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# Categorized Preoperative Estimated Glomerular Filtration Rate as a Criterion for Choosing Between Radical or Partial Nephrectomy for Renal Tumor

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## Abstract

**Purpose:** We examined retrospectively whether outcomes of radical nephrectomy (RN) and partial nephrectomy (PN) are predictable on the basis of preoperative estimated glomerular filtration rate (eGFR) classifications.

**Material and methods:** The study included 284 patients with renal tumor who underwent RN (n=195) or PN (n=89) at our institution. Preoperative eGFRs were categorized to reflect the stages of chronic kidney disease (CKD). The primary endpoint was postoperative onset of CKD stage 3b (eGFR<45 mL/min/1.73 $m^2$). Also examined were the incidence of postoperative cardiovascular (CV) events, overall survival (OS), and cause-specific survival (CSS). The outcomes of RN and PN were compared per the preoperative eGFR categories.

**Results:** PN was found to prevent postoperative CKD ≥ stage3b when the preoperative eGFR indicated CKD stage 2. The incidence of CV events was significantly low among patients with an eGFR indicative of CKD stage 3a and treated by RN. Regardless of patients' pre-operative eGFR, there was no significant difference between procedures in OS or CSS. Multivariate analysis showed RN to be an independent risk factor for CKD ≥ stage 3b in patients with a preoperative eGFR indicative of CKD stage 2.

**Conclusions:** In terms of postoperative renal function and CV events, the prognosis is equivalent for PN and RN when preoperative eGFR indicates CKD stage 1. However, PN is advisable when preoperative eGFR indicates CKD stage 2, and RN may be the better option when preoperative eGFR indicates CKD stage 3a. Categorized preoperative eGFR can serve as a reliable criterion for choosing between RN and PN.

**Keywords:** Kidney; Renal neoplasm; Nephrectomy; Preoperative; Renal function

## Abbreviations and Acronyms

CKD: Chronic Kidney Disease; CSS: Cancer Specific Survival; CV events: Cardiovascular events; eGFR: Estimated Glomerular Filtration Rate; OS: Overall Survival; PN: Partial Nephrectomy; RN: Radical Nephrectomy

## Introduction

For treatment of small renal tumors, partial nephrectomy (PN) yields the same oncological results as radical nephrectomy (RN), and it yields favorable outcomes in terms of overall survival (OS) as well as the incidences of chronic kidney disease (CKD) and postoperative cardiovascular (CV) events [1-7]. Thus, PN is generally preferred over RN. However the prospective, randomized, controlled European Organization for Research and Treatment of Cancer (EORTC 30904) study reported opposite outcomes in terms of 10 year OS and freedom from CV death [6,7]. Therefore no patterns were identified. It has been reported that when the post-RN or post-PN estimated glomerular filtration rate (eGFR) is <45 mL/minute/1.73 $m^2$, the OS decreases significantly; thus, the low eGFR indicates a rise in measured independent risk factors and risk of postoperative CV events. This value has been reported as a possible critical cut-off value [4,8-14].

In several previously reported studies that compared prognoses between PN and RN, we had doubts about the common lumping all preoperative renal function values together although the patients had a variety of preoperative eGFR values and the common use of a postoperative eGFR of <60 mL/min/1.73 $m^2$ as a study endpoint [5,6,15-17]. To date, there have been no reported studies that used preoperative renal function to compare the prognoses associated with RN and PN, much less to evaluate patients with a renal tumor to determine which procedure is appropriate. In addition, it is unclear whether PN actually decreases the risk of CV events and/or improves life expectancy.

If preoperative renal function were to be classified and postoperative onset of CKD ≥ stage 3b (postoperative eGFR of <45 mL/min/1.73 $m^2$) were to be used as a study endpoint, would new light would be shed on the commonly accepted advantages of each procedure? Furthermore, what new light would be shed on each procedure in terms of the incidence of postoperative CV events, OS, and cause-specific survival (CSS)? To answer these questions, we categorized preoperative eGFRs as indicative of the stages of CKD [18,19] and performed a

retrospective study comparing the surgical procedures in terms of postoperative renal function, postoperative CV events, and OS and CSS in light of patients' preoperative eGFRs. We also examined whether preoperative RN or PN was most beneficial for patients in light of the preoperative eGFRs.

