a tumor-stimulating effect. This phenomenon is best studied in colon cells, mainly with the participation of TLR4 and TLR2 [23].

On the other hand, TLRs are involved in antitumor immunity: TLRs are capable of activating various links of cellular immunity firstly [24]. A number of studies have shown that the development of a colorectal tumor is associated with an increased level of TLR4 expression, which is an unfavorable clinical factor [25–28]. Some studies have shown that the interaction of TLR9 with CD4+ T-cells can enhance and accelerate antitumor responses [29].

Findings:

A comparative analysis of immunological parameters, depending on the tumor location on the right or left sides of the colon, showed:

1. Tissues of the right-sided tumors had a higher T-lymphocytic infiltration, compared to the left-sided tumors, while the latter showed a higher B-lymphocytic infiltration ($p = 0.025$).

2. Peritumoral zone tissues of left-sided tumors demonstrated a decrease of lymphocytes levels ($p = 0.027$), NKT – ($p = 0.035$), NK – ($p = 0.041$) and B lymphocytes ($p = 0.038$), and a significant increase in CD8+- ($p = 0.02$) and DP cells ($p = 0.0018$).

3. Left-sided tumors showed a percentage decrease of CD45- cells expressing TLR4 and TLR8, compared to right-sided tumors, by 38% ($p = 0.038$) and 25% ($p = 0.043$).

4. There was a decrease in the number of CD45+ cells expressing TLR2 and TLR4 in left-sided tumors by 54% ($p = 0.035$) and 33% ($p = 0.04$) respectively, than in right-sided tumors.

5. The percent of CD45 cells expressing TLR4 in the perifocal tissues of left-sided tumors decreased by 61% (p = 0.031) in comparison to the corresponding tissues in right-sided tumors.

6. The numbers of CD45+ cells expressing TLR2 and TLR4 were 81% (p = 0.02) and 87% (p = 0.018) lower respectively in the peritumoral tissues of left-sided tumors, compared to the corresponding tissues in right-sided tumors.

Conclusion

The revealed characteristics of the local subpopulations of immunocompetent cells and the numbers of CD45+/- cells expressing TLRs depending on the tumor location on the right or left sides of the colon can serve as a prognosis of the disease clinical course and the choice of further treatment tactics. The data obtained will form the basis for our further research in this area.

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