Int Urol Nephrol (2012) 44:745–751
DOI 10.1007/s11255-011-0058-z

UROLOGY – ORIGINAL PAPER

Renal function and adaptive changes in patients after radical or partial nephrectomy

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Received: 5 July 2011 / Accepted: 8 September 2011 / Published online: 21 September 2011

Abstract
Introduction Renal function after renal surgery depends on the volume of renal parenchyma loss and improves in the postoperative period. However, the knowledge on kidney function after radical (RN) and partial (PN) nephrectomy is still insufficient. The aim of this study is to analyze the global renal function and compensatory hyperfunction of the non-operated kidney in patients with renal cancer after RN or PN.
Methods Fifty-one patients of mean age 62.2 years with renal cancer were included. Thirty-three RN and eighteen PN were performed. We measured creatinine serum concentrations, and we estimated glomerular filtration rate (eGFR) preoperatively and postoperatively at two time intervals: 3 and 12 months after surgery. Additionally, we assessed effective renal plasma flow (ERPF) in dynamic scintigraphy preoperatively and 12 months after surgery.
Result At the baseline, all mean measured values were comparable in RN and PN groups ($P > 0.05$). Three months after surgery, creatinine level increased in both groups, more remarkably in RN group (128 mmol/l vs. 95 mmol/l; $P < 0.05$), while eGFR diminished (47 ml/min/1.73 m^2 vs. 70 ml/min/1.73 m^2; $P < 0.05$). Similar biochemical values were observed 12 months after surgery. The mean ERPF of the non-operated kidney 12 months after surgery in RN and PN groups increased by 3.8% (232 ml/min) and 0.1% (200 ml/min), respectively ($P > 0.05$). The mean ERPF of the operated kidney in PN group decreased by 24.7% (149 ml/min).
Conclusion The deterioration of renal function after partial nephrectomy is nearly insignificant clinically. In 1-year postoperative observation, the renal function does not improve. This causes potential compensatory mechanisms to be insufficient.

Keywords Renal cancer · Kidney function tests · Nephrectomy · Glomerular filtration rate · Effective renal plasma flow

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Introduction

The first planned successful nephrectomy was performed in 1869 by Gustav Simon [1]. Over time, we have expanded our knowledge and refined surgical techniques, oncological results, and follow-up protocols. However, the knowledge of renal function and compensatory mechanisms following nephrectomy in renal cancer patients has not progressed much further than what Simon had learned from the experiments performed in the seventeenth century by Hendrik von Roonhuysen, Giuseppe Zambeccarius, Stephan Blankaard, and others. These researchers proved that it was possible to live with a single kidney and demonstrated limited compensative hypertrophy in the residual kidney [2].

Renal cancer is one of the most frequently occurring neoplasms. Its incidence is still on the rise, contributing to renal surgery becoming increasingly more common [3]. One of the most interesting and important observations derived from the clinical data of patients qualified for nephrectomy or nephrectomized is the influence exerted by renal parenchyma reduction on global renal function. Our current working hypothesis is that patients undergoing renal surgery suffer from deterioration of renal function depending on the volume of renal parenchyma loss but that the global renal function during long-term follow-up improves as a consequence of the compensatory mechanism produced by contralateral kidney hyperfunction [4]. The extent of our knowledge on kidney function after radical (RN) and partial (PN) nephrectomy as a consequence of renal cancer, however, is insufficient and must be expanded.

Aim

The aim of the study is to analyze the impact exerted by renal surgery on global renal function and the compensatory hyperfunction of the non-operated kidney in radical and partial nephrectomy surgery.

Materials and methods

Population

62 white race patients with renal cancer were enrolled in the study prospectively. All the patients gave written consent to participate in the study. Mean tumor size was 5.3 × 4.4 × 4.5 cm. One-year follow-up was performed completely in 51 patients (28 men and 23 women). RN was performed in 33 patients (2 T1a, 17 T1b, 10 T2, and 4 T3 tumors) and PN in 18 patients (18 T1a tumors). The mean age in the cohort was 62.2 years (42–78). Table 1 summarizes basic demographic and clinical data of the cohort. Hypertension was defined as systolic pressure over 140 mmHg and diastolic pressure over 90 mmHg at two visits or hypotensive therapy, hypercholesterolemia as total cholesterol serum concentration >5.17 mmol/l or hypolipemic therapy, hyperuricemia as uric acid serum concentration >428 mmol/l, diabetes as hypoglycemic therapy.

