RESEARCH ARTICLE

The Correlates of Kidney Dysfunction – Tumour Nephrectomy Database (CKD-TUNED) Study: Protocol for a Prospective Observational Study

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Abstract

Background: Tumour nephrectomy conveys a significant risk of adverse renal functional outcomes postoperatively, however there are limited strategies for predicting patients at increased risk of these outcomes. The Correlates of Kidney Dysfunction – Tumour Nephrectomy Database (CKD-TUNED) study is a prospective observational study evaluating the risk of chronic kidney disease and end-stage kidney disease in tumour nephrectomy patients. **Methods:** The CKD-TUNED study involves analysis of clinical data and collection of tissue, urine and blood samples for the purposes of forming a tissue repository resource for future investigation. Recruitment began in 2013 and is expected to continue until 2023, with a projected sample size between 700-1000 subjects. **Results:** All relevant ethics and site-specific approvals have been granted and all relevant infrastructure is in place. Study methods are undergoing validation and refinement. As of June 2017 there are 267 participants enrolled in the study. **Conclusion:** It is anticipated that this study will have the potential to identify risk factors for adverse renal functional outcomes following tumour nephrectomy, which can be used in the development of predictive models with clinical utility, and in turn improve patient outcomes.

Keywords: Kidney cancer- renal cell carcinoma- chronic kidney disease- nephrectomy- glomerular filtration rate

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Introduction

The gold-standard management for localised renal cell carcinoma (RCC) and other malignant kidney mass lesions is tumour nephrectomy, which involves the removal of part or all of a kidney (Ljungberg et al., 2015). Historically, most patients were expected to retain the majority of their kidney function postoperatively, due to parallels being drawn between tumour and donor nephrectomies, however it is now established that many tumour nephrectomy patients have worse postoperative renal outcomes compared to live kidney donors (Lee et al., 2015; Gazel et al., 2015; Etafy et al., 2015), and that this is likely due to a substantially higher comorbidity burden (Timsit et al., 2012).

Development and progression of chronic kidney disease (CKD) is a significant potential complication following tumour nephrectomy. In Australia, approximately one in ten adults has clinical features of CKD and one in three has at least one major risk factor (Kidney Health Australia, 2015). This prevalence is expected to rise with an increasingly aging population, mainly due to increased incidence of lifestyle-associated metabolic diseases (such as diabetes mellitus, hypertension and obesity) which are associated with or contribute to the development of CKD (Levey and Coresh, 2012). The identification of risk factors which may predispose patients to the development of adverse renal functional outcomes is of significant importance when planning management strategies for patients with renal tumours. Postoperative CKD in tumour nephrectomy patients is associated with increased risk of all-cause mortality and cardiovascular disease-related mortality (Weight et al., 2010). It is apparent that loss of functional renal parenchyma is one of the driving forces behind adverse events, as radical tumour nephrectomy is associated with significantly increased risk of adverse events compared to partial nephrectomy (Thompson et al., 2008; Miller et al., 2008).

Patients undergoing tumour nephrectomy can also consequently progress to end-stage kidney disease (ESKD), requiring either dialysis or kidney transplant. A recent study from the USA utilising data from the United

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States Renal Data System identified that, between 1983 and 2007, 0.49% of patients with ESKD developed this as a consequence of renal tumour management (Nguyen et al., 2017). In Australia, based on Australian and New Zealand Dialysis and Transplant Registry (ANZDATA) annual reports (http://www.anzdata.org.au/v1/annual_reports_download.html), in the five years from 2011 to 2015, 0.63 and 0.77% of patients who commenced treatment for ESKD did so as a consequence of RCC and urogenital malignancy (RCC and transitional cell carcinoma of the urinary tract), respectively (Table 1). There have been many studies assessing the risk of CKD progression in both radical and partial nephrectomy patients. Increasing age, proteinuria, the presence of diabetes mellitus, obesity and hypertension, as well as behavioural factors such as tobacco use, are associated with CKD progression (Jeon et al., 2009; Klarenbach et al., 2011; Satasivam et al., 2015). There is substantial contiguity with risk factors associated with CKD in the general population (Levey and Coresh, 2012).

