

Regional differences in practice patterns and associated outcomes for upper tract urothelial carcinoma in Canada

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Abstract

Introduction: We delineated Canadian regional differences in practice patterns in the management of upper tract urothelial carcinoma (UTUC) after nephroureterectomy and relate these to patient outcomes.

Methods: A database was created with 1029 patients undergoing radical nephroureterectomy for UTUC between 1994 and 2009 at 10 Canadian centres. Demographic, clinical and pathological variables were collected from chart review. Practice pattern variables were defined as: open versus laparoscopic nephroureterectomy, management strategy for the distal ureter, performance of lymphadenectomy and administration of chemotherapy and/or radiation therapy. The outcome measures were overall (OS), disease-specific (DSS) and recurrence-free survival (RFS). The centres were divided into three regions (West, Central, East). Cox proportional multivariable linear regression analysis was used to determine the association between regional differences in practice patterns and clinical outcomes.

Results: There was a significant difference in practice patterns between regions within Canada for: time from diagnosis to surgery ($p = 0.001$), type of surgery (open vs. laparoscopic, $p < 0.01$) and method of management of the distal ureter ($p = 0.001$). As well, there were significant differences in survival between regions across Canada: 5-year OS (West 70%, Central 81% and East 62%, $p < 0.0001$) and DSS (West=79%, Central=85%, East=75%, $p = 0.007$) were significantly different, but there was no difference in RFS (West 47%, Central 48%, East 46%, $p = 0.88$). Multivariable linear regression analysis demonstrated that the differences in survival were independent of region OS ($p = 0.78$), DSS ($p = 0.30$) or RFS ($p = 0.43$).

Conclusion: There is significant disparity in practice patterns between regions within Canada, but these do not appear to have an effect on survival. We believe that the variability in practice is a reflection of the lack of standardized treatments for UTUC and underlines the need for multi-institutional studies in this disease.

Introduction

Upper tract urothelial carcinoma (UTUC) is rare and comprises only 5% of urothelial cancers.¹ This low incidence makes it relatively difficult to study and, as a result, much of our understanding of its natural history and pathology is extrapolated from bladder cancer.² Currently, the gold standard treatment for UTUC is nephroureterectomy with excision of the bladder cuff. However, many aspects of the diagnosis and treatment of UTUC, such as the management of the distal ureter and bladder cuff, are specific to its anatomic location in the upper tract. The current evidence to address many of these management questions is derived from single or multi-institutional retrospective series. In this context, we wanted to study the current practice patterns across Canada in the management of UTUC.

The European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN) have developed guidelines for the diagnosis and treatment of UTUC.^{2,3} These sources are consistent with each other on most issues, but they avoid concrete recommendations on many important questions. This is due mostly to the lack of quality evidence to support such recommendations. It would appear from multiple retrospective series, for example, that laparoscopic nephroureterectomy is equivalent to open nephroureterectomy, but this has not been evaluated prospectively.⁴⁻⁷ The most recent EAU guidelines state that there is limited data for laparoscopic versus open nephroureterectomy (grade B evidence), lymphadenectomy (Grade C evidence), and technique of bladder cuff excision (Grade C evidence). Other critical questions, such as the use of perioperative chemotherapy, have even less evidence.

We hypothesize that there is considerable variability in the management of UTUC primarily by nephroureterectomy across Canada and that this has a direct effect on patient outcome. We aim to define regional differences in practice patterns across Canada and relate these to patient survival.

Methods

Canadian Upper Tract Collaboration

The Canadian Upper Tract Collaboration (CUTC) includes 10 Canadian centres. Each centre performed a chart review for predefined demographic, clinical and pathologic variables in all patients who underwent nephroureterectomy from 1990 to 2010. Participating sites included: University of British Columbia, University of Alberta, University of Winnipeg, University of Western Ontario, McMaster University, University of Ottawa, University of Montreal, McGill University, Laval University and Dalhousie University. All participating sites obtained necessary institutional data use approval prior to their involvement in the CUTC.

