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- To promote the development of oncological medicine in the South of Russia and the implementation of its achievements in practice.
- High-quality published content that includes the latest and trustworthy scientific papers, research or work on oncology issues.

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- Facilitating the exchange of experience and transfer of advanced knowledge between specialists;
- Informing readers about the results of major medical forums;
- Giving scientists the opportunity to publish the results of their research;
- Achieving an international level in scientific publications;
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Журнал входит в рекомендованный ВАК РФ перечень рецензируемых научных журналов и изданий для опубликования основных научных результатов диссертаций на соискание учёной степени кандидата и доктора наук.

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- Содействие обмену опытом и передаче передовых знаний между специалистами;
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Журнал принимает к публикации: результаты оригинальных исследований, обзоры литературы, описание клинических случаев.

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ORIGINAL ARTICLE

Features of occult hepatitis B diagnostics in cancer patients

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ABSTRACT

Purpose of the study. Analysis of the frequency of detection of HBsAg-negative hepatitis B serological and molecular biological markers in cancer patients.

Materials and methods. The blood serum samples of patients hospitalized at the National Medical Research Centre for Oncology in 2016–2023 were studied. 41,523 samples were tested for HBsAg, 2,035 for anti-HBcore, of which 958 were tested simultaneously for both markers using the enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay (CLIA). 1,380 samples were tested for the presence of hepatitis B virus (HBV) DNA in blood plasma using real time polymerase chain reaction (qPCR).

Results. The HBsAg prevalence in cancer patients accounted for 2.5 % (1051/41523), 23.7 % (483/2035) for anti-HBcore. Simultaneous examination for HBsAg and anti-HBcore revealed various combinations of markers. Among HBV-positive variants, the most common was the combination anti-HBcore+HBsAg-. The average number of such patients was 20.6 % (197/958). The simultaneous presence of both markers was noted in 4.6 % of patients (44/958). There were no isolated HBsAg detection cases. The total number of HBV+ individuals was 25.2 % (241/958). 81.7 % out of these (197/241) were HBsAg-negative. 219 samples with the HBV DNA presence in the blood plasma were identified. 19 of these were examined simultaneously for HBsAg, anti-HBcore. The majority (78.9 %) had all three markers. 21.1 % were HBsAg-negative but DNA-positive (latent form of infection), 15.8 % of which were anti-HBcore-positive, and 5.3 % did not have a single serological marker.

Conclusion. The detection of anti-HBcore in the absence of HBsAg can indicate the presence of occult forms of hepatitis B, which under conditions of drug immunosuppression can be reactivated. The identified significant percentage of cancer patients with occult hepatitis B variants highlights the necessity to expand the number of diagnostic markers for screening. Additional testing for anti-HBcore can significantly increase the likelihood of detecting HBV during prehospital testing.

Keywords: occult viral hepatitis B, HBV reactivation, oncological diseases

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki (1964, ed. 2013) were observed in the work. The study was approved by the Committee on Ethics at the Rostov Research Institute of Oncology (extract from the protocol of the meeting No. 30/1 dated 15/12/2015). Informed consent was obtained from every participant of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Особенности диагностики скрытой формы гепатита В у онкологических больных

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РЕЗЮМЕ

Цель исследования. Анализ частоты выявления серологических и молекулярно-биологических маркеров HBsAg-негативного гепатита В среди онкологических больных.

Материалы и методы. Исследовали сыворотки крови больных, госпитализированных в ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации с 2016 по 2023 гг. Исследовано 41523 образца на HBsAg, 2035 – на суммарные анти-HBcore, из них 958 – одновременно на HBsAg и анти-HBcore методами иммуноферментного (ИФА) или иммунохемилюминесцентного анализа (ИХЛА), 1380 образцов – на наличие ДНК вируса гепатита В (ВГВ) в плазме крови методом полимеразной цепной реакции в режиме реального времени (ПЦР-РВ).

Результаты. Распространенность HBsAg среди онкологических больных составила 2,5 % (1051/41523), анти-HBcore – 23,7 % (483/2035). Одновременное обследование на HBsAg и анти-HBcore позволило выявить различные сочетания маркеров. Среди вариантов, положительных хотя бы по одному маркеру, самым распространенным оказался HBsAg-негативный, но анти-HBcore-позитивный. Количество таких больных в среднем составило 20,6 % (197/958). Одновременное присутствие обоих маркеров было отмечено в среднем у 4,6 % больных (44/958). Не было выявлено ни одного случая изолированного выявления HBsAg. Всего число лиц, инфицированных ВГВ, составило 25,2 % (241/958). Из них HBsAg-негативными оказались 81,7 % (197/241).

Было выявлено 219 образцов с наличием ДНК ВГВ в плазме крови. Из них 19 были обследованы одновременно на наличие HBsAg, анти-HBcore. У большинства (78,9 %) присутствовали все три маркера. HBsAg-негативными, но ДНК-позитивными были 21,1 % (скрытая форма инфекции), из них 15,8 % – анти-HBcore-позитивными, а 5,3 % не имели ни одного серологического маркера.

Заключение. Обнаружение антител к HBcoreAg при отсутствии HBsAg может свидетельствовать о наличии скрытой формы гепатита В, которая в условиях медикаментозной иммуносупрессии способна перейти в активную форму. Выявленный существенный процент онкологических больных со скрытым вариантом гепатита В подчеркивает необходимость расширения числа диагностических маркеров для скрининга. Дополнительное тестирование на анти-HBcore может существенно повысить вероятность выявления ВГВ на этапе догоспитального обследования.

Ключевые слова: скрытый вирусный гепатит В, реактивация ВГВ, онкологические заболевания

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INTRODUCTION

One of the most important problems of modern diagnosis of chronic hepatitis B is the ability of the pathogen to cause the so-called occult form of infection. The following synonyms are used in scientific publications to refer to it: "occult", "silent" and "latent", as well as different definitions are applied in accordance with various guidelines [1–3].

Therefore, according to the recommendations of the European Association for the Study of the Liver [1], "occult hepatitis B virus (HBV) infection" is simply the fifth and final phase of the development of chronic hepatitis B. This is the HBsAg-negative phase, which is characterized by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). Patients in this phase have normal ALT values and usually, but not always, undetectable serum HBV DNA. Hepatitis B virus DNA (in covalently closed form) is often found in the liver. It is emphasized that the absence of HBsAg can often be associated with the use of insufficiently sensitive methods for its detection. Thus, it is assumed that occult hepatitis B is either one of the outcome options for chronic HBV infection, or it is the result of a virus mutation that "eludes diagnosis", which, obviously, is not the same thing [3]. In the Chinese guidelines for the prevention and treatment of chronic hepatitis B, the occult form is mentioned as one of the types of clinical diagnosis with special characteristics (the surface antigen of the virus is not detected in blood serum, but its DNA can be detected in blood and/or liver tissue) [4]. The World Health Organization, as part of the annual meeting of the Asia-Pacific Association for the Study of the Liver (APASL), presented updated guidelines on hepatitis B, according to which the occult form is the fourth phase of chronic infection and is defined as the persistence of HBV DNA in the liver or blood serum in people in whom HBsAg is not detectable in the blood [5]. As for the Guidelines of the American Association for the Study of Liver Diseases (AASLD), in its latest edition, occult hepatitis B is mentioned only as a possible risk factor in organ transplantation [6].

Based on the results of two international seminars in Taormina devoted specifically to the issue of occult hepatitis B, in 2008 and 2019, the following definition of occult HBV infection was formulated [7, 8]. Occult HBV infection is defined as the presence of replication-competent HBV DNA (i. e. episomal covalently closed circular HBV DNA [cccDNA]) in the liver and/or HBV DNA in the blood of people with a negative test result for hepatitis B virus surface antigen (HBsAg) using currently available assays. Based on the profiles of HBV-specific antibodies, occult hepatitis B can be divided into the following types:

- serum positive: positive for anti-HBc and/or anti-HBs, the most common form of infection that accounts for about 78 % of cases. The serological profile of occult HBV infection may include anti-HBc (50 %), anti-HBs (35 %);
- serum negative: anti-HBc and anti-HBs negative [8].

The origin of the occult form of HBV infection is considered insufficiently studied. It is assumed that there are several possible mechanisms of its occurrence, including, first of all, pronounced suppression of viral replication and/or inhibition of S gene expression, mutations in the regulatory regions of the HBV genome, persistence of Ig-associated HBV immune complexes, viral interference, coincidence of the time of the study with the phase of the serological "window", integration of the viral DNA in the cellular genome, long-term persistence in the hepatocyte nucleus of cccDNA in the form of a stable episome, and others [9]. According to Semenov A. V. et al., the occult form of hepatitis B can be considered as the result of the implementation of various scenarios of interaction between the virus and the immune system, expressed in extremely diverse patterns in terms of the results of the determination of laboratory markers [10].

Since a fairly wide range of clinical conditions fall under the formal definition of "occult HBV infection" as the absence of HBsAg in the presence of DNA in serum or liver biopsy, it is not surprising that data on its prevalence in the world vary widely (from 1 to 87 %) and depend on the region, the method of determining the virus genome, the markers studied, and the diversity commercial kits for detecting HBV markers, the sensitivity of the analysis, the study population, and the availability of studies at different points in time are more likely to identify low-copy samples [3, 10]. Many studies have shown that HBV DNA is only occasionally detected in serum/plasma,

and when detected, its concentration is low, usually less than 200 IU/ml (about 1000 copies/ml) [8]. Due to the factors listed above, the prevalence of occult hepatitis B is difficult to summarize. It is most often observed in people with liver diseases, for example, in HBsAg–negative hepatocellular carcinoma, its frequency reaches 70 %, after liver transplantation reaches up to 64 %, and barely reaches 5 % in blood donors [8].

Increasing numbers of the modern literature sources suggest that in areas of medicine where immunosuppressive therapy is actively used, standard screening for infection by the main marker (HBsAg) does not provide sufficient assurance of the absence of an active infectious process in liver tissue [10]. Reactivation of viral hepatitis is particularly dangerous for cancer patients due to the need to interrupt chemotherapy and the high incidence of deaths. HBV reactivation can occur in 40 % of people with latent infection when using powerful immunosuppressive therapy. The issue has been studied in more detail in patients with oncohematological pathology, since they are at the highest risk (especially when using rituximab), but it is also described against the background of treatment of solid tumors [11]. At the same time, the issues of reactivation of latent HBV in cancer patients remain poorly understood [9].

The phenomenon of occult HBV infection is largely a diagnostic problem. The search for suitable diagnostic markers of occult form of HBV is actively continuing. In particular, test systems are being developed to determine the presence of covalently closed circular HBV DNA in liver tissues [10]. This study is considered the gold standard on which both the concept and diagnosis of occult hepatitis B are based. The importance of testing this marker is due to the fact that it is this form of DNA that allows the virus to remain inaccessible in liver tissue after functional healing and elimination of the virus from the blood. Covalently closed viral DNA in hepatocytes remains stable, difficult to detect and not yet available for medication therapy, while fully ready for replication, and it can resume at any time if the body's immune system weakens and cannot suppress it. However, in practice, the detection of this form of viral DNA in the liver is often inapplicable due to its invasive approach and lack of standardized methods [8].

The relatively new indicators correlating with the presence of an active infectious process in the liver include the determination of HBcore-related antigen. It is a composite antigen that includes three proteins: nuclear antigen (HBcAg), a nucleocapsid containing viral DNA; E-antigen (HBeAg), a circulating protein that is expressed from the core gene, then modified and secreted by liver cells; auxiliary precore-bound antigen (PreC), found in the virus-similar particles that do not contain DNA. In general, the HBcore-bound antigen is a surrogate marker of intrahepatic HBV replication, correlating with viral DNA and HBsAg levels, and can also serve as an additional marker for detecting infection phases [12, 13]. Other promising types of markers associated with the transcriptional activity of cccDNA virus in the liver include HBV RNA [14, 15] and quantification of anti-HBc levels [16]. However, such markers are not yet available in clinical practice.

Screening for anti-HBc in the blood as a surrogate marker is especially important both for donors and for people who are going to receive immunosuppressive therapy, since liver tissue is often unavailable, access to HBV DNA tests in the blood may be limited or delayed, and undetectable HBV DNA in the blood, tested in one the moment in time does not exclude the presence of infection. Indeed, HBV reactivation was recorded in HBsAg-negative and anti-HBc-positive individuals whose viral DNA was not detected in their blood. Taking into account that the detection of anti-HBc is not an absolute proof of the presence of a occult form of infection (since they continue to be detected even after full clearance of the virus), we have to admit that so far this remains one of the few available options for primary screening of the population for the prevalence of occult hepatitis B [10].

The World Health Organization's guidelines for the treatment of HBV, updated in 2024, also emphasize the importance of identifying the occult form of infection and the risk of its reactivation in patients with immunosuppressive therapy. HBV reactivation can occur spontaneously or can be caused by chemotherapy to lead to the fatal development of acute or chronic hepatitis, therefore, proactive therapy with nucleosi(t)de analogues is used [5].

The purpose of the study was to analyze the frequency of detection of HBsAg-negative hepatitis B serological and molecular biological markers among cancer patients.

MATERIALS AND METHODS

Blood samples of patients with oncological diseases who were admitted to the National Medical Research Center of Oncology, the Russian Federation Ministry of Health, in the period from 2016 to 2023 were examined. All patients signed an informed consent to participate in the study at the screening stage. HBsAg was determined (with a confirmatory test for positive samples), anti-HBcore was determined using enzyme immunoassay systems (Vector-Best JSC, Russia; recording of the results – Infinite F50, Tecan Austria GmbH, Austria) or the Vitros 3600 immunochemiluminescence analyzer (Ortho Clinical Diagnostics, USA). The sensitivity of the methods was at least 0.01 IU/ml.

A total of 41,523 blood serum samples of patients with HBsAg were examined, of which 26,724 were men, 14,799 were women, and the median age was 58 years. 2,035 samples were tested for total anti-HBcore (the study was assigned to people with onco-hematological diseases), of which 958 samples were simultaneously tested for HBsAg and anti-HBcore.

Additionally, 1,380 studies were performed on the presence of HBV DNA in blood plasma, reagent kits for the MagNAPure Compact automatic isolation station (Roche Diagnostics Ltd, Switzerland) were used to isolate DNA, AmpliSens HBV-FL was used to determine DNA, and AmpliSens HBV-monitor-FL was used for quantitative determination., Russia), the sample extraction volume was 1 ml. Amplification was performed by polymerase chain reaction (PCR) in real time with hybridization-fluorescence detection using a Rotor-Gene Q thermal cycler (Qiagen GmbH, Germany). The sensitivity of the method at an extraction volume of 1 ml for a qualitative test was 10 IU/ml, the linear measurement range for a quantitative test was within 15–100 000 000 IU/ml.

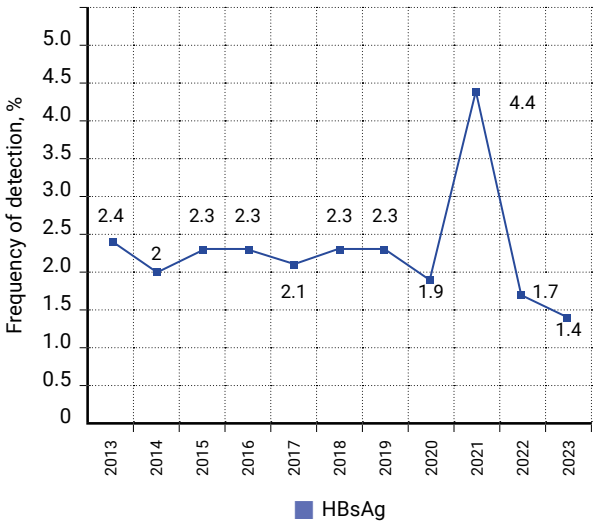

Fig. 1. Dynamics of HBsAg detection among cancer patients

Statistical analysis

Statistical data processing was carried out using the Microsoft Office Excel and STATISTICA 10.0 application software package. Descriptive statistics for categorical variables are presented in the form of absolute and relative frequencies (percentages, %). To study the relationship of categorical variables, the χ^2 test and the Fisher exact criterion were used, the association was considered statistically significant at $p < 0.05$.

STUDY RESULTS

The prevalence of HBsAg among cancer patients was 2.5 % (1051/41523, Fig. 1). It was found in men twice as often as in women: in 2.7 % of cases versus 1.1 % ($p = 0.0001$, $\chi^2 = 15.37$). The largest proportion of HBsAg-positive samples was detected in 2021 (4.4 %), the smallest in 2023 (1.4 %).

The frequency of HBsAg detection was also analyzed depending on the department profile: the 2 % prevalence threshold was exceeded in several of them, the highest frequency was for people with hematological diseases (Fig. 2).

The overall frequency of anti-HBcore detection ranged from 18.5 % (2022) to 27.1 % (2021) and averaged 23.7 % (483/2035, Fig. 3).

Simultaneous examination for HBsAg and anti-HBcore revealed various combinations of markers. Among the variants with at least one hepatitis B marker, "HBsAg- anti-HBcore+" turned out to be the most common. The number of such patients ranged from 15.9 % in 2022 to 24.5 % in 2016 and 2019, with an average of 20.6 % (197/958). The simultaneous presence of both markers was noted in an average of 4.6 % of patients (44/958): the maximum such variant was detected in 2017 (8.5 %), the minimum in 2019. (2,8 %). No isolated cases of HBsAg have been identified.

The total number of people with at least one HBV serological marker was 25.2 % (241/958). 81.7 % of

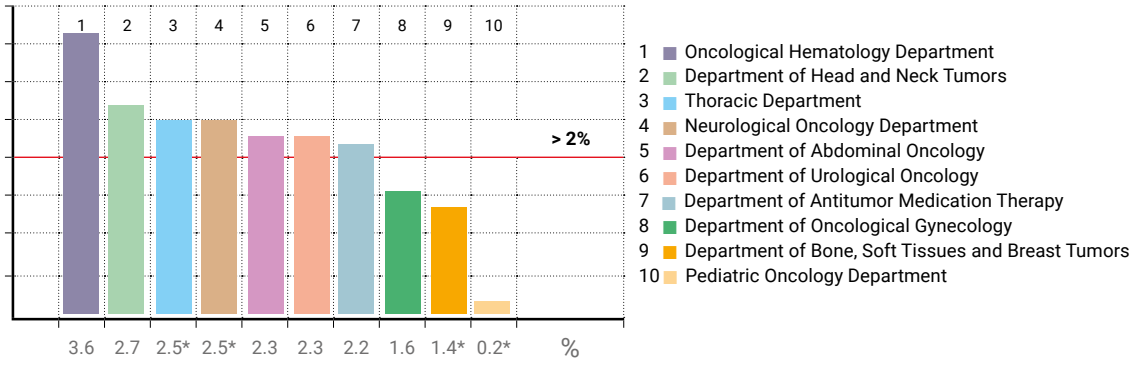

Fig. 2. Frequency of HbsAg detection depending on the department profile
Notes: * – statistically significant difference compared to the Department of Hematology ($p < 0.05$)

these turned out to be HBsAg-negative (197/241). Which means that during a standard screening examination, these patients would have remained undetected.

A study was also carried out for the viral DNA presence in the blood serum: a total of 219 positive samples were found. The viral load level was in a wide range of values: there were samples outside the linear measurement range (less than 15 IU/ml – 23.2 %, more than 100,000,000 IU/ml – 6.5 %), the median values within the linear range was 1020.0 IU/ml [148.5; 14084.0]. Of these, 19 samples were examined simultaneously for the presence of HBsAg, anti-HBcore. Taking into account the presence of viral DNA, the patient profiles were distributed as follows (Table 1).

