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Association between symptomatic versus asymptomatic recurrence and survival in bladder cancer

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Abstract

Introduction—The benefit of surveillance after curative cystectomy in bladder cancer is unproven, but might be justified if detection of asymptomatic recurrence improves survival. Prior studies demonstrating a benefit of surveillance may have been impacted by lead-time or length-time bias.

Materials and Methods—We conducted a retrospective cohort study among 463 cystectomy patients at the University of Pennsylvania. Patients were followed by standardized protocol and classified by asymptomatic or symptomatic recurrence detection. Primary outcome was all-cause mortality. Adjusted Cox regression models were used to assess the impact of mode of recurrence on survival from time of cystectomy (model 1) and time of recurrence (model 2) in order to account for lead and length time.

Results—197 patients (42.5%) recurred; 71 were asymptomatic (36.0%), 107 were symptomatic (54.3%), and 19 (9.6%) were unknown. Relative to patients with asymptomatic recurrence, patients with symptomatic recurrence had significantly increased risk of death (Model 1 HR 1.67, 95% CI 1.07–2.61, Model 2 HR 1.74, 95% CI 1.13–2.69) and had lower 1 year overall survival from time of recurrence (29.37% vs. 55.66%). Symptomatic patients were diagnosed with recurrence a median of 1.7 months *prior to* asymptomatic patients, yet their median survival from recurrence was 8.2 months *less*.

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Conclusions—Symptomatic recurrence is associated with worse outcomes than asymptomatic recurrence, which cannot be explained by lead- or length-time bias. Similar methods to account for these biases should be considered in studies of cancer surveillance. Shortening surveillance intervals may allow for detection of more recurrences in an asymptomatic phase.

Keywords

Bladder cancer; epidemiologic methods; cancer surveillance; lead- time bias

Introduction

Bladder cancer accounts for about 5% of all new cancers in the United States, with an estimated 76,960 new cases and 16,390 deaths in 2016.¹ Treatment of bladder cancer comes at considerable expense, owing partially to high recurrence rates and frequent invasive surveillance regimens.^{2,3} However, these costs may be justified if early detection of cancer recurrence in the absence of symptoms is more amenable to treatment and associated with improved survival.

Among patients with muscle-invasive bladder cancer treated with radical cystectomy, post-cystectomy surveillance for the detection of cancer recurrence is standard and consists of routine office visits and cross-sectional imaging. These recommendations are based largely on consensus opinion⁴; however the benefit of surveillance remains unproven. Because randomized trial data comparing surveillance strategies are not available, the evidence-base for surveillance has relied on observational data that are susceptible to lead-time and length-time biases. Lead-time bias is a systematic overestimation of survival duration due to the early detection of asymptomatic disease (e.g., surveillance- detected cancer recurrence),⁵ while length-time bias overestimates survival of surveillance-detected recurrence due to the relatively higher probability of detecting slow-growing cancers with more favorable tumor biology.

A few prior studies have demonstrated improved survival associated with surveillance-detected relative to symptom-detected recurrence.^{6,7,8} However, none of these studies attempted to account for both lead-time and length time bias. In this study, we compared survival between symptom-detected and surveillance-detected cancer recurrence among a cohort of cystectomy patients using different cohort-entry times to adjust for the possible effects of lead-time and length-time bias.

Materials and Methods

Study design and population

We performed a retrospective cohort study to compare differences in overall survival (OS) between patients who presented with symptomatic cancer recurrence and those whose recurrence was detected during routine post- cystectomy surveillance. The study population was obtained from a database of patients who underwent radical cystectomy by four surgeons for bladder cancer between 02/01/1987 and 10/31/2011 at the Hospital of the University of Pennsylvania. This database has been used for several prior studies.^{9,10}

Patients were included in the study if they were 18 years of age or older, had a biopsy confirmed diagnosis of muscle-invasive bladder cancer, and were status post radical cystectomy. Patients were excluded if distant metastatic disease was present prior to cystectomy. The study protocol was approved by the Institutional Review Board at the University of Pennsylvania.

Surveillance protocol, exposure ascertainment, and primary outcome definition

All patients were recommended to undergo routine post-cystectomy surveillance involving an excretory urogram 6 weeks postoperatively, a renal ultrasound 3 months postoperatively, CT urogram and chest x-ray every 6 months and routine blood work every 4 months for the first 2 years and annually thereafter. Additional studies, such as brain imaging and bone scans, were performed as clinically indicated.

