Pathology (January 2019) **51(1)**, pp. 32–38

ANATOMICAL PATHOLOGY

Chronic kidney cortical damage is associated with baseline kidney function and albuminuria in patients managed with radical nephrectomy for kidney tumours

Robert J. Ellis[1,2,3], Benjamin Kalma[2,3], Sharon J. Del Vecchio[1,2,3], Danielle N. Aliano[2,3], Keng Lim Ng[1,2,3], Goce Dimeski[1,2,3], Li Ma[1], David Guard[1], John F. Bertram[4], Christudas Morais[1,2,3], Kimberley Oliver[1], Simon T. Wood[1,2,3], Glenda C. Gobe[1,2,3,5,6], Ross S. Francis[1,2,3]

[1]Princess Alexandra Hospital, Brisbane, Qld, Australia; [2]Centre for Kidney Disease Research, University of Queensland, Brisbane, Qld, Australia; [3]Translational Research Institute, Brisbane, Qld, Australia; [4]Biomedicine Discovery Institute and Department of Anatomy and Developmental Biology, Monash University, Melbourne, Vic, Australia; [5]School of Biomedical Sciences, University of Queensland, Brisbane, Qld, Australia; [6]NHMRC Chronic Kidney Disease Centre for Research Excellence, University of Queensland, Brisbane, Qld, Australia

Summary

This study evaluated the relationship between histological markers of chronic kidney damage in patients undergoing radical nephrectomy for kidney tumours and preoperative kidney function, degree of albuminuria, and changes in glomerular volume. A schema to grade chronic kidney damage could be used to identify patients at risk of developing CKD following nephrectomy. Non-neoplastic cortical tissue was sourced from 150 patients undergoing radical nephrectomy for suspected kidney cancer. This tissue was evaluated for indicators of chronic damage, specifically: glomerulosclerosis, arteriosclerosis, interstitial fibrosis, and tubular atrophy. Glomerular volume was determined using the Weibel and Gomez method. Associations between these parameters and both estimated glomerular filtration rate (eGFR) and albumin-creatinine ratio (ACR) were determined using either a Mann–Whitney U-test or a Kruskal–Wallis ANOVA. Associations between both eGFR and ACR and glomerular volume were assessed using linear regression. eGFR was inversely associated with the degree of glomerulosclerosis ($p < 0.001$), vascular narrowing ($p = 0.002$), tubular atrophy ($p < 0.001$), and interstitial fibrosis ($p < 0.001$). ACR was associated only with the degree of interstitial fibrosis ($p = 0.02$) and tubular atrophy ($p = 0.02$). Glomerular volume was greater for males, diabetics, hypertensive patients, and patients with a greater degree of interstitial fibrosis. Glomerular volume was positively associated with ACR. A schema to grade chronic damage was developed. The proposed schema is associated with baseline clinical indices of kidney function and damage. Longitudinal validation is necessary to determine the prognostic utility of this schema.

Key words: Radical nephrectomy; renal cell carcinoma; tubulointerstitial fibrosis; glomerulosclerosis; arteriosclerosis.

Received 27 June, revised 16 October, accepted 18 October 2018
Available online 23 November 2018

INTRODUCTION

In Australia, despite an increase in the use of nephron-sparing surgery in recent years, radical nephrectomy remains the most common approach for management of kidney tumours.[1–3] Although curative for the large majority of localised tumours, loss of functional kidney parenchyma increases the risk of chronic kidney disease (CKD) development or progression.[4] This is particularly true for elderly patients and patients with comorbidities which increase CKD risk, such as diabetes mellitus, obesity, and hypertension.[4,5] Notwithstanding, the identification of patients who are at risk of developing adverse kidney functional outcomes following radical nephrectomy is not as clear-cut as limiting to elderly/comorbid patients.

Histopathological evaluation of chronic parenchymal changes has been suggested as a potential approach to risk-stratifying patients who have undergone radical nephrectomy, with regard to potential future adverse events.[5,6] Several studies have assessed the predictive utility of non-neoplastic cortical parenchyma in patients managed with radical nephrectomy.[7–11] Global glomerulosclerosis and arteriosclerosis have both been shown to associate with worse postoperative kidney function.[7–9] A limitation of these studies is that there is no standardised approach to semi-quantitatively assess chronic pathological change across studies. There has also been no consideration of quantitative assessment of other parameters related to early glomerular damage or loss, such as glomerular hypertrophy.

