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The long-term outcome of surgical treatment of kidney cancer complicated by tumor thrombosis

Relevance: *Kidney cancer ranks 10th and accounts for 2-3% of all oncological diseases. In oncourology, it ranks 3rd after prostate cancer and bladder cancer. 1163 primary cases of kidney cancer were detected in 2017 in the Republic of Kazakhstan.*

Kidney cancer mainly affects people from 40 to 60. The frequency in males is 4.4‰, what is 2-3 times more often than in females – 3‰.

The peculiarity of kidney cancer vs. other tumors is its frequent spread through the venous collectors as the path of least resistance to invasive growth, namely, through the renal (25-30% cases) and inferior vena cava (IVC) (4-10% cases) up to the right atrium.

Purpose of the study *is to evaluate the results of treatment of patients with kidney cancer and venous tumor thrombosis.*

Results. *The tumor with thrombus was radically removed in all 68 treated patients. A standard nephrectomy with thrombectomy was sufficient for patients with a thrombus of the renal vein (27 patients). Nephradrenalectomy was performed in case of adrenal lesions. 1-year survival with different vascular invasions varied from 62% with IVC lesion up to 77% with the renal vein lesion. 5-year survival differed significantly (26.8% and 63%, respectively). Overall survival varied from 26.8% in case of invasions into the IVC to 63.0% with the thrombus in the renal vein. Median survival in months amounted to 36.8 and 72.4, respectively (p~0.02). Median survival without metastases was 52.8 months vs. 40.3 months with metastases at diagnosis. The latter data was not statistically significant (p = 0.36) due to a small sample.*

Conclusions: *Despite recent advances in the combined treatment of kidney cancer, the kidney removal with thrombectomy remains an effective method of treating patients with kidney cancer complicated by venous tumor thrombosis.*

Keywords: *renal cell carcinoma, vascular invasion, surgical treatment, metastases, survival.*

Introduction. Kidney cancer (KC) ranks 10th and accounts for 2-3% of all oncological diseases. In oncourology, it ranks 3rd after prostate cancer and bladder cancer. Annually, around 400,000 new cases of renal cell carcinoma (RCC) are detected worldwide. RCC ranks 9th in the structure of oncopathologies in men, and 14th in women [1]. According to the cancer register - 2017, RCC ranked 10th in the structure of cancer diseases in the Republic of Kazakhstan [2].

KC is mainly detected in patients aged 40 to 60 years, 2-3 times more often in men than in women [1]. Compared to other tumors, KC spreads more frequently through the veins due to their least resistance to invasive growth. It mostly invades into the renal vein (25-30% of cases) and inferior vena cava (IVC) (4-10% of cases) till the right atrium [3]. "Venous invasion" means the penetration of the tumor into the lumen of blood vessel (continued growth) without a mandatory invasion of the vascular wall. Such thrombus can reach 20 cm. They are fixed to the tumor in kidney parenchyma and float at different levels in the lumen of the renal vein and the IVC.

91.1 thousand patients die from this disease worldwide each year [3]. 5-10% of patients with KC have vessel invasion what substantiates the relevance of the problem of treatment of advanced forms of KC [4]. Untreated RCC with venous tumor thrombosis has a very unsatisfactory picture.

In the recent study in RCC patients with venous tumor thrombosis, the median survival was 5 months, and the annual specific survival was only 29% [5]. Some studies have shown a stable disease-free survival after radical nephrectomy with tumor thrombectomy [6].

Radical surgical treatment of KC with tumor thrombus in IVC has proven its efficiency. Today, tumor thrombus is not the cause to refuse in the surgical treatment of such patients. Today, surgical treatment remains the only way to prolong life and improve its quality in patients with advanced KC and its most complicated case - with venous tumor invasion and spread of thrombi via the renal vein and IVC till the right atrium [7].

Purpose of the study is to evaluate the results of treatment of patients with kidney cancer complicated by venous tumor thrombosis.

