THE INFLUENCE OF PARTIAL NEPHRECTOMY ON FUNCTIONAL STATUS OF PATIENTS WITH RENAL CELL CARCINOMA

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Resection of kidney is by far the operation of choice in localized forms of renal cell carcinoma (RCC) with diameter up to 4 cm, which not only provides satisfactory cancer, but functional results. Recent studies have shown that tumor resection, performed with a negative surgical margin, provides excellent local control of tumor. However, its performance depends on several factors: size, location, morphological structure of the tumor, surgeon's experience and others. On the other hand, absence of clear standardization of anatomical changes in renal cell carcinoma impedes the right choice of surgical treatment [1].

The study advantages of resection of kidney include: preservation of functional state of kidney that allows reducing the risk of emergence of kidney failure and complications associated with other organs and systems, providing good rates of overall survival compared with radical nephrectomy [2]. However, kidney resection is technically more difficult operation and is characterized by a higher frequency of surgical complications that often require repeated surgery [3-6].

One standard approach for resection of kidney is to stop the blood flow by the way of clamping the vascular pedicle during the operation, which enables to minimize blood loss. However, kidney ischemia often leads to irreversible ultrastructural changes in the renal parenchyma with subsequent deterioration or even loss of function and development of chronic renal failure. To reduce the effect of ischemia on renal are often used various nephroprotection measures, including: renal hypothermia, reducing the time of ischemia, infusion of mannitol [7], but carrying out the above procedures can not fully ensure leveling the

pernicious influence of ischemia on the function of kidney. Therefore, a promising direction in the treatment of RCC is the development of methods of antiischemic protection of kidney and the development of new surgical approaches that would ensure the preservation of kidney function in its resection.

The purpose of work: to study the influence of ischemia on the functional state of kidney during its resection with tumor in the remote postoperative period.

Material and methods. The work was performed at the premises of National Cancer Institute, Research Department of Plastic and Reconstructive Oncourology. For the purpose of adjuvant therapy, aimed at preservation and improving kidney function and prevention of symptoms of kidney failure in the future, all patients who acted from 2012 and who were planned to perform resection of kidney, were randomized into two groups. The study group included patients whom, at the time of resection of kidney with tumor, ischemia of kidney was not performed; in control – patients to whom organ-preserving surgical treatment was carried out using the ischemia of kidney with temporary clamping of renal artery. Randomization was performed using the method of random numbers in the randomization center of the National Cancer Institute.

During 2012- 013 the study included 221 patient with RCC. All patients were planned to undergo resection of kidney, but in 50 (22,6 %) patients surgery was done with nephrectomy, so in the further analysis they were not included. Thus kidney resection was performed in 171 (77,4 %) patients, outcomes of which were the subject of further analysis.

Men were 88 (51,5 %), women – 83 (48,5 %). The age of patients ranged from 20 to 79 years, on average (54,6 ± 11,6) years. Disease duration from the time of first complaints averaged (4,9 ± 3,1) months.

Tumor size ranged from 10 to 208 mm (40,4 ± 23,5). Tumor 4 cm or less was diagnosed in 67 (39,2%), 4 to 7 cm – in 77 (45%) and 7 cm or more – in 27 (15,8%) patients.

75 (43,9 %) patients had comorbidities of other organs and systems that affect the kidney function in both pre- and postoperative period. They included:

arterial hypertension occurred in 58 (33,9 %), diabetes mellitus – in 10 (5,8 %), obesity – in 6 (3,5%) patients, cysts of contralateral kidney – 15 (8,8 %), urinary stone disease – in 3 (1,7%), hypoplasia of contralateral kidney – in 3 (1,7%) patients.

In the study group were randomized 87 (50,9 %) patients, including 48 (55,2 %) – males, 39 (40,8 %) – women. The age of patients ranged from 25 to 79 years and averaged (54,3 ± 11,8) years, duration of disease (6,9 ± 12,9) months, ECOG status (0,5 ± 0,5) points. Size of tumor lesion ranged from 10 to 153 mm on average (42,0 ± 22,1).

