World Journal of Clinical Urology

Submit a Manuscript: http://www.wjgnet.com/esps/

*World J Clin Urol* 2017 March 24; 6(1): 10-17

DOI: 10.5410/wjcu.v6.i1.10

ISSN 2219-2816 (online)

MINIREVIEWS

# Chronic kidney disease after radical nephrectomy for suspected renal cancers

Tuck Y Yong, Kareeann SF Khow

Tuck Y Yong, Internal Medicine, Flinders Private Hospital, Bedford Park, South Australia 5042, Australia

Kareeann SF Khow, Adelaide Geriatrics Teaching and Research with Aged Care, the University of Adelaide, Paradise, South Australia 5075, Australia

Author contributions: Yong TY and Khow KSF designed, performed the research and wrote the paper.

Conflict-of-interest statement: The authors have no financial relationships to disclose.



Manuscript source: Invited manuscript

Correspondence to: Dr. Tuck Y Yong, FRACP, Internal Medicine, Flinders Private Hospital, Flinders Drive, Bedford Park, South Australia 5042, Australia. tyyong@hotmail.com
Telephone: +61-8-82412121
Fax: +61-8-82400879

Received: August 28, 2016
Peer-review started: September 1, 2016
First decision: November 30, 2016
Revised: December 29, 2016
Accepted: January 11, 2017
Article in press: January 13, 2017
Published online: March 24, 2017

## Abstract

Nephrectomy is the treatment of choice for early stage renal cell carcinoma. However, radical nephrectomy is consistently associated with higher rates of new-onset chronic kidney disease (CKD) than the general population, regardless of the method used in measuring renal function. The higher rates of CKD are associated with worsened survival because of increased risk of cardiovascular diseases and mortality. Comorbidities and adjacent non-neoplastic kidney diseases are important risk factors for the development of CKD after nephrectomy. Partial nephrectomy has become the standard of care for patients with stage 1a tumours (diameter < 4 cm) and an attractive option for those with stage 1b (diameter 4-7 cm). Therefore stratifying the risk of postoperative CKD before surgery is important and ongoing monitoring of kidney function after radical nephrectomy is needed in addition to oncological surveillance. More research is needed to better understand the risk of CKD after radical nephrectomy and develop effective strategies to optimize kidney function after such surgery.

**Key words:** Nephrectomy; Renal function; Renal cell carcinoma; Chronic kidney disease; Prevention



**Core tip:** Chronic kidney disease (CKD) is an important complication associated with radical nephrectomy. CKD post-nephrectomy is associated with increased risk of cardiovascular diseases. Risk factors for CKD should be assessed thoroughly before radical nephrectomy. Where possible, nephron-sparing treatment should be used to mitigate the onset of CKD after tumour resection.

Yong TY, Khow KSF. Chronic kidney disease after radical nephrectomy for suspected renal cancers. *World J Clin Urol* 2017; 6(1): 10-17 Available from: URL: http://www.wjgnet.com/2219-2816/full/v6/i1/10.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i1.10

## INTRODUCTION

Renal cell carcinoma (RCC) is the third most common urological cancer but has the highest mortality rate[1]. The five-year survival of late stage RCC is 5%-10%[1]. Radical or partial nephrectomy is the preferred treatment for the majority of patients with RCC or other renal malignancies. Although outcomes are favourable for early stage RCC treated with unilateral radical nephrectomy, concerns are emerging about the adverse impact on long-term renal function and survival. Nephrectomy for renal malignancies has been recognized as an independent risk factor for developing chronic kidney disease (CKD)[2,3] whilst nephrectomy for other indications such as living kidney donation has a more benign long-term renal outcome[4]. CKD is defined as kidney damage for more than 3 mo (either confirmed by indicators of kidney injury such as proteinuria, or pathological disease in biopsy samples) with or without changes in estimated glomerular filtration rate (eGFR), or eGFR < 60 mL/min per 1.73 $m^2$ for more than 3 mo[5].

In the United States, 75%-80% of patients with renal cancer are diagnosed incidentally with disease localized to the kidney[6]. This observation is largely attributable to a 73% rise in imaging of the abdomen with CT and MRI[6]. In parallel with increased detection of renal neoplasms, benign renal tumours such as oncocytoma, angiomyolipoma and simple renal cysts, have been diagnosed increasingly[7]. More than 20% of incidental renal masses are benign but current radiological investigations cannot accurately differentiate malignant from benign tumours[8].

In this review, we will describe the epidemiology of CKD after radical nephrectomy for renal tumours and ways to prevent the development of this condition after surgery.

## EPIDEMIOLOGY

Evidence from observational studies support the finding that radical nephrectomy is associated with higher rates of CKD, regardless of the method used in measuring renal function. Klarenbach *et al*[9] used a large Canadian population-based database of subjects who underwent nephrectomy between 2002 and 2007 to evaluate kidney outcomes after a mean follow-up of 2 years and 8 mo. Among those who underwent radical nephrectomy, 106 out of 921 (11.5%) experienced adverse renal outcomes, which was defined as end-stage renal disease (ESRD), acute dialysis, CKD (eGFR < 30 mL/min per 1.73 $m^2$), and rapidly progressive CKD (eGFR < 60 mL/min per 1.73 $m^2$ and eGFR loss $\geqslant$ 4 mL/min per 1.73 $m^2$ per year)[9].

In the Memorial Sloan-Kettering Cancer Center (MSKCC) study, about a quarter of patients with T1a RCC (tumour diameter < 4 cm) had CKD (eGFR < 60 mL/min per 1.73 $m^2$) prior to surgery despite preoperative serum creatinine within the normal range[2] (Table 1). In a study of patients who had nephrectomy for T1a RCC using the linked Surveillance, Epidemiology and End Results (SEER)-Medicare database in the United States between 1998 and 2005, an increased rate of new-onset CKD was observed in patients who had radical nephrectomy (20%) compared with partial nephrectomy (11%)[10]. Using data from this study, the authors estimated that the five-year rate of new-onset CKD was 18% for radical nephrectomy and 9% for partial nephrectomy.

