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TREATING COMMON FORMS OF RENAL CELL CARCINOMA WITH USE OF CHEMICAL EMBOLIZATION (lecture)

Currently, diagnosis of kidney cancer in early stages (I-II) stage and its timely radical treatment remains relevant, unfortunately, despite the rapid development of modern diagnostic equipment (ultrasound, CT, MRT, etc.) the rate of detection of patients with early stages of the disease is still low due to asymptomatic course the process in its earliest stages.

In the present lecture material reflects issues of etiology, classification, clinical picture and diagnostics, modern methods of treatment for kidney cancer. It regards the problems of targeted therapies and methods of combined treatment for patients with metastatic kidney cancer. Special attention is given to historical aspects, indications and contraindications for chemoembolization in treatment of renal cancer.

The author reviews his personal experience upon the results of treatment of 15 patients with advanced renal cancer, using the procedure of renal artery chemoembolization in combination with other therapies, presents cases of treatment of patients with kidney cancer.

Key words: *kidney cancer, treatment, metastases, embolization, targeted therapy.*

Renal cancer makes about 3.2 per cent of all malignancies. Each year there are nearly 189-190 thousand new cases of renal cancer registered worldwide, that takes 2.2-2.7% of the malignancies in men, 1.5% – in women. Men suffer 2 times more often than women. Each year, kidney cancer takes away 91 thousand lives. In 1998, there were 30 thousand new cases of renal cancer registered in the United States, and in 2002 their number reached almost 32 thousand, indicating progression of the disease. In 2002 1200 patients died from renal cancer in this country. In the CIS countries also there is an increase in the proportion of renal cancer in the structure of oncological diseases. Renal cell carcinoma enters the 2nd place on the growth rate among all malignancies, showing an annual increase of 2%.

Renal cancer occupies the 3rd place by frequency among the urogenital malignancies, behind prostate cancer and bladder cancer. The average age of patients with kidney cancer is 50-60 years. About 830-840 kidney cancer patients are identified annually in the Republic of Kazakhstan and 50-55 kidney cancer patients are registered by the South Kazakhstan region, 15-17% of which are in stage IV.

Over the past 10-15 years there has been a significant increase in the incidence of this tumor. Every year it grows by 1-5 percent that amounted to about 50 percent over the past 10 years.

ETIOLOGY

It is a proven fact today that tobacco smoking is one of the most significant risk factors for development of various malignancies. The risk of kidney tumors in smokers of both sex groups grows from 30 to 60% compared with non-smoker population. Smoking cessation reduces the probability of the disease development. Obesity leads to an increase in the incidence of renal cell carcinoma by 20%.

Weight fluctuations, as well as a significant increase in body weight in adults are independent risk factors for development of this disease. Several epidemiological studies have indicated a 20% increased risk of kidney cancer development in hypertensive patients. It remains an open question, whether the reason for the development of renal cell cancer the hypertension itself or whether tumor development is actually potentiated by using a variety of antihypertensive drugs. Many authors attribute the appearance of renal cell carcinoma with the use of diuretics. The risk of the disease developing in patients receiving diuretics for various indications is over 30%.

An increased risk of renal cell carcinoma development is marked in the end-stage of a chronic renal failure. A number of studies have noted an increase in the incidence of renal cell carcinoma in patients with diabetes.

CLASSIFICATION

For practical purposes, it is advisable to allocate tumors of renal parenchyma and renal pelvis tumors, because they differ from each other in structure, propagation paths, diagnosis and treatments. Kidney tumors can be benign or malignant, primary as well as secondary (i.e., metastatic or germinating from adjacent organs).

The morphological (histological) classification of renal cancer includes four options:

1 Clear cell renal cancer (classic hyper-nephroid cancer);

2 Granular cell renal cancer (dark-cell cancer);

3 Spindle cell renal cancer (polymorph-cell, solid-tubular cancer);

4 Glandular renal cancer.

Clear cell variant is most common among the primary structure of renal cancer.

The grading of malignancy (histopathological grading J) has been included into the morphological characteristics of tumor process in the recent years:

- Gx – degree of differentiation can not be defined;
- G1 – highly differentiated tumor;
- G2 – moderately differentiated tumor;
- G3 – poorly differentiated tumor;
- G4 – nondifferentiated tumor.

In clinical practice, oncologists use the International TNM classification of renal cell cancer, where T is the spread of the

primary tumor, N is the involvement of regional lymph nodes, M means remote metastases. The T category is estimated on the basis of physical examination and radiological methods of diagnosis, the N category is set on the basis of physical examination and radiological methods, the M category is estimated on the basis of physical examination and radiological methods. Regional lymph nodes are the reniportal nodes, abdominal, para-aortic and para-caval nodes. Histological confirmation of the diagnosis and the division of a tumor in histological types are mandatory.

- T – primary tumor:
- Tx – Primary tumor can not be assessed.
- To – No evidence of primary tumor.
- T1 – tumor is not more than 7 cm in greatest dimension and is bounded by a kidney.
- T2 – tumor more than 7 cm in greatest dimension and is bounded by a kidney.
- T3 – Tumor extends into major veins or invades the adrenal gland or surrounding tissues but not beyond Gerota's fascia.
- T3a – Tumor invasion of the adrenal gland or perirenal tissue within the Gerota's fascia.
- T3b – Tumor extends to the renal vein or inferior vena cava below the diaphragm.
- T3c – tumor extends into the inferior vena cava above the diaphragm.
- N – Regional lymph nodes:
- Nx – regional lymph nodes can not be assessed.
- No – no metastases in regional lymph nodes.
- N1 – metastasis in a single regional lymph node.
- N2 – metastasis in more than one regional lymph node.
- M – remote metastases:
- MX – remote metastases can not be assessed.
- Mo – No distant metastases.
- M1 – remote metastases.
- P – histological categories defined after the surgery (the pT, pN, pM categories correspond the T, N and M categories).

Renal cancer can affect any kidney segments. Kidney tumor growth is possible towards the fibrous capsule as well as in the direction of pyelocaliceal system. In some patients, the tumor grows into the kidney vein, and then – into the lower vena cava. The tumor may contain foci of necrosis, old and recent hemorrhages areas of calcification. Cystic cavities containing clear, hemorrhagic or chocolate-colored liquid and sometimes even gelatinous mass are formed in the decay centers. Kidney tumors of small size are usually surrounded by a visible dense capsule representing the renal tissue atrophied due to compression. This allowed S. Petcovic to develop a classification of kidney tumors basing on the presence of a tumor capsule.

The following tumors are identified according to this classification:

- first, when there is a tumor inside capsular not germinating in "its" capsule;
- second, in which the tumor grows into the renal parenchyma, but does not grow beyond it;
- third, when the tumor invades the fibrous renal capsule surrounding the kidney tissue, involving regional lymph nodes;
- fourth, in which the remote metastases of the tumor are observed.

