

Efficiency and Safety of Nephron-Sparing Surgery for Localized Kidney Cancer

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Introduction. There are numerous publications demonstrating contradictory outcomes of kidney cancer surgery.

Objective. To evaluate the efficiency of surgical treatment in patients with localized kidney cancer (KC), comparing the immediate and long-term results of nephron-sparing surgery (NSS) and radical nephrectomies (RN).

Patients and methods. The results of surgical treatment were analyzed in 251 patients with KC who had undergone NSS ($n = 124$) or RN ($n = 27$). The groups were matched for gender, age, stage, and baseline glomerular filtration rate. Surgical complications were evaluated according to the Clavien–Dindo classification. Survival rates were calculated using the Kaplan–Meier method.

Results. There were no significant differences between the two groups of patients in the amount of blood loss (median 300 ml) and in the hospital length of stay (LOS). The median renal ischemia time was 15.0 ± 3.4 min. Complications after NSS and nephrectomies occurred in 10.4 % and 4.7 % of cases respectively. The patients of NSS group were found to have higher 5-year overall survival rates (89.1 %) than the patients of RN group (70.6 %) ($p = 0.248$). The NSS group was found to have higher 5-year overall and relapse-free survival rates than the nephrectomy group ($p > 0.05$).

Conclusion. NSS is an effective and safe method of treatment for RCC, however it still has insufficient and limited application in clinical practice.

Key words: kidney cancer; localized renal cell carcinoma (RCC); surgical treatment; nephrectomy; nephron-sparing surgery (NSS); resection; partial nephrectomy (PN), surgical complications; hospital length of stay; amount of blood loss; therapy; renal ischemia; survival rate

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Introduction

The incidence of kidney cancer (KC) has been increasing in the past decade in Russia and worldwide. In 2013 in Primorye (the region in the Russian Far East), 269 new cases of KC were detected (in 2004–192 cases), KC morbidity rate has increased by 40.1 % over the past 10 years (in Russia – by 27.8 %), from 6.9 per 100,000 to 10.0 per 100,000 (in Russia – from 7.5 to 9.0). In Primorye in 2013, stage I KC was diagnosed in 36.8 % ($n = 99$) new patients, stage II KC – in 18.6 % ($n = 50$), stage III KC – in 14.1 % ($n = 38$), and stage IV – in 30.5 % ($n = 82$) patients. Low – stage KC was diagnosed in 55.4 % (in Russia – 56.6 %) new cases. In 2013 the KC mortality rate was 4.4 per 100,000 in Primorye (in Russia – 3.4), one – year mortality rate was 19.3 % (in Russia – 18.0 %) [1, 2].

Surgery is considered the most effective treatment for KC [3], however there is a lot of debate about techniques and extent of the surgical intervention [4]. Nephron – sparing surgery (NSS) advantages, the tumor size and localization [5, 6], safe renal ischemia time [7], effective hemostasis techniques, the surgical complications rate [8, 9], the development of chronic kidney disease (CKD), survival and patients' quality of life [10, 11] represent some of the most often clinicians' concerns and debates. The only randomized study of efficiency of radical nephrectomy

(RN) and nephron-sparing surgery (NSS) in KC revealed contradictory results [11]. S.P. Kim et al reported of similar efficiency of NSS and RN in terms of disease – specific survival [12], while C.J. Weith et al. found overall survival (OS) increase after NSS [13]. In Russia during the past 10 years the NSS rate in KC has increased only by 15.5 %. [14]. The clinical database of Primorye demonstrates similar rates: 3524 new patients were diagnosed with KC from 1999 to 2013, 2230 (63.3 %) of these patients were operated on for KC – 1889 (84.7 %) patients underwent radical nephrectomy (RN) while NSS was performed only in 341 (15.3 %) cases.

Objective. To assess the effectiveness of surgical treatment in patients with the localized renal cell carcinoma (RCC) comparing the NSS and RN immediate and long – term results.