Recently, the importance of standardised grading of native kidney biopsy specimens was discussed by Sethi *at al*., as chronic cortical changes are generally irreversible, reasonably homogeneous across different aetiologies of kidney disease, and can be readily and reproducibly characterised by experienced pathologists.[12] With this in mind, we set out to develop a schema which could be used to assess non-neoplastic cortical parenchyma from radical nephrectomy specimens. A standard compartment model was used to

Print ISSN 0031-3025/Online ISSN 1465-3931
DOI: https://doi.org/10.1016/j.pathol.2018.10.009

assess chronic pathological changes. This was based on the results of previous studies, as well as existing schemas.[7–13]

The aim of the present study was to evaluate the association between chronic histopathological damage in the cortex of the kidney, and both kidney function and the extent of albuminuria, in order to develop a schema for grading chronic cortical damage in nephrectomised kidneys. In addition, the association between average glomerular volume, and kidney function, albuminuria, and other measures of chronic parenchymal damage was assessed.

PATIENTS AND METHODS

Study population

Patients were recruited from the CKD-TUNED study, a prospective observational study conducted at a single tertiary hospital in Brisbane, Australia, capturing all patients managed surgically for kidney tumours at this centre.[14] Of 267 patients managed between June 2013 and June 2017, there were 150 patients who underwent radical nephrectomy for whom non-neoplastic cortical tissue was available. Clinical characteristics were recorded from patient interviews and chart review. Albumin-creatinine ratio (ACR) was determined from urine samples taken at the time of surgery, and estimated glomerular filtration rate (eGFR) was calculated from serum creatinine concentrations recorded within one preoperative month, using the CKD-EPI equation.[15]

Ethical considerations

This study was approved by the Metro South Health Human Research Ethics Committee (HREC/05/QPAH/95; HREC/16/QPAH/353). All patients were aged ≥18 years, and written informed consent was a requirement for inclusion.

Tissue collection and slide preparation

Non-neoplastic cortical tissue was randomly sampled from an area distal to the tumour, to minimise any potential mass effects.[16,17] After resection, kidneys were immediately bisected and non-neoplastic cortical tissue was excised with a scalpel and placed on ice. Tissue was placed in 4% formalin for 24 h at 4°C for fixation; formalin was then replaced with phosphate-buffered saline and tissue was stored at 4°C. Samples were embedded in paraffin using a Leica EG1150 Tissue Embedder and 4μm sections were cut onto glass slides using a Leica RM2245 Semi-Motorized Rotary Microtome (Leica, Germany). Haematoxylin and eosin staining was performed using a Tissue-Tek Prisma Automated Slide Stainer and G2 Coverslipper (Sakura, The Netherlands).

Histopathology scoring

Scoring was undertaken by one of three pathologists, who were blinded to identifying and clinical information, using the schema in Table 1. This grading schema considered the degree of glomerulosclerosis, vessel lumen narrowing, tubular atrophy, and interstitial fibrosis (see Fig. 1 for example micrographs). Glomerulosclerosis was determined by a formal count. A senior renal pathologist was consulted if there was any uncertainty about the score of specimens, particularly regarding the degree of tubular atrophy and interstitial fibrosis, as the potential for misclassification was higher due to the relative subjectivity of these measures.

Estimation of glomerular volume

Average glomerular volume was estimated using the Weibel and Gomez method,[18] evaluating a minimum of 15 glomerular profile areas per patient. The following equation was used, where β is a shape coefficient and K is a size distribution coefficient.

$$\text{Volume} = \text{Profile Area}^{1.5} \times \frac{\beta}{K}$$

The value of β was 1.38 as this is the shape coefficient for a sphere; and 1.01 was selected for K, which assumes a 10% coefficient of variation.[18]

The profile area of the entire renal corpuscle and the capillary tuft (Fig. 2) was calculated using Olympus cellSens Software (Olympus. Australia).