The CKD-TUNED study aims to identify factors which associate with adverse renal functional outcomes following tumour nephrectomy surgery, with a goal of developing clinical tools with for identifying patients at increased risk of these outcomes. This will be carried out through analysis of clinical factors, compared to longitudinal measures of renal function. Urine, blood and tissue samples are being analysed using validated and exploratory methods for predicting kidney function change.

This study will evaluate postoperative renal function within various timeframes; specifically:

i) Short Term: immediate postoperative changes in renal function within seven days of surgery;

ii) Mid Term: renal function assessed two-three years postoperatively;

iii) Long Term: renal function assessed greater than five years postoperatively.

Materials and Methods

Patients and Methods

Study Design and Sampling

This protocol describes a single centre prospective cohort study of patients undergoing tumour nephrectomy, utilising a convenience sampling strategy. All patients undergoing tumour nephrectomy at the study centre are approached for enrolment. The study began in June 2013 and recruitment is expected to continue until 2023. Based on the average number of cases per year between 2013 and 2016, it is estimated that the ten year recruitment period will yield between 700 and 1,000 participants.

Recruitment

Patients undergoing tumour nephrectomy surgery at the Princess Alexandra Hospital are approached for inclusion in the study by a treating clinician. Written informed consent is necessary for enrolment. Participants are able to withdraw at any stage without consequence.

Inclusion and Exclusion Criteria

All participants must be aged ≥18 years and undergoing a tumour nephrectomy procedure; all consenting patients fitting these criteria are included in the database.

Exclusion criteria for the primary analysis of renal function include: any previous nephrectomy procedures, patients requiring kidney replacement therapy (stage 5 CKD), renal transplant recipients, and perioperative mortality. Participants with limited data availability for outcomes and predictors are considered for inclusion on a case-by-case basis. Preoperative values must be available within one month before surgery. Participants excluded from renal function analyses may be included in other analyses, hence the rationale for inclusion in the database.

Subgroups

Patients undergoing partial and radical nephrectomy will be compared in separate subgroups. Those with advanced oncological disease will also be compared in different groups based on tumour-node-metastasis (TNM) stage. Patients will be compared by preoperative level of kidney function, grouped according to CKD stage (Table 2). These distinctions will also be applied to new baseline kidney function established after surgery.

Results

Data Collection

Baseline characteristics data for this study are collected from three main sources: i) directly from the patient, in the form of a structured interview, concurrent with medical, surgical, social and family history, recorded by the treating clinician; ii) chart review, with particular focus on the most recent years, to corroborate the accuracy and expand upon the information provided by the patient; and iii) pathology tests undertaken prior to surgery (including full blood count, routine biochemistry, and urinalysis). Tumour histopathology is recorded postoperatively. Information from all sources is compared to improve accuracy and minimise missing data. Preoperative pathology tests are considered as 'baseline' only if obtained within one month prior to surgery.

Short-term follow-up data are collected from chart review and pathological tests in the postoperative period prior discharge of each participant. Serum creatinine will be recorded from postoperative day one until day seven, unless discharged prior to this point. After discharge, follow-up data will be recorded at either: i) scheduled follow-up outpatient clinics at the Princess Alexandra Hospital, related to surgery; ii) relevant pathology tests performed during unscheduled or unrelated admissions (in- or outpatient) to the Princess Alexandra Hospital or another Queensland Health Facility; or iii) by contacting other health care providers of the participant, when that participant has not been attending regular follow-up appointments or is followed up in a private centre. If renal follow-up data are recorded due to an acute hospitalisation it will not be included in the analysis if associated with acute kidney injury.

