J Cancer Res Clin Oncol (2015) 141:169–176
DOI 10.1007/s00432-014-1793-1

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Adjuvant chemotherapy after radical cystectomy for bladder cancer: a comparative study using inverse-probability-of-treatment weighting

Taekmin Kwon · In Gab Jeong · JungBok Lee · Chunwoo Lee · Dalsan You · Bumsik Hong · Jun Hyuk Hong · Hanjong Ahn · Choung-Soo Kim

Received: 4 June 2014 / Accepted: 3 August 2014 / Published online: 14 August 2014

Abstract
Objectives The role of adjuvant chemotherapy (AC) after radical cystectomy for bladder cancer remains unclear. This study evaluated the benefits of cisplatin-based AC plus surgery versus surgery alone in patients with bladder cancer.
Materials and methods The medical records of 746 patients who underwent radical cystectomy for bladder cancer were reviewed. The association between AC and survival was analyzed using Cox regression models. To reduce the impact of treatment selection bias and potential confounding in an observational study, significant differences in patient characteristics were rigorously adjusted using inverse-probability-of-treatment weighting (IPTW).
Results The cohort consisted of 746 patients (664 men and 82 women) of mean age 62.4 years and median follow-up of 64.3 months (range, 1–231.4 months). Of these patients, 176 (23.6 %) received AC after cystectomy and 570 (76.4 %) underwent cystectomy alone. Patients who received AC were significantly younger (60 vs. 63 years, $p = 0.001$) and significantly more likely to have high pathologic T stage ($p = 0.001$), lymph node metastasis ($p = 0.001$), high grade ($p = 0.001$), and lymphovascular invasion ($p = 0.001$) than patients who underwent cystectomy alone. Multivariable analysis showed a cancer-specific survival (CSS) benefit for AC [hazard ratio (HR) 0.56, 95 % confidence interval (CI) 0.39–0.80, $p = 0.002$], as did low pathologic T stage, absence of lymph node metastasis, and absence of lymphovascular invasion. After IPTW adjustment for baseline characteristics, AC remained an independent predictor of CSS (HR 0.83, 95 % CI 0.69–0.99, $p = 0.043$).
Conclusions Cisplatin-based AC after radical cystectomy had survival benefits in patients with bladder cancer, even after IPTW adjustment for confounding variables.

Keywords Adjuvant chemotherapy · Urinary bladder neoplasm · Cystectomy · Prognosis · Cisplatin

T. Kwon · I. G. Jeong · C. Lee · D. You · B. Hong · J. H. Hong · H. Ahn · C.-S. Kim (✉)
Department of Urology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap 2 dong Songpa-gu, Seoul 138-736, Korea
e-mail: rozy308@nate.com; cskim@amc.seoul.kr

J. Lee
Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Introduction

The incidence of several types of cancers, such as bladder cancer, is increasing in the USA. Bladder cancer is the fourth most common cancer in men and accounts for 4.4 % of all primary malignancies in the USA, with approximately 54,610 men and 17,960 women newly diagnosed annually (Siegel et al. 2013). Muscle-invasive bladder cancer (MIBC) accounts for 25 % of newly diagnosed bladder cancers (Leow et al. 2014). Radical cystectomy alone can result in a 5-year survival rate in patients with organ-confined lymph node-negative MIBC of up to 80 %. This rate, however, decreases to 40–50 % in patients with extravesical disease, with a further reduction to 15–35 % if lymph node metastases are present (Stein et al. 2001).

Distant recurrences have been observed to occur more frequently than locoregional recurrences in 20–50 and 5–15 % of patients, respectively, suggesting that perioperative systemic therapy may improve outcomes (Quek et al. 2003; Shariat et al. 2006; Stein et al. 2001). The current

National Comprehensive Cancer Network (NCCN) guidelines recommend radical cystectomy as the standard of care for all patients with nonmetastatic MIBC and sufficient performance status. Cisplatin-based neoadjuvant chemotherapy (NC) is strongly recommended based on level 1 evidence showing a survival benefit (Advanced Bladder Cancer Meta-analysis 2005b; Sternberg et al. 2013). Recent studies, however, demonstrate the underutilization of this treatment strategy. For example, a retrospective multi-institutional study of 4,541 patients across 14 academic centers in the USA from 2003 to 2008 found that only 12 % of patients received NC and 22 % received AC (Feifer et al. 2011).

