Natural history of pT3-4 or node positive bladder cancer treated with radical cystectomy and no neoadjuvant chemotherapy in a contemporary North-American multi-institutional cohort

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Abstract

Background: The present study documents the natural history and outcomes of high-risk bladder cancer after radical cystectomy (RC) in patients who did not receive neoadjuvant chemotherapy during a contemporary time period.

Methods: We analyzed 1180 patients from 1993 to 2008 with ≥pT3N0 or pT0-4N+ bladder cancer who underwent RC ± standard (sLND) or extended (eLND) lymph node dissection from 8 Canadian centres.

Results: Of the 1180 patients, 55% (n = 643) underwent sLND, 34% (n = 402) underwent ePLND and 11% did not undergo a formal LND. Of the total number of patients, 321 (27%) received adjuvant chemotherapy. The median follow-up was 2.1 years (range: 0.6 to 12.9). Overall 30-day mortality was 3.2%. Clinical and pathological stages T3-4 were present in 6.1% and 86.7% of the patients, respectively; this demonstrates a dramatic understaging. Overall survival (OS) at 2 and 5 years was 60% and 43%, respectively. Patients who received adjuvant chemotherapy had a 2- and 5-year disease-specific survival (DSS) of 72% and 57% versus 64% and 51% for those who did not (log-rank $p = 0.0039$). The 2- and 5-year OS for high-risk node-negative disease was 67% and 52%, respectively, whereas for node-positive patients, the OS was 52% and 32%, respectively ($p < 0.001$). The OS, DSS and RFS for patients with pN0 were significantly improved compared to those who did not undergo a LND (log-rank $p = 0.0035$, 0.0241 and 0.0383, respectively).

Interpretation: This series suggests that bladder cancer outcomes in advanced disease have improved in the modern era. The need for improved staging investigations, use of neoadjuvant chemotherapy and performance of complete LND is emphasized.

Introduction

An estimated 77 630 new bladder cancer diagnoses and 20 188 deaths will occur in the United States and Canada in 2010.[1] Most new cases will be lower grade and stage but 20% to 40% will present or progress to muscle invasive disease. Up to 50% of these patients will harbour metastases.[2,3] Radical cystectomy (RC) and bilateral pelvic lymph node dissection (PLND) have become the standard treatment option over the past 30 years with 30-day overall mortality of 1.5% to 2% and morbidity ranging from 30% to 64%.[2,4] All major publications of RC series include patients treated prior to 2005.[5] Most of these publications do not specifically address the natural history of high-stage or lymph-node positive patients. Very few studies have assessed the impact of whether overall bladder cancer treatment during this time period has actually improved outcomes. Population-based retrospective studies suggest, at least in males, that there has been a 5% reduction in cancer-specific death from 1990 to 2006.[1] This improvement is modest at best. The present study aims to document the natural history and outcomes of high-stage (pT3-4) and/or node positive bladder cancer after surgical therapy in the modern era in those patients who did not undergo neoadjuvant chemotherapy. Subgroup analysis attempts to identify the role of adjuvant chemotherapy, as well as the effect of node-positive disease on survival.

Patients and methods

Between 1993 and 2008, 1180 patients underwent RC with curative intent for pT3-4 N0-3 or pT0-4 N1-3 urothelial carcinoma of the bladder in 8 Canadian centres. These

patients did not receive neoadjuvant chemotherapy. After Institutional Research Board (IRB) approval, clinical and pathological information was obtained. Of the total number of patients, 74% (874/1180) were treated after 2005. The median follow-up was 2.1 years (range: 0.6 to 12.9). Clinical staging was obtained from preoperative cross sectional imaging (computed tomography scan or magnetic resonance imaging) to rule out metastases and pathologic staging was performed according to 1997 TNM classification and grading according to the 2004 WHO system.[6,7]

The indications for cystectomy included muscle invasive and/or intravesical therapy refractory bladder cancer. Overall, 75.4% of patients had high-grade bladder tumours. The extent and performance of a lymph node dissection (LND) was physician- and institution-dependent. Standard LND (sLND) boundaries were defined as distally the circumflex vein and the node of Cloquet, laterally the external iliac artery, medially the bladder and prostate and proximally the internal iliac (hypogastric) artery. Extended LND (eLND) included a farther dissection proximally to include nodal tissue to the bifurcation of the aorta and laterally to the genitofemoral nerve. All patients were referred to medical oncology for consideration of adjuvant chemotherapy. The details of regimens received were not available.

