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

DURATION OF DRUG FIXATION AT THE EDGE OF RESECTION DURING TARGETED CHEMOEMBOLIZATION

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The aim: to determine the duration of drug presence in the parenchyma, introduced into the edge of resection and fixed with a hemostatic suture.

Materials and methods. The present study is based on the results of 13 experimental operations on patients with malignant neoplasms of the renal parenchyma. A dynamic assessment of the content of contrast agents at the edge of the resection, after their introduction through the renal artery, was performed.

Results and discussion. Transarterial injection of a contrast agent into the renal parenchyma and its subsequent fixation at the edge of resection with a hemostatic suture, maintains a high concentration of the drug for a week after surgery Conclusion. The presence of high concentrations of the targeted drug at the margin of the kidney resection in the early postoperative period will create an additional barrier of anti-contraction protection.

Keywords: Kidney cancer, balloon targeted chemoembolization.

Introduction. In the Russian Federation in 2018, kidney cancer was diagnosed for the first time in 23,157 people; the mortality rate in the first year of life after diagnosis was 14.5%. In the structure of cancer incidence, kidney cancer is 4.7% [3].

In the tumor tissue, which has an increased mitotic potential, angiogenesis constantly occurs to meet the metabolic needs of the growing tumor. In this regard, in the new millennium, drugs have become widespread - inhibitors of vascular growth factors that block angiogenesis [5].

Despite the success of targeted therapy, the studies of the last decade demonstrate insufficient effectiveness of the treatment, which is due to the multifactorial nature of the causes of oncoangiogenesis [1, 2, 6]. Also, one cannot ignore the toxicity of targeted drugs, the low sensitivity of certain forms of cancer to inhibitors of angiogenesis, as well as the high likelihood of relapses against the background of targeted therapy [7, 11]. Bevacizumab, a humanized anti-VEGF monoclonal antibody, was the first drug approved by the Food and Drug Administration (FDA) for the treatment of metastatic colon, ovarian, kidney, non-squamous cell lung cancer, and glioblastoma multiforme [9, 10]. However, it has not shown clinical significance when used as monotherapy, with the exception of glioblastoma [8].

Dissatisfaction with the results of targeted therapy prompted the search for new areas of application of antiangiogenic drugs based on the mechanism of their action. An example of such an innovative approach was the method of balloon chemoembolization and resection of malignant tumors of parenchymal organs, in essence of which the authors received a patent for invention of the Russian Federation No. 2711549 [4]. The essence of the method consists in the transarterial injection of an angiogenesis inhibitor into the parenchyma segment of the organ with a tumor through the coaxial canal of a balloon catheter installed and inflated in the segmental branch of the artery to provide local and reversible intraoperative ischemia of the segment. After the injection of the targeted drug, tumor resection is performed, followed by suturing the parenchymal wound with a hemostatic suture and immediate removal of the embolizing balloon catheter. As is known, as a result of ischemia, tumor tissue secretes vascular endothelial growth factor (VEGF). The introduction of the antiangiogenic drug Bevazuzimab directly at the time of tumor ischemia inactivates the synthesized VEGF, depriving the prospects of continued growth or recurrence of a malignant tumor.

It is also impossible not to take into account the high margin of vitality of malignant cells - the oncocytes remaining in the margin of the organ resection under conditions of ischemia continue to release vascular growth factor, which can provoke tumor recurrence or activation of possible metastatic foci. Our study is aimed at determining the duration of fixation of the preparation at the edge of the resection.

Materials and research methods. In the urology department of GAU Republican Hospital No. 1 - National Center of Medicine in 2018-2019, kidney resections were performed in 13 patients with a diagnosis of renal cell carcinoma T1 N0 M0. In 10 patients, the histological report showed clear cell carcinoma, in 3 operated patients papillary variant of kidney cancer was revealed. All patients gave written consent to participate in the experimental study.

In 8 patients, the tumor was localized in the left kidney, in 5 - right-sided lesion. The sizes of the formations ranged from 18 to 56 mm. According to computed tomography data, the mean score on the morphometric scale R.E.N.A.L. was estimated at 5.6 points. Surgical support was performed by lumbotomy access, in a lateral position, with isolation and clamping of the renal artery. No additional arteries feeding the kidney were found in any case. After resection and removal of the preparation, U- and Z-shaped hemostatic

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** – 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 Gavrilyevna** – 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; **KLADKIN Nyurgun Pavlovich** – urologist of the urology department of Republican Hospital №1 – National Medical Center, e-mail: nyrgunprogib@mail.ru

sutures were applied to the wound edges, the duration of thermal ischemia did not exceed 20 minutes.