AC has several putative advantages compared with NC, including its administration to selected patients, based on factors predictive of relapse, and its lack of delay of definitive treatment. Since many patients are unwilling to accept NC, clinicians must decide whether to recommend AC to moderate- to high-risk patients previously unexposed to NC. Although several randomized trials have investigated the efficacy and safety of AC after radical cystectomy (Lehmann et al. 2006; Resorlu et al. 2010), almost all these studies have provided insufficient evidence to support routine AC, due to small sample sizes, early stopping of patient entry, confusing analyses and terminology, and the reporting of questionable conclusions (Boccardo and Palmeri 2006; Sylvester and Sternberg 2000). Meta-analyses that included several trials each have been performed to evaluate AC for bladder cancer (Advanced Bladder Cancer Meta-analysis 2005a; Leow et al. 2014). However, these meta-analyses have limitations, such as significant heterogeneity among trials, lack of access to individual patient data, different chemotherapy regimens, and different definitions of outcomes.

In assessing the efficacy of AC, we rigorously adjusted for significant differences in patient characteristics by using inverse-probability-of-treatment weighting (IPTW), reducing the impact of treatment selection bias and potential confounding factors in an observational study. Using IPTW, we therefore evaluated the benefits of cisplatin-based AC plus surgery versus surgery alone in patients with bladder cancer.

Materials and methods

Study participants

This study was performed with the approval and oversight of the Institutional Review Board of the Asan Medical Center, which waived the requirement for informed consent due to the retrospective design of the study. The medical records of 756 consecutive patients who underwent radical cystectomy for bladder cancer between 1990 and 2012 were retrospectively reviewed. Patients receiving NC or radiotherapy were excluded. Finally, a total of 746 patients who received radical cystectomy for bladder cancer were included in this study. Patient demographic and clinical characteristics were evaluated. All patients underwent preoperative chest X-ray, computerized tomography of the abdomen and pelvis, and bone scan for disease staging. No patient showed evidence of metastatic disease on physical examination or staging.

Surgical procedures and pathological evaluation

Radical cystectomy and pelvic lymphadenectomy were performed by two senior surgeons (C.S.K. and H.A.) as previously described in detail (Jeong et al. 2011). Urinary diversions, including ileal conduit diversion, and orthotopic bladder substitution were performed following radical cystectomy and bilateral pelvic lymphadenectomy (Jeong et al. 2012). All surgical specimens were processed according to standard pathological procedures. Tumor grade was determined according to the 2004 WHO grading system (Montironi and Lopez-Beltran 2005), and pathological stage was reassigned according to the 2010 American Joint Committee on Cancer tumor node metastasis (TNM) staging system (Edge and Compton 2010). Positive soft tissue surgical margin status was defined as the presence of tumor in inked areas of soft tissue of cystectomy specimens; urethral or ureteral margin status was not considered positive in this analysis (Novara et al. 2010). Lymphovascular invasion was defined as the unequivocal presence of tumor cells in an endothelium-lined space without underlying muscular walls.

Adjuvant chemotherapy

AC at our institute is routinely recommended with full counseling for pathologic $\geq$T3 and/or node-positive patients, except for those who are medically intolerant or who refuse this treatment. Within 3 months of surgery, all patients started AC, consisting of three to six cycles of MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin, $n = 45$) or GC (gemcitabine and cisplatin, $n = 131$). Patients treated with MVAC received methotrexate 30 mg/m^2 on days 1, 15, and 22; vinblastine 3 mg/m^2 on days 2, 15, and 22; doxorubicin 30 mg/m^2 on day 2; and cisplatin 70 mg/m^2 as a 1–8 h infusion on day 2. Patients treated with GC received gemcitabine 1,000 mg/m^2 over 30–60 min on days 1, 8, and 15, plus cisplatin 70 mg/m^2 on day 2. Cisplatin was administered with adequate pre- and post-hydration. Cycles were repeated every 28 days (von der Maase et al. 2000). From 1992 to 2000, only MVAC regimens were used. GC and MVAC regimens have similar

survival benefits, but GC has a better safety profile and is better tolerated by patients with advanced or metastatic bladder cancer; therefore, only GC regimens were administered from 2001 to 2011 (von der Maase et al. 2000).