Study design

This is a retrospective study cohort of a multi-institutional database. The patient cohort was divided into three geographic regions: (1) West (British Columbia, Alberta and Manitoba); (2) Central (Ontario), and (3) East (Quebec and Maritime Provinces). Practice patterns were defined as: time from diagnosis to surgery, open versus laparoscopic nephroureterectomy, method of management of the distal ureter, performance of lymphadenectomy, use of neo-adjuvant and adjuvant chemotherapy, and use of radiation therapy. Baseline demographic, clinical and pathological parameters were collected. Demographic variables included age, gender, race and body mass index (BMI). Clinical variables included smoking history (never, quit and current), previous abdominal radiation exposure, presence of hydronephrosis, presence of symptoms (local vs. systemic), and a prior history of urothelial cancer (with associated stage, grade and treatment parameters). Pathological variables included

Table 1. Baseline characteristics and practice patterns for patients who underwent nephroureterectomy for UTUC in Canada, divided by geographical region

		Central	East	West	<i>p</i> value	
Demographic characteristics						
Total number		252	488	289		
Age	Mean	70.2 (SD 10.5)	69.8 (SD 10.4)	69.1 (11.2)	0.231	
	Male	159/252 (63%)	320/488 (65%)	174/288 (60%)	0.340	
Gender	Female	93/252 (36.9%)	168/488 (34.4%)	114/288 (40%)		
Past smoking history		183/285 (78%)	298/443 (67%)	165/247 (67%)	0.870	
Body mass index (mg/m ²)		Mean	28.9 (SD 8.6)	26.8 (SD 5.4)	27.1 (SD 5.4)	0.008
Clinical characteristics						
History of abdominal radiation		8/249 (3.2%)	30/352 (8.5%)	42/282 (15%)	<0.001	
Presence of hydronephrosis		149/235 (63.4%)	152/349 (42.9%)	151/285 (53%)	<0.001	
Presence of symptoms	None	35/247 (14%)	44/455 (10%)	27/278 (10%)	0.083	
	Local	205/247 (83%)	385/455 (85%)	231/278 (83%)		
	Systemic	7/247 (3%)	26/455 (6%)	20/278 (7%)		
History of bladder cancer		69/249 (28%)	124/479 (26%)	75/283 (26.5%)	0.870	
History of UTUC		18/247 (7.29%)	28/353 (7.9%)	33/282 (11.7%)	0.142	
Management of prior UTUC	Endoscopic	11/16 (69%)	13/27 (48%)	23/33 (70%)	0.177	
	Percutaneous	1/16 (6%)	5/27 (19%)	0/33 (0%)		
	Distal	3/16 (19%)	6/27 (22%)	5/33 (15%)		
	Segmental	1/16 (6%)	3/27 (11%)	5/33 (15%)		
Grade of highest previous cancer	Low	28/54 (52%)	36/101 (35.6%)	37/71 (52%)	0.049	
	High	26/54 (48%)	65/101 (64.4%)	34/71 (48%)		
Stage of highest previous cancer	Ta, Tis and T1	41/47 (87%)	71/85 (83.5%)	50/67 (75%)	0.188	
	T2, T3 or T4	6/47 (13%)	14/85 (16.5%)	17/67 (25%)		
Pathological characteristics						
Presence of CIS		18/58 (31%)	13/100 (13%)	20/66 (30%)	0.007	
Tumour location	Renal Pelvis	129/245 (53%)	272/470 (58%)	137/286 (48%)	<0.001	
	Prox. ureter	52/245 (21%)	109/470 (23%)	89/286 (31%)		
	Pelvis + ureter	64/245 (26%)	89/470 (19%)	60/286 (21%)		
Presence of multifocality		94/246 (38%)	63/340 (19%)	82/285 (29%)	<0.001	

UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ.

tumour location within the renal pelvis or ureter, stage, grade, multifocality, carcinoma in situ (CIS), the presence of lymphovascular invasion, architecture (papillary vs. sessile), lymph node status, and surgical resection margin status. Outcome measures were overall survival (OS), disease-specific survival (DSS) and recurrence-free survival (RFS) at 5 years after nephroureterectomy. All surgical pathology was examined according to usual clinical practice at each individual institution.