Exposure was defined as the mode of diagnosis of cancer recurrence ascertained by chart abstraction. Cancer recurrence was categorized as asymptomatic if disease was detected during routine surveillance, and as symptomatic if the presence of new symptoms prompted additional testing beyond the routine surveillance protocol.

Primary outcome was all-cause mortality, which was based on death certificates or physician correspondence.

Covariates

The following potential confounding variables were collected from the database at time of cystectomy: patient age, gender, race, smoking status, and body mass index, as well as clinical and pathological tumor characteristics including histology (pure urothelial cell carcinoma vs. mixed), pathologic tumor stage, presence of nodal disease, presence of lymphovascular invasion, and presence of positive surgical margins. Additional variables measured at tumor recurrence included recurrence type (distant vs. local) and recurrence location (visceral vs. nodal). Some patients recurred at multiple anatomic sites concurrently; these recurrences were categorized as visceral if at least one anatomic site involved was not nodal. Time from the date of cystectomy to the date of recurrence was used as a surrogate for the rate of tumor progression (i.e., length-time).

Statistical analysis

Separate Cox regression models with different cohort entry times assessed the association of mode of recurrence detection (symptomatic versus asymptomatic) on mortality. Accordingly, hazard ratios (HRs) and 95% confidence intervals (CIs) for death were computed from time of cystectomy (first model) and from time of cancer recurrence (second model). Cox regression models were adjusted for all patient and tumor variables described above and the second model was additionally adjusted for the time-interval between cystectomy and recurrence. A sensitivity analysis assessed the impact of residual or metastatic disease present at cystectomy on the observed associations. In this analysis, we repeated the primary analysis after excluding patients with positive surgical margins at cystectomy or disease recurrence within 1 month from cystectomy.

All statistical tests were two-sided and considered significant when $p < 0.05$. All statistical analyses were performed using STATA version 12.0 (StataCorp, CollegeStation, TX).

Results

A total of 463 patients were included in this study, of which 197 patients (42.5%) developed recurrent disease following cystectomy. 71 (36.0%) of these patients were diagnosed with recurrence through asymptomatic routine surveillance, 107 (54.3%) through symptom-driven testing, and 19 (9.6%) had an unknown mode of recurrence detection. Median follow-up time for the entire cohort was 18 months. Of the 266 patients that did not recur, 37 (13.9%) had follow up of less than 1 year after surgery. Baseline patient and tumor characteristics were generally similar between the asymptomatic and symptomatic groups (Table 1). Median time from cystectomy to recurrence was longer for patients with asymptomatic recurrence compared to patients with symptomatic recurrence, although this was not statistically significant (11.5 months (5 months – 24.6 months) versus 9.7 months (3.5 months – 20.5 months), $p = 0.49$).

Figure 1 demonstrates survival curves following cystectomy (1a) and recurrence (1b). From both the date of cystectomy and the date of recurrence, survival for asymptomatic recurrence was longer relative to symptomatic recurrence (median OS: 24.8 months vs. 15.6 months, $p = 0.022$, and 5y OS: 14.1% vs. 10.3%, Figure 1a, respectively; median OS: 13.7 months vs. 5.2 months, $p < 0.001$, and 1y OS: 55.7% vs. 29.4%, Figure 1b, respectively).

In analyses adjusted for patient and tumor characteristics, relative to asymptomatic patients, patients with symptomatic recurrence had significantly increased risk of death from the time of cystectomy (Model 1 HR 1.67, 95% CI 1.07–2.61, table 2). Similar results were seen from the time of recurrence, adjusted for time from cystectomy to recurrence as a marker of the rate of tumor progression (Model 2 HR 1.74, 95% CI 1.13–2.69, table 2). The between-group difference (symptomatic vs. asymptomatic) in median time from surgery to recurrence detection was 1.7 months, while the difference in median time from recurrence detection to death was 8.2 months (Figure 2).

To determine whether the increased risk of death among symptomatic patients could be explained by inclusion of patients likely to have residual or metastatic disease present at cystectomy, we repeated the primary analysis excluding patients with positive surgical margins at cystectomy or disease recurrence within 1 year from cystectomy ($n=41$). In this sensitivity analysis, HRs for death were not appreciably different from time of recurrence to death (Model 2 HR 1.95, 95% CI 1.21 – 3.13), but were attenuated from time of cystectomy to death (Model 1 HR 1.29, 95% CI 0.80 – 2.06).

