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Prevalence of Baseline Chronic Kidney Disease in Patients Presenting with Solid Renal Tumors

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Abstract

Objectives—Serum creatinine (sCr) inadequately reflects renal function. Estimated glomerular filtration rate (eGFR) and CKD stage are more clinically relevant parameters to reflect the risk of morbidity and mortality in patients following nephron loss. Comparing sCr and eGFR, we evaluated the prevalence of baseline CKD in a large cohort of patients presenting with renal masses to a tertiary care center.

Methods—Using the prospectively maintained Fox Chase Kidney Cancer Database, we identified patients undergoing kidney surgery between 1/2000– 5/2010. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) and the CKDEpidemiology formulas. CKD stages I–V were defined using the National Kidney Foundation definitions.

Results—1114 patients had adequate data available to calculate a preoperative eGFR (ml/min). Although 88% of all patients presenting for surgery at our institution had a “normal” baseline sCr (≤ 1.4 mg/dl), 22% of patients had CKD Stage III or greater. Moreover, of the 282 patients 70 years and older, 40% (113/282) had CKD stage III. 23% (51/220) of patients older than 70 years had a CKD stage III with a seemingly normal sCr.

Conclusions—Many patients with a normal sCr have CKD III or higher, particularly patients older 70 years old. Given the high prevalence of baseline CKD in patients with a solid renal tumor, a concerted effort must be made to preserve renal function when surgically treating solid renal masses.

Keywords

kidney cancer; chronic kidney disease; serum creatinine; glomerular filtration rate

INTRODUCTION

The incidence of renal cell carcinoma (RCC) continues to rise due to the widespread use of cross-sectional imaging¹ with the greatest absolute increase noted in renal tumors sized 2–4 cm.² The AUA has recently published guidelines outlining their recommendations for the treatment of the clinical T1 renal mass.³ At present, a renal lesion less than 4 cm (cT1a),

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treated by radical nephrectomy (RN), partial nephrectomy (PN), or thermal ablation (TA) has a recurrence-free survival rate ranging from 87–99%.³ Also, increasing data suggest that selected patients with prohibitive medical co-morbidities or those who do not desire surgery may have such small renal masses (SRMs) followed on an active surveillance (AS) protocols with a low likelihood of progression over one to three years.⁴

The recent systematic review by the guidelines committee of the AUA highlight the priority of goals when managing localized RCC: (1) optimize cancer treatment, (2) preserve renal function, and if the first two goals are met, (3) utilize a minimally-invasive technique while minimizing the risk of adverse post-operative events.³ Published series have established the oncologic efficacy of nephron-sparing surgery (NSS) for pT1a and more recently pT1b renal tumors.^{5–8} Furthermore, emerging data suggest that NSS may be an acceptable treatment option for anatomically appropriate pT2 tumors.^{9–10} Despite these findings and other data indicating that PN confers a non-oncological survival advantage, nationally the use of PN for tumors less than 4 cm continues to be less than 30%.¹¹

As more incidental renal masses continue to be detected and the adverse relationship between long term CKD and morbidity/mortality is uncovered, the importance of renal functional preservation will continue to be stressed. Recent data suggest that the serum creatinine measurements are a poor tool to estimate the degree of renal impairment.^{12–13} In fact, in a recent cross-sectional analysis comparing the National Health and Nutrition Examination Surveys (NHANES) between 1988–1994 and 1999–2004 consisting of approximately 29,000 patients, 25% of patients with a “normal” serum Cr (sCr) had chronic kidney disease (CKD) stage 3 or greater, as defined by the National Kidney Foundation.¹⁴ Therefore, the socioeconomic and health implications of significant national under-utilization of NSS are likely clinically underestimated. We evaluated the baseline renal functional parameters of patients presenting to our institution for evaluation of an enhancing renal mass and determined the prevalence of baseline chronic kidney disease in this large case specific cohort of patients with SRM.

MATERIALS AND METHODS

Information regarding patients undergoing renal surgery between 2000 and 2010 are recorded in our prospectively maintained kidney cancer database in accordance with institutional review board guidelines. All consented patients evaluated for a suspicious renal mass and managed by excision, ablation or active surveillance were included in this study cohort. Standard evaluation included medical history, physical examination, routine laboratory studies including serum creatinine level and appropriate radiographic testing (contrast based CT scan or MRI of the abdomen and staging studies).

