



Which treatment is best for patients with AJCC stage IV bladder cancer?

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Abstract

Purpose We sought to identify the method that could obtain the best survival rate for AJCC stage IV bladder cancer (BCa) patients.

Methods Patients with AJCC stage IV BCa diagnosed between 2004 and 2015 were identified using the Surveillance, epidemiology and end results (SEER) database. Kaplan–Meier curves and log-rank test were used for overall survival (OS) and cancer-specific survival (CSS). Multivariable Cox regression was used to determine factors associated with all-cause mortality (ACM) and cancer-specific mortality (CSM).

Results We found that among the 11824 patients, the number of patients who received chemotherapy (CT), radiotherapy (RT) and radical cystectomy (RC) was 6243 (52.8%), 2005 (17.0%) and 4987 (42.2%), respectively. Patients who received CT or RC had improved OS (26.4% vs. 11.7%, $p < 0.001$ and 27.3% vs. 13.7%, $p < 0.001$, respectively), but patients who underwent RT alone had lower OS (14.4% vs. 20.5%, $p < 0.001$). Furthermore, CT combined with RC was associated with the lowest ACM (hazard ratio (HR) = 0.26, 95% CI 0.24–0.28, $p < 0.001$) and the lowest CSM (HR = 0.24, 95% CI 0.22–0.26, $p < 0.001$). Patients who only received RT had the highest ACM (HR = 0.84, 95% CI 0.77–0.92, $p < 0.001$) and the highest CSM (HR = 0.85, 95% CI 0.77–0.94, $p = 0.002$).

Conclusions We concluded that CT combined with RC was the best method with the highest survival rate for patients with AJCC stage IV BCa and that CT combined with RC had more benefits in improving OS and CSS than did RT alone.

Keywords Bladder cancer · Radical cystectomy · Chemotherapy · Radiotherapy · SEER

Abbreviations

CT Chemotherapy

RT Radiotherapy

RC Radical cystectomy

SEER Surveillance, epidemiology and end results

OS Overall survival

CSS Cancer-specific survival

ACM All-cause mortality

CSM Cancer-specific mortality

BCa Bladder cancer

AJCC American joint committee on cancer

Introduction

Bladder cancer (BCa) is the ninth most common cancer worldwide and the fourth most common malignant tumour in the United States with an estimated 81190 new cases diagnosed and 17240 cancer deaths in 2018 [1, 2]. There are two known histopathological stages, non-muscle-invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC). Approximately 70% of patients with BCa present with a disease confined to NMIBC, including stage Ta, carcinoma in situ (CIS) or stage T1 [3]. Transurethral resection of bladder tumours (TURBT) is the main treatment for NMIBC, but the recurrence rate was 15–75% within 5 years, with 15% of cases progressing to MIBC and

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metastatic cancer [4, 5]. Overall, 10–15% patients with BCa had metastases at the time of diagnosis, and for metastatic BCa patients, the 5-year survival was only approximately 8.1% [6, 7].

For MIBC patients, surgery is the preferred treatment, including partial cystectomy and radical cystectomy (RC). Currently, the gold standard for tumour control and eventual cure for MIBC is RC [8]. Chemotherapy (CT), radiotherapy (RT) and surgery are the main treatments for patients with AJCC stage IV BCa or metastatic BCa [9]. RC and systemic CT have been demonstrated to be effective in the treatment of MIBC, but radiation therapy remains controversial [10, 11].

According to the American joint committee on cancer (AJCC) cancer staging atlas, 2nd edition staging for BCa (https://link.springer.com/chapter/10.1007/978-1-4614-2080-4_45), stage IV included T4b N0 M0, Any T N1-3 M0 and Any T Any N M1. The purpose of this study was to use the Surveillance, epidemiology and end results (SEER) database to characterize the different treatment methods and find the best treatment method for AJCC stage IV BCa patients on a population-based level.

Patients and methods

Data source and patients

The SEER database of the National Cancer Institute covers approximately 28% of the US population and collects incidence, treatment and survival data from 18 tumour registries [12]. For all cancer patients, the SEER registries collect data on patient social demographic characteristics, disease diagnosis time, site and extent, clinical and pathological stages, treatment, and follow up vital status. SEER*Stat software, version 8.3.5 was used to access the SEER 18 Regs Custom Data (with additional treatment field), Nov 2017 Sub (1973–2015 varying) database using SEER*Stat's client-server mode. For this study, the data used included patients diagnosed between 2004 and 2015. Patients were excluded if they had unknown survival time, were under 18 years old, were diagnosed at autopsy, or had unknown TNM stage. Within the SEER database, we identified 11824 patients 18 years or older who were diagnosed with AJCC stage IV BCa between 1 January 2004 and 31 December 2015.

Study variables

Overall survival (OS) and cancer-specific survival (CSS) were the primary study end points. In our study, we categorized patients by various patient factors such as year of diagnosis (2004–2006, 2007–2009, 2010–2012, 2013–2015), age at

diagnosis (18–40, 41–60, 61–80, > 80), gender, race (white, black, others), marital status (married, unmarried, unknown) and state (West, Northeast, South, Midwest). Variables about the tumour included tumour primary site, tumour grade (well differentiated, moderately differentiated, poorly differentiated, undifferentiated, unknown), histology type (transitional cell carcinoma, squamous cell carcinoma, adenocarcinoma, others), T-stage (T0, T1, T2, T3, T4), N-stage (N0, N1, N2, N3) and M-stage (M0, M1).

Statistical analysis

Patients were followed up until the end of statistical analysis. We provide Chi-square test statistical analysis of our cohort on whether AJCC stage IV BCa patients underwent CT, RT, or RC. Kaplan–Meier curves and log-rank test were used to evaluate the association between covariates and OS or CSS. Multivariable Cox regression was used to determine factors associated with all-cause mortality (ACM) and cancer-specific mortality (CSM). A p -value < 0.05 was considered to be significant. All statistical analyses were performed using the Statistical package for the social sciences (SPSS, version 20.0, Chicago, IL, USA).