With variable duration of follow-up after radical nephrectomy, ESRD has been reported in 0%-4% of patients in various studies[2,9-11]. In a Canadian study involving 1151 subjects with kidney lesions who have undergone nephrectomy, 2% developed ESRD requiring dialysis within a median period of 32 mo after surgery[9]. However ESRD was not considered as a specific renal outcome due to its low incidence. In the SEER-Medicare (1988-2005) linked cohort, 2% of patients who had partial nephrectomy and 4% of radical nephrectomy developed ESRD when the data was censored in 2008[10]. However there was no statistical difference between these two treatment groups. In the subgroup analysis of the European Organisation for Research and Treatment of Cancer (EORTC) trial, the incidence of ESRD was low in the radical nephrectomy group at 1.5% and was not significantly different from those who had partial nephrectomy[11]. In the MSKCC study, none of the included subjects required renal replacement therapy, acute or chronic[2].

Recent studies have provided new insight into differences between patients with CKD caused by medical conditions and those after nephrectomy. One study found that CKD related to nephrectomy was associated with annual kidney function decline of 0.7%, which is significantly lower than the 4.7% observed in medical-related CKD[12].

Most studies have used either creatinine or eGFR to determine kidney function. Nonetheless serum creatinine alone does not reliably reflect kidney function due to variations in between days, extremes of age and people with different muscle mass[13]. More recent studies have found that using serum creatinine and eGFR have underestimated the real effect on kidney function[14]. By measuring 24-h urinary creatinine clearance, one study has shown a decline in renal function by 31.6% after radical nephrectomy[15].

## PREDISPOSING FACTORS FOR CKD POST-NEPHRECTOMY

Patients with renal tumours tend to be older resulting in a higher prevalence of cardiovascular diseases. As a result, this group of patients may have a greater degree of renal disease even when their creatinine concentration is still within the reference interval.

Similar systemic comorbidities and intrinsic renal risk factors might predispose people to develop both renal malignancies and CKD[16,17]. These factors include patient characteristics (such as age, sex and ethnicity), genetic predisposition, medical comorbidities (such as hypertension, diabetes mellitus and other chronic

**Table 1 The incidence or prevalence of chronic kidney disease or end-stage renal disease before and after radical or partial nephrectomy for suspected renal cancers**

| Population | Incidence or prevalence | Ref. |
|---|---|---|
| CKD in patients with T1a RCC before surgery | 26% | Huang *et al*[2] |
| New-onset CKD after radical nephrectomy (SEER-Medicare database) | 20% | Sun *et al*[10] |
| New-onset CKD after partial nephrectomy (SEER-Medicare database) | 11% | Sun *et al*[10] |
| ESRD after radical nephrectomy | 2%-4% | Sun *et al*[10] |
| | | Scosyrev *et al*[11] |
| ESRD after partial nephrectomy | 2% | Sun *et al*[10] |

CKD: Chronic kidney disease; ESRD: End-stage renal disease; RCC: Renal cell carcinoma; SEER: Surveillance, Epidemiology and End Results.

**Table 2 Risk factors associated with new-onset chronic kidney disease or acceleration of pre-existing chronic kidney disease after radical nephrectomy**

| Risk factor | Odds ratio (95%CI); *P*-value | Ref. |
|---|---|---|
| Diabetes mellitus | 11.60 (1.39-97.04); $P = 0.024$ | Brandina *et al*[24] |
| | 2.74 (1.07-6.98); $P = 0.035$ | Cho *et al*[30] |
| Hypertension | 3.67 (1.28-10.48); $P = 0.015$ | Brandina *et al*[24] |
| Low preoperative GFR (< 90 mL/min per 1.73 $m^2$) | 3.30 (1.16-9.37); $P = 0.025$ | Brandina *et al*[24] |
| Preoperative GFR (per 10 mL/min per 1.73 $m^2$ rise) | 0.47 (0.36-0.60); $P = 0.0001$ | Cho *et al*[30] |
| Postoperative AKI | 4.24 (2.28-7.89); $P = 0.0001$ | Cho *et al*[30] |
| Adjacent non-neoplastic kidney parenchyma abnormalities | | |
| Arteriosclerosis > 50% | 3.33 (1.03-10.79); $P = 0.045$ | Brandina *et al*[24] |
| Interstitial fibrosis (present) | 3.78 (1.32-10.76); $P = 0.013$ | |
| Glomerulosclerosis ⩾ 5% | 3.78 (1/24-11.50); $P = 0.0061$ | |

AKI: Acute kidney injury; GFR: Glomerular filtration rate.

or acute diseases), coexisting pathologies in adjacent non-neoplastic renal parenchyma and environmental exposures (such as nutrition and smoking status)[18,19] (Table 2).

### *Non-neoplastic renal parenchymal disease*

Several studies have shown that arterionephrosclerosis and glomerular diseases frequently coexist with RCC[20-22]. In resected tumour specimens, up to 90% have been reported to have coexisting non-neoplastic renal disease in the adjacent parenchymal tissue[21]. Clinically significant intrinsic renal abnormalities, such as glomerular hypertrophy, diabetic nephropathy, mesangial expansion and diffuse glomerulosclerosis were evident in more than 60% of these specimens[21].

From a study of 110 neoplasm-related nephrectomy, people with significant abnormal renal parenchyma showed a higher decrease in kidney function at 6 mo after surgery in comparison to those with normal adjacent renal tissue (increase in serum creatinine by 97.24 ± 159.12 μmol/L *vs* 17.68 ± 17.68 μmol/L)[20]. Nonetheless, a limitation of this study was the small sample of serum creatinine measurement on follow-up. In another study of 156 patients after tumour nephrectomy who had follow up for 12 mo or more, findings of severe arteriosclerosis or arteriolosclerosis, tubular atrophy or interstitial fibrosis, or glomerulosclerosis in nephrectomy specimens were associated with significantly lower renal function after surgery[22].

