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DEVELOPMENT OF NEW APPROACHES IN TREATMENT OF METASTATIC RENAL CELL CARCINOMA

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Abstract:

According to the WHO, Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018, and renal cell cancer accounts for about 3% of all malignant neoplasms in adults in the world and takes approxiately 97% of all kidney tumors[1]. The incidence of kidney cancer has significant geographic variability. The same trend is observed with the pain index. The problem of kidney cancer in Uzbekistan has the following tendency: if in 2013 there were 8.4 per 100,000 of the population, then at the end of 2019 this indicator was noted at the level of 8.9. In 2013, the 1-year mortality rate was within 0.5%, in 2019, the data had not changed and the 1-year mortality was athe same 0.5%, which indicates an improvement in diagnosis and treatment[2]. In this regard, research on this scientific problem requires further studies of the features of surgical treatment tactics depending on the changes in the immuno-morphological features of the tumor process, and therefore, it is planned to study the features of the immunohistochemical status of RCC patients, cytogenetic study, search for informative oncomarker, as well as specific diagnostic tests to determine and assess the proper use of a particular treatment strategy. Conducting research in this field will allow determining the features of surgical treatment tactics in terms of performing operations in case of metastatic RCC, as well as solve the issues of the most specific IHC markers for selecting and determining further tactics of surgical treatment of this category of patients. All this on the whole determines the expediency of conducting a new study to solve the problem posed.

Keywords: metastatic, renal cell, carcinoma.

According to Ganesh S Palapattu et all., The role of lymph node dissection (LD) for patients with a diagnosis of renal cell carcinoma (RCC) is uncertain[3]. LD leads to a more accurate diagnosis and may reduce the risk of a positive field, which will lead to a lower risk of local recurrence. LD can also be performed in patients with metastatic lesions in the form of lymphadenectomy.

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Nowadays, available evidence suggests that extended LD may be useful when it is technically possible to remove LN in patients with locally advanced disease (T3-T4) and / or poor clinical and pathological characteristics (high Fuhrman level, large tumors, presence of sarcomatoid signs and / or coagulation tumor necrosis). Although patients with lymph node metastases often also have distant metastases, most retrospective non-randomized studies indicate the potential benefit of regional LD even for this group of patients[4].

In a single randomized study addressing this problem, concerns were expressed regarding EORTC 30881 and its ability to determine the role of LD during nephrectomy. The main limitation of the study was the relatively low risk of patients (70% with the T1-2 stage).

According to some authors, after extended LD, pelvic lymphatic complications are observed three times more often. Other authors report a higher rate of lymphorrhea in patients underwent laparoscopic nephrectomy with LD, compared with patients who underwent only nephrectomy.

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In healthy adult tissues, expression of VEGFR3 is mainly restricted to lymphatic endothelial cells (LEC) and its activation is responsible for the proliferation, migration and survival of LEC. Several reports have shown that expression of VEGF-C in cancer cells correlates with lymphangiogenesis, accelerated tumor progression and / or poor clinical outcome.

Determination of molecular genetic prediction factors (inducer of apoptosis of p53, inhibitor of apoptosis of Bsl 2 and proliferation marker Ki-67) in tumor cells of patients with primary generalized forms of renal cell cancer allows not only to evaluate the activity of tumor cells, but also to predict the patient's life expectancy[6]

Aim of the study. Improving the results of diagnosis and treatment of renal cell cancer with metastases in regional lymph nodes through the development and implementation of modern advances in pathological and immuno-histochemical research methods.

Matherial end methods:

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Object of study: 130 patients with renal cell carcinoma with and without metastases to regional lymph nodes investigated, who received treatment in at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology for the period from 2009 to 2019.

Subject of research: histological material for the determination of immunohistochemical tumor markers (based on retrospective data) obtained from RCC patients with a verified diagnosis, medical history, outpatient cards, data from the Cancer Registry.

Research methods: To achieve the goal of the study and to solve the tasks, the following methods were used: x-ray, ultrasound, morphological, immunohistochemical, radiation, surgical and statistical methods.

Affection of the right kidney was noted in 72 (55.4%), left 58 (44.6%) cases. Patients were conditionally divided into 3 groups, in accordance with the volume of lymph node dissection.

