

## Comparison of Overall Survival after Nephron-Sparing Surgery and Radical Nephrectomy on the Basis of Preoperative Renal Function and Tumor Size

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### Abstract

**Objective:** To compare the overall survival (OS) between radical nephrectomy (RN) and nephron-sparing surgery (NSS) by preoperative estimated glomerular filtration rate (eGFR) and tumor size.

**Methods:** Patients with cT1 renal tumors (N0M0) treated by RN or NSS between 1994 and 2014 were included. OS was compared by the surgical technique using Kaplan- Meier curves for the whole population. Then, subgroup analyses for OS were performed by the presence (< 60 ml/min/1.73 m<sup>2</sup>) or absence (≥ 60 ml/min/1.73 m<sup>2</sup>) of preoperative chronic kidney disease (CKD) and by cT1a and cT1b disease status. Multivariate analysis was also performed.

**Results:** 440 patients were included. There was no significant difference in OS by the surgical technique, including in patients with CKD. However, the group without CKD had a significantly better OS than the group with CKD. Moreover, compared with RN, the use of NSS was associated with a significantly better OS for patients without CKD, including those with cT1a tumors. There were no significant differences when OS was compared by the surgical technique in patients with CKD or cT1b tumors. Multivariate analysis showed that preoperative eGFR and tumor size were independent risk factors in the total population and the group without CKD, respectively.

**Conclusion:** We have shown that NSS can be beneficial for patients with preoperative non-CKD and stage cT1a tumors. RN and NSS produce comparable OS in patients with unfavorable preoperative renal function or tumor size. Further investigation is needed with larger populations.

**Keywords:** Chronic kidney disease; Nephron-sparing surgery; Overall survival; Preoperative renal function; Radical nephrectomy; Renal cell carcinoma; Tumor size

### Introduction

Nephron-sparing surgery (NSS) is considered preferable to radical nephrectomy (RN) for small renal tumors. NSS offers the same oncological benefits as RN, including low onset of postoperative chronic kidney disease (CKD), good overall survival (OS), and few cardiovascular events [1-11].

Interestingly, Thompson et al. reported that NSS offered superior OS than RN in patients with T1a tumors [2]; however, there was no significant difference between NSS and RN in those with T1b tumors [6]. However, the only prospective, randomized comparative trial (EORTC 30904) has indicated that although NSS offered better postoperative renal function, the 10 year OS rate was significantly improved after RN [12,13]. The reasons for the results of the EORTC study are discussed in a study by Lane et al. [14]. They investigated whether CKD, which developed before or after kidney surgery, affected survival and reported that no correlation existed between the postoperative estimated glomerular filtration rate (eGFR) and OS in patients with a preoperative eGFR ≥ 60 ml/min/1.73 m<sup>2</sup>.

To date, there has been no direct comparison of OS between RN and NSS considering the role of preoperative eGFR and tumor size using Kaplan- Meier curve analyses. Therefore, we studied patients with cT1a and cT1b tumors, with and without preoperative CKD, to compare OS following RN and NSS according to preoperative eGFR and tumor size.

### Materials and Methods

#### Patients

Patients with cT1a or T1b (all N0M0) malignant renal tumors who underwent RN or NSS between 1994 and 2014 at Kyorin University Hospital were included. Patients observed for fewer than 6 months and those with missing data were excluded. Selection of NSS or RN was determined based on tumor size, position within the kidney, and patient status. Either open or laparoscopic surgery was performed.

#### Procedures

eGFR values were categorized relative to surgery as preoperative (most recent eGFR before surgery), postoperative (eGFR obtained after surgery).

Our analysis was based on the methods used by Lane [14]. First, OS was compared on the basis of the surgical technique in the parent population. Next, the sample population was divided into two groups to compare OS on the basis of preoperative eGFR as follows: a group with a preoperative eGFR  $\geq 60$  ml/min/1.73 m<sup>2</sup> (i.e., the non-CKD group) and a group with a preoperative eGFR  $< 60$  ml/min/1.73 m<sup>2</sup> (i.e., the CKD group). OS was also compared on the basis of the surgical technique in both the CKD and non-CKD groups, and then the CKD and non-CKD groups were divided into cT1a and cT1b groups for further comparison.

