Radical cystectomy for the treatment of T1 bladder cancer: the Canadian Bladder Cancer Network experience

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Abstract

Background: Radical cystectomy may provide optimal survival outcomes in the management of clinical T1 bladder cancer. We present our data from a large, multi-institutional, contemporary Canadian series of patients who underwent radical cystectomy for clinical T1 bladder cancer in a single-payer health care system.
Methods: We collected a pooled database of 2287 patients who underwent radical cystectomy between 1993 and 2008 in 8 different centres across Canada; 306 of these patients had clinical T1 bladder cancer. Survival data were analyzed using Kaplan-Meier method and Cox regression analysis.
Results: The median age of patients was 67 years with a mean follow-up time of 35 months. The 5-year overall, disease-specific and disease-free survival was 71%, 77% and 59%, respectively. The 10-year overall and disease-specific survival were 60% and 67%, respectively. Pathologic stage distribution was p0: 32 (11%), pT1: 78 (26%), pT2: 55 (19%), pT3: 60 (20%), pT4: 27 (9%), pTa: 16 (5%), pTis: 28 (10%), pN0: 215 (74%) and pN1-3: 78 (26%). Only 12% of patients were given adjuvant chemotherapy. On multivariate analysis, only margin status and pN stage were independently associated with overall, disease-specific and disease-free survival.
Interpretation: These results indicate that clinical T1 bladder cancer may be significantly understaged. Identifying factors associated with understaged and/or disease destined to progress (despite any prior intravesical or repeat transurethral therapies prior to radical cystectomy) will be critical to improve survival outcomes without over-treating clinical T1 disease that can be successfully managed with bladder preservation strategies.

Cite as: *Can Urol Assoc J* 2011;5(2):83-7; DOI:10.5489/cuaj.10040

Résumé

Contexte : La cystectomie radicale peut donner des résultats optimaux en lien avec la survie dans la prise en charge d'un cancer de la vessie de stade clinique T1. Nous présentons ici les données provenant d'une récente étude multicentrique de grande envergure portant sur des patients canadiens ayant subi une cystectomie radicale pour le traitement d'un cancer de la vessie de stade clinique T1 dans un système de santé à payeur unique.
Méthodologie : Nous avons cumulé les données provenant de 2 287 patients ayant subi une cystectomie radicale entre 1993 et 2008 dans 8 centres différents au Canada; 306 de ces patients présentaient un cancer de la vessie de stade clinique T1. Les données liées à la survie ont été analysées à l'aide de la méthode de Kaplan-Meier et du modèle de régression de Cox.
Résultats : L'âge médian des patients était de 67 ans, et la durée moyenne du suivi, de 35 mois. La survie globale, la survie spécifique à la maladie et la survie sans maladie après 5 ans étaient de 71 %, 77 % et 59%, respectivement. La survie globale et la survie spécifique à la maladie après 10 ans étaient de 60 % et 67 %, respectivement. Les stades pathologiques se répartissaient ainsi : p0 : 32 (11 %), pT1 : 78 (26 %), pT2 : 55 (19 %), pT3 : 60 (20 %), pT4 : 27 (9 %), pTa : 16 (5 %), pTis : 28 (10 %), pN0 : 215 (74 %) et pN1-3 : 78 (26 %). Seulement 12 % des patients ont reçu une chimiothérapie adjuvante. À l'analyse multivariée, seuls le statut des marges chirurgicales et le stade pN étaient indépendants de la survie globale, la survie spécifique à la maladie et la survie sans maladie.
Interprétation : Ces résultats indiquent que le stade d'un cancer de la vessie d'abord classé comme T1 peut avoir été grandement sous-évalué. L'identification des facteurs associés à un cancer dont le stade a été sous-évalué et/ou à une maladie destinée à évoluer (malgré un traitement intravésical antérieur ou des traitements transurétraux répétés avant la cystectomie radicale) jouera un rôle crucial dans la hausse des taux de survie sans surtraiter la maladie clinique de stade T1 pouvant être prise en charge de façon efficace par des stratégies de conservation de la vessie.