The first group consisted of 35 (26.9%) patients who underwent conventional (without lymph node dissection) nephrectomy. Among the patients of the first group, there was a predominance of women 18 (51.4%) versus 17 (48.6%) men, a ratio of 1: 1.1. The age range is from 21 to 78 years, the average age of patients was 55.3 ± 1.4 years. The right kidney was affected in 17 (48.6%) men and 13 (37.1%) women, and the left kidney 2 (5.7%) in men and in women 3 (8.6%).

The second group consisted of 42 (32.3%) patients, to whom nephrectomy was supplemented with selective lymph node dissection. In this group, the same number of men and women is noted - 21 (50.0%), the ratio is 1: 1. The age range is from 21 to 78 years, the average age of patients was 54.0 ± 1.6 years. Cancer of the right kidney was diagnosed in 8 (19.0%) men and 10 (23.8%) women, cancer of the left kidney was diagnosed in 10 (23.8%) men and 14 (33.3%) women.

The third group consisted of 53 (40.8%) patients, they underwent nephrectomy with extended lymph node dissection. In this group, there is a predominance of men 28 (52.8%) against 25 (47.2%) women, the ratio is 1: 1.1. The age range is from 21 to 75 years, the average age of patients was 52.0 ± 1.3 years. In men, cancer of the right kidney is set in 12 (22.6%) cases, and left in 16 (30.2%). For women, these figures were 12 (22.6%) and 13 (24.5%), respectively.

In stages, the distribution of patients was as follow: with the second stage, 65 (46.1%) patients; with the third - 45 (34.6%) and with the fourth stage - 18 (13.8%) patients. In all the compared groups, the greatest number of patients was with the second stage of the disease: in the first group in 10 (30.3%) patients, in the second - in 18 (42.8%), and in the third in 32 (58.2%) .

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The number of patients with metastatic lesions of regional lymph nodes revealed: N1 - 32 (24.6%), N2 - 8 (6.2%). In the remaining 90 (69.2%) patients, the regional lymph nodes were intact.

The results of the histological examination of the surgical material obtained by performing nephrectomy in patients showed a different histological structure of renal cell carcinoma.

The most frequent type of renal cell carcinoma was detected in 109 (83.8%) patients.

Systemic immunotherapy and targeted therapy was performed in the postoperative period. Immunotherapy was performed with the drug "Roferon-A" by intramuscular injection of 3 million IU intramuscularly per day for 10 days. The break between courses was 3 weeks. The effectiveness of treatment was evaluated after 4 courses (according to international criteria). Targeted therapy was performed by Pazopanib according to the 80 mg / day oral schedule. Immunohistochemical study (IHC) of operational material was performed on serial paraffin sections in the laboratory: Premium Diagnostics LLC, address: Tashkent Uchtepa district, ul. Uigur 618A. License number 1260-00 series A№005951. The preparation has the registration certificate Number Tv / X 00058/03/15, the date of registration is 13.03.2015 with the term of registration certificate 13.03.2020. Manufacturer: Dako Denmark A / S, Dania Dakoproduktionsvej 42, DK-2600 Glostrup Denmark

As mentioned above, all patients were divided into groups based on the volume of lymph node dissection.

In the first group, normal (without lymph node dissection) nephrectomy with a median approach was performed.

In the second group, nephrectomy was supplemented with selective lymphodissection. After laparotomy, the abdominal cavity was examined by a median approach. The retroperitoneal space was opened, then when lymph nodes were enlarged or suspected of metastatic lymph node lymphadenectomy of one package of lymphatic collectors was performed, after which nephrectomy was performed.

In the third group, nephrectomy was performed with extended lymph node dissection. Technique: after laparotomy, the loop of the intestines is retracted medially, the pancreas, the fiber that surrounds the aorta and the inferior vena cava are also mobilized. After that, the back sheet of the peritoneum is opened over the projection of the aorta from the level of the bifurcation upwards with dissection of the Traineal ligament, the retroperitoneal space is revealed. The left renal vein stands out and is taken to the turnstile, after which lymphadenectomy begins. First order lymph nodes, lateroaortic lymph nodes located from the aortic intersection of the left renal vein to the beginning of a.mesenteria inferior in the amount of 6-7, retro-aortic (1-2), preaortic

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(10-12), second-order lymph nodes : retro-caval lymph nodes up to the level of the superior mesenteric artery (2-4), interortoaval lymph nodes - 3, upper ileal artery - 3, for a total of 24-30 lymph nodes.

