Renal functional outcomes after surgery for renal cortical tumors
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Purpose of review
To review the established literature on renal functional outcomes and related pathologies after surgery for renal cortical tumors.

Recent findings
Recent data support the prevailing notion that radical nephrectomy is associated with higher rates of chronic kidney disease, regardless of the metric used in determining renal function. Furthermore, higher rates of chronic kidney disease in patients receiving radical nephrectomy have been associated with more noncancer deaths and higher rates of cardiovascular mortality.

Summary
Patients undergoing radical nephrectomy are at an increased risk of noncancer mortality, and in some cases, cardiovascular events and death. A comprehensive preoperative risk assessment is paramount in managing newly diagnosed patients with small renal masses.

Keywords
chronic kidney disease, nephrectomy, renal cell carcinoma, renal function, small renal mass

Introduction
In 2010, there were 54,000 new diagnoses and 12,000 deaths from renal cell carcinoma (RCC) [1]. The vast majority of these newly diagnosed tumors are small renal masses discovered incidentally on cross-sectional imaging [2]. This large subgroup of localized RCC was historically treated with radical nephrectomy, and continues to be treated this way in many parts of the US and the world [3]. However, over the past 10 years, there has been a paradigm shift in the surgical management of renal cortical tumors.

Currently, the three most important factors that should play a role in treatment decision-making for these patients are obtaining cancer control, minimizing morbidity, and preserving renal function. Partial nephrectomy has been shown to confer similar cancer control rates to radical nephrectomy for T1a RCC since the late 1990s [4]. More recently, partial nephrectomy has been shown to have equivalent oncologic outcomes for larger T1b (4–7 cm) tumors as well [5]. Whereas in its infancy, partial nephrectomy may have been a more morbid procedure, in the hands of an experienced surgeon operative complications rates now mirror those traditionally seen following radical nephrectomy [6,7]. Given these findings, in 2009 the American Urological Association (AUA) endorsed clinical guidelines that suggested partial nephrectomy should be the standard of care for T1a (<4 cm) RCC and a viable option for T1b tumors.

Although advocacy for partial nephrectomy originally hinged on proving noninferiority in terms of cancer control and operative morbidity. As further research emerged, however, it became evident that partial nephrectomy resulted in superior renal functional outcomes; these findings were the primary reason the AUA ultimately adopted partial nephrectomy as the preferred treatment modality for small renal tumors. Certainly, both within the nephrology and urology communities, the past decade has witnessed a paradigm shift in the understanding of how renal volume affects renal function, and how renal function in turn affects cardiovascular competence. Having less renal parenchyma, it now seems, does not merely worsen renal function, but it is a poor prognostic indicator for cardiac function and overall survival. It is against this backdrop that a review of renal functional outcomes following surgery for renal cortical tumors can be undertaken.

Chronic renal insufficiency after partial versus radical nephrectomy
The early work on renal function in the patient undergoing surgery for kidney cancer began as an effort to...
chronicle the prevalence and timing of chronic kidney disease (CKD) postoperatively. Then, as now, there is no standardized way to measure kidney function, although the literature has gradually progressed to incorporate more accurate means to assay such function. In one of the early studies on this topic, McKiernan et al. [8] selected 290 patients with T1a (<4 cm) RCC and a preoperative serum creatinine less than 1.5 mg/dl, and tracked the timing of postoperative ‘chronic renal insufficiency’ (CRI) (defined as creatinine >2 mg/dl). The rate of freedom from CRI at 5 years was 100% in partial nephrectomy versus 84.8% in radical nephrectomy. These findings were validated in a level 2 prospective cohort study by Huang et al., whereby estimated glomerular filtration rate (eGFR) lower than 60 ml/min per 1.73 m² was used as a more precise index to define CKD stage III or higher [9]. Among 662 patients with a normal serum creatinine undergoing surgery for RCC, they found freedom from new-onset CKD to be 80% after partial nephrectomy versus just 35% among the radical nephrectomy cohort [10]. Furthermore, after controlling for relevant clinical and pathologic differences between the two groups, patients receiving radical nephrectomy were at four-fold higher risk of having postoperative CKD compared with those undergoing partial nephrectomy. Similar findings were substantiated using creatinine clearance, yet another measurement of kidney function [11].

Whereas the findings in support of partial nephrectomy are compelling regardless of the renal functional metric that is employed, as alluded to previously, there is no clear consensus on the most accurate means of approximating renal function. In fact, a recent comparison of GFR estimates in patients undergoing partial nephrectomy, the Chronic Kidney Disease Epidemiology Collaboration equation categorized 7% fewer patients as CKD stage III in comparison to the Modification of Diet in Renal Disease (MDRD) equation [12]. Furthermore, eGFR is notoriously difficult to estimate in the elderly and chronically ill, and studies utilizing eGFR in this group should be interpreted with caution. As these authors note, despite the inaccuracies of eGFR, it is often interpreted as a continuous value, and not merely as a rough estimate of CKD. These findings cumulatively highlight the importance of critically interpreting the renal functional measurements used in contemporary reports.