The control group randomly assigned 84 (49,1 %) patients: 40 (47,6 %) – men, 44 (52,4 %) – women. The age of patients ranged from 25 to 80 years and averaged (54,9 ± 11,5) years, duration of disease (5,4 ± 13,3) months, ECOG status does not exceed 2 points and averaged (0,45 ± 0,5). Size of tumor lesion ranged from 10 to 208 mm on average (46,8 ± 26,2), comparative data are presented in Table 1.

Table 1 – Comparative evaluation of the outcome data by sex, age, stage of disease, general condition according to ECOG, total renal function in the comparison groups

Index		Study group n = 87 (%)	Control group n = 84 (%)	Authenticity
Age, years		54,3 ± 11,8	54,9 ± 11,5	t-test; p > 0,7
Gender	male, n (%)	48 (55,2)	40 (47,6)	x^2 = 0,9 p > 0,3
	female, n (%)	39 (40,8)	44 (52,4)	
Duration of disease, months		6,9 ± 3,2	6,4 ± 4,1	t-test; p > 0,5
Maximum size of tumor, cm.		42 ± 22,1	46,8 ± 26,2	t-test; p > 0,2
GF (total), ml/min		91,3 ± 20,6	91,3 ± 21,0	t-test; p > 0,99
ECOG, points		0,5 ± 0,5	0,45 ± 0,5	t-test; p > 0,4
Comorbidities, n (%)		38 (43,8)	37 (44,0)	x^2 = 0,002; p > 0,9

Presented in the table data indicate the absence of statistically significant difference in the comparison group by sex, age, tumor size, total renal function, general condition according to ECOG and frequency of comorbidity before the surgery.

Assessment of functional state of kidney was held according to the results of dynamic nephroscintigraphy which necessarily was performed at each follow-up (3 months and 1 year after surgery) and allowed to estimate not only the total cleansing function of the body, but also separate for each kidney.

Statistical analysis of obtained results was performed using the software Excel 2003 and STATISTICA 8.0. Comparison of quantitative indexes in the groups was performed by using Mann-Whitney test. Statistically significant differences were considered to be probability of error of the first kind less than 5%, $p < 0,05$.

Results.

Comparative analysis of total glomerular filtration rate (GFR) in the preoperative stage and the overall impact of ischemic kidney on its functional status in both study groups are given in Table 2.

Table 2 – Indexes of total GFR in the study and control groups, n = 171

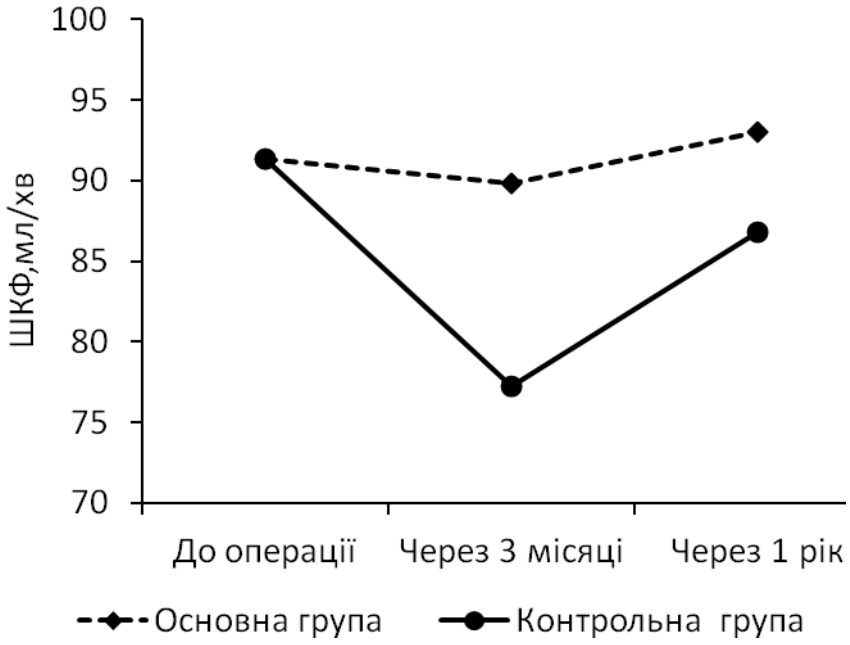
Total GFFR, ml/min.	Study group, n = 87	Control group, n = 84	Authenticity
Before the surgery	91,3 ± 20,7	91,3 ± 21,0	t-test; $p > 0,05$
3 months after the surgery	89,8 ± 16,3	77,2 ± 13,4	t-test; $p < 0,05$
1 year after the surgery	93,0 ± 16,1	86,8 ± 14,9	t-test; $p > 0,05$

