Original Article

Delays in Diagnosis and Bladder Cancer Mortality

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BACKGROUND: Mortality from invasive bladder cancer is common, even with high-quality care. Thus, the best opportunities to improve outcomes may precede the diagnosis. Although screening currently is not recommended, better medical care of patients who are at risk (ie, those with hematuria) has the potential to improve outcomes. **METHODS:** The authors used the Surveillance, Epidemiology, and End Results-Medicare linked database for the years 1992 through 2002 to identify 29,740 patients who had hematuria in the year before a bladder cancer diagnosis and grouped them according to the interval between their first claim for hematuria and their bladder cancer diagnosis. Cox proportional hazards models were fitted to assess relations between these intervals and bladder cancer mortality, adjusting first for patient demographics and then for disease severity. Adjusted logistic models were used to estimate the patient's probability of receiving a major intervention. **RESULTS:** Patients (n = 2084) who had a delay of 9 months were more likely to die from bladder cancer compared with patients who were diagnosed within 3 months (adjusted hazard ratio [HR], 1.34; 95% confidence interval [CI], 1.20-1.50). This risk was not markedly attenuated after adjusting for disease stage and tumor grade (adjusted HR, 1.29; 95% CI, 1.14-1.45). In fact, the effect was strongest among patients who had low-grade tumors (adjusted HR, 2.11; 95% CI, 1.69-2.64) and low-stage disease (ie, a tumor [T] classification of Ta or tumor in situ; adjusted HR, 2.02; 95% CI, 1.54-2.64). **CONCLUSIONS:** A delay in the diagnosis of bladder cancer increased the risk of death from disease independent of tumor grade and or disease stage. Understanding the mechanisms that underlie these delays may improve outcomes among patients with bladder cancer. *Cancer* **2010;116:5235–42.** *© 2010 American Cancer Society.*

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Nearly 1 in 10 patients with hematuria have an associated life-threatening disease.[1] However, although hematuria is a common manifestation of an underlying bladder neoplasm, it is a symptom shared with many other diseases, including urinary tract infection. Because of its lack of specificity, some physicians may procrastinate with regard to the evaluation of hematuria,[2] for which current clinical guidelines recommend urine cytologic evaluation, upper urinary tract imaging, and cystoscopy.[3] The implications of a delay in the diagnosis of bladder cancer are not entirely clear.[4,5]

Earlier evaluation and intervention for patients with bladder cancer potentially can improve their outcomes. For example, delays in definitive treatment (ie, from transurethral resection to radical cystectomy) have been associated with worse outcomes.[6] On average, patients who wait for >3 months between diagnosis and radical cystectomy are at 20% to 90% greater risk of mortality,[7,8] at 60% greater risk of disease progression,[9] and are more likely to have advanced disease (ie, with lymph node involvement).[8-11] In this context, 1 potential mechanism to improve patient outcomes is to ensure timely intervention as necessary.

However, even in the best of hands, a cure for many patients with bladder cancer remains elusive, and nearly 33% of all patients die from disease within 5 years of the diagnosis.[12] Invariably, tumor biology plays an important role in determining the ultimate outcome regardless of the type and timing of treatment. Thus, it seems logical that opportunities to

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improve bladder cancer outcomes may be greatest upstream from the diagnosis. Screening for bladder cancer may identify more patients at a curable stage of the disease, but this approach is not yet ready to be implemented at the population level.[13] Alternatively, better recognition and timely intervention before the diagnosis afford the possibility of immediate improvements in outcomes. For this reason, we used national cancer registry data to evaluate relations between a delay in diagnosis and outcomes among patients with bladder cancer.

MATERIALS AND METHODS

Study Population

We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database for the years 1992 through 2002 to identify patients with bladder cancer. These files provide information on Medicare patients who are included in SEER,[14] which is a nationally representative collection of population-based registries of all incident cancers that comprised approximately 26% of the US population by the end of the study period.[15] For each Medicare patient in SEER, the SEER-Medicare linked files contain 100% of Medicare claims from the inpatient, outpatient, and national claims history files. From these files, all Medicare patients aged $\geq$66 years with incident cases of bladder cancer were identified by the appropriate code in SEER. Only fee-for-service beneficiaries with coverage for both Parts A and B of Medicare were included in this study.