## Methods

### Patients

Our study group comprised 284 patients with a renal tumor treated by RN (n=95) or PN (n=89) between 1994 and 2013 at Kyorin University Hospital. Patients with a preoperative eGFR of <45 mL/min/1.73 $m^2$ or who had been monitored for less than 6 months were excluded from the study. Selection between RN and PN was based on the size of the tumor, its location in the kidney, and its characteristics. Surgery was performed by laparotomy or by laparoscopy.

### Variables examined

Patients' clinical characteristics were reviewed, and preoperative and postoperative eGFRs were calculated according to the Modification of Diet in Renal Disease (MDRD) Study equation: eGFR=186 × sCr - 1.154 × age - 0.203 (× 0.742, for females) [20]. Staging was based on the National Kidney Foundation guidelines [18,19] that is, CKD stage 1 (eGFR ≥ 90 mL/min/1.73 $m^2$), stage 2 (eGFR 60-89 mL/min/1.73 $m^2$), stage 3a (eGFR 45-59 mL/min/1.73 $m^2$) and ≥ stage 3b (eGFR ≤ 45 mL/min/1.73 $m^2$). The primary endpoint was onset of CKD stage 3 or higher (eGFR <45 mL/min/1.73 $m^2$). Secondary endpoints were a postoperative CV event, OS, and CSS. Postoperative eGFR was measured at 1 month, 3 months, 6 months and 1 year after surgery and every year thereafter.

## Statistical Analysis

Group differences in continuous variables were analyzed by Mann-Whitney U test and ANOVA, and in categorical variables were analyzed by chi-square test. Kaplan-Meier curves were drawn for postoperative onset of CKD ≥ stage 3b, postoperative CV events, OS, and CSS and were analyzed by log rank test. Univariate and multivariate Cox proportional hazards regression analysis was carried out to investigate whether the type of procedure (RN or PN) had an effect on the postoperative onset of CKD ≥ stage 3b or postoperative CV events. All statistical analyses were carried out with SAS *vs.* 9.4 (SAS Institute Inc., Cary, NC, USA). A p value <0.05 was accepted as statistically significant.

## Results

Patients' clinical characteristics are shown in table 1.Median age was 62.5 years and 65 years in the RN and PN groups, respectively, and male patients made up 67.2% and 68.5% of the groups, respectively. Median body mass index was 22.1 kg/$m^2$ and 23.8 kg/$m^2$, respectively. Preoperative CKD stages (based on eGFR classification) were as follows: stages 1 to 3a, n=284 (stage 1, n=52 (18.3%); stage 2, n=171 (60.2%); stage 3a, n=61 (21.5%). There were no significant differences in the tumor size (p=0.73) and ischemic time of PN (p=0.99) among CKD stage 1, 2 and 3a. The proportion of patients with hypertension was 46.1% and 37.2%, respectively (p=0.17).

The proportion of patients with diabetes was 13.0% and 21.0%, respectively (p=0.08). The proportion with hyperlipidemia was 11.7% and 15.7%, respectively (p=0.35). The proportion of patients who has previously suffered a CV event was 11.7% and 15.7%, respectively (p=0.35), and that of patients with non-clear cell cancer was 22.6% and 30.3%, respectively (p=0.18). The proportions of patients with a malignant tumor differed significantly (95.4% *vs.* 82.0%, respectively; p<0.001). The median follow-up period for RN and PN was 51.6 months and 43.6 months, respectively.

