Partial cystectomy for urothelial carcinoma of the bladder: Practice patterns and outcomes in the general population

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Abstract

Introduction: Partial cystectomy (PC) for urothelial carcinoma (UC) in selected patients may avoid the morbidity of radical cystectomy (RC). We describe utilization and outcomes of PC for UC in routine clinical practice.
Methods: All patients with urothelial carcinoma of the bladder (UCB) undergoing PC or RC in Ontario from 1994–2008 were identified using the Ontario Cancer Registry and linked electronic records. Pathology reports were reviewed. Variables associated with PC use were identified using logistic regression. Cox proportional hazards model identified factors affecting cancer-specific (CSS) and overall survival (OS).
Results: A total of 3320 patients underwent PC (n=181; 5%) or RC (n=3139; 95%) from 1994–2008. PC patients were older (36% 80+ years vs. 19%; p<0.001) and more likely to have organ-confined (<pT3) disease (54% vs. 36% RC; p<0.001). Two-thirds (67%) of

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PC patients did not undergo lymph node dissection (24% for RC; p<0.001). Factors associated with having PC included older age (odds ratio [OR] 1.55; 95% confidence interval [CI] 0.96–2.51 for 70+ years), moderate comorbidity (OR 1.95; 95% CI 1.13–3.37), and surgery outside of a comprehensive cancer centre (OR 1.44; 95% CI 1.03–2.01). Unadjusted five-year OS for PC and RC cases was 34% and 33%, respectively (p=0.455); CSS at five years was 43% and 37% (p=0.045). On adjusted analysis, PC was associated with comparable CSS (hazard ratio [HR] 0.87, 95% CI 0.70–1.09) and OS (HR 0.95, 95% CI 0.79–1.14) as RC.

Conclusions: In routine clinical practice, PC is not common. A substantial proportion of patients treated with PC achieve long-term survival. PC remains a treatment option in selected patients with UCB.

Introduction

Bladder cancer is a disease of the elderly who often have concomitant frailty and comorbidity[1]. Radical cystectomy (RC), long the standard management of muscle-invasive bladder cancer (MIBC), is a morbid procedure with a major complication rate even in high-volume centers of over 30%[2]. We have previously reported that among patients older than 80 years, 90-day postoperative mortality following radical cystectomy is 15%. Moreover, 5-year overall survival and cancer-specific survival are lower than in younger patients[3]. The morbidity of major exenterative and reconstructive surgery has led to the use of bladder-sparing techniques and protocols for some patients with MIBC, including maximal transurethral resection, radiation and chemotherapy[4,5]. However, many patients are not candidates for chemotherapy and therefore ineligible for optimal bladder sparing approaches[6]. Partial cystectomy (PC), ideally in conjunction with pelvic lymph node dissection (PLND), remains an option for highly selected patients with MIBC.

A handful of published reports have suggested that PC has comparable oncologic and survival outcomes to RC, however these reports predominately come from single-center series[7-9]. Partial cystectomy data often includes non-urothelial cancers and are therefore difficult to compare with radical cystectomy. Only a handful of studies have described utilization and outcome of PC in routine clinical practice[7,10,11]. We undertook a population-based retrospective cohort study to describe the use and outcomes of PC in the Canadian province of Ontario.

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Methods

Study design and population

This is a secondary report of a population-based, retrospective cohort study of all patients with bladder cancer treated with cystectomy in the Canadian province of Ontario. Detailed methodology and primary results have been reported elsewhere[12]. Ontario has a single-payer universal health insurance program that covers a population of approximately 13.5 million. All incident cases of urothelial bladder cancer in Ontario who underwent cystectomy in 1994-2008 were identified using the Ontario Cancer Registry and linked treatment records. Surgical pathology reports were obtained for all cystectomy cases.

The primary objectives of this study were to describe the utilization and outcomes of PC in the surgical management of UCB at the population level, and compare these to patients undergoing RC. Ethics approval was obtained from the Research Ethics Board of Queen's University.

