



Risk of Chronic Kidney Disease After Nephrectomy for Renal Cell Carcinoma

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The incidence of low-stage renal cell carcinoma is rising and is observed to demonstrate excellent prognosis following surgical treatment irrespective of method. However, several epidemiologic observational and population-based studies suggest that radical nephrectomy is associated with increased adverse renal outcomes such as chronic kidney disease (CKD) compared with partial nephrectomy. This is suggested in turn to lead to increased mortality via an increase in cardiovascular complications and mortality. Prospective data are scarce, and there are conflicting data as well on whether surgically induced CKD is as debilitating as medically induced CKD. Further research is needed to assess the presence and the extent of the relationship between nephrectomy, CKD, and noncancer mortality.

Keywords: Nephrectomy; Renal cell carcinoma; Renal insufficiency, chronic

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INTRODUCTION

Renal cell carcinoma (RCC) is the third most common malignancy in the genitourinary tract [1]. Its incidence has been rising, especially in the past 2 decades, mainly owing to advancements in diagnostic radiographic modalities and increased utilization of abdominal imaging for unrelated purposes. In Korea in the past decade alone, the incidence rate increased from 3.0 per 100,000 in 1999 to 5.2 per 100,000 in 2010 in both sexes [2]. In 2010, a total of 3,598 new cases were diagnosed, and the annual percentage rate increase was estimated at 6.1%. As a result of the increase in incidentally detected renal tumors, stage at RCC diagnosis has decreased, with T1 tumors making up more than half of the newly diagnosed cases [3,4].

Current guidelines from the American Urological Association or the European Association of Urology for the management of T1 RCC recommend nephron-sparing surgery for all T1a and amenable T1b cases [5,6]. These recommendations were based on the demonstration of oncological equivalence of partial nephrectomy compared to radical nephrectomy for these tumors and the rising recognition of the health significance of chronic kidney disease (CKD) following radical nephrectomy. T1 tumors are more

intensely investigated because they constitute the majority of cases, are technically amenable for nephron-sparing surgery, and demonstrate excellent prognosis with adequate surgical intervention alone, which thus mandates long-term consideration of other competing risks for survival and quality of life.

In this review, we describe the epidemiology of CKD, discuss the risks and consequences of CKD following radical or partial nephrectomy for RCC, and present controversial issues that remain to be elucidated with the aim of better understanding the natural history and progression of CKD after nephrectomy.

CKD AS A PUBLIC HEALTH PROBLEM

The definition of CKD is kidney damage for longer than 3 months confirmed by pathologic abnormalities in biopsy samples or by markers of kidney damage such as proteinuria, with or without changes in the glomerular filtration rate (GFR), or GFR less than 60 mL/min/1.73 m² for longer than 3 months with or without kidney damage [7]. CKD is increasingly being recognized as a significant public health problem in Korea as well as worldwide [8]. The incidence and prevalence have been steadily and continuously rising,

followed by an increase in associated complications and deteriorations in general health conditions. In Korea, the number of people with newly diagnosed end-stage renal disease (ESRD) requiring some form of renal replacement therapy was over 10,000 in 2011, totaling 63,000, which was more than 0.1% of the entire population. Comparing the number to the total of 2,500 patients in 1986, the annual rate increase was estimated to be approximately 5%, which is higher than in other countries [9]. Extrapolating from this data, the number of patients with CKD could be estimated to be over 100,000, approximating 1% of the population, and also increasing.

Survival of patients with ESRD is reported to be lower than in the general population by 30%, most importantly because of the increase in associated complications. In a recent report, 51% and 47% of Korean patients receiving hemodialysis and peritoneal dialysis, respectively, had vascular diseases including hypertension and cerebrovascular accident [10]. Furthermore, with an additional 17% and 18% of patients complicated with cardiac disease, the most common cause of death in this population was cardiovascular disease.