By analyzing the data in Table 2 it is shown that in patients of the study group, where during surgery total ischemia of kidney was not used, significant difference in total GFR in the preoperative stage, 3 months and 1 year after the surgery was not found ($p > 0,05$), indicating a positive functional outcome of kidney resection without ischemia.

By analyzing the indexes of the control group was shown statistically significant decrease of index of total GFR 3 months and 1 year after the surgery compared with preoperative data ($p < 0,05$), indicating a negative influence of kidney on its ischemia functional status.

In conducting statistical analysis was showed significant difference ($p < 0,05$) between the indexes of total GFR of the study and control group in the period of 3 months and 1 year after the surgery.

A visual dynamic performance of indexes of total GFR can be analyzed in graphic form, which is shown in Picture 1.



Picture 1 – Indexes of total GFR in dynamics before and after resection of kidney in the comparison group

ШКФ, мл/хв - GFR, ml/min

До операції - Before the surgery

Через 3 місяці - 3 months after the surgery

Через 1 рік - 1 year after the surgery

Основна група - Study group

Контрольна група - Control group

Thus, the total GFR in the group where the kidney resection was performed without ischemia, in dynamics over time was not significantly changed, whereas in the control group (ischemia of kidney) it decreased by 15.4% after 3 months ($p < 0,05$), and 5% – after 1 year ($p > 0,05$), compared with the preoperative parameters (91,3 ± 21,0) ml/min, and amounted to (77,2 ± 15,4) and (86,8 ± 18.9) ml/min.

More interesting was to analyze the indexes of GFR on the side of kidney resection, because of the dynamic data of renoscintigraphy allowed to do so. The results are presented in Table 3.

Table 3 – Indexes of GFR on the side of kidney resection in the study and control groups, n = 171

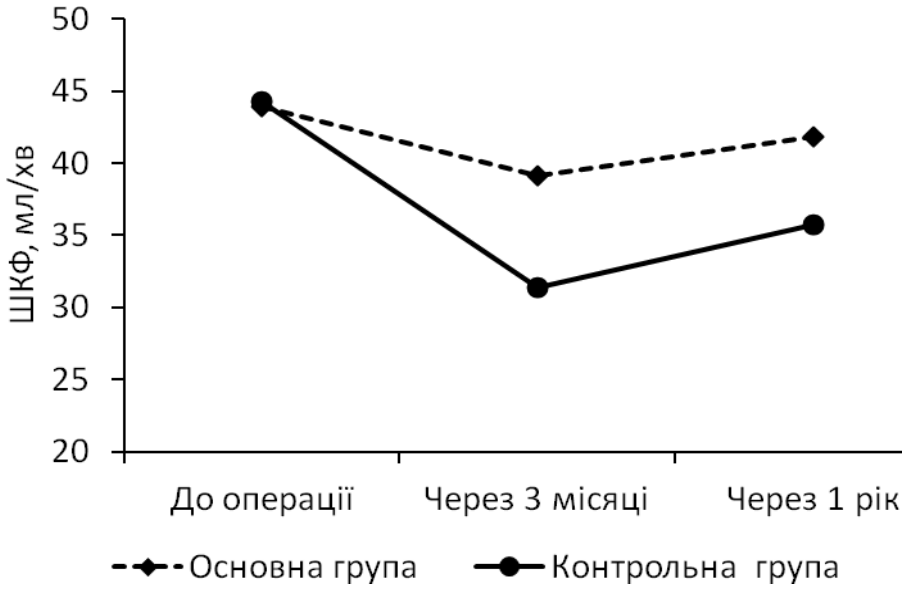
GFR on the side of resection, ml/min.	Study group, n = 87	Control group, n = 84	Authenticity
Before the surgery	43,9 ± 10,2	44,3 ± 12,4	t-test; $p > 0,05$
3 months after the surgery	39,1 ± 10,2	31,4 ± 10,2	t-test; $p < 0,05$
1 year after the surgery	41,8 ± 7,2	35,7 ± 11,4	t-test; $p < 0,05$

