Long-term outcomes after radical or partial nephrectomy for T1a renal cell carcinoma: A population-based study

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Abstract

Introduction: The benefit of partial nephrectomy (PN) compared to radical nephrectomy (RN) for T1a renal cell carcinoma (RCC) remains uncertain, with observational studies conflicting with level 1 evidence. Therefore, the purpose of this population-based study was to compare long-term outcomes in patients undergoing PN or RN for T1a RCC.
Methods: We studied 5670 patients in Ontario, Canada undergoing PN or RN for T1a RCC. The primary outcome was overall survival (OS). Secondary outcomes were cancer-specific survival (CSS), chronic kidney disease (CKD), end-stage renal disease (ESRD), and myocardial infarction (MI). We used multivariable Cox proportional hazard models to evaluate the association between PN or RN and these outcomes. A sensitivity analysis was performed in patients with a preoperative serum creatinine available.
Results: Median followup was 77 months. Compared to RN, PN was associated with significantly improved OS (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.63–0.84), reduced risk of CKD (HR 0.18; 95% CI 0.12–0.27) and improved CSS (HR 0.45; 95% CI 0.30–0.65). The risk of myocardial infarction was not significantly different between groups (HR 0.91; 95% CI 0.62–1.34). Few patients (n=15) required renal replacement therapy. In the sensitivity analysis, the association between type of surgery and OS and CKD persisted, while the association with CSS did not.

Conclusions: Our study found that in patients undergoing surgery for T1a RCC, PN was associated with improved OS and reduced risk of CKD compared to RN. However, few patients in either group developed ESRD requiring renal replacement therapy.

Introduction

The incidence of kidney cancer is increasing in several countries[1]. This increase is thought to be due to the rising prevalence of obesity and hypertension, both of which are established risk factors for kidney cancer[2], and the increased use of diagnostic imaging[3]. The increased use of diagnostic imaging may explain the stage migration that has been observed over time, with the vast majority of tumours detected in the modern era being stage T1a tumours (tumours less than 4cm)[4].

Several guidelines recommend that patients with clinical stage T1a tumours be managed preferentially with partial nephrectomy (PN) over radical nephrectomy (RN)[5-7]. This recommendation is based on several observational studies demonstrating that PN is associated with a reduced risk of renal dysfunction and improved overall survival compared to RN[8]. However, many of these observational studies have been limited by sample size, follow-up, and inclusion of patients with heterogenous kidney cancer characteristics. Furthermore, few have been population-based, limiting their generalizability. The only randomized trial comparing these surgical approaches validated the increased risk of renal dysfunction with RN[9]; however, overall survival in this trial was improved in the RN arm[10].

Given that the therapeutic benefit of PN remains uncertain[8] in patients presenting with clinical stage T1a kidney cancer, the most common stage of presentation in the present era, we performed a population-based study evaluating long-term survival and renal disease following PN compared to RN in these patients.

Methods

Setting and design

We performed a population-based cohort study of kidney cancer patients undergoing nephrectomy for stage T1a kidney cancer between 1995 and 2014 using linked administrative databases from Ontario, Canada. Our study was approved by the Research Ethics Board at the University Health Network, Toronto, Ontario, Canada.

Data sources

We used the Canadian Institute for Health Information Discharge Abstract Database, Same Day Surgery Database, National Ambulatory Care Reporting System, and Ontario Health Insurance Plan databases to obtain information on use of health-care services and hospitalizations, the Ontario Cancer Registry to obtain information on cancer diagnosis date and cause of death,

where applicable, and the Registered Person's Database to obtain patient demographics including date of birth, gender, place of residence via postal code, and date of death. We abstracted pathology records from Cancer Care Ontario, and linked them with the administrative database records. Several of these databases have been validated and have been described in detail elsewhere[11].

Study patients

To derive a cohort of patients undergoing a single nephrectomy for stage T1a renal cell carcinoma, we first identified hospitalizations containing a record for a PN or RN. We then linked these records with the Ontario Cancer Registry and only records with a kidney cancer diagnosis date within 14 days of nephrectomy date were kept. These records were linked to abstracted pathology reports, which contained information on histology and tumour size, and only records with histology consistent with renal cell carcinoma and maximal tumour size ≤ 4.0cm were kept. To compare only a single partial vs. radical nephrectomy, we further excluded patients with any nephrectomy prior to or following the initial nephrectomy for kidney cancer.

