## Title

Carbonic anhydrase-IX score is a novel biomarker that predicts recurrence and survival for high-risk, nonmetastatic renal cell carcinoma: Data from the phase III ARISER clinical trial



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## Authors

Chamie, Karim
Klöpfer, Pia
Bevan, Paul
et al.

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# Treatment and survival in patients with recurrent high-risk non–muscle-invasive bladder cancer

**Karim Chamie, M.D., M.S.H.S.**[a,b,*], **Eric Ballon-Landa**[a], **Timothy J. Daskivich, M.D.**[a,b], **Jeffrey C. Bassett, M.D., M.P.H.**[a,b], **Julie Lai, M.S.**[c], **Jan M. Hanley, M.S.**[c], **Badrinath R. Konety, M.D., M.B.A.**[d], **Mark S. Litwin, M.D., M.P.H.**[a,b,c,e], **Christopher S. Saigal, M.D., M.P.H.**[a,b,c], and **Urologic Diseases in America Project**

[a] Health Services Research Group, Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles, CA

[b] Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at UCLA, Los Angeles, CA

[c] *RAND Corporation, Santa Monica, CA*

[d] Department of Urology, University of Minnesota, Minneapolis, MN

[e] Department of Health Services, University of California Los Angeles, School of Public Health, Los Angeles, CA

## Abstract

**Background—**Multiple recurrences develop in patients with high-risk non–muscle-invasive bladder cancer. As neither the association of recurrences with survival nor the subsequent aggressive treatment in individuals with recurrent high-grade non–muscle-invasive bladder cancer has ever been quantified, we sought to determine whether the increasing number of recurrences is associated with higher subsequent treatment and mortality rates.

**Methods—**Using linked Surveillance, Epidemiology, and End Results–Medicare data, we identified subjects with recurrent high-grade, non–muscle-invasive disease diagnosed in 1992 to 2002 and followed up until 2007. Using competing-risks regression analyses, we quantified the incidence of radical cystectomy, radiotherapy, and systemic chemotherapy after each recurrence. We then performed a propensity-score adjusted competing-risks regression analysis to determine whether the increasing recurrences portend worse survival.

**Results—**Of 4,521 subjects, 2,694 (59.6%) had multiple recurrences within 2 years of diagnosis. Compared with patients who only had 1 recurrence, those with ≥4 recurrences were less likely to undergo radical cystectomy (hazard ratio [HR] = 0.73, 95% CI: 0.58–0.92), yet more likely to undergo radiotherapy (HR = 1.51, 95% CI: 1.23–1.85) and systemic chemotherapy (HR = 1.58, 95% CI: 1.15–2.18). For patients with ≥4 recurrences, only 25% were treated with curative intent. The 10-year cancer-specific mortality rates were 6.9%, 9.7%, 13.7%, and 15.7% for those with 1, 2, 3, and ≥4 recurrences, respectively.



* Corresponding author. Tel.: +1-310-794-2526; fax: +1-310-794-2538. kchamie@mednet.ucla.edu (K. Chamie)..

**Conclusions—**Only 25% of patients with high-risk non–muscle-invasive bladder cancer who experienced recurrences at least 4 times underwent radical cystectomy or radiotherapy. Despite portending worse outcomes, increasing recurrences do not necessarily translate into higher treatment rates.

### Keywords

Urinary bladder neoplasms; Recurrence; Progression; Bladder cancer mortality; Quality of healthcare

## 1. Introduction

Over the last 15 years, bladder cancer–related mortality has reduced by only 5%, whereas cancer-specific mortality rates have decreased more precipitously for other malignancies [1]. Despite established best-practice guidelines, widespread adoption of effective measures has lagged [2,3]. In a prior study examining claims from 4,514 patients with high-risk, non–muscle-invasive bladder cancer, we found that only 1 patient received all elements of recommended treatment, despite a process-outcome link [4,5]. The improved survival following more frequent surveillance and instillation of intravesical therapy is partly attributable to the nature of the disease—recurrence is seen in nearly three-fourths of the patients, and disease progression is seen in a significant number [6].

Although the timing of aggressive intervention is debated, the fact that progression is associated with increased cancer-related mortality is not; therefore, the goal is to administer definitive treatment before the onset of muscle invasion [7]. Patients who experience a delay in receiving definitive treatment, in favor of less effective intravesical therapy, have worsened survival rates [8–10].