SYMPTOMATOLOGY

The symptomatology of kidney cancer in adults is extremely diverse. The clinical picture of the disease allocates the "classic triad" of symptoms (pain, macrohematuria and a palpable tumor). These symptoms are considered to be local. However, the above described classic triad of symptoms, occurs only in 15% of patients with renal cancer. Presently, the "classic triad" is rare. In most cases the disease proceeds asymptomatically. Along with this, the so-called "common" symptoms are often observed in patients with kidney cancer. These are: high body temperature, weight loss, anemia, renal dysfunction, secondary erythrocytosis, hypercalcemia. The local symptoms of kidney cancer also include varix dilatation of seminal vesicle excretory ducts. Hematuria is observed in 50-65% of patients with kidney cancer and almost equally often at all stages of the disease. It is important to note that total painless hematuria is the first indication of the disease in one third of patients, but many patients at stages I and II can have single cases of hematuria, which often causes delays in seeking medical attention. Not all patients with renal tumor have hematuria accompanied by the attack of renal colic due to obstruction of the ureter by a blood clot, i.e. is often "silent." We also can not agree with the opinion of some authors who attribute haematuria to the later signs of the disease, since this symptom is quite often (more than in half of the patients) observed in the first and second stages of the disease. The causes of hematuria in renal cancer are the destruction of vessels by the tumor tissue, tumor invasion into the wall of the calyx or pelvis, venous hypertension in the kidney due to compression of the renal tissue tumor, and microscopic hematuria (red blood cell uria).

Pain in the lumbar region should be attributed to late manifestations of the disease. It is extremely rare then the pain in the kidney may be the first sign of the disease. Usually pains are dull or aching and depend on stretching while tumor is invading the fibrous capsule of the kidney.

The tumor is rarely determined by palpation, mostly at stages III or IV, during the blastomatous process development. A tumor-bearing kidney retains its mobility for a long period. The tumor is often palpable as a dense lumpy body and has clear contours.

One of kidney cancer symptoms is arterial hypertension. This symptom is observed in 10-15% of patients.

If kidney cancer is complicated by formation of a thrombus in the inferior vena cava (the large vein, collecting blood from almost the entire lower half of the body and lower limbs), this may arise the "syndrome of the inferior vena cava removal", which is a set of symptoms caused by a sharp slowdown and a decrease in the volume of blood flow in this vessel. This causes swollen feet, expansion of abdominal subcutaneous veins, varicose veins in the lower extremities, thrombosis of deep veins in lower limbs, an increase in size of feet.

The variety of clinical manifestations of kidney cancer in some patients is associated with metastases. Kidney cancer metastases were observed in more than half of the patients. Metastases are most frequently detected in lungs, then – in pelvis, spine, ribs, hip, collarbone, calvaria and less frequently – in liver and brain. Regional metastases of renal cancer are localized in para-caval and para-aortic lymph nodes near the renal sinus. Less

often they happen in the lymph nodes of the mediastinum, neck, iliac and inguinal nodes. In addition, renal cancer may cause the so-called local metastases outside the lymph nodes – in perirenal adipose tissue, in a post-operative scar.

A special place in the clinical picture of kidney cancer is occupied by symptoms associated with metastasis, as more than 25% of patients have distant metastases at the moment of the diagnosis. The first manifestation of lung lesion is cough and hemoptysis. Bone metastases can manifest by pain syndrome, by development of pathological fractures or spinal brain compression, by appearance of palpable tumors. Brain injury is accompanied by rapid emergence and increase of neurological symptoms. Multiple liver metastases can manifest themselves with jaundice.

Such common symptoms, as anemia, high erythrocyte sedimentation rate, loss of appetite, weight loss, weakness, are signs of the later stages.

Speaking about the course of metastatic disease in renal cancer, we can not help mentioning the cases of spontaneous regression and stabilization. Spontaneous regression is observed in 0.4-0.8% of patients with renal cell carcinoma. This in the majority of cases applies to regression of pulmonary metastases. Disease stabilization, defined as the absence of growth and emergence of new metastases, is observed in 20-30% of patients. With the same frequency of disease stabilization (lack of growth of the primary tumor) is noted in patients with renal cell carcinoma without metastasis. This phenomenon should be taken into account when deciding on surgery or systemic treatment of patients, which is associated with high risks, as in reality such patients can survive longer without any treatment.

DIAGNOSTICS

Recognition of kidney cancer is rather complicated. Methods of kidney cancer diagnostics are divided into clinical, laboratory, ultrasound, radioisotope and radiological.

General clinical methods imply survey, palpation. Typically, patients with tumors complain of poor general condition, decreased interest in the environment, decreased performance and appetite and other common symptoms of life discomfort. Special attention during a survey should be paid to the general appearance of a patient, the color of his skin. Laboratory methods for diagnosing help detecting kidney tumor to a certain extent. Urinalysis reveals erythrocyteuriah, but this is usually normal without hematuria. Common blood tests reveal the increased erythrocyte sedimentation rate (ESR) and anemia. ESR is one of the indicators suggestive of a tumor presence in general and kidney cancer in particular. An increase in alkaline phosphatase activity and lactate dehydrogenase of blood serum was observed in many patients with renal cell carcinoma. Ultrasound scanning has a high resolving power. Moreover it is safe and requires no prior preparation of a patient. In the presence of a tumor kidney contours tend to be deformed, heterogeneity of the echo signal is characteristic due to areas of necrosis, hemorrhages, and tumor's abrupt sound absorption. It is believed that renal ultrasound examination in the first stage is paramount.

X-ray examination is the final stage of kidney cancer diagnostics. Radiographic signs of kidney cancer are an increased size of the kidney and change of its contours, deformation and filling defects of the pyelocaliceal system. The signs of tumor on renal angiograms are extension of the main renal artery lumen, disorderly pathological vascularization in the tumor mass, segmental premature renogram, increased tumor shadow. The leading method of X-ray diagnosis of renal parenchyma cancer is renal angiography. This method allows to determine the character of the volume process in the kidney and to distinguish a tumor from a cyst; to recognize smaller tumors localized in the cortical layer, which are not deforming the pyelocaliceal system of the kidney; to ascertain the status of the renal vein and to confirm the presence or absence of tumor thrombus in its lumen; to detect tumor invasion into adjacent organs and metastases in the opposite kidney.

Modern methods of renal cancer diagnosis also include computer tomography, and magnetic resonance imaging. These study methods allow to determine the existence of kidney tumors less than 2 cm in diameter, tumor localization in relation to the kidney segment, its surface and the pyelocaliceal system gate, to determine the depth of germination into renal parenchyma, the structure of the tumor, possible infiltration of the perirenal tissue, presence of a thrombus in the Renal vein and inferior vena cava, to detect an increase of regional lymph nodes, their consistency and size, tumor invasion into the abdominal cavity, as well as metastases in the liver and bones.

TREATMENT

Standard methods of treatment:

1 Radical nephrectomy with removal of the renal vein and, if necessary, resection of the inferior vena cava. Radical nephrectomy with lymph node dissection.

2 Preoperative embolization of renal artery and radical nephrectomy.

3 External radiation therapy (palliative)

4 Tumor embolization (palliative)

5 Palliative nephrectomy

6 External radiation therapy before or after surgery and radical nephrectomy

7 Adjuvant therapy with interferon-alpha is undergoing clinical trials, targeted therapy with Sorafenib (Nesavar) and Sunitinib (Sutent) drugs is also applicable for advanced renal cancer.