As shown in Table 3, during the GFR comparison on the side of resection of the study group at the preoperative stage with indexes after 3 months, we received a statistically significant its decrease of 10.9% (43,9 ± 10,2) ml/min to (39 1 ± 10,2) ml/min ($p < 0,05$), which was associated with postoperative kidney injury, but after 1 year its function was not significantly different from the preoperative ($p > 0,05$), it was close to original values and showed (41,8 ± 7,2) ml/min.

By analyzing the indexes of the control group was shown statistically significant decrease of GFR index on the side of resection 3 months and 1 year after the surgery compared with preoperative data, indicating a negative effect of kidney ischemia on its functional status.

In conducting statistical analysis was shown a significant difference ($p < 0,05$) between the indexes of total GFR of the study and control groups in the period of 3 months and 1 year after the surgery.

Clearly dynamic of GFR indexes on the side of resection are analyzed in graphic form, which is shown in Picture 2.



Picture 2 – Indexes of GFR on the side of resection in dynamics before and after resection of kidney in the comparison groups

ШКФ, мл/хв - GFR, ml/min

До операції - Before the surgery

Через 3 місяці - 3 months after the surgery

Через 1 рік - 1 year after the surgery

Основна група - Study group

Контрольна група - Control group

Thus GFR on the affected side in the control group significantly ($p < 0,05$) decreased compared with the preoperative indexes by 29,1 % after 3 months and 19,4 % – after 1 year and amounted to (44,3 ± 12,4); (31,4 ± 10,2) and (35,7 ± 11,4) ml/min, respectively.

Comparing the indexes in the study and control groups, it was found that despite the lack of significant difference of indexes of the total GFR and GFR on the affected side in the preoperative period, after 3 months and 1 year, kidney ischemia during resection significantly reduces its function in the postoperative period.

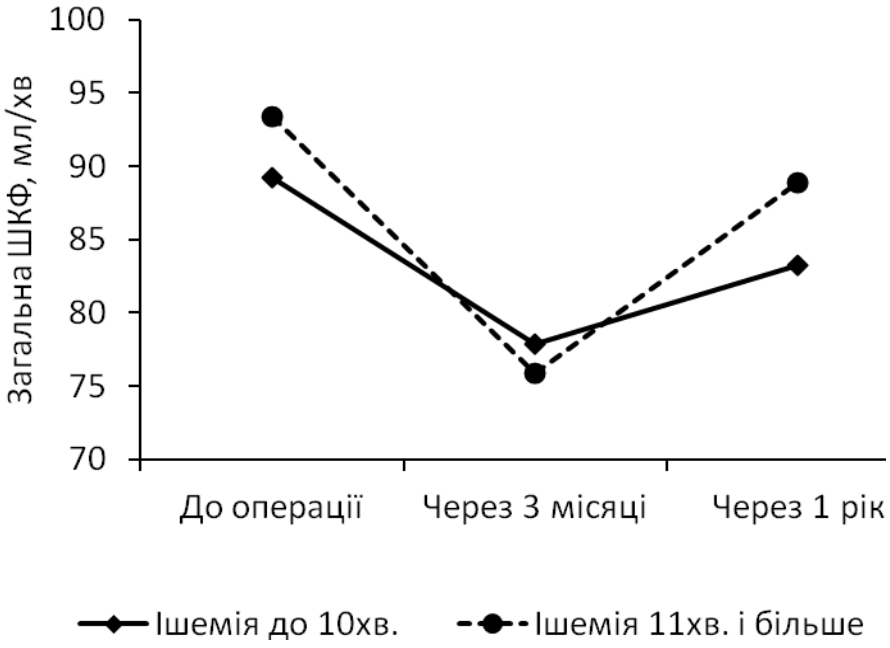
Separately is proved analysis of depending kidney function on the duration of ischemia (see Table 5). Generally during resection in patients in the control

group kidney ischemia lasted from 5 to 21 minutes and averaged to (10,6 ± 3,4) min.