Statistical analysis

Data were analyzed using Statistical Analysis Software version 9.1.3 (SAS Institute, Cary, NC). The Fisher's exact and chi-squared tests were used to evaluate differences between geographical regions. Univariable and multivariable cox proportional regression analyses were performed to determine the association between practice patterns and clinical outcomes. All significant or borderline significant variables from the univariable analysis were included in the multivariable model. A two-sided p value <0.05 defined

statistical significance, and a p value <0.2 defined borderline significance. The Kaplan-Meier method was used to estimate survival functions; differences were assessed with the Log-rank statistic.

Results

Baseline characteristics

The CUTC included data on 1029 patients who underwent nephroureterectomy from 10 different Canadian centres. There were 289 patients from the West, 252 patients from Central Canada and 488 patients from the East. The mean follow-up was 2.2 years (range: 0.6-5.0 years) for all patients. It was 1.8 years in Western Canada (range: 0.5-4.9), 2.1 years in Central Canada (range: 0.7-4.4), and 2.0 in Eastern Canada (range: 0.7-4.8). Demographics were similar between the three study regions (Table 1). However, patients from Central Canada had a statistically significantly higher BMI. Clinical parameters that carried statistical significance

Table 1. Baseline characteristics and practice patterns for patients who underwent nephroureterectomy for UTUC in Canada, divided by geographical region (cont'd)

Pathological characteristics (cont'd)		Central	East	West	p value
Architecture	Papillary	215/251 (86%)	286/488 (59%)	240/288 (83%)	<0.001
	Sessile	9/251 (4%)	11/488 (2%)	5/288 (1.7%)	
	Other	27/251 (10%)	191/488 (39%)	43/288 (15%)	
Presence of lymphovascular invasion		38/252 (15%)	79/488 (16%)	50/289 (17%)	<0.001
Presence of positive surgical margins		20/244 (8%)	10.3/443 (10.3)	34/281 (12%)	0.341
Presence of positive lymph nodes	No	60/252 (24%)	59/488 (12%)	67/289 (23%)	<0.001
	N1	19/252 (8%)	38/488 (7.8%)	21/289 (7.3%)	
	Nx	173/252 (69%)	391/488 (80%)	201/289 (70%)	
Stage	T1	130/235 (55%)	204/440 (46%)	129/246 (52%)	<0.144
	T2	43/235 (18%)	81/440 (18%)	36/246 (14%)	
	T3	48/235 (20%)	131/440 (30%)	65/246 (26%)	
	T4	14/235 (5%)	24/440 (5%)	16/246 (6.5%)	
Grade	Low	99/243 (40%)	123/477 (26%)	90/281 (32%)	<0.001
	High	144/243 (59%)	453/477 (74%)	191/281 (68%)	
Practice pattern					
Time from diagnosis to surgery (days)		92.8 (92.4)	36.8 (57)	68.4 (104)	<0.001
Surgery type	Open	91/252 (36%)	197/309 (64%)	115/288 (40%)	<0.001
	Laparoscopic	161/252 (64%)	112/309 (36%)	173/288 (60%)	
Management of distal ureter	Extravesical	67/252 (27%)	105/299 (35%)	144/284 (51%)	<0.001
	Internal/external	103/252 (41%)	184/299 (62%)	119/284 (42%)	
	Endoscopic	77/252 (31%)	8/299 (3%)	13/284 (5%)	
	Other	5/252 (2%)	2/299 (1%)	8/284 (3%)	
Lymphadenectomy		79/251 (31%)	99/481 (21%)	98/283 (35%)	<0.001
Neoadjuvant chemotherapy		3/248 (1.2%)	13/353 (3.7%)	15/289 (5.2%)	0.042
Adjuvant chemotherapy		21/249 (8.4%)	53/479 (11%)	38/289 (13%)	0.219
Salvage chemotherapy		32/234 (14%)	18/352 (5.1%)	25/289 (8.7%)	<0.001
Salvage radiation therapy		15/241 (6.2%)	31/352 (9%)	23/289 (8.0%)	0.513

UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ.

between regions were: previous abdominal radiation, the presence of hydronephrosis and highest grade of any prior tumour. Pathological parameters that were statistically different between regions included: presence of CIS, multifocality, tumour location, architecture, lymphovascular invasion, tumour node status and tumour grade.

