

**RENAL FUNCTIONAL STATUS AFTER NEPHRON-SPARING SURGERY VERSUS  
RADICAL NEPHRECTOMY FOR RENAL CELL CARCINOMA: A RANDOMIZED  
CLINICAL TRIAL STUDY**

Dr. SM Ramiz Ahmed<sup>\*1</sup>, Dr. Md. Abdul Quiyum<sup>2</sup>, Dr. Mohammad Zahirul Islam<sup>3</sup>, Dr. Md. Mostafa Kamal<sup>4</sup>,  
Dr. Nirupom Mondal<sup>5</sup> and Dr. Md. Tazrul Islam<sup>6</sup>

<sup>1</sup>MBBS, MS, Resident Medical Officer, Department of Urology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

<sup>2</sup>MBBS, MS (Hepatobiliary surgery), Resident Medical Officer (A-59368), Department of Hepatobiliary, Pancreatic & Liver Transplant Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

<sup>3</sup>MBBS, MS, Resident Medical Officer, Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh.

<sup>4</sup>MBBS, MS (Urology), EMO, Shaheed Ziaur Rahman Medical College Hospital, Bogura, Bangladesh.

<sup>5</sup>MBBS, MS (Urology), Registrar, Urology, Khulna Medical College Hospital, Khulna, Bangladesh.

<sup>6</sup>MBBS, MS (Urology), IMO, Khulna Medical College, Khulna, Bangladesh.

**\*Corresponding Author: Dr. SM Ramiz Ahmed**

MBBS, MS, Resident Medical Officer, Department of Urology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

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**ABSTRACT**

**Introduction:** Localized RCC can be managed by surgery, ablative therapy and active surveillance. Radical nephrectomy (RN) has long been the standard treatment for renal cell carcinoma (RCC). Whether NSS is a better than RN for RCC still remains controversial. Evaluate the renal function changes in the follow up period after NSS and RN for RCC can be done with various method including by MDRD-eGFR preoperatively and postoperatively.

**Objective:** To compare estimated glomerular filtration rate (eGFR) after nephron-sparing surgery and radical nephrectomy (RN) for renal cell carcinoma (RCC). **Methods:** We evaluated renal function of NSS and RN in 52 patients having renal cell carcinoma ( $\leq 7$  cm, cT1b) and normal contralateral kidney using eGFR in different hospitals and institutes, Dhaka, from January, 2017 to September, 2018. After surgical intervention with different surgeons, MDRD-eGFR was measured postoperatively 1, 3, 7 days, and 3 monthly for one year. MDRD-eGFR declining is assessed from the preoperative value (eGFR0) to the last post operative value (eGFR12) at the end of follow up. **Results:** Demographic characteristics, BMI, pre and post operative symptoms and sign of the patients, most of the tumor characteristics were not statistically significant in both groups but statistically significant changes are found in tumor size ( $p=0.004$ ) and tumor type ( $p=0.013$ ). There is no significant difference in preoperative eGFR in both groups. The mean eGFR decreased more significantly in RN (18.56 ml/min) than NSS patients (6.31 ml/min) from preoperative to 12 months after operation and shows statistically significant differences between and within both groups ( $p < 0.001$ ,  $< 0.001$ ,  $0.001$  respectively). **Conclusion:** NSS is the superior protective technique for improving renal function than RN for RCC.

**KEYWORD:** RCC, radical nephrectomy, nephron sparing surgery, MDRD, eGFR.

**INTRODUCTION**

Renal cell carcinoma (RCC) is the most common malignancy of the kidney (90-95%) Due to the progress in radiological imaging, the majority of renal tumors are detected incidentally (>50%) in asymptomatic early stage. The triads of symptoms only occur in minority of patients (7-10%) and are usually a sign of locally advanced disease.<sup>[1]</sup>