Table 1 Scoring criteria for radical nephrectomy specimens

Scoring criteria	
Tubular atrophy score	
t0	No tubular atrophy
t1	Tubular atrophy in ≤25% of the area of cortical tubules
t2	Tubular atrophy in 26–50% of the area of cortical tubules
t3	Tubular atrophy in >50% of the area of cortical tubules
Interstitial fibrosis score	
i0	Interstitial fibrosis in ≤5% of the cortical area
i1	Interstitial fibrosis in 6–25% of the cortical area
i2	Interstitial fibrosis in 26–50% of the cortical area
i3	Interstitial fibrosis in >50% of the cortical area
Vasculopathy score	
v0	No significant chronic vascular changes
v1	Luminal area reduction of 25% in worst affected vessels
a	Area reduction of 10–25% in less than half of total vessels in section
b	Area reduction of 10–25% in more than half of total vessels in section
v2	Luminal area reduction of 26–50% in worst affected vessels
a	Area reduction of 10–50% in less than half of total vessels in section
b	Area reduction of 10–50% in more than half of total vessels in section
v3	Luminal area reduction of >50% in worst affected vessels
a	Area reduction of >10% in less than half of total vessels in section
b	Area reduction of >10% in more than half of total vessels in section
Glomerulopathy score	
g0	Sclerosis of <20% of glomeruli
a	Sclerosis of <10% of glomeruli
b	Sclerosis of 10–20% of glomeruli
g1	Sclerosis of 20–50% of glomeruli
a	<50% sclerotic glomeruli globally affected
b	≥50% sclerotic glomeruli globally affected
g2	Sclerosis of 51–90% of glomeruli
a	<50% sclerotic glomeruli globally affected
b	≥50% sclerotic glomeruli globally affected
g3	Sclerosis of >90% of glomeruli
a	<50% sclerotic glomeruli globally affected
b	≥50% sclerotic glomeruli globally affected

Measurements were undertaken by a single investigator who was blinded to identifying and clinical information.

Statistical analysis

Each histopathological score category was compared on eGFR and ACR, using a Kruskal–Wallis ANOVA or Mann–Whitney U-test. In addition, clinical characteristics and histopathological score categories were compared on glomerular volume, using a Mann–Whitney U-test. Associations between glomerular volume and both ACR and eGFR were evaluated using multivariable linear regression, adjusting for age and sex. ACR was log-transformed for this analysis. Statistical analysis was performed using Stata 14.0 (StataCorp, USA).

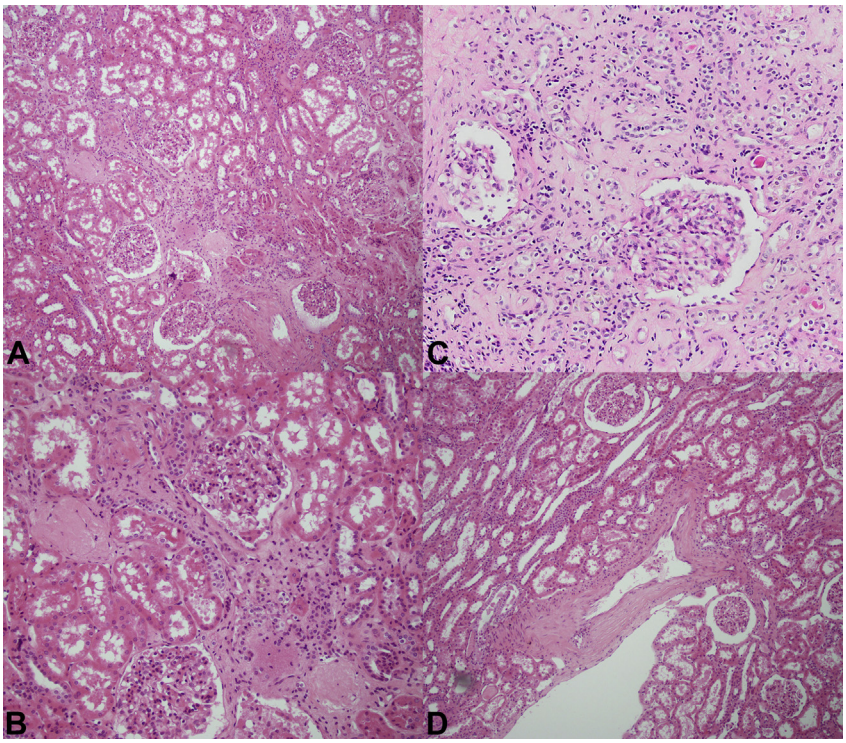

Fig. 1 Example micrographs demonstrating chronic damage. (A) Low-power, and (B) high-power fields, demonstrating mild interstitial fibrosis (i1) and tubular atrophy (t1). Globally sclerosed and functional glomeruli are both present. (C) High-power field demonstrating extensive tubular atrophy (t3) and interstitial fibrosis (i3) with viable glomeruli present. (D) Low-power field demonstrating mild arteriosclerosis (v1).

RESULTS

Clinical characteristics of the study population are presented in Table 2 and comparisons between histopathology score and kidney function measures are presented in Table 3. As expected, eGFR was inversely associated with the degree of glomerulosclerosis ($p < 0.001$), vessel narrowing ($p = 0.002$), tubular atrophy ($p < 0.001$), and interstitial fibrosis ($p < 0.001$). ACR was associated only with the degree of interstitial fibrosis ($p = 0.02$) and tubular atrophy ($p = 0.02$, when comparing scores of 0 and ≥ 1).

