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Original Article

Treatment trends of muscle invasive bladder cancer: Evidence from the Surveillance, Epidemiology, and End Results database, 1988 to 2013

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Practice trends;
Kaplan-Meier survival curves

Abstract *Objective:* Guidelines for muscle-invasive bladder cancer (MIBC) recommend that patients receive neoadjuvant chemotherapy with radical cystectomy as treatment over radical cystectomy alone. Though trends and practice patterns of MIBC have been defined using the National Cancer Database, data using the Surveillance, Epidemiology, and End Results (SEER) program have been poorly described.
Methods: Using the SEER database, we collected data of MIBC according to the American Joint Commission on Cancer. We considered differences in patient demographics and tumor characteristics based on three treatment groups: chemotherapy (both adjuvant and neoadjuvant) with radical cystectomy, radical cystectomy, and chemoradiotherapy. Multinomial logistic regression was performed to compare likelihood ratios. Temporal trends were included for each treatment group. Kaplan-Meier curves were performed to compare cause-specific survival. A Cox proportional-hazards model was utilized to describe predictors of survival.
Results: Of 16 728 patients, 10 468 patients received radical cystectomy alone, 3236 received chemotherapy with radical cystectomy, and 3024 received chemoradiotherapy. Patients who received chemoradiotherapy over radical cystectomy were older and more likely to be African American; stage III patients tended to be divorced. Patients who received chemotherapy with radical cystectomy tended to be males; stage II patients were less likely to be Asian than Caucasian. Stage III patients were less likely to receive chemoradiotherapy as a treatment option than stage II. Chemotherapy with radical cystectomy and chemoradiotherapy are both underutilized treatment options, though increasingly utilized. Kaplan-Meier survival curves showed significant differences between stage II and III tumors at each interval. A Cox proportional-hazards model showed differences in gender, tumor stage, treatment modality, age, and marital status.

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Conclusion: Radical cystectomy alone is still the most commonly used treatment for muscle-invasive bladder cancer based on temporal trends. Significant disparities exist in those who receive radical cystectomy over chemoradiotherapy for treatment.

1. Introduction

In the United States for 2019, bladder cancer (BC) is expected to account for 80 470 new cancer cases [1]. BC based on the tumor-node-metastasis stage system can be described into three chief groups: muscle-invasive bladder cancer (MIBC), non-MIBC, and metastatic BC. Non-MIBC is classified as stage I (Ta, Tis, and T1) and accounts for approximately 75% of cases [2,3]. The rest of cases are either considered MIBC, classified as stage II to III, or metastatic BC, classified as stage IV [3,4]. Primary treatments for MIBC, based on National Comprehensive Cancer Network (NCCN) guidelines, differs based on stage. For stage II tumors, treatment consists of 1) neoadjuvant chemotherapy (NAC) plus radical cystectomy, 2) NAC plus partial cystectomy (for highly selected patients), 3) radical cystectomy, and 4) concurrent chemoradiotherapy [5]. For stage III, NCCN lists treatment guidelines as 1) NAC with radical cystectomy and 2) concurrent chemoradiotherapy [5].

NAC with radical cystectomy has become the standard treatment for MIBC over radical cystectomy alone. The first study of NAC plus radical cystectomy was conducted by the Medical Research Council and European Organization for Research and Treatment of Cancer in 1999 [6]. In this phase III trial, roughly half of the 976 patients with high grade T2—T4a, N0—Nx, M0 urothelial carcinoma were selected for either radical cystectomy alone or three cycles of NAC (cisplatin, methotrexate, and vinblastine [CMV], with folinic acid rescue) plus radical cystectomy and/or radiation therapy [6]. An 8-year follow-up showed a statistically significant 16% improvement in survival outcome [7]. In a 2003 randomized phase III trial from the Southwest Oncology Group (SWOG), 317 patients considered to have MIBC (stages T2—T4a) were randomly assigned to either radical cystectomy alone or three cycles of NAC (methotrexate, vinblastine, doxorubicin, and cisplatin [MVAC]) followed by radical cystectomy [8]. Compared to NAC with radical cystectomy, patients who received radical cystectomy alone were associated with a 33 percent greater risk of death (hazard ratio: 1.33). A randomized control trial by Sherif et al. [9] showed that patients who received NAC with radical cystectomy were associated with a 20% risk reduction compared to radical cystectomy alone. A subsequent meta-analysis supported the combination use of NAC with a 5% absolute improvement in survival 5 years after surgery [10]. A randomized prospective study by Rosenblatt et al. [11] found that pathologic downstaging rates increased significantly with NAC, in particular for T3 tumors. Despite CMV and MVAC being used in the phase III trials described above, healthcare providers have preferred the combination of gemcitabine and cisplatin NAC in clinical setting due to its better tolerability and similar efficacy [12]. Comparing gemcitabine and cisplatin to MVAC has shown similar likelihood of downstaging primary tumors and eliminating muscle-invasive disease while also showing less toxicity [13].

