

Increased utilization of external beam radiotherapy relative to cystectomy for localized, muscle-invasive bladder cancer: a SEER analysis

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Abbreviations used: ACM, all-cause mortality; CSM, cause-specific mortality; CSS, cause-specific survival; MIBC, muscle-invasive bladder cancer; OS, overall survival; RT, radiotherapy; SEER, surveillance, epidemiology, and end results program

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ABSTRACT

OBJECTIVE: To assess recent utilization patterns of radiotherapy (RT) relative to cystectomy for muscle-invasive bladder cancer (MIBC) and evaluate survival trends over time in patients receiving RT.

MATERIALS AND METHODS: The surveillance, epidemiology, and end results program (SEER) was used to identify patients diagnosed between 1992 and 2013 with localized MIBC. Patients with a prior history of non-bladder malignancy, who received no treatment, or did not have available treatment information, were excluded. Treatment utilization patterns were assessed using Cochran-Armitage tests for trend, and patient characteristics were compared using chi-square tests. Overall survival (OS) and cause-specific survival (CSS) were estimated using the Kaplan-Meier method. All-cause (ACM) and cause-specific mortality (CSM) were evaluated with multivariable Cox proportional hazards regression.

RESULTS: Of 16175 patients analyzed, 11917 (74%) underwent cystectomy, and 4258 (26%) were treated with RT. Patients who received RT were older (median age 79 vs. 68, $P < 0.01$). Over time, the proportion of patients receiving RT relative to cystectomy increased (24% 1992–2002 vs. 28% 2003–2013, $P < 0.01$), despite median patient age throughout the study period remaining unchanged (71 for each 1992–2002 and 2003–2013, $P = 0.41$). For RT, compared with patients diagnosed earlier, those diagnosed from 2010–2013 showed improved OS (64% vs. 60% at 1 year, $P < 0.01$; 38% vs. 29% at 3 years, $P < 0.01$) and CSS (71% vs. 67% at 1 year, $P = 0.01$; 51% vs. 40% at 3 years, $P < 0.01$). On multivariable analysis, diagnosis from 2010–2013 was associated with a lower estimated risk of ACM (hazard ratio 0.77; 95% confidence interval 0.66–0.89, $P < 0.001$) and CSM (hazard ratio 0.81; 95% confidence interval 0.67–0.97, $P = 0.02$).

CONCLUSION: Utilization of RT for localized MIBC increased relative to cystectomy from 1992 to 2013, despite the median age of treated patients remaining unchanged. More recent survival outcomes for patients receiving RT were improved, supporting continued use of bladder preservation strategies utilizing RT.

Keywords: bladder cancer, SEER, radiotherapy, cystectomy

INTRODUCTION

Bladder cancer will afflict an estimated 80000 patients in 2017 and result in 17000 deaths [1]. While most patients present with superficial tumors that are highly treatable, 30% have muscle-invasive disease that carries a higher risk of progression and mortality [2]. For patients with

muscle-invasive bladder cancer (MIBC), radical cystectomy is the most commonly used definitive treatment, and large surgical series report 5-year overall survival (OS) rates nearing 60% [3–6]. However, for appropriately selected patients, bladder preservation therapy consisting of maximal transurethral resection of bladder tumor followed by external beam radiotherapy (RT) typically with concurrent chemotherapy stands

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as a reasonable alternative [7,8].

Multiple prospective trials have demonstrated bladder preservation therapy to be feasible, with favorable results that are comparable to those obtained with cystectomy [8-12]. Nonetheless, prior population-based studies showed that RT for bladder preservation is infrequently utilized as compared with surgery. A Surveillance, Epidemiology, and End Results program (SEER) analysis of patients with localized MIBC diagnosed from 1988 to 2006 showed that 86% of patients had surgery, 11% received RT, and that utilization rates of RT did not increase over that timeframe [13]. A notable limitation of that study was that RT was compared to a broad, poorly defined category of surgery that included procedures ranging from radical cystectomy to non-definitive local treatments, such as transurethral resection. We aimed to perform an updated SEER analysis to determine whether the utilization rate of RT for bladder preservation therapy in direct comparison to surgery had changed more recently. Furthermore, we sought to evaluate trends in recent survival outcomes for patients receiving RT.

