



CKD Outcomes after Nephron Sparing Surgery with Non-Ischemia vs. Radical Nephrectomy for Renal Cell Carcinoma

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Abstract

Purpose: Recently, Partial Nephrectomy (PN) is not inferior to Radical Nephrectomy (RN) concern about cancer specific survival in small renal cell. PN is now standard for clinical stage T1 Renal Cell Carcinoma (RCC). We evaluate whether no-ischemic PN provided keeping renal functional outcomes compared with RN.

Material and Methods: From 1993 to 2009, 226 patients with RCC underwent extirpative surgery, PN (75) or RN (151). PN was treated with non-ischemic procedure. The inclusion criteria were as follows: Patients have been inspected regularly more than three years, and end-point was to ten years. Renal function (eGFR) was measured at pre-operation, 1-month, 1-year, 3-years, 5-years and 10-years after operation.

Results: Preoperative e-GFR of PN and RN are similar (74.9 ± 14.8 to 74.4 ± 24.8 ml/min/1.73 m²). However, e-GFR of RN is lower than that of PN (1 month 48.8/71.1, 1 year 49.7/68.0, 3 years 50.5/69.1, 5 years 51.5/67.9, 10 years 50.0/66.9 ml/min/1.73 m²). Preoperative CKD G1+G2 rate of PN and RN were similar (23% + 49% and 22% + 52%). But, the rate of RN at 1 month after operation was deteriorated comparison with PN through all periods until ten years. CKD G4+G5 rate of RN is increased at ten years later (14%) comparison with preoperative rate (3%). While, that of PN is not changed between preoperative rate (3%) and ten years later (4%).

Conclusion: Renal functional of PN is superior to RN for clinical stage T1. PN is complete surgical excision and should be strongly considered for prevention of postoperative CKD. PN should be recommended in most patients with small RCC.

Keywords: CKD outcomes; Partial nephrectomy; Radical nephrectomy; Renal cell carcinoma

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Introduction

At the present, an abdomen ultrasound test and CT have been used abundantly as primary diagnostic apparatus in medical treatment. As a result, diagnosis of a small renal tumor (cT1) has increased. About surgical treatment for cT1 renal cell cancer, there were Partial Nephrectomy (PN) and Radical Nephrectomy (RN). Traditionally, for solitary located small renal tumor, radical nephrectomy is gold standard operative strategy for recent 40 years. Partial nephrectomy is indicated for patients in whom radical nephrectomy would result to end stage renal failure [1], such as patients with solitary kidney, bilateral renal tumors and conservative renal injury. In recent years, health check is popular using Ultra-Sonic tomography (US) or Computed Tomography (CT) recently, and the incidental renal tumor has been increased. More than 70% of diagnosed renal cell cancer is small cT1 renal carcinoma [2]. In late years there are a lot of literatures that PN is better renal function compared with RN. For important point, PN is equivalent oncological outcomes to RN [3,4]. PN is now recognized as recommended standard surgical treatment of small renal cell tumor (T1a) as nephron sparing technique [5].

Microwave Tissue Coagulation (MTC) is useful to control bleeding in case of vessel abundant solid organ surgery such as liver. As for this surgical technique, it is adapted to PN with small renal tumor in Japan [6]. And, this procedure with MTC is applied to non-ischemic PN because of control bleeding. The other side, there is limit for PN with clumping the renal vessels as ischemic methods.

Concrete limit time is less than 30 min [7], but it is very difficult to resect tumor and control hemorrhage in limited time.

In comparison to radical nephrectomy, partial nephrectomy is associated with a lower risk of postoperative renal insufficiency [8]. Additionally, recent efforts have demonstrated that outcomes after RN is higher risk about cardio vascular events and survival rate [9].

By focusing on CKD of renal insufficiency after PN and RN, we discuss the predominance of long time follow-up post these operations.

Material and Methods

From 1993 to 2009, 75 PN patients (55 men and 20 women: mean age 62.1 ± 12.3 years) and 151 RN patients (112 men and 39 women: mean age 61.3 ± 12.3 years) with renal mass underwent each surgery in Nara Medical University Hospital.