Of the 2006 patients in our database, patients who did not undergo surgery or had urothelial histology, metastatic disease to the kidney, or no demonstrable pathology were excluded from the analysis. Another 75 patients did not have adequate data available to calculate a preoperative eGFR (ml/min), leaving 1114 patients who formed the basis of our analysis. Estimated GFR was calculated using the both the MDRD equation $GFR (ml \text{ per minute per } 1.73 \text{ m}^2) = 186 \times sCr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$ and the CKD-Epidemiology Study equation as described previously¹⁵. Chronic kidney disease stages I–V were defined according to the definition provided by the National Kidney Foundation.¹⁶ CKD stages were stratified by age and gender. The two equations were compared to determine if one equation was more sensitive in detecting CKD in patients presenting with a solid renal mass.

Management by excision, ablation or observation was based on clinical assessments including performance status, co-morbidity calculations, nephrometry scores¹⁷ and interactive patient trade off decisions. A descriptive analysis of the type of 1178 surgical procedures performed on the 1114 patients with renal function data available is presented. An analysis of the overall trends in the type of renal surgery performed at our institution over the time interval based on eGFR, CKD stage and nephrometry is presented to determine if there has been a trend toward renal parenchymal preservation and its interaction with nephrometry.

RESULTS

Of the 1114 patients who formed the basis of this analysis, 66% were male and 87.5% were Caucasian (10% African-American, 2.5% other). The mean age for this cohort was 62 (range=24–88). Table 1 stratifies the patient population by age, baseline serum Cr value, baseline CKD stage, and type of surgical procedure performed. 833 patients (67%) were older than 55 years of age, and 983 patients (88%) had a normal serum Cr, using equal to or less than 1.4 mg/dl as an accepted cutoff. In contrast to serum Cr, the prevalence of baseline chronic kidney disease in the whole patient population as defined by the National Kidney Foundation by estimating an individual's glomerular filtration rate using both the MDRD and the CKD-epi equations results in 22% of all patients presenting to our tertiary care center as having CKD stage III or higher: 226 patients (20%) had CKD stage III, 11 patients (1%) had CKD stage IV, and 11 patients (1%) had CKD stage V. 597 patients (48%) underwent a radical nephrectomy to treat their renal mass while 52% (660 patients) had a partial nephrectomy or an ablative procedure.

Table 2a examines the underestimation of CKD in patients with a normal sCr. Of the 1114 patients in our cohort, 983 (88%) patients had a serum creatinine at presentation of ≤ 1.4 mg/dl. Of these 983 patients, 124 (12.5%) patients had unrecognized CKD stage III. Similarly, there were 282 (25%) patients in our cohort who were 70 years old or greater. Of these 282 patients, 113 patients (40%) had CKD stage III or greater at the time of discovery of their solid renal mass. More importantly, of the 220 patients older than 70 years of age with a sCr ≤ 1.4 mg/dl, 51 (23%) people had CKD stage III, accounting for over half of all patients > 70 with CKD III+. We could not identify a greater prevalence in higher CKD stages in men compared to women (Table 2b). Furthermore, we identified no difference in the distribution of CKD staging comparing the MDRD to the CKD-epi equations (Table 2c).

Tables 3a and 3b examine the relationship between surgical procedure, nephrometry score, and CKD stage. Of the 529 patients with nephrometry scores available for their renal mass, 350 (66%) patients had a partial nephrectomy and 179 (34%) patients had a radical nephrectomy. When stratifying by complexity of the mass using nephrometry score, i.e, low, medium, and high, 113 masses were scored as low complexity; 244 were scored as medium complexity; and, 171 masses were scored as high complexity. Of the low complexity masses, 94% were excised using nephron-sparing techniques. Conversely, for high complexity masses, 68% were treated with a radical nephrectomy even though 13% of patients with high complexity masses had CKD stage III prior to surgery. 6% of patients with high complexity masses had CKD stage III pre-operatively and were treated with a partial nephrectomy. Of the 244 medium complexity masses, 23% were treated with complete kidney removal while the remaining 77% underwent a partial nephrectomy. Finally, closer examination of this subset of patients reveals that 11.5% of patients with a medium complexity mass and CKD stage III underwent a partial nephrectomy whereas 4.5% of comparable patients underwent a radical nephrectomy.

