

An analysis of preoperative delays prior to radical cystectomy for bladder cancer in Quebec

Nader Fahmy, MD;* Wassim Kassouf, MD;* Suganthiny Jeyaganth, MS;* Moamen Amin, MD;* Salaheddin Mahmud, MD;† Jordan Steinberg, MD;* Simon Tanguay, MD;* Armen Aprikian, MD*

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Abstract

Background: The province of Quebec has the highest incidence of urothelial tumours in Canada. Radical cystectomy remains the standard treatment for invasive bladder cancer. We have previously observed that prolonged delays between transurethral resection of bladder tumour (TURBT) and radical cystectomy lead to worse survival in Quebec.

Objective: The aim of our study was to characterize the various periods of delay sustained by bladder cancer patients before radical cystectomy across Quebec and to determine their relation to survival.

Methods: We obtained the billing records for all patients treated with radical cystectomies for bladder cancer across Quebec from 1990 to 2002. Collected information included patient age and sex; dates of family physician (FP) and specialist visits with accompanying diagnoses; dates of cystoscopy, TURBT and CT scanning; surgeon age; surgical volume and dates of death.

Results: We analyzed a total of 25 862 visits for 1633 patients. Median diagnostic delays from FP to specialist, then to cystoscopy, then to TURBT and finally from TURBT to CT were 20, 11, 4 and 14 days, respectively, over the entire study period. Median overall delay from FP visit to radical cystectomy was 93 days. In addition, median FP to radical cystectomy delay progressively increased from 1990 to 2000 from 58 to 120 days ($p < 0.01$). Multivariate analyses showed that patients with an overall delay of either < 25 or > 84 days had a 2.1 and 1.4 times increased risk of dying, respectively ($p \leq 0.01$).

Conclusion: Preoperative delays have been progressively increasing over time. Overall, delays from FP to radical cystectomy of < 25 and > 84 days may translate into worse outcomes. Poor survival in cases with < 25 days delay may be attributed to case selection, with more advanced cases being managed much quicker. Poor survival in cases with delays of > 84 days may be attributed to disease progression while awaiting completion of management.

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Introduction

Bladder cancer is the sixth most common cancer in Canada, the eighth most common cause of cancer death in males and the thirteenth in

females.¹ About one-half of people with muscle-invasive bladder tumour have occult metastases at presentation, which reflects the aggressive nature of these tumours.² Hence, it is preferable to avoid delays in definitive treatment once a diagnosis of invasive cancer has been made. Unfortunately, delays are sometimes unavoidable because of patient^{3,4} or health provider factors.⁵

Delays related to access to medical care have become a major concern in Canada. In Quebec, for all specialties combined, the median wait time from family physician (FP) referral until treatment more than doubled between 1993 and 2004, rising from 7 to 18 weeks. Median delays that are specifically related to urology have also increased by 5 weeks in 12 years.⁶ Several studies, including 1 from Quebec, have suggested that delays greater than 3 months between transurethral resection of bladder tumour (TURBT) and radical cystectomy were significantly associated with worse clinical outcome and mortality.^{3,4,7-11} However, bladder cancer patients may be subjected to significant delays before TURBT for several reasons, including patients seeking additional advice, sick patients requiring medical optimization, delayed FP referral, delay in seeing a urologist and delay in obtaining investigations such as cystoscopy and imaging. To date, only a few publications included delays before TURBT in their outcome analyses.¹²⁻¹⁵ However, it is difficult to draw conclusions from these studies because of diverse study cohorts, different treatment protocols and lack of population perspective. Therefore, the

objectives of our study were to characterize and measure the contribution of the different components of delay experienced by bladder cancer patients before radical cystectomy in Quebec, to identify predictors of longer delays and to determine the impact of the various components of delay on mortality.

