Oncourology

COMPLICATIONS OF PARTIAL NEPHRECTOMY AT OPERATIVE TREATMENT OF RENAL CELL CARCINOMA

O.A. Voylenko, P.S. Vukalovych, Y.V. Vitruk,
O.E. Stakhovsky, V.A. Kotov, E.O. Stakhovsky.
National Cancer Institute, Kyiv

Address:
Eduard Oleksandrovych Stakhovsky,
03022, Kyiv, Lomonosova Str., 33/43,
National Cancer Institute
Tel.: (044) 259-01-86
E-mail: estakhovsky@yahoo.com

Abstract

The article presents treatment outcomes in 316 renal cell carcinoma patients who underwent partial nephrectomy. Kidney function was studied; postoperative complications and their relationship with tumor size as well as with volume of functioning parenchyma and nephrometry index (R.E.N.A.L. score) were analyzed. It was established that postoperative complications occurred in 7.9% of patients. The most common complication was urinary fistula, which occurs in 2.8% of patients and directly correlates with tumor size.

Keywords: renal cell carcinoma, partial nephrectomy, complications, tumor size, renal function.

Introduction

Implementation in general medical practice of radically new methods to diagnose and monitor treatment effectiveness (ultrasound, CT and magnetic resonance imaging, and others) enables cancer detection in early stages. This in turn raises interest in the development of organ-preserving approach to cancer treatment.

Partial nephrectomy to date has become a welcome alternative to radical nephrectomy for stage T1 tumors [1]. Organ-sparing surgery compared with radical nephrectomy showed equivalent oncologic outcome for tumors less than 4 cm in diameter [2, 3]. The proximity of the tumor to the collecting system or renal vessels, doubts about the multifocality of the tumor, and the intent to leave a 1 cm margin of healthy parenchyma are the factors that hindered the success of the surgery in the past [4]. Recent studies have shown that tumor resection performed with negative surgical edge provides excellent local control of the tumor even in the absence of 1 cm of healthy parenchyma along the tumor edge [5]. This primarily relates to intrarenal tumors. In these cases, the use of intraoperative ultrasound makes possible to localize the tumor without much difficulty. Availability of modern suture material helps to restore kidney collecting system, vessels and renal parenchyma integrity. On the other hand, possibility to perform resections for tumors with nonperipheral localization increases the risk of intra- and postoperative complications. Thus determining factors that may affect the possible development of complications are: tumor size, location and relation to the main renal structures (vascular pedicle and abdominal systems). According to the world literature the complications rate during organ-sparing surgery for kidney tumors does not exceed 10% [6].

Based on the above, the purpose of the work was to improve the effectiveness of treatment for patients with localized renal cell cancer by analyzing complications during partial resection, and to develop measures for their prevention.

Material and methods.

A retrospective clinical analysis was performed in 727 RCC patients who in the period from 2008 to 2012 underwent examination and surgical treatment in the research department of plastic and reconstructive oncourology in National Cancer Institute. Partial nephrectomy as a main treatment was performed in 316 (44.1%) cases. This group of patients was used for further analysis of intra- and post-operative complications.

The group contained 203 men (64.2%), and 113 women (35.6%). Age of patients ranged from 19 to 78, the average is (54.2 ± 11.2) years. Disease duration since the time of the first complaints made 1-18 months, the average is (3.9 ± 2.7) months.

Tumor size ranged from 12 to 157 mm (40.1 ± 19.4). Unilateral tumoral lesions were diagnosed in 288 (91.1%) patients, bilateral - in 20 (6.3%) patients, horseshoe kidney tumor - in 4 (1.3%) cases, single kidney tumor – in 4 (1.3%) patients. Extrarenal tumor more than 50% was found in 157 (49.7%) patients, extrarenal localization less than 50% - in 125 (39.5%) cases and completely intrarenal was found in 34 (10.8%) patients.

156 (49.4%) patients had comorbidities that affected kidney function: hypertension - in 84 (26.6%), contralateral kidney cyst - in 31 (9.8%), alimentary-constitutional obesity - 20 (6.3%), diabetes - in 17 (5.4%), urolithiasis - in 13 (4.1%), contracted contralateral kidney - in 5 (1.6%) cases. Chronic kidney disease was in 17 (5.4%) patients.