The diabetic patients were excluded to evaluate renal functions in this study. These patients could follow up more than three years after operation, and cancer death cases were not included in this study. And, contralateral nephrectomy cases in PN patients were excluded, because renal function could not assess. After operation of both groups, the renal function of estimated Glomerular Filtration Rate (eGFR) measured it as follows at a period, pre-operation, 1 month, 1 year, 3 years, 5 years and 10 years after each surgery.

Characteristics of PN group and RN group

There were no significant difference about age and gender. The rate of Incidental tumors to symptomatic tumors is 90.7% (68/75) in PN group, and that of RN group is 47.7% (72/151). There is significant difference between two groups ($p < 0.0001$). Concerning about T staging of each group, almost cases were low stage in PN group, but there were many high stage in RN group ($p < 0.0001$). Tumor size of PN group is smaller than that of RN group ($p < 0.0001$).

Pre-operative eGFR of PN groups were $73.5 \text{ mL/min/1.73 m}^2$, and that of RN were $74.4 \text{ mL/min/1.73 m}^2$, there was no significant difference in both groups. The distribution of pre-operative CKD staging was similar in both groups, and there was no significant difference in both groups (Table 1).

Operative method of PN

PN has been accepted as nephron sparing surgery for small renal cell carcinoma recently. And PN is recommended because of chronic renal disease for long time outcomes. In our institute, PN was performed using microwave coagulation without occlusion of the renal vasculature [6]. The coagulation line was marked by electrocautery surround renal tumor with surgical margin of 5 mm from the tumor edge. Kidney microwave coagulation was performed using a Microtaze AMZ-520[®] (Alfresa-Pharma, Osaka, Japan) with monopolar needle electrode 15 mm long and 0.6 mm diameter. Kidney was punctured along coagulation line with the needle electrode. And the kidney parenchyma was coagulated, and the tumor was excised with scissors by cutting middle line of the coagulated zone.

Statistical analysis

Unadjusted statistical association between the type or renal surgery and patient characteristics were analyzed using chi-square test and adjusted association were estimated using Mann-Whitney test. We used the Wilcoxon T test to compare the renal function of pre and post-operation in both groups of RN and PN.

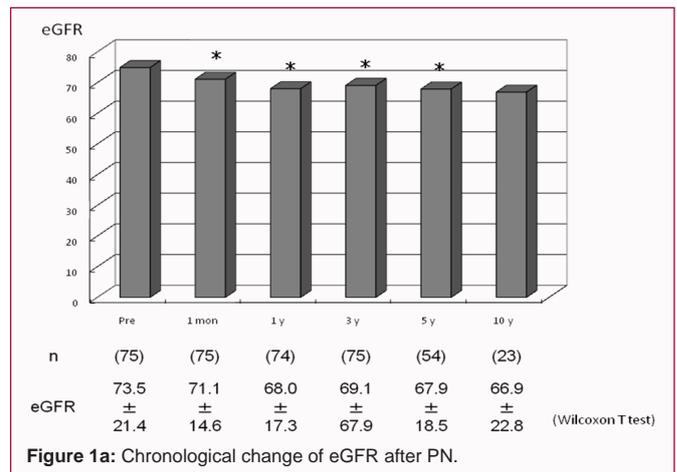


Figure 1a: Chronological change of eGFR after PN.

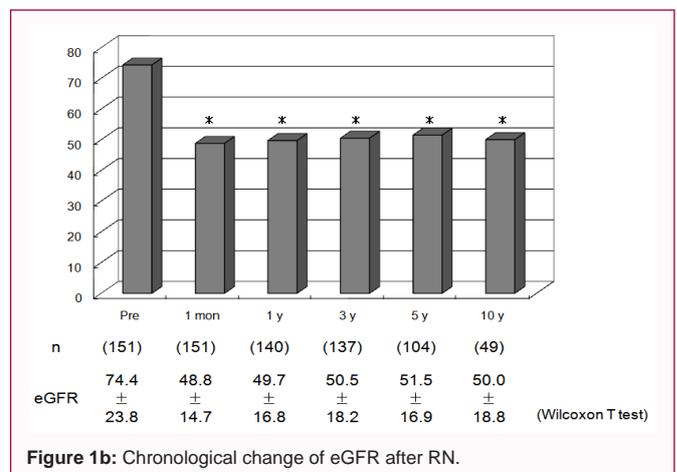


Figure 1b: Chronological change of eGFR after RN.