CKD AND NEPHRECTOMY

Since 1969 and until recently, the standard treatment for all renal masses presumed to be RCC was radical nephrectomy [11]. Radical nephrectomy results in adequate long-term cancer control, and observations from large-scale kidney donor studies have suggested that the health effects of rendering these patients with a single renal unit were not significant [12-14]. However, RCC patients differ from kidney donors. Whereas kidney donors are a screen-selected group of people in good health, of a younger age, and with good health habits, patients with RCC are often older and frequently have various medico-surgical comorbidities including hereditary disorders and social as well as lifestyle risk behaviors. Kidney donors are selected on the basis of their good baseline kidney function, whereas kidney function is deteriorated in up to 30% of RCC patients ($\text{GFR} < 60 \text{ mL/min/1.73 m}^2$) at diagnosis before surgery [15,16]. Furthermore, in contrast to preexisting studies, contemporary evidence suggests that not only several donor subgroups [17,18] but the entire donor population itself is at higher risk for ESRD compared with matched healthy nondonors, as early as at a median of 7.6 years [19].

Patients with RCC are especially at higher risk for development and progression of CKD after nephrectomy, even when other risk factors are accounted for. In a retrospective analysis comparing 173 patients who underwent radical nephrectomy with 117 patients who underwent partial nephrectomy, McKiernan et al. [20] reported that after a median follow-up of 25 months postoperatively, 16 patients (9%) after radical nephrectomy had developed CKD (Table 1). No one after partial nephrectomy had developed CKD and serum creatinine was significantly higher in patients who underwent radical nephrectomy (1.5 mg/dL vs.

1.0 mg/dL, $p < 0.001$) despite similar preoperative creatinine concentrations (1.0 and 0.98 mg/dL, $p=0.4$) and risk factors for renal insufficiency in the two groups. In this single-center analysis, patients in the study differed in terms of age (radical vs. partial, 63 years vs. 57 years, $p < 0.001$) and tumor size (2.9 cm vs. 2.3 cm, $p < 0.001$). Also, use of serum creatinine as a marker of renal function in the study limits the study results because serum creatinine is influenced substantially by muscle mass, body habitus, and food contents. Day-to-day variability is substantial and the value itself may be inaccurate in the extremes of age [21].

Using estimated GFR as a measure of renal function in a retrospective cohort of 662 patients who had normal preoperative creatinine, Huang et al. [15] compared the impact of partial or radical nephrectomy for T1a RCC on the risk of postoperative CKD. Despite a normal serum creatinine level before surgery, CKD was present in 26% of the patients. Following surgery, the 3-year probability of freedom from new onset CKD was 35% after radical nephrectomy compared with 80% after partial nephrectomy. Three years after surgery, radical nephrectomy was estimated to increase the risk of developing CKD 3.8 folds compared with partial nephrectomy (95% confidence interval [CI], 2.75-5.32). The results were similar after longer follow-up. In another study from a cohort of 328 patients who underwent radical or elective partial nephrectomy for T1a RCC between 1966 and 1969 and who were followed for 10 years, patients were matched for pathology, tumor size, age, and gender [22]. The 10-year follow-up cumulative incidence of chronic renal insufficiency was 22.4% and 11.6% following radical and partial nephrectomy, respectively (hazard ratio [HR], 3.7; 95% CI, 1.2-11.2).

Studies on Korean data are scarce and current reports are limited in sample size and retrospective design. However, the results are similar to what has been published previously. In 89 Korean patients who underwent radical nephrectomy and were followed for longer than 5 years, CKD was observed in 43 patients (48.3%) at the end of follow-up [23]. In 561 patients with T1a RCC, the mean GFR decreased from 83.0 mL/min/1.73 m² before surgery to 58.4 mL/min/1.73 m² at 1 year after radical nephrectomy [24]. In 76 patients who underwent radical nephrectomy and inferior vena cava thrombectomy, the incidence of postoperative CKD was 32.9% with a mean follow-up of 22.9 months [25]. In a retrospective comparative study of 79 and 29 Korean patients who underwent radical and partial nephrectomy with normal baseline renal function, 36.1% and 3.8%, respectively, were found to have new onset CKD after surgery ($p < 0.001$) [26]. In a recent analysis of 1676 patients with T1a RCC who underwent radical or partial nephrectomy, Kim et al. [27] reported a CKD incidence of 34.8% for radical nephrectomy and 5.4% for partial nephrectomy and that radical nephrectomy was associated with an increased risk of CKD (odds ratio [OR], 11.89; 95% CI, 7.98-17.69; $p < 0.001$).

