Does prolonging the time to bladder cancer surgery affect long-term cancer control: a systematic review of the literature

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Background: *Prolonged surgical wait times have significant effects on a patient's psychological well-being and a negative impact on quality of life but the effect on long-term cancer control is controversial. We conducted a systematic review of the bladder cancer literature to examine the best available evidence addressing the following key questions:*

- *What is the reported time interval for bladder cancer patients from the decision to operate until the day of bladder cancer surgery?*
- *Are there recommendations/guidelines in the urological cancer literature and, if so, how do the Canadian times compare?*
- *Is there a known association between duration of wait time beyond the recommended standard and clinical outcome (i.e., recurrence-free survival, overall survival)?*

Methods: *A structured literature search PubMed, Embase, the Cochrane Database and Google Scholar from January 1965 to January 2006 was conducted for published studies and international guidelines/consensus documents that evaluated surgical wait times for bladder cancer. Data extracted from eligible studies included median time to bladder cancer surgery from diagnosis and key patient outcomes, such as survival rate or adjusted hazard ratios (HR).*

Results: *Eighteen studies evaluating wait times for bladder cancer surgery were identified, ten of which measured the association between prolonged waiting time and overall survival or tumor grade. Differences in study data availability, method of analysis and wait time definitions precluded statistical pooling of the findings. Median wait times from various points of patient contact ranged from 29 days (urologist consultation to transurethral resection) to 164 days (general practitioner referral to surgery). In the lone Canadian epidemiological study, which focused on all types of urological cancer, median wait time was 64 days from referral to surgery. This was in contrast to national and international guidelines, which recommended a maximum wait time between 2 and 4 weeks for all cancer surgeries. The association between surgical delay and overall survival remained controversial with some studies reporting a reduced overall survival in patients with prolonged delays, while others failed to find such associations. However, the three studies that measured the association between a delay of ≥ 3 months and tumor grade reported that patients in the prolonged delay groups had an overall poorer tumor grade.*

Conclusions: *In Canada, it appears that current wait times for urological surgeries, such as for bladder cancer, are beyond the threshold recommended by national and international expert bodies. Even though the association between surgical delay and overall survival remains inconclusive, there is evidence to suggest that prolonged delays are associated with an overall poorer tumor grade. To provide the necessary guidance and recommendations on these issues to the federal and provincial governments, the surgical wait times (SWAT) initiative was developed. Through a partnership of the key stakeholders, it is the vision of SWAT to ultimately improve the care and quality of life of bladder cancer patients and their families.*

Key Words: bladder cancer, surgery, wait time, delay

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Introduction

It is estimated that bladder cancer is the ninth most common cancer in the world and the sixth most common in Canada.[1,2] Five thousand new cases are expected to be diagnosed in Canada in 2006, with almost three times as many occurring in men as in women.[2] Described as having a "fairly good prognosis", the number of deaths from bladder cancer is approximately 34% of the number of newly diagnosed cases.[2]

Bladder cancer can present at a variety of stages. Staging is most commonly done using the TNM classification, where T stages the primary tumor, N identifies whether regional lymph nodes are affected, and M indicates distant metastasis. Histopathological grading is often included in tumor descriptions: GX classifies that cell differentiation cannot be assessed, and G1 to G3-4, classify well differentiated to poorly differentiated or undifferentiated cells.[3] The National Comprehensive Cancer Network (NCCN), in its latest practice guidelines, neatly summarized the probability of recurrence and progression of bladder cancers. Tumors graded as Ta, G1 would have a 50% probability of recurrence and a minimal probability of progressing to muscle invasion; those graded T1, G3 have 70% recurrence and high progression rate, and carcinoma in situ (CIS) has a 50%-90% recurrence and high probability of progression; other grades fall somewhere in between.[3] The organization further simplifies bladder cancers into three broad groupings: non-invasive tumors, invasive tumors, and tumors with metastatic lesions.

Surgery is the primary treatment for all grades of bladder tumors.[4,5] Approximately 70% to 80% of all patients present with superficial tumors.[4,6] For these the definitive treatment is transurethral resection of the bladder tumor (TURBT); furthermore, TUR is indicated for all bladder cancers in order to obtain pathology samples for tumor staging.[3-5,7,8] Unfortunately, tumor resection is not always curative and additional treatments, such as radiation or chemotherapy, may be required, as could a radical cystectomy if it was not the primary treatment. Furthermore, there remains the possibility of error in clinical staging of the tumor, which after resection may be pathologically graded as higher.[9,10] Such a delayed finding could result in changes in patient outcome vis-à-vis the original diagnosis and possibly repeated surgery.

How quickly a patient progresses from their first visit to the family doctor, to complain of symptoms suggestive of some sort of urological problem, through to specialist referral, diagnosis and treatment is not well documented. The Progress Report on Cancer Control in Canada notes: "Excessive waiting is attributable to increased incidence and prevalence of cancer, insufficient facilities (operating rooms, radiotherapy equipment), human resource shortages, inefficient health care delivery systems, increased screening, new clinical care indications, or a combination of these factors."[11] Although suggestions or recommendations for shortened and "timely" access to health care have been made, complete data is not presented to substantiate these recommendations.

The impact of surgical delays remains controversial and appropriate wait times for treatments are currently unknown. Determining whether a delay is appropriate or not, or whether a delay affects patient outcome, is especially problematic, considering the various stages of cancer and possible co-morbid conditions with which patients may present.