One study with a follow-up of an average 19.7 mo found that after laparoscopic radical nephrectomy, the change in eGFR was significantly associated with the severity of glomerulosclerosis or the finding of interstitial fibrosis[23]. For every ten percent rise in the degree of glomerulosclerosis, eGFR dropped by 9% post-surgery compared with baseline.

Another study of 65 individuals who had radical nephrectomy for RCC, elevated risk of new-onset CKD (eGFR less than 60 mL/min per 1.73 $m^2$) was observed in association with abnormal pathology in adjacent non-neoplastic parenchyma[24]. A multivariate analysis in this study showed that arteriosclerosis of more than 50% (odds ratio, OR = 3.3), presence of interstitial fibrosis (OR = 3.8) and glomerulosclerosis of 5% or greater (OR = 3.8) were associated with significant loss in renal function after radical nephrectomy.

Findings from these studies have led the College of American Pathologists to recommend reporting of non-neoplastic renal parenchyma for examination of all tumour nephrectomy and nephroureterectomy specimens[25]. However, no study has reported any correlation between adjacent non-neoplastic renal disease and the development of ESRD or cardiovascular diseases after nephrectomy.

### *Co-existing morbidities*

After nephrectomy, co-existing morbidities are important contributing factors to deterioration in kidney function

after nephrectomy because of their effects on remaining renal parenchyma. Diabetes mellitus, hypertension and cigarette smoking have been independently linked with the decrease in renal function after nephrectomy for kidney tumours[9,26]. These factors can lead to *de novo* development of CKD or acceleration of decline in pre-existing CKD. Studies have pointed towards a progressive increase in the risk of RCC with worsening hypertension but the pathophysiological mechanism for this relationship is still unclear[17,19,27]. Diabetes mellitus is present in 6.8%-23.0% of patients with RCC undergoing surgery[27,28]. A prior diagnosis of diabetes has been found to be a predisposing factor for development of stage Ⅲ CKD after radical nephrectomy[29].

### *Postoperative acute kidney injury*

Acute kidney injury (AKI) after radical nephrectomy among patients diagnosed with RCC has been found to be a significant risk factor for new-onset CKD[30]. This study also found that about one-third of patients experienced post-operative AKI when they underwent radical nephrectomy. A year post-surgery, median GFR was lower in the AKI group compared to those without AKI. Advanced age, male gender, increased body mass index, low presurgical GFR and small size of RCC were identified as predisposing factors for postoperative AKI[30]. Uncertainty remains about how these factors are associated with inadequate compensation of the remaining kidney and adaptive hyperfiltration[30]. Additional research is required to identify ways of preventing AKI after radical nephrectomy as a strategy to prevent new-onset CKD after this procedure.

### *Characteristic of renal tumour*

One study has found that larger kidney tumour diameter was independently associated with decreased preoperative estimated GFR even after adjusting for hypertension and race[31]. The findings of this study suggest that either the growth of a tumour or displacement of the non-tumour renal parenchyma affects kidney function.

On the other hand, two other studies found that small tumour size was associated with significant deterioration in renal function after radical nephrectomy[32,33]. Therefore, researchers in these studies have advocated that partial nephrectomy are more appropriate in patients with tumour size 7 cm or less.

## POST-NEPHRECTOMY CKD, CARDIOVASCULAR DISEASES AND MORTALITY

Higher rates of CKD in patients who had radical nephrectomy have been associated with increased risk of cardiovascular diseases and mortality[2,34]. Using Medicare data, Huang *et al*[2] found that the risk of cardiovascular events and non-cancer mortality was increased in the group that had radical nephrectomy. This finding was corroborated by a study from Weight and colleagues[34]. In their study, they evaluated the overall and disease-specific survival in 1004 subjects with T1b RCC (tumour of 4-7 cm in diameter) who had either radical or partial nephrectomy. This study found that a significant drop in renal function was observed in those who had radical nephrectomy, over a follow-up period of 4 years. In addition, this differing rate of decline in kidney function was associated with a 25% increase in cardiovascular-related mortality and a 17% rise of all-cause mortality.

## PREVENTION OF CKD AFTER RADICAL NEPHRECTOMY

In the past decade, partial nephrectomy has emerged as the standard treatment for most small kidney masses of less than 4 cm in size[35-37]. Available evidence strongly supports the notion that control of cancer and risk of cancer-associated mortality for tumours up to 7 cm are not compromised by partial nephrectomy when compared with the radical procedure[38,39].

The EORTC is the only randomized trial comparing partial and radical nephrectomy in patients with solitary kidney lesions[40]. This study randomized 541 participants with solitary renal tumours with a diameter of 5 cm or less and normal contralateral kidney to receive either radical or partial nephrectomy. After a median follow-up period of over 9 years, this trial showed an inferior outcome after partial nephrectomy in comparison with radical nephrectomy (mortality of 25.0% compared with 18.3%). However the trial closed prematurely due to low recruitment and was confounded by a large number of crossover in between the two arms of treatment.

A subsequent subgroup analysis of the EORTC study found that after a median follow-up of 6.7 years, nephron-sparing surgery was associated with a lower absolute risk (21%) of developing stage Ⅲ CKD[11]. In addition, stage Ⅳ and Ⅴ CKD (eGFR < 30 mL/min per 1.73 $m^2$) were observed in 10.0% of participants who had radical nephrectomy compared with 6.3% of those who had nephron-sparing surgery.