The majority (78.9 %) had all three markers, which was regarded as a clear variant of the disease. HBsAg-negative, but DNA-positive was 21.1 %, which is a occult form of infection that could not be detected with standard screening. 15.8 % of this number were anti-HBcore-positive, and 5.3 % had no serological markers. As for the level of viral load, within the linear range, the median value was 413.0 IU/ml [389.0; 5968.0], 21.0 % had less than 15 IU/ml. Among the HBsAg-negative variants, 75.0 % (3/4) of patients had a viral load below the linearity limit, and one patient (25.0 %) had a viral load of 403 IU/ml.

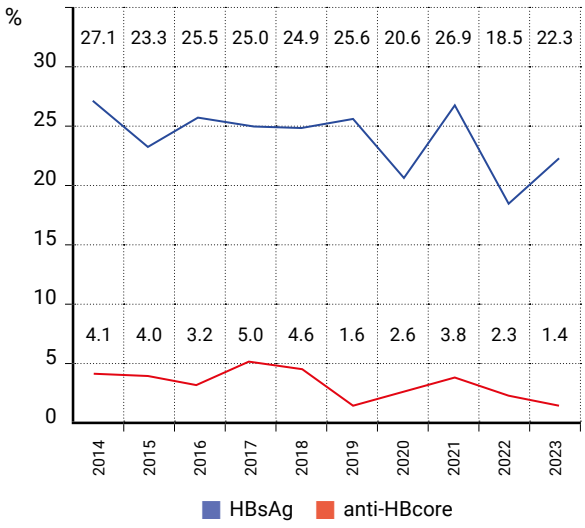

Fig. 3. Dynamics of HBsAg and anti-HBcore detection in oncohematological patients

DISCUSSION

According to our data, the prevalence of HBsAg among cancer patients was 2.5 % overall, which exceeds the detection rate in conditionally healthy individuals and donors (from 0.07 % to 0.25 %) and correlates with the available literature data [17]. The dynamics of the indicator was relatively stable with the exception of the one in 2021: during this period, there was an unexplained increase in other parameters of pre-hospital screening, including hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis.

There is evidence that in patients with a negative HBsAg test result, but with other markers of HBV infection (anti-HBcore IgG+, anti-HBs IgG+/-), the use of immunosuppressive therapy causes reactivation of chronic hepatitis with a typical serological and molecular biological profile of active infection (HBsAg+, anti-HBe IgG+, anti-HBcore IgG+, HBV DNA+, ALT↑↑). These data convincingly demonstrate the importance of dynamic monitoring of patients with occult form of hepatitis B [10]. If we talk about the experience of our institution, epi-

sodes of reactivation were also recorded in previous studies [18], in all cases all three markers were identified. A sharp increase in the viral load was noted, including to a value exceeding 100 million IU/ml. Patients received antiviral therapy along with antitumor treatment, as a result of which the majority of patients managed to reduce the viral load to undetectable, and only one patient failed to stabilize the situation, and chemotherapy was interrupted.

In the study of Semenenko T. A. et al. analysis of the results of serological testing revealed 13 hematological patients with HBV DNA, but with a different serological profile: five people with HBsAg–/HBV DNA+ (group 1) and eight people with HBsAg+/HBV DNA+ (group 2) [10]. The authors considered it important to note that HBV DNA was contained in very low concentrations (< 102 IU/ml) in the blood serum of patients negative for HBsAg, while in three cases (2.3 %) HBV DNA served as the only marker of HBV infection. In our study, the detected concentration of HBV DNA was also at a low level (less than 100 IU/ml) in the absolute majority of cases (75.0 %). These results are consistent with data from other researchers who have shown that the viral load in occult HBV infection is extremely low [8, 9].

It should be noted that the documents regulating the stages of hepatitis B diagnosis, which include recommendations from foreign and domestic oncological associations and clinical guidelines, do not mention occult forms of hepatitis B as such, but in most cases they all indicate the need to study additional markers besides HBsAg. In particular, in the recommendations of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), the volume of additional studies is determined depending on the therapy used and the associated risk [19, 20]. In addition to the degree of risk of the planned antitumor therapy, the serological status and the level of viremia are taken into account by the Russian Society of Clinical Oncology (RUSSCO) in the recommendations updated in 2023. In particular, it highlights the high incidence of patients who lack HBsAg in their blood, but at the same time anti-HBc is detected. For immunocompromised individuals, including those receiving antitumor treatment, the risk of HBV reactivation is: in the presence

Table 1. Variants of HBV marker combinations in oncohematological patients

The combination of markers	abs. / n	%	% out of positives at least to one HBV marker
Serological markers exclusively			
HBsAg+ anti-HBc+	44 / 958	4.6	18.3
HBsAg- anti-HBc+	197 / 958	20.6 $p^1 < 0.0001$ $\chi^2 = 111.11$	**81.7**
HBsAg- anti-HBc-	717 / 958	74.8 $p^1 < 0.0001$ $\chi^2 = 987.32$; $p^2 < 0.0001$ $\chi^2 = 565.70$	
Serological and molecular biology markers			
HBV DNA + HBsAg+ anti-HBc+	15 / 19	78.9	78.9
HBV DNA + HBsAg- anti-HBc+	3 / 19	15.8 $p^3 = 0.0001$ F = 0.40	**21.1**
HBV DNA + HBsAg- anti-HBc-	1 / 19	5.3 $p^3 < 0.0001$ F = 0.557	

Notes: abs. is the number of identified samples, *n* is the total number of examined, p^1 is a statistically significant difference compared to the "HBsAg+ anti-HBc+" variant, p^2 is a statistically significant difference compared to the "HBsAg- anti-HBc+" variant, p^3 is a statistically significant difference compared to the "HBV DNA+" variant. HBsAg+ anti-HBc+"

of anti-HBc – 5 %, and in the absence – in 14 % of patients. The risk of reactivation is higher in patients with oncohematological diseases: from 18 % in people with only antibodies to HBcore, up to 48 % in people with chronic HBV. In patients with solid tumors, the risk of HBV reactivation is ~3 % in patients with HBcore antibodies and up to 25 % in patients with chronic hepatitis B [11]. And the data we have obtained on such a high percentage of occult form of hepatitis B among cancer patients fully confirm the need for them to comply with more extensive screening, as shown in the recommendations mentioned above.

CONCLUSIONS

The detection of antibodies to HBcoreAg in the absence of HBsAg, as a rule, may indicate the presence of a occult form of hepatitis B, which, under conditions of drug immunosuppression, is capable of becoming active. The revealed significant percentage of cancer patients with a occult variant of hepatitis B is of concern and highlights the need to expand the number of diagnostic markers for screening. Additional testing for anti-HBcore and HBV DNA can significantly increase the likelihood of detecting HBV at the prehospital examination stage.

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ORIGINAL ARTICLE

Quality of life of gastric cancer patients after radical surgery depending on the status of the duodenal passage

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ABSTRACT

Purpose of the study. To assess the impact of preservation of the duodenal passage on the quality of life (QOL) after total gastrectomy (TGE) in patients with gastric cancer (GC).

Patients and methods. The study included 55 patients with GC who underwent TGE: group I (*n* = 29) included patients with preservation of the duodenal passage (PDP) using the double tract reconstruction method; Group II (*n* = 26) included those with standard Roux-en-Y reconstruction. QOL was assessed using the EORTC QLQ-C30 questionnaire with the QLQ-STO22 module for GC patients.

Results. Changes in QOL in patients 3 months after TGE were expressed in a statistically significant decrease in scores of all functional scales (QL, PF, RF, EF, CF and SF), and an increase in the scores of symptom scales (FA, NV, PA, DY, SL, AL, CO, DI, FI), to the same extent for both groups. After 6 months, an increase in the scores of functional scales was noted; statistically significant differences between the groups were identified on the QL, RF, CF and SF scales in favor of the group with PDP. In the group with PDP, a more significant decrease in the level of most symptomatic scales was also noted. After 12 months, a statistically significant advantage remained on functional and symptomatic scales for patients in the group with PDP. Assessment of QOL using the scales of the QLQ-STO22 module showed similar trends: after a sharp increase in symptom values at 3 months after surgery, equally pronounced in both groups, there was a decrease at 6 months, more pronounced in the group with PDP. At 12 months postoperatively, the overall trend towards an advantage in the PDP group continued.

Conclusion. The dynamics of QOL recovery in patients with GC after surgical treatment depends on the status of the duodenal passage: in the group of patients with PDP, faster positive dynamics are observed on all scales of functioning and symptoms than in patients without duodenal passage. Preservation of duodenal passage during surgical treatment of GC has a positive effect on the dynamics of recovery of the QOL of patients with GC, providing a positive contribution to improving the results of antitumor treatment.

Keywords: gastric cancer, total gastrectomy, quality of life, duodenal passage

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Compliance with ethical standards: this research has been carried out in compliance with the ethical principles set forth by the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Committee on Ethics at the Kuban State Medical University (extract from the protocol of the meeting No. 107 dated 28/01/2022). Informed consents were received from all the participants of the study

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Качество жизни больных раком желудка после радикального хирургического лечения в зависимости от статуса восстановления дуоденального пассажа

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РЕЗЮМЕ

Цель исследования. Оценка влияния на качество жизни (КЖ) сохранения дуоденального пассажа в хирургическом лечении больных раком желудка (РЖ).
Пациенты и методы. В исследование включены 55 больных РЖ, которым выполнена гастрэктомия (ГЭ): I группа (*n* = 29) – с сохранением дуоденального пассажа (СДП) методом реконструкции «двойной тракт»; II группа (*n* = 26) – со стандартной реконструкцией по Ру. Оценка КЖ проводилось с помощью опросника EORTC QLQ-C30 с модулем для РЖ QLQ-STO22.
Результаты. Изменения КЖ у пациентов через 3 месяца после ГЭ выражались в статистически значимом снижении показателей всех функциональных шкал (QL, PF, RF, EF, CF и SF), и повышении значений шкал симптомов (FA, NV, PA, DY, SL, AP, CO, DI, FI), в одинаковой степени для обеих групп. Через 6 месяцев отмечено повышение значений функциональных шкал, статистически значимые различия между группами выявлены по шкалам QL, RF, CF и SF в пользу группы с СДП. В группе с СДП отмечено также более значительное снижение уровня большинства симптоматических шкал. Через 12 месяцев сохранилось статистически значимое преимущество пациентов группы с СДП по функциональным и симптоматическим шкалам. Оценка КЖ по шкалам модуля QLQ-STO22 показала аналогичные тенденции: после резкого роста значений симптомов в сроки 3 месяца после операции, одинаково выраженного в обеих группах, отмечалось их понижение к сроку 6 месяцев, более выраженное в группе с СДП. Через 12 месяцев после операции общая тенденция к преимуществу группы с СДП сохранялась.
Заключение. Динамика восстановления КЖ у больных РЖ после хирургического лечения зависит от статуса дуоденального пассажа: в группе пациентов с СДП отмечается более быстрая позитивная динамика по всем шкалам функционирования и симптомов, чем у пациентов без включения двенадцатиперстной кишки (ДПК). Сохранение дуоденального пассажа при хирургическом лечении РЖ положительно влияет на динамику восстановления КЖ пациентов после радикального хирургического лечения РЖ, обеспечивая позитивный вклад в улучшение результатов противоопухолевого лечения.

Ключевые слова: рак желудка, гастрэктомия, качество жизни, дуоденальный пассаж

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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 Независимым этическим комитетом ФГБОУ ВО «Кубанский государственный медицинский университет» Министерства здравоохранения Российской Федерации (протокол № 107 от 28.01.2022 года). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Quality of life (QOL) assessment is an important component for determining optimal therapy in both radical and palliative care programs for patients with cancer, including gastric cancer [1–5]. It is important that QOL is a patient-oriented variable reflecting the functional impact of the disease and its treatment process on the patient in the system of his goals, expectations, standards and problems [6–8]. At the same time, as emphasized by B. Alkhaffaf et al. (2020), the patient's priorities regarding treatment outcomes may differ and be broader than traditional oncological criteria and priorities of oncologists [9]. At the present stage, there is an increasing demand for functional treatment outcomes, including surgical ones, both from oncologists and patients. This determines the search for functionally optimal methods of reconstructing the digestive tract in the surgical treatment of GC, one of the options of which is the restoration of the duodenal passage [10–13]. The importance of QOL assessment in oncology is outlined by the randomized clinical trial R. van Amelsfoort et al. (2022), which showed that a decrease in QOL was associated with worse event-free and overall survival in patients with GC [14]. In this regard, the introduction of new or improved treatment methods into clinical practice should be accompanied by a thorough and objective study of their effects on QOL.

The purpose of the study was to evaluate the effect on quality of life (QOL) of maintaining the duodenal passage in the surgical treatment of patients with gastric cancer (GC).

PATIENTS AND METHODS

The study included 55 patients with histologically verified gastric cancer who underwent gastrectomy (GE) surgery. The study was prospective in nature, patients were randomized into 2 groups according to the study design: group I (29 patients) included patients with GE performed with restoration of the duodenal passage using the "double tract" reconstruction method (DT); II group was presented by 26 patients with GE performed with standard reconstruction according to Roux-en-Y (Fig. 1). The examination was conducted in 3, 6, and 12 months after surgery. The study was performed on the basis of the Clinical Oncological Dispensary in Krasnodar in the period from 2020 to 2024. The work followed the ethical principles set forth in the Helsinki Declaration of the World Medical Association (1964, ed. 2013), the study was approved by the Independent Ethics Committee of the Kuban State Medical University (Protocol No. 107 dated 01/28/2022). Informed consent was obtained from all participants in the study. Inclusion criteria: age over 18, GE surgery, obtained written informed consent to participate. Exclusion criteria: stage IV of GC cancer (with distant metastases), presence of decompensated chronic and acute concomitant diseases, refusal to participate. There were no statistically significant differences between the groups in terms of the main clinical characteristics (Table 1).

Surgical treatment was performed in accordance with the clinical recommendations of the Ministry of Health of the Russian Federation for the diagnosis and treatment of patients with gastric cancer. In patients with stage IB and higher, diagnostic laparoscopy with cytological examination of peritoneal flushes for the presence of free tumor cells was performed before planning treatment. Patients with positive (Cyt+) flushes were classified as having M1 and excluded from the study. Perioperative chemotherapy, according to the "Clinical guidelines for the treatment of gastric cancer", was performed in 37 patients with tumors of stages II and III (37/44. 84 % of the total number, the differences between the groups are statistically unreliable). The preferred regimen was the FLOT regimen:

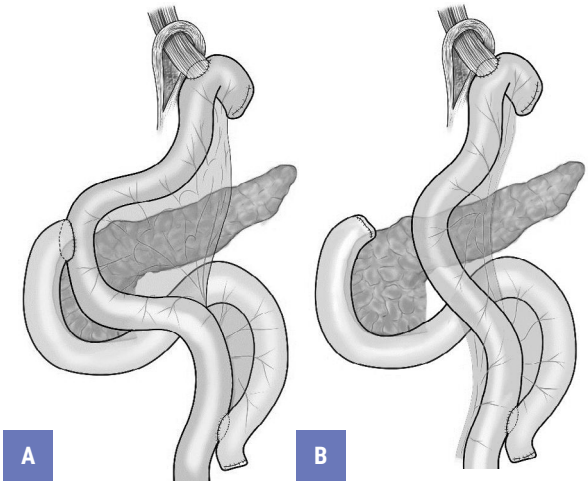

Fig. 1. The scheme of the operation: A – GE with the reconstruction of the double tract (DT); B – GE with the Roux-en-Y reconstruction

4 courses preoperatively, 4–6 weeks after surgery, 4–8 weeks after surgery – 4 more courses in the FLOT regimen, regardless of the therapeutic pathomorphosis of the tumor. In somatically burdened patients, FOLFOX (4 + 4 cycles), XELOX (3 + 3 cycles), cisplatin and fluorouracil (3 + 3 cycles) combinations were used with the onset of the postoperative stage 4–6 weeks after surgery. There were no statistically significant differences in access, volume of organ removal, and volume of lymph dissection in both groups. Laparotomy access was used in 27 (93.1 %) patients of group I and in 23 (88.5 %) of group II (p = 0.550). In 2 cases (6.9 %) in group I and 3 (11.5 %) in group II, abdominal-mediastinal access was used to resect the abdominal esophagus and form an esophageal-intestinal anastomosis in the lower mediastinum. The volume of lymph dissection corresponded to the volume of D2: lymph nodes of groups No. 1–7, 8a, 9, 10, 11p, 11d and 12a were removed, with the spread above the cardia, lymph dissection expanded at the expense of groups No. 19, 20, 110 and No. 111 (according to the classification of the Japanese Association for the Study of Gastric Cancer). There were no deaths after surgery in both groups. The length of hospital stay was similar for patients of both groups: 7.4 ± 1.2 days for GE with DT reconstruction vs 7.6 ± 1.9 days for GE according to Roux-en-Y (p = 0.632). Postoperative complications were noted in 2 patients of group I and 2 in group II. In group II, a surgical complication was registered, which led to re-operation (perforation of the stump of the loop). In other cases, the development of pneumonia was diagnosed, and in 2 of them, pneumonia had a viral etiology (COVID-19).

We used a Quality of Life Questionnairy – Core 30, EORTC QLQ-C30 to assess the quality of life [15, 16], which includes 30 questions and consists of multiposition scales and individual indicators. The estimated indicators include: 1) Global health/quality of life scale (quality of life, QOL); 2) five functional scales – physical functioning (PF), role function-

Table 1. Characteristics of operated patients who underwent GE with DT reconstruction (group I) and Roux-en-Y (group II)

Parameter	I group (n = 29)	II group (n = 26)	p
Age, years	61.21 (9.42)	57.4 (11.4)	0.191
Body mass, kg; ave. (SD)	71.0 (11.1)	74.4 (17.6)	0.244
BMI, ave. (SD)	24.3 (3.61)	26.2 (4.8)	0.464
Sex, n (%)			
M	18 (62.1)	16 (61.4)	0.968
F	11 (37.9)	10 (38.5)	
TNM staging, n (%)			
IA	3 (10.3)	4 (15.3)	0.978
IB	2 (6.9)	2 (7.7)	
IIA	4 (13.8)	3 (11.5)	
IIB	3 (10.3)	3 (11.5)	
IIIA	9 (31.0)	6 (23.1)	
IIIB	4 (13.8)	4 (15.4)	
IIIC	4 (13.8)	4 (15.4)	
Tumor localization, n (%)			
Cardia, fundus	8 (27.6)	5 (19.2)	0.685
Body	17 (58.6)	16 (61.5)	
Antrum	1 (3.4)	1 (3.8)	
A lesion that spread beyond one location	3 (10.3)	4 (15.3)	

ing (RF), emotional functioning (EF), cognitive functioning (CF) and social functioning (SF) functioning; 3) three scales of symptoms – fatigue (FA), nausea and vomiting (NV), pain (PA); 4) six separate items – dyspnea (dyspnea, DY), sleep disorder (SL), loss of appetite (AP), constipation (CO), diarrhea (DI), financial difficulties (FI). In addition to the main questionnaire, the QLQ-STO22 module was also used, a validated QOL assessment tool specific to patients with GC [17], consisting of 22 items and mainly focused on symptoms specific to GC: pain, dysphagia, reflux and early satiety, as well as addressing emotional problems (including body image changes, weight loss and the patient's thoughts about his illness). The scale scores were calculated based on the official EORTC QLQ-C30 Scoring Manual [16]. As a result of the calculation procedure, all scales and measures for individual items ranged from 0 to 100 points.