Follow-up

After radical cystectomy, patients were generally followed up every 3 months during the first year, every 6 months during years 2–6, and annually thereafter. Follow-up consisted of a medical history and a physical examination, as well as blood laboratory assays, urine sedimentation, culture, and cytology. All patients were assessed by imaging modalities, including chest radiography, computed tomography of the abdomen and pelvis, and bone scanning, at 6 and 12 months postoperatively, and annually thereafter. Recurrence was defined as local recurrence at or below the common iliac bifurcation or distant metastasis documented by imaging and biopsy, if indicated. Detection of cancer in the ureter or urethra was recorded as a second primary tumor rather than as local or distant recurrence. The median follow-up duration was 64.3 months (range, 1–231.4 months).

Statistical analysis

Clinicopathological features in the two groups were compared using Pearson's chi-square test for categorical variables and Student's *t* test for continuous variables. Quantitative data are expressed as the mean ± standard deviation. Recurrence-free survival (RFS) was calculated as the interval from radical cystectomy to the first documented clinical recurrence. Patients who died before any clinical recurrence were censored at death. Cancer-specific survival (CSS) was measured from the date of initiation of treatment to the date of death from bladder cancer. To evaluate the effect of AC according to pathologic status and to reduce the impact of treatment selection bias and potential confounding in an observational study, significant differences in patient characteristics were rigorously adjusted using multivariable model and IPTW method of propensity scores (Robins et al. 2000). For multivariate analyses, the Cox proportional hazards model was fitted with time to recurrence and death with and without variables selection procedure. As well as multivariable model, the propensity score was calculated to account for the confounding arising from differences in clinical characteristics. Propensity scores were estimated by multiple logistic-regression analysis. Significant differences of clinical/pathological characteristics are identified in Tables 1 and 2 and were used to calculate propensity scores of likelihood of AC. To evaluate the discrimination and calibration abilities of propensity scores, C statistics and the Hosmer–Lemeshow test were used. The model was well calibrated (Hosmer–Lemeshow test; $p = 0.732$) with reasonable discrimination (C statistic = 0.763). IPTW for AC use was applied to estimate hazard ratios of treatment effect in Cox's proportional hazard model. All reported p values are two-sided, with p values <0.05 considered statistically significant. All statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

Results

The descriptive characteristics of the 746 patients are shown in Table 1. Of these patients, 176 (23.6 %) received AC after radical cystectomy and 570 (76.4 %) received radical cystectomy alone. The mean age of the entire cohort was 62.4 ± 9.7 years (range: 29–85 years), with patients receiving AC being significantly younger at the time of radical cystectomy ($p = 0.001$). Patients in the cystectomy with AC group were also significantly more likely to have higher pathologic T stage ($p = 0.001$), lymph node metastasis ($p = 0.001$), and lymphovascular invasion ($p = 0.001$) than patients undergoing cystectomy alone. However, there were no between group differences in the number of positive lymph nodes and removed lymph nodes.

Of all, 253 patients had died. Tumor was the cause of death in 166 patients in the cystectomy alone group and in 87 patients in the cystectomy with AC group. The overall 5- and 10-year survival rates were 70.7 % and 65.1 %, respectively. However, the 5-year overall survival rate was significantly lower for patients with than without node metastasis (37.8 vs. 80.6 %, $p < 0.001$). Table 2 shows a Cox regression analysis of the effects of AC on RFS and CSS according to pathologic status. AC improved RFS (HR 0.50, $p = 0.004$) and CSS (HR 0.32, $p = 0.001$) only in patients with pathologic N2 stage or greater. In these patients, the 5-year RFS (21.9 vs. 16.4 %, $p = 0.003$, Fig. 1a) and CSS (32.5 vs. 12.6 %, $p = 0.001$, Fig. 1b) rates were significantly higher in patients who received AC than in those who underwent surgery alone.