| | **Total patients*** | **RN** | **PN** | |
|---|---|---|---|---|
| | **n=284** | **n=195** | **n=89** | **p Value** |
| | | | | - |
| Preoperative eGFR: CKD1 | 52 | 31 | 21 | - |
| Preoperative eGFR: CKD2 | 171 | 118 | 53 | - |
| Preoperative eGFR: CKD3a | 61 | 46 | 15 | - |
| Median age (IQR | 62.5 (51.25-71) | 65 (54-72) | 60 (48-71) | 0.151 |
| % Male (n) | 67.6 (192) | 67.2 (131) | 68.5 (61) | 0.821 |
| Median body mass index (IQR, Kg/m2) | 22.7 (20.6-25.2 | 22.1 (20.1-23.4) | 23.8 (21.3-24.3) | 0.26 |
| % Hypertension | 41.4 | 46.1 | 37.2 | 0.167 |
| % Diabetes mellitus | 15.4 | 12.95 | 20.93 | 0.089 |
| % Hyperlipidemia | 13.7 | 13 | 15.1 | 0.64 |
| % Cardiovascular disease | 12.9 | 11.64 | 15.73 | 0.345 |

| | | | | |
|---|---|---|---|---|
| Median pre eGFR (IQR, mL/min/1.73 m2) | 71.9 (61.5-85.7) | 69.3 (60.6-79.7) | 76.5 (65.6-89.7) | 0.005 |
| Median follow-up (IQR, months) | 49.0 (31.2-71.5) | 51.6 (32.2-75.9) | 43.624.5-62 | 0.085 |
| % Non-clear cell type (n) | 25.0 (71) | 22.6 (44) | 30.3 (27) | 0.184 |
| % Carcinoma (n) | 91.2 (259) | 95.4 (186) | 82.0 73 | 0.001 |
| *The 284 study patients were treated between 1994 and 2013 and did not include 15 patients with a preoperative eGFR < 45 mL/min/m2 (CKD3b-5) and treated during the same period.<br>eGFR, estimated glomerular filtration rate; CKD1, CKD2, CKD3, chronic kidney disease stages 1, 2, 3. | | | | |

**Table 1:** Clinical characteristics of study patients treated by radical or partical nephrectomy (RN or PN).

Kaplan-Meier curves for the onset of CKD ≥ stage 3b are shown per preoperative eGFR classification in When the preoperative eGFR was indicative of CKD stage 2, onset of CKD ≥ stage 3b was seen significantly fewer patients in the PN group than in the RN group (p<0.001) (Figure 1). When the preoperative eGFR was indicative of CKD stage 1 or stage 3a, there was no significant difference in the onset of CKD ≥ stage 3b between the 2 groups. In addition, the results of univariate and multivariate analyses showed RN to be an independent risk factor for postoperative CKD ≥ stage 3b when the preoperative eGFR was indicative of CKD stage 2 (Table 2).

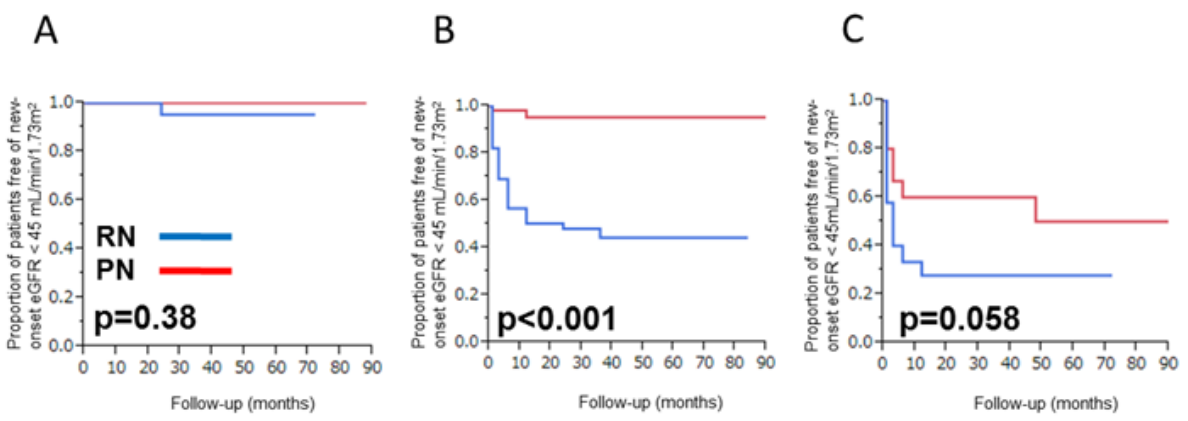


**Figure 1:** Kaplan-Meier curves for the new onset of CKD ≥stage 3b are shown per preoperative eGFR classification. A, preoperative eGFR: CKD stage 1. B, preoperative eGFR: CKD stage 2. C, preoperative eGFR: CKD stage 3a. With a preoperative eGFR indicative of CKD stage 2, onset of CKD ≥stage 3b was seen in significantly fewer patients in the PN group than in the RN group (p<0.001). With a preoperative eGFR indicative of CKD stage 1 or stage 3a, there was no significant difference in the onset of CKD ≥stage 3b between the 2 groups.

