Clinical outcomes following laparoscopic management of pT3 renal masses: A large, multi-institutional cohort

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Abstract

Introduction: We described the clinical and oncological outcomes of patients treated by laparoscopic surgery for non-metastatic pT3 renal cell carcinoma (RCC).

Methods: We queried a multi-institutional database for patients diagnosed with non-metastatic pathological T3 RCC from 13 Canadian centres treated laparoscopically (radical or partial nephrectomy) between 2008 and 2014. Clinical and pathological outcomes were evaluated. Progression was defined as the development of recurrence or metastatic disease. Log-rank testing and Kaplan-Meier statistical methods assessed for differences and estimated progression-free survival (PFS).

Results: In total, 176 patients were identified with a median age of 64 years. The median tumour size was 7.0 cm. Pre-clinical stage was cT1 to cT4 in 39%, 28%, 30% and 3%, respectively. The median blood loss was 150 mL (range: 0–6000) and the median operative time was 124 minutes (range: 60–360). Most lesions were clear cell RCC (80%). After a median follow-up of 17.6 months (range: 0.2–75.0), disease progression occurred in 26% (46/176) of patients, consisting of local recurrence in 7% (3/46), and metastatic disease in 93% (43/46). The 3-year PFS was 67%, with a median PFS of 49 months. Of those who progressed, the median time to progression was 10.3 months.

Conclusions: This study is the largest cohort of pT3 RCC patients treated laparoscopically in the literature and suggests that for properly selected patients, laparoscopic management of locally advanced renal masses yields acceptable short-term oncological outcomes.

Introduction

Surgical management is the primary treatment modality for localized renal cell carcinoma (RCC). Since its introduction in 1991,[1] laparoscopic surgery has become widely used to treat renal masses when technically feasible. The reduced morbidity with laparoscopic surgery compared to traditional open surgery is well-established, with less blood loss, decreased analgesic requirements, less disfigurement, shorter hospital admissions, and shorter periods of convalescence.[2-4] Additionally, oncological outcomes between laparoscopic and open techniques for T1 and T2 RCC are similar.[5-7] Yet, current literature examining the laparoscopic management of advanced RCC remains sparse, but promising.

Pathological T3 (pT3) disease includes renal tumours with venous invasion or peri-nephric tissue involvement. The 5-year disease-free survival for pT3 disease ranges from 30% to 85%.[8-13] Among patients who recur, the median time to recurrence ranges from 11 to 22 months.[8,9,12-14] If oncological efficacy can be demonstrated, a minimally invasive approach to pT3 disease would be preferred. However, current literature examining outcomes in this patient population are limited to small, single-centre analyses.[15-19] In this study using a large, multi-institutional design in a contemporary cohort, we described the oncological outcomes of patients with locally advanced, non-metastatic RCC treated laparoscopically.

Methods

A multi-institutional database, the Canadian Kidney Cancer Information System (CKCis), was developed to compile clinical characteristics and outcomes among patients with RCC from 13 centres in 6 Canadian provinces. This database has

been prospectively collected and maintained since January 2011, with retrospective data collection for preceding years. Institutional review board approval was obtained from each contributing site. We included patients who underwent laparoscopic partial (LPN) or radical nephrectomy (LRN) between January 2008 and August 2014 for pathological T3 disease. The choice of procedure was non-randomized and dependent on the preferences of the patient and surgeon. Patients were excluded if they had known metastatic disease prior to surgery, if metastatic disease was found intraoperatively, or if the case was converted to open surgery.

All patients were staged according to the American Joint Committee of Cancer Staging manual, 7th edition.[20] Cancer-specific survival and overall survival were not assessed due to the low number of deaths. Progression-free survival (PFS) was calculated based on the time from surgery to the development of metastatic disease, local recurrence, or cancer-related death. Patients were censored at last follow-up or at non-cancer related death. The Kaplan-Meier method was used to estimate survival, and log-rank testing was used to assess for differences in PFS. Cox-proportional hazard ratios and 95% confidence intervals were determined. Statistical analysis was performed using R statistical environment, with statistical significance set at $p < 0.05$.

Results

Of the 651 patients with pT3 disease, 176 patients met the inclusion criteria with non-metastatic RCC treated laparoscopically. The cohort consisted of predominantly Caucasian males with normal baseline renal function and clinical T1/2 disease (Table 1).

The median tumour diameter was 7.0 cm with most patients treated by LRN, for predominantly clear cell RCC. Blood loss was minimal and surgery was completed at a median of about 2 hours. Surgical margins were negative in 158 (90%), positive in 13 (7%), and unknown in 5 patients (3%). For the 13 patients with a positive margin, 8 had a LRN and 5 had a LPN. The positive margin rate stratified by procedure type was 5% (8/155) for LRN and 24% (5/21) for LPN (Table 2).