Multivariable analysis showed that factors significantly predictive of RFS and CSS included age (RFS HR 1.01, $p = 0.013$; CSS HR 1.03, $p = 0.001$), body mass index (RFS HR 0.89, $p = 0.001$; CSS HR 0.86, $p = 0.001$), pathologic T stage (RFS HR 0.53, 95 % CI 0.39–0.71, $p = 0.001$; CSS HR 0.49, $p = 0.001$), lymph node metastasis (RFS HR 0.40, $p = 0.001$; CSS HR 0.28, $p = 0.001$), and lymphovascular invasion (RFS HR 0.52, $p = 0.001$; CSS HR 0.65, $p = 0.004$) (Tables 3, 4). In multivariable analysis, AC after radical cystectomy correlated significantly with CSS (HR 0.56, 95 % CI 0.39–0.80, $p = 0.002$). AC also correlated significantly with CSS when the significance of each variable affecting CSS was assessed by IPTW using propensity score (HR 0.83, 95 % CI 0.69–0.99, $p = 0.043$).

Table 1 Clinical/pathological characteristics of the patient cohort

	Overall	Cystectomy alone	Cystectomy with adjuvant chemotherapy	*p* value
Number of patients	746	570	176	
Mean age ± SD (year)	62.4 ± 9.7	63.1 ± 9.6	60.2 ± 9.8	0.001
Gender, *n* (%)				
Male	664 (89.0)	502 (88.1)	162 (92.0)	0.168
Female	82 (11.0)	68 (11.9)	14 (8.0)	
Diabetes, *n* (%)	99 (13.3)	75 (13.3)	24 (13.6)	0.899
Hypertension, *n* (%)	203 (27.2)	166 (29.3)	37 (21.0)	0.033
ECOG performance status, *n* (%)				0.266
0	640 (85.8)	484 (84.9)	156 (88.6)	
≥1	106 (14.2)	86 (15.1)	20 (11.4)	
Serum albumin level (gm/dl), *n* (%)				0.893
<3.5	94 (12.6)	72 (12.6)	22 (12.5)	
3.5 or greater	652 (87.4)	498 (87.4)	154 (87.5)	
Mean hemoglobin ± SD (g/dl)	12.6 ± 2.1	12.5 ± 2.1	12.8 ± 2.0	0.157
Mean serum creatinine ±SD (mg/dl)	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.2	0.932
Mean body mass index ±SD (kg/m^2)	23.4 ± 3.3	23.6 ± 3.4	22.9 ± 2.8	0.064
Pathologic T stage, *n* (%)				0.001
≤T2	386 (51.7)	385 (67.5)	23 (13.1)	
≥T3	338 (45.3)	185 (32.5)	153 (86.9)	
Lymph node metastases, *n* (%)				0.001
N0	556 (74.5)	508 (89.1)	48 (27.3)	
N1	64 (8.6)	24 (4.2)	40 (22.7)	
N2 or greater	126 (16.9)	38 (6.7)	88 (50.0)	
Mean positive lymph nodes ±SD (median, range)	5.2 ± 7.5 (3, 1–58)	3.7 ± 3.7 (2, 1–22)	5.9 ± 8.8 (3, 1–58)	0.065
Mean lymph node removed ±SD (median, range)	20.7 ± 15.1 (17, 1–118)	18.2 ± 10.2 (22, 1–45)	21.9 ± 16.8 (25, 1–118)	0.113
Grade, *n* (%)				0.001
Low	108 (14.5)	103 (18.16)	5 (2.8)	
High	636 (85.5)	467 (81.9)	171 (97.2)	
Lymphovascular invasion, *n* (%)				0.001
Yes	310 (41.6)	182 (31.9)	128 (72.7)	
No	436 (58.4)	388 (68.1)	48 (27.3)	
Carcinoma in situ, *n* (%)				0.490
Yes	189 (25.3)	141 (24.7)	48 (27.3)	
No	557 (74.7)	429 (75.3)	128 (72.7)	
Soft tissue surgical margin status, *n* (%)				0.621
Positive	23 (3.1)	19 (3.3)	4 (2.3)	
Negative	723 (96.9)	551 (96.7)	172 (97.7)	