Multivariate Cox proportional hazards regression analysis was performed on the total sample population and on the CKD and non-CKD groups. Preoperative eGFR was calculated using the abbreviated equation from the Cleveland Clinic Laboratory for the Modification of Diet in Renal Disease Study [15]:  $eGFR = 186 \times sCr^{-1.154} \times age^{-0.203}$  ( $\times 0.742$  if female). Tumor size was defined as the maximum tumor diameter according to preoperative images. The characteristics of renal tumors were quantified using the RENAL nephrometry score [16]. The comorbidities were measured by the Charlson index [17].

### Statistical analysis

For comparisons between RN and NSS, continuous variables were examined using the Mann–Whitney U test, and categorical variables

were examined using the chi-square test. OS was analyzed using Kaplan–Meier curves and compared with the log-rank test. Cox proportional hazards regression analyses were performed to investigate independent risk factors for OS. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and a p-value  $< 0.05$  was considered statistically significant.

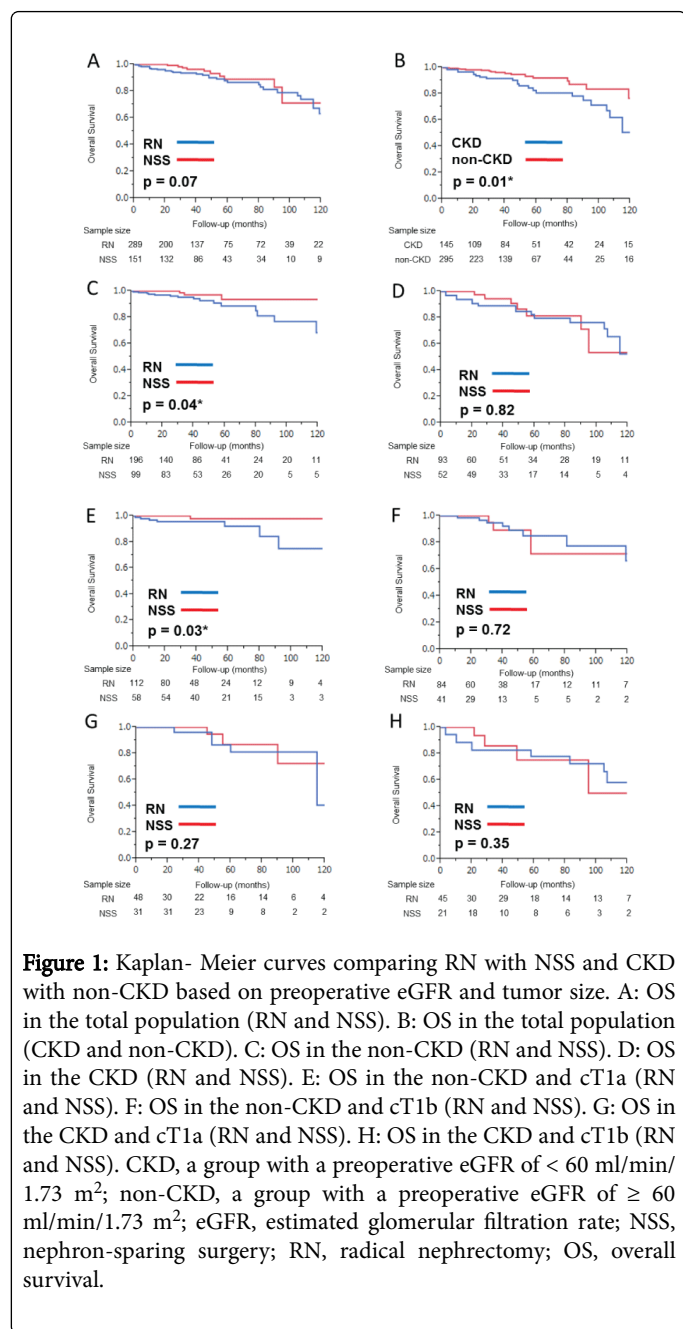
## Results

### Participants

The clinical characteristics of the 440 participants are shown in Table 1. Among these, RN and NSS were performed on 289 and 151 patients, respectively. Compared with the NSS group, the age of the RN group was slightly higher ( $p = 0.02$ ). Although there was a male preponderance in both groups, there was no significant between-group difference. There were also non-significant, minor differences in the median body mass index and mean Charlson comorbidity index as well as in the proportions of patients with hypertension, diabetes mellitus, and non-clear cell cancer. However, there were significant differences in the median preoperative eGFR, median tumor size, and median RENAL nephrometry score.

