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ONE YEAR DECLINE IN ESTIMATED GFR AFTER NEPHRECTOMY IN PATIENTS WITH RENAL MASSES AND MATCHED LIVING KIDNEY DONORS IS THE SAME

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ABSTRACT

Objectives

To determine short-term differences in renal function evolution between renal cell carcinoma (RCC) patients submitted to radical nephrectomy (RN) and living kidney donors matched for age and gender and to assess the role of co-morbidity as risk factor for developing an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73m².

Patients and Methods

In this retrospective study patients undergoing RN between January 2000 and February 2011 for suspicion of localized RCC were matched by age and gender to living kidney donors. Renal function was compared between the groups using the Modification in Diet and Renal Disease (MDRD) equation at 1 year postoperative. Charlson co-morbidity score, incidence of hypertension, diabetes and cardiovascular diseases (CVD) were compared and assessed as predictors for developing an eGFR below 60 ml/min/1.73m².

Results

In total 196 patients were included, 98 in each group. Mean age was respectively 60.6 (RCC group) and 59.1 years (donors). One year postoperative mean eGFR (available in 89 RCC patients and 87 donors) was comparable in both groups (56.7±16.4 ml/min/1.73m² in RCC patients and 56.2±9.8 ml/min/1.73m² in donors (p=0.83)). In RCC patients the incidence and severity of co-morbidities was significantly higher. Preoperative eGFR 60-89 ml/min/1.73 m² was the only independent risk factor for developing postoperative eGFR below 60 (OR=4.4, CI=2.1-9.5, p<0.001).

Conclusions

In our cohorts with advanced age 1 year follow up eGFR was comparable in both groups. In spite of increased co-morbidity in the RCC group there was no increased decline in renal function. Only reduced preoperative eGFR could be identified as risk factor for developing postoperative eGFR below 60.

INTRODUCTION

Various studies have shown that radical nephrectomy (RN) for renal cell carcinoma (RCC) may lead to long term adverse renal outcomes, such as deterioration of the estimated glomerular filtration rate (eGFR) or hospitalisation^{1,2}. An eGFR below 60 ml/min/1.73 m² has been described in 45% - 70% of the patients after RN^{3,4}. Although the number of patients that eventually requires renal replacement therapy is low (2.0% - 6.2%)^{1,2}, chronic kidney disease (CKD) deteriorates the quality of life and is a risk factor for cardiovascular disease (CVD) and overall mortality⁵.

In contrast to patients undergoing RN for RCC, living kidney donors rarely develop end stage CKD (0.3%-0.5%) after nephrectomy^{6,7}. The fact that donor selection is primarily based on good health and limited co-morbidity, has been the advocated reason⁶.

In contrast, Timsit et al⁸ reported that donors and RCC patients with a low co-morbidity load presented with the same percentage of decrease in renal function at 1 to 4 years following nephrectomy, in spite of older age and lower baseline renal function in the RCC patients.

Our primary objective was to determine short-term differences in renal function evolution between RCC patients submitted to RN and living kidney donors at the age when RCC is predominant. Secondary objective was to assess the role of co-morbidity as risk factor for developing an eGFR below 60 ml/min/1.73m².

PATIENTS AND METHODS

Patient selection

For this single center retrospective longitudinal cohort study all patients between 18 and 75 years who underwent (open or laparoscopic) RN for suspicion of RCC between January 2000 and February 2011 in our center were identified. Patients with an abnormal contralateral radiological kidney, solitary kidney or synchronous RCC, patients with metastatic or locally advanced cancer at nephrectomy (pT4/N1-2), previous surgery for RCC and pre-existing severe renal insufficiency (defined as an eGFR below 30 ml/min/1.73m²) were excluded.

In addition, we retrieved all living kidney donors between 18 and 75 years operated upon in our hospital during the same period from a prospective database.

Selected patients undergoing nephrectomy for solitary renal masses (RCC group) were matched for age and gender to the most suitable group of kidney donors (donor group).

Due to the retrospective nature of this study approval of the medical ethics committee was not required.

Outcomes

Renal function was evaluated by calculating the eGFR using the 4 variable Modification in Diet and Renal Disease (MDRD) equation⁹. To obtain maximal follow-up measurements we contacted patient's general practitioners for creatinine values. The eGFR was assessed preoperative, at 6 months and 1 year postoperative. To mirror the stages of kidney disease defined by the National Kidney Foundation¹⁰, the eGFR was divided in the following stages ≥ 90 ; 60-89; 30-59; 15-29; < 15 ml/min/1.73m².

