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COMPARATIVE ANALYSIS OF ONCOLOGIC OUTCOMES OF RADICAL NEPHRECTOMY AND NEPHRON-SPARING SURGERY IN PATIENTS WITH INTRAVENOUS EXTENSION OF TUMOR INTO THE RENAL VEIN

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Abstract

Over recent years, there has been a considerable expansion of indications for nephron-sparing surgery in patients with renal cell carcinoma, including cases of local tumor extension. We have analyzed survival rates of patients with intravenous renal cell carcinoma extension into intrarenal tributaries or the main trunk of the renal vein, who underwent nephron-sparing surgery with thrombectomy or nephrectomy with thrombectomy.

All patients were divided into two groups: I – nephron-sparing surgery (n=19) and II – radical nephrectomy (n=53). The average follow-up period in I group varied from 10 to 72 months and averaged 30.4±2.8 months, in II group – from 9 to 66 months (average 34.0±4.2 months) (p>0.680). Tumors in I group had smaller diameter, higher degree of differentiation and less frequently extended into the fatty tissue. Thrombi, limited by intrarenal part of the renal vein (78.9% vs. 16.9%, respectively for I and II groups) prevailed in the nephron-sparing surgery group. All other clinical and pathological characteristics in patients of both groups were similar.

The disease progression was recorded in 3 (15.8%) patients out of 19 in I group, and 34 (64.2%) patients out of 53 in II group (p<0,001). In I group only distant metastases were noted, while local recurrence in the remnant kidney was absent. All 3 patients with metastatic progression from I group had imperative indications for nephron-sparing surgery, the tumor size over 7.0 cm, neoplastic invasion into the fatty tissue and into the segmental renal vein wall. In II group local recurrence was identified in 3 (5.7%) cases. All of these recurrences were not isolated and were combined with distant metastasis.

The 5-year survival rate was significantly better in I group patients. This included both overall survival parameters (89.5% vs. 47.2%; p<0.042), and the level of progression-free survival (84.2% vs. 35.8%; p<0.046).

Nephron-sparing surgery may be used for certain patients with intravenous extension of renal cell carcinoma, which is limited by intrarenal branches of the renal vein. Oncologic efficacy and safety of this type of surgery warrants further study.

Keywords: *renal cell carcinoma, nephron-sparing surgery, tumor thrombus, intravenous extension of the tumor.*

Introduction

Over recent years, there has been a considerable expansion of indications for nephron-sparing surgery in patients with renal cell carcinoma, including cases of local tumor extension [*Leibovich B et al., 2004; Fergany A et al., 2006; Margulis V et al., 2007*]. This is due to actively increasing experience of this type of surgery and analysis of long-term oncological outcomes in such patients. Many clinicians hold the view that treatment results are more dependent on the biological features of tumor, rather than the type of surgical intervention. However, by now, there have been very few clinical trials, that investigated the oncological effectiveness of nephron-

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sparing surgery with intravenous extension of kidney tumors [*Angermeier K et al., 1990; Pruthi R et al., 1999; Sengupta S et al., 2005; Tollefson M et al., 2005; Kemmer H et al., 2007; Margulis V et al., 2007; Kolla S et al., 2010; Woldu S et al., 2010; Kim E et al., 2012, Abaza R, Angell J, 2013; Stakhovsky E et al., 2016*]. So far, there are no literature data directly comparing the results of nephrectomy with those of nephron-sparing surgery in these patients.

Sparing the kidney with tumor penetrating into the venous system and into the inferior vena cava is quite complex and not always a feasible task. Many of these cases, particularly those relating to the inferior vena cava injury, are casual and do not reflect any mature surgical strategy. However, at this time there is certain experience in organ-sparing surgeries in the group of patients with imperative indications with intravenous invasion of renal cell carcinoma. On the other hand, this approach is often reflexively used in the group of patients with elective indications for nephron-sparing surgery, when venous invasion is detected intraoperatively or postoperatively. Certainly, in vast majority of cases this concerns the tumor thrombi, limited by segmental renal vein or initial part of the main renal vein.

Rationality of organ-sparing surgical approach, which allows to avoid the renoprival condition, is undoubtedly justified for the imperative group patients. The safety of this approach in patients without contralateral kidney impairment is yet to be assessed. This type of surgery requires development of indications for its use and requires improvement of surgical techniques.

We have analyzed survival rates of patients with intravenous renal cell carcinoma extension into the intrarenal tributaries or the main trunk of the renal vein, who underwent nephron-sparing surgery with thrombectomy or nephrectomy with thrombectomy.

Material and methods

All patients were divided into two groups: I – nephron-sparing surgery (n=19) and II – radical nephrectomy (n=53). The survival study included patients without distant or regional metastases. Both groups included patients with intravenous extension of renal cell carcinoma, confined to the intrarenal tributaries or the main trunk of the renal vein. The average follow-up period in I group varied from 10 to 72 months and averaged 30.4±2.8 months, in II group – from 9 to 66 months (average 34.0±4.2 months) (p>0.680). Comparative characteristics of patients in both groups are presented in table 1.

