

Temporal Trends in Selecting Patients for Partial Nephrectomy for Small Renal Cell Carcinomas in Alberta, Canada

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Derek Tilley¹
Taylor Remondini²
John Van Tuyl²
Wendy Pak¹
Geoffrey T Gotto³ 

¹Alberta Health Services, Cancer Control, Holy Cross Centre, Calgary, AB, Canada; ²Cumming School of Medicine, University of Calgary, Calgary, AB, Canada; ³Department of Surgery, University of Calgary, Calgary, AB, Canada

Background: When technically feasible, partial nephrectomy (pN) is preferred over radical nephrectomy (rN) due to similar oncological control with preservation of renal function. Here, we evaluate the incorporation of pN into practice for small renal masses and examine the associated outcomes.

Methods: We included patients who had undergone either a partial or radical nephrectomy in Alberta, Canada for renal cell carcinomas with pathology tumor stage T1a between 2002 and 2014 (N=1449). Patients were excluded if they had multiple tumors or if they were on dialysis prior to nephrectomy.

Results: pN use increased over the duration of the study period. Patients treated after the introduction of guidelines (2007) recommending the use of pN were significantly more likely to receive a pN (OR: 2.709, 95% CI: 1.944–3.775; $p<0.001$) after adjusting for baseline estimated glomerular filtration rate (GFR), age, and sex. Patients who received rN were at significantly increased risk of death (HR: 1.528, 95% CI: 1.029–2.270; $p=0.036$) after controlling for baseline GFR, age, and sex. Baseline GFR significantly affected odds of receiving pN ($p<0.050$) in the entire cohort, but subgroup analysis of more recently diagnosed patients (2011–2014) showed that only patients with kidney failure (GFR <15) were less likely to have received pN.

Discussion: The utilization of pN for patients with pT1a renal cell carcinoma has increased significantly over time and has been accelerated by the introduction of guideline recommendations. Patients treated with pN over the study period had superior overall survival.

Keywords: nephrectomy, T1a, renal cell carcinoma, guideline, survival, adherence

Background

Renal cell carcinoma (RCC) is responsible for between 80% and 85% of all primary renal neoplasms. In Canada, approximately 6600 new kidney cancer diagnoses were made in 2017 and 1900 patients died from their disease.¹ The increased utilization of diagnostic imaging in general has resulted in more small renal masses being detected,² allowing for early intervention.

In the absence of metastatic disease, surgery is the preferred treatment approach for eligible patients with small renal masses <4 cm. After nephrectomy, 10-year overall survival rates of 75–80% have been reported.³ Partial nephrectomy (pN), if technically feasible, is preferred over radical nephrectomy (rN) because pN is associated with similar oncologic outcomes but significantly lower rates of chronic renal dysfunction.^{3,4} The benefits of pN may extend beyond renal preservation.

Correspondence: Geoffrey T Gotto
Department of Surgery, University of
Calgary, Suite 6625 - 7007 14th Street
SW Calgary, Calgary, AB T2V 1P9,
Canada
Tel +1 403 943-8921
Fax +1 403 943-8667
Email drgotto@gmail.com

Patients who undergo pN may be at a decreased risk of cardiovascular disease, anemia, malnutrition, and neuropathy compared to patients who undergo rN.⁵

These findings have led to American⁶ and European⁷ guidelines recommending pN as the standard of care for small renal tumors where technically feasible.

In our jurisdiction (Alberta, Canada), pN was initially recommended as the standard treatment for T1a RCC in 2007. Although some controversy remains regarding the optimal surgical approach for small RCC masses,⁸ pN has become the primary treatment approach in most jurisdictions.^{6,7} The goal of this study was to evaluate uptake of pN over time and to investigate current pN/rN practice patterns and outcomes in T1a disease.