Baseline co-morbidity load was assessed by the Charlson co-morbidity score¹¹ and by a history of hypertension, diabetes and cardiovascular disease (CVD).

RCC tumours were staged according to the 2009 TNM¹².

Statistical analysis

Propensity score matching utilizing a multivariate logistic regression model to create single scores was used for matching the RCC patients with kidney donors in a 1:1 ratio based on age and sex.

To assess the differences between the RCC and donor group the independent samples T- test was used for continuous (normal) variables and the Chi-square test for categorical variables.

Independent risk factors for developing an eGFR < 60 ml/min/1.73m² 1 year postoperative, were evaluated by univariate analyses using the independent samples T- test for continuous (parametric) variables (age and BMI) and the Chi-square test and odds ratio for categorical variables (preoperative eGFR stage, presence of diabetes, hypertension, CVD and Charlson score of 2 or higher and gender). Multivariate analyses (preoperative eGFR stage, age, BMI, Charlson score of 2 or higher and gender) were done using logistic regression (all variables entered). Variables included in the multivariate analyses were statistically significant on univariate analyses or known with relation to renal function deterioration.

A multiple imputation and subsequent analyses with the pooled data were done to assess the effect of missing data on eGFR outcomes.

All tests were two-tailed and a p-value < 0.05 was considered statistically significant. Matching was done using R statistical software version 2.13.2. Data was analyzed using Predictive Analytics Software Statistics 18.0.2 (Armonk, New York, United States of America).

RESULTS

Both the RCC and living donor group contained 98 patients. Baseline characteristics of both groups are shown in Table 1. None of the living donors had proteinuria at baseline and donor nephrectomy was performed laparoscopic.

RCC group consisted of 92 RCCs and 6 benign tumours. Pathological T-stage was divided as followed T1a 14 (15.2%); T1b 28 (30.4%); T2a 11 (12.0%); T2b 9 (9.8%); T3a 28 (30.4%); T3b 2 (2.2%).

Characteristics	RCC group (n=98)	Donor group (n=98)	p- value
Age (years) [*]	60.6 (9.9)	59.1 (9.1)	0.25
Gender			0.56
- male (n (%))	63 (64.3%)	59 (60.2%)	
- female (n (%))	35 (35.7%)	39 (39.8%)	
BMI (kg/m ²) ^{1, *}	26.8(5.1)	25.8 (3.0)	0.11
Charlson score			$< 0.001^*$
- 0-1	75 (76.5%)	96 (98.0%)	
- ≥ 2 (n (%))	23 (23.5%)	2 (2.0%)	
ASA score (n (%)) ²			$< 0.001^*$
- I	20 (21.7%)	70 (73.7%)	
- II	52 (56.5%)	24 (25.2%)	
- III	19 (20.7%)	1 (1.1%)	
- IV	1 (1.1%)	-	
Diabetes (n (%))	10 (10.2%)	0 (0%)	0.001*
Hypertension (n (%))	36 (36.7%)	19 (19.4%)	0.007*
Cardiovascular disease (n (%))	22 (22.4%)	1 (1.0%)	$< 0.001^*$
Preoperative creatinine (μ mol/L) [*]	82.1 \pm 19.5	73.3 \pm 11.0	$< 0.001^*$
Preoperative renal function MDRD (ml/min/1.73m ²) [*]	84.7 (21.0)	92.3 (14.2)	0.003*
Preoperative eGFR (MDRD) (ml/min/1.73m ²), (n (%))			$< 0.001^*$
- ≥ 90	36 (36.7%)	55 (56.1%)	
- 60-89	47 (48.0%)	42 (42.9%)	
- 30-59	15 (15.3%)	1 (1.0%)	

Table 1. Differences in baseline characteristics of RCC and donor nephrectomy patients

^{*} mean (standard deviation).

^{*} p < 0.05

¹ BMI was available in 96 RCC patients and in 94 donors. ² ASA score was available in 92 RCC patients and 95 donors.

^{*} Renal function was estimated using the MDRD equation.

Postoperative differences in renal function are displayed in Table 2. In 89 RCC patients and 87 donors creatinine measurements were available 1 year after nephrectomy. Four RCC patients died before 1 year follow-up was reached (2 from other causes and two from progressive RCC). From 5 RCC patients and 6 donors renal function measurements were not available in the hospital or with the general practitioner. Five donors had no general practitioner or came from abroad.