Statistical analysis

The statistical analysis was carried out using the following methods: analysis of four-field and multipole arbitrary conjugacy tables using the Pearson chi-square (χ^2) criterion, the Kruskal-Wallis H-test, the t-test for independent samples, and the t-test for paired samples. The threshold criterion for statistical significance is $p < 0.05$. For statistical analysis, the IBM® SPSS Statistics 23.0 software package for statistical data processing for Windows (IBM, USA) was used.

STUDY RESULTS AND DISCUSSION

Changes in QOL parameters in patients after GE in the early stages after surgery (3 months) were expressed in a statistically significant decrease in all six functional scales (QL, PF, RF, EF, CF, and SF), and an increase in the values of the symptom scales (FA, NV, PA) and individual questionnaire items (DY, SL, AP, CO, DI, FI). These changes affected patients of both groups to the same extent, and there were no statistically significant differences between them in any of the indicators during this period (Fig. 2).

By the time of 6 months after surgery, the QOL parameters were transformed towards their improvement, with an increase in the values of all functional scales, statistically significant differences were noted between the groups on the functional scales QL ($p < 0.001$), RF ($p = 0.028$), CF ($p = 0.009$), SF ($p < 0.001$), in In favor of the group with PDP, there was no statistically significant difference on the PF and EF scales. In the group of patients with PDP, there was also a more pronounced decrease in the values of the symptomatic scales compared to the Roux-en-Y group: FA ($p = 0.001$), NV ($p = 0.003$), PA ($p = 0.010$), DY ($p = 0.001$), SL ($p < 0.001$), CO ($p = 0.001$), DI ($p = 0.004$), FI ($p < 0.001$), the difference was statistically insignificant only in the symptom of loss of appetite (AL) ($p = 0.092$) (Fig. 3).

When evaluated after 12 months in both groups, the indicators on the scales of the EORTC QLQ-C30 questionnaire did not change significantly, and the statistically significant advantage of patients with PDP remained in such parameters as the functional scales QL ($p < 0.001$), PF ($p < 0.001$), RF ($p < 0.001$), EF ($p < 0.001$), CF ($p <0.001$), SF ($p < 0.001$), symptomatic scales FA ($p < 0.001$), NV ($p < 0.001$), PA ($p < 0.001$), DY ($p <0.001$), SL ($p < 0.001$), CO ($p = 0.002$), DI ($p = 0.010$). There was no statistically significant difference in the symptoms of AL and the FI issue (Fig. 4).

The assessment of QOL dynamics on the scales of the QLQ-STO22 module showed similar trends.

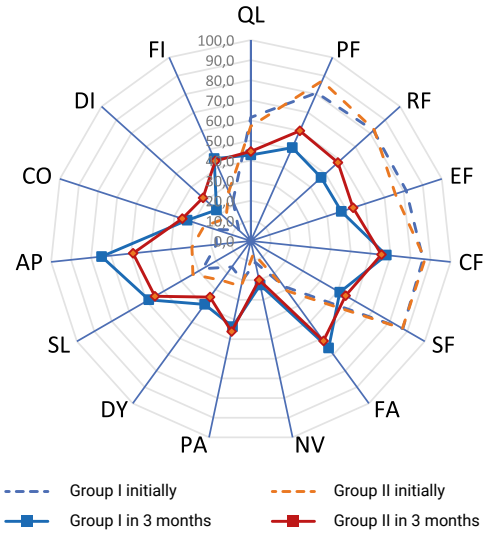

Fig. 2. Dynamics of quality of life according to the scales of the EORTC QLQ-C30 questionnaire in patients after GE, depending on the method of reconstruction 3 months after surgery. Group I – with preservation of the duodenal passage, group II – with reconstruction according to Roux-en- Y. QL – global state of health / quality of life; PF – physical functioning; RF – role functioning; EF – emotional functioning; CF – cognitive functioning; SF – social functioning; FA – fatigue; NV – nausea and vomiting; PA – pain; DY – dyspnea; SL – sleep disorders; AL – appetite loss; CO – constipation; DI – diarrhea; FI – financial difficulties

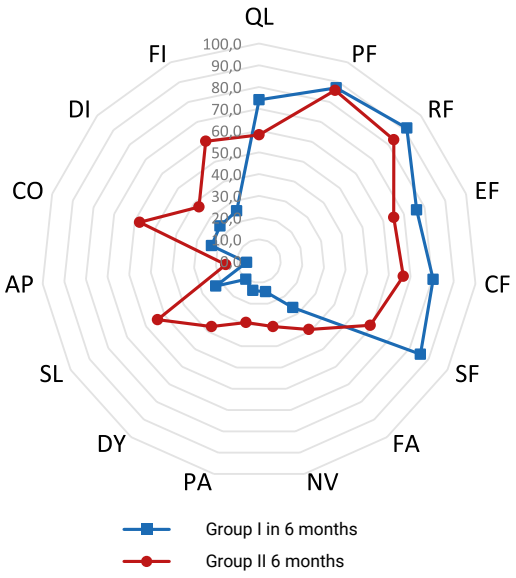

Fig. 3. Dynamics of quality of life according to the scales of the EORTC QLQ-C30 questionary in patients after GE, depending on the method of reconstruction 6 months after surgery. Group I – with preservation of the duodenal passage, group II – with reconstruction according to Roux-en- Y. QL – global state of health / quality of life; PF – physical functioning; RF – role functioning; EF – emotional functioning; CF – cognitive functioning; SF – social functioning; FA – fatigue; NV – nausea and vomiting; PA – pain; DY – dyspnea; SL – sleep disorders; AL – appetite loss; CO – constipation; DI – diarrhea; FI – financial difficulties

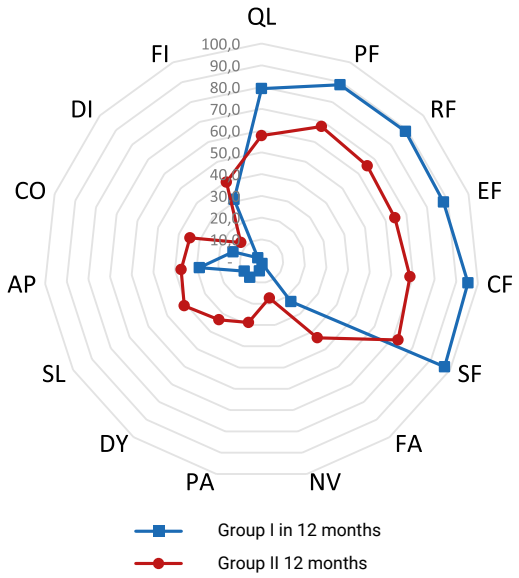

Fig. 4. Dynamics of quality of life according to the scales of the EORTC QLQ-C30 questionnaire in patients after GE, depending on the method of reconstruction 12 months after surgery. Group I – with preservation of the duodenal passage, group II – with reconstruction according to Roux-en- Y. QL – global state of health / quality of life; PF – physical functioning; RF – role functioning; EF – emotional functioning; CF – cognitive functioning; SF – social functioning; FA – fatigue; NV – nausea and vomiting; PA – pain; DY – dyspnea; SL – sleep disorders; AL –appetite loss; CO – constipation; DI – diarrhea; FI – financial difficulties

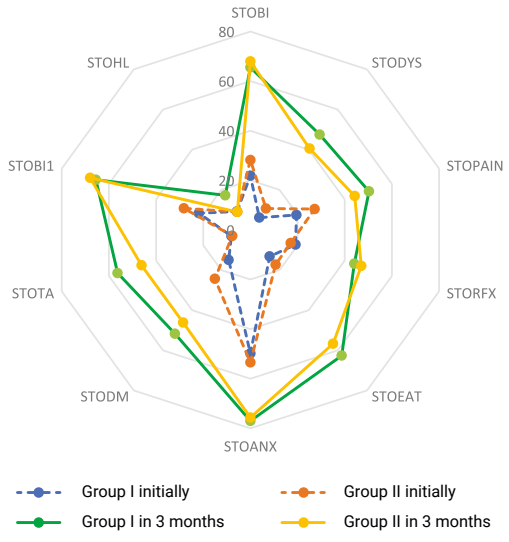

Fig. 5. Dynamics of QL values according to the scales of the QLQ-STO22 module in patients after GE, depending on the method of reconstruction 3 months after surgery. Group I – with preservation of the duodenal passage, group II – with reconstruction according to Roux-en- Y. STOBI – change in appearance; STODYS – dysphagia; STOPAIN – pain; STORFX– reflux symptoms; STOEAT – dietary restrictions; STOANX – anxiety; STODM– dry mouth; STOTA– taste change; STOHL – hair loss

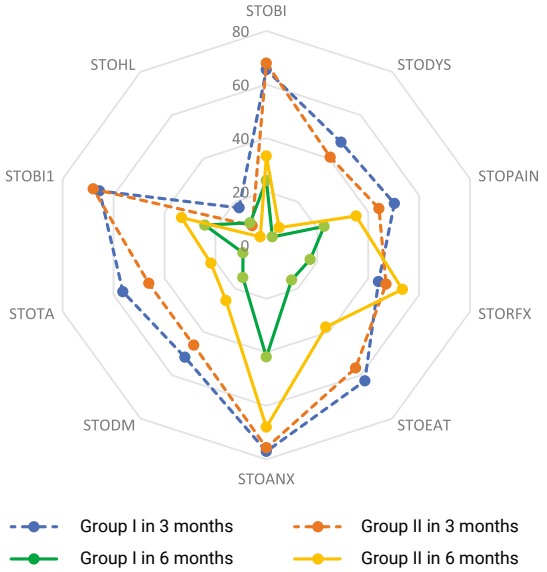

Fig. 6. Dynamics of QL values according to the scales of the QLQ-STO22 module in patients after GE, depending on the method of reconstruction 6 months after surgery. Group I – with preservation of the duodenal passage, group II – with reconstruction according to Roux-en- Y. STOBI – change in appearance; STODYS – dysphagia; STOPAIN – pain; STORFX– reflux symptoms; STOEAT – dietary restrictions; STOANX – anxiety; STODM– dry mouth; STOTA– taste change; STOHL – hair loss

After a sharp increase in the scales of symptoms within 3 months after surgery, which was equally pronounced in both groups of patients (Fig. 5), there was a decrease in the severity of symptoms by the time of 6 months, and this decrease was more pronounced in the group of patients after GE with PDP.

Statistically significant differences between the groups were noted on the scales of STODYS ($p = 0.007$), STOPAIN ($p = 0.038$), STORFX ($p < 0.001$), STOEAT ($p < 0.001$), STOANX ($p < 0.001$), STODM ($p = 0.045$), STOTA ($p = 0.004$). The differences were unreliable on the scales of STABI ($p = 0.135$) and STAHL ($p = 0.149$) (Fig. 6).

12 months after surgery, the general trend towards the advantage of the duodenal passage restoration group persisted. Statistically significant differences between the groups were noted on the scales of STODYS ($p = 0.007$), STOPAIN ($p = 0.038$), STORFX,000 STOEAT ($p < 0.001$), STOANX ($p < 0.001$), STODM ($p = 0.045$), STOTA ($p = 0.004$). The differences were not significant on the STOBI ($p = 0.135$) and STOHL ($p = 0.149$) scales. The differences on the STOBI scale reached the limits of statistical significance ($p < 0.001$), and the statistically significant advantage of the PDP group remained in terms of STODYS, STOPAIN, STORFX, STOEAT, STOANX, and STOTA. The differences in symptoms of STODM and STOHL were not significant (Fig. 7).

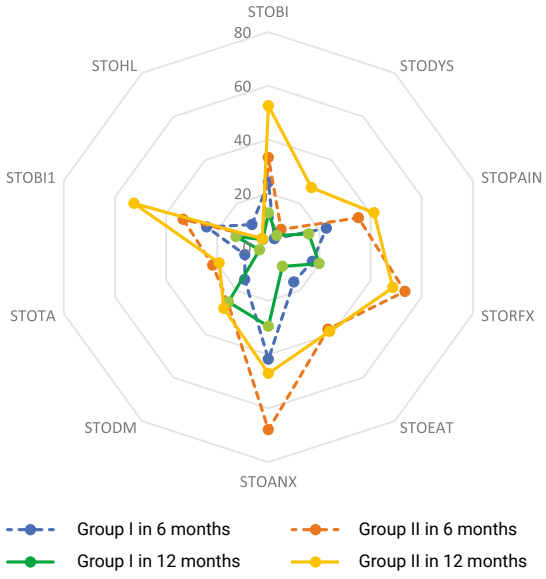

Fig. 7. Dynamics of QL values according to the scales of the QLQ-STO22 module in patients after GE, depending on the method of reconstruction 12 months after surgery. Group I – with preservation of the duodenal passage, group II – with reconstruction according to Roux-en- Y. STOBI – change in appearance; STODYS – dysphagia; STOPAIN – pain; STORFX– reflux symptoms; STOEAT – dietary restrictions; STOANX – anxiety; STODM – dry mouth; STOTA – taste change; STOHL – hair loss

CONCLUSION

The dynamics of quality of life on the EORTC QLQ-C30 scale with the STO22 module in patients with GC in the early stages after surgery (3 months) is characterized by a sharp decrease in total QOL and all scales of functioning and an increase in values on the scales of symptoms, later (6 and 12 months after surgery), the QOL parameters transform towards their improvements.

The dynamics of recovery of QOL parameters in patients with GC after surgical treatment depends on the status of the duodenal passage: in the group of patients with duodenal passage preservation, there is a faster positive dynamic of recovery of indicators on the scales of functioning and reduction of symptomatic scales than in patients without duodenal passage. Thus, the preservation of the duodenal passage during surgical treatment of GC has a positive effect on the dynamics of restoring the quality of life of patients, providing a positive contribution to the quality and results of antitumor treatment.

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Asipovich O. M. – performed development of the research design, data collection, analysis and interpretation, writing the draft;
Uvarov I. B. – performed development of the research design, analysis of the obtained data, writing the draft, critical revision with the introduction of valuable intellectual content;
Porkhanov V. A. – performed development of the research design, critical revision with the introduction of valuable intellectual content, final approval of the published version of the manuscript.

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ORIGINAL ARTICLE

Local levels of lymphocytes and cytokines in colon cancer patients with bowel obstruction

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ABSTRACT

Purpose of the study. To study local immunity and cytokine levels in colon cancer patients with subcompensated intestinal obstruction.

Patients and methods. In 60 patients with locally advanced left-side colon carcinoma (30 with and 30 without bowel obstruction) during the surgery samples of tumor, peritumoral area and resection line tissue were obtained. After disintegration of tissue samples T-, B-, NK-lymphocytes` subsets (CD3+, CD4+, CD8+, CD4+CD25+CD127dim, CD19+, CD16+CD56+) were studied by flow cytometry and inflammatory cytokines` content (TNF-α, IL-1α, IL-6, IL-8) via ELISA test.

Results. Higher levels of interleukins were shown in the tumors of patients in both groups compared to the tumor-free tissue samples. In the presence of subcompensated intestinal obstruction, local levels of proinflammatory cytokines were higher than in patients who did not have it: IL-6 and IL-1a in all tissues studied, IL-8 in tumor and peritumoral zone samples; TNF-α – in the tumor and the resection line. In the absence of intestinal obstruction in the tumor tissue, compared with non-tumor samples, the content of T-lymphocytes was increased due to CD4+ and CD8+, and Tregs levels were lower. These differences were leveled in the presence of intestinal obstruction, i. e. accumulation of T-lymphocytes in the tumor, providing adaptive immunity, was not observed in such patients. Their lower levels of CD8+ T cells and higher levels of Tregs in the tissue of the resection line form a low cytotoxic potential of the tissue remaining after surgery.

Conclusions. The presence of subcompensated intestinal obstruction in patients with colon cancer leads to a number of quantitative changes in local immunity factors compared with patients in whom it was not detected or was compensated. Among these changes, a particularly unfavorable content of pro-inflammatory cytokines, in particular IL-6, in the tissue of the resection line, along with a lower number of CD8+ T lymphocytes and a higher number of Tregs, which suggests a decrease in antiproliferative potential not only in the tumor, but also in non-tumor tissues.

Keywords: colon cancer, bowel obstruction, cytokines, lymphocytes, local immunity

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Локальные уровни лимфоцитов и цитокинов у больных раком ободочной кишки при субкомпенсированной кишечной непроходимости

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РЕЗЮМЕ

Цель исследования. Изучение факторов локального иммунитета и состава ряда интерлейкинов у больных раком ободочной кишки при субкомпенсированной кишечной непроходимости.
Пациенты и методы. У 60 больных местнораспространенным раком левого фланга ободочной кишки (30 с субкомпенсированной кишечной непроходимостью и 30 без нее) при проведении операции, выполненной первым этапом лечения, брали образцы тканей опухоли, перитуморальной зоны и линии резекции, в которых методом проточной цитометрии изучали состав субпопуляций Т-, В-, NK-лимфоцитов (CD3+, CD4+, CD8+, CD4+CD25+CD127dim, CD19+, CD16+CD56+), иммуноферментным методом – уровни цитокинов (IL-6, TNF-α, IL-1α, IL-8).
Результаты. Исследования показали более высокие уровни интерлейкинов в опухолях больных обеих групп, чем в неопухолевых тканевых образцах. При наличии субкомпенсированной кишечной непроходимости локальные уровни провоспалительных цитокинов были выше по сравнению с больными, у которых она не выявлена: IL-6 и IL-1α во всех исследованных тканях, IL-8 – в образцах опухоли и перитуморальной зоны; TNF-α – в опухоли и линии резекции. При отсутствии кишечной непроходимости в опухолевой ткани по сравнению с неопухолевыми образцами было повышено содержание Т-лимфоцитов за счет CD4+ и CD8+, а уровни Tregs были ниже. Эти различия нивелировались при наличии кишечной непроходимости, т. е. накопления в опухоли Т-лимфоцитов, обеспечивающих адаптивный иммунитет, у таких больных не наблюдалось. Более низкий уровень у них CD8+ Т-клеток и более высокий – Tregs в ткани линии резекции формирует низкий цитотоксический потенциал ткани, остающейся после операции.
Заключение. Наличие у больных раком ободочной кишки субкомпенсированной кишечной непроходимости приводит к ряду количественных изменений факторов локального иммунитета по сравнению с больными, у которых она не выявлена или была компенсированной. Среди этих изменений представляются особенно неблагоприятными более высокое содержание провоспалительных цитокинов, в частности, IL-6, в ткани линии резекции, наряду с более низким количеством CD8+ Т-лимфоцитов и более высоким – Tregs, что предполагает снижение антипролиферативного потенциала не только в опухоли, но и в неопухолевых тканях.

Ключевые слова: рак ободочной кишки, кишечная непроходимость, цитокины, лимфоциты, локальный иммунитет

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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 медицинской этике ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (выписка из протокола заседания № 2 от 22.01.2021 г.). Информированное согласие получено от всех участников исследования

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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Bowel obstruction (BO) is one of the most common complications. It is described in 20 % of cases of colon cancer, with the predominant frequency in its left flank [1]. Mechanical BO is a consequence of the cessation of the passage of chyme through the intestine due to complete or partial obstruction of its lumen, accompanied by intoxication and several metabolic, microbiological, immunological, and other disorders. As indicated in the Clinical Recommendations of 2023, the modern classification of BO that occurs in patients with colon cancer divides it according to the degree of compensation into compensated (intermittent constipation accompanied by delayed stools and difficulty in gas discharge; abdominal X-ray may show pneumatization of the colon with single fluid levels in it); subcompensated (delayed bowel movements, stool and gases for less than 3 days, small intestinal arches, pneumatosis and Cloiber's bowls in the right half of the abdomen are determined on the X-ray; there are no signs of polycranial dysfunctions; conservative therapy is effective); decompensated (retention of stool and gases for more than 3 days; radiological signs of both large and small intestinal obstruction with localization of small intestinal levels and arches in all parts of the abdominal cavity; vomiting with stagnant contents; the presence of organ dysfunctions [2]. Disorders caused by BO affect various processes. Stretching of the proximal intestine leads to stagnation of intestinal contents, buildup of toxic products, and increased inflammatory processes [3]. At the same time, the barrier function of the intestinal mucosa suffers, dysbiotic changes and bacteremia develop with the risk of peritonitis and endotoxemia [4], which are accompanied by a massive release of cytokines [5]. Many of them are tropic to vascular endothelium and cause microcirculation disorders with microthrombosis, which can also lead to necrosis of the intestinal wall with the possibility of perforation.

