

Chapter 15: Workup and Management of “Small” Renal Masses

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INTRODUCTION

Nephrologists are frequently asked by urology and oncology colleagues to participate in the management of patients diagnosed with a renal mass. This is especially the case when there is associated CKD, hypertension, and/or other medically challenging comorbidities. Renal masses are classified as large and small. Small renal masses, defined as T1a (≤ 4 cm) with no metastases or contralateral kidney involvement, have a 5-year survival rate approaching 100% in most studies. Therefore, as the vast majority of these patients are cured of their kidney cancer, the maintenance of renal function is becoming the major determinant of clinical outcomes. In this era of almost indiscriminate use of diagnostic imaging, $>50\%$ of renal masses are incidentally discovered (1,2) and 16%–23% of these are benign (3,4). Given the rise of incidental tumors, nephron-sparing procedures (partial nephrectomy, cryoablation, radiofrequency ablation, or thermal ablation) are increasingly replacing traditional radical nephrectomy (RN), and even diagnostic renal biopsies are a viable option as the concept of tumor seeding along the needle track has been largely unfounded (5).

Cancer-specific survival and overall survival between radical nephrectomy and nephron-sparing surgery are comparable (6). For poor or nonsurgical candidates, greater consideration is being given to ablative therapies or even active surveillance, given that small renal masses grow very slowly at an average rate of 1.3 mm/yr (7). This population (with small renal masses) who remain renal cancer free, are dying of other causes, most frequently due to cardiovascular events (8). With improving survival, morbidity related to CKD from nephron mass loss, as well as comorbid disease–induced complications, has become more relevant and ultimately impacts survival (with increased risk for cardiovascular

death) (9). Consideration of preoperative kidney function, comorbidities (10), nephron-sparing surgical methods, and tumor size (11) should be made when determining the management plan for patients with small renal masses.

EPIDEMIOLOGY

Individuals with small renal tumors are older (average age of 60 years), predominantly white men (12–14) with notable comorbidity (13,14). In the Medicare-linked US Surveillance Epidemiology and End Results (SEER) database, $>10,000$ individuals with small tumors ≤ 7 cm surveyed had an average tumor size of 4 cm, had a higher median age of 74, were predominantly white, 8.7% were African American, and 65% were male. In this population with high burden of comorbid diseases, almost half had diabetes mellitus (DM) or chronic obstructive pulmonary disease, a third had cerebrovascular disease, and approximately 15% had peripheral vascular disease or preexisting CKD (14). The study population of the sole prospective randomized controlled multicenter trial, European Organization for Research and Treatment of Cancer (EORTC) trial, which included small renal masses (≤ 5 cm), had substantial comorbid disease (36%), which was largely cardiovascular disease (8).

Overlapping risk factors between renal cell carcinoma and CKD may account for the high prevalence for CKD and cardiovascular disease in this population (Figure 1). Risk factors for renal cell carcinoma in the general population have traditionally

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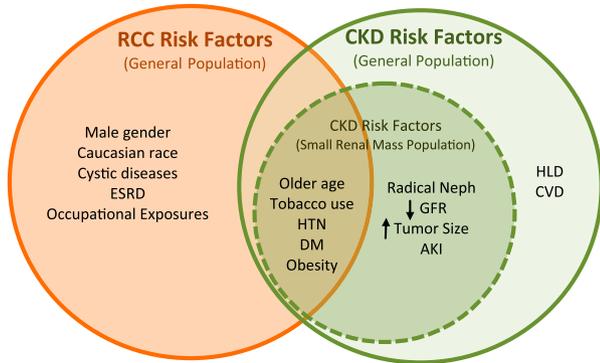


Figure 1. Overlapping risk factors for renal cell carcinoma and CKD in the general population and among those with small renal masses. DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; Neph, nephrectomy.

included tobacco exposure, obesity, DM, and hypertension (HTN) (15). Cystic disease and ESRD patients have a greater predisposition to renal tumors (16). This risk is 100-fold for ESRD patients (16) and a lesser but significant risk has been identified for stage 3 and 4 CKD (17). Therefore, the risk factors for CKD seem to also predispose one to the development of renal cell carcinoma.

With extension of survival, quality-of-life issues shaped by postoperative chronic disease burden, primarily CKD, and cardiovascular disease have increasingly become an important factor in the care of these patients.