Several studies have found that partial nephrectomy can be expanded safely to patients with tumours of 4-7 cm in size (T1bN0M0)[35,41-43]. One study has extended these findings on partial nephrectomy in patients with T1b to the population level, using analyses from the SEER registry[44]. Using propensity scoring, this study found no overall survival difference between partial and radical nephrectomy in a matched cohort of patients with T1bN0M0 staging. One meta-analysis of 39 studies and 41010 individuals who had surgery for small renal neoplasms found that nephron-sparing surgery had a 19% lower all-cause mortality (hazard ratio, HR = 0.81; $P < 0.0001$)[45]. However, this finding has to be interpreted cautiously due to the heterogeneity in study population and the inclusion of retrospective studies.

In a meta-analysis of 26 studies (27845 radical nephrectomy and 8201 partial nephrectomy), nephron-

sparing surgery was associated with a 73% risk reduction of new-onset CKD (eGFR < 60 mL/min per 1.73 $m^2$) in all included patients (HR = 0.27; $P$ < 0.0001) compared with radical nephrectomy[46]. In patients with tumours > 4 cm, partial nephrectomy was associated with a 65% risk reduction of new-onset CKD compared to radical nephrectomy. However this systematic review was not able to assess the incidence of ESRD (eGFR < 15 mL/min per 1.73 $m^2$) after surgery because of a lack of relevant data.

In one study, patients treated with nephron-sparing surgery have about half the risk of developing cardiovascular events compared with radical nephrectomy[47]. After adjusting for clinical characteristics, comorbidities, and cardiovascular risk at diagnosis, nephron-sparing surgery was independently associated with a lower risk of cardiovascular events compared to radical nephrectomy.

However, in a meta-analysis of 6 studies (16745 radical nephrectomy and 5403 partial nephrectomy), there was no significant difference between radical and partial nephrectomy in relation to post-surgery cardiovascular events (HR = 0.86; $P$ = 0.24) and cardiovascular death (HR = 0.71; $P$ = 0.20)[46]. However, these results are still contentious because of the limited number of studies.

The most likely mechanism of how partial nephrectomy confer the kidney function advantage is through preservation of a larger renal volume or some may refer to a functional volume. Among people with a single kidney undergoing nephron-sparing surgery, a larger preserved kidney volume is independently associated with better renal function[48,49]. An increase of 5% in the volume of preserved kidney was associated with a reduction in the risk of new-onset stage IV CKD by 17%[50].

After nephron-sparing surgery, the integrity and quality of the remaining parenchyma is predictive of CKD risk. In one study of 1169 subjects, a greater decline in kidney function was observed during open or laparoscopic partial nephrectomy with increased duration of warm ischaemia greater than 20 min[51]. This study also showed that the duration of warm ischaemia was correlated with nadir eGFR decline after surgery and the magnitude of this reduction was associated with progression to CKD[51]. Furthermore, duration of warm ischaemia of more than 25 min has been demonstrated to double the risk of severe CKD[52]. However, even with prolonged ischaemic time during partial nephrectomy (> 30 min), kidney function outcomes were still better than radical nephrectomy[53].

Cryoablation and radiofrequency ablation are emerging as other nephron-sparing therapies for localized kidney neoplasms[54-56]. However ablative procedure often precludes definitive pathological staging. Although a promising option for small lesions, the efficacy in terms of oncological and renal outcomes have not yet been established due to small study cohort and the absence of long-term data. Therefore surgical resection remains the preferred treatment modality in most cases of suspected kidney malignancy.

Active surveillance can be considered the preferred "nephron-sparing" procedure in patients with limited life expectancy due to comorbidities or advanced age. Lane *et al*[57] have demonstrated that for patients 75 years or older, the renal function deterioration after radical nephrectomy is associated with higher risk of cardiovascular death. In this older age group, neither radical nor partial nephrectomy conferred a significant survival advantage over active surveillance. In the largest prospective observational study using the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry, the 5-year overall survival was lower in the active surveillance (75% *vs* 92%) but no difference in cancer-specific survival[58].

## RISK STRATIFICATION BEFORE NEPHRECTOMY

Comprehensive stratification of risk before nephrectomy is vital to ensure patients achieve the best functional renal outcomes. One of the risk stratification tool is the Screening for Occult Renal Disease (SCORED) which uses factors such as patient age, gender, anemia, proteinuria and cardiovascular comorbidities[59]. This tool has been validated in patients with small kidney masses undergoing nephrectomy and those in the high risk category (SCORED $\geqslant$ 4) were three times more likely to develop Stage Ⅲ CKD[60]. Another group has proposed an alternative instrument for risk prediction. Sorbellini *et al*[61] have devised a nomogram to predict decline in kidney function, which was defined as two or more creatinine measurements of 176 μmol/L within a month after surgery. This nomogram takes into account the change in kidney volume and pre-surgery creatinine but does not include preoperative comorbidities which can be important risk factors for CKD.

Other models of risk prediction have used information from renal parenchyma surrounding the tumour[23]. The presence and extent of glomerulosclerosis in adjacent parenchyma has been found to correlate with decline in kidney function after nephrectomy but this relationship is not observed with arteriosclerosis, interstitial fibrosis or tubular atrophy[23]. Brandina *et al*[24] have proposed a nomogram using age-adjusted Charlson comorbidity index, percentage of glomerulosclerosis in the adjacent non-neoplastic parenchyma and baseline eGFR before surgery to predict the probability of developing CKD after nephrectomy. However this nomogram has not been validated for clinical use.

## KNOWLEDGE GAP AND FUTURE RESEARCH

The evidence to support nephron-sparing surgery in patients with suspected RCC has been derived mainly from single-centre cohort studies. Consequently these studies lack standardisation in the definition for renal impairment, method in assessing kidney function and varying cutoff or stages of CKD as the primary outcome.

**Table 3 Questions to be addressed by future studies**

| |
|---|
| How is long-term cardiovascular health affected by radical nephrectomy? |
| What is the incidence of end-stage renal disease and renal replacement therapy after radical or partial nephrectomy? |
| What reliable investigations can be used to identify patients with renal cell carcinoma prior to surgery? |
| How does the contralateral kidney compensate after radical nephrectomy? |
| How can kidney function be preserved after nephrectomy? |

Furthermore there is also disparities between studies in terms of eligibility criteria and duration of follow-up after surgery.

