

tem, immunity and nonspecific resistance in dental patients and methods of their correction/I.S. Pinelis//Transbaikal Medical Journal. – 2004. – №4. – Pages 80-82.

35. Pinelis I.S. Features of bioregulatory therapy of dental diseases/I.S. Pinelis, B.I. Kuznik, Yu.I. Pinelis//Transbaikal Medical Bulletin. – 2019. – №1. – Pages 173-186.

36. Pinelis Yu.I. Pathogenetic mechanisms of chronic generalized periodontitis in patients of old and senile age: dissertation... Doctors of Medical Sciences/Yu.I. Pinelis. - Chita, 2013. – 237 pages.

37. Simanovskaya O.E. Impact of dental health on quality of life/O.E. Simanovskaya//

Dentistry. – 2008. – V.87, No. 5. – Pages 75-77.

38. Tarasova Yu.G. The significance of social factors in determining the life quality in patients with chronic generalized periodontitis/Yu.G. Tarasova//Institute of Dentistry. – 2011. – №2. – 51. – Pages 22-23.

39. Frequency and structure of pathological processes of periodontal tissues of inflammatory-destructive nature in the population of the Far Eastern region/M.B. Suvyrina, I.D. Ushnitsky, A.V. Yurkevich [et al.]/Yakutsk medical journal. – 2018. – №3. – Pages 71-74. DOI: 10.25789/YMJ.2018.63.24

40. IRF6 Regulates the Expression of IL-36 by human oral epithelial cells in response to Porphy-

romonas gingivalis / Huynh J., G.M. Scholz, J. Aw [et. al.] // The journal of immunology. – 2016. – Vol.196. – №5. – P.2230.

41. Olsen I. Modulation of inflammasome activity by Porphyromonas gingivalis in periodontitis and associated systemic diseases / I. Olsen, O. Yilmaz // Journal of oral microbiology. – 2016. – №8. – P.383-385. DOI: org/10.3402/jom.v8.30385.

42. Periodontitis induced by Porphyromonas gingivalis drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response / Blasco-Baque V., Garidou L., Pomie C. [et al.] // Gut. February. – 2016, DOI: 10.1136/gutjnl-2015-309897.

DOI 10.25789/YMJ.2021.73.09

A.V. Maksimov, P.M. Ivanov, F.G. Ivanova, P.A. Neustroev

ANTI-RELAPSE TARGETED CHEMOEMBOLIZATION AS AN ADJUNCT TO RENAL CANCER RESECTION

Aim: to assess the saturation of the surgical margin of the kidney resection with a chemotherapy drug in order to determine the effectiveness of targeted balloon chemoembolization during parenchymal organ resection for the prevention of tumor recurrence

Materials and methods. The study is based on the results of experimental experiments on laboratory animals. The concentration of the marker in the parenchyma of the organ was determined for 8 days with its transarterial administration when simulating the resection process followed by wound closure.

Results and discussion. The data obtained clearly demonstrated the prolonged fixation of the marker in the tissues of the surgical edge of the resected organ.

Conclusion. Transarterial balloon embolization with a targeted drug for resection of the parenchymal organ may be effective for the prevention of tumor recurrence due to the duration of high concentrations in the surgical margin of resection.

Keywords: Kidney cancer, renal tumor recurrence, targeted balloon chemoembolization

Introduction. Kidney cancer occupies 2–3% of all human malignant neoplasms, and 90% of kidney tumors are localized in the renal parenchyma. The annual global increase in the incidence of kidney tumors is 2%, [13]. In Russia, this figure is slightly higher and amounts to about 3–4% [2]. Given the high growth rates of this pathology, the search for the most effective methods of treatment is an urgent problem of modern medicine.

