with an average correlation strength ($\chi 2 = 11.374$, $r = 0.118$, $p = 0.044$).

Elderly patients more often have an intima-media thickness of 0.9 cm, and senile patients - more than 0.9 cm thickness. The age distribution showed that the older the subjects are, the higher the thickness of their intima-media is.

Thus, the age factor enhances the degree of remodeling of the vascular wall of the carotid arteries, which is consistent with the works of other authors [3,4].

Comparative analysis of IMT as a function of gender shows that IMT in men is, on average, statistically significantly higher than in women. (1.11 ± 0.31; 1.18 ± 0.31 versus 1.08 ± 0.31 and 1.14 ± 0.30, $p = 0.04$).

Conclusion. Ethnicity-dependent variability of intima-media thickness of the common carotid artery was revealed in elderly and senile residents of the Republic of Sakha (Yakutia). Indirect changes in cerebral blood flow, which influenced the formation and development of cerebrovascular disorders, are due to ethnic, age and gender characteristics.

An analysis of intima-media thickness demonstrated that the Yakuts and Russians have significantly greater IMT than the Evens. In all groups with the second stage of chronic cerebral ischemia, hypoheterogeneous and large atherosclerotic plaques were the most common. When compared by gender, it is significantly higher in men. With age, a remodeling and thickening of this indicator in the form of an increase and hardening of plaques was observed.

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CREATION OF A MODEL OF OVARIAN CANCER IN IMMUNODEFFICIENT MICE OF THE BALB / C NUDE LINE

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The purpose of this study was to create an in vivo model of ovarian cancer allowing control of the dynamics of tumor growth and adequate data on its size. As a model Balb/c Nude mouse lines were used. Removal of the mouse ovary with an implanted tumor fragment under the skin made it easier to visualize and to control the dynamics of xenograft growth.

Keywords: ovarian cancer, PDX model, patient-derived xenograft, Balb/c Nude, xenograft, in vivo models.

Ovarian cancer (OC) is the fifth most common malignant tumor in females aged 55 to 69 years, and the fourth most common cancer in females aged 40-54 years. According to the data on the world morbidity, OC is diagnosed in 9.1 cases per 100 000 female population. According to the Rosstat statistics, 17.8 cases on average were registered per 100 thousand female population in 2016. OC causes more deaths than any other cancer of the female reproductive system in Russia: 7 616 women died from OC in 2018 [6].

OC has several histological and molecular subtypes. Serous carcinomas are the main group of malignant epithelial tumors of the ovaries. Low-grade serous carcinoma consists of cystic, papillary and solid components [11,13]. Early diagnosis of OC is complicated, and its therapy effect is poor, so it is important to study the nature of this disease and develop methods for its treatment using various biological models [7,8].

Today, one of the tasks of researchers creating various animal tumor models is to reproduce the complexity of the tumor

microenvironment. Different experimental models have their own advantages and disadvantages which may influence the subsequent results of translational studies of new chemotherapy and immunotherapy agents [9].

The development of PDX (patient-derived xenograft) models for cancer research is based on the assumption that these models are close to the original donor tumors. Transplantation of cancer cells or tissues can be heterotopic or orthotopic, and each method has its advantages and disadvantages. Heterotopic method is characterized by an easy implantation and accurate monitoring of the tumor size. Orthotopic transplantation is technically more complicated and often requires ultrasound or exploratory laparotomy to monitor the dynamics of the tumor node growth; however, the advantage of this method is the preservation of the microenvironment of human tumors [3]. Similar microenvironment and carcinogenesis of the xenograft and the donor tissue allow assessment of drug effectiveness by determining the degree of inhibition of tumor growth by studying the dynamics of tumor growth [2]. Tumor visualization is one of the main difficulties in creating an adequate PDX model of OC. Being unable to visualize the tumor in vivo, some researchers performed necropsy at the end of the experiment and measured the isolated fragments of xenografts [10,15]. Such method of measurements does not allow registering the individual dynamics of the xenograft growth.

That is why the aim of this study was to create an *in vivo* OC model allowing control of the dynamics of tumor growth and adequate data on its size.

Material and methods. Prior to the experiment, an approval of the ethics committee of National Medical Research Centre for Oncology № 4/82 from 30.06.2020 was obtained.