When the tumor of the right kidney, lymph nodes of the first order were removed: precaloids in an amount of 2-3, laterocaval - 3-4, retrocaval - 2-4, then lymph nodes of a second order: interortoaval in number 3 to the level of the superior mesenteric artery and 3 superior iliac lymph nodes a total of 14-19 lymph nodes, with the left-sided location of the tumor, the descending, transverse colon is mobilized.

Resalts:

To assess the immediate results of surgical treatment, we used the generally accepted classification of Clavien-Dindo. Early postoperative complications were detected in 47 patients (15.7%). In group 1, early postoperative complications developed in 5 (15.1%) patients. Renal failure was detected in 1 (3.0%) patient. In the postoperative period, multiple organ failure and acute cerebrovascular accident developed in 1 (3.0%) case, eventration of abdominal organs was observed in 2 (6%) cases, postoperative wound suppuration was detected in 2 (6.0%) patients. Late complications in the form of postoperative fistula were observed in 2 (6.0%) and hydrocele in 1 (3%) patient. Thus, in group 1 for surgical complications in Clavien-Dindo, grade 1 -8 (24.2%) is noted.

In group 2, a common early postoperative complication developed in 7 (16.7%) patients. Acute renal failure developed in 1 (2.4%) patient. The development of the eventration of the abdominal organs was noted in 2 (4.8) cases. Suppuration of the postoperative wound was found in 2 (4.8%) cases, pyelonephritis of the only kidney was noted in 1 (2.4%) patient. Of the late complications, postoperative hernia occurred in 1 (2.4%) patient, exacerbation of chronic pyelonephritis was observed in 2 (4.8%) cases, the development of chronic renal failure was observed in 1 (2.4%) patient. In this group, there were only 4 (9.5%) cases of late postoperative complications.

It should be noted that during the eventration of abdominal organs, which occurred in 2 (4.8%) patients, relaparotomy and closure of the abdominal wall were performed. In the second group, the evaluation of surgical complications according to Clavien-Dindo was 1st degree 11 (26.1%) patients, and 3rd degree 2 (4.9%)

In group 3, common early postoperative complications developed in 10 (18.2%) patients. Acute renal failure developed in 2 (3.6%) patients. Multiple organ failure was observed in 1 (1.8%) patient. Pyelonephritis of a single kidney developed in 2 (3.6%) patients. Suppuration of the postoperative wound was found in 3 (5.4%) cases. Postoperative bleeding began in 2 (3.6%) patients, due to inadequate final hemostasis, and a postoperative hematoma formed in the area of the kidney bed (according to clinical data and ultrasound data), and therefore relaparatomy was required. Of the late

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complications, exacerbation of chronic pyelonephritis was noted in 2 (3.6%) cases, the development of chronic renal failure was observed in 1 (1.8%) patients. Dropsy of the testicle was developed in 1 (1.8%) patient. In this group, there were a total of 5 (9.1%) cases of late postoperative complications. Summarizing surgical complications according to Clavien-Dindo, grade 1 occurred in 15 (25.4%) patients, grade 3 was noted in 2 (3.6%).

Table 2

The distribution of patients depending on the development of late postoperative complications

	First Group, n=53		Second Group, n=42		Third Group, n=35		Total, n=130	
CHRF	1	1,9	0	0,0	2	5,7	3	2,3
Adhesive Disease	3	5,7	2	4,8	2	5,7	7	5,4
No data	4	7,5	5	11,9	2	5,7	11	8,5
No Complication	43	81,1	34	81,0	29	82,9	106	81,5
In total	48	90,6	41	97,6	35	100,0	124	95,4

A comparative analysis of the direct results of surgical treatment of kidney cancer in each group showed a rather low incidence of the development of various postoperative complications. So only in 34 patients, which was only 26.1%, the postoperative period proceeded with the development of any complications, only early postoperative complications developed in 12 (9.2%) of 130 patients. It should be noted that the most common early postoperative complications were found in patients undergoing selective lymphadenectomy - 5 (9.1%) out of 42, while in the group of patients who underwent nephrketomy with extended lymph node dissection and without lymph node dissection, complications were noted in 8 cases in total (9.1% - n = 55 - the third group; 9% - n = 33 - the first group), which statistically is not reliable $p \leq 0.05$ (Table 2).