Data sources

The Ontario Cancer Registry (OCR) is a passive registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer diagnosed in the province of Ontario[13]. The following data was obtained via the OCR: International Classification of Disease, version 9 (ICD-9) code; the ICD-O histology code; date of diagnosis; date of birth; place of residence at diagnosis; vital status; date of death; and cause of death. Vital status was available up to December 31, 2010 and cause of death was available up to December 31, 2008. Socioeconomic status (SES) data of the community in which patients resided at time of diagnosis were linked to the OCR as described previously, divided into quintiles (Q) of median household income as compared to the entire province[14]. Q1 represents the communities where the poorest 20% of the Ontario population resided. Hospitalization records obtained from the Canadian Institute for Health Information (CIHI) included surgical interventions, length of stay and repeat admission to hospital. Hospital participation in collection of records is consistent and complete throughout Ontario[15]. Chemotherapy use was identified through provincial physician billing records and treatment records from Ontario's regional cancer centers. Surgical pathology reports were obtained from the Ontario Cancer Registry (OCR). An electronic database was created by a team of trained data abstractors who reviewed and abstracted data from the pathology reports. In this study we use pathologic (not clinical) stage.

Comorbidity was classified by the Charlson Comorbidity Index, based on non-cancer diagnoses recorded within 5 years of surgery[16]. Neoadjuvant chemotherapy (NACT) was defined as occurring ≤16 weeks before surgery, and adjuvant chemotherapy (ACT) within 16 weeks following surgery. Pre-operative radiotherapy (RT) was defined

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as RT giving within 16 weeks before cystectomy; post-operative RT was given within 16 weeks after cystectomy. RT beyond 16 weeks from surgery was considered to be salvage RT.

Statistical analysis

Overall (OS) and cancer-specific (CSS) survival were determined from date of surgery using the Kaplan-Meier technique and comparisons between groups were made using the log-rank test. Factors associated with PC were evaluated with logistic regression analyses. The association between patient-, disease-, and treatment-related factors with overall/cancer-specific survival was evaluated using the Cox proportional hazards regression model. The survival analyses were restricted to patients that did not receive NACT or pre-operative radiotherapy, because information about pathologic stage for these patients would be less reliable. As per institutional privacy policy, patient sub-groups with <6 cases are suppressed to preserve patient confidentiality. Results were considered statistically significant at p-value < 0.05. As per institutional privacy policy we do not report any data with cell sizes <6. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Results

Study population

We identified 3320 patients who underwent PC or RC for urothelial cancer of the bladder in Ontario between 1994 and 2008. Five percent (181/3320) of cases underwent PC. Characteristics of the study population are shown in Table 1. A higher proportion of PC vs RC patients were octogenarians (36% vs 19%, p<0.001). PC patients were more likely to have organ-confined (<pT3) disease (54% vs 36%, p<0.001) than patients with RC. Two thirds of patients with PC (121/181, 67%) did not have lymph nodes resected at the time of surgery; conversely, 24% (741/3139, p<0.001) of patients with RC were NX. Surgical margins were positive in a higher proportion of PC patients compared to patients with total cystectomy (18% vs 12%, p=0.013).

Practice patterns

Use of peri-operative chemotherapy was less common among patients treated with PC. Eighteen percent (553/3139) of patients with total cystectomy had adjuvant chemotherapy compared to 12% (22/181) of PC patients (p=0.059). Neoadjuvant chemotherapy was delivered to 4% of cases with total cystectomy (128/3139); 1% (<6/181) patients with PC received neoadjuvant chemotherapy (p=0.009). Post-operative RT [3% (6/181) vs 1% (23/3319), p=0.004] and salvage RT [4% (7/181) vs 2% (61/3319), p=0.096] was more common among patients with PC compared to RC.