Surgical treatment

Surgical treatment is indicated for most patients with renal cell carcinoma. The main operative method is radical nephrectomy. During its execution the kidney is removed along with and perirenal retroperitoneal adipose tissue, regional lymph nodes from the diaphragm to the aortic bifurcation and the confluence of the common iliac veins in a single block. When performing this operation any manipulations on the kidney prior to ligation of the renal vessels must be avoided. When choosing an operative access for radical nephrectomy, it is necessary to observe the basic postulate of Oncology – ablasticness as well as minimal invasiveness and the availability of the operation objects.

Transperitoneal access has certain advantages compared with the lyumbotomic one. These include direct access to main vessels of the kidney, significant atraumaticness and ablasticness, feasibility of a detailed revision of the abdominal

cavity and, if necessary, removal of the spleen, bowel, liver and pancreas resection. Certain difficulties for transperitoneal approach arise in cases of infiltration of the renal vessels by tumor masses.

Treatment of renal cell carcinoma depending on the stage of the disease

Stage I (T1-2, N0, M0)

The main method of treatment is radical nephrectomy.

Partial nephrectomy is applied for tumors smaller than 4 cm.

Stage II (T3a, N0. M0) Radical nephrectomy remains the main treatment for tumors at this stage. Lymphadenectomy is also performed, but its effectiveness has not been confirmed.

Organ-sparing surgery (partial nephrectomy) is performed only in cases of bilateral lesions and tumors of a solitary kidney.

Stage III (T3b, N0, M0)

T3b, N0, M0

Radical nephrectomy remains the main method of treatment. During the operation, there often appears a necessity for removal of an adrenal gland or tumor thrombus from the renal vein and inferior vena cava, for resection of inferior vena cava walls. Embolization of renal arteries is strongly recommended before the surgery. The effectiveness of pre-and post-operative radiotherapy, recommended by some authors, at this stage of tumor has not been confirmed.

2) Any T, T1-3, M0

The prognosis for patients with this tumor stage is unfavorable. Radical nephrectomy also remains the procedure of choice. Extended lymphadenectomy is necessary during the operation. Arterial embolization of the tumor before the surgery is used to reduce blood loss during nephrectomy or as a palliative treatment for inoperable patients.

Stage IV (T4, N0, M0, any T, any N, M1)

The prognosis for patients with advanced renal cell carcinoma is extremely unfavorable. Arterial embolization of the tumor and nephrectomy can be applied as palliative treatment. A significant improvement in survival rate of patients with advanced renal cell carcinoma after nephrectomy was noted in cases, when the tumor did not exceed 7 cm in diameter. It is proved that nephrectomy in some cases can cause spontaneous regression of metastases. However, regression of remote metastases was noted without performing any intervention as well. In some patients with a limited number of distant metastases increase survival rate can be achieved by nephrectomy and surgical removal of metastases. Resection of metastases in patients with prolonged (more than 2 years) interval between primary nephrectomy and the development of distant metastases tends to be more effective. No change in the survival rate was observed upon removing one or several metastases. Surgical resection can be performed even in patients with brain metastases, but the best results are obtained by removing the lung metastases. Great importance attaches to immunotherapy in patients with metastatic renal cancer. Alpha-interferon is effective in about 15% of patients. The best results were observed in patients with sporadic pulmonary metastases and without cachexia. However, remission was often short-term. The use of interleukin-2 is more promising as it causes long-term complete remission in 5% of patients. The optimal dose of IL-2 is not completely clear. Some reports indicate that low doses of interleukin-2 are just as effective as high doses but have fewer side effects. Combined immunotherapy with interleukin-2 and interferon-alpha was effective in 18% of patients, and prolonged complete remission was achieved in 6%. A combination of chemotherapy and immunotherapy in the treatment of patients with metastatic renal cancer has proved its effectiveness in recent years. Interleukin-2 and interferon alpha in combination with 5-fluorouracil are most commonly used. This therapy is effective in 19% of patients. However, some researchers doubt the validity of combined chemoimmunotherapy, indicating that its long-term results are no better than that those of a single immunotherapy.

Targeted Therapy

Over the last 5-7 years the so-called purposeful therapy, or targeted therapy, further and further used every year, has become a new trend in treatment of metastatic renal cancer.

Presently, the Office of the Food and Drug Administration USA (FDA) has approved several drugs from the targeted therapy class for use in the later stages of kidney cancer. Targeted therapy drugs are often used as first-line therapy for advanced renal cancer.

Physicians are still studying the best ways to use targeted therapy in renal cancer. At the moment these are used one at a time. If one is not effective, it is possible to use other. Currently, there are ongoing researches studying the tactics of targeted therapy application in renal cancer.

There are several targeted therapy drugs for treatment of advanced renal cancer endorsed presently. These are: Sorafenib (Nexavar), Sunitinib (Sutent), Temsirolimus (Torisel), Everolimus (Afinitor), Bevacizumab (Avastin), Pazopanib (Votrient), Aksitinib (Inlita).

Sorafenib (Nexavar).

Sorafenib was approved by the FDA for treatment of metastatic renal cancer in 2005. Sorafenib comes in tablet form. The study, which was attended by more than 900 people with advanced renal cancer, proved that Sorafenib slows the progression of kidney cancer. In addition, Sorafenib has shown its effectiveness in slowing tumor growth. Sorafenib affects one of the mechanisms of tumor growth. A tumor requires blood supply as well as healthy tissues. Blood vessels grow in several ways. One of the mechanisms is VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor) – the proteins that stimulate the growth of blood vessels. These proteins stimulate the vessels to grow into the tumor. When cancer cells begin to spread in the body, they secrete VEGF and PDGF for the formation of new blood vessels. Sorafenib blocks VEGF and PDGF, disrupting the formation of new blood vessels needed for tumor blood supply. Sorafenib also blocks the formation of molecules that promote the growth of cancer cells. As healthy tissues have stable blood supply, they are not affected during the therapy. Side effects of Sorafenib are: fatigue, rash, diarrhea, high blood pressure, hand-foot syndrome.

Sunitinib (Sutent). In 2006 the FDA approved Sunitinib for treatment of metastatic kidney cancer. Sunitinib comes in tablet form, as well as Sorafenib. Sunitinib is taken once a day for four weeks, a four-week course of therapy is repeated after a two week break. In clinical studies comparing treatment with immunotherapy by interferon, Sunitinib showed a slowdown in growth of metastatic tumors renal cancer by half, compared with interferon. Due to its efficiency, Sunitinib is often used as first-line therapy for metastatic renal cancer. Studies have shown that Sunitinib reduces the size of tumors in patients whose previous therapy was ineffective. For example, in one of studies, patients, who had previously received immunotherapy, received Sunitinib. During the two months of receiving Sunitinib more than 40% of these patients had a considerable tumor decrease. Tumor also decreased in another 25% of patients, but to a lesser extent. The response to treatment lasted for a year.

Side effects of Sunitinib include fatigue, diarrhea, high blood pressure, pains in arms and legs, and pain in the mouth cavity.

