

MAJOR AND MINOR POPULATIONS OF LYMPHOCYTES: LOCAL FEATURES IN DIFFERENT STAGES OF COLON CANCER

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ABSTRACT

Purpose of the study. Was to reveal characteristics of the immunocompetent cells in colon cancer (CC) according to the disease stage, and to identify prognostic factors of cancer development.

Materials and methods. The study included 50 patients with CC: stage I – 4 patients (8 %), II – 25 (50 %), III – 21 (42 %). All patients underwent standard surgical intervention at the initial stage, the obtained material was used for subsequent studies: a cell suspension was obtained from the tumor tissue, peritumoral zone (1–3 cm from the tumor), which was treated with an antibody panel (Becton Dickinson, USA) to identify the main subpopulations of leukocytes and lymphocytes.

Results. The tumor tissues of patients with stages I + II showed a decrease in the relative number of DP, DN, NKT and CD19+, compared to peritumoral tissues, by 33 %, 42 %, 31 % and 82 % respectively. Tumor tissues of stage III patients demonstrated elevated relative numbers of CD3+, CD4+, NK by 57 %, 34 %, 48 %, and decreased DP, DN, NKT, CD19+ by 33 %, 74 %, 31 %, 59 %, compared to peritumoral tissues. DP, DN, NKT and CD19+ in the tumor decreased by 78 %, 74 %, 39 %, 60 %, respectively, and the relative number of lymphocytes increased by 138 %, compared to the tissues of the resection line. A comparative analysis of local immunological parameters in the tumor tissues of patients with CC revealed that the relative numbers of lymphocytes and CD19+ were 58 % and 87 % higher, and DP and DN were 33 % and 27 % lower in tumor tissues of stage III patients, compared to tumor tissues of stage I + II patients.

Conclusion. Thus, the obtained features of the local population and subpopulation composition of immunocompetent cells in CC, depending on the stage of the tumor process, can be used to predict the clinical course of the disease.

Keywords:

oncology, colon cancer, local cellular immunity

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The work followed the ethical principles set forth by the Helsinki Declaration of the World Medical Association (World Medical Association Declaration of Helsinki, 1964, ed. 2013). The study was approved by the Ethics Committee of the National Medical Research Centre for Oncology (Protocol No. 32 of 10/08/2020). Informed consent was obtained from all participants of the study.

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ОСНОВНЫЕ И МИНОРНЫЕ ПОПУЛЯЦИИ ЛИМФОЦИТОВ: ЛОКАЛЬНЫЕ ОСОБЕННОСТИ ПРИ РАЗЛИЧНЫХ СТАДИЯХ РАКА ОБОДОЧНОЙ КИШКИ

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РЕЗЮМЕ

Цель исследования. Выявить особенности состава иммунокомпетентных клеток при раке ободочной кишки (РОК) в зависимости от стадии процесса и выделить прогностические факторы течения заболевания.

Материалы и методы. В исследование включено 50 пациентов РОК: I стадия – 4 пациента (8 %), II – 25 (50 %), III – 21 (42 %). Всем больным на начальном этапе было выполнено стандартное оперативное вмешательство. Полученный материал был использован для последующих исследований: из ткани опухоли, перитуморальной 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.

Результаты. В тканях опухолей группы пациентов I + II стадии отмечено уменьшение относительного количества ДП, ДН, NKT и CD19+ по сравнению с перитуморальной зоной на 33 %, 42 %, 31 % и 82 % соответственно. В тканях опухолей пациентов с III стадией выявлено повышение относительного количества CD3+, CD4+, NK на 57 %, 34 %, 48 % и снижение ДП, ДН, NKT, CD19+ на 33 %, 74 %, 31 %, 59 % по сравнению с тканью перитуморальной зоны. В опухолях выявлено уменьшение ДП, ДН, NKT, CD19+ на 78 %, 74 %, 39 %, 60 %, а также увеличение относительного количества лимфоцитов по сравнению с линией резекции на 138 % соответственно. При проведении сравнительного анализа локальных иммунологических показателей в тканях опухолей больных РОК выявлено, что в тканях опухолей группы пациентов III стадии отмечено увеличение относительного количества лимфоцитов и CD19+ на 58 % и 87 % и снижение ДП и ДН на 33 % и 27 % по сравнению с тканями опухолей группы I + II стадии.