TABLE 1. Summary of comparative studies assessing CKD after radical and partial nephrectomy

Source	Period	Design	Patient sample	Patients	Variable	Results of CKD	Follow-up (mo)
McKiernan et al. [20]	1989-2000	Retrospective	Single institution	RN 173 PN 117	Serum creatinine	Sixteen patients (9%) after RN had developed CKD. No one after PN had developed CKD.	Median, 25
Huang et al. [15]	1989-2005	Retrospective	Single institution	RN 204 PN 287	eGFR	The 3-year probability of freedom from new onset CKD was 35% after RN compared to 80% after PN. RN was estimated to increase the risk of developing CKD 3.8 folds compared to PN, 3 years after surgery.	Median, 19
Lau et al. [22]	1966-1999	Retrospective, matched	Single institution	RN 164 PN 164	Serum creatinine	The cumulative incidence of CKD was 22.4% and 11.6% following RN and PN, respectively.	10 yr after surgery
Kim et al. [27]	2001-2011	Retrospective	Single institution	RN 605 PN 1071	eGFR	Surgical type (PN or RN; OR, 11.89) was significant as postoperative risk factor for CKD.	Mean, 37-47
Kong et al. [26]	2003-2010	Retrospective	Single institution	RN 79 PN 29	eGFR	Patients who underwent RN and PN with normal baseline renal function, 36.1% and 3.8% respectively were found to have new onset CKD after surgery.	-
Sun et al. [28]	1988-2005	Retrospective, matched	Population based	RN 840 PN 840	eGFR	CKD was observed in 20.1% of patients after RN and 11.4% of patients after PN. RN increased the risk of CKD 1.9 fold compared to PN.	60 after surgery
Klarenbach et al. [32]	2002-2007	Retrospective	Population based	Total 1,151 RN 80% PN 20%	eGFR	RN (vs. PN) was associated with increased risk of developing composite adverse renal outcomes with a hazard ratio of 1.75.	Median, 32
Mariusdottir et al. [33]	2000-2010	Retrospective, matched	Population based	RN 44 PN 44	eGFR	RN was associated with increased risk of CKD development, at 6 months postoperatively.	Median, 44
Van Poppel et al. [35]	1992-2003	Prospective, randomized	EORTC-GU trial 30904	RN 273 PN 268	eGFR	PN reduced risk of CKD by 21% at 6.7 years. However, at 9.3 years after surgery, 25% of patients after PN and 18.3% of patients after RN died, both most commonly due to cardiovascular disease.	Median, 9.3 yr

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PN, partial nephrectomy; RN, radical nephrectomy; OR, odds ratio.

POPULATION-BASED STUDIES OF CKD AFTER NEPHRECTOMY

Risk of CKD after nephrectomy for RCC was confirmed in several retrospective population-based studies. Using the data of 4633 T1a RCC patients from the United States (US) Surveillance Epidemiology and End Results (SEER)-Medicare-linked cohort, Sun et al. [28] demonstrated that radical nephrectomy increased the risk of CKD 1.9 folds compared to partial nephrectomy. In the analytic cohort, which included 840 patients carefully matched on propensity scores, CKD was observed in 20.1% of patients after radical nephrectomy and 11.4% of patients after partial nephrectomy, and the difference in CKD development between the surgical methods was observed as soon as 36 months after surgery and increased thereafter. Additional population-based studies from the US have shown similar results. However, all of the study populations were derived from the SEER registry at different but overlapping time

periods. Whereas all of the SEER-linked cohort studies point to radical nephrectomy as an independent risk factor for postoperative CKD and increased mortality by approximately 30% [29-31], caution needs to be taken in interpreting these studies because they all came from the same data source.

On the other hand, in a retrospective study using the population-based data of 1,151 Canadian patients treated between 2002 and 2007, Klarenbach et al. [32] demonstrated that radical nephrectomy was associated with increased risk of developing composite adverse renal outcomes, which included acute dialysis, CKD, rapidly progressive CKD, and ESRD (radical vs. partial; HR, 1.75; 95% CI, 1.02-2.99). Adverse renal outcomes were observed in 10.5% of the entire study cohort at less than 3 years after surgery and patients with lower baseline GFR or proteinuria were shown to be at higher risk. Another retrospective study from Iceland that included all Icelandic patients who underwent partial nephrectomy for RCC between 2000 and

2010, and corresponding radical nephrectomy patients matched for tumor size, TNM stage, and time of operation, also reported that radical nephrectomy was associated with increased risk of CKD development at 6 months post-operatively (GFR < 60 mL/min/1.73 m²; HR, 3.07; 95% CI, 1.03–9.79). The study population was small with a total of 88 patients but it included every member of the population who was operated on during the designated time period, and postoperative creatinine was uniformly measured at 6 months after surgery [33]. Six months after nephrectomy may not be sufficient, but as the investigators suggested, it has been reported that patients who develop CKD 6 months after surgery are unlikely to improve with further follow-up [34]. Further change may be difficult to attribute to one risk factor, especially when the patients are frequently complicated by various other medico-surgical comorbidities.

