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Non-neoplastic parenchymal changes in kidney cancer and post-partial nephrectomy recovery of renal function

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Abstract

Objective—To explore the association of non-neoplastic parenchymal changes (nNPC) with patients' health and renal function recovery after partial nephrectomy (PN).

Materials and methods—This retrospective review identified 800 pT1a patients who underwent PN at Memorial Sloan Kettering Cancer Center from 2007 to 2012. Pathology reports were reviewed for nNPC graded as mild or severe: vascular sclerosis (VS), glomerulosclerosis (GS), and fibrosis/scarring. Correlations between nNPC and known preoperative predictors of renal function [age, sex, African-American race, estimated glomerular filtration rate (eGFR), American Society of Anesthesiologists (ASA) score, body mass index, coronary artery disease, and hypertension (HTN)] were assessed using Spearman's rank correlation (ρ). Multivariable linear regression, adjusted for the described known preoperative risk predictors, was performed to evaluate whether the parenchymal features were able to predict 6-month postoperative eGFR.

Results—In this study, 46 % of tumors had benign surrounding parenchyma. We noted statistically significant yet weak associations of VS with age ($\rho = 0.19$; $p < 0.001$), ASA ($\rho = 0.09$; $p < 0.001$), preoperative eGFR ($\rho = -0.14$; $p < 0.001$), and HTN ($\rho = 0.14$; $p < 0.001$). GS also significantly correlated with HTN, but the correlation was again small ($\rho = 0.12$; $p < 0.001$). After adjusting for known risk predictors, only GS was a significant predictor of 6-month postoperative eGFR. When compared with no GS, mild and severe GS were negatively associated with a decrease of 4.9 and 10.8 mL/min/1.73 m² in 6-month postoperative eGFR, respectively.

Conclusions—Presence of VS and GS correlated with patients' baseline health, and presence of GS predicted postoperative renal function recovery.

Keywords

Kidney diseases; Kidney neoplasms; Renal insufficiency

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Compliance with ethical standards

Conflict of interest: All authors declare no conflicts of interests.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Introduction

Mounting evidence supports the association of chronic kidney disease (CKD) with kidney cancer [1]. Numerous proposed mechanisms include ineffective clearance of circulating toxins with an ensuing pro-neoplastic uremic state and/or neoplasia developing from parenchymal damage secondary to chronic medical diseases [2, 3]. Bijol et al. [4] demonstrated that only 10 % of 110 nephrectomy specimens resected for renal cell carcinoma (RCC) had normal renal parenchyma surrounding the tumor; the rest had an array of abnormalities including nephrosclerosis and glomerular changes. These findings were later corroborated by other centers [5, 6]; hence, the reporting of surrounding nNPC is now highly encouraged [7, 8].

In their pathologic review of 381 nephrectomies for non-neoplastic parenchymal changes (nNPC), Salvatore et al. [6] noted that severe arteriosclerosis/arteriolosclerosis, >5 % glomerulosclerosis (GS), and >10 % interstitial fibrosis/tubular atrophy were all associated with worse post-nephrectomy renal function recovery irrespective of whether the patient underwent a partial or radical nephrectomy. In this report, we review Memorial Sloan Kettering Cancer Center pathologic reporting of nNPC and explore those findings for associations with patients' health and renal function after partial nephrectomy (PN).

Materials and methods

After institutional review board approval was obtained, we performed retrospective chart review for patients who underwent a PN at our institution between January 2007 and July 2012. Inclusion criteria included final pathologic size ≤ 4 cm and malignant stage of pT1a according to American Joint Committee on Cancer (AJCC) 2010 staging ($n = 800$) [9]. Size ≤ 4 cm was chosen to limit the tumor size effect on preoperative [10] and postoperative renal function. Pathology reports were reviewed for comments on three parenchymal features in the non-neoplastic kidney: vascular sclerosis (VS) (arteriosclerosis and arteriolosclerosis), GS, and fibrosis/scarring (FS). Parenchymal features were graded by our genitourinary pathologists as either mild or severe using standard periodic acid-Schiff staining. We investigated the relationship between nNPC and known preoperative predictors of renal function to determine whether benign parenchymal features can predict renal function outcomes after nephrectomy.