The analysis of clinical and pathological categorical variables was performed using Fisher and chi-squared tests. Kaplan-Meier curves were used to estimate the overall survival (OS), recurrence-free survival (RFS) and disease-specific survival (DSS) of all patients and for subgroups classified according to nodal status and whether adjuvant chemotherapy was received. Multivariate analysis was performed according to the Cox proportional hazard regression model. A p value of less than 0.05 was considered statistically significant. All analyses were performed using the SAS version 9.1.3 Service Pack 4, windows platform (SAS Institute Inc., Cary, NC).

Results

The overall male-to-female ratio was 3.3:1. Median patient age was 69 years. Mean Charlson comorbidity score was 4.9. Most patients underwent a sLND (55%, n= 643), whereas 34% (n = 402) underwent eLND. Only 11% of patients did not undergo a formal LND. Of the total 1180 patients, 321 (27%) received adjuvant chemotherapy, whereas 859 (73%) did not. A further 91 (9%) received salvage/palliative chemotherapy (Table 1).

The pathological stages of the RC specimens were mainly pT3-4 (85%), demonstrating a very significant clinical understaging due to most patients being clinical stage T2 (75%). A significant number of cases, however, did not have a cT stage assigned (32%). Thirty-four percent of patients were stage pN1-3 with a median number of 8 positive nodes.

Table 1. Clinical and pathological characteristics in 1180 patients who underwent radical cystectomy for bladder urothelial carcinoma

	No. patients	Percent
Clinical characteristics		
Sex		
Female	266	22.5
Male	914	77.5
Clinical tumour stage		
cTis	16	1.4
cTa	13	1.1
cT1	104	8.8
cT2	596	50.5
cT3	35	3.0
cT4	36	3.1
Missing	380	32.2
Clinical nodal stage		
cN0	456	38.6
cN1	15	1.3
cN2	2	0.2
cNX	166	14.1
Not recorded	541	45.8
Clinical carcinoma in situ		
Positive	346	29.5
Negative	590	50.0
Missing	244	20.7
Clinical tumour grade		
Low	193	24.6
High	785	75.4
Pathological characteristics		
Surgical technique		
No PLND	123	10.5
Standard PLND	643	55.1
Extended PLND	402	34.4
Final tumour stage		
pT0	18	1.5
pTa	6	0.5
pTis	13	1.1
pT1	23	1.9
pT2	83	7
pT3	699	59.2
pT4	325	27.5
Not recorded	13	1.1
Final nodal stage		
pN0	578	49
pN1	231	19.6
pN2	233	19.7
pN3	19	1.6
pNX	116	9.8
Not recorded	3	0.3
Surgical margin		
Negative	1037	87.9
Positive	129	12.1
LVI		
Negative	540	45.8
Positive	390	54.2

PLND: pelvic lymph node dissection; LVI: lymphovascular invasion.

