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Impact of Radical Nephrectomy on Renal Function in patients with Renal Cell Carcinoma

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Abstract
Objective: *To find out the pattern of change in post-operative renal function in patients who underwent radical nephrectomy for renal cell carcinoma.*
Patients and Methods: *A retrospective review of histological and biochemical findings in all patients who underwent RN for RCC over a period of 4 years was done. Study group comprised of 106 cases. Estimated glomerular filtration rate (eGFR) was calculated pre-operatively, 2 weeks and 3 months postoperatively and 6 monthly thereafter with a median follow up period of 24 months. Clinical variables that were evaluated included the age, sex, co-morbidities particularly diabetes mellitus (DM) and hypertension, tumor size, tumor stage, and preoperative estimated GFR(eGFR).*
Results: *The incidence of a moderate decrease in GFR after RN was 44 (48.88%). Patients with pT1a tumors had significantly higher mean baseline pre-operative eGFR compared to other T stages and the eGFR decline was also highest for T1a cases. There was significant negative correlation between tumor size and pre-operative eGFR. Age, DM, preop GFR, tumor size and tumor stage were found to be strong determinants of decline in GFR postoperatively.*
Conclusions: *eGFR decline seems to be more for those with small renal tumors and they might derive the most benefit from NSS.*
Keywords: *Renal function, Renal cell Carcinoma, Radical Nephrectomy, Glomerular filtration rate.*

Introduction

Renal cell carcinoma (RCC) accounts for 2% to 3% of all adult malignant neoplasms and is the most lethal of the common urologic cancers[1]. In patients diagnosed between 2002 to 2008, the five-year relative survival rates were 71% for kidney cancer, 78% for bladder cancer (excluding carcinoma in situ), and 99% for prostate cancer[2]. The majority of cases of RCC are diagnosed in the 6th and 7th decades of life[3]. With a higher incidence of hypertension, diabetes mellitus and cardiovascular disease which are known risk factors for chronic kidney disease (CKD) in this age group, there is arising concern about the additional impact of radical nephrectomy (RN) on renal function. Age, comorbidities mainly diabetes mellitus, pre-existing kidney disease and the type of surgery were the major determinants of post-operative renal function as per conclusions of previous studies. These conclusions were based

mainly on donor nephrectomies done on relatively healthy individuals whose characteristics are quite different from those suffering from renal cancer. Progression of post-operative CKD in patients who underwent RN for RCC is slower than in those with CKD due to medical causes[4] even though RN is identified as an independent risk factor for development of CKD. In addition, small tumor size was associated with a higher risk of new onset CKD after radical nephrectomy compared with larger tumors. Nephron sparing surgery (NSS) would circumvent this problem in a selected group of patients[5]. There have been relatively few studies examining the magnitude of decline in renal function following radical nephrectomy for renal cancer. Furthermore, understanding the likely patterns of change in renal function following radical nephrectomy will help determine the type of surveillance required for patients.

In the present study we aimed to examine the impact of RN in post-operative renal function in patients with RCC over a median follow up period of 2 years at our institution and the association between tumor size, stage and preoperative glomerular filtration rate(GFR) with the change in GFR after radial nephrectomy.

Materials and Methods

Patients

All patients with localized RCC who underwent radical nephrectomy in the Urology department, Government Medical College, Kozhikodefrom January 2012 to December 2015 were taken up for the study.

Exclusion Criteria

Metastatic RCC,
Transitional cell carcinoma in biopsy report,
Bilateral renal tumors,
Solitary kidney,
Stage IV CKD
Those on preoperative hemodialysis.

Basic patient profile atthe time of surgery was recorded including age and gender. Biochemical profiles, blood pressure and albuminuria ofall patients were documented. Serum creatinine values were recorded at several key timepoints: pre-operatively, 2 weeksand 3 months postoperatively and 6 monthly thereafter.

Clinical variables that were evaluated included the age,sex, co-morbidities particularly diabetes mellitus (DM) and hypertension, tumor size, tumor stage,and preoperative estimated GFR(eGFR).

Size of tumor was calculated as the longest dimension of the tumor on computerized tomography images taken preoperatively.The T stage of the tumor was evaluated as per the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

GFR was estimatedusing the Modified Diet in Renal Disease (MDRD) 4 variable formula,taking account of gender and ethnicity.

$GFR = 186 \times \text{Serum Cr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female)

Chronic kidney diseasewas defined based on the National Kidney Foundation KidneyDisease Outcomes Quality Initiative (NKF-KDOQI) from stage 0(eGFR>90 mL/min/1.73 m^2, no disease) to stage 5 (eGFR < 15mL/min/1.73 m^2, established renal failure).

The study was observational and no intervention were done except for the addition of formalized data collection.