Modeling of targeted balloon chemoembolization was performed in the following way. After isolation of the renal pedicle, the renal artery was clamped with a Satinsky vascular forceps. Thus, the kidney was completely excluded from the main blood flow. Distal to the clamping, closer to the kidney, the artery was punctured with an infusion cannula of the "needle-butterfly" type to a depth of 3-4 mm, and a solution of contrast agent was injected through it. To quantify the densitometric density of the contrast fixed in the renal parenchyma by computed tomography, Ultravist was used in an amount of 20 ml, diluted in 50 ml of saline in 7 patients. To qualitatively determine the duration of fixation of the substance at the edge of resection in 6 patients by magnetic resonance imaging, a preparation containing gadolinium - Gadovist 7.5 ml, also diluted in 50 ml of saline was used. Immediately after the introduction of the marker, an atypical resection of the formation within the healthy tissue was performed, followed by suturing of the parenchymal wound. 7 patients were examined by computed tomography on the day of surgery and on the 6th day of the postoperative period on a 64-slice General Electric Optima 660 apparatus without the use of contrast enhancement. A qualitative assessment of the degree of saturation with the inserted marker of the resection margin was performed in 6 patients on the 2nd and 6th days by means of magnetic resonance imaging on a Siemens Magnetom Avanto tomograph. The studies were carried out in coronal and axial projections with 3 mm sections, according to the T1 vibe protocol and with a tension of 1.5 Tesla.

Results and discussion. In response to acute hypoxia during surgical removal of the tumor, malignant cells secrete special substances that prevent the development of hypoxia. There are several varieties of them, the most active of which is vascular endothelial growth factor (VEGF). Its production occurs immediately in response to hypoxia of tumor tissue, acting on the corresponding receptors, vascular growth factor triggers a cascade of reactions that activate neoangiogenesis. In the presence of metastatic foci or perico-multiple oncological process in the body, the effect of VEGF on them is a prognostically unfavorable factor.

Based on the understanding of this mechanism, a new method is proposed that combines the antiangiogenic effect with the surgical method of eliminating the oncological focus. Transarterial administration of an angiogenesis blocker, which has a direct inhibitory effect on vascular growth factor at the very moment of active production of the latter, eliminates one of the main mechanisms for the further spread of the malignant process.

To assess the amount of the substance injected into the parenchyma and fixed at the edge of the resection with a hemostatic suture, an Ultravist iodine-containing contrast was used. We compared the densitometric density of the kidney parenchyma with the injected contrast and the density of the contralletral healthy kidney in dynamics 6 days after the operation.

Figure 1 shows a CT scan of a patient with a tumor of the left kidney that underwent resection within a healthy tissue with a preliminary intra-arterial injection of Ultravist. On the day of surgery, 4 hours later, this patient underwent computed tomography. A snapshot of the tomogram is shown in Figure 2, where the following are marked: a - the area of the resection edge with the injected contrast agent; b - an area of healthy kidney tissue outside the field of surgical manipulation; c - parenchyma of the contralateral organ for control measurement.

On the 6th day after the operation, a similar computed tomography (Fig. No. 3) was performed to determine the densitometric density (DMP) of the renal parenchyma at the previous points. Analysis of PMD indicators was performed using statistical packages SPSS (Windows version 7.5.2). The significance of differences between quantitative indicators was assessed using the Student's t test for normally distributed values. Differences were considered significant at $p < 0.03$.

The obtained values of densitometric density are presented in table No. 1. For a dynamic assessment of the degree of saturation with a contrast agent, the DMP index of the area of the opposite kidney not exposed to surgery was taken as 100%, which made it possible to assess the content of the marker in the resection margin relative to the intact parenchyma in dynamics.

The introduction of a contrast agent into the edge of the resection increases its densitometric density by 3 times compared to the intact tissue - the DMP values at the edge of the resection are 222.51% higher than the density of a healthy kidney. Restoration of blood flow after performing the main surgical technique washes out the contrast agent from the kidney tissue not stitched with a suture - the DMP of the parenchyma of the operated kidney outside the field of surgical manipulation is 25.83% higher than the DMP of a healthy kidney. 6 days

Fig. 1. Tumor of the left kidney.