Variables associated with the use of partial cystectomy are shown in Table 2. Use of PC has decreased over time (p<0.001). On adjusted analyses, patients 70+ years of age

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(OR 1.55, 95%CI 0.96-2.51) and those with greater co-morbidity (OR 1.95, 95%CI 1.13-3.37) were more likely to have PC. Patients who underwent surgery at a comprehensive cancer center were less likely to have PC (OR 0.70, 95%CI 0.50-0.97). More advanced tumours (T3-4) were less likely to be managed with PC (OR 0.49, 95%CI 0.36-0.67). There was no significant regional variation in use of PC. Gender was not associated with use of PC. No patients with PC subsequently underwent salvage cystectomy in our data. Fewer than 5%of patients underwent salvage RC after PC in this cohort.

Outcomes

Outcomes of patients treated with PC and RC are shown in Table 3. Median length of stay was shorter for PC patients (8 days vs 11 days; $p<0.001$). Readmission rate and early postoperative mortality were similar between groups. Unadjusted five-year OS for PC and RC cases was 34% and 33% respectively ($p=0.455$); CSS at 5 years was 43% and 37% ($p=0.045$).

Adjusted overall and cancer-specific survival analyses for patients treated with PC are shown in Table 4. Among patients treated with PC, more advanced disease (T stage and N stage) and LVI were associated with inferior survival; age, co-morbidity, and margin status were not associated with outcome.

Adjusted survival analyses for all patients having cystectomy (partial and radical) are shown in Table 5. Among PC and RC patients greater age and co-morbidity are associated with inferior survival; T stage, N stage, and lymphovascular invasion are also associated with inferior outcomes. Adjusted analyses do not suggest any significant difference in CSS (HR 0.87, 95%CI 0.70-1.09) or OS (HR 0.95, 95%CI 0.79-1.14) among patients treated with partial cystectomy versus radical cystectomy.

Discussion

In this study we describe utilization of partial cystectomy for urothelial cancer of the bladder and outcomes achieved in routine clinical practice. Several important findings have emerged. First, PC is not common in the general population and utilization has decreased over time. In the most recent study (2004-2008) era only 4% of patients treated with cystectomy had PC. Second, factors associated with having PC include older age, greater co-morbidity, less extensive disease, and treatment outside a comprehensive cancer center. Third, 67% of patients with PC did not have lymph nodes resected at the time of surgery. Fourth, among patients treated with PC, T stage, N stage and LVI are associated with survival. Finally, in adjusted analyses, the long-term survival of patients treated with PC is comparable to those treated with RC.

Partial cystectomy is an understandably attractive option for patients with MIBC as compared to a radical cystectomy given the less disruptive surgical procedure and the functional bladder left *in situ*. PC is associated with earlier post-surgical recovery, avoidance of stigma and management issues that may accompany urinary diversion and

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the possible retention of sexual function[11,17]. PC is likely only feasible in a small proportion of MIBC patients (less than 10%), as indications are limited to those with a small solitary mass favorably located to allow adequate post-operative capacity, away from the trigone and in the absence of associated carcinoma in situ[8,11].

Partial cystectomy for UCB is relatively uncommon in the province of Ontario, and its use appears to be decreasing in more recent years. Several other series have observed similar rates of PC. Fedeli et al noted a decrease in PC as a proportion of all cystectomies in Italian centers, from 5.5% during 2000-2002 to 3.3% during 2006-2008[18]. Two population-level studies from the United States and from the Canadian province of Quebec found 18-30% of patients underwent PC, however these studies may have included non-urothelial histologies.[10,11]. Moreover, because these studies classified cystectomy based on administrative data sources, they may over-estimate the use of PC due to misclassification bias. Extent of cystectomy in the present study was established based on review of the surgical pathology report. Moreover, our study assessed only urothelial cancer. Removing other less aggressive or benign histology provides more clarity into the outcomes of PC in this context.