When comparing the median (interquartile range) glomerular volume, males had a greater corpuscle and capillary tuft volume than females [6.6 (4.9–8.3) vs 5.1 (4.3–6.9) $\times 10^6$ μm^3, $p = 0.02$; and 3.7 (2.7–5.0) vs 3.0 (2.1–4.2) $\times 10^6$ μm^3, $p = 0.007$], patients with diabetes mellitus tended to have a larger corpuscle and capillary tuft volume than non-diabetic patients [6.8 (5.5–8.5) vs 5.7 (4.4–7.8) $\times 10^6$ μm^3, $p = 0.06$; and 4.1 (3.3–5.7) vs 3.4 (2.6–4.7) $\times 10^6$ μm^3, $p = 0.05$], and hypertensive patients tended only to have a larger corpuscle volume than normotensive patients [6.7 (5.1–8.4) vs 5.0 (4.4–7.8), $p = 0.05$].

There was no association between eGFR and glomerular volume. Patients with an ACR >3 mg/mmol appeared to have larger glomeruli, although this did not achieve statistical significance ($p = 0.08$ and 0.06 for corpuscle and capillary tuft volume, respectively). On adjusted linear regression analysis, however, both corpuscle and capillary tuft volumes were positively associated with log-transformed ACR [β (per unit volume) 0.17, 95% confidence interval (CI) 0.05–0.28; and β 0.26, 95% CI 0.09–0.42, respectively]. There was no association between glomerular volume and eGFR on linear regression analysis.

When considering histopathology scores, only an interstitial fibrosis score ≥ 1 was associated with a larger corpuscle and capillary tuft volume [7.0 (5.0–9.3) vs 5.5 (4.4–7.0) $\times 10^6$ μm^3, $p = 0.004$; and 3.9 (2.5–5.7) vs 3.3 (2.6–3.8) $\times 10^6$ μm^3, $p = 0.007$] (Table 4).

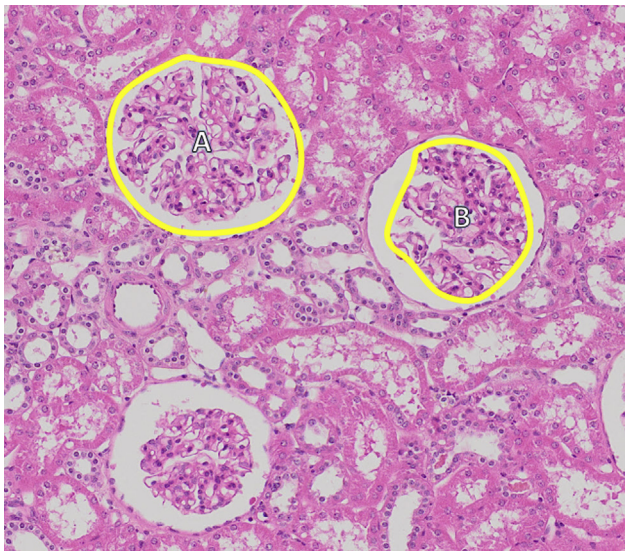

Fig. 2 Measurement of glomerular area. Example micrograph demonstrating the procedure for measuring the profile area of the renal corpuscle, (A) encompassing the entire border of Bowman's space and (B) the glomerular capillary tuft.

DISCUSSION

The goal of this study was to evaluate the correlation between chronic histopathological damage, and both baseline kidney

Table 2 Characteristics of study population

	n (%)
Age, years	
<65	90 (60)
≥65	60 (40)
Sex	
Female	59 (39)
Male	91 (61)
Body mass index, kg/m^2	
<30	85 (57)
≥30	58 (39)
Missing	7 (5)
Diabetes mellitus	
No	114 (76)
Yes	29 (19)
Uncertain	7 (5)
Hypertension	
No	44 (29)
Yes	94 (63)
Uncertain	12 (8)
Tumour size, mm	
≤40	50 (33)
>40	96 (64)
Missing	4 (3)
eGFR, mL/min per 1.73m^2	
≥60	105 (70)
<60	36 (24)
Missing	9 (6)
ACR, mg/mmol	
≤3	79 (53)
>3	45 (30)
Missing	26 (17)

ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

function and albuminuria, with the aim of developing a standard schema for scoring chronic pathological changes to non-neoplastic kidney cortical tissue in radical nephrectomy specimens. We additionally aimed to investigate whether glomerular volume was associated with either eGFR, albuminuria, or degree of chronic damage.