Methods

Study population

We obtained complete billing records for 1633 patients who underwent radical cystectomy for bladder cancer in Quebec between 1990 and 2002 from the Quebec provincial database of physician fee-for-service claims (Régie de l'Assurance Maladie du Québec). Data received included patient age and sex, patient vital status and date of death, dates of FP and specialist visits, diagnoses coded using the International Classification of Diseases (ICD-9-CM) in each visit, dates of relevant diagnostic and therapeutic procedures (cystoscopy, TURBT, intravesical therapy, CT and radical cystectomy), anonymous unique identifier, age group of the urologist who provided the service and hospital name. The data set excluded patients aged less than 18 years and those preceded by any neoadjuvant therapy.

We measured several components of delay for each patient. Period 1 (FP or referral delay) is defined as the period from the first FP (office or emergency) visit where a diagnostic code associated with a bladder tumour (e.g., hematuria, cystitis) was recognized, until the first urologist visit. Period 2 (cystoscopy delay) is the period from the first urologist visit until the first cystoscopy. Period 3 (TURBT delay) is the period from the most recent cystoscopy until the first TURBT. Period 4 (imaging delay) is the period from the most recent TURBT until the date of CT imaging. To allow comparison with other reports we also examined the following: period 5 (diagnostic delay), defined as the period from the first urologist visit to CT imaging; period 6 (radical cystectomy delay), defined as the period from the first cystoscopy to the radical cystectomy; and period 7 (overall urologist delay), defined as the period from the first urologist visit to the radical cystectomy. We then integrated all delay periods together and examined

period 8 (overall delay), defined as the period from the first FP visit to the radical cystectomy (Fig. 1).

For some patients, visits did not follow the chronological order shown in Figure 1. These visits were excluded from the calculation of their respective delays. For example, patients who had a urologist visit before their FP visit were excluded from the period 1 (FP or referral) delay analysis.

To minimize the effects of outliers (patients with unusually long delays), we excluded patients in whom delays were longer than the upper quartile of the preoperative delay period plus 3 times the interquartile range.¹⁶ Because we lacked information on tumour stage, patients who had more than 1 TURBT more than 4 months apart were classified as having a history of superficial tumours. All patients who had a history of superficial disease according to this criterion were excluded from the analysis of delay periods 5 to 8.

Statistical analyses

Results were expressed as means and standard deviations (SDs). We first conducted both graphical (box plots) and statistical univariate analyses (Kruskal–Wallis test) to assess for the relationship between each delay variable and the following characteristics: patient sex, patient age, presence of hematuria, hospital radical cystectomy volume, surgeon radical cystectomy volume, surgeon age groups, and year, season and month of the tested procedure (cystoscopy, TURBT, CT or radical cystectomy). Using Cox regression and a stepwise modelling approach, variables with independent prognostic significance in relation to delay were identified and hazard ratios were generated for each variable.

To calculate overall survival in relation to delay,

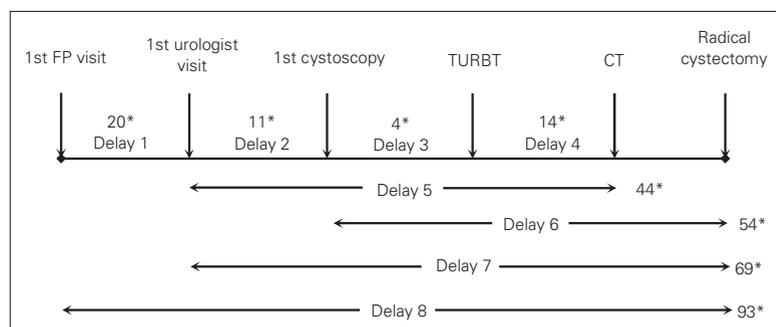


Fig. 1. Types of delays described and their median. FP = family physician; TURBT = transurethral resection of bladder tumour. *Median delay in days.

we excluded patients who died within 90 days after radical cystectomy since these patients are

more likely to have died because of operative complications. We then examined the association between various delay variables and overall survival computed from the date of the first FP visit to either the date of death or the date of censoring (Dec. 31, 2003). We used the Cox proportional hazards model with the shared frailty to assess the effect of preoperative delays on long-term survival. Models with shared frailty were used to allow for within-group correlation (among patients treated by the same surgeon). We assessed the assumption of proportional hazards for each of the covariates by examining graphs of scaled Schoenfeld residuals and by using appropriate statistical tests. All models were estimated using Stata 9 (Stata Corp., College Station, Texas).