Temsirolimus (Torisel). In May 2007, the FDA approved Temsirolimus for treatment of metastatic kidney cancer. Temsirolimus is available as a solution for intravenous administration. Temsirolimus works by blocking the action of MTOR, a substance that stimulates growth and cell division. According to clinical testing, patients who received Temsirolimus lived longer, compared to those treated with interferon. Temsirolimus side effects are similar to the side effects of other drugs of targeted therapy used for treatment of metastatic kidney cancer. Side effects of Temsirolimus include rash, oral ulcers, fatigue, nausea, low blood count, high blood sugar and blood cholesterol levels.

Everolimus (Afinitor). In 2009, the FDA approved Everolimus for treatment of advanced kidney cancer. Everolimus is received in the form of tablets twice a day. Everolimus blocks the MTOR protein. Everolimus refers to the second-line of targeted therapy in renal cancer. Side effects of Everolimus include oral ulcers, increased risk of infections, loss of appetite, rash, fatigue, weakness, edema.

Bevacizumab (Avastin). Bevacizumab was approved by the FDA for treatment of advanced renal cancer in 2009. Bevacizumab is a preparation for intravenous administration. Bevacizumab is a monoclonal antibody that selectively binds to the receptors that are sensitive to vascular endothelial growth factor, blocking them, which leads to disruption of new blood vessels formation in tumors. Recent studies have demonstrated that Bevacizumab is more effective in its combination with alpha-interferon. Bevacizumab is usually well tolerated by patients.

Side effects of Bevacizumab are the increase of blood pressure, blood clotting disorders, and problems with wound healing.

Pazopanib (Votrient). In 2009, FDA approved Pazopanib for the treatment of metastatic kidney cancer. Pazopanib blocks several tyrosine kinases, substances that are involved in the formation of new tumor blood vessels and growth of cancer cells. Pazopanib is administered in the form of tablets once a day.

Side effects of Pazopanib include increased blood pressure, nausea, vomiting, diarrhea, headache, low blood cell counts and hepatic disorders.

Aksitinib (Inlita). Aksitinib also inhibits several tyrosine kinases including those involved in the formation of new blood vessels. Aksitinib is administered in the form of tablets twice a day.

Side effects of Aksitinib are: high blood pressure, fatigue, nausea and vomiting, diarrhea, loss of appetite and weight loss, hand-foot syndrome, blood clotting disorders, laboratory indicators failure of hepatic function.

Sorafenib (Nexavar), Sunitinib (Sutent), Everolimus (Afinitor), Bevacizumab (Avastin), Pazopanib (Votrient) only are of all the above-mentioned drugs registered in Kazakhstan and are widely used by oncologists and are also available for free in all cancer institutions of our country.

THE MAIN THERAPEUTIC APPROACHES IN DIFFERENT VARIANTS OF THE ADVANCED KIDNEY CANCER:

1. Palliative nephrectomy.
2. Radical nephrectomy (in some patients with T4, M0).
3. Nephrectomy and resection of metastases (in some patients with M1).
4. Monotherapy with interleukin-2.
5. Monotherapy with interferon alpha.
6. Combined immunotherapy with interleukin-2 and interferon alpha.
7. Combined chemoimmunotherapy.
8. Arterial chemoembolization.
9. Surgical resection of metastases.

ARTERIAL CHEMOEMBOLIZATION (method history)

Firstly renal artery embolization in the experiment has been performed by A. Lalli et al. (1969). In clinics L. Almgard et al. (1973) firstly used the renal artery embolization in renal cancer for relief of hematuria and significant tumor size, and in metastatic stage of the disease in order to stimulate antitumor activity of the immune system of the body by self-immunization. The most extensive use of this technique reached its peak in the middle of 1980s. In Central Research

Institute of Roentgenology and Radiology transcatheter interventions in kidneys cancer have been used since 1979 [Granov A.M. et al., 1996].

Initially, arterial occlusion of the renal artery was intended only for the reduction of blood supply to the kidney to form ischemic necrosis of the tumor [Wallace S. et al., 1987]. Further development of methods has led to a deeper and a reasonable estimate of the pathogenetic mechanisms. It is primarily concerned with the development of the method of chemical and oil embolization, in which the conditions for deeper necrotic of tumor tissue are created, since feature of this embolizat is a combination of long, local, cytotoxic action of chemical agent with prolonged blockade of arterial blood flow in the tumor. Furthermore, it is important to note that deposition of the drug in the oil precludes systemic toxic effects of cytostatic agent.

TECHNIQUE OF ARTERIAL CHEMOEMBOLIZATION

After puncture of the femoral artery by Seldinger (Fig. 1) the head end of the catheter renal double, hook, cobra 4-5 F is set in the aorta at the level of origin of the renal arteries, and then a selective catheterization of the renal artery on the affected side is implemented, and when necessary, and of additional vessels participating in the blood supply to the tumor. 15-20 ml of the contrast agent (Ultravist 300, 370) at a rate of 5-6 ml / s should be administered in selective angiography of diseased kidney.

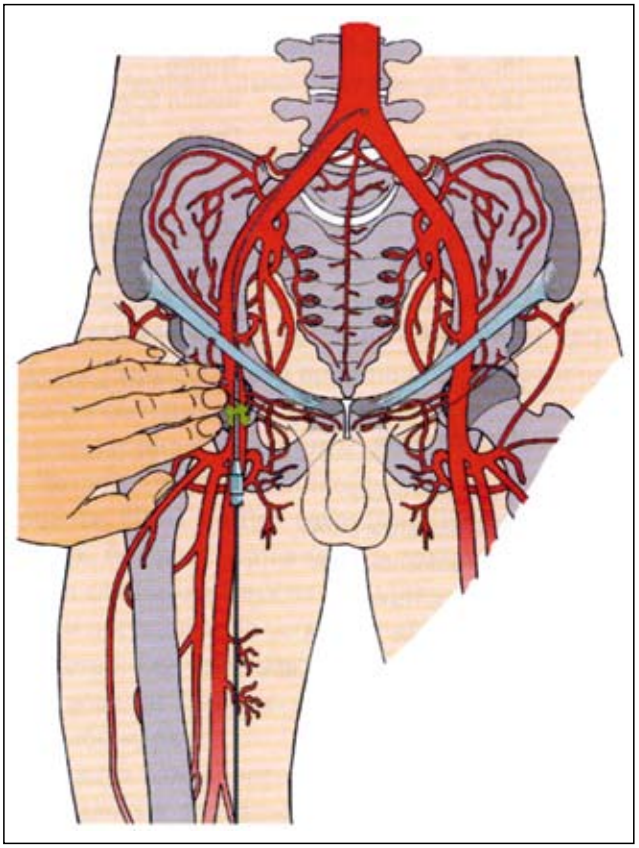

Figure 1 – Access to renal arteries through the catheterization of femoral artery by Seldinger

Using angiograms the size and vascularization of neoplasms, the sources and nature of its blood supply, involvement in the neoplastic process of adjacent organs shall be assessed, as well as identify the invasion to the venous system of the kidney in the degree of renal vein opacification.

INDICATIONS AND CONTRAINDICATIONS (Mavrichev A.S., 1996; Granov A.M. et al., 1997)

INDICATIONS:

Locally advanced renal cell carcinoma (RCC) with spread to adjacent organs.

Kidney tumors with multiple distant metastases.

Presence of severe concomitant somatic pathology in patients with localized forms of RCC.