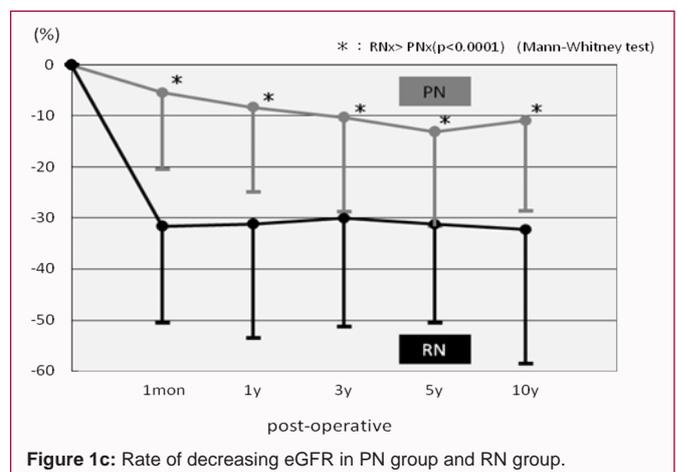


Figure 1c: Rate of decreasing eGFR in PN group and RN group.

Results

Chronological changes of eGFR after PN and RN

Previously it was mentioned that the mean preoperative eGFR of each groups were almost same, and there was no significant difference. But, each chronological changes of eGFR after PN and RN were remarkable different. The mean preoperative eGFR was $73.5 \text{ mL/min/1.73 m}^2$ in PN group, and its level of eGFR decreased to $71.1 \text{ mL/min/1.73 m}^2$ one month later, and there was significant decreasing renal function. The increase degree of renal function lasted afterward to 10 years later. On the other hand, the mean preoperative

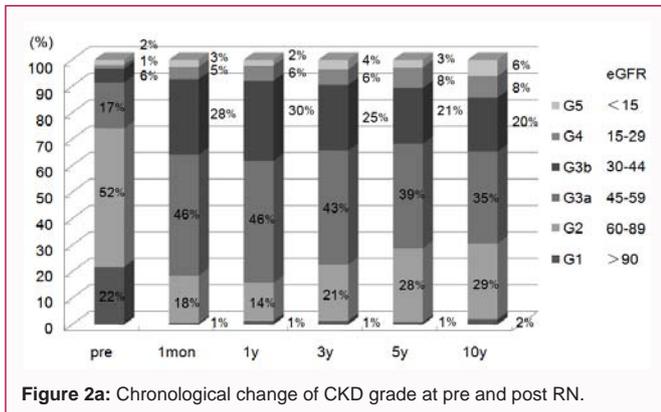


Figure 2a: Chronological change of CKD grade at pre and post RN.

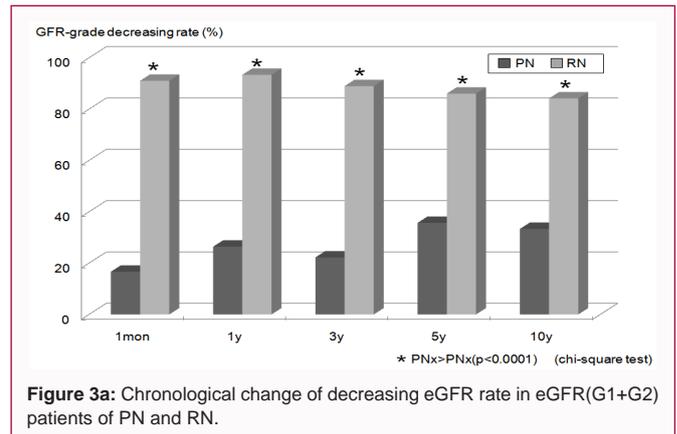


Figure 3a: Chronological change of decreasing eGFR rate in eGFR(G1+G2) patients of PN and RN.