Immunological changes, especially local ones, in BO have been studied poorly and mainly experimentally. Therefore, an experimental model of partial obstruction of the distal colon has shown that it causes depletion of both B-lymphocytes and both major T-cell subpopulations in lymphoid organs [6]; the authors attribute this to a violation of the composition of the microbiota, hyperproduction of IL-6, corticosterone and osteopontin. The BO model shows an increase in the permeability of the colon mucosal barrier and translocation of the microbiota, which, according to the authors, also causes adverse immunological changes [7].

However, when analyzing the clinical material, attention is paid to many factors of the development of BO in patients with colon cancer (late diagnosis, macroscopic tumor morphology, vascularization and thickness of the intestinal wall, peristalsis activity), but the state of immunity is not mentioned, which indicates the unexplored nature of this problem, as shown in a recent review [1]. Only a few studies can be indirectly related to this topic: for example, the difference in the metabolome in patients with non-cancerous and tumor BO was considered, and in the latter case, the predominance of tryptophan metabolism disorders was noted [8], and, as is known, the products of altered metabolism of this amino acid have significant immunosuppressive and pro-oncogenic effects [9].

The purpose of the study was to study the factors of local immunity and the composition of several interleukins in the tissues of patients with colon cancer with subcompensated intestinal obstruction.

PATIENTS AND METHODS

The study included 2 groups of patients with locally advanced colon cancer (left side): 30 patients with subcompensated BO and 30 patients without obstruction (total n = 60). The study was approved by the Committee on Medical Ethics of the National Research Medical Center for Oncology (extract from the minutes of meeting No. 2 dated 01/22/2021. Informed consent was received from all participants in the study. Female patients prevailed in each group (54 and 56 %, respectively), the average age was 64 ± 5.5 and 65 ± 6.3 years, respectively. There were no significant differences between the groups in terms of gender, age, and the presence of concomitant diseases. Radical surgical interventions were performed in all patients during the first stage of treatment.

The exclusion criteria were the presence of preoperative drug treatment, the presence of infectious complications and peritonitis, tumor localization in the right side of the colon, decompensated intestinal obstruction.

The diagnosis of BO caused by a tumor was established preoperatively clinically and radiographically.

To assess local cellular immunity and cytokine composition, tumor tissue samples (TTS) were taken during surgery, as well as visually unchanged tissue sections, moving away proximally 1–3 cm (peritumoral zone, PZ) and 10 cm (resection line, RL) from the edge of the tumor. The concentration of interleukins (IL-1α, IL-6, IL-8) and tumor necrosis factor (TNF-α) was determined in the homogenates of the obtained tissue samples by ELISA using Vector-Best test systems (Novosibirsk) with the calculation of the specific content (per 1 g of protein determined by the biuretic method). The levels of lymphocytic subpopulations were determined in the homogenates of tissue samples using flow cytometry (FACS Canto II, BD) using the T-B-NK panel, the results were expressed as a percentage.

Statistical analysis

Statistical analysis of the results of the study was carried out using the Statistica 13.3 program (StatSoft, USA). The normality of the distribution was checked using the Shapiro-Wilk criterion. Since the distribution of the data was not normal, the Mann-Whitney criterion was used for their statistical processing; quantitative indicators were presented as the median of both the lower and upper quartiles (Me; LQ; UQ). Intergroup differences were considered statistically significant at $p < 0.05$.

STUDY RESULTS

The amount of total protein in the studied tissues did not differ significantly, the variability of data on this indicator is insignificant. The specific content of pro-inflammatory cytokines in the homogenates of the studied tissue samples of patients in the main and control groups is shown in Table 1.

As can be seen from the data presented in Table 1, the content of the studied cytokines in the tumor was statistically significantly higher than their levels in samples of both non-tumor tissues, and this was observed in both compared groups regardless of the presence of BO. Thus, in patients of both groups, the content of all cytokines studied did not differ between the peritumoral region and the resection line, and in the tumor tissue it was higher than in both non-tumor tissues.

An intergroup comparison of tissue cytokine levels revealed that the presence of BO is accompanied by a higher content of TNF-α, IL-6, IL-8, and IL-1a in tumor tissue (by 1.7, 2.2, 1.7, and 2.6 times, respectively) than in the absence of BO (for all cytokines, $p < 0.05$). The levels of IL-6, IL-8, and IL-1a in the PZ tissue of patients with BO were also statistically significantly higher than in patients without BO: 6.3, 2.3, and 2 times, respectively. In the tissue of the resection line with BO, the levels of IL-1a were 2.7 times

Table 1. Specific cytokine content in colon tumor tissues, peritumoral zone, and resection line of colon cancer patients with absence and presence of BO

Tissue samples	Specific content of cytokines (pg/g protein)							
	TNF-α		IL-6		IL-8		IL-1α	
	No BO	BO	No BO	BO	No BO	BO	No BO	BO
Tumor, Me	1.5* **	2.6* ** Δ	7.0* **	15.5* ** Δ	23.2* **	41.3* ** Δ	20.3* **	52.3* **Δ
LQ	1.0	2.3	4.5	12.8	19.5	33.4	13.5	38.9
UQ	2.1	3.1	10.0	18.7	28.7	45.8	23.6	60.7
Peritumoral zone, Me	0.5	0.9	0.8	5.1 Δ	8.2	19.2 Δ	9.2	18.1Δ
LQ	0.2	0.5	0.3	3.2	5.5	15.5	5.7	14.0
UQ	1.0	1.5	1.0	11.4	11.2	22.7	13.1	26.2
Resection line, Me	0.5	1.3 Δ	1.2	5.5 Δ	10.1	13.0	7.0	19.0 Δ
LQ	0.3	1.0	0.6	3.5	6.7	9.7	4.8	15.7
UQ	1.0	1.8	1.4	8.9	12.5	15.5	10.2	22.6

Note: * – differences from the PZ indicator; ** – differences from the RL indicator; Δ – differences between groups ($p < 0.05$)

higher, and IL-6 was 4.6 times higher than in patients without BO ($p < 0.05$). As can be seen from Table 1, the IL-6 content had the maximum differences between the compared groups in the samples of non-tumor tissues (PZ and RL) (in all cases, $p < 0.05$), and the differences in TNF-α were minimal.

The content of T-lymphocytes of the main subpopulations in the studied tissue samples of patients of the compared groups is shown in Table 2, which shows that the total number of T-cells (CD3+) in the tumor tissue of patients without BO was statistically significantly higher than in patients with subcompensated BO. These differences were observed due to higher levels of both major T-lymphocyte subpopulations (CD4+ and CD8+), while the Tregs content in these patients was 2 times lower; for all T cells, $p < 0.05$. There were no statistically significant differences between the groups in PZ, however, higher Tregs levels with lower CD8+ levels were detected in the RL tissue of patients with BO. It should be noted that in the presence of BO, the T-cell composition of PZ and RL had no statistically significant differences from the tumor tissue, whereas in the absence of BO, it was expressed in CD3+, CD4+ and CD8+ levels, which in the tumor tissue exceeded their content in non-tumor samples by 1.5–2 times.

The assessment of the content of natural killers in tumor tissue samples of patients without BO showed its higher value in PZ tissue compared with the tumor (Me 10.1 [6.4;12.5] and 4.1 [2.9;5.0] %), respectively ($p < 0.05$), which was not observed in patients with BO, in whom the level of these cells in the tumor, although it was slightly higher than in the non-tumor samples, however, without statistical significance. There were also no intergroup differences in this indicator.

The content of B-lymphocytes in the PZ and RL of both patients with and without BO was statistically significantly higher than in the tumor. Their level was minimal in the tumor samples of patients with BO (Me 4.7 [3.3;6.0] versus 19.2 [11.0;23.5] % with BO), and there were no intergroup differences in the tissues of PP and LP (in PZ of patients with BO 37.0 [24.4;41.2] versus 29.3 [15.5;34.2] without BO; in RL 37.2 [28.5;41.4] versus 29.2 [20.2;33.5] %, respectively, $p > 0.05$).

DISCUSSION

We noted a number of differences between cellular and cytokine factors in patients with colon cancer of the left flank with the presence of subcompensated BO and the absence or compensated BO. Subcompensated BO is accompanied by a number of unfavorable differences. First of all, it is a high level of tissue pro-inflammatory cytokines, including IL-6, which is

Table 2. The content of T-lymphocyte subpopulations in colon cancer tissues, peritumoral zone, and resection line of colon cancer patients with absence and presence of BO

Tissue samples	T-lymphocyte subsets (%)							
	CD3+		CD4+		CD8+		Tregs	
	No BO	BO	No BO	BO	No BO	BO	No BO	BO
Tumor, Me	88.0* **	62.2 Δ	51.4* **	39.2 Δ	38.2*	21.5 Δ	7.1	15.2 Δ
LQ	69.2	50.4	46.3	29.3	31.3	15.2	3.3	11.4
UQ	91.1	67.6	59.8	45.0	44.6	28.3	9.1	21.0
Peritumoral zone, Me	63.0	55.2	33.5*	34.3	26.2	19.9	4.4	12.0
LQ	55.4	48.4	27.4	24.2	18.0	13.3	3.1	5.8
UQ	67.2	66.1	40.1	38.1	30.4	31.4	4.9	14.9
Resection line, Me	65.6	60.2	25.1*	27.4	44.5**	25.8 Δ	3.9	9.8 Δ
LQ	61.5	52.9	14.9	21.1	35.2	18.9	1.9	4.7
UQ	68.0	69.9	30.7	30.2	47.9	30.3	4.6	12.5

Note: * – differences from the PZ indicator; ** – differences from the RL indicator; Δ – differences between groups ($p < 0.05$)

well known to have pro-oncogenic and pro-angiogenic effects, contributing to invasion, metastasis, and epithelial-mesenchymal transition [10– 11]. Its high content not only in the tumor, but also in non-cancerous tissues, primarily in the resection line, may characterize the condition of the latter as less favorable than in patients without BO. Other cytokines we studied also create a microenvironment that promotes tumor growth and spread. The pro-oncogenic effect of IL-6 is mediated through the transcription factor STAT3, and TNF-α through NF-kB, the synergistic activation of which causes the growth of colorectal cancer cells [24]. Similar properties have been described for IL-1 [25] and IL-8 [26].

As for the local content of lymphocytes, the differences we found between patients with and without BO relate primarily to the T cell population: in the presence of subcompensated BO, their levels turned out to be lower than in the absence of it, due to the lower content of both T helper cells and cytotoxic lymphocytes (CTL). The higher Tregs level found in patients with BO, along with a low CD8+ cell count, suggests a low cytotoxic potential of the tissue, which is especially important for the resection line. The importance of the immunological microenvironment of the tumor has been repeatedly described in the literature both in terms of prognosis and for effective immunotherapy, in particular, with immune checkpoint inhibitors, as well as chemotherapy [12, 13–16]. The literature attaches great prognostic importance to locally present T lymphocytes – their number and subpopulation composition, primarily the content of CD8+ T cells, as well as their functional activity [17–22]. In the occurrence and progression of a malignant tumor, in the colon, "immunoredaction" plays an important role, i. e. The accumulation of immune system factors in it that can exhibit pro-oncogenic rather than antitumor effects [23]. Apparently, BO, which causes a violation of the composition of the microbiota and passage of intestinal contents, contributes to the development of this process.

CONCLUSION

Thus, we have established that the presence of subcompensated intestinal obstruction in patients with colon cancer leads to a number of quantitative changes in local immunity factors and tissue cytokine content compared with patients in whom it was not detected or was compensated. Among these changes, the higher content of pro-inflammatory cytokines (IL-6, IL-1a, TNF-α) in the tissue of the resection line is particularly unfavorable, along with a lower number of CD8+ T lymphocytes and a higher number of Tregs, which suggests a decrease in the antiproliferative potential of the tissue remaining in the patient's body after surgery. interventions in patients with colon cancer complicated by intestinal obstruction.

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Bondarenko E. S. – conducting studies;
Maksimov A.Yu. – development of the concept;
Maslov A. A. – statistical analysis, analysis of the results;
Snezhko A. V. – statistical analysis, analysis of the results.

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ORIGINAL ARTICLE

In vivo microcomputed tomography visualization of a hepatocellular carcinoma orthotopic model using a contrast based on LaF_3:Ce(5 %)Tb(15 %) nanoparticles

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ABSTRACT

Purpose of the study. To investigate the effectiveness of a new contrast agent based on LaF_3:Ce(5 %)Tb(15 %) nanoparticles on a hepatocellular carcinoma orthotopic model.

Materials and methods. The experiment was performed on female BALB/c Nude mice. The subcutaneous model was created by injecting Hep G2 tumor cell culture into the right side of the animals. The orthotopic models were obtained by implanting a fragment of a subcutaneous Hep G2 xenograft into the left lobe of the liver of mice. Colloidal water solutions of LaF_3:Ce(5 %) Tb(15 %) nanoparticles were prepared by dispersing the nanoparticle powder in bidistilled water using an ultrasonic tube for 30 minutes. Two samples with different nanoparticle sizes (13 and 60 nm) were administered to mice intravenously in a volume of 200 µl at a concentration of 40 mg/ml. The assessment of changes in radiopacity of the internal organs of animals was carried out at different points in time (before nanoparticle injection, at 5 min, 30 min, 1 h, 2 h, 4 h, 24 h, 48 h, and 7 days after inlection) using microcomputer tomography on a Quantum GX2 device. On the 7th day of the experiment, animals were euthanized by dislocation of the cervical vertebrae, organs (liver and spleen) were collected and fixed in a 10 % solution of neutral formalin. Sections for histological examination and their staining were made according to the standard method.

Results. Microcomputer tomography (micro-CT) results indicated accumulation of both contrast samples in the spleen and healthy liver tissue within 5 minutes after intravenous injection, maintaining X-ray contrast for the 7-days. However, no specific accumulation of nanoparticles in the tumor was observed. Histological analysis revealed minimal impact on the liver structure and cells, with a more pronounced effect in the spleen.

Conclusion. These findings suggest that LaF_3:Ce(5 %)Tb(15 %) metal nanoparticles can be used in *in vivo* experiments for liver and spleen visualization after further investigation of their long-term effects.

Keywords: microcomputed tomography, hepatocellular carcinoma, HepG2, CDX model, mouse model, nanoparticles

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Compliance with ethical standards: the study was reviewed and approved by the local bioethical committee of the National Medical Research Centre for Oncology (Protocol No. 9/219). All animal experiments were performed in accordance with the ethical principles established by the European Convention for the Protection of Vertebrates

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Микрокомпьютерная визуализация *in vivo* ортотопической модели гепатоцеллюлярной карциномы с применением контраста на основе наночастиц LaF_3:Ce(5 %)Tb(15 %)

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РЕЗЮМЕ

Цель исследования. Исследование эффективности нового контрастного агента LaF_3:Ce(5 %)Tb(15 %) на ортотопической модели гепатоцеллюлярной карциномы.

Материалы и методы. Эксперимент выполнен на самках мышей линии BALB/c Nude. Подкожная модель была получена введением в правый бок животных опухолевой культуры клеток Hep G2. Модель ортотопической гепатоцеллюлярной карциномы получили путем имплантации в левую долю печени мышей фрагмента подкожного ксенографта Hep G2. Коллоидные водные растворы наночастиц LaF_3:Ce(5 %)Tb(15 %) готовили путем диспергирования порошка нанокристаллов в бидистиллированной воде с помощью ультразвуковой трубки в течение 30 минут. Два образца наночастиц с разными размерами (13 и 60 нм) однократно вводили мышам внутривенно в объеме 200 мкл в концентрации 40 мг/мл. Оценка изменения рентгеноконтрастности внутренних органов животных проводилась в разных временных точках (до введения наночастиц, через 5 мин., 30 мин., 1 ч., 2 ч., 4 ч., 24 ч., 48 ч. и 7 дней после введения) с помощью микрокомпьютерной томографии на приборе Quantum GX2. На 7-й день эксперимента выполняли эвтаназию животных методом дислокации шейных позвонков, забор и фиксацию в 10 % растворе нейтрального формалина органов (печень и селезенка). Изготовление срезов для гистологического исследования и их окрашивание проводилось по стандартной методике.

Результаты. Микрокомпьютерная томография показала накопление обоих образцов контраста в селезенке и здоровой ткани печени уже через 5 минут после его внутривенного введения животным с сохранением рентгенконтраста в течение всех 7 дней эксперимента. Однако не было замечено специфического накопления наночастиц в опухоли. Гистологический анализ показал слабое воздействие на структуру и клетки печени и более выраженное – в селезенке.

Заключение. Наши результаты показывают, что металлические наночастицы LaF_3:Ce(5 %)Tb(15 %) могут быть использованы в экспериментах *in vivo*, где требуется визуализация печени и селезенки, после дополнительных исследований их долгосрочного влияния.

Ключевые слова: микрокомпьютерная томография, гепатоцеллюлярная карцинома, HepG2, CDX-модель, мышиная модель, наночастицы

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Соблюдение этических стандартов: исследование было рассмотрено и одобрено локальным биоэтическим комитетом ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации (протокол № 9/219). Все эксперименты на животных были выполнены в соответствии с этическими принципами, установленными Европейской конвенцией по защите позвоночных животных

Финансирование: исследование выполнено при финансовой поддержке Министерства науки и высшего образования Российской Федерации в рамках государственного задания в сфере научной деятельности № FENW-2023-0019

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

In vivo models on small laboratory animals have made a significant contribution to the study of the pathogenesis and development of cancer treatment methods, including liver cancer, which, according to Global Cancer Statistics for 2022, is the third leading cause of cancer death among both sexes [1]. Hepatocellular carcinoma (HCC) is the main histological type of liver cancer characterized by rapid progression and unfavorable prognosis. Despite the fact that new opportunities for screening programs, advanced diagnostic methods and treatments for HCC have emerged over the past decade, morbidity and overall survival rates remain unsatisfactory [2–3].

The creation of new drugs to improve the results of HCC treatment requires easily reproducible adequate models that are created by injecting tumor cell culture or implanting a tumor fragment in immunocompromised mice at a heterotopic (most often subcutaneous) or orthotopic site. The first option is easy to implement, the tumor nodes are available for measurements, which makes it easy and effective to track the response to treatment. The second option has the advantage of simulating the tumor-host interaction, organ-specific conditions, invasion and metastasis, and responses to therapy. However, it is technically more difficult: certain skills are required from the researcher, and tumor growth must be controlled using additional equipment [4].

Over the past decade, the number of publications using microcomputer tomography (micro-CT) in *in vivo* significantly increased. Even though micro-CT initially showed good images of only high-contrast structures, noticeable improvements in spatial and temporal resolution were achieved, which allowed researchers to obtain detailed anatomical images and track the progression of the disease in small laboratory animal models. In addition, contrast agents are used to increase the contrast of soft tissues [5–6].