Feature	RN (n = 289)	NSS (n = 151)	p value
	Mean (median; range)		
Age at surgery, years	63.3 (65; 26-86)	60.4 (60; 33- 86)	0.02
Body mass index, kg/m <sup>2</sup>	23.1 (22.3; 13.6- 38.9)	23.3 (22.9; 17.6- 32.5)	0.2
Charlson comorbidity index	0.63 (0; 0- 1)	0.52 (0; 0- 1)	0.18
Preoperative eGFR, ml/min/1.73 m <sup>2</sup>	70.6 (68.2; 45.2- 121.4)	78.8 (76.5; 49.1- 120.9)	$< 0.001$
Clinical tumor, cm	4.6 (4.0; 1.2- 7.0)	3.0 (2.8; 1.0- 7.0)	$< 0.001$
RENAL nephrometry score	8.25 (9; 4- 11)	6.55 (6; 4- 11)	$< 0.001$
Gender (%)			0.72
Male	70.3	72	
Female	29.7	28	
Hypertension (%)	44.4	40.3	0.41
Diabetes mellitus (%)	14.6	16.6	0.22
Non-clear cell type (%)	13.5	11.3	0.3
Operation (%)			
Open	87.3	54.6	$< 0.001$
Laparoscopic	12.7	45.4	$< 0.001$

**Table 1:** Patient characteristics based on the type of surgery. eGFR: Estimated glomerular filtration rate, RN: Radical nephrectomy, NSS: Nephron-sparing surgery.



**Figure 1:** Kaplan- Meier curves comparing RN with NSS and CKD with non-CKD based on preoperative eGFR and tumor size. A: OS in the total population (RN and NSS). B: OS in the total population (CKD and non-CKD). C: OS in the non-CKD (RN and NSS). D: OS in the CKD (RN and NSS). E: OS in the non-CKD and cT1a (RN and NSS). F: OS in the non-CKD and cT1b (RN and NSS). G: OS in the CKD and cT1a (RN and NSS). H: OS in the CKD and cT1b (RN and NSS). CKD, a group with a preoperative eGFR of < 60 ml/min/1.73 m<sup>2</sup>; non-CKD, a group with a preoperative eGFR of ≥ 60 ml/min/1.73 m<sup>2</sup>; eGFR, estimated glomerular filtration rate; NSS, nephron-sparing surgery; RN, radical nephrectomy; OS, overall survival.

### Comparison of RN and NSS overall and by subgroup

When the RN and NSS groups were compared in the total population, there was no significant difference in OS between the groups (p = 0.07, Figure 1A). However, when that population was then divided into non-CKD and CKD groups, OS was significantly better in the non-CKD group (p = 0.01, Figure 1B). Comparing OS according to the surgical technique in each group, OS was significantly better for NSS than for RN in the non-CKD group (p = 0.04, Figure 1C), but there was no significant difference between RN and NSS in the CKD group (p = 0.82, Figure 1D).

Further analysis by dividing the non-CKD group into cT1a and cT1b groups indicated that OS was significantly better for NSS than for

RN in the cT1a group (p = 0.03, Figure 1E) but that there was no significant difference between RN and NSS in the cT1b group (p = 0.72, Figure 1F). A similar investigation was then performed in the CKD group, but no significant difference was found in terms of OS according to the surgical technique between the cT1a and cT1b groups (p = 0.27, p = 0.35; Figures 1G, 1H).