CONFLICTING VIEWS

While the results of most existing studies evaluating and comparing outcomes between radical and partial nephrectomy consistently agree that partial nephrectomy is associated with a decreased risk of CKD development and improved overall survival, all of these studies are limited in that they were single-center, retrospective analyses. To date, only one prospective, randomized clinical trial has compared long-term nononcological morbidity and mortality between radical and partial nephrectomy: the European Organisation for Research and Treatment of Cancer (EORTC) trial. A total of 541 patients with solitary renal tumors ≤ 5 cm were randomized to radical or partial nephrectomy and followed for a median of 9.3 years post-operatively [35]. The trial was closed prematurely because of poor accrual, and there was high crossover between the treatment groups. Notwithstanding the limitations, the results from EORTC trial were in clear contrast to previous studies and suggested more favorable outcomes after radical nephrectomy than partial nephrectomy. The intention-to-treat analysis showed that 10-year overall survival was 81% in the radical nephrectomy patients compared with 75% in the partial nephrectomy patients (HR, 1.5; 95% CI, 1.03–2.16). In a subgroup analysis, risk of CKD development was observed to be 85.7% following radical nephrectomy and 64.7% following partial nephrectomy, demonstrating that partial nephrectomy reduced the risk of CKD by 21% (95% CI, 13.8–28.3) at 6.7 years. Advanced CKD defined as GFR < 30 mL/min/1.73 m² was observed in 10% of radical nephrectomy patients and 6.3% of partial nephrectomy patients (95% CI, -1.0 to 8.5). At 9.3 years after surgery, 25% of patients after partial nephrectomy and 18.3% of patients after radical nephrectomy died, both most commonly due to cardiovascular disease. The discrepant finding of the EORTC trial that partial nephrectomy is associated with decreased risk of CKD development but increased all-cause mortality is in contrast to preexisting studies.

In all of the preexisting retrospective studies examining the impact of declining renal function on cardiovascular events, CKD was consistently demonstrated to be an independent risk factor for cardiovascular disease [36–38]. Nephrectomy and sudden reduction in renal unit could adversely impact patient's survival outcomes. However, current evidence suggests that these effects may be selective. In a single-center cohort of 648 patients with normal baseline renal function who underwent radical or partial nephrectomy for T1a RCC, radical nephrectomy was demonstrated to be associated with higher overall mortality (risk ratio, 2.02–2.34, with adjustment for variables that included year of operation, preoperative creatinine, Charlson-Romano index, sex, symptoms at presentation, constitutional symptoms at presentation, and malignant histology). But the association was observed only in the subset of patients less than 65 years of age and not in older patients or the entire cohort [39]. On the other hand, Huang et al. [29] analyzed SEER-Medicare linked data of 2991 patients older than 66 years treated for T1a renal tumors between 1995 and 2002 demonstrating that radical nephrectomy was associated with increased risk of overall mortality (HR, 1.38; 95% CI, 1.13–1.69) after adjustment for demographic and comorbid variables. In this study, radical nephrectomy was associated with increased risks of cardiovascular events after surgery; probabilities of 3- and 5-year freedom from events were 86% and 82% after partial nephrectomy and 82% and 75% after radical nephrectomy, respectively. However, with respect to time to first cardiovascular event or cardiovascular death, no association was found. Hence, the association between nephrectomy-induced CKD and cardiovascular outcomes or overall survival may be weak if present and the differences in study population characteristics, especially the presence of comorbidities, which have a direct influence on renal function or follow-up duration in currently available literature limit generalization.