Hitherto, none of the studies have used ESRD after nephrectomy as the primary endpoint. Future work is needed to evaluate the effects of nephrectomy on patients, particularly with ESRD as the main endpoint, and the possible two-way relationship between RCC and CKD. Further research is required to better understand how CKD develops or progresses after nephrectomy and identify effective measures to prevent CKD and associated adverse effects in this setting. While comorbidities such as hypertension and diabetes mellitus are cited as risk factors for new-onset CKD or worsening kidney function after radical nephrectomy, no study have evaluated how interventions to control these risk factors may potentially influence outcome.

Assessment of kidney function before and after nephrectomy is still largely based on serum creatinine measurement. Although serum cystatin C has been found to be a good predictor of AKI in different settings[62-64], its use has not been evaluated in those undergoing nephrectomy. Similarly, another marker, neutrophil gelatinase-associated lipocalin (NGAL), has not been studied in patients having nephrectomy.

The increased incidence of CKD after radical nephrectomy also highlights the need for more research to distinguish between high- and low-risk renal tumours before surgery to better select patients who will require surgical management. Clinical trials are currently investigating gene alterations such as chromatin remodelling and microsatellite instability as tool for such differentiation (NCT02204800 and NCT01305330). Urinary biomarkers such as aquaporin-1 and perilipin-2 have demonstrated early promise in differentiating benign tumours from malignant RCC[65]. Newer markers such as decreased expression of small non-coding RNAs known as PIWI-interacting RNAs have also been associated with poor survival in RCC[66]. However more research is required to validate the accuracy of these markers in the pre-surgical diagnosis of RCC.

Future studies are needed to address a number of important gaps in knowledge for patients who had radical nephrectomy. Table 3 summaries a few key questions about kidney function and adaptation after radical nephrectomy that warrants further research.

## CONCLUSION

Consistently, patients who have undergone radical nephrectomy for a suspected kidney malignancy are at increased risk of CKD. The concern with the deterioration in kidney function after radical nephrectomy is that this group of patients are at increased risk of ESRD and adverse cardiovascular outcomes. Coexisting medical disorders including diabetes mellitus, hypertension and abnormalities in the remaining kidney parenchyma are risk factors for new-onset CKD after radical nephrectomy. A comprehensive assessment of developing CKD after radical nephrectomy should be undertaken in every patient in whom this procedure is being considered so that management decisions can be better informed.

## REFERENCES


1 **Siegel R**, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10-29 [PMID: 22237781 DOI: 10.3322/caac.20138]

2 **Huang WC**, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, Scardino PT, Russo P. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006; **7**: 735-740 [PMID: 16945768 DOI: 10.1016/S1470-2045(06)70803-8]

3 **Leibovich BC**, Blute ML. Surgical management of renal cell carcinoma. *Semin Oncol* 2006; **33**: 552-562 [PMID: 17045084 DOI: 10.1053/j.seminoncol.2006.06.007]

4 **Ibrahim HN**, Foley R, Tan L, Rogers T, Bailey RF, Guo H, Gross CR, Matas AJ. Long-term consequences of kidney donation. *N Engl J Med* 2009; **360**: 459-469 [PMID: 19179315 DOI: 10.1056/NEJMoa0804883]

5 K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002; **39**: S1-266 [PMID: 11904577 DOI: 10.1053/ajkd.2002.30940]

6 **Jewett MA**, Zuniga A. Renal tumor natural history: the rationale and role for active surveillance. *Urol Clin North Am* 2008; **35**: 627-634 [PMID: 18992616 DOI: 10.1016/j.ucl.2008.07.004]

7 **Murphy AM**, Buck AM, Benson MC, McKiernan JM. Increasing detection rate of benign renal tumors: evaluation of factors predicting for benign tumor histologic features during past two decades. *Urology* 2009; **73**: 1293-1297 [PMID: 19371933 DOI: 10.1016/j.urology.2008.12.072]

8 **Akdogan B**, Gudeloglu A, Inci K, Gunay LM, Koni A, Ozen H. Prevalence and predictors of benign lesions in renal masses smaller than 7 cm presumed to be renal cell carcinoma. *Clin Genitourin Cancer* 2012; **10**: 121-125 [PMID: 22401753 DOI: 10.1016/j.clgc.2012.01.005]

9 **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**: 333-339 [PMID: 21109345 DOI: 10.1016/j.eururo.2010.11.013]

10 **Sun M**, Bianchi M, Hansen J, Trinh QD, Abdollah F, Tian Z, Sammon J, Shariat SF, Graefen M, Montorsi F, Perrotte P, Karakiewicz PI. Chronic kidney disease after nephrectomy in patients with small renal masses: a retrospective observational analysis. *Eur Urol* 2012; **62**: 696-703 [PMID: 22483407 DOI: 10.1016/j.eururo.2012.03.051]

11 **Scosyrev E**, Messing EM, Sylvester R, Campbell S, Van Poppel H. Renal function after nephron-sparing surgery versus radical nephrectomy: results from EORTC randomized trial 30904. *Eur Urol* 2014; **65**: 372-377 [PMID: 23850254 DOI: 10.1016/j.eururo.2013.06.044]

12 **Lane BR**, Demirjian S, Derweesh IH, Takagi T, Zhang Z, Velet L, Ercole CE, Fergany AF, Campbell SC. Survival and functional stability in chronic kidney disease due to surgical removal of nephrons: Importance of the new baseline glomerular filtration rate. *Eur Urol* 2015; **68**: 996-1003 [PMID: 26012710 DOI: 10.1016/j.eururo.2015.04.043]