Intervention

The influence of surgery on renal function was compared generally between RN group and PN group, as well as regarding to age (patients younger and older than 60 years) and arterial hypertension (hyper- and normotensive patients). The kidney function was assessed preoperatively and postoperatively in two time intervals: at 3 and 12 months after surgery by measuring serum creatinine concentration, and subsequently by calculating the estimated glomerular filtration rate (eGFR) using the Modification of Diet Renal Disease (MDRD) formula. Additionally, effective renal plasma flow (ERPF) in dynamic scintigraphy with technetium-99 m ethylenedicysteine

Table 1 Basic demographic and clinical data of the cohort

	RN group ($n = 33$)	PN group ($n = 18$)	P value
Mean age	61.9	62.7	0.77
Female to male ratio	1:1.4	1:1.3	0.95
Number of pts aged >60 years	20 (61%)	10 (56%)	0.73
Number of hypertensive pts	22 (67%)	12 (67%)	1.00
Number of pts with hypercholestrolemia	11 (33%)	4 (22%)	0.41
Number of pts with hyperuricemia	4 (12%)	4 (22%)	0.34
Number of diabetic pts	6 (18%)	3 (17%)	0.89

The unpaired t test was used for age comparison, and the χ^2 test was used for all qualitative variables

(^{99m}Tc-EC) as a radiopharmaceutical was measured preoperatively and postoperatively 12 months after surgery to assess the differences in each kidney separately.

Statistical analysis

The paired t test was used to compare the measured values at different follow-up points within study groups. To compare selected parameters in partially versus radically nephrectomized patients, the unpaired t test was used for quantitative variables and χ^2 test for qualitative variables. Normal distribution was confirmed by the Shapiro–Wilk test, while the equality of variances was assessed using Levene's test before all the t tests were performed. The differences were considered to be statistically significant when the P value was <0.02. The measurement results are expressed as mean values and standard deviations; in addition, range and/or percentage of change are presented for selected parameters.

Results

The differences between the RN and PN groups in the mean values were not statistically significant at the baseline. Statistically significant results are summarized in Tables 2 and 3.

Serum creatinine concentration

Patients in both groups had a high baseline serum creatinine concentration, at the upper limit of the reference range (44–94 mmol/l). Thus, surgery is very important for renal function measured by serum creatinine concentration. Postoperative mean values were above normal in both groups with the difference between the baseline and the measured results 3 months after surgery being statistically significant in RN group ($P < 0.02$).

Estimated glomerular filtration rate

According to chronic kidney disease classification, patients in our cohort suffered stage one of this disease preoperatively (eGFR under 90 ml/min/1.73 m^2 and over 60 ml/min/1.73 m^2). However, surgery significantly deteriorated renal function, shifting our patients to more advanced stages of chronic kidney disease. The drop in the first 3 months of observation is statistically significant in RN group ($P < 0.02$), as opposed to subsequent growth over the following 9 months.

Effective renal plasma flow

The preoperative differences in mean global ERPF in the RN and PN groups were not statistically significant. During the 1-year postoperative follow-up, we noticed a decrease in global ERPF in both groups, by 38% in the RN group and 11% in the PN group. The final differences in global ERPF between the groups under analysis are statistically significant ($P < 0.02$), as are the differences between pre- and postoperative values in the RN group ($P < 0.02$). Twelve months after surgery, the mean ERPF of the

Table 2 Mean serum creatinine concentration and estimated glomerular filtration rate values with standard deviations (in brackets) at follow-up points

	Creatinine (mmol/l)			eGFR (ml/min/1.73 m^2)		
	RN	PN	*P* value (RN vs. PN)	RN	PN	*P* value (RN vs. PN)
Visit 1	90.5 (19.5)	89.4 (23.3)	0.86	70.8 (18.4)	74.0 (21.1)	0.57
Visit 2	128.1 (25.0)	94.9 (27.3)	**<0.01**	47.1 (9.5)	69.6 (18.4)	**<0.01**
Visit 3	126.4 (24.7)	95.1 (34.9)	**<0.01**	48.1 (10.2)	70.5 (22.8)	**<0.01**
P value (visit 1 vs. visit 2)	**<0.01**	0.08		**<0.01**	0.10	
P value (visit 1 vs. visit 3)	**<0.01**	0.43		**<0.01**	0.66	

Visit 1 preoperative levels, *visit 2* postoperative levels 3 months after surgery, *visit 3* postoperative levels 12 months after surgery. *GFR* glomerular filtration rate, *RN* radical nephrectomy group, *PN* partial nephrectomy group

Paired t test and unpaired t test were used to compare creatinine concentration and eGFR at different follow-up points within and between study groups, respectively

Table 3 Mean effective renal plasma flow values with standard deviations (in brackets) at follow-up points (ml/min)