After a median follow-up of 22.6 months (range: 0.2–75.0), 43 (24%) patients developed metastatic disease and 3 (2%) patients had an isolated local recurrence. Lung (70%, 32/46), bone (39%, 18/46), and lymph nodes (30%, 14/46) were the most common sites of metastases. Isolated lymph node recurrences were found in 3 patients. Overall, 6/176 patients (3%) died from kidney cancer, and 1/176 patient (1%) died from other causes. The 3-year estimated PFS was 67%, with a median progression survival of 49 months (Table 3). Of those who progressed, the median time to progression was 10.3 months. Figure 1 shows the Kaplan-Meir PFS estimates for the overall cohort and subgroup comparisons.

Discussion

Minimally invasive surgery has gone through many years of advances. With growing experience, more advanced tumours are likely to be managed by this approach; however, there is limited data examining oncological outcomes in the locally advanced RCC population. Using a large, multi-institutional design, our study represents the largest cohort of pT3 RCC treated laparoscopically in the literature. The estimated 3-year PFS was 67%, with a median PFS of 49 months, suggesting that adequate short-term oncological outcomes can be achieved with laparoscopic management of locally advanced RCC.

Some studies have attempted to demonstrate the efficacy and safety of laparoscopic surgery in a similar population;[16,17,21-23] however, single-centre analyses, minimal patient numbers or short follow-up periods limit their generalizability. Our multi-institutional design allows us to include many patients in a contemporary time period, not easily accomplished in single-centre studies. Further, including multiple institutions allows us to widen the application of our results by reducing potential patient selection or referral biases inherent in smaller studies. Additionally, single centres may have a certain element of standardization of surgical techniques, which further minimizes generalization of their results.

Table 1. Patient and clinical preoperative characteristics (n = 176)

Variable	Median (IQR) or n (%)
Age	64 (57–64)
Male	117 (66)
Ethnicity	
Caucasian	121 (69)
Asian	6 (3)
Aboriginal	5 (3)
Other	3 (2)
Unknown	41 (23)
Preoperative creatinine (μmol/L)	83 (71–99)
Estimated glomerular filtration rate (mL/min)	78 (61–90)
Preoperative hemoglobin (g/L)	137 (122–145)
Laterality	
Left kidney	98 (56)
Right kidney	78 (44)
Preoperative clinical stage	
T1	57 (39)
T2	42 (28)
T3	45 (30)
T4	35(3)
Missing	28
IQR: Interquartile range.	

Table 2. Operative and pathological characteristics for 176 patients undergoing laparoscopic surgery for pT3 RCC

Variable	Median (range) or n (%)
Tumour size (cm)	7.0 (1.6–15.0)
Surgical approach	
Partial nephrectomy	21 (12)
Radical nephrectomy	155 (88)
Blood loss (cc) median	150 (0–6000)
Skin-to-skin OR duration (minutes)	124 (60–360)
Positive surgical margin	
Overall	13 (7)
LRN	8 (5)[a]
LPN	5 (24)[b]
Histological subtype	
Clear cell RCC	140 (80)
Papillary RCC	13 (7)
Chromophobe	5 (3)
RCC unclassified	9 (5)
Sarcomatoid	2 (1)
Other	7 (34)
Furhman grade	
1	5 (43)
2	53 (31)
3	83 (48)
4	31 (18)
Missing	4
Pathological stage	
pT3a	150 (85)
pT3b	16 (9)
pT3 (unspecified)	10 (6)

[a]Compared to total number of LRN (n = 155); [b]Compared to total number of LPN (n = 21). OR: operation room; LRN: laparoscopic radical nephrectomy; LPN: laparoscopic partial nephrectomy; RCC: renal cell carcinoma.

Table 3. Subgroup analysis of estimated 3-year PFS

Group	Median time to progression (months)	3-year estimated PFS	p value
All lap treated pT3	49	67%	N/A
Pathological stage			0.09
pT3a	46	63%	
pT3b	N/Aa	86%	
Clinical stage			0.08
cT1	N/Aa	80%	
cT2	42	67%	
cT3 and cT4	45	58%	
Surgical approach			0.27
LPN	N/Aa	83%	
LRN	49	65%	

PFS: progression-free survival; LRN: laparoscopic radical nephrectomy; LPN: laparoscopic partial nephrectomy; N/A: not available; aMedian time to progression not assessed due to a greater than 50% survival rate at the end of the follow-up period.