Rudolf Virchow in 1865 noted the abundant blood supply to tumor tissue, but only 100 years later J. Folkman in 1971 suggested the dependence of tumor growth on the development of capillary blood supply, under the influence of certain substances produced by the tumor itself [7]. Since that time, an extensive search for angiogenesis inhibitors and their use in the treatment of oncological diseases began. For a long time, it was believed that a tumor mass with a volume of less than 2 mm³ does not have its own blood supply and that vital functions in it are supported by its own supply of energy substrates and diffusion of oxygen from the surrounding tissue. When a tumor grows beyond this volume, oncocytes located in the center of the formation undergo acute hypoxia and stimulate the processes of oncoangiogenesis [8]. The results of studies of C. Li showed that oncoangiogenesis is triggered in a formation consisting of 100–300 cells, when microvessels are formed to feed the tumor mass [12]. Substances that activate angiogenesis were first described by N. Ferrara in 1989 and constitute a group of vascular endothelial growth factors (VEGF) [6].

When VEGF interacts with the corre-

sponding receptor on the endothelial cell surface, the receptor is activated, which leads to the launch of a cascade of intracellular mediators reaching the cell nucleus and the final result of which is the initiation of genes responsible for angiogenesis [15]. Disclosure of the mechanisms of oncoangiogenesis led to the creation of a whole group of drugs that block angiogenesis in malignant tumors of various localization [1].

The first targeted drug, bevacizumab, which is a monoclonal antibody, was presented in 2003 and showed an increase in oncological patient survival in clinical studies [9, 14]. In the treatment of advanced renal cell carcinoma, the use of bevacizumab led to a decrease in tumor size and increased the duration of the relapse-free period [5]. Inhibitors of vascular endothelial growth factors block the site that binds to the corresponding receptor and thereby prevent its activation and further transmission of the angiogenic impulse, which in turn inhibits the proliferation of endothelial cells, preventing the formation of a pathological vascular network. In addition, the action of bevacizumab induces apoptosis of endothelial cells of tumor vessels [4]. It is noteworthy that the effect of antiangiogenic therapy

MAKSIMOV Alexander Vasilievich - Head of the Urology Department of the State Autonomous Institution of the Republic of Sakha (Yakutia) Republican Hospital No. 1 - National Center of Medicine, maximov_alex1971@mail.ru; **IVANOV Petr Mikhailovich** - Doctor of Medical Sciences, Professor, Head of the Department of Oncology of the Medical Institute of the North-Eastern Federal University named after M.K. Ammosov, petr_ivanov_38@mail.ru; **IVANOVA Feodosia Gavril'yevna** - PhD, Head of the Department of Anticancer Drug Therapy of the State Budgetary Institution of the Republic of Sakha (Yakutia) Yakutsk Republican Oncological Dispensary, feodossiaiv@inbox.ru; **NEUSTROEV Petr Afanasyevich** - PhD, Associate Professor of the Department of Hospital Surgery and Radiation Diagnostics of the Medical Institute of the North-Eastern Federal University named after M.K. Ammosov, neusman14@gmail.com.

with monoclonal antibodies develops on the first day after the start of treatment [10], which is associated with the extracellular mechanism of action of drugs of this series.

Materials and research methods.

The currently existing methods of organ-preserving operations for malignant neoplasms, with all their positive characteristics, are devoid of a specific anti-relapse component. Prevention of relapse consists in resection of the affected area of the organ with a supply of healthy tissue, determined macroscopically, and removal of the tissues adjacent to the formation. As a result, the inevitable acute ischemia of tumor tissue is accompanied by a massive release of vascular endothelial growth factors, which, entering the systemic circulation, act on the receptors of epithelial cells, and thereby trigger recurrent neo-oncoangiogenesis. At the same time, relapse can give not only marginal continued growth from the remaining tumor, but also the emergence of a tumor de novo from microscopic oncocytes located outside the resection zone in the primary-multiple nature of the disease.

Taking into account the mechanism of oncoangiogenesis and the principle of antiangiogenic targeted therapy, a method of balloon chemoembolization and resection of malignant tumors of parenchymal organs has been proposed (RF patent for invention No. 2711549 "Method for balloon chemoembolization and resection of malignant tumors of parenchymal organs", Maksimov A.V., Neustroev P.A., 17.01.2020, State Register of Inventions of the Russian Federation).