Patients and methods

We analyzed and compared the clinical data and information about the surgical treatment outcomes of 251 KC patients from 2004 to 2013. According to the KC patients program of navigating, scheduling and guidance, the patients underwent surgery at the Regional Clinical Oncology Center of Primorye and Vladivostok Clinic – 2, performed using the endovideosurgery equipment,

Table 1. Investigation groups of KC patients

	Total	Group I (PN)	Group II (RN)	<i>p</i>
Patients, <i>n</i> (%)	251 (100,0)	124 (100,0)	127 (100,0)	—
Males, <i>n</i> (%)	183 (72,9)	90 (72,6)	93 (73,2)	0,957
Females, <i>n</i> (%)	68 (27,1)	34 (27,4)	34 (26,8)	0,915
Age, median \pm δ , yrs	56 \pm 10,4	55 \pm 10,9	57 \pm 9,6	0,124
Renal damage, <i>n</i> (%):				
right (R)	117 (46,6)	62 (50,0)	55 (43,3)	0,288
left (L)	127 (50,6)	57 (46,0)	70 (55,1)	0,149
both (bilateral)	7 (2,8)	5 (4,0)	2 (1,6)	0,235
Tumor size, median \pm δ , mm	45,0 \pm 18,9	35,0 \pm 13,9	58,0 \pm 18,5	0,001

ultrasonic, radio-frequency ablator and argon plasma scalpels. In the investigation group there were 2.7 times as many males as females (table 1). The age of the patients varied from 22 to 87 years (mean 56.0 ± 10.4). All the patients were divided into two clinical groups. Patients in Group I ($n = 124$) underwent NSS, while RN was carried out in all the patients of Group II ($n = 127$). Right kidney tumors were almost as frequent as left kidney tumors: 117 (46.6 %) and 127 (50.6 %) cases respectively. Bilateral KC was detected in 7 (2.8 %) patients. The size of tumors of patients in Group I was significantly smaller ($p = 0.001$) (median 35.0 ± 13.9 cm) than that in Group II (median 58.0 ± 18.5 cm).

The majority of patients in Group I had stage I KC. The rate of stage I–II KC in both groups was almost identical – 118 and 117 patients respectively. There were more patients with II stage KC in the RN Group – 35 ($p = 0.001$) cases (table 2).

Clear-cell carcinoma (RCC) was the most common type of KC – representing 56.9 % of cases (in Group I – 58.9 %, in Group II – 55.1 %). The mixed type cancer was detected in 27.5 % (in Group I – 25.0 %, in Group II – 29.9 %), a papillary carcinoma – in 10.8 % (in Group I – 13.3 %, in Group II – 10.2 %), chromophobe RCC – in 3.6 % (in Group I – 4.0 %, in Group II – 3.2 %) and Bellini ducts cancer – in 1.2 % of cases (in Group I –

0.8, in Group II – 1.6 %). As for the grades of tumor differentiation, both groups had very similar rates. High differentiated carcinoma (G1) was diagnosed in 76.5 % (192) cases, moderately differentiated carcinoma (G2) – in 21.1 % (53), low differentiated carcinoma (G3) – in 1.6 % (4) and undifferentiated carcinoma (G4) – in 0.8 % (2).

Surgical complications were ranked and estimated according to Clavien-Dindo classification [9]. Renal function was controlled calculating the glomerular filtration rate (GFR) before and after surgery and long-term postoperatively. The grade of GFR damage was estimated according to the KDOQI (Kidney Disease Outcomes Quality Initiative) classification. Overall survival (OS) was calculated using the Kaplan-Meier estimator. The significance of differences was evaluated with the *log-rank* test and Student's *t*-test. The investigation materials and findings were statistically processed and analyzed with *STATISTICA 6.0*, *MS Excel*, *MS Office* and *BIOSTAT* programs.

Discussion of results

NSS in most patients ($n = 79$; 63.7 %) was performed on elective indications. 25 (20.2 %) patients had absolute surgical indications, 20 (16.1 %) patients had relative indications for their operations. Of 189 cases of stage I KC, 107 (56.6 %) patients underwent NSS. Of 46 stage II KC cases,

Table 2. Patients in KC stages

KC Stages		Total, <i>n</i> (%)	Group I (NSS), <i>n</i> (%)	Group II (RN), <i>n</i> (%)	<i>p</i>
I	pT1aN0M0 pT1bN0M0	189 (75,3)	107 (86,3)	82 (64,6)	0,061
II	pT2aN0M0 pT2bN0M0	46 (18,3)	11 (8,9)	35 (27,5)	0,001
III	pT3aN0M0	16 (6,4)	6 (4,8)	10 (7,9)	0,315

only 11 (23.9 %) patients had NSS, of 16 stage IIIa KS cases – 6 (37.5 %) patients (table 2). RN was carried out very often in stage I and II KC – in 43.4 % ($n = 82$) and 76.1 % ($n = 35$) cases respectively, in stage III KC – in 62.5 % ($n = 10$) cases. These findings have demonstrated the limited application of organ-sparing surgery in the low-stage KC that is confirmed by O.I. Apolikhin et al who have revealed that most patients (77.0 %) with localized KC are exposed to an unreasonable RN [14].