To address the issue of wait times for the key urological disease sites: prostate, bladder, kidney and testes - a Canadian surgical wait times (SWAT) initiative was undertaken. The SWAT initiative is composed of a steering committee and a scientific advisory committee. The SWAT initiative, whose members consist of urological oncologists, surgeons and methodologists, is mandated to review the current literature on the surgical wait times for urological cancers and then develop a consensus document that can serve as a guide for patients, physicians and other key stakeholders in the Canadian health care system. To begin this process, a review of bladder cancer literature was performed to determine the recommendations currently available regarding appropriate wait times for TURBT or cystectomy, and to quantify the overall risk of disease recurrence and overall survival in patients who have wait times beyond a recommended threshold. In this paper, the results of the systematic review of the literature addressing the key questions in bladder cancer are described.

Methods

Objectives

A systematic literature review was conducted to obtain the best available published articles in the medical literature to address the following questions:

- What is the reported time interval for bladder cancer patients from the decision to operate until the day of bladder cancer surgery?
- Are there recommendations/guidelines in the urological cancer literature and, if so, how do the Canadian times compare?
- Is there a known association between duration of wait time beyond the recommended standard and clinical outcome (i.e. recurrence free survival,

overall survival)?

Data sources, study selection and data extraction and synthesis

A structured literature search was conducted of PubMed, Embase, Cochrane Database and Google Scholar from January 1965 to December 2005 to obtain published epidemiological studies and international guidelines/consensus documents that evaluated surgical wait times for bladder cancer. An additional PubMed search was performed to cover July to January 2006. Furthermore, an "in press" article was forwarded from a member of the advisory committee. The following inclusion criteria were used: 1) The document was available as a full report; 2) The document was developed in North or South America, Western Europe, Australia or New Zealand; 3) Patients undergoing bladder cancer surgery must have been considered and 4) The primary outcome of interest for epidemiological studies was the association between surgical wait times from the initial surgical consultation until the day of surgery and clinical outcomes. Care was undertaken to avoid the inclusion of duplicate publications.

Searches of the listed databases, as well as of government reports, took place between June and October 2005, and again in December 2005. Information was extracted from full copies of all primary study reports and included tables that summarized key study characteristics and data. The definition of wait time varied among the studies, and those that characterized it differently from "surgical consultation until the day of surgery" were evaluated and their data also included. Key findings from each study were documented in summary tables. Studies evaluating the natural history of bladder cancer were considered and particular note was made of those that placed patients into risk groups.

Results

Surgical wait time

Eighteen studies reporting wait times for bladder cancer surgery were identified. Differences in available study data, method of analysis, wait time definitions and grades of disease precluded statistical pooling of the data. Wait time definitions consisted of the following time intervals: from general practitioner (GP) referral to surgery, from surgeon consultation date to hospital admission, from referral to surgery, from diagnosis to surgery, and from diagnosis to hospital admission. The most common intervals reported were the time between primary diagnosis, surgery and the time from family physician referral to definitive treatment with surgery and from the onset of symptoms until treatment. Some studies reported all

TABLE 1. **Reported wait times for bladder cancer surgery in various countries**

Reference	Country	No. patients (n) and year	Wait time definition used	Median duration
Dickinson[14a]	England	n = 186; 1989	GP referral to definitive treatment	114 d
		n = 199; 1993	GP referral to definitive treatment	96 d
Gulliford[15]	England	n = 430; 1982	GP referral to first definitive treatment (TURBT)	48 d
MacArthur[16]	England	n = 330; 1977-1979	GP referral to definitive hospital treatment[b]	≤ 2 mo[b]
Simunovic[12]	Canada	n = 58; Jan-May 2000	Referral to surgery (from referral to treating surgeon to surgery)	64 d[c]
Spurgeon[17]	England	n = 627; Oct 1997	GP referral to first definitive treatment - urgent[d]	57 d
			GP referral to first definitive treatment - non-urgent[d]	82 d
Subramonian[18]	United Kingdom	n = 40; Before Dec 2000	GP referral to surgery	165 d
Wallace[19]	England	n = 1537; Jan 1991-June 1992	GP referral to first treatment (TURBT)	68 d

TUR = transurethral resection, TURBT = transurethral resection of bladder tumor, GP = general practitioner or family physician
[a]Patient selection was for muscle-invasive bladder cancer, excluding recurrent cases. Patients had cancer stages T2-T3. There were 15 primary cystectomies in 1989 and 21 in 1993.
[b]Sixty-eight percent of patients had surgical excision. Just over half of the patients were treated within 2 months of referral.
[c]The authors reported on urological cancer surgeries, without further specification.
[d]Definitions of "definitive treatment" and "urgent/non-urgent" were not provided.

