The association of baseline health and gender with small renal mass pathology

Wassim M. Bazzi, MD,[1] Sheila Z. Dejbakhsh, MD,[2,3] Melanie Bernstein,[1] Paul Russo, MD[1]

[1]Urology Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York, USA
[2]University of California San Diego School of Medicine, La Jolla, California, USA
[3]Columbia University Mailman School of Public Health, New York, New York, USA

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Introduction: *To explore further the association of baseline health and gender with small renal mass pathology as approximately 20% of those masses are benign and women are twice as likely as men to have benign pathology.*

Materials and methods: *We conducted retrospective chart reviews of patients with renal masses ≤ 4 cm who underwent partial and radical nephrectomy from 1998 to 2012. Multivariable logistic regression analysis was performed to determine demographic and clinicopathologic factors associated with malignant pathology.*

Results: *In our cohort of 1726 patients, compared to patients with benign pathology, those with malignant pathology included a higher proportion of men (64.3% versus 42.7%, p < 0.01) and high American Society of Anesthesiologists class (43.8% versus 37.3%, p = 0.04), and had higher preoperative serum creatinine levels (1.1 mg/dL versus 1.0 mg/dL, p < 0.01) and larger tumors (2.5 cm versus 2.2 cm, p < 0.01). Gender-specific multivariable logistic regression analysis showed that in women factors associated with malignant pathology were high American Society of Anesthesiologists class (OR 1.57, 95% CI 1.07-2.32, p = 0.02) and tumor size (OR 1.46, 95% CI 1.19-1.79, p < 0.01). In men, factors associated with malignant pathology were tumor size (OR 1.33, 95% CI 1.06-1.67, p = 0.01) and age (OR 0.97, 95% CI 0.95-0.99, p < 0.01).*

Conclusions: *Our results are consistent with prior reports, in which male gender and larger tumor size are significantly associated with malignant small renal masses. In addition, poor baseline health as represented by a high American Society of Anesthesiologists class is significantly associated with malignant pathology in women.*

Key Words: kidney neoplasms, kidney diseases

Introduction

In 2013, there was an estimated 65,150 new cases and 13,680 resultant deaths from kidney cancer in the United States.[1] The widespread availability of cross-sectional imaging for unrelated conditions has caused a marked rise in incidentally discovered small renal masses (SRM) ≤ 4 cm,[2] of which nearly a fifth are likely to be benign.[3] In addition, women have been shown to have a higher likelihood of having a benign SRM.[4–6]

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Address correspondence to Dr. Paul Russo, Urology Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 USA

The association of baseline health with SRM pathology has not been fully explored. On re-examination of 110 nephrectomy specimens of renal cell carcinoma (RCC), Bijol et al[7] demonstrated that only 10% had benign renal parenchyma surrounding the tumor; the remaining specimens had nephrosclerosis and glomerular pathological changes consistent with common medical conditions, including diabetes, hypertension, and vasculopathy from cigarette smoking. These findings have been confirmed by other investigators.[8,9] Although the link between chronic kidney disease (CKD) and kidney cancer is not fully established, it could potentially relate to ineffective clearance of circulating toxins by the kidneys and uremic immunosuppression.[10,11]

In this report we closely examine the association of baseline health, as represented by preoperative renal function and American Society of Anesthesiologists (ASA) classification for medical comorbidities,[12] with malignant SRM for each gender.

Material and methods

After institutional review board approval, we conducted a retrospective chart review of patients with SRM who underwent nephrectomy at Memorial Sloan Kettering Cancer Center from 1998 to 2012 (n = 3874). Tumor stage, if malignant, was pT1a, according to the American Joint Committee on Cancer 2010 classification.[13] Tumor size cutoff was ≤ 4 cm (n = 1900). Patients with solitary kidney, multiple and bilateral tumors, and a history of prior kidney surgery were excluded from the analysis (n = 174). Collected data included age at time of surgery, gender, race, ASA classification for medical comorbidities,[12] which were divided into low (I-II) and high (III-IV), preoperative serum creatinine (Cr) [mg/dL], preoperative estimated glomerular filtration rate (eGFR) [mL/min/1.73 m^2], procedure, side of procedure, tumor size (diameter in cm), and final pathology. Malignant pathology included clear cell RCC, papillary RCC, and chromophobe RCC; benign pathology included oncocytoma, angiomyolipoma, and other benign pathology. eGFR was calculated using the Chronic Kidney Disease – Epidemiology Collaboration formula.[14] CKD was defined as eGFR < 60 mL/min/1.73 m^2.[15]