Results

Demographic and clinicopathological characteristics of the AJCC stage IV BCa patients

According to the screening criteria in Fig. 1, 11824 AJCC stage IV BCa patients were included in the final study cohort. Among them, 6243 (52.8%) patients received CT (CT group), 2005 (17.0%) patients received RT (RT group) and 4987 (42.2%) patients underwent RC (RC group) (Table 1). Among all 11824 patients, over time, the proportion of patients receiving CT increased, while the rate of RT or RC decreased. The vast majority of our cohort was 60–80 years of age (57.6%), male (71.0%), white (85.8%), married (54.4%) and diagnosed in the West (51.6%) with an undifferentiated grade (53.6%). As shown in Table 1, the categorical variables of year of diagnosis, age at diagnosis, sex, race, marital status, state, tumour grade, histology type and TNM stage were associated with both CT and RC. All variables were statistically significantly different (Chi-square test: $p < 0.05$). The categorical variables of sex, race, marital status and tumour primary site were not associated with RT.

Effects of different variables on all-cause survival and BCa-caused survival in patients with AJCC stage IV

Of the 11824 patients, 9524 (80.5%) died of all causes, while 7181 (75.7%) died of BCa (Fig. 1; Table 2). Patients

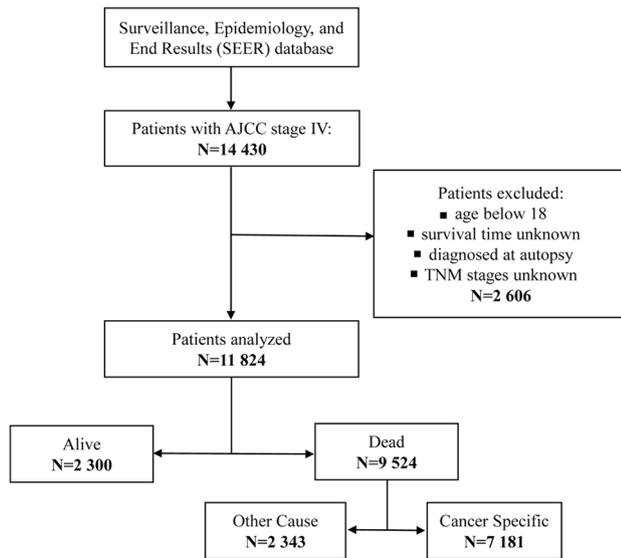


Fig. 1 Schematic flow diagram of inclusion and exclusion criteria for our study cohort

who live over 80 years of age and live in the northeast have higher mortality rates than unmarried black women. In addition, there was a higher mortality rate in patients with T4N0 M1 poorly differentiated squamous cell carcinoma located at the ureteric orifice. On univariate analysis, patients who received CT had improved OS (26.4% vs. 11.7%, $p < 0.001$) and CSS (31.4% vs. 15.4%, $p < 0.001$). RC improved OS (27.3% vs. 13.7%, $p < 0.001$) and CSS (33.5% vs. 17.3%, $p < 0.001$). However, patients who underwent RT had lower OS (14.4% vs. 20.5%, $p < 0.001$) and CSS (17.5% vs. 25.7%, $p < 0.001$). CT combined with RC was associated with the highest OS (36.2% vs. 8.2%, $p < 0.001$) and CSS (42.4% vs. 11.0%, $p < 0.001$). In contrast, OS at 144 months was decreased in patients who received RT, 6.4% versus 8.2% ($p < 0.001$) and CSS at 144 months was also decreased in patients who received RT alone, 8.2% versus 11.0%, ($p < 0.001$).

Survival

A Kaplan–Meier curve depicting OS and CSS among patients with AJCC stage IV BCa who underwent different treatment methods is shown in Fig. 2. The median survival in the entire cohort was 9.0 months. Patients who received CT or RC had significantly better survival in months (21.05 ± 24.93 vs. 12.23 ± 21.74 ; 24.88 ± 28.46 vs. 11.05 ± 17.76) and median survival time (12 months vs. 4 months; 14 months vs. 5 months) than those who did not receive CT or RC. Patients who received RT had reduced survival months (13.73 ± 18.49 vs. 17.53 ± 24.79) and median survival time (8 months vs. 9 months)

(Table 3). CT combined with RC showed the longest median survival of 18.0 months and mean survival months (29.12 ± 29.76 months) (Table 3). Patients who only received RT and those who did not receive any treatment had similar median survival periods of 3 months and 2 months, respectively.

Identification of prognostic factors for patients with AJCC stage IV BCa patients

After adjusting for the age at diagnosis, sex, race, marital status, state, primary site, grade, histology type and T/N/M stage, the multivariate Cox regression analysis showed that treatment method is an independent prognostic factor for ACM and CSM (Table 4). It showed a significant protective effect for CT combined with RC treatment (ACM: HR = 0.26, 95% CI 0.24–0.28, $p < 0.001$; CSM: HR = 0.24, 95% CI 0.22–0.26, $p < 0.001$) and a counter effect for RT treatment (ACM: HR = 0.84, 95% CI 0.77–0.92, $p < 0.001$; CSM: HR = 0.85, 95% CI 0.77–0.94, $p < 0.001$).