Clinical diagnosis of local complications of the wound process was not difficult. We believe that this group of complications is not related to technical features or errors of the operation, but is a reflection of the problem of hospital infection in surgery. Conservative treatment of local wound complications was a success in all cases.

Such terrible complications as eventration of abdominal organs and postoperative bleeding were the most frequent - in 3% and 1.5%, respectively. Within a year after surgery, no patient died due to decompensation of concomitant somatic pathology.

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We performed an immunohistochemical analysis with VEGF-C in 40 patients from 130. The patients were divided into 3 conditional groups: 1 group - 10 patients without relapse and metastases, group 2 - 20 patients with metastases to the lymph nodes and group 3 - 10 patients who have metastasis or relapse in the postoperative period.

In the immunohistochemical study, a positive reaction with high expression of VEGF was observed mainly in the degree of differentiation of the tumor G-3 and G-4, which accounted for 28 (55%) patients. In group 1, negative expression was observed in highly and moderately differentiated tumors 3 (30%). At low and undifferentiated tumors, moderate and high expression of VEGF was observed (50%), with further observation in these patients a locoregional recurrence or distant metastasis was observed.

In the second group of patients in whom postoperative histopathological examination revealed metastasis to the lymph nodes, high expression of VEGF-C with G-4 was observed in 16 (75%), and in G-3 there was a moderate expression in 15% of cases. Negative expression was observed only in 1 (5%) with G3. As can be seen from Table 4, lymphogenous metastasis did not reveal negative expression of VEGF-C.

Table 3.

The study of the relationship of the level of differentiation of the tumor and VEGF expression in RCC patients.

Tumor differentiation	Patients without recurrence and metastasis, n = 10					
	Negative		Modern Expression		High Expression	
	abs	%	abs	%	abs	%
G-1	2	20,0	0	0	0	0
G-2	1	10,0	1	10,0	1	10,0
G-3	0	0	1	10,0	1	10,0
G-4	0	0	1	10,0	2	20,0
Total	3	30,0	3	30,0	4	40,0
	Patients with verified metastasis in lymph /n, n = 20					
G-1	0	0	0	0	2	10,0
G-2	0	0	1	5,0	2	10,0
G-3	1	5,0	1	5,0	5	20,0
G-4	0	0	1	5,0	7	35,0
Total	1	5,0	3	15,0	16	75,0
	Patients with separated metastases and relapses of the postoperative period n = 10					
G-1	0	0	0	0	1	10,0
G-2	0	0	0	0	1	10,0

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G-3	0	0	1	10,0	2	20,0
G-4	1	10,0	1	10,0	3	30,0
Total	1	10,0	2	20,0	7	70,0

Patients in group 3 with metastases and locoregional recurrences in the late postoperative period showed high expression of VEGF-C in low and undifferentiated forms 5 (50%), and no negative reaction was detected.

Among 40 patients with kidney cancer, the expression index of VEGF-C antigen in 4 (10%) patients was negative, in 8 (20%) - moderately positive, in 28 (70%) - highly positive.

A comparative analysis of the data obtained, according to the degree of expression of VEGF-C antigen, showed that the frequency of negative results of this symptom of the tumor process of the kidney in patients with cancer was more significant and statistically significant ($p < 0.05$).

The high expression level of VEGF-C in patients correlated with an unfavorable prognosis regarding survival.

The increase in the expression of endothelial growth factor of the lymphatic vessels of VEGF-C in renal cell carcinoma may be due to even more obvious mutations, which play a central role in lymphoangiogenesis. Overexpression of this protein indicates the beginning of invasion into the lymph nodes or metastasis. Thus, there is a tendency to increase VEGF-C with increasing stage, including with obvious metastases in the lymph nodes.

Thus, the relationship between the expression of VEGF-C protein and the development of relapses and metastasis after radical nephrectomy has been shown, which may be one of the prognostic criteria. As noted above, there is a correlation between the level of cell differentiation and protein expression.

A total of 67 patients from 130 patients in the postoperative period received adjuvant therapy. They were divided into four groups:

- the first group - 21 (31.2%) with verified lymphogenous metastasis, which underwent immunotherapy with interleukins in the postoperative period.
- the second group - 19 (28.3%) patients with verified lymphogenous metastasis who underwent immunotherapy in the postoperative period and with sorafenib (nexewar);
- the third group - 15 (22.3%) patients, with verified lymphogenous metastasis, who in the postoperative period underwent targeted therapy with pazopanib (votrient.);
- the fourth group - 12 (17.9%) patients, with positive expression of VEGF-C without lymphogenous metastasis.