TABLE 1 (cont'd): **Reported wait times for bladder cancer surgery in various countries**

Reference	Country	No. patients (n) and year	Wait time definition used	Median duration
Chang[20e]	United States	n = 153; Jan 1998-Dec 2001	Referral to surgery (from TUR diagnosis of muscle-invasive disease to radical cystectomy)	42 d
Dickinson[14a]	England	n = 186; 1989 n = 199; 1993	Diagnostic cystoscopy to definitive treatment Diagnostic cystoscopy to definitive treatment	55 d 44 d
Mahmud[40]	Canada	n = 1592; 1990-2002	Cystoscopy or TURBT to radical cystectomy	33 d
Hautmann[20f]	Germany	n = 213; Apr 1986-Sept 1994	Primary diagnosis to cystectomy	14.4 mo[f]
May[29]	Germany	n = 189; Feb 1992-Aug 2002	Diagnosis to radical surgery	1.8 mo
Subramonian[18]	United Kingdom	n = 40; Before Dec 2000	Diagnosis to radical surgery	73 d
Liedberg[41]	Sweden	n = 139; 1990-1997	Pathology confirmation of invasive disease to cystectomy	49 d
Lee[42]	United States	n = 214; 1990-2004	Diagnosis of T2 disease to cystectomy	61 d
Gschwend[22]	United States	n = 634; 1980-1990	First muscle invasion to cystectomy	67 d
Stower[25]	England	n = 100; Before Mar 1988[g]	Onset of symptoms to diagnosis	18 wk (= 126 d)
Mommsen[23]	Denmark	n = 212; 1977-1980	Onset of symptoms to treatment[h]	15 wk (= 105 d)
Paul	Scotland	n = 19; 1988-1989 n = 22; 1990	Onset of symptoms to treatment (TURBT)	60 ± 31 d[i] 33 ± 12 d[i]
Esmail[13j] Fraser Institute	Canada	2005	Specialist to TUR Specialist to radical cystectomy	29 d 32 d

TUR = transurethral resection, TURBT = transurethral resection of bladder tumor, GP = general practitioner or family physician
[a]Patient selection was for muscle-invasive bladder cancer, excluding recurrent cases. Patients had cancer stages T2-T3. There were 15 primary cystectomies in 1989 and 21 in 1993.
[b]Sixty-eight percent of patients had surgical excision. Just over half of the patients were treated within 2 months of referral.
[c]The authors reported on urological cancer surgeries, without further specification.
[d]Definitions of "definitive treatment" and "urgent/non-urgent" were not provided.
[e]Patient selection was for muscle-invasive bladder cancer.
[f]This study focused on patients with cancer stages T2-T3 and N0M0 and subsequently having either an ileal neobladder or a conduit procedure. The wait time was given as an average, and ranged from 0 - 128 months. There was a significant difference in wait times between patients having a neobladder procedure (shorter interval) and those having an ileal conduit.
[g]No dates of data collection were specified, however the short report was accepted for publication in March 1988.
[h]Treatment was radiotherapy followed by cystectomy.
[i]This number is the mean ± SD.
[j]Patient numbers were not reported. The wait times are calculated as a weighted median for nine provinces.

three outcomes and, for ease of comparison and review, the findings have been separated within Table 1.

There were two published epidemiological studies from Canada.[12,40] Simunovic et al evaluated wait times for urological cancers in the province of Ontario, without specifying the types of cancer. The small cohort of 58 cases from the first half of the year 2000 had a median waiting time of 64 days between referral and surgery.[12] Mahmud et al, reported on findings from the provincial billing database in Quebec, reporting on 1592 patients who had undergone radical cystectomy between 1990 and 2002. Their median pre-

operative waiting time was 33 days.[40] Most recently, the Fraser Institute released a document on wait times in Canada, using a survey-based approach, for all medical procedures (surgery, radiation therapy, etc).[13] For all of the Canadian provinces, they report that wait times between GP referral to specialist and from specialist to treatment have increased between 1993 and 2005, but have fallen slightly between 2004 and 2005. Using the responses from 179 urologists from across Canada (without a further breakdown by disease site), the 2005 median waiting period between GP referral and treatment was 12.8 weeks, 7.5 weeks between GP to specialist consultation and 5.3 weeks from consultation to actual treatment. The median waiting time for TUR after a specialist appointment can be calculated to be approximately 29 days among nine provinces. The median waiting time for radical cystectomy after a specialist appointment can be calculated to be an average of 32 days among nine provinces, which matches with the Mahmud et al, findings from Quebec.

The majority of studies within this review (i.e., eight) were from the United Kingdom; six of these provided data from England (often from a specific region or hospital group). The median wait times from GP referral to surgery ranged from 48 days (Gulliford, data from 1982) to 165 days (Subramonian, data from before 2000).[14-19] Dickinson et al found that this time interval decreased in 1993 (to 96 days) from their study sample in 1989 (from 114 days).[14] Liedberg et al reported on cases from their hospital practice in Sweden, where the median delay between pathology confirmed invasive bladder cancer and cystectomy was 49 days.[41]

In one study from the United States, a 42-day median interval between diagnosis after a TUR to radical cystectomy was reported.[20] However, the German study by Hautmann et al is an outlier, with a median delay of 14.4 months.[21] It is included here for completeness. Hautmann's patients were all referred because of the possibility of the specialty ileal neobladder procedure available; and the time period of their review spans eight and a half years. Once again, Dickinson et al found a decreased waiting time in 1993 (44 days) from 1989 (55 days).[14] Gschwend et al, from the Memorial Sloan-Kettering Cancer Centre, found that the median time between first muscle invasion and cystectomy was 67 days (in 634 bladder tumor patients followed for at least 5 years).[22] The time lag between onset of patient symptoms to either diagnosis or treatment was the sole parameter reported by Mommsen, Paul and Stower.[23-25] These were shorter than the waiting times identified through patient interviews after diagnosis. Paul et al in Edinburgh monitored patients within a hematuria clinic and reported "mean" (rather than "median") time to treatment.[24] Considering all studies, the waiting time interval from diagnosis to surgery ranged from 42 days to 14.4 months, Table 1.