Bladder preservation therapy that consists of chemoradiation therapy, also called combined modality therapy when combined with maximal transurethral resection of bladder tumor (TURBT), has traditionally been considered a regimen for highly-selected patients with MIBC who are poor surgical candidates or for quality-of-life purposes (*i.e.* those who prefer to preserve their native bladder) [14]. While no randomized trials of patients with MIBC have directly compared radical cystectomy and bladder preservation therapy, meta-analysis has shown similar overall 5-year and 10-year survival rates [15].

The purpose of our study was to compare trends in three major options of care for MIBC using the Surveillance, Epidemiology, and End Results (SEER) database: radical cystectomy alone, chemotherapy (both neoadjuvant and adjuvant) with radical cystectomy, and chemoradiotherapy with and without TURBT. Additionally, we intended to consider survival trends amongst stage II and III MIBC cases as well as to describe demographic and clinical factors that impact mortality. Previous studies have investigated, using the National Cancer Database (NCDB), tumor characteristics, and patient demographic in NAC in combination with radical cystectomy [16—21]. This is the first study to our knowledge to use SEER, a more appropriate database for considering sociodemographic disparities [22]. This is the largest study to directly compare utilization of radical cystectomy with or without chemotherapy to a bladder-preservation approach for MIBC, though the second largest to look at tumor characteristics and patient demographics between these two groups [23,24]. We hypothesized that the use of radical cystectomy alone would decline in lieu of the rise in popularity of alternative treatments.

2. Methods

The SEER program is a national cancer database in the United States, a part of the National Cancer Institute, which provides cancer incidence and survival. SEER contains information not available in other national registries

including stage of cancer. SEER contains deidentified data and is compliant with the Health Insurance Portability and Accountability Act.

Our study was based on incident cases of BC diagnosed among patients of 18 geographic regions, which included the chemotherapy recode, covered by the SEER program (November 2015 submission). Eligible BC cases were identified using the International Classification of Diseases for Oncology (ICD-O-3) topography code C67.0-C67.9.

Patients with the American Joint Commission on Cancer clinically staged T2–T4a, N0, M0 were included in the study and considered to have MIBC. Cases of T4b MIBC were excluded due to metastasis. Cancers of unknown stage were excluded. Patients who underwent radical cystectomy without radiation therapy were included in the study based on the 2-Digit Site-Specific Surgery Codes from 1973 to 1997 listed as 40, 50, and 70. The SEER 2003+ Site-Specific Surgery of Primary Site Codes listed as 50, 60, and 70 were also included. Additionally, patients who received solely chemotherapy plus radiation with or without TURBT were also included in the study within the chemoradiotherapy group. For 1973–1997, the 2-Digit Site-Specific Surgery Codes for TURBT were listed under 10 and for SEER 2003+ listed as 20.

Descriptive statistics were compiled using the Statistical Package for the Social Sciences (SPSS) in order to summarize patient demographics, tumor-node-metastasis stage and grade, and treatment characteristics. Associations of cases were compared using Chi-squared as well as multinomial logistic regression, due to more than two sample groups. Usage rate was compared using 5-year intervals in order to better group and to aid in analysis. Kaplan-Meier curves were performed to compare stage II versus stage III cause-specific survival. A Cox proportional-hazards model was utilized to describe predictors of survival.

3. Results

Between the years 1988 and 2013, there were 360 559 cases of BC in the SEER program that were initially queried for our study. Within each group there resulted in 10 468 radical cystectomy cases, 3236 radical cystectomy with chemotherapy cases, and 3024 chemotherapy plus radiation cases for a total of 16 728 cases that met selection criteria (Fig. 1). Patients were stratified based on stage in order to control for progression of the cancer. The SEER program does not provide a specific patient age, but instead provides age ranges of 5-years. To calculate median ages of each treatment, averages were created for each patient. After separating by stage, there were significant differences between the groups according to patient demographics and tumor characteristics (Tables 1 and 2). Patients were also compared based on the treatment groups between stage II and III (Table 3). Patients in both stage II and III who received chemoradiotherapy were more likely to be older (median age: stage II was 72.1 years old and stage III was 71.9 years old) compared to radical cystectomy (median age: stage II was 66.2 years old and stage III was 68.9 years old) or radical cystectomy plus chemotherapy (median age: stage II was 63.8 years old and stage III was 65.5 years old) with highly significant p-value (<0.001). There was also a difference in the number of patients who received chemoradiotherapy. Although 2443 stage II cases (26.4%) received chemoradiotherapy for treatment of MIBC, only 581 stage III