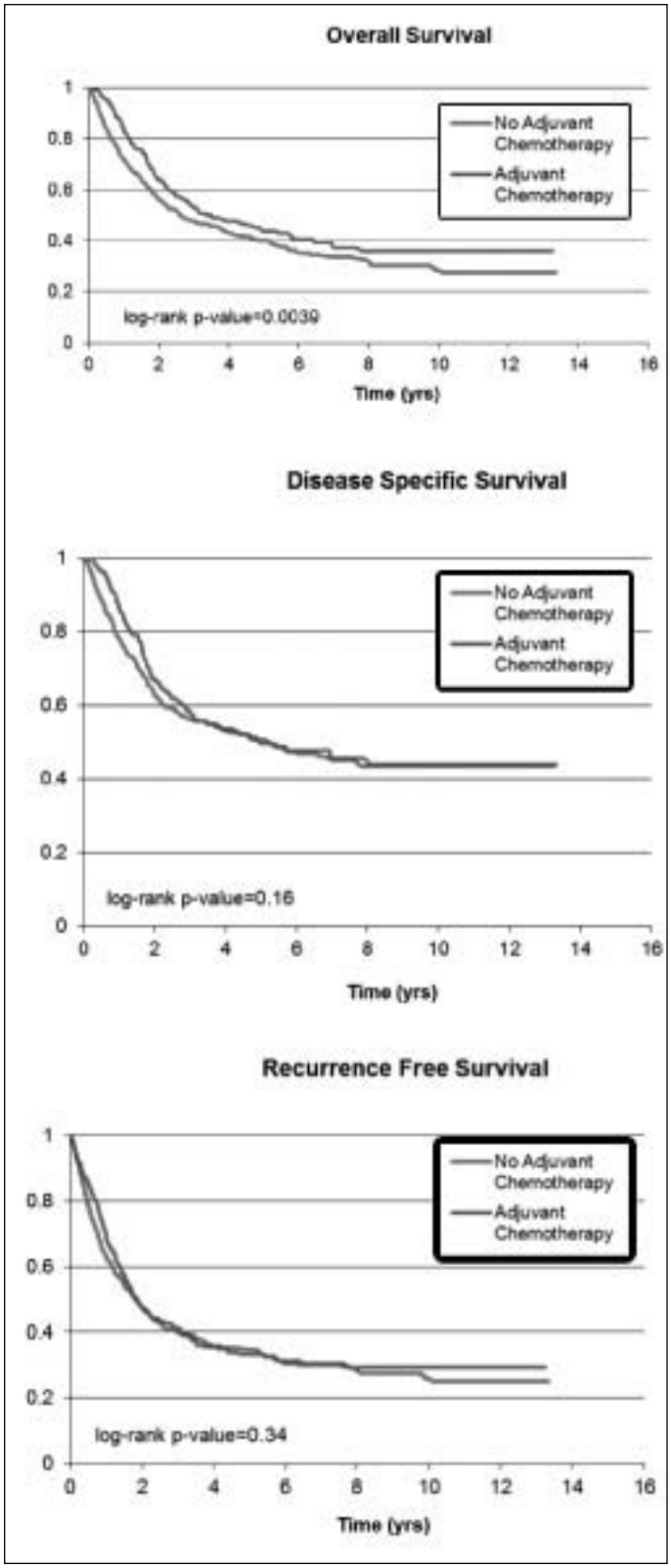

Fig. 1. Kaplan-Meier estimates of overall, disease-specific and recurrence-free survival probabilities in patients treated with radical cystectomy according to the use of adjuvant chemotherapy.

