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Pattern of Change in Renal Function Following Radical Nephrectomy for Renal Cell Carcinoma

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Abstract

Radical nephrectomy (RN) is an independent risk factor for the development of chronic kidney disease (CKD) in those with renal cell carcinoma (RCC). We aimed to examine the pattern of change in post-operative renal function in patients who underwent RN for RCC over a 3 year period at our institution. We performed a retrospective review of histological and biochemical findings in patients undergoing RN for RCC over a 38 month period. Estimated glomerular filtration rate (eGFR) was recorded pre- and post-operatively and at follow-up. We analysed data on 131 patients (median follow-up 24 months). The proportion of patients with advanced CKD increased significantly at follow-up with 48 (85.7%) patients, classified as having stage 2 CKD pre-operatively, being re-classified as stage 3-5. Mean eGFR was significantly lower pre-operatively (76.6 mL/min/1.73 m²) compared to hospital discharge (61 mL/min/1.73 m², p<0.001) and follow-up (55.5 mL/min/1.73 m², p<0.001). Those with pT1 tumours sustained a significantly greater decline in eGFR compared to other stages. In conclusion, patients with pT1a and pT1b tumours sustain a disproportionate decline in renal function and may benefit the most from NSS.

Introduction

Renal cell carcinoma (RCC) is the 7th most common cancer diagnosed in Ireland and is the 10th most common cause of solid-organ cancer death¹. Recent reports have identified an average of 341 new cases each year in Ireland. Rates of diagnosis have been steadily rising over the last decade due to increased use of abdominal radiological imaging and incidental "pick-ups", with a rise of 3.0-3.5% per annum being recorded annually². The most significant increase has been noted in T1 (TNM classification system, AJCC, 2010) disease, which accounted for 5% of all cases in 1994-1998, but now accounts for 37% of new diagnoses². This trend is mirrored internationally with renal tumour size at presentation steadily and consistently decreasing³. T1 disease is associated with a 5 year survival of 81%, as compared to 53% and 8% for T3 and T4 disease respectively, suggesting

that the increased detection of smaller renal masses could lead to an overall reduction in mortality for RCC⁴. When organ-confined (T1-T2), RCC is treated with curative intent, traditionally with radical nephrectomy (RN). Nephron sparing surgery (NSS) has now emerged as the preferential operative treatment for small renal masses (T1a) in appropriate cases⁵. In patients with metastatic disease, cytoreductive RN has a role in reducing disease burden when used in conjunction with systemic therapy⁶.

The majority of RCC diagnoses occur in the 6th and 7th decades of life^{7,8}. Given the higher incidence of risk factors for chronic kidney disease (CKD) in this age group, such as hypertension, diabetes mellitus and cardiovascular disease, there is just concern about the impact of RN on renal function. CKD is associated with a significant burden of morbidity and mortality⁹. This burden increases incrementally with reducing

estimated glomerular filtration rate (eGFR)¹⁰. Both declining eGFR and microalbuminuria have been reported as independent determinants of cardiovascular outcome in those with CKD. Given that RN – itself an independent risk factor for the development of CKD – essentially only impacts on the eGFR, progression of post-operative CKD may be slower in these individuals than in those with CKD due to medical causes¹¹⁻¹³. Of concern, however, is that patients with small tumours may be more likely to develop new-onset CKD following RN and appear to have proportionately worse outcomes in this regard than those with more advanced tumours^{14,15}. The advent of NSS in selected patients reduces the incidence of post-operative CKD¹⁵. However, its routine use is still controversial for those with tumours greater than 4cm in size or in those in whom the location of the tumour makes NSS technically difficult^{5,16-18}. There have been relatively few studies examining the pattern and magnitude of decline in renal function following RN across the full spectrum of patients undergoing RN. Furthermore, understanding the likely patterns of change in renal function following RN will help determine the schedule and type of surveillance required for patients. We aimed to examine the pattern of change in post-operative renal function in patients who underwent RN for RCC over a 3 year period at our institution, with specific reference to tumour size and stage.