Wait time guidelines and recommendations from the literature

Many government health services agencies (in Europe, North America, Australia) have identified the need to shorten wait times for patients to receive treatment. However, documents generally refer to the "need" and the "plan" without providing a definite waiting time threshold. When they do, it is for specific diseases or interventions, such as cardiac surgery, breast cancer treatment, and radiotherapy or surgery for cancer; let alone bladder cancer surgery, is usually not on the "action list". One professional organization and two government bodies have developed recommendations for a maximum wait time for cancer surgery in general, Table 2.[26-28] The Canadian Society of Surgical Oncology (CSSO) and the United Kingdom National Health Service made similar recommendations, where the maximum wait time for referral from a general practitioner (GP) to an oncology specialist should be 2 weeks.[26,27] The position statement of the CSSO states that cancer patients should be seen in consultation within 2 weeks of referral and that surgery should be initiated within 2 weeks after preoperative tests.[26] The United Kingdom National Health Service specifies in its Cancer Plan that there should be a maximum wait of 2 weeks from the time of the GP referral to the time for a specialist's assessment, a maximum 1-month wait between diagnosis and treatment, and a maximum 2-month wait between an urgent GP referral and actual treatment.[27] The Saskatchewan Surgical Care Network's recommendations for delay between diagnosis and treatment lie between the other two groups' guidelines at 3 weeks.[28] These recommendations are for all cancer types, with no specific guidelines for bladder cancer. Regarding bladder cancer-specific recommendations, the Fraser Institute has just released the results of their 2005 cross-Canada survey where specialists indicated that a reasonable wait time from specialist visit to treatment should be an average of 2.4 weeks for TUR and 2.7 weeks for radical cystectomy.[13]

Is there an association between wait time and clinical outcome?

One of the main objectives of the current study was

TABLE 2. **Recommended maximum wait times from the literature**

Reference	Wait time definition	Recommended maximum wait time	Type of surgery
CSSO[26]	Referral to consultation	2 weeks	All cancer surgeries
	Conclusion of preoperative tests to treatment	2 weeks	All cancer surgeries
United Kingdom National Health Service[27]	GP referral to specialist assessment	2 weeks	All cancer surgeries
	Diagnosis to treatment	1 month	All cancer surgeries
	Urgent GP referral to treatment	2 months	All cancer surgeries
SSCN	Diagnosis to treatment	3 weeks	95% of all cancer and suspected cancer surgeries
	Diagnosis to treatment	18 months	All cases (including cancers)
Esmail[13]*	Specialist to treatment	2.4 weeks	TUR bladder
	Specialist to treatment	2.7 weeks	Radical cystectomy

GP = general practitioner or family physician
*Numbers are from information received through a cross-Canada survey of specialists and are an average of the results from nine provinces. The recommended maximum wait time is described as: "Median Reasonable Wait for Treatment after Appointment with Specialist".

to evaluate the epidemiological literature that measured the association between prolonged wait times and patients' clinical outcomes. Ten studies falling within the search parameters were identified, as well as one abstract with sufficient reported data, Table 3a. All of the studies used retrospective designs, with the primary outcome being survival. Five studies applied Cox regression analysis, adjusted for known prognostic factors to measure the hazard ratio (HR), in patients with prolonged wait times compared to those with shorter delays.[29,30,40-42] Three studies compared the survival of groups of patients with a delay between diagnosis of muscle invasive bladder cancer to treatment with cystectomy of ≤ 3 months or > 3 months (90 days in May et al and 12 weeks in Sánchez-Ortiz et al and Mahmud et al). Liedberg et

TABLE 3a. **Epidemiological studies evaluating the association between wait time and patient clinical outcome**

Reference	No. patients	Years	Key groups evaluated	Key outcome
May[29]	189	Feb 1992-Aug 2002	Initial diagnosis of muscle invasion to cystectomy:	5-year PF survival[a]
				HR (univariate) / HR (multivariate)
			≤ 3 months (n = 147)	1.00 / 1.00
			> 3 months (n = 42)	1.64 (1.01-2.67) / 1.62 (0.99-2.66)
			Initial diagnosis of muscle invasion to cystectomy:	5-year PF survival:
			≤ 3 months (n = 147)	55%
			> 3 months (n = 42)	34%
Sánchez-Ortiz[30]	189	Feb 1987-July 2000	Initial diagnosis of muscle invasion to cystectomy:	3-year survival[b]
				HR (univariate) / HR (multivariate)
			≤ 12 weeks (n = 170)	1.00 / 1.00
			> 12 weeks (n = 19)	2.51 (1.30-4.83) / 1.93 (0.99-3.76)
Gschwend[22]	634	1980-1990	Initial diagnosis of muscle invasion to cystectomy:	mean disease-specific survival[c]
			≤ 3 months	9.4 years
			> 3 months	6.7 years

TABLE 3a (cont'd): **Epidemiological studies evaluating the association between wait time and patient clinical outcome**