In this context, we sought to answer the questions, “Are patients with multiple recurrences more likely to receive aggressive treatment? Also, are increasing number of recurrences necessarily associated with worse outcomes?” Although we hypothesized that patients with high-risk non– muscle-invasive bladder cancer with recurrent disease would be undertreated with respect to these aggressive modalities, we anticipated that with increasing recurrences, the incidence of aggressive treatment would increase correspondingly.

## 2. Materials and methods

### 2.1. Data source

We used the linked Surveillance, Epidemiology, and End Results (SEER)–Medicare database of the National Cancer Institute to identify patients diagnosed with bladder cancer in 1992 to 2002. SEER data are linked with 100% of Medicare claims from inpatient, outpatient, and national claims history files. The study was restricted to subjects who had Medicare Fee-for-Service coverage, and for whom Medicare Parts A and B claims data were available 12 months before bladder cancer diagnosis [11].

### 2.2. Study population

The cohort comprised individuals of 66 years of age or older, with at least 1 recurrence of nonmetastatic, high-grade, non–muscle-invasive urothelial bladder cancer diagnosed between January 1, 1992 and December 31, 2002, for whom claims data were available through 2007. We limited our cohort to those 66 years or older to allow at least 1 year of eligibility in Medicare before diagnosis to ascertain comorbidity data.

### 2.3. Study variables

We determined patient age, sex, race/ethnicity, marital status, tumor grade, tumor stage, and year of diagnosis. We imputed subject socioeconomic status using 2000 US Census data to derive quartiles of ZIP code-level median household income and percentage of residents ≥25 years of age with at least 4 years of college education [12]. We used the modification by Klabunde et al. [14] of the Charlson comorbidity index to quantify severity of preexisting comorbidities [13]. We limited our cohort to those who have had least one additional transurethral resection of a bladder tumor beyond 60 days but within 2 years of an initial diagnosis. The purpose of this was to capture new recurrences outside the 60-day claims window of the initial resection but within 2 years of diagnosis—when patients often declare themselves either with aggressive tumors necessitating definitive treatment, or those following a more indolent course.

We stratified our cohort based upon the number of recurrences, and observed the probability of receiving subsequent treatment. Treatment was defined as the receipt of radical cystectomy, radiotherapy, or systemic chemo-therapy anytime in the follow-up period. Treatment was defined in a hierarchical manner with radical cystectomy first, followed by radiotherapy, and systemic chemotherapy. Radical cystectomy included those who underwent a radical cystectomy alone, radical cystectomy and radiotherapy (before or after cystectomy), radical cystectomy and systemic chemotherapy (before or after cystectomy), and radical cystectomy in combination with radiotherapy and systemic chemotherapy. Radiotherapy included those who underwent a radiotherapy alone, as well as radiotherapy with systemic chemotherapy (before or after radiotherapy). Systemic chemotherapy included only those who underwent systemic chemotherapy alone.

We performed further analyses of treatment in conditions conducive to aggressive treatment, defined as those patients with characteristics most suited for aggressive intervention: age <70 years, without any comorbid conditions, with undifferentiated T1 tumors treated at an academic cancer centers.

### 2.4. Statistical analysis

Correlation between categorical variables and the number of recurrences was derived by chi-square analyses. As patients may die, we used a maximum likelihood, competing-risks regression model as described by Fine and Gray [15] to determine aggressive treatment rates. We performed competing-risks regression analyses to characterize the incidence of radical cystectomy, radiotherapy, and systemic chemotherapy. Estimates are reported as subhazard ratios, with corresponding 95% CIs that accounted for potential clustering using the Huber-White sandwich variance estimator.

To quantify the association of recurrence with bladder cancer mortality, we generated multivariate multinomial inverse probability of treatment weights. This multivariate multinomial model sought to examine the association of recurrences with bladder cancer mortality, after adjusting for covariates. The inverse probability of treatment weights was then included in the competing-risks regression analysis.

We conducted all analyses with STATA software 13.0 (StataCorp, College Station, TX). All statistical tests were 2 tailed, and the probability of a type I error was set at 0.05. The institutional review board at University of California, Los Angeles exempted our study.

## 3. Results

Cohort characteristics are listed in Table 1. Within 2 years of diagnosis, 1,827 patients (40.4%) experienced 1 recurrence, 1,071 (23.7%) experienced 2 recurrences, 616 (13.6%) experienced 3 recurrences, and 1,007 (22.3%) experienced ≥4 recurrences (Table 2). On bivariate analysis, we found that the increased incidence of recurrence was associated with younger age (<75), marital status (married), median household income (>$45,000 per year), region (Midwest and Northeast), year of diagnosis (before 1998), institution type (academic centers), and tumor grade (poorly differentiated).