It is perhaps unsurprising that patients chosen for partial cystectomy are older and greater comorbidity than RC patients. However, previous population level data using the Surveillance Epidemiology and End Results (SEER) database have shown inconsistent effects of age, gender and comorbidity on the choice to use PC[7,11]. Our results also suggest that PC is more often used in patients with less extensive disease. This, as well as the generally more elderly and unwell patients, may explain the decreased use of adjuvant chemotherapy in PC patients. These population data show a slightly higher local stage at PC than prior published population and single-center series, likely reflecting the analysis of urothelial cancer in isolation, while suggesting differences in patient selection or time to surgery in the population at large[8,9,19-21]. It is notable that no lymph node pathologic data was available for 67% of PC cases in our series (and 24% of RC), suggesting that PLND was not considered part of the surgical procedure, possibly to decrease operative time and/or morbidity. Prior studies have shown highly variable use of PLND in other settings[8,10,20]. It is clear that PLND is a critical component of definitive surgical management of MIBC from a risk stratification and prognostic perspective, and these data point to a deficit in current practice[3,22,23]. The decision to forego PLND at partial cystectomy, given its relatively benign nature, may compromise long-term outcome in these patients.

Adjusted analyses in our study suggest that patients who have PC have comparable survival to RC. These data however must be interpreted in light of the fact that age, comorbidity, and extent of disease were very different between the 2 groups and the analyses are therefore prone to residual confounding. Patients with PC were older than those with RC; this might explain the fact that PC was not associated with any

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substantial reduction in post-operative re-admission rates or mortality. The low rate of lymph node dissection is also notable and suggests the need for future quality improvement initiatives. Outcomes observed in our cohort of PC patients are inferior to single-center series which have reported 58-70% OS at 5 years, and 65-87% DSS, as compared to 34% and 43%, respectively in our study. This likely reflects selection bias and the different case mix of patients treated in single centers compared to care in the general population.[8,9,19,20].

Our results need to be considered in the context of study limitations. As with all retrospective cohort studies, our results are prone to bias by confounding. Although the pathology reports were individually reviewed by a trained team of abstractors, surgical specimens did not undergo central pathology review. While our existing data-sets allow us to describe practice and outcomes for all patients treated with cystectomy in Ontario, we do not have granular details regarding patient performance status, previous transurethral resection history, location of disease, tumour size, carcinoma-in-situ or bladder/renal function. This limits our ability to evaluate appropriateness of case selection for PC. We also do not have information on date of disease recurrence so cannot describe relapse-free survival.

This database has significant strengths as compared to other population data sets. Detailed pathologic information from abstracted reports and complete chemotherapy data are distinguishing characteristics that provide a uniquely comprehensive window into routine urologic practice in the general population.

Conclusion

The decision to choose PC over RC in patients with UCB is complex and relates to disease characteristics and patient preference. While partial cystectomy is not used commonly in the general population, adjusted outcomes suggest that survival is comparable to RC. Our data suggest that lymph node dissection may be underutilized in PC.

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Figures and Tables

Table 1. Characteristics of 3320 patients with urothelial bladder cancer treated with cystectomy in Ontario from 1994–2008				
Variable	**Value**	**Radical cystectomy**	**Partial cystectomy**	**Total**
		n=3139	n=181	n=3320
Patient-related				
Age, years	20-49	110 (4%)	6 (3%)	116 (3%)
	50-59	389 (12%)	15 (8%)	404 (12%)
	60-69	806 (26%)	36 (20%)	842 (25%)
	70-79	1,243 (40%)	58 (32%)	1,301 (39%)
	80+	591 (19%)	66 (36%)	657 (20%)
Sex	F	761 (24%)	51 (28%)	812 (24%)
	M	2,378 (76%)	130 (72%)	2,508 (76%)
SES quintile [1]	1	613 (20%)	38 (21%)	651 (20%)
	2	706 (22%)	41 (23%)	747 (23%)
	3	699 (22%)	46 (25%)	745 (22%)
	4	592 (19%)	35 (19%)	627 (19%)
	5	<530 (17%)	21 (12%)	<550 (17%)
Charlson score	0	2,184 (70%)	122 (67%)	2,306 (69%)
	1-2	795 (25%)	42 (23%)	837 (25%)
	≥3	160 (5%)	17 (9%)	177 (5%)
Disease-related				
T-stage (categorized)	<T3	1,144 (36%)	97 (54%)	1,241 (37%)
	T3-T4	1,995 (64%)	84 (46%)	2,079 (63%)
T-stage	0	94 (3%)	9 (5%)	103 (3%)
	I	282 (9%)	31 (17%)	313 (9%)
	II	768 (24%)	57 (31%)	825 (25%)
	III	1,262 (40%)	76 (42%)	1,338 (40%)
	IV	733 (23%)	8 (4%)	741 (22%)
N-stage	N negative	1,558 (50%)	42 (23%)	1,600 (48%)
	N positive	840 (27%)	18 (10%)	858 (26%)
	NX	741 (24%)	121 (67%)	862 (26%)
LVI	No	839 (27%)	35 (19%)	874 (26%)