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The results of the treatment were evaluated according to the following indicators: three-year patient survival after treatment; median life expectancy and average life expectancy.

Previously studied the effectiveness of the treatment method for each group separately, and then conducted a comparative analysis of the results of treatment between groups.

The median of time to progression (TTP) was considered the primary reference point for the assessment. The secondary control points were the median of the OS in 1 and the frequency of general responses (OA + stabilization) and objective answers (OA = PA+ PR).

To determine and build graphs of survival, the Kaplan – Meier method was used; differences in survival were compared using a log-rank test. The differences between the compared values at a significance level of $P < 0.05$ were considered statistically significant. Mathematical processing of the results obtained was carried out using Statistica software.

The average duration of treatment was 23.0 (4.0–32.9) months. The effectiveness and frequency of general responses depending on the drug and the line of treatment are presented in Figure 1. Only with the use of pazopanib, complete regression was observed in 6 patients. In addition, pazopanib (37.0%) and sorafenib (29.0%) showed the largest proportion of objective responses. The smallest number of objective responses was obtained in patients who received a IT (9.1%).

In every 3rd patient, against the background of IT (29.1%), the maximum response to treatment was progression, while on other drugs it did not exceed 13.7%. Nevertheless, the frequency of general responses achieved at IT was 70.9%. In 8 patients, a prolonged stabilization of the process was registered (more than 5 years).

To evaluate the indicators of the median time to progression (TTP) and the OS median in the treatment, 3 drugs were used, represented by the largest sample: interferon 2β (n = 21), sorafenib (n = 19) and pazopanib (n = 15). TTP median was 13 months (95% confidence interval (CI) 8–12). The duration of treatment ranged from 1 to 30 months.

Targeted therapy demonstrated a significantly significant superiority in TTP ($P < 0.0001$) over IT: 16 months (95% CI 10–21) and 12 months (95% CI 10–16) in pazopanib and sorafenib, respectively, compared to 7 months (95% CI 5–9) on IT.

The median OS in the pazopanib group was higher and amounted to 37.2 months (95% CI 18.6–46.2). In the INF and sorafenib group, this indicator corresponded to 29.9 months (95% CI 31.6–42.7) and 24.4 months (95% CI 23.3–36.0). Statistical significance was not achieved ($P = 0.43$).

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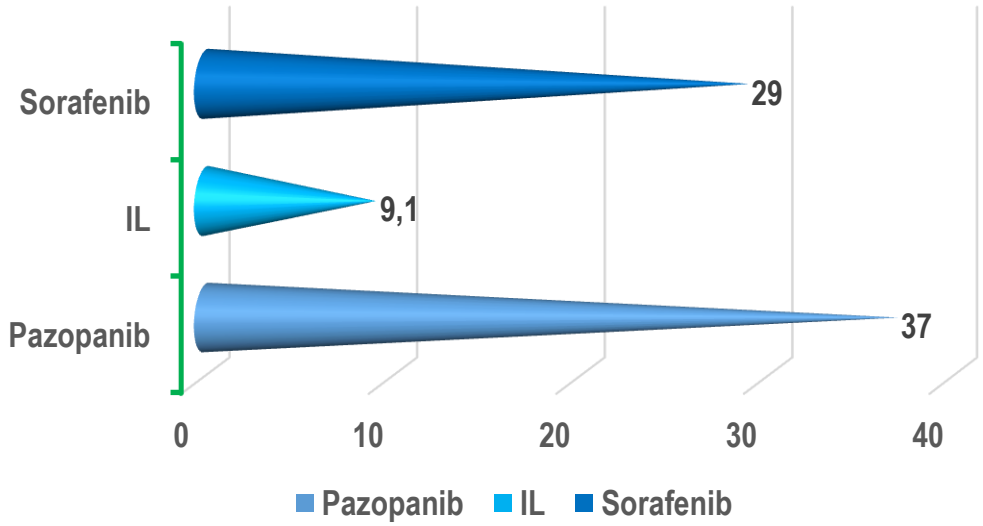

Fig.1. Characteristics for an objective response

Evaluation of treatment results was performed in 23 patients. Of these, 4 (17%) patients registered partial regression (PR), 16 (70%) - stabilization and 3 (13%) - disease progression.