Introduction

Bladder cancer has a significant impact on cancer mortality and morbidity from a global perspective. In the United States, it ranks fourth in terms of incidence, and eighth in terms of mortality among males.[1] However, in other areas, such as Northern Africa, it is the leading cause of cancer mortality.[2] Such figures underscore the need for focusing on the primary objective of improving overall survival when-

ever treating patients with bladder cancer.

From a clinical decision making standpoint, one of the most difficult groups of bladder cancer patients to treat are those with clinical T1 urothelial cancer (T1). These patients have traditionally been placed into the "superficial" bladder cancer category, and the current standard treatment is transurethral resection and then intravesical immunotherapy. A recent population-based study, from the northeastern United States, found the prevalence of newly diagnosed T1 bladder cancer to be 20.8% of all newly diagnosed bladder cancers.[3] The mortality rate, however, belies the use of the word "superficial" for this group of patients; the 5-year survival rate for T1 tumours was 75%, as reported in the literature from a large national registry.[4] Patients also endure significant morbidity, even when managed without cystectomy, with current guidelines recommending that patients undergo a repeat transurethral resection, subsequent intravesical bacillus Calmette-Guerin (BCG) immunotherapy for at least 1 year, in addition to cystoscopies every 3 months (European Association of Urology guidelines March 2009.[5] The high mortality and morbidity rates of current treatment paradigms have led some urologists to question whether patients should be offered early radical cystectomy, in particular to improve overall survival,[6] rather than being treated with intravesical immunotherapy.

Previous studies of patients with clinical T1 urothelial cancer undergoing radical cystectomy have found survival rates which are not as high as might be expected for patients with superficial disease.[7] Bianco and colleagues reviewed the outcomes of 66 patients who underwent radical cystectomy for clinical T1 disease between 1990 and 2000, and found a cancer-specific mortality rate of 22% at a median follow-up of 4 years.[8] Gupta and colleagues reviewed the outcomes of 167 patients with clinical T1G3 disease, from a total pool of 202 patients with clinical T1 disease who underwent radical cystectomy between 1984 and 2003 at 3 different academic medical centres.[9] The cancer-specific 5-year and 7-year survival rates were 79% and 71%, respectively. Most previous studies have been single institution-based studies, raising the possibility of selection bias, and also have not had a large number of patients. The aim of this study was to analyze survival outcomes for patients with clinical T1 disease undergoing radical cystectomy from a large multi-provincial database, which is likely to be a more representative sampling of the broader community.

Methods

The Canadian Bladder Cancer Network database consists of 2287 patients who underwent radical cystectomy between 1993 and 2008 in 8 different centres across Canada (University of Western Ontario, McGill University, University of Montreal, Laval University, University of Alberta, University of Ottawa, Dalhousie University and University of Manitoba). These 8 centres represent 5 out of the 10 provinces in Canada. Collected variables included age, race, gender, presence of hydronephrosis, clinical stage and nodal status, concomitant carcinoma in situ (CIS), histology, Eastern Cooperative Oncology Group performance, smoking, pelvic lymph node dissection, pathologic stage and nodal status, grade, surgical margins, postoperative chemotherapy/radiation, recurrence and salvage therapy.

From this database, there were 306 patients who underwent radical cystectomy for clinical stage T1 bladder cancer, and they formed the study population for our analysis. There were no standardized inclusion or exclusion criteria, as this was a retrospective pooled database from several institutions. However, standard practice in Canada is for patients with clinical stage T1 bladder cancer to have undergone transurethral resection of the tumour followed by a trial of intravesical immunotherapy or chemotherapy prior to undergoing radical cystectomy. This cohort, therefore, mostly represents patients who have failed intravesical therapy, although the prior number of intravesical therapies is not known.

Clinical and pathological staging was according to the 2002 American Joint Committee on Cancer TNM classification. Pathological examination of specimens was performed at each institution by university pathologists. Grading was done using the 1998 World Health Organization (WHO) grading system. Radical cystectomy and pelvic lymph node dissection was performed as per Canadian standards. Neoadjuvant or adjuvant chemotherapy was administered at the discretion of the treating urologist.