In 309 (97.8%) cases a unilateral partial resection was performed, bilateral resection was performed in 4 (1.3%) cases; in 3 (0.9%) cases simultaneous resection was performed on one side and nephrectomy - on the other. In 36 (11.4%) patients, partial nephrectomy had cytoreductive character. In all cases surgery was done by transabdominal access that allowed of controlling renal vessels and was fully compliant with the laws of ablation. In unilateral tumors preference was given to subcostal and anterior-lateral incisions. In case of bilateral tumors such incision continued on the opposite side.

Primary diagnostics included, on a mandatory basis, the study of complaints, patient history, physical examination data, laboratory analysis, MSCT (multispiral computed tomography) with bolus enhancement. Identification of kidney function both before and after surgery was performed using dynamic nephroscintillography by the rate of total and divided glomerular filtration. Monitoring survey was conducted in 3 and 12 months, further it was done on the annual base with the obligatory local control with MSCT and functional control according to the data of dynamic nephroscintillography. Statistical analysis of the results was performed using Excel 2003 and STATISTICA 8.0 software. Statistically significant differences were considered as type I error probability less than 5%, $p < 0.05$

Patients were divided into three groups depending on tumor stage. The first group included 142 (44.9%) patients with T1a, the second - 141 (44.6%) with T1b, and the third - 33 (10.5%) T2 stage patients with tumor size over 7 cm.

Baseline data were compared in groups by gender, age, duration of disease, general condition by ECOG and total kidney function (Table 1).

Table 1. Comparative evaluation of baseline data by sex, age, stage, general condition by ECOG, total kidney function in the control group

Indicator		T1a, n=142	T1b, n=141	T2, n=33	Statistical significance
Age, years		54.5 ± 11.1	55.5 ± 10.5	49.6 ± 13.9	t-test; p > 0.3
Sex	Men, n (%)	95 (66.9 %)	85 (60.3 %)	23 (69.7 %)	$x^2 = 1.83$ p > 0.4
	Women, n (%)	47 (33.1 %)	56 (39.7 %)	10 (30.3 %)	
Duration of disease, months		3.8 ± 3.1	3.5 ± 2.6	2.35 ± 2.1	t-test; p > 0.25
GFR (total), ml/min		90.1 ± 19.8	85.8 ± 18.2	84.8 ± 19.5	t-test; p > 0.1
GFR < 60 ml/min, n (%)		5 (3.5 %)	10 (7.1 %)	2 (6.1 %)	$x^2 = 1.81$; p > 0.1
ECOG, score		0.67 ± 0.5	0.72 ± 0.57	0.81 ± 0.54	t-test; p > 0.35
Comorbidity, n (%)		62 (43.7 %)	80 (56.7 %)	19 (57.6 %)	$x^2 = 5.5$; p > 0.05

Data presented in the table indicate that there is no statistically significant difference in control groups by gender, age, and total kidney function prior to the

surgery, number of patients with chronic renal failure, general condition by ECOG, and frequency of comorbidity.

Results.

In order to determine the risk of complications after partial resection in all the cases we identified nephrometry indicators using R.E.N.A.L. score method [7] and evaluated the volume of functioning renal parenchyma; the results are shown in Table 2 and 3.

Table 2. Dependence of nephrometry index (R.E.N.A.L. score) on the size of kidney tumor, n = 316

Nephrometry index (R.E.N.A.L. score)	T1a, n = 142 (%)	T1b, n = 141 (%)	T2, n = 33 (%)
Low (4-6 points)	96 (67.6)	61 (43.3)	10 (30.3)
Medium (7-9 points)	35 (24.6)	56 (39.7)	11 (33.3)
High (10-12 points)	11 (7.7)	24 (17)	12 (36.4)
Statistical significance	$x^2 = 31.99$; $p < 0.001$		

As seen from the data presented in Table 2 when the clinical study is performed according to nephrometry index (R.E.N.A.L. score), statistically significant direct proportional dependence of higher risk of complications in partial resection on bigger tumor size is observed.

Table 3. Dependence of volume of functioning renal parenchyma on the volume of functioning renal parenchyma on the affected side, n = 316

	T1a, n = 142 (%)	T1b, n = 141 (%)	T2, n = 33 (%)
Volume of functioning renal parenchyma, %	93.5 ± 6.3	77.6 ± 14.6	55.7 ± 14.0
Statistical significance	t-test; $p < 0.01$		

Data presented in Table 3 indicate statistically significant directly proportional dependence of tumor size on the volume of functioning parenchyma

on the affected side that justifies the use of this indicator in determining the indications for kidney resection.