Table 1. ESKD Incidence in Australia by Year

Year	New Patients	Due to Renal Cell Carcinoma	Due to Urogenital Malignancy
2015	2,654	19 (0.72)	22 (0.82)
2014	2,610	23 (0.88)	27 (1.03)
2013	2,544	16 (0.62)	20 (0.79)
2012	2,534	13 (0.51)	16 (0.63)
2011	2,453	9 (0.37)	14 (0.57)
2010	2,257	10 (0.44)	14 (0.62)
2009	2,337	10 (0.43)	15 (0.64)
2008	2,476	6 (0.24)	14 (0.57)
2007	2,311	6 (0.26)	12 (0.52)
2006	2,378	14 (0.59)	17 (0.71)

Total number of new patients undergoing treatment for end-stage kidney disease (ESKD) by year; and the number (%) of those for whom this was due to renal cell carcinoma, and urogenital malignancy. Summary data were retrieved from the 30th to 39th (2007-2016) ANZDATA annual reports and interpreted by the authors.

Table 2. Chronic Kidney Disease (CKD) Staging

Stage	eGFR (ml/min per 1.73m^2)
1	> 90 *
2	60-90 *
3a	45-59
3b	30-44
4	15-29
5	< 15

* Only considered CKD with other evidence of kidney damage. eGFR, estimated glomerular filtration rate.

Data Management

Data are stored in hard copy, in potentially-identifiable form. Electronic data are de-identified and managed using Microsoft Access software.

Tissue Repository

In addition to the collection of data, blood, urine and tissue samples are collected intraoperatively from consenting patients, where feasible, and stored for future study.

Approximately 10 ml of venous blood is collected from a peripheral cannula or central line into EDTA (ethylenediaminetetraacetic acid) tubes and centrifuged at 1,200 rpm for 10 minutes at 25°C. Buffy coat, erythrocytes and plasma are stored separately at -80°C. Approximately 15-20 ml of urine is collected from the catheter bag perioperatively, centrifuged at 1,200 rpm for 10 minutes at 25°C, and stored as 1 ml aliquots at -80°C.

Normal renal parenchyma (where possible), perinephric fat, and tumour tissue are collected following surgical resection of the specimen. Normal parenchyma is sampled from an area as far as possible from the primary tumour, to minimise any potential mass effects as a consequence of the tumour. Samples are stored as formalin-fixed or fresh-frozen. Formalin-fixed samples are fixed in 4% formalin and stored at 4°C for 24 hours, before being transferred to phosphate-buffered saline and stored at 4°C, prior to being embedded in paraffin. Fresh-frozen samples are stored at -80°C.

Table 3. Acute Kidney Injury Staging

Stage	Serum Creatinine	Urine Output
1	Increase 1.5-1.9 times the baseline; or absolute increase ≥26.5μM	<0.5 ml/kg/h (6-12 hrs)
2	Increase 2.0-2.9 times the baseline	<0.5 ml/kg/h (>12 hrs)
3	Increase ≥3.0 times the baseline; or absolute increase ≥353.6μM; or initiation of kidney replacement therapy	<0.3 ml/kg/h (>24 hrs); or anuria (≥12 hrs)

Only relative serum creatinine change is assessed in the CKD-TUNED study when evaluating short-term changes in kidney function.

Discussion

Outcomes

Short-Term Outcomes

Short-term renal function change is determined from the zenith serum creatinine within seven postoperative days. Acute kidney injury is characterised by transient loss of renal function with potential for recovery. It is staged by both relative and absolute change in serum creatinine, and urine output (Table 3). In this study, only relative change in serum creatinine will be evaluated as an outcome, where a value of ≥50% of baseline within the first seven postoperative days will be used as a measure of acute kidney injury, as per Kidney Disease: Improving Global Outcomes (KDIGO) practice guidelines (Table 3) (KDIGO AKI Workgroup, 2012). Due to the fact that patients are undergoing a procedure which reduces nephron mass, decreased kidney function is expected. It is therefore important to differentiate this outcome from transient acute kidney injury, which occurs without surgical removal of nephron mass. One potential way to evaluate this is to assess for reversibility. Serum creatinine increased ≥50% from baseline following radical nephrectomy has been reported to predict CKD (defined as an estimated glomerular filtration rate [eGFR] <60 ml/min per 1.73 m^2) three years following surgery (Cho et al., 2011). Serum creatinine change is also assessed as a continuous variable, standardised as a percentage increase from baseline, to increase statistical power for detecting an effect.