Materials and methods. The total of 68 patients with RCC complicated by tumor renal and inferior vena cava thrombosis (IVC) treated at the Kazakh Institute of Oncology and Radiology (Almaty, the Republic of Kazakhstan) in 2007-2016 (10 years) were included in the retrospective study. Age of the patients – 35 to 84 years; the median age – 54 years.

The tumor thrombosis of renal veins and IVC in patients with kidney cancer was diagnosed using standard methods of RCC diagnostics and identification of the venous invasion and the thrombus upper level such as ultrasonography of kidneys, ultrasonic Doppler examination of the vascular system, multi-layer spiral CT of abdominal organs and retroperitoneal space with bolus contrast enhancement. The additional methods of examination used in certain cases included the selective vasography with ascending IVC-graphy in order to determine the extension of tumor thrombus, and MRI with contrast enhancement.

The main clinical symptom was the lumbar pain. 14 (20%) patients had no clinical symptoms. Some patients had such symptoms of IVC thrombosis as: hepatomegaly – 9 (13.2%), caput medusae – 5 (7%), pampinocele – 4

(5.9%), ascites – 3 (4.4%). Pre-operative lab tests: anemia – 52 (76.5%), leukocytosis – 12 (17.6%), thrombocytosis – 17 (25%); hyperglycemia – 6 (8.8%), elevated ALT and AST levels – 28 (41.1%) patients; as well as some cases of micro-hematuria and high creatinine.

The concomitant pathologies included: arterial hypertension – 62 (91.2%); DM type 2 – 6 (8.8%); hepatitis B and C – 13 (19.1%) patients.

Table 1 shows the clinical profile of patients with venous tumor thrombosis.

Table 1 – Clinical profile of patients with RCC complicated by venous tumor thrombosis, n = 68

	Criteria	Total, n	%
Sex	Male	43	63.2
	Female	25	36.8
Age	≤50 years	11	16.2
	50 to 60 years	39	57.3
	>60 years	18	26.5
Side of lesion	Right kidney	36	52.9
	Left kidney	32	47.1
Thrombus localization levels	Renal vein	27	39.7
	Inferior vena cava (IVC)	41	60.3
Thrombus invasion in IVC	Infrahepatic	27	39.7
	Retrohepatic	11	16.2
	Suprahepatic	3	4.4
Distant metastases	M_0	52	76.5
	M_+	16	23.5

According to Table 1, the tumor venous invasion was more frequent in men (63.2%). The frequency of lesions was the same on the right and left side (52.9 and 47.1%, respectively). The median length of the thrombus was 7 cm (4 to 16 cm); the median diameter –2 cm (2 to 4 cm).

The venous tumor thrombosis was found in the renal vein in 27 (39.7%) cases, and in IVC level – in 41 (60.3%) cases. In 4 cases, the tumor thrombus was not diagnosed by standard X-ray imaging methods. During surgery, the tumor thrombi were found in the mouth of the renal veins; in 2 cases, they were floating in the IVC lumen. All those cases were noted in patients with rightward kidney cancer. The diagnostics was complicated by a large volume of the kidney tumor and/or the conglomerate of lymphatic nodes in the hilum of the kidney. One patient had a tumor thrombus in the retrohepatic segment, and a formed blood clot below the renal vein level. His IVC was ligated below the renal vessels transposition level due to a high risk of post-surgical thromboembolic complications, the infeasibility of thrombectomy, and the presence of formed collateral blood flow. In all cases, the surgery was completed by removing the kidney with tumor thrombosis.

52 patients had no distant metastasis during the examination; 16 (23.5%) patients had lung metastases at diagnosis.

SPSS Statistics 2017 was used for graphic processing of data. The statistical significance between the survival curves was calculated by the Pearson's chi-square test with CI 95% or higher.