Reference	No. patients	Years	Key groups evaluated	Key outcome		
Lee[42]	214	1990-2004	Diagnosis of T2 disease to cystectomy: ≤ 93 days (n = 88) > 93 days (n = 26)	Overall survival HR (multivariate) 1.00 1.96; P = 0.04		
Liedberg[41]	139	1990-1997	Pathology confirmation of muscle invasion to cystectomy: ≤ 60 days (n = 86) > 60 days (n = 53)	5-year survival[h] HR (multivariate) 1.00 1.05 (0.61-1.82)		
Mahmud[40]	1315	1990-2000	Cystoscopy or TURBT to radical cystectomy ("pre-operative delay"): ≤ 12 weeks (n = 1405) > 12 weeks (n = 187)	5-year survival[g] HR (crude) 1.00 1.3 (1.1-1.6)	HR (multivariate) 1.00 1.2 (1.0-1.6)	
Mommsen[23]	212	1977-1980	Onset of symptoms to definitive treatment for stage T1-T2[c] ≤ 20 weeks = 21 - 52 weeks > 52 weeks	4-year crude survival for 100 patients[d] 57% 22% 21%		
Wallace[31]	10,015[f]	1944-1962	Onset of symptoms to first treatment: ≤ 1 month > 1 month	3-year crude survival: 65% 25%		
Wallace[19]	1537	Jan 1991-June 1992	Onset of symptoms To first treatment (TURBT)[e] ≤ 110 days (n = 757) > 110 days (n = 754) GP referral to first treatment (TURBT)[e] ≤ 68 days (n = 757) > 68 days (n = 747)	Survival[e] 1-year 82% 87% 82% 88%	2-year 67% 72% 66% 73%	3-year 59% 63% 57% 65%

TCC = transitional cell carcinoma, PF = progression free, HR = hazard ratio

[a]Analysis was of 5-year progression-free survival. Numbers in parentheses after the HR are the 95% Confidence Interval. Hazard ratios were significantly different in analysis of the effect of the delay (p = 0.04); however multivariate progression analysis did not show a significant difference between the two groups (p = 0.057).

[b]Patients were stage T2 or higher. Numbers in parentheses after the HR are the 95% Confidence Interval. Both analyses found a significant difference between the waiting periods (univariate, p = 0.006; multivariate, p = 0.05).

[c]There was a significant difference in survival between the two waiting time groups, including overall survival (p < 0.0007).

[d]Treatment was radiotherapy followed by cystectomy if residual tumor was found at 3-month follow-up. Cumulative survival rates were calculated "according to the life table (actuarial) method".

[e]There was no significant difference in survival for each time period between the two key groups for either wait category. There was no significant difference in survival between the two "onset to first treatment" wait time groups when stratified by tumor category (pTa, pT1, T2-t4). There was a significant difference in survival between the two "GP referral to first treatment" wait time groups overall when stratified by tumor category (pTa, pT1, T2-t4), (p = 0.01); only the time between GP referral and first attendance at hospital was significantly different (p = 0.001), but not the time between first hospital visit and first treatment.

[f]Data on epithelial bladder tumors from English and Welsh registries was reported, with the range of source dates spanning 1944 to 1962.

[g]Overall survival was plotted as a function of pre-operative delay (Kaplan-Meier plot), with a statistically significant decrease in survival for patients with a delay of over 12 weeks (p = 0.007 by log-rank test).

[h]Treatment delay of more than 60 days did not affect disease-specific survival (p = 0.85).

al used a cut-off of 60 days' delay between confirmation of invasive disease by pathology and cystectomy, with no significant difference between groups in disease-specific survival.[41] May et al reported on 5-year progression-free survival, showing a statistically significant difference as a result of the delay (55% versus 33%; p = 0.04), but no significant difference when multivariate analysis was done (p = 0.057).[29] In contrast, Sánchez-Ortiz et al, Mahmud et al and Lee et al found statistically significant difference in both univariate and multivariate analyses, showing worse prognosis with a delay in treatment.[30,40,42]

One of the most cited papers on this subject was by Wallace and Harris, which was published in 1965.[31] The investigators reported a 3-year survival rate of 65% for patients who had a delay of 1 month or less between the onset of their symptoms and their first treatment. The rate decreased to 25% for those with a delay of more than 1 month (statistical analysis was not reported). Overall, none of the other studies analyzed such a short time period; the delays ranged from 68 days (approximately 2 months) to 52 weeks (1 year). Survival was calculated using the Kaplan-Meier method for the Wallace et al (1991-1992) data, and crude survival estimates were made by Mommsen et al and Wallace et al.[23,31] Wallace et al, in a more recent study, had one of the largest patient samples available for evaluation (n = 1537).[19] In their patient population, stratified by tumor category, they found that the statistically significant interval affecting survival was the wait time between GP referral and first attendance at hospital: 14 days or fewer versus over 14 days. Other delays evaluated in the analysis were not statistically significant.

Chang,[20] May[29] and Sánchez-Ortiz[30] evaluated the association between wait time and tumor grade, Table 3b. Chang et al reported that a statistically greater percentage of patients had a higher tumor grading (> pT3) when the time between diagnosis and cystectomy was more than 90 days.[20] Similarly, May et al found a significant difference in pT staging between their waiting time cohorts, with pT4 staging showing the biggest difference.[29] Sánchez-Ortiz et al noted that there was a greater incidence of extravesical disease in patients waiting more than 12 weeks between diagnosis of muscle invasive bladder tumors and cystectomy.[30]

Unfortunately, the studies presented here are variable in their definitions, available details, patient subgroups and disease stages. As Gschwend et al noted, "stratification variables" are probably of value when trying to analyze patient outcomes in bladder cancer treatment.[32] Differences in the waiting time subgroups and the lack of

TABLE 3b. **Epidemiological studies evaluating the association between wait time and tumor status**