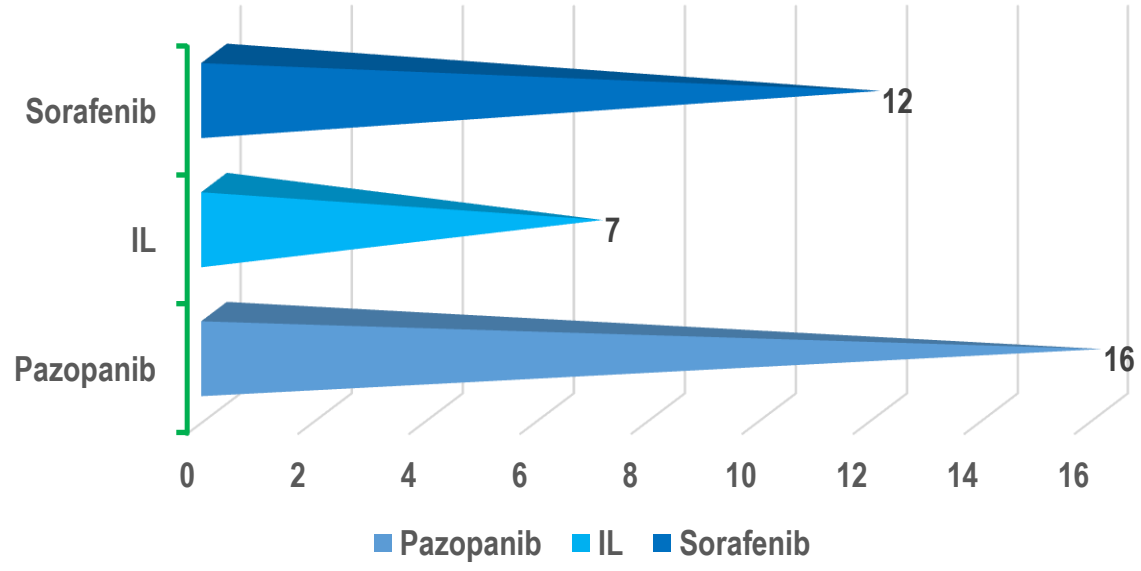

Fig. 2. Median time to progress

After discontinuation of therapy, the severity of adverse events decreased, but the persisting proteinuria did not allow to conduct retreatment.

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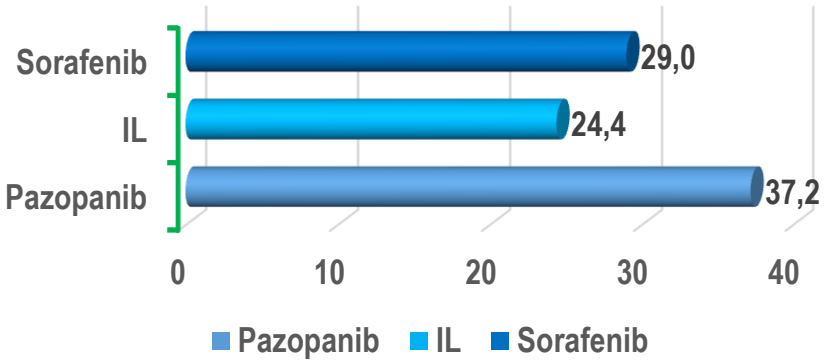

Fig. 3. Median overall survival

Sorafenib + IFN combination therapy has a favorable safety profile. The purpose of IFN in low doses allows you to minimize its side effects.

Tolerance to pazopanib as monotherapy was better than IFN-α. Side effects of III – IV degrees of severity were less common in patients with pazopanib (57%) than in IFN-α (78%; p = 0.02). The main non-desirable events in patients were hypertension (55%), hepatotoxicity (47%) and nosebleeding (35%).

The above side effects were due to inhibition of mTOR-regulated glucose and fat metabolism. Respiratory symptoms such as coughing and shortness of breath were recorded in approximately 15% of patients (26 and 28%, respectively). In the Global ARCC study, the incidence of nausea and diarrhea in the pazopanib group was 29%, while in the IFN-α group it was 6%. The majority of adverse events during therapy with pazopanib were easily stopped and managed. Acceptance of pazopanib compared with IFN-α therapy is associated with an increase in liver, in particular bilirubin and ALT-AST. An isolated increase in ALT levels correlated with longer life expectancy.