Table 1. Univariate relation between delays and study characteristics

Variable	No. of patients, n = 866	Median delay, d (95% CI)	p value (Kruskal-Wallis test)
Period 1 (FP to urologist)			
Sex			
Female	273	29 (23–34)	< 0.001
Male	593	18 (15–21)	
Hematuria			
No	399	21 (19–24)	< 0.001
Yes	467	10 (4–20)	
Year of specialist visit			
1990–1995	376	18 (14–21)	0.008
1996–2002	490	23 (20–28)	
Period 3 (cystoscopy to TURBT)			
Sex			
Female	369	4 (3–6)	0.6
Male	930	4 (3–5)	
Hematuria			
No	94	4 (3–5)	0.25
Yes	1205	2 (1–5)	
Year of TURBT			
1990–1995	577	1 (1–1)	< 0.001
1996–2002	722	8 (7–8)	
Period 4 (TURBT to CT)			
Sex			
Female	323	11 (4–35)	0.12
Male	757	15 (4–36)	
Hematuria			
No	68	14 (4–36)	0.22
Yes	1012	8 (2–37.5)	
Year of CT			
1990–1995	504	8 (4–27.5)	0.01
1996–2002	576	19 (4–42)	
Period 8 (FP to radical cystectomy)			
Sex			
Female	209	96 (82–117)	0.81
Male	452	92 (84–104)	
Hematuria			
No	214	79 (62–93)	0.002
Yes	447	101 (91–114)	
Year of radical cystectomy			
1990–1995	307	75 (62–84)	< 0.001
1996–2002	354	115 (104–129)	

CI = confidence interval; FP = family physician; TURBT = transurethral resection of bladder tumour.

Results

Patient characteristics

The mean patient age was 66.4 (SD 10.1) years and the median age was 69 years. Male to female ratio was 2.6:1. A total of 25 862 visits were analyzed. Of the 1633 patients who had a radical cystectomy for bladder cancer included in this study, billing records revealed that 1288 (78.9%) patients had FP visits, 1360 (83.3%) had urologist visits, 1169 (71.6%) had CT and 1516 (92.8%) had TURBT. The overall 5-year survival rate was 51%. Table 1 illustrates the relation of various parameters to individual preoperative periods in univariate analysis.

Variables affecting each delay type

Period 1 (FP to urologist)

The number of patients who had complete information allowing for calculation of this period was 866. The median delay was 20 days (range 0–231 d). In the multivariate analysis, the odds of having delays shorter than 20 days were significantly associated with male sex (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.48–0.87, $p = 0.005$), or with the presence of hematuria (HR 0.55, 95% CI 0.34–0.75, $p < 0.001$). Patients seen by a urologist after 1995 were significantly associated with longer delays (HR 1.38, 95% CI 1.05–1.83, $p = 0.02$).

Period 2 (urologist to cystoscopy)

The number of patients who had complete information for this period was 720. The median delay was 11 days (range 0–128 d). This delay had no correlation with any patient or provider characteristics.

Period 3 (cystoscopy to TURBT)

The number of patients who had complete information for this period was 1299. The median delay was 4 days (range 1–57 d). Multivariate analyses showed that the odds of having greater delays significantly correlated with TURBT performed after 1995 (HR 4.03, 95% CI 3.17–5.14, $p < 0.001$).

Period 4 (TURBT to CT imaging)

The number of patients who had complete information for this period was 1080. The median delay was 14 days (range 1–189 d). Multivariate analyses revealed that delays longer than 14 days were significantly associated with CT performed after 1995 (HR 1.95, 95% CI 1.44–2.64, $p < 0.001$).

Periods 5, 6 and 7

These periods had no independent correlation with any variable. However, it was observed that these median delays significantly increased with time (Fig. 2).