Discussion

BCa is the second most common cancer after prostate cancer in the urinary system and the eighth leading cause of cancer-related deaths in American men [13]. Population-based data from the United States showed a 5-year cancer-specific survival rate of only 8.1% after the diagnosis of a metastatic bladder with no improvement over time [7]. David et al. [14] examined the National Cancer DataBase and reported AJCC stage IV BCa relative survival of about 17.4% from 1993 to 2000. Therefore, for AJCC stage IV BCa patients, management of metastatic bladder represents a great challenge, and more effective treatment strategies or better management methods are needed.

For patients with MIBC, surgery, CT and RT are the main treatments. From our research, over time, the proportion of patients receiving CT increased gradually, while the proportion of patients receiving RT and RC decreased as age increased. The percentage of CT, RT and RC also decreased. In this study, we found that both CT and RC can improve the median survival of patients with AJCC stage IV BCa to 12 months (vs. 4 months) with CT and 14 months (vs. 5 months) with RC. However, median survival time of patients receiving RT decreased (8 months vs. 9 months). In addition, patients with CT combined with RC treatment had the longest median survival (18 months). Patients who only received RT treatment and those who did not receive any treatment had similar median survival periods of months and 2 months, respectively. Our group found a significant increase in HR (0.26–0.84; $p < 0.001$) for ACM and for CSM (0.24–0.58; $p < 0.001$) in the CT combined with RC

Table 1 Characteristics for bladder cancer patients stratified by chemotherapy (CT), radiotherapy (RT) and radical cystectomy (RC) (Chi-square test)

Characteristics	Total	CT N (%)	No CT N (%)	p	RT N (%)	No RT N (%)	p	RC N (%)	No RC N (%)	p
Total	11,824	6243 (52.8)	5581 (47.2)		2005 (17.0)	9819 (83.0)		4987 (42.2)	6837 (57.8)	
Year of diagnosis										
2004–2006	2504	1173 (46.8)	1331 (53.2)	<0.001	432 (17.3)	2072 (82.7)	0.032	1188 (47.4)	1316 (52.6)	<0.001
2007–2009	2892	1426 (49.3)	1466 (50.7)		477 (16.4)	2415 (83.5)		1282 (44.3)	1610 (55.7)	
2010–2012	3103	1723 (55.5)	1380 (44.5)		572 (18.4)	2531 (81.6)		1265 (40.8)	1838 (59.2)	
2013–2015	3325	1921 (57.8)	1404 (42.2)		524 (15.8)	2801 (84.2)	0.011	1252 (37.7)	2073 (62.3)	<0.001
Age at diagnosis										
18–40	111	79 (71.2)	32 (28.8)	<0.001	24 (21.6)	87 (78.4)	0.484	52 (46.8)	59 (53.2)	0.042
41–60	2658	1784 (67.1)	874 (32.9)		444 (16.7)	2214 (83.3)		1291 (48.6)	1367 (51.4)	
61–80	6811	3805 (55.9)	3006 (44.1)		1109 (16.3)	5702 (83.7)		3095 (45.4)	3716 (54.6)	
> 80	2244	575 (25.6)	1669 (74.4)	<0.001	428 (19.1)	1816 (80.9)		549 (24.5)	1695 (75.5)	
Sex										
Male	8392	4601 (54.8)	3791 (45.2)	<0.001	1436 (17.1)	6956 (82.9)	0.057	3589 (42.8)	4803 (57.2)	<0.001
Female	3432	1642 (47.8)	1790 (52.2)		569 (16.6)	2863 (83.4)		1398 (40.7)	2034 (59.3)	
Race										
White	10,141	5426 (53.5)	4715 (46.5)	<0.001	1687 (16.6)	8454 (83.4)	0.076	4379 (43.2)	5762 (56.8)	<0.001
Black	1111	517 (46.5)	594 (53.5)		215 (19.4)	896 (80.6)		359 (32.3)	752 (67.7)	
Other	572	300 (52.4)	272 (47.6)		103 (18.0)	469 (82.0)		249 (43.5)	323 (56.5)	
Marital status										
Yes	6429	3755 (58.4)	2674 (41.6)	<0.001	1046 (16.3)	5383 (83.7)	0.005	3018 (46.9)	3411 (53.1)	<0.001
No	4974	2304 (46.3)	2670 (53.7)		889 (17.9)	4085 (82.1)		1808 (36.3)	3166 (63.7)	
Unknown	421	184 (43.7)	237 (56.3)		70 (16.6)	351 (83.4)		161 (38.2)	260 (61.8)	
State										
West	6096	3187 (52.3)	2909 (47.7)	<0.001	986 (16.2)	5110 (83.8)	0.158	2775 (45.5)	3321 (54.5)	<0.001
Northeast	2054	1048 (51.0)	1006 (49.0)		330 (16.1)	1724 (83.9)		767 (37.3)	1287 (62.7)	
South	2395	1233 (51.5)	1162 (48.5)		457 (19.1)	1938 (80.9)		918 (38.3)	1477 (61.7)	
Midwest	1279	775 (60.6)	504 (39.4)		232 (18.1)	1047 (81.9)		527 (41.2)	752 (58.8)	
Primary Site										
Trigone of bladder	705	391 (55.5)	314 (44.5)	0.156	137 (19.4)	568 (80.6)	0.158	296 (42.0)	409 (58.0)	<0.001
Dome of bladder	510	272 (53.3)	238 (46.7)		77 (15.1)	433 (84.9)		209 (41.0)	301 (59.0)	
Lateral wall of bladder	1490	804 (54.0)	686 (46.0)		270 (18.1)	1220 (81.9)		649 (43.6)	841 (56.4)	
Anterior wall of bladder	324	187 (57.7)	137 (42.3)		68 (21.0)	256 (79.0)		138 (42.6)	186 (57.4)	
Posterior wall of bladder	758	382 (50.4)	376 (49.6)		133 (17.5)	625 (82.5)		337 (44.5)	421 (55.5)	
Bladder neck	438	239 (54.6)	199 (45.4)		77 (17.6)	361 (82.4)		145 (33.1)	293 (66.9)	
Ureteric orifice	189	105 (55.6)	84 (44.4)		29 (15.3)	160 (84.7)		65 (34.4)	124 (65.6)	