Therefore, for a more accurate staging process, it is advisable to perform selective lymph dissection with the removal of first-order lymphocollectors.

When discussing the results of lymphadenectomy, it should be emphasized that probably the most important basis for lymphadenectomy is the improvement of treatment results after the removal of macroscopically and microscopically affected lymph nodes.

VEGF overexpression was observed in 61.4% of cases of clear cell RCC (in 27 of 40 observations). In patients without recurrence, overexpression was observed in 40% of patients, in 60% of cases negative or moderate expression was encountered.

A high level of protein expression in the group with lymph node metastases or in case of distant metastasis may be associated with a more aggressive course of these carcinomas, compared with the control group. The lack of expression in clear cell

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carcinoma can probably be explained by the small number of studied tumors or the expression of other protein isoforms by the tumor cells.

Significant differences in the expression of VEGF in tumors of different stages both in the whole sample and in each studied group were revealed.

VEGF overexpression is characteristic for all variants of advanced cell-renal cell carcinomas and is practically undetectable in the early stages of the disease.

The dependence of VEGF overexpression on the degree of differentiation was observed.

Among the highly and moderately differentiated carcinomas, a high level of VEGF expression was noted in 20% of cases, in the low-differentiated group - in 27% (in 11 out of 40). The assessment revealed a significant predominance of overexpression of VEGF in low-grade tumors.

The results of the analysis suggest that VEGF-C overexpression is associated with a reduction in the relapse-free survival time. This figure was 26 months in patients with low levels of VEGF-C 4 expression and 18 months with high marker expression. The predicted 5-year survival with overexpression of protein was 18%, with a low level of expression - 70%.

The result obtained is significant and allows us to attribute the overexpression of VEGF-C to independent factors of unfavorable course of clear cell RCC.

It is noted that in clear cell carcinomas, VEGF-C is expressed more intensely with G4 than with other G.

Among tumors with a low level of protein expression in all histological variants, stage III – IV carcinomas prevailed.

Thus, with an increase in the tumor stage in PKR, the expression of VEGF-C is significantly increased.

CONCLUSION

On the basis of the research we the following conclusions were made:

1. It has been established that the overexpression of VEGF-C is an independent adverse criterion for the prediction of clear cell RCC. This protein is significantly more frequently detected in clear cell carcinoma, and its expression level increases with G3-G4. Proteins can be considered as potential prognostic markers of RCC, as their level of expression is significantly associated with the degree of differentiation: VEGF-C overexpression increases as the degree of differentiation decreases.
2. In case of locally advanced renal cell carcinoma, performing a nephrectomy with extended lymphadenectomy does not increase the incidence of post-operative complications compared to non-lymph node dissection and selective lymphadenectomy. When evaluating surgical complications according to the

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classification of Clavien-Dindo, grade 1 was noted in group 1 in 8 (24.2%) patients; in the group with selective lymph node dissection (group 2) in 11 (26.1%) patients, at the same time grade 3 in 2 (4.9%) patients; Group 3, generalizing surgical complications according to Clavien-Dindo, grade 1 in 15 (25.4%), grade 3 in 2 (3.6%) patients. Also for access to the main vessels of the kidney and lymphatic collectors of the kidney, we recommend cutting the Trayce ligament before mobilizing the kidney.

3. Nephrectomy with extended lymphadenectomy in renal cell carcinoma can significantly improve long-term results of treatment: three-year survival in the group of patients with simple nephrectomy was 54.5%; in the group of patients with selective lymph node dissection - 69.0%, and when conducting advanced lymph node dissection - 78%.
4. Expression of VEGF-c protein was detected at G1-20%, G2-30%, G3- 50%, G4- 85%. This protein is significantly more frequently detected in G3-4. The VEGF-C protein can be considered as a potential prognostic marker of RCC, since its level of expression depends on the degree of differentiation. It is established that the overexpression of VEGF-C is an independent adverse criterion for the prediction of RCC.
5. Targeted therapy demonstrated a significantly significant superiority of VDP (P <0.0001) over BMI: UAR in patients in the pazopanib and sorafenib groups reached 16 and 12 months, respectively, whereas in the group of BMI - only 7 months. At the same time, there was no significant difference in the OV between the drugs. The ORR in patients taking pazopanib was slightly higher and amounted to 30%.

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