Discussion

Bladder cancer is a potentially lethal disease, with as many as one-quarter of patients who undergo cystectomy having micrometastatic disease at the time of surgery (International Bladder Cancer Nomogram et al. 2006). Bladder cancer can progress quickly and may justify some form of systemic treatment for tumor eradication and improved survival. This study evaluated the survival benefits of cisplatin-based AC in a large cohort of patients treated at a single institution with radical cystectomy and lymphadenectomy, with some also receiving AC. In addition, patients were compared after IPTW, thus controlling for potentially confounding covariables affecting survival, including age, sex, comorbidities, and pathologic status. Propensity scores were used to reduce any biases due to differences in the

Table 2 Effect of adjuvant chemotherapy on survival according to pathologic status

Subgroup	Recurrence-free survival		Cancer-specific survival	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Pathologic T stage				
≤T2	4.28 (2.36–7.76)	0.001	4.03 (2.18–7.48)	0.001
≥T3	1.24 (0.92–1.67)	0.160	0.85 (0.63–1.17)	0.329
Lymph node metastases				
N0	2.23 (1.40–3.56)	0.001	1.81 (1.10–2.97)	0.018
N1	0.83 (0.40–1.69)	0.601	0.56 (0.26–1.19)	0.136
N2 or greater	0.50 (0.31–0.81)	0.004	0.32 (0.20–0.51)	0.001
Grade				
Low	4.87 (1.67–14.19)	0.003	5.20 (1.80–15.01)	0.002
High	2.61 (1.94–3.42)	0.001	1.94 (1.48–2.55)	0.001
Lymphovascular invasion				
Yes	1.79 (1.62–2.43)	0.001	1.37 (0.99–1.90)	0.054
No	2.26 (1.37–3.75)	0.001	1.72 (1.02–2.91)	0.040
Carcinoma in situ				
Yes	3.22 (1.91–5.44)	0.001	2.29 (1.24–4.24)	0.008
No	2.77 (2.08–3.69)	0.001	2.08 (1.56–2.78)	0.001
Soft tissue surgical margin				
Yes	4.59 (1.19–17.60)	0.026	2.81 (0.50–15.82)	0.239
No	2.80 (2.17–3.61)	0.001	2.08 (1.56–2.78)	0.001

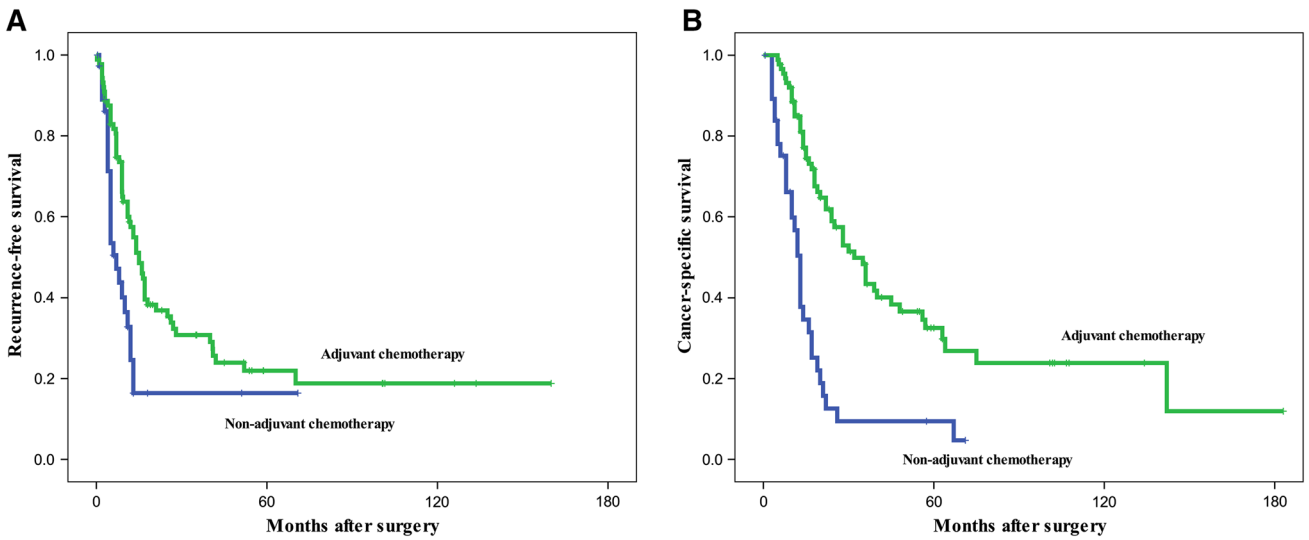

Fig. 1 **a** Recurrence-free survival and **b** cancer-specific survival in 126 patients with bladder cancer of pathologic stage N2 or greater

