Outcomes of pT0N0 at radical cystectomy: The Canadian Bladder Cancer Network experience

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Abstract

Introduction: Radical cystectomy is the standard treatment for muscle invasive bladder cancer. We assessed clinical outcomes in patients found to have no evidence of disease (i.e., pT0N0) following radical cystectomy.

Methods: We collected and pooled a database of 2287 patients who underwent radical cystectomy between 1993 and 2008 in eight centres across Canada. Of this number, 135 patients were found to have pT0N0 bladder cancer at the time of cystectomy. Survival data and prognostic variables were analyzed using Kaplan-Meier method and Cox proportional hazard regression analysis.

Results: Median patient age was 66 years with a mean follow-up of 42 months. Clinical stage distribution was Tis 8.9%, Ta 1.5%, T1 20.7%, T2 45.2%, T3 5.2%, and T4 5.2%. The five-year recurrence-free survival (RFS), disease-specific survival (DSS) and overall survival (OS) were 83%, 96%, and 88%, respectively. The 10-year RFS, DSS and OS were 66%, 92%, and 70%, respectively. On Cox proportional regression analysis, no variables were associated with disease recurrence and only patient age was associated with overall survival.

Interpretation: Patients with pT0N0 pathology after cystectomy have excellent outcomes with high five- and 10-year RFS, DSS and OS. However, there is still a risk of tumour recurrence in this patient population and thus postoperative surveillance is still required.

Introduction

In 2012, there will be an estimated 73,510 people diagnosed with bladder cancer and approximately 14,880 deaths due to this disease."[1] Bladder cancer is the fourth most common cancer in men and eighth most common in women.[2] While most patients presenting with bladder cancer have superficial disease (<cT2), about 25% of these individuals will have at least muscle invasive (≥cT2) or node positive (N+) disease.[3] Currently, radical cystectomy (RC) is the standard of care for the management of organ-confined muscle invasive or high-risk superficial disease.[4-8] About 10% of patients (range: 5-20) will have no evidence of tumour at pathological examination of the cystectomy specimen; such patients are designated stage pT0.[6,8-10]

The clinical outcomes and significance of patients with stage pT0 disease at cystectomy is unclear. Thrasher and colleagues[11] reviewed survival outcomes in these patients and found that survival in this population was determined by the presenting clinical stage. However, Palapattu and colleagues[9] found that survival in patients with pT0 is similar to those with pTa and pTis (in situ) and Cho and colleagues[12] found survival to be similar to those with pTis and T1 disease.

In an effort to help clarify the clinical significance of patients with stage pT0N0 disease at cystectomy, we assessed clinical outcomes of these patients following RC using a contemporary series of bladder cancer patients treated by urologic oncologists from multiple Canadian academic centres.

Methods

Retrospective clinical and pathological data were collected on 2287 patients who underwent RC for bladder cancer from eight academic centres across Canada between 1993 and 2008 as part of the Canadian Bladder Cancer Network. Institutional research ethics board approval was obtained at all centres. Data were collected using a standardized template. Guidelines for cystectomy were similar across all institutions, with indications including those patients with muscle invasive disease based on clinical staging, and non-muscle invasive tumours that were either recurrent or refractory to transurethral resection and/or intravesical chemo/immunotherapy. Clinical staging was done according to the TNM

system and included histologic diagnosis with transurethral resection of a bladder tumour (TURBT), abdominal/pelvic imaging and/or bimanual examination under anesthesia. Imaging of the abdomen and pelvis was done with at least one of the following: computerized tomography (CT), magnetic resonance imaging (MRI), ultrasonography or excretory urography. The choice of imaging modality depended on the surgeon or institutional guidelines at the time.

Variables that were analyzed included patient age, gender, smoking history, clinical stage, nodal status, histologic type, prior history of superficial transitional cell carcinoma (TCC) and carcinoma in situ (CIS), use of neoadjuvant chemotherapy, mode of pelvic lymph node dissection (PLND) (none, standard, extended), disease recurrence and death. The use of neoadjuvant chemotherapy was at the discretion of the surgeon. The extent of lymph node dissection was surgeon and institution-dependent.