Table 5 – Influence of ischemia on the functional state of kidney after resection

Index		Ischemia before 10 min, n = 39	Ischemia 10 – 21 min, n = 45	Authenticity
Before the surgery	Total GFR, ml/min	89,2 ± 19,1	93,4 ± 22,8	t-test; p > 0,05
	GFR on the affected side, ml/min	44,2 ± 10,5	44,4 ± 14,1	t-test; p > 0,05
3 months after	Total GFR, ml/min	77,9 ± 16,4	75,9 ± 17,0	t-test; p > 0,05
	GFR on the affected side, ml/min	30,9 ± 7,0	31,1 ± 11,4	t-test; p > 0,05
1 year after	Total GFR, ml/min	83,2 ± 23,9	88,9 ± 10,8	t-test; p > 0,05
	GFR on the affected side, ml/min	35,4 ± 17,3	39,5 ± 10,7	t-test; p > 0,05

Analyzing the data in Table 5, we can say that as in the group of patients who have ischemia which lasted 10 min and in patients who have ischemia which lasted 10 - 21 min. kidney function in the postoperative period was significantly decreased ($p < 0,05$). Thus the significant difference between the groups regarding the comparison of indexes of total GFR and GFR on the side of resection 3 months and 1 year after the surgery was not found, indicating a negative effect of kidney ischemia on its functional status, regardless of the duration of ischemia (see Pic. 3, Pic. 4).



Picture 3 – Indexes of total GFR depending on the duration of ischemia

Загальна ШКФ, мл/хв - total GFR, ml/min

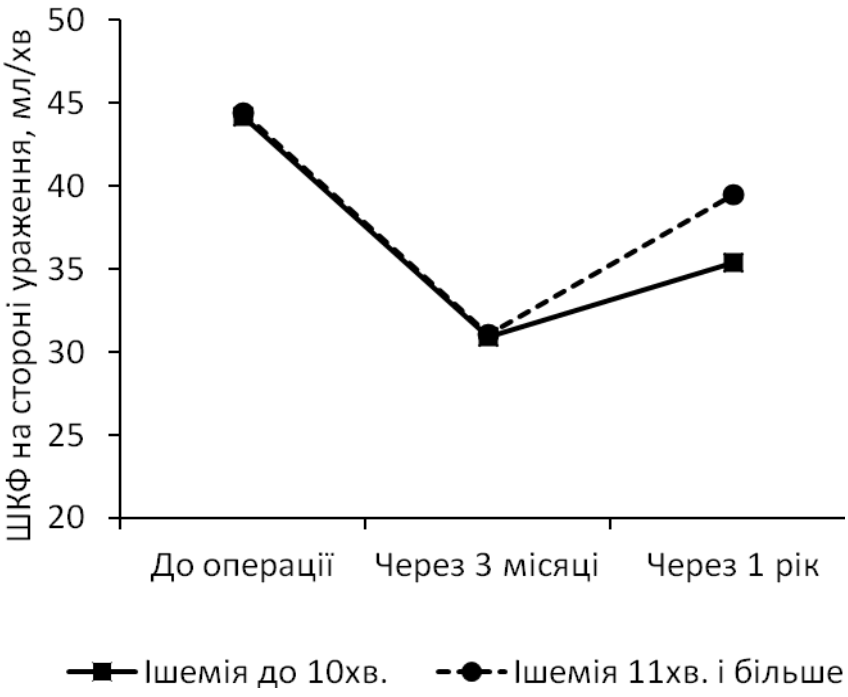
До операції - Before the surgery

Через 3 місяці - 3 months after the surgery

Через 1 рік - 1 year after the surgery

Ішемія до 10 хв - Ischemia before 10 min

Ішемія 11хв і більше - Ischemia 10 – 21 min



Picture 4 – Indexes of GFR on the side of resection, depending on the duration of ischemia