In 68 (21.5%) patients surgery was carried out with overall kidney ischemia by renal artery cross-clamping, which lasted from 5 to 27 minutes (15 ± 5.7). In 248 (78.5%) cases the overall kidney ischemia was not used during resection, the hemostasis was carried out by local ischemia thus ensuring maximum preservation of functional capacity of parenchyma that became a preventive measure for kidney failure.

It was required to restore the integrity of the hollow renal system in 74 (23.4%) patients; out of them in six (1.9%) cases the kidney was intraoperatively stented. Intraoperative mortality was 0%.

Intraoperative complications during resection of kidney with tumor occurred in 55 (17.4%) patients. In one case (0.3%) during surgery the spleen was injured that became an indication for splenectomy. It should be noted that partial resection without ischemia was accompanied by greater blood loss from parenchyma. It was considered as complication at the blood loss level of more than 500 ml; it was observed in 54 (17.1%) cases and required transfusion of blood components only in 7 (2.2%) cases with bleeding over 800 ml. Blood loss rate was analyzed depending on the tumor size, its location, and the volume of functioning parenchyma. The results are presented in Table 4, 5, and 6.

Table 4. Volume of intraoperative blood loss during partial resection depending on the size of kidney tumor, n = 316

Stage	T1a, n = 142	T1b, n = 141	T2, n = 33	Statistical significance
Volume of blood loss, ml	321.2 ± 146.3	377.7 ± 182.7	426.2 ± 198.2	t-test; $p < 0.01$
Blood loss> 500 ml, n (%)	16 (11.3)	26 (18.4)	12 (36.4)	$x^2 = 12.2$; $p < 0.005$

As seen in Table 4, the volume of blood loss had directly proportional dependence on the tumor size and progressively increased from 321.2 ± 146.3 ml

with tumor size less than 4 cm to 426.2 ± 198.2 ml with tumor size greater than 7 cm ($p < 0.01$). Similar data for the control groups were received after analyzing the number of patients with blood loss exceeding 500 ml ($p < 0.005$). The data showed the allowable volume of blood loss during kidney resection with blood loss level increase being directly proportional to the bigger size of kidney tumor.

Table 5. Volume of intraoperative blood loss during kidney resection, depending on tumor location, n = 316

Location	Over 50% extrarenal, n = 157	Less than 50% extrarenal, n = 125	Intrarenal, n = 34	Statistical significance
Volume of blood loss, ml	325.5 ± 134.4	402.7 ± 212.5	427.0 ± 218.1	t-test; $p < 0.01$
Blood loss> 500 ml, n (%)	16 (10.2)	23 (18.4)	15 (44.1)	$x^2 = 22,9$; $p < 0.0001$

Our data showed a significant increase in bleeding in tumors, which were located more than 50% extrarenal compared with intrarenal ones, and those which were located less than 50% extrarenal, while the number of patients with significant blood loss increased in direct proportion from 10.2% in the extrarenal tumors to 44.1% in intrarenal ones that was primarily due to the technical difficulties of both the resection and the size of the wound surface of the kidney.

Table 6. Volume of intraoperative blood loss, depending on the volume of functioning parenchyma on the affected side, n = 316

Volume of functioning parenchyma	55 - 70%, n = 43	71 – 85%, n = 95	86 – 100%, n = 178	Statistical significance
Volume of blood loss, ml	460.5 ± 275.7	379.8 ± 168.2	401.5 ± 218.7	t-test; $p > 0.5$

The analysis of the volume of intraoperative blood loss, depending on the volume of functioning parenchyma on the affected side showed no significant differences, indicating the possibility of resection even with the parenchyma lesion up to 45%.

In our opinion it was interesting to find out whether the preoperative level of nephrometry index (R.E.N.A.L. score) had any effect on blood loss. Results are presented in Table 7.

Table 7. Volume of intraoperative blood loss during kidney resection, depending on nephrometry index (R.E.N.A.L. score), n=316

Nephrometry index (R.E.N.A.L. score)	Low (4-6 points), n = 167	Medium (7-9 points), n = 102	High (10-12 points), n = 47	Statistical significance
Volume of blood loss, ml	327.1 ± 143	363.3 ± 183.3	450.9 ± 207.5	t-test; $p < 0.05$
Blood loss> 500 ml, n (%)	16 (9.5)	22 (21.6)	16 (34.0)	$x^2 = 17.6$; $p < 0.001$

The results were similar in nature; they indicated directly proportional dependence of blood loss volume and the number of patients with significant blood loss on nephrometry index (R.E.N.A.L. score) $p < 0.05$. The data show promising outlook of using nephrometry to forecast intraoperative volume of blood loss.

