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BASELINE GFR IMPACTS SURVIVAL IN PATIENTS UNDERGOING PARTIAL OR RADICAL NEPHRECTOMY FOR RENAL CORTICAL TUMORS

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Abstract

Background—We evaluated the impact of baseline renal function and comorbidity index on survival in patients with renal tumors.

Methods—We identified 1479 patients who underwent partial or radical nephrectomy between 1995 and 2005 for localized renal tumors. Demographic, clinicopathologic, body mass index (BMI) and comorbidity data (assessed by Charlson-Romano index and hypertension) were retrieved. We used the abbreviated modified diet and renal disease (MDRD) equation to estimate glomerular filtration rate (GFR) using the last preoperative serum creatinine. BMI and GFR time trends were analyzed with linear regression. The impact of BMI, comorbidity, and baseline GFR on disease-free and overall survival was studied using Cox regression controlling for pathologic stage, node and metastatic status.

Results—Over a 10 year interval, median BMI increased from 27 (Interquartile Range [IQR]: 24,31) to 28 (IQR: 25,31, $p=0.004$), and median baseline GFR fell from 70 (IQR:58,80) to 63cc/min/1.73m² (IQR: 57,78, $p<0.001$). Multivariable regression demonstrated an association between year of surgery and baseline GFR ($p<0.001$) even after adjusting for age, sex, comorbidity, BMI, and tumor size. We repeated the analysis for patients aged 18–70, and this association persisted ($p<0.001$). Baseline GFR, BMI, and comorbidity were not associated with disease-free-survival after controlling for stage. However, moderately reduced baseline GFR (45–60cc/min/1.73m²) and severely reduced GFR (<45cc/min/1.73m²) were significantly associated with overall survival (hazard ratio [HR] 1.5, $p<0.003$ and 2.8, $p<0.001$, respectively).

Conclusions—There has been a time-dependent decline in baseline GFR over the last decade. Baseline GFR is an important preoperative consideration independently affecting overall survival.

Keywords

GFR; renal cortical tumor; renal cell carcinoma

Introduction

The last two decades have heralded significant changes in the treatment of localized renal cortical tumors (RCT). Considerable stage migration has occurred as a result of increased use of abdominal imaging, manifesting as incidental detection of smaller tumors.^{1–4} Despite this trend, cancer-specific and overall mortality have actually increased.^{4, 5} Decreased survival is

most evident in patients with tumors >7cm, but has been observed across all sizes of tumors.^{4, 5} The reason for this trend is not clear, but may be related to non-oncologic factors such as chronic kidney disease (CKD), and obesity. We previously recently reported that 26% patients who underwent radical or partial nephrectomy for RCT had baseline CKD.⁶

CKD, defined as an estimated glomerular filtration rate (GFR) <60cc/min/1.73m², has been associated with an increase in all-cause mortality, particularly cardiovascular death. Go and colleagues⁷ studied a cohort of over a million patients and found a graded, non-linear relationship between all-cause mortality, all-cause hospitalizations, cardiovascular death and CKD.

The United States is experiencing a national epidemic of obesity. Data from the National Health and Nutrition Examination Study (NHANES) indicate that more than 70% of patients over the age of 40 were either overweight or obese. Furthermore, obesity is increasing across all races.⁸ The incidence of CKD is increasing among the general population, largely driven by obesity-related diabetes, hypertension, and peripheral vascular disease, yet CKD remains under-appreciated in the US.⁹

The purpose of this study was to identify potential trends in comorbidity over time in a large cohort of patients treated for localized renal cancer and determine whether comorbidity, and particularly CKD, may impact disease-free or overall survival.