Заключение. Таким образом, полученные особенности локального популяционного и субпопуляционного состава иммунокомпетентных клеток при РОК в зависимости от стадии опухолевого процесса могут быть использованы при прогнозировании клинического течения заболевания.

Ключевые слова:
онкология, рак ободочной кишки, локальный клеточный иммунитет

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В работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено этическим комитетом ФГБУ «НМИЦ онкологии» Минздрава России (протокол № 32 от 08.10.2020 г.). Информированное согласие получено от всех участников исследования.

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RELEVANCE

Colorectal cancer (CRC) occupies one of the first places in the structure of morbidity from cancer in the Russian Federation [1; 2]. About 60 % of cases of CRC occur in colon cancer (CC), which occupies the 4th place in the structure of female cancer incidence, the 5th place – male cancer incidence [3].

To date, there are a large number of modern methods of diagnosing the oncoprocess. However, despite this, the level of neglect of colon tumors remains quite high. As a rule, at the time of treatment of patients, the cancer process has advanced stages [4; 5].

More and more research in oncology is associated with the study of the role of the links of the immune system in the occurrence, course, and progression of the cancer process. Its dual role has been proven: on the one hand, the presence of antitumor effects, on the other – tumor-activating. This fact determines the relevance of studying the role of individual components of both innate and adaptive immunity in colocalization.

The immune system of the gastrointestinal tract plays an important role in protecting the body from the action of infectious agents and toxins, their inactivation and elimination is carried out. It has been proven that both local and systemic inflammatory reactions play an important role in the progression of the tumor process, thereby affecting the outcome of the disease [6; 7]. Colorectal tumors are infiltrated by immune and inflammatory cells, the most significant of which are T-lymphocytes. It is also known that the tissue of tumors of the colon and rectum contains a small number of T-lymphocytes with CD4+ and CD8+ receptors [8].

Infiltration by macrophages of the tumor and peritumoral zone is used as a prognostic factor: low infiltration density is associated with high invasive properties of tumors [9; 10]. There are a number of works in the literature devoted to the study of tumor-infiltrating immunocompetent cells and the assessment of their prognostic significance in CRC, which are very contradictory [11–13]. There is no doubt about the high importance of studying the role of tumor infiltration of lymphocytes, which determine the biological properties of the tumor and the features of the clinical course of the disease. At the same time, there is a small amount of information reflecting the features of lymphocytic infiltration in the tumor tissue, peritumoral zone, resection line, depending on the stage of the disease, which determines the purpose of the study.

Purpose of the study was to identify the features of the population and subpopulation composition of immunocompetent cells locally in colon cancer, depending on the stage of the process and to identify prognostic factors of the course of the disease.

MATERIALS AND METHODS

The study included 50 patients with CC who were treated at the National Medical Research Centre for Oncology: 26 of them were women (52 %), whose average age was 67 ± 0.4 years and 24 men (48 %), the average age was 66 ± 0.3 years.

According to the results of postoperative histological analysis, the following distribution was revealed by stages of CC: I – 4 patients (8 %), II – 25 (50 %), III – 21 (42 %), subsequently patients of groups I and II were combined (Fig. 1).

The spread of the tumor within the intestinal wall (T1–3) was noted in 38 (76 %) patients, and a tumor that sprouted into other organs and/or visceral peritoneum T4 – in 12 (24 %). Regional lymph nodes (l.n.) (N+) were affected in 27 patients (54 %). At the 1st stage of treatment, all patients underwent surgical intervention with the collection of material for subsequent studies. A cell suspension was obtained from tumor tissues, the peritumoral zone, and the resection line, processed using an antibody panel (Becton Dickinson, USA) in order to identify the main populations and subpopulations of leukocytes and lymphocytes using a BD FACSCanto flow cytometer (Becton Dickinson, USA). The results were expressed in the relative number of the main populations and