Practice patterns varied significantly across Canada. Differences in the time from diagnosis to surgery, proportion of open versus laparoscopic nephroureterectomy, method of distal ureteral management, performance of lymphadenectomy and use of chemotherapy were statistically significant between regions.

Clinical outcomes stratified by geographic region

We used the Kaplan-Meier method OS (Fig. 1), DSS (Fig. 2) and RFS estimates (Fig. 3), stratified by geographical region. The predicted 5-year OS (West 69.6%, Central 80.6% and East 62.3%, $p < 0.0001$, log rank statistic= 0.014) and DSS (West 79.2%, Central 84.9%, East 75.0%, $p = 0.007$, log rank=0.13) differed significantly by region, but the RFS (West 46.7%, Central 47.6%, East 45.7%, $p = 0.88$ log rank=0.40) did not.

Association between geographic region and clinical outcomes

Table 2 presents the results of the univariable analysis examining predictors of clinical outcomes. Geographic region was associated with 5-year OS ($p < 0.001$) and DSS ($p = 0.007$), but not with RFS ($p = 0.88$). Table 3 presents the results of the multivariable analysis examining predictors of clinical outcomes. Geographic region was included in the multivariable analysis, but it did not make the final model. It was not independently associated with OS ($p = 0.78$), DSS ($p = 0.30$) or RFS ($p = 0.43$).

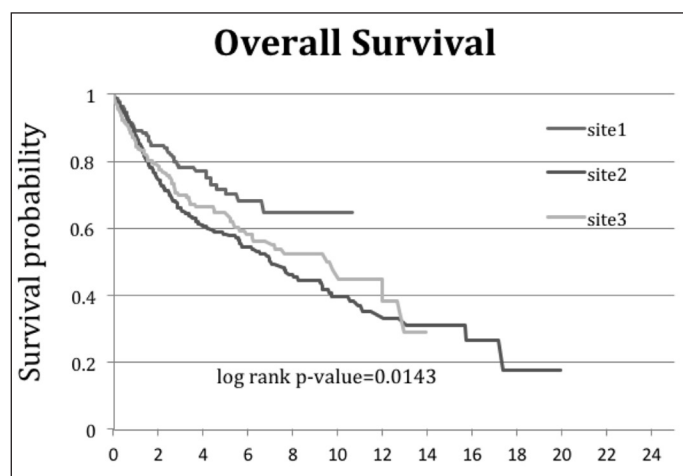


Fig. 1. Kaplan-Meier curve for overall survival stratified by geographic region.

Discussion

In this study, we analyzed practice patterns across Canada with respect to the management of UTUC and correlated these to clinical outcomes. We found that practice patterns varied considerably by region, but there was no significant difference in outcome after controlling for demographic, clinical and pathological variables. Baseline variability for clinical and pathological parameters was surprising, but can likely be explained by cultural, genetic, and socio-economic variability, in addition to referral patterns to the respective centres. The differences in pathologic parameters could also be due to variability at the individual centres for determining the indication for nephroureterectomy. The regional differences in practice patterns pertained particularly to surgical wait times, laparoscopic versus open nephroureterectomy, management of the distal ureter and the use of chemotherapy and radiation therapy.