Methods

We obtained Institutional Review Board approval prior to initiating this study. We queried our nephrectomy database for patients who underwent partial or radical nephrectomy from 1995 to 2005. De-identified demographic and clinicopathologic data were retrieved. Body mass index (BMI) was calculated as weight (Kg)/(height [m])². GFR was estimated using the abbreviated Modified Diet and Renal Disease (MDRD) equation, which is a function of age, race, and serum creatinine.¹⁰ For this calculation, the last serum creatinine prior to surgery was used. Charlson-Romano index^{11, 12} was calculated as an instrument for objective comparison of comorbidity. Patients with evidence of nodal or metastatic involvement at time of surgery and those with incomplete data were excluded.

We used linear regression to test for trends in age, BMI and baseline GFR over time. Logistic regression was employed to test for trends in Charlson-Romano index and hypertension. For this purpose, the Charlson-Romano index was dichotomized into >2 and ≥2; hypertension, which is not included in the Charlson-Romano index, was recorded separately as a binary variable and defined as requiring medication for blood pressure control. A multivariable linear regression model was fit to test for association between BMI and GFR, controlling for year of surgery, age, sex, Charlson-Romano score, hypertension, and pathologic tumor size. Cox regression analysis was used to test whether baseline GFR, comorbidity, and BMI had impact on disease-free and overall survival, controlling for pathologic stage. For this purpose, baseline GFR was tested as an ordinal variable: GFR>60, GFR 45–60, and GFR <45 cc/min/m². We used Kaplan-Meier analysis to estimate survival and the log-rank test for equality. All statistics were performed using Stata (College Station, TX). P-values of <0.05 were considered statistically significant.

Results

A total of 1479 patients with complete data were identified for analysis. The demographic and pathologic data are summarized in Table 1 and Table 2, respectively. During the study period, a modest but statistically significant increase in median BMI was observed from 27 kg/m² (Interquartile range [IQR]: 24, 31) in 1995 to 28 kg/m² in 2005 (IQR= 25, 31, p=0.004, Figure

1). Baseline GFR decreased from a median of 70 (IQR 58, 80) to 63 cc/min/1.73m² (IQR: 57, 78, Figure 2). Increasing age (coefficient: -5.4 per decade, $p<0.001$), a Charlson-Romano score >2 (coefficient: -1.2, $p<0.001$), and increasing tumor size (coefficient: -0.5, $p=0.009$) were all associated with a lower baseline GFR, the increase in BMI by itself was not. However, year of surgery was also independently associated with a lower baseline GFR (coefficient: -1.0, $p<0.001$), suggesting that some untested variables may might explain, at least in part, the observed decline in GFR over time (Table 3). These associations remained significant when the analysis was repeated for only patients 18–70 years old indicating that extremes of age are not responsible for the associations.

There was no association between baseline GFR, Charlson-Romano index, hypertension, or BMI with disease-free survival after adjusting for stage (Table 4). However, lower baseline GFR was associated with reduced overall survival (Table 4). For example, a moderately decreased baseline GFR (45–60cc/min/1.73m²) was associated with a 1.5-fold increased hazard ($p=0.008$) of all-cause mortality and severely decreased GFR (<45 cc/min/1.73m²) was associated with a 2.9-fold increased hazard of all-cause mortality. ($p<0.001$). Actuarial estimates of overall survival are presented in Figure 3.

DISCUSSION

Diminished renal function has been associated with increased mortality in several large studies, 7, 9, 13, 14 and a significant proportion of patients diagnosed with renal cortical tumors may have baseline CKD.⁶ Since both partial or radical nephrectomy adversely affect the GFR over time,^{6, 15} with radical nephrectomy having a significantly larger effect,⁶ we hypothesized that baseline GFR may impact overall survival in patients undergoing extirpative surgery for RCT. Our study suggests that GFR may be declining in patients presenting with localized RCT and this trend may be translated into a reduction in overall survival in these patients. These findings underscore the importance of considering baseline GFR when devising treatment plans for management of RCTs.

