Original Article

Understanding Bladder Cancer Death

Tumor Biology Versus Physician Practice

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BACKGROUND: To the authors' knowledge, the extent to which death from bladder cancer is attributable to tumor biology or physician practice patterns is unknown. For this reason, the relative importance of broadening indications for aggressive therapy has unclear implications. **METHODS:** Patients whose deaths were caused directly by bladder cancer were identified using institutional (n = 126 patients) and administrative (n = 6326 patients) data sources. By using implicit review (clinical data, 2001-2005) and explicit algorithms (Surveillance, Epidemiology, and End Results [SEER]-Medicare, 1992-2002), the authors estimated the proportion of potentially avoidable deaths from bladder cancer. **RESULTS:** After an implicit review of clinical data, 40 of 126 deaths (31.7%) were classified as potentially avoidable. Compared with those patients who were deemed unsalvageable, these patients generally presented with nonmuscle-invasive disease (80% vs 25.6%; $P < .001$), received multiple courses of intravesical therapy (32.5% vs 1.2%; $P < .001$), and had a more protracted course from diagnosis to aggressive treatment (median, 23 months vs 2 months; $P < .001$). An explicit review of claims data indicated that between 31.6% and 46.8% of the 6326 bladder cancer deaths identified in the SEER-Medicare data potentially were avoidable, depending on the survivorship threshold chosen. Patients whose deaths potentially were avoidable more commonly presented with nonmuscle-invasive disease (66.7% vs 24.7%; $P < .0001$) and lower grade disease (35.1% vs 15.1%; $P < .0001$). **CONCLUSIONS:** The greatest inroads into reducing death from bladder cancer likely hinge on earlier detection or improvement of systemic therapies. However, changing physician practice may translate into nontrivial reductions in bladder cancer mortality. **Cancer 2009;115:1011–20. © 2009 American Cancer Society.**

KEY WORDS: bladder cancer, mortality, practice pattern, Surveillance, Epidemiology, and End Results-Medicare.

In theory, treatment decisions are relatively straightforward for many patients with bladder cancer. Those with muscle-invasive (bladder carcinoma stage II [tumor invading muscle; T2], no regional lymph node metastasis [N0], and no distant metastasis [M0] according to the American Joint Committee on Cancer *Cancer Staging Manual*, sixth edition[1]) or more advanced disease are treated best with aggressive local therapy (eg, radical cystectomy, radiotherapy) and/or systemic chemotherapy.[2] In contrast, for patients with nonmuscle-invasive disease (ie, superficial bladder cancer), the current paradigm generally favors

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See editorial on pages 914-7, this issue.

Received: May 29, 2008; **Revised:** July 17, 2008; **Accepted:** August 4, 2008

Published online: January 17, 2009, © 2009 American Cancer Society

DOI: 10.1002/cncr.24136, www.interscience.wiley.com

endoscopic resection with or without intravesical therapy.[3,4] In both cases, cancer biology likely will determine the ultimate outcome for the majority of patients.

However, there are occasions in which the optimal treatment approach is unclear or is rejected by the patient or physician, thereby prompting deviation from the traditional paradigm. Some patients with muscle-invading cancers do not receive aggressive therapy for a variety of patient or physician factors.[5] Conversely, among patients with clinical stage T1 disease, the indications to proceed with 'early' cystectomy, although soundly based on medical theory and nonexperimental data, are speculative, and their application likely varies considerably between physicians.[6-12] Among patients in whom the cancer biology is uncertain, physician decision making likely plays a greater role in determining the course of the disease.

Although the decision for and timing of radical cystectomy can be a source of considerable debate, the extent to which clinical judgment ultimately contributes to bladder cancer death is unclear. For this reason, we sought to gain a better understanding of the magnitude of potentially avoidable deaths among patients who died of bladder cancer. On the one hand, cancer biology may be the primary mediator of mortality in the majority of patients regardless of the timing and nature of the decisions made by clinicians. In this case, only better systemic therapies would reduce bladder cancer-related deaths. Conversely, the persistent use of conservative measures or an insufficient appreciation of the future risk of disease that delays necessary, aggressive therapy may constitute a substantial proportion of those who ultimately die from bladder cancer. In this case, changing clinician decision making or practice patterns would help to decrease mortality. To understand the relative importance of these mechanisms, we used both clinical and medical claims data comprised of patients who died from bladder cancer to estimate the proportion of potentially avoidable deaths.