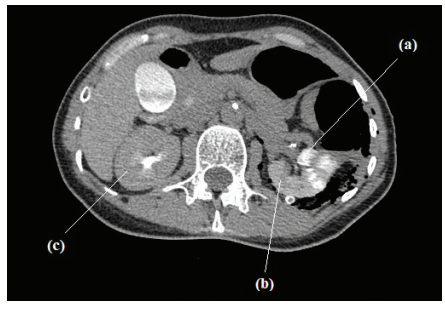


Fig. 2. Computer tomography image right after surgery. a - kidney resection area with a fixation of a contrast agent; b - zone of intact parenchyma, not exposed to surgical intervention; c - an area of the parenchyma of the contralateral kidney for control measurement.

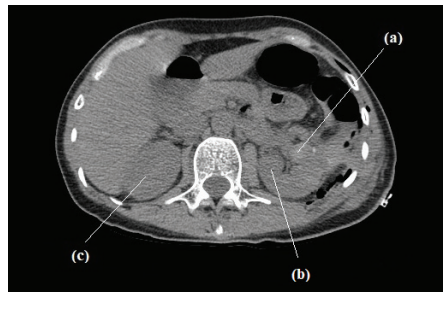
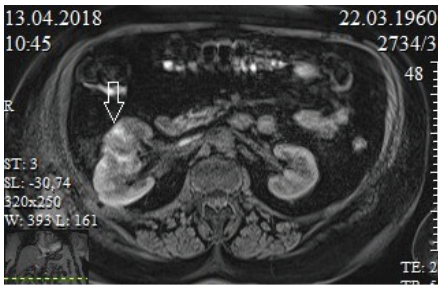


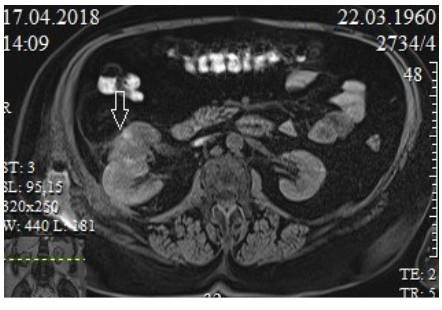
Fig. 3. Computed tomogram on the 6th day after surgery

Densitometric density of various parts of the kidney over time (*p=0,021*)

	0 day		6-th day	
	D.M.P.	%	D.M.P.	%
Parenchyma zone of the contralateral kidney (c)	75,5	100	32,5	100
Zone of intact renal parenchyma (b)	95	125,83	33,5	103,07
Resection and hemostasis area (a)	243,5	322,51	71	218,46



a



b

Fig. 4. MRT on the 2nd day, 6th day

after the operation, the measurement of the densitometric density showed a high density of the resection edge sutured with a hemostatic suture - 118.46% higher than the density of the unoperated organ, while the DMP of the intact parenchyma of the operated kidney is higher than the healthy organ by only 3.07%.

The presented data clearly demonstrate that the substance introduced into the arterial bed of the kidney and fixed in the tissues with a hemostatic suture is fixed in them for a long period of time. The coefficient of elimination of the substance was 1.47. This means that 6 days after the operation, more than half of the substance introduced transarterially into the resection margin remains in the tissue.

For a qualitative assessment of the degree of fixation of the substance at the edge of the resection, magnetic resonance imaging was performed in patients who underwent kidney resection on the 2nd and 6th days after the operation according to the method described above, with the difference that instead of Ultravist, Gadovist in volume 7 was introduced into the renal artery. , 5 ml. This study is based on the registration of a magnetic resonance signal from kidney tissues with an injected paramagnet. The study was carried out on a Siemens Magnetom Avanto magnetic resonance imager with 1.5 Tesla strength according to the T1-vibe protocol with a slice thickness of 3 mm in coronary and axial projections.

The obtained tomograms clearly show the areas of accumulation of paramagnet by the kidney tissue in the resection zone (Fig. No. 4 and Fig. No. 5). In dynamics, 6 days after the operation, the presence of residual contrasting at the edge of the resection is noted, which indicates its insignificant elimination. The leaching of the substance occurs mainly by diffusion, at a very low rate, as indicated by a decrease in the concentration of the substance introduced into the kidney parenchyma by no more than half during the first week.

Conclusion. The performed study of prolongation of the injected substance convincingly proved the presence of high concentrations of the marker at the edge of resection of the parenchymal organ during the first week of the postoperative period. This gives reason to hope that the targeted drug Bevatsimab, injected into the segment affected by the malignant tumor, will also maintain a high concentration at the resection margin for a sufficient time to provide additional anti-angiogenic protection after surgical resection of the malignant neoplasm.

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