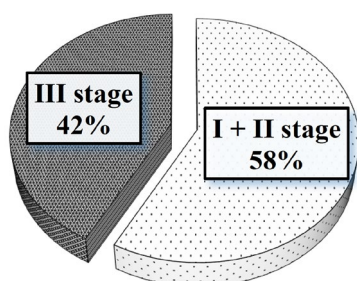


Fig. 1. Distribution of patients according to their disease stage.

subpopulations of lymphocytes: CD45+ – total number of lymphocytes (Lymph), CD3+ – T-lymphocytes, CD3+CD4+ – T-lymphocytes helper, CD3+CD8+ – cytotoxic T-lymphocytes, CD3+CD4+CD8+ – double positive lymphocytes (DP), CD3+CD4-CD8- – double negative lymphocytes (DN), CD3-CD56+CD16+ – NK lymphocytes, CD3+CD56+CD16+ – NKT lymphocytes, CD19+ – B lymphocytes relative to the total number of lymphocytes.

Statistical processing of the obtained results was carried out using the STATISTICA 13.3 package (StatSoft Inc., USA), which involved calculating the main statistical characteristics of the samples, determining the nature of the distribution of the determined indicators using the Shapiro-Wilk criterion. Due to the fact that the obtained results did not obey the law of normal distribution, the reliability of the differences between the samples was evaluated using the nonparametric Mann-Whitney criterion. The results were considered statistically significant at $p < 0.05$.

RESEARCH RESULTS AND DISCUSSION

We conducted a comparative analysis of the relative number of the main populations and subpopulations of lymphocytes, depending on the stage, the depth of the lesion of the intestinal wall tumor (T), the presence or absence of lesion of regional lymph nodes (N).

When analyzing the data, depending on the stage of the tumor process, it was revealed that in the tumor tissues of the group of patients of stage I–II, there was a decrease in the relative number of DP and DN cells, NKT and CD19+ lymphocytes compared with similar indicators in the peritumoral zone by 33 %, 42 %, 31 % and 82 %, respectively ($p < 0.05$). Compared with conditionally healthy tissue, tumor fragments showed an increase in the relative number of T-lymphocytes, CD3+ and NK cells by 41 %, 35 %, 50 %, while the content of DP-, DN-, NKT-, CD19+ lymphocytes was reduced by 33 %, 42 %, 31 %, 82 % ($p < 0.05$).

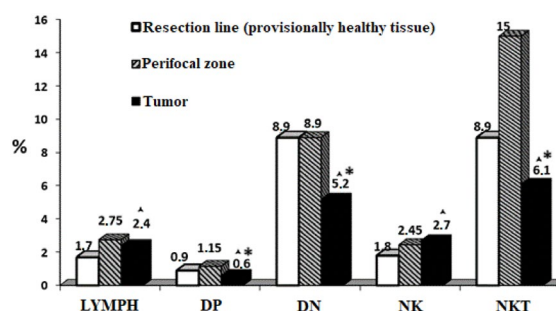
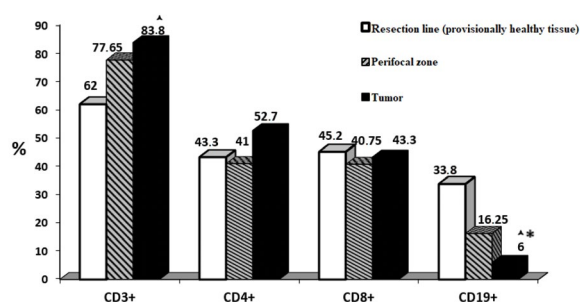


Fig. 2. Subpopulation composition in the tissues of patients with stage I – II colon cancer.

Note: Δ – statistically significant differences from the indicators of the resection line (conditionally healthy tissue); * – statistically significant differences from the indicators of the peritumoral zone.

