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A.V. Maksimov, P.M. Ivanov, L.N. Afanasyeva, E.V. Tapyev

RENAL CANCER RESECTION WITH TARGETED BALLOON CHEMOEMBOLIZATION

The purpose of the study was to evaluate the content of endothelial vascular growth factor in the tissues of the kidney parenchyma, in the thickness of the tumor and in the blood serum of a patient during partial nephrectomy with intra-arterial administration of an anti-angiogenic drug.

Materials and research methods. The present study was carried out on the basis of an analysis of the results of surgical treatment of patients with kidney cancer. 8 patients with renal cell carcinoma in stage T 1 a N 0 M 0 organ-preserving surgery was performed in the amount of kidney resection with intra-arterial injection of the targeted drug Bevacizumab into the kidney artery. The concentration of vascular growth factor in the tumor, in the renal parenchyma, and in venous blood from the kidney was studied before the renal artery was clamped, during renal ischemia, and after the injection of Bevacizumab into the renal artery.

Results and discussion. With a sudden cessation of blood flow, the tumor releases the amount of vascular growth factor several times higher than the initial values: an increase in the concentration in the thickness of the tumor by 3 times, in the kidney parenchyma - 1.5 times, and in the venous blood - 3.5 times higher than before ischemia. Inactivation of the growth factor by the targeted drug caused a decrease in its level in the tumor tissue by 25%, in the kidney parenchyma by 10% and in the blood serum by 85.35%.

Conclusion. Intraoperative administration of a targeted drug at the time of acute tumor ischemia irreversibly binds the vascular growth factor released during hypoxia, and thus prevents neoangiogenesis in potential metastatic foci.

Keywords: kidney cancer, vascular endothelial growth factor, kidney resection.

Introduction. The discovery of the mechanisms of oncoangiogenesis has led to the creation of new approaches in the treatment of malignant neoplasms. Targeted drugs have firmly entered the routine practice of pharmacotherapy for various types of cancer. Various combinations of targeted and chemotherapy show ambiguous results, which encourages the search for new, non-trivial solutions in the fight against oncology. With regards to renal cell carcinoma, the situation is exacerbated by the peculiarities of the pathogenesis of kidney cancer. There is a lot of evidence in the literature of aggressive metastasis of kidney cancer - up to 30% of all newly diagnosed patients at the time of diagnosis have metastatic lesions of varying severity [2, 4, 10], and, despite the radical nature of the operation performed, these metastases progress to 20-40% of cases of all operations [1, 7]. Such an aggressive course of the disease requires systemic postoperative therapy [3]. In addition, after organ-preserving surgery, a third of patients may experience a relapse [8].

Thus, the treatment of renal cell carcinoma is a complex, completely unresolved problem of both surgical treatment and conservative therapy, since long-term targeted therapy has numerous side effects [9], affecting a wide variety of organs and systems. In some cases, these side effects can lead to death [5].

The threat of activation of kidney cancer metastases or tumor recurrence led to the invention of a new combined method of surgical treatment of malignant tumors of the renal parenchyma [6], which provides additional anti-relapse and antimetastatic protection of the body in organ-preserving surgical treatment of kidney cancer. It is well known that during acute ischemia, a cancerous tumor secretes special biologically active substances that promote the growth of additional vessels to improve the blood supply to the ischemic tumor. The group of these substances includes vascular endothelial growth factor (VEGF), which has the most active effect on neoangiogenesis. In this regard, substances were synthesized that inactivate VEGF by irrevers-

MAKSIMOV Alexander Vasilievich – PhD, Head of the Urology Department of the State Autonomous Institution of the Republic of Sakha (Yakutia) Republican Hospital №1 - National Center of Medicine, maximov_alex1971@mail.ru; **IVANOV Petr Mikhailovich** - MD, Professor, Head of the Department of Oncology of the Medical Institute of M.K. Ammosov North-Eastern Federal University, petr_ivanov_38@mail.ru; **AFANASYEVA Lena Nikolaevna** – PhD, Associate Professor of the Department of Oncology of the Medical Institute of M.K. Ammosov North-Eastern Federal University, lenanik2007@mail.ru; **TAPYEV Evgeny Viktorovich** – doctor of the Medical Genetic Center of the Republican Hospital №1 - National Center of Medicine, junior researcher, Research Laboratory Molecular Medicine and Human Genetics of the M.K. Ammosov North-Eastern Federal University, t-evgeniy@list.ru

ible binding to it, and thus prevent further growth of tumor vessels. Local injection of a targeted angiogenesis inhibitor into an artery feeding a segment of the kidney with a tumor at a precisely chosen time of acute ischemia of the tumor during resection of the tumor will lead to the fact that the released growth factor will be immediately inactivated by irreversible binding to the targeted drug, which will minimize the possibility of growth pathological vessels for tumor recurrence or growth of metastatic foci.