We considered damage in the four major cortical compartments: glomeruli, vasculature, tubules, and interstitium. As expected, the degree of chronic damage strongly associated with eGFR in all compartments. However, only the degree of tubular atrophy and interstitial fibrosis was associated with albuminuria. Interstitial fibrosis was also associated with a larger glomerular volume. Males, and patients with diabetes mellitus or hypertension also tended to have larger glomeruli. Although glomerular volume was not associated with eGFR, it was positively associated with ACR.

Chronic parenchymal changes are generally ubiquitous in CKD regardless of the underlying aetiology.[12] The extent of damage has been demonstrated to have prognostic value in deceased donor kidney pre-implantation biopsies,[19] allograft pathology,[20,21] IgA nephropathy,[22] lupus nephritis,[23] and diabetic nephropathy.[24] Similar associations between cortical histopathology and kidney function have been demonstrated in patients undergoing nephrectomy for kidney tumours. In a study of 110 cases from a single centre in the USA, Bijol *et al.*[9] found that >20% glomerulosclerosis was associated with a higher postoperative serum creatinine concentration. In a single-centre study evaluating 49 cases in the USA with a mean follow-up of 19.7 months, Gautam *et al.*[8] demonstrated that for each 10% increase in sclerosed glomeruli, percentage decline in eGFR increased by 9% ($p = 0.03$). Similarly, in a Japanese single-centre study evaluating 100 nephrectomy cases with a median follow-up duration of 84.2 months, Sejima *et al.*[11] demonstrated that global glomerulosclerosis was associated with greater decline in eGFR. In a single-centre study of 156 patients with a mean follow-up of 49 months, Salvatore *et al.*[7] showed that severe arteriosclerosis (>50% luminal narrowing) associated with a greater mean pre-to-postoperative change in serum creatinine (0.9 mg/dL vs 0.2–0.3 mg/dL in patients without severe arteriosclerosis). Based on the significant correlation between the thresholds for histopathology categorisation and baseline kidney function and albuminuria in the present study, and previous associations between similar

Table 3 Histopathology score compared on kidney function and albuminuria

	n[a]	eGFR, mL/min per 1.73m^2	*p* value	ACR, mg/mmol	*p* value
Glomerulopathy (score)					
0	102	80.5 (66.0–94.0)	<0.001	1.8 (0.6–5.9)	0.56
1	22	63.0 (37.0–76.0)		1.0 (0.6–3.2)	0.88[b]
≥2	9	43.0 (37.0–51.0)		1.7 (1.3–7.7)	
Vasculopathy (score)					
0	41	85.0 (73.0–96.0)	0.002	1.4 (0.5–3.8)	0.23
1	50	72.0 (58.0–85.0)		2.5 (1.0–11.0)	0.07[b]
2	21	70.0 (54.0–92.0)		1.7 (0.8–4.8)	
3	15	58.0 (38.0–77.0)		1.4 (1.1–3.8)	
Tubular atrophy (score)					
0	30	81.5 (70.0–95.0)	<0.001	0.8 (0.4–3.0)	0.09
1	82	79.5 (63.0–94.0)		1.8 (0.8–5.9)	0.02[b]
2	13	60.0 (51.0–74.0)		2.0 (1.3–7.5)	
3	14	37.5 (33.0–65.0)		2.6 (1.3–7.7)	
Interstitial fibrosis (score)					
0	72	83.0 (70.5–95.5)	<0.001	1.2 (0.5–3.3)	0.02
1	40	70.5 (57.5–82.5)		3.2 (0.8–11.0)	0.002[b]
2	10	66.0 (54.0–105.0)		2.0 (1.8–4.0)	
3	17	38.0 (37.0–65.0)		2.6 (1.1–7.7)	

Data presented as median (interquartile range).
ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.
[a] Some compartments were unable to be assessed in all patients; total $n = 150$.
[b] p value calculated by comparing scores of 0 and ≥1, using a Mann–Whitney U-test.