To date, comparative studies between laparoscopic and open surgery for pT3 disease have shown similar outcomes, but have been limited predominantly to retrospective reviews.[17,24] One study used a prospective cohort matched analysis of 25 pairs.[23] Although a comparative group is lacking in the present study, our short-term results are concurrent with literature on open surgery.[23,24] However, the possibility than open surgery may confer a long-term survival advantage should not be disregarded. In fact, open surgery may be more advantageous as it affords a greater opportunity for retroperitoneal lymph node dissection that offers both diagnostic and therapeutic advantages. In the current study, less than half of the patients had node dissections of which the extent is uncertain. While the role for lymphadenectomy in laparoscopic renal surgery has been debated,[25] much of the opposing literature arises from predominantly clinically localized (pT1–2) disease that is likely to have a different biological natural history than pT3 disease. Further, 2% (3/176) patients developed isolated local lymph node recurrences in our cohort and conceivably may have derived benefit from a lymph node dissection.

Nonetheless, our multicentre results corroborate the findings of two recent single-centre series. Guzzo and colleagues evaluated 32 patients undergoing laparoscopic management for non-metastatic pT3b renal cancers, of whom 3 developed recurrences at a mean time of 11 months.[16] Stewart and colleagues retrospectively reviewed 77 patients who underwent laparoscopic management of pT3 RCC (36% pT3a and 62% pT3b),[19] and after a median follow-up of 17 months, 28.6% of patients developed disease recurrence after a median 13.9 months. Their median predicted PFS was 48 months.

LPN, in select patients, yields similar results to those treated by LRN. In our current study, 12% of patients underwent LPN presumably due to clinical under-staging on preoperative imaging. With microscopic involvement of the venous system, including segmental vessels, it is not uncommon for a partial nephrectomy to be performed with final pathology demonstrating occult adverse pathological features. In fact, 81% of our LPN patients were at clinical stage T1/2, suggesting that the surgeons may have been unaware of the locally advanced nature of the disease. Although, the overall numbers of positive margins were low, the rate of margin positivity was markedly higher in the LPN group, which may reflect clinical under-staging and/or suboptimal patient selection. However, the risk of local recurrence in those with a positive margin remains controversial.[26,27] Much of the data on positive margins after partial nephrectomy indicate that these margins do not predict worse outcomes,[28] although most of this data were collected in patients with lower risk tumours. It is possible that positive margins are biologically more relevant in pT3 tumours. The difference in positive margins between LRN and LPN in our series was not reflected in the 3-year PFS (Fig. 1, p = 0.27), concurrent with other findings.[29] Importantly, one might expect a worse

outcome after LRN due to selection for larger tumours, and one could speculate that the absence of this difference could be due to the positive margins.

Clinical under-staging is an important phenomenon to discuss. Larger tumours in particular are associated with an elevated risk of being identified as pT3 on final pathologi-