Reference	No. patients	Years	Key groups evaluated	Tumor grade
Chang[20]	153	Jan 1998-Dec 2001	Referral to surgery (from TUR diagnosis of muscle-invasive disease to radical cystectomy):	> pT3[a]
			≤ 90 days	52%
			> 90 days	81%
May[29]	189	Feb 1992-Aug 2002	Initial diagnosis of muscle invasion to cystectomy:	pT4[b]
			≤ 3 months (n = 147)	14%
			> 3 months (n = 42)	31%
Sánchez-Ortiz[30]	189	Feb 1987-July 2000	Initial diagnosis of muscle invasion to cystectomy:	Extravesical extension[c]
			≤ 12 weeks (n = 170)	48.2%
			> 12 weeks (n = 19)	84%

TUR = transurethral resection

[a]There was a significant difference between the two wait time groups (p = 0.01), with a higher percentage of patients having a tumor grade higher than pT3 if they waited over 3 months for radical cystectomy.

bThere was a significant difference in pT stages between the two groups (p = 0.009), with a higher percentage of pT4 in those having a delay of over 3 months.

[c]This included patients with pathology stage ≥ P3a or with node positivity (p < 0.01). However, there was no significant difference between clinical stage and time lag to cystectomy (p = 0.3).

TABLE 4. **Qualitative insights on the impact of wait time on clinical outcomes as reported by experts in the field**

Reference	Key opinion
Bishop[34]	More timely investigation of potential symptoms of bladder cancer seems desirable to allay the patient's anxiety, although it will probably do little to alter the prognosis.
Chang et al[10]	Unfortunately, pathologic staging at the time of cystectomy indicates that 35% to 50% of these patients, in fact, harbor muscle invasive disease,…. In addition, patient outcomes seem to be directly related to the pathologic stage, implying an adverse effect owing to a delay in treatment.
Gulliford et al[15]	Our results suggest that patients with the worst prognosis were selected for early treatment, and there was little evidence to suggest that the prognosis deteriorated with increasing delay.
Paul et al[24]	In the absence of major advances in the management of bladder cancer we believe that reduction in the delay before diagnosis and treatment of bladder cancer is a worthwhile aim.
Spurgeon et al[17]	We do not suggest that there are "across the board" implications for clinical outcome in the wait times reported.
Wallace et al[31]	Patients with hematuria treated within a month of onset of symptoms will include some with good and some with bad biological potential. With delay, growths with bad potential will have spread beyond local control; with still longer delay, only patients with a good biological potential will be available for treatment.

detailed data in most of the studies precluded data pooling for meta-analysis.

Qualitative insights from experts in the field

Where there is limited, ambiguous, and even controversial data, expert opinion is often sought. Some qualitative insights from authors of the reviewed studies and epidemiological investigations are presented in Table 4. The comments vary, yet there remain some who believe that surgical delays of a few months do not appear to negatively affect recurrence-free survival in most patients. Yet we do not know which patients can safely wait for longer periods, nor what the waiting time threshold should be. Therefore, initiatives such as SWAT need to consider published epidemiological data, the reported impact of delays on patient quality of life, the various patient risk groups, and the health care resources available in order to develop reasonable wait time benchmarks for bladder cancer surgery in Canada.

Discussion

We conducted a systematic review of the literature to identify current wait times for bladder cancer surgery, recommendations on what the maximum wait time should be and to assess the possible association between surgical delays and patient clinical outcomes. Our findings revealed that wait times for bladder cancer surgery in Canada may be shorter than those in comparable countries. In addition, as reported by Statistics Canada for the year 2003, the median wait time for a specialist visit for a new illness or condition was 4.0 weeks and the median wait time for non-emergency surgeries was 4.3 weeks.[33] Using these estimates, they suggest that the median wait time between GP referral and surgery for bladder cancer in Canada could be 8.3 weeks, i.e., still lower than the often cited "3 months" in the studies reviewed here?

Recommendations for maximum wait times are rare, and there are no standards for "acceptable" surgical delays. It is therefore difficult to conclude whether currently documented delays are appropriate and if they have a true negative impact on patient outcome. The association between prolonged wait times and overall survival is contentious. Although some reports find that a delay of a few weeks, or even months, does not have a negative impact on outcome,[19,30,41] there is other evidence suggesting poorer outcomes with prolonged delays, particularly in patients considered to be high risk, i.e., with muscle invasive disease.[23,29,40] In addition to the potential clinical impact of a prolonged surgical delay, there is concern about the effect on patient health associated with the psychological stress from waiting. Widespread agreement exists that delays to surgery have significant effects on psychological well being, and reduced wait times may result in decreased psychological

morbidity.[17,34] Furthermore, the issue of palliative surgery was not been addressed in this review.