While the association between nephrectomy, CKD, and mortality remains controversial, a study reported from Cleveland Clinic may help to provide insight. Analyzing data from 4,180 patients who underwent renal surgery between 1999 and 2008, Lane et al. [16] compared the impact of nephrectomy on annual renal functional change and overall survival between patients with preexisting CKD (medical CKD) and postoperatively developed CKD (surgical CKD). Similar to what was previously suggested, medical CKD was present in 28% of the patients before surgery. Among patients with normal preoperative renal function, 22% developed de novo CKD after surgery. However, on subsequent follow-up, annual renal functional decline was 4.7% for patients with medical CKD but 0.7% for patients with surgical CKD. Furthermore, surgical CKD was not a significant predictor of overall survival in those without medical CKD before surgery, and survival of surgical CKD patients was observed to be similar to those without postoperative CKD. While radical nephrectomy was a predictor of increased all-cause mortality in both

medical CKD patients and those with normal preoperative renal function (OR, 2.89; 95% CI, 2.49-3.37), for patients with normal preoperative renal function, neither postoperative GFR nor the development of surgical CKD was associated with reduced survival [40].

These studies underscore the significance of medical renal disease, which could accelerate progression of CKD after renal surgery. Several others have suggested that in the noncancerous parenchyma of the kidneys adjacent to the RCC, only about 10% had completely normal histology. In more than 60% of the specimens, significant histologic abnormality could be identified, which included glomerular hypertrophy, mesangial expansion, and diffuse glomerulosclerosis, even in the specimens of patients without a known medical comorbidity [41-44]. The presence of histologic change in the noncancerous parenchyma was directly related to greater decline in postoperative renal function, especially after radical nephrectomy. Such prevalent renal parenchymal abnormality explains *de novo* CKD occurring after an uncomplicated partial nephrectomy. Similarly, it has also been suggested that compared with patients with lower GFR preoperatively or medical CKD, patients with normal preoperative GFR exhibited significantly better postoperative renal function recovery and less perioperative GFR decline, thus demonstrating an essentially different renal functional outcome [45]. Amount of renal parenchyma spared during partial nephrectomy is increasingly recognized as the most important determinant of postoperative renal functional outcome [46,47]. It seems that not only the quantity but also the quality of the preserved parenchymal volume matters, especially in the long term.

Contemporary people generally live longer and more frequently acquire various degenerative medical conditions that influence renal function. Many such conditions require long-term medical or surgical intervention, which also has the potential for additional renal functional decline. Whether the occurrence of RCC in the kidney is associated with additional histologic change in the entire renal parenchyma is unclear, but the presence of RCC is associated with deteriorated renal function. Surgical intervention for the renal tumor results in additional functional decline. Patients with RCC are at increased risk of CKD development and progression, especially after treatment. Thus, future research should be extended to evaluate not only the long-term impact of nephrectomy on CKD, but also the potential bidirectional and causal relationship between RCC and CKD [40]. CKD itself is a health hazard that may influence various systemic conditions downstream and accordingly quality of life. Also, it is probable that another prospective randomized clinical trial comparing radical versus partial nephrectomy for T1 renal tumors to compare renal functional outcomes and subsequent all-cause mortality will be extremely difficult to conduct. In light of these findings, even in the absence of a stronger level of evidence or the demonstration of a solid association between surgical CKD and all-cause mortality, partial nephrectomy

should be considered with priority for all surgical candidates with T1 tumors.