Methods

We identified 1679 patients diagnosed between 2002 and 2014 that received a pN or rN for T1a RCC through the Alberta Cancer Registry (ACR). Patient/treatment data were collected from the Discharge Abstract Database (DAD), the National Ambulatory Care Reporting System Database (NACRS), ACR, and through manual chart review. Patients were excluded (n=230) for inaccessible or incomplete medical records, multiple tumors, actual tumor size >4 cm after chart review, if they never underwent pN/rN, or because they were on dialysis prior to nephrectomy. This led to a final cohort of N=1449.

Patients were stratified into pre-/post-guideline eras (2002–2007 and 2008–2014, respectively) based on the

Table 1 Patient Characteristics

	Total		Partial Nephrectomy		Radical Nephrectomy		p
	(N=1449)		(n=879)		(n=570)		
	n	%	n	%	n	%	
Age (years) Median (Range)	59 (21–87)		59 (21–86)		60 (23–87)		0.033
Sex							0.210
Male	873	60.2	541	61.5	332	58.2	
Female	576	39.8	338	38.5	238	41.8	
GFR							<0.001
Median	75.9		78.4		71.7		
Mean	76.5		80.1		70.9		
≥90	349	24.8	248	28.5	101	18.8	
60–89	760	54	476	54.7	284	52.8	
45–59	180	12.8	99	11.4	81	15.1	
30–44	84	6	42	4.8	42	7.8	
15–29	17	1.2	5	0.6	11	2.0	
<15	18	1.3	0	0.0	19	3.5	
Unknown	41		9		32		
Year of Diagnosis							<0.001
2002	29	2	7	0.8	22	3.9	
2003	45	3.1	18	2.0	27	4.7	
2004	31	2.1	5	0.6	26	4.6	
2005	50	3.5	23	2.6	27	4.7	
2006	46	3.2	22	2.5	24	4.2	
2007	104	7.2	44	5.0	60	10.5	
2008	136	9.4	67	7.6	68	11.9	
2009	160	11	70	8.0	91	16.0	
2010	166	11.5	95	10.8	71	12.5	
2011	172	11.9	127	14.4	45	7.9	
2012	167	11.5	118	13.4	49	8.6	
2013	190	13.1	165	18.8	25	4.4	
2014	153	10.6	118	13.4	35	6.1	

introduction of clinical practice guideline recommendations for pN use in T1a tumors. Patients were also stratified into “modern era” based on >70% pN rates (2011–2014).

GFR was calculated according to Levey et al⁹ or Levey et al¹⁰ where appropriate.

Patient and treatment characteristics were compared using monovariate (Chi-square, *t*-test, or Mann–Whitney, where appropriate), or multivariate analyses (logistical regression). Survival was compared using Kaplan–Meier estimates, Log-rank, and Cox Regression. Statistics were performed using SigmaPlot V13.0 (Systat Software Inc.; Chicago, Illinois) or SPSS V19.0 (IBM; Armonk, New York).

This study did not meet the requirement for ethics board review. The study was determined to be low risk as assessed by the ARECCI ethical review system.¹¹

Results

The entire cohort had a mean follow-up of 54 months. Median age was 59 years (range: 21–87 years) with 39.8% females, and a median GFR of 75.9 mL/min/1.73m² (Table 1).

In total, n=879 patients received pN and n=570 patients received rN. In general, pN utilization increased over time (Figure 1A). The lowest utilization of pN occurred in 2004 (16.1% of nephrectomies were pN), and the highest in 2013 (86.8% of nephrectomies were pN). Year-over-year significant increases/decreases in pN use occurred in 2004, 2005, 2009, 2010, 2011, 2013, and 2014 (all *p*<0.050).

Overall, patients who received pN had similar sex compared to rN patients (38.5% vs 41.8% female, respectively, *p*=0.202); however, pN patients were significantly younger (median 59 vs 60 years, respectively, *p*=0.033) and had significantly higher baseline GFR (median 78.4 mL/min/1.73m² vs 71.6 mL/min/1.73m², respectively, *p*<0.001).