Localized RCC can be managed by surgery and ablative therapy. Although radical nephrectomy (RN) considered as the standard treatment last 30-40 years, nephron-

sparing surgery (NSS) for localized RCC become popular over the last decades. Though it remains controversial,<sup>[2]</sup> the improved overall survival and health-related quality of life, better preservation of renal function, better safety and oncological efficacy seen after NSS. Previously renal function after surgery for RCC has usually been assessed by serum creatinine level alone but it is affected by factors which generate it such as muscle mass and dietary intake. Recently renal function is accurately measured by eGFR from MDRD equation which depends on serum creatinine concentration, age, sex and race.<sup>[3]</sup>

In different hospitals and institutes, Dhaka, Bangladesh, nephron sparing surgery is started in recent years along with radical nephrectomy for localized RCC. As renal function deteriorates more or less in both cases of NSS and RN, it is now necessary to determine which procedures conserve renal function better and causes less complication. As NSS is currently an underutilized procedure, this study data will highlight the importance of performing NSS regularly in our country.

## MATERIALS AND METHODS

This randomized controlled clinical trial study was conducted in the Department of Urology, BSMMU and other institutes-National Institute of Kidney Disease and Urology (NIKDU), Dhaka Medical College Hospital (DMCH), Comfort Nursing Home (Pvt.) Ltd, Dhaka, from January, 2017 to September, 2018. Total 52 patients were selected by purposive sampling technique having age 35-75 years; solitary renal cell carcinoma ( $\leq 7$  cm) and radiographically normal contralateral kidney. Patients who have preoperative serum creatinine level  $>1.5$  mg/dl, MDRD-eGFR  $<30$  ml/min/1.73m<sup>2</sup>, tumor in a solitary kidney, bilateral or multiple renal tumors, overweight or obese patient BMI  $> 25$  kg/m<sup>2</sup>, pregnant

patient, patients who refused to give consent or missing or dead during flow up were excluded. 46 patients are randomly allocated into group-A (NSS) and group-B (RN). The enrolled 23 patients in each group were evaluated preoperatively with standard protocol along with MDRD-eGFR. Then surgical intervention was performed in patients of both groups by different surgeons and patients were followed up postoperatively on 1, 3, 7 days and 3 monthly for one year with standard protocol along with measuring MDRD-eGFR. MDRD-eGFR declining was assessed from the preoperative value (eGFR<sup>0</sup>) to the last post operative value (eGFR<sup>12</sup>) at the end of follow up.

Statistical analysis was done by SPSS 20.0. Results are expressed as mean ( $\pm$ SD) and compared by Student's unpaired (independent) and paired (dependent) t-test for continuous variables and Chi square test for categorical variables. A 'p' value of  $< 0.05$  was considered as significant.

## RESULTS

There are no statistically significant differences in demographic characteristic between two groups.

**Table I: Patients characteristics in both groups (n=46).**

	Group-A(Nephron-Sparing Surgery) (n=23)	Group-B(Radical Nephrectomy) (n=23)	P- value
<b>Sex</b>			
Male	14 (60.9)	15 (65.2)	0.760
Female	9 (39.1)	8 (34.8)	
<b>Age (years) (mean<math>\pm</math>SD)</b>	48.91 $\pm$ 8.79	50.70 $\pm$ 12.23	0.573
<b>Range (years)</b>	35-65	35-74	
<b>BMI (kg/m<sup>2</sup>) (mean<math>\pm</math>SD)</b>	20.70 $\pm$ 2.36	21.22 $\pm$ 6.36	0.714

Table-II & III showed no statistically significant differences in pre and post operative clinical symptoms

and signs of the patients and tumor characteristics between two groups.