One of the main causes of delayed treatment for bladder cancer is delayed diagnosis, and the time it takes a patient to seek medical care is often an important factor.[23,25,35] Encouraging patients to come for regular urological check-ups is beyond the scope of most health care systems. Nevertheless, some urologists have proposed the establishment of hematuria clinics, which could more quickly perform follow-up on patients with abnormal symptoms. This could increase the identification of new bladder cancer cases, thereby shortening the hospital portion of waiting time.[24,36,37] Additional delays occur when patients seek a second opinion or by not following-up on referral.[30]

Subramonian et al observed that the 2-week waiting rule from GP referral to specialist assessment will do nothing to improve other steps in the pathway to surgery.[17] Their study demonstrated that the longest waiting time for all urological surgeries (except orchidectomy) is from diagnosis to surgery, which is the key time interval that needs to be shortened. Sikora et al, in their overview publication, Cancer Care in the NHS, write: "Perhaps the biggest disappointment has been the inability to reduce the delay from referral or diagnosis to first treatment".[38]

Overall, more well-designed epidemiological studies are needed to examine the association between wait time and clinical outcomes, with the ultimate objective being the identification of a delay threshold, which would assist in the development of surgical guidelines for informed health policy decision making. As a caution, the review conducted by Hanning et al on the initiative for reducing wait times for a variety of conditions and treatments, not including cancer, in Sweden should be considered.[39] The investigators found that surveyed physicians were initially very happy to implement shorter wait times. Over time, however, there was increased demand, decreased health care expenditure and new patient priorities, all of which required some change in clinical practice. These changes "did not coincide with the physicians' professional values" resulting in their abandonment of the original agreement.

A final factor that needs to be considered by health policy decision makers when establishing benchmarks is overall quality of care, during and following the surgical procedure. There is a growing body of evidence in the urological surgery literature that the hospital and an individual surgeon's volume are directly related to post operative complications, overall hospital length of stay and even mortality.[43-45] In one recent study evaluating 1302 bladder carcinoma patients who underwent cystectomy, treatment in high-volume hospitals was associated with lower risks of mortality (odds ratio [OR] = 0.35; P = 0.02) and complications (OR = 0.53; P = 0.01). Hospitals with a high registered nurse-to-patient ratio also had a lower mortality risk (OR = 0.43; P = 0.04). The investigators concluded that referral should only be to those centers that perform more than 10 cystectomies per year.[46] The failure to consider overall quality of care when establishing wait time benchmarks may actually increase patient morbidity and mortality.

Conclusions

The findings of our systematic literature review revealed that the national and international guidelines are few, and those that exist recommend a maximum wait time between referral and bladder surgery, be it TURBT or radical cystectomy, of about 4 weeks. In addition, the association between surgical delay and overall survival is inconclusive. To address the important issues related to surgical delays, the SWAT initiative is mandated to provide the necessary guidance and recommendations to the federal and provincial governments. Through a partnership among key stakeholders, it is the vision of SWAT to ultimately improve the care and quality of life of cancer patients.

References

1. National Cancer Institute of Canada: International variation in cancer incidence, 1993-1997, 9 March 2005. Available at: http://www.ncic.cancer.ca; accessed 2005 October 13.
2. Canadian Cancer Society/National Cancer Institute of Canada: Canadian Cancer Statistics 2005. Available at: http://www.ncic.cancer.ca; accessed 2005 October 13.
3. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology - v.1.2005. Bladder Cancer. Including Upper Tract Tumours and Urothelial Carcinoma of the Prostate. Available at: www.nccn.org; accessed 2005 July 31.
4. Herr HH. Surgical factors in the treatment of superficial and invasive bladder cancer. *Urol Clin N Am* 2005;32:157-164.
5. National Cancer Institute. Bladder Cancer (PDQ®): Treatment. Health Professional Version. 19 April 2005. Available at: http://www.cancer.gov; accessed 2005 July 29.
6. UroToday. Bladder Cancer - Treatment, 13 November 2003. Available at: http://www.urotoday.com; accessed 2005 July 19.
7. National Institute for Clinical Excellence, NHS. Guidance on Cancer Services. Improving Outcomes in Urological Cancers. The Manual. September 2002. Available at: http://www.nice.org.uk; accessed 2005 July 29.