Metal nanoparticles are a suitable candidate for use as contrast agents for micro-CT. Metal atoms have high atomic numbers and exceptional X-ray attenuation properties, therefore they provide a higher contrast enhancement than iodine preparations used in medical practice at the same concentration [7]. Depending on the purpose of the study, they can be modified: the size of the nanoparticles is changed, they are coated with organic molecules to increase biocompatibility, functional groups are added to increase specificity to certain tissues, which expands the possibility of their use not only in diagnosis, but also in cancer therapy [8–9].

The purpose of the study was to evaluate the effectiveness of a new contrast agent based on nanoparticles – LaF_3:Ce(5 %)Tb(15 %) on an orthotopic model of hepatocellular carcinoma.

MATERIALS AND METHODS

Female Balb/c Nude mice aged 10–12 weeks were taken into the experiment. The animals were kept at a temperature of 22 °C ± 1 °C, humidity 55 % ± 15 % and a 12/12-hour day/night cycle. Food and water were provided to the animals "ad libitum".

The culture of human hepatocellular carcinoma Hep G2 was used in the work. Tumor cells were cultured in DMEM medium (Gibco, Thermo Fisher Scientific), with 10 % veal serum (Gibco, Thermo Fisher Scientific) and 1 % antibiotic (penicillin/streptomycin), in a CO2 incubator (series 8000W, Thermo Fisher Scientific, USA) with a content of 5 % CO2 and a temperature of 37 °C.

All manipulations were performed under sterile conditions. Two female Balb/c Nude mice were subcutaneously injected with a tumor culture of Hep G2 cells at a concentration of 5×10^6 cells in 200 µl (Fig. 1a) in the right side. When the tumor nodes reached a volume of about 100 mm³, the animals were euthanized by dislocation of the cervical vertebrae, the xenographs were extracted and cut into fragments of 1 mm³ in size. Donor animals (10♀) were anesthetized according to the protocol described earlier [10].

Mice were placed on their backs, the skin and abdominal wall were excised along a white line of the abdomen measuring 30–40 mm and the left lobe of the liver was exposed, into which a previously isolated tumor fragment was implanted (Fig. 1b). Next, the liver was returned to the abdominal cavity, the abdominal wall and skin were sutured with a continuous surgical suture.

Measurement of the linear dimensions of subcutaneous xenografts was performed twice a week. The tumor volume was determined according to the formula:

$V = LW^2/2$,

where *L*, *W*, represent the linear sizes of the tumor nodes.

Two samples of LaF_3:Ce(5 %)Tb(15 %) nanoparticles were used in the work with different sizes (13 and 60 nm), which were obtained by hydrothermal synthesis. To obtain nanoparticles with different average sizes, synthesis was carried out at room temperature (size ~ 13 nm) and at 400 °C (size ~ 60 nm). Colloidal water solutions of LaF_3:Ce(5 %)Tb(15 %) nanoparticles were prepared by dispersing nanocrystal powder in bidistilled water using an ultrasonic tube for 30 minutes. The resulting solutions were administered once intravenously to mice in a volume of 200 µl at a concentration of 40 mg/ml (two groups of 5 animals each).

Microcomputer tomography was performed on a Quantum GX2 microCT device (Perkin Elmer, USA). During the scan, the animals were anesthetized with 2 % isoflurane (Laboratories Karizoo, S.A., Spain) using a RAS-4 anesthesia device (Perkin Elmer, USA). A total of 9 scans were performed for each mouse: before nanoparticle injection, 5 min, 30 min, 1 h, 2 h, 4 h, 24 h, 48 h and 7 days after administration. The scanning parameters were as follows: voltage – 80 kV, current – 90 µA, field of view – 86 mm × 72 mm, voxel size – 140 microns, scanning mode – high resolution, time – 4 min, 360° gentry rotation. The resulting images were analyzed in the Quantum GX2 software (Perkin Elmer, USA). The data was analyzed using Statistica 10 and presented as the "mean ± standard error of the mean".

7 days after the introduction of contrasts and the final scan, the animals were euthanized by dislocation of the cervical vertebrae. Fragments of the spleen and liver with tumor nodules were placed in a 10 % formalin solution for 24 hours. The fixed tissues were then poured into paraffin wax and, using a microtome, sections with a thickness of 5 microns were made onto positively charged specimens. The specimens were stained with hematoxylin and eosin. The finished histological preparations were examined by a pathologist.

STUDY RESULTS

A significant increase in contrast between the spleen and normal liver tissue was observed compared with the results obtained before the administration of the studied substances as early as 5 minutes after the introduction of 60 nm nanoparticles and 30 minutes after the introduction of 13 nm nanoparticles. The following scans, after 1, 2 and 4 hours, show the accumulation of contrasts in these organs (Fig. 2). There was no change in radiopaque contrast in the tumor tissue. After 24 hours, nanoparticles are slightly washed out of the liver,

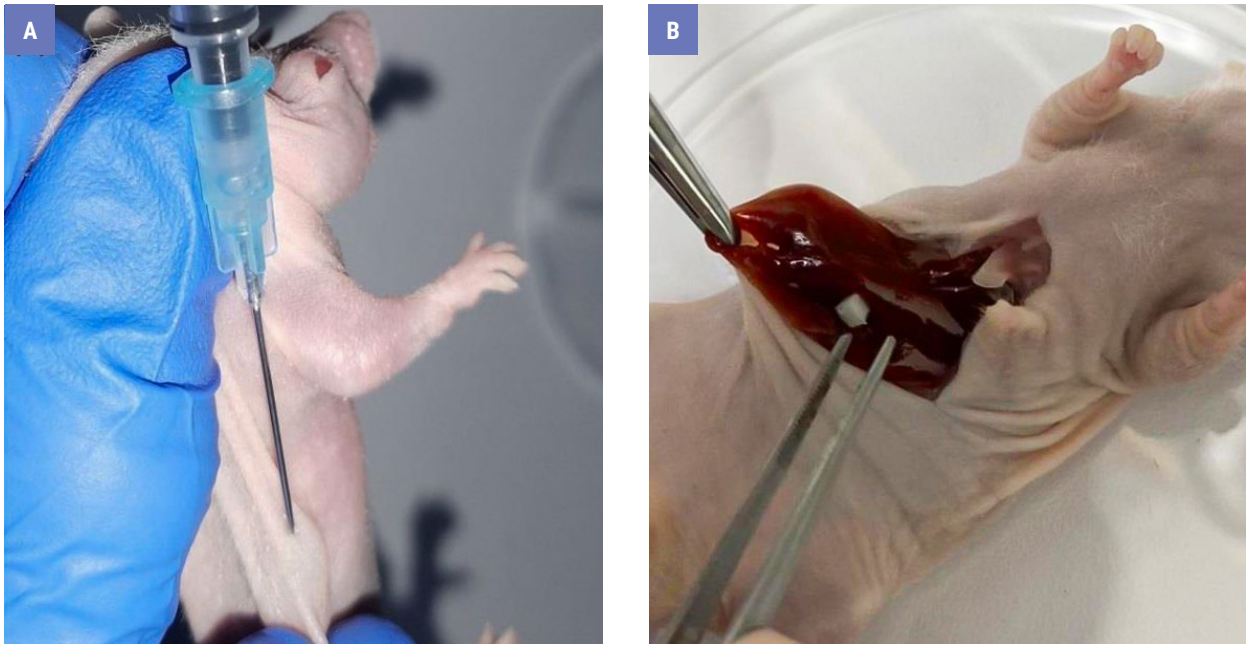

Fig. 1. The stages of an orthotopic HCC CDX model creation: a – subcutaneous injection of the HepG2 cell line with a sterile insulin syringe; b – transplantation of a tumor fragment into the left lobe of the liver

but they continue to accumulate in the spleen. The same dynamics is observed on scans performed after 48 hours and 7 days. There was no significant difference between the measured contrast enhancement of organs such as tumors, heart, and kidneys during the entire experiment.

The weight of the injected animals decreased slightly on the first and second days after the administration of contrasts and stopped after the 3rd day of the experiment (the total weight loss for each mouse was less than 10 %). On day 6, the weight of the mice returned to their initial values. There were no changes in other physical parameters and behavior of the animals during 7 days.

Before organ sampling, a macroscopic examination was performed for histological analysis. The liver of the mice had a red-brown color, and a tumor node was clearly visible in the left lateral lobe. The remaining 3 lobes of the liver – the right inner one with a mastoid process, the right lateral one with a caudate process and the left inner one were unchanged. The spleen of both animals was lighter than normal, enlarged, and free of blotches. No other internal organs were found to have pathological changes caused by the introduction of nanoparticles.

On all histological preparations, the liver retains its histostructure. Hepatocytes are arranged in thin trabeculae separated by sinusoidal vessels. The triads, portal tracts, and central veins are clearly distinguishable (Fig. 3a, b). Histological preparations (Fig. 3b, d) show that the tumor is clearly bounded from the normal liver tissue. Histopathological examination 7 days after the introduction of contrasts (Fig. 3c, d) showed that ectasia of the central veins is observed in the liver, mild inflammation, hepatocytes are slightly enlarged, their nuclei are larger with a finely dispersed chromatin distribution. In all samples, the lymphoid tissue of the spleen was divided by thin trabeculae and had the same density as the follicles in it. Reactive hyperplasia of lymphoid tissue and weak infiltration by macrophages were observed in the spleens of mice injected with contrast (Fig. 3g, h).

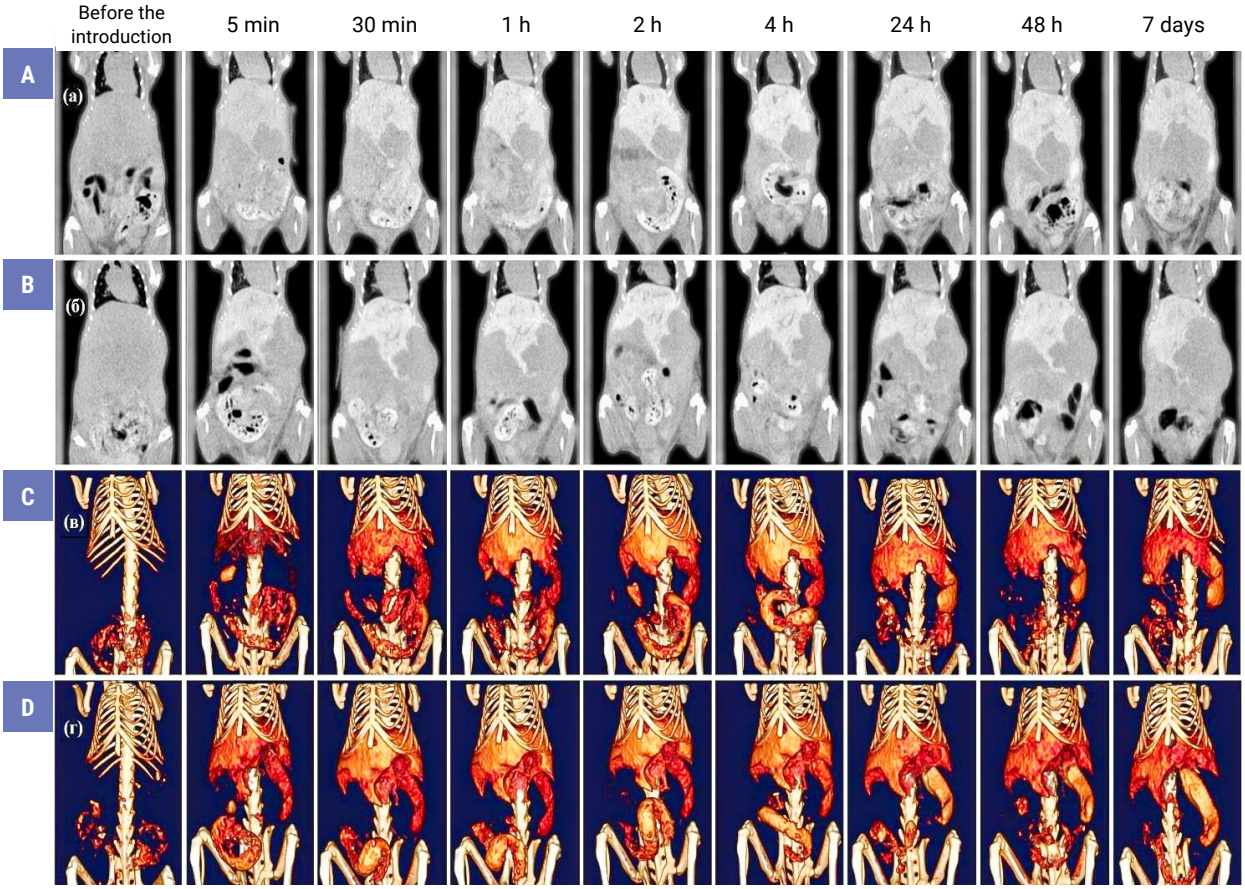

Fig. 2. *In vivo* microcomputer tomography results in 5 min, 30 min, 1 h, 2 h, 4 h, 24 h, 48 h and in 7 days after administration of LaF3: Ce(5 %)Tb(15 %) with nanoparticle size: a, c – 13 nm; b, d – 60 nm. a, b – CT images in coronal projection; c, d – 3D images

DISCUSSION

X-ray microcomputer tomography has gained great importance in recent decades. *In vivo* visualization of soft tissues of small laboratory animal models has become popular due to the introduction of various radiopaque substances that help to circumvent the limitation of low contrast of internal organs [6]. Metal nanoparticles can be used for this purpose, since metals have high X-ray attenuation and high density. Nanoparticles can also provide X-ray contrast for a long time [9].

In our work, we used LaF_3:Ce(5 %)Tb(15 %) nanoparticles of different sizes in orthotopic tumor models of HCC. The Hep G2 tumor cell line was used to create them. However, when trying to create a HCC model using the injection method, negative consequences arise: leakage of cell suspension from the puncture site and ingress into the abdominal cavity and, as a result, the formation of tumor nodules in other tissues and organs of the animal [11]. Therefore, in our work, we first obtained a subcutaneous xenograft from a cell line, and then it was used to create an orthotopic model of HCC.

Basic images (before contrasting) of xenographs were made on micro-CT for further visual and quantitative assessment of the effectiveness of the tested contrasts. After the introduction of LaF_3:Ce(5 %)Tb(15 %) nanoparticles showed rapid distribution in the tissues of the spleen and nor-

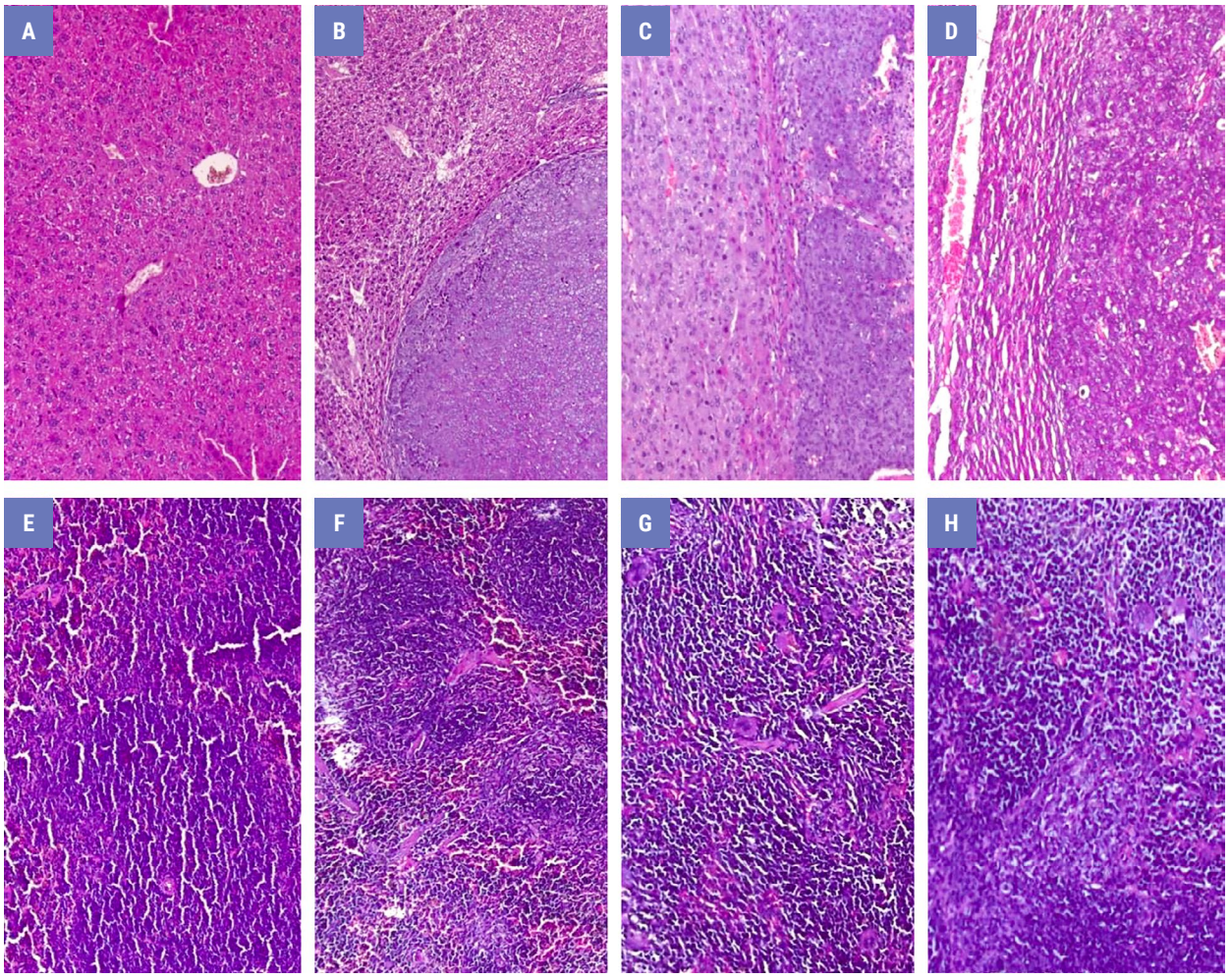

Fig. 3. Histopathological examination of the liver and spleen (100x): a – normal liver; b – liver with tumor without exposure; c – liver with tumor 7 days after administration of LaF3 nanoparticles: Ce(5 %)Tb(15 %) with a size of 13 nm; d – liver with a tumor 7 days after administration of LaF3: Ce(5 %)Tb(15 %) nanoparticles 60 nm in size; e – normal spleen; f – spleen taken from a mouse with a tumor in the liver, without exposure; g – spleen 7 days after administration of LaF3: Ce(5 %)Tb(15 %) nanoparticles with a size of 13 nm; h – spleen 7 days after administration of LaF3: Ce(5 %)Tb(15 %) nanoparticlessize 60 nm

mal liver tissue, high absorption in the X-ray range, and provided X-ray contrast during 7 days of the experiment. Nanoparticles with a size of 13 nm reached their maximum accumulation in the liver (241.18 ± 6.07 HU) 4 hours after their administration. Then there was a slow weakening of the radiopaque contrast in the organ. Accumulation in the spleen occurred gradually, and the maximum value of HU units was obtained on the last day of the experiment (272.4 ± 9.9 HU). A similar dynamic was observed for the second sample with a nanoparticle size of 60 nm. The maximum accumulation in the liver (230.19 ± 8.84 HU) was reached 30 minutes after the introduction of contrast, after which the radiopaque contrast in the organ weakened. For the spleen, the maximum value of HU units was also obtained on the last day of the experiment, but it was higher than the results obtained from the first sample (311.95 ± 9.36 HU).