Assessment of exposure

The type of nephrectomy, PN vs. RN, was based on the recorded procedure code during the relevant hospitalization. The date of nephrectomy was considered the index date.

Assessment of outcomes

The primary outcome was overall survival, defined as the time from the date of nephrectomy to death from any cause, or December 31st, 2016, whichever came first. The secondary outcomes were time to diagnosis of chronic kidney disease (CKD), defined as time from nephrectomy to date of CKD diagnosis, or March 31st, 2015, whichever came first; time to renal replacement therapy, defined as time from nephrectomy to first hospitalization code for kidney transplant or dialysis, or March 31st, 2015, whichever came first; time to myocardial infarction, defined as time from nephrectomy to date of myocardial infarction diagnosis, or March 31st, 2015, whichever came first; and cancer-specific mortality, defined as time from nephrectomy to death from kidney cancer, or December 31st, 2011, whichever came first. Deaths within 30 days of nephrectomy were attributed to death from kidney cancer[12]. The end dates were chosen based on the last update for the relevant databases at the time that the study cut-off date.

Statistical analysis

We compared baseline characteristics using standardized differences, whereby a threshold of >0.10 indicated a significant difference[13]. We conducted time-to-event analysis using multivariable Cox proportional hazard regression to estimate the association of type of nephrectomy on the risk of the primary and secondary outcomes. The proportional hazards assumption was verified by evaluating Schoenfield residuals[14]. For the secondary outcomes, we estimated the cause-specific hazard as we were interested in understanding the potential etiology of kidney cancer survival outcomes related to type of nephrectomy[15]. Covariates in the

multivariable model were chosen *a priori* and included age, income quintile, Charlson score, year of surgery, tumour size, and histology. We confirmed the absence of significant collinearity based on the variance inflation factor[16]. For the renal function outcomes, we excluded patients with any previous history of diabetes, hypertension, CKD, or renal replacement therapy to avoid potential bias of preferential use of partial nephrectomy based on specific comorbidities.

All statistical analyses were performed using SAS (version 9.3; SAS Institute, Cary, NC).

Sensitivity analysis

We repeated the analyses adjusting for serum creatinine within one year prior to nephrectomy in patients in whom this data was available.

Results

A total of 5,670 patients met the inclusion criteria, of which 3,167 (55.9%) underwent RN and 2,503 (44.1%) underwent PN (Table 1). Other than income quintile, all other baseline characteristics were significantly different between the PN and RN groups. The analyses for the renal function outcomes included 2,110 patients.

Primary outcome

Median follow-up for overall survival was 77 months, during which there were 1,187 deaths, 260 in the PN group and 927 in the RN group. Compared to RN, PN was associated with significantly improved overall survival (hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.63 to 0.84), supplemental table).

Secondary outcomes

The results for the secondary outcomes are summarized in Table 2 and detailed in the supplemental table. Multivariable Cox proportional hazard models found that compared to RN, PN was associated with significantly reduced risk of CKD (HR 0.18, 95% CI 0.11 to 0.27) and significantly improved cancer-specific mortality (HR 0.45, 95% CI 0.30 to 0.65). The risk of myocardial infraction was not significantly different between groups (HR 0.91, 95% CI 0.62 to 1.34). The number of patients (n=15) requiring renal replacement therapy was limited, precluding multivariable analysis; univariable analysis found that type of surgery was not associated with renal replacement therapy (HR 0.25, 95% CI 0.06 – 1.12).

Serum creatinine within 1 year prior to surgery was available in 2,411 (43%) patients. A multi-variable sensitivity analysis further adjusting for pre-operative serum creatinine demonstrated that OS remained significantly improved in the PN group. Due to the limited number of cancer-specific deaths (n=31) and patients diagnosed with CKD (n=46), these models included only type of surgery and serum creatinine as covariates; PN was associated with a reduced risk of CKD (HR 0.09, 95% CI 0.04 to 0.20) but not improved cancer-specific survival (HR 0.84, 95% CI 0.42 to 1.72). In this sensitivity analysis, only 2 patients were diagnosed with an myocardial infarction, both in the PN group, and 2 patients required renal replacement therapy, 1 in each group.