Next, we identified 29,740 of 37,972 patients (78%) who had a claim that included a physician-ascribed diagnosis of hematuria (International Classification of Diseases, Ninth Revision [ICD-9] diagnosis code 599.7x) within the year preceding a bladder cancer diagnosis. The initial claim for hematuria was determined according to the claim that was the most removed in terms of date from the date of the bladder cancer diagnosis within the 12-month window. We limited our retrospection to 1 year before diagnosis for 2 reasons. First, looking back further would require additional patient exclusions, thereby reducing our sample size and generalizability. For example, a 2-year window would necessitate limiting our population to patients aged $\geq$67 years to ensure that all patients had similar entitlements to Medicare coverage during the period at risk. Second, the vast majority of patients (75%) aged $\geq$70 years (those with at least 5-years of prediagnosis claims) had their initial claim for hematuria within the 12-month period before their bladder cancer diagnosis.

Finally, we sorted patients into 4 groups based on the interval between the date of their initial claim for hematuria and the date of their bladder cancer diagnosis (<3 months, 3 months to <6 months, 6 months to <9 months, and 9 months to 12 months). We chose this classification scheme for 2 reasons. First, the literature is replete with studies that support a 3-month interval between diagnosis and treatment as a clinically important threshold, indicating that greater delays may have a negative impact on outcomes.[6-10,16] Second, this methodology enables us to contrast the extremes in the interval between the initial hematuria claim and the bladder cancer diagnosis and to articulate more easily the clinical relevance of the problem.

Outcomes

Our primary outcome was bladder cancer-specific mortality as determined by SEER's cause-of-death variable. Given concerns surrounding the attribution of the cause-of-death,[17] we also assessed all-cause mortality. Survival time was measured from the date of bladder cancer diagnosis, as determined by the date of biopsy or transurethral resection, to the date of death, and surviving patients were censored on September 30, 2005 (ie, the date of the most recent death). In addition, patients who died were censored for the cancer-specific survival analyses if their cause of death site was listed as anything other than the urinary system. Secondarily, we also identified the receipt of a major medical intervention (as evidenced by a claim for radical cystectomy, systemic chemotherapy, or radiation therapy) in the inpatient, national claims history, and outpatient files. All outcomes, for which the patient was the unit of analysis, were measured between January 1, 1992 and December 31, 2005.

Statistical Analysis

For all of our analyses, our exposure was the interval between the initial claim for hematuria and bladder cancer diagnosis, which was divided into 3-month intervals (<3 months, 3 months to <6 months, 6 months to <9 months, and 9 months to 12 months). First, we examined differences in patient demographics according to this interval. Next, we evaluated the extent to which disease characteristics and survival varied according to the interval. For all of these comparisons, statistical inference was made using chi-square tests or log-rank tests, as appropriate.

For the purpose of understanding the relation between the delay interval and bladder cancer mortality, we fit a Cox proportional hazards model adjusting for patient characteristics, including patient age, sex, race, and comorbidity. The last variable was identified using healthcare encounters (both inpatient and outpatient) in the 12-month period preceding the bladder cancer diagnosis using an adaptation of the Charlson Comorbidity Index[18] as described by Klabunde and colleagues.[19] In addition, we adjusted for socioeconomic status using a composite measure assessed at the zip code level, as described by Diez-Roux et al.[20]

To evaluate the extent to which differences in disease severity might explain any disparity in survival because of a delay in diagnosis, a second model was fit adjusting for the above covariates and for cancer grade and stage. The relative attenuation of the hazard ratio (HR) was measured as $(HR_R - HR_F)/(HR_R - 1)$, where HR_R is the adjusted HR of mortality for diagnosis delay ignoring disease severity measures, and HR_F is the HR for diagnosis delay after including the disease severity measures.

For each of our secondary outcomes (all-cause mortality and the use of major interventions), we fit separate models adjusting for the same covariates that were used in our primary analysis. For all Cox models, the assumption of proportionality was confirmed by visual inspection of the hazard plots and goodness-of-fit testing.[21] The use of a major medical intervention was determined by fitting adjusted logistic models and then back-transforming these models to estimate each patient's probability of undergoing the intervention.