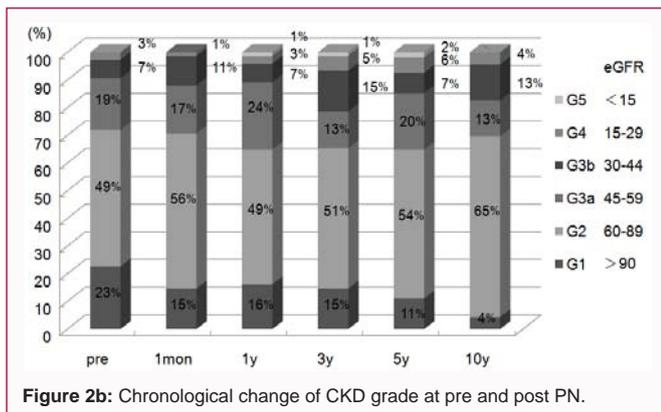


Figure 2b: Chronological change of CKD grade at pre and post PN.

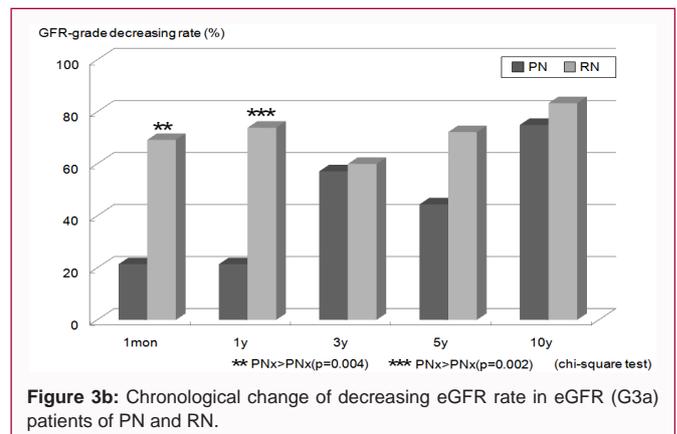


Figure 3b: Chronological change of decreasing eGFR rate in eGFR (G3a) patients of PN and RN.

eGFR was 74.4 mL/min/1.73 m² in RN, and its level eGFR after one month decreased same as PN significantly. However, the degree of the decreasing eGFR after one month was more remarkable than PN. After then, the degree of the degradation of eGFR lasted until the tenth year without being improved (Figure 1a and 1b). Through all course of two groups until post-transplantation tenth year, a significant difference was recognized for renal function of an eGFR marker. As for the renal function of eGFR, 34.4% decreased in RN group after renal transplantation one month later. However, the decrement rate was 3.3% in PN group (Figure 1c).

Chronological change of CKD grade at pre and post RN and PN

A change of postoperative CKD grade is important for the patient. At a time when grade of CKD became grade 5 after operation, the patient must consider the therapy such as dialysis or renal transplantation for end stage renal failure disease state. In this study of RN and PN, there were no cases of dialysis therapy becomes necessary. Concerning about CKD, a ratio of preoperative CKD grade 1+2 was 74%, but it was decreased to 19% at one month later post RN group. And, a ratio of preoperative CKD grade 4+5 was 3%, but it was increased to 8% at one month later post RN. And the deterioration of CKD was maintained to postoperative 10 years. A matter is that the patients of CKD grade 5 are increasing in number with 6% ten years after a postoperative (Figure 2a). The patient of this CKD grade 5 has a high turn probability to renal replacement therapy.

On the other hand, in the PN group, a ratio of preoperative CKD grade 1+2 was 72%, and the ratio of postoperative 1 month was 71% which was almost same with the preoperative ratio. This tendency was maintained till 10 years after PN. And a ratio of preoperative CKD grade 4+5 was 3%, its ratio was not changed in all the course up

to 10 years (Figure 2b).