Tumor material. Patient V. diagnosed with serous ovarian carcinoma Gx T2-3NxM0 was the donor of the tumor material. The patient gave her informed consent for the use of the biological material. The ovarian tumor was surgically removed, and its fragment was placed in nutrient RPMI medium containing gentamicin (5%); the resulting material was purified from elements of necrotic masses and connective tissue and divided into fragments with a volume of 8 mm^3. The time from the moment of resection of the tumor material to the moment of its transplantation did not exceed 20 minutes, which is an important condition for the successful engraftment.

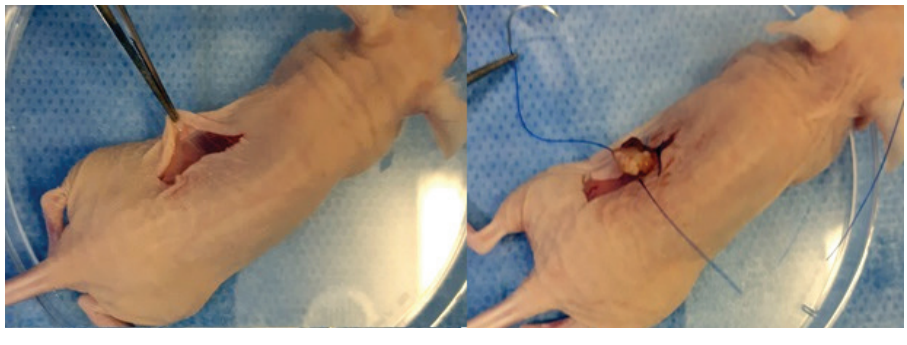
Animals. The experiment was carried out in accordance with the guidelines for the care and use of laboratory animals [1]. An orthotopic model of ovarian cancer was created in 20 female Balb/c Nude mice. The key characteristics of this strain is partial immunodeficiency of animals [5]. The age of the mice was 5 weeks, and their average weight was 22-24 g. The animals were kept in the SPF vivarium of the National Medical Research Centre for Oncology in individually ventilated cages at a temperature of 21-23 °C, with free access to food and water.

Creation of the PDX model of ovarian cancer. The animals were anesthetized prior to the implantation of tumor fragments. This procedure consisted of two stages: premedication with xylazine (injected at a dose of 1.5 ml/kg of body weight of Balb/c Nude mice) and anesthesia with zoletil (injected at a dose of 67.5 mg/kg of body weight of Balb/c Nude mice) [4]. After the mouse entered the surgical stage of anesthesia, it was placed on the operating table in a prone position. The skin of the animal was dissected parallel to the spine, below the costal arch; to make the manipulation easier, a second skin incision was made, 10 mm long, perpendicular to the first one. The skin flap was lifted to visualize the ovary (figure 1A) which was located between the spleen, pancreas (located above the ovary) and the kidney (located closer to the spine).

Then the abdominal wall was dissected parallel to the spine, and the ovary was removed into the surgical wound; the serous membrane was incised with a scalpel along the edge opposite to the vascular pedicle for 2 mm in the implantation area. The ovary was fixed from above to the peritoneum with a ligature, thus leaving it between the abdominal wall and the skin. A tumor fragment was implanted into the ovarian incision, sutured using a 6-0 suture under the control of an operating microscope (figure 1B). The abdominal wall and skin were sutured with a furrier's suture, a 4-0 ligature.

Subcutaneous tumor growth was observed during 8 weeks after xenotransplantation; measurements were performed twice a week using a caliper (GRIFF, Russia). Then necropsy was performed. The resected ovary was examined histologically.

Histological analysis. Tumor fragments were fixed in 10% formalin solu-



A B

Fig. 1. Surgical manipulations in the model creation. A - visualization of the ovary under the peritoneum of a Balb/c Nude mouse; B - implantation of tumor material into the ovary of an immunodeficient mouse