		RCC	Donor	p-value
6 months	number	86	87	
	creatinine ($\mu\text{mol/L}$)	116.8 (31.6)	113.4 (19.2)	0.40
	eGFR MDRD ($\text{ml/min}/1.73\text{m}^2$)*	57.0 (16.4)	55.9 (11.0)	0.62
	% decrease eGFR (compared to baseline)	31.3 (14.0)	39.0 (8.0)	<0.001
1 year	number	89	87	
	creatinine ($\mu\text{mol/L}$)	117.4 (36.8)	111.4 (19.0)	0.16
	eGFR MDRD ($\text{ml/min}/1.73\text{m}^2$)*	56.6 (16.4)	56.2 (9.8)	0.87
	% decrease eGFR (compared to baseline)	31.4 (16.3)	38.3 (8.6)	0.001

Table 2. Postoperative renal function and changes compared to baseline renal function, 6 months and 1 year postoperatively (variables are reported as mean (standard deviation)).

In RCC patients eGFR 1 year postoperative was divided as followed; ≥ 90 $\text{ml/min}/1.73\text{m}^2$ in 4 (4.5%); 60-89 $\text{ml/min}/1.73\text{m}^2$ in 29 (32.6%); 30-59 $\text{ml/min}/1.73\text{m}^2$ in 52 (58.4%); 15-29 $\text{ml/min}/1.73\text{m}^2$ in 4 (4.5%) patients. In the donor group 33 (37.9%) had an eGFR 60-89 $\text{ml/min}/1.73\text{m}^2$ and 54 (62.1%) an eGFR 30-59 $\text{ml/min}/1.73\text{m}^2$ ($p=0.04$). Figure 1 illustrates changes from preoperative to postoperative renal function per preoperative stage.

Four RCC patients developed an eGFR between 15 and 29 $\text{ml/min}/1.73\text{m}^2$ postoperatively. Their preoperative eGFRs were 42, 44, 46 and 61 $\text{ml/min}/1.73\text{m}^2$. Postoperative evaluation of the renal function showed hypertension in all of them associated to nephrosclerosis (1), diabetes type II and micro-albuminuria (1), metabolic syndrome (1) and diabetes type II and chronic NSAID use (1).

When assessing patients with a preoperative eGFR ≥ 60 $\text{ml/min}/1.73\text{m}^2$, new onset of an eGFR < 60 $\text{ml/min}/1.73\text{m}^2$ developed in 41 of 74 RCC patients (55.4%) and 54 of 86 donor patients (62.8%) ($p=0.34$).

Univariate analyses demonstrated significant associations between developing an eGFR < 60 $\text{ml/min}/1.73\text{m}^2$ ($p < 0.001$), gender ($p=0.01$) and a preoperative eGFR between 60-89 $\text{ml/min}/1.73\text{m}^2$ ($p < 0.001$). In multivariate analyses (with patients who had all data available at baseline and 1 year control ($n=155$)) including preoperative eGFR stage, age, BMI, Charlson score ≥ 2 and gender the only independent factor associated to developing postoperative eGFR below 60 ml/min was a preoperative eGFR between 60-89 ml/min (OR 4.5, CI 2.1-9.5, $p < 0.001$).