OS and DSS, but not RFS, correlated with geographic region. However, when geographic region was included in the multivariable analysis, it did not independently predict survival. Patients in central Canada had the longest 5-year OS and DSS, despite some adverse characteristics, such as increased BMI and smoking history as well as more frequent hydronephrosis and more delays in treatment. Other disease- and treatment-related factors appear to have compensated for this, including more frequent low-grade disease with papillary architecture and more frequent N0 status. The time from diagnosis to surgery demonstrated remarkable variance across Canada. Patients in Central Canada waited 2.5 times longer (92.8 days) and patients in Western Canada 1.9 times (68 days) longer than patients in Eastern Canada (36.8 days) to reach the operating theatre ($p = 0.001$). However, wait time did not correlate with OS (hazard ratio [HR]=0.999), DSS (HR=0.998) or RFS (HR=0.998). We know from studies in urothelial carcinoma of the bladder that delays in radical cystectomy greater than 12 weeks lead to decreased

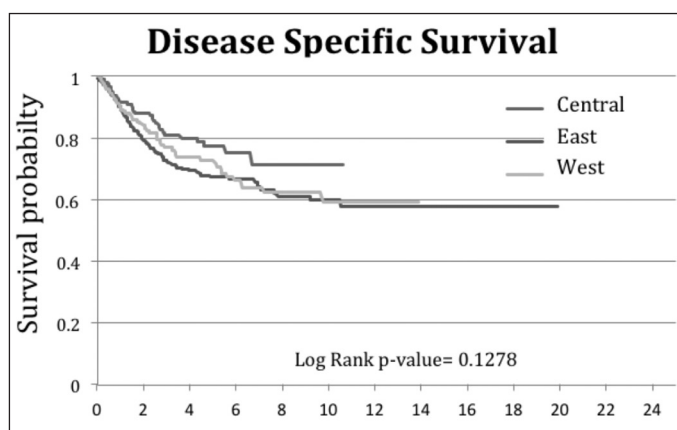


Fig. 2. Kaplan-Meier curve for disease specific survival stratified by geographic region.

Table 2. Univariable analysis

Demographic variables		5-year OS	p value	5-year DSS	p value	5-year RFS	p value
Site	West	201/289	69.6%	229/289	79.2%	135/289	46.7%
	Central	203/252	80.6%	214/252	84.9%	120/252	47.6%
	East	304/488	62.3%	366/488	75.0%	223/488	45.7%
Sex	Male	444/653	68.0%	507/653	77.6%	308/653	47.2%
	Female	263/375	70.1%	301/375	80.2%	169/375	45.1%
Smoking history	Non-Smoker	213/279	76.3%	236/279	84.6%	144/279	51.6%
	Smoker	433/646	67.0%	498/646	77.1%	283/646	43.2%
Clinical variables							
Hydronephrosis	None	213/279	76.3%	347/422	82.0%	209/422	49.5%
	Hydronephrosis	433/646	67.0%	349/452	78.2%	196/452	43.4%
Previous abdominal radiation	None	575/803	71.6%	643/803	80.1%	380/803	47.3%
	Prior RT	56/79	70.8%	61/80	76.2%	32/80	40.0%
Previous UTUC	None	574/803	71.4%	638/803	79.5%	375/803	46.7%
	Prior	56/79	70.8%	66/79	83.5%	37/79	46.8%
History of bladder cancer	None	473/634	74.6%	598/743	80.5%	360/743	48.5%
	Yes	170/268	63.4%	198/268	73.9%	108/268	60.3%
Symptoms from UTCC	None	86/106	81.1%	90/106	84.9%	61/106	57.5%
	Local	570/821	69.4%	654/821	79.7%	381/821	46.4%
	Systemic	34/53	64.2%	37/53	69.8%	24/53	45.3%
Pathological variables							
Tumour location	Renal pelvis	394/538	73.2%	446/538	82.8%	285/538	53.0%
	Ureter	174/250	69.6%	196/250	78.4%	119/250	47.6%
	Both	126/213	59.2%	146/213	68.5%	66/213	31.0%
Multifocal disease	None	473/634	74.6%	598/743	81.5%	302/634	47.6%
	Yes	156/239	65.2%	198/268	73.9%	78/239	32.6%
Tumour pathology stage	T1	357/463	75.8%	403/463	87.0%	256/463	55.3%
	T2	114/160	71.3%	128/160	80.0%	72/160	45.0%
	T3	140/244	57.4%	169/244	69.3%	153/244	37.3%
	T4	26/54	48.1%	31/54	57.4%	16/54	29.6%
Tumour grade	Low	251/312	80.4%	274/312	87.8%	171/312	54.8%
	High	442/689	64.1%	516/689	74.9%	392/689	43.1%
Lymphovascular invasion	Absent	460/615	74.8%	515/615	83.7%	304/615	49.4%
	Present	149/247	60.3%	107/167	64.1%	118/247	47.7%
Architecture	Papillary	554/741	74.7%	615/741	83.0%	364/741	49.1%
	Sessile	11/25	44.0%	13/25	52.0%	6/25	24.0%
CIS	Absent	490/650	75.3%	542/650	83.4%	341/650	52.5%
	Present	139/215	64.6%	159/215	74.0%	68/215	31.6%
Surgical margins	Negative	620/868	71.4%	704/868	81.1%	426/868	49.1%
	Positive	47/100	47.0%	59/100	59.0%	21/100	21.0%
Lymph node status	No	132/186	71.0%	148/186	79.6%	87/186	46.8%
	N1	33/78	42.3%	39/78	50.0%	15/78	19.2%
	Nx	543/765	71.0%	622/765	81.3%	376/765	49.2%