Cystectomy specimens were processed and evaluated by staff pathologists with genitourinary expertise. Pathologic staging was in accordance with the 1997 TNM classification. Postoperative surveillance consisted of routine history and physical examination, blood chemistry analysis, abdominal/pelvic imaging, urinary cytology and chest x-ray. All assessments were repeated every three to six months for the first five years and at increasing intervals thereafter. Any additional evaluation was done on an individual basis at the discretion of the treating physician.

Measured survival outcomes included recurrence-free survival (RFS), disease-specific survival (DSS) and overall survival (OS). Time to recurrence was calculated as the time interval from surgery to evidence of clinical recurrence or last follow-up in the absence of any recurrence. Time to DSS was determined as the time interval from surgery to the date of death from bladder cancer or last follow-up if the patients had not died of bladder cancer. Time to OS was assessed as the time from surgery to the date of death, regardless of cause of death. The Kaplan-Meier method was used to estimate the RFS, DSS and OS. Prognostic variables for RFS and OS were analyzed using Cox proportional hazard regression models. Statistical significance was considered at $p < 0.05$. All analyses were performed using the SAS version 9.1.3 Service Pack 4 statistical (Windows platform, SAS Institute, Cary, NC).

Results

Patient and clinical characteristics

The entire study cohort consisted of 2287 patients, of which 135 (5.9%) patients had pT0N0 disease and 25 (1.1%) patients had pT0N+ disease. No patients with pT0 had metastatic disease. Of the 135 patients with pT0N0, TCC was the primary histology in 68.9% (83), and 80% (108) were male (Table 1). Median age was 66 years (range: 39-72) and median follow-up of living patients was 42 months (range: 3-180). Most patients had either clinical T1 or T2 stage disease (65.9% of 135 patients). There was a history of concomitant CIS in 24% and a history of previous superficial TCC in 35% of patients. Very few patients did not receive a lymph node dissection (7.4%). Neoadjuvant chemotherapy was offered to 11 (8.1%) of 135 patients with pT0N0, and 71 (3.1%) patients in the entire study cohort. Adjuvant chemotherapy was not offered to any patients in the pT0N0 group.

Clinical outcomes with pT0N0 pathology

The five- and 10-year RFS for pT0N0 was 83% and 66%, respectively; moreover, the five- and 10-year DSS for pT0N0 was 96% and 92%, respectively. The five- and 10-year OS was 88% and 70%, respectively (Fig.1). The five-year RFS, DSS and OS for the entire study population (2287) were 57%, 48% and 67%, respectively.

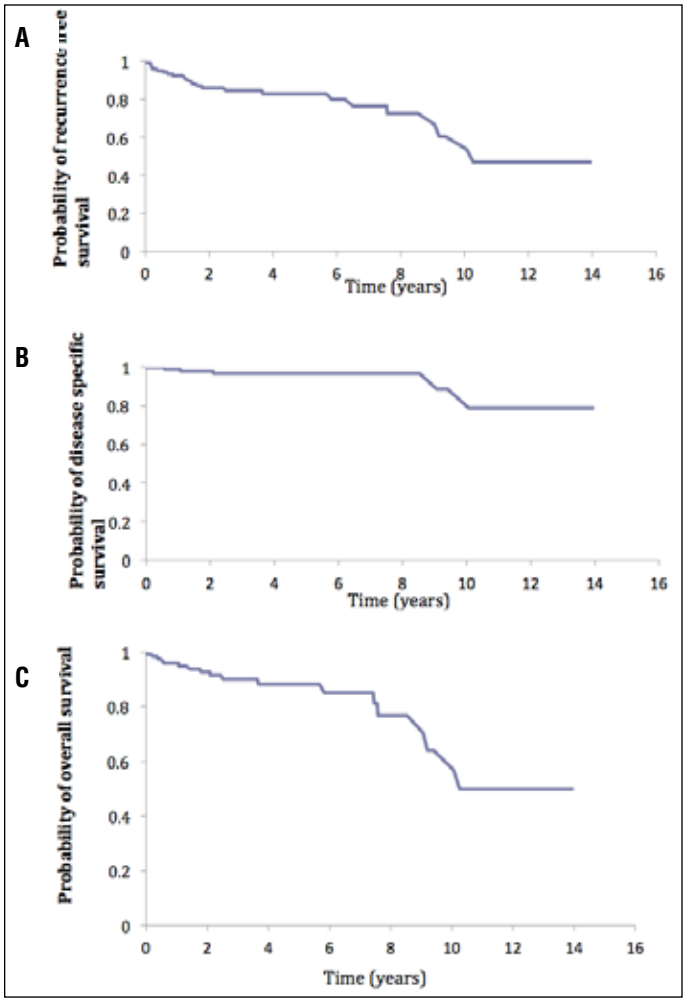

Fig. 1. Probability estimates of recurrence-free (A), disease specific (B) and overall survival (C) in 135 patients with pT0N0 disease at radical cystectomy.