Preoperative CKD and comorbidity

Prevalence of CKD seems to vary, considerably ranging from 10% to 52% (18–21) for those with small renal masses, similar to that of all-comers with all sizes of renal masses (11%–32%) depending on the cutoff GFR and age of the general population (22–24). When examining older subgroups, CKD prevalence nearly doubled (19,23), consistent with the finding that increasing age raises CKD risk. Of known CKD risk factors, the most important two, DM and HTN, were also highly prevalent in this population, where 9%–22% had diabetes and 23%–59% were hypertensive (18,20,24–26). The extent of DM and HTN was greater not only among those with a diagnosis of preexisting CKD, but also among those with renal cell carcinoma. Not surprisingly, preexisting CKD patients had more DM (26%) and HTN (60%) in a Korean cohort with small renal masses ($n = 1,928$) than those without CKD (DM, 12.7%; HTN, 32%) (19). In a case-matched Taiwanese cohort of 26,460 patients, those diagnosed with renal cell carcinoma had greater burden of DM (19.6%) and HTN (30.6%) compared with case-matched controls (DM, 7.7%; HTN, 14%) without renal cell carcinoma (10).

CKD risk factors

Predictive factors for new-onset CKD or progression of CKD after therapeutic intervention include older age, male sex (6), tobacco use (27), obesity (27,28), and concomitant DM or

HTN, which are reflective of the predominant features defining the renal mass cohort, and also include lower baseline estimated GFR and larger tumor size (10,11,20). Hypoalbuminemia (19) and postoperative AKI (29) are other likely determinants of GFR decline (Table 1). With tumor resection, CKD prevalence increased anywhere from 10%–24% to 16%–52% after treatment (18–20). Others reported a mean GFR decrease of 13 mL/min per 1.73 m², corresponding to a 30% drop in GFR after partial nephrectomy (PN), and renal volume reduction seemed to be a prognostic factor for GFR decline (30). Furthermore, among diabetics, 60% developed CKD compared with only 43% of the entire cohort; the 2-year probability of absence of CKD was poor among patients with diabetes (47%) in contrast to those without DM (76%, $P = 0.006$) (20). Incidence of ESRD was 5.6 times greater among renal cell carcinoma patients (4.05%) than for a comparable control group (0.68%) (10). In the US Renal Data System (USRDS), renal cell carcinoma has been reported as a cause for ESRD in 0.5% of the 360,000 patients, with a higher mortality compared with other causes of ESRD (28).

MANAGEMENT

Preoperative evaluation

Historically, small renal mass identification by imaging studies nearly always led to surgical intervention with the possible exception of an angiomyolipoma, which can be suspected when there is a significant component of adipose tissue. However, active surveillance and percutaneous kidney biopsies are viable options that are increasingly utilized, as up to 23% of patients will have benign small renal masses (oncocytoma or angiomyolipoma) and can be spared any additional surgery (3,4). The diagnostic rate of kidney biopsies approaches 80% in experienced centers (31), and the concordance rate approaches 100% compared with the surgical resection specimen (32).

Preoperative evaluation of potentially modifiable risk factors including DM, HTN, and CKD may play a role in the preservation of renal function. Optimizing glycemic and BP control, as well as estimation of GFR and prevention of AKI, may minimize risk for deterioration of GFR postoperatively. Prevention of AKI can be achieved through proper medical management to avoid nephrotoxic exposure and renal

Table 1. Risk factors for CKD

Older age (>65 years)
Male sex
Tobacco use
Comorbid diseases
Diabetes mellitus
Hypertension
Obesity
Lower baseline GFR
Larger tumor size
Surgical procedure: radical nephrectomy
Postoperative AKI

hypoperfusion (33). Renal nuclear scintigraphy has been used to help determine proportional GFR of each kidney to better assess the potential impact of renal resection (partial or radical nephrectomy). Preoperative proportional GFR assessment used to calculate the expected postoperative GFR tended to underestimate the actual postoperative GFR by 12% in one study (34), presumably due to compensatory hyperfiltration and hypertrophy. Additionally, one study examining pre- and postoperative differential function with nuclear scintigraphy found that postsurgical differential function inversely correlated best with ischemia time and tumor size, which may be more predictive of intraoperative renal damage (35). Evaluation of differential function remains a useful tool in assessing operative risk for CKD, providing we recognize these limitations of total GFR underestimation (due to hyperfiltration by the preserved kidney) and relative GFR overestimation in the surgical kidney.

Treatment of small renal masses and outcomes

RN has been the mainstay of therapy for generations and remains an essential therapy for those with larger renal masses or with lesions extending beyond the affected kidney. Small renal masses have favorable prognosis and survival, which do not necessitate radical nephrectomy. Partial nephrectomy has equivalent/comparable oncologic and overall survival and greater renal preservation (6,36,37).