MATERIALS AND METHODS

Study population and study design

We used the SEER database to identify 275843 patients diagnosed from 1992 to 2013 with localized MIBC (stages II-III; topography codes C67.0-C67.9) and urothelial carcinoma, squamous cell carcinoma, or adenocarcinoma histology [14]. Patients with noninvasive or T1 disease were not included. The SEER program is sponsored by the National Cancer Institute and is comprised of 18 cancer registries. Its database includes population-based cancer incidence, treatment, and survival data covering approximately 28% of the United States population. We selected 1992 as the first year of this study since it is when a number of new registries joined the program, and it allowed for analysis of a sufficient duration of time to assess trends. Patients were eligible for inclusion if they received either RT or cystectomy as initial definitive treatment. Cystectomy was defined as radical or partial. Patients were excluded who had a prior history of non-bladder malignancy or who were younger than age 18 at time of diagnosis. Patients who had initial treatment other than cystectomy or RT, had no treatment, or for whom treatment information was not available were also excluded, leaving 16175 patients for the primary analysis.

Statistical analyses

Patient and tumor characteristics were compared using chi-square tests and Student's *t*-test. Treatment utilization patterns over time were assessed using Cochran-Armitage tests for trend. OS and cause-specific survival (CSS) were estimated using the Kaplan-Meier method. All-cause (ACM) and cause-specific mortality (CSM) were evaluated using multivariable Cox proportional hazards regression, adjusting for age, sex, race, marital status, tumor grade, histology, year of diagnosis, and stage. All *P* values reported were two-sided, with those ≤ 0.05 deemed statistically significant. Statistical analyses were performed using SAS statistical software (SAS version 9.4; SAS Institute Inc., Cary, NC). As this study used de-identified SEER data, it did not require Institutional Review Board approval.

RESULTS

Patient characteristics

Patient and tumor characteristics are shown in **Table 1**. The total study population consisted of 16175 patients, of whom 11917 (73.6%) received cystectomy and 4258 (26.3%) received RT. Statistically significant differences between these two groups were noted with regard to age, sex, race, marital status, tumor grade, histology, and stage ($P < 0.0001$ for each variable). Patients who received RT were older (median age 79 vs. 68, $P < 0.01$), and the only age group of patients in which the majority received RT was those 80 years or older. Other variables associated with a higher likelihood of receipt of RT were black race, widowed or unmarried marital status, and increasing tumor grade. Patients of all stages were more likely to receive cystectomy than RT, but of patients who received RT, the majority had T2 disease (76.2%, compared to 50.1% in patients who had cystectomy). T4 disease was present in relatively few patients included for analysis (5.9% of total).

Utilization of RT over time

Figure 1 shows the percent utilization of RT for localized MIBC over time compared with cystectomy. While cystectomy was utilized more frequently than RT throughout the study period, there was a statistically significant increase in the proportion of patients receiving RT (24% in 1992–2002 vs. 28% in 2003–2013, $P < 0.01$) over time. This increase occurred in the context of no change in median patient age (71 for each 1992–2002 and 2003–2013, $P = 0.41$). The median patient age by treatment group over the study period is shown in **Figure 2**. Over the study period, the number of patients treated with either modality increased from 1.66 per 100000 person-years in 1992 to 3.24 per 100000 person-years in 2013; the yearly average for the cohort (1992–2013) was 2.70 per 100000 person-years.

Overall and cause-specific survival with RT

Figure 3 shows 3-year OS (**Fig. 3A**) and CSS (**Fig. 3B**) for patients receiving RT, and not cystectomy, for localized MIBC. Patients are stratified into five groups based on year of diagnosis to highlight observed differences in outcome over time. Compared with patients diagnosed from 1992 to 2009, those diagnosed from 2010 to 2013 had improved OS (64% vs. 60% at 1 year, $P < 0.01$; 38% vs. 29% at 3 years, $P < 0.01$) and CSS (71% vs. 67% at 1 year, $P = 0.01$; 51% vs. 40% at 3 years, $P < 0.01$).