CONCLUSIONS

Patients with RCC are at increased risk for CKD development and progression especially after treatment. At the same time, these patients are more likely to have medical as well as social risk factors for renal functional decline. Nephron-sparing surgery is associated with a significantly reduced risk of developing CKD compared to radical nephrectomy for patients with T1 RCC. Hence, a nephron-sparing approach should be the primary consideration for all amenable T1 tumors. The relationship between surgically induced CKD and increased all-cause mortality or the beneficial effect of nephron-sparing surgery on reducing overall survival needs to be demonstrated further.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Evenski A, Ramasunder S, Fox W, Mounasamy V, Temple HT. Treatment and survival of osseous renal cell carcinoma metastases. *J Surg Oncol* 2012;106:850-5.
2. Jung KW, Won YJ, Kong HJ, Oh CM, Seo HG, Lee JS. Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2010. *Cancer Res Treat* 2013 ;45:1-14.
3. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. *JAMA* 1999;281:1628-31.
4. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst* 2006;98:1331-4.
5. Campbell SC, Novick AC, Belldegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. *J Urol* 2009;182:1271-9.
6. Ljungberg B, Cowan NC, Hanbury DC, Hora M, Kuczyk MA, Merseburger AS, et al. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010;58:398-406.
7. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39(2 Suppl 1):S1-266.
8. United States Renal Data System. USRDS 2012 Annual Data Report: atlas of chronic kidney disease and end-stage renal disease in the United States, 2012 [Internet]. Ann Arbor, MI: USRDS Coordinating Center; [cited 2014 May 8]. Available from: <http://www.usrds.org/atlas12.aspx>.
9. Park JT, Oh HJ, Kang SW. Cardiovascular disease in end-stage renal disease. *J Korean Med Assoc* 2013;56:576-82.
10. Jin DC, Ha IS, Kim NH, Lee SW, Lee JS, Yoon SR, et al. Brief report: renal replacement therapy in Korea, 2010. *Kidney Res Clin Pract* 2012;31:62-71.
11. Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1969;101:297-301.
12. Fehrman-Ekholm I, Duner F, Brink B, Tyden G, Elinder CG. No evidence of accelerated loss of kidney function in living kidney donors: results from a cross-sectional follow-up. *Transplantation* 2001;72:444-9.