Statistical analysis

Preoperative and operative variables were described using descriptive statistics. Continuous variables, including age, preoperative Cr, preoperative eGFR, and tumor size, were described by median and interquartile range (IQR). Categorical variables, including gender, race, ASA class, surgical procedure, side of procedure, CKD stage,[14] and tumor pathology, were described by frequency and percent of total. Univariate analyses between study variables and benign versus malignant pathology were performed using Mann-Whitney rank sum analysis for continuous variables and chi-square analysis for categorical variables. A multivariable logistic regression analysis was performed to analyze the crude association of predictors with malignant pathology (main effect model). To preserve independence between variables in the logistic regression model, Cr, age, gender, and race were included in the model separately in lieu of eGFR. Subsequent interaction analysis was performed using all variables in the main effect model with the addition of the interaction variable (gender x ASA class). Stratified subgroup analyses, by gender, were completed to measure the association between ASA class and malignant pathology. All probabilities were two-sided, and a p value < 0.05 was considered significant for all analyses. Receiver operating characteristic (ROC) curve analysis was used to assess model goodness-of-fit. All data were analyzed using STATA 13.0 (Stata Corp., College Station, TX, USA).

TABLE 1. **Baseline and disease characteristics for 1726 patients expressed as median (IQR) or frequency (%)**

Age at surgery	60.5 (51.6, 69.1)
Gender	
Male	1045 (60.5%)
Female	681 (39.5%)
Race	
White	1553 (90.0%)
Black	78 (4.5%)
Other	95 (5.5%)
ASA class	
I-II	990 (57.4%)
III-IV	736 (42.6%)
Surgical procedure	
Partial	1540 (89.2%)
Radical	186 (10.8%)
Side of procedure	
Right	875 (50.7%)
Left	851 (49.3%)
Preoperative Cr (mg/dL)	1.1 (0.9, 1.2)
Preoperative eGFR (mL/min/1.73 m^2)	68.5 (57.7, 81.8)
≥ 60	1201 (69.6%)
< 60	525 (30.4%)
CKD stage	
I	266 (15.4%)
II	937 (54.3%)
III	500 (29.0%)
IV	20 (1.1%)
V	3 (0.2%)
Pathology	
Benign	**300 (17.4%)**
Oncocytoma	162 (9.4%)
Angiomyolipoma	63 (3.7%)
Other benign	75 (4.3%)
Malignant	**1426 (82.6%)**
Clear cell RCC	1008 (58.4%)
Papillary RCC	260 (15.1%)
Chromophobe RCC	158 (9.1%)
Size of pathological specimen (cm)	2.5 (1.8, 3.2)

Cr = creatinine; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; RCC = renal cell carcinoma

Results

Our cohort consisted of 1726 patients, Table 1, of which 60.5% (n = 1045) were men and 90.0% (n = 1553) were Caucasian. Median age at nephrectomy was 60.5 years (IQR 51.6, 69.1) and 89.2% (n = 1540) underwent partial nephrectomy. High ASA class (III-IV) was seen in 42.6% (n = 736) of patients. Median preoperative Cr was 1.1 mg/dL (IQR 0.9, 1.2) and median preoperative eGFR was 68.5 mL/min/1.73 m^2 (IQR 57.7, 81.8). Pre-existing CKD was present in 30.4% (n = 525) of patients, and 83.3% (n = 1437) had CKD stage II-III (eGFR 30-89 mL/min/1.73 m^2). Benign pathology was present in 17.4% (n = 300) of patients (oncocytoma, 9.4%; angiomyolipoma, 3.7%; and other benign pathology, 4.3%); the remaining 82.6% (n = 1426) had malignant pathology (clear cell RCC, 58.4%; papillary RCC, 15.1%; and chromophobe RCC, 9.1%). The median tumor size on final pathologic examination was 2.5 cm (IQR 1.8, 3.2).

The results of the univariate analysis are shown in Table 2. When compared to patients with benign SRM, those with malignant SRM included a higher proportion of men (64.3% versus 42.7%, p < 0.001), higher ASA class (43.8% versus 37.3%, p = 0.041), and larger tumor size 2.5 cm (IQR 1.9, 3.2) versus 2.2 cm (IQR 1.5, 3.0) (p < 0.01). There was no association between age, race, median eGFR, or proportion of patients with CKD.