Results and discussion. All patients underwent radical tumor removal (nephrectomy with thrombectomy). A standard nephrectomy was sufficient for the patients with renal vein thrombosis. Nephradrenalectomy was required in some cases due to the lesion of the adrenal. The main operative approaches used were median laparotomy and Cherni operative approach. Chevron or Mercedes laparotomy was also used in case of large formations and local advancement; however, those approaches were associated with a longer-term postoperative wound healing.

Contralateral renal vein thrombectomy was accompanied by heparinization after IVC compression above and below the thrombus. In some cases, after IVC mobilization, it was possible to distally shift the top of the thrombus by fingers, permitting to locate the clamp at a lower level. In case the thrombus was advancing to the retrohepatic segment and higher, the liver was mobilized and its vasculature isolated during the thrombus evacuation from the IVC (including the clamping of the hepatoduodenal ligament).

The patients with thrombi above the diaphragm were not admitted to the hospital due to the lack of opportunities for auxiliary and artificial blood circulation, temporary bypass surgery, and the lack of cardiac surgeons.

The average intra-operational blood loss was 950 ml (400 to 2500 ml).

Heparin was administered in therapeutic dose 1-2 days after the intervention affecting the IVC. Then the dosage was changed to prophylactic or a fractionated heparin was administered. Indirect anticoagulants were prescribed on individual bases.

Some complications were observed in the early postoperative period. 1 patient died due to acute DIC. 4 cases of bleeding from the tumor bed during the first postoperative day required immediate recurrent operation for bleeding control.

The histopathological examination showed RCC in all preparations (clear cell – 52 (76.5%), papillary –

9 (14.7%), chromophobic – 2 (4.4%), formation of renal collecting tubules – 1 (1.4 %)). The tumor thrombus structure was similar to the renal neoplasm structure.

23 (33.8%) patients had metastases in regional lymph nodes (pN +).

Long-term surgical treatment results were analyzed by the one-year and five-year survival rates (see Table 2).

Table 2 – Review of long-term surgical treatment results in patients with RCC complicated by venous tumor thrombosis, n = 68

Criteria		One-year survival %	Overall sur-vival %	Median sur-vival, months	Chi-square	P-value
Sex	Male	76	41,9	51,2	0,107	0,744
	Female	56	40,0	50,0		
Side of lesion	Right kidney	68	50,0	50,9	0,41	0,52
	Left kidney	69	31,2	47,2		
Level of thrombus localization	Renal vein	77	63,0	72,4	9,2	0,02
	inferior vena cava (IVC)	62	26,8	36,8		
Level of thrombus invasion into the IVC	Infrahepatic	74	37,0	42,2	5,41	0,06
	Retrohepatic	36	0	22,1		
	Suprahepatic	50	50,0	7,7		
Distant metastases	M_0	72	52	52,8	0,82	0,36
	M_+	56	37,5	40,3		