Chronological decreasing change of CKD grade 1+2 and CKD grade 3a

CKD grade 1+2 has a normal renal function, and CKD grade 3a is a pathosis that mild renal function is impaired. In this condition of CKD 1+2+3a, renal replacement therapy is not required. Preoperative CKD 1+2 number was 112 in RN and 91.0% of these cases has deteriorated below CKD 3a after 1 month post RN. But, PN preoperative number was 54 cases of CKD 1+2, and only 16.6% of these cases did worse below CKD 3a after 1 month post PN (Figure 3a).

Concerning about CKD grade 3a, this grade cases before surgery in RN was 23 cases. 67% of these 23 cases had become worse in the following CKD 3b after 1 month post-surgery. In addition, 76% of these cases had become worse in the following CKD 3b after 1 year post-surgery. On the other hand, in PN this grade 3a cases before surgery was 19 cases. 20% of these 19 cases had become worse in the following CKD grade 3b after 1 month post-surgery. And 20% of these cases had become worse in the following CKD grade 3b after 1 year post-surgery. Both of PN and RN went worse from 3 years after surgery up to 10 years. But RN is tended worse than PN (Figure 3b).

Analysis of risk factor deteriorating less than postoperative CKD 3b in preoperative CKD 1+2+3a

If CKD grade 1+2+3a case once worth to CKD grade 3b+4+5, it becomes necessary to various treatment. For example a case of CKD grade 3b is required stricter renal functions to rage treatment. And, CKD grade 4+5 is necessary to consider a renal replacement therapy in the near future. The risk factors for the development of renal

Table 1: Characteristics of PNx and RNx.

	RNx (n=151)	PNx (n=75)	p-value
Age	61.3 ± 12.3	62.1 ± 12.3	0.654
Gender (M/F)	112/39	55/20	0.892
Pre-ope eGFR (mL/min/ 1.73m ²)	74.4 ± 23.8	73.5 ± 21.4	0.786
Pre-ope CKD stage (1/2/3a/3b/4/5)	33/79/26/8/2/3	17/37/14/5/2/0	0.803
Incidental/Symptomatic	72/79	68/7	<0.0001
T staging (1/2/3/4)	89/19/39/4	70/2/0/0	<0.0001
Grading (1/2/3)	15/113/17	15/53/3	0.031
Histology (clear/not clear)	122/26	57/7	0.337
Tumor size (mm)	59.2 ± 30.2	28.9 ± 12.3	<0.0001
Ope methods (open/laparo)	145/5	72/3	0.799
Ope time (mins)	216 ± 98.8	176 ± 58.3	0.001
Bleeding (mL)	929 ± 3182	371 ± 426	0.135

Table 2: Analysis of the risk factors deteriorating less than postoperative CKD3b in preoperative CKD1+2+3a.

Variables		Univariate analysis		Multivariate analysis		
		Hazard ratio	p value	Hazard ratio	95% C.I.	p value
Age	60	1		1		
	60-69	3.542	<0.0001	2.293	1.142-4.605	0.02
	70	4.688	<0.0001	3.426	1.623	0.001
Gender	M	1				
	F	0.853	Ns			
Preoperative CKD stage	G1	1		1		
	G2	5.09	0.003	3.266	1.090-9.790	0.035
	G3a	12.339	<0.0001	8.12	2.718-24.258	<0.001
Operative method	PNx	1		1		
	RNx	2.805	0.004	3.533	1.737-7.270	0.001
Operation	open	1				
	Lapalo	1.292	ns			
Ope time	<190 min	1				
	≥ 190 min	1.248	ns			
Bleeding	<350 mL	1				
	≥ 350 mL	1.205	Ns			

insufficiency have analyzed in preoperative CKD 1+2+3a cases. The factors of age of over 60 years old (yo), gender, preoperative CKD at aging, operative methods of PN and RN, operative procedure of open and lapalo, operation time and amount of bleeding were analyzed by both of Univariate Analysis (UA) and Multivariate Analysis (MA) of Hazard Ratio (HR). Consequently, the influence factor for renal insufficiency were the age of over 60 yo (60 to 69 yo: $p < 0.0001$, over 70 yo: $p < 0.0001$ by UA of HR. $p = 0.02$ $p = 0.001$ by MA), the preoperative CKD stage of G2 and G3a for G1 (G2: $p = 0.003$, G3a: $p < 0.0001$ by UA of HR. $p = 0.035$ $p < 0.0001$ by MA of HR). This result showed that HR of RN against PN was 2.805 by UA, and that by MA was 3.533 respectively. Comparing the PN and RN, RN is factors which predominantly worsen renal function (Table 2).