Period 8 (FP to radical cystectomy)

The number of patients who had complete information for this period was 661. The median delay was 93 days (range 11–307). Multivariate analysis showed that delays shorter than 93 days were significantly associated with male sex (HR 0.65, 95% CI 0.48–0.87, $p = 0.005$), the presence of hematuria (HR 0.50, 95% CI 0.34–0.75, $p < 0.001$) or urologists aged > 59 years (HR 0.25, 95% CI 0.09–0.65, $p = 0.005$). Radical cystectomies performed after 1995 were significantly associated with increased risks of been delayed more than 92 days (HR 1.38, 95% CI 1.05–1.83, $p = 0.022$).

Overall survival

Period 8 and overall survival ($n = 491$) are shown in

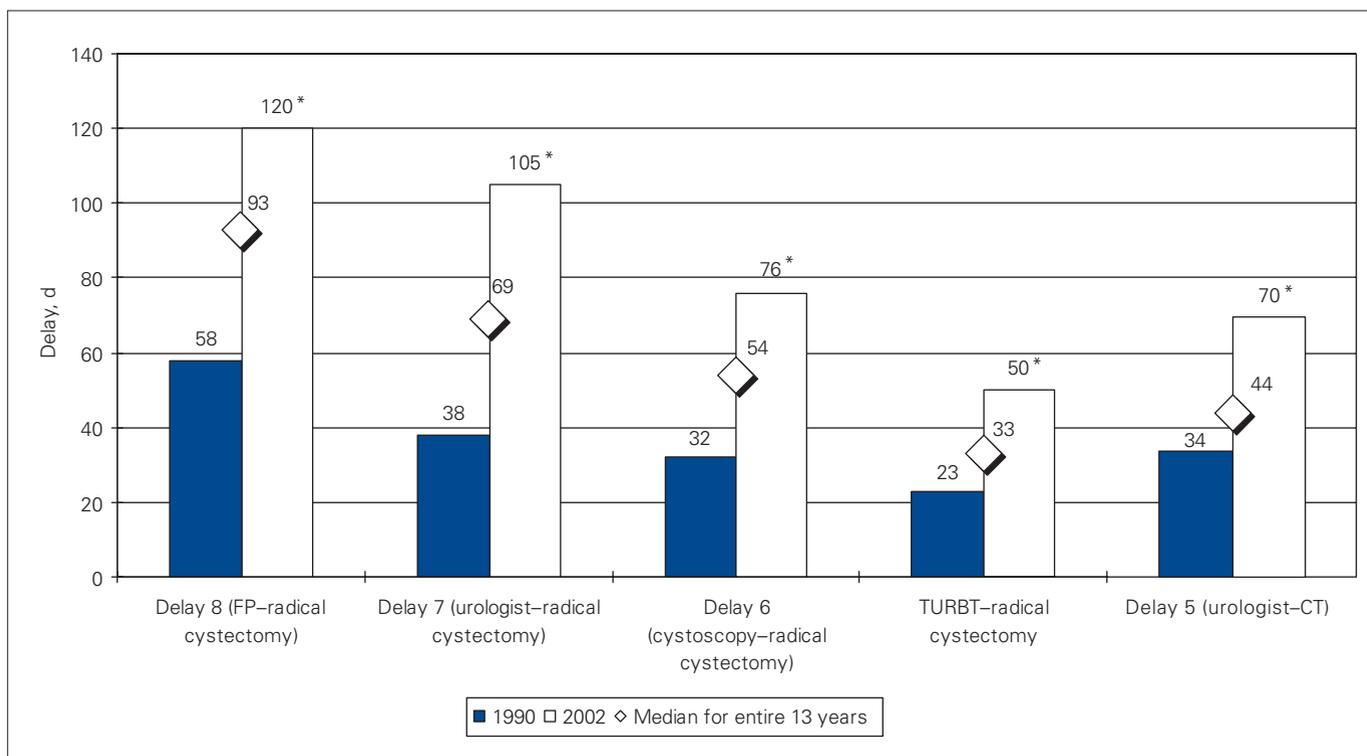


Fig. 2. Median delays investigated. FP = family physician. * $p = 0.01$.