OS: overall survival; DSS: disease-specific. UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ; RFS: recurrence-free survival; UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ.

survival.⁸ There is limited data for such a relationship in UTUC. One study showed an increased risk of upstaging with delays in nephroureterectomy greater than 45 days, however there was no correlation with survival.⁹ A small retrospective review demonstrated that, in carefully selected patients, including some after neoadjuvant chemotherapy,

a prolonged surgical wait time has no effect on survival.¹⁰ The difference with UTUC is that tumours are more likely low grade and more often non-muscle invasive, whereas in the bladder, tumours are almost all high grade, and many are muscle invasive. Wait time may not be as critical for the lower risk tumours in the upper tract.

Table 2. Univariable analysis (cont'd)

Practice pattern		5-year OS	p value	5-year DSS	p value	5-year RFS	p value
Surgery type	Open	265/403	66.0%	310/403	80.5%	179/403	44.4%
	Laparoscopic	365/446	82.1%	387/446	73.9%	234/446	62.5%
Lymphadenectomy	None	525/739	71.0%	600/739	82.2%	362/739	49.0%
	Performed	175/276	63.4%	198/276	71.7%	108/276	39.1%
Distal ureter management	Extravesical	236/316	74.7%	263/316	83.2%	146/316	46.2%
	Transvesical	314/406	77.3%	339/406	83.5%	217/406	53.4%
	Endoscopic	8/15	53.3%	82/98	83.4%	43/98	43.8%
Neoadjuvant chemotherapy	None	617/859	71.8%	691/859	80.5%	406/859	47.3%
	Given	20/31	64.5%	20/31	64.5%	10/31	32.3%
Adjuvant chemotherapy	None	631/905	69.7%	726/905	80.2%	453/905	51.1%
	Given	68/112	60.7%	72/112	64.3%	21/112	78.7%
Salvage chemotherapy	None	591/800	73.9%	664/800	83.0%	410/800	51.2%
	Given	33/75	44%	33/75	54.0%	0/75	0%
Salvage radiotherapy	None	612/813	75.3%	685/813	84.3%	414/813	51.0%
	Given	18/69	26.1%	19/69	27.5%	0	0%
Time from diagnosis to surgery (days)		641/924	64.6	731/924	63.9	431/924	66.06

OS: overall survival; DSS: disease-specific. UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ. survival; RFS: recurrence-free survival; UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ.