The incidence of kidney cancer is rising.¹ Hollingsworth et al⁴ observed that disease specific death increased 155% and overall death increased 323% among renal cancer patients between 1983–2002. Patients with tumors >7 cm accounted for the greatest increase in overall death, but overall mortality increased over all groups except those with tumors smaller than 2cm, despite more incidental detection and subsequent surgical resection. Competing risk analysis demonstrates an inverse relationship between tumor size and disease-specific survival and a direct relationship between age and competing-risk mortality.⁵ Our data support this finding since age was associated with Charlson-Romano index ($p<0.001$) and baseline GFR ($p<0.001$), both of which were associated with overall but not disease-specific survival.

Go et al⁷ studied over one million patients and found that all-cause mortality and hospitalization were associated with decreasing estimated GFR. In that study, the authors controlled for diabetes, coronary heart disease, stroke and other comorbidities and found an independent, graded relationship between GFR and cardiovascular events and mortality. Fried and associates found that CKD was associated with non-cardiovascular mortality.¹⁶ Interestingly, most patients with severely decreased renal function will die from comorbid conditions prior to the initiation of dialysis or undergoing transplantaton; Keith and colleagues showed that 45% of stage 4 CKD (GFR 15–30cc/min/m²) died before dialysis was initiated.

Surgical treatment of RCT is not inconsequential. We recently showed a significant difference in rates of moderate and severe chronic renal disease in patients operated with radical nephrectomy for tumors <4 cm and found that the median time to CKD (<60 cc/min/m²) was 18 months postoperatively in radical nephrectomy patients while it was never reached in partial

nephrectomy patients.⁶ Patients undergoing radical nephrectomy were 11.8 times more likely to develop $\text{GFR} < 45 \text{ cc/min/m}^2$ than patients undergoing partial nephrectomy. It remains unclear whether surgically-induced CKD has the same implications as disease-induced CKD, but it does prompt concern that in many patients surgically induced CKD may result in more medical harm than oncologic benefit. Our data beg the question of whether patients with CKD and small “incidentalomas” might be best managed with active surveillance and intervention reserved for patients where progressive tumor growth is documented.

Partial nephrectomy is oncological control similar to radical nephrectomy for tumors of 7cm or less, including the most malignant variant clear cell carcinoma.^{17–19} The decline in GFR is markedly reduced with partial nephrectomy compared to radical nephrectomy⁶ and is not dependent on tumor location.¹⁹ Despite abundant data supporting partial nephrectomy, partial nephrectomy accounted for only 7.5% of extirpative renal operations done between 1988–1992 in the US.²⁰ Furthermore, even among 2–4cm tumors only 20% were treated with partial nephrectomy between 2000–2001 according to Surveillance Epidemiology and End Results (SEER) data.² The results of this study the importance of performing partial nephrectomy whenever technically feasible since decreased pre-treatment GFR is associated with increased overall mortality and the baseline GFR has decreased over time.

This study shows that baseline GFR may be decreasing among patients who present with localized RCT. Baseline GFR was associated with the presence of hypertension, comorbidity, tumor size, and age. These factors do not completely account for the decrease in GFR over time because the year of surgery remained significantly associated with baseline GFR. This finding implies that there is another variable contributing to the GFR decrease. These observations are consistent with the increase in CKD prevalence over time reported from the NHANES data.⁹

We observed that BMI had increased over time in our cohort but was not associated with baseline GFR, probably because hypertension and comorbidity were included in the model. Over an 18-year period, Fox et al demonstrated that age, increasing BMI, hypertension, mildly diminished GFR ($> 90 \text{ cc/min/1.73m}^2$) are all associated with progression to chronic kidney disease, defined as $\text{GFR} < 60 \text{ cc/min/1.73m}^2$.¹³ BMI has previously been shown not to affect disease-free survival, but obesity does add an element of difficulty to surgery and may lead to unnecessary perioperative morbidity.²¹