Figure 3. Multivariate survival analyses have shown a significantly increased risk of overall mortality associated with patients who were aged > 69 years (HR 2.3, 95% CI 1.4–3.9, $p = 0.002$), patients who were delayed < 25 days (HR 2.1, 95% CI 1.3–3.3, $p = 0.001$) or those who were delayed > 84 days (HR 1.4, 95% CI 1.1–1.8, $p = 0.014$).

Discussion

Since invasive bladder tumours are known to possess an aggressive nature from the time of presentation, it is expected that delaying definitive therapy might lead to worse outcome. Only a few publications included delays before TURBT in their outcome analyses.^{12–15} These publications had important variations, including diverse studied cohorts, inconsistent durations and types of delays, variable treatments, dissimilar investigated end points and different statistical methods used. Moreover, these studies were not conducted in Canada.

Our study has demonstrated that bladder cancer

pretreatment delays have significantly increased over time in Quebec. A particularly long delay appears to occur between the FP visit and the urologist visit. The fact that younger age, female sex and absence of hematuria significantly correlated with longer delays could be in part due to the failure of the FP to appreciate the seriousness of the presenting symptom. Additionally, these delays might also occur in part because of difficulty in getting a timely urologist appointment. The second longest delay appears to be associated with prolonged CT scheduling that may be in part because of limited access to radiological resources.

Our analysis revealed that various delays were not associated with surgeon volume, surgeon age, hospital volume, the number of TURBTs, intravesical therapy, the season and the month of the procedure, or the type of diversion. In contrast, Hautmann and Paiss¹⁷ have shown that orthotopic bladders were significantly associated with shorter delays compared with ileal conduits.

Interestingly, ours is the first publication that studied the outcomes of delays from the FP visit