	Global ERPF			ERPF in operated kidney			ERPF in non-operated kidney		
	RN	PN	*P* value (RN vs. PN)	RN	PN	*P* value (RN vs. PN)	RN	PN	*P* value (RN vs. PN)
Visit 1	394.0 (97.2)	391.3 (132.0)	0.94	170.2 (53.4)	197.2 (69.2)	0.15	223.4 (62.1)	199.3 (64.3)	0.21
Visit 3	239.0 (84.5)	348.0 (85.0)	**<0.01**	0.0 (0.0)	148.5 (47.7)	**<0.01**	232.1 (86.8)	199.5 (43.5)	0.18
P value (visit 1 vs. visit 3)	**<0.01**	**0.02**		**<0.01**	**<0.01**		0.80	0.72	

Visit 1 preoperative levels, *visit 3* postoperative levels 12 months after surgery. *ERPF* effective renal plasma flow, *RN* radical nephrectomy group, *PN* partial nephrectomy group

Paired *t* test and unpaired *t* test were used to compare ERPF at different follow-up points within and between study groups, respectively

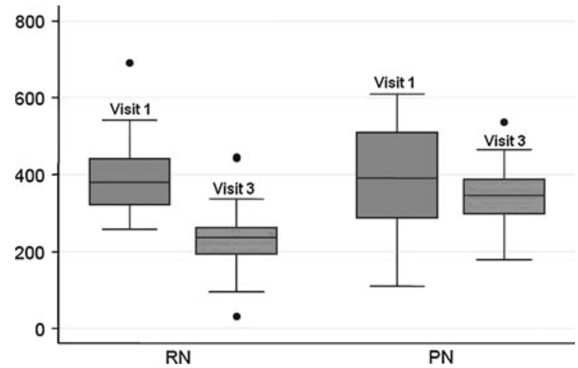

Fig. 1 Global effective renal plasma flow values (ml/min). *Visit 1* preoperative levels, *visit 3* postoperative levels 12 months after surgery. *RN* radical nephrectomy group, *PN* partial nephrectomy group

operated kidney in the PN group decreased by 24.7%. The mean ERPF of the contralateral kidney in the RN and PN groups grew 3.8 and 0.1%, respectively. The difference between the ERPF values for the contralateral kidney in the two groups 1 year after surgery is not statistically significant ($P > 0.02$) (Fig. 1).

Age effect on effective renal plasma flow after renal surgery

Under the hypothesis that the non-operated kidney's compensatory hyperfunction is less effective in older patients, we compared postoperative changes in ERPF in patients aged $\leq$60 and >60 years. Our statistical analysis has demonstrated that the measured differences in patients younger and older than 60 are not significant. At the baseline, mean ERPF was 410.2 and 381.9 ml/min ($P > 0.02$), while 12 months after surgery decreased to 309.7 and 255.0 ml/min ($P > 0.02$), respectively. Analogous conclusions come when analyzing these two groups of patients regarding to the type of operation.

Arterial hypertension effect on effective renal plasma flow after renal surgery

Finally, we performed an analysis to assess whether hypertensive patients have less effective renal compensatory mechanisms due to hypertensive nephropathy. Just as with the age effect on ERPF after renal surgery, the measured differences between normotensive and hypertensive patients are not statistically significant. At the baseline mean ERPF in normotensive and hypertensive patients was 394.9 and 389.2 ml/min ($P > 0.02$), while 12 months after surgery decreased to 247.0 and 286.8 ml/min ($P > 0.02$), respectively.

Discussion

Our results prompt one to question our current way of thinking about nephrectomy. The conclusion that kidney removal deteriorates renal function is not surprising or insightful. It is apparent, however, that our knowledge on the long-term effect of renal surgery is insufficient.

One year after renal surgery, we observed a mean increase of 27% in serum creatinine concentration. Simultaneously, we recorded a decrease of 22% in eGFR and 30% in effective renal plasma flow. All these changes were more clinically and statistically significant in radically nephrectomized patients than in partially nephrectomized patients.

First, our results confirm the appropriateness of nephron-sparing surgery and the need to perform partial nephrectomy on appropriate patients to avoid the removal of normal renal parenchyma and consequently excessive deterioration of renal function. At the 1-year observation point, we recorded a 32% decrease in eGFR in radically nephrectomized patients, compared to a mere 5% decrease in partially nephrectomized patients. Similar conclusions stem from the study published by Clark et al. comparing creatinine clearance in patients undergoing RN or PN at the 1-year observation point. The authors demonstrated a 32% decrease in the RN group and a 6% decrease in the PN group [5]. The values reported by Tanaka et al. [6] based on follow-up at 2–4 weeks were 37 and 5%, respectively. Shirasaki et al. [7] published a study based on 1-year observation of 30 radically nephrectomized patients reporting a 33% increase of serum creatinine concentration. Cozzi et al. [8] observed 16 radically and 10 partially nephrectomized children and recorded 36 and 24% growth in serum creatinine concentration, respectively, 1 year after surgery.