Materials and methods. To assess the effectiveness of intra-arterial administration of a targeted drug at the time of resection of a kidney tumor, the content of VEGF was measured in the thickness of the tumor tissue, in the renal parenchyma adjacent to the tumor, and in the venous blood serum taken from the lumen of the renal vein. The studied samples were taken 3 times during lumbotomy resection of a kidney with a malignant tumor: in the native state - before clamping the vascular pedicle of the kidney, a fragment of tumor tissue measuring 5 x 5 x 5 mm, a similar size area of the renal parenchyma, in close proximity to the tumorous tissue and venous blood aspirated with a syringe in a volume of 3 ml from the renal vein. Immediately after taking the first batch of material, a clamp was applied to the vascular pedicle, stopping the blood flow in the kidney. After an exposure time of 5 minutes, the second batch of laboratory material was taken: similar samples were taken from the thickness of the tumor mass, from the kidney tissue and venous blood by puncture of the renal vein distal to the clamp. After the removal of the material was completed, the lumen of the renal artery distal to the clamp was punctured, and the targeted drug Bevacizumab 2.5 mg, dissolved in 10 ml of saline, was injected into the artery. solution. After 5 minutes of exposure with a fringing incision, 5 mm away from the edge of the tumor, the formation was resected within healthy tissue. After suturing the wound of the parenchyma of the kidney with P- and Z - shaped interrupted sutures, before starting the blood flow, the renal vein was repeatedly punctured and 3 ml of venous blood from the kidney was drawn into the syringe.

The obtained material was labeled in test tubes and sent to a specialized laboratory in its native state.

The above study was performed in 8 patients with a diagnosed kidney tumor stage T 1 a N 0 M 0, in whom, according to the results of computed tomography, malignant neoplasms were found, 2.4–4.8 cm in size, with signs of contrast accumulation, subject to organ-preserving surgery. All patients gave their consent to conduct a scientific study and signed the ethical protocol of the North-Eastern Federal University named after M.K. Ammosov.

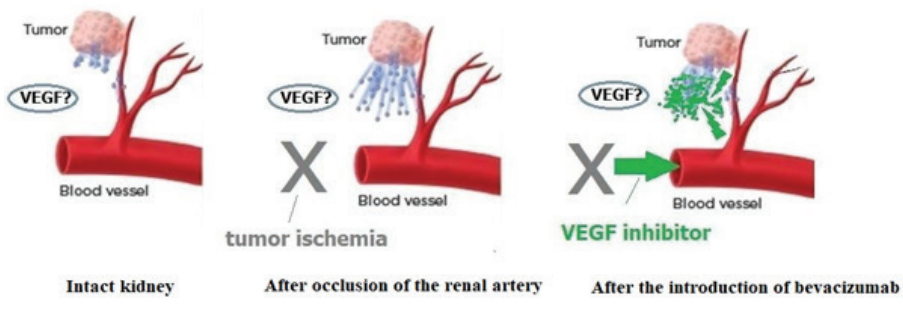

Fig. 1. Scheme for assessing the level of endothelial growth factor in the experiment

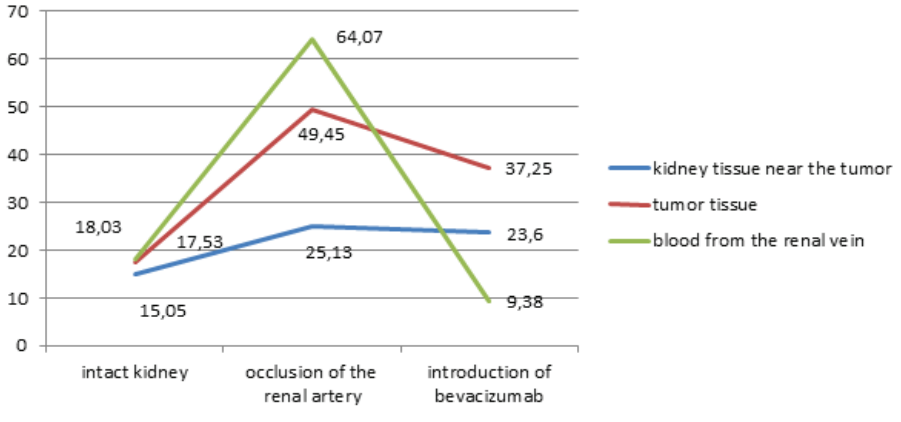

Fig. 2. Dynamics of VEGF content in preparations during the experiment (pg/ml)