**Table II: Pre and post operative symptoms & sign of the patients in both groups (n=46).**

	Group-A (Nephron-Sparing Surgery) (n=23)	Group-B(Radical Nephrectomy) (n=23)	p-value
<b>Pre operative</b>			
<b>Flank pain</b>			
Yes	18 (78.3)	16 (69.6)	0.502
No	5 (21.7)	7 (30.4)	
<b>Hematuria</b>			
Yes	5 (21.7)	7 (30.4)	0.502
No	18 (78.3)	16 (69.6)	
<b>Diabetes</b>			
Yes	6 (26.1)	5 (21.7)	0.730
No	17 (73.9)	18 (78.3)	
<b>Hypertension</b>			
Yes	10 (43.5)	10 (43.5)	1.000
No	13 (56.5)	13 (56.5)	
<b>Post operative</b>			
<b>Fever</b>			
Yes	3 (13.0)	2 (8.69)	1.000
No	20 (87.0)	21 (91.30)	

Table III: Distribution of the patients according to tumor characteristics in both groups (n=46)

	Group-A (Nephron-Sparing Surgery) (n=23)	Group-B (Radical Nephrectomy) (n=23)	p-value
<b>Tumor size (cm)</b>	4.28 ± 0.91	5.08 ± 0.89	0.004
<b>Range(cm)</b>	(2.60 – 6.30)	(2.90 – 6.90)	
<b>Tumor location</b>			
<b>Upper pole</b>	9 (39.1)	12 (52.2)	0.563
<b>Lower pole</b>	10 (43.5)	9 (39.1)	
<b>Interpolar</b>	4 (17.4)	2 (8.7)	
<b>Tumor type</b>			
<b>Exophytic</b>	19 (82.6)	5(21.7)	0.013
<b>Endophytic</b>	4 (17.4)	13 (78.3)	
<b>Hydronephrosis</b>			
<b>Yes</b>	1 (4.3)	2(8.6)	0.187
<b>No</b>	22 (95.7)	21 (91.3)	
<b>Enhancement</b>			
<b>Yes</b>	23 (100.0)	21 (91.3)	0.489
<b>No</b>	0 (0.0)	2 (8.7)	

During evaluation of patient's eGFR status before operation, mean (±SD) eGFR in group-A, 75.22 ± 14.48 ml/min and in group-B, 73.17 ± 17.74 ml/min (table-V) but there are no significant differences preoperatively (p=0.671). After operation, the time depended changes of eGFR at 1st POD was not significant (p= 0.116, table-V). At 3rd, 7th POD and 3, 6, 9, 12 months follow up period after operation, time depended mean (±SD) eGFR status decreased gradually and become statistically

significant ('P' value in 3rd, 7th, 3, 6, 9 and 12 months POD = 0.012, 0.053, 0.002, 0.001, <0.001, <0.001 respectively; table-V). The mean (±SD) eGFR status decreased from preoperative to 12 months after operation in group-A 6.31±1.62 and in group-B 18.56±6.88 which shows statistically significant differences in eGFR status between and within the groups (p= <0.001, <0.001, 0.001 respectively; table-V)

Table IV: eGFR status before and time depended changes after operation (at different follow up) in both groups (n=46).

eGFR	Group		p-value
	Nephron-Sparing Surgery (NSS) (n=23) [Mean±SD]	Radical Nephrectomy (RN) (n=23)[Mean±SD]	
<b>Before operation</b>	75.22 ± 14.48	73.17 ± 17.74	0.671
<b>After operation</b>			
<b>At 1st POD</b>	64.39 ± 16.05	57.78 ± 11.50	0.116
<b>At 3rd POD</b>	67.52 ± 15.24	57.43 ± 10.23	0.012
<b>At 7th POD</b>	67.96 ± 13.66	60.13 ± 13.08	0.053
<b>After 3 months of POD</b>	69.65 ± 14.81	56.61 ± 11.58	0.002
<b>After 6 months of POD</b>	68.39 ± 13.61	55.91 ± 9.49	0.001
<b>After 9 months of POD</b>	68.52 ± 12.52	54.83 ± 10.44	<0.001
<b>After 12 months of POD</b>	68.91 ± 12.86	54.61 ± 10.86	<0.001
<b>Decrease in eGFR(ml/min)</b>	6.31 ± 1.62	18.56 ± 6.88	<0.001
<b>p-value (before op vs after 12 months of POD)</b>	<0.001	0.001	<0.001