To assess whether nNPC is associated with preoperative and postoperative renal function, we assessed correlations between parenchymal features and known preoperative predictors using Spearman's rank correlation (ρ). Known predictors of renal function include age, sex, African-American race, preoperative glomerular filtration rate (eGFR) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11], American Society of Anesthesiologists (ASA) score [12], body mass index (BMI), history of coronary artery disease (CAD), and hypertension (HTN). To evaluate whether the parenchymal features were able to predict 6-month postoperative eGFR, we used multivariable linear regression adjusted for the described known preoperative predictors. ASA score was categorized in the models as low (I–II) versus high (III–IV). Each parenchymal feature was analyzed in the models separately. Fuhrman grade [13] was assessed for conventional clear

cell RCC. Differences in the prevalence of parenchymal features were described by histologic type and Fuhrman grade (1–2 vs. 3–4). All statistical analyses were conducted using STATA 12.0 (Stata Corp., College Station, TX, USA).

Results

Patient characteristics are given in Table 1. The median age of patients was 59 years, and median preoperative eGFR was 71 mL/min/1.73 m². HTN was present in 51 % of patients and CAD in 7 %. As shown in Table 2, the most common pathologic finding in nNPC was VS. Of nephrectomy specimens, 23 % showed VS, whereas the prevalence rate of any GS was 12 % and any FS was 9 %. Severe VS was found in 4 % of patients, and severe GS was present in 2 % of patients. Completely benign surrounding parenchyma was present in 46 % of patients.

As shown in Table 3, we found statistically significant but weak relationships between VS and age ($\rho = 0.19$; $p < 0.001$), preoperative eGFR ($\rho = -0.14$; $p < 0.001$), high ASA ($\rho = 0.09$; $p < 0.001$), and HTN ($\rho = 0.14$; $p < 0.001$). GS was significantly correlated with high ASA and HTN, but the correlations were again small ($\rho = 0.10$, $p < 0.007$ and $\rho = 0.12$, $p < 0.001$, respectively).

On multivariable regression analysis for the prognostic significance of presence of nNPC features in 6-month postoperative eGFR (Table 4), only GS was a significant predictor of postoperative eGFR after adjusting for age, sex, African-American race, preoperative eGFR, ASA, BMI, CAD, and HTN. When compared with the absence of GS, mild and severe GS were negatively associated with eGFR, with a 4.89 mL/min/1.73 m² (95 % CI -7.89, -1.90; $p = 0.001$) and 10.83 mL/min/1.73 m² (95 % CI -18.33, -3.32; $p = 0.005$) decrease in 6-month postoperative eGFR, respectively.

Discussion

In this study, we used the 4-cm cutoff size to minimize the possible independent effect of tumor size on preoperative renal function [10, 14] caused by direct tumor destruction of kidney parenchyma [10] and/or tumor neovascularity shunting blood flow away from normal kidney parenchyma [14, 15]. We noted significant yet weak associations of nNPC with patients' health. The presence of VS correlated with older age, lower preoperative eGFR, high ASA class, and HTN. GS correlated with high ASA class and HTN, but not with age. This latter finding contrasts with Rule et al's [16] study of renal biopsies in kidney transplantation donor patients where the authors noted an increase in the incidence of GS with age independent of renal function; however, they do state that their findings are limited by the generally good health of kidney donor patients, and renal biopsies do not provide full pathologic interpretation.

Salvatore et al. [6] reported that the degrees of VS, GS, and fibrosis/tubular atrophy were all associated with elevated postoperative serum creatinine levels. In this study, the renal function was evaluated at 6 months post-operatively to allow enough time for its recovery [11]. We noted similar findings for presence of GS as patients with mild and severe GS, when compared with patients with no GS, had a 6-month decline in eGFR of 4.9 and 10.8

mL/min/1.73 m², respectively. The presence of VS and FS, in contrast, did not correlate with postoperative renal function recovery.

To our knowledge, this is the largest clinical series in the literature that correlates nNPC, patients' health, and renal functional outcomes after PN. As part of the preoperative medical assessment routine, calculation of eGFR should be an essential part of the urologic surgeon's preparation. In patients who may be seemingly otherwise well and without obvious renal disease, our data indicate that nNPC, particularly mild and severe GS, can affect postoperative renal function. These data reemphasize the fact that renal tumor patients are subject to medical comorbidities that can cause intrinsic renal damage and affect long-term renal function after PN. These data also confirm that renal tumor patients are clearly a population distinct from carefully selected kidney donors. Careful assessment and reporting of nNPC at the time of tumor pathologic examination is valuable information that will allow the urologic surgeon an opportunity to counsel the patient and possibly refer the patient to nephrologic specialists should a serious decline in renal function be documented after kidney-sparing surgery.