Then, we performed several sensitivity analyses to assess the robustness of our findings. First, we adjusted our final models for whether the patient underwent cystoscopy at the time (within 30 days) of the initial hematuria claim. Second, we treated our time-to-diagnosis exposure as a continuous variable in lieu of categorizing it into 3-month groups. Third, we attempted to adjust for the severity of hematuria (eg, gross vs microscopic); however, 99.95% of 353,091 claims that were submitted for hematuria within national claims history files were for ICD-9 code 599.7 (hematuria unspecified). Fourth, to determine the extent to which lead-time bias might account for any observed differences in survival between groups (ie, patients with shorter intervals would appear to have longer survival even if the actual survival times from initial hematuria claim were equal), we assessed survival from the date of first hematuria claim until death. Finally, we assessed survival according to diagnosis delay among patients with no comorbid conditions (ie, those in whom the probability of unmeasured confounding is smallest). In all patients, the magnitude and significance of the effects were nearly identical to those in our primary analyses.

All analyses were carried out using computerized statistical software (SAS Institute, Cary, NC). All tests were 2-tailed, and the probability of Type 1 error was set at .05. The study protocol was approved by the Institutional Review Board of the University of Michigan.

RESULTS

Of 29,826 patients with bladder cancer, we identified 7004 (24%) whose diagnosis was made $\geq$3 months after an initial physician claim with a hematuria diagnosis, including 2084 patients (7%) whose interval was $\geq$9 months. The median survival for the cohort ranged from 50.9 months for patients who had an interval $\geq$9 months to 70.9 months for those whose diagnosis was made within 3 months (log-rank $P < .001$). On the basis of our sensitivity analysis assessing median survival from the first hematuria claim until death, lead-time bias played a minor role in explaining differences in survival between the groups (<3-month group: survival, 70.9 months; 3 to 6-month group: survival, 62.6 months; 6 to 9-month group: survival, 60.7 months; 9 to 12-month group: survival, 59.9 months; log-rank $P < .001$). Table 1 shows that patients who had longer delays tended to be older men with more comorbid illnesses. However, the distributions of cancer grade and stage were similar across all diagnostic delay intervals. Finally, almost all patients (93.5%) underwent cystoscopy within 30 days of their initial claim for hematuria, although small but significant differences were evident according to delay intervals.

Table 2 highlights the finding that longer delays in diagnosis were associated with increased risk of bladder cancer-specific and all-cause mortality. Compared with patients who were diagnosed within 3 months, patients who had delays $\geq$9 months were 34% more likely to die from bladder cancer after adjusting for patient demographics (adjusted HR, 1.34; 95% confidence interval [CI], 1.20-1.50). After incorporating disease severity measures into the model, the risk was attenuated by only 14.7%, suggesting that differences in tumor grade and disease stage explained little of the observed differences in bladder cancer mortality across diagnostic delay strata. Among the patients who had no comorbid conditions, those who had delays $\geq$9 months were 38% more likely

Table 1. Patient Characteristics According to the Interval Between an Initial Claim for Hematuria and Bladder Cancer Diagnosis

Characteristic	Interval Between Hematuria Claim and Diagnosis: Delay <3 mo	Delay 3 to <6 mo	Delay 6 to <9 mo	Delay 9-12 mo	*P*
No. of patients	22,736	2904	2016	2084	
Median survival, mo	70.9	59.6	54.7	50.9	<.001
Age, y, %					<.001
66-69	14.2	12.3	12.9	10.7	
70-74	23.8	21.5	21.7	20.8	
75-79	25.7	25.6	24.9	24.8	
80-84	20.1	21.7	22.7	23.3	
≥85	16.2	18.9	17.8	20.4	
Women, %	27.4	27.9	26.2	23.5	<.001
Race, %					<.001
White	94.1	91.6	91.7	92.2	
Black	3.4	5.3	4.5	4.5	
Other	2.5	3.1	3.8	3.3	
Socioeconomic status, %					
Low	32.5	33.8	35.6	33.5	.06
Medium	34.2	34.2	33.0	32.6	
High	33.3	32.0	31.4	33.9	
No. of comorbidities, %					<.001
0	56.8	50.9	48.4	47.2	
1	20.2	21.3	22.6	22.5	
2	11.2	12.0	13.7	13.9	
≥3	11.8	15.8	15.3	16.4	
Tumor grade, %					.11
Low	53.7	51.9	54.4	51.5	
High	46.3	48.1	45.6	48.5	
Tumor stage, %					.66
Ta/Tis	52.6	52.8	54.1	52.3	
T1	20.3	20.6	20.6	19.5	
T2	17.5	17.2	16.6	17.5	
≥T3	9.6	9.4	8.7	10.7	
Cystoscopy within 30 d of initial hematuria claim, %	97.4	95.0	94.7	95.3	<.001

Tis indicates tumor in situ.

to die from bladder cancer after adjusting for patient demographics (adjusted HR, 1.38, 95% CI, 1.17-1.63) compared with those who were diagnosed within 3 months.