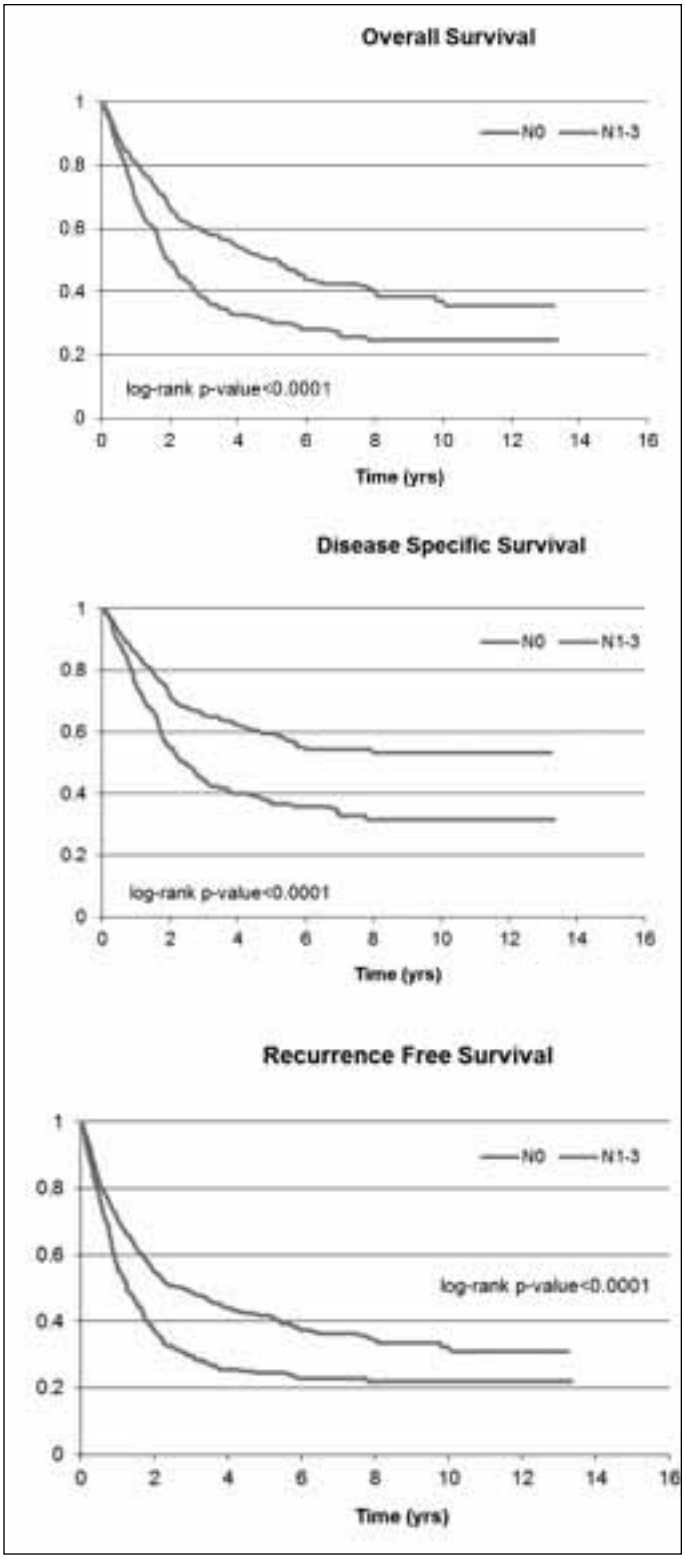

Fig. 2. Kaplan-Meier estimates of overall, disease-specific and recurrence-free survival probabilities in patients treated with radical cystectomy according to pathologic lymph node status.

Table 2. Multivariate Cox regression analysis of clinical and pathological characteristics for predicting overall survival, disease-specific survival, recurrence-free survival in 1180 patients treated with radical cystectomy for bladder urothelial carcinoma