The results of the multivariable logistic regression analysis are shown in Table 3. In this main effects model, malignant SRM was significantly associated with male gender (Odds ratio $[OR]_{crude}$ 0.44, 95% confidence interval [CI] 0.34-0.58, p < 0.01), larger tumor size (OR_{crude} 1.40, 95% CI 1.20-1.62, p < 0.01), and high ASA class (OR_{crude} 1.37, 95% CI 1.04-1.80, p = 0.02). There were no significant associations with age, race, or Cr. The area under the ROC curve on logistic regression was 0.65 (95% CI 0.62-0.69).

To further describe the effect of baseline health, as represented by ASA class, on pathological diagnosis, an interaction analysis was completed by adding an interaction term 'gender x ASA class' as a variable in the multivariable logistic regression model. The interaction variable was statistically significant (p = 0.03), representing a significant effect measure modification of gender on the association between ASA class and malignant pathology. To better quantify the effect measure modification of gender, a subgroup analysis was preformed whereby males and females were analyzed separately.

In women, gender-specific logistic regression analysis, Table 4 showed that high ASA class and

TABLE 2. **Univariate analysis of baseline and pathology characteristics expressed as median (IQR) or frequency (%)**

Characteristic	Benign	Malignant	p value
Age at surgery	61.2 (52.8, 69.3)	60.5 (51.4, 69.2)	p = 0.40[a]
Gender			**p < 0.01[b]**
Male	128 (42.7%)	917 (64.3%)	
Female	172 (57.3%)	509 (35.7%)	
Race			p = 0.98[b]
Caucasian	270 (90.0%)	1283 (90.0%)	
African-American	14 (4.7%)	64 (4.5%)	
Other	16 (5.3%)	79 (5.5%)	
ASA class			**p = 0.04[b]**
I-II	188 (62.7%)	802 (56.2%)	
III-IV	112 (37.3%)	624 (43.8%)	
Cr (mg/dL)	1.0 (0.9, 1.2)	1.1 (0.9, 1.2)	**p < 0.01[a]**
eGFR (mL/min/1.73 m^2), median	66.6 (57.7, 79.7)	68.9 (57.5, 82.2)	p = 0.12[a]
≥ 60	196 (65.3%)	1005 (70.5%)	p = 0.08[b]
< 60	104 (34.7%)	421 (29.5%)	
Size (cm)	2.2 (1.5, 3.0)	2.5 (1.9, 3.2)	**p < 0.01[a]**

ASA = American Society of Anesthesiologists; Cr = creatinine; eGFR = estimated glomerular filtration rate
[a]Mann-Whitney rank sum analysis
[b]Chi-square analysis

TABLE 3. **Main effect model with multivariable logistic regression analysis of the entire cohort for association with malignant small renal mass**

Parameter	OR†	95% CI	p value
Age at surgery*	0.99	0.98, 1.00	p = 0.14
Race			
African-American versus Caucasian	1.02	0.55, 1.87	p = 0.96
Other versus Caucasian	0.95	0.54, 1.68	p = 0.86
Tumor size* (cm)	**1.40**	**1.20, 1.62**	**p < 0.01**
Cr* (mg/dL)	1.07	0.73, 1.55	p = 0.74
Gender (female versus male)	**0.44**	**0.34, 0.58**	**p <0.01**
ASA class (III-IV versus I-II)	**1.37**	**1.04, 1.80**	**p = 0.02**

Cr = creatinine; ASA = American Society of Anesthesiologists
†crude OR (calculated prior to interaction analysis)
*continuous variable

larger tumor size were significantly associated with malignant SRM with OR 1.57 (95% CI 1.07-2.32, p = 0.02) and OR 1.46 (95% CI 1.19-1.79, p < 0.01), respectively. Age, race, and preoperative Cr were not significantly associated. The area under the ROC curve on logistic regression was 0.62 (95% CI 0.57 - 0.67).

In men, gender-specific logistic regression analysis, Table 5 showed that older age and larger tumor size were significantly associated with malignant SRM with OR 0.97 (95% CI 0.95-0.99, p < 0.01) and OR 1.33 (95% CI 1.06-1.67, p = 0.01), respectively. Race, ASA class, and preoperative Cr were not significantly associated. The area under the ROC curve on logistic regression was 0.60 (95% CI 0.55-0.66).