Methods

A comprehensive, retrospective review of histological findings and biochemical profiles was undertaken for all patients undergoing RN for RCC at our institution, a tertiary referral centre, over a 38 month period from January 2009 to March 2012. This population included a very small proportion of patients whose surgery was performed with cytoreductive rather than curative intent. However, it excluded patients with transitional cell carcinoma and those undergoing NSS. The decision to perform RN rather than NSS in patients with small renal masses was based on patient characteristics, tumour characteristics (e.g. location) and surgeon's preference. The study population included those undergoing both open and laparoscopic RN. Basic patient demographics at the time of surgery were identified including age and gender. Histological findings recorded for all specimens included side, size, TNM stage and Fuhrman grade. Biochemical profiles of all patients were examined for patterns of change over time. Specifically, we recorded serum creatinine at several key time points: pre-operatively, at the time of hospital discharge post-operatively, and at most recent follow-up. GFR was estimated using the Modified Diet in Renal Disease (MDRD) formula, taking account of gender and ethnicity. Chronic kidney disease was defined based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) from stage 0 (eGFR >90 mL/min/1.73 m², no disease) to stage 5 (eGFR < 15 mL/min/1.73 m², established renal failure). Data recording and statistical analysis were accomplished using a standard statistical software package (SPSS version 18.0).

Results

Clinicopathological characteristics

We examined follow-up data for 131 RN carried out over a 38 month period. The median follow-up of biochemical data was 24 months (0-58 months). The median age at surgery was 64 years (30-84 years). There was a modest male preponderance in the population and right sided tumours were more common than left (see Table 1). Most tumours were histologically T1 (T1a 39 tumours [29.8%], T1b 24 tumours [18.3%]) or T3 (T3a 39 tumours [29.8%], T3b 8 tumours [6.1%], T3c 2 tumours [1.5%]). Only 2 patients (1.5%) had T4 tumours. Over half of all tumours were Fuhrman grade 2 (75 specimens [57.3%]) while grade 1 and grade 4 disease were least common. Four tumours (3.1%) were appropriately not subject to the Fuhrman grading system.

CKD following RN

Pre-operatively, 42 patients (32.1%) had no biochemical evidence of CKD, while 57 (43.5%) had mild (stage 1 and stage 2) CKD, and 32 (24.4%) had stage 3 CKD. There was a significant increase in the advanced stages of CKD at follow-up. In the group

with no CKD pre-operatively (n=42), only 4 (9.5%) continued to meet the biochemical criteria for stage 0 CKD at follow-up, 26 (61.9%) had stage 2 CKD, and 12 (28.6%) had stage 3 CKD. At follow-up, 5 patients with stage 3 CKD pre-operatively sustained a sufficient deterioration in renal function to be re-classified as stage 4 CKD (4 patients) or stage 5 CKD (1 patient). Similar trends were observed across the cohort with 43 (76.8%) of those with stage 2 CKD pre-operatively being re-classified as having stage 3 CKD at follow-up (Figure 1).

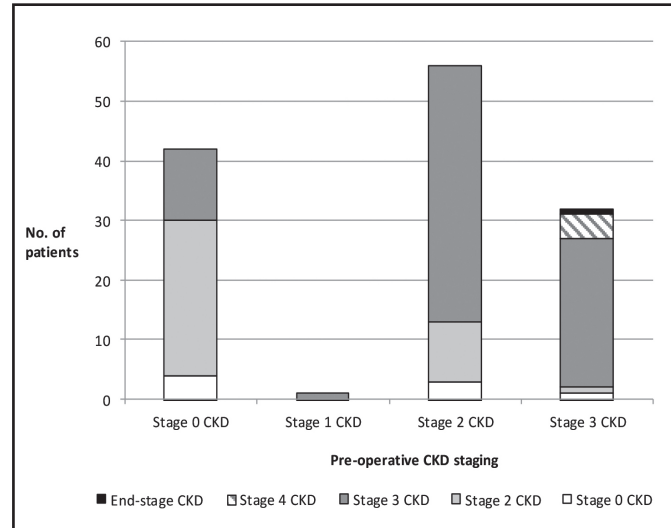


Figure 1 Outcome of patients following radical nephrectomy regarding progression of CKD at follow-up