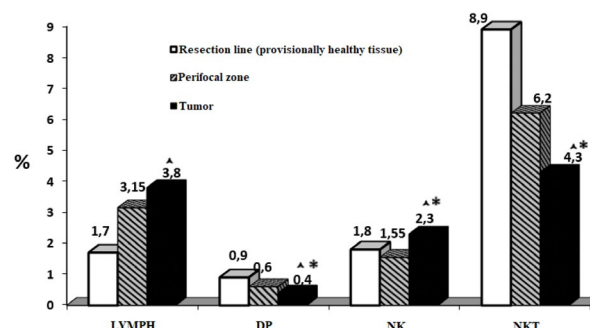
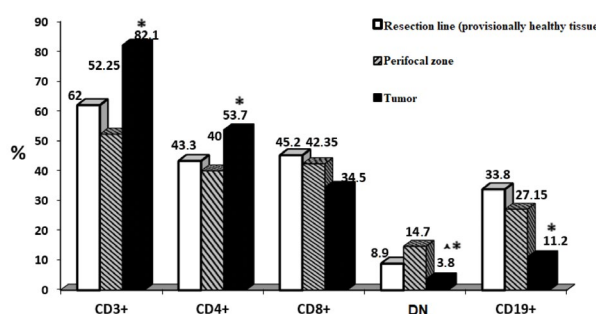


Fig. 3. The subpopulation composition in the tissues of the group of patients with stage III colon cancer.

Note: Δ – statistically significant differences from the indicators of the resection line (conditionally healthy tissue); * – statistically significant differences from the indicators of the peritumoral zone.

In the peritumoral zone, a low content of CD19+ (by 52 %) was noted, as well as an increased content of lymphocytes, CD8+, DP, NK, NKT on 62 %, 25 %, 27 %, 36 % and 69 %, respectively, compared with the indicators in the resection line ($p < 0.05$) (fig. 2).

Analysis of the results of the study of tissues of patients with stage III CC showed that in the tumor tissue there is an increase in the relative number of CD3+, CD4+, NK lymphocytes by 57 %, 34 %, 48 % and a decrease in DP, DN, NKT, CD19+ cells by 33 %, 74 %, 31 %, 59 % by compared with the tissue of the peritumoral zone ($p < 0.05$). In the tumor, there is a decrease in DP, DN, NKT, CD19+ by 78 %, 74 %, 39 %, 60 %, against this background, an increase in the relative number of lymphocytes compared to the resection line was revealed by 138 %, respectively ($p < 0.05$) (Fig. 3).

A comparative analysis of local immunological parameters in the tumor tissues of CC patients revealed that in the tumor tissues of the group of stage III

patients there was an increase in the relative number of lymphocytes and CD19+ cells by 58 % and 87 % and a decrease in DP and DN of lymphocytes by 33 % and 27 % compared with the tissues of tumors of stage I and II ($p < 0.05$) (fig. 4).

Based on the data obtained, it was revealed that the tumor is characterized by the accumulation of T-lymphocytes, in particular, T-helper-inductor and B-cells (CD19+), which is especially pronounced in stage III of the disease in patients with CC and a low content of DP and DN lymphocytes, as well as NKT cells.

The existing data in the literature indicate that the tissue of tumors of the colon and rectum is infiltrated by a small number of T-lymphocytes. In 1987, J. R. Jass et al. It has been shown that pronounced lymphocytic infiltration of the perifocal zone is a prognostic factor for longer overall survival of CRC patients [11–13]. It has been proven that the pronounced accumulation of CD8+ T cells in tumor tissue correlates with longer survival of patients [14; 15].