Mid- and Long-Term Outcomes

eGFR calculated using the CKD-EPI equation was used to assess changes in kidney function in mid-long term (Levey et al., 2009).

Normalised eGFR as a continuous variable will be assessed. Adjustment will be made for preoperative eGFR, depending on the analysis being undertaken. Change in eGFR is also assessed categorically, based on clinical definitions of CKD (KDIGO CKD Workgroup, 2013). Clinically-defined outcomes include stage 3 and 5 CKD (Table 2); or up- or down-staging of CKD. The rationale for this approach is to maximise the likelihood of detecting

an effect by using a continuous measure, whilst also maintaining a clinical focus by evaluating a validated risk stratification model for kidney function. Stage 3 CKD is a clinically significant outcome as it indicates the threshold that CKD can be diagnosed based on eGFR alone (if persisting ≥3 months). Stage 5 CKD provides a clinically significant outcome as it indicates onset of ESKD, where either dialysis or renal transplant (kidney replacement therapy) is required for the continuation of life, with associated reduction in quality-of-life and significant financial burden.

Additional outcomes include oncological and urological events of significance, such as disease recurrence/metastasis, additional nephrectomy procedures, or other urological procedures evaluated on a case-by-case basis. Acute kidney injury, initiating kidney replacement therapy for non-acute events, all-cause mortality, and cardiovascular events/mortality are also considered outcomes of interest.

Analysis Plan

Baseline Characteristics

Continuous variables will be assessed visually for normality. Nonparametric tests will be used for data that is not normally distributed or for analysis of subgroups with small sample sizes.

Short-Term

Continuous outcomes will be assessed with univariable and multivariable linear regression whereas dichotomous outcomes will be assessed using univariable and multivariable logistic regression. Multivariable models will be developed based on biological significance of predictors and p-values from simple regression.

Mid-Long-Term

Continuous and dichotomous outcomes will be assessed as previously described. The timing of each follow-up point is recorded as days following surgery. One month is defined as 30.4375 (365.25÷12) days. There are two options for analysis, depending on follow-up time homogeneity: i) follow-up time categorised by six-monthly intervals, with follow-up measures ±3 months rounded accordingly and variation reported as median follow-up time, analysed multivariable regression models; ii) time reported as a continuous variable, analysed using mixed models with each observation considered a random effect. All models assessing kidney function will be used and compared for appropriateness of fit.

Outcomes not related to kidney function will be assessed using logistic regression, or survival analysis (e.g. Kaplan-Meier estimator or Cox proportional hazards model) depending on event numbers. This approach may also be taken for new-onset stage 3 or 5 CKD.

Statistical analysis will be performed using Stata Version 14 (StataCorp, College Station, TX).

Missing Data

For demographic and regression analysis, if there are missing data for exposures or potential confounders the entire observation will be dropped from the relevant model and sample size adjusted to reflect this. For longitudinal analysis, a multiple imputation model may be used to estimate missing values.

Ethical Considerations

This study has received institutional ethics approval from the Metro South Human Research Ethics Committee (for patients enrolled prior to October 2016: HREC/05/QPAH/95; and after October 2016: HREC/16/QPAH/353). Institutional human research ethics approval was also obtained from the University of Queensland (Approval No. 2016001215). Written informed consent is a requirement for inclusion in this study and participants are given the option to withdraw at any time.

Significance

During surgical management of renal neoplasia there is limited focus placed on outcomes relating to kidney function when making clinical decisions regarding management plans. This is in part due to a lack of knowledge on the subject, combined with the lack of clinically-oriented predictive models which can be used for CKD risk stratification. Greater knowledge about CKD risk in tumour nephrectomy patients may lead to additional considerations in relation to surgical management decisions, follow-up periods, specialist referral, or early implementation of disease-modifying or preventative measures.

Disclosure Statement

The authors report no relevant disclosures.

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