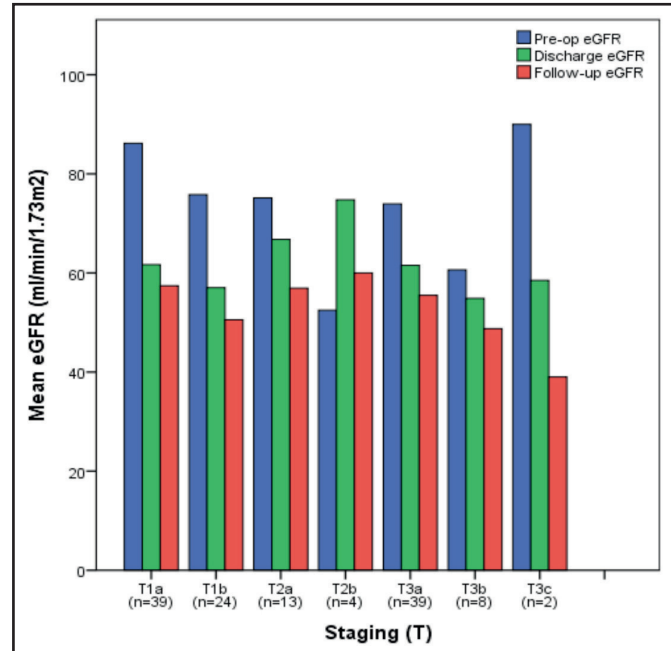


Figure 2 Mean eGFR by tumour stage (T-stage)

Tumour stage and renal function

For the population as a whole (n= 131), compared to pre-operatively, there was a significant decline in mean eGFR both at hospital discharge (76.6 mL/min/1.73 m² vs. 61 mL/min/1.73 m², p<0.001) and at follow-up (76.6 mL/min/1.73 m² vs. 55.5 mL/min/1.73 m², p<0.001). Patients with pT1a tumours had significantly higher mean baseline pre-operative eGFR compared to those with pT2b (p<0.001), pT3a (p=0.004) and pT3b tumours (p<0.001). Similar trends of decline in eGFR were observed for all tumour stages except those with pT2b tumours (Figure 2). The magnitude of decline was highest in those with

T1a (n=39), and T1b (n=24) tumours relative to other stages (Figure 3). In particular, eGFR decline in those with T1a tumours was significantly greater than that seen in patients with T2a ($p=0.026$), T2b ($p<0.001$), T3a ($p=0.009$), and T3b ($p=0.002$), but was similar to that seen those with T1b tumours ($p=0.411$, see figure 3). There was a weak negative correlation between tumour size and both pre-operative eGFR ($R=-0.227$, $p=0.009$) and the magnitude of decline in eGFR seen at follow-up ($R=-0.36$, $p<0.001$).