MATERIALS AND METHODS

Conceptual Model of Potentially Avoidable Bladder Cancer Deaths

Conceptually, there are several factors that plausibly contribute to death from bladder cancer, including access to healthcare, comorbidity,[13] tumor biology,[7,14] and physician or patient decision making. Whereas the first of these factors influences diagnosis and the downstream consequences related to treatment delay, the latter 3 factors likely play a greater role in the insured (ie, Medicare) population, although the magnitude of the relation is unknown.

To understand the theoretical implications of reducing or expanding the role of aggressive therapy, consider a model of all bladder cancer patients who present for treatment. Broadening the indications for aggressive therapy likely will decrease the number of bladder cancer deaths while understandably increasing the cumulative morbidity of the bladder cancer population, as illustrated in Figure 1. Performing a cystectomy at diagnosis in all patients with bladder cancer could decrease bladder cancer mortality; however, such a strategy clearly would be over treatment for some patients. Furthermore, such an approach would have extraoncologic consequences among survivors, including a deleterious impact on quality of life. In contrast, abandoning aggressive therapy altogether likely would result in greater bladder cancer mortality regardless of stage.

Applying the current treatment paradigm (ie, aggressive therapy for those with muscle-invasive disease and those with high-risk or refractory nonmuscle-invasive disease), a minority of patients with nonmuscle-invasive disease and approximately half of those with muscle-invasive disease ultimately will die of bladder cancer.[15,16] Under this algorithm, it is unclear whether this 'minority' of patients with nonmuscle-invasive bladder cancer constitutes a small or large number of patients. The ultimate objective of the current study was to quantify the magnitude of patients whose deaths may have been avoided if aggressive therapy had been applied as soon as feasible based on current indications.

Patient and Disease Course Ascertainment

Implicit review of clinical data

For this study, we used both clinical and administrative data. First, we used our institutional cancer registry to identify all patients who died because of bladder cancer between 2001 and 2005. During the period of our study, the institution's comprehensive cancer center averaged approximately 200 new bladder cancer patients annually. The cancer registry ascertains vital status using both the