13 **Patel SS**, Molnar MZ, Tayek JA, Ix JH, Noori N, Benner D, Heymsfield S, Kopple JD, Kovesdy CP, Kalantar-Zadeh K. 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 [PMID: 22777757 DOI: 10.1007/s13539-012-0079-1]

14 **Kim HL**, Shah SK, Tan W, Shikanov SA, Zorn KC, Shalhav AL, Wilding GE. Estimation and prediction of renal function in patients with renal tumor. *J Urol* 2009; **181**: 2451-2460 [PMID: 19371883 DOI: 10.1016/j.juro.2009.01.112]

15 **McKiernan J**, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. *Urology* 2002; **59**: 816-820 [PMID: 12031359 DOI: 10.1016/S0090-4295(02)01501-7]

16 **Chow WH**, Gridley G, Fraumeni JF, Järvholm B. Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* 2000; **343**: 1305-1311 [PMID: 11058675 DOI: 10.1056/NEJM200011023431804]

17 **Chow WH**, Dong LM, Devesa SS. Epidemiology and risk factors for kidney cancer. *Nat Rev Urol* 2010; **7**: 245-257 [PMID: 20448658 DOI: 10.1038/nrurol.2010.46]

18 **Macleod LC**, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, White E. Risk factors for renal cell carcinoma in the VITAL study. *J Urol* 2013; **190**: 1657-1661 [PMID: 23665301 DOI: 10.1016/j.juro.2013.04.130]

19 **Setiawan VW**, Stram DO, Nomura AM, Kolonel LN, Henderson BE. Risk factors for renal cell cancer: the multiethnic cohort. *Am J Epidemiol* 2007; **166**: 932-940 [PMID: 17656615 DOI: 10.1093/aje/kwm170]

20 **Bijol V**, Mendez GP, Hurwitz S, Rennke HG, Nosé V. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. *Am J Surg Pathol* 2006; **30**: 575-584 [PMID: 16699311 DOI: 10.1097/01.pas.0000194296.74097.87]

21 **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**: 1703-1708 [PMID: 18059227 DOI: 10.1097/PAS.0b013e31804ca63e]

22 **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**: 531-540 [PMID: 23544942 DOI: 10.5858/arpa.2012-0070-OA]

23 **Gautam G**, Lifshitz D, Shikanov S, Moore JM, Eggener SE, Shalhav AL, Chang A. Histopathological predictors of renal function decrease after laparoscopic radical nephrectomy. *J Urol* 2010; **184**: 1872-1876 [PMID: 20850146 DOI: 10.1016/j.juro.2010.06.145]

24 **Brandina R**, Moreira Leite KR, Gregório EP, Fernandes KB, Srougi M. Histologic abnormalities in non-neoplastic renal parenchyma and the risk of chronic kidney disease following radical nephrectomy. *Urology* 2017; **100**: 158-162 [PMID: 27725235 DOI: 10.1016/j.urology.2016.09.041]

25 **Srigley JR**, Amin MB, Delahunt B, Campbell SC, Chang A, Grignon DJ, Humphrey PA, Leibovich BC, Montironi R, Renshaw AA, Reuter VE. Protocol for the examination of specimens from patients with invasive carcinoma of renal tubular origin. *Arch Pathol Lab Med* 2010; **134**: e25-e30 [PMID: 20367296 DOI: 10.1043/1543-2165-134.4.e25]

26 **Barlow LJ**, Korets R, Laudano M, Benson M, McKiernan J. Predicting renal functional outcomes after surgery for renal cortical tumours: a multifactorial analysis. *BJU Int* 2010; **106**: 489-492 [PMID: 20039869 DOI: 10.1111/j.1464-410X.2009.09147.x]

27 **Schlehofer B**, Pommer W, Mellemgaard A, Stewart JH, McCredie M, Niwa S, Lindblad P, Mandel JS, McLaughlin JK, Wahrendorf J. International renal-cell-cancer study. VI. the role of medical and family history. *Int J Cancer* 1996; **66**: 723-726 [PMID: 8647639 DOI: 10.1002/(SICI)1097-0215(19960611)66: 6<723: : AID-IJC2>3.0.CO; 2-1]

28 **Lindblad P**, Chow WH, Chan J, Bergström A, Wolk A, Gridley G, McLaughlin JK, Nyrén O, Adami HO. The role of diabetes mellitus in the aetiology of renal cell cancer. *Diabetologia* 1999; **42**: 107-112 [PMID: 10027588 DOI: 10.1007/s001250051122]

29 **Lane BR**, Russo P, Uzzo RG, Hernandez AV, Boorjian SA, Thompson RH, Fergany AF, Love TE, Campbell SC. Comparison of cold and warm ischemia during partial nephrectomy in 660 solitary kidneys reveals predominant role of nonmodifiable factors in determining ultimate renal function. *J Urol* 2011; **185**: 421-427 [PMID: 21167524 DOI: 10.1016/j.juro.2010.09.131]

30 **Cho A**, Lee JE, Kwon GY, Huh W, Lee HM, Kim YG, Kim DJ, Oh HY, Choi HY. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. *Nephrol Dial Transplant* 2011; **26**: 3496-3501 [PMID: 21406544 DOI: 10.1093/ndt/gfr094]

31 **Donin NM**, Suh LK, Barlow L, Hruby GW, Newhouse J, McKiernan J. Tumour diameter and decreased preoperative estimated glomerular filtration rate are independently correlated in patients with renal cell carcinoma. *BJU Int* 2012; **109**: 379-383 [PMID: 21851533 DOI: 10.1111/j.1464-410X.2011.10331.x]

32 **Jeon HG**, Choo SH, Sung HH, Jeong BC, Seo SI, Jeon SS, Choi HY, Lee HM. 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**: 64-69 [PMID: 24060356 DOI: 10.1016/j.ejca.2013.08.018]