Presence of severe concomitant somatic pathology in patients with localized forms of RCC.

Superselective palliative embolization is carried out when both kidneys are affected by tumor.

Tumors with a diameter of more than 4 cm in a functionally or anatomically single kidney.

Preoperative embolization.

Improving conditions of ablastics.

CONTRAINDICATIONS

1. Very severe general condition of the patient.
2. Multiple organ failure.
3 Impaired function of the contralateral kidney.
4 Hypo vascular and cystic forms of tumors.

PALLIATIVE EMBOLIZATION

Follow-ups of such interventions is continued to be debated. In a review of the literature it notes that palliative embolization is required to stop the severe hematuria, but its impact on the improvement in survival has not been proven [Kalman D., 1999]. The same opinion belongs to other authors [Roy S. et al., 1999].

On the other hand, S. Bache et al. (1992), comparing follow-ups of 57 patients who passed palliative embolization by them mixture of Histoacryl (Histoacryl blau) and Lipiodol (Lipiodol Ultrafluid), and 58 patients who underwent nephrectomy for cancer, it should be noted a significant improvement in life expectancy: 16.0 and 10.6 months respectively. T. Onishi et al. (2001) indicated increase in median survival from 4.0 to 7.0 months and figures 1-, 2- and 3 year survival rates to 13, 7 and 3% to 29, 15 and 10% respectively after embolization of inoperable kidney cancer by ethanol. Table 1 shows the follow – ups in patients with renal cancer according to the Russian Scientific Center of Radiology and Surgical Technologies [Granov A.M., Tarazov P.G. et al., 2008].

Table 1 – **Follow-ups of embolization in patients with renal cell carcinoma**

Embolization types		Survival rate,%	
		3-year	5-year
Preoperative (dg. II-III)	mechanical	57,8±6,6	51,2±6,9
	Chemical embolization	79±4,9	72,1±5,3
Palliative (dg. III-IV)	mechanical	10,6±4,2	0
	Chemical embolization	33,1±6,9	24,5±6,7

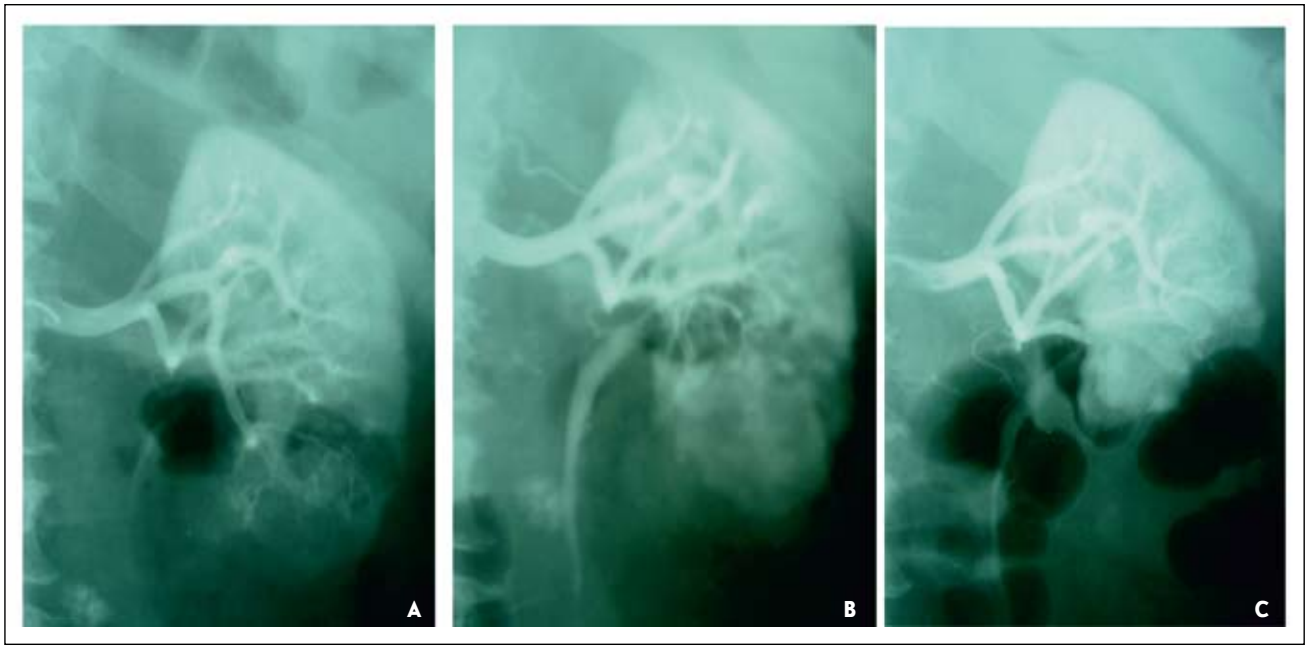

Figure 2 – The angiogram of the left kidney of the patient a., 71 years old.
A – before embolization (tumor of the lower pole of the left kidney). B – after selective chemoembolization.
C – a control angiography at 3 months (the function of the upper pole of the left kidney is preserved)

EXPERIENCE OF CHEMOEMBOLIZATION IN THE COMBINED TREATMENT IN PATIENTS WITH ADVANCED KIDNEY CANCER IN THE SOUTH KAZAKHSTAN REGIONAL ONCOLOGY CENTER.

The purpose of palliative embolization in renal cancer in our clinic was the opportunity to reduce the effect of "live" kidney tumor on organisms as a whole. Blocking blood flow and thus a sharp decline in the influence of biological, predict tumor agents (proteins "catalyst", "stimulators") of neoangiogenesis and neoblastomgenesis in the body and promotion of their growth and tumor metastasis.

From 2008 to 2013 we have experience in treating 42 patients with advanced kidney cancer; including 15 patients were applied with combined treatment through catheter chemoembolization of renal tumors. All patients were aged 35-87 years. Men is 11, women is 4. All 5 patients were diagnosed with advanced kidney cancer T3NxM1, cancer of the right kidney was observed in 5 patients, cancer of the left kidney in 9 patients, 1 patient had 2-sided renal disease. 7 patients had metastases in the bones of the skeleton (lumbar and sacral spine, ribs, pelvis), 6 patients had lung metastases, 2 patients had metastases in the brain. The common status by Karnovsky in all 15 patients was rated higher than 80% at the starting date of treatment.

All patients passed combined multistage treatment: the first stage – 4 patients passed oil chemoembolization of renal tumor. Lipiodol 5 ml + Vinblastine 5 mg with doembolization by hemostatic sponge to complete reduction of blood flow of blood vessels, as well as palliative radiotherapy for the purpose of coping with pain syndrome metastases of the spine, total tumor dose (SOD) 25 Gray. 2 patients have passed selective embolization of the lower pole vessels of the renal artery with partial preservation of affected kidney function (Fig. 2), 1 patient has passed simultaneously mechanically total embolization of the right kidney and selective chemoembolization by doxorubicin 50 mg of the lower pole of the left kidney functioning only with preservation of its functions, the remaining 8 patients were passed total mechanical embolization of renal artery on the affected side.