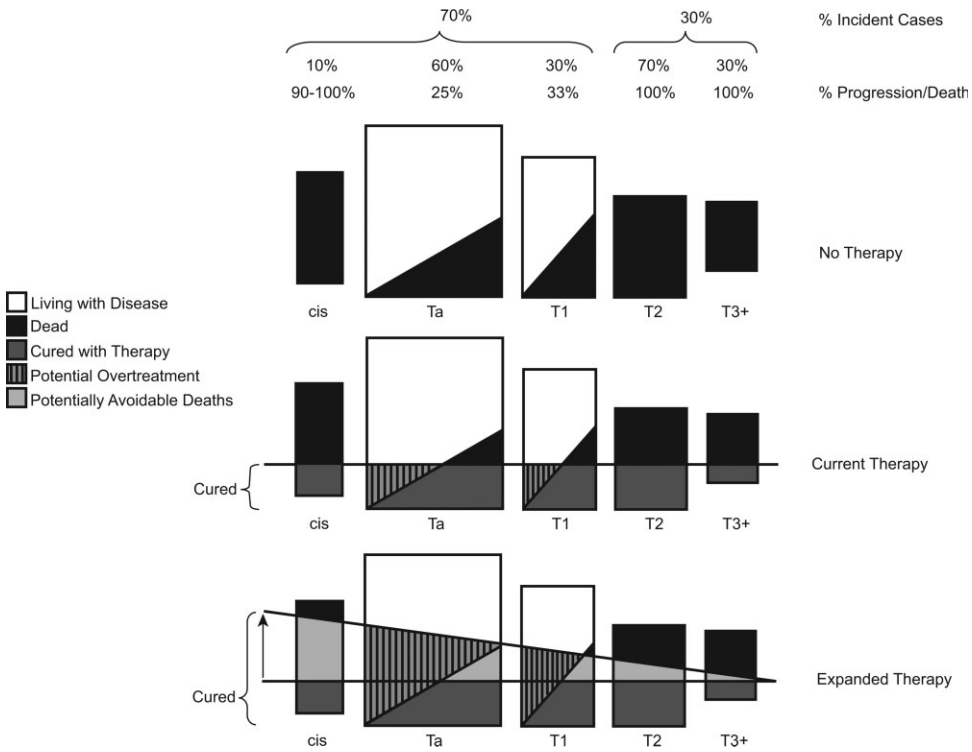

FIGURE 1. Conceptual model of bladder cancer presentation[25,28] and treatment paradigms. The size of each box approximates the number of patients in each primary tumor (T) classification according to the American Joint Committee on Cancer staging manual.[1] Cis indicates carcinoma in situ.

Social Security Death Index and communications from referring physicians and families. The cause of death was identified according to the patient's death certificate.

We identified 144 patients whose deaths initially were attributed to bladder cancer. Of these, 18 patients were excluded from the study for the following reasons: inadequate documentation within external medical records (n = 2), misclassification of cause of death based on medical record review (n = 5), nonurothelial (histologic subtypes were not excluded) variants (n = 2), and the presence of a primarily upper tract urothelial disease (n = 9). Then, paper and electronic medical records were reviewed, and relevant data were abstracted using a standardized form that was developed by the investigators. The form was designed to capture rich demographic and cancer-related detail to facilitate the implicit review of a patient's treatment course. Information that was abstracted included demographic data, comorbid conditions, treatment recommendations, patient compliance, dates and pathology for all surgical procedures, dates of intravesical chemotherapy, clinical stage, and dates and types of systemic chemotherapy regimens.

A panel of 4 experts (J.E.M., B.K.H., A.Z.W., and D.S.M.) independently reviewed each patient's clinical course that ultimately culminated in bladder cancer-related mortality. The criteria used to determine potentially avoidable deaths included clinical stage, the temporal relation between diagnosis and death, the time between treatments, recurrence patterns, the use of intravesical therapy, and patient preferences, as indicated in the medical record. On the basis of an implicit review, each expert made a judgment regarding whether a death potentially would have been avoidable if the patient had received an alternative course of aggressive therapy (cystectomy, systemic chemotherapy, or radiotherapy as opposed to more conservative therapies). A kappa statistic was calculated to determine the agreement of this initial review among the experts. Then, consensus was achieved by simple majority and through a group meeting and rereview of each case. If the panel was split evenly, then the

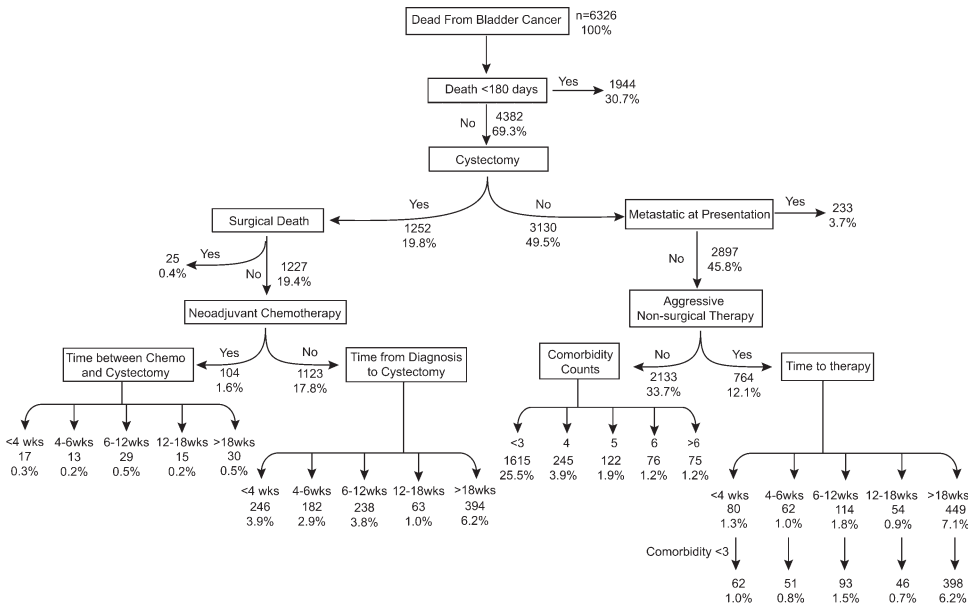

FIGURE 2. Algorithm used to ascertain the avoidability of death among patients in the Surveillance, Epidemiology, and End Results-Medicare database using a survivorship threshold of 180 days. For example, based on our assumptions described in the text, potentially avoidable deaths include 0.4% (surgical deaths) + 0.7% (delay from chemotherapy) + 7.2% (delay from diagnosis to cystectomy) + 7.0% (delay from diagnosis) + 25.5% (healthy and no therapy) or 40.8% of all patients dying of bladder cancer. Chemo indicates chemotherapy.