Histological examination of the surgical material in all resected formations revealed a clear cell variant of kidney cancer. The early postoperative period was uneventful, and all patients after control studies were discharged for outpatient follow-up.

Quantitative assessment of the VEGF content in the studied samples was performed by enzyme immunoassay using diagnostic reagents HEA 143 Hu (Cloud - Clone Corp., USA). The standard sample preparation consisted in separating the material in a centrifuge with an acceleration of 1000 G for 20 min at a temperature of plus 4°C. The separated serum was analyzed immediately or, if necessary, kept at minus 20°C for a week.

The material obtained before grinding in a homogenizer was washed with chilled phosphate-buffered saline according to the instructions (Invitrogen , USA) and mixed with lysis buffer IS 007 (Cloud - Clone Corp. , USA). The resulting suspension was homogenized on ice using Qsonica ultrasound. Q 125 (Qsonica , USA) with parameters of pulse duration of 5 min, amplitude of 50% and a break of 5 min 2 times. The homogenizate was separated in a centrifuge with an acceleration of 1000 G for 5 min at a temperature not exceeding 4°C. The supernatant after sample preparation was subjected to enzyme immunoassay immediately or delayed, with storage conditions at t -20 °C for no more than 7 days. The results obtained by enzyme immunoassay were

VEGF levels in preparations (pg/ml)

	Intact kidney	Occlusion of the renal artery	Introduction of bevacizumab
Kidney tissue near the tumor	15.04	25.13	23.6
Tumor tissue	17.53	49.45	37.25
Blood from the renal vein	18.03	64.07	9.38

recorded with an SLT plate photometer. Spectra II (Tecan , USA) according to the instructions, with data processing by the MultiCalc software package (Wallac, Finland) .

The analysis of the obtained data was carried out using SPSS statistical packages (Windows version 7.5.2). The significance of differences between quantitative indicators was assessed by Student's t test for normally distributed values. Differences were considered significant at $p < 0.03$.

Results and discussion. The histological conclusion of all operated tumors showed the presence of a clear cell variant of renal cell carcinoma.

The obtained concentration of vascular growth factor in the course of experimental work is presented in Table No. 1 and the dynamics of its changes is shown in Figure No. 2. At the initial point, without any effect on the organ with the tumor, the levels of the growth factor in the tumor, in the peritumorous renal parenchyma and in the venous blood are at the same level (15.4-18.03 pg/ml). As mentioned above, acute ischemia of a cancerous tumor leads to a sharp hyperproduction of VEGF by oncocytes in a state of hypoxia: an increase by 182.08% is noted in the tumor itself, by 66.97% in the parenchyma tissue adjacent to the neoplasm, and an increase by 255.35%. Such an uneven increase in vascular endothelial growth factor is associated with the peculiarity of the redistribution of the produced substance under conditions of cessation of blood flow - the most active deposition occurs in venous blood, its least diffusion occurs in the tissue of the surrounding parenchyma of the kidney.

Based on the mechanism of its interaction, the targeted antiangiogenic drug bevacizumab, injected into the renal artery, irreversibly binds to the released vascular growth factor. It should be noted that the receptors of the monoclonal antibody produced by VEGF were immediately captured by the receptors - already 5 minutes after the administration of the drug, a significant decrease in the level of growth factor was recorded in the studied tissue samples: in the renal vein, a decrease by 85.35%, in the tumor tissue - by 24.67% and in peritumorous in the kidney parenchyma, the concentration of growth factor is reduced by 6.08%.

In the postoperative period, all operated patients did not show any shifts from the usual course of the postoperative period; the performed control studies of general clinical analyzes did not differ from the preoperative ones. All patients were discharged home in a satisfactory condition after removal of postoperative sutures.