Discussion

This population-based study spanning nearly 20 years found that compared to RN, PN for T1a kidney cancer was associated with significantly improved overall-survival and reduced risk of CKD. The association with cancer-specific mortality was inconsistent; type of surgery was not associated with risk of myocardial infarction, and the requirement for renal replacement therapy occurred infrequently in either group. These findings reaffirm the preferred use of partial nephrectomy for stage T1a kidney cancer, when feasible.

To date, EORTC 30904 is the only randomized trial that has compared RN vs. PN[10]. This multi-centre trial randomized 541 patients with tumours <5cm suspicious for renal cell carcinoma to RN vs. PN. Median follow-up was 9.3 years for overall survival. In the intention-to-treat analysis, PN was associated with significantly worse overall survival but there was no significant difference in cancer-specific mortality (only 2% of patients died of cancer). In the subgroup analysis of patients with confirmed renal cell carcinoma histology, the association for overall survival was not statistically significant. This trial also found that cardiovascular deaths were less common in the RN group[10], RN was favourable in terms of lower perioperative morbidity[17], while PN provided better renal function outcomes[9]. The results of this trial have been controversial and several criticisms, including premature study closure, cross-over between groups, the design of a non-inferiority trial but the overall survival benefit with RN being based on a test of superiority, among others, have made it difficult to interpret the results.

Despite the only level 1 evidence on this topic supporting the use of RN over PN for small renal masses, several guidelines recommend the preferential use of PN, when feasible[5-7]. This is based on the biological rationale and several observational studies demonstrating the benefit of PN over RN. A systematic review and meta-analysis was published in 2012 included 36 studies evaluating 31,729 RN and 9,281 PN patients undergoing surgery for localized kidney cancer[18]. This study found that PN was associated with significantly improved overall survival, improved cancer-specific mortality, and reduced risk of CKD. A more recent meta-analysis also found a reduced risk of CKD associated with PN, but no difference in cardiovascular outcomes between PN and RN[19].

The reduced risk of CKD related to PN is biologically plausible given the nephron-sparing concept behind PN. In our study, the reduced risk of CKD in patients undergoing PN may have contributed to the observed benefit in overall survival. Indeed, the landmark study by Go et. al. found that increasing glomerular filtration rate was inversely associated with risk of death[20]. Their study also found that increasing glomerular filtration rate was inversely associated with cardiovascular outcomes[20]; despite the associated observed benefit in risk of CKD provided by PN in our study, there was no association with myocardial infarction, consistent with the previously described meta-analysis[19]. This can be explained by the proposed theory that the biology of CKD associated with surgery may be different than that of CKD associated with medical conditions[21], as those medical conditions, such as diabetes and hypertension, continue to contribute to the risk of cardiovascular outcomes. It is worth noting that the requirement for renal

replacement therapy occurred infrequently. The results of our large population-based study support a previous analysis of 514 patients from EORTC 30904, which found that only 4 patients in each group developed end-stage renal disease. Put together, these results suggest that although RN likely increases the risk of CKD compared to PN, the risk of end-stage renal disease requiring renal replacement therapy after RN may be low. Therefore, in select cases, such as those with complex tumours, the risk of PN may outweigh the benefit and RN remains an option in these select cases for the management of stage T1a kidney cancer.

In the overall cohort, cancer-specific mortality was significantly improved in the PN arm, consistent with the findings of a meta-analysis[18]. This likely represents selection bias as there is no biological rationale supporting PN as a more oncologic effective procedure. We attempted to reduce selection bias by restricting our cohort to patients with pathologic tumour size <4cm and further adjusting for histology and tumour size; however, the possibility of residual confounding remains. In our sensitivity analysis restricting to patients with pre-operative serum creatinine, there was no association between type of surgery and cancer-specific mortality, though this should be interpreted with caution given the limited number of events.