Multivariable analyses of ACM and CSM are shown in **Table 2** and **Table 3**, respectively. Increasing age, as compared with the reference group of 21–49 years old, was associated with an increased risk for both ACM and CSM. While there was no observed difference in ACM with regard to sex, CSM was less in men relative to women (adjusted HR 0.86, $P < 0.01$). With regard to race, outcomes in black patients and relative white patients were significantly worse for both ACM (adjusted HR 1.22, $P < 0.01$) and CSM (adjusted HR 1.31, $P < 0.01$). Similarly, as compared with patients who were married, outcomes were worse for patients who were single (adjusted HR for ACM 1.24, $P < 0.01$; adjusted HR for CSM 1.18, $P < 0.05$) or divorced (adjusted HR for ACM 1.35, $P < 0.001$; adjusted HR for CSM 1.35, $P < 0.001$).

While there was no observed association between tumor grade and survival, there were higher estimates of mortality for squamous cell histology as compared with urothelial carcinoma (adjusted HR for ACM 1.38, $P < 0.001$; adjusted HR for CSM 1.34, $P < 0.01$). Relative to

urothelial histology, the proportion of non-urothelial cancers decreased from 11.4% in 1992 to 6.0% in 2013 ($P < 0.001$), with a gradual decline over the study period. Another tumor feature significantly associated with adverse outcomes was T4 disease (adjusted HR for ACM 1.38, $P < 0.001$; adjusted HR for CSM 1.57, $P < 0.001$). When assessing year of diagnosis in multivariable analysis, those diagnosed from 2010 to

2013 had lower estimates of mortality as compared with the reference group of 1992 to 1996 (adjusted HR for ACM 0.77, $P < 0.001$; adjusted HR for CSM 0.81, $P = 0.02$). For all other years of diagnosis evaluated (1997 to 2001, 2002 to 2005, and 2006 to 2009), ACM and CSM did not differ significantly from the reference range.

Table 1. Patient and tumor characteristics by treatment received.

Characteristic	No. of patients (%)	Radiotherapy (%)	Cystectomy (%)	P value*
Total	16175 (100)	4258 (26.3)	11917 (73.6)	< 0.0001
Age (years)				< 0.0001
21–50	836 (5.2)	67 (8.0)	769 (92.0)	
50–59	2311 (14.3)	253 (10.9)	2058 (89.1)	
60–69	4346 (26.9)	645 (14.8)	3701 (85.2)	
70–79	5130 (31.7)	1292 (25.2)	3838 (74.8)	
80–89	3191 (20.3)	1726 (54.1)	1465 (45.9)	
≥ 90	361 (2.2)	275 (76.2)	86 (23.8)	
Sex				< 0.0001
Male	11781 (72.8)	2974 (25.2)	8807 (74.8)	
Female	4394 (27.2)	1284 (29.2)	3110 (70.8)	
Race				< 0.0001
White	13488 (83.4)	3524 (26.1)	9964 (73.9)	
Hispanic	860 (5.3)	192 (22.3)	668 (77.7)	
Black	1046 (6.5)	357 (34.1)	689 (65.9)	
Asian or Pacific Islander	701 (4.3)	168 (24.0)	533 (76.0)	
Other or unknown	80 (0.4)	17 (21.2)	63 (78.8)	
Marital status				< 0.0001
Single	1680 (10.4)	413 (24.6)	1267 (75.4)	
Married	9802 (60.6)	2185 (22.3)	7617 (77.7)	
Separated	146 (0.9)	27 (18.5)	119 (81.5)	
Divorced	1387 (8.6)	324 (23.4)	1063 (76.6)	
Widowed	2664 (16.5)	1167 (43.8)	1497 (56.2)	
Unmarried or domestic partner	8 (0.05)	3 (37.5)	5 (62.5)	
Unknown	488 (3.0)	139 (28.5)	349 (71.5)	
Tumor differentiation				< 0.0001
Well	157 (1.0)	29 (18.5)	128 (81.5)	
Moderately	1165 (7.2)	237 (20.3)	928 (79.7)	
Poorly	6828 (42.2)	1796 (26.3)	5032 (73.7)	
Undifferentiated	7442 (46.0)	1988 (26.7)	5454 (73.3)	
Histology				< 0.0001
Urothelial cell carcinoma	14895 (92.1)	4038 (27.1)	10857 (72.9)	
Squamous cell carcinoma	779 (4.8)	169 (21.7)	610 (78.3)	
Adenocarcinoma	501 (3.1)	51 (10.2)	450 (89.8)	
Stage				< 0.0001
T2	9219 (57.0)	3245 (35.2)	5974 (64.8)	
T3	6000 (37.1)	784 (13.1)	5216 (86.9)	
T4	956 (5.9)	229 (24.0)	727 (76.0)	