cal analysis.[27] While surgical planning is highly dependent on preoperative imaging, it should be noted that segmental renal vein involvement and fat invasion are often difficult to identify with current cross-sectional imaging techniques. In fact, two-thirds of our cohort had clinical stage T1/2 disease. While clinical stage was not a significant predictor
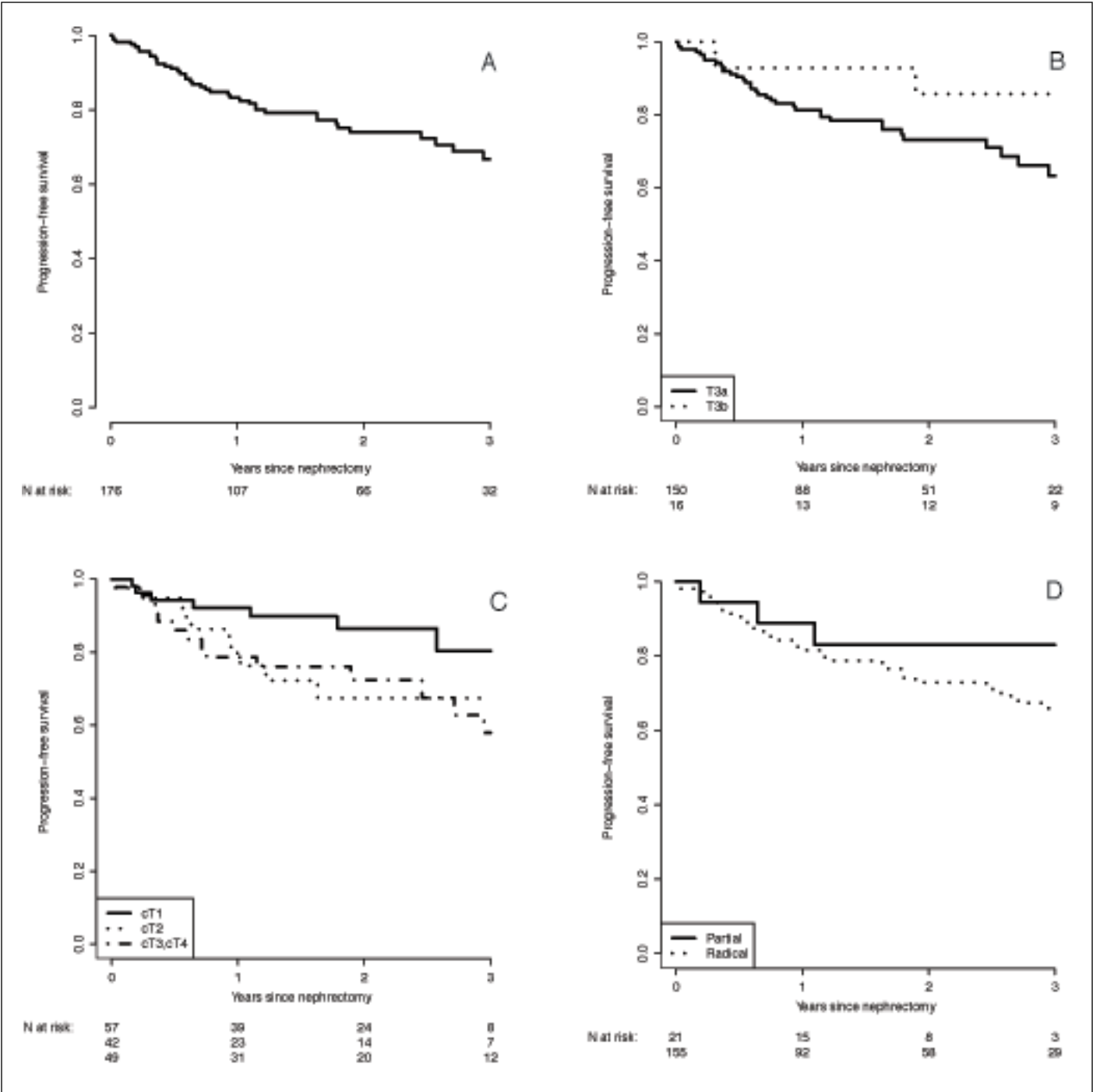
Fig. 1. Kaplan-Meier curve for progression free survival for (A) all pT3 renal cell carcinoma treated laparoscopically; (B) those with pT3a and pT3b disease (*p* = 0.09); (C) stratified according to clinical stage (*p* = 0.08); and (D) sub-stratified according to surgical approach (*p* = 0.27).

of progression, patients with cT1 tumours trended towards improved outcomes with an 80% 3-year PFS compared to 67% and 58% in those with cT2 and cT3/4, respectively (p = 0.08). This may be related to the prognostic value of tumour size. In fact, when accounting for size in regression modelling, this trend was no longer appreciated (p = 0.36).

We acknowledge that a number of tumour characteristics present risk factors for pathological upstaging from cT1 to pT3 disease, including high tumour complexity, increasing tumour diameter and hilar location.[30] While we have not compared the rates of margin positivity between LPN and open partial nephrectomy, as this would be limited by selection bias, it is worth considering whether the tumours in this series may have been better managed with open partial nephrectomy if the indication was truly mandatory. It must also be acknowledged that this is a very select group of patients, with most being treated for presumed clinical T1/2 disease. We are not suggesting that T3 disease be managed by partial nephrectomy. However, should pT3 disease be identified on final pathological analysis, acceptable short-term oncological outcomes can be achieved.

While operating time and blood loss only represent a portion of the morbidity associated with this procedure, in our experience, reduced operative times and comparable blood loss to other studies were seen, despite similar tumour sizes.[16,21] In this regard, laparoscopic surgery appears technically safe and feasible in this population.

There are a number of limitations. First, the multi-institutional design, while advantageous to reduce biases found within single-centre studies, is also subject to heterogeneity in data collection and follow-up. Second, we did not capture data on specific postoperative complications, although others have shown similar complication rates between laparoscopically treated pT1, pT2 and pT3 disease.[11,21] Third, we acknowledge that pT3 RCC includes a heterogeneous population, including those with both venous and fat invasion, whose differential prognoses are debatable. Fourth, there is an inherent selection bias in those selected for laparoscopic surgery, which we are unable to adjust. Fifth, the median follow-up in our study was 22.6 months and the median PFS was 49 months, so that further cases of local recurrence or metastatic disease will be anticipated with longer follow-up. Lastly, cancer-specific survival and overall survival were not assessed due to the low number of deaths, precluding any meaningful conclusions in this regard.

Conclusion

This multi-centered study constitutes the largest cohort of patients to have undergone laparoscopic renal surgery for pT3 RCC. For properly selected patients, our findings provide preliminary evidence that laparoscopic management of locally advanced renal masses yields acceptable oncological outcomes, and may be considered in the treatment paradigm on locally advanced disease. Under-staging in patients undergoing laparoscopic partial nephrectomy remains a concern.

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