In the total population there were significant differences in the median preoperative eGFR and tumor size (Table 1). However OS was compared between RN and NSS with using stratified preoperative eGFR and tumor size. Therefore in each subgroup there was no significant difference in the preoperative eGFR and tumor size between RN and NSS (data not shown).

### Multivariate analysis

The results of multivariate Cox proportional hazards regression analysis showed that preoperative eGFR (p = 0.03) and tumor size (p < 0.001) were independent risk factors in the total population and non-CKD groups, respectively. There were no significant factors in the CKD group (Table 2).

	All Pts		CKD		non-CKD	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.05 (0.98-1.12)	0.1542	0.96 (0.78-1.21)	0.6978	1.15 (1.00-1.40)	0.0147
Gender	0.46 (0.09-3.39)	0.3972	-	0.6124	0.35 (0.02-4.65)	0.3143
Body mass index	0.92 (0.76-1.11)	0.4135	1.01 (0.69-1.47)	0.9216	0.72 (0.41-1.16)	0.0715
Charlson comorbidity index	0.32 (0.09-0.83)	0.0179	3.03 (0.18-122.9)	0.7227	-	0.0572
Preoperative eGFR	0.94 (0.88-0.99)	0.0306	0.69 (0.42-1.00)	0.061	0.90 (0.77-0.99)	0.0214
Clinical tumor size	1.01 (0.99-1.02)	0.4944	1.01 (0.97-1.04)	0.5255	1.16 (1.07-1.34)	0.0001
Nephrectomy (vs. NSS)	1.02 (0.28-4.24)	0.9777	0.24 (0.35-0.01)	0.3507	0.50 (0.02-15.10)	0.7497

**Table 2:** Multivariate Cox regression analysis of risk factors for overall survival. CI: Confidence interval, CKD: a group with a preoperative eGFR of < 60 ml/min/1.73 m<sup>2</sup>, non-CKD: a group with a preoperative eGFR of ≥ 60 ml/min/1.73 m<sup>2</sup>, eGFR: estimated glomerular filtration rate, HR: Hazard ratio, RN: Radical nephrectomy, NSS: Nephron-sparing surgery.

### Discussion

In the present study, OS was compared according to the surgical technique, preoperative eGFR and tumor size in patients with cT1a

and cT1b renal cell carcinoma (cT1N0M0). Our major results are summarized in Table 3. We report that NSS was associated with better OS in the non-CKD group with cT1a tumors and that there were no

significant differences in OS according to the surgical technique between the non-CKD group with cT1b tumors and the CKD group.

cT1N0M0 RCC patients			
OS: no significant difference			
preoperative eGFR < 60 ml/min/1.75 m <sup>2</sup> (CKD)		preoperative eGFR < 60 ml/min/1.75 m <sup>2</sup> (non-CKD)	
OS: no significant difference		OS: RN < NSS	
Tumor size: cT1b	Tumor size: cT1a	Tumor size: cT1b	Tumor size: cT1a
OS: no significant difference	OS: no significant difference	OS: no significant difference	OS: RN < NSS

**Table 3:** Summary of the main results. CKD: A group with a preoperative eGFR of < 60 ml/min/1.73 m<sup>2</sup>; non-CKD: A group with a preoperative eGFR of ≥ 60 ml/min/1.73 m<sup>2</sup>; eGFR: Estimated glomerular filtration rate; NSS: Nephron-sparing surgery; RN: Radical nephrectomy; OS: Overall survival.

In the total population there were significant differences in the median preoperative eGFR and tumor size (Table 1). However OS was compared between RN and NSS with using stratified preoperative eGFR and tumor size. Therefore in each subgroup there was no significant difference in the preoperative eGFR and tumor size between RN and NSS.