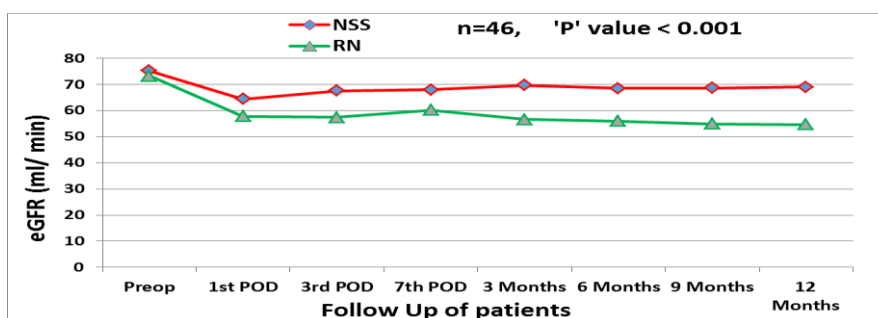


Fig-I: Time dependent changes of eGFR after NSS and RN in all patients.

## DISCUSSION

According to EAU guideline (2014), nephron sparing surgery is the first treatment option for cT1a tumor (<4 cm) and a viable option for cT1b lesions (> 4 cm) when technically feasible.<sup>[4]</sup>

In this prospective study, preoperative and post operative time dependent changes of renal function up to 12 months after NSS(Group-A) and RN(Group-B) are assessed by measuring eGFR using MDRD formula as renal function tends to be overestimated by using serum creatinine which is affected by several factors affecting creatinine generation. In this study, the risk factors for the development of new onset of CKD (eGFR< 60 ml/min) after operation are observed.

With regard to patient baseline characteristics (age, sex, BMI) in the current study, no significant differences ( $p=0.760$ ,  $0.573$ ,  $0.714$  respectively) are noted that can affect renal function. An interesting finding is that the age ranges in group-A, (35-65) years and in group-B, (35-74) years but classically renal tumors occur in sixth and seventh decades of life. The early occurrence of tumors in the current study perhaps due to easier access or exposure to carcinogen (smoking, industrial chemicals) and more rapid diagnostic and therapeutic methods available currently; additionally, many patients are diagnosed incidentally during medical evaluation for other symptoms.<sup>[5]</sup> Although compensatory hypertrophy occurs in all age groups after nephrectomy due to increased renal plasma flow and more pronounce in <30 years of age, effective renal plasma flow is known to decrease with patient age resulting in decreased compensatory hypertrophy with increased age and progressive deterioration of renal function.<sup>[6]</sup>

Most of the patients in both groups are male.<sup>[7]</sup> The male predominance in our country may be due to more exposure to cigarette smoking, industrial chemical exposure. Male patients had a significantly greater increase in effective renal plasma flow as well creatinine clearance than female patients at 1 week ( $p<0.005$ ) and at 1 year ( $p<0.0001$ ) after nephrectomy due to more compensatory hypertrophy than female.<sup>[6]</sup>

Flank pain is predominant present study (in group-A 78.3%, group-B 69.6% respectively) because they are more diagnosed incidentally and may get immediate management for pain.<sup>[8]</sup> Though hematuria is the late presentation but within this study, hematuria is higher in group-B than group-A (21.7% vs. 30.4%) because most of the tumors are larger and endophytic in group-B which may involve the PCS and may causes hematuria slightly differ from others. Minorities of the patients in this study have hypertension and diabetes that are well controlled preoperatively, intraoperatively and postoperatively up to follow up period by measuring regular blood pressure with getting anti hypertensive drugs, measuring blood sugar level with giving short acting insulin, oral hypoglycemic agents and advice is

given to control hypertension, blood sugar strictly in life time.<sup>[9]</sup> Hypertension was reported 44% in NSS, 60.8% in RN by Liss et al compared to 43.5% in both groups of current study due to their sedentary life styles and consumption of lipid rich food.<sup>[10]</sup> Several conflicting studies examined the long-term effects of renal donation on the contralateral kidney.