*Chi square value pertaining to treatment and variable of interest.

Table 2. Multivariable Cox model of all-cause mortality for patients receiving RT for bladder cancer.

Variable	HR (95% CI)	P value
Age (years)		
21–49	1.00 (ref)	
50–59	1.21 (0.84–1.74)	0.309
60–69	1.55 (1.10–2.20)	0.013
70–79	2.31 (1.65–3.25)	< 0.001
80–89	2.86 (2.04–4.01)	< 0.001
≥ 90	3.96 (2.7565.69)	< 0.001
Sex		
Female	1.00 (ref)	
Male	0.98 (0.90–1.07)	0.627
Race		
White	1.00 (ref)	
Hispanic	0.94 (0.78–1.13)	0.527
Black	1.22 (1.06–1.39)	0.004
Asian	0.84 (0.69–1.02)	0.077
Other or unknown	0.92 (0.47–1.77)	0.791
Marital status		
Married	1.00 (ref)	
Single	1.24 (1.09–1.42)	0.002
Separated	1.26 (0.82–1.94)	0.302
Divorced	1.35 (1.16–1.57)	< 0.001
Widowed	1.04 (0.94–1.14)	0.448
Unmarried	1.07 (0.15–7.64)	0.947
Unknown	1.15 (0.93–1.43)	0.187
Tumor differentiation		
Well	1.00 (ref)	
Moderately	1.30 (0.83–2.06)	0.255
Poorly	1.23 (0.79–1.90)	0.357
Undifferentiated	1.20 (0.77–1.85)	0.419
Unknown	1.39 (0.87–2.20)	0.165
Histology		
Urothelial carcinoma	1.00 (ref)	
Adenocarcinoma	0.85 (0.59–1.23)	0.395
Squamous cell carcinoma	1.38 (1.15–1.65)	< 0.001
Year of diagnosis		
1992 to 1996	1.00 (ref)	
1997 to 2001	1.01 (0.88–1.15)	0.936
2002 to 2005	0.98 (0.86–1.12)	0.777
2006 to 2009	0.92 (0.80–1.05)	0.207
2010 to 2013	0.77 (0.66–0.89)	< 0.001
Stage		
T2	1.00 (ref)	
T3	1.08 (0.98–1.19)	0.132
T4	1.38 (1.17–1.62)	<0.001

DISCUSSION

Despite longstanding efforts to establish bladder preservation utilizing RT as an alternative to cystectomy for the initial management of muscle-invasive bladder cancer, adoption of this approach has primarily been limited to patients who are deemed medically inoperable. Our data from a large national registry are the first to show that utilization of RT for localized MIBC has increased relative to cystectomy. This trend occurred with no associated change in median patient age throughout the study period of 1992 to 2013, which mitigates the potential confounding effect of age on this comparison. Our analysis is the most recent to evaluate trends of RT for bladder preservation in the United States and is the first to compare these directly with rates of definitive surgery (*i.e.*, cystectomy or partial cystectomy). While the observed absolute magnitude of increase was modest (4% over the study period), it suggests a positive trend that may reflect clinical incorporation of the growing body of literature supporting bladder preservation.