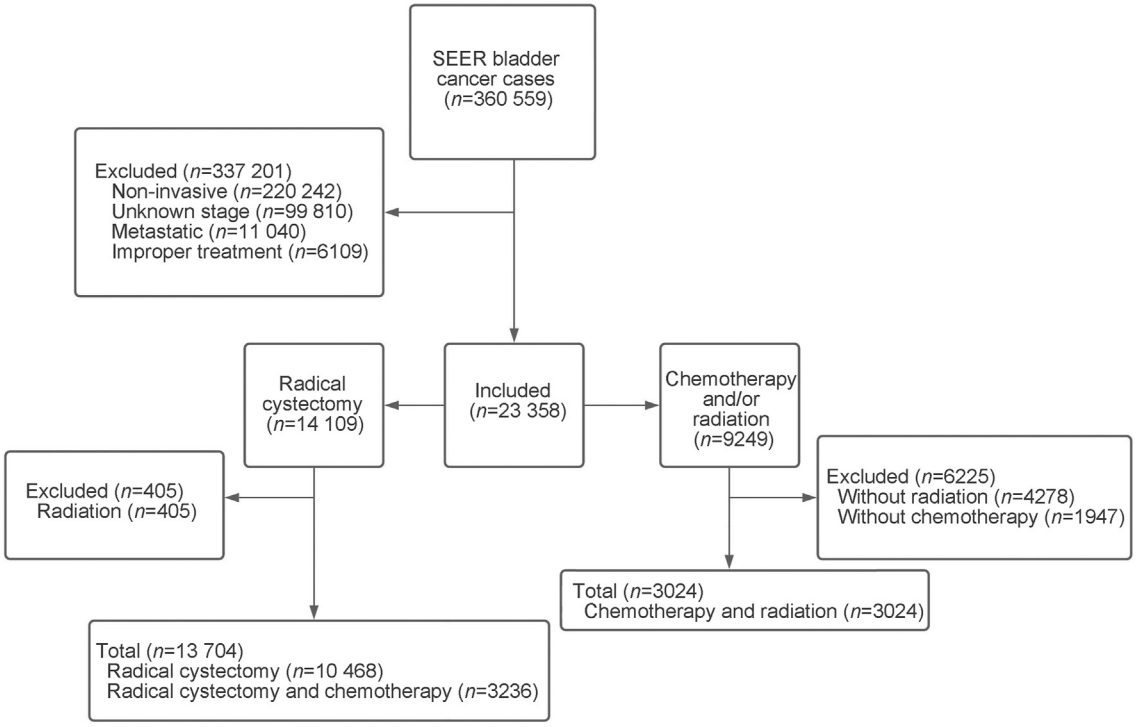

Figure 1 Case flow diagram. SEER, the Surveillance, Epidemiology, and End Results.

Table 1 Patient demographics and tumor characteristics based on treatment groups for stage II.

Patient demographic	Treatment ($n=9243$)			p-Value[a]
	Radical cystectomy; $n=5185$ (56.1%)	Radical cystectomy + chemotherapy; $n=1615$ (17.5%)	Chemotherapy + radiation; $n=2443$ (26.4%)	
Age at diagnosis				<0.001
Population age, mean, year	66.2	63.8	72.1	
85+ years old, *n* (%)	165 (3.2)	15 (0.9)	384 (15.7)	
Sex, *n* (%)				<0.001
Male	3918 (75.6)	1264 (78.3)	1785 (73.1)	
Female	1267 (24.4)	351 (21.7)	658 (26.9)	
Race, *n* (%)				<0.001
Caucasian	4663 (89.9)	1482 (91.8)	2179 (89.2)	
Asian or Pacific Islander	221 (4.3)	48 (3.0)	82 (3.4)	
African American	275 (5.3)	74 (4.6)	170 (7.0)	
Unknown	26 (0.5)	11 (0.7)	2 (0.5)	
Marital status, *n* (%)				<0.001
Married	3382 (65.2)	1108 (68.6)	1383 (56.6)	
Widowed	613 (11.8)	122 (7.6)	532 (21.8)	
Divorced	460 (8.9)	147 (9.1)	211 (8.6)	
Single	510 (9.8)	163 (10.1)	209 (8.6)	
Unknown	220 (4.2)	75 (4.6)	108 (4.4)	
Primary site, *n* (%)				<0.05
Trigone of bladder	329 (6.3)	89 (5.5)	177 (7.2)	
Dome of bladder	194 (3.7)	63 (3.9)	124 (5.1)	
Bladder wall	1607 (31.0)	505 (31.3)	847 (34.7)	
Overlapping lesion of bladder	881 (17.0)	278 (17.2)	375 (15.4)	
Unknown	2174 (41.9)	680 (42.1)	920 (37.7)	
Grade, *n* (%)				<0.001
Moderately differentiated	387 (7.5)	51 (3.2)	94 (3.8)	
Poorly differentiated or undifferentiated	4553 (87.8)	1450 (89.8)	2187 (89.5)	
Unknown	245 (4.7)	114 (7.1)	162 (6.6)	