Second, our study underlines the inefficiency of potential compensatory mechanisms improving renal function in the postoperative period. The non-operated kidney's compensatory hypertrophy seems not to be associated with hyperfunction. By definition, hypertrophy entails nephron enlargement, not an increase in the number of nephrons. However, we intuitively think that hypertrophy causes hyperfunction. In 1-year observation, we observed a 4% increase in the non-operated kidney's ERPF in radically nephrectomized patients and a 0.1% increase in partially nephrectomized patients. It is worth remembering that the operated kidney's ERPF in partially nephrectomized patients simultaneously fell by just 25%. Finally, the deterioration of global renal function measured by the decrease in global ERPF was three times more significant in radically nephrectomized patients than in partially nephrectomized patients. Previously published studies have focused mainly on the value of renal scintigraphy in assessing renal insufficiency after renal surgery. However, they present important data for discussion of our results. The lack of significant renal compensatory mechanisms is confirmed by the study published by Groshar et al. [9] reporting no changes regarding the non-operated kidney's renal volume and the percentage injected dose per cubic centimeter of renal tissue of operated and non-operated kidneys in 24 patients examined preoperatively and 1–6 months after partial nephrectomy. Ben-Haim et al. [10] reported a 9% increase in the non-operated kidney's volume accompanied by a 29% increase in the percentage injected dose per cubic centimeter of renal tissue in 30 patients examined preoperatively and 2–23 months after radical nephrectomy. It is hard to ascertain the underlying cause for the results of Ben-Haim's study and our study differing from one another in this way. The primary difference rests in the radionucleotide used for renal scintigraphy and the lack of protocol for follow-up points in Ben-Haim's study. Another important aspect is that, even though the results of his scintigraphy were more optimistic than ours, Ben-Haim et al. reported a surprisingly more significant increase in serum creatinine concentration (49% increase). The authors concluded that compensatory hyperfunction occurs soon after surgery, which is totally at odds with our study's findings, and that the postoperative hyperfunction remains intact for at least 1 year, which also seems to be consistent with our observations.

Our results stand in opposition to some other studies published in recent years. Anderson et al. [11] recorded a 33% increase in the non-operated kidney's ERPF 1 week after nephrectomy in 55 patients, Bieniasz et al. [12] reported a 30% decrease in creatinine clearance in 46 patients 3 months after nephrectomy, and Goldfarb et al. [13] observed a 28% decrease in 24-h urinary creatinine clearance in 70 patients 25 years after nephrectomy. All these studies were based, however, on living kidney donors. These patients have attributes that are incomparable with renal cancer patients. Usually, they are healthy young people with a potentially greater ability for compensation.

The most important limitations of our study are the small number of patients in the PN group, the length of follow-up, and the reliance on serum creatinine concentration/eGFR as sole measure of renal function. During data collection, 18 partial and 33 radical nephrectomies were performed, illustrating the stage of renal cancer at the time of diagnosis in Poland. In the contemporary cohort, 90% of T1a patients were qualified for partial nephrectomy.

The study protocol called for three control points with the last one being 1 year after surgery. Renal function deterioration proved to be slightly more advanced 3 months after surgery compared to renal function deterioration 12 months after surgery. Although the differences between the postoperative measurements at 3 and 12 months are not statistically significant, it may be interesting that renal function significantly retarded immediately after surgery improves in subsequent months. An important question that must be posed is whether the compensatory mechanisms analyzed in our study were insufficient because of their limited capacity or because of the observation period was too short. However, even if compensation becomes effective only after the elapse of more than a year, we think our conclusions are correct.

The number of tests assessing renal function is still rising. However, in the present study, we used only creatinine serum concentration and eGFR calculated by MDRD formula. Despite their limitations, these tests are one of most commonly used in urological departments in every day practice. While we think that more specific tests would not change our results substantially, their use could consolidate our findings and increase the scientific value of the report.

Conclusions

Renal surgery deteriorates global kidney function proportionately to the volume of renal parenchyma loss. While a tumor does not produce urine, the deterioration of renal function after partial nephrectomy is nearly insignificant clinically. At 1-year observation, potential compensatory mechanisms are totally insufficient and global renal function does not improve. The hypothesis regarding hyperfunction of contralateral kidney should be revised because hyperfunction is not clinically or statistically significant. Having regard for the study's methodological limits, further investigation is needed to confirm the results and conclusions definitively.

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