Discussion

In this era of increasing focus on cost-conscious medicine, routine surveillance regimens to detect asymptomatic cancer recurrence following curative surgery have come under scrutiny. However, these significant expenses may be justified if they lead to improved patient survival.

This current study adds to a growing but divided body of literature evaluating whether asymptomatic detection of bladder cancer recurrence is associated with improved outcomes compared to detection based on symptoms. A retrospective study of 1270 German patients by Volkmer et al¹¹ found no difference in overall survival from time of recurrence, however they did not examine survival from time of cystectomy. In contrast, Boorjian et al⁶ evaluated 1599 US patients and found significantly increased overall survival from time of cystectomy for patients with asymptomatic compared to symptomatic recurrence and Giannarini et al⁷ noted similar findings among a cohort of 479 patients as well. Our findings are in line with these latter two studies, however importantly, we examined survival from both time of cystectomy and time of recurrence.

A criticism of many cancer surveillance regimens is that they are influenced by lead-time bias and length-time bias, wherein survival appears to improve with earlier disease detection by increasing the length of time that a patient is aware of a disease without extending overall years of life and by disproportionally detecting slower growing tumors with a longer asymptomatic period as well as a more favorable biology. In contrast to prior studies examining survival differences with surveillance- versus symptom-detected recurrence, the present study examined the potential influence of these biases by measuring survival from both time of curative cystectomy and from time of cancer recurrence to account for lead-time, and by adjusting for the time interval to recurrence to account for length-time. Notably, there was no evidence of either lead-time or length-time bias given that symptomatic patients in our study were diagnosed with recurrence a median of 1.7 months *prior to* asymptomatic patients, yet their median survival from recurrence was 8.2 months *less*. Thus, asymptomatic recurrence detection was still associated with improved overall survival.

One potential explanation for the improved survival observed in patients with asymptomatic recurrence relates to intrinsic differences in the tumor biology between asymptomatic and symptomatic tumors. Because fast growing tumors generally have a shorter asymptomatic phase than slow-growing tumors, fast growing tumors have a shorter time period in which recurrence can be detected by surveillance. Consequently, recurrence detected through symptoms is likely to include more patients with fast growing and potentially more aggressive disease that carries a worse prognosis. Furthermore, visceral recurrence is more likely to cause symptoms than lymph node recurrence, and nodal-only disease is known to have an improved prognosis compared to visceral disease.¹² For these reasons, it is highly likely that asymptomatic and symptomatic patients represent two distinct categories of tumor biology with inherently different natural histories and outcomes.

Additionally, patients with asymptomatic recurrence may be more likely to have better performance status and lower overall tumor burden compared to patients with symptoms, thus allowing the opportunity for greater therapeutic options and consequently improved treatment response and outcomes. Indeed, the recent approval of immunotherapy for the management of metastatic bladder cancer will also likely have a significant impact on overall survival for all patients going forward.^{13,14}

Alternatively, the increased risk of death observed amongst patients with symptomatic recurrence could be partially explained by those with positive surgical margins or rapid

disease recurrence within 1 month of cystectomy, as demonstrated by results from sensitivity analyses. Indeed, this population likely harbored residual or metastatic disease at the time of surgery.

Therefore, the current data could be interpreted as supportive of more intense post-cystectomy surveillance in an effort to detect recurrence of aggressive tumors earlier in the asymptomatic phase with the aim of preserving treatment options and performance status. However, this must be balanced against both the financial and patient-level costs of increased imaging, particularly surrounding scan anxiety.¹⁵ Promising research is currently underway to identify biomarkers at time of cystectomy, such as circulating tumor cells, that could predict aggressive disease and thereby further personalize the intensity of post-cystectomy surveillance based on tumor biology.^{16,17}

Each of the prior studies investigating the relationship between detection of asymptomatic bladder cancer recurrence and survival utilized different post-cystectomy surveillance strategies, suggesting that further investigation is needed to determine the optimal modality and timing of testing. Current guidelines recommend surveillance imaging more frequently (every 3–6 months) during the first two years post-cystectomy and less frequently (annually) for years 3–5. Similar to prior studies, few patients (18 patients, 9.1%) in our study developed cancer recurrence more than 3 years post-cystectomy,^{6,11,18} supporting the National Comprehensive Cancer Network (NCCN) guidelines for a less intensive surveillance regimen after this time.