There were no changes in the contrast ability of the other organs of the animals during the entire observation period. There was also no accumulation of contrast in tumor tissues, as, for example, in a study where gold nanoparticles with an average size of 50 nm were used, which were injected intravenously into a mouse model of breast cancer at a concentration of 4.8 mg/kg and a mouse model of fibrosarcoma at a concentration of 9.6 mg/kg [12]. The researchers noted the accumulation of nanoparticles in the tumor tissue of both models. The biodistribution could be influenced by the difference in the metals included in the nanoparticles, the presence of polyethylene glycol (PEG) coating on gold nanoparticles, the use of different tumor models, etc. We assume that the non-penetration of nanoparticles into the tumor nodes was due to their low vascularization. Therefore, additional studies using other *in vivo* tumor models are required.

Histological analysis revealed that both samples did not affect tumor cells, but caused mild inflammation in the liver and reactive hyperplasia in the spleen. As a rule, nanoparticles are removed from the bloodstream mainly by Kupffer cells of the liver and macrophages of the spleen [13], which explains the presence of the latter on histological preparations.

CONCLUSION

Both samples of LaF_3:Ce(5 %)Tb(15 %) nanoparticles have proven to be effective contrast agents for micro-CT imaging. Depending on the size of the nanoparticles, the time of their maximum accumulation in the liver and the maximum value of HU units in the spleen varied. Further work is required to study their safety profile and study the effects on the liver and spleen with a longer follow-up period. It is also promising to study possible modifications of some characteristics of nanoparticles, which will increase their accumulation directly in the tumor tissue.

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Gurova S. V. – conducting an experiment on animals;
Gadzhimagomedova Z. M. – editing and translation of the text of the article;
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Kecheryukova T. M. – researching the literature resources.

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ORIGINAL ARTICLE

Analysis of additional prognostic factors in patients with renal cancer metastases to the liver

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ABSTRACT

Purpose of the study. Was to identify additional prognostic factors in patients with renal cell cancer metastases to the liver influencing survival rates.

Patients and methods. In patients with renal cell cancer (RCC) metastases to the liver, a search for new prognostic factors affecting survival rates is needed. The retrospective analysis of data of 141 patients with liver metastases of RCC treated at the Moscow City Oncological Hospital No. 62 in Moscow and the City Clinical Oncological Dispensary (St. Petersburg) from 2006 to 2022 was carried out. Men prevailed (66.7 %), age 60–74 years in 51.1 %, low-differentiated tumors (56,0 %) and multiple metastases (83.7 %) were detected more often. The study investigated clinical and morphological prognostic factors influencing survival rates in patients with liver metastases of RCC. Statistical analysis was performed using Statistica 10.0 software packages (StatSoft, USA) by constructing Kaplan-Meier curves and survival tables, building a mathematical model of survival.

Results. The 3- and 5-year OS in patients with liver metastases of RCC (n = 141) was 42.4 % and 23.7 %, respectively, with a median OS of 22 months.

In a single-factor analysis in patients with renal cancer metastases to the liver, it was found that ECOG status ($p < 0.001$), histological subtype ($p = 0.01$) had a negative impact on survival rates, Fuhrman tumor differentiation ($p < 0.001$), type ($p < 0.001$) and number of metastases ($p = 0.024$), metastases to lymph nodes ($p = 0.006$), IMDC prognosis ($p < 0.001$), nephrectomy ($p < 0.001$) and metastasectomy ($p = 0.0006$).

In multivariate analysis, ECOG status [HR = 10.09 (95 % CI = 1.31–77], histological subtype [HR = 3,45 (95 % CI = 1.77–6.71], lymph node metastasis [HR = 1.93 (95 % CI = 1.21–3.07], hemoglobin level [HR = 2.44 (95 % CI=1.39–4.29], and undergoing nephrectomy [HR = 2.10 (95 % CI = 1.16–3.79] were additional predictors affecting OS rates in patients with liver metastases of RCC.

Conclusion. In our study, ECOG status, histological subtype, lymph node metastasis, hemoglobin level and nephrectomy were additional independent prognostic factors affecting AE rates in patients with RCC liver metastases. Further studies are needed to identify additional prognostic factors in patients with RCC liver metastases to improve the efficacy of personalized treatment.

Keywords: renal cell cancer, liver metastases, overall survival rate, prognostic factors

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Compliance with ethical standards: the study was carried out in compliance with the World Medical Association Declaration of Helsinki, 1964, ed. 2013. The study was approved by the Ethics Committee of the St. Petersburg Oncological Dispensary (extract from the protocol of the meeting No. 3872 dated 09/22/2022). Informed consent was received from all participants of the study

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Анализ дополнительных факторов прогноза у больных с метастазами рака почки в печень

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РЕЗЮМЕ

Цель исследования. Выявить дополнительные прогностические факторы у больных с метастазами рака почки в печень, влияющие на показатели выживаемости.

Пациенты и методы. У пациентов с метастазами в печень почечноклеточного рака (ПКР) необходим поиск новых прогностических факторов, влияющих на показатели выживаемости. Проведен ретроспективный анализ данных 141 пациента с метастазами в печень ПКР, получавших лечение в ГБУЗ «Московская городская онкологическая больница № 62 Департамента здравоохранения города Москвы», г. Москвы и СПбГУЗ «Городской клинический онкологический диспансер», г. Санкт-Петербург с 2006 по 2022 гг., из которых преобладали мужчины (66,7 %), возраст 60–74 года, у 51,1 %, чаще выявлены низкодифференцированные опухоли (56,0 %) и наличие множественных метастазов (83,7 %). В исследовании изучены клинико-морфологические факторы прогноза, влияющие на показатели выживаемости у больных с метастазами в печень ПКР. Статистический анализ проводился с использованием пакетов программного обеспечения Statistica 10.0 (StatSoft, США) посредством построения кривых Каплана-Мейера и таблиц дожития, построение математической модели дожития.

Результаты. 3- и 5-летняя общая выживаемость (ОВ) у больных с метастазами в печень ПКР (n = 141) составила 42,4 и 23,7 % соответственно, при этом медиана ОВ составила 22 месяца.

В однофакторном анализе у больных с метастазами рака почки в печени выявлено, что отрицательное влияние на показатели выживаемости оказывали статус по ECOG (p < 0,001), гистологический подтип (p = 0,01), степень дифференцировки опухоли по Fuhrman (p < 0,001), тип (p < 0,001) и количество метастазов (p = 0,024), метастазы в лимфатические узлы (p = 0,006), прогноз по IMDC (p < 0,001), проведение нефрэктомии (p < 0,001) и метастазэктомии (p = 0,0006).

При многофакторном анализе ECOG статус [HR = 10,09 (95 % ДИ = 1,31–77], гистологический подтип [HR = 3,45 (95 % ДИ = 1,77–6,71], метастазы в лимфатические узлы [HR = 1,93 (95 % ДИ = 1,21–3,07], уровень гемоглобина [HR = 2,44 (95 % ДИ = 1,39–4,29], а также проведение нефрэктомии [HR = 2,10 (95 % ДИ = 1,16–3,79] были дополнительными предикторами влияющими на показатели ОВ у пациентов с метастазами в печень ПКР.

Заключение. В нашем исследовании ECOG статус, гистологический подтип, метастазы в лимфатические узлы, уровень гемоглобина и проведение нефрэктомии были дополнительными независимыми прогностическими факторами, влияющими на показатели ОВ у пациентов с метастазами в печень ПКР.

Ключевые слова: почечноклеточный рак, метастазы в печень, общая выживаемость, прогностические факторы

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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 этическим комитетом СПБ Онкологического Диспансера (выписка из протокола заседания № 3872 от 22.09.2022 г.). Информированное согласие получено от всех участников исследования

Финансирование: финансирование данной работы не проводилось

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Renal cell carcinoma of the kidney (RCC) accounts for about 2 % of the total number of diagnosed and deceased cancers worldwide [1]. The 5-year survival in patients with metastatic RCC (mRCC) is 12 % [2, 3], and 25–30 % of patients with RCC have metastatic disease at initial diagnosis [4, 5]. The liver is one of the common locations for metastasis and affects 20 % of patients with mRCC [6]. Unfortunately, the development of liver metastases is considered a poor prognostic factor and is often associated with low survival rates [7, 8]. The median progression-free survival in patients with RCC was significantly shorter in the presence of liver metastases, and the median overall survival in patients was less than 12 months [9–10]. For a long time, the selection of patients with mRCC was based on the IMDC prediction model, which is now insufficient in the era of immuno-oncological drugs. In our study, we analyzed additional prognostic factors in patients with kidney cancer metastases to the liver.

The purpose of the study was to identify additional prognostic factors in patients with kidney cancer metastases to the liver that affect survival rates.

Table 1. Patients' characteristics (*n* = 141)

Characteristic	Number of patients (*n* (%))
Sex:	
male	94 (66.7)
female	47 (33.3)
Age, years:	
18–44	9 (6.4)
45–59	54 (38.3)
60–74	72 (51.1)
≥75	6 (4.3)
Histological type:	
clear-cell carcinoma	118 (83.7)
non-clear-carcinoma	23 (16.3)
Differentiation grade:	
G1	19 (13.5)
G2	43 (30.5)
G3	79 (56.0)
ECOG status:	
0	5 (3.5)
1	43 (30.5)
2	46 (32.6)
3	47 (33.3)
Number of metastases:	
solitary	5 (3.5)
single	18 (12.8)
multiple	118 (83.7)
IMDC prognosis:	
favorable	26 (18.4)
intermediate	40 (28.4)
poor	75 (53.2)
Metastasis type:	
metachronous	66 (46.8)
synchronous	75 (53.2)
Prior nephrectomy:	
yes	117 (83.0)
no	24 (17.0)
Normal hemoglobin	70 (49.6)
Anemia	71 (50.4)

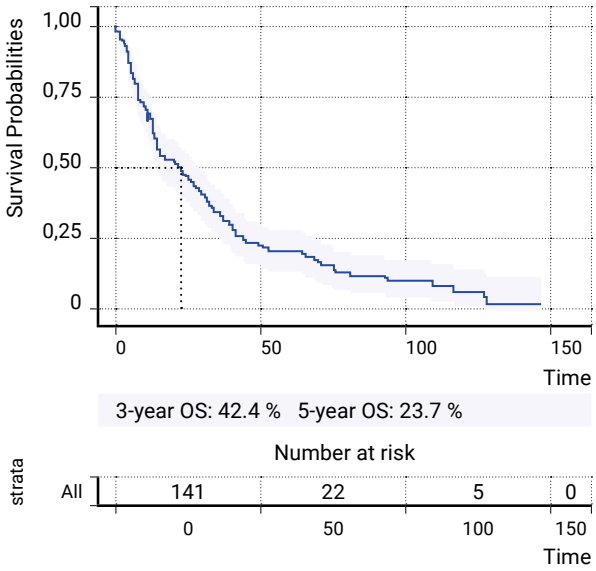


Fig. 1. OS rate of patients with liver metastases of RCC (n = 141)
Note: Median of the OS was 22 months

PATIENTS AND METHODS

A retrospective analysis of the data of 141 patients with liver metastases of RCC treated at the Moscow City Oncological Hospital No. 62 in Moscow and the City Clinical Oncological Dispensary (St. Petersburg) from 2006 to 2022 was carried out. Males (66.7 %) predominated, the age of 60–74 years in 51.1 %, low-grade tumors were more often detected (56.0 %) and the presence of multiple metastases (83.7 %). The study examined the clinical and morphological prognostic factors affecting survival rates in patients with liver metastases of RCC.

Statistical analysis

Statistical analysis was carried out using Statistica 10.0 software packages (StatSoft, USA) by constructing Kaplan-Meyer curves and survival tables, and constructing a mathematical survival model. All patients received systemic antitumor therapy. Detailed characteristics of the patients are given in Table 1.

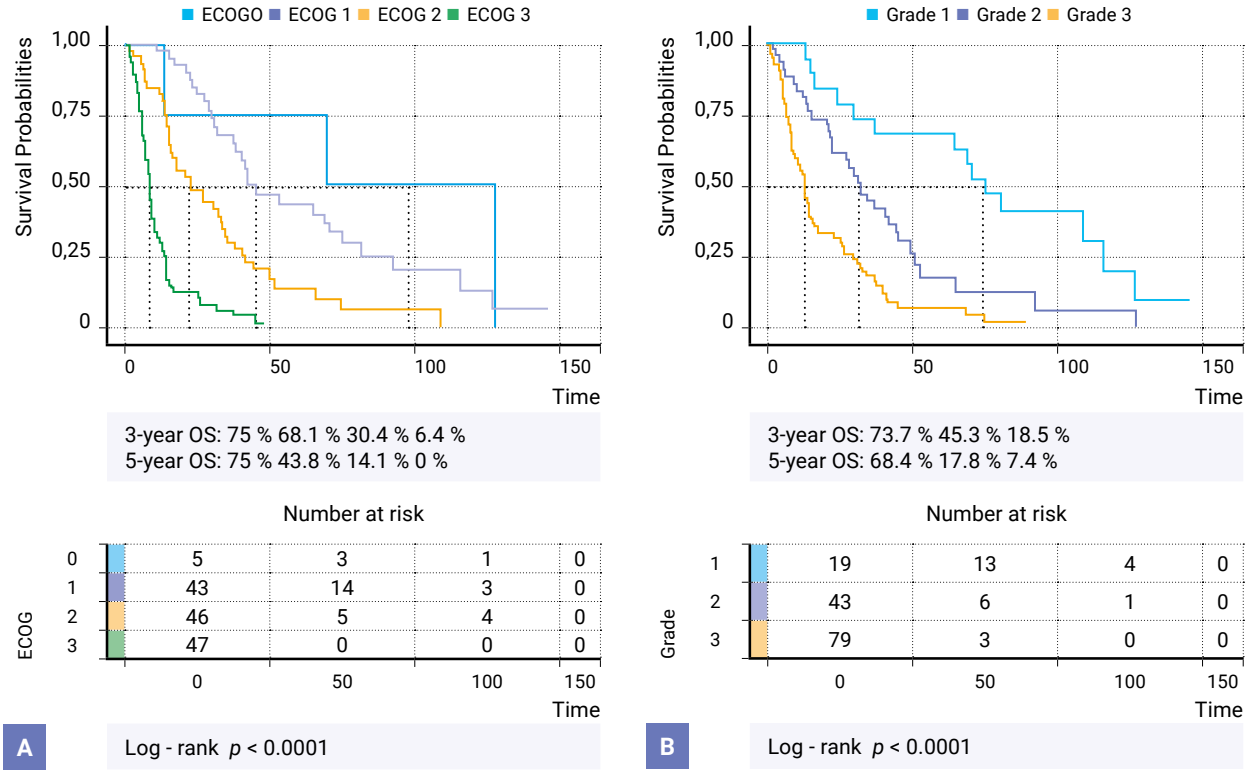


Fig. 2. Overall survival (OS) in patients with RCC liver metastases depending on ECOG status (a) and Fuhrman tumor differentiation (b) (n = 141)
Note: the median OS for ECOG 0.1.2 and 3 was 98.6, 45, 22 and 7.9 months, and for G1, G2 and G3 it was 74.8, 31.9 and 13 months, respectively

Table 1 shows that low-grade tumors (56 %), multiple metastases (83.7 %), and an unfavorable IMDC prognosis (53.2 %) were the most common.

Patient data was consolidated in the form of spreadsheets and analyzed using the Statistica 12 for Windows program. Life expectancy was calculated from the date of diagnosis to the date of last observation or death. Survival was assessed using the Kaplan-Mayer method, survival differences were determined using the log-rank test; Cox regression analysis was used to exclude factors that do not have independent prognostic significance. A single-factor analysis was used to determine whether there were statistically significant differences between two or more groups in one independent variable. A multifactorial analysis was used to determine the effect of several factors on the dependent variable. The analysis of OS indicators in patients with nmPCR was carried out depending on clinical and morphological parameters. The analysis of the risk ratio of an event at a certain point in time t in one group compared with another group (Hazard Ratio (HR)) was performed.

STUDY RESULTS

The clinical and morphological characteristics of the patients are presented in Table 1. The study was dominated by 90 men (66.7 %). 75 (53.2 %) patients had an unfavorable prognosis according to IMDC, while 79 (56 %) were diagnosed with low-grade tumors. Multiple metastases were detected in 118 (83.7 %) patients. These data indicate that the group of patients with nmPCR has a pronounced metastatic load.

In a one-factor analysis in patients with kidney cancer metastases in the liver, it was revealed that ECOG status ($p < 0.001$), histological subtype ($p = 0.01$), degree of tumor differentiation according to Fuhrman ($p < 0.001$), type ($p < 0.001$) and number of metastases ($p = 0.024$), lymph node metastases ($p = 0.006$), IMDC prognosis ($p < 0.001$), nephrectomy ($p < 0.001$) and metastasectomy ($p = 0.0006$) (Table 1, Fig. 2–6).

In multivariate ECOG analysis, the status [HR = 10.09 (95 % CI = 1.31–77], histological subtype [HR = 3.45 (95 % CI = 1.77–6.71], lymph node metas-

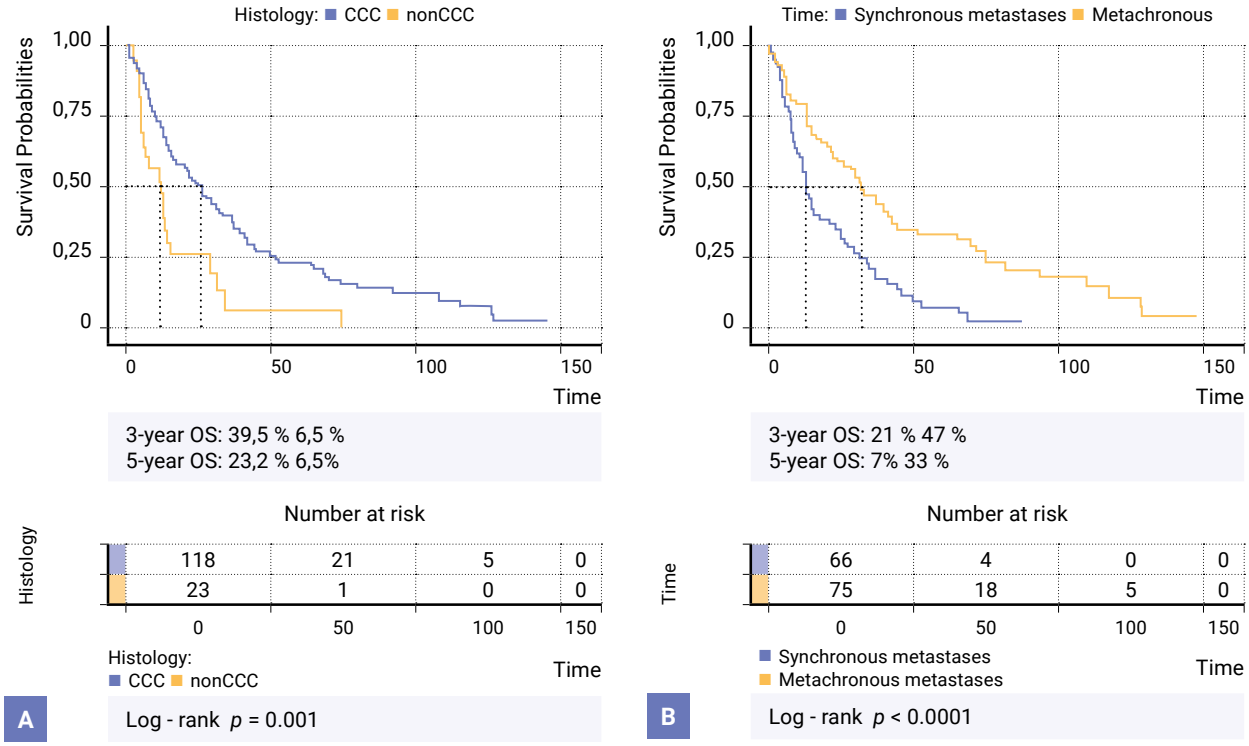


Fig. 3. Overall survival (OS) in patients with RCC liver metastases as a function of histologic subtype dependency (a) and time of metastasis occurrence (b) ($n = 141$)
Note: the median OS for clear-cell and non-clear-cell RCC was 26.3 and 12 months, respectively, and for synchronous and metachronous metastases, 13.2 and 31.4 months, respectively