Despite this controversy, partial nephrectomy is associated with improved long-term renal function in comparison to radical nephrectomy, a finding that continues to be validated by several recent analyses. [13–16]. Although there were initially concerns that hilar clamping during partial nephrectomy might increase the renal insufficiency rate secondary to cold ischemia time, in patients with healthy functioning kidneys, clamp time was shown not to be associated with long-term renal functional outcomes. In fact, Yossepowitch et al. [17] demonstrated that in healthy patients with two kidneys new-onset renal insufficiency is primarily a transient postoperative phenomenon. Whereas it appears nonmodifiable, factors such as the amount and quality of renal parenchyma preserved in conjunction with preoperative eGFR are more predictive of postoperative renal function, there are no level 1 data to further inform this topic [18,19].

### Key points
- Radical nephrectomy confers poor long-term renal function compared with partial nephrectomy.
- Inferior renal functional outcomes after radical nephrectomy increases risk of cardiovascular events and death.
- Although a new European Organization for Research and Treatment of Cancer (EORTC) trial suggests similar rates of overall death between radical and partial nephrectomy, renal function was not addressed in this study.
- Patients with small renal masses should undergo a renal functional risk assessment preoperatively to ensure that those at risk for CKD avoid total kidney removal.

### Chronic kidney disease as a harbinger of cardiovascular disease and death
In 2002 Go et al. [20] first identified declining renal function as a risk factor for cardiovascular events in a cohort of over one million patients of Kaiser Permanente. This large, retrospective cohort study was one of the first to demonstrate that the risk of cardiovascular events increased proportionally with a decline in eGFR. In fact, patients with a GFR less than 60 ml per min were at 1.4 times increased risk of cardiovascular events as compared to counterparts with normal renal function, and those with GFR less than 30 ml per min were at a 2.8 times increased risk of primary cardiac events. In light of this and similar emerging evidence, the National Kidney Foundation, American Heart Association, and the Seventh Joint National Committee on prevention, Detection, Evaluation, and Treatment of High Blood Pressure deemed CKD as an independent risk factor for cardiovascular disease [21–23]. The implications of this work, namely that renal insufficiency was a harbinger of heart disease, remains particularly relevant in the management of renal cancer, because patients with early-stage RCC and significant cardiovascular comorbidities may be more likely to die of noncancer-related diseases in the long term.
Poor renal functional outcomes after nephrectomy increases risk of cardiovascular events and death

Several studies have demonstrated an increase in non-cancer-related deaths in patients undergoing radical nephrectomy as compared to partial nephrectomy [24,25]. Whereas many postulated this increased mortality was likely due to CKD, and by extension cardiovascular disease, this was largely unproven until recently. Weight et al. [26*] studied overall and disease-specific outcomes in 1004 patients treated either with radical nephrectomy or partial nephrectomy for T1b RCC (4–7 cm), and over a median follow-up of 4 years observed a significantly decreased level of renal function in the radical nephrectomy cohort. This difference in renal function was associated with a 25% increased risk of cardiovascular death and a 17% risk of death from any cause. The findings of this single-institution study were substantiated by Huang et al. [27] in a population-based study of Medicare beneficiaries, which found radical nephrectomy was associated with an increased risk of cardiovascular events and non-cancer mortality within this cohort. Contemporary work continues to support the worsened overall and cardiovascular survival from radical nephrectomy, and Table 1 summarizes the data in this field.

Case in point: renal function, surgery, and the elderly

In the initial studies on postnephrectomy renal function by McKiernan et al. [8] and Huang et al. [10], the vast majority of these patients with declining renal function were diagnosed with CKD within less than 3 years of their initial surgery. The ‘long-term’ benefit from nephron-sparing surgery is therefore not long-term at all, but occurs within a few years after surgery. An older patient, even with a relatively short life expectancy would be expected to benefit from partial nephrectomy, especially considering recent evidence that there is no greater risk of complication from partial nephrectomy among patients over 75 years of age [28]. This precedent with regard to risk stratification and surgical outcomes is significant given urologists’ hesitation to perform a partial nephrectomy in the elderly, a historic disparity that has continued well into this decade [3,29].

Recently, Lane et al. [30*] have shown that for patients at least 75 years of age, the decline in renal function that occurs after radical nephrectomy is associated with increased cardiovascular death. In this older cohort of patients with local RCC 7 cm or less, there was no statistically significant difference in survival between patients treated with extirpative surgery, partial nephrectomy or radical nephrectomy, as opposed to active surveillance. This finding suggests that nonoperative management may be indicated for a subset of appropriately selected elderly patients, as active surveillance may be the proverbial ‘maximal nephron-sparing procedure’ within this population.