Table 1 (continued)

Characteristics	Total	CT N (%)	No CT N (%)	<i>p</i>	RT N (%)	No RT N (%)	<i>p</i>	RC N (%)	No RC N (%)	<i>p</i>
Urachus	70	40 (57.1)	30 (42.9)		8 (11.4)	62 (88.6)		11 (15.7)	59 (84.3)	
Overlapping lesion of bladder	2404	1282 (53.3)	1122 (46.7)		395 (16.4)	2009 (83.6)		1130 (47.0)	1274 (53.0)	
Bladder, NOS	4936	2541 (51.5)	2395 (48.5)		811 (16.4)	4125 (83.6)		2007 (40.7)	2929 (59.3)	
Grade				<0.001			0.006			<0.001
Well differentiated	100	38 (38.0)	62 (62.0)		22 (22.0)	78 (78.0)		21 (21.0)	79 (79.0)	
Moderately differentiated	486	178 (36.6)	308 (63.4)		95 (19.5)	391 (80.5)		189 (38.9)	297 (61.1)	
Poorly differentiated	3635	1813 (49.9)	1822 (50.1)		625 (17.2)	3010 (82.8)		1557 (42.8)	2078 (57.2)	
Undifferentiated	6335	3653 (57.7)	2682 (42.3)		1015 (16.0)	5320 (84.0)		3012 (47.5)	3323 (52.5)	
Unknown	1268	561 (44.2)	707 (55.8)		248 (19.6)	1020 (80.4)		208 (16.4)	1060 (83.6)	
Histology type				<0.001			0.002			<0.001
Transitional cell carcinoma	9898	5372 (54.3)	4526 (45.7)		1631 (16.5)	8267 (83.5)		4406 (44.5)	5492 (55.5)	
Squamous cell carcinoma	580	215 (37.1)	365 (62.9)		118 (20.3)	462 (79.7)		242 (41.7)	338 (58.3)	
Adenocarcinoma	325	154 (47.4)	171 (52.6)		49 (15.1)	276 (84.9)		99 (30.5)	226 (69.5)	
Others	1021	502 (49.2)	519 (50.8)		207 (20.3)	814 (79.7)		240 (23.5)	781 (76.5)	
T-stage				<0.001			<0.001			<0.001
T0	51	25 (49.0)	26 (51.0)		10 (19.6)	41 (80.4)		1 (2.0)	50 (98.0)	
T1	1250	534 (42.7)	716 (57.3)		222 (17.8)	1028 (82.2)		110 (8.8)	1140 (91.2)	
T2	3859	2187 (56.7)	1672 (43.3)		759 (19.7)	3100 (80.3)		902 (23.4)	2957 (76.6)	
T3	2832	1580 (55.8)	1252 (44.2)		280 (9.9)	2552 (90.1)		2137 (75.5)	695 (24.5)	
T4	3832	1917 (50.0)	1915 (50.0)		734 (19.2)	3098 (80.8)		1837 (47.9)	1995 (52.1)	
N-stage				<0.001			<0.001			<0.001
N0	4215	1859 (44.1)	2356 (55.9)		951 (22.6)	3264 (77.4)		556 (13.2)	3659 (86.8)	
N1	3778	2096 (55.5)	1682 (44.5)		521 (13.8)	3257 (86.2)		2215 (58.6)	1563 (41.4)	
N2	3669	2199 (59.9)	1470 (40.1)		506 (13.8)	3163 (86.2)		2134 (58.2)	1535 (41.8)	
N3	162	89 (54.9)	73 (45.1)		27 (16.7)	135 (83.3)		82 (50.6)	80 (49.4)	
M-stage				<0.001			<0.001			<0.001
M0	6191	3452 (55.8)	2739 (44.2)		840 (13.6)	5351 (86.4)		4099 (66.2)	2092 (33.8)	
M1	5633	2791 (49.5)	2842 (50.5)		1165 (20.7)	4468 (79.3)		888 (15.8)	4745 (84.2)	

CT chemotherapy; RT radiotherapy; RC radical cystectomy

Table 2 Univariate survival analyses of AJCC stage IV bladder cancer patients according to various clinicopathological variables