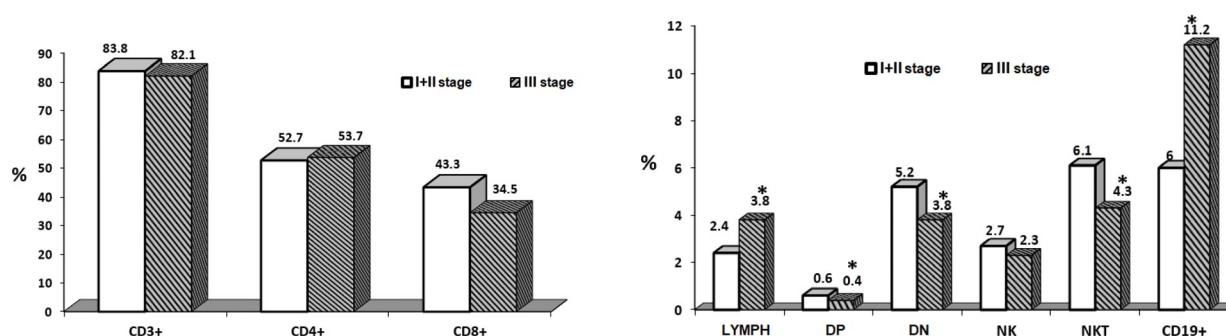


Fig. 4. The subpopulation composition in the tumor tissues of a group of colon cancer patients, depending on the stage. Note: * – statistically significant differences ($p < 0.05$).

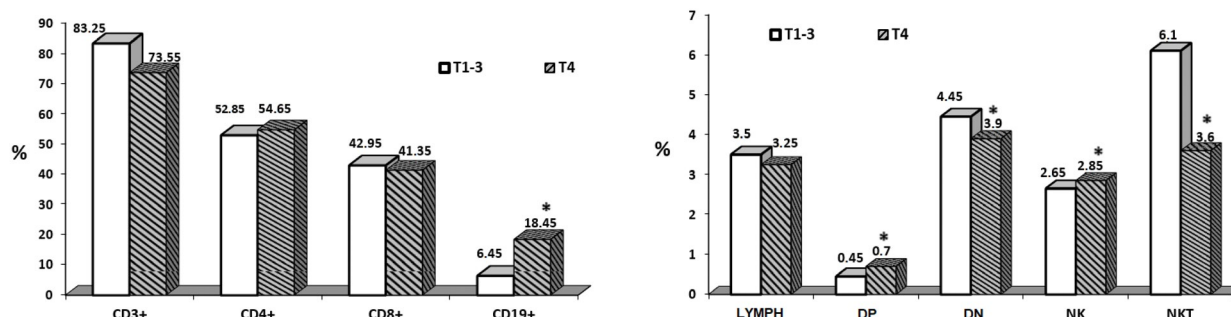


Fig. 5. The subpopulation composition in the tumor tissues of a group of colon cancer patients, depending on the criterion T. Note: * – statistically significant differences ($p < 0.05$).

Analysis of the subpopulation composition of lymphocytes in tumor tissue, depending on the criterion of the level of invasion of the intestinal wall tumor (T), showed that in the tumor tissues of the T4 patient group, an increase in the relative number of DP cells and CD19+ lymphocytes was noted compared to the tissues of the T1-3 group by 56 % and 186 %, respectively ($p < 0.05$), and also, a decrease in the relative number of NKT lymphocytes by 41 % ($p < 0.05$) (fig. 5).

When comparing the results obtained, depending on the lymph node lesion, it was noted that in the tumor tissues of the group of patients with node lesion (N+), an increase in the relative number of lymphocytes and CD19+ was noted by 96 % and 97 %, as well as a decrease in the relative number of NKT lymphocytes by 32 % compared with the tumor tissues of the group of patients N0 ($p < 0.05$) (Fig. 6).

Our results somewhat contradict the data of Tachibana T. et al., according to which tumor infiltration by NKT cells positively correlated with a smaller number of lymph node metastases [16].

By a group of authors A. C. Diederichsen et al. It has been demonstrated that a low CD4+/CD8+ ratio, i.e. the prevalence of cytotoxic T-lymphocytes in the tumor against the background of a decrease in T-cells with helper-inductor function, is a prognostic factor for long-term survival of CRC patients [17]. The data obtained in our study, indicating certain features of the tissue composition of immunocompetent cells in the tumor and its microenvironment, in some cases agree with the data of other authors and may, in our opinion, be the basis for the development of criteria for the prognosis of the development of CRC metastases [18].

DN lymphocytes – Pinocchio cells (Pinocchio cells) are intermediate elements of differentiating T-lymphocytes. This type of cells resembles cells of innate immunity in functional activity, they form early barrier formations aimed at maintaining immune homeostasis [19].

When studying the features of the immunological organization of soft tissue sarcomas, it was shown that in the tissue of recurrent sarcomas there is a high level of DN T-lymphocytes, which belong to a subpopulation of T cells with TCR $\gamma\delta$ and may have the properties of T-regs [20]. An increase in their level in the blood in some malignant tumors presupposes some negative changes in the immune status [21].