The main outcomes for the analysis were overall survival (OS) and disease specific survival (DSS). Secondary outcomes were predictors for OS and DSS. Survival data were analyzed using the Kaplan-Meier method and Cox regression analysis. Categorical data were evaluated using the chi-squared test and continuous data with the Student's t-test. Statistical significance was set at 0.05, and the software used was SAS 9.1.3 Service Pack 4 (Windows platform, SAS Institute, Inc, Cary, NC).

Results

We outline the baseline characteristics of the group (Table 1). The median age was 67 years (interquartile range 60-72.5 years). Most patients were male (81.7%) with CIS present on the pre-cystectomy biopsies in 24.3%, and the mean follow-up was 3.1 years. A minority of patients (32 patients, 12.1%) received adjuvant chemotherapy.

Pathological outcomes are noteworthy for the high proportion of patients for whom upstaging was noted (Table 2). Local tumour staging remained as T1 in 78 patients (26.4%), was downstaged in 48 patients (16.2%) to pTa or pT0, and was upstaged in 142 patients (48%) to pT2-4.

Table 1. Baseline characteristics for the 306 patients with clinical stage T1 disease undergoing cystectomy	
Variable	
Mean Age ± (SD), years	66 ± (9.6)
Mean follow-up ± (SD), years	3.1 ± (3.0)
Sex	
Male, n (%)	250 (81.7%)
Female, n (%)	56 (18.3%)
Hydronephrosis	
Present, n (%)	47 (24.5%)
Absent, n (%)	145 (75.5%)
CIS on preoperative biopsies	
Present, n (%)	58 (24.3%)
Absent, n (%)	181 (75.7%)
Extent of lymphadenectomy	
None, n (%)	32 (10.8%)
Pelvic lymphadenectomy, n (%)	184 (62.2%)
Extended pelvic lymphadenectomy, n (%)	80 (27%)

SD: standard deviation; CIS: carcinoma in situ.

Most patients upstaged had extra-vesical disease (87 of 142 patients). Pelvic lymph node dissection, either standard or extended, was performed in 264 patients (89.2%) and lymph node metastasis was present in 58 patients (19.9%). A small number of patients had positive margins (6.6%). We did not find a statistically significant higher rate of pathologic upstaging in those patients with pre-cystectomy CIS.

At the time of data extraction, 73 patients were deceased and 220 patients were still alive (75.1%). Kaplan-Meier OS rates (Fig. 1) at 2, 5 and 10 years were 0.81 (95% confidence interval [CI] 0.76-0.85), 0.71 (95% CI 0.64-0.77), and 0.60 (95% CI 0.50-0.69), respectively. Disease-specific survival rates (Fig. 1) at 2, 5 and 10 years were 0.83 (95% CI 0.78-0.87), 0.77 (95% CI 0.70-0.82) and 0.67 (95% CI 0.57-0.76), respectively.

Multivariable Cox regression modelling for OS was performed, adjusting for age and gender. The model included all variables which showed a $p < 0.25$ on univariate Cox regression analysis. In this model, only positive margin status (hazard ratio [HR] 3.0, 95% CI 1.3-7.0; $p = 0.01$) and positive lymph nodes (HR 3.6, 95% CI 1.9-6.7; $p < 0.001$) remained as independent predictors of decreased OS. Similar findings were noted in the Cox multivariable model for DSS, with positive margin status (HR 2.6, 95% CI 1.0-6.6; $p = 0.047$) and positive lymph nodes (HR 4.5, 95% CI 2.3-8.9; $p < 0.001$) remaining as independent predictors of worse DSS. Local pathologic staging ("T" staging) did not remain an independent predictor after adjusting for margins and nodal status. Of note, neither the presence of CIS nor the performance of an extended pelvic lymphadenectomy were independent predictors of OS or DSS. Clinical CIS was not associated with pathologic upstaging; however, we did note that pathologic CIS was associated with upstaging ($p = 0.03$).