33 **Ohno Y**, Nakashima J, Ohori M, Hashimoto T, Iseki R, Hatano T, Tachibana M. Impact of tumor size on renal function and prediction of renal insufficiency after radical nephrectomy in patients with renal cell carcinoma. *J Urol* 2011; **186**: 1242-1246 [PMID: 21849191 DOI: 10.1016/j.juro.2011.05.087]

34 **Weight CJ**, Lieser G, Larson BT, Gao T, Lane BR, Campbell SC, Gill IS, Novick AC, Fergany AF. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. *Eur Urol* 2010; **58**: 293-298 [PMID: 20546991 DOI: 10.1016/j.eururo.2010.04.033]

35 **Patard JJ**, Shvarts O, Lam JS, Pantuck AJ, Kim HL, Ficarra V, Cindolo L, Han KR, De La Taille A, Tostain J, Artibani W, Abbou CC, Lobel B, Chopin DK, Figlin RA, Mulders PF, Belldegrun AS. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol* 2004; **171**: 2181-2185, quiz 2435 [PMID: 15126781 DOI: 10.1097/01.ju.0000124846.37299.5e]

36 **Thompson RH**, Ordonez MA, Iasonos A, Secin FP, Guillonneau B, Russo P, Touijer K. Renal cell carcinoma in young and old patients--is there a difference? *J Urol* 2008; **180**: 1262-1266; discussion 1266 [PMID: 18707708 DOI: 10.1016/j.juro.2008.06.037]

37 **Becker F**, Siemer S, Humke U, Hack M, Ziegler M, Stöckle M. Elective nephron sparing surgery should become standard treatment for small unilateral renal cell carcinoma: Long-term survival data of 216 patients. *Eur Urol* 2006; **49**: 308-313 [PMID: 16359779 DOI: 10.1016/j.eururo.2005.10.020]

38 **Dash A**, Vickers AJ, Schachter LR, Bach AM, Snyder ME, Russo P. Comparison of outcomes in elective partial vs radical nephrectomy for clear cell renal cell carcinoma of 4-7 cm. *BJU Int* 2006; **97**: 939-945 [PMID: 16643474 DOI: 10.1111/j.1464-410X.2006.06060.x]

39 **Leibovich BC**, Blute M, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. *J Urol* 2004; **171**: 1066-1070 [PMID: 14767272 DOI: 10.1097/01.ju.0000113274.40885.db]

40 **Van Poppel H**, Da Pozzo L, Albrecht W, Matveev V, Bono A, Borkowski A, Colombel M, Klotz L, Skinner E, Keane T, Marreaud S, Collette S, Sylvester R. 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**: 543-552 [PMID: 21186077 DOI: 10.1016/j.eururo.2010.12.013]

41 **Mitchell RE**, Gilbert SM, Murphy AM, Olsson CA, Benson MC,

McKiernan JM. Partial nephrectomy and radical nephrectomy offer similar cancer outcomes in renal cortical tumors 4 cm or larger. *Urology* 2006; **67**: 260-264 [PMID: 16461075 DOI: 10.1016/j.urology.2005.08.057]

42 **Becker F**, Siemer S, Hack M, Humke U, Ziegler M, Stöckle M. Excellent long-term cancer control with elective nephron-sparing surgery for selected renal cell carcinomas measuring more than 4 cm. *Eur Urol* 2006; **49**: 1058-1063 [PMID: 16630686 DOI: 10.1016/j.eururo.2006.03.003]

43 **Kim JM**, Song PH, Kim HT, Park TC. Comparison of partial and radical nephrectomy for pT1b renal cell carcinoma. *Korean J Urol* 2010; **51**: 596-600 [PMID: 20856643 DOI: 10.4111/kju.2010. 51.9.596]

44 **Badalato GM**, Kates M, Wisnivesky JP, Choudhury AR, McKiernan JM. Survival after partial and radical nephrectomy for the treatment of stage T1bN0M0 renal cell carcinoma (RCC) in the USA: a propensity scoring approach. *BJU Int* 2012; **109**: 1457-1462 [PMID: 21933334 DOI: 10.1111/j.1464-410X.2011.10597.x]

45 **Kim SP**, Thompson RH, Boorjian SA, Weight CJ, Han LC, Murad MH, Shippee ND, Erwin PJ, Costello BA, Chow GK, Leibovich BC. Comparative effectiveness for survival and renal function of partial and radical nephrectomy for localized renal tumors: a systematic review and meta-analysis. *J Urol* 2012; **188**: 51-57 [PMID: 22591957 DOI: 10.1016/j.juro.2012.03.006]

46 **Wang Z**, Wang G, Xia Q, Shang Z, Yu X, Wang M, Jin X. Partial nephrectomy vs. radical nephrectomy for renal tumors: A meta-analysis of renal function and cardiovascular outcomes. *Urol Oncol* 2016; **34**: 533.e11-533.e19 [PMID: 27776978 DOI: 10.1016/j.urolonc.2016.07.007]

47 **Capitanio U**, Larcher A, Terrone C, Antonelli A, Volpe A, Fiori C, Furlan M, Dehò F, Minervini A, Serni S, Porpiglia F, Trevisani F, Salonia A, Carini M, Simeone C, Montorsi F, Bertini R. End-stage renal disease after renal surgery in patients with normal preoperative kidney function: Balancing surgical strategy and individual disorders at baseline. *Eur Urol* 2016; **70**: 558-561 [PMID: 27021797 DOI: 10.1016/j.eururo.2016.03.023]

48 **Fergany AF**, Saad IR, Woo L, Novick AC. Open partial nephrectomy for tumor in a solitary kidney: experience with 400 cases. *J Urol* 2006; **175**: 1630-1633; discussion 1633 [PMID: 16600716 DOI: 10.1016/S0022-5347(05)00991-2]

49 **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**: 1284-1288 [PMID: 18280508 DOI: 10.1016/j.juro.2007.11.071]