The essence of the method is as follows: under X-ray control, selective angiography is performed, which determines the segmental artery of the organ supplying blood to the segment with the formation. A balloon catheter with a central channel for the administration of drugs, with a balloon size sufficient to block blood flow, is inserted into the selected artery under X-ray control. Inflation of the balloon stops arterial blood flow in the parenchyma segment of the organ. Then, bevacizumab is injected through the central canal of the balloon catheter into the ischemic segment, after which the tumor is resected within the intact tissue. The wound of the organ parenchyma is sutured with hemostatic sutures, after which the balloon is deflated and removed from the vessel lumen.

The current practice of prescribing targeted chemotherapy in the long term after the operation is not effective enough due to the late onset: the vascular growth

factor formed as a result of acute hypoxia of tumor tissue provides active growth of the pathological vascular network, and the action of angiogenesis antagonists does not apply to already formed tumor vessels, which contributes to the recurrence of the oncological process. Thus, the timely saturation of the parenchyma adjacent to the tumor with a targeted drug creates a trap barrier for the VEGF secreted by the formation, thereby preventing its influence on potential recurrent foci.

An important role in this protection is played by the time factor - how long the targeted drug can persist in the resection margin, since oncocytes have an increased potential for survivability. In this regard, the goal of our study is to assess the saturation of the surgical margin with a chemotherapy drug and the duration of saturation during resection of the parenchymal organ for the prevention of tumor recurrence. To assess the duration of drug fixation in the surgical margin of resection of the parenchymal organ, we performed an experiment on laboratory animals, simulating the transarterial administration of the drug during resection by the example of using a marker - food dye Ponso S introduced into the parenchyma of the kidney of laboratory rabbits.

We used 14 laboratory rabbits weighing 2400-2600 g, New Zealand White breed. When working with laboratory animals, we used the recommendations of the "Animals in Research: Reporting In Vivo Experiments" manual [11], in compliance with international standards and bioethical norms, in accordance with the European Convention for the Protection of Vertebrate Animals used for Experiments or Scientific Purposes, Declaration of Helsinki on the Humane Treatment of Animals [3].

A diagram of the experimental operations is shown in Fig. № 1. Laparotomy was performed on two rabbits under mask ether anesthesia (Fig. №. 1) with further isolation of both kidneys. After isolation, the upper third of both kidneys were sutured with U-shaped sutures, in the transverse direction, while the nodes were not tightened. Then a 21 G cannula, 25 mm long, was inserted into the lumen of the aorta below the renal artery discharge, its end was inserted proximally, above the renal arteries. Through the cannula into the lumen of the aorta, a jet infusion of a solution of food coloring Ponso S in physiological saline was carried out at a rate of 100 mg / l in a volume of 5 ml. At the time of administration of the marker solution, knots were tied on the renal parenchyma, so as to