| | | **Univariate** | | **Multivariate** | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p Value | HR (95% CI) | p Value |
| **Preoperative eGFR: CKD1** | | | | | |
| | Operation (RN vs. PN) | - | 0.999 | - | - |
| | Age | 1.02(0.85-1.25) | 0.753 | - | - |
| | Sex | - | 0.999 | - | - |
| | BMI | 0.95(0.37-1.78) | 0.882 | - | - |
| | Hypertension | - | 0.999 | - | - |
| | Diabetes mellitus | - | 1 | - | - |
| | Hyperlipidemia | - | 1 | - | - |

| | | | | | |
|---|---|---|---|---|---|
| **Preoperative eGFR: CKD2** | | | | | |
| | Operation (RN vs. PN) | 32.2 (8.32-223) | <0.001 | 28.57 (8.22-181) | <0.001 |
| | Age | 1.03 (1.00-1.07) | 0.038 | 1.04 (1.01-1.07) | 0.01 |
| | Sex | 0.75 (0.32-1.72) | 0.496 | - | - |
| | BMI | 1.00 (0.96-1.00) | 0.757 | - | - |
| | Hypertension | 1.71 (0.75-3.93) | 0.204 | - | - |
| | Diabetes mellitus | 2.36 (0.73-8.67) | 0.167 | - | - |
| | Hyperlipidemia | 0.73 (0.27-2.30) | 0.585 | - | - |
| **Preoperative eGFR: CKD3** | | | | | |
| | Operation (RN vs. PN) | 1.41 (0.23-7.87) | 0.697 | - | - |
| | Age | 1.04 (0.97-1.11) | 0.295 | - | - |
| | Sex | 0.69 (0.19-2.59) | 0.58 | - | - |
| | BMI | 1.00 (0.04-1.16) | 0.964 | - | - |
| | Hypertension | 3.36 (0.85-15.6) | 0.096 | - | - |
| | Diabetes mellitus | 1.67 (0.29-14.2) | 0.591 | - | - |
| | Hyperlipidemia | 0.57 (0.10-3.31) | 0.519 | - | - |

eGFR, estimated glomerular filtration rate; CKD1, CKD2, CKD3, chronic kidney disease stages 1, 2, 3; RN, radical nephrectomy; PN, partial nephrectomy; BMI, body mass index.

**Table 2:** Results of univariate and multivariate analysis of risk factors for new-onset eGFR <45 mL/min/1.73 $m^2$.

Kaplan-Meier curves for postoperative CV event-free survival are shown per preoperative eGFR classification. There were no deaths from postoperative CV events. When the preoperative eGFR was indicative of CKD stage 3a, the incidence of postoperative CV events was higher in the PN group than in the RN group. When the preoperative eGFR was indicative of CKD stage 1 or stage 2, there was no significant between-group difference in post-procedural CV events. Hypertension was identified as a risk factor when the preoperative eGFR was indicative of CKD stage 2 (p<0.001), and RN was identified as a risk factor when the preoperative eGFR was indicative of CKD stage 3a (p<0.001) (Table 3).