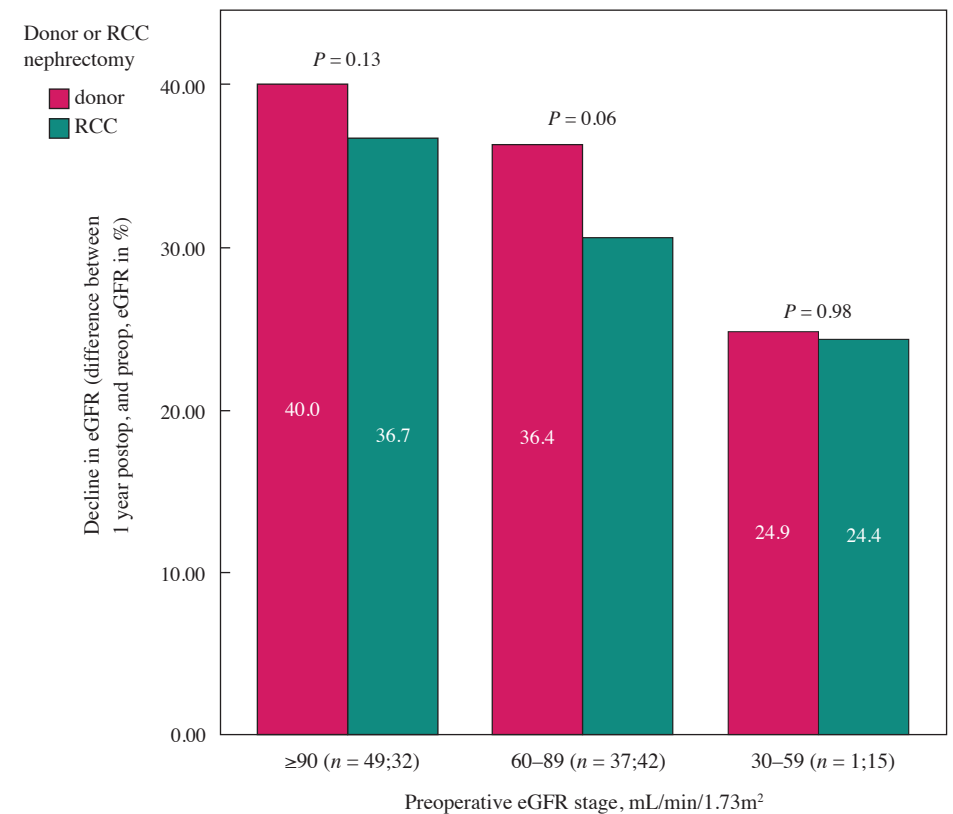


Figure 1. Mean decline in eGFR (difference between 1 year postoperative and preoperative eGFR in percentage). Displayed per preoperative eGFR stage for RCC patients and living kidney donors separately. P-values for the difference between RCC patients and donors are shown in the figure above each eGFR stage. The delta eGFR (1 year postoperative eGFR minus preoperative eGFR in $\text{ml/min}/1.73\text{m}^2$) in the eGFR stage > 90 was -40,5 for RCC patients and -39,3 for donors ($p=0.64$); in the 60-89 stage -29,1 for RCC patients and -23,8 for donors ($p=0.03$) and in the 30-59 stage -14,4 for RCC patients and -11,9 for donors ($p=0.77$).

Calculations for postoperative renal function outcomes using pooled multiple imputation results were similar to results with original data. With the imputed data one-year postoperative eGFR was 56.6 and 56.8 ml/min/1.73m² respectively in RCC patients and donors (p=0.93); creatinine was 118.6 and 111.1 µmol/L (p=0.09); and percentage decrease in eGFR compared to baseline resp. 32.1% and 38.0% (p=0.003).

DISCUSSION

In the current study we assessed the evolution of the renal function after nephrectomy at the age in which RCC is predominant. Our results suggest that nephrectomy at advanced age results in a significant one-year decline in renal function in both RCC patients and living kidney donors independently of the presence of co-morbidity.

Preoperative eGFR between 60 and 89 ml/min/1.73m² predicted the development of a post-nephrectomy eGFR below 60 ml/min/1.73m².

After nephrectomy, decrease in renal function has been reported in both RCC patients and living kidney donors^{6,13-15}. However mean age and co-morbidity of living donors were traditionally considerably lower than the correspondent figures in RCC patients. In older living donors, with a mean age in the range of our cohort, a similar eGFR decrease has been reported^{16,17}. The renal function decline in previous studies seemed to be dependent on age at donation^{3,13}. It was more prominent in donors aged ≥60 years than in younger ones. Up to 80% of the elderly might develop a post nephrectomy eGFR<60 ml/min/1.73 m² while this figure accounts for 31% in the younger¹⁶.

Conversely when post RN renal function is compared among living kidney donors and “healthy” RCC patients (meeting criteria for living donation), no difference in renal function decrease (around 30% in both groups) has been found in spite of significant differences in mean age at RN (57.9 years in RCC patients vs. 48.5 years in donors) and baseline renal function⁸. This later study suggests that age and co-morbidity might not be the most important determinants in renal function outcomes after RN either for donation or because RCC.

We hypothesized that matching groups for age should minimize its effect as a risk factor on the post nephrectomy renal function outcomes and underscore the effect of the co-morbidity. As renal function is subjected

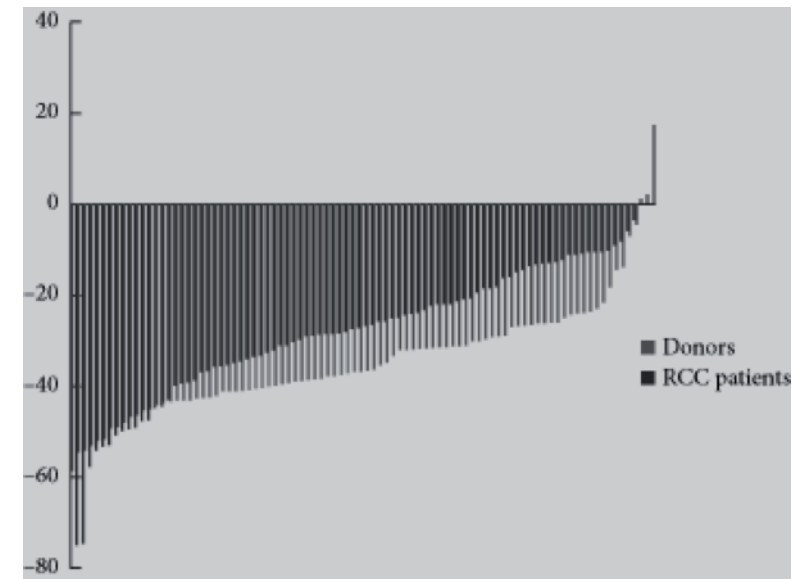


Figure 2. 'Per patient' differences (percentage) between baseline eGFR and eGFR at 1 year after RN.