A comment on the EORTC randomized trial

This year the results of the first randomized controlled trial comparing nephron-sparing surgery (NSS) to radical nephrectomy were published [31**]. This phase 3 EORTC intergroup study recruited 541 patients with renal masses 5 cm or less between 1992 and 2003. Patients were randomized to receive NSS (n = 268) or radical nephrectomy (n = 273). In an intention-to-treat analysis including all patients receiving surgery, those patients receiving radical nephrectomy had better 10-year overall survival compared to NSS (log-rank test: P = 0.03). This survival difference, however, became insignificant when the cohort of interest was relegated to patients with RCC (P = 0.07) and patients with complete clinical and pathologic eligibility (P = 0.17).

The fact that renal function was not studied limits the conclusions that can be drawn about nononcologic outcomes. Only a small portion of cardiovascular morbidity and mortality can be attributed to CKD at baseline; as a result, there would need to be many cases of CKD to observe a single CKD-related cardiovascular event. The study reported no differences in cardiovascular survival between the two operations. However, given that the EORTC trial was underpowered due to its premature closing from poor accrual (541 versus 1300 patients), the small number of overall deaths (117), and particularly cardiovascular-related deaths (45), should be interpreted with caution. Nevertheless, as the only current level 1 evidence on the subject, this trial cannot be easily dismissed [32].

Renal functional risk profiling for patients with renal cortical tumors

An extensive preoperative risk assessment of patients undergoing kidney surgery is paramount, with

### Table 1 Open series outcomes (overall and cardiovascular mortality)

| Study        | Year | Age | Tumor size (cm) | Patients (n) | Overall death HR | CV events/death HR |
|--------------|------|-----|-----------------|--------------|------------------|--------------------|
|              |      |     |                 | RN | PN |
| Thompson [24]| 2008 | <65 | ≤4              | 140 | 187 | 2.16                | –                  |
| Weight [25]  | 2010 | –   | ≤7              | 111 | 388 | 2.5                 | –                  |
| Weight [26*] | 2010 | –   | 4–7             | 480 | 525 | 1.17                | 1.25               |
| Huang [27]   | 2009 | >65 | ≤4              | 2547 | 556 | 1.38                | 1.4                |

PN, partial nephrectomy; RN, radical nephrectomy.

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a particular emphasis on renal function. It has recently been reported by Clark et al. [33] that up to one-third of patients with pre-existing CKD stage I or II will go on to develop CKD stage III (GFR <60). There are several risk factors for developing stage III CKD postoperatively, most notably diabetes [18]. Some have advocated for using composite risk profiles preoperatively to predict a patient’s risk of CKD. One such risk stratification method is the Screening for Occult Renal Disease (SCORED) tool. This clinical prediction tool uses variables of patient age, sex, and symptomatology (anemia, proteinuria, and comorbidities) to stratify them into risk groupings for the development of CKD. Lucas et al. [34] validated the SCORED criteria in patients with small renal masses undergoing kidney surgery. They determined that patients in high-risk groups (SCORED ≥4) were three-fold more likely to develop stage III CKD, with rates as high as 73% for those undergoing radical nephrectomy and 17% for those undergoing partial nephrectomy [34]. Sorbellini et al. [35] have also put forth a nomogram to predict renal insufficiency, which the authors defined as two or more recordings of a creatinine of 2.0 mg/dl at least 1 month postoperatively. However, whereas this nomogram takes into account the change in kidney volume, a relevant and useful datapoint, it also relies on creatinine and does not include preoperative comorbidity information, criteria that are known harbingers of CKD.

The renal parenchyma itself at the time of surgical resection may also afford a useful tool in predicting renal functional outcomes in patients undergoing kidney surgery. In fact, the presence and extent of glomerulosclerosis in non-neoplastic renal parenchyma appears to be correlated with a deterioration in postoperative kidney function, although this trend was not noted for features of arteriosclerosis or interstitial fibrosis/tubular atrophy [36,37].

Conclusion

It is now accepted that patients undergoing radical nephrectomy for renal cortical tumors are at an increased risk for the long-term development of CKD, compared to those patients who undergo nephron-sparing surgery or no surgery at all. The implications of this deterioration in renal function continues to be an area of concern, as new evidence suggests that radical nephrectomy and CKD may lead to adverse cardiovascular outcomes in addition to eventual end-stage renal disease. A comprehensive assessment for the risk of developing CKD should be undertaken in every patient presenting with a small renal mass, as these data remain critical in informing management decisions.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest
• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 440–441).

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