During the second stage 4 patients have passed 4-6 courses of immunochemotherapy: Vincristine 2 mg at the 1st and the 8th day intravenously + Roferon 4.5 million ME subcutaneously 1-10 days + Therapy with Bonefos 1,500 mg intravenously at 1 day, followed by 1600 mg orally starting from 2nd day constantly, for 1 year, 4 patients have passed only outpatient immunoglobulin monotherapy Alpha 2-b interferon by 3 million ME subcutaneously 3 times a week, continuously for up to 6-8 months until disease progression. 1 patient with metastases to the lungs and bones has passed combined treatment: immunotherapy Alpha 2-b interferon by 3 million ME subcutaneously daily for 10-12 days with an interval of 2 weeks, 400 mg of Bevacizumab / drip 1 times for 21 days, Zolendronovaya acid 4 mg / drip 1 time for 28-30 days. Treatment lasted for 8 months, after which the patient demonstrated complete regression of all tumor lesions, and disease control had been achieved.

6 patients after palliative embolization are transferred for the target therapy, 3 of them receive 800 mg/day of Sorafenib tab., 3 patients – 50 mg/day of Sorafenib dr. in the morning, one-time dose. Among 6 patients, receiving the target therapy, 1 patient has appealed with a progression of disease after 1,5 hours, for whom the 2-nd line of target therapy was started with 250 mg/day of Everolimus tab.

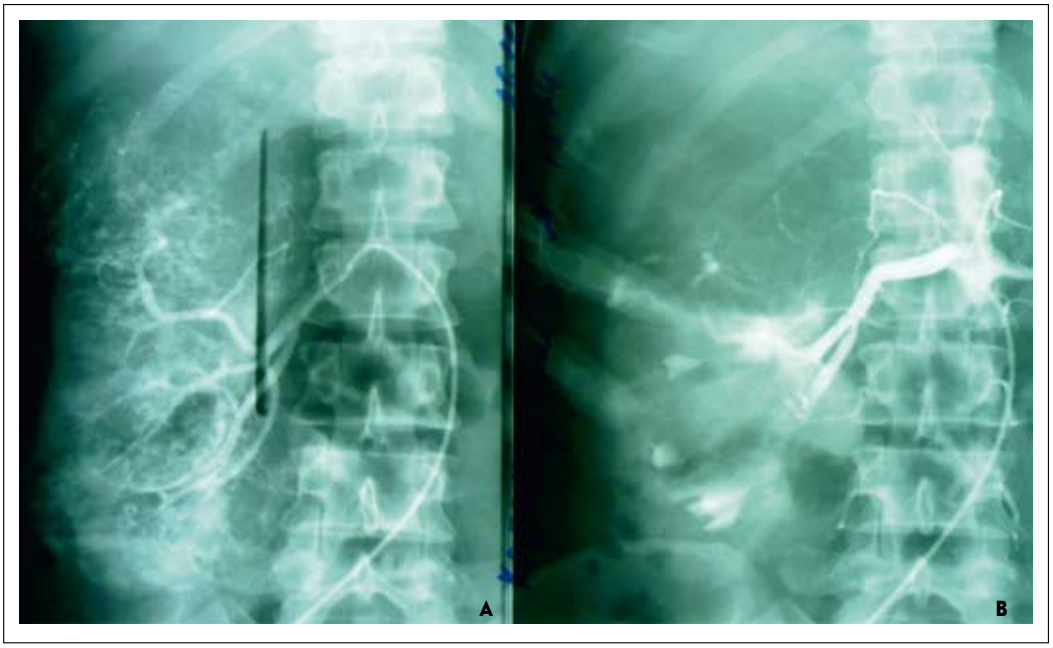

Figure 3 – Angiograms of the right kidney of K. patient, female, 35 years old:
A – before embolization (the right kidney tumour with the absence of an excretory function).
B – after total embolization

BILATERAL TUMOURS AND A TUMOUR OF THE SINGLE KIDNEY

In the case of kidneys' bilateral involvement, the following is applied:

Bilateral resection of kidneys.

Kidney resection and radical nephrectomy at the opposite side.

Bilateral radical nephrectomy with subsequent hemodialysis and kidney transplantation.

In the case of a tumour of the single kidney, it is possible to execute kidney resection, or radical nephrectomy with subsequent hemodialysis and kidney transplantation.

Difficulties in the treatment of patients with bilateral tumours and a tumour of the single kidney are conditioned by the necessity to combine, on the one hand, the adequacy of tumour resection, and, from the other hand, – the maximum possible preservation of kidney tissue. The main criterion for a choice of a treatment tactic for such patients is predictable survival rate in the case of each method of the treatment. Not the least importance has the age of a patient.

However, last years, many authors, dealing with tumours' treatment with the application of the methodology of chemical embolization, in increasing frequency, demonstrate opportunities of interventianal procedures applying in the treatment of this difficult category of patients. In the case of bilateral lesions, different methods of the treatment could be applied, for instance: per saltum embolization of the most affected kidney and selective embolization of less affected kidney with subsequent nephrectomy of the afunctional kidney. Other variant – kidney resection with subsequent immunochemotherapy or target therapy. All of that are in the hands of clinicians themselves, and depends only on the opportunities of a clinic, where a patient is, itself.

To demonstrate the possibilities of chemical embolization method with bilateral kidney lesion, the clinical case is given below.

K. patient, 39 years old.

From the anamnesis: the patient has been ill from September 2009, when at USE, CT and angiography of kidneys, it was diagnosed: left kidney cancer T3N1M1 IV St. in the left kidney lower pole. Tumour's sizes at the right kidney are 19,5x11 cm, at the left kidney – 7x8x6 cm. Right kidney function – Abs. The patient was sent according to the quota to the KazRDIO&R of the MH RK, where the sympthomatic therapy was recommended in the home area of the SKR.

The patient was hospitalized in the SKR OC, where 1 course of immunochemotherapy was held, without a sufficient effect. She came for a continuation of the treatment on 16.11.2009, she was hospitalized in the Chemotherapy Department.

Treatment

Taking into account the young age, the «safekeeping» of the patient and the consent to be treated, council of ROC's physicians has decide: as for the first stage – to conduct per saltum embolization of the right kidney's tumour and selective embolization of the left kidney lower pole's tumour with subsequent nephrectomy of the right kidney, aiming the cytoreduction. Then, immunochemotherapy's continuation.

26.11.2009, per saltum embolization of the right kidney artery and selective embolization of the left kidney lower pole's tumour were performed (the only kidney that is functioning) (Fig. 3, 4).