Decreased incidence of radical cystectomy was observed with advancing age (≥70 y), male sex, non-married status, comorbid conditions (Charlson 1), and people experiencing 4 or more recurrences within 2 years of diagnosis (Table 3). Conversely, increased incidence of radical cystectomy was associated with female sex, married status, median household income (>$55,000), unknown institution type, and tumor stages Tis and T1. Decreased incidence of radiotherapy was only observed with year of diagnosis (for each year after 1992); increased incidence of radiotherapy was observed with unknown institution type, undifferentiated tumor grade, tumor stage T1, and people experiencing 2 or more recurrences. Treatment with systemic chemotherapy was more frequent with black race, median household income ($35,000–$45,000), and people experiencing 4 or more recurrences within 2 years of diagnosis.

The cumulative incidence of undergoing aggressive treatment at 2, 5, and 10 years from the competing-risks regression analyses was derived for the group as a whole (Fig. 1). The incidence of radical cystectomy at 10 years was 10%, 9%, 9%, and 7% in patients with 1, 2, 3, and ≥4 recurrences, respectively. Correspondingly, The incidence of radiotherapy at 10 years was 13%, 16%, 17%, and 18%. The incidence of systemic chemotherapy at 10 years was 4%, 4%, 4%, and 7%, respectively. Therefore, the incidence of treatment for curative intent (radical cystectomy and radiotherapy) at 10 years was 23%, 25%, 26%, and 25% after 1, 2, 3, and ≥4 recurrences, respectively.

As the decision to pursue aggressive medical intervention must consider many factors, we restricted our analysis to treatment practices in an environment conducive to aggressive treatment (Fig. 2). Among this group of patients most amenable to aggressive intervention, at 10 years, 38%, 37%, 35%, and 30% underwent radical cystectomy after 1, 2, 3, and ≥4 recurrences, respectively. Correspondingly, the incidence of radiotherapy at 10 years was

9%, 11%, 12%, and 13% and the incidence of systemic chemotherapy at 10 years was 8%, 7%, 8%, and 13%. In this ideal cohort of patients, the incidence of treatment for curative intent at 10 years was 47%, 48%, 47%, and 43% after 1, 2, 3, and ≥4 recurrences, respectively.

After 5 years, when compared with patients who had 1 recurrence (4.3%), those with 2 (6.1%, $P = 0.03$), 3 (8.6%, $P < 0.01$), and at least 4 recurrences (9.9%, $P < 0.01$) were more likely to die of bladder cancer (Table 4). After 10 years, the mortality rates were 6.9% (referent), 9.7% ($P = 0.03$), 13.7% ($P < 0.01$), and 15.7% ($P < 0.01$) for patients with 1, 2, 3, and ≥4 recurrences, respectively.

## 4. Discussion

Our study has 4 principal findings. Firstly, we demonstrated that among patients with recurrent high-grade non–muscle-invasive bladder cancer, 60% experienced more than 1 recurrence during this time. In light of widespread provider noncompliance, it reaffirms the importance of frequent surveil-lance as recommended by multiple urologic associations [2,3].

Secondly, we found broad divergence in the aggressive treatment of patients with bladder cancer. With increasing recurrences, patients are more apt to receive radiotherapy or systemic chemotherapy and less likely to undergo radical cystectomy. Although the incidence of cystectomy is much higher in conditions conducive for aggressive treatment, the inverse association between recurrence and cystectomy is preserved. Therefore, if patients undergo cystectomy, they tend to have the procedure after the first recurrence. Specifically, patients that are concerned about progression —owing to grade, stage, or relative discomfort with the risk of tumor progression—will likely choose to proceed with aggressive therapy much earlier, leaving the rest of the cohort to continue the endoscopic management of these tumors. We can speculate whether the patient or the provider dictates this discordance; yet in the context of optimal conditions, so favorable to aggressive treatment, the fact that the cystectomy rates do not increase accordingly suggests that patients and their providers may become increasingly comfortable with bladder preservation. Alternatively, patients may be unwilling or unable to endure the effect that adverse events associated with aggressive treatment may have on their psychological well-being.