All of the patients underwent surgery with curative intent at a tertiary center, so referral and selection bias may limit the interpretation of our data to surgical candidates. In addition, during the study period, an increasing number of patients at our center had partial nephrectomy each year, making it difficult to draw conclusions about the effect of nephron sparing on overall survival because of the selection bias. The proportion of patients managed with surveillance during the study period is unknown. If untreated patients had been included, our results may have been more pronounced in terms of decreasing baseline GFR and overall survival since those patients tend to be older and have more comorbidity. Finally, subtle changes in creatinine measurement may have influenced our GFR results, but standardizing the creatinine levels would likely have made the GFR trends more pronounced.⁹

CONCLUSION

Decreased baseline glomerular filtration rate is associated with reduced overall survival following subsequent definitive surgery for renal cortical tumors. This should be considered in deciding who is appropriate for definitive surgery, and may have an important role in identifying optimal candidates for active surveillance.

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Figure 1.

Figure 2.

FIGURE 3.

Table 1

Demographics N=1479			
Age, years (IQR)		63	(54,71)
Sex (%)	Female	555	(38)
	Male	924	(62)
Laterality (%)	Left	723	(49)
	Right	756	(51)
	White	1,300	(88)
	Black	73	(5)
	Other	106	(7)
Baseline GFR, cc/min/1.73m² (%)	>60	1005	(68)
	45–60	363	(25)
	<45	111	(7)
Charlson Score (%)	<2	848	(57)
	≥2	631	(43)
BMI, kg/m², median, (IQR)		28	(25,31)

Table 2

Pathologic Characteristics N=1479			
Pathologic Stage (%)	T1	1045	(71)
	T2	127	(8)
	T3	299	(20)
	T4	8	(1)
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Pathologic Size, cm median (IQR)		4	(2.5, 6.2)
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Histology	Clear Cell Carcinoma	904	(61)
	Papillary	202	(14)
	Chromophobe	150	(10)
	Oncocytoma	158	(11)
	Other	65	(4)

Table 3

Impact on Baseline GFR			
	Coefficient	95% CI	P-Value
Year	−1.0	(−1.3, −0.7)	<0.001
Age (per decade)	−5.4	(−6.1, −4.6)	<0.001
Sex (male vs female)	0.9	(−1.0, 2.7)	0.4
Tumor Size	−0.5	(−0.8, −0.2)	<0.001
BMI	0.1	(−0.1, 0.3)	0.20
Charleson-Romano (>2 vs ≤2)	−1.2	(−1.8, −0.6)	<0.001
Hypertension	−4.6	(−6.6, −0.6)	<0.001

The coefficient is interpreted as units of change per increment in continuous variables and for the presence of a factor for binary. For instance, GFR decreases 5.4cc/min/1.73m² for each additional decade of life and decreases 1.2cc/min/1.73m² for having a Charleson-Romano index >2

Table 4

Disease-Free Survival				
		HR	95% CI	P-value
BMI		1.0	(1.0, 1.1)	0.7
Baseline GFR	45–60	1.5	(0.9, 2.5)	0.088
	<45	1.1	(0.4, 3.1)	0.9
Charleson-Romano (>2 vs ≤2)		0.7	(0.4, 1.2)	0.16
Hypertension (yes vs no)		0.9	(0.6, 1.5)	0.79
Pathologic Stage	T2	4.8	(2.6, 8.8)	<0.001
	T3	4.0	(2.4, 6.5)	<0.001
	T4	29.5	(8.8, 100.0)	<0.001
Overall Survival				
		HR	95% CI	P-Value
BMI		1.0	(1.0, 1.0)	0.9
Baseline GFR	45–60	1.5	(1.1, 2.0)	0.008
	<45	2.8	(1.9, 4.1)	<0.001
Charleson-Romano (>2 vs ≤2)		2.0	(1.5, 2.7)	<0.001
Hypertension (yes vs no)		1.0	(0.8, 1.4)	0.7
Pathologic Stage	T2	2.1	(1.4, 3.2)	<0.001
	T3	1.6	(1.2, 2.2)	0.001
	T4	10.5	(4.5, 24.1)	<0.001