[a] p-Value evaluated level of significance between treatment and patient demographic or tumor characteristic.

cases (7.8%) received the same treatment. The values of chemoradiotherapy as a treatment option between stage II and III showed high levels of significance (<0.001) (Table 3).

A multinomial logistic regression for each stage was performed in order to compare likelihood of patient demographic or tumor characteristic listed to receive any of the three treatments (Table 4). Compared to the reference category of radical cystectomy alone, patients who received chemoradiotherapy had 1.3 higher odds of being African American than Caucasian for stage II tumors (95% CI 1.1—1.6) and 1.6 higher odds for stage III tumors (95% CI 1.2—2.2); stage II showed a higher level of significance (stage II: ≤0.001; compared to stage III: <0.05). Stage II patients who received chemoradiotherapy had 8.7 higher odds of being 75—85 years old compared to the reference age of 55—65 (95% CI 7.0—10.7). Stage III patients who received chemoradiotherapy had 1.4 higher likelihood of being divorced rather than married (95% CI 1.0—1.8). For the treatment group of chemotherapy with radical cystectomy, patients of both stage II and III groups had lower likelihood of being female, compared to radical cystectomy alone, with highly significant values ($p<0.001$). The stage II group of chemotherapy with radical cystectomy had a lower likelihood of being Asian than Caucasian ($p<0.001$). Compared to the reference group, both the radical cystectomy and chemoradiotherapy treatment groups had a higher likelihood of being poorly or undifferentiated grade tumors ($p<0.001$).

Practice trends were calculated for each treatment option based on the year of diagnosis and separated based on stage (Figs. 2 and 3). Based on stage II cases from 1988 to 1992, the usage of chemotherapy with radical cystectomy (7.6%) initially dropped and then began rising in 2003—2007 (12.4%) and 2008—2013 (26.5%). Compared to 1988—1992, the usage of chemoradiotherapy (11.9%) initially stayed the same in 1993—1997 and then has consistently risen over the years to 2008—2013 (32.1%). In contrast, the usage of radical cystectomy alone has dropped over the years compared to the other treatment options. For 2003, the percentage of patients elected for chemotherapy with

Table 2 Patient demographics and tumor characteristics based on treatment groups for stage III.

Patient demographic	Treatment ($n=7485$)			p-Value[a]
	Radical cystectomy; $n=5283$ (70.6%)	Radical cystectomy + chemotherapy; $n=1621$ (21.7%)	Chemotherapy + radiation; $n=581$ (7.8%)	
Age at diagnosis				<0.001
Population age, mean, year	68.9	65.5	71.9	
85+ years old, *n* (%)	229 (4.3)	20 (1.2)	78 (13.4)	
Sex, *n* (%)				<0.001
Male	3707 (70.2)	1216 (75.0)	438 (75.4)	
Female	1576 (29.8)	405 (25.0)	143 (24.6)	
Race, *n* (%)				<0.05
Caucasian	4728 (89.5)	1462 (90.2)	499 (85.9)	
Asian or Pacific Islander	214 (4.1)	66 (4.1)	27 (4.6)	
African American	317 (6.0)	84 (5.2)	53 (9.1)	
Unknown	24 (0.5)	9 (0.6)	2 (0.3)	
Marital status, *n* (%)				<0.001
Married	3275 (62.0)	1104 (68.1)	325 (55.9)	
Widowed	870 (16.5)	146 (9.0)	122 (21.0)	
Divorced	471 (8.9)	134 (8.3)	64 (11.0)	
Single	487 (9.2)	174 (10.7)	49 (8.4)	
Unknown	180 (3.4)	63 (3.9)	21 (3.6)	
Primary site, *n* (%)				NS
Trigone of bladder	317 (6.0)	263 (16.2)	42 (7.2)	
Dome of bladder	263 (5.0)	67 (4.1)	16 (2.8)	
Bladder wall	1509 (28.6)	459 (28.3)	147 (25.3)	
Overlapping lesion of bladder	1146 (21.7)	343 (21.2)	111 (19.1)	
Unknown	2048 (38.8)	489 (30.2)	265 (45.6)	
Grade, *n* (%)				<0.001
Moderately differentiated	418 (7.9)	80 (4.9)	30 (5.2)	
Poorly differentiated or undifferentiated	4700 (89.0)	1479 (91.2)	510 (87.8)	
Unknown	165 (3.1)	62 (3.8)	41 (7.1)	

NS, no significance.
[a] p-Value evaluated level of significance between treatment and patient demographic or tumor characteristic.