COMMENT

While renal physiologists have long recognized the limitations of serum creatinine (sCr) in estimating glomerular filtration, only in the last 2 to 3 years have physicians begun to focus on the clinical implications of this concern. Traditionally, sCr has been used to measure the presence or absence of renal dysfunction, however this can be a misleading value, since sCr can be affected by age, gender, muscle mass, and dietary intake of meat. Furthermore, since creatinine is both secreted and reabsorbed by renal tubules, certain medications, such as cimetidine and bactrim, can alter sCr by inhibiting its tubular secretion. With recent data underscoring the prevalence of CKD in the general population, attention has focused on estimating the glomerular filtration rate (GFR) as a measure of a patient's renal function. More precise measures of GFR have recently been adopted including the MDRD and CKD-epi, since these equations incorporate a patient's age, gender, body-surface area, and race.

As oncologic data have become available demonstrating equivalency of nephron-sparing surgery compared with radical approaches in most cases of localized RCC, increased attention has focused on the under-utilization of NSS techniques. A recent examination of the National Cancer Database (NCDB) between 1993–2005 revealed that only 27.1% of tumors less than 4.0 cm were being treated with NSS techniques.¹⁸ At the beginning of this time period, a paltry 5.9% of T1a lesions were being treated with NSS approaches. The SEER registry data shows similar trends. Examining the SEER data from 1999–2006 for over 18,000 lesions less than 4.0 cm, the rate of PN only increased from 20.0% to 40.0%.¹¹ Finally, an analysis of over 66,000 patients from the Nationwide Inpatient Sample from 1988 to 2002 revealed a 7.5% national rate of PN.¹⁹

The risk of postoperative chronic kidney disease after RN when compared to PN has been well studied. McKiernan et al. showed that the risk of having a postoperative baseline sCr greater than 2.0 mg/dL was significantly greater following RN when compared to a PN.²⁰ A more precise quantification of chronic kidney disease after nephrectomy was undertaken by Huang et al. Using the MDRD equation to estimate GFR, the authors found in a multivariable analysis that RN was an independent risk factor for patients developing an eGFR of less than 60 mL/min and less than 45 mL/min.²¹ The incidence of baseline renal dysfunction (eGFR < 60) in their study was 26%.

The relationship between chronic kidney disease on risks of death, cardiovascular events, and hospitalization rates is clinically relevant but has previously not received much attention because it is often an event that occurs well past the initial surgical loss of nephrons. With each 15 mL/min diminution of eGFR below 60 mL/min, the risk of death, cardiovascular events, and hospitalization increases.²² For example, the adjusted hazard ratio for death in a patient with an eGFR of 45 to 59 mL/min is 1.2 while it is 5.9 for an eGFR less than 15 mL/min.²² Furthermore, the interaction between age and CKD and their effects on survival requires the urologist to diligently assess an elderly patient's renal function preoperatively. In one study, more than 50% of patients older than 75 years died within 2 years after starting dialysis.²³ The median survival time for this aged population on dialysis was 22 months.

There is mounting published evidence suggesting that radical nephrectomy even in the setting of a normal contralateral kidney predisposes a patient to decreased overall survival and decreased cardiac specific survival, although the mechanism for this relationship is unclear.^{24–26} Most recently, Weight et al. published the Cleveland Clinic's follow-up comparing survival outcomes in patients who underwent a RN or a PN for a cT1b renal mass. In this cohort of 1,004 patients, postoperative eGFR was an independent predictor on multivariate analysis of overall survival and cardiac specific survival. Patients treated with a PN had a statistically significant improved 5-year OS compared to patients treated with RN,

85% versus 78% ($p=0.01$).²⁶ Interestingly, of the 175 deaths in this cohort, 48 were due to cardiovascular events and 19 were related to renal failure.