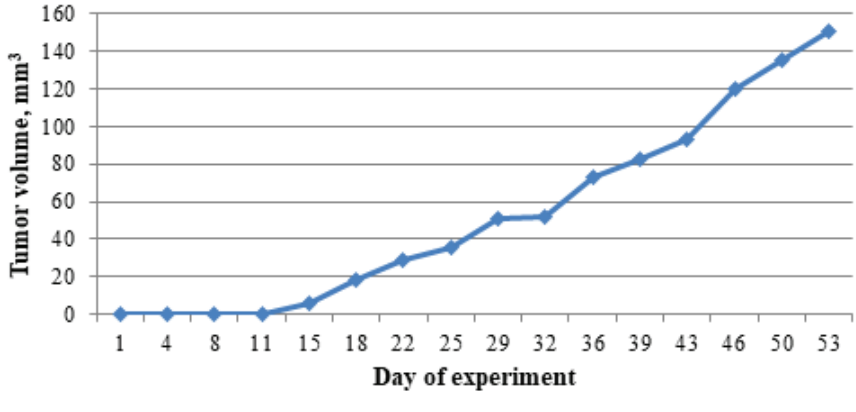


Fig. 2. Dynamics of the growth of an orthotopic xenograft of ovarian cancer during 8 weeks of observation.

tion for 24 h and dehydrated in alcohol and xylene baths. Then the tumor was embedded in paraffin, and micropreparations were prepared. Obtained sections were stained with hematoxylin and eosin. Histological preparations were examined under a light microscope. The primary tumor, PDX and the murine intact ovaries were analyzed histologically.

Results and discussion. During the observation of mice with implanted ovarian cancer, tumor growth was registered in 17 out of 20 operated mice, which accounted for 85% xenograft engraftment. After 8 weeks from the moment of inoculation, tumor nodules could be determined; their volume ranged from 130.43 to 170.1 mm^3. Figure 2 demonstrates the xenorgaft growth dynamics.

Note. Data are presented as averages. At necropsy, the tumor was separated from the ovary to create subsequent passages. Histological examination revealed that the donor tumor had the structure of serous carcinoma with the presence of psammoma bodies. Areas of solid structure were identified in the tumor. No foci of necrosis were found (figure 3 A).

Examination of a xenograft fragment revealed single tumor cells and their accumulations of various sizes and shapes infiltrating the ovarian stroma. Malignant cells were characterized by the presence of distinct small nucleoli and moderate nuclear polymorphism. Foci of cells with karyorrhexis and karyolysis, as well as rather extensive necrotic areas, were noted in the tissue. The data were obtained by light microscopy, and it showed that the tumor reproduced in the created PDX model was identical to the donor one. The histological picture in the experimentally reproduced tumor corresponded to serous carcinoma, and papillary and solid structures were determined in it. In addition, the solid component contained small psammoma bodies (figure 3 B, C).

One of the main disadvantages of creation of an orthotopic model of ovarian cancer is the complexity of visualizing the growth of a tumor node [14]. To solve this problem, we used a new approach to creating an OC model, and the ovary was transposed under the skin of the animal. The access of our laboratory to resected donor tumors ensured the timely delivery of biological material. This allowed xenograft engraftment in 85% cases. According to the literature, the engraftment of an ovarian cancer xenograft in the body of a recipient animal depends on the type of tumor, the transplantation site and the strain of immunodeficient mice; the period averages from 2 to 4 months, and the xenograft engraftment averages about 50% [3,12]. In our experiment, a high engraftment percentage was registered, and after 8 weeks the tumor node reached an average size sufficient for subsequent transplantation, which allowed creation of a model of ovarian cancer with adapted growth for its further use in experimental studies.

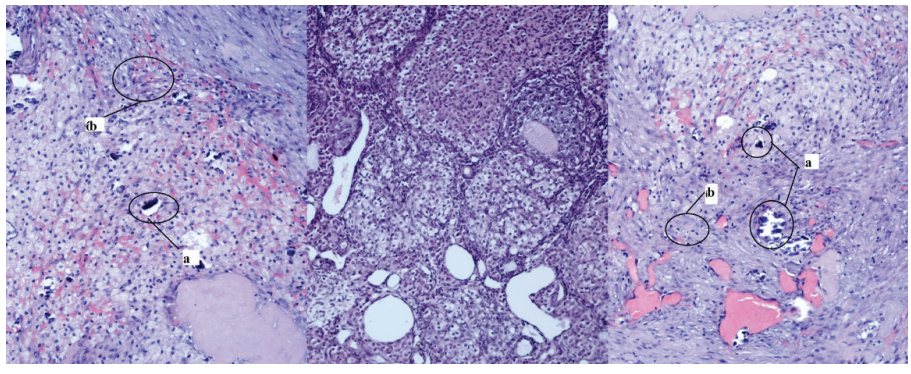


Fig. 3. Histological preparations of the patient's tumor, control ovarian tissue and xenograft. A - serous ovarian carcinoma (donor): a - psammary bodies; b – cancer cells; B - normal tissue of the murine ovary (control); C - tissue of ovarian cancer xenograft after the first passage in the recipient animal with the subcutaneous transposition of the ovary with the tumor: a - psammary bodies; b – cancer cells. Staining with hematoxylin and eosin. Magnification: x200.