Table 3 Treatment groups were separated into stage II and III.

Stages	Treatment			Total
	Radical cystectomy	Radical cystectomy + chemotherapy	Chemotherapy + radiation	
II	5185 (56.1)	1615 (17.5)	2443 (26.4)	9243
III	5283 (70.6)	1621 (21.7)	581 (7.8)	7485
p-Value[a]	NS	NS	<0.001	

NS, no significance.
[a] p-Value evaluated level of significance between treatment and stage.

radical cystectomy showed a jump (9.3% based on 344 cases) compared to the previous year (6.8% based on 324 cases).

For stage III cases from 1988 to 1992, the usage of chemotherapy with radical cystectomy (11.8%) initially dropped in 1993–1997 (10.3%) and then began rising each 5-year increment to 2008–2013 (33.6%). For stage III cases of chemoradiotherapy, the usage rate was rising till 2003–2007 when the usage dropped slightly (8.9%). In contrast, stage III cases of radical cystectomy alone slightly rose in 1993–1997 (82.8%) and then rates had been dropping in 2008–2013 (57.2%). Again for 2003, the percentage of patients elected for each treatment option was obtained. In 2003, there was an increase in chemotherapy with radical cystectomy (13.8% based on 465 cases) compared to the previous year (11.7% based on 418 cases). Kaplan-Meier survival curves showed significant differences ($p<0.05$) between stage II and stage III groups at each 5-

Table 4 Cox proportional hazards model indicating likelihood of group receiving either chemotherapy with radical cystectomy or chemotherapy plus radiation compared to reference radical cystectomy group.

Patient demographic	Likelihood ratio (95% CI) of stage II patients			Likelihood ratio (95% CI) of stage III patients		
	Radical cystectomy + chemotherapy	Chemotherapy + radiation	*p*-Value	Radical cystectomy + chemotherapy	Chemotherapy + radiation	*p*-Value
Sex			<0.001			<0.001
Male	Reference	Reference		Reference	Reference	
Female	0.9 (0.8–1.0)	1.1 (1.0–1.2)		0.8 (0.7–0.9)	0.8 (0.6–0.9)	
Age, year			<0.001			<0.001
55–65	Reference	Reference		Reference	Reference	
65–75	1.1 (0.9–1.2)	2.0 (1.6–2.4)		0.7 (0.6–0.9)	1.1 (0.8–1.4)	
75–85	2.3 (1.9–2.7)	8.7 (7.0–10.7)		0.4 (0.4–0.5)	2.0 (1.5–2.6)	
85+	Reference	Reference		1.0 (0.5–1.9)	0.1 (0.1–0.2)	
Race			<0.001			<0.05
Caucasian	Reference	Reference		Reference	Reference	
Asian	0.7 (0.5–0.9)	0.8 (0.6–1.0)		1.0 (0.8–1.3)	1.2 (0.8–1.8)	
African American	0.8 (0.7–1.1)	1.3 (1.1–1.6)		0.9 (0.7–1.1)	1.6 (1.2–2.2)	
Marital status			<0.001			<0.001
Married	Reference	Reference		Reference	Reference	
Divorced	0.9 (0.7–1.2)	1 (0.7–1.4)		0.84 (0.7–1.0)	1.4 (1.0–1.8)	
Grade			<0.001			<0.001
Moderately differentiated	Reference	Reference		Reference	Reference	
Poorly or undifferentiated	2.4 (1.8–3.3)	2 (1.6–2.5)		1.6 (1.2–2.0)	1.7 (1.1–2.6)	

CI, confidence interval.