Table 4 Clinical characteristics compared on average glomerular volume

	Glomerular volume ($\times 10^6$ μm^3)			
	Corpuscle	*p* value	Capillary tuft	*p* value
Age, years				
<65	6.2 (4.6–8.4)	0.25	3.4 (2.7–4.9)	0.25
≥65	5.9 (4.4–7.3)		3.3 (2.4–4.2)	
Sex				
Female	5.1 (4.3–6.9)	0.02	3.0 (2.1–4.2)	0.007
Male	6.6 (4.9–8.3)		3.7 (2.7–5.0)	
Body mass index, kg/m^2				
<30	5.7 (4.4–8.0)	0.34	3.3 (2.4–4.9)	0.23
≥30	6.2 (5.1–7.8)		3.8 (3.0–4.8)	
Diabetes mellitus				
No	5.7 (4.4–7.8)	0.06	3.4 (2.6–4.7)	0.05
Yes	6.8 (5.5–8.5)		4.1 (3.3–5.7)	
Hypertension				
No	5.0 (4.4–7.8)	0.05	3.4 (2.6–4.5)	0.40
Yes	6.7 (5.1–8.4)		3.7 (2.9–5.0)	
Tumour size, mm				
≤40	5.7 (4.4–7.7)	0.64	3.3 (2.7–4.9)	0.94
>40	6.2 (4.8–8.1)		3.4 (2.6–4.7)	
eGFR, mL/min per 1.73m^2				
≥60	6.4 (3.5–8.1)	0.73	3.4 (2.7–4.9)	0.50
<60	6.2 (4.8–8.0)		3.7 (2.1–4.3)	
ACR, mg/mmol				
≤3	5.5 (4.6–7.5)	0.08	3.3 (2.6–4.3)	0.06
>3	7.1 (5.4–8.6)		4.0 (2.7–5.2)	
Glomerulopathy (score)				
0	6.3 (4.7–8.0)	0.15	3.4 (2.6–4.8)	0.36
≥1	5.1 (4.1–6.6)		3.1 (2.0–4.2)	
Vasculopathy (score)				
0	6.3 (4.7–7.7)	0.93	3.8 (2.7–4.9)	0.33
≥1	6.0 (4.4–8.2)		3.3 (2.5–4.6)	
Tubular atrophy (score)				
0	5.6 (4.4–6.9)	0.20	3.2 (2.7–3.6)	0.14
≥1	6.2 (4.7–8.3)		3.6 (2.4–5.0)	
Interstitial fibrosis (score)				
0	5.5 (4.4–7.0)	0.004	3.3 (2.6–3.8)	0.007
≥1	7.0 (5.0–9.3)		3.9 (2.5–5.7)	

Data presented as median (interquartile range); $n = 113$.
ACR, albumin-creatinine ratio; eGFR, estimated glomerular filtration rate.

thresholds and worse postoperative kidney function, we conclude that using the proposed schema (Table 1) to report non-neoplastic pathology in radical nephrectomy specimens is likely to provide important information to clinicians, and provide an estimate of the degree of chronic histopathological changes present in the contralateral kidney. Notwithstanding, longitudinal kidney function data are required to confirm this assertion.

The relatively weak association between albuminuria and the histological findings may be explained by the fact that the presence of a kidney tumour could contribute to the development of albuminuria by directly damaging nephron structures, without any concomitant chronic damage.[25,26] This was not able to be assessed in this study, as cortical tissue was sampled from areas distal to the tumour.

Our finding that certain clinical characteristics were associated with glomerular volume was reasonably predictable, as larger glomerular volumes have previously been reported in males,[27] diabetics,[28] and hypertensive patients.[29,30] Mechanisms of glomerular hypertrophy vary by aetiology, but are thought in general to be mediated by functional stress, as a consequence of prolonged hyperperfusion and hyperfiltration (as seen in obesity and hypertension), progressive nephron loss, or low starting nephron number.[31] When comparing glomerular volume by histopathology scores, only interstitial fibrosis was associated with increased glomerular volume, whereas vascular changes were not associated. The amount of interstitial fibrosis is likely to correlate well with the degree of nephron loss,[32] and it is unsurprising that this was also associated with larger glomeruli. The fact that arteriosclerosis was not associated with glomerular volume may be because arteriosclerosis leads to glomerular ischaemia, with subsequent capillary tuft shrinkage and glomerular volume reduction.[33]

The correlation between glomerular volume and albuminuria also supports the glomerular stress paradigm, as hyperfiltration is generally associated with albuminuria.[34] Based on the results of this study, it is apparent that glomerular volume may provide additional prognostic information, compared with assessing chronic damage and fibrotic change alone, as early glomerular damage may only manifest as glomerular enlargement. This method requires a substantial amount of time to undertake, and significant inter- and intra-individual variability in glomerular volume may introduce difficulty if translating this approach into clinical applications.