Characteristics	All-cause		<i>p</i>	Bladder cancer cause		<i>p</i>
	Dead	Alive		Dead	Alive	
	<i>N</i> (%)	<i>N</i> (%)		<i>N</i> (%)	<i>N</i> (%)	
Total	9524 (80.5)	2300 (19.5)		7181 (75.7)	2300 (24.3)	
Age at diagnosis			<0.001			<0.001
18–40	73 (65.8)	38 (34.2)		58 (60.4)	38 (39.6)	
41–60	2013 (75.7)	645 (24.3)		1610 (71.4)	645 (28.6)	
61–80	5446 (80.0)	1365 (20.0)		4061 (74.8)	1365 (25.2)	
>80	1992 (88.8)	252 (11.2)		1452 (85.2)	252 (14.8)	
Sex			<0.001			<0.001
Male	6686 (79.7)	1706 (20.3)		4984 (74.5)	1706 (25.5)	
Female	2838 (82.7)	594 (17.3)		2197 (78.7)	594 (21.3)	
Race			<0.001			<0.001
White	8151 (80.4)	1990 (19.6)		6188 (75.7)	1990 (24.3)	
Black	941 (84.7)	170 (15.3)		590 (80.2)	170 (19.8)	
Other	432 (75.5)	140 (24.5)		303 (68.4)	140 (31.6)	
Marital status			<0.001			<0.001
Yes	5055 (78.6)	1374 (21.4)		3818 (73.5)	1374 (26.5)	
No	4127 (83.0)	847 (17.0)		3109 (78.6)	847 (21.4)	
Unknown	342 (81.2)	79 (18.8)		254 (76.3)	79 (23.7)	
State			<0.001			<0.001
West	4800 (78.7)	1296 (21.3)		3677 (73.9)	1296 (26.1)	
Northeast	1707 (83.1)	347 (16.9)		1240 (78.1)	347 (21.9)	
South	1970 (82.3)	425 (17.7)		1492 (77.8)	425 (22.2)	
Midwest	1047 (81.9)	232 (18.1)		772 (76.9)	232 (23.1)	
Primary site			0.04			0.04
Trigone of bladder	568 (80.6)	137 (19.4)		411 (75.0)	137 (25.0)	
Dome of bladder	398 (78.0)	112 (22.0)		291 (72.2)	112 (27.8)	
Lateral wall of bladder	1178 (79.1)	312 (20.9)		906 (74.4)	312 (25.6)	
Anterior wall of bladder	246 (75.9)	78 (24.1)		198 (71.7)	78 (28.3)	
Posterior wall of bladder	605 (79.8)	153 (20.2)		475 (75.6)	153 (24.4)	
Bladder neck	350 (79.9)	88 (20.1)		236 (72.8)	88 (27.2)	
Ureteric orifice	160 (84.7)	29 (15.3)		123 (80.9)	29 (19.1)	
Urachus	50 (71.4)	20 (28.6)		36 (64.3)	20 (35.7)	
Overlapping lesion of bladder	1961 (81.6)	443 (18.4)		1507 (77.3)	443 (22.7)	
Bladder, Nos	4008 (81.2)	928 (18.8)		2998 (76.4)	928 (23.6)	
Grade			<0.001			<0.001
Well differentiated	85 (85.0)	15 (15.0)		64 (81.0)	15 (19.0)	
Moderately differentiated	410 (84.4)	76 (15.6)		314 (80.5)	76 (19.5)	
Poorly differentiated	3109 (85.5)	526 (14.5)		2356 (81.7)	526 (18.3)	
Undifferentiated	4849 (76.5)	1486 (23.5)		3702 (71.4)	1486 (28.6)	
Unknown	1071 (84.5)	197 (15.5)		745 (79.1)	197 (20.9)	
Histology type			<0.001			<0.001
Transitional cell carcinoma	7868 (79.5)	2030 (20.5)		5949 (74.6)	2030 (25.4)	
Squamous cell carcinoma	526 (90.7)	54 (9.3)		426 (88.8)	54 (11.2)	
Adenocarcinoma	261 (80.3)	64 (19.7)		186 (74.4)	64 (25.6)	
Others	869 (85.1)	152 (14.9)		620 (80.3)	152 (19.7)	
T-stage			<0.001			<0.001
T0	43 (84.3)	8 (15.7)		18 (69.2)	8 (30.8)	
T1	1024 (81.9)	226 (18.1)		740 (76.6)	226 (23.4)	
T2	3036 (78.7)	823 (21.3)		2376 (74.3)	823 (25.7)	

Table 2 (continued)

Characteristics	All-cause		<i>p</i>	Bladder cancer cause		<i>p</i>
	Dead	Alive		Dead	Alive	
	<i>N</i> (%)	<i>N</i> (%)		<i>N</i> (%)	<i>N</i> (%)	
T3	2129 (75.2)	703 (24.8)		1591 (69.4)	703 (30.6)	
T4	3292 (85.9)	540 (14.1)		2456 (82.0)	540 (18.0)	
N-stage			<0.001			<0.001
N0	3698 (87.7)	517 (12.3)		2802 (84.4)	517 (15.6)	
N1	2897 (76.7)	881 (23.3)		2131 (70.8)	881 (29.2)	
N2	2792 (76.1)	877 (23.9)		2142 (71.0)	877 (29.0)	
N3	137 (84.6)	25 (15.4)		106 (80.9)	25 (19.1)	
M-stage			<0.001			<0.001
M0	4646 (75.0)	1545 (25.0)		3435 (69.0)	1545 (31.0)	
M1	4878 (86.6)	755 (13.4)		3746 (83.2)	755 (16.8)	
CT			<0.001			<0.001
No	4928 (88.3)	653 (11.7)		3578 (84.6)	653 (15.4)	
Yes	4596 (73.6)	1647 (26.4)		3603 (68.6)	1647 (31.4)	
RT			<0.001			<0.001
No	7808 (79.5)	2011 (20.5)		5822 (74.3)	2011 (25.7)	
Yes	1716 (85.6)	289 (14.4)		1359 (82.5)	289 (17.5)	
RC			<0.001			<0.001
No	5899 (86.3)	938 (13.7)		4479 (82.7)	938 (17.3)	
Yes	3625 (72.7)	1362 (27.3)		2702 (66.5)	1362 (33.5)	
Treatment method			<0.001			<0.001
No CT and no RT and no RC	2544 (91.8)	228 (8.2)		1839 (89.0)	228 (11.0)	
CT	1938 (79.8)	492 (20.2)		1527 (75.6)	492 (24.4)	
RT	595 (93.6)	41 (6.4)		462 (91.8)	41 (8.2)	
RC	1701 (82.1)	370 (17.9)		1205 (76.5)	370 (23.5)	
CT and RT	822 (82.3)	177 (17.7)		651 (78.6)	177 (21.4)	
CT and RC	1625 (63.8)	921 (36.2)		1251 (57.6)	921 (42.4)	
RT and RC	88 (86.3)	14 (13.7)		72 (83.7)	14 (16.3)	
CT and RT and RC	211 (78.7)	57 (21.3)		174 (75.3)	57 (24.7)	

AJCC American joint committee on cancer; *CT* chemotherapy; *RT* radiotherapy; *RC* radical cystectomy; *IV* T4b, and/or positive nodes and/or positive metastases

treatment group compared with the RT treatment alone group.