| | | **Univariate** | | **Multivariate** | |
|---|---|---|---|---|---|
| | | HR (95% CI) | p Value | HR (95% CI) | p Value |
| **Preoperative eGFR: CKD1** | | | | | |
| | Operation (RN vs. PN) | <0.00 | 1.000 | - | - |
| | Age | 5.77 | 1.000 | - | - |
| | Sex | <0.00 | 1.000 | - | - |
| | BMI | 0.16 | 1.000 | - | - |
| | Hypertension | 0.18 | 1.000 | - | - |
| | Diabetes mellitus | <0.00 | 1.000 | - | - |
| | Hyperlipidemia | 6 | 1.000 | - | - |
| **Preoperative eGFR: CKD2** | | | | | |
| | Operation (RN vs. PN) | 0.26 (0.06-1.07) | 0.063 | - | - |
| | Age | 1.03 (0.96-1.10) | 0.441 | - | - |

| | | | | | |
|---|---|---|---|---|---|
| | Sex | - | - | - | - |
| | BMI | 1.00 (1.00-1.01) | 1 | - | - |
| | Hypertension | 0.04 (0.00-0.31) | 0.008 | 15.48 (2.85-288) | 0.010 |
| | Diabetes mellitus | 1.26 (0.25-7.47) | 0.783 | - | - |
| | Hyperlipidemia | 0.33 (0.06-1.75) | 0.178 | - | - |
| **Preoperative eGFR: CKD3** | | | | | |
| | Operation (RN vs. PN) | 0.04 (0.00-0.03) | 0.009 | 0.15 (0.03-0.64) | 0.012 |
| | Age | 1.06 (0.97-1.18) | 0.239 | - | - |
| | Sex | 3.60 (0.47-41.5) | 0.238 | - | - |
| | BMI | 1.09 (0.93-1.30) | 0.305 | - | - |
| | Hypertension | 1.02 (1.23-9.73) | 0.985 | - | - |
| | Diabetes mellitus | 5.53 (0.79-55.4) | 0.100 | - | - |
| | Hyperlipidemia | 0.282 (0.02-2.94) | 0.330 | - | - |

eGFR, estimated glomerular filtration rate; CKD1, CKD2, CKD3, chronic kidney disease stages 1, 2, 3; RN, radical nephrectomy; PN, partial nephrectomy; BMI, body mass index.

**Table 3:** Results of univariate and multivariate analysis of risk factors for new-onset cardiovascular events after renal surgery.

Comparison of the Kaplan-Meier curves for OS per preoperative eGFRs showed no significant difference in between RN and PN. Likewise, comparison of the Kaplan-Meier curves for CSS per preoperative eGFRs showed no significant difference between RN and PN (Figure 2).

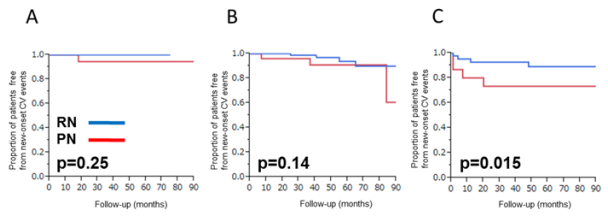


**Figure 2:** Kaplan-Meier curves for postoperative CV event-free survival are shown per preoperative eGFR classification. A, preoperative eGFR: CKD stage 1. B, preoperative eGFR: CKD stage 2. C, preoperative eGFR: CKD stage 3a. There were no deaths from postoperative CV events. With a preoperative eGFR indicative of CKD stage 3a, the incidence of postoperative CV events was higher in the PN group than in the RN group. With a preoperative eGFR indicative of CKD stage 1 or stage 2, there was no significant between-group difference in post-procedural CV events.

## Discussion

This investigation was based on categorization of preoperative eGFR, a factor not previously emphasized, to compare the prognoses associated with RN and PN. Our study results suggest the following: First, with respect to the likelihood of non-development of CKD ≥ stage 3b, PN is more effective than RN only when the preoperative eGFR indicates CKD stage 2. There is no significant difference when the preoperative eGFR indicates CKD stage 1 or 3a. The type of procedure is an independent risk factor only when the preoperative eGFR indicates CKD stage 2. Second, with respect to postoperative CV events, there is no significant difference in the incidence when the preoperative eGFR indicates CKD stage 1 or 2. However, when the preoperative eGFR indicates CKD stage 3a, CV events are more likely after PN than after RN. The results of multivariate analysis show that the type of procedure is an independent risk factor when preoperative eGFR indicates CKD stage 3a. Third, there is no significant difference in the OS or CSS, regardless of the preoperative eGFR.