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	Yes	1,485 (47%)	68 (38%)	1,553 (47%)
	Unstated	815 (26%)	78 (43%)	893 (27%)
Margin status	Negative/unstated	2,762 (88%)	148 (82%)	2,910 (88%)
	Positive	377 (12%)	33 (18%)	410 (12%)

[1]SES quintile 1 represents patients from the poorest communities in Ontario. SES data were not available for <6 patients.

Table 2. Variables associated with use of partial cystectomy (PC) among patients with urothelial bladder cancer treated with cystectomy in Ontario, 1994–2008 (n=3185[*])

	Proportion PC	**Multivariate analysis**	
		OR (95% CI)	**p**
Patient-related			
Study Period			
1994-1998	9%	Ref	<0.001
1999-2003	5%	0.57 (0.39-0.83)	
2004-2008	4%	0.45 (0.31-0.65)	
Sex			
Male	5%	Ref	0.276
Female	6%	1.21 (0.86-1.70)	
Age, years			
20-59	4%	Ref	0.026
60-69	4%	0.97 (0.55-1.70)	
70+	7%	1.55 (0.96-2.51)	
Charlson comorbidity score			
0	6%	Ref	0.042
1-2	5%	0.94 (0.65-1.36)	
3+	10%	1.95 (1.13-3.37)	
System-related			
Region[†]			
A	6%	Ref	0.183
B	7%	1.10 (0.71-1.70)	
C	8%	1.66 (0.98-2.82)	
D	6%	1.20 (0.61-2.35)	
E	4%	0.95 (0.22-4.11)	
F	2%	0.35 (0.08-1.45)	
G	7%	1.23 (0.69-2.19)	
H	4%	0.69 (0.41-1.16)	
Cancer centre surgical hospital			
No	7%	Ref	0.035

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Yes	4%	0.70 (0.50-0.97)	
Disease-related			
Pathologic T stage			
<T3	8%	Ref	<0.001
T3-4	4%	0.49 (0.36-0.67)	

*135 patients with NACT and/or pre-operative RT are removed from the analysis since T stage does not reflect actual surgical pathologic stage. †Region data were not available for <6 patients.

Table 3. Unadjusted outcomes of patients with urothelial bladder cancer treated with partial or radical cystectomy in Ontario, 1994–2008 (n=3320)

	Partial n=181	**Radical n=3139**	**p**
Outcome			
Mean/median LOS (days)*	11/8	15/11	<0.001
30 day re-admission N (%)	21 (12%)	494 (16%)	0.135
90 day re-admission N %)	43 (24%)	1017 (32%)	0.015
30 day mortality N (%)	<=5 (<3%)	79 (3%)	0.196
90 day mortality N (%)	8 (4%)	263 (8%)	0.059
5 year OS (95%CI)*	34% (27-41%)	33% (31-35%)	0.455
5 year CSS (95%CI)†	43% (34-51%)	37% (35-39%)	0.045

†p values for 5 year OS and CSS are based on log-rank test. *p value for mean LOS is Kruskal Wallis test. Others are Chi-square test. Fisher's exact test was used for 30-day mortality because expected cell size was <5.