This study aimed to evaluate the feasibility of a novel schema for assessing cortical histopathological changes in nephrectomised kidneys with cortical tumours, and how well these changes correlated with baseline kidney function and albuminuria. Based on the findings of this study we conclude

that using a schema such as this to report non-neoplastic histopathology in radical nephrectomy specimens may provide important information to the treating clinician in terms of future risk of kidney function deterioration. Longitudinal validation of this schema using the same dataset is currently underway. The limitations of using a semi-quantitative schema include the possibility for inter-observer and inter-centre variability, which was not evaluated in this study. Although some parameters (such as glomerulosclerosis) are reasonably objective, the degree of interstitial fibrosis is more subjective, and therefore more likely subject to misclassification.[35] Additional staining methods (e.g., Masson's trichrome or periodic acid–Schiff staining) may provide more information than haematoxylin and eosin staining in cases of uncertainty. Another possible limitation is that the cortical tissue sampled from the excised kidney was not reflective of the level of damage in the cortex of the contralateral kidney, due to effects of the tumour that are not related to mass, for example inflammation. Nonetheless, in this clinical scenario, there are no better methods of estimating the degree of chronic kidney damage without subjecting patients to further invasive procedures. These results should be interpreted in the context of the relatively small sample size of this study, particularly analyses involving comparisons between subgroups.

CONCLUSION

This study showed that histological evidence of cortical parenchymal damage was strongly associated with poorer baseline kidney function in patients managed with radical nephrectomy for kidney tumours. A standardised schema to score cortical parenchymal damage is proposed, and longitudinal follow-up of patients recruited into this study will allow for validation of this schema for prognostication of patients at risk of CKD.

Conflicts of interest and sources of funding: RJE was supported by an Australian Government Research Training Stipend and a scholarship from the Royal College of Pathologists of Australasia during the conduct of this study. This research was supported by a grant awarded by Metro South Hospital and Health Service – Study, Education and Research Trust Account (SERTA). The authors state that there are no conflicts of interest to disclose.

Address for correspondence: Mr Robert Ellis, Level 5 Translational Research Institute, 37 Kent Street, Woolloongabba, Brisbane, Qld, 4102, Australia. E-mail: r.ellis1@uq.edu.au