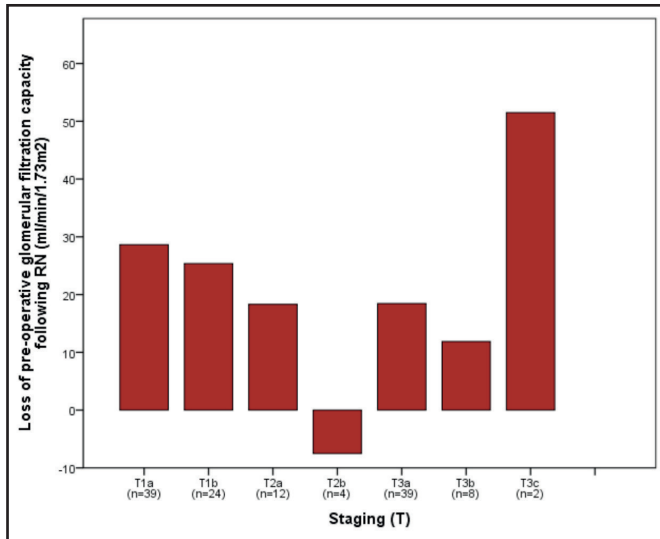


Figure 3 Measured decline in eGFR by tumour stage

Discussion

To our knowledge, this is the largest such national series examining the renal profiles of patients undergoing RN for RCC. Many studies have examined the prognostic value of pre- and post-operative renal function for RCC. There is consensus agreement that NSS leads to a less sustained decline in renal function post operatively than RN for patients with small localised renal tumours^{5,19}, which is in turn associated with a reduced risk of cardiovascular events and increased mortality¹⁵. Determining which cohort of patients with RCC will benefit most from NSS in terms of renal function, without compromising oncological outcomes, is imperative. Present guidelines recommend NSS as the treatment of choice for small renal masses (T1a, <4cm in size), those with an affected solitary functioning kidney and those with bilateral RCC⁵. It is also relatively indicated in those in whom the contralateral kidney is poorly functioning or threatened by a disease process likely to lead to diminished function such as diabetes mellitus or hypertension or nephrolithiasis, as well as those with hereditary forms of RCC (e.g. Von Hippel Lindau gene)^{16,20}. RN is still the most commonly performed surgical procedure of choice in those with tumours larger than 4cm and a normally functioning contralateral kidney⁵. The role of RN in the treatment of RCC has been somewhat bolstered by recent level 1 evidence demonstrating that, despite improved nephrological outcomes, nephron sparing surgery did not result in improved overall 10 year survival in a cohort of patients with small (< 5cm) tumours²¹. It is widely acknowledged that further prospective studies are needed to examine morbidity outcomes and give greater context to this evidence.

Our findings suggest that, at follow-up, nadir eGFR is similar for patients with different tumour sizes. However, patients with T1a tumours suffer a proportionately greater decline in mean eGFR compared to those with tumours >7cm in size (Stage T2a and greater). The disproportionate effects of RN on loss of renal function in those with T1a and T1b tumours demonstrated in our study suggests that this sub-group of patients will benefit the most from NSS. Tumour size was noted to be inversely proportional to the magnitude of decline in eGFR observed. We

hypothesize that larger tumours cause a greater destruction of normally functioning parenchyma resulting in a lower eGFR at presentation. Our study is limited by its retrospective nature, the relatively short period of follow-up, and the absence of data regarding the prevalence of pertinent medical co-morbidities such as diabetes mellitus and hypertension. Comparison of oncological and renal biochemical outcomes in our population with those of a population undergoing NSS is warranted and we are now doing NSS where possible for small renal masses, even with a normal contralateral kidney. We intend to study this prospectively in the future, with particular regard to clinical and biochemical risk factors for progression of CKD, such as microalbuminuria.

In summary, a substantial proportion of patients with stage 2 CKD pre-operatively were reclassified as having stage 3 CKD following RN, at which stage the effects of CKD become clinically significant in those with risk factors for renal disease progression. While patients with RCC collectively sustain a decline in eGFR following RN, those with T1a and T1b tumours appear to be disproportionately affected and stand to derive the most benefit from NSS, given the recognition of its oncological equivalence to RN at this disease stage.

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Evolution of Carotid Surgical Practice in the last Decade

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Abstract

Stroke units provide immediate care and appropriate intervention in the evolving stroke. The aims of this study were to review the practice of carotid endarterectomy (CEA) before and after the establishment of a Stroke Unit in St. James's Hospital. Prior to the introduction of the Stroke Unit, 263 CEAs were performed over a five-year period. 139/263 (53%) of these were for symptomatic disease. 229 were performed in the five years since. 179/229 (78%) of these were for symptomatic disease. The 30-day stroke and death rates were <2% before the introduction of the Stroke Unit, and have remained unchanged. Since the introduction of the Stroke Unit, there has been a slight decrease in the overall number of CEAs performed with a 25% increase in the proportion of endarterectomies performed for symptomatic disease. Despite the reduction in surgery for asymptomatic disease the overall 30-day stroke and death rate remains excellent at 2/229 (2%).