Statistical Analyses

Statistical analysis was done using SPSS version 16.0. Qualitative data was expressed as frequency and percentage and quantitative data as median and inter quartile range (IQR). Paired data was compared using Wilcoxon Signed Rank test and independent groups were compared using Mann Whitney U test and Kruskal Wallis test. All tests were two sided and a p value<0.05 was considered to indicate statistical significance.

Results

Between 2012 to 2015, there were 148 cases that satisfied our inclusion criteria. We examined follow-up data of these cases over a median period

of 24 months. 23 cases couldnot be followed up due to discrepancies in the data furnished. 19 patients who died during the follow up period were excluded from the study. Hence the remaining 106 patients were considered as the study group.

Patient Profile

Age of the patients was between 24 to 75 years with median age 55 years (45 – 63). 27 (25.47%) patients were diabetic and 49 (46.2%) patients had hypertension. 59 (55.66%) patients had RCC right and 47 (44.34%) had RCC left. There was a clear male preponderance (79.2%) among the patients in study group. Male to Female ratio in the study group was 3.8:1.

The median (IQR) preoperative serum creatinine(S.Cr) level was 1.1 (0.9 - 1.2)mg/dL and the median (IQR) preoperative eGFR was 75 (65 - 90)mL/min/1.73m^2.

The pre-existing eGFR was<60mL/ min/1.73m^2 before RN in16 (15.09%).

Pathological Characteristics

More than half of the cases were T1 tumors with T1a lesions being slightly more than T1b lesions (Table 1). Considering the histology, clear cell carcinoma was the commonest type with about 91.5% of cases. Rest of the cases were constituted by papillary type (6.6%) and chromophobe (1.8%).

Table 1: Case distribution as per T stage

Type	Frequency (%)
T1a	34 (32.07)
T1b	29 (27.35)
T2a	22 (21.6)
T2b	14 (13.2)
T3a	3 (2.83)
T3b	1 (0.9)
T4	2 (1.88)

Serum Creatinine & GFR following RN

The median (IQR) follow upS.Cr level was 1.3 (1.2 - 1.4)mg/dL and the median (IQR) follow up eGFR was 59 (53- 67)mL/min/1.73m^2. The incidence of a moderate decrease in GFR after RN was 44 (48.88%). There was no case of severe decrease in GFR among the cases. The median (IQR) eGFR decline was 14 (8 - 26) mL/min/1.73m^2. Median followup eGFR was significantly lower compared to median pre-operative eGFR, p<0.0001.

Association of tumor Stage &eGFR

Variation of eGFR in accordance with T stage of the tumor are depicted in Table 2 and Table 3.Patients with pT1a tumors had significantly higher mean baseline pre-operative eGFR compared to other T stages and the eGFR decline was also the highest for T1a cases.

Baseline eGFR showed a progressive decline as the stage of disease advanced and similar trends of decline in eGFR were observed for all tumor stages (Figure 1).

Table 2: Mean eGFR by tumor stage (T-stage)

Type	Pre operative eGFR	Follow up eGFR
T1a	90 (73.5 - 104)	59 (54 - 69)
T1b	79 (66 - 90)	62 (56 - 69)
T2a	70 (60 - 83)	63 (50 - 67)
T2b	67 (57.25 - 72.25)	54.5 (50.75 - 59.25)
T3a	59 (48)*	48 (45)*
T3b	65$^+$	58$^+$
T4	68.5 (64)*	53.5 (53)*

Data expressed as median and IQR

*Upper quartile cannot be calculated as there were only 2patients

$^+$ IQR cannot be calculated as there were only 1 patient

Table 3: Decline in eGFR with Tumor Stage

Type	Decline in eGFR
T1a	27 (14.5 - 36.5)
T1b	13 (7 - 26)
T2a	10 (7 - 16)
T2b	10 (5.75 - 14)
T3a	7 (3)*
T3b	7$^+$
T4	15 (11)*