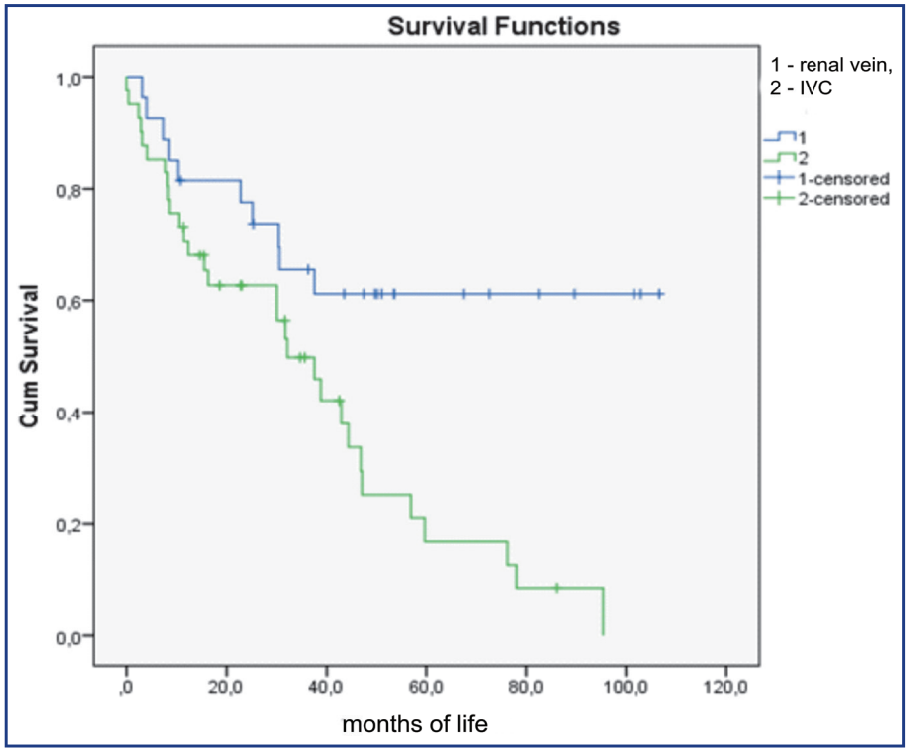

Figure 1 – Kaplan-Meier survival curves of patients with RCC complicated by venous tumor thrombosis depending on the lesion: 1 - renal vein, 2 - IVC

One-year survival rates varied depending on the vascular invasions: from 62% with IVC lesion to 77% with the renal vein lesion.

The figures of overall survival differed significantly. Overall survival varied from 26.8 % in case of IVC lesion to 63.0% with the renal vein lesion. Median survival in months was 36.8 and 72.4, respectively (p = 0.02) (Figure 1).

We assessed the survival rates depending on the level of IVC lesion. In case of infrahepatic IVC lesion, the overall survival of patients amounted to 37.0%, and in case of suprahepatic lesion – to 50.0% (median survival – 42.2 and 7.7 months, respectively) (p ~ 0.06). Figure 2 shows the survival curves depending on the level of IVC thrombus localization.

We have also analyzed the survival of RCC patients with venous tumor invasion depending on the presence or absence of metastases at the time of diagnosis (see Figure 3).

One-year survival of patients was equal to 56% with metastases vs. 72% without metastases. Overall survival

was equal to 37.5% with metastases vs. 52% without metastases (median survival was 40.3 and 52.8 months, respectively) (p ~ 0.36) (Table 2). All patients with distant metastases received targeted postoperative therapy what could have a positive impact on the survival of that group of patients.