However, there is also an opposite opinion, according to which both DN and DP lymphocytes, being cells of innate immunity, have the opposite effect. In our study, the opposite trend was found – in the case of disease progression, its later stages or the presence of metastases, it was accompanied by an increase in the content of these cells, which, however, does not allow us to draw a final conclusion about the functional significance of this fact.

Currently, there is no clear opinion about the role of B-lymphocytes in the development of tumors and sensitivity to therapy. It has been shown that the number of circulating antibodies increases in the blood of cancer patients, and in the tumor tissue of tumor-infiltrating B-lymphocytes, which perform a protective function [22]. According to another opinion, B cells increase the aggressiveness of the tumor, thereby worsening the prognosis [23]. Under certain conditions, B cells can perform the function of antigen-presenting cells: express stimulating CD80, CD86 and ICOS molecules and activate CD4+, CD8+ T cells [24].

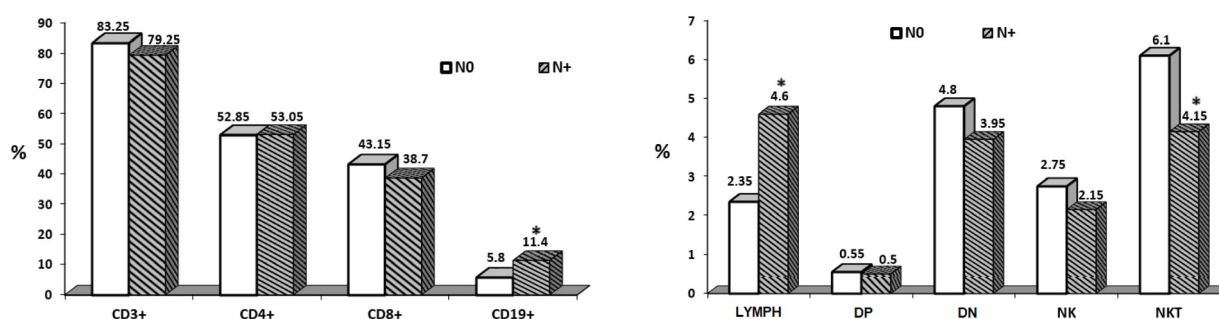


Fig. 6. The subpopulation composition in the tumor tissues of the CC patient group, depending on criterion N. Note: * – statistically significant differences ($p < 0.05$).

However, activated B-lymphocytes and plasmocytes synthesize antibodies that block the antigens of tumor cells, disrupting their recognition [25]. It has been shown that one of the varieties of B-lymphocytes are cells with high regulatory potential, which is expressed in the secretion of IL-10, IL-35, IL-6, transforming growth factor- β (TGF- β), which causes immunosuppression of antitumor immunity [26]

Despite certain differences in the results of studying the immunological microenvironment of various malignant tumors obtained by various research groups, understanding the mechanisms involved in the interaction between tumor cells and the microenvironment opens up a great prospect for changing the treatment strategy that will help fight tumors more effectively [27].

CONCLUSION

1. The tumor tissue in CC is characterized by the accumulation of T-helper-inductor lymphocytes and

B cells (CD19+) and depletion of DP and DN lymphocytes, as well as a decrease in the number of NKT cells, which is more pronounced in stage III of the disease in patients with CC.

2. At the III stage of the disease, in CC, there is a decrease in the activity of local innate immunity, which is manifested in a decrease in the content of NKT cells in the primary tumor, as well as the tension of the humoral link of immunity, due to the high content of tumor CD19+ lymphocytes, the same trend is observed with the defeat of regional lymph nodes (N+).

3. It is possible that an increased number of CD19+ cells is a factor predisposing to the occurrence of lymphogenic metastasis, and is also associated with a more advanced stage of CC.

Thus, the data obtained on the features of the local population and subpopulation composition of immunocompetent cells in colon cancer, depending on the stage, T and N, can be used in the prognosis of the clinical course of the disease.

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