final judgment coincided with the opinion of the member (J.E.M.) who had the most years of clinical experience in treating patients with bladder cancer.

Explicit review of administrative data

In addition, we identified patients in the Surveillance, Epidemiology, and End Results (SEER)-Medicare-linked database who were newly diagnosed with bladder cancer between 1992 and 2002. These files, as detailed elsewhere,[17] provide a rich source of information on Medicare patients who are included in the SEER data, a nationally representative collection of population-based registries of all incident cancers from diverse geographic areas in the US. By the end of the study period, the SEER registries captured approximately 26% of the US population.[18] For each Medicare patient in SEER, the SEER-Medicare-linked files contain 100% of Medicare claims from the inpatient (Medicare Provider and Analysis Review [MEDPAR]), outpatient (OUT), and physician National Claims History (NCH) files.

From these files, all Medicare patients with incident cases were identified by the appropriate bladder cancer code within the Patient Entitlement and Diagnosis Summary file from SEER. By using the SEER cause-of-death variable, we identified patients whose deaths were attributable to bladder cancer. Patient comorbidities were enumerated by examining healthcare encounters that preceded the bladder cancer diagnosis using the methods described by Elixhauser et al.[19] For each patient, the nature, extent, and timing of all bladder cancer-related therapies were identified using International Classification of Diseases, ninth revision (MEDPAR) and Common Procedural Terminology, fourth edition (NCH and OUT) codes. Then, algorithms were developed to estimate the proportion of bladder cancer deaths that potentially were avoidable using clinical characteristics, disease severity, treatment course, and timing of therapy.

The cornerstone of the algorithms was the survivorship threshold, which we defined as the time from bladder cancer diagnosis until death. Deaths among patients who survived for less than the survivorship threshold were considered unavoidable deaths, regardless of their treatment course, because of the apparent aggressive nature of the disease. Lacking empiric support for any specific survivorship threshold, we tested 3 values (<90 days, <180 days, and <365 days). Patients who lived longer than the threshold then proceeded through the algorithms, as demonstrated in Figure 2 (survivorship threshold, 180 days).

Table 1. Characteristics of Patients From a Clinical Registry According to Classification of Death

Variable	No. of Patients (%)		*P*
	Potentially Avoidable Deaths	Unavoidable Deaths	
Age, y			
<60	6 (15)	28 (32.6)	.017
60-69	17 (42.5)	24 (27.8)	
70-79	16 (40)	22 (25.6)	
>80	1 (2.5)	12 (14)	
Sex			
Men	38 (95)	65 (76)	.012
Women	2 (5)	21 (24)	
Race			
Black	1 (2.5)	8 (9.3)	.043
Other	—	8 (9.3)	
White	39 (97.5)	70 (81.4)	
Socioeconomic status			
Low	15 (38.5)	27 (31.4)	.440
Medium	10 (25.6)	32 (37.2)	
High	14 (35.9)	27 (31.4)	
Tumor classification at diagnosis*			
Ta/Tis	11 (27.5)	4 (4.7)	<.001
T1	21 (52.5)	18 (20.9)	
T2	8 (20)	49 (57)	
T3+	—	15 (17.4)	
Intravesical chemotherapy			
None	19 (47.5)	83 (96.5)	<.001
Any no. of courses	21 (52.5)	3 (3.5)	
None	19 (47.5)	83 (96.5)	<.001
1 course	8 (20)	2 (2.3)	
2 courses	8 (20)	—	
≥3 courses	5 (12.5)	1 (1.2)	
Treatment			
Cystectomy	27 (67.5)	43 (50)	.066
No surgery	13 (32.5)	43 (50)	
Neoadjuvant chemotherapy	10 (35.7)	14 (25)	.320
Adjuvant chemotherapy	18 (64.3)	42 (75)	