Discussion

There is increasing evidence in the literature for the association of early-stage CKD with cancer.[10,16–18] In a study linking the Blue Mountains Eye Study with the New South Wales Cancer Registry, Wong et al[16] noted that in approximately 3500 individuals aged 49 to 97, older men with an eGFR of < 55 mL/min/1.73 m^2 were at increased risk for developing cancer (hazard ration [HR] 1.39, 95% CI 1.00-1.92, p = 0.04), with the greatest risk at an eGFR < 40 mL/min/1.73 m^2 (HR 3.01, 95% CI 1.72-5.27, p < 0.01). Lung and urinary tract cancers were the most likely diagnoses. Similarly, in a longitudinal follow up (median, 7 years) of 123,717 Taiwanese adults,

TABLE 4. **Stratified multivariable logistic regression analysis of female gender only, in association with malignant small renal mass**

Female

Parameter	OR‡	95% CI	p value
Age at surgery*	1.01	0.99, 1.02	p = 0.35
Race			
African-American versus Caucasian	1.17	0.54, 2.55	p = 0.69
Other versus Caucasian	0.92	0.43, 1.99	p = 0.84
ASA class (III-IV versus I-II)	**1.57**	**1.07, 2.32**	**p = 0.02**
Tumor size* (cm)	**1.46**	**1.19, 1.79**	**p < 0.01**
Cr* (mg/dL)	1.15	0.67, 2.00	p = 0.31

ASA = American Society of Anesthesiologists; Cr = creatinine
‡stratum-specific OR, specific to female gender only
*continuous variable

TABLE 5. **Stratified multivariable logistic regression analysis of male gender only, in association with malignant small renal mass**

Male			
Parameter	**OR§**	**95% CI**	**p value**
Age at surgery*	**0.97**	**0.95, 0.99**	**p < 0.01**
Race			
African-American versus Caucasian	0.79	0.30, 2.10	p = 0.64
Other versus Caucasian	1.09	0.45, 2.62	p = 0.85
ASA class (III-IV versus I-II)	1.16	0.78, 1.71	p = 0.46
Tumor size* (cm)	**1.33**	**1.06, 1.67**	**p = 0.01**
Cr* (mg/dL)	1.01	0.60, 1.72	p = 0.96

ASA = American Society of Anesthesiologists; Cr = creatinine
§stratum-specific OR, specific to male gender only
*continuous variable

Weng et al[17] noted that CKD was associated with an increased kidney cancer mortality risk (HR 3.3, 95% CI 1.24-8.81, p = 0.02). In a recently reported study by Christensson et al[18] involving 24,552 participants from the Malmo Prevention Project cohort in Sweden with a median follow up of 28 years, 6595 participants were diagnosed with cancer and 3.5% had CKD at the time of enrollment. Although there was no association between CKD and long term cancer risk, there was an association between CKD in younger men (median age 47 years) and subsequent risk of developing kidney cancer (HR 3.38, 95% CI 1.48-7.71, p < 0.01). In this study, consistent with our previous report,[19] 30% of patients had preoperative CKD as defined by eGFR < 60 mL/min/1.73 m^2 yet we did not find statistically significant differences in median preoperative eGFR or percentage with CKD between patients with benign SRM and those with malignant SRM. Furthermore, while we noted a statistically significant difference in preoperative Cr on univariate analysis, there was no statistically significant association on multivariable logistic regression analyses. Though we failed to detect an association of preoperative renal function with SRM pathology, we believe this is probably related to the size of our cohort and this may need to be further investigated using large multi-institutional databases.

Consistent with previous reports, in this study malignant SRM was associated with male gender SRM,[4-6] larger tumor size,[3] and older men after subgroup analysis though the latter finding carries little clinical relevance (OR 0.97, 95% CI 0.95-0.99, p < 0.01). While the main effects model renders significant association of ASA class and malignant SRM, further analysis showed that in fact there is an effect measure modification of gender. Hence after performing gender specific subgroup analysis, we noted that the association of high ASA class with malignant SRM differed by gender, whereby it holds true for women but not for men. This association in women remains unclear and to our knowledge has never been reported before.

In this study, to limit the independent impact of tumor size on preoperative renal function as demonstrated as demonstrated by numerous investigators,[20-23] we analyzed renal masses ≤ 4 cm or staged as pT1a if malignant. Our study is however limited by its retrospective nature and surgical selection bias as patients with serious medical comorbidities at risk for surgical complications were often managed by active surveillance only. Nevertheless, 43% of our patients had a high ASA class indicating that this might not have been the case.

Conclusions

Consistent with prior reports, our results show that male gender and larger tumor size are significantly associated with malignant SRM. In addition, we show that among women, those with high ASA have a higher likelihood of malignant SRM pathology. □

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