Result: for 5-7 days patient's state is in dynamics, without worsening, with phenomena of post-embolization syndrome of a light stage on the background of remedial therapy and anal-

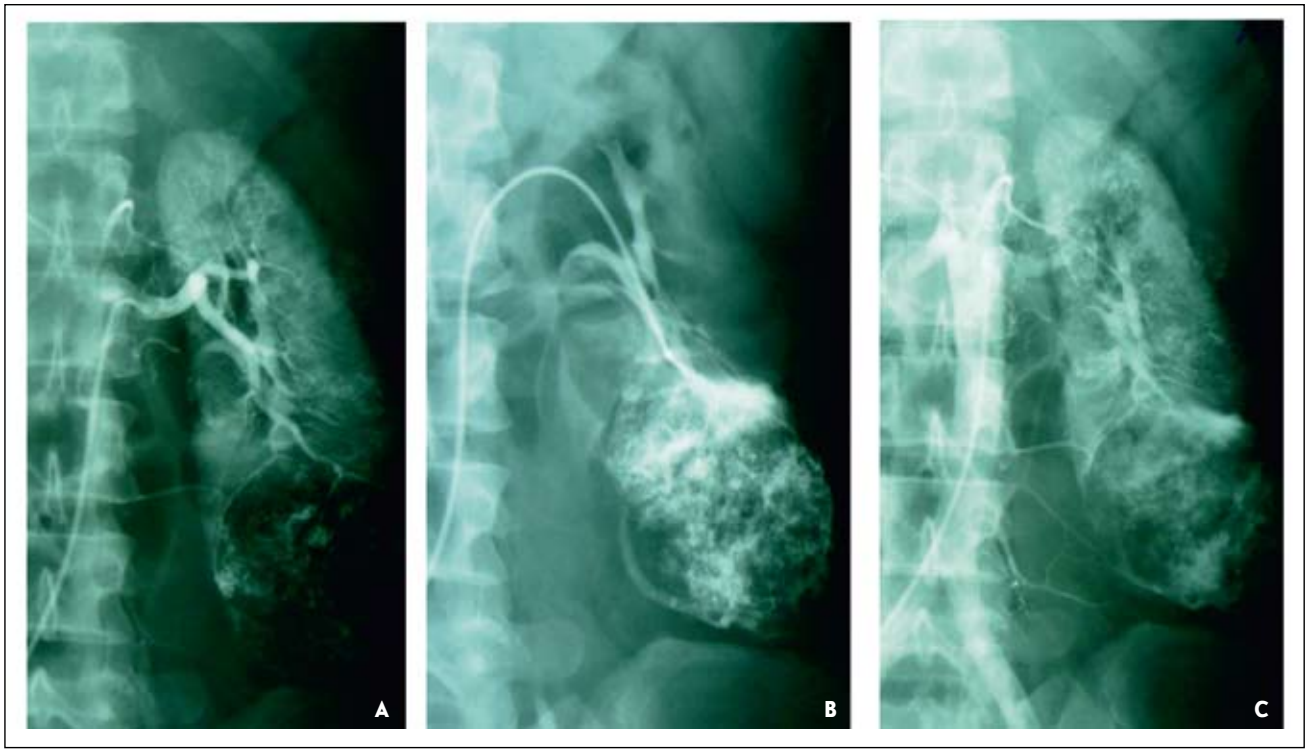

Figure 4 – Angiograms of the left kidney of K. patient, female, 35 years old:
A – before embolization (the tumour of left kidney's lower pole).
B – selective chemical embolization. C – after chemical embolization

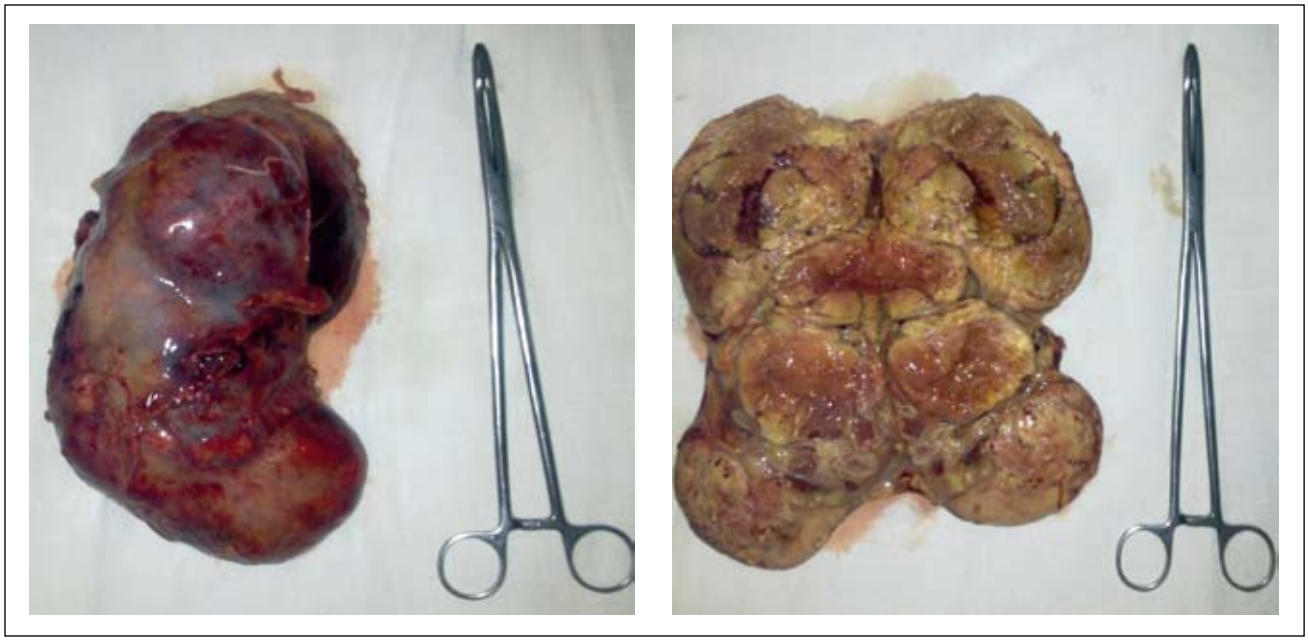

Figure 5 – Extracted gross specimen of the right kidney of K. patient, female, 35 years old

gesics. 08.12.2009. The scheduled nephrectomy is performed, right side (Fig. 5).

The patient received, according to the schedule, the target therapy with 400 mg of Nexavar preparation, twice a day, during 18 months, during the control examination, data of progressing was not detected, at the control angiography of the left kidney, the tumour is in dynamics, without marks of revascularization and a growth (Fig. 6, 7). Currently, the patient is under the dynamic observation. Disease control until July 2014 is 55 months (4,5 years).

Figure 6 – Control angiography of the left kidney of K. patient, female, 39 years old, in 54 mon. after selective embolization of loser pole's tumour

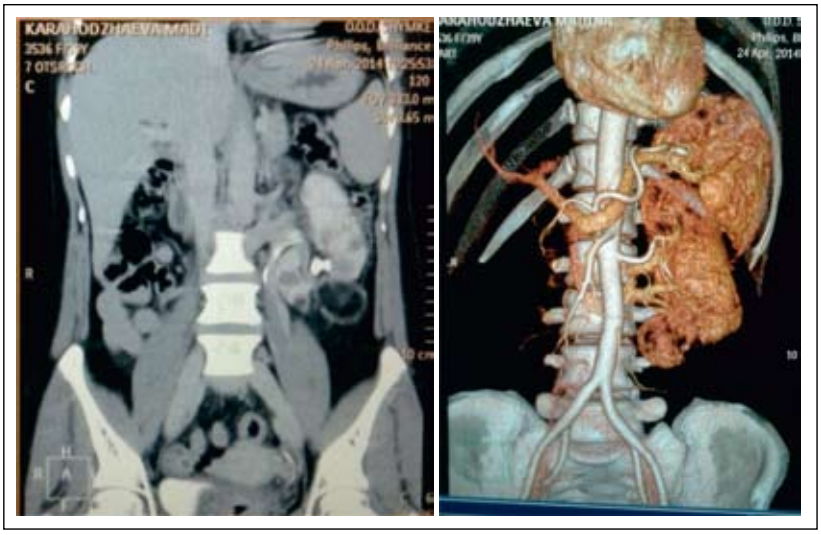

Figure 7 – Control computer tomography of abdominal cavity organs and retroperitoneal space of K. patient, female, 39 years old, in 54 mon. Left kidney lower pole's tumour is observed, at 3D-reconstruction without marks of pathological vascularization

CONCLUSION

Currently, the diagnostics of renal cell carcinoma at the early (I-II) stages and its timely radical treatment remains urgent, unfortunately, despite the rapid development of modern diagnostic equipment (USE, CT, MRT etc.), the percentage of identifying patients at the early stages of disease is still low due to asymptomatic process at its earlier stages.