Most recent studies have used a new onset of postoperative eGFR <60 mL/min/1.73 $m^2$ as the endpoint and the postoperative eGFR as an evaluation index. Huang et al. reported that patients treated by RN have a 36% probability and patients treated by PN have a 5% probability of developing an eGFR of <45 mL/min/1.73 $m^2$ within 3 years. RN is a significant risk factor for the postoperative development of CKD [15]. The risk is 13%, 61%, 24%, and 2% when the preoperative eGFR indicates CKD stage 1, 2, 3a, and 3b, respectively [15]. This could be attributed to the fact that CKD stage 2 patients accounted for more than 60% of the patients. Sun et al. compared RN and PN and reported that patients who underwent RN were 1.9 times more likely than those who underwent PN to have a postoperative eGFR of <60 mL/min/1.73 $m^2$ [16]. But in their study, CKD stage 2 patients were also the most numerous, and the postoperative renal function of these patients who underwent RN was significantly better than that of patients who underwent PN. Therefore, the results for this group are consistent with previously reported results. The meta-analysis conducted by Kim et al. showed a 61% decrease in postoperative CKD for patients who underwent PN rather than RN [5]. However, there was also a 29% decrease in CSS, which might have influenced the outcomes. We investigated preoperative renal function and found that patients with

CKD stage 1 or 3a who underwent PN did not necessarily have better renal function than that of patients who underwent RN.

Second, the EORTC 30904 prospective randomized controlled study reported 117 fatalities, 20 of which were post-RN CV-related deaths and 25 of which were post-PN CV-related deaths [6]. Although we had no CV-related deaths, this greater number of deaths in the PN group is consistent with results of our study. However, Kates et al. reported a rise in the risk of overall mortality and CV mortality in their RN group compared to the risk among their patients who underwent PN for small renal tumors [17]. In addition, Takeshita et al. reported a significant increase in the incidence of CV events when post-RN eGFR indicated CKD ≥ stage 3b; they showed postoperative but not preoperative eGFR to be a significant predictive factor [11]. These reports lump all preoperative renal function values together, and in the latter report, there was no comparison with a PN group.

Factors that are related to a decline in renal function and increase CV events include hyperfunction of the renin-angiotensin system and intravascular inflammation due to cytokine-induced oxidative stress [21]. The high incidence of CV events associated with a preoperative eGFR indicative of CKD stage 3a in our PN group point to ischemic stress related to the kidney surgery. Other factors may be necrosis of surrounding renal tissue caused by the sutures and thrombus formation. Performance of PN when the preoperative eGFR indicates CKD ≥ stage 3b leaves the patient with renal dysfunction and possibly a negative outcome.

Third, the results we obtained are consistent with previous reports of absence of a significant difference in oncological outcomes between RN and PN [1,2]. In the intention to treat analysis, the EORTC 30904 reported 81.1% OS in the RN group and 75.5% OS in the PN group 10 years after surgery, with a 1.59 (p=0.03) relative risk [6]. However, preoperative renal function was not considered; serum creatinine was used, making it impossible for us to perform a simple comparison.

Our study is the first to show that the preoperative eGFR can be categorized and used for patient evaluation when determining either RN or PN is appropriate. Categorizing the preoperative eGFR is particularly useful because it is reflects the CKD stage. Furthermore, results of this study were useful in describing the results of previous studies that did not show a pattern.

Our study was limited first by the fact that it was a retrospective, single-institution study. Second, the observation period was relatively short. The time required for evaluating postoperative renal function [22,23] and the time required for observation are unclear. The use of new-onset CKD ≥ stage3b compensates somewhat for the short observation time. Further investigations may make it possible to identify more specific evaluation criteria when choosing between RN and PN. It may even become possible to practice individualized treatment based on the various renal tumors.

## Conclusions

In terms of postoperative renal function and postoperative CV events, the prognosis is the same for PN and RN when preoperative eGFR indicates CKD stage 1. However, PN appears to be advisable when preoperative eGFR indicates CKD stage 2, and RN may be the better option when preoperative eGFR indicates CKD stage 3a. This is the first report to show that categorized preoperative eGFR can be used as a reliable criterion for choosing between RN and PN in patients with a renal tumor.

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