This finding stands in contrast to that of Kozak *et al.*, whose analysis of an earlier era found that RT utilization remained unchanged [13]. There are several plausible explanations for increased utilization rates of RT for MIBC. Over the time period studied, there may have been increasing awareness, both among patients and physicians, of bladder preservation therapy as a feasible alternative to cystectomy. Also possible is that as physicians whose training incorporated increased utilization of bladder preservation therapy entered clinical practice, the appeal of this treatment approach increased. Additionally, it is possible that the continued improvements in other fields of medicine better enabled management of comorbid conditions and subsequently increased the number of patients who were eligible for bladder preservation with RT. Due to the limitations of data available in the SEER, our study cannot definitively provide insight into this trend, which is likely to be multifactorial.

The second aim of our study was to evaluate survival outcomes over time for patients receiving RT, and we found that both CSS and OS were improved for patients diagnosed after 2010 as compared with earlier years. This finding is consistent with the largest published institutional experience of bladder preservation therapy to date, which showed that 5-year disease-specific survival improved from 60% in 1986–1995 to 84% in 2005–2013 [15]. Those outcomes are notably better than our reported rates of CSS, but may reflect a more selective group of patients treated at a single institution with demonstrated expertise in bladder preserving therapy. In contrast, our SEER results are representative of a more geographically diverse patient population and clinical practice types.

One likely explanation for the observed improvements in survival outcomes is wider incorporation of RT delivered with concurrent chemotherapy as evidence emerged supporting the superiority of this approach as compared with RT alone. In 2012, a randomized trial by James *et al.* showed a 32% benefit in disease-free survival with the addition of concurrent fluorouracil and mitomycin C to RT, without a significant increase in treatment-related adverse events [8]. Based on these results and other studies [16–19], patients treated more recently were probably more likely to receive concurrent chemotherapy with RT, but unfortunately this information is not available in SEER. Additionally, there have also been improvements in RT technique, such as image-guided treatment and intensity-modulated RT, which over time have become more widely adopted. These technological advantages

can allow more accurate targeting of bladder tumors and delivery of higher doses of more conformal radiation, which could further improve treatment efficacy. Recent clinical improvements could also be related

to increased use of maximal safe transurethral resection, stage migration, and improved patient selection due to improved and increasingly utilized diagnostic imaging.

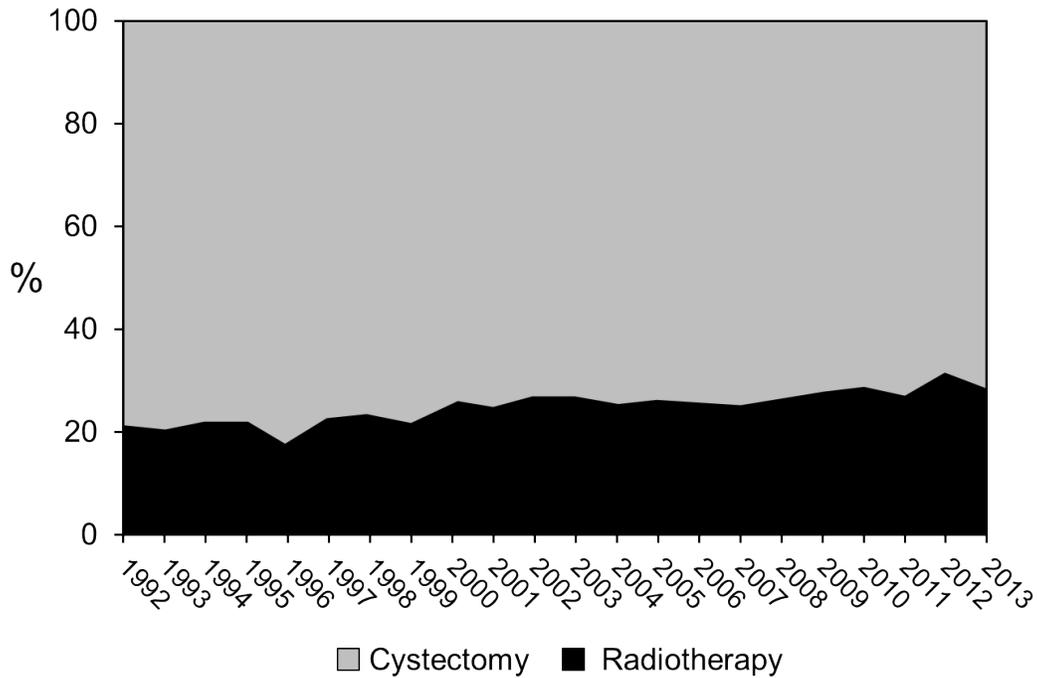


Figure 1. Percent utilization of RT compared with cystectomy over time. Gray, cystectomy; black, radiotherapy.