Table 2. Post-cystectomy pathological outcomes	
Pathological stage	
pT0, n (%)	32 (10.8%)
pCIS only, n (%)	28 (9.5%)
pTa, n (%)	16 (5.4%)
pT1, n (%)	78 (26.4%)
pT2, n (%)	55 (18.6%)
pT3, n (%)	60 (20.3%)
pT4, n (%)	27 (9.1%)
CIS, n (%)	114 (43.5%)
Nodal stage	
pNX, n (%)	19 (6.5%)
pN0, n (%)	215 (73.6%)
pN1-3, n (%)	58 (19.9%)
Grade	
Low, n (%)	51 (22.2%)
High, n (%)	179 (77.8%)
Margins	
Positive, n (%)	18 (6.6%)
Negative, n (%)	255 (93.4%)
Lymphovascular invasion	
Present, n (%)	50 (29.6%)
Absent, n (%)	119 (70.4%)
Histology	
Urothelial, n (%)	246 (85.4%)
Non-urothelial, n (%)	42 (14.6%)

CIS: carcinoma in situ.

Discussion

The main findings from our study have been the poor OS and DSS rates at 5 years, which were 0.71 (95% CI 0.64-0.77) and 0.77 (95% CI 0.70-0.82), respectively, in a cohort of 306 patients who underwent radical cystectomy for clinical T1 disease. These findings are similar to published survival rates in the literature. The largest published cohort, a multinational study by Fritsche and colleagues of 1135 patients with T1G3 disease, had a cancer-specific survival rate of 64.5% at 8 years.[10] Denzinger and colleagues, in a non-randomized comparison, found 5-year DSS rates of 0.83 in 54 patients who underwent early cystectomy, versus 0.67 in 51 patients who underwent deferred cystectomy;[7] these results fall just outside the upper and lower end of our confidence interval, respectively. The cohort of Gupta and colleagues (167 patients with T1G3 disease) had a 5-year DSS rate of 0.79,[9] while the cohort of Bianco and colleagues (66 patients with T1 disease) had a DSS rate of about 0.78.[8] Given that all of these studies concur with our findings, this suggests that this cohort of patients need to be informed about the potential lethality of their disease early in the decision-making process.

The other major finding of this study has been the high proportion of pathological upstaging (48%) and the surpris-

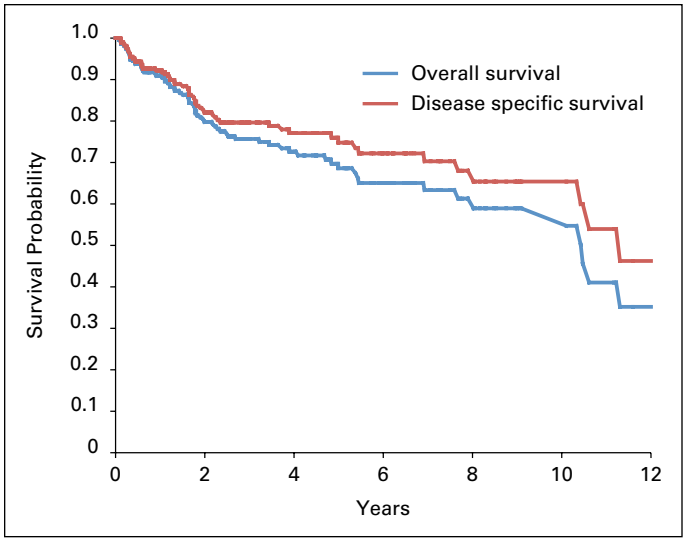

Fig. 1. Disease-specific survival and overall survival rates.

ingly high proportion of patients with positive lymph nodes (20%) at the time of radical cystectomy. This has been a common finding in the last 2 decades, despite improvements in the imaging used; similar findings have been previously reported.[9,11] The high rate of pathological upstaging, along with the low rate of adjuvant chemotherapy, are possible explanations for the overall low survival rate. Unlike earlier studies, we did not find CIS to be an independent predictor of OS or DSS.[7,12] One possible reason for this discrepancy is that previous studies which have noted this observation have been smaller; other possible reasons include inaccurate initial staging on our part or possibly more widespread usage of random bladder biopsies prior to radical cystectomy at other institutions.