While several observational studies have compared survival outcomes following RN or PN, our study has several strengths. Our population-based study design in a universal health-care setting improves generalizability. Furthermore, we used regularly updated administrative databases, several of which have been validated, allowing us to accurately capture various outcomes over a prolonged period of time. We also had detailed information on various baseline characteristics allowing us to restrict our study to a homogenous population of patients undergoing a single nephrectomy for renal cell carcinoma tumours <4cm, and to further adjust for differences in characteristics between patients undergoing RN or PN. Finally, we did a sensitivity analysis adjusting for pre-operative creatinine; albeit, this information was available in a reduced cohort.

This study is not without limitations. Although we attempted to reduce confounding by adjusting for known prognostic factors, the possibility of residual confounding remains. Additionally, our cohort may have included patients with solitary kidney prior to nephrectomy, though this is expected to be infrequent. We were unable to evaluate additional cancer-related outcomes such recurrence or metastasis as these are difficult to define using administrative databases. Finally, there may be subsets of patients for whom there is no benefit of PN or RN; this was not an objective of this study but is an area of future research given the potential increased risk of perioperative morbidity associated with PN[17,22,23].

Conclusions

Our population-based study of patients undergoing nephrectomy for T1a kidney cancer found that compared to radical nephrectomy, partial nephrectomy was associated with significantly improved overall survival and reduced the risk of chronic kidney disease. However, few patients in either group developed end-stage renal disease requiring renal replacement therapy. These findings reaffirm the preferred use of partial nephrectomy for these patients.

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Figures and Tables

Table 1. Cohort characteristics of 5670 patients undergoing nephrectomy for pT1a renal cell carcinoma between 1995 and 2015 in Ontario, Canada			
	Partial nephrectomy (n=2503)	**Radical nephrectomy (n=3167)**	**Standardized difference**
Gender, n (%)			0.61
Female	959 (38.3)	1354 (42.8)	
Male	1544 (61.7)	1813 (57.3)	
Age group, n (%)			0.30
18–39	191 (7.6)	148 (4.7)	
40–44	153 (6.1)	181 (5.7)	
45–49	277 (11.1)	249 (7.9)	
50–54	348 (13.9)	311 (9.8)	
55–59	366 (14.6)	428 (13.5)	
60–64	353 (14.1)	447 (14.1)	
65–69	337 (13.5)	507 (16.0)	
70–74	248 (9.9)	396 (12.5)	
75–79	161 (6.4)	322 (10.2)	
80+	69 (2.8)	178 (5.6)	
Income quintile, n (%)			0.09
1 (lowest)	442 (18)	632 (20)	
2	504 (20)	679 (21)	
3	500 (20)	647 (20)	
4	515 (21)	613 (19)	
5 (highest)	542 (22)	596 (19)	
Charlson score, median (interquartile range)	2 (2–3)	2 (2–3)	0.15
Year of surgery, n (%))			0.78
1995–2000	144 (6)	876 (28)	
2001–2005	232 (9)	520 (16)	
2006–2010	790 (32)	979 (31)	
2011–2014	1337 (53)	792 (25)	
Tumour size, median (interquartile range)	2.5 (2.0–3.2)	3.0 (2.5–3.6)	0.61
Histology, n (%)			0.16
Clear-cell	1817 (73)	2510 (79)	
Papillary	527 (17)	402 (13)	
Chromophobe	157 (6)	150 (5)	
Other	102 (4)	105 (3)	

Table 2. Long-term outcomes in 5670 patients undergoing partial vs. radical nephrectomy for pT1a renal cell carcinoma		
Outcome	**Partial nephrectomy (n=2503)**	**Radical nephrectomy (n=3167)**
Chronic kidney disease # of events Hazard ratio* (95% CI)	 26 0.18 (0.11–0.27)	 223 Reference
Renal replacement therapy # of events Hazard ratio± (95% CI)	 2 0.25 (0.06–1.12)	 13 Reference
Myocardial infarction # of events Hazard ratio* (95% CI)	 42 0.91 (0.62–1.34)	 131 Reference
Death from kidney cancer # of events Hazard ratio* (95% CI)	 36 0.45 (0.30–0.65)	 184 Reference

*Adjusted for gender, age group, income quintile, Charlson score, year of surgery, tumour size, and histology. ±Univariate model due to low number of events. CI: confidence interval.