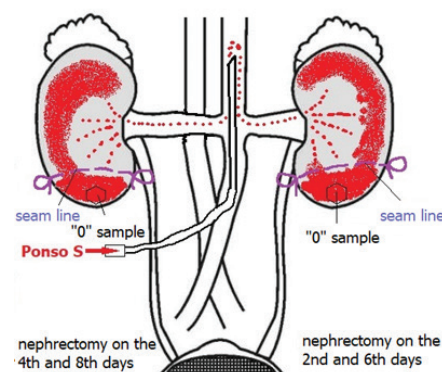


Fig. 1. Scheme of the operation on experimental animals

cause ischemia of the organ site. The resulting model of kidney resection with preliminary saturation of the parenchyma of the resection zone with a marker and with the imposition of hemostatic sutures clearly demonstrated the process of fixation of the targeted drug injected through the artery into the parenchyma adjacent to the tumor. After suturing the kidney, a 2 x 3 mm tissue fragment was taken from the ischemic region of the kidney for an initial assessment of the concentration of the marker in the parenchyma and a similar fragment of the parenchyma from the blood supplied part of the organ. In this way, zero dye values were obtained. The operation was completed by suturing the abdominal wound. After 2 days, one rabbit underwent nephrectomy of kidney №1, after 4 days, the same animal underwent nephrectomy of kidney №2 on the other side. In the second rabbit, the kidneys №3 and №4 were removed after 6 and 8 days. At the end of the last operation, all experimental animals were injected into the aorta with a solution of potassium chloride for cardioplegia, whereby the animals were removed from the experiment.

Thus, we obtained the values of the Ponso S marker concentration in the parenchyma of the ischemic and blood-supplied areas of the kidneys at the time of dye injection and with the dynamics of elimination within 2, 4, 6 and 8 days after the operation.

Results and discussion. The quantitative assessment of the concentration of the introduced dye into the renal parenchyma and the determination of the rate of marker elimination from the resection margin made it possible to estimate the duration of high concentrations of the chemotherapy drug in the organ parenchyma. For this, the initial specific gravity of the marker in the parenchyma at the time of administration was determined in both experimental animals, then the con-

Ponceau S concentration in kidney parenchyma, mg/l (p=0,024)

	Kidney №1	Kidney №2	Kidney №3	Kidney №4
Initial, on the day of administration	27,25 (100)	26,4 (100)	22,96 (100)	28,4 (100)
Study timing	2-й	4-й	6-й	8-й
Ischemized parenchyma (margin of resection)	16,55 (60,73)	15,18 (57,5)	12,65 (55,09)	14,82 (52,85)
Healthy parenchyma	7,7 (28,25)	3,36 (12,72)	2,45 (10,67)	2,46 (8,77)

tent of the substance in the tissue was assessed after 2 and 4 days in one rabbit, after 6 and 8 days in the second of this pair. For comparison, the concentration of the dye in the healthy, non-ischemic part of the kidneys was evaluated. Data were analyzed using statistical packages SPSS (Windows version 7.5.2). The reliability of differences in quantitative indicators was determined by the Student's t test for normally distributed values. Differences were recognized as significant at $p < 0.05$. The data obtained as a result of the experiments are presented in table.

Taking the initial, on the day of administration, the content of the marker in the parenchyma as 100%, to eliminate the effects of individual characteristics (age, condition of the animal, organ size, speed and amount of the injected drug), the concentration of the substance can be presented as a percentage of the initial one. The data obtained as a result of the experiments are presented in table No. 1. A clear dynamics of elimination is shown in Figure 2.

The graph shows that the clearance of the drug injected into the parenchyma and fixed with sutures at the edge of the resection is less than the separation from the parenchyma marker, the blood-supplied part of the organ. The quantitative

expression of this process: the concentration of the substance in the stitched part of the organ decreases after 2 days by 1.64 times, and in the blood-supplied part of the kidney - a decrease from the initial figures by 3.57 times. Elimination of the drug from the kidneys continues throughout the observation period, but its rate in the zone of organ ischemia is less than the rate of decrease in the concentration of the substance from the tissue of the intact kidney area.

The presented data prove the fact of long-term persistence of the substance introduced into the renal parenchyma through the arterial bed and fixed with hemostatic sutures. Moreover, more than 50% of the initial level remains for 8 days. A substance introduced into an organ and not fixed by sutures loses more than 90% of its original concentration.

Conclusion. The performed study proves that the duration of high concentrations of targeted chemotherapy drugs in the surgical margin of resection may be sufficient for effective prevention of tumor recurrence.

Methods of nephrons-sparing surgery have recently firmly occupied their niche in the arsenal of surgical treatment of malignant kidney tumors. The functional safety, low invasiveness and radicality of these methods

certainly deserve the highest assessment, but at the same time one important aspect of the treatment of malignant neoplasms of the parenchymal organs is missed - the danger of tu-

mor recurrence. Supplementing surgical organ-preserving treatment with local targeted chemotherapy, based on one of the mechanisms of tumor recurrence and the principles of antiangiogenic therapy, will block this vector of disease recurrence.