Longer diagnostic intervals were associated most strongly with bladder cancer-specific mortality among patients with low-grade and low-stage disease (Table 3). Among those with low-grade disease, patients who had a delay ≥9 months were more than twice as likely to die from bladder cancer compared with patients who had a delay <3 months (adjusted HR, 2.11; 95% CI, 1.69-2.64). The corresponding relation among patients who had high-grade disease was more modest (adjusted HR, 1.10; 95% CI, 0.95-1.27). Similar relations were evident for patients who had a diagnosis delay >6 months. For our sensitivity analysis using the time between first hematuria claim and diagnosis as a continuous exposure, we observed an increased risk of death from bladder cancer (adjusted HR, 1.01; 95% CI, 1.01-1.03) and death from all causes (adjusted HR, 1.01; 95% CI, 1.01-1.02). That is, each day of delay was associated with an approximately 1% greater risk of death.

Compared with patients whose diagnosis was made within 3 months of the initial claim for hematuria, those who had a delay ≥9 months were more likely to undergo radical cystectomy (5.8% vs 6.2%; $P = .04$; c-index,

Table 2. Relation Between Delays in Diagnosis and Mortality

	HR (95%CI)		
Model	Unadjusted	Adjusted[a]	Adjusted[b]
Cancer-specific mortality			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.09 (0.99-1.20)	1.00 (0.89-1.11)	1.05 (0.93-1.18)
Delay 6 to <9 mo	1.19 (1.07-1.33)	1.16 (1.03-1.31)	1.30 (1.15-1.48)
Delay 9-12 mo	1.39 (1.26-1.54)	1.34 (1.20-1.50)	1.29 (1.14-1.45)
All-cause mortality			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.13 (1.07-1.19)	1.06 (1.00-1.12)	1.06 (1.00-1.13)
Delay 6 to <9 mo	1.21 (1.14-1.29)	1.15 (1.07-1.23)	1.19 (1.11-1.28)
Delay 9-12 mo	1.28 (1.21-1.36)	1.15 (1.08-1.23)	1.12 (1.04-1.20)

HR indicates hazard ratio; CI, confidence interval.
[a] Adjusted for age, sex, race, socioeconomic status, and comorbidity.
[b] Adjusted for the same variables stated above plus grade and stage.

Table 3. Relation Between Diagnosis Delays and Cancer-Specific Mortality by Cancer Grade and Stage

	HR (95% CI)		
Stratified Model	Unadjusted	Adjusted[a]	Adjusted[b]
Grade			
Low-grade			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.19 (0.95-1.48)	1.03 (0.79-1.34)	1.05 (0.81-1.36)
Delay 6 to <9 mo	1.47 (1.17-1.86)	1.61 (1.26-2.07)	1.61 (1.25-2.06)
Delay 9-12 mo	2.31 (1.90-2.81)	2.21 (1.78-2.75)	2.11 (1.69-2.64)
High-grade			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.02 (0.92-1.15)	0.98 (0.86-1.11)	1.05 (0.93-1.20)
Delay 6 to <9 mo	1.13 (0.99-1.29)	1.07 (0.92-1.24)	1.21 (1.04-1.41)
Delay 9-12 mo	1.18 (1.04-1.33)	1.13 (0.98-1.30)	1.10 (0.95-1.27)
Tumor classification			
Ta/Tis			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.46 (1.18-1.82)	1.29 (0.99-1.67)	1.26 (0.96-1.66)
Delay 6 to <9 mo	1.85 (1.47-2.33)	1.86 (1.44-2.42)	1.85 (1.40-2.45)
Delay 9-12 mo	2.07 (1.66-2.58)	2.22 (1.75-2.83)	2.02 (1.54-2.64)
T1			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.25 (1.00-1.57)	1.14 (0.87-1.49)	1.19 (0.91-1.56)
Delay 6 to <9 mo	1.31 (1.00-1.70)	1.39 (1.05-1.84)	1.40 (1.05-1.87)
Delay 9-12 mo	1.63 (1.28-2.07)	1.48 (1.12-1.96)	1.50 (1.12-1.99)
T2			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	0.99 (0.84-1.18)	0.87 (0.71-1.07)	0.90 (0.73-1.10)
Delay 6 to <9 mo	1.15 (0.94-1.40)	1.16 (0.92-1.45)	1.14 (0.90-1.44)
Delay 9-12 mo	1.37 (1.14-1.63)	1.23 (1.00-1.51)	1.25 (1.02-1.53)
≥T3			
Delay <3 mo	1.0	1.0	1.0
Delay 3 to <6 mo	1.04 (0.87-1.23)	1.05 (0.87-1.28)	1.02 (0.83-1.25)
Delay 6 to <9 mo	1.11 (0.90-1.37)	1.08 (0.85-1.38)	1.12 (0.87-1.43)
Delay 9-12 mo	1.02 (0.83-1.23)	0.93 (0.74-1.16)	0.98 (0.78-1.23)