	Overall survival			Disease-specific survival			Recurrence-free survival		
	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value
Age	1.01	1.00 – 1.02	0.08	1.00	0.99 – 1.02	0.50	1.01	1.00 – 1.02	0.04
LND									
Standard LND		Referent			Referent			Referent	
No LND	1.46	0.88 – 2.43	0.15	1.57	0.89 – 2.75	0.12	1.39	0.85 – 2.27	0.20
Extended LND	1.07	0.85 – 1.36	0.55	1.23	0.94 – 1.59	0.12	1.03	0.83 – 1.29	0.80
Pathological stage									
≤T2		Referent			Referent			Referent	
>T2	3.19	1.40 – 7.24	0.01	2.89	1.17 – 7.12	0.02	2.81	1.31 – 6.01	0.01
Pathological nodal status									
pN0	Referent	Referent	Referent						
pN1-3	2.07	1.67 – 2.57	<0.01	2.15	1.68 – 2.74	<0.01	1.85	1.51 – 2.26	<0.01
No. nodes +	1.00	0.98 – 1.01	0.01	0.99	0.98 – 1.01	0.42	1.00	0.98 – 1.01	0.71
Grade	0.85	0.58 – 1.26	0.43	0.88	0.57 – 1.36	0.57	0.83	0.57 – 1.20	0.32
Margins	1.70	1.29 – 2.25	<0.01	1.95	1.44 – 2.64	<0.01	1.52	1.17 – 1.98	<0.01
Adjuvant chemotherapy	0.53	0.42 – 0.68	<0.01	0.55	0.42 – 0.71	<0.01	0.64	0.51 – 0.79	<0.01
Salvage chemotherapy	1.46	1.09 – 1.95	0.01	1.79	1.32 – 2.42	<0.01	2.31	1.79 – 2.98	<0.01

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

Clinical staging suggested that only 3% were positive. The surgical margins were positive in 12.1% of the cases, but these included ureteral, urethral and soft tissue margins, not delineated during initial data collection (Table 1).

The 2- and 5-year OS was 60% and 43%. The RFS was 50% and 36% at 2 and 5 years, respectively. The 2- and 5-year DSS was 67% and 53%, respectively. Univariate analysis identified increased age, higher Charlson score, node positive disease, positive surgical margin (SM), lymphovascular invasion (LVI) and administration of salvage chemotherapy as significant factors contributing to worse OS, RFS and DSS. On multivariate analysis, patients with lower pT and pN stages, negative SMs, salvage chemotherapy and adjuvant chemotherapy experienced better OS, RFS and DSS (Table 2).

The subset analysis for patients that received adjuvant chemotherapy identified significant differences between the groups. Those who were more likely to receive adjuvant chemotherapy had lower age, pathologic high grade disease, LVI, eLND, lower Charlson comorbidity score, higher number of nodes positive, higher pT stage ($p = 0.05$), higher pN stage and positive SM (all p<0.001 unless stated otherwise). The Kaplan-Meier analysis for adjuvant chemotherapy versus no adjuvant chemotherapy failed to show improvement in DSS (log-rank $p = 0.16$) and RFS (log-rank $p = 0.34$) but did show a significant improvement in OS (log-rank $p = 0.0039$) (Fig. 1).

Nodal status survival was also analyzed separately. For pT3-4 node negative disease, the 2 and 5 year OS was 67% and 52%, RFS was 56% and 43%, and DSS was 73% and 61%, respectively. For node-positive disease, the 2- and 5-year OS was 52% and 32%, RFS was 39% and 25%, and DSS was 58% and 40%, respectively. Overall, node-negative patients had a significantly better OS, RFS and DSS than node-positive (log-rank $p < 0.001$) (Fig. 2).

By comparing pN0 patients (having either standard or extended LND) to pNX patients who did not undergo a LND, a significantly improved survival was found in OS, DSS and RFS (log-rank $p = 0.0035$, 0.0241 and 0.0383, respectively) (Fig. 3).

Discussion

A recent review by Lerner highlights the major publications addressing the role and extent of LNDs in bladder cancer.[5] All of these series from high-volume tertiary care centres do not include any patients treated after 2005, with most patients treated before 2002. In contrast, this current study is comprised mostly (71.4%) of patients who were treated after 2005. No patient underwent neoadjuvant chemotherapy. The present study provides a realistic cross-section and contemporary analysis of patients undergoing RC and LND with curative intent who ultimately are found to have high tumour stage or positive lymph node involvement in their pathological specimens. It highlights the poor accuracy of clinical staging and emphasizes the need for consideration of neoadjuvant chemotherapy to improve outcomes. From this series, adjuvant chemotherapy is suggested to be of benefit

