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 use 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 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 centres of over 30%.[2] We have previously reported that among patients older than 80 years, 90-day postoperative mortality following RC is 15%. Moreover, five-year overall survival (OS) and cancer-specific survival (CSS) 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 oncological and survival outcomes to RC; however, these reports predominately come from single-centre series.[7-9] PC data often includes non-urothelial cancers and are therefore difficult to compare with RC. Only a handful of studies have described use 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.

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 carcinoma of the bladder (UCB) in Ontario who underwent cystectomy

from 1994–2008 were identified using the Ontario Cancer Registry (OCR) and linked treatment records. Surgical pathology reports were obtained for all cystectomy cases.

The primary objectives of this study were to describe the use 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 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 centres. Surgical pathology reports were obtained from the 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 pathological (not clinical) stage.

Comorbidity was classified by the Charlson Comorbidity Index, based on non-cancer diagnoses recorded within five years of surgery.[16] Neoadjuvant chemotherapy (NACT) was defined as occurring ≤16 weeks before surgery, and adjuvant chemotherapy (ACT) within 16 weeks following surgery. Preoperative radiotherapy (RT) was defined as RT giving within 16 weeks before cystectomy; postoperative RT was given within 16 weeks after cystectomy. RT beyond 16 weeks from surgery was considered to be salvage RT.

Statistical analysis

OS and CSS 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 OS/CSS was evaluated using the Cox proportional hazards regression model. The survival analyses were restricted to patients that did not receive NACT or preoperative RT because information about pathological stage for these patients would be less reliable. As per institutional privacy policy, patient subgroups with <6 cases are suppressed to preserve patient confidentiality. Results were considered statistically significant at $p<0.05$. 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, U.S.).

Results

Study population

We identified 3320 patients who underwent PC or RC for UCB 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 perioperative chemotherapy was less common among patients treated with PC. Eighteen percent (553/3139) of patients with total cystectomy had ACT compared to 12% (22/181) of PC patients ($p=0.059$). NACT was delivered to 4% of cases with total cystectomy (128/3139); 1% (<6/181) of patients with PC received NACT ($p=0.009$). Postoperative 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 (odds ratio [OR] 1.55; 95% confidence interval [CI] 0.96–2.51) and those with greater comorbidity (OR 1.95; 95% CI 1.13–3.37) were more likely to have PC. Patients who underwent surgery at a comprehensive cancer centre 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

Table 1. Characteristics of 3320 patients with urothelial bladder cancer treated with cystectomy in Ontario, 1994–2008

Variable	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	1243 (40%)	58 (32%)	1301 (39%)
80+	591 (19%)	66 (36%)	657 (20%)
Sex			
Female	761 (24%)	51 (28%)	812 (24%)
Male	2378 (76%)	130 (72%)	2508 (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	2184 (70%)	122 (67%)	2306 (69%)
1–2	795 (25%)	42 (23%)	837 (25%)
≥3	160 (5%)	17 (9%)	177 (5%)
Disease-related			
T-stage (categorized)			
<T3	1144 (36%)	97 (54%)	1241 (37%)
T3–T4	1995 (64%)	84 (46%)	2079 (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	1262 (40%)	76 (42%)	1338 (40%)
IV	733 (23%)	8 (4%)	741 (22%)
N-stage			
N negative	1558 (50%)	42 (23%)	1600 (48%)
N positive	840 (27%)	18 (10%)	858 (26%)
NX	741 (24%)	121 (67%)	862 (26%)
LVI			
No	839 (27%)	35 (19%)	874 (26%)
Yes	1485 (47%)	68 (38%)	1553 (47%)
Unstated	815 (26%)	78 (43%)	893 (27%)
Margin status			
Negative/unstated	2762 (88%)	148 (82%)	2910 (88%)
Positive	377 (12%)	33 (18%)	410 (12%)

*SES quintile 1 represents patients from the poorest communities in Ontario. SES data were not available for <6 patients. LVI: lymphovascular invasion.

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.

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
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 neoadjuvant chemotherapy and/or preoperative radiotherapy are removed from the analysis since T stage does not reflect actual surgical pathologic stage.
†Region data were not available for <6 patients. CI: confidence interval; OR: odds ratio.

Outcomes

Outcomes of patients treated with PC and RC are shown in Table 3. Median length of stay was shorter for PC patients (8 vs. 11 days; p<0.001). Re-admission 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 five years was 43% and 37%, respectively (p=0.045).

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 (%)†	≤6 (<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 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. **p values for 5-year OS and CSS are based on log-rank test. CI: confidence interval; CSS: cancer-specific survival; LOS: length of stay; OS: overall survival.

Adjusted OS and CSS 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 lymphovascular invasion (LVI) were associated with inferior survival; age, comorbidity, 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 comorbidity are associated with inferior survival; T stage, N stage, and LVI are also associated with inferior outcomes. Adjusted analyses do not suggest any significant difference in CSS (hazard ratio [HR] 0.87; 95% CI 0.70–1.09) or OS (HR 0.95; 95% CI 0.79–1.14) among patients treated with PC vs. RC.

Discussion

In this study, we describe use of PC for UCB and outcomes achieved in routine clinical practice. Several important findings have emerged. First, PC is not common in the general population and use has decreased over time. In the most recent study era (2004–2008), only 4% of patients treated with cystectomy had PC. Second, factors associated with having PC include older age, greater comorbidity, less extensive disease, and treatment outside a comprehensive cancer centre. 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,

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)	
Comorbidity 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 neoadjuvant chemotherapy and/or preoperative radiotherapy were excluded from this analysis, as T and N stage at time of surgery would not accurately reflect extent of disease. CI: confidence interval; HR: hazard ratio; LVI: lymphovascular invasion.

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 Multivariate analysis		OS 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 neoadjuvant chemotherapy and/or preoperative radiotherapy were excluded from this analysis, as T and N stage at time of surgery would not accurately reflect extent of disease. CI: confidence interval; HR: hazard ratio; LVI: lymphovascular invasion.

in adjusted analyses, the long-term survival of patients treated with PC is comparable to those treated with RC.

PC is an understandably attractive option for patients with MIBC as compared to RC, 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 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 favourably located to allow adequate postoperative capacity, away from the trigone and in the absence of associated carcinoma in situ.[8,11]

PC 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 centres, from 5.5% during 2000–2002 to 3.3% during 2006–2008.[18] Two population-level studies from the U.S. 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 PC are older and have greater comorbidity than RC patient; 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 ACT in PC patients. These population data show a slightly higher local stage at PC than previously published population and single-centre 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 pathological 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 PC, 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 two 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 substantial reduction in postoperative 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-centre series, which have reported 58–70% OS at five years, and 65–87% CSS, 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 centres 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 pathological information from abstracted reports and complete chemotherapy data are distinguishing characteristics that provide a uniquely comprehensive window into routine urological 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 PC 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 underused in PC.

Competing interests: Dr. Leveridge has been an advisor for Astellas. Dr. Siemens has participated in clinical trials supported by Astellas, Janssen, and Sanofi. The remaining authors report no competing personal or financial interests.

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