Tis, indicates tumor in situ.
*See Green 2002.[1]

For the purpose of estimating potentially avoidable death, we used a threshold of <3 comorbid medical conditions (we assumed that patients who had more comorbid conditions were not candidates for aggressive therapy) and an interval between therapies of <12 weeks (we assumed that patients who had longer delays resulted in potentially avoidable deaths). Other thresholds for each of these parameters also were examined (eg, <2 comorbid conditions) but did not substantially alter the overall estimates of avoidable deaths (data not shown). A range of potentially avoidable deaths was estimated depending on the survivorship threshold chosen.

Statistical Analysis

To lend validity to our implicit and explicit reviews, we examined clinical, disease, and treatment characteristics according to whether a death was classified as potentially avoidable or not. Chi-square tests were used to test for the independence of death status categorization and these

characteristics. We also estimated each group's time to death using Kaplan-Meier estimation methods. The log-rank test was used to test the independence of the survival curves. All statistical testing was 2-sided, was completed using computerized software (SAS version 9.1; SAS Institute, Cary, NC), and was performed at the 5% significance level. The Institutional Review Board of the University of Michigan approved the study protocol.

RESULTS

Clinical Data

Between 2001 and 2005, we identified 126 patients from the University of Michigan cancer registry data who ultimately died of bladder cancer and met our inclusion criteria. Among these, the year of bladder cancer diagnosis ranged from 1965 to 2005, and the duration of survivorship ranged from 1 month to 451 months (mean ± standard deviation, 38 ± 63 months). After independent review by 4 clinicians, we estimated that between 38 (30.2%) and 44 (34.9%) of 126 bladder cancer deaths potentially would have been avoidable if an alternative treatment course had been implemented. Agreement between the 4 panel members was high with kappa statistics ranging from 0.74 to 0.96. After a consensus conference, we determined that 40 deaths (31.7%) potentially were avoidable. Among those 40 deaths, all 4 reviewers agreed on 30 deaths (75%), 3 reviewers agreed on 8 deaths (20%), and reviewers were split on 2 deaths (5%), with the vote ultimately was decided by the reviewer who had the most clinical experience (J.E.M.). Of the 86 patient deaths that were deemed unavoidable, reviewers were evenly split on only 3 deaths (3%).

To explore the validity of our implicit review, we measured differences in patient characteristics according to our classification scheme (Table 1). Not surprisingly, patients whose deaths were classified as potentially avoidable generally presented with nonmuscle-invasive disease (80% vs 25.6%; $P < .001$), received ≥2 courses of intravesical therapy (32.5% vs 1.2%; $P < .001$), and had a more protracted clinical course between diagnosis and death (median, 58 months vs 10 months; log-rank test, $P < .001$) (Fig. 3A). Among the patients who underwent cystectomy, the median time between diagnosis to cystectomy was 23 months versus 2 months for patients whose deaths were classified as potentially avoidable and as unavoidable, respectively (log-rank test; $P < .001$).