Discussion

Before various clinical diagnostic imaging becomes possible, it was difficult to diagnose kidney cancer. Initial symptoms of kidney cancer were abdominal mass and hematuria. And, when kidney

cancer could be diagnosed, it had already progressed in many cases. In recent years, advances in medical devices have been remarkable in diagnosis and staging for various diseases. These days, in the inspection of a general complete physical examination, ultrasonic diagnostic equipment is always used. For a whole body inspection, all the internal organs are inspected and the kidney is inspected correctly similarly.

Detection of small renal tumor has been increased because that Computed tomography and ultrasound have been popular for healthy check. The progress in ultrasonographic image diagnosis is astonishing. As a result, surgery number of cases with small renal tumor has been gradually increased. Especially in the advanced nations where medical technology progressed, the diagnostic rate of a small renal cancer is high by the spread of medical checkups. Ultrasonic examination is now common, and any small clinic is equipped with this medical machine. It is not uncommon for small kidney cancer to be found during examination of organs other than kidney. Furthermore, ultrasound examination is almost indispensable

in general group health examination. Now, it has also been installed in most of the facility CT examination, and it is not a rare chance that small renal tumor is found in the inspection of other diseases [10].

There are some various operative methods for renal tumor, such as radical nephrectomy, partial nephrectomy (nephron sparing surgery) and cryosurgery. Traditionally these tumors have been treated most often with radical nephrectomy. But radical nephrectomy disposes these patients to chronic kidney disease with attendant cardiovascular diseases [11]. In relation of risk factor of chronic renal failure, RN is about 12 times higher than PN. PN is recommended if the size of a renal cancer is from 4 cm to 7 cm (4 Thompson RH). Current guideline of the American Urological Association and the European Association of Urology for the management of T1 RCC recommend nephron-sparing surgery for small RCC (all T1a and amenable T1b cases) [5,12]. The PN rates in the management of small renal masses have increased remarkably in the 21 century, and this phenomenon show a paradigm shift in the treatment of small renal masses [13].

Regarding surgical methods of small kidney cancer, endoscopic surgery has become popular recently from invasive open surgery. The surgical treatment of a small renal cancer has come to be performed by robotic surgery Robot Assisted Partial Nephrectomy (RAPN) in a recent [14]. Compared to open surgery, endoscopic surgery including robotic surgery has become less frequent in bleeding volume and it became a very safe surgical method.

Small renal cancer may be benign histologically but there are cases where there is no need for surgery in all cases compared with small kidney cancer showing malignant findings.

A renal carcinoma small has many cases of a benign tumor at the histologic diagnosis in recent reports [15,16]. Therefore, when a small renal carcinoma is diagnosed, the patient does an active surveillance in many cases without undergoing an operation [13]. Active surveillance should be an initial management option for patients who have significant comorbidities and limited life expectancy [17,18].

The most important goal is maintaining a renal function post renal surgery. Generally, as for the patient who experienced radical nephrectomy and partial nephrectomy, the number of nephrons decreases as compared with the status of a preoperative [19]. Nephron sparing surgery provides effective therapy for patients in whom preservation of renal is relevant clinical consideration [20].