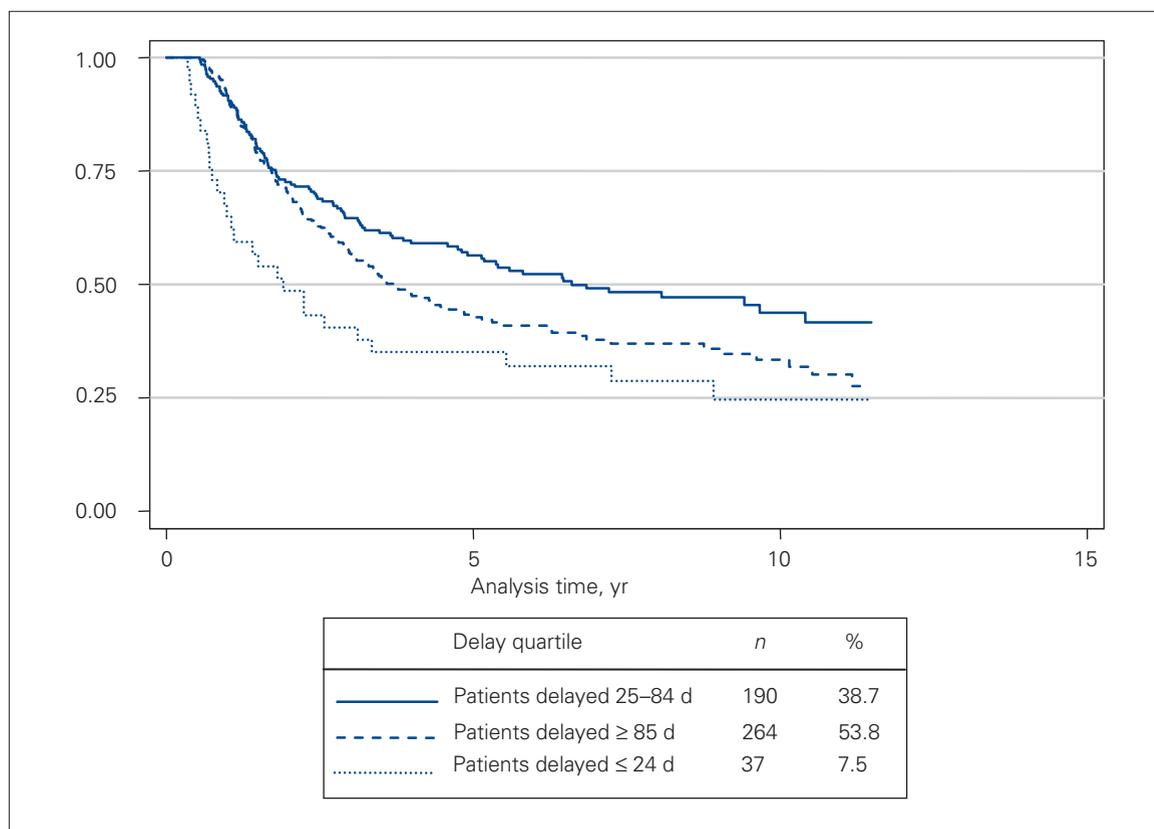


Fig. 3. Kaplan–Meier curves showing age adjusted overall survival of patients in relation to delays. $p = 0.014$.

until radical cystectomy that is not preceded by any neoadjuvant therapy. Few publications have investigated survival in relation to delays beyond the TURBT to radical cystectomy interval¹²⁻¹⁵ with significant variations among the reported delays, rendering comparison very difficult. Delays from the onset of symptoms to TURBT¹⁵ or to radiotherapy followed by radical cystectomy¹⁴ were not associated with a survival effect. These publications included patient delays that were based entirely on subjective assumptions. On the other hand, shorter delays from the first FP referral or first hospital appointment to TURBT^{13,15} or to radical cystectomy^{12,18} were associated with worse survival in some studies. The seemingly paradoxical worse survival associated with shorter delays was also noticed in our study where patients delayed ≤ 24 days had higher mortality. This could be explained in part by a selection bias, where patients with higher-stage disease could have been expedited to receive faster treatment and ultimately died earlier. Conversely, we also observed significantly worse survival in patients delayed > 84 days (12 wk). This observation may represent a true effect of disease progression while waiting for definitive therapy.

Causes for delays were reported in several studies^{3,4,9,10,14,19} and ranged from patient to provider factors. Some of these delays can be reduced by increasing patients' awareness about early symptoms of bladder cancer, such as hematuria; by stressing the importance of early referral by FPs, especially for elderly female patients with hematuria, persistent cystitis, or both^{14,19,20}; by initiating hematuria clinics, which have been shown to reduce delays caused by patient and FP factors²⁰⁻²³; and by addressing organizational and resource issues behind system or provider delays, or both.^{9,20,24}

Finally, it should be noted that delay is not the only prognostic factor. There are other important predictors of survival, including clinical and surgical factors that could not be evaluated in our study.

This was a retrospective study that was based entirely on billing records that lacked information on disease-specific survival, disease stage and grade. Our study also cannot be accurately used to assess the existence of comorbidities. In addition, many of the provided visits were not valid for delay interpretation. The major strengths of our

study lay in its provincial coverage and relatively large number of cases.

Conclusion

Bladder cancer pretreatment delays in Quebec have progressively increased over time. Younger age, female sex, the absence of hematuria and cystectomies performed after 1995 were significantly associated with longer delays between the FP visit and the radical cystectomy. Even though it is wise to encourage treatment as soon as the diagnosis of invasive bladder cancer is reached, this is unfortunately not always possible because of several factors including patient- or health care provider-related issues. Delays of more than 84 days between FP visit and radical cystectomy were significantly associated with a 40% increased risk of dying.

From the *Department of Surgery (Urology), McGill University, Montréal, Que., and the †Department of Community Health Sciences, University of Manitoba, Winnipeg, Man.

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Correspondence: Dr. Armen Aprikian, Head, Division of Urology, McGill University, Montreal General Hospital, L8-309, 1650 Cedar Ave., Montréal QC H3G 1A4; armen.aprikian@muhc.mcgill.ca

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