The regional differences in wait times presumably result from local logistics related to access to imaging studies, operating room time and other such variables. We acknowledge that our data are taken from 10 tertiary care referral centres and this may have a large impact on wait times and may not be representative of community centres across Canada.

This study parallels a previous Canadian study on wait times for bladder cancer patients undergoing cystectomy. In a mix of community and academic centres, there was a large variability in wait times.¹¹ Because Canadian centres were previously beyond the recommended threshold of the 40-day wait time,^{12,13} in 2006 the surgical wait times initiative (SWAT) was developed to expedite surgery for all genitourinary malignancies.¹⁴ The patients from the current study were treated between 1990 and 2009, which mostly pre-dates SWAT.

There were significant differences in the surgical techniques used across the country. The diminished use of laparoscopy in Eastern Canada (36%) compared to western (60%) and central (64%) regions may reflect a delayed adoption of laparoscopy in general, or a hesitation to adopt this technique specifically for nephroureterectomy. We now know from our own collaboration¹⁵ and from other series^{6,16,17} that the oncologic control for laparoscopic and open nephroureterectomy appears to be the same, but this was previously debated. Interestingly, the rate of laparoscopic cases done in Canada in the 10-year study period was much higher than the number reported in the largest multi-institutional series published, where only 28% (270/1249) of patients from 9 centres underwent laparoscopic nephroureterectomy from 1987 to 2007.⁷

Regional differences in the management of the distal ureter and bladder cuff are not surprising, as there are numerous options for this part of the surgery, and there is little evidence to support one over another. There has also likely been some evolution in practice over the study period. As with laparoscopy, it is noteworthy that Canadian urologists are excising the distal ureter and bladder cuff more frequently than was reported by the largest multi-institutional series, in which 32.2% (403 of 1249) of patients underwent a bladder cuff excision.⁷

The regional differences in the management of the distal ureter and bladder cuff underline a common theme that is apparent throughout the management of patients with UTUC: *poor standardization of practices*. Highly variable practice patterns are likely a reflection primarily of the low level of evidence guiding practice for UTUC. Few prospective or randomized studies have been conducted in this

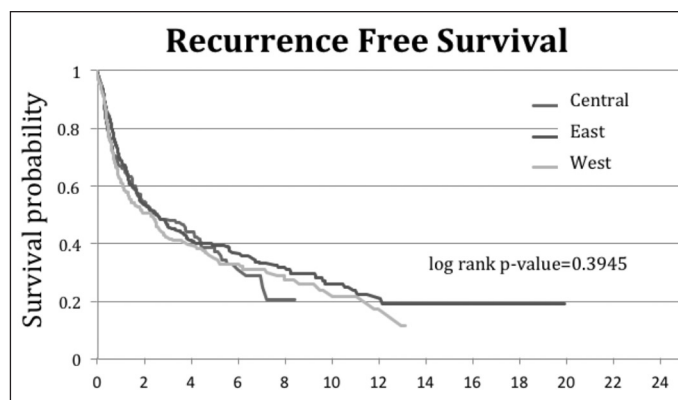


Fig. 3. Kaplan-Meier curve for recurrence free survival stratified by geographic region.