Data expressed as median and IQR

*Upper quartile cannot be calculated as there were only 2patients

$^+$ IQR cannot be calculated as there were only 1 patient

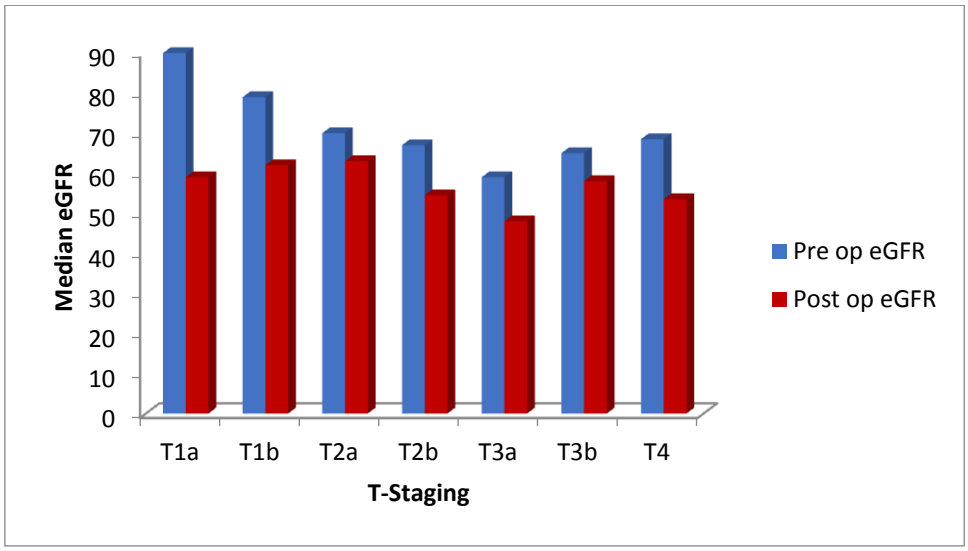

Figure 1: Mean eGFR by tumor stage (T-stage)

The median decline in eGFR was significantly higher among T1a type patients, p=0.001(Figure2).

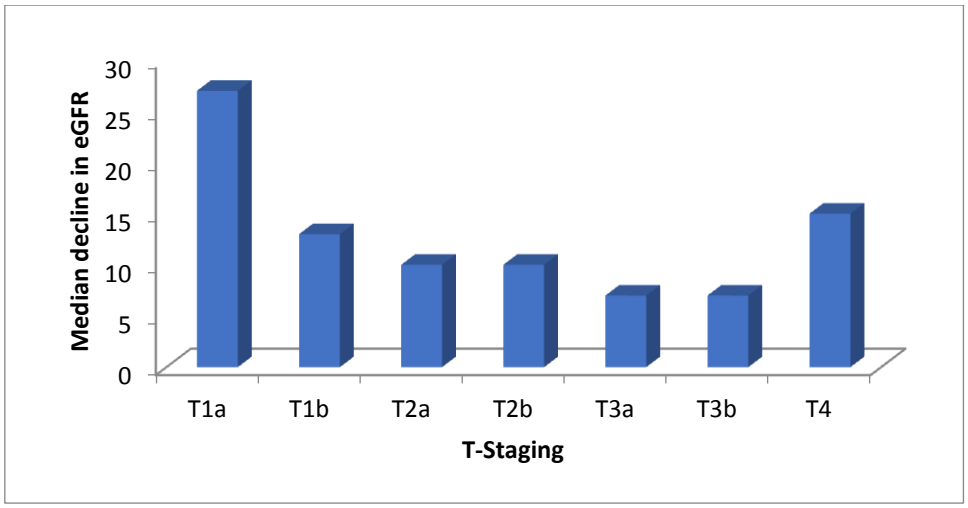

Figure 2: Measured decline in eGFR by tumor stage

Correlation between tumor size and pre-operative eGFR

There was significant negative correlation between tumor size and pre-operative eGFR, correlation coefficient = 0.389, p < 0.0001. As the tumor size increases pre-operativeeGFR decreases (Figure 3).

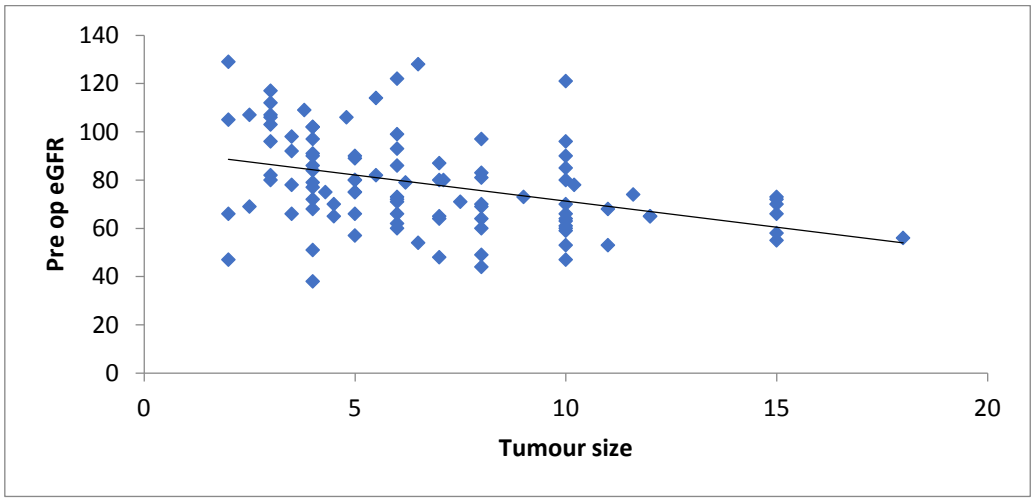

Figure 3: Relationship between preoperative GFR and tumor size.