Thirdly, we found that the cumulative incidence of aggressive treatment of any type was surprisingly low. Even for patients who have experienced ≥4 recurrences, only 25% were treated with radical cystectomy or radio-therapy within 10 years of diagnosis, whereas 43% were similarly treated in an environment conducive for aggressive treatment. Some have attributed it on an overreliance of intravesical therapy with subsequent delay to cystectomy and worsened survival [10,19]. We found that a minority of patients (14% overall, 27% in an environment conducive for aggressive treatment) receive treatment within this critical period.

Fourthly, with increasing recurrences, we find an increase in the incidence of cancer-related death. Although we are clearly not the first to demonstrate the association of recurrence with

mortality, this is the first population-level analysis to demonstrate this finding. There is a 2% absolute increase in the incidence of bladder cancer death per recurrence at 5 years and 3% absolute increase per recurrence at 10 years. Catalona et al. [20] demonstrated that with every increase in intravesical therapy, the risk of metastases increases from 5% at entry to 11% after 1 failed course to 50% after 2 or more failed courses. Herr and Sogani [9] noted that even in patients with noninvasive tumors, early cystectomy (within 2 y) was associated with improved survival when compared with those who had a delay (92% vs. 56%, log-rank $P = 0.003$). Lambert et al. [10] found that the 5-year disease-free survival rate decreased from 69.7% to 39.6% (log-rank $P = 0.05$), with the use of additional courses of intravesical therapy and delay in treatment. Although our population-level analysis demonstrates that the 5- and 10-year cancer-specific mortality rates increase with more frequent recurrences, the effect size was not quite as profound as the aforementioned single-institution series. Although increasing recurrences portend worse bladder cancer–specific survival, the magnitude is significantly diminished in the context of overall survival. Only patients with 4 or more recurrences within a 2-year period have worse overall survival (data not shown).

Although our sample size was large and our statistical methodology was robust, our study has methodological limitations. Particularly, patient preferences for conservative management may have eroded our rates of aggressive therapy. For instance, this is a cohort with at least 1 recurrence and a nonnegligible proportion may have had aggressive treatment up front before proceeding. A second limitation was the use of the SEER-Medicare database, whereby our patient population was restricted to those ≥66 years old. However, because bladder cancer is most frequent in this cohort, our findings remain generalizable to the broader population [21]. A third limitation is the use of treatment codes to define recurrence and treatment. Coding may imperfectly reflect the medical decision making of providers, who may administer treatments for various reasons. Some endoscopic procedures may be performed for suspicious lesions that ultimately turn out to be benign; conversely, some patients may not receive treatment for small, asymptomatic papillary lesions. Nevertheless, in the absence of restaging data, we anticipate that most patients with high-grade non–muscle-invasive cancer who have experienced recurrence will be treated or, if left untreated, will ultimately progress and die of their disease. Similarly, our definition of recurrence does not account for restaging endoscopic resections. However, although some of these patients may have undergone a restaging resection for high-grade disease [22], Skolarus et al. [23] have found that this is rarely done (<8% of patients with high-grade disease). However, this does not detract from our principal finding, that more recurrences were no more likely to undergo aggressive treatment. Fourth, SEER captures staging and treatment data during the first 6 months after diagnosis. Therefore, staging beyond the 6-month period is not available, and we may be overstating the underutilization rate among patients who may have had recurrence with lower grade and stage disease. Furthermore, the reason for treatment may not always be for a curative intent (such as palliative cystectomy or radiotherapy for bleeding). However, this would suggest that the treatment rate for curative intent may actually be lower than our reported findings. Finally, the study is limited by the absence of detailed information on the World Health Organization grading of urothelial carcinoma, amount of carcinoma in situ as well as the type, number and size of cancer, and duration of intravesical therapy. Either this information is not available in SEER

data (SEER grading used in lieu of World Health Organization grading and absence of amount of carcinoma in situ) or it is outside the scope of this article (type, number, and duration of intravesical therapy). It is very probable that smaller and more indolent high-grade tumors are more likely to be treated with endoscopic resections and intravesical therapy. Although we do not have information on size or quantity of tumors, we do have information on grade and stage. Using grade and stage as a proxy for tumor aggressiveness, then we partially adjust for this limitation. In Table 3, we have demonstrated that patients with more aggressive disease (e.g., higher grade and stage) were more likely to undergo aggressive treatment with radiation and cystectomy.