baseline characteristics of the two patient groups (Joffe and Rosenbaum 1999). Although matching was an option, weights based on propensity scores reduce the possibility that matching might exclude a substantial sample size of patients whose disease experience could make a valid contribution. Considering weights based on both the standardized morbidity ratio and the inverse probability of treatment (Robins et al. 2000; Sato and Matsuyama 2003), we chose the latter. These weights yield cohorts that are effectively from a common population, except for the difference in the propensity score response variable. Following IPTW, AC significantly improved CSS (HR 0.83, 95 % CI 0.69–0.99, $p = 0.043$).

Cisplatin-based combination NC has been shown to result in a 5 to 7 % absolute survival benefit in patients undergoing radical cystectomy for bladder cancer (Advanced Bladder Cancer Meta-analysis 2005b; Sternberg et al. 2013). Cisplatin-based NC is therefore an

Table 3 Multivariable analysis of factors influencing recurrence-free survival

	Without variable selection		With variable selection[a]		IPTW using propensity score	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Adjuvant chemotherapy (yes)	0.82 (0.57–1.17)	0.285			1.107 (0.925–1.324)	0.266
Age (continuous)	1.01 (1.00–1.03)	0.031	1.01 (1.00–1.03)	0.013		
Sex (male)	0.72 (0.48–1.06)	0.097				
Diabetes (yes)	1.19 (0.82–1.75)	0.349				
Hypertension (no)	0.88 (0.66–1.78)	0.394				
ECOG performance status (≥1)	1.11 (0.78–1.57)	0.558				
Body mass index (continuous)	0.88 (0.85–0.92)	0.001	0.89 (0.85–0.92)	0.001		
Pathologic T stage (≤T2)	0.51 (0.37–0.71)	0.001	0.53 (0.39–0.71)	0.001		
Lymph node metastases (no)	0.34 (0.24–0.49)	0.001	0.40 (0.30–0.54)	0.001		
Grade (low)	1.08 (0.71–1.64)	0.705				
Lymphovascular invasion (no)	0.54 (0.39–0.72)	0.001	0.52 (0.39–0.70)	0.001		
Carcinoma in situ (no)	1.17 (0.86–1.58)	0.309				
Soft tissue surgical margin (no)	1.02 (0.51–2.03)	0.955				

IPTW Inverse-probability-of-treatment weighting, *HR* Hazard ratio, *CI* Confidence interval, *ECOG* Eastern Cooperative Oncology Group

[a] Backward elimination

Table 4 Multivariable analysis of factors influencing cancer-specific survival

	Without variable selection		With variable selection[a]		IPTW using propensity score	
	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value	HR (95 % CI)	*p* value
Adjuvant chemotherapy (yes)	0.57 (0.39–0.83)	0.003	0.56 (0.39–0.80)	0.002	0.83 (0.69–0.99)	0.043
Age (continuous)	1.03 (1.01–1.04)	0.001	1.03 (1.01–1.04)	0.001		
Sex (male)	0.71 (0.46–1.11)	0.239				
Diabetes (yes)	1.33 (0.85–2.09)	0.497				
Hypertension (no)	0.96 (0.68–1.34)	0.611				
ECOG performance status (≥1)	1.05 (0.71–1.57)	0.365				
Body mass index (continuous)	0.86 (0.82–0.89)	0.001	0.86 (0.82–0.89)	0.001		
Pathologic T stage (≤T2)	0.52 (0.38–0.72)	0.001	0.49 (0.34–0.70)	0.001		
Lymph node metastases (no)	0.27 (0.18–0.39)	0.001	0.28 (0.19–0.39)	0.001		
Grade (low)	1.02 (0.68–1.51)	0.937				
Lymphovascular invasion (no)	0.65 (0.48–0.87)	0.004	0.65 (0.48–0.87)	0.004		
Carcinoma in situ (no)	1.47 (1.05–2.05)	0.024	1.03 (1.06–2.21)	0.022		
Soft tissue surgical margin (no)	1.32 (0.57–2.99)	0.515				