In baseline tumor characteristics, mean tumor size differs according to type of surgery in which larger tumor in group-B (5.08 cm) than group-A (4.28 cm) which influence the renal function in the present study ( $p = 0.004$ ) because larger tumor reduce more functional renal parenchyma. 4 cm or smaller RCC showed better quality of life and less renal impairment for NSS than for RN.<sup>[11]</sup> Comparable result is observed from the study by Kim et al which reported that mean tumors size in NSS was 3.63 cm and in RN 5.54 cm and there was statistically significant difference ( $p<0.001$ ).<sup>[12-13]</sup>

Most of the renal tumors are exophytic (82.6%) in group-A and endophytic (78.3%) in group-B. Although NSS is technically more difficult in centrally located lesions leading to longer ischemia times and increased incidence of collecting system injuries.<sup>[14-15]</sup>

In general, it is accepted that renal tumor enhancement of >15 Hounsfield units (HU) in CT is suggestive of a malignancy.<sup>[16]</sup> Usually, heterogeneous enhancement pattern is seen in clear-cell RCC compared with chromophobe and papillary RCCs.<sup>[17]</sup> In this study, almost all of the tumors had contrast enhancement and rest of the tumors have USG features of RCC but statistically no significant difference was present ( $p=0.489$ ). No study was reported relating to contrast enhancement, hydronephrosis and renal function.

In preoperative period, mean eGFR is more in group-A (75.22 ml/min) than in group-B (73.17 ml/min) due to small tumor size and more functioning renal parenchyma and have no significant difference ( $p>0.671$ ). Similar eGFR results were observed in the studies (71.4 vs. 71.3 ml/min,  $p>0.05$ )<sup>2</sup> and (80.2 vs. 78.2 ml/min;  $P >0.05$ )<sup>[18]</sup> The time depended changes of mean eGFR status at 1<sup>st</sup> POD is not significant ( $p=0.116$ ) but at 3<sup>rd</sup>, 7<sup>th</sup> POD and 3, 6, 9, 12 months, it becomes significant in both groups ( $p<0.05$ ) because of more residual functioning renal parenchyma present after NSS. Comparable result are noted by Mariusdottir et al. in which significant differences was observed postoperatively and after 6 months (56 vs. 44 ml/min,  $p<0.001$ ; 59 vs. 45 ml/min;  $p<0.001$ ). The mean eGFR decreased more significantly in group-B (18.56 ml/min) than group-A (6.31 ml/min) from preoperative to 12 months after operation and have significant differences ( $p<0.001$ ; table-V).

The time-dependent changes of eGFR after RN showed (Fig-I) plateau form initially and then gradually declining from the first postoperative day to the 12 postoperative months. In case of NSS, a lowest eGFR is observing in

postoperative day 1 and gradually recovered to near preoperative level for 12 months. eGFR in NSS patients were higher than RN in postoperatively. The compensatory hypertrophy after donor nephrectomy has previously been believed to be beneficial but compensatory hyperfiltration due to arterial vasodilatation with increased flow and pressure in the capillaries of the remnant glomeruli resulting in progressive sclerosis and eventually proteinuria, azotemia and hypertension but does not lead to long term decrease in renal function.<sup>[18]</sup>

Limitation of our study was small sample size, lack of longer follow up (only 12 months), surgery is performed by multiples surgeons, associated risk factors are not evaluated by logistic regression analysis.

## CONCLUSION

Although compensatory hypertrophy occurs in the early postoperative day in RN than NSS, renal functional outcome (eGFR) is more stable in NSS than RN due to functioning residual renal parenchyma. NSS is therefore the effective procedure for conservation of renal function.

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