8. Oosterlinck W, Lobel B, Jakse G et al. European Association of Urology. Guidelines on Bladder Cancer. Eur J Urol 2002;41(2):105-112. Also available at: http://www.uroweb.org; accessed 2005 July 31.
9. Pagano F, Bassi P, Prayer Galetti T et al. Results of contemporary radical cystectomy for invasive bladder cancer: a clinicopathological study with an emphasis on the inadequacy of the tumor nodes and metastases classification. *J Urol* 1991;145:45-50.
10. Chang SS, Cookson MS. Radical cystectomy for bladder cancer: the case for early intervention. *Urol Clin N Am* 2005;32:147-155.
11. Public Health Agency of Canada. Progress Report on Cancer Control in Canada. 19 October 2004. Available at: http://www.phac-aspc.gc.ca/publicat/prccc-relccc/chap_5_e.html; accessed 2005 July 31.
12. Simunovic M, Gagliardi A, McCready D et al. A snapshot of waiting times for cancer surgery provided by surgeons affiliated with regional cancer centres in Ontario. *CMAJ* 2001;165:421-425.
13. Esmail N, Walker M. Waiting Your Turn: Hospital Waiting Lists in Canada, 15th Edition. The Fraser Institute, October, 2005. Available at: http://www.fraserinstitute.ca; accessed 2005 October 20.
14. Dickinson AJ, Howe K, Bedford C et al. A retrospective study of the investigation and management of muscle-invasive bladder cancer in the South West Region. *Br J Urol* 1996;77:70-75.
15. Gulliford MC, Petruckevitch A, Burney PGJ. Survival with bladder cancer, evaluation of delay in treatment, type of surgeon, and modality of treatment. *BMJ* 1991;303:437-440.
16. MacArthur C, Pendleton LL, Smith A. Treatment delay in patients with bladder tumours. *J Epidemiol Community Health* 1985;39:63-66.
17. Spurgeon P, Barwell F, Kerr D. Waiting times for cancer patients in England after general practitioners' referrals: retrospective national survey. *BMJ* 2000;320:838-839.
18. Subramonian KR, Puranik S, Mufti GR. How will the two-week wait rule affect delays in management of urological cancers. *J R Soc Med* 2003;96:398-399.
19. Wallace DMA, Bryan RT, Dunn JA et al. Delay and survival in bladder cancer. *BJU Int* 2002;89:868-878.
20. Chang SS, Hassan JM, Cookson MS et al. Delaying radical cystectomy for muscle invasive bladder cancer results in worse pathological stage. *J Urol* 2003;170:1085-1087.
21. Hautmann RE, Paiss T. Does the option of the ileal neobladder stimulate patient and physician decision toward earlier cystectomy? *J Urol* 1998;159(6):1845-1850.
22. Gschwend JE, Vieweg J, Fair WR. Early vs. delayed cystectomy for invasive bladder cancer - impact on disease specific survival. *J Urol* 1997;157(4 Suppl):385;abstract 1507.
23. Mommsen S, Aagard J, Sell A. Presenting symptoms, treatment delay and survival in bladder cancer. *Scand J Urol Nephrol* 1983;17:163-167.
24. Paul AB, Wild SR, Chisholm GD. An integrated haematuria clinic. *Br J Clin Pract* 1993;47(3):128-130.
25. Stower MJ. Delays in diagnosing and treating bladder cancer. *BMJ* 1988;296:1228-1229.
26. Canadian Society for Surgical Oncology position statement. Available at: http://www.cos.ca/csso/; accessed 2005 October 8.
27. Department of Health, National Health Service. Cancer waiting targets: A guide (Version 4). 2005. Available at: www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4116412&chk=9Sf2EG; accessed 2005 October 8.
28. Saskatchewan Surgical Care Network, Saskatchewan Health, Government of Saskatchewan. Target time frames for surgery. 2003. Available at: http://www.sasksurgery.ca/target_timeframes.htm; accessed 2005 October 8.
29. May M, Nitzke T, Helke C et al. Significance of the time period between diagnosis of muscle invasion and radical cystectomy with regard to the prognosis of transitional cell carcinoma of the urothelium in the bladder. *Scand J Urol Nephrol* 2004;38:231-235.
30. Sánchez-Ortiz RF, Huang WC, Mick R et al. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. *J Urol* 2003;169:110-115.
31. Wallace DM, Harris DL. Delay in treating bladder tumours. *BMJ* 1965;19:332-334.
32. Gschwend JE, Dahm P, Fair WR. Disease specific survival as endpoint of outcome for bladder cancer patients following radical cystectomy. *Eur Urol* 2002;41:440-448.
33. Sanmartin C, Gendron F, Berthelot J-M, Murphy K. Health Analysis and Measurement Group. Statistics Canada. Access to health care services in Canada, 2003. Catalogue no. 82-575-XIE. Minister of Industry, 2004. Available at: http://www.statcan.ca/english/freepub/82-575-XIE/82-575-XIE2003001.pdf; accessed 2005 October 8.
34. Bishop MC. The dangers of a long urological waiting list. *BJ Urol* 1990;65:433-440.
35. Mohamed SR, Mishriki SF, Persad RA et al. Urological audit: the role for an aggressive approach to high grade superficial bladder tumours. *BJ Urol* 1992;70:156-160.
36. Turner AG, Hendry WF, Williams GB, Wallace DM. A haematuria diagnostic service. *BMJ* 1977;2:29-31.
37. Lynch TH, Waymont B, Dunn JA et al. Rapid diagnostic service for patients with haematuria. *BJ Urol* 1994;73:147-151.
38. Sikora K, Slevin M, Bosanquet N. Cancer Care in the NHS. Reform, February 2005. Available at: www.reform.co.uk; accessed 2005 October 8.
39. Hanning M, Winblad Spångberg U. Maximum waiting time - a threat to clinical freedom? Implementation of a policy to reduce waiting times. *Health Policy* 2000;52:15-32.
40. Mahmud SM, Fong B, Fahmy N, Tanguay S, Aprikian AG. Effect of preoperative delay on survival in patients with bladder cancer undergoing cystectomy in Quebec: a population-based study. *J Urol* 2006;175:78-83.
41. Liedberg F, Anderson H, Månsson W. Treatment delay and prognosis in invasive bladder cancer. *J Urol* 2005;174:1777-1781.
42. Lee CT, Madii R, Daignault S, et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in diminished disease specific and overall survival. *J Urol* 2006;175;1262-1267.
43. Joudi FN, Konety BR. The impact of provider volume on outcomes from urological cancer therapy. *J Urol* 2005;174:432-438.
44. Nuttall M, van der Meulen J, Phillips N et al. A systematic review and critique of the literature relating hospital or surgeon volume to health outcomes for 3 urological cancer procedures. *J Urol* 2004;172:2145-2152.
45. Konety BR, Dhawan V, Allareddy V, Joslyn SA. Impact of hospital and surgeon volume on in-hospital mortality from radical cystectomy: data from the health care utilization project. *J Urol* 2005;173:1695-700.
46. Elting LS, Pettaway C, Bekele BN et al. Correlation between annual volume of cystectomy, professional staffing, and outcomes: a statewide, population-based study. *Cancer* 2005;104:975-984.