Our study is limited by its retrospective nature, with patient case selection bias likely present. Patients with severe CKD and small renal masses would likely be managed non-operatively by active surveillance. In addition, nNPC severity was assigned in qualitative terms by degree rather than percentages, and special staining and routine electron microscopy for a more complete nephropathologic assessment was not performed. We also do recognize inter- and intra-observer variability among pathologists, and the volume of neo-neoplastic parenchyma present for pathologic examination was highly variable. Similarly the nNPC could be related to tumor compression and/or surgical procedure rather than a reflection of medical co-morbidities.

Conclusions

The presence of GS correlated with postoperative renal function recovery. Reporting of nNPC at time of tumor pathologic interpretation, coupled with renal functional assessment using eGFR, provides valuable information to the urologic surgeon and may lead to further nephrologic assessment and intervention.

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Table 1
Preoperative characteristics of patients included in this study

Age at surgery (years)	59 [51–68]
Male sex	518 (65 %)
African-American race	35 (4 %)
Preoperative eGFR (mL/min/1.73 m ²)	71 [60–83]
ASA score	
I	31 (4 %)
II	393 (49 %)
III	370 (46 %)
IV	6 (1 %)
Body mass index (kg/m ²)	29 [26–33]
Coronary artery disease	54 (7 %)
Hypertension	405 (51 %)

All values presented are median (interquartile range [IQR]) or frequency (percent)

ASA American Society of Anesthesiologists, eGFR estimated glomerular filtration rate

Table 2
Non-neoplastic renal parenchyma and pathologic features

Characteristics	<i>n</i> (%)
Non-neoplastic parenchymal changes (nNPC)	
Vascular sclerosis	
Absent	618 (77 %)
Mild	152 (19 %)
Severe	30 (4 %)
Glomerulosclerosis	
Absent	705 (88 %)
Mild	83 (10 %)
Severe	12 (2 %)
Fibrosis/scarring	
Absent	728 (91 %)
Mild	72 (9 %)
Severe	0 (0 %)
Tumor features	
Histology	
Clear cell RCC	506 (63 %)
Papillary RCC	107 (13 %)
Chromophobe	72 (9 %)
Oncocytoma	49 (6 %)
Cystic RCC	38 (5 %)
Other	28 (4 %)
Fuhrman grade ^a	
1	13 (3 %)
2	320 (64 %)
3	162 (32 %)
4	4 (1 %)

^aClear cell renal cell carcinoma (RCC) types only

Table 3
Spearman's correlation coefficients between additional pathologic features and known predictors of postoperative renal function

	Age	Male Sex	African-American race	Preoperative eGFR	ASA III–IV	BMI	Coronary artery disease	Hypertension
Vascular sclerosis	0.19 (<0.001)	−0.05 (0.12)	−0.03 (0.5)	−0.14 (<0.001)	0.09 (0.008)	0.03 (0.5)	−0.01 (0.8)	0.14 (<0.001)
Glomerulosclerosis	0.01 (0.8)	0.02 (0.6)	0.03 (0.4)	−0.05 (0.13)	0.10 (0.007)	0.00 (0.9)	0.06 (0.10)	0.12 (<0.001)
Fibrosis/scarring	−0.01 (0.7)	0.03 (0.4)	−0.02 (0.5)	−0.01 (0.8)	0.01 (0.8)	0.01 (0.8)	0.00 (0.9)	0.06 (0.11)

Statistically significant results are in bold

ASA American Society of Anesthesiologists, BMI/body mass index, eGFR estimated glomerular filtration rate

Table 4
Multivariable regression analyses of the prognostic significance of benign parenchymal features in 6 months postoperative estimated glomerular filtration rate

Parenchymal feature	Coefficient	95 % CI	<i>p</i> value
Vascular sclerosis			
Absent	–	–	–
Mild	–0.68	–3.07, 1.71	0.6
Severe	–2.64	–7.56, 2.27	0.3
Glomerulosclerosis			
Absent	–	–	–
Mild	–4.89	–7.89, –1.90	0.001
Severe	–10.83	–18.33, –3.32	0.005
Fibrosis/scarring ^a			
Absent	–	–	–
Mild	–2.00	–5.21, 1.21	0.2

Each of the features was modeled separately, adjusting for known predictors of renal function. The estimates give the change in postoperative glomerular filtration rate (mL/min/1.73 m²) for no presence of the feature to mild or severe grades of the feature

Statistically significant results are in bold

^aNo patients have severe fibrosis