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Table 4. Factors associated with cancer-specific (CSS) and overall survival (OS) among patients treated with partial cystectomy for bladder cancer in Ontario, 1994–2008 (n=181)*

Characteristic	CSS		OS	
	Multivariate analysis		Multivariate analysis	
	HR (95% CI)	p trend	HR (95% CI)	p trend
Patient-related				
Age, years		0.414		0.112
20-59 (n=21)	Ref		Ref	
60-69 (n=35)	1.63 (0.72-3.70)		1.21 (0.61-2.43)	
70+ (n=124)	1.62 (0.78-3.37)		1.74 (0.94-3.22)	
Co-morbidity score		0.462		0.252
0 (n=57)	Ref		Ref	
>0 (n=15)	1.18 (0.76-1.85)		1.24 (0.86-1.78)	
Disease-related				
T stage		0.002		0.040
<T3 (n=96)	Ref		Ref	
T3-T4 (n=84)	2.10 (1.32-3.34)		1.49 (1.02-2.19)	
N stage		0.077		0.001
N negative (n=42)	Ref		Ref	
N positive (n=17)	2.43 (1.11-5.31)		3.45 (1.80-6.63)	
NX (n=121)	1.56 (0.86-2.83)		1.49 (0.92-2.41)	
LVI		0.011		0.024
No (n=35)	Ref		Ref	
Yes (n=68)	2.00 (1.03-3.87)		1.49 (0.90-2.46)	
Unstated (n=77)	0.94 (0.49-1.82)		0.83 (0.50-1.36)	
Margin status		0.548		0.380
Negative/unstated (n=147)	Ref		Ref	
Positive (n=33)	0.84 (0.47-1.48)		1.22 (0.78-1.90)	

*≤5 cases with NACT and/or pre-op RT were excluded from this analysis as T and N stage at time of surgery would not accurately reflect extent of disease.

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Table 5. Factors associated with cancer-specific (CSS) and overall survival (OS) among all patients treated with cystectomy for bladder cancer in Ontario, 1994–2008 (n=3320)[*]

Characteristic	CSS		OS	
	Multivariate analysis		Multivariate analysis	
	HR (95% CI)	p trend	HR (95% CI)	p trend
Age, years		<0.001		<0.001
20-59 (n=480)	Ref		Ref	
60-69 (n=804)	1.11 (0.94-1.30)		1.21 (1.04-1.40)	
70+ (n=1901)	1.39 (1.20-1.61)		1.64 (1.44-1.87)	
Comorbidity score		0.003		<0.001
0 (n=2198)	Ref		Ref	
>0 (n=987)	1.17 (1.05-1.29)		1.28 (1.17-1.40)	
T stage		<0.001		<0.001
<T3 (n=1185)	Ref		Ref	
T3-T4 (n=2000)	2.01 (1.79-2.25)		1.83 (1.66-2.01)	
N stage		<0.001		<0.001
N negative (n=1529)	Ref		Ref	
N positive (n=825)	1.58 (1.40-1.78)		1.52 (1.37-1.69)	
NX (n=831)	1.41 (1.26-1.59)		1.42 (1.28-1.58)	
LVI		<0.001		<0.001
No (n=830)	Ref		Ref	
Yes (n=1497)	2.08 (1.81-2.39)		1.79 (1.60-2.02)	
Unstated (n=858)	1.31 (1.13-1.52)		1.20 (1.06-1.36)	
Surgery		0.224		0.568
Total cystectomy (n=3005)	Ref		Ref	
Partial cystectomy (n=180)	0.87 (0.70-1.09)		0.95 (0.79-1.14)	

[*]135 cases with NACT and/or pre-op RT were excluded from this analysis as T and N stage at time of surgery would not accurately reflect extent of disease.

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