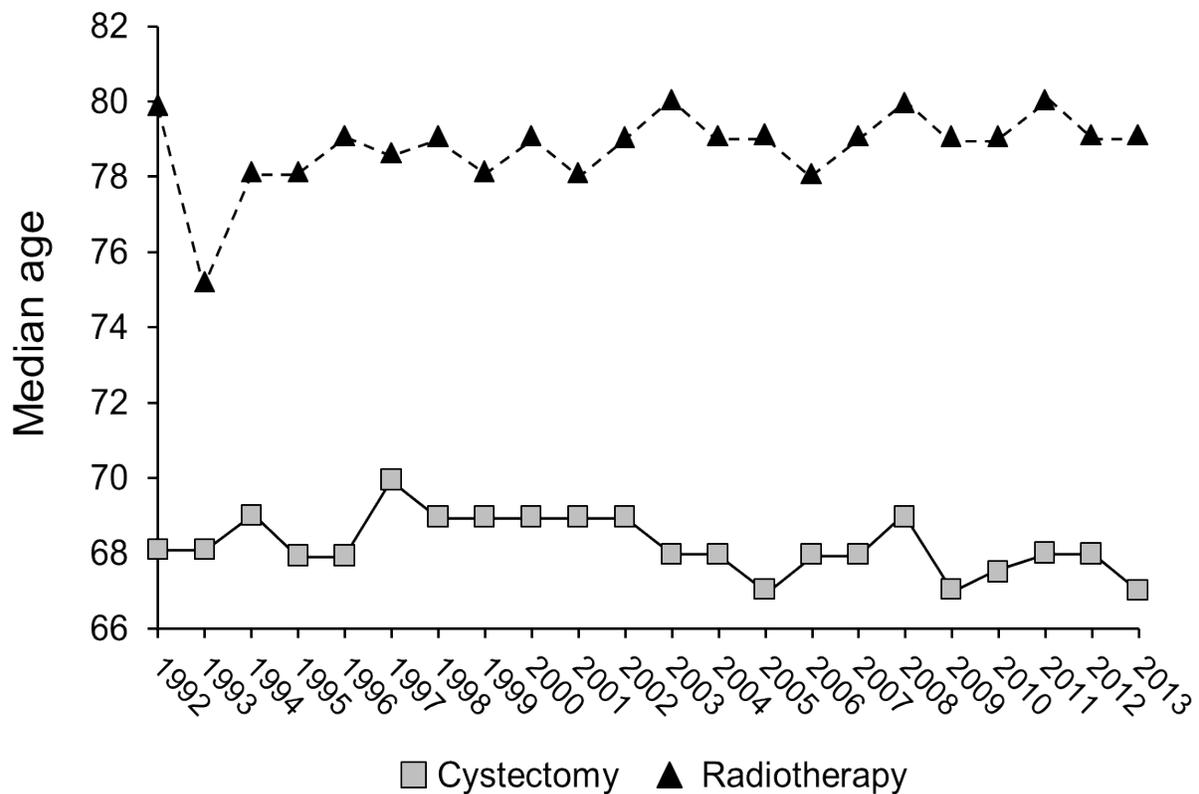


Figure 2. Median patient age by treatment group over the study period. Squares, cystectomy; triangles, radiotherapy.

Table 3. Multivariable Cox model of cancer-specific mortality for patients receiving RT for bladder cancer.