Despite these limitations, we have identified several important findings in the management of patients with high-risk non–muscle-invasive bladder cancer: first, recurrence will occur more than once within 2 years of diagnosis in most patients who experience it; second, with multiple recurrences the probability of radical cystectomy decreases, whereas the probability of radiotherapy and systemic chemotherapy increases; third, three-quarters of patients who have experienced at least 4 recurrences do not receive treatment with curative intent within 10 years of diagnosis; and fourth, more frequent recurrences portend a worse prognosis. Physicians should closely monitor such patients for recurrence, and they should offer aggressive therapy to patients before they progress to invasive disease, thereby greatly diminishing the risk of bladder cancer–related death.

## 5. Conclusion

Only 25% of patients with high-risk non–muscle-invasive bladder cancer underwent radical cystectomy or radio-therapy after experiencing a recurrence 4 or more times. Increasing recurrences did not alter the aggressive treatment rate, despite the clear association between recurrences and worse survival.

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**Precis**

Despite portending worse outcomes, approximately 75% of patients with high-risk non–muscle-invasive bladder cancer who recur 4 or more times within 2 years of diagnosis do not undergo aggressive treatment.

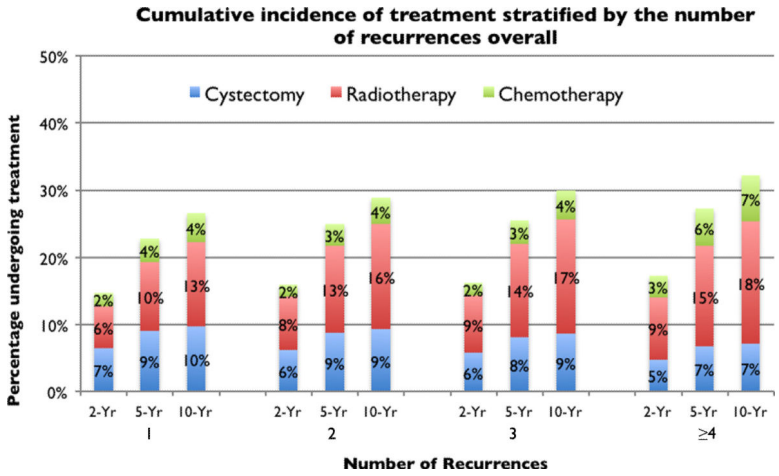


**Fig. 1.**

Cumulative incidence of treatment stratified by the number of recurrences overall. (Color version of figure is available online.)

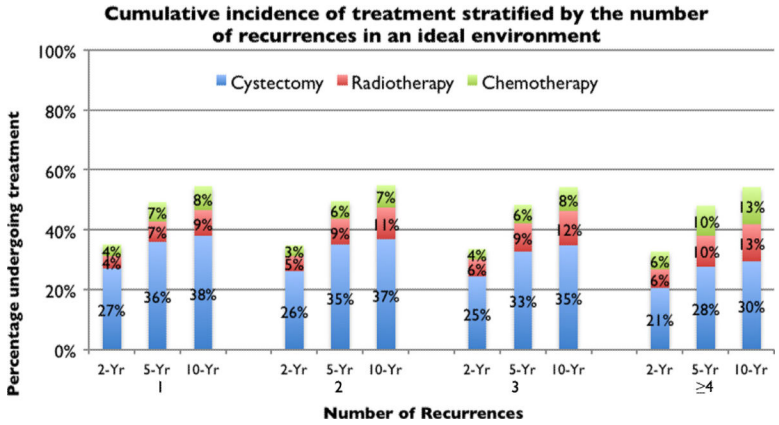


**Fig. 2.**

Cumulative incidence of treatment stratified by the number of recurrences in an ideal environment. (Color version of figure is available online.)

## Table 1

Cohort characteristics ($n$ = 4,521)