Introduction

Dublin has a high incidence of stroke compared to other European cities. Over a one-year period, 701 patients were diagnosed with new strokes or transient ischaemic attacks (TIAs) in a North Dublin population. At 28 days, 40% of patients with ischaemic strokes had not regained independence and 16% had died¹. The healthcare costs of stroke are high, and continue to increase as the number of patients with newly diagnosed strokes and the numbers of stroke survivors escalate worldwide². Internal carotid artery stenosis is responsible for approximately 19% of acute ischaemic strokes in men and a further 8% in women³. The symptomatic carotid trials demonstrate a six to ten-fold reduction in long-term risk of stroke in symptomatic patients with >70% ipsilateral stenosis treated with carotid endarterectomy (CEA) and best medical therapy (BMT) compared to those treated with BMT alone⁴⁻⁶. In the NASCET trial, the number of CEAs required to prevent one stroke (the number needed to treat, NNT) was five⁵. After analysis of these trials, Rothwell has demonstrated that carotid endarterectomy (CEA) was of marginal benefit in symptomatic patients with a 50-69% stenosis⁷ and that ideally, patients should undergo carotid endarterectomy within two weeks of symptoms⁸. Carotid endarterectomy for asymptomatic patients remains controversial. Two randomised controlled trials have shown a reduction in the risk of ipsilateral ischemic stroke from 2% per year with best medical therapy (BMT) to 1% with CEA and BMT in patients with high-grade stenoses^{9,10}. In ACST, the number of CEAs required to prevent one stroke was nineteen¹⁰.

Since the publication of these trials, BMT has improved, leading to a reduction in the average annual rate of ipsilateral ischaemic stroke in asymptomatic patients with high-grade carotid stenoses to just 0.34%. In this paper, Rothwell and his colleagues defined BMT as antiplatelet agents (aspirin plus/ minus clopidogrel for 30 days, followed by aspirin plus dipyridamole for the long-term), simvastatin 40mg/day, antihypertensive agents (to keep blood pressure below the target 130/80mmHg), glycaemic control

and smoking cessation¹¹. This improvement in BMT has certainly been reflected by a change in surgical practice in Europe, with Ross Naylor's unit in Leicester reporting an asymptomatic carotid endarterectomy rate of just 14% from 1995 to 2012¹². This change, however, has not been instituted worldwide. In a recently published American study from 2000-2009 involving more than 220,000 patients who underwent carotid endarterectomy, more than 90% of patients had surgery for asymptomatic disease¹³. Many trials have been conducted to evaluate the safety of carotid stenting. Although the most recent randomised controlled trial (CREST 2010)¹⁴ showed no significant difference between the stenting and CEA arms in terms of a primary composite end-point of peri-procedural stroke, myocardial infarction or death, the peri-procedural stroke rate was lower in the CEA group. The ESVS guidelines (2009)¹⁵ advocate that stenting should be performed in high volume centres or inside a randomised controlled trial. In our centre, all carotid interventions are performed by conventional endarterectomy.

A stroke unit consists of a hospital ward that exclusively takes care of stroke patients and is staffed by a specialist multidisciplinary team. A stroke unit should have constant access to a stroke specialist, as well as imaging and thrombolysis facilities. As well as acute care, access to rehabilitation facilities is often required¹⁶. Stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke¹⁷. Since the introduction of the Stroke Unit in St James's Hospital, there is a weekly multidisciplinary meeting (MDMT) involving the Stroke and Vascular services. All patients under consideration for CEA are discussed at this meeting, and a treatment plan for each patient is decided by a consensus based decision-making process involving the full team. The aim of this study was to review CEA practice over the five-year period since the Stroke Unit was established and to compare results to the five-year period prior to this.