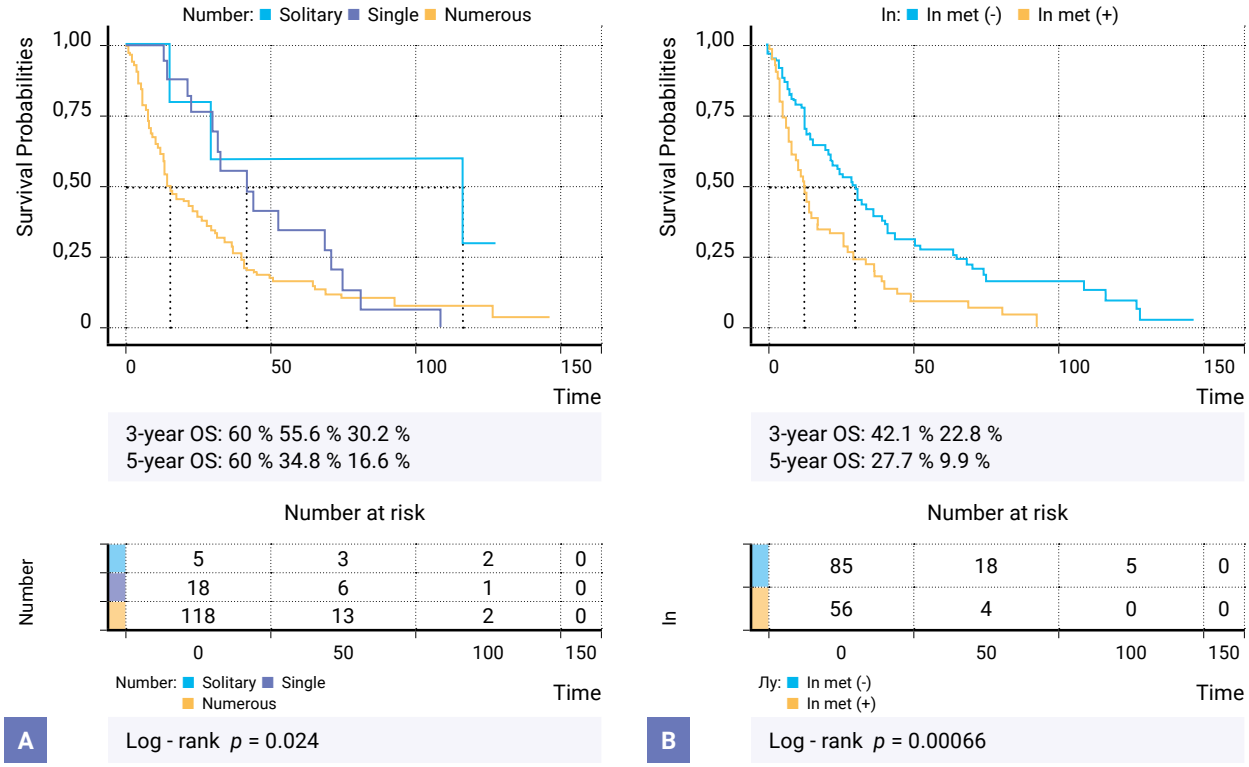
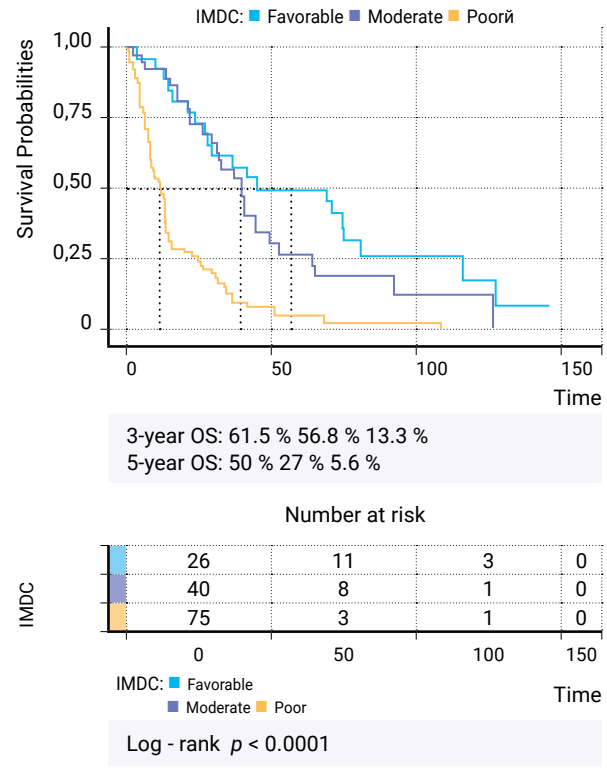


Fig. 4. Overall survival (OS) in patients with liver metastases of RCC depending on the number of metastases (a) and with and without lymph node metastases (b) (n = 141)
Note: the median OS in patients with solitary, single, and multiple metastases was 116.6, 41.8, and 15.5 months, respectively, and in the absence and presence of lymph node metastases, 30.9 and 13.4 months, respectively



tases [HR = 1.93 (95 % CI = 1.21–3.07], hemoglobin level [HR = 2.44 (95 % CI = 1.39–4.29], as well as nephrectomy [HR = 2.10 (95 % CI = 1.16–3.79] were additional factors that had an independent negative effect on OS in patients with liver metastases of RCC (Table 2).

DISCUSSION

RCC is a highly vascularized tumor and is prone to the appearance of distant metastases [11]. About 30 % of new cases are metastatic at the time of diagnosis [12]. The liver is one of the most common locations of RCC metastases, including 23.6 % of newly diagnosed cases of metastatic RCC and is associated with poor overall survival rates [13]. Despite the fact that treatment strategies for mRCC have improved significantly over the past decade,

Fig. 5: Overall survival (OS) in patients with RCC liver metastases according to IMDC prognosis (n = 141)
Note: the median OS for favorable, intermediate, and poor IMDC prognosis was 57.1, 39.8, and 12 months, respectively

there is still no consensus on the optimal clinical strategy for the treatment of liver metastases of RCC [14–16]. A prognostic model for liver metastases of RCC would be very useful for personalized treatment [17].

In our work, we have shown that the IMDC model, which was developed to analyze the forecast of mRCC [18, 19] is insufficient. In our study, ECOG status, histological subtype, lymph node metastases, hemoglobin levels, and nephrectomy were important prognostic factors in RCC liver metastases. Most of these predictors are not taken into account in modern forecasting models. It is interesting to note that the IMDC prognosis, type and number of metastases were not prognostic predictors in patients with RCC with liver metastases.

This study also has some limitations. First of all, because of the retrospective nature. Further multicenter studies are needed to determine the clinical, pathomorphological and molecular prognostic factors in patients with kidney cancer metastases to the liver.

CONCLUSIONS

In our study, ECOG status, histological subtype, lymph node metastases, hemoglobin level, and nephrectomy were additional independent prognostic factors affecting OS in patients with liver metastases of RCC. Further studies are needed to identify additional prognostic factors in patients with liver RCC metastases in order to increase the effectiveness of personalized treatment.

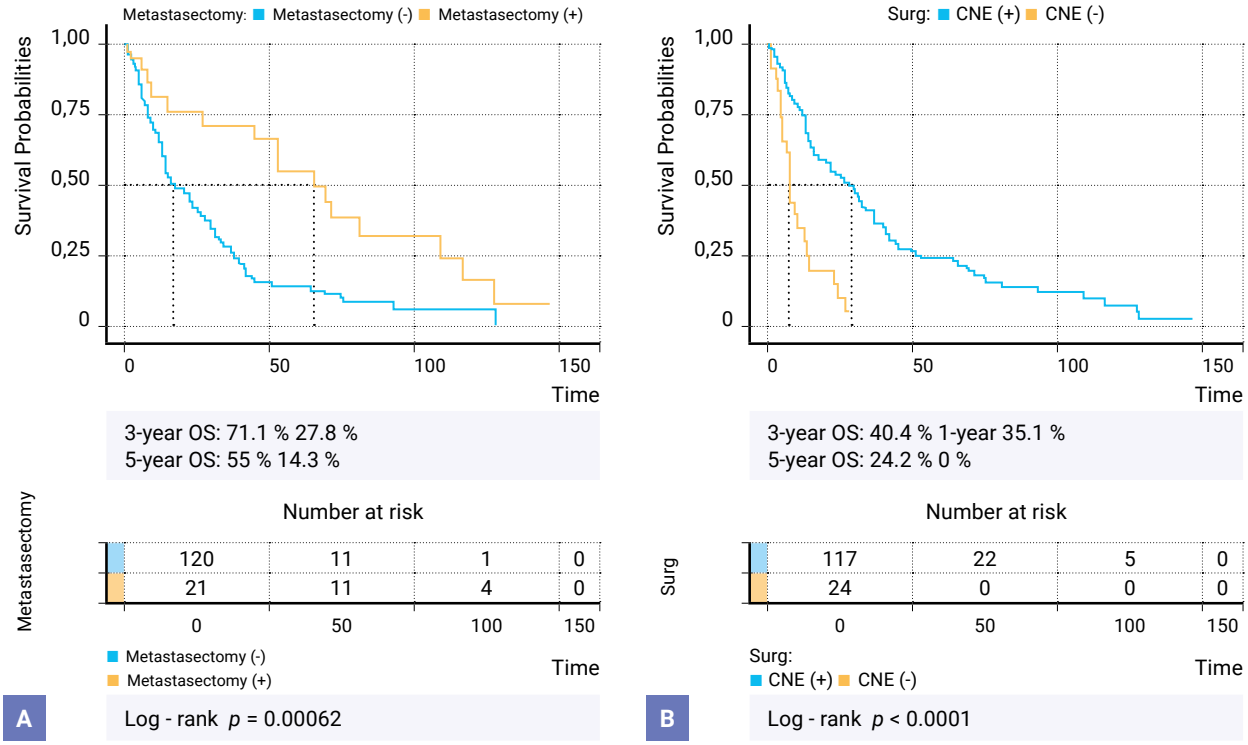


Fig. 6. Overall survival (OS) in patients with RCC liver metastases when metastasectomy is performed (a) and with and without CNE (b) (n = 141)
Note: the median OS in the absence and performance of metastasectomy was 17.5 and 65.2 months, respectively, and in the absence and performance of CNE was 29.3 and 8.1 months, respectively

Table 2. Predictive factors for overall survival rate for patients with liver metastases of RCC (*n* = 141) (single-factor and multifactor analysis)

Factor	Number of patients (%)	Hazard ratio (95 % confidence interval)	
		Univariate test	Multivariate test
ECOG status: 1 2 3	 5 (3.5) 43 (30.5) 46 (32.6) 47 (33.3)	– 1.66 (0.49–5.61, *p* = 0.417) 4.07 (1.1913.98, *p* = 0.026) 13.99 (4.0048.89, *p* < 0.001)	– 1.16 (0.18–7.51, *p* = 0.880) 2.37 (0.34–16.68, *p* = 0.388) 10.09 (1.31–77.63, *p* = 0.026)
Histological type: clear-cell carcinoma non-clear-carcinoma	 118 (83.7) 23 (16.3)	– 2.20 (1.36–3.58, *p* = 0.001)	– 3.45 (1.77–6.71, *p* < 0.001)
Differentiation grade: G1 G2 G3	 19 (13.5) 43 (30.5) 79 (56.0)	– 2.33 (1.21–4.46, *p* = 0.011) 5.24 (2.79–9.83, *p* < 0.001)	– 1.70 (0.69–4.22, *p* = 0.251) 1.59 (0.61–4.11, *p* = 0.342)
Metastasis type: metachronous synchronous	 66 (46.8) 75 (53.2)	– 0.45 (0.31–0.67, *p* < 0.001)	– 1.13 (0.66–1.96, *p* = 0.649)
Lymph nodes metastases: present absent	 85 (60.3) 56 (39.7)	– 1.90 (1.31–2.77, *p* = 0.001)	– 1.93 (1.21–3.07, *p* = 0.006)
Hemoglobin: yes – normal no – anemia	 70 (49.6) 71 (50.4)	– 3.04 (2.05–4.50, *p* < 0.001)	– 2.44 (1.39–4.29, *p* = 0.002)
Prior nephrectomy: yes no	 117 (83.0) 24 (17.0)	– 3.57 (2.14–5.97, *p* < 0.001)	– 2.10 (1.16–3.79, *p* = 0.014)
Metastasectomy: yes no	 120 (85.1) 21 (14.9)	– 0.39 (0.23–0.68, *p* = 0.001)	– 0.58 (0.26–1.30, *p* = 0.186)

Note: the table only presents factors with prognostic significance

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Orlova R. V. – development of the study design, analysis of the obtained data, editing of the manuscript;
Shirokorad V. I. – development of study design, obtaining data for analysis, analysis of the obtained data, editing of the manuscript;
Kostritsky S. V. – collection of material, analysis of data.

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ORIGINAL ARTICLE

Free radical oxidation and antioxidant defense in uterine myoma and endometrioid adenocarcinoma depending on its degree of differentiation

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ABSTRACT

Purpose of the study. To evaluate the features of free radical oxidation (FRO) and the principal enzymatic and non-enzymatic links of antioxidant defense in proliferating tissues of benign myoma and malignant endometrioid adenocarcinoma (EA) with varying degrees of differentiation.

Patients and methods. Patients who received surgical treatment for EA (n = 42) and uterine myoma (n = 14) were examined. Patients with stage Ia (n = 26) and stage Ib (n = 16) of disease were selected. 16 patients had highly differentiated (G1) EA, 12 had moderately differentiated (G2) EA, and 14 had low-differentiated (G3) EA. The activity of superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), glutathione transferase (GST), reduced glutathione (GSH), vitamins A and E, lipid peroxidation products diene conjugates (DC) and malondialdehyde (MDA) were determined colorimetrically in the tissues of EA, myoma and intact uterus.

Results. Compared with the level in intact tissue, SOD decreased by 3.2 times and GST increased by 2.7 times in myoma ($p < 0.01$). Similar changes were noted for EA G1 – on average by 5.3 times ($p < 0.01$) and also DC increased by 2.2 times ($p < 0.05$). In EA G2 tissue, SOD and GPx activities were lower than in the intact tissue, by 5.7 and 4.5 times, respectively ($p < 0.05$), and lower GST, GPx and GSH than in the EA G1, by 4.9, 8.9 and 1.6 times, respectively ($p < 0.05 – p < 0.01$). In EA G3 tissue, there was an increase in GSH, GPx and GST from 1.5 to 7.1 times ($p < 0.05 – p < 0.01$) and lipid peroxidation products by an average of 2.5 times ($p < 0.05$), as well as a decrease in vitamins A and E by 2.9 and 4.6 times, respectively ($p < 0.05$) compared with the intact tissue. The tissue of the EA G2 had a minimal level of activity of the GSH-dependent system.

Conclusion. The results reflect the differences in the mechanisms of proliferation regulation by FRO in myomas and in the EA tissue with changes in its differentiation. Knowledge of the characteristics of individual links in the regulation of FRO can play a certain role in the use of antioxidant therapy for benign or malignant tumors of the uterus.

Keywords: endometrial cancer, uterine myoma, endometrioid adenocarcinoma, degree of differentiation, free radical oxidation, antioxidant enzymes, glutathione-dependent system, vitamins A and E

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013, were observed in the work. The study was approved by the Ethics Council of the National Medical Research Center for Oncology (Protocol No. 22 dated 09/05/2023). Informed consent was received from all participants of the stud

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3.1.6. Онкология, лучевая терапия
ОРИГИНАЛЬНАЯ СТАТЬЯ

Состояние процессов свободнорадикального окисления и антиоксидантной защиты в миоме матки и в эндометриоидной аденокарциноме в зависимости от ее степени дифференцировки

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РЕЗЮМЕ

Цель исследования. Оценить особенности свободнорадикального окисления (СРО) и основных ферментативных и неферментативных звеньев антиоксидантной защиты в пролиферирующих тканях доброкачественной миомы и злокачественной эндометриоидной аденокарциномы (ЭА) с различной степенью ее дифференцировки.
Пациенты и методы. Обследованы больные, получившие хирургическое лечение по поводу ЭА (n = 42) и миомы матки (n = 14). Больные с ЭА Ia (n = 26) и Ib (n = 16) стадией. У 16 больных была высокодифференцированная (G1) ЭА, у 12 умереннодифференцированная (G2) ЭА, у 14 низкодифференцированная (G3) ЭА. В тканях ЭА, миомы, интактной матки колориметрически определяли активность ферментов супероксиддисмутазы (СОД), каталазы, глутатионпероксидазы (ГПО), глутатионтрансферазы (ГТ), содержание восстановленного глутатиона (GSH), витаминов А/Е, продуктов перекисного окисления липидов (ПОЛ) диеновых конъюгатов (ДК) и малонового диальдегида (МДА).
Результаты. По сравнению с уровнем в интактной ткани в миоме снижалась СОД в 3,2 раза и увеличивалась ГТ в 2,7 раза (p < 0,01). Аналогичные изменения отмечены для ЭА G1 – в среднем в 5,3 раза (p < 0,01) и увеличение ДК в 2,2 раза (p < 0,05). В ткани ЭА G2 активность СОД и ГПО была ниже, чем в интактной ткани, соответственно в 5,7 и 4,5 раза (p < 0,05) и более низкие ГТ, ГПО и GSH, чем при ЭА G1, соответственно в 4,9, 8,9 и 1,6 раз (p < 0,05 – p < 0,01). В ткани ЭА G3 отмечен рост GSH, ГПО и ГТ от 1,5 до 7,1 раза (p < 0,05 – p < 0,01) и продуктов ПОЛ в среднем в 2,5 раза (p < 0,05), а также снижение витаминов А и Е в 2,9 и 4,6 раза соответственно (p < 0,05) по сравнению с интактной тканью. Ткань ЭА G2 отличалась минимальным уровнем активности GSH-зависимой системы.
Заключение. Результаты отражают различия механизмов регуляции пролиферации посредством СРО в миомах и в ткани ЭА при изменении ее дифференцировки. Знание особенностей отдельных звеньев регуляции СРО может играть определенную роль в назначении антиоксидантной терапии доброкачественных или злокачественных опухолей матки.

Ключевые слова: рак эндометрия, миома матки, эндометриоидная аденокарцинома, степень дифференцировки, свободнорадикальное окисление, антиоксидантные ферменты, глутатионзависимая система, витамины А и Е

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Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

Endometrial cancer (EC) is one of the most common malignancies of the female reproductive system, ranking second in frequency after cervical cancer in the world. EC is formed from the mucous membrane of the uterine body, and the most common histological type is endometrioid adenocarcinoma (EA), the detection rate of which can reach up to 80–90 % of all cases of EC [1]. There is no tendency to decrease the incidence of EC, which is explained, on the contrary, by an increase in the prevalence of risk factors that create conditions for the occurrence of disorders in the body that contribute to endometrial malignancy (aging of women, a decrease in the number of births, an increase in the number of abortions, inflammatory diseases of the uterus), and directly affect endometrial malignancy (hyperestrogenism, metabolic disorders associated with obesity, diabetes mellitus).