Conclusion. A PDX model of ovarian cancer with orthotopic implantation of tumor material was created during the study. The originality of this work consists in a non-standard solution: transposition of the mouse ovary with a tumor fragment under the skin of an experimental animal, which allowed monitoring the development of an orthotopic xenograft without laparotomy or additional expensive equipment. This achievement contributes to the application of such a model in multiple studies.

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INTERRELATION OF THE CONTENT OF TRANSFERRIN, ERYTHROCYTES WITH THE FUNCTIONAL ACTIVITY LEUKOCYTES OF PERIPHERAL VENOUS BLOOD IN RESIDENTS OF THE EUROPEAN NORTH OF THE RUSSIAN FEDERATION

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The aim is establish the relationship between the content of transferrin, erythrocytes and the functional activity of leukocytes of peripheral venous blood in residents of the European North of the Russian Federation. Study included analysis of immunological parameters of 765 people, aged 18 to 89 years, living in the Arkhangelsk, of which 553 women aged 18-89 years and 212 men aged 18-84 years. It was found that increase in 49.21% of the examined individuals, the iron-containing protein increases against the background of a decrease in the content of the membrane transferrin receptor (CD71+). An increase in the content of transferrin is associated with an increase in the concentration of circulating IgG immune complexes in 44.21% of cases. With an increase in the concentration of transferrin in the blood in 27.95% of cases it is associated with a decrease in platelet count and in 24.08% - with a decrease in hemoglobin, mainly in men with increasing age. In 8.06% of the examined individuals, an increase in the level of transferrin is interrelated with an increase in the concentration of reagins. In 5.12% of cases, an increase in the transferrin content is associated with the activation of cell-mediated cytotoxicity, which is mainly supported by the pro-inflammatory cytokine IL-6. No association has been established between the increase in transport protein and the concentration of IL-10.

Keywords: transferrin, erythrocytes, hemoglobin, lymphocytes, cytokines, IgE, circulating immune complexes.

Background. The functions of the iron transport protein are not limited to participation in iron homeostasis [1]. Reference range of transferrin on the serum content is 170-340 mg / dL, in the bloodstream it is in a state of apo-, mono-, or bi-iron transferrin [2] and half-life is 8-12 days [3]. Normally, transferrin is saturated with iron by 20-30% [4,5], therefore, the iron-binding capacity is used only by 1/3. Iron transport protein with partial saturation, being a component of the antioxidant system, binds blood plasma iron and protects cell from disrupting membrane structures and reducing cell energy supply when intensifying lipid peroxidation processes [6]. In addition, iron binds to complexes with albumin, low molecular weight organic compounds, forming a pool of nontransferrin-bound iron [7,8]. The content of iron-binding protein is interrelated with the content of cells with a membrane receptor for transferrin [9,10]. In addition, when binding to receptors on the cell surface, transferrin is involved in the transport of metals: Zn, Co, Ga, Al. It should be taken into account that the content of transport proteins in the inhabitants of the North fluctuates within wide limits due to the pronounced photoperiodicity and intensity of the geomagnetic field [11,12].

The aim of the study was to establish the relationship between the content of transferrin and erythrocytes with the functional activity of leukocytes in peripheral venous blood in residents of the European North of the Russian Federation.

Material and methods. The immunological results of preanalytical and analytical stages of examination of 765 people were analyzed, including 553 women aged 18-89 years and 212 men aged 18-84 years, living in Arkhangelsk, who applied to the center of professional diagnostics "Biolam". The inclusion criteria are residence of the examined persons in Arkhangelsk and voluntary consent to the examination.

All stages of clinical laboratory examination were performed by medical workers of the laboratory of the center "Biolam": instruction on the rules of preparation for laboratory research, taking of biomaterial and its preliminary processing, application of analytical technology using appropriate reagents and equipment, obtaining examination results. Clinical and

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