Effect of Various Clinical Factors on decline in eGFR after RN

Clinical variables other than tumor size and stage have also been studied and results are compiled in Table 4.

Table 4: Other clinical variables and eGFR decline

Variable		Median Decline (IQR)	P value
Pre operative eGFR	< 60	5 (1 - 9)	<0.0001*
	>= 60	16 (10 - 28.75)	
DM	Yes	15 (9.5 - 29.5)	0.03*
	No	10 (6.5 - 16)	
HTN	Yes	16 (11 - 26)	0.111
	No	12 (6.25 - 27.5)	
Age (yrs)	< 60	16.5 (10 - 33)	0.02*
	60 - 69	11 (7 - 20)	
	>= 70	8 (5 - 14)	

*statistically significant

eGFR decline was significantly higher among patients having pre-operativeeGFR>= 60

eGFR decline was significantly higher among diabetic patients

eGFR decline was significantly higher among patients of lower age group, ie; < 60 yrs

Discussion

We evaluated eGFR to determine postoperative changes in renal function and investigated clinical factors affecting post-operative renal function. eGFR was calculated using MDRD formula which utilizes S. Cr values. Renal scan is said to be an accurate method[6] but in clinical practice it is not feasible to get a renal scan done routinely. After nephrectomy. S. Cr values correspond more to the renal function of the solitary kidney.

As per previous studies, the prevalence of eGFR of less than 60mL/min/1.73m^2 preoperatively was 10-30%.[7,8]The prevalence of pre-existing renal insufficiency in our study was 15.09% and median (IQR) preoperative eGFR in our study group was 75 (65 - 90)mL/min/1.73m^2 which were comparable to other large RCC cohorts whose preoperative GFR values were 73.3–74.8mL/min/1.73m^2.[8]

In addition to age, DM, HTN and Preoperative GFR, which are well documented risk factors related to CKD after radical nephrectomy, we evaluated the correlation of worsening of renal parameters with tumor size and stage. In our study group, age, DM, preop GFR, tumor size and tumor stage were found to be strong determinants of decline in GFR postoperatively. Our study shows that there was significant eGFR decline postoperatively in T1a tumors though there were only a few cases with advanced stage RCC.

Tumor size was noted to be inversely proportional to the magnitude of decline in eGFR observed. It is known from previous studies that there occurs a functional adaptation in the remaining kidney as a consequence of nephron loss.[9,10] Large renal tumors increase the renal parenchymal destruction resulting in decreased GFR pre-operatively itself. Hence, hypertrophy and hyperfiltration are induced in the remaining kidney according to tumor size. It was observed in our study that, there was a higher eGFR decline in case of smaller renal tumors. It may be due to the fact that in patients with larger tumors, the remaining kidney initiates an adaptation in renal function even before surgery as a result of greater loss of parenchyma on the tumor side.When it comes to small tumors, it could be seen that contralateral normal kidney was not compensating for the diseased kidney since the normal parenchymal loss in the tumor side was smaller in this group.

RN is still the most commonly performed surgical procedure in cases of RCC worldwide. Several previous reports have identified RN to be an independent risk factor for worsening of GFR in cases of RCC. It is said that for small renal tumors, NSS leads to a less sustained decline in GFR when compared to RN.[11] It is imperative to identify the group of patients who will benefit from partial nephrectomy in terms of renal function without compromising oncological outcomes. Present guidelines recommend NSS as

the treatment of choice for small renal masses (T1a, <4cm in size), those with an affected solitary functioning kidney, those with bilateral RCC5, in those in whom the contralateral kidney is poorly functioning or threatened by a disease process likely to lead to diminished function such as diabetes mellitus or hypertension or nephrolithiasis, as well as those with hereditary forms of RCC (e.g. Von Hippel Lindau gene).[12,13] However, partial nephrectomy for stage T1 stage is still underutilized in the United States.[14] The role of RN in the treatment of RCC has been somewhat bolstered by recent level 1 evidence demonstrating that, despite improved nephrological outcomes, nephron sparing surgery did not result in improved overall 10 year survival in a cohort of patients with small (< 5cm) tumours.[15]According to a meta-analysis of comparative studies, NSS is said to be a treatment option for even larger renal tumors, but the surgeon should be more selective and specific patient and tumor factors should be considered.[16] Prospective randomized studies, are warranted to better define the role of PN in the challenging clinical scenario and to document the survival benefits for the patients.

Limitations

First, it was a retrospective study performed at a single institution. Second, median(IQR)follow-up of 24months, may not be long enough to draw conclusions on long-term post-operative renal function. Thirdly, GFR were calculated using S. Cr values.

Conclusion

A significant proportion of patients developed moderate decrease in GFR following radical nephrectomy. eGFR decline seems to be more for those with small renal tumors and they might derive the most benefit from NSS, given the recognition of its oncological equivalence to RN at this disease stage.

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