The patients in Group I most often had a lower segment tumor ($n = 55$; 44.4 %) and upper-pole tumor ($n = 37$; 29.8 %), sometimes the mid-renal tumor ($n = 31$; 25.0 %), 1 patient (0.8 %) had a tumor in the central (pelvic) segment. Most patients in Group II had the mid-renal tumor ($n = 58$; 45.7 %), sometimes a lower segment tumor ($n = 25$; 19.7 %) and an upper-pole tumor ($n = 24$; 18.9 %).

The main types of organ-sparing surgery in KC included various kidney resections ($n = 113$; 91.1 %): wedge ($n = 54$; 43.6 %), frontal ($n = 27$; 21.8 %), atypical ($n = 17$; 13.7 %), planar ($n = 15$; 12.1 %) resections. The enucleation of tumor node was carried out in 11 (8.9 %) cases with no tumor capsule invasion that corresponded to recommendations of J.-J. Patard et al.

Nephrectomy was more often carried out in mid-renal ($n = 58$; 45.7 %) and basilar tumor cases ($n = 25$; 19.7 %), and only sometimes in upper – pole tumors ($n = 24$; 18.9 %) and central (pelvic) tumors ($n = 13$; 10.2 %) ($p = 0.001$). RN was performed after partial nephrectomy (PN) in 2 patients when cancerous cells were found in the kidney resection line after the urgent histological investigations. These findings were not confirmed after the planned histological test that proved false-positive results. Endovideosurgical RN was performed only in 5 (3.9 %) patients due to the beginning of endosurgery application in the State medical clinics of Primorye just in 2011. Regional lymph nodes were excised during NSS in 4 (3.2 %) patients, during RN – in 11 (8.9 %) patients. Progress and development of X-ray and radioisotope diagnostics in KC allowed abandoning unreasonable lymphadenectomies.

The time median of nephron-sparing surgeries was more (87.5 ± 30.5 min.) than that of nephrectomies (65.0 ± 21.3 min.) ($p = 0.001$), that was caused by the period of surgeons' mastering the NSS technique in KC. NSS in 90.4 % ($n = 112$) cases was carried out with the blocked blood flow by the tourniquet on a vascular pedicle; in 5.6 % ($n = 7$) cases artery forceps such as «bulldog» were used; in 4.0 % ($n = 5$) cases there was digital occlusion of a renal parenchyma in a resection zone applied without ischemia. Now we perform primarily only a renal artery clamping, as simultaneous clamping of both arteries and veins more often results in a damage of the renal parenchyma [15].

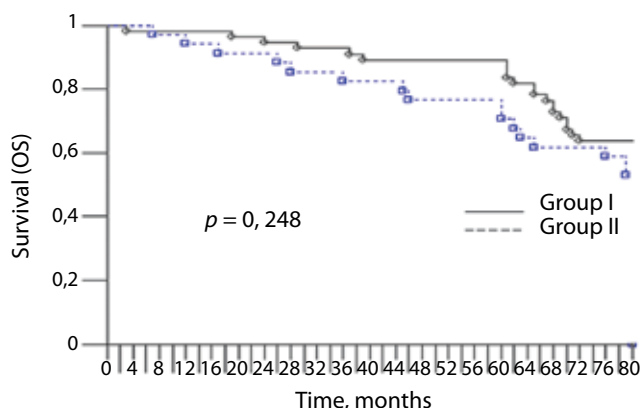
The median renal ischemia time was 15.0 ± 3.4 (from 8 to 20) minutes. In literature there are still discussions about safe and accepted time of warm and cold ischemia. Most authors define mean safe duration of renal parenchyma ischemia no more than 25–30 min. [16]. However according to the recent publications, the renal ischemia should be minimized, as zero-ischemia is the best [17]. The n-shaped, the double modified loop haemostatic suture or some other sutures were used to secure complete hemostasis based on operating surgeon's technical possibilities and preferences.

The amount of blood loss median in RN and PN was identical (300.0 ± 145.5 ml). According to various authors' reports, the amount of blood loss in NSS is from 200.0 [18] to 700.0 ml [19] and depends on many factors, including calculation method. The transfused erythromass median in Group I was 750.0 ± 297.5 ml, in Group II – 1000.0 ± 409.4 ml ($p = 421$).