IPTW Inverse-probability-of-treatment weighting, *HR* Hazard ratio, *CI* Confidence interval, *ECOG* Eastern Cooperative Oncology Group

[a] Backward elimination

option for patients with localized cT2–4 urothelial carcinoma of the bladder (Sternberg et al. 2007); it should be 'considered' for patients with cT2N0M0 and 'strongly considered' for patients with cT3N0M0 disease (Montie et al. 2009). However, NC for all patients undergoing radical cystectomy has not been widely adopted, due to concerns about unnecessary treatment of patients who may not benefit from NC and disease progression that may result from delays in surgery caused by chemotherapy, especially if NC is ineffective. Furthermore, AC may be as effective as NC if the former is administered selectively based on adverse pathologic characteristics (Ruggeri et al. 2006). Nevertheless, the role of AC in patients with high-risk urothelial carcinoma of the bladder has not been well defined. Although a recent meta-analysis of individual patient data from available trials reported a 23 % relative reduction in the risk of death in patients receiving AC compared with those undergoing surgery

alone (Leow et al. 2014), this analysis was limited by the methodological flaws of individual trials and their inclusion of insufficient numbers of patients and events. Thus, the routine use of AC for patients undergoing radical cystectomy has not gained widespread acceptance. Moreover, these trials were performed in highly selected patients and under favorable conditions. The results of these trials are therefore difficult to apply to patients in everyday practice, who may be older, have increased comorbidities, and may receive suboptimal chemotherapy regimens or doses (Markman 2007). This has increased the importance of rigorous adjustment for differences in patient characteristic by IPTW. In our study, using IPTW, AC after radical cystectomy improved survival in the entire cohort, with subgroup analysis showing that AC improved RFS and CSS in patients with a pathologic N2 or greater. Thus, the benefit of AC depended primarily on disease progression. Selective administration of AC to patients at higher risk of disease progression, such as those with pathologic N2 or greater, may optimize the therapeutic benefits of AC.

Patients with $N \geq 2$ disease had poorer survival. In our study, all single positive lymph nodes were found below the aortic bifurcation, consistent with previous studies (Abol-Enein et al. 2004; Leissner et al. 2004). For example, one study reported that none of 290 patients who underwent extended lymphadenectomy had a single nodal metastasis located above the aortic bifurcation or in the presacral triangle (Leissner et al. 2004). A second study reported a single nodal metastasis in the endopelvic region, except for one in the common iliac chain (Abol-Enein et al. 2004). Therefore, patients with a single positive lymph node had less advanced disease than patients with N2 patients, and N2 disease is more likely to lead to systemic metastasis. In addition, the 5-year RFS and CSS rates in patients with $N \geq 2$ disease were 18 and 26 %, respectively. The CSS rate was likely higher than the RFS rate because tumors were likely the cause of death in most of these patients.

This study had several limitations, including its retrospective nature, the relatively small patient cohort, and the significant differences in certain variables between patient groups. Residual confounding is anticipated as many patients undergoing radical cystectomy have significant age-related comorbidities that influence their ability to be selected for and/or tolerate AC and are casually related to outcomes (Koppie et al. 2008). Unfortunately, the comorbidity status of patients was not collected during data acquisition. The absence of this information would likely systematically bias the results in favor of AC because it is more likely administered to healthier patients. In addition, our estimates for the effect of AC in the low-risk subgroup were underpowered because of the lack of events in this population, enabling no conclusions to be drawn with respect to the advantages or disadvantages of AC in this population. Nevertheless, the clinical results obtained from this single group of patients over an extended period of time demonstrate that AC after radical cystectomy provides good survival results after controlling for potentially confounding covariables affecting survival, including age, sex, comorbidities, and pathologic status by IPTW.

Conclusions

Our results showed that, after adjusting for confounding variables using IPTW analysis, cisplatin-based AC showed survival benefit in patients with bladder cancer after radical cystectomy. Although AC was associated with a significant improvement in survival in the entire patient cohort, its benefits depended primary on disease progression. Selective administration of AC to patients at highest risk of disease progression, such as those with pathologic N2 or greater, may reinforce the therapeutic benefit of AC.

Conflict of interest The authors have no conflict of interest or financial disclosures.

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