to gender differences a further match on gender would overcome this confounder^{18,19}. However in our population a similar eGFR at 1 year after RN in living donors and RCC groups was observed in spite of the higher co-morbidity load in the RCC group. Furthermore the decline of renal function of the donor group was higher than of the RCC group. The later phenomenon may be explained by the better preoperative renal function of the donor group and subsequent lesser decrease among patients with lower baseline renal function as displayed in Figure 1. As a relative high percentage of our tumours were staged pT1b or higher we think that the tumour process had been replacing a considerable amount of kidney and the relatively lesser functioning kidney was removed at RN.

While we did not expect any effect of age in our analysis, the striking point is that in these two age/gender matched cohorts we could not demonstrate any association between co-morbidity and development of an eGFR <60 ml/min/1.73m². In the age range of our study baseline eGFR was the only predictive factor for development of an eGFR below 60 ml/min/1.73m² after RN. Specifically a baseline eGFR between 60-89 ml/min was associated with a fourfold times higher chance of developing an eGFR below 60 ml/min one year after RN.

While the 1 year postoperative eGFR > 90 ml/min/1.73m² in 4.5% of patients with RN because RCC is anecdotic and responds to the normal range variations, the 4.5% of patients with a severe CKD at 1 year is of concern. Of these four RCC patients three had a low eGFR prior to nephrectomy (between 42 and 46 ml/min) and two of them presented micro-albuminuria. No patient in the donor group developed an eGFR below 30 ml/min/1.73m².

Our results, reinforced by the lack of progression to severe CKD in the donor group, suggest that criteria for living donor may expand to those elderly patients with a certain degree of co-morbidity provided their baseline eGFR is above 89 ml/min/1.73m². Consequently an increasing pool of individuals with advanced age may still be considered for living kidney donation under strict respect of pre-donation screening guidelines including evaluation of proteinuria/micro-albuminuria²⁰⁻²². Conversely, under the urological point of view our results are a plea for expanding the pool of nephron sparing surgery in an attempt to avoid detrimental quality of life or serious events²³.

We do acknowledge that the above conclusions deserve critical considerations. Firstly, renal function was assessed at short follow-up hindering conclusions on the influence of co-morbidity on long-term outcomes. However several studies indicated that changes in the renal function occur mainly during the first year after nephrectomy^{8,17,24}. Secondly proteinuria determination was not available in all our RCC patients precluding assessment of its weighted value on renal function outcomes. Macro-albuminuria (≥300mg albumin/24h urine) has a higher impact on the risk for decline in renal function than impaired baseline renal function²⁵ and recent data points out its usefulness on the decision treatment algorithm in patients with suspected RCC¹. Thirdly, in the current study eGFR was used as a proxy for CKD stages. We applied the MDRD formula that is known to increase the accuracy when eGFR is <60 ml/min/1.73m² with respect to the Cockcroft and Gault formula²⁶. Fourth, the study sample is relatively small. However age and gender matching allowed for independent assessment on the value of co-morbidity as a predictor in a given age range. Lastly 1 year renal function was not available in a small number of patients whether for medical or social reasons. Efforts were maximized to collect follow-up data and rates of eGFR below 60 ml/min/1.73m² were similar in both cohorts. Noteworthy after multiple imputation our results did not change.

In spite of these limitations our results suggest that living donation

programs may expand at the expenses of elderly patients and support the current policy on NSS in RCC when feasible. Further prospective research on the long-term effects of co-morbidity and other factors, such as proteinuria on renal function in RCC patients and elderly living donors should be pursued.

CONCLUSIONS

After nephrectomy RCC patients and living kidney donors matched for age and gender developed equal renal function at 6 months and 1 year postoperatively in spite of a higher co-morbidity load and lower baseline renal function in RCC patients. Only preoperative eGFR between 60 and 89 ml/min/1.73m² was an independent risk factor for developing a renal function below 60 ml/min/1.73m². No association was found between the presence of co-morbidity and renal function outcomes.

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