Variable	HR (95% CI)	P value
Age (years)		
21–49	1.00 (ref)	
50–59	1.31 (0.86–1.98)	0.207
60–69	1.33 (0.89–1.98)	0.163
70–79	1.75 (1.19–2.59)	0.005
80–89	2.23 (1.51–3.30)	< 0.001
≥ 90	2.82 (1.86–4.29)	< 0.001
Sex		
Female	1.00 (ref)	
Male	0.86 (0.78–0.95)	0.004
Race		
White	1.00 (ref)	
Hispanic	1.10 (0.89–1.35)	0.390
Black	1.31 (1.13–1.53)	< 0.001
Asian	0.99 (0.79–1.24)	0.913
Other or unknown	0.82 (0.37–1.83)	0.627
Marital status		
Married	1.00 (ref)	
Single	1.18 (1.01–1.38)	0.041
Separated	1.35 (0.82–2.22)	0.241
Divorced	1.35 (1.13–1.61)	< 0.001
Widowed	0.95 (0.85–1.07)	0.423
Unmarried	1.34 (0.19–9.57)	0.774
Unknown	1.16 (0.91–1.49)	0.237
Tumor differentiation		
Well	1.00 (ref)	
Moderately	1.19 (0.70–2.02)	0.517
Poorly	1.19 (0.72–1.97)	0.489
Undifferentiated	1.15 (0.70–2.02)	0.576
Unknown	1.41 (0.83–2.39)	0.206
Histology		
Urothelial carcinoma	1.00 (ref)	
Adenocarcinoma	0.76 (0.48–1.19)	0.231
Squamous cell carcinoma	1.34 (1.08–1.66)	0.008
Year of diagnosis		
1992 to 1996	1.00 (ref)	
1997 to 2001	1.09 (0.92–1.29)	0.348
2002 to 2005	1.02 (0.87–1.21)	0.809
2006 to 2009	1.03 (0.87–1.23)	0.699
2010 to 2013	0.81 (0.67–0.97)	0.021
Stage		
T2	1.00 (ref)	
T3	1.13 (1.01–1.28)	0.036
T4	1.57 (1.31–1.88)	< 0.001

On multivariable analysis, we did find race, marital status, and histology to be statistically significantly associated with ACM and CSM. Black race was associated with worse oncologic outcomes. This finding is aligned with prior SEER analyses and may be related to socioeconomic factors, accessibility of care, and potential differences in tumor biology [20]. Outcomes were improved in married patients, which is also likely multifactorial [21]. In our data, squamous cell histology was associated with adverse outcomes, which is also aligned with previous studies [22]. After adjusting for these factors, we did find that compared with patients diagnosed 1992 to 1996, those diagnosed 2010 to 2013 showed improved ACM and CSM. For all other years evaluated, the differences were not statistically significant, suggesting that recent outcomes for patients receiving bladder preservation therapy might be improved.

Unfortunately, there is no randomized data comparing bladder preservation therapy with cystectomy. One attempted study, the Selective Bladder Preservation Against Radical Excision (SPARE) trial, was terminated after failing to accrue: the majority of patients refusing randomization at the time of consent expressed a preference for bladder preservation therapy [23]. Although non-randomized comparisons between RT and surgery are inherently biased to favor surgery, systematic literature review and meta-analysis does not support the notion that better outcomes result from a particular approach [24–26]. We did not attempt to use SEER to compare survival outcomes between patients receiving RT and cystectomy, because the SEER Program will no longer include the “receipt of radiation” variable without signed recognition from the investigator of the “potential biases associated with radiation data”—an explicit acknowledgement of bias [27].

Limitations of this study are primarily related to the absence of complete patient characteristics data and clinical details that are not included in SEER. As such, our analysis was unable to incorporate patient comorbidities, performance status, dose of RT delivered (e.g., curative versus palliative), and information regarding chemotherapy. Another limitation is that in comparing staging between treatment groups, patients who received RT were clinically staged, whereas cystectomy patients were surgically staged. Additionally, for the purposes of reporting CSS, patients were excluded who had a history of non-bladder malignancy prior to our evaluation of utilization rates of RT. However, patients with multiple malignancies would seem less likely to be considered favorable surgical candidates so that exclusion likely does not detract from our conclusion of there being increased utilization of RT relative to cystectomy over time.