Table 1

Comparative characteristics of patients in both groups

Characteristics		I group (n=19)	II group (n=53)	p
Average age (*years*)		59.3±7.2	59.1±8.4	>0.979
Sex	male	9 (47.4%)	41 (77.4%)	<0.018
	female	10 (52.6%)	12 (22.6%)	<0.018
ECOG score	0	16 (84.2%)	40 (75.6%)	>0.640
	1	3 (15.8%)	11 (20.8%)	>0.640
	2	0 (0%)	2 (3.8%)	>0.445
Lesion side	right	6 (31.6%)	34 (64.2%)	>0.095
	left	13 (68.4%)	19 (35.8%)	>0.068
Symptoms	local	13 (68.4%)	37 (69.8%)	>0.871
	general	6 (31.6%)	18 (34.0%)	>0.875
	no symptoms	5 (26.3%)	4 (7.5%)	>0.067
Fuhrman grade	1	5 (26.3%)	1 (1.9%)	<0.026
	2	9 (47.4%)	24 (45.3%)	>0.697
	3	5 (26.3%)	28 (52.8%)	<0.047
Average tumor size (*cm*)		6.2±0.56	10.0±1.4	<0.038
Adipose tissue invasion		4 (21.1%)	29 (54.7%)	<0.013
Collecting system invasion		5 (26.3%)	7 (13.2%)	>0.194
Invasion of tumor thrombus into the renal vein wall		4 (21.1%)	25 (47.2%)	>0.051

ECOG score is used to assess how a patient's disease is progressing. Fuhrman grade is the most popular and widely used system for grading renal cell carcinoma [*Sorensen J et al., 1993, Fuhrman S et al., 1982*].

Tumors in I group had smaller diameter, higher degree of differentiation and less frequently extended into the fatty tissue. The levels of tumor thrombi extension differed significantly in both groups (in I group thrombi of intrarenal part of the renal vein prevailed) (Table 2). All other clinical and pathological characteristics in patients of both groups were similar.

Table 2

Levels of intravenous extension of tumor thrombi

Levels of thrombi		I group (n=19)	II group (n=53)	p
Parts of the renal vein	Intrarenal	15 (78.9%)	9 (16.9%)	<0.272
	Segmental	10 (52.6%)	2 (3.8%)	<0.034
	Polar	5 (26.3%)	7 (13.1%)	>0.682
	Extrarenal	4 (21.1%)	44 (83.1%)	<0.217

In 8 (42.1%) patients of I group, nephron-sparing surgery was performed based on absolute imperative indications (the solitary kidney tumor – 4, bilateral tumors – 2, renal failure – 2).

Prior to the operation, tumor penetration into the lumen of the venous system was found only in 3 (15.8%) patients of I group. In other cases, intravenous extension of the renal cell carcinoma was revealed during surgery (14 (73.7%) patients) or at the final histological examination (2 (10.5%) cases).

Surgical technique of nephron-sparing surgery included enucleoresection of tumor using warm ischemia in all cases. During warm ischemia, enucleoresection of the renal mass, repairing of the damaged blood vessels and the collecting system were immediately performed. Afterwards, the renal artery was unclamped, additionally the bleeding vessels were sutured with twin 8-shaped seams, and the renal parenchyma wound was repaired with horizontal mattress and locking stitches.

In case of small thrombi of the segmental veins (up to 5 *mm* long) the surgical technique did not differ from the standard technique of enucleoresection, with tumor thrombus being removed together with the wall of the affected vessel. In situations of tumor extension to the main renal vein or the segmental vessel as long as over 5 *mm* and in the absence of signs of invasion into the venous wall, the segmental vein opening with intrarenal thrombectomy was performed. Then, the thrombus was easily evacuated out of the vein lumen. In case of detection of the tumor growing to the venous wall the segmental or polar vein was completely removed up to the level of the distal end of the tumor thrombus.

Statistical analysis of the obtained results was performed using Statistica 5.5, 6.0 applications, Excel 2007, Windows 2007 programs. The average values of each index and average error of the mean were calculated. All the samples were evaluated by normal distribution of variants according to Kolmogorov-Smirnov and Shapiro-Wilk's tests. In case the samples met the criteria, the methods of parametric statistics (Student's t-test for dependent or independent groups) were used in the compared groups. If at least one of the groups failed to meet the criteria of normal distribution of variants the nonparametric statistical methods (Mann-Whitney criteria) were used.

All patients were observed from the time of diagnosis until death or until the date of censoring (the patient was seen as alive). The patients with observation period less than 6 months were not included in the analysis of censored data. Overall survival was calculated from the date of surgery up to the date of the last visit or death. Progression-free survival was defined as the period between the surgery and the tumor local relapse or metastases. Survival curves were calculated according to the Kaplan-Meier method using the censored data. For their comparison the log-rank test was used. P value less than 0.05 was considered as characteristics of reliability differences.