There are several important limitations of this study. As with all observational studies, there is risk of residual confounding. We did not have complete information regarding neoadjuvant, adjuvant, or salvage therapy received by each patient. Although platinum-based neoadjuvant chemotherapy improves survival,¹⁹ the greatest survival benefit is limited to a small proportion of patients achieving a complete pathologic response to chemotherapy. Because analyses were adjusted for pathologic stage, whether a patient received neoadjuvant treatment is less likely a potential confounder in this study, and whether adjuvant chemotherapy influences survival remains unclear.²⁰

We did not have available the number of surveillance tests obtained per patient; thus, we could not assess for the impact of surveillance intensity on post-cystectomy survival. Although we were unable to assess the optimal surveillance timing, our results suggest that a surveillance strategy more intensive compared to that which was performed in our protocol may be beneficial. As the surveillance protocol used in this study was an institutional standard, we expect surveillance intensity to be uniform across cohort subjects. Because aggressive tumors are more likely to be symptom-detected, these results also highlight the need to identify biomarkers predictive of aggressive tumor biology to select patients at the highest risk of symptomatic recurrence and most likely to benefit from intensive surveillance.

Conclusions

In summary, asymptomatic as compared to symptom detected recurrence was associated with improved survival. This translated to a between-group difference in median survival of 9.2 months from cystectomy and 8.5 months from recurrence. However, the earlier time to recurrence of the symptomatic tumors implies a more aggressive biology such that it is not possible to know whether the longer survival after detection of recurrence is related to the underlying tumor biology or the early intervention offered to those with asymptomatic recurrences. Up to this point, all studies examining this issue have been retrospective. As such, prospective, randomized studies are needed to provide a higher level of evidence to support or refute the routine use of surveillance following cystectomy with curative intent for bladder cancer.

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Clinical Practice Points

- Routine surveillance of patients with muscle-invasive bladder cancer is standard practice after curative cystectomy to screen for cancer recurrence. However, current recommendations are based largely on consensus opinion and the benefit of surveillance remains unproven.
- The current study demonstrates that patients with symptomatic recurrence had significantly increased mortality from time of cystectomy and time of recurrence compared to asymptomatic patients, despite being diagnosed with recurrence earlier.
- Shorter initial surveillance intervals may allow more patients to be detected during the asymptomatic phase, potentially improving outcomes.
- A prospective, randomized study is still needed to provide a higher level of evidence to support the use of routine surveillance following curative cystectomy.

Figure 1.
Kaplan-Meier curves for overall survival from (A) time of cystectomy and (B) time of cancer recurrence

Figure 2.
Schematic representation of time to cancer recurrence and survival.

Table 1

	Entire Cohort (n = 463)	Asymptomatic (n = 71; 39.9%)	Symptomatic (n = 107; 60.1%)
Median age at radical cystectomy (years)	65.4	66.9	65.8
Female gender	104 (22.5%)	13 (18.3%)	33 (30.8%)
Pathologic (p) tumor (T) stage			
<pT2	140 (33.5%)	12 (18.8%)	19 (17.6%)
pT2	75 (17.9%)	13 (20.3%)	13 (12.0%)
pT3	129 (30.9%)	25 (35.9%)	34 (31.5%)
pT4	74 (17.7%)	16 (25.0%)	42 (38.9%)
Positive lymph nodes present	133 (29.0%)	25 (35.7%)	46 (43.4%)
Lymphovascular invasion present	157 (34.4%)	29 (40.9%)	52 (49.5%)
Pure urothelial cell carcinoma		53 (75.7%)	79 (73.8%)
Distant recurrence		31 (46.3%)	55 (53.4%)
Visceral recurrence		31 (46.3%)	63 (61.2%)
Median time to recurrence (mos)		11.5	9.7

Baseline patient and tumor characteristics.

Table 2

Model	Unadjusted HR (95% CI), for death	Adjusted HR (95% CI), for death*
Cohort entry time from date of surgery	1.22 (0.89 – 1.67)	1.67 (1.07 – 2.61)
Cohort entry time from date of recurrence*	1.46 (1.06 – 2.03)	1.74 (1.13 – 2.69)

Association between symptomatic relative to asymptomatic recurrence and the risk of death, using varying cohort-entry times.

Models both adjusted for pathologic tumor stage, presence of positive lymph nodes, presence of lymphovascular invasion, presence of positive surgical margins, histology (pure UCC vs. mixed), recurrence site (local vs. distant), recurrence type (visceral vs. nodal), gender, age at time of cystectomy, presence of obesity, and race

* Additionally adjusted for time from cystectomy to recurrence