Overall survival (OS) was higher in patients who received pN compared to those who received rN (94.8% vs 87.0%, respectively, *p*=0.002) (Figure 1B). Multivariate analysis identified rN use (HR 1.528, 95% CI: 1.029–2.270, *p*=0.036), lower GFR (HR: 4.080, 95% CI: 1.673–9.951, *p*=0.002), older age (60–<80 years) (HR: 2.775, 95% CI: 1.767–4.358, *p*<0.001) and (≥80 years) (HR: 6.688, 95% CI 3.258–13.729, *p*<0.001) as factors significantly associated with poorer survival outcomes. Female sex was associated with significantly superior outcomes (HR: 0.600, 95% CI: 0.397–0.906, *p*=0.015). Guideline era (2002–2006 vs 2007–2014) did not significantly impact survival outcomes (*p*=0.345) (Table 2).

Patients who received nephrectomies in the pre-guideline era (2002–2006) were significantly less likely to have received pN compared to patients receiving nephrectomies in the post-guideline era (pre: 37.3%, post: 64.4%, *p*=0.001). In the pre-guideline era pN patients were significantly younger than rN patients (median 53 years vs 60 years; *p*=0.015) and had higher baseline GFR (median 68 mL/min/1.73m² vs 59 mL/min/1.73m²). Patient age (*p*=0.896) and sex (*p*=0.888) were similar between guideline eras; however, baseline GFR was

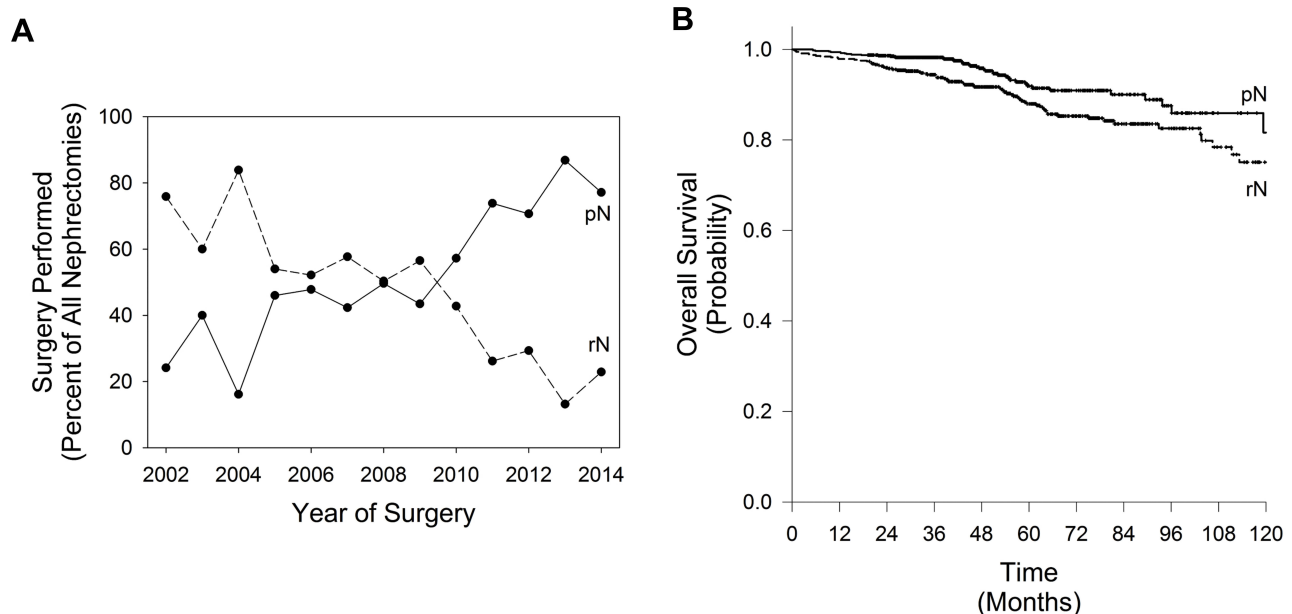


Figure 1 Partial (pN) and Radical (rN) Nephrectomy Utilization and Outcomes. **(A)** Illustrates the shift in pN/rN utilization over time. **(B)** Depicts a Kaplan–Meier estimate of survival (Log-Rank *p*=0.002). In both panels: rN (dashed line) and pN (solid line).