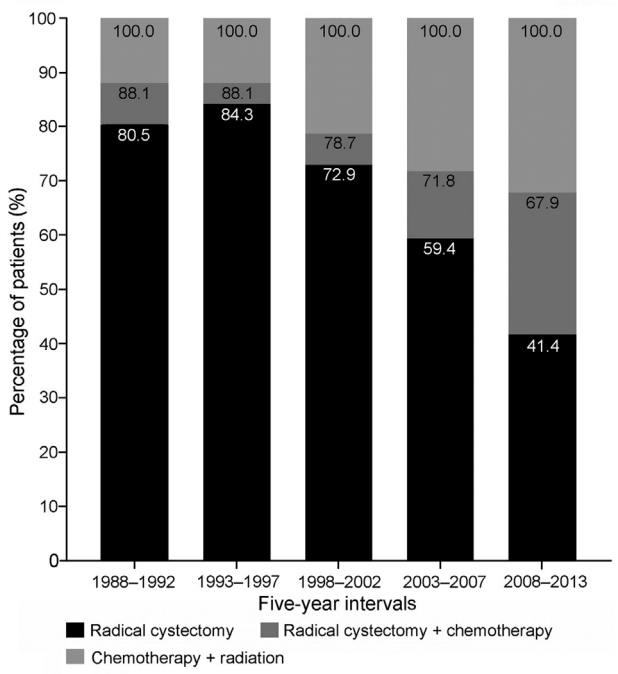

Figure 2 Percentage of patients by treatment group treated for stage II MIBC from 1988 to 2013 based on 5-year intervals. For 1988–1992, $n=399$; 1993–1997, $n=597$; 1998–2002, $n=1186$; 2003–2007, $n=2848$; 2008–2013, $n=4213$ (highly significant of p-values of <0.001).

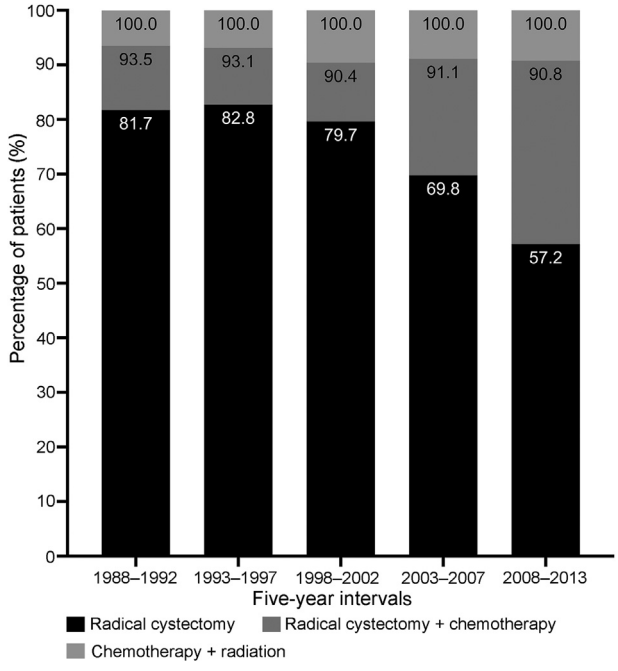

Figure 3 Percentage of patients by treatment treated for stage III MIBC from 1988 to 2013 based on 5-year intervals. For 1988–1992, $n=478$; 1993–1997, $n=743$; 1998–2002, $n=1666$; 2003–2007, $n=2060$; 2008–2013, $n=2538$ (highly significant of p-values of <0.001).

year time point (Fig. 4). A Cox proportional-hazards model was utilized to look at survival differences in each time period using clinical and demographic factors. Significant differences were found in survival based on gender ($p<0.05$), tumor stage ($p<0.001$), treatment modality ($p<0.001$), age at diagnosis ($p<0.001$), and marital status ($p<0.001$) (Table 4). No significance was found amongst racial groups in survival.

4. Discussion

The purpose of this study was to compare practice trends in patients with clinically staged T2–T4a, N0, M0 MIBC treated in the United States with three major treatment options from 1988 to 2013 using the SEER database. Although radical cystectomy plus chemotherapy and chemoradiotherapy are both category 1 treatment options for MIBC according to NCCN guidelines, our results showed that they were both underutilized, with highly significant p-values (<0.001).

Despite practice patterns having changed in the last two decades, clinicians have continued to use the previously standard treatment of radical cystectomy for MIBC. The landmark article published in 2003 from Grossman et al. [8] has made an immediate impact on the usage of NAC with radical cystectomy. Our results reflect this change in clinical knowledge. In 2003–2007, the use of radical cystectomy plus chemotherapy doubled for both stage II and stage III data compared to the previous interval. For 2003 specifically, the use of radical cystectomy plus chemotherapy as a treatment option increased for both stages.