References

1. Patel MI, Strahan S, Bang A, *et al*. Predictors of surgical approach for the management of renal cell carcinoma: a population-based study from New South Wales. *ANZ J Surg* 2016; 87: E193–8.
2. Ta AD, Bolton DM, Dimech MK, *et al*. Contemporary management of renal cell carcinoma (RCC) in Victoria: implications for longer term outcomes and costs. *BJU Int* 2013; 112 (Suppl 2): 36–43.
3. Ellis RJ, Edey DP, Del Vecchio SJ, *et al*. End-stage kidney disease following surgical management of kidney cancer. *Clin J Am Soc Nephrol* 2018; 13: 1641–8.
4. Ellis RJ, Joshi A, Ng KL, *et al*. Optimising assessment of kidney function when managing localised renal masses. *Med J Aust* 2017; 207: 127–33.
5. Hu SL, Chang A, Perazella MA, *et al*. The nephrologist's tumor: basic biology and management of renal cell carcinoma. *J Am Soc Nephrol* 2016; 27: 2227–37.
6. Henriksen KJ, Meehan SM, Chang A. Nonneoplastic kidney diseases in adult tumor nephrectomy and nephroureterectomy specimens: common, harmful, yet underappreciated. *Arch Pathol Lab Med* 2009; 133: 1012–25.
7. Salvatore SP, Cha EK, Rosoff JS, *et al*. Nonneoplastic renal cortical scarring at tumor nephrectomy predicts decline in kidney function. *Arch Pathol Lab Med* 2013; 137: 531–40.
8. Gautam G, Lifshitz D, Shikanov S, *et al*. Histopathological predictors of renal function decrease after laparoscopic radical nephrectomy. *J Urol* 2010; 184: 1872–6.
9. Bijol V, Mendez GP, Hurwitz S, *et al*. Evaluation of the nonneoplastic pathology in tumor nephrectomy specimens: predicting the risk of progressive renal failure. *Am J Surg Pathol* 2006; 30: 575–84.
10. Sarsik B, Simsir A, Yilmaz M, *et al*. Spectrum of nontumoral renal pathologies in tumor nephrectomies: nontumoral renal parenchyma changes. *Ann Diagn Pathol* 2013; 17: 176–82.
11. Sejima T, Yumioka T, Yamaguchi N, *et al*. Characterization of mild and severe post-radical nephrectomy renal functional deterioration utilizing histopathological evaluation of non-neoplastic nephrectomized renal parenchyma. *Int J Clin Oncol* 2016; 21: 588–94.
12. Sethi S, D'Agati VD, Nast CC, *et al*. A proposal for standardized grading of chronic changes in native kidney biopsy specimens. *Kidney Int* 2017; 91: 787–9.
13. Racusen LC, Solez K, Colvin RB, *et al*. The Banff 97 working classification of renal allograft pathology. *Kidney Int* 1999; 55: 713–23.
14. Ellis RJ, Del Vecchio SJ, Ng KL, *et al*. The Correlates of Kidney Dysfunction – Tumour Nephrectomy Database (CKD-TUNED) study: protocol for a prospective observational study. *Asian Pac J Cancer Prev* 2017; 18: 3281–5.
15. Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–12.
16. Khemees TA, Lam ET, Joehlin-Price AS, *et al*. Does the renal parenchyma adjacent to the tumor contribute to kidney function? A critical analysis of glomerular viability in partial nephrectomy specimens. *Urology* 2016; 87: 114–9.
17. Bonsib SM, Pei Y. The non-neoplastic kidney in tumor nephrectomy specimens: what can it show and what is important? *Adv Anat Pathol* 2010; 17: 235–50.
18. Weibel ER. *Stereological Methods. Volume 1: Practical Methods for Biological Morphometry*. London: Academic Press Inc, 1979.
19. Liapis H, Gaut JP, Klein C, *et al*. Banff histopathological consensus criteria for preimplantation kidney biopsies. *Am J Transplant* 2017; 17: 140–50.
20. Nicholson ML, McCulloch TA, Harper SJ, *et al*. Early measurement of interstitial fibrosis predicts long-term renal function and graft survival in renal transplantation. *Br J Surg* 1996; 83: 1082–5.
21. Diaz Encarnacion MM, Griffin MD, Slezak JM, *et al*. Correlation of quantitative digital image analysis with the glomerular filtration rate in chronic allograft nephropathy. *Am J Transplant* 2004; 4: 248–56.
22. Vleming LJ, de Fijter JW, Westendorp RG, *et al*. Histomorphometric correlates of renal failure in IgA nephropathy. *Clin Nephrol* 1998; 49: 337–44.
23. Austin 3rd HA, Muenz LR, Joyce KM, *et al*. Prognostic factors in lupus nephritis. Contribution of renal histologic data. *Am J Med* 1983; 75: 382–91.
24. Bohle A, Wehrmann M, Bogenschutz O, *et al*. The pathogenesis of chronic renal failure in diabetic nephropathy. Investigation of 488 cases of diabetic glomerulosclerosis. *Pathol Res Pract* 1991; 187: 251–9.
25. Jorgenson L, Heuch I, Jenssen T, *et al*. Association of albuminuria and cancer incidence. *J Am Soc Nephrol* 2008; 19: 992–8.
26. Vaglio A, Buzio L, Cravedi P, *et al*. Prognostic significance of albuminuria in patients with renal cell cancer. *J Urol* 2003; 170: 1135–7.
27. Puelles VG, Douglas-Denton RN, Zimanyi MA, *et al*. Glomerular hypertrophy in subjects with low nephron number: contributions of sex, body size and race. *Nephrol Dial Transplant* 2014; 29: 1686–95.
28. Zhu WW, Chen HP, Ge YC, *et al*. Ultrastructural changes in the glomerular filtration barrier and occurrence of proteinuria in Chinese patients with type 2 diabetic nephropathy. *Diabetes Res Clin Pract* 2009; 86: 199–207.
29. Hoy WE, Hughson MD, Diouf B, *et al*. Distribution of volumes of individual glomeruli in kidneys at autopsy: association with physical and clinical characteristics and with ethnic group. *Am J Nephrol* 2011; 33 (Suppl 1): 15–20.

30. Puelles VG, Zimanyi MA, Samuel T, *et al*. Estimating individual glomerular volume in the human kidney: clinical perspectives. *Nephrol Dial Transplant* 2012; 27: 1880–8.
31. Hoy WE, Bertram JF, Denton RD, *et al*. Nephron number, glomerular volume, renal disease and hypertension. *Curr Opin Nephrol Hypertens* 2008; 17: 258–65.
32. Zeisberg M, Neilson EG. Mechanisms of tubulointerstitial fibrosis. *J Am Soc Nephrol* 2010; 21: 1819–34.
33. Tighe JR. The pathology of renal ischaemia. *J Clin Pathol Suppl (R Coll Pathol)* 1977; 11: 114–24.
34. Palatini P. Glomerular hyperfiltration: a marker of early renal damage in pre-diabetes and pre-hypertension. *Nephrol Dial Transplant* 2012; 27 (1708–14).
35. Farris AB, Chan S, Climenhaga J, *et al*. Banff fibrosis study: multicenter visual assessment and computerized analysis of interstitial fibrosis in kidney biopsies. *Am J Transplant* 2014; 14: 897–907.