| Variables | Distribution | % |
|---|---|---|
| Age group, y | | |
| 66–69 | 616 | 13.6 |
| 70–74 | 1,138 | 25.2 |
| 75–79 | 1,148 | 25.4 |
| ≥80 | 1,619 | 35.8 |
| Sex | | |
| Male | 3,441 | 76.1 |
| Female | 1,080 | 23.9 |
| Race/ethnicity | | |
| White | 4,141 | 91.6 |
| Black | 133 | 3.0 |
| Hispanic | 101 | 2.2 |
| Other | 146 | 3.2 |
| Marital status | | |
| Other | 1,643 | 26.3 |
| Married | 2,878 | 63.7 |
| Charlson score | | |
| 0 | 3,039 | 67.2 |
| 1 | 990 | 21.9 |
| 2 | 326 | 7.2 |
| ≥3 | 166 | 3.7 |
| % With ≥ 4 y of college education | | |
| <15% | 953 | 21.1 |
| 15%–25% | 1,161 | 25.7 |
| 25%–35% | 965 | 21.3 |
| > 35% | 1,442 | 31.9 |
| Median household income | | |
| < $35,000 | 749 | 16.6 |
| $35,000–$45,000 | 1,060 | 23.5 |
| $45,000–$55,000 | 1,150 | 25.4 |
| > $55,000 | 1,562 | 34.5 |
| Region | | |
| West | 2,117 | 46.8 |
| Midwest | 999 | 22.1 |
| South | 417 | 9.2 |
| Northeast | 988 | 21.9 |
| Year of diagnosis | | |
| 1992–1997 | 1,809 | 40.0 |
| 1998–2002 | 2,712 | 60.0 |

| Variables | Distribution | % |
|---|---|---|
| Institution type | | |
| Nonacademic noncancer center | 3,102 | 68.6 |
| Academic noncancer center | 1,023 | 22.6 |
| Academic cancer center | 108 | 2.4 |
| Unknown | 288 | 6.4 |
| Grade | | |
| Poorly differentiated | 3,552 | 78.6 |
| Undifferentiated | 969 | 21.4 |
| Stage | | |
| Ta | 1,414 | 31.3 |
| Tis | 440 | 9.7 |
| T1 | 2,667 | 59.0 |

## Table 2

Cohort characteristics stratified by recurrences

| Variables | 1 Recurrence (*n* = 1,827) | 2 Recurrences (*n* = 1,071) | 3 Recurrences (*n* = 616) | ≥ 4 Recurrences (*n* = 1,007) | *P* value |
|---|---|---|---|---|---|
| Age group, y | | | | | < 0.01 |
| 66–69 | 248 (13.6%) | 137 (12.8%) | 87 (14.1%) | 144 (14.3%) | |
| 70–74 | 399 (21.8%) | 272 (25.4%) | 163 (26.5%) | 304 (30.2%) | |
| 75–79 | 465 (25.5%) | 284 (26.5%) | 153 (24.8%) | 246 (24.4%) | |
| ≥80 | 715 (39.1%) | 378 (35.3%) | 213 (34.6%) | 313 (31.1%) | |
| Sex | | | | | 0.16 |
| Male | 1,367 (74.8%) | 811 (75.7%) | 474 (76.9%) | 789 (78.3%) | |
| Female | 460 (25.2%) | 260 (24.3%) | 142 (23.1%) | 218 (21.7%) | |
| Race/ethnicity | | | | | 0.19 |
| White | 1,659 (90.8%) | 976 (91.1%) | 569 (92.4%) | 937 (93.0%) | |
| Black | 53 (2.9%) | 29 (2.7%) | 20 (3.3%) | 31 (3.1%) | |
| Hispanic | 44 (2.4%) | 24 (2.3%) | 12 (1.9%) | 21 (2.1%) | |
| Other | 71 (3.9%) | 42 (3.9%) | 15 (2.2%) | 18 (1.8%) | |
| Marital status | | | | | 0.04 |
| Other | 705 (38.6%) | 389 (36.3%) | 209 (33.9%) | 340 (33.8%) | |
| Married | 1,122 (61.4%) | 682 (63.7%) | 407 (66.1%) | 667 (66.2%) | |
| Charlson score | | | | | 0.25 |
| 0 | 1,190 (65.1%) | 717 (67.0%) | 424 (68.8%) | 708 (70.3%) | |
| 1 | 420 (23.0%) | 237 (22.1%) | 136 (22.1%) | 197 (19.6%) | |
| 2 | 147 (8.1%) | 76 (7.1%) | 34 (5.5%) | 69 (6.8%) | |
| ≥3 | 70 (3.8%) | 41 (3.8%) | 22 (3.6%) | 33 (3.3%) | |
| % With ≥4 y of college | | | | | 0.08 |
| <15% | 399 (21.8%) | 249 (23.2%) | 119 (19.3%) | 186 (18.5%) | |
| 15%–25% | 472 (25.8%) | 257 (24.0%) | 145 (23.5%) | 287 (28.5%) | |
| 25%–35% | 390 (21.4%) | 230 (21.5%) | 136 (22.1%) | 209 (20.7%) | |
| > 35% | 566 (31.0%) | 335 (31.3%) | 216 (35.1%) | 325 (32.3%) | |
| Median household income | | | | | 0.03 |
| < $35,000 | 306 (16.8%) | 197 (18.4%) | 104 (16.9%) | 142 (14.1%) | |
| $35,000–$45,000 | 454 (24.8%) | 261 (24.4%) | 123 (20.0%) | 222 (22.1%) | |
| $45,001–$55,000 | 464 (25.4%) | 254 (23.7%) | 159 (25.8%) | 273 (27.1%) | |
| > $55,000 | 603 (33.0%) | 359 (33.5%) | 230 (37.3%) | 370 (36.7%) | |
| Region | | | | | < 0.01 |
| West | 927 (50.7%) | 513 (47.9%) | 274 (44.5%) | 403 (40.0%) | |
| Midwest | 389 (21.3%) | 222 (20.7%) | 134 (21.7%) | 254 (25.2%) | |
| South | 164 (9.0%) | 111 (10.4%) | 64 (10.4%) | 78 (7.8%) | |
| Northeast | 347 (19.0%) | 225 (21.0%) | 144 (23.4%) | 272 (27.0%) | |
| Year of diagnosis | | | | | < 0.01 |
| 1992–1997 | 699 (38.3%) | 384 (35.9%) | 253 (41.1%) | 473 (47.0%) | |
| 1998–2002 | 1,128 (61.7%) | 687 (64.1%) | 363 (58.9%) | 534 (53.0%) | |