Most retrospective studies of the preferred surgical technique for obtaining the best OS have reported that RN is inferior to NSS [1-11]. Among these, Thompson et al. reported that in patients with T1a tumors, NSS offered superior OS than RN [2], whereas there was no significant difference between NSS and RN in patients with T1b tumors [6]. These studies also indicated that tumor size had a major influence on OS [2,6]. In comparison, the EORTC 30904 study indicated that RN was superior [12,13], showing postoperative 10 year OS rates of 81.1% and 75.5% for RN and NSS, respectively, with a relative risk of 1.59 (p = 0.03). This was explained by Lane et al. [14], who showed no correlation between postoperative renal function and OS in patients without medically induced CKD [Lane described with surgically induced CKD (CKD-S)]. However, Thompson [18] indicated that it remained questionable whether the results of the EORTC 30904 study [12,13] could be applied to the CKD-S model because the EORTC study evaluated preoperative renal function with creatinine rather than eGFR, and they included creatinine scores that were higher than normal; moreover, although tumor size in the EORTC study was limited to < 5 cm, some patients with T1b tumors would have been included in addition to those with T1a tumors. Furthermore, Lane et al. did not perform a direct comparison between OS for RN and NSS using Kaplan-Meier curves, and they did not investigate the effect of tumor size. When comparing OS for RN and NSS, it is necessary to consider at least the preoperative eGFR and tumor size in the total population.

Our data support and build upon the previous research. No significant difference between RN and NSS was showed in the total population when it was not classified based on preoperative eGFR and tumor size (p = 0.07, Figure 1A), which was consistent with the results of the EORTC 30904 report [12,13]. When the total population was then divided into non-CKD and CKD groups, the finding that OS was better in the non-CKD group (p = 0.01, Figure 1B) was consistent with the results of the Lane et al. study [14]. However, we also report the following new findings, in addition to those described in the previous research: OS was significantly better for NSS than for RN in the non-

CKD group (p = 0.04, Figure 1C); there was no significant difference between RN and NSS in the CKD group (p = 0.82, Figure 1D); OS was significantly better for NSS than for RN in the non-CKD group with cT1a tumors (p = 0.03, Figure 1E); and, there were no significant differences between RN and NSS in the non-CKD group with cT1b tumors, the CKD group with cT1a tumors, and the CKD group with cT1b tumors (p = 0.72, p = 0.27, p = 0.35; Figure 1F, 1G, 1H). Multivariate Cox proportional hazards regression analysis of OS in the non-CKD group was used to confirm that tumor size was the strongest independent risk factor (p < 0.001, Table 2).

Thus, OS is expected to change with the distributions of preoperative eGFR and tumor size in the population. It is plausible that this may have influenced the various conflicting results seen in previous studies. Indeed, when compared with RN, NSS is expected to impose greater stress on the residual renal parenchyma (e.g., ischemia and sutures) and to have greater potential for causing hypertension and major injury to the vascular and collecting systems in the early postoperative period [19-22]. In addition, the pathological stage of the tumor increases as the tumor diameter increases, thereby lowering OS. When preoperative renal function is adequate and the tumor size is small, there is a large amount of postoperative renal reserve. Therefore, the remnant renal tissue may be able to compensate for the harmful effects that occur after NSS, and it may be that the full benefits of NSS are being achieved. Meanwhile, because there is little postoperative renal reserve in patients with poor preoperative renal function or large tumors, the harmful effects of NSS may not be able to be compensated for, which probably decreases OS.

This study has some limitations. Notably, it was a retrospective study conducted at a single facility and with a small patient population. However, compared with the study by Lane et al., which was based on the OS results in the EORTC, our investigation increased the number of variables considered. If our findings can be confirmed and expanded upon in a larger sample, preoperative criteria for RN and NSS that are associated with improved outcomes could be identified.

## Conclusion

In the present study, OS was compared according to the surgical technique in patients with stage cT1N0M0 renal cell carcinoma using preoperative eGFR and tumor size for subgroup analyses. We showed that the benefits of NSS apply to patients with a preoperative eGFR ≥

60 ml/min/1.73 m<sup>2</sup> and stage cT1a tumors, and that there was no difference in OS between RN and NSS in patients with an unfavorable preoperative renal function or tumor size. Further investigation in larger populations is needed in the future.

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Study concept and design, analysis and interpretation of data, drafting of the manuscript, statistical analysis: Yamaguchi.

**Critical revision of the manuscript for important intellectual content:** Okegawa, Nutahara, Yamaguchi.

**Supervision:** Yamaguchi, Okegawa and Nutahara.

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