Studies looking at chemotherapy with radical cystectomy showed results comparable to our own with some caveats. Zaid et al. [21] looked at trends of 5692 patients who received either radical or partial cystectomy alone combined with NAC for MIBC in the NCDB from 2006 to 2010. Duplisea et al. [17] identified 18 188 patients who underwent either radical or partial cystectomy combined with NAC using NCDB from 2006 to 2014. The current study looked solely at radical cystectomy. Reardon et al. [20] looked at 5692 patients with MIBC treated with radical cystectomy alone or with perioperative chemotherapy in the same timeframe. Our study similar to Zaid et al. [21], Reardon et al. [20], and Duplisea et al. [17] all showed an increase in chemotherapy with radical cystectomy after clinical guidelines changed. While Zaid et al. [21] and Duplisea et al. [17] showed that neither patient sex or race was associated with NAC, our study showed that patients who received chemotherapy with radical cystectomy were less likely to be female or Asian compared to radical cystectomy alone. Compared to Zaid et al. [21] and Reardon et al. [20], our study included more patients in each treatment group. Duplisea et al. [17] included more patients in each treatment group than our own [17]. Compared to studies that looked at chemotherapy with radical cystectomy, our study covered the longest timeframe.

Chemoradiotherapy overall has shown increased utilization. We suggest that chemotherapy and radiation have greatly improved when it comes to not only targeting the cancer, but also reducing the amount of side effects leading to increased usage for otherwise difficult to manage MIBC

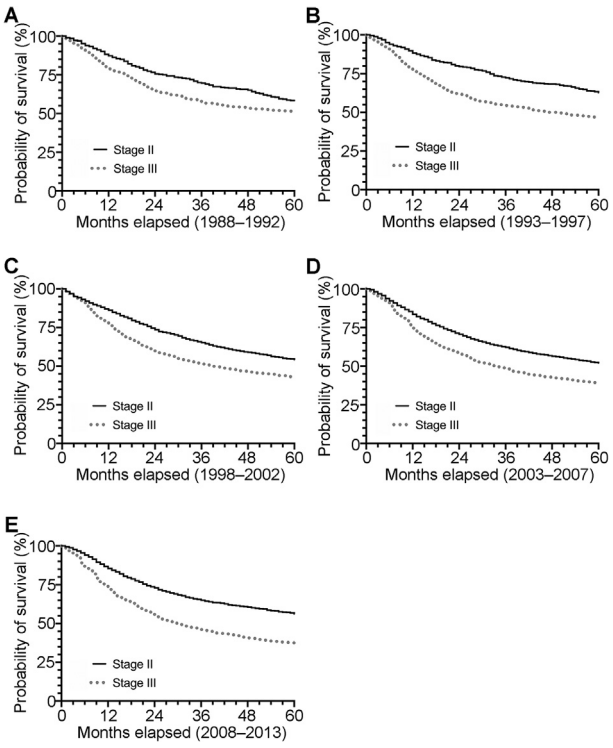

Figure 4 5-year cause-specific survival curves of muscle-invasive bladder cancer for stage II versus stage III from 1988 to 2013 at 5-year intervals. Cases from (A) 1988–1992, $n=877$; (B) 1993–1997, $n=1340$; (C) 1998–2002, $n=2852$; (D) 2003–2007, $n=4908$; (E) 2008–2013, $n=6751$ (p-values <0.05).

cases, especially older patients who would have poorer quality of life after a radical cystectomy surgery. Trenta et al. [25] suggest that clinical treatment of MIBC using chemotherapy has made great strides from using the single platinum agent cisplatin to the development of effective drug combinations that improve safety profiles and thus survival. Along with this, Sandler and Mirhadi [26] suggest that radiotherapy has also improved and led to better outcomes in the treatment of MIBC through an improved understanding of fractionation and tumor response. The continued improvement in chemoradiotherapy may help explain its increased utilization. However, our results have shown a significant difference in the number of patients who have received chemoradiotherapy for stage II compared to III ($p<0.001$). While chemoradiotherapy for both stages of MIBC is suggested, it is less likely to be utilized for stage III. We also considered patient demographics based on each treatment group. Our findings suggest that clinicians are more likely to choose one treatment over another based on a variety of factors. Patients who were more likely to receive chemoradiotherapy were more commonly African American and aged 75–85 years old, compared to the radical cystectomy reference group. According to a phase II study that evaluated 31 elderly patients treated with bladder preservation therapy for MIBC, treatment showed acceptable toxicity with good survival and response rate [27].