| Variables | 1 Recurrence (*n* = 1,827) | 2 Recurrences (*n* = 1,071) | 3 Recurrences (*n* = 616) | ≥ 4 Recurrences (*n* = 1,007) | *P* value |
|---|---|---|---|---|---|
| Institution type | | | | | < 0.01 |
| Nonacademic noncancer | 1,302 (71.3%) | 744 (69.5%) | 408 (66.2%) | 648 (64.3%) | |
| Academic noncancer | 367 (20.1%) | 250 (23.3%) | 153 (24.8%) | 253 (25.1%) | |
| Academic cancer | 35 (1.9%) | 19 (1.8%) | 22 (3.6%) | 32 (3.2%) | |
| Unknown | 123 (6.7%) | 58 (5.4%) | 33 (5.4%) | 74 (7.4%) | |
| Grade | | | | | < 0.01 |
| Poorly differentiated | 1,410 (77.2%) | 821 (76.7%) | 503 (81.7%) | 818 (81.2%) | |
| Undifferentiated | 417 (22.8%) | 250 (23.3%) | 113 (18.3%) | 189 (18.8%) | |
| Stage | | | | | 0.64 |
| Ta | 576 (31.5%) | 337 (31.5%) | 182 (29.5%) | 319 (31.7%) | |
| Tis | 169 (9.3%) | 96 (9.0%) | 65 (10.6%) | 110 (10.9%) | |
| T1 | 1,082 (59.2%) | 638 (59.6%) | 369 (59.9%) | 578 (57.4%) | |

## Table 3

Multivariate competing-risks regression analysis of incidence of subsequent treatment