The study clearly demonstrates the process of triggering oncological neoangiogenesis - acute hypoxia of cancer cells immediately leads to the production of substances aimed at the growth of new blood vessels to improve tumor nutrition. The obtained evidence of immediate activation of tumor angiogenesis explains the reason for the increased growth of metastases in 30% of cases after organ-preserving surgery: acute ischemia of the tumor during the temporary shutdown of blood flow in the operated organ is accompanied by a sharp release of VEGF , the start of blood flow after the completion of the main surgical procedure spreads the growth factor accumulated in the kidney throughout body and promotes additional vascularization of possible metastatic lesions.

Taking into account the above time factor of the mechanism of activation of possible metastases or relapses of a malignant neoplasm, it is advisable to introduce a commercial antiangiogenic drug into the arterial bed of the operated organ immediately at the time of acute ischemia during surgical treatment.

To achieve this goal, a technique for balloon chemoembolization and resection of malignant tumors of parenchymal organs has been developed and patented [6]. The essence of the technique is as follows: immediately before the operation, by means of selective renal angiography, a segmental branch of the renal artery is selected, feeding the segment with the tumor. Its location and diameter are estimated. Under x-ray control, a coronary balloon catheter with a coaxial channel is inserted into the established segment of the segmental artery (Figure No. 3). A solution of bevacuzimab, a monoclonal antibody that binds to vascular endothelial growth factor, is injected through the canal into the segment of the kidney with the tumor (Figure 4). Immediately after the injection of the drug, the balloon is inflated and thereby occludes the lumen of the artery, stopping the blood flow in the segment. Acute tumor ischemia, as mentioned above, entails a sharp release of VEGF , which irreversibly binds to the injected target substance. After achieving chemoembolization of the kidney parenchyma, the tumor is resected within healthy tissues by laparoscopic access (Figure No. 5). After reaching the final hemostasis, the balloon is deflated and removed from the artery, resuming the blood supply to the kidney (Figure #6).

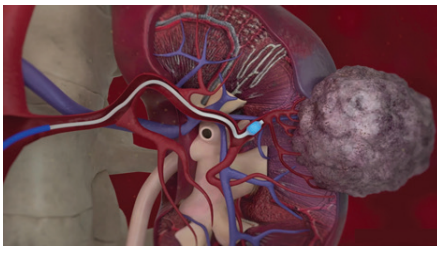

Fig. 3. Superselective balloon embolization of the renal artery

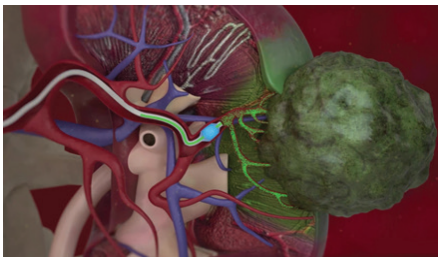

Fig. 4. Introduction of a targeted drug into a segment of the kidney with a tumor

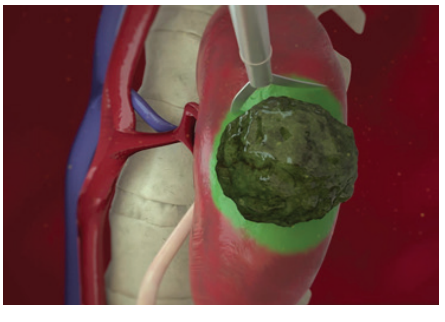

Fig. 5. Resection of the kidney tumor

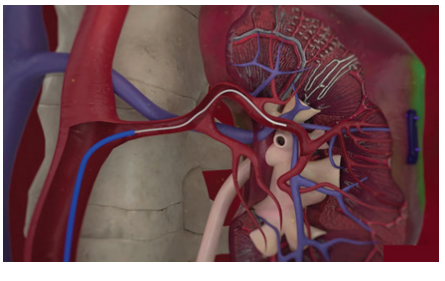

Fig. 6. Removing the balloon and starting blood flow

Thus, the presented method of resection of kidney tumors with preliminary balloon embolization and with the introduction of a targeted drug into the tumor provides an opportunity for minimally invasive, low-traumatic, functionally oriented, radical and carcinoprotective removal of a malignant formation of the renal parenchyma, based on the principles of laparoscopic surgery using transluminal endovascular aids, supplemented targeted, dosed and accurately timed administration of a chemotherapy drug that has an anti-relapse and anti-metastatic effect.

