Original Study

Association Between Symptomatic Versus Asymptomatic Recurrence and Survival in Bladder Cancer

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Abstract

Routine surveillance after curative cystectomy in bladder cancer might be justified if detection of asymptomatic recurrence improves survival. We conducted a retrospective cohort study of 463 patients classified according to asymptomatic or symptomatic recurrence detection. Asymptomatic compared with symptom-detected recurrence was associated with improved survival. Shortening surveillance intervals might allow for detection of more recurrences in an asymptomatic phase.

Background: The benefit of surveillance after curative cystectomy in bladder cancer is unproven, but might be justified if detection of asymptomatic recurrence improves survival. Previous studies showing a benefit of surveillance might have been affected 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 according to a standardized protocol and classified according to asymptomatic or symptomatic recurrence detection. Primary outcome was all-cause mortality. Adjusted Cox regression models were used to assess the effect of mode of recurrence on survival from time of cystectomy (model 1) and time of recurrence (model 2) to account for lead and length time. **Results:** One hundred ninety-seven 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: hazard ratio [HR], 1.67; 95% confidence interval [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 before asymptomatic patients, yet their median survival from recurrence was 8.2 months less. **Conclusion:** 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 might allow for detection of more recurrences in an asymptomatic phase.

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Introduction

Bladder cancer accounts for approximately 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 might 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, postcystectomy surveillance for the detection of cancer recurrence is standard and consists of routine office visits and

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cross-sectional imaging. These recommendations are largely on the basis of consensus opinion[4]; 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 because of the early detection of asymptomatic disease (eg, surveillance-detected cancer recurrence),[5] whereas length-time bias overestimates survival of surveillance-detected recurrence because of the relatively higher probability of detecting slow-growing cancers with more favorable tumor biology.

A few previous studies have shown improved survival associated with surveillance-detected relative to symptom-detected recurrence.[6-8] However, none of these studies attempted to account for lead-time as well as 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 Method

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 postcystectomy surveillance. The study population was obtained from a database of patients who underwent radical cystectomy by 4 surgeons for bladder cancer between February 1, 1987 and October 31, 2011 at the Hospital of the University of Pennsylvania. This database has been used for several previous 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 before 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 postcystectomy surveillance involving an excretory urogram 6 weeks postoperatively, a renal ultrasound 3 months postoperatively, computed tomography 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 on the basis of death certificates or physician correspondence.

Covariates

The following potential confounding variables were collected from the database at time of cystectomy: patient age, sex, 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 1 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 (ie, length-time).

Statistical Analysis

Separate Cox regression models with different cohort entry times were used to assess the association of mode of recurrence detection (symptomatic vs. 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 previously and the second model was additionally adjusted for the time-interval between cystectomy and recurrence. A sensitivity analysis assessed the effect 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 2-sided and considered significant when $P < .05$. All statistical analyses were performed using STATA version 12.0 (StataCorp, College Station, TX).

Results

A total of 463 patients were included in this study, of whom 197 patients (42.5%) developed recurrent disease after cystectomy. Seventy-one of these patients (36.0%) 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 who did not have disease recurrence, 37 (13.9%) had follow-up of < 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 with patients with symptomatic recurrence, although this was not statistically significant (11.5 months [range, 5-24.6 months] vs. 9.7 months [range, 3.5-20.5 months], $P = .49$).

Figure 1 shows survival curves after cystectomy (Figure 1A) and recurrence (Figure 1B). From the date of cystectomy as well as the date of recurrence, survival for asymptomatic recurrence was longer relative to symptomatic recurrence (median OS, 24.8 months vs. 15.6 months; $P = .022$, and 5-year OS, 14.1% vs. 10.3%, respectively; Figure 1A; median OS, 13.7 vs. 5.2 months; $P < .001$, and 1-year OS, 55.7% vs. 29.4%, respectively; Figure 1B).

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