Supplementary Table 1. Multivariable Cox proportional hazard model evaluating the association between partial or radical nephrectomy and outcomes in patients with pT1a renal cell carcinoma

	Outcome (hazard ratio [95% confidence interval])			
Predictor	**OS**	**CKD**	**MI**	**CSS**
Partial nephrectomy	0.73 (0.63–0.84)	0.18 (0.11– 0.27)	0.92 (0.62–1.35)	0.45 (0.30–0.65)
Female gender	0.81 (0.72–0.92)	0.72 (0.55–0.94)	0.58 (0.42–0.80)	0.65 (0.48–0.85)
Age				
18–39	Reference	Reference	Reference	Reference
40–44	1.8 (0.75–4.6)	0.79 (0.36–1.74)	0.95 (0.24–3.80)	1.12 (0.25–5.03)
45–49	2.7 (1.2 –6.2)	1.35 (0.70–2.62)	1.46 (0.45–4.75)	2.45 (0.69–8.71)
50–54	4.8 (2.2–10.4)	2.17 (1.16–4.05)	1.43 (0.45–4.57)	3.13 (0.92–10.6)
55–59	7.8 (3.6–16.8)	2.29 (1.24–4.25)	1.88 (0.63–5.65)	3.19 (0.96–10.6
60–64	10.7 (5.0–22.9)	2.84 (1.54–5.24)	2.21 (0.75–6.52)	4.88 (1.50–15.9)
65–69	13.8 (6.5–29.4)	2.68 (1.44–5.00)	3.77 (1.34–10.6)	3.70 (1.13–12.1)
70–74	20.4 (9.6–43.4)	2.55 (1.30–5.00)	4.28 (1.51–12.2)	4.42 (1.35–24.5)
75–79	33.8 (15.9–71.8)	3.32 (1.64–6.73)	5.27 (1.85–15.0)	6.06 (1.85–19.9)
80+	53.1 (24.7–114.1)	3.73 (1.59–8.74)	3.27 (1.00–10.68)	8.82 (2.59–30.1)
Income quintile				
1 (lowest)	Reference	Reference	Reference	Reference
2	0.84 (0.71–1.00)	1.16 (0.78–1.71)	0.72 (0.46–1.13)	1.27 (0.83–1.96)
3	0.83 (0.69–0.98)	1.03 (0.68–1.55)	0.79 (0.50–1.23)	1.42 (0.93–2.15)
4	0.82 (0.68–0.98)	1.06 (0.70–1.62)	0.70 (0.43–1.11)	1.31 (0.84–2.04)
5 (highest)	0.75 (0.62–0.89)	0.88 (0.58–1.33)	0.59 (0.37–0.96)	1.10 (0.70–1.74)
Charlson score	1.34 (1.30–1.37)	0.84 (0.72–0.98)	1.05 (0.96–1.16)	1.37 (1.30–1.45)
Year of surgery				
1995–2000	Reference	Reference	Reference	Reference
2001–2005	0.95 (0.81–1.11)	1.04 (0.72–1.51)	0.86 (0.58 –1.27)	1.07 (0.75 –1.54)
2006–2010	0.71 (0.60–0.83)	1.66 (1.18–2.34)	0.55 (0.36–0.85)	0.68 (0.46–1.00)
2011–2014	0.55 (0.44–0.69)	2.14 (1.35–3.42)	0.59 (0.32–1.09)	6.42 (3.88–10.61)
Tumor size	1.09 (1.01–1.17)	1.05 (0.89–1.24)	1.05 (0.86–1.28)	1.18 (0.99–1.41)
Histology				
Clear-cell	Reference	Reference	Reference	Reference
Papillary	0.96 (0.81–1.14)	1.16 (0.82–1.65)	0.85 (0.55–1.31)	0.96 (0.65–1.41)
Chromophobe	0.80 (0.57–1.12)	0.89 (0.47–1.70)	1.34 (0.65–2.77)	0.38 (0.12–1.19)
Other	1.22 (0.95–1.58)	1.02 (0.52–1.99)	0.32 (0.10–1.00)	1.95 (1.16–3.27)

CKD: chronic kidney disease; CSS: cancer-specific survival; MI: myocardial infarction; OS: overall survival