Table 1. Characteristics in 135 patients with pT0N0 pathology after radical cystectomy	
pT0N0 Cohort	
Age (median, years)	66.0
Gender	**N (%)**
Male	108 (80)
Clinical tumour stage	**N (%)**
Ta	2 (1.5)
Tis	12 (8.9)
T1	28 (20.7)
T2	61 (45.2)
T3	7 (5.2)
T4	7 (5.2)
Missing	18 (13.3)
Histology	**N (%)**
Transitional cell carcinoma	83 (68.9)
Mixed	23 (17.0)
Non-transitional cell	19 (14.1)
Lymph Node Dissection	**N (%)**
No nodes examined	10 (7.4)
Standard node dissection	85 (63.0)
Extended node dissection	40 (29.6)

Predictors of recurrence free survival and overall survival with pT0N0 pathology

No variables were found to be associated with disease recurrence, including patient age, histology, clinical tumour stage and PLND on univariable or multivariable analysis (Table 2).

On univariable analysis, patient age was associated with OS ($p = 0.009$). Other variables, including histology, clinical tumour stage and extent of PLND, were not associated with OS on univariable analysis ($p > 0.05$ for all) (Table 3). Traditional predictors of OS were included in a multivariable model and only patient age remained a significant predictor of OS ($p = 0.002$) (Table 3).

Discussion

The frequency of pT0 pathology at RC has been reported to range from 5% to 20%.[8-11] The frequency of 5.9% of pT0 disease from the Canadian Bladder Cancer Network is in keeping with the published range. There are a number of causes of a pT0 RC specimen, including effective neoadjuvant therapy, complete endoscopic resection prior to cystectomy, residual tumour that is too small to be detected, and misdiagnosis at TURBT.[12-14] Neoadjuvant chemotherapy was administered to 3.1% of our entire study population, with only 8% of the 135 patients with pT0N0 disease being so treated. Neoadjuvant chemotherapy has been shown to result in a much higher rate of pT0 cystectomy specimens than that of surgery alone, 38% vs. 15%.[15] Additionally, the range of neoadjuvant chemotherapy use in cystectomy series is 14-37%.[6,8,9,16] There may have been an increased frequency of pT0 pathology in our cohort had there been a higher utilization of neoadjuvant chemotherapy in our series.

The significance of pT0 in terms of oncologic outcomes has been debated. In 1994, Thrasher and colleagues reported that stage pT0 bladder cancer patients have a survival that is determined by clinical stage at presentation.[11] They found no survival difference between patients who were downstaged to pT0 when compared to those in whom the clinical and final pathologic stage were consistent. More recent reviews highlight the importance of downstaging as survival outcomes are determined by pathological staging. In 2006, Palapattu and colleagues reviewed cancer-specific outcomes in 59 patients with pT0 disease following RC, with eight patients having received neoadjuvant chemotherapy.[9] At a median follow-up of 56 months, in those patients alive at last follow-up, the five- and 10-year DSS were 95% and 85%, respectively. These outcomes were statistically similar to those of their patients with pTa and pTis disease. Similarly, Cho and colleagues in 2008 found that five-year DSS was similar between pT0 (88%) and pTis-T1 (92%),