In the case of radical nephrectomy, its nephron number will be about half. Therefore, radical nephrectomy is more likely to become renal failure in the future as compared with partial nephrectomy. Compared with RN, PN was associated with a marked reduction in the incidence of clinically significant CKD and with enhanced survival [21]. And the 3-year probability of freedom from new onset of GFR less than 60 mL/min/1.73 m² was 80% after partial nephrectomy but only 35% after radical nephrectomy (P<0.01) [9]. Also in our study renal function was good even with partial resection for 10 years. The renal function decreased by about 5% in the third month after surgery and decreased to 12% in the fifth year, but there was no downward trend thereafter. While radical nephrectomy decreased its renal function by 30% after 1 month, and reduced renal function did not improve thereafter. Renal function between the 2 groups showed a significant difference at any time after surgery. And, concerning about the chronological change of CKD grade at pre and post RN, the proportion of CKD G1 decreases 10 years after PN, but the ratio of CKD 1+2 does not change. On the other hand, about the kidney

total extirpation, although the percentage of preoperative CKD 1+2 was 74%, the ratio of ten years after was getting worse with 31%. The impairment of CKD which needs a kidney alternative therapy is grade 4+5. The percentage of postoperative 10 year CKD 4+5 of a RN is 14%, and it of a PN is 4%. As mentioned above, the PN is more useful to the renal function of a long term than to RN. Even when PN was performed with extended ischemia, PN is associated with renal function outcomes superior to those of RN for small renal cell cancers [22].

CKD is recognized as illness which threatens the health of much global population. The age-adjusted mortality rate of CKD patients is still high and comparable to that of many malignancies, in spite of marked improvements in renal replacement therapy for these 20 to 30 years. Persistent inflammation is increasingly recognized as most complications of CKD, accounting in part for endothelial dysfunction, vascular calcification, cardiovascular and all-cause mortality. Renal insufficiency has significant impact of mortality on cardiovascular events in patients with RN for renal cancer [23]. In a community-based cohort with mild renal insufficiency, renal insufficiency is common and is associated with CKD [24]. Cardiovascular Disease (CVD) remains the major cause of morbidity and mortality in CKD patients. It was explained that the malnutrition-inflammation-atherosclerosis syndrome was the cause as an aggravation factor of CVD in CKD patients [25]. CKD is characterized by an exceptional high risk of mortality; the cause of a disease which should be apprehended is a result of aggravation of CVD [26]. The risks of death and cardiovascular events were evident at an estimated GFR of less than 60 ml per minute per 1.73 m² and substantially increased with an estimated GFR of less than 45 ml per minute per 1.73 m². And an independent, graded association was recognized between decreased eGFR and risks of mortality and cardiovascular event [27]. The nephrectomy patient has a high possibility that the renal function is decreasing. The nephrectomy patient has a high possibility that the renal function is decreasing. On the other hand, Najarian et al. [28] reported that average serum creatinine level was 1.1 mg/dL and GFR was only reduced 20% following up for a minimum of 20 years after kidney transplant donor nephrectomy. However, the donor's renal function was normal completely, and their average age of donors was 43 years compared with 61.2 years in our RN group. Considering having always merged Acute Kidney Injury (AKI), the nephrectomy patient cannot generally compare a donor patient with a nephrectomy patient.

Although PN for small renal cancer is associated with better Overall Survival (OS) compared with RN, recurrence of postoperative cancer is also an important problem after PN and RN. There are uncertainties about oncological outcomes for PN and RN of small localized RCC. Positive surgical margins in PN specimens do not uniformly portend an adverse prognosis [29]. And, it was reported that the Cancer-Specific Survival (CSS) and Recurrence-Free Survival (RFS) seem to be similar for patients underwent PN and RN [30]. From this report, it became clear that the oncological outcomes of PN were not inferior as compared with RN. RN contributes a survival advantage and a reduction of CKD disease after operation [19].

Conclusion

The various guidelines have recommended the partial nephrectomy for a small renal cancer. The most important reason is preservation of the renal function after PN. It is necessary to also take introduction of a kidney alternative therapy into consideration

according to aggravation of CKD.

Furthermore, a morbidity and mortality also becomes high. In this study, patients that received a PN had a reduced risk of CKD when compared with patient of RN. PN to a small renal cancer is a cure advanced from a viewpoint of renal function preservation.

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