ШКФ на стороні ураження, мл/хв - GFR on the affected side GFR, ml/min

До операції - Before the surgery

Через 3 місяці - 3 months after the surgery

Через 1 рік - 1 year after the surgery

Ішемія до 10 хв - Ischemia before 10 min

Ішемія 11хв і більше - Ischemia 10 – 21 min

Summarizing the data, we can conclude that conduction of kidney resection with ischemia leads to reduction of total GFR by 15,4 % after 3 months and 5 % – after 1 year, and GFR on the affected side – by 29,1 % and 19,4 %, respectively ($p < 0,05$).

Discussion.

The main advantage of resection of kidney before nephrectomy is preservation of the maximum amount of functioning parenchyma [8]. 10 years after surgical treatment the development of renal failure in patients, undergoing nephrectomy, is 2 times more frequently than in patients who underwent resection of kidney.

The only large randomized research that compares the results of nephrectomy and resection of kidney with tumor size to 5 cm in diameter is the EORTC protocol 30904. Preliminary results of this research indicate no difference in survival of patients in the groups with significantly greater frequency of complications after organ-preserving operations. In this regard, organ treatment in the presence of normal functioning of the second kidney is legitimate. In most studies it is argued that the small size of tumor (4 cm) is the main criterion that provides satisfactory long-term results of organ treatment [9].

Circulatory arrest in the kidney during resection improves visualization of its structures that allow performing radical removal of tumor, making adequate

suturing of pyelocaliceal system and performing qualitative hemostasis. However, thermal ischemia more than 30 minutes may be connected with irreversible changes in the proximal collecting tubules and associated with a significant increase in the incidence of renal failure in the postoperative period from 1,7 to 10,2%. Use of local hypothermia reduces the intensity of energetic metabolism processes in the kidney, significantly reducing the likelihood of developing chronic renal failure to 3 - 8%. Using the local ischemia and nephroprotection therapy, when doing organ-preserving surgeries in patients with RCC, will allow minimizing the likelihood of renal failure [10, 11].

In general, the limited use of thermal ischemia or hypothermia reduces its consequences and is temporary and reversible. In most cases, renal function is restored to the original level if the number of surviving parenchyma is sufficient [12].

Researchers from California have studied the clinical impact of reduction of glomerular filtration (GF) for a long time in 1120295 patients in the period from 1996 to 2000 who did not receive dialysis. The authors examined multivariable associations between calculated GF level and the risk of death, cardiovascular accident or hospitalization. The average age of patients was 52 years, 55 % of patients were women and the average follow-up period was 2,84 years. The risk of death increased with the decrease of calculated GF below 60 ml/min/1,73m^2 with established risk ratio 1,2 (GF 45 – 59 ml/min/1,73m^2), 1,8 (GF 30- 4 ml/min/1,73 m^2), 3,2 (GF 15-29 ml/min/1,73m^2), and 5,9 (GF < 15 ml/min/1,73m^2), respectively [13].

Presented in the work results of randomized research of the effect of ischemia on the function of kidney in its resection shows that even short duration ischemia (10 minutes) ultimately leads to deterioration of kidney function in the remote postoperative period compared with resection without ischemia. Therefore, the most promising way to minimize the negative impact of kidney ischemia is its absence.

Conclusion.

This paper presents the results of randomized research, where for the first time on the basis of evaluation of permission function of kidneys in the remote postoperative period was demonstrated the negative influence of ischemia on the functional state of kidney after resection in patients with renal cell carcinoma.

Thus, kidney resection without use of ischemia results after 3 months of surgery in decreasing of glomerular filtration rate on the affected side 10,9 % ($p < 0,05$). Significant decrease of total glomerular filtration rate was not found, which can be regarded as compensatory mechanisms of the body.

Kidney ischemia during resection of up to 20 minutes causes decrease in total glomerular filtration rate by 15,4 % at 3 months and 5 % – 12 months, and glomerular filtration rate on the affected side – by 29,1 % and 19,4 %, respectively ($p < 0,05$).

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