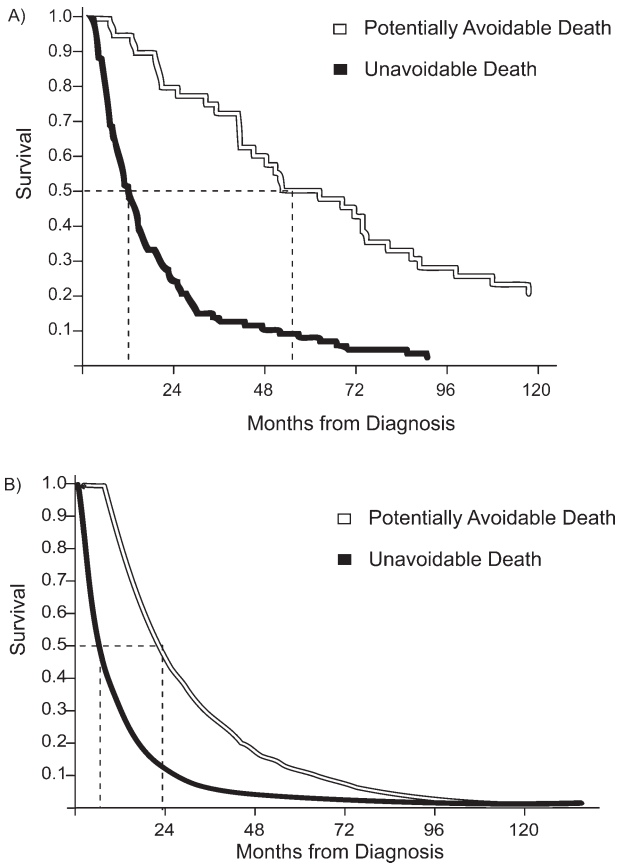

FIGURE 3. These Kaplan-Meier plots demonstrate the differences in survival among patients who died of bladder cancer according to the avoidability of death using (A) clinical data and (B) and claims data.

Administrative Data

Among those who were diagnosed with bladder cancer between 1992 and 2003, we identified 6326 patients who died of bladder cancer before 2005. By using our algorithms to classify all deaths, we estimated that 31.2% and 46.8% of bladder cancer deaths potentially were avoidable among those who survived for at least 365 days and 90 days after diagnosis, respectively (Table 2), depending on the survivorship threshold.

Regardless of the survivorship threshold that was chosen, avoidable deaths, in large part, included patients who were relatively healthy (≤3 comorbid conditions) and did not receive any form of aggressive therapy (radical cystectomy, systemic chemotherapy,

Table 2. Estimating Avoidability of Death Among 6326 Patients Within a Surveillance, Epidemiology, and End Results–Medicare Data Population Who Died of Bladder Cancer

	Survivorship Threshold: No. of Patients (%)					
	>90 Days		>180 Days		>365 Days	
Criteria	Potentially Avoidable Death	Unavoidable Death	Potentially Avoidable Death	Unavoidable Death	Potentially Avoidable Death	Unavoidable Death
Interval <survivorship threshold		1060 (16.8)		1944 (30.7)		3293 (52.1)
Surgical death	39 (0.6)		25 (0.4)		16 (0.3)	
Metastases at diagnosis		386 (6.1)		233 (3.7)		95 (1.5)
Cystectomy						
Delay since diagnosis	467 (7.4)	802 (12.7)	457 (7.2)	666 (10.5)	401 (6.3)	417 (6.6)
Delayed by preceding chemotherapy	45 (0.7)	60 (0.9)	45 (0.7)	59 (0.9)	41 (0.6)	43 (0.7)
Other aggressive therapy						
Delay since diagnosis, otherwise healthy	457 (7.2)		444 (7)		368 (5.8)	
Delay since diagnosis, otherwise too unhealthy for cystectomy		65 (1)		64 (1)		49 (0.8)
No delay, otherwise healthy		243 (3.8)		206 (3.3)		117 (1.8)
No delay, otherwise too unhealthy for cystectomy		64 (1)		50 (0.8)		27 (0.4)
No aggressive therapy						
Otherwise healthy	1951 (30.8)		1615 (25.5)		1149 (18.2)	
Otherwise too unhealthy for cystectomy		687 (10.9)		518 (8.1)		310 (4.9)
Totals	2959 (46.8)	3367 (53.2)	2586 (40.8)	3740 (59.1)	1975 (31.2)	4351 (68.8)

external-beam radiotherapy). For example, if we assume that a patient who dies of cancer within 90 days of diagnosis is not salvageable by contemporary therapies, then the 1951 patients (30.8% of all patients who died of bladder cancer) who did not receive any form of aggressive therapy accounted for 65.9% of the potentially avoidable deaths under this assumption. In contrast, if we assume that the threshold for salvageability is living for at least 1 year, then 1149 patients (18.2% of all patients who died of bladder cancer), or 58.2% of potentially avoidable deaths, received no form of aggressive therapy. In contrast, the significance of delays in treatment to the bottom line of potentially avoidable deaths appeared to have a more limited impact. Although patients who had delays accounted for 41% (810 of 1975) of potentially avoidable deaths among the patients who lived for at least 1 year, this assumption represented only 12.8% (810 of 6326) of all bladder cancer deaths. In Figure 2, we provide an explicit breakdown of the assumptions that were used to generate the data for Table 2 for patients who had a survivorship threshold of >180 days.