Although metastatic BC is an aggressive tumour with rapid systemic transmission, some patients with locally advanced disease will benefit from surgical resection. Several studies have shown that surgery for locally advanced and metastatic BCa may affect survival. Herr et al. [15] reported 207 patients with unresectable or regional metastatic BCa, and 80 (39%) underwent surgery after CT with cisplatin. Results showed no viable cancer was present at post-CT surgery in 24 of the 80 cases (30%), and 14 of the 24 cases (58%) survived for 9 months to 5 years. This finding suggests that surgical resection of residual cancer after CT may result in disease-free survival in some patients.

Radical surgical procedures include open radical cystectomy (ORC), laparoscopic radical cystectomy (LRC) and robot-assisted radical cystectomy (RARC) [16, 17]. ORC

plus pelvic lymphadenectomy is currently the gold standard for high-grade invasive transitional cell carcinoma of the bladder and provides good local cancer control [18]. Ashok et al. [17] found that LRC can reduce perioperative morbidity and provides another treatment for locally advanced BCa patients. In addition, many studies have shown that LRC and RARC have no significant advantages in reducing postoperative complications compared with ORC [19, 20].

BCa is a chemosensitive tumour, and for locally advanced and metastatic BCa patients, RC alone is rarely curative [21], while CT remains the preferred treatment. For locally advanced and metastatic BCa patients, the median survival is 3–6 months without treatment, and the median survival with treatment was approximately one year [22]. CT options, such as methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine and cisplatin (GC), are widely used in locally advanced and metastatic BCa patients.

Fig. 2 Survival curves in AJCC stage IV BCa according to different treatment methods.

a, b Kaplan–Meier curves among patients stratified by CT/No CT for OS (**a**, $p < 0.001$) and CSS (**b**, $p < 0.001$). **c, d** Kaplan–Meier curves among patients stratified by RT/No RT for OS (**c**, $p < 0.001$) and CSS (**d**, $p < 0.001$). **e, f** Kaplan–Meier curves among patients stratified by RC/No RC for OS (**e**, $p < 0.001$) and CSS (**f**, $p < 0.001$). **g, h** Kaplan–Meier curves among patients stratified by different treatment methods for OS and CSS. Abbreviations: AJCC, American Joint Committee on Cancer; CT, chemotherapy; RT, radiotherapy; RC, radical cystectomy

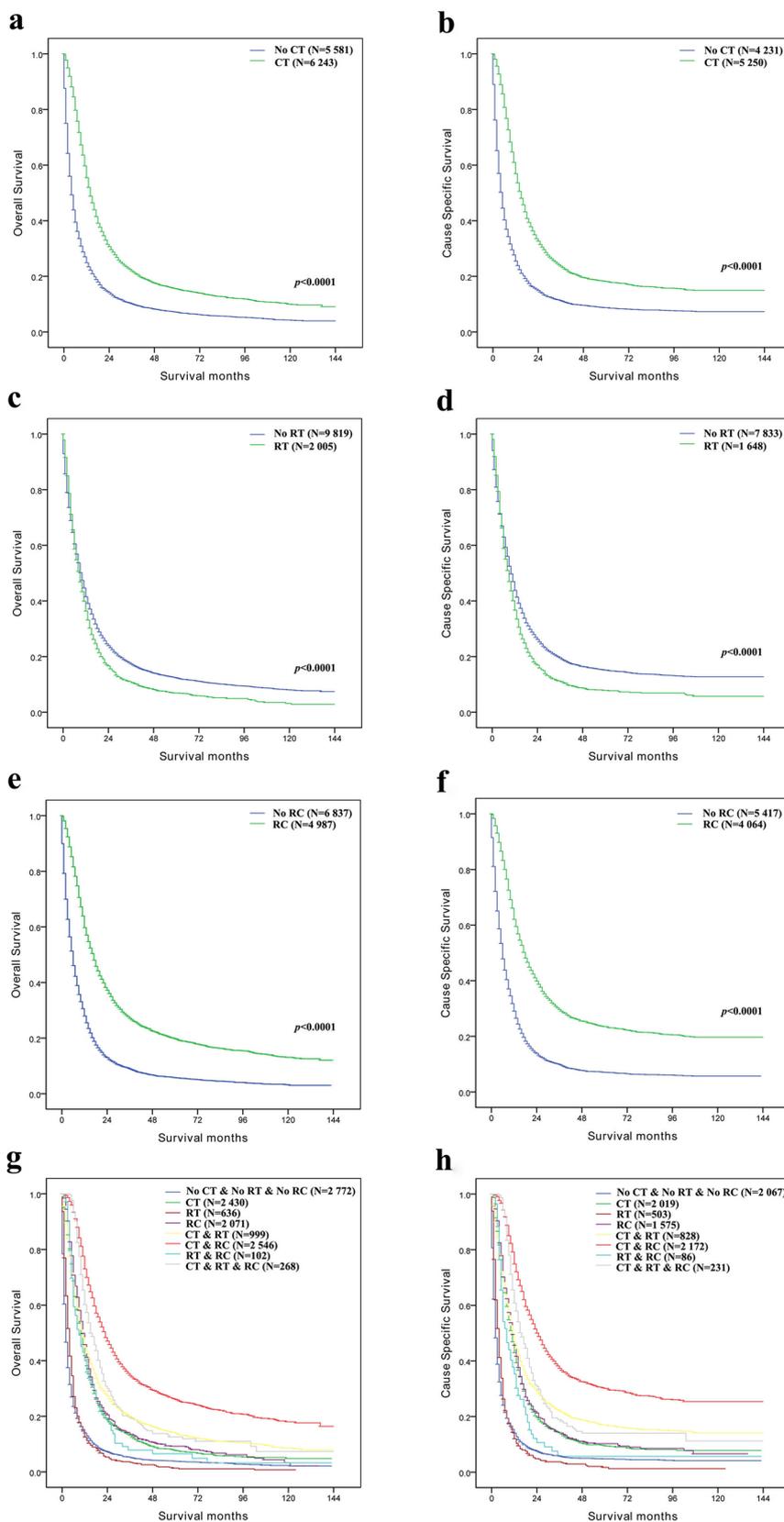


Table 3 Median survival and survival months of bladder cancer patients with AJCC stage IV