The results of many years of research have helped to understand the important role of free radical oxidation (FRO) and reactive oxygen species (ROS) processes both in the normal physiology of the female reproductive system and in the development of its pathology – the involvement of ROS in the regulation of the ovarian cycle, the initiation of endometrial rejection, the development of infertility, endometriosis. The balance of pro- and antioxidants in uterine tissue is regulated by interrelated signaling cascades of inflammation, hypoxia, and angiogenesis [2, 3]. The uterus is particularly sensitive to the effects of hormonal factors, as well as various external lifestyle-related factors, which activate free radical processes that are inhibited by the body's antioxidant system. In particular, it was found that obesity, by inducing a pro–inflammatory environment and oxidative stress, promotes the transformation of myometrial stem cells into leiomyoma and endometrial into adenocarcinoma, activating proliferation and angiogenesis [4, 5]. It was found that the transcriptional activity of the genes responsible for estrogen reception and metabolism changes depending on the degree of tumor differentiation and the age of the affected women [6]. The occurrence of an imbalance in the processes of FRO, turning into oxidative stress, through complex mechanisms contributes to the formation of fibroids or leads to neoplastic transformation of the endometrium, the development of hyperplasia and the active growth of malignant tumors [3, 7, 8]. All these pathologies of the uterus have a common basis – increased activity of proliferative processes. However, as a result of such activation, tumors that are fundamentally different in nature are formed – benign fibroids or malignant carcinoma. Since FRO and the antioxidant system are important links in the pathogenesis of proliferation-related processes, it would be interesting to evaluate the features of FRO and the main enzymatic and non-enzymatic components of the antioxidant defense system in proliferating tissues of benign fibroids and malignant endometrioid adenocarcinoma with varying degrees of its differentiation, which was **the purpose of this study**.

PATIENTS AND METHODS

The present study included 42 patients with endometrioid adenocarcinoma (average age 60.8 ± 2.9years) and 14 patients with uterine fibroids (average age 49.4 ± 2.5 years) who underwent special treatment at the National Medical Research Centre for Oncology of the Ministry of Health of the Russian Federation, Rostov-on-Don. All patients signed a voluntary informed consent for medical intervention and the use of biological material for scientific purposes. The study was approved by the Ethics Council of the National Medical Research Centre for Oncology, Rostov-on-Don (Protocol No. 22 dated 09/05/2023).

The average body mass index of women with EC was 39.8 (from 24.3 to 49.7), the Quetelet index formula was used to calculate it, 12 women had type 2 diabetes mellitus, 10 had impaired glucose tolerance. The average body mass index in patients with uterine fibroids was 31.4 (from 21.9 to 38.4). Type 2 diabetes occurred in 2 patients with uterine fibroids, and in 2 patients with impaired glucose tolerance. In 9 patients, uterine fibroids were combined with genital endometriosis.

In patients with EC, the prevalence of the tumor process was within the Ia and Ib stages. In the group with G1 EA (n = 16), there were 14 patients with stage Ia and 2 with stage Ib. With G2 EA (n = 12) – 7 patients with Ia and 5 with stage Ib. In the group with G3 EA (n = 14), there were 5 with Ia and 9 with Ib.

Biomaterial (fibroids and intact uterus, EA tumor) was obtained during surgical treatment of these women. They did not receive neoadjuvant treatment. The biomaterial of all patients with EC was divided into 3 groups according to the degree of tumor differentiation – G1, G2, G3. 10 % homogenates were prepared from tumor tissues (fibroids, EA) and intact uterine tissue obtained during the removal of fibroids (uterine body tissue unaffected by the tumor process, containing endometrium and myometrium) obtained during the surgical stage, in which a number of indicators characterizing the intensity of FRO and the functioning of the antioxidant system by colorimetric methods were studied: superoxide dismutase (SOD) activity (EC 1.15.1.1) [9], the amount of enzyme that caused 50 % inhibition of the reaction was taken as the unit of activity and expressed in units/ml of homogenate; catalase activity (EC 1.11.1.6.) [10], expressed in μ mol H_2O_2/ min•mg of protein; glutathione peroxidase (GPx) activity (EC 1.11.1.9.) [11] and glutathione transferase (GST) activity (EC 2.1.5.18) [12], the activity of these enzymes was expressed in IU/ mg of protein. The state of the non-enzymatic link of the antioxidant system was assessed by the content of reduced glutathione (GSH) [12], expressed in μ mol/ mg of protein, and vitamins A and E [13], expressed in units/ml of homogenate. The intensity of lipid peroxidation (LPO) was assessed by the content of primary products in tumor tissues, diene conjugates (DC) [14] and the most stable secondary product, malondialdehyde (MDA) [12]. Protein concentration was determined by biuretic method, expressing it in mg/ml of homogenate. The results of colorimetric studies were evaluated using a U-2900 bi-beam spectrophotometer with UV Solutions software (Hitachi, Japan) and an INFINITE M NANO microplate automatic analyzer (Tecan Austria GmbH, Austria).

Statistical analysis

Statistical analysis of the results was carried out using Statistica 6.0. The Shapiro-Wilk test was used for testing the data sample normality, and using the Levene's test was checked the equality of variances. The data in the tables are presented as median and quartiles (Me; Q1; Q3). The statistical significance of the differences was assessed using the Mann-Whitney test, and the Holm-Bonferroni method was used for multiple comparisons to correct the achieved significance level of p. The critical level of significance of the differences is $p \leq 0.05$.

STUDY RESULTS AND DISCUSSION

During the study of the characteristics of FRO and the activity of individual links of the antioxidant system in benign and malignant proliferative processes, it was found that only the activity of SOD in fibroids significantly changed – a decrease of 3.2 times, and the activity of GST – an increase of 2.7 times compared with the level in intact tissue (Table 1). There were no significant changes in other links of the antioxidant system and the content of LPO products. (Tables 1, 2). A similar pattern was observed in the tissue of highly differentiated EA G1: lower SOD activity and higher GST activity, on average 5.2 times, than in intact tissue (Table. 1), however, in contrast to fibroids, there was a 2.2-fold increase in the level of DC compared with the level in intact tissue (Table. 2), which may indicate the appearance of an imbalance and an increase in FRO processes.

In the tissue of moderately differentiated EA G2, in addition to the lower activity of SOD – 5.7 times lower than the level in intact tissue, there was also a lower activity of GPx – 4.5 times lower than in intact tissue, at the same time, the activity of GST, GPx and the content of GSH were significantly lower than in EA G1 – b tissue. 4.9, 8.9, and 1.6 times, respectively (Table 1). There were no statistically significant changes in the content of vitamins and LPO products in EA G2 tissue (Table 2).

In the tissue of low–grade EA G3, a generally different picture of the state of the antioxidant system was observed than in fibroids and with EA of a higher degree of differentiation: the activity of SOD and catalase did not significantly differ from the level in intact tissue, but activation of all components of the glutathione-dependent system was noted – an increase in the content of GSH and the activity of GPx and GST, respectively, by 2.1, 1.5 and 7.1 times (Table 1). The content of vitamins A and E was 2.9 and 4.6 times lower, respectively, and the level of LPO products was 2.5 times higher on average than in intact tissue (Table. 2), which may reflect an increasing imbalance between FRO and antioxidant protection despite an increase in the activity of the glutathione-dependent system.

Analyzing the results, we can note the similarity of the state of the antioxidant system in fibroids and EA G1 tissue. With a decrease in the degree of tumor differentiation and intensification of proliferation, the balance in the system of enzymatic and non-enzymatic antioxidants and in the processes of FRO changes, which is manifested by an increase in the level of LPO products. It is noteworthy that in EA G2 tissue, the activity of the glutathione system is significantly lower than in EA G1 tissue – the GSH content is 1.6 times lower, the activity of GPx and GST is 8.9 and 4.9 times lower, respectively (Table 1). At the same time, in EA G3 tissue, compared with the level in EA G2 tissue, the activity of SOD and catalase was higher, respectively, by 6.2 and 2.5 (p = 0.0516) times, as was the activity of the glutathione-dependent system – the activity of GPx and GST was on average 6.8 times higher, and the level of GSH was 2.7 times above (Table. 1), while the content of vitamins A and E, on the contrary, was lower – 3.6 and 2.5 (p = 0.0501) times, respectively (Table. 2), and the level of LPO products is 6.3 (DC) and 2.1 (MDA) times higher (Table 2).

As a result of long-term studies, the great importance of the processes of free radical oxidation and redox of tissues in the physiological regulation of the female reproductive system and their imbalance in the process of pathological changes, in particular in the development of hyperplastic processes and oncogynecological pathology, has been established [2, 3, 15]. It was found that fibroids, hyperplasia, and endometrial adenocarcinoma are characterized by a decrease in mRNA levels, expression, and/or activity of the antioxidant enzymes SOD and catalase, which contributes to the creation of pro-oxidant conditions in the tissue that stimulate proliferation and tumor formation [16, 17]. Our results were somewhat similar – we observed a decrease in SOD activity in both benign fibroids and malignant high- and moderate-grade EA tissue, but not in low-grade EA, however, we did not find a significant decrease in catalase activity in any group. The change in SOD activity is adaptive in nature and its decrease may reflect both a decrease in the generation of superoxide anion radical and inhibition by the reaction product, H_2O_2, which suppresses proliferation, unlike

Table 1. Indicators of the antioxidant system and the content of lipid peroxidation products in tumor tissue in patients with uterine fibroids and patients with EC of varying degrees of differentiation

	SOD activity, units/ml	Catalase activity, μ mol H_2O_2/ min•mg protein	GSH content, μ mol/mg of protein	GPx activity, IU/ mg of protein	GST activity, IU/mg of protein
Intact uterine tissue n = 12	15.5; (12.5; 20.7)	2.2; (1.7; 2.7)	33.6; (32.4; 40.5)	181.6; (144.9; 224.6)	39.8; (29.4; 58.7)
Myomatous node n = 14	4.8; (2.1; 6.5) p = 0.0082	1.9; (1.8; 3.1)	30.6; (30.2; 61.8)	179.8; (120.2; 390.6)	107.6; (72.8; 157.9) p = 0.0065
EA G1 n = 16	2.9; (1.4; 4.5) p = 0.0105	3.6; (1.6; 6.7)	40.2; (31.4; 68.9)	360.0; (200.0; 415.4)	200.4; (175.0; 284.7) p = 0.0027
EA G2 n = 12	2.7; (2.4; 3.3) p = 0.0209	1.7; (1.3; 2.1)	25.8; (17.6; 26.8) p^1 = 0.0118	40.2; (28.8; 52.4) p = 0.0209 p^1 = 0.0105	41.1; (28.5; 43.8) p^1 = 0.0045
EA G3 n = 14	16.9; (13.1; 17.9) p^2 = 0.0143	4.3; (2.5; 5.6) p^2 = 0.0516	70.4; (64.9; 78.4) p = 0.0143 p^2 = 0.0139	272.2; (252.2; 286.1) p = 0.0500 p^2 = 0.0147	281.2; (137.1; 297.8) p = 0.0062 p^2 = 0.0090

Note: the achieved level of statistical significance of the differences: p – compared with the level of the indicator in the intact uterine tissue, p^1 – compared with the level of the indicator in EA G1, p^2 – compared with the level of the indicator in EA G2

superoxide anion radical, and activates apoptosis. Thus, a decrease in the production of H_2O_2 with low SOD activity and while maintaining catalase and GPx activity can contribute to a decrease in the content of H_2O_2 and an increase in the superoxide content in the tissue. Studies of the role of hypoxia in the pathogenesis of fibromyoma have shown, for example, a violation of the innate antioxidant mechanism occurs, aggravated by hypoxia, which manifests itself in the constant suppression of SOD and catalase mRNA expression in fibromyoma cells compared with cells of the normal myometrium after exposure to hypoxia [16, 18]. As suggested by the authors, hypoxia can stimulate the proliferation of fibroids cells, and possibly transformed endometrial cells, through the activation of the HIF-1α/TGF-β3/Smad3 signaling pathway and the expression of NADPH oxidase-4 (NOX4) enzymes, generating superoxide ions, as well as through the expression of double oxidase (DUOX1), generating H_2O_2, the activity of which contributes to the creation of pro-oxidant conditions [16].

As our results showed, higher SOD and catalase activity was observed in EA G3 tissue than in the tissues of moderately differentiated endometrial tumors, as well as significantly higher activity of glutathione-dependent antioxidant enzymes GPx and GST and a higher content of GSH itself, even compared with the tissue of the intact uterus. Obviously, this adaptive increase in the activity of protective antioxidant systems is associated with increased generation of ROS (especially superoxide) and FRO processes while reducing tumor differentiation to a low-grade state to ensure rapid proliferation and protect tumor cells from apoptosis. This assumption is supported by the accumulation of LPO – DC and significantly more stable MDA products in the tissue of low-grade EA. This was not observed in fibroids, which suggests that there may be different mechanisms of proliferation activation during the development of fibroids and EA. As is known, GSH and its associated enzymatic system are of key importance in maintaining the intracellular redox state, which regulates signaling pathways, gene expression, and cell death, and the functioning of its redox cycle is a cytoprotective mechanism for limiting FRO in various cells, especially tumor cells [19]. In this regard, the content of glutathione and related enzymes is often increased in a number of tumors – GSH exhibits antioxidant activity, restoring H_2O_2, lipid hydroperoxides and peroxynitrite, and GPx, metabolizing H_2O_2 and lipid hydroperoxides, increases cell resistance to oxidative damage [19].

Table 2. Indicators of the glutathione-dependent system in tumor tissue in patients with uterine fibroids and patients with EC of varying degrees of differentiation

	Vitamin A content, unit/ml	Vitamin E content, unit/ml	DC content, μ mol/ml	The content of MDA, nmol/mg of tissue
Intact uterine tissue *n* = 12	2.21; (2.06; 2.96)	5.61; (2.92; 5.81)	0.80; (0.18; 1.38)	2.31; (1.60; 3.14)
Myomatous node *n* = 14	3.58; (1.56; 3.97)	2.22; (1.04; 4.33)	0.74; (0.16; 2.65)	2.05; (1.92; 3.08)
EA G1 *n* = 16	2.54; (1.68; 4.65)	4.35; (2.94; 5.94)	1.78; (1.57; 2.57) *p* = 0.0233	2.30; (1.54; 3.59)
EA G2 *n* = 12	2.74; (2.66; 3.91)	3.05; (2.06; 6.61)	0.35; (0.25; 0.79)	2.18; (1.54; 2.56)
EA G3 *n* = 14	0.75; (0.59; 1.02) *p* = 0.0119 p^2 = 0.0163	1.21; (0.88; 1.94) *p* = 0.0275 p^2 = 0.0501	2.20; (1.29; 2.98) *p* = 0.0373 p^2 = 0.0233	4.87; (4.10; 6.41) *p* = 0.0179 p^2 = 0.0339

Note: the achieved level of statistical significance of the differences: *p* – compared with the level of the indicator in intact uterine tissue, p^2 – compared with the level of the indicator in EA G2

An interesting result was higher GST activity in both low-grade (maximum) and high-grade EA tissue, as well as in fibroid tissue (minimum). Glutathione transferase is a superfamily of enzymes representing the main cellular defense system that detoxify various hydrophobic and electrophilic endogenous compounds formed during metabolism [20]. In addition, GST, participating in a wide range of signaling mechanisms of mitogen-activated protein kinases (MAPK), such as c-Jun N-terminal kinase (JNK), apoptosis signaling kinase 1 (ASK1), and the 4-hydroxy-2-transnonenal pathway, ensure cell survival, thus playing a significant role in both in tumor formation and in established tumors [19, 21]. This role of GST in activating cellular maintenance, proliferation, and avoidance of apoptosis leads to an increase in GST expression in many malignant tumors, which is associated with a decrease in patient survival, in particular, in the work of Singh R. R. and Reindl K. M. (2021) provide information on a negative correlation between increased GSTA1 expression and survival in patients with endometrial cancer [20], and in the study Checa-Rojas A. et al. (2018) knockdown of GSTM3 and GSTP1 proteins showed increased apoptosis of cervical cancer cells of different lines and suppression of cell survival through various signaling pathways [22]. Thus, by regulating the activation of cellular stress signaling pathways, GST contributes to the adaptation of tumor cells to stressful conditions in the tumor microenvironment and their survival, and may be a common mechanism for avoiding apoptosis in fibroids.

In the study of Obukhova L. and co-authors. (2022) [23] showed consistent changes in free radical activity and glutathione metabolism in glioma tissue as their malignancy increased from Low Grade (I, II) to High Grade (III, IV), although these changes were not similar to those we found, which may be due to the peculiarities of local regulatory mechanisms.

Analyzing the results obtained, attention is drawn to the significantly lower content of vitamins A and E in the tissue of low-grade EA and the absence of significant changes in it in the tissues of higher-grade EA and fibroids, which is obviously related to the role of these vitamins in the processes of development and cellular differentiation, as well as participation in antioxidant protection. Vitamin A is classified as morphogens, metabolites that are of key importance in the processes of embryogenesis and tissue differentiation [24], which is consistent with our results, which showed no differences in its levels in the tissues of the intact uterus, fibroids and highly differentiated EA G1 and significantly lower levels in the tissue of low-differentiated EA G3. To date, it has been established that retinol metabolites, acting through genomic and non-canonical mechanisms, can have the opposite effect on tumor development: they participate in the induction of genes that activate cell differentiation, and their low levels in cells can stimulate proliferation through the MAPK signaling mechanism; they provoke an increase in the expression of the estrogen receptor α, which stimulates the progression of hormone-dependent tumors [24]. Under the influence of retinol metabolites, a change in the activity of aldehyde dehydrogenase 1, a key marker of malignant stem cells, weakens the signaling of the ALDH1/FoxM1/Notch1 pathway, thereby suppressing tumor growth in ovarian cancer; in the endometrium, vitamin A metabolites control the expression of the enzyme 17β-hydroxysteroid dehydrogenase type 2, involved in the cyclic change of estrogen-dependent proliferative and progesterone- dependent secretory phases [25]. Cellular components such as retinoic acid binding protein 1 (CRABP1) and fatty acid binding protein 5 (FABP5) mediate the ability of retinoic acid to cause differentiation, cell cycle arrest, and apoptosis: this metabolite has an enhanced apoptotic effect in cells with a high CRABP1/FABP5 ratio [26].

The importance of vitamin E in tumors is primarily associated with antioxidant properties and its antitumor effect: a number of studies have confirmed a link between high intake of vitamin E and a reduced risk of cervical cancer and endometrial cancer, and the established mechanisms of action of vitamin E include inhibition of the pro-tumor pathway NF-kB, suppression of the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and neutralization of reactive oxygen species and nitrogen. However, a number of studies have shown opposite results [25, 27].

CONCLUSION

The presented very little information about the currently known molecular mechanisms of the involvement of FRO, the glutathione-dependent system, vitamins A and E in the processes regulating the

development and progression of malignant tumors, in particular, endometrial cancer, and benign fibroids leads to an understanding of the results obtained in this study as a reflection of differences in the mechanisms of regulation of proliferation by FRO in fibroids. and in the EA tissue with a consistent decrease in its differentiation. At the same time, knowledge of the features of individual links in the regulation of FRO can play a role in prescribing antioxidant therapy for benign or malignant uterine tumors, when not only the type of antioxidant, but also the stage of tumor development at which its use is expected may be important. The results obtained in the study of moderately differentiated EA, which was characterized by significantly lower activity of the glutathione-dependent system in comparison with the tissue of highly and low differentiated EA, look particularly interesting. In our opinion, this group of tumors is interesting because they change the ratio of biochemical processes that still regulate tissue-specific functions and already provide the main signs of malignancy (active proliferation, attenuation of apoptosis, activation of neoangio- and neurogenesis), which entails morphological changes.

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