Table 2 Cox Regression for Factors Associated with Risk of Death from Any Cause

	Univariate				Multivariate			
	HR	95% CI		P	HR	95% CI		P
Nephrectomy								
Partial	Reference				Reference			
Radical	1.778	1.225	2.580	0.002	1.528	1.029	2.270	0.036
GFR								
≥90	Reference				Reference			
60–89	0.931	0.543	1.597	0.770	0.713	0.413	1.232	0.225
45–59	1.972	1.088	3.576	0.025	1.266	0.686	2.339	0.450
30–44	1.747	0.856	3.564	0.125	0.831	0.919	2.000	0.831
15–29	7.841	3.425	17.949	<0.001	4.080	1.673	9.951	0.002
<15	2.842	0.840	9.614	0.093	1.679	0.485	5.819	0.414
Age								
<60	Reference				Reference			
60 to <80	3.254	2.105	5.029	<0.001	2.775	1.767	4.358	<0.001
≥80	8.653	4.608	16.247	<0.001	6.688	3.258	13.729	<0.001
Sex								
Male	Reference				Reference			
Female	0.649	0.440	0.956	0.029	0.600	0.397	0.906	0.015
Era								
2002–2006	Reference				Reference			
2007–2014	0.685	0.447	1.050	0.083	0.797	0.499	1.275	0.345

significantly higher in the post-guideline era patients (median GFR pre: 62.9 mL/min/1.73m², post: 77.5 mL/min/1.73m², $p<0.001$). Multivariate analysis of the entire cohort found that baseline GFR significantly affected the relative odds of receiving a partial nephrectomy with decreasing GFR values associated with decreasing likelihood of receiving a pN, with the exception of GFR values in the 30–44 mL/min/1.73m² range (GFR ≥90 reference, GFR 60–89: OR: 0.716, GFR 45–59: OR 0.597, GFR 15–29: OR 0.249, GFR <15: OR <0.001, all $p<0.05$; GFR 30–44: OR 0.607 $p=0.064$). The relative odds of receiving a pN in the entire cohort was also significantly affected by pre/post-guideline era, with patients in the post-guideline era significantly more likely to receive a pN (OR: 2.709, 95% CI: 1.944–3.775, $p<0.001$). Patient sex or age did not affect the relative odds of receiving a pN in the entire cohort ($p>0.05$) (Table 3). In the modern era (2011–2014), the odds of receiving a pN were not significantly affected by GFR, Age, or Sex, with the exception of patients with kidney failure

(GFR <15), who remained significantly less likely to receive a pN (OR: <0.001, $p<0.001$).

Discussion

The management of small renal masses has rapidly evolved. Relative to rN, pN is often a more technically challenging procedure; however, the benefits from preserving renal function have led to wide-spread adoption into clinical practice.