Innumerable studies have emerged examining these outcomes over the last couple of decades with similar findings and may be best illustrated in a meta-analysis performed by Kim *et al.* Risk reduction with nephron-sparing surgery assessed from 36 studies (40,000 patients; 31,000 RN and 9,300 PN) was 19% for all-cause mortality, 29% for cancer specific mortality, and 61% for CKD (37). On the contrary, the EORTC study, which was a clinical trial of 541 patients with solitary unilateral small renal masses (≤ 5 cm), found that overall 10-year survival was slightly higher for RN (81.1%) than nephron-sparing surgery (75.7%), with a hazard ratio (HR) of 1.5 (95% CI, 1.03–2.16). The small difference in mortality was no longer present when only patients diagnosed with renal cell carcinoma were considered. Progression of disease and renal cell carcinoma death were no different between the two therapies (8).

In the same EORTC study, risk of CKD was retrospectively examined and demonstrated that partial nephrectomy (PN) preserved GFR (baseline creatinine < 1.25 times the upper normal range), particularly early on where the difference of patients reaching GFR < 60 mL/min per 1.73 m² between RN (85.7%) and PN (64.7%) was 21%. However, over time, this difference of progressive decline to lower GFRs < 30 (RN 10%, PN 6.3%) and < 15 mL/min per 1.73 m² (RN 1.5%, PN 1.6%) became insignificant. The steeper GFR decline observed initially with RN was not associated with an increase in mortality (36), potentially suggesting that GFR loss from nephrectomy did not confer the same risk of death usually seen with GFR decline from traditional causes of CKD such as DM or HTN (9). The cohort studies, however, generally showed a survival

advantage in addition to GFR preservation with nephron-sparing surgery (37), which is clearly limited by its retrospective design.

The increased mortality seen with CKD has been attributed to high cardiovascular disease risk typically associated with advanced GFR (9). Among 1,004 case-matched patients with relatively small renal mass size (T1b, 4–7 cm), an association of greater cardiovascular death and GFR decline was observed. GFR loss was measured using the difference between extrapolated values of preoperative and (> 3 weeks) postoperative GFRs. The average GFR loss was less for those who had partial nephrectomy (16.6 mL/min) as opposed to radical nephrectomy (23.5 mL/min, $P < 0.0001$). GFR decline generally occurred within 3 weeks and then stabilized thereafter. Each excess loss of GFR of 7 mL/min per 1.73 m² resulted in a 17% increase risk of death as well as a 25% greater cardiovascular disease risk. Cancer-specific survival was not different, but overall survival was better for partial nephrectomy (85% versus RN 78%, $P = 0.01$) (38).

The hard end point of ESRD has also been examined in a Taiwanese incident cohort with 10-year follow-up in a newly diagnosed renal cell carcinoma group ($n = 2940$) and a control group ($n = 23,520$). Progression to ESRD occurred in 4.05% of the renal cell carcinoma group compared with only 0.68% of the control group (HR, 5.63; 95% CI, 4.37–7.24) with the same risk factors (DM, preexisting CKD) for CKD progression (10). In the USRDS, the higher mortality noted with ESRD from renal cell carcinoma compared with other causes was not observed for those who had undergone nephrectomy, suggesting that even though progression to ESRD from renal cell carcinoma could not be prevented, nephrectomy may still confer a lower risk for mortality (28).

Alternative therapy for small renal masses in individuals with high operative risk includes nonsurgical ablative therapies such as radiofrequency ablation and cryoablation, which are currently the two most common approaches used. Older patients were more likely to receive radiofrequency ablation (RFA) with fewer major complications (RFA 3.1% versus PN 7.2%–7.9%, $P < 0.001$), but with higher local progression of disease (RFA 4.6% versus PN 1.2%–1.9%, $P < 0.001$) than seen with partial nephrectomy (39). In one series, however, oncologic outcomes were no different when excluding those with high risk for recurrence (40). Cryoablation was also utilized more frequently for older patients with higher operative risk. In addition to fewer procedural complications, shorter length of hospital stay was noted; however, this was also associated with higher local (relative risk [RR], 9.39; $P < 0.0001$) and metastatic progression of disease (RR, 4.68; $P = 0.01$) after cryoablation compared with partial nephrectomy (both performed laparoscopically) (41). Last, active surveillance with judicious monitoring of tumor size and sometimes with delayed surgical intervention resulted in acceptable outcomes particularly among those age > 75 , which was no worse than surgical resection for select populations (14). Although oncologic outcomes for ablative therapies may not be as favorable as surgical resection, they provide viable therapeutic options

with less complications and likely greater renal parenchymal (thus also GFR) preservation for nonoperative candidates.