The reasons for the high proportion of tumour and nodal upstaging are likely to be the same reasons for which survival is not optimal in the published literature and in our study among patients with clinical T1 disease. Selection bias is a possible reason that would account for these findings, as invariably the patients who undergo radical cystectomy for non-invasive disease are those who have failed intravesical therapy, and so may represent a biologically more aggressive cohort. Also, most of the studies are from university centres, which may also get patients who have higher risk disease. Other possible reasons include delay in definitive treatment due to the usage of multiple trials of intravesical therapy, variation in pathological reporting of transurethral biopsy specimens, variation in the usage of clinical staging modalities (such as computer tomography [CT] scanning) for patients with T1 disease, under-utilization of repeat transurethral resection to ensure accurate initial local staging, and clinician and patient complacency with regards to the lethality of the disease process.

We feel that the external validity of this study is high for Western countries, as the sampled patient population is likely to be broadly representative of the target population, as this is not a single institution or single province study. This is one of the strengths of a multi-institutional database across geographically diverse areas of Canada. However, the results are not generalizable to areas where squamous cell cancer of the bladder is highly prevalent, such as Egypt.

As with any multi-institutional retrospective cohort, there are a number of limitations in our study which need to be acknowledged. The number of previous endoscopic resections or intravesical therapies is not known for our cohort, and the variation in intravesical therapy usage across Canada was not recorded in this database. Routine repeat transurethral resection was not standard practice in the early part of this series. There was no centralized pathological review of the initial biopsy or of the subsequent cystectomy specimen, and data collection was incomplete for some variables. The definitions of some variables, for instance extended pelvic lymph node dissection, was based on the surgeon's description of the procedure, rather than on the number of nodes collected or the template used.

A prospective community or registry based cohort study, including all patients with an initial diagnosis of clinical T1 disease, would be very useful to clarify the overall mortality for this group of patients, although it would need a sufficient long time frame to provide meaningful results. Given the findings from our study and those of earlier studies, the role of neoadjuvant chemotherapy for patients with clinical T1 disease undergoing radical cystectomy needs to be addressed as a possible method to improve survival. The usage of early radical cystectomy, as compared to intravesical immunotherapy or repeat intravesical therapy,[13] also needs to be addressed in a randomized trial. Until then, the dilemma remains for clinicians when attempting to identify which patients with clinical T1 disease will benefit most from early radical cystectomy. Possible factors warranting further study to identify these patients include the presence of lymphovascular invasion in the biopsy specimen,[14,15] the use of histological substaging of the transurethral biopsy specimen,[11] the presence of urethral involvement[16] and divergent histology,[16,17] size and number of T1 lesions,[11] and the presence of de-novo/primary clinical T1G3 disease.[18]

Other implications from this study are the issue of clinical staging for patients initially diagnosed with T1 disease, and the need for better diagnostic methods to identify those patients with T1 disease who would be better served by immediate cystectomy. Current guidelines, such as those from the National Comprehensive Cancer Network (NCCN),[19] recommend staging studies such as CT or magnetic resonance image scanning in patients with muscle invasive disease. Consideration should be given to extending this recommendation to patients with newly diagnosed T1 disease as well, as radiographic features such as perivesical

stranding, thickening of the bladder wall and the presence of hydronephrosis[20] will alert the clinician to the possible presence of higher stage disease. Newer imaging modalities, such as fludeoxyglucose-positron emission tomography/CT, warrant further study in the subgroup of patients with newly diagnosed clinical T1 disease.[21]

Conclusion

This study has confirmed that patients undergoing radical cystectomy for clinical T1 disease have a high proportion of both pathological upstaging and lymph node metastases, and should be added to the counselling information provided to patients considering bladder preservation strategies with immunotherapy. Consideration should be given to offering patients early radical cystectomy, as salvage is by no means certain for patients with clinical T1 disease. Further studies are needed to identify patients who should proceed directly to radical cystectomy, as opposed to receiving intravesical immunotherapy.

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Competing interests: None declared.

This paper has been peer-reviewed.

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