Treatment method	Patients, no	Median survival months
CT		
Yes	6243	12 (21.05 ± 24.93)
No	5581	4 (12.23 ± 21.74)
RT		
Yes	2005	8 (13.73 ± 18.49)
No	9819	9 (17.53 ± 24.79)
RC		
Yes	4987	14 (24.88 ± 28.46)
No	6837	5 (11.05 ± 17.76)
Treatment method		
No CT and no RT and no RC	2772	2 (7.25 ± 16.85)
Only CT	2430	9 (14.55 ± 18.36)
Only RT	636	3 (6.55 ± 11.14)
Only RC	2071	10 (20.54 ± 26.92)
CT and RT	999	10 (15.97 ± 19.12)
CT and RC	2546	18 (29.12 ± 29.76)
RT and RC	102	8 (14.19 ± 19.28)
CT and RT and RC	268	14 (22.23 ± 23.46)

AJCC American joint committee on cancer; CT chemotherapy; RT radiotherapy; RC radical cystectomy

MVAC has long been regarded the gold standard for first-line treatment for locally advanced and metastatic BCa [23, 24], but MVAC has serious side effects such as neutrophilia, thrombocytopenia, anaemia, nausea and others. In 2000, a large, international, multi-centre phase III randomized clinical study demonstrates that GC and MVAC have similar survival of 13.8 months (95% CI, 12.3–15.8 months) with GC and 14.8 months (95% CI, 13.2–16.8 months) with MVAC, but GC has become the main choice because of its tolerability and security [25]. Resorlu B et al. [26] proved that adjuvant CT improved the outcome of local treatment and reduced the incidence of distant metastasis. In addition, the role of neoadjuvant CT has also been reported. In a retrospective study, Dash et al. [27] demonstrated that both GC and MVAC methods of neoadjuvant CT could downstage the primary tumours and prolong disease-free survival with minimal or no residual disease.

RT is an alternative to RC in patients with MIBC [28]. There are few studies of RT alone with AJCC stage IV BCa patients. The application of RT in BCa is mainly used for preoperative or postoperative RT, and the role of preoperative RT for BCa is still controversial. Diaz et al. [29] retrospectively analysed 5562 cases of BCa and also suggested that preoperative RT could reduce cause-specific mortality (CSM) and overall mortality (OM) in cT2b/T3 patients. However, some research results do not support the use of preoperative RT for patients with MIBC. Skinner et al. [30]

performed RC after 16 Gy/4 F RT in 97 patients with high-stage MIBC compared with those who only underwent RC. There was no difference in survival rate, local control rate and distant transfer rate between the two groups. A retrospective analysis of 170 locally advanced BCa (T3–T4, N0/N1, M0) patients was carried out by Yasser et al. [31]. Among them, 92 patients received RC and postoperative RT, and 78 cases received RC alone. The local recurrence rates of the two groups were 33% and 55%, disease-free survival (DFS) was 65% and 40% and OS was 52% and 38%, respectively. Moreover, EI-Monim et al. [32] studied 100 patients with MIBC between May 2004 and June 2007, and preoperative RT and postoperative RT have similar OS, disease-free survival and complication rates.

Among the entire cohort, we demonstrated that CT combined with RT or RC is essential for long-term survival compared with RT alone. In addition, we presented that receiving RT alone reduced median survival (8 months vs 9 months) and increased ACM (HR = 0.84, 95% CI 0.77–0.92) and CSM (HR = 0.85, 95% CI 0.77–0.94). The results of this study suggest that RT alone may increase the risk of death and reduce survival time in patients with AJCC stage IV BCa, which may be inconsistent with other studies, possibly because the subjects in this study were patients with a higher level of bladder tumour and had a higher risk of recurrence and mortality than previous subjects. Furthermore, the treatment of BCa patients varies from person to person, and further research is needed.

Limitations

This study is a population-based retrospective study with limitations inherent in retrospective design. For the type of RC, we did not get detailed information on whether it was ORC, LRC or RARC, and we cannot further evaluate the effects of three RC methods on patients with AJCC stage IV. For CT and RT, we did not distinguish whether it was adjuvant or neoadjuvant therapy. Therefore, we cannot analyse in more detail the effect of adjuvant or neoadjuvant therapy, and there is no information on specific RT technique (dose, fractionation, beam energy) in the SEER database. The SEER database does not provide specific information on chemotherapies used for treatment, thus limiting our interpretation of the findings.