HR indicates hazard ratio; CI, confidence interval; Tis, tumor in situ.
[a] Adjusted for age, sex, race, socioeconomic status, and comorbidity.
[b] Adjusted for the same variables stated above plus stage (in grade strata) or grade (in stage strata).

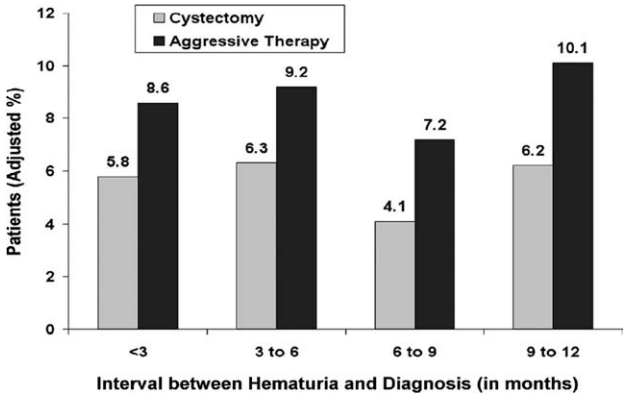

Figure 1. This bar chart illustrates the percentages of patients undergoing radical cystectomy and receiving any aggressive therapy (radical cystectomy, systemic chemotherapy, or radiation therapy). Analyses were adjusted for age, sex, race, socioeconomic status, and comorbidity. An increasing diagnostic delay interval was associated both with undergoing radical cystectomy ($P = .04$) and with the receipt any aggressive therapy ($P = .04$).

0.66) or any major intervention (8.6% vs 10.1%; $P = .04$; c-index, 0.63) after adjusting for patient differences (Fig. 1). Among the patients who underwent the intervention, the median time from bladder cancer diagnosis to radical cystectomy for those whose diagnosis was made within 3 months was 2.4 months compared with 2.6 months for patients who had a delay $\geq$9 months (log-rank $P = .44$). The corresponding times to any major intervention were 2.3 months and 2.6 months, respectively (log-rank $P = .62$).

DISCUSSION

Patients with protracted delays between an initial claim for hematuria and the diagnosis of bladder cancer are at 34% higher risk of dying from the disease and are more likely to undergo major interventions, including radical cystectomy. Although the latter differences are of debatable clinical significance, the observed mortality differences are robust. The increasing risk of mortality with longer diagnosis delays was not directly attributable to greater disease severity as measured by cancer grade and stage. Surprisingly, delays in diagnosis appeared to exert the strongest effects among those with low-grade and low-stage disease.

That diagnosis delays are associated with lower rates of survival is not surprising in light of the rich literature describing the effects of prolonged intervals between diagnosis and radical cystectomy.[5,6,8,10,16] For example, in 1 study, patients who had treatment delays >3 months were more than twice as likely to die from their cancers compared with those who had more prompt intervention.[16] However, although it is generally believed that such relations are mediated by disease progression, our data do not necessarily support this mechanism upstream from the cancer diagnosis. Patients who had more protracted intervals between an initial claim for hematuria and bladder cancer diagnosis had similar grade and stage distributions relative to those with shorter intervals. Furthermore, we observed only a 15% reduction in the risk of cancer-specific mortality after accounting for these disease severity measures.