Table 3. Multivariable analysis examining predictors of clinical outcomes

Variable	OS			DSS			RFS		
	HR	95% CI		HR	95% CI		HR	95% CI	
Region									
Central	1.0			1.0			1.0		
East	1.105	0.707	1.727	1.097	0.658	1.827	0.796	0.575	1.103
West	1.124	0.744	1.698	0.892	0.540	1.473	0.726	0.519	1.016
Age									
<65	1.0			1.0			1.0		
>65	1.045	1.027	1.063	1.034	1.013	1.055	1.023	1.010	1.035
Symptoms									
None	1.0			1.0			1.0		
Local/Systemic	–	–	–	1.725	0.906	3.282	1.740	1.166	2.595
Surgical Approach									
Open	1.0			1.0			1.0		
Laparoscopic	0.866	0.618	1.270	–	–	–	1.142	1.085	1.839
Tumour location									
pelvis	1.0			1.0			1.0		
ureter	1.165	0.770	1.762	1.246	0.754	2.058	–	–	–
ureter and pelvis	2.021	1.395	2.927	2.379	1.484	3.814	1.779	1.345	2.354
pT stage									
1	1.0			1.0			1.0	–	–
2	0.987	0.606	1.606	1.145	0.634	2.069	–	–	–
3	2.564	1.748	3.759	2.935	1.810	4.758	–	–	–
4	4.326	2.427	7.714	3.660	1.723	7.777	–	–	–
Tumour grade									
Low	1.0			1.0			1.0	1.059	1.839
High	2.158	1.426	3.265	2.158	1.273	3.658	1.395	–	–
Concomitant CIS									
None	1.0			1.0			1.0	–	–
Present	0.819	0.566	1.184	0.847	0.547	1.311	–	–	–
History of bladder cancer									
None	1.0			1.0			1.0	0.845	1.496
Yes	1.313	0.946	1.822	1.367	0.910	2.052	1.124	–	–
Neoadjuvant chemotherapy									
None	1.0			1.0			1.0	0.457	1.998
Yes	–	–	–	2.573	0.981	6.748	0.995	–	–
Adjuvant chemotherapy									
None	1.0			1.0			1.0	1.089	2.231
Yes	–	–	–	–	–	–	1.559	–	–
Salvage chemotherapy									
None	1.0			1.0	1.0		1.0	1.601	3.424
Yes	1.187	0.719	1.960	1.744	1.021	2.978	2.341	–	–
Salvage radiation therapy									
None	1.0			1.0			1.0	1.661	3.497
Yes	3.586	2.272	5.662	4.018	2.419	6.675	2.410	–	–
Surgical margins									
Negative	1.0			1.0			1.0	0.995	2.050
Positive	–	–	–	1.342	0.790	2.279	1.428	–	–
Smoking history									
None	1.0			1.0			1.0	1.010	1.035
Yes	–	–	–	–	–	–	1.023	–	–
Previous abdominal RT									
None	1.0			1.0			1.0	0.936	1.578
Yes	–	–	–	1.0	–	–	1.254	–	–
Tumor node status									
Negative	1.0			1.0			1.0	0.171	10.987
Positive	–	–	–	–	–	–	1.372	–	–

OS: overall survival; DSS: disease-specific. UTUC: upper tract urothelial carcinoma; SD: standard deviation; CIS: carcinoma in situ. survival; RFS: recurrence-free survival; CIS: carcinoma in situ; HR: hazard ratio; CI: confidence interval; RT: radiation therapy.

disease, and some practices are simply extrapolated from the management of bladder cancer. There are no Canadian guidelines for UTUC, although the NCCN and EAU have guidelines. Unfortunately, neither guideline makes strong recommendations for specific treatment paradigms due to the lack of evidence. An analysis of practice patterns in Canada could, in principle, uncover deficiencies in current practice, but a practice can only be deemed deficient if there is clearly a better alternative. This cannot be claimed for most interventions related to UTUC. The high variability in management of UTUC in Canada underlines the urgent need for more multi-institutional controlled trials which may aid in the development of specific best practice guidelines.

The strength of this study is that it represents a broad spectrum of practice across many geographical regions. The data is Canadian and can be directly applied to our practices and patient populations. It is multi-institutional and includes a large number of patients. Limitations in this study include its retrospective design and the potential for inconsistencies in data entry between centres. Since all contributing centres in this study are academic institutions, the results do not necessarily reflect community practice.

Conclusion

There is significant variability in practice patterns for UTUC across Canada. However, when accounting for demographic, clinical and pathological variables, there was no significant difference seen in clinical outcomes that could be accounted for by the variability in practice patterns. We believe that the variability in practice patterns is primarily a reflection of the lack of treatment standards for UTUC due to the relative paucity in clinical evidence demonstrating the superiority of one practice over another. More large-scale controlled trials are required for UTUC to improve patient care.

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