Similar conclusions were reached by Thompson et al. and Huang et al. when examining the Mayo Clinic nephrectomy registry as well as the SEER cancer database. The data from the Mayo clinic demonstrated that in patients younger than 65 years treated for a pT1a renal mass, RN was significantly associated with death from any cause (RR 2.16, $p=0.02$).²⁴ Also, a query of the SEER cancer registry showed a statistically significant increase in the risk of cardiovascular events ($p < 0.05$) and all cause mortality (HR 1.46, $p < 0.001$) for patients treated with RN for a pT1a renal mass.²⁵

The prevalence of CKD stage III or higher based on NHANES 1999–2004 data has increased to over 8%.¹⁴ It is unclear if a population enriched for patients with radiographically concerning RCC reflects this trend or has a potentially higher risk of CKD. In this study, we demonstrate that although 88% of all patients presenting for surgery with a solid renal mass at our institution had a “normal” sCr (≤ 1.4 mg/dl), 12.5% of these patients had CKD Stage III when estimating GFR. Moreover, 23% of patients 70 years old or greater with a seemingly normal sCr had CKD Stage III. These findings support reports by other authors who have argued for more precise measurement of a patient's renal function, either by the MDRD equation or the newly developed Chronic Kidney Disease-Epidemiology Study equation, to better assess a patient's renal function.¹³ Finally, the national average of NSS, ranging from 27% to 40%¹¹ for pT1a tumors, is concerning in light of our findings showing an underestimation of chronic kidney disease by routine serum creatinine monitoring. We believe, especially in the elderly, that this study highlights the fact that both eGFR and CKD stage must be routinely calculated and clinical decisions based on these variables not sCr.

The nephrometry score of a given renal mass is an objective and reproducible system to standardize the description of salient tumor anatomy. Our data was unique in that we explored the relationship between a tumor's nephrometry score, type of surgical procedure chosen, and a patient's CKD stage. As expected, low complexity tumors were almost universally treated by NSS. Similarly, the preponderance of high complexity tumors—68%—were treated by radical nephrectomy even in patients with CKD stage III. In fact, twice as many patients with CKD stage III and high complexity masses were treated by radical nephrectomy, highlighting the difficult tumor anatomy of these masses which may preclude renal parenchymal preservation. Medium complexity tumors appear to be the group of masses that offer the greatest opportunity to intervene in a manner that maximizes renal functionality. In our data, 77% of these masses were treated with NSS, including 11.5% of medium complexity masses in patients with CKD stage III. Only 4.5% of medium complexity masses in patients with CKD stage III were treated with radical nephrectomy. Although challenging, it appears technically possible, oncologically sound and functionally imperative to perform a partial nephrectomy in patients with medium and even high complexity masses, especially when chronic kidney disease exists.

The retrospective nature of this analysis is an inherent limitation of this single institution study. Although the findings in this observational study are novel, the ability to generalize them is limited. Despite the finding of almost half the population over 70 years of age having CKD, this study lacks prospective correlation. Meaningful conclusions could best be drawn if preoperative renal assessment were done more precisely^{12,13} in concert with an objectification of the salient anatomy of the renal mass that has been advocated by us¹⁷ and others²⁷. By codifying surgical decision-making based on preoperative renal function and an objective measure(s) of the renal mass in question, one could better objectify surgical decision-making.²⁸ Finally, as a tertiary care center with a large volume of complex kidney

cases, there may be a bias toward NSS in complex tumors that may not be generalizable to the average practitioner. This possibility argues for standardization, i.e, nephrometry scores, so that these complex cases are sent to referral centers rather than subjecting a patient to a radical nephrectomy and its possible long term deleterious health risks.

CONCLUSIONS

We demonstrate a high prevalence of baseline chronic kidney disease in patients presenting to a tertiary referral center with a renal mass, particularly in the elderly (>70) where nearly half of all patients had CKD III+ of which nearly half had a normal sCr. Our data underscores the shortcomings of serum Cr measurements given that the absolute Cr value is an inexact measure of a patient's true renal function. This data is especially relevant given underutilization of nephron sparing surgery and robust emerging data regarding inferiority of radical nephrectomy when compared to NSS with regard to long-term morbidity and overall survival. Continued objectification of clinical decision making including measurements of performance status, eGFR, CKD stage and nephrometry are imperative to improving rates of nephron preservation for RCC.