The median of the preoperative glomerular filtration rate (GFR) was 98.3 ml/min./1.73 sq. m and had no significant differences in both groups of patients ($p > 0.05$). Postoperatively the GFR decrease was revealed in 20 (7.9 %) patients: after PN – to 81.2 ml/min./1.73 sq. m, after RN – to 84.3 ml/min./1.73 by sq. m. The most evident GFR decrease (< 30 ml/min./1.73 sq. m) was registered in 1 patient after RN that corresponded to stage IV CKD in the KDOQI classification. 19 (7.6 %) of 251

Table 3. Surgical complications (in Clavien–Dindo classification)

Complications	Total, n (%)	Group I (NSS), n (%)	Group II (RN), n (%)	p
G1	9 (3,6)	7 (5,6)	2 (1,6)	0,088
G2	5 (2,0)	3 (2,4)	2 (1,6)	0,650
G3a	3 (1,1)	3 (2,4)	0	0,079
G3b	1 (0,4)	0	1 (0,7)	0,351
G5	1 (0,4)	0	1 (0,7)	0,351
Total	19 (7,6)	13 (10,4)	6 (4,7)	$> 0,05$



Overall survival (OS) curves of localized kidney cancer patients after nephron-sparing surgery (NSS) and nephrectomy (RN)

patients had various complications of surgery (table 3) registered.

Most often Grade I–II complications ($n = 14$; 73.7 %) were detected; sometimes Grade III ($n = 4$; 21.0 %); and 1 (5.3 %) case presented Grade V (lethal outcome). Complications of Grade IVa – IVb were not registered. The complications rate in Group I was higher ($n = 13$; 10.4 %) than in Group II ($n = 6$; 4.7 %) mainly during the period of surgeons' mastering of the NSS method. After PN 4 patients had got urinary fistula (a ureteric stent was required in 1 case). 1 patient had got hemorrhage of the renal resection zone, 5 patients had chronic pyelonephritis exacerbation, 2 patients had a retroperitoneal hematoma, 1 patient had pneumonia. In RN Group grades I–IIIb complications were registered: some cases of renal hemorrhage ($n = 1$), the organized hematoma ($n = 1$), suture sinus ($n = 1$), pneumonia ($n = 1$), a stroke ($n = 1$); Grade V complications – progressing chronic renal failure with lethal outcome ($n = 1$). The surgical lethality after radical nephrectomy was 0.04 %. The hospital length of stay (LOS) median after NSS was less (12 days), than after RN (15 days).

The postoperative follow – up median was 50.0 months. During 1.5 years after PN, 2 KC relapses were re-

vealed and followed by the RN with relapse – free condition. Now 229 of these 251 KC postoperative patients are alive (91.2 %): complete clinical remission was registered in 222 (88.5 %) patients, progression of the disease was in 7 (2.8 %) patients. In total 22 (8.8 %) patients died: due to progressing KC – 18 (7.2 %) patients (8 after PN, 10 after RN), due to some other reasons – 4 (1.6 %) patients. In the NSS group one-year overall survival rate was 98.2 %, three-year OS rate – 93.5 % and five-year OS rate – 89.1 %, for pT1aN0M0 G1–100.0 %. After nephrectomy OS rates were 99.2; 92.5 and 70.6 % respectively (fig. 1).

One-year relapse-free survival (RFS) rate in Group I was 99.1 %, 3-year RFS rate – 92.5 % and 5-year RFS rate – 91.1 %; in Group II – 98.3; 88.7 and 70.6 % respectively ($p > 0.05$).

Five-year OS and RFS rates after NSS were higher, than after RN.

Conclusions

The navigating, scheduling and guidance program for KC patients is extremely significant for the individualized approach to the surgical treatment of localized RCC. RN and NSS are the most effective methods of treatment in kidney cancer.

NSS and endovideo-NSS still have limited and insufficient application in clinical practice. A half of stage I KC patients is still exposed to an unreasonable nephrectomy. NSS should be preferred in extrarenal upper-pole and lower segment tumors. About 10.0 % of KC patients could have enucleation of an extracapsular tumor if there is no tumoral invasion of a renal parenchyma. Early detection of KC tumors at low-stages expands elective indications to NSS, as this method has the low complications rate and demonstrates no surgical lethality. Most complications are registered in the period of surgeons' mastering of the NSS techniques. Ischemia time minimizing due to the effective and quick hemostasis provides very low risk of CKD development. Organ – sparing surgical treatment has many advantages for overall and relapse – free survival (OS & RFS) in patients with localized kidney cancer.

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