13. Ibrahim HN, Foley R, Tan L, Rogers T, Bailey RF, Guo H, et al. Long-term consequences of kidney donation. *N Engl J Med* 2009;360:459-69.
14. Segev DL, Muzaale AD, Caffo BS, Mehta SH, Singer AL, Taranto SE, et al. Perioperative mortality and long-term survival following live kidney donation. *JAMA* 2010;303:959-66.
15. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7:735-40.
16. Lane BR, Campbell SC, Demirjian S, Fergany AF. Surgically induced chronic kidney disease may be associated with a lower risk of progression and mortality than medical chronic kidney disease. *J Urol* 2013;189:1649-55.
17. Fehrman-Ekholm I, Norden G, Lennerling A, Rizell M, Mjornstedt L, Wramner L, et al. Incidence of end-stage renal disease among live kidney donors. *Transplantation* 2006;82:1646-8.
18. Cherikh WS, Young CJ, Kramer BF, Taranto SE, Randall HB, Fan PY. Ethnic and gender related differences in the risk of end-stage renal disease after living kidney donation. *Am J Transplant* 2011;11:1650-5.
19. Muzaale AD, Massie AB, Wang MC, Montgomery RA, McBride MA, Wainright JL, et al. Risk of end-stage renal disease following live kidney donation. *JAMA* 2014;311:579-86.
20. McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002;59:816-20.
21. Patel SS, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D, et al. Serum creatinine as a marker of muscle mass in chronic kidney disease: results of a cross-sectional study and review of literature. *J Cachexia Sarcopenia Muscle* 2013;4:19-29.
22. Lau WK, Blute ML, Weaver AL, Torres VE, Zincke H. Matched comparison of radical nephrectomy vs nephron-sparing surgery in patients with unilateral renal cell carcinoma and a normal contralateral kidney. *Mayo Clin Proc* 2000;75:1236-42.
23. Ahn JS, Kim HJ, Jeon HG, Jeong BC, Seo SI, Lee HM, et al. Predictive preoperative factors for renal insufficiency in patients followed for more than 5 years after radical nephrectomy. *Korean J Urol* 2013;54:303-10.
24. Jeon HG, Choo SH, Sung HH, Jeong BC, Seo SI, Jeon SS, et al. Small tumour size is associated with new-onset chronic kidney disease after radical nephrectomy in patients with renal cell carcinoma. *Eur J Cancer* 2014;50:64-9.
25. Shin S, Han Y, Park H, Chung YS, Ahn H, Kim CS, et al. Risk factors for acute kidney injury after radical nephrectomy and inferior vena cava thrombectomy for renal cell carcinoma. *J Vasc Surg* 2013;58:1021-7.
26. Kong HJ, Park JS, Kim DY, Shin HS, Jung HJ. Renal function following curative surgery for renal cell carcinoma: who is at risk for renal insufficiency? *Korean J Urol* 2013;54:830-3.
27. Kim SH, Lee SE, Hong SK, Jeong CW, Park YH, Kim YJ, et al. Incidence and risk factors of chronic kidney disease in Korean patients with t1a renal cell carcinoma before and after radical or partial nephrectomy. *Jpn J Clin Oncol* 2013;43:1243-8.
28. Sun M, Bianchi M, Hansen J, Trinh QD, Abdollah F, Tian Z, et al. Chronic kidney disease after nephrectomy in patients with small renal masses: a retrospective observational analysis. *Eur Urol* 2012;62:696-703.
29. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors: is there a difference in mortality and cardiovascular outcomes? *J Urol* 2009;181:55-61.
30. Zini L, Perrotte P, Capitanio U, Jeldres C, Shariat SF, Antebi E, et al. Radical versus partial nephrectomy: effect on overall and noncancer mortality. *Cancer* 2009;115:1465-71.
31. Miller DC, Schonlau M, Litwin MS, Lai J, Saigal CS; Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. *Cancer* 2008;112:511-20.
32. Klarenbach S, Moore RB, Chapman DW, Dong J, Braam B. Adverse renal outcomes in subjects undergoing nephrectomy for renal tumors: a population-based analysis. *Eur Urol* 2011;59:333-9.
33. Mariusdottir E, Jonsson E, Marteinsson VT, Sigurdsson MI, Gudbjartsson T. Kidney function following partial or radical nephrectomy for renal cell carcinoma: a population-based study. *Scand J Urol* 2013;47:476-82.
34. Roos FC, Brenner W, Thomas C, Jager W, Thuroff JW, Hampel C, et al. Functional analysis of elective nephron-sparing surgery vs radical nephrectomy for renal tumors larger than 4 cm. *Urology* 2012;79:607-13.
35. Van Poppel H, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, et al. A prospective, randomised EORTC intergroup phase 3 study comparing the oncologic outcome of elective nephron-sparing surgery and radical nephrectomy for low-stage renal cell carcinoma. *Eur Urol* 2011;59:543-52.
36. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
37. McCullough PA, Jurkovitz CT, Pergola PE, McGill JB, Brown WW, Collins AJ, et al. Independent components of chronic kidney disease as a cardiovascular risk state: results from the Kidney Early Evaluation Program (KEEP). *Arch Intern Med* 2007;167:1122-9.
38. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culeton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003;108:2154-69.
39. Thompson RH, Boorjian SA, Lohse CM, Leibovich BC, Kwon ED, Chevillet JC, et al. Radical nephrectomy for pT1a renal masses may be associated with decreased overall survival compared with partial nephrectomy. *J Urol* 2008;179:468-71.
40. Li L, Lau WL, Rhee CM, Harley K, Kovesdy CP, Sim JJ, et al. Risk of chronic kidney disease after cancer nephrectomy. *Nat Rev Nephrol* 2014;10:135-45.
41. Bijol V, Mendez GP, Hurwitz S, Rennke HG, Nose V. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. *Am J Surg Pathol* 2006;30:575-84.
42. Henriksen KJ, Meehan SM, Chang A. Non-neoplastic renal diseases are often unrecognized in adult tumor nephrectomy specimens: a review of 246 cases. *Am J Surg Pathol* 2007;31:1703-8.
43. Salvatore SP, Cha EK, Rosoff JS, Seshan SV. Nonneoplastic renal cortical scarring at tumor nephrectomy predicts decline in kidney function. *Arch Pathol Lab Med* 2013;137:531-40.
44. Garcia-Roig M, Gorin MA, Parra-Herran C, Garcia-Buitrago M, Kava BR, Jorda M, et al. Pathologic evaluation of non-neoplastic renal parenchyma in partial nephrectomy specimens. *World J Urol* 2013;31:835-9.
45. Takagi T, Kondo T, Iizuka J, Omae K, Kobayashi H, Hashimoto Y, et al. Better recovery of kidney function in patients with de novo chronic kidney disease after partial nephrectomy compared with those with pre-existing chronic kidney disease. *Int J Urol*

- 2014;21:613-6.
46. Sharma N, O'Hara J, Novick AC, Lieber M, Remer EM, Herts BR. Correlation between loss of renal function and loss of renal volume after partial nephrectomy for tumor in a solitary kidney. *J Urol* 2008;179:1284-8.
47. Thompson RH, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, et al. Renal function after partial nephrectomy: effect of warm ischemia relative to quantity and quality of preserved kidney. *Urology* 2012;79:356-60.