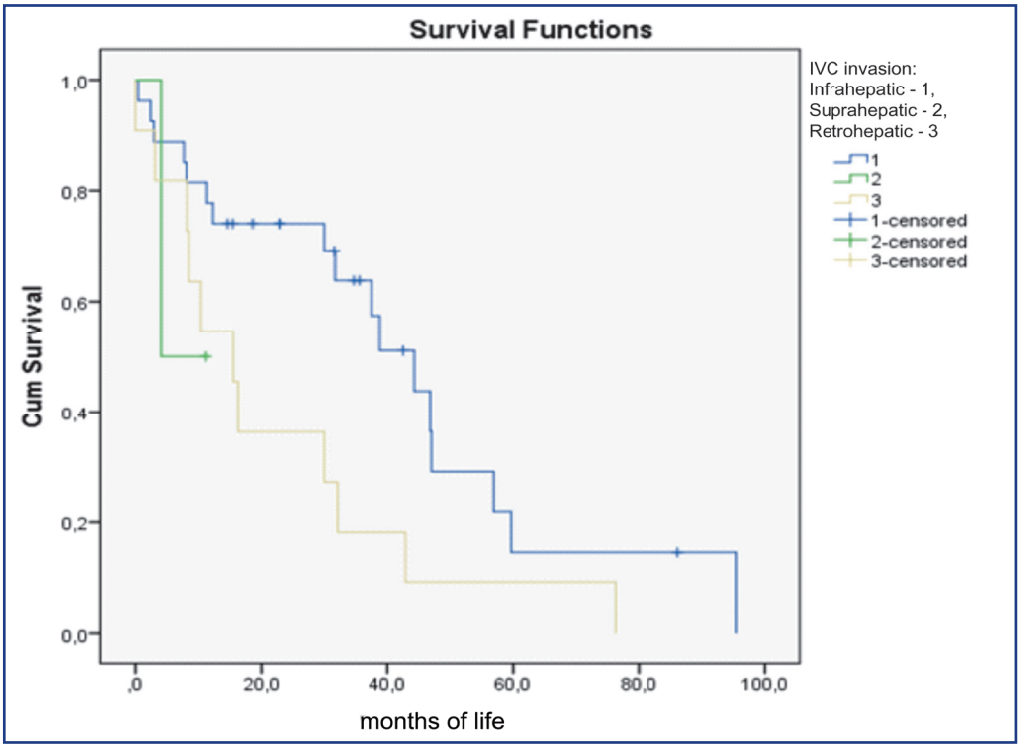

Figure 2 – Kaplan-Meier survival curves of patients with RCC complicated by venous tumor thrombosis depending on the level of IVC thrombus localization

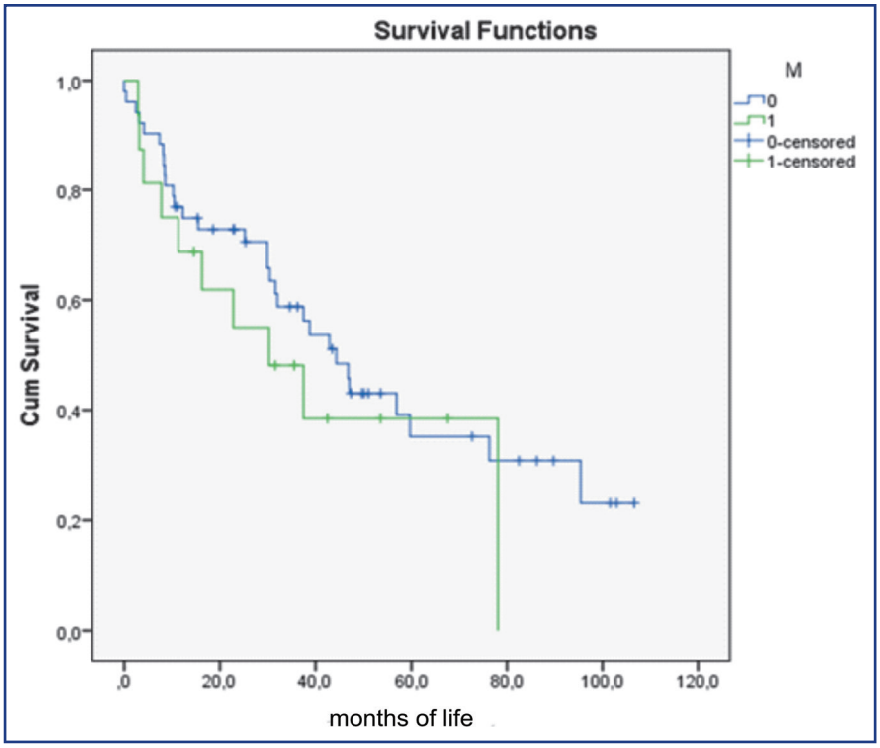

Figure 3 – Kaplan-Meier survival curves of patients with RCC complicated by venous tumor thrombosis depending on the presence of metastases

Conclusions. Although venous invasion deteriorates the survival of patients with RCC, radical surgery gives a chance to prolong their life and recovery regardless of the dimension of the tumor thrombi. Despite recent advances in the combined treatment of kidney cancer, nephrectomy with thrombectomy remains an effective treatment method for patients with kidney cancer complicated by venous tumor thrombosis. Age, gender, and

side of lesion do not influence the patients' survival. According to the study results, the survival is dependent on the thrombus localization in the IVC, and the presence of distant metastases.

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