In conclusion, it is worth saying that the embolization of kidney artery is not complicated procedure for an experienced physician-interventionist. However, in day-to-day work, before supporting its application, it is reasonable to take into account the following practical situations:

If the disease is at TlaNOMO stage, superselective embolization before organ-preserving operation could be applied in order to increase the ablastic of a surgery intervention, all the more, this methodology is not excluded in a case of the single functioning kidney disease. It needs to be taken into account that if there is TlbNOMO, in this group could be the patients both with a tumour of 4,5 cm in extrarenal location, and with a tumour of 7 cm in intra-organ location. In the case of patient with TlbNOMO diagnosis with tumour's sizes 6-7 cm, especially located in the central part of a kidney, this methodology could be reasonable enough.

At the II stages of disease, when tumour's diameter reaches more than 25 cm, distal & proximal variants of pre-operational chemical embolizationcould of the affected kidney could not be excluded. The main aim in these cases could be in the prevention of intraoperational dissemination of tumour cells from an initial nidus.

A clinical appraisal of T3 stage of diseases is characterised by the invasion of initial tumour in a capsule or by the spread of tumour's clot through the venous collector up to the atrium. Advisability of the chemical emobilization in these conditions increases, but terms of a surgery intervention after the procedure rises.

At IV stage of the renal cell carcinoma, to which, as it is known, the patients with locally advanced process, and also with single and multiply distant metastases are included, palliative embolization is suggested, especially for the patients of T4N0M0 category.

In the case of bilateral affection or a tumour of the single kidney, it is possible to use the superselective embolization of hepatic artery's branches, supplying blood to the neoplasm.

The development of world pharmaceutical industry, and rapid coming into being of the target therapy of malignant tumours for the last 10 years, gives the opportunity for oncologists to treat patients with metastatic cancer wider and to use various combinations of target preparations. Nowadays, for the renal cell carcinoma, as for no other tumour, more than 7 target preparations exists and yet about 6-7 new target preparations are investigated in different clinical researches. Currently, there are 3 lines of the target therapy for kidney cancer, starting from Sunitinib – 1 line, continuing with Everolimus, Sorafenib, Pazopanib in 2 lines, and also with the possibility to continue the treatment with Axitinib and other agents in 3 lines of a treatment. Except this, there is a variety of schemes and combinations of a treatment with these target preparations. All of this gave the opportunity to control a disease in the case of disseminating and metastatic kidney cancer for the period from 3 up to 10 years and more, providing a good quality of patient's life and survival. The only problem in the case of metastases kidney cancer still remains the treatment of patients with metastases into the brain, when, unfortunately, it is not possible to provide a prolonged control of a disease.

Thus, renal cell carcinoma, nowadays, is a controllable disease at all stages of the process. Nevertheless, it is worth emphasizing that a treatment of patients must be performed by specialized centres and clinics (oncology centre and dispensary), where the wide capacity to treat this difficult category of patients exists. Kidney cancer treatment at the initial stage should be radical, and at the «advanced» stages, it should be complex and combined, including the application of modern endovascular technologies.

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ТҰЖЫРЫМ

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Оңтүстік-Қазақстандық мемлекеттік фармацевтикалық академия,
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ХИМИОЭМБОЛИЗАЦИЯЛАУДЫ ҚОЛДАНА ОТЫРЫП, БҮЙРЕК ОБЫРЫНЫҢ ТАРАЛҒАН ФОРМАЛАРЫН ЕМДЕУ (дәріс)

Қазіргі уақытта ерте сатылардағы бүйрек обырын диагностикалау (I-II) және оны уақтылы радикальды емдеу, бүгінгі күнгі диагностикалық аппаратураның (УЗИ, КТ, МРТ және т.б.) қарқынды дамуына қарамастан, өкінішке орай, өзекті болып қалуда, аурудың ерте сатыларындағы науқастарды анықтау пайызы оның ерте сатыларындағы үрдістің симптомсыз өтуімен байланысты әлі төмен болып қалуда.

Ұсынылған дәрістік материалда этиология, жіктеулер, клиника және диагностика, бүйрек обырының сатылары бойынша емдеудің бүгінгі күнгі әдістері сұрақтары көрсетілген. Таргетті терапия және бүйректің метастатикалық обыры кезіндегі аралас емдеу сұрақтары қарастырылған. Бүйрек обыры кезіндегі химиоэмболизацияның тарихи аспектілері, көрсетілімдері және қарсы көрсетілімдері жеке қарастырылған. Бүйрек таралған обыры бар 15 науқастарды емдеудің басқа әдістерімен бірге бүйрек артериясын химиэмболизациялау әдісін қолдана отырып емдеу нәтижелері бойынша автордың жеке тәжірибесі ұсынылған. Бүйрек обырымен ауыратын науқастарды емдеудің клиникалық жағдайлары ұсынылған.

Негізгі сөздер: *бүйрек обыры, емдеу, метастазы, эмболизация, таргетті терапия.*

РЕЗЮМЕ

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ЛЕЧЕНИЕ РАСПРОСТРАНЕННЫХ ФОРМ РАКА ПОЧКИ С ПРИМЕНЕНИЕМ ХИМИОЭМБОЛИЗАЦИИ (лекция)

В настоящее время диагностика рака почки в ранних стадиях (I-II) стадии и ее своевременное радикальное лечение остается актуальной, к сожалению, несмотря на бурное развитие современной диагностической аппаратуры (УЗИ, КТ, МРТ и др.), процент выявления больных в ранних стадиях заболевания все еще остается низким в связи с бессимптомным течением процесса в ранних его стадиях.

В представленном лекционном материале отражены вопросы этиологии, классификации, клиники и диагностики, современных методов лечения по стадиям рака почки. Рассмотрены вопросы таргетной терапии и методов комбинированного лечения при метастатическом раке почки. Отдельно рассмотрены исторические аспекты, показания и противопоказания химиоэмболизации при раке почки.

Представлен личный опыт автора по результатам лечения 15 больных с распространенным раком почки с применением методики химиоэмболизации почечной артерии в комплексе с другими методами лечения. Представлены клинические случаи лечения больных раком почки.

Ключевые слова: *рак почки, лечение, метастазы, эмболизация, таргетная терапия.*

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