Next, as we did with the clinical data, we measured the differences in patient and disease characteristics according to survivorship thresholds (Table 3). Similar to the clinical data, patients whose deaths were classified as potentially avoidable had nonmuscle-invasive disease (66.7% vs 24.7%; $P < .0001$) and lower grade disease (35.1% vs 15.1%; $P < .0001$). The median survival for patients who had potentially avoidable and unavoidable deaths according to survivorship threshold were >90 days (18 months vs 6.7 months, respectively; log-rank test, $P < .0001$), >180 days (20.9 months vs 5.6 months, respectively; log-rank test, $P < .0001$), and >365 days (27.3 months vs 6.8 months, respectively; log-rank test, $P < .0001$). In Figure 3B, we illustrate the Kaplan-Meier plots for patients who had a survivorship threshold of >180 days.

Finally, we explored in detail, those patients who presented without metastatic disease and received no aggressive therapy for their lethal bladder cancer (n = 2133; 48.7% of all bladder cancer deaths using a threshold of >180 days). Approximately 25% of these patients were aged <75 years, 33% presented with low-grade disease, and 59.6% had nonmuscle-invasive disease at some point during evaluation. Nonetheless, 1615 patients (72.9%) who received no therapy had ≤3 comorbidities

Table 3. Patient Demographics from Surveillance, Epidemiology, and End Results–Medicare Population

		Interval Between Diagnosis and Death								
		>90 Days			>180 Days			>365 Days		
Variable	Overall Population	Potentially Avoidable Death, %	Unavoidable Death, %	*P*	Potentially Avoidable Death, %	Unavoidable Death, %	*P*	Potentially Avoidable Death, %	Unavoidable Death, %	*P*
Age, y										
65-69	13.6	12.5	14.6	.007	13.1	14	.420	14.6	13.2	<.001
70-74	20.5	19.6	21.3		20.3	20.7		21.8	20	
75-79	22.8	22.6	23		23.2	22.5		23.9	22.3	
80-84	21	22.3	19.7		21.9	20.3		20.7	21.1	
≥85	22.1	22.9	21.4		21.5	22.5		19	23.5	
Sex										
Men	63.7	67.5	60.5	<.001	69.3	59.9	<.001	70.6	60.6	<.001
Women	36.3	32.5	39.5		30.7	40.1		29.4	39.4	
Race										
Black	6.5	5.7	7.3	.010	5.5	7.3	.010	5.1	7.2	<.001
Other	4.5	4.1	4.9		4.3	4.7		3.6	4.9	
White	89	90.2	87.9		90.3	88.1		91.3	87.9	
Socioeconomic status										
Low	33.3	32	34.5	.020	31.6	34.6	.240	30.2	34.8	<.001
Medium	33.3	33	33.6		33.5	33.2		33.5	33.2	
High	33.3	35	31.9		36	32.2		36.4	32	
Tumor classification*										
Ta/T1	37.9	55.1	22.9	<.001	59.2	23.1	<.001	66.7	24.7	<.001
T2	20.5	23.4	17.9		21.8	19.5		18.2	21.5	
T3	14.7	11.3	17.7		9.8	18.2		7.9	17.9	
T4	26.9	10.3	41.5		9.2	39.2		7.2	35.9	
Grade										
High	78.7	71.2	85.3	<.001	68.9	85.5	<.001	64.9	84.9	<.001
Low	21.3	28.8	14.7		31.2	14.5		35.1	15.1	

*See Green 2002.[1]

and potentially were candidates for some form of definitive therapy.

DISCUSSION

Roughly 33% of the 67,000 estimated new cases of bladder cancer in 2007 would present with muscle-invasive disease which, on average, affords a survival rate of 50% at 5 years.[20-22] The remaining 67% have nonmuscle-invasive disease that invariably recurs but generally is nonlethal if treated.[23] However, this population, in whom cancer-related mortality should be the exception, is typified by an equally dismal prognosis upon progression to muscle-invasive disease.[22,24] In both groups, a variety of considerations contribute to the lethality of bladder cancer, including patient (eg, comorbidity precluding treatment), physician (eg, conservative practice styles), and cancer biology,[5] among others. Ultimately, understanding these mechanisms of mortality is vital for focusing resources to reduce bladder cancer-related deaths. For example, if tumor biology is the predominant determinant of mortality, then developing new systemic agents and combinations would have the greatest impact. Conversely, if physician decision making plays a significant role, then altering current practice patterns (eg, lowering therapeutic thresholds for aggressive therapy) may afford the most efficient means of reducing mortality.