PATHOLOGIC EVALUATION OF TUMOR NEPHRECTOMY

The evaluation of tumor nephrectomy specimens has always centered around the renal mass, but careful assessment of the nonneoplastic kidney parenchyma reveals the presence of common yet undiagnosed nonneoplastic renal diseases. Therefore, the synoptic reports established by the College of American Pathologist required in 2010 that the nonneoplastic parenchyma should be evaluated and reported for every renal malignancy (42). Also, the Accreditation Council for Graduate Medical Education will require that nephropathology be part of the curriculum for all anatomic pathology residents effective July 1, 2015, as the vast majority of pathologists do not receive any exposure to this subspecialty. Several large studies found that diabetic nephropathy and hypertensive nephropathy (or arterionephrosclerosis) can be identified in 8%–20% and 3%–14% of specimens, respectively (43–45), and 60%–88% of these diagnoses were not identified during the initial evaluation. With nearly 350,000 kidney cancer survivors in the United States, the CKD burden will only increase, especially as more attention is given to the nonneoplastic parenchyma examined by pathologists. In addition, there still remains much room for improvement regarding the coordination of urologists, pathologists, and especially nephrologists in the preoperative and postoperative management of kidney cancer patients.

CONCLUSIONS

The majority of renal tumors are small renal tumors discovered on routine imaging with excellent oncologic and overall survival. The prolonged survival with earlier discovery has resulted in higher likelihood of nononcologic death, where patients are saddled instead with CKD and associated increased cardiovascular morbidity and mortality. Minimally invasive techniques for diagnosis and nephron-sparing surgery have minimized nephron mass and functional loss. Recognizing and assessing modifiable risk factors for CKD such as HTN, DM, and cardiovascular disease may potentially allow for greater preservation of GFR and reduction of cardiovascular disease-related death. To achieve this goal, communication and coordination of management is essential within the specialty care team, which is comprised of nephrologists, oncologists, urologists, and pathologists.

TAKE HOME POINTS

- Early diagnosis of small renal tumors is rising due to incidental discovery with favorable prognosis.
- New-onset CKD is fairly common after nephrectomy with overlapping risk factors for CKD and renal cell carcinoma.

- Older age, male sex, comorbid diseases including diabetes mellitus, hypertension, preexisting CKD, and larger tumor size increase risk for postoperative CKD.
- Nephron-sparing surgery (partial nephrectomy) among patients with small renal masses has equivalent cancer-specific survival, practically similar overall survival, and better GFR preservation compared with radical nephrectomy.

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REVIEW QUESTIONS

1. What are the common risk factors for both CKD and renal cell carcinoma (RCC)?
 - a. Obesity
 - b. Diabetes mellitus
 - c. Hypertension
 - d. All of the above

Answer: d is correct. Diabetes, hypertension, and obesity are independent risk factors for renal cell carcinoma. Diabetes and hypertension can be found in 25% and up to 60% of kidney cancer patients, respectively. These are also the two most common causes of ESRD. Given the link between CKD and RCC, it is not surprising to find these common overlapping risk factors. Obesity is a lesser but also significant risk factor common to both CKD and RCC.

2. Which of the following is the most common pathologic finding in tumor nephrectomy specimens?
 - a. Diabetic nephropathy
 - b. Membranous nephropathy
 - c. IgA nephropathy
 - d. Focal segmental glomerulosclerosis
 - e. Minimal change disease

Answer: a is correct. Diabetes is an independent risk factor for RCC and is found in up to 25% of kidney cancer patients. Therefore, diabetic nephropathy is common and can be identified in 8%–20% of tumor nephrectomy specimens (depending on the definition of diabetic nephropathy). IgA

nephropathy occurs in <2% of specimens. Amyloidosis occurred in 3% of specimens according to a study in the late 1980s, but is much less common due to the significant stage migration that has occurred toward smaller neoplasms as a result of early detection. Membranous nephropathy and pauci-immune crescentic glomerulonephritis rarely occur in the setting of kidney cancer, with only case reports being available in the literature.

3. Which of the following statements is true regarding outcomes in the management of small renal masses?
 - a. Cancer-specific survival and overall survival is superior with radical nephrectomy, which should be considered primarily in this population
 - b. Partial nephrectomy is associated with GFR preservation and comparable cancer-specific survival and overall survival to that of radical nephrectomy
 - c. Ablative therapies are associated with increased treatment-related complication rates but less disease progression
 - d. Active surveillance is not indicated for management of small renal masses

Answer: b is correct. Cancer-specific survival and overall survival are equivalent between partial and radical nephrectomy. GFR preservation is greater with partial nephrectomy. For small renal masses, nephron-sparing procedure should be considered first. Ablative therapies have worse oncologic outcomes but lower treatment-related complications. Active surveillance in select populations such as older poor operative candidates have been shown to have comparable outcomes.