Previous studies have shown results similar for chemoradiotherapy utilization. In a study with 15 510 cases comparing radical cystectomy and chemoradiotherapy for MIBC between 2004 and 2013, patients who underwent chemoradiotherapy tended to be older, female, and African American [18]. This is in line with results from the current study. Our study, however, found that patients tended to be male rather than female after controlling for stage III patients. Unlike their study, ours also compared bladder preservation therapy to chemotherapy with radical cystectomy as separate treatment options for MIBC. To go along with ours and the study by Haque et al. [18] that showed patients who received chemoradiotherapy for MIBC tended to be African American, the Gray et al. [24] and Fedeli et al. [28] studies found that the rate of cystectomy decreased with age and among ethnic and racial minorities. The Gray et al. [24] study looked at 28 691 patients from the NCDB between 2003 and 2008 who received aggressive therapy that included radical cystectomy or partial cystectomy, chemotherapy, or radiotherapy as treatment options for MIBC. Although their study included more patients who received treatment for MIBC, ours had larger pools of data for treatment of radical cystectomy or chemoradiotherapy. Fedeli et al. [28] looked at 40 388 patients from the NCDB between 2003 and 2007 who received either cystectomy, chemoradiotherapy, or no treatment for MIBC. Their study similar to our own showed an increase in chemotherapy for radical cystectomy due to NAC [28]. Although their study considered many similar patient demographics as the present study and included more patients, our own study controlled for stage when considering patient demographics [28]. Cahn et al. [16] looked at contemporary use trends between radical cystectomy and bladder preservation therapy for MIBC that included 32 300 from the NCDB between 2004 and 2013. Their study included more patients in radical cystectomy and bladder preservation therapy, when looking at patient and tumor characteristics. Cahn et al. [16], however, did not include a group for chemotherapy with radical cystectomy or control by stage. Compared to all previous studies, ours looked at greater temporal trends. Our study uniquely found a drop in chemoradiotherapy in stage III tumors.

While NAC with radical cystectomy is the preferred treatment for MIBC, a significant portion of the BC population may be ineligible to receive chemotherapy. Several retrospective studies have shown that approximately 40% of patients who received radical cystectomy were ineligible to receive cisplatin chemotherapy treatment due to poor renal function [29,30]. Other co-morbidities including hearing loss and cardiac dysfunction may similarly prevent patients from receiving standard cisplatin-based chemotherapy [31]. The usage of a bladder-preservation approach with chemoradiotherapy for MIBC may be underutilized for the same reason. Data have identified basal and luminal subgroups of MIBC based on survival and chemotherapy response [32]. Seiler et al. [33] have shown that the basal subtype of MIBC derived the most benefit from NAC while luminal nonimmune-infiltrated may not derive any benefit despite having the best outcomes. In a similar mechanistical approach, Vollmer et al. [34] identified the prognostic role of the intratumoral CXCR3alt-CXCL11 biomarker in CD8+ T-cell subpopulations in predicting NAC responsiveness in MIBC. The identification of molecular markers in these subtypes of MIBC, however, has been variable in

predicting response to NAC, proven to be difficult to account for in clinical practice, and further has few mechanistic connections to the tumor immunological microenvironment; therefore, future development will be needed to merit their use in practice.

As an analysis of a national oncologic registry, our study has several limitations that extend to all cohort studies. Our study is limited in the patients that were recorded in the registry. The SEER database itself has several limitations especially on radiotherapy and chemotherapy information. Data stemming from radiotherapy treatment can be underreported. As radiotherapy is commonly administered in an outpatient setting, the SEER database may not capture all data especially being driven by hospital-based registries. The SEER database also lacks radiotherapy doses and intent of treatment as either curative or palliative regimens. Data submitted to SEER in terms of chemotherapy options are limited, being listed solely as either "yes" or "no-unknown". While there is confidence that a patient received chemotherapy after the box was marked as "yes", there is less confidence that a patient who was marked as "no-unknown" did not actually receive chemotherapy. For this reason, the data for radical cystectomy alone would be most affected as the patients may actually have received chemotherapy. In the SEER database, we are unable to know whether a patient received NAC or adjuvant chemotherapy; therefore, both groups have been included together.

5. Conclusion

Although considered the standard treatment prior to 2003, radical cystectomy is still the most commonly utilized treatment for MIBC. Chemotherapy with radical cystectomy and chemoradiotherapy are still underutilized. Differences in chemoradiotherapy as a treatment option are especially noticeable between stage II and III tumors, with stage III cases less likely to receive this treatment. Significant disparities exist in those who receive radical cystectomy over chemoradiotherapy for treatment. More research is still needed to understand what treatment delivers better survival outcomes.

Author contributions

Study concept and design: Victor Chalfant, Peter Silberstein.
Data acquisition: Victor Chalfant.
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Conflicts of interest

The authors declare no conflict of interest.

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