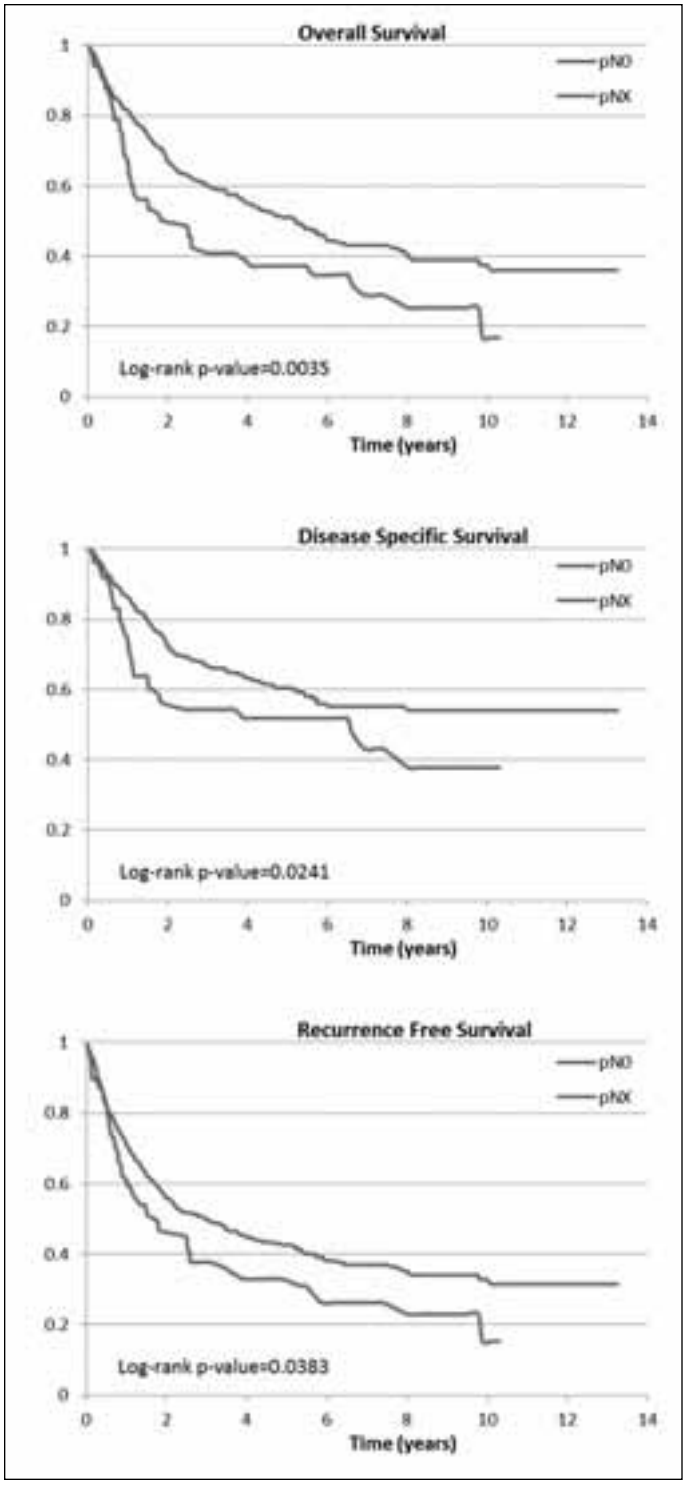

Fig. 3. Kaplan-Meier estimates of overall, disease-specific, and recurrence-free survival probabilities in patients with lymph node-negative disease versus those who did not undergo lymph node dissection.

in terms of OS, however, the patient subsets are significantly different. Therefore, this makes interpreting results difficult. Pathologic node negative disease appears to portend a better prognosis, although the extent of LND varies significantly. It does seem that there are improved outcomes over time when comparing this cohort with traditional publications. The value of this series is its description of a true, modern era, large general population of how high metastatic risk bladder cancer patients fare when they do not receive neo-adjuvant chemotherapy. This description aids both in counselling patients and in identifying quality care improvement possibilities within the urological community.