| Variables | Radical cystectomy HR (95% CI) | Radiotherapy HR (95% CI) | Systemic chemotherapy HR (95% CI) |
|---|---|---|---|
| Age group, y | | | |
| 66–69 | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| 70–74 | 0.70 (0.56–0.89)[a] | 0.97 (0.74–1.27) | 1.14 (0.75–1.74) |
| 75–79 | 0.59 (0.46–0.75)[a] | 1.14 (0.87–1.48) | 1.03 (0.67–1.60) |
| ≥80 | 0.22 (0.16–0.29)[a] | 1.22 (0.94–1.57) | 0.73 (0.47–1.14) |
| Sex | | | |
| Male | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Female | 1.27 (1.03–1.59)[a] | 0.99 (0.81–1.20) | 1.06 (0.76–1.48) |
| Race/ethnicity | | | |
| White | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Black | 0.72 (0.38–1.34) | 1.45 (0.95–2.22) | 2.25 (1.25–4.05)[a] |
| Hispanic | 1.02 (0.57–1.82) | 0.91 (0.52–1.59) | 0.74 (0.23–2.34) |
| Other | 1.00 (0.62–1.60) | 1.17 (0.75–1.81) | 0.65 (0.24–1.79) |
| Marital status | | | |
| Other | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Married | 1.26 (1.02–1.55)[a] | 0.98 (0.82–1.17) | 1.10 (0.81–1.49) |
| Charlson score | | | |
| 0 | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| 1 | 0.72 (0.57–0.91)[a] | 1.01 (0.83–1.22) | 1.20 (0.88–1.64) |
| 2 | 0.83 (0.57–1.21) | 0.95 (0.69–1.29) | 0.94 (0.54–1.64) |
| ≥3 | 0.62 (0.34–1.12) | 1.02 (0.67–1.54) | 0.25 (0.06–1.04) |
| % With ≥4 y of college | | | |
| <15% | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| 15%–25% | 1.03 (0.78–1.36) | 1.16 (0.92–1.48) | 0.93 (0.60–1.43) |
| 25%–35% | 0.77 (0.55–1.07) | 1.00 (0.75–1.33) | 1.36 (0.84–2.19) |
| > 35% | 0.91 (0.64–1.27) | 1.00 (0.74–1.36) | 1.01 (0.59–1.73) |
| Median household income | | | |
| < $35,000 | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| $35,000–$45,000 | 0.98 (0.71–1.35) | 0.91 (0.70–1.19) | 1.74 (1.07–2.82)[a] |
| $45,000–$55,000 | 1.22 (0.88–1.69) | 1.05 (0.80–1.39) | 1.38 (0.82–2.33) |
| > $55,000 | 1.49 (1.04–2.13)[a] | 0.93 (0.67–1.27) | 1.26 (0.70–2.27) |
| Region | | | |
| West | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Midwest | 0.94 (0.73–1.20) | 1.00 (0.80–1.25) | 1.31 (0.90–1.90) |
| South | 1.08 (0.79–1.47) | 0.99 (0.74–1.32) | 1.42 (0.86–2.35) |
| Northeast | 0.93 (0.73–1.19) | 1.18 (0.95–1.46) | 1.16 (0.79–1.71) |

| Variables | Radical cystectomy HR (95% CI) | Radiotherapy HR (95% CI) | Systemic chemotherapy HR (95% CI) |
|---|---|---|---|
| Year of diagnosis | | | |
| 1992 | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Subsequent year thereafter | 0.98 (0.95–1.01) | 0.97 (0.95–1.00)[a] | 1.00 (0.96–1.04) |
| Institution type | | | |
| Nonacademic noncancer | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Academic noncancer | 1.00 (0.79–1.27) | 0.93 (0.76–1.13) | 1.24 (0.88–1.73) |
| Academic cancer | 1.49 (0.93–2.38) | 0.60 (0.33–1.10) | 1.79 (0.89–3.61) |
| Unknown | 1.41 (1.02–1.94)[a] | 1.35 (1.01–1.82)[a] | 1.32 (0.78–2.21) |
| Grade | | | |
| Poorly differentiated | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Undifferentiated | 1.18 (0.96–1.45) | 1.22 (1.01–1.48)[a] | 1.23 (0.89–1.71) |
| Stage | | | |
| Ta | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Tis | 3.04 (2.13–4.34)[a] | 0.86 (0.61–1.20) | 0.97 (0.58–1.64) |
| T1 | 3.57 (2.73–4.66)[a] | 1.50 (1.25–1.80)[a] | 1.14 (0.84–1.55) |
| Recurrence | | | |
| 1 | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| 2 | 0.96 (0.77–1.21) | 1.28 (1.04–1.58)[a] | 0.89 (0.61–1.31) |
| 3 | 0.89 (0.68–1.16) | 1.39 (1.09–1.76)[a] | 0.97 (0.62–1.52) |
| ≥4 | 0.73 (0.58–0.92)[a] | 1.51 (1.23–1.85)[a] | 1.58 (1.15–2.18)[a] |

[a]Statistical significance with a $P < 0.05$.

## Table 4

Propensity-score adjusted competing-risk regression analysis quantifying the association of number recurrences with cancer-specific survival

| | HR (95% CI) | P value | 5-y Mortality (%) | 10-y Mortality (%) |
|---|---|---|---|---|
| 1 Recurrence | Referent | Referent | 4.3 | 6.9 |
| 2 Recurrences | 1.44 (1.03–2.01) | 0.03 | 6.1 | 9.7 |
| 3 Recurrences | 2.06 (1.45–2.92) | <0.01 | 8.6 | 13.7 |
| ≥4 Recurrences | 2.39 (1.78–3.21) | <0.01 | 9.9 | 15.7 |