Table 2. Univariable and multivariable Cox regression analysis predicting disease recurrence in 135 patients with pT0N0 pathology at radical cystectomy			
Recurrence-free survival			
Univariable analysis			
Variable	**HR**	**95% CI**	***p* value**
Age (per year older)	1.04	0.997-1.09	0.07
Histology			
Transitional cell	Referent	–	–
Non-transitional cell	0.91	0.28-2.95	0.87
Clinical tumour stage			
Ta, Tis, T1	Referent	–	–
T2	1.19	0.40-3.57	0.75
T3, T4	2.21	0.58-8.38	0.25
PLND			
Extended	Referent	–	–
None	2.06	0.41-10.39	0.38
Standard	1.11	0.43-2.88	0.83
Multivariable analysis			
Variable	**HR**	**95% CI**	***p* value**
Age (per year older)	1.05	0.98-1.12	0.21
Histology			
Transitional cell	Referent	–	–
Non-transitional cell	1.36	0.15-12.46	0.79
Clinical tumour stage			
Ta, Tis, T1	Referent	–	–
T2	2.31	0.47-11.43	0.30
T3, T4	4.85	0.84-28.13	0.08

PLND: Pelvic lymph node dissection; HR: hazard ratio; CI: confidence interval.

Table 3. Univariable and multivariate Cox regression analysis predicting overall survival in 135 patients with pT0N0 pathology at radical cystectomy

Overall mortality			
Univariable analysis			
Variable	**HR**	**95% CI**	***p value***
Age (per year older)	1.08	1.02-1.15	0.009
Histology			
Transitional cell	Referent	--	--
Non-transitional cell	0.82	0.21-3.24	0.77
Clinical tumour stage			
Ta, Tis, T1	Referent	--	--
T2	0.92	0.26-3.31	0.90
T3, T4	1.04	0.18-5.84	0.97
PLND			
Extended	Referent	--	--
None	2.53	0.49-13.11	0.27
Standard	0.65	0.23-1.83	0.41
Multivariable analysis			
Variable	**HR**	**95% CI**	***p value***
Age (per year older)	1.13	1.05-1.22	0.002
Histology			
Transitional cell	Referent	--	--
Non-transitional cell	0.55	0.12-2.56	0.45
Clinical tumour stage			
Ta, Tis, T1	Referent	--	--
T2	2.93	0.33-25.77	0.33
T3, T4	2.50	0.21-29.39	0.47

PLND: Pelvic lymph node dissection; HR: hazard ratio; CI: confidence interval.

with both groups being significantly higher than pT2 (65%).[12] Improved outcomes with pT0N0 pathology have also been corroborated in multi-institutional studies.[17] Our results also revealed excellent DSS and OS outcomes in patients with pT0N0 pathology.

In spite of good outcomes in patients with pT0, there remains a risk of recurrence, which has been attributed to occult metastatic disease at the time of surgery. This risk of recurrence, 17% at 5 years in our study, highlights the need for ongoing surveillance of those patients with pT0 disease. We were unable to identify factors that were associated with an increased risk of recurrence in our study. Rodriguez Faba and colleagues identified clinical factors associated with worse DSS in patients with pT0 disease; these include a progression to muscle invasive disease from previously non-invasive disease, a history of 5 or more recurrences and lymphovascular invasion in the TURBT specimen.[18] Multi-institutional reviews have also found that female gender, posterior tumour location and absence of lymph node dissection are associated with increased disease recurrence.[17,19] These patients may benefit from more stringent surveillance to allow identification of recurrence earlier with subsequent initiation of additional therapy.

We also attempted to identify predictors of OS in this patient group with pT0N0 pathology. Our analysis revealed that only patient age was associated with OS. Clinical tumour stage was not predictive of OS in our study, which refutes the aforementioned findings of Thrasher and colleagues[11] that survival outcomes in this group of patients were dictated by clinical stage. Clinical stage was also not found to be associated with OS in a multi-institutional series.[19]

Our study has several limitations. It is a retrospective analysis, with accompanying inherent bias. Further, the patients in this study were treated over a long study period, during which time staging modalities have improved and treatment strategies have evolved. However, most patients were treated after 2000. This is a multicentre, multi-surgeon study where the operative technique may have varied and there was no centralized pathology core. However, we believe this represents a "real world" experience with bladder cancer patients treated with cystectomy.

Conclusions

The results of this large multicentre study suggest that patients with pT0N0 have excellent outcomes from cystectomy with high five- and 10-year RFS, DSS and OS; however, there still remains a risk of tumour recurrence in this patient population. Given that patients with pT0N0 pathology are a heterogeneous group, ongoing postoperative surveillance is required for these patients.

Competing interests: None declared.

This paper has been peer-reviewed.

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