The cited male-to-female ratio for all bladder cancer cases for 2010 is 2.9:1, whereas for our series it is 3.3:1.[8] This suggests that not only are males at an increased risk for bladder cancer, they are at even higher risk of having unsuspected advanced disease.

Most patients prior to RC had clinically localized disease with cT1-2 tumours (91%) and cN0 (71%). This contrasts greatly with postoperative findings (87% pT3-4 and 41% N1-3) emphasizing the drastic understaging that occurs. Despite 32% missing clinical staging, as many as 79% of patients were upstaged at surgery in T stage category alone. For all bladder cancer patients, the rate of upstaging cited in the literature is 31% to 50%.[9,10] These figures, at a minimum, underscore the need for improved staging techniques, particularly in this subset of patients with high-risk disease.

The overall 30-day mortality is similar to published reports (3.4%),[2,4] however, the Charlson comorbidity scores in the present series provide a sobering view of the typical high overall 1-year mortality rate. For instance, with the current series average age of 67.3 years and an average Charlson comorbidity score of 4.9, the original Charlson literature cited an estimated 59% 1-year mortality for a similar general hospitalized population.[11,12] The age-adjusted Charlson comorbidity index (AACI) predicts 1-year mortality as high as 88%. The actual 1-year mortality rate for our highly selected subset capable of undergoing a physiologically complex operation is 29%. More recently, investigators at Memorial Sloan-Kettering Cancer Center cited a dismal 1.7-year median OS in patients with AACI of >5 undergoing RC for clinically localized bladder cancer (the average AACI for the present series is calculated as 7.6).[13] Their article suggests, however, that RFS is significantly underestimated in this patient population due to the large number of censoring occurring secondary to competing causes of death. Prout and colleagues examined the SEER database and found that older patients with more comorbidity were less likely to undergo RC, even in the presence of invasive disease.[14] This tendency to defer definitive therapy may account for the association of higher comorbid disease with more advanced stages of bladder cancer observed in the present cohort.

The long-term results from radical cystectomy patients from 1971 to 1997 by Stein and colleagues from the University of Southern California provide a temporal comparison for our 1993-2008 cohort.[2] In this study, Stein and

colleagues found that the 5-year RFS and OS in extravesical node-positive patients was 30% and 25%, respectively.[2] The 5-year RFS and OS from this current series are 39% and 52%, respectively. Similar rates of adjuvant chemotherapy were used (26% for Stein and colleagues[2] and 27% for the present series). Considering the slightly different patient study subsets, the outcomes appear to have improved over time. Using SM status as a surrogate marker for quality of surgery, the 12.1% positive SM rate here is lower than published literature that suggests 12.3% to 15% as a threshold.[15,16]

The extent of PLND and its therapeutic role in bladder cancer is debatable. Suffice it to say that the presence of LN metastasis is one, if not the most, important prognostic indicator for RFS and OS in patients undergoing RC for clinically localized disease.[17,18] This is certainly revealed in the improved OS, DSS and RFS for patients with node-negative disease in the present series. It must be conceded, however, that the variability of ePLND (34%) and sPLND (55%) performance clouds interpretation. On a positive note, only 10.5% of the present overall cohort had no formal PLND. The authors agree a LND should be performed in all patients; our rate is an improvement over United States Surveillance, Epidemiology and End Results (SEER) database trends over time; this SEER database showed that 37% of patients had no PLND in 1988; this number decreased over time to 16% in 2004.[19] On average, the present Canadian cohort had a better overall PLND rate. Interestingly enough, the performance of a PLND and the number of positive nodes were not significantly associated with improved RFS, OS or DSS in any of the present multivariate models. This suggests that with advanced bladder cancer, the role of PLND may only serve prognostic value and not infer any therapeutic benefit. However, when we compared those patients who were pN0 to those patients who did not undergo LND, there was a statistically significant improvement in OS, DSS and RFS on univariate analysis. Due to the unknown nodal staging of the comparison group, it is difficult to extrapolate a therapeutic benefit, but this does, again, stress the importance of performing the LND.