Conclusions

Multimodal treatment has become a standard of care for some malignancies. Patients with AJCC stage IV BCa have poor prognosis, and it is necessary to find the best treatment method for the best survival rate. Our study concluded that

Table 4 Risk factors for survival: outcome is all-cause mortality and bladder cancer specific mortality (Multivariate Cox regression analysis)

Characteristics	All-cause mortality		Cancer-specific mortality	
	Hazard ratio (95% CI)	<i>p</i>	Hazard ratio (95% CI)	<i>p</i>
Age at diagnosis				
18–40	Reference		Reference	
41–60	1.14 (0.90–1.45)	0.265	1.12 (0.86–1.46)	0.398
61–80	1.35 (1.07–1.71)	0.011	1.33 (1.02–1.73)	0.033
> 80	1.67 (1.32–2.11)	<0.001	1.68 (1.29–2.20)	<0.001
Sex				
Male	Reference		Reference	
Female	1.05 (1.00–1.10)	0.037	1.07 (1.02–1.13)	0.008
Race				
White	Reference		Reference	
Black	0.99 (0.92–1.06)	0.773	1.00 (0.92–1.08)	0.914
Other	0.88 (0.80–0.97)	0.012	0.83 (0.74–0.94)	0.002
Marital status				
Yes	Reference		Reference	
No	1.10 (1.05–1.15)	<0.001	1.11 (1.06–1.17)	<0.001
Unknown	1.09 (0.98–1.22)	0.111	1.05 (0.93–1.20)	0.44
State				
West	Reference		Reference	
Northeast	1.02 (0.96–1.08)	0.593	1.01 (0.95–1.08)	0.745
South	1.15 (1.09–1.21)	<0.001	1.11 (1.05–1.19)	0.001
Midwest	1.08 (1.01–1.16)	0.022	1.08 (0.99–1.16)	0.074
Primary site				
Trigone of bladder	Reference		Reference	
Dome of bladder	0.89 (0.78–1.01)	0.064	0.93 (0.80–1.08)	0.336
Lateral wall of bladder	1.04 (0.94–1.15)	0.458	1.09 (0.97–1.22)	0.153
Anterior wall of bladder	0.89 (0.76–1.03)	0.118	0.90 (0.76–1.07)	0.216
Posterior wall of bladder	1.05 (0.94–1.18)	0.382	1.08 (0.94–1.23)	0.283
Bladder neck	0.93 (0.81–1.06)	0.251	0.95 (0.81–1.11)	0.52
Ureteric orifice	1.04 (0.88–1.24)	0.64	1.12 (0.92–1.37)	0.271
Urachus	0.62 (0.46–0.84)	0.002	0.59 (0.41–0.85)	0.004
Overlapping lesion of bladder	1.11 (1.01–1.22)	0.029	1.16 (1.04–1.30)	0.007
Bladder, NOS	1.08 (0.99–1.18)	0.087	1.10 (1.00–1.22)	0.062
Grade				
Well differentiated	Reference		Reference	
Moderately differentiated	1.18 (0.94–1.50)	0.162	1.17 (0.89–1.54)	0.251
Poorly differentiated	1.56 (1.25–1.94)	<0.001	1.53 (1.19–1.97)	0.001
Undifferentiated	1.49 (1.19–1.85)	<0.001	1.44 (1.11–1.85)	0.005
Unknown	1.56 (1.25–1.95)	<0.001	1.48 (1.14–1.92)	0.003
Histology type				
Transitional cell carcinoma	Reference		Reference	
Squamous cell carcinoma	1.92 (1.74–2.12)	<0.001	1.98 (1.78–2.21)	<0.001
Adenocarcinoma	0.83 (0.72–0.95)	0.007	0.82 (0.70–0.97)	0.017
Others	1.20 (1.12–1.30)	<0.001	1.21 (1.11–1.32)	<0.001
T-stage				
T0	Reference		Reference	
T1	1.23 (0.90–1.67)	0.196	1.50 (0.94–2.40)	0.092
T2	1.33 (0.98–1.81)	0.065	1.68 (1.05–2.69)	0.02
T3	1.53 (1.13–2.08)	0.007	1.93 (1.20–3.09)	0.006
T4	1.95 (1.44–2.65)	<0.001	2.52 (1.58–4.03)	<0.001

Table 4 (continued)

Characteristics	All-cause mortality		Cancer-specific mortality	
	Hazard ratio (95% CI)	<i>p</i>	Hazard ratio (95% CI)	<i>p</i>
N-stage				
N0	Reference		Reference	
N1	0.96 (0.90–1.02)	0.144	0.97 (0.91–1.04)	0.344
N2	1.09 (1.03–1.16)	0.003	1.10 (1.03–1.18)	0.003
N3	1.18 (0.99–1.41)	0.059	1.28 (1.05–1.56)	0.015
M-stage				
M0	Reference		Reference	
M1	1.71 (1.63–1.80)	<0.001	1.79 (1.69–1.90)	<0.001
Treatment method				
No CT and no RT and no RC	Reference		Reference	
CT	0.43 (0.40–0.46)	<0.001	0.41 (0.38–0.44)	<0.001
RT	0.84 (0.77–0.92)	<0.001	0.85 (0.77–0.94)	0.002
RC	0.43 (0.40–0.46)	<0.001	0.41 (0.38–0.45)	<0.001
CT and RT	0.41 (0.38–0.45)	<0.001	0.40 (0.37–0.44)	<0.001
CT and RC	0.26 (0.24–0.28)	<0.001	0.24 (0.22–0.26)	<0.001
RT and RC	0.49 (0.40–0.61)	<0.001	0.56 (0.44–0.71)	<0.001
CT and RT and RC	0.32 (0.28–0.37)	<0.001	0.32 (0.27–0.38)	<0.001

CT chemotherapy; RT radiotherapy; RC radical cystectomy; NA not applicable

CT combined with RC was the best treatment method and provided the highest survival rate for patients with AJCC stage IV BCa. CT combined with RC has more benefits in improving OS and CSS than RT alone.

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Author contributions WM, JF and JG were involved in the study conception and design. WM collected and assembled data. WM, BM, XH, SG, ML and JG were involved in data analysis and interpretation WM wrote the manuscript.

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Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest.

Ethical approval No ethics approval was required as this study was an economic analysis without human subjects.

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