50 **Thompson RH**, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, Gill IS, Blute ML, Campbell SC. Renal function after partial nephrectomy: effect of warm ischemia relative to quantity and quality of preserved kidney. *Urology* 2012; **79**: 356-360 [PMID: 22310752 DOI: 10.1016/j.urology.2011.10.031]

51 **Lane BR**, Babineau DC, Poggio ED, Weight CJ, Larson BT, Gill IS, Novick AC. Factors predicting renal functional outcome after partial nephrectomy. *J Urol* 2008; **180**: 2363-2368 [PMID: 18930264 DOI: 10.1016/j.juro.2008.08.036]

52 **Thompson RH**, Lane BR, Lohse CM, Leibovich BC, Fergany A, Frank I, Gill IS, Blute ML, Campbell SC. Every minute counts when the renal hilum is clamped during partial nephrectomy. *Eur Urol* 2010; **58**: 340-345 [PMID: 20825756 DOI: 10.1016/j.eururo.2010.05.047]

53 **Lane BR**, Fergany AF, Weight CJ, Campbell SC. Renal functional outcomes after partial nephrectomy with extended ischemic intervals are better than after radical nephrectomy. *J Urol* 2010; **184**: 1286-1290 [PMID: 20723936 DOI: 10.1016/j.juro.2010.06.011]

54 **Raman JD**, Raj GV, Lucas SM, Williams SK, Lauer EM, Ahrar K, Matin SF, Leveillee RJ, Cadeddu JA. Renal functional outcomes for tumours in a solitary kidney managed by ablative or extirpative techniques. *BJU Int* 2010; **105**: 496-500 [PMID: 19681900 DOI: 10.1111/j.1464-410X.2009.08776.x]

55 **Tracy CR**, Raman JD, Donnally C, Trimmer CK, Cadeddu JA. Durable oncologic outcomes after radiofrequency ablation: experience from treating 243 small renal masses over 7.5 years. *Cancer* 2010; **116**: 3135-3142 [PMID: 20564644 DOI: 10.1002/cncr.25002]

56 **Mitchell CR**, Atwell TD, Weisbrod AJ, Lohse CM, Boorjian SA, Leibovich BC, Thompson RH. Renal function outcomes in patients treated with partial nephrectomy versus percutaneous ablation for renal tumors in a solitary kidney. *J Urol* 2011; **186**: 1786-1790 [PMID: 21944103 DOI: 10.1016/j.juro.2011.07.036]

57 **Lane BR**, Abouassaly R, Gao T, Weight CJ, Hernandez AV, Larson BT, Kaouk JH, Gill IS, Campbell SC. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. *Cancer* 2010; **116**: 3119-3126 [PMID: 20564627 DOI: 10.1002/cncr.25184]

58 **Pierorazio PM**, Johnson MH, Ball MW, Gorin MA, Trock BJ, Chang P, Wagner AA, McKiernan JM, Allaf ME. Five-year analysis of a multi-institutional prospective clinical trial of delayed intervention and surveillance for small renal masses: the DISSRM registry. *Eur Urol* 2015; **68**: 408-415 [PMID: 25698065 DOI: 10.1016/j.eururo.2015.02.001]

59 **Bang H**, Vupputuri S, Shoham DA, Klemmer PJ, Falk RJ, Mazumdar M, Gipson D, Colindres RE, Kshirsagar AV. SCreening for Occult REnal Disease (SCORED): a simple prediction model for chronic kidney disease. *Arch Intern Med* 2007; **167**: 374-381 [PMID: 17325299 DOI: 10.1001/archinte.167.4.374]

60 **Lucas SM**, Nuss G, Stern J, Lotan Y, Sagalowsky AI, Cadeddu JA, Raj GV. The screening for Occult Renal Disease (SCORED) value is associated with a higher risk for having or developing chronic kidney disease in patients treated for small, unilateral renal masses. *Cancer* 2008; **113**: 2681-2686 [PMID: 18853420 DOI: 10.1002/cncr.23850]

61 **Sorbellini M**, Kattan MW, Snyder ME, Hakimi AA, Sarasohn DM, Russo P. Prognostic nomogram for renal insufficiency after radical or partial nephrectomy. *J Urol* 2006; **176**: 472-476; discussion 476 [PMID: 16813869 DOI: 10.1016/j.juro.2006.03.090]

62 **Zhang Z**, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. *Am J Kidney Dis* 2011; **58**: 356-365 [PMID: 21601330 DOI: 10.1053/j.ajkd.2011.02.389]

63 **Zhang Z**, Xu X, Ni H, Jin N. Serum cystatin C is associated with renal function recovery in critically ill patients undergoing continuous renal replacement therapy. *Nephron Clin Pract* 2012; **122**: 86-92 [PMID: 23594833 DOI: 10.1159/000350245]

64 **Zhang Z**. Biomarkers, diagnosis and management of sepsis-induced acute kidney injury: a narrative review. *Heart Lung Vessel* 2015; **7**: 64-73 [PMID: 25861592]

65 **Morrissey JJ**, Mellnick VM, Luo J, Siegel MJ, Figenshau RS, Bhayani S, Kharasch ED. Evaluation of urine aquaporin-1 and perilipin-2 concentrations as biomarkers to screen for renal cell carcinoma: A prospective cohort study. *JAMA Oncol* 2015; **1**: 204-212 [PMID: 26181025 DOI: 10.1001/jamaoncol.2015.0213]

66 **Iliev R**, Fedorko M, Machackova T, Mlcochova H, Svoboda M, Pacik D, Dolezel J, Stanik M, Slaby O. Expression levels of PIWI-interacting RNA, piR-823, are deregulated in tumor tissue, blood serum and urine of patients with renal cell carcinoma. *Anticancer Res* 2016; **36**: 6419-6423 [PMID: 27919963 DOI: 10.21873/antic anres.11239]

**P- Reviewer**: Friedman EA, Naselli A, Talas ZS, Wang F, Zhang ZH
**S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com