Overall postoperative complications occurred in 25 (7.9%) patients, that is far below the published data and is due to effective surgical technique, use of local ischemia, quality sutures, new hemostatic means, modern antibiotics, and the early activation of patients. Analysis of postoperative complications is presented in Table 8.

Table 8. Postoperative complications in kidney resection, depending on kidney tumor size, n = 316

Postoperative complications	T 1a, n = 142	T 1в, n = 141	T 2, n = 33	Total, n=316
Urinary fistula, n (%)	1 (0.7)	5 (3.5)	3 (9.0)	9 (2.8)
Postoperative bleeding, n (%)	6 (4.2)	2 (1.4)	-	8 (2.5)
Acute pyelonephritis, n (%)	4 (2.8)	1 (0.7)	2 (6.0)	7 (2.2)
Suppuration of post-op. wound, n (%)	3 (2.1)	-	1 (3.0)	4 (1.3)
Acute renal failure, n (%)	1 (0.7)	2 (1.4)	-	3 (0.9)
Stricture of ureter, n (%)	-	1 (0.7)	-	1 (0.3)
Total, n (%)	11 (7.7)	9 (6.4)	5 (15.2)	25 (7.9)
Statistical significance	$x^2 = 2.83$; $p = 0.24$			

Thus the data presented in the table show that the most frequent complication was postoperative urinary fistula, which was observed in 9 (2.8%) patients; it was eliminated in 7 (2.2%) cases within 7-21 days with the use of stenting; in 2 (0.6%) cases, due to the ineffectiveness of conservative treatment it served as an indication to perform nephrectomy. The incidence of urinary fistulas directly correlated to the tumor size and was observed in 1 (0.7%), 5 (3.5%), and 3 (9.0%) cases, respectively, for stage T1a, T1b, and T2.

Postoperative bleeding in the period from 1 hour to 2 days was diagnosed in 8 (2.5%) patients. It was arrested in 4 (1.3%) cases with conservative means. In 3 (0.9%) cases it led to kidney revision, parenchyma re-suturing, and in 1 (0.3%) case - to nephrectomy.

Purulent septic complications were generally quite rare: pyelonephritis with hyperthermia of over 5 days was diagnosed only in 7 (2.2%) cases, and suppuration of wound – in 4 (1.3%) cases. In general no correlation was found of bleeding, pyelonephritis and wounds suppuration that depended on the tumor size.

Out of 7 cases of bilateral surgery (4 cases - bilateral resection of kidneys, 3 cases - kidney resection on one side and nephrectomy on the other) in 3 (42.9%) cases postoperative progress was complicated by acute renal failure, which was arrested within 2-3 days without dialysis. Given the high risk of acute renal failure in these situations, the surgery should be performed in specialized centers with hemodialysis.

Only in 1 case in the presence of prolonged urinary fistula due to uroplania and subsequent cicatricial deformity the ureteral stricture occurred in the area of pelvis-ureteral segment with the development of hydronephrosis that subsequently required surgical correction.

The use of ischemia in resection of kidney with tumor prevented acute renal failure development; our study had no acute renal failure occurrence even in cases of bilateral resection.

The postoperative hospital stay was 10.1 ± 3.4 days with no correlation with the tumor size; it was more dependent on the complications occurrence.

Discussion.

Today, complications associated with partial resection are the major challenge for many urologists. They are divided into three main groups: hemorrhage, urinary fistula and infectious complications. MSKCC researchers from New York found 361 patients after partial resection and 688 patients who underwent radical nephrectomy during the period of 1995-2002. Complications related to surgery included urinary fistulas, acute renal failure, retroperitoneal hematoma, pneumothorax, trauma of adjacent organs and small bowel obstruction. Urinary fistula was defined as a constant leakage of urine over 7 days after surgery or accumulation of urine, which required percutaneous drainage. 235 complications occurred in 180 patients (17%).

3 cases of perioperative deaths were noted. Partial resection of kidney was not associated with more complications compared to radical nephrectomy, but it had more complications related to surgery itself (9% vs. 3%), mainly due to urinary fistulas with the rate of repeated interventions 2.5% vs. 0.6% in the group of radical nephrectomy. Only one complication required the intervention. No link of complications with the size, localization, imperative or elective indications for kidney resection was found. Multivariate analysis showed that the timing of surgery and the presence of a single functioning kidney were significantly associated with complications [8]. Complications requiring special attention were: constant leakage of urine, in particular, when the patient had to be discharged home with drainage.