In the current study, we used 2 distinct sources of data to estimate empirically the percentage of bladder cancer deaths that potentially were avoidable. Although our criteria to classify patients and the absolute magnitude of the problem certainly are arguable, the conclusions are

supported by the similarity of the findings between the clinical and claims data. The implicit medical record review by a panel of 4 experts demonstrated that 31.7% of deaths potentially were avoidable at some point during their clinical course among patients who were treated at a tertiary care center. Similarly, medical claims data using explicit criteria to classify bladder cancer deaths revealed that between 31.2% and 46.8% of bladder cancer deaths potentially were avoidable, depending on the survival threshold chosen. Thus, although the majority of deaths appear to be because of the biologic properties of the bladder cancer, a significant percentage of patients may have died unnecessarily because of insufficiently aggressive therapy early in the disease course.

Collectively, these data support a 2-pronged approach to reducing bladder cancer mortality. First, improvements in chemotherapies clearly are needed to rescue patients who have unsalvageable disease. Treatment delays notwithstanding, approximately 50% of patients undergoing radical cystectomy for muscle-invasive disease ultimately die of bladder cancer, underscoring the shortcomings of the current paradigm.[16,22,25] On the basis of our implicit review of clinical data, 68.3% of patients received timely and appropriate therapy for their bladder cancer based on the extent of disease and contemporary practice patterns. These findings generally were confirmed by our review of claims data, which suggested that improvements in systemic therapy are necessary to making the greatest inroads into bladder cancer mortality. Second, alterations in the physician decision-making process are warranted. This would include improving the understanding of the biologic risks of conservative therapy and broadening the indications for aggressive therapy, including proceeding to cystectomy earlier in the disease evolution. Although the specter of over treatment must be considered, our clinical review suggests that the overuse of intravesical therapy and the underuse of systemic therapy may be contributory. Alternatively, improving the accuracy of clinical staging, with restaging transurethral resection or biomarkers of disease aggressiveness, might improve risk stratification and facilitate more tailored therapy to minimize over treatment.

We acknowledge that the magnitude of the avoidable death problem is arguable. Implicit reviews of clinical data are subjective, and our criteria used in claims data to identify the avoidability of death are only as good as the medical evidence and theory on which they are based.[26] However, the validity of our classification of death in the clinical review and claims algorithms is supported by the divergent time courses to death, as illustrated in the Kaplan-Meier plots and the patient characteristics of our cohorts. Furthermore, the purpose of the current study was not to quantify precisely the magnitude of avoidable deaths but rather to understand the extent to which current practice patterns play a contributory role in death. Thus, although our survivorship thresholds are arbitrary and our classifications of avoidable death imprecise, this study does serve to inform the popular debate surrounding the role of early cystectomy or other aggressive therapy. Finally, our estimates ignore patient preference for undergoing an alternative treatment course. Although previous reports clearly demonstrated the relative underuse of aggressive therapy in the elderly, it is possible that patient preference drove the observed treatment patterns.[5,27]

Despite these limitations, the current study demonstrates the significant contribution of both physician practice patterns and tumor biology to bladder cancer death. On the basis of clinical and administrative data, we estimate that between 31.2% and 46.8% of deaths potentially were avoidable. The validity of our findings is supported by the similarity of magnitude of the estimates between clinical and claims populations. Not surprisingly, patients with potentially avoidable deaths had a significantly prolonged course, suggesting that there was ample opportunity for aggressive therapy. Nonetheless, the majority of bladder cancer deaths in both patient populations most likely were the result of aggressive tumor biology, suggesting that better systemic therapies also are needed.

Conflict of Interest Disclosures

Supported by the American Cancer Society Pennsylvania Division.

Dr. Hollenbeck was supported by the Dr. William and Rita Conrady Mentored Research Scholar Grant (MSRG-07-006-01-CPHPS), the American Urological Association Foundation, and Astellas Pharma US, Inc.

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