Although the mechanisms underlying these mortality differences are unclear, there are at least 2 possibilities. On 1 hand, patients with longer diagnosis delays may have access to care issues beyond those of insurance entitlement that also translate into delays in definitive local therapy for patients who need it. However, among the patients who underwent major interventions, we observed no differences in the time to treatment according to the diagnostic delay interval, and in all patients, the median time to treatment was <3 months.

Alternatively, the observed relations between diagnosis delay and mortality may reflect the quality of care provided. Specifically, it is plausible that patients who have more protracted delays may receive their care in lower quality settings. For example, patients with more pronounced delays were less likely to undergo cystoscopy around the time of hematuria. Although differences in cystoscopy use were quite small and lacked clinical significance, they may reflect other disparities in quality (eg, physician practice styles) that were not readily appreciable in the data. This may explain why those with lower risk bladder cancer (ie, low grade and stage) have the most to lose. Arguably, the goal with these patients is to prevent disease recurrence and progression, because those who progress fare no better than those who present initially with invasive disease.[22] In lower risk patients, physician decision making surrounding the nature and extent of treatment likely plays a primary role in determining outcomes, whereas the effects of tumor biology are more pronounced for those who have muscle invasion. Examples in which questionable decision making may contribute to missing the window for cure include continued use of intravesical therapy despite multiple failures or frequent fulguration of recurrent disease without pathologic assessment. Regardless, the finding that almost everyone with a delay underwent cystoscopy within 30 days of their initial hematuria claim means that many of these cancers

presumably are being missed despite theoretically appropriate evaluation—a problem that might be tough to remedy unless better diagnostic tools become available.

A central concern when using observational data is the possibility that patient heterogeneity may explain in part the relation between exposure and outcomes.[23] Specifically, although observational studies are able to account for measurable characteristics that mediate relations between diagnosis delay and mortality, they cannot account for potentially important factors that are unmeasured. For example, patients with protracted delays may have more aggressive bladder cancers, which naturally would result in higher disease mortality. However, we addressed this limitation by using a clinical cancer registry that captures both cancer grade and stage, arguably the most important mediators of bladder cancer-specific survival.[12,24] Furthermore, we used robust methods to adjust for patient comorbidity[19] and socioeconomic status,[20] 2 well described predictors of long-term mortality.[25,26] Nonetheless, it is possible that unmeasured characteristics of tumor biology, such as lymphovascular invasion[27] and microvessel density,[28] may explain some of our findings relative to the grade and stage effects. Perhaps it is such unmeasured machinery that, over time, enables disease progression and whose effects may be most apparent for those with seemingly curable disease (eg, low grade and stage).

Another concern centers on our use of the cause-of-death variable as measured by SEER and the possibility of attribution bias.[17] Specifically, deaths among patients with longer diagnosis delays may be attributed preferentially to bladder cancer relative to those with shorter delays. Although this theoretically is possible, we know of no biologic rationale why such differential attribution might exist. Furthermore, the approach used by the SEER registries to identify cause of death has been well vetted in patients with other nonhematopoietic malignancies,[29,30] and its extension to the bladder cancer population seems reasonable. Next, because we assessed survival from diagnosis (ie, the date of transurethral resection) to death, it is possible that differences in lead time (ie, between the date of hematuria and diagnosis) may explain part of the observed survival differences between groups. However, we assessed this as part of a sensitivity analysis and observed that the survival benefit for those with the shortest interval between hematuria and diagnosis persisted even after considering the differences in lead time. A final consideration stems from the use of the Medicare population. Because we studied patients aged $\geq$66 years, our findings may not be generalizable to a younger group. However, because nearly 75% of bladder cancers occur in Medicare-aged patients,[15] our findings are pertinent to (arguably) the most important group with the disease, and their applicability to the larger population of patients with bladder cancer seems appropriate.

In conclusion, nearly 1 in 4 patients who ultimately are diagnosed with bladder cancer has a delay >3 months between their first provider claim for hematuria and diagnosis. Those with more protracted delays have significantly higher rates of mortality from the disease and are more likely to undergo a major intervention, such as radical cystectomy. These mortality differences do not appear to be caused by disease progression, at least as measured by cancer grade and stage. Although the mechanisms underlying this relation are unclear, future work should explore both the evaluation of these patients upstream from the diagnosis and the care provided to those with lower risk disease downstream from the diagnosis, for whom the delay seems to matter the most.

CONFLICT OF INTEREST DISCLOSURES

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