Conclusion. The study showed an immediate massive release of endothelial vascular growth factor by tumor tissue in the event of acute ischemia, and its equally immediate inactivation by a targeted drug, which indicates the need for timely, targeted and dosed administration of a chemotherapy drug. The proposed method of targeted chemoembolization most fully meets the above criteria and, together with superselective balloon embolization, allows the most minimally traumatic, with maximum preservation of organ function, safely, economically, and at the same time, radically and carcinoprotectively, to remove a malignant tumor of the kidney. In the context of the growing incidence of kidney cancer throughout the world, with the expansion of the arsenal of radiation diagnostic methods, the need for organ-preserving operations on the kidney increases every year, and this technique can significantly help in solving this problem.

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ORGANIZATION OF HEALTHCARE, MEDICAL SCIENCE AND EDUCATION

L.N. Afanasyeva, A.V. Alekhnovich, A.A. Kalininskaya, A.V. Lazarev, M.V. Kizeev

MEDICAL AND DEMOGRAPHIC SITUATION IN THE REPUBLIC OF SAKHA (YAKUTIA)

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УДК 614.2

AFANASYEVA Lena Nikolaevna – M.K. Ammosov North-Eastern Federal University, Medical Institute (Yakutsk). SPIN: 5567-4610, AuthorID: 536271 https://orcid.org/0000-0003-2592-5125; **ALEKHNOVICH Alexander Vladimirovich** – MD, Professor, deputy head for Research and Scientific Work, Federal State Budgetary Institution A.I. A.A. Vishnevsky Central Military Clinical Hospital No3, Ministry of Defense, Russia, 143420, Russia, city district Krasnogorsk, e-mail: vmnauka@mail.ru, https://orcid.org/0000-0002-8942-2984; **KALININSKAYA Aleftina Aleksandrovna** – MD, Professor, chief researcher, Public Health Research Department, Federal State Budgetary Scientific Institution N.A. Semashko National Research Institute of Public Health, e-mail: akalininskya@yandex.ru, https://orcid.org/0000-0002-6984-6536, SPIN: 3315-1595, Scopus Author. ID: 55791248200; **LAZAREV Andrey Vladimirovich** – PhD, researcher, N.A. Semashko National Research Institute of Public Health, e-mail: andrey.v.lazarev@gmail.ru. https://orcid.org/0000-0001-6574-7875; **KIZEEV Mikhail Vladimirovich** – PhD, researcher, Department of Medical and Social Problems, Federal State Budgetary Scientific Institution N.A. Semashko National Research Institute of Public Health, (https://orcid.org/0000-0002-0293-8372

In the Republic of Sakha (Yakutia) for the period 2015-2020, an increase in mortality and a decrease in fertility were noted, as well as higher rates of primary morbidity, including in the class of respiratory diseases, 1.4 times higher than in the Russian Federation, while the incidence rate of COVID-19 was higher; also, higher incidence of digestive diseases was noted (1.7 three times higher than in the Russian Federation). Indicators of primary morbidity of children and adolescents are higher than those of the total population in almost all classes of diseases for all 6 years of analysis (2015-2020). Differences in the indicators of primary morbidity in uluses (regions) of the Republic of Sakha (Yakutia) are higher by 3.3 times, which is associated with difference in availability of medical care in different areas of residence. The information obtained is important for development of management decisions at the regional level.

Keywords: medical and demographic situation, mortality, morbidity, age groups, uluses.

Introduction. The key objectives of the national project «Demography» are to improve the medical and demographic situation, reduce the morbidity of the population, increase the birth rate and healthy life expectancy [7, 4, 12, 8].

Geographical, climatic, territorial, national and ethnic features in Russia determine the inequality in the provision of medical care to the population [9]. The Far Eastern Federal District (FEFD) is the largest and most strategically important region in Russia and in the Asia-Pacific area. Since the 1990s, there has been a decline in population at a catastrophic rate in the Far Eastern Federal District, including the Sakha Republic (Yakutia) [11, 3, 10].

The COVID-19 pandemic has exacerbated the challenges of rising noncommunicable diseases (NCDs); scientific studies have shown that NCDs are risks of poor outcome [2, 6]. The way out of the demographic crisis requires an increase in the effectiveness of assistance, taking into account the regional characteristics of the territories [5].

Purpose of the Study. Based on the study of demographic indicators and a comparative analysis of the incidence in the Sakha Republic (Yakutia), in the Far Eastern Federal District and in the Rus-