Today urologists perform more and more complex kidney resections followed by damage of hollow renal system; the damage increases the risk of urinary fistula. Analysis of 127 patients operated between 2001 and 2007 who underwent kidney resection (70 open and 57 laparoscopic) by Meeks J.J. & colleagues, identified the fistula as leakage of urine during more than 48 hours after surgery. In general, in their study, the presence of such complications was observed in 21 (13.3%) patients. Factors that were associated with the risk of such complications were tumor size, endophytic tumors and restoration of the integrity

of the hollow renal system during resection. Not risk-related factors were: the number of operated tumors, blood loss, ischemia timing, body mass index, age, and other surgical complications. The average duration of urine leakage was 20 days. Most cases of leakage were arrested by drainage. Ten patients required re-intervention to install the ureteral stent (8 cases) and percutaneous nephrotomy (2 cases). No nephrectomy or repeated surgery was made in this study [9].

In another MSKCC study 1118 kidney resections were analyzed. Urinary fistula was identified by urine leakage for more than 2 weeks after surgery or the presence of urinoma after removal of drainage that required additional drainage. 52 patients developed postoperative urinary fistula (4.4%) with a constant leakage of urine, and out of these the delayed urinary fistula occurred only in 0.4% of cases. Factors that have been associated with the development of fistulas were: tumors larger in size (3.5 cm vs. 2.6 cm), operations with greater blood loss (400 ml vs. 300 ml), and longer ischemia of vascular pedicle (50 minutes versus 39 minutes). In total, in 36 patients the healing proceeded without additional intervention, but 16 patients required re-intervention, which included kidney stenting in 8 cases and nephrotomy in 2 cases. No nephrectomy was performed, and in no case kidney function was permanently lost [10].

The results of our study showed that due to local ischemia the intraoperative bleeding rate was slightly higher, that was compensated by a significant decrease in the number of postoperative complications and thus improved the life quality for patients. Therefore, the proposed method is a promising trend in treatment of patients with renal cell cancer; it needs further development, kidney function and long-term outcomes study.

Conclusions:

1. Use of local ischemia during organ-sparing surgery for kidneys is followed by greater blood loss from parenchyma that was observed in 54 (17.1%) cases, and required transfusion of blood components only in 7 (2.2%) cases with bleeding more than 800 ml.
2. Directly proportional dependence was found of the blood loss volume on the tumor size, its location, and the nephrometry index (R.E.N.A.L. score) $p < 0.05$.
3. Postoperative complications of partial resection were diagnosed only in 25 (7.9%) patients. The most frequent complication was postoperative urinary fistula, which occurred in 9 (2.8%) patients; it directly correlated with the tumor size, and was observed in 1 (0.7%), 5 (3.5%), and 3 (9.0 %) cases, respectively, for stage T1a, T1b, and T2.
4. No correlation dependence was found of postoperative bleeding (2.5%), pyelonephritis (2.2%) and suppurating wounds (1.3%) on the tumor size.
5. High risk of acute renal failure after partial resection on both sides simultaneously (42.9%) dictates the need for such surgery to be performed in specialized centers with hemodialysis.

List of References:

1. Russo P., et al., Partial nephrectomy: the rationale for expanding the indications. Annals of surgical oncology, 2002. 9(7): p. 680-7.
2. Lee C. T., et al., Surgical management of renal tumors 4 cm. or less in a contemporary cohort. The Journal of urology, 2000. 163(3): p. 730-6.
3. Leibovich B. C., et al., Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. The Journal of urology, 2004. 171(3): p. 1066-70.
4. Gilbert B. R., Russo P., Zirinsky K., et al., Intraoperative sonography: application in renal cell carcinoma. The Journal of urology, 1988. 139(3): p582-584.
5. Timsit M. O., et al., Prospective study of safety margins in partial nephrectomy: intraoperative assessment and contribution of frozen section analysis. Urology, 2006. 67(5): p. 923-6.
6. Stephenson A. J., et al., Complications of radical and partial nephrectomy in a large contemporary cohort. The Journal of urology, 2004. 171(1): p. 130-4.
7. Kutikov A. and Uzzo R. G., The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. The Journal of urology, 2009. 182(3): p. 844-53.
8. Meeks J. J., et al., Risk factors and management of urine leaks after partial nephrectomy. The Journal of urology, 2008. 180(6): p. 2375-8.
9. Kundu S. D., et al., Urinary fistulae after partial nephrectomy. BJU international, 2010. 106(7): p. 1042-4.