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Table 1

Patients stratified by Age, pre-operative serum Cr, pre-operative CKD stage, and type of surgical procedure

Age	No. (%)
18–35	30 (2)
36–45	131 (10)
46–55	260 (21)
56–65	397 (32)
66–75	293 (23)
76–85	142 (11)
>85	1 (1)
Serum Creatinine (mg/dl)	No. (%)
≤1.0	667 (60)
1.1–1.4	316 (28)
1.5–1.8	89 (8)
1.9–2.2	22 (2)
2.3–2.6	4 (<1)
>2.7	16 (2)
CKD Stage	No. (%)
Stage I (eGFR ≥90)	294 (26)
Stage II (eGFR 60–89)	572 (52)
Stage III (eGFR 30–59)	226 (20)
Stage IV (eGFR 15–29)	11 (1)
Stage IV (eGFR <15 or dialysis)	11 (1)
Type of Procedure	No. (%)
Nephrectomy	597 (48)
Partial Nephrectomy	606 (48)
Ablative Therapy	54 (4)

Table 2A

CKD Stages in Patients Presenting to a Tertiary Care Center for Evaluation of a Solid Renal Mass Stratified by Age

CKD (All patients)	Overall No. (%)	Patients with “normal” sCr (<1.4mg/dl) (n=983)
Stage I (eGFR ≥90)	294 (26)	293 (29.5)
Stage II (eGFR 60–89)	572 (52)	570 (58)
Stage III (eGFR 30–59)	226 (20)	124 (12.5)
Stage IV (eGFR 15–29)	11 (1)	0 (0)
Stage IV (eGFR <15 or dialysis)	11 (1)	0 (0)
CKD (Patients > 70 years old)	No. (%)	Patients with “normal” sCr <1.4mg/dl) (n=220)
Stage I (eGFR ≥90)	34 (12)	34 (16)
Stage II (eGFR 60–89)	135 (48)	135 (61)
Stage III (eGFR 30–59)	102 (36)	51 (23)
Stage IV (eGFR 15–29)	5 (2)	0 (0)
Stage V (eGFR <15 or dialysis)	6 (2)	0 (0)

Table 2B

CKD Stages in Patients Presenting to a Tertiary Care Center for Evaluation of a Solid Renal Mass Stratified by Gender

CKD (All patients)	No (%)	Male (%)	Female (%)
Stage I (eGFR $\geq$ 90)	294 (26)	199 (27)	95 (25)
Stage II (eGFR 60–89)	572 (52)	368 (50)	204 (54)
Stage III (eGFR 30–59)	226 (20)	152 (21)	74 (19)
Stage IV (eGFR 15–29)	11 (1)	6 (1)	5 (1)
Stage V (eGFR <15 or dialysis)	11 (1)	8 (1)	3 (1)
CKD (Patients > 70 years old)	No. (%)	Male (%)	Female (%)
Stage I (eGFR $\geq$ 90)	34 (12)	20 (11)	14 (13)
Stage II (eGFR 60–89)	135 (48)	86 (48)	49 (47)
Stage III (eGFR 30–59)	102 (36)	66 (37)	36 (35)
Stage IV (eGFR 15–29)	5 (2)	2 (1)	3 (3)
Stage V (eGFR <15 or dialysis)	6 (2)	4 (2)	2 (2)

Table 2C

Comparison of MDRD and CKD-epi equations in determining CKD Stages in Patients Presenting to a Tertiary Care Center for Evaluation of a Solid Renal Mass

CKD (All patients)	MDRD equation	CKD-epi equation
Stage I (eGFR ≥ 90)	294 (26)	294 (26)
Stage II (eGFR 60–89)	572 (52)	572 (52)
Stage III (eGFR 30–59)	226 (20)	226 (20)
Stage IV (eGFR 15–29)	11 (1)	11 (1)
Stage V (eGFR <15 or dialysis)	11 (1)	11 (1)

Table 3A

NSS trends based on nephrometry score and CKD stage

N=350	Low (4–6)	Medium (7–9)	High (10–12)
CKD Stages I/II	83 (74%)	160 (66%)	43 (25%)
CKD Stage III	23 (20%)	28 (12%)	11 (6%)
CKD Stages IV/V	0	1 (<1%)	1 (<1%)

Table 3B

Radical nephrectomy trends based on nephrometry score and CKD stage

N=179	Low (4–6)	Medium (7–9)	High (10–12)
CKD Stages I/II	4 (4%)	41 (17%)	92 (54%)
CKD Stage III	2 (2%)	11 (5%)	22 (13%)
CKD Stages IV/V	1 (<1%)	4 (<1%)	2 (1%)