The utilization of pN as a proportion of total nephrectomies for T1a RCC generally increased over time from 2002 to 2014 (Figure 1); however, from 2002 to 2009 6 of 8 years had pN utilization rates between 40% and 50%. In 2007, Van Poppel et al¹² reported positive complications/safety outcomes from the Phase III EORTC intergroup trial which led to adoption of pN as standard of care in our local consensus/evidence-based clinical practice guidelines; however, this did not correlate with immediate

Table 3 Relative Odds (Adjusted) of Receiving a Partial Nephrectomy

	Entire Cohort (2002–2014)				Modern Era (2011–2014)			
	OR	95% CI		P	OR	95% CI		P
GFR								
≥90	Reference				Reference			
60–89	0.716	0.541	0.949	0.020	0.900	0.585	1.384	0.631
45–59	0.597	0.403	0.886	0.010	1.076	0.520	2.223	0.844
30–44	0.607	0.358	1.029	0.064	0.992	0.338	2.911	0.988
15–29	0.249	0.082	0.756	0.014	0.543	0.048	6.182	0.623
<15	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Age								
<60	Reference				Reference			
60 to <80	1.013	0.801	1.281	0.915	1.201	0.809	1.783	0.364
≥80	0.599	0.308	1.165	0.131	0.687	0.227	2.080	0.507
Sex								
Male	Reference				Reference			
Female	0.875	0.696	1.099	0.251	0.960	0.653	1.410	0.835
Era								
2002–2006	Reference				NA			
2007–2014	2.709	1.944	3.775	<0.001				

significant increases in pN use when comparing year-over-year use. Major year-over-year increases in pN use become apparent post-2009, perhaps representing a delay in surgeon uptake¹³ or correlating with the reporting of oncological outcomes from the EORTC intergroup phase III trial.³ Regardless, patients treated in the pre-guideline era, when compared to the post-guideline era, were significantly (OR: 2.709, $p < 0.001$) less likely to receive a pN.

In our cohort, pN patients had significantly improved overall survival (Figure 1), which is likely associated with patient selection as phase III randomized data have shown equivalent outcomes in clinically and pathologically eligible patients,³ however, pN's superiority did persist when controlled for baseline GFR, age, sex, and guideline era (Table 2). As expected, low baseline GFR (15–29 mL/min/1.73m²) was associated with decreased survival. Patients with kidney failure at presentation (GFR <15 mL/min/1.73m²) were not at a significantly increased risk of death, likely due to limited statistical power ($n=18$). Also expected, older age was associated with increased risk of death from any cause and like others,¹⁴ we

found that women had significantly reduced risk of death when compared to males.

Early studies evaluating pN recommended that the procedure should be reserved for highly selected patients.¹⁵ Over time these recommendations shifted to include all patients who are surgically eligible if the procedure is technically feasible. This transition was apparent in our cohort. In our overall cohort, the adjusted odds of receiving a pN was significantly associated with baseline GFR, with a clear trend towards decreasing pN use with decreased baseline GFR (Table 3). Age or gender did not appear to affect the odds of receiving a pN in the entire cohort; however, patients aged ≥80 years did trend towards higher rN use ($p=0.131$).

To evaluate more recent practice patterns we subdivided our cohort into the “modern era” which consisted of all years where pN represented at least 70% of nephrectomies performed in T1a patients (2011–2014). In this subgroup, no patients with baseline kidney failure (GFR <15 mL/min/1.73m²) received a pN, but otherwise, GFR, age, or sex had no effect on the relative odds of receiving a pN (all $p > 0.050$). This suggests that local guideline recommendations (that all surgically eligible patients

should receiving a pN where technically feasible) were adopted within 4 years.

As pN use has now been adopted in most jurisdictions, it is important to analyze how that adoption took place as the focus now shifts to utilizing pN for larger renal masses.¹⁶ Despite consensus on evidence-based guidelines in our jurisdiction, a clear lag in uptake was apparent before fairly rapid adoption of recommendations.

This major limitations for this study include the inability to adjust for all clinically relevant patient characteristics and decisions that influence the use of pN vs rN. Also, we did not examine the effects of the surgical approach used (open vs laparoscopic vs robot-assisted laparoscopic). Additionally, ablation techniques that may have been used to treat small renal cell carcinomas were not analyzed. However, we do report on a relatively large real-world population of patients with sufficient time to allow for analysis of temporal trends.

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Disclosure

The authors report no conflicts of interest in this work.

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