References

1. Banyra O.B., Shulyak A.V. Angiogenesis Inhibition in Renal Cell Carcinoma (RCC) Treatment: Mechanisms, Especialities and Perspectives. *Experimental and Clinical Urology*. 2011; 1: 59–68.
2. Kaprin A.D., Apolikhin O.I., Sivkov A.V. Analysis of urological morbidity and mortality in Russian Federation for 2003–2013. *Experimental and Clinical Urology*. 2015; 2: 4–12.
3. European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS No.123). *Appendix A «Guidelines for the maintenance and care of animals»*. Strasbourg, 18.03.1986.
4. Bergers G., Benjamin L.E. Tumorigenesis and the angiogenic switch. *Nature Rev. Cancer*. – 2003. – № 3 (6). – p. 401–410.
5. Costa J.L., Drabkin H.A. Renal cell carcinoma: new developments in molecular biology and potential for targeted therapies. *The oncologist*. 2007; 12: 1404–15.
6. Ferrara N., Carver-Moore K., H. Chen, et al. Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature*. 1996; 380(6573): 439–42.
7. Folkman J. The vascularization of tumors. *Sci Am*. 1976; 234(5): 58–64.
8. Folkman J. Fighting cancer by attacking its blood supply. *Sci Am*. 1996; 275: 150–4.
9. Gunther J.B., Gunther M.M., Altaweel Bevacizumab (Avastin) for the treatment of ocular disease. *Survey of Ophthalmology*. 2009; 54(3): 372–400. doi: 10.1016/j.survophthal.2009.02.004
10. Inai T., Mancuso M., Hashizume H. et al. Inhibition of vascular endothelial growth factor (VEGF) signaling in cancer causes loss of endothelial fenestrations, regression of tumor vessels, and appearance of basement membrane ghosts. *Am. J. Pathol*. 2004; 165(1): 35–52.
11. Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research / C. Kilkenny, William J. Browne et al. *PloS Biol*. 2010. 8 (6): 94–9
12. Li C.Y., Shan S., Huang Q., et al. Initial stages of tumor cell-induced angiogenesis: evaluation via skin window chambers in rodent models. *J. Nat. Cancer Inst*. 2000; 92(2): 143–7.
13. Ljungberg B., Bensalah K., Canfield S. et al. EAU Guidelines on Renal Cell Carcinoma: 2014 Update. *Eur. Urol*. 2015; 67(5): 913–24. doi: 10.1016/j.eururo.2015.01.005.
14. Mukherji S.K. Bevacizumab (Avastin). *American journal of neuro-radiology*. 2009; 31(2): 235–6. doi: 10.3174/ajnr.a1987
15. Rosen L.S. Clinical experience with angiogenesis signaling inhibitors: focus on vascular endothelial growth factor (VEGF) blockers. *Cancer Control*. 2002; 9: 36–44.

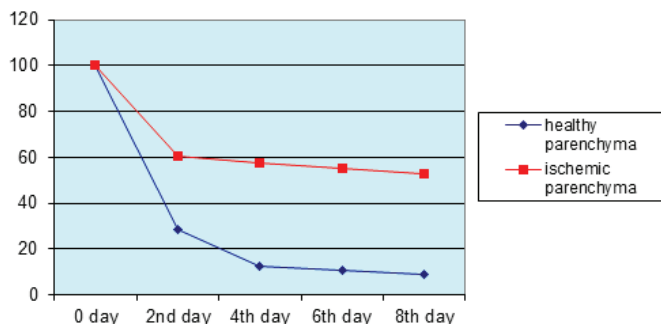


Fig. 2. The dynamics of Ponceau S elimination from kidney parenchyma, %.