Results

Disease progression was recorded in 3 (15.8%) patients out of 19 in the group of nephron-sparing surgery and 34 (64.2%) patients out of 53 in the group of nephrectomy ($p<0.001$) (Table 3). In I group only distant metastases were noted, while local recurrence in the remaining kidney was absent. In II group local recurrence was identified in 3 (5.7%) cases. All of these recurrences were not isolated and were combined with distant metastases.

Table 3

Characteristics of tumor progression in patients of both groups

Characteristics of disease progression	I group (n=19)	II group (n=53)	p
Isolated local recurrence	0 (0%)	0 (0%)	>0.990
Local recurrence in combination with metastases	0 (0%)	3 (5.7%)	>0.279
Lymph node metastases	1 (5.3%)	2 (3.8%)	>0.854
Lung metastases	2 (10.5%)	22 (41.5%)	<0.017
Liver metastases	0 (0%)	1 (1.9%)	>0.537
Other localizations	0 (0%)	1 (1.9%)	>0.537
Multiple metastases of various localization	0 (0%)	5 (9.4%)	>0.180
Total	3 (15.8%)	34 (64.2%)	<0.001

All 3 patients with metastatic progression of I group had imperative indications for nephron-sparing surgery, the tumor size over 7.0 *cm*, neoplastic invasion into the fatty tissue and into the segmental renal vein wall. In two (10.5%) cases the tumor thrombi reached the main trunk of the renal vein, in one (5.3%) case – the segmental vein. In these patients kidney resection was combined with resection of the vein up to the level of the apex of the thrombus.

Five-year survival rates were significantly better in patients of I group. This included both overall survival (89.5% vs. 47.2%; p<0.042), and the level of progression-free survival (84.2% vs. 35.8%; p<0.046).

Discussion

It should be noted, that our work had significant limitations, which were associated with differences in relation between the levels of extension of the intravenous part of the tumor, the frequency of invasion into the fatty tissue, the size and histological grading of the tumors in both groups. In the population of patients who underwent radical nephrectomy, these parameters were significantly worse. Therefore, the priorities of survival in patients of nephron-sparing surgery group were not surprising, since most likely they were due to the abovementioned differences, rather than to the type of surgical intervention.

Though, the main goal of our work was to demonstrate the oncological efficacy and safety of nephron-sparing surgery in patients with intravenous extension of renal cell carcinoma. The results of the present study showed that survival of patients after nephron-sparing surgery of renal tumors mostly with intrarenal intravenous invasion was not worse, than survival rate of patients after nephrectomy, who had tumors invading the main trunk of the renal vein. From our point of view, these data are important, since the overall experience of nephron-sparing surgery in patients with intravenous invasion of renal cell carcinoma, which is presented in the literature, is extremely limited [*Angermeier K et al., 1990; Pruthi R et al., 1999; Sengupta S et al., 2005; Tollefson M et al., 2005; Kemmer H et al., 2007; Margulis V et al., 2007; Kolla S et al., 2010; Woldu S et al., 2010; Kim E et al., 2012, Abaza R, Angell J, 2013; Stakhovsky E et al.*, 2016].

The method of kidney preservation in the presence of intravenous tumor thrombus (even if only in the segmental vein) has got not only supporters, but also radical opponents. An objective solution of this dispute warrants further prospective study of basic oncological parameters in these patients, including overall and progression-free survival. The comparative analysis of the results of nephrectomy and nephron-sparing surgery in patients with similar morphological parameters of the tumor and the levels of its intravenous extension should be considered as the most objective. Unfortunately, in our study we were not able to perform direct comparison of survival rates in patients with the same size tumor thrombi. This was due to retrospective nature of the work and a small amount of intrarenal thrombi in the group of nephrectomy (16.9% vs. 78.9%, respectively for II and I groups).

In our opinion, nephron-sparing surgery is a feasible variation of surgical treatment in certain patients even if they have only elective indications. This concerns the patients with tumor thrombi of small size, that penetrate no further than the intrarenal tributaries of the main trunk of the renal vein and do not invade the venous wall. In present work, no signs of local recurrence of the tumor were detected in all patients of nephron-sparing surgery group; 11 (57.9%) out of these patients underwent surgery based on elective indications. Though, tumor progression was not detected in any of these patients with an average follow-up period of 30.4±2.8 months.

It should be kept in mind that intravenous extension of the tumor, which was not identified during surgery, may be one of the reasons for local recurrence of the disease after nephron-sparing surgery. The main condition of oncologic safety for this kind of surgeries is good visibility in the zone of resection. Therefore, we believe that nephron-sparing surgery for renal tumors must be carried out under conditions of renal ischemia ensuring bloodless operational fields in the area of interface between tumor, renal parenchyma and renal sinus tissue. Another important condition is careful examination of the resection zone in the area of the intersection of forniceal and segmental veins to detect possible intravenous part of the tumor. The most careful search of intravenous tumor thrombi must be carried out mostly in case of intraparenchymal tumors contacting with sinus fat tissue.

Thus, nephron-sparing surgery may be used for some patients with intravenous extension of renal cell carcinoma, which is limited by intrarenal branches of the renal vein. Oncologic efficacy and safety of this type of surgery warrants further study.

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