Neoadjuvant chemotherapy has Level 1 evidence to support its use. Cisplatin-based regimens followed by RC and PLND improve OS by 4% to 6%, according to the major publications.[20,21] Adjuvant chemotherapy in high-risk bladder cancer is much more contentious. Trials thus far have lacked methodological rigor and robust patient numbers.[22-25] Despite criticisms, many of the individual trials do show a statistically significant survival improvement. The present series revealed that most patients with high-risk bladder cancer (73%) did not receive adjuvant chemotherapy. One reason is decreased renal function in older patients with increased comorbidities. Dash and colleagues determined that 40% of patients >70 years old postoperatively from RC were rendered ineligible to receive cisplatin-based chemotherapy (based on a lower limit creatinine clearance of 60 cc/min/1.73m^2).[26] Another, less quantifiable reason, is individual surgeon practice.

The decision to offer adjuvant chemotherapy has a number of competing aspects. Patients who received adjuvant chemotherapy in this cohort were significantly younger and healthier ($p < 0.001$), however they still averaged a poor mean Charlson comorbidity score overall (4.3, SD 1.4). Extended PLND was also associated with receiving adjuvant chemotherapy and reflects an increased chance of finding occult metastases with a more extensive dissection. Improved RFS, OS and DSS, however, were shown in multivariate analysis only in patients receiving adjuvant chemotherapy. Overall survival in Kaplan-Meier analysis was also significantly improved. The discrepancy that arises of adjuvant chemotherapy being non-significant on univariate Kaplan-Meier analysis (but significant in multivariate analysis) may be explained due to selection bias favouring adjuvant chemotherapy and inherent biases of pooled cohorts. Indeed, our cohort demonstrates that 51% (245 patients) of LN+ patients versus only 19% (108 patients) of LN negative patients received adjuvant chemotherapy. From clinical experience, adjuvant chemotherapy is offered mostly to patients with lymph node positive disease after surgery. Therefore, the favourable effect of adjuvant chemotherapy may be counteracted by the higher risk patient population receiving it. When the nodal stage was added to the multivariate model, adjusting for correlations between the variables, adjuvant chemotherapy obtained significance. We attempted to perform a time-dependent analysis to account for immortal time bias,[27] another potential confounder that can explain this discrepancy in cohort analysis, but the dates of receipt of chemotherapy were not collected in the original dataset. It remains to be determined in prospective, randomized clinical trials whether the improved RFS, OS and DSS were due to the adjuvant chemotherapy or the population characteristics.

The limitations of this retrospective study include the 15-year time span where numerous facets of bladder cancer treatment evolved, both on the surgical and medical oncology fronts. The high rate of positive SM is an issue as rates of soft tissue SM are reported from 2% to 6% in major published series.[15] This major limitation may be explained due to the data collection that did not differentiate between soft tissue, ureteral and urethral margins. The limited median follow-up time, explained by most patients being treated after 2005, is too short to capture all events. Also, there was no central pathological review of all surgical specimens, therefore analyses of lymph node density on various outcomes was not possible, and no data was available regarding type of urinary diversion.

Conclusion

This large, contemporary series suggests that bladder cancer outcomes in advanced disease have improved over time. It also suggests areas requiring quality improvement. The need for improved staging investigations, use of neoadjuvant chemotherapy and performance of complete lymph node dissections is highlighted in the current series. Adjuvant chemotherapy is shown to improve survival outcomes in multivariate analysis, but patient characteristics introduce significant bias. Node-positive disease remains a poor prognostic indicator.

Competing interests: None declared.

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