In conclusion, our analysis of a large set of cancer registries in the United States provides an update on the use of RT for localized MIBC across the United States and demonstrates that utilization has increased over time relative to cystectomy. Although this increase was modest, it stands in contrast to prior analyses that showed RT utilization rates to be unchanged over time. Moreover, survival outcomes for patients diagnosed after 2010 were improved, perhaps as a result of more uniform adoption of concurrent chemotherapy with RT, as well as higher prevalence of urothelial histology, but also likely at least in part due to better patient selection and improved treatment technique. These findings are notable and support continued efforts to improve and employ bladder preservation strategies utilizing RT for patients with localized MIBC who favor an organ-sparing curative treatment approach.

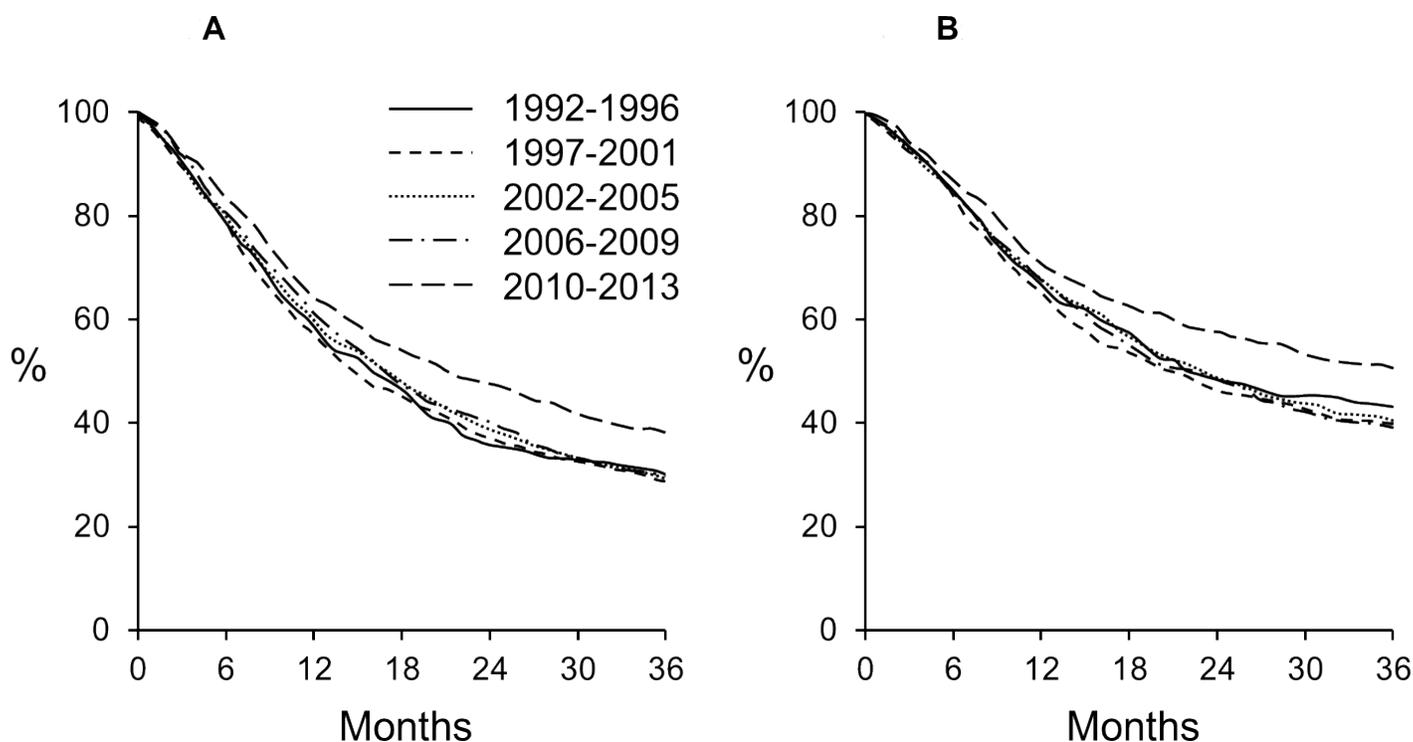


Figure 3. Three-year OS (A) and CSS (B) of patients receiving RT for bladder cancer stratified by year of diagnosis.

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