Gang Li, M.Sc.^{1, #}
Hui-min Niu, M.Sc.^{2, #}
Hong-tao Wu, MD, Ph.D.³
Bao-yu Lei, M.Sc.¹
Xiao-hua Wang, M.S.¹
Xiao-bo Guo, M.S.¹,
Shu-lin Feng, M.D.¹

#These authors contributed equally to this work

¹Department of Urology, Heji Hospital Affiliated with Changzhi Medical College, Changzhi, Shanxi 046011, P.R. China.

²Department of Nephrology, Peace Hospital Affiliated with Changzhi Medical College, Changzhi, Shanxi, 046000, P.R.China.

³Department of Urology, Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, P.R. China.

Effect of cisplatin-based neoadjuvant chemotherapy on survival in patients with bladder cancer: a meta-analysis

Abstract

Purpose: Cisplatin-based neoadjuvant chemotherapy (NAC) has been shown to improve survival in patients with muscle-invasive bladder cancer (MIBC) who underwent radical cystectomy as compared with patients who underwent surgery alone. It has also been suggested as current standard of care in surgically-fit patients with MIBC. This meta-analysis assessed the effect of cisplatin-based NAC on survival in patients with bladder cancer.

Source: PubMed, CENTRAL, and Embase were searched until November 22, 2016. Two-arm randomized controlled trials that compared cisplatin-based neoadjuvant chemotherapy plus local treatment *versus* the same local treatment without neoadjuvant chemotherapy were selected. Patients with histologically-confirmed bladder cancer (adenocarcinoma, transitional, or squamous-cell carcinoma) were included. The primary outcome was overall survival (OS).

Principal findings: Of the 292 articles initially identified, 14 were included in the final analysis. Patients in the NAC group had similar OS as the local treatment (i.e., radiation therapy or cystectomy) group (pooled hazard ratio [HR] = 0.92, 95% confidence interval [CI]: 0.84 to 1.00, $P=0.056$). No difference in progress-free survival between two groups was observed ($P=0.725$). Subgroup analysis showed that OS was similar in patients treated with NAC plus radiotherapy or cystectomy compared with patients who received local treatment alone.

Conclusions: Platinum-based NAC was associated with similar survival benefit as patients undergoing cystectomy and/or radiotherapy. No conclusion can be drawn about the optimal platinum-based combination to be used in the neoadjuvant setting.

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Correspondence to:

Gang Li
Department of Urology, Heji Hospital Affiliated with Changzhi Medical College, Changzhi, Shanxi 046011, P.R. China.
E-mail: woshilg@163.com

Bladder cancer is the ninth most common cancer, with a peak incidence in the seventh to eighth decade of life, and is three to four times more common in males than in females [1]. Urothelial cell carcinoma is the most common type of bladder cancer in Western countries, and accounts for approximately 95% of cases [1]. Urothelial cell carcinoma is clinically classified as non-muscle-invasive and muscle-invasive because muscle layer invasion is the primary factor for performing a cystectomy [1]. The 5-year relative survival rates range from 97% for stage I disease to 22% for stage IV disease [1].

Radical cystectomy with regional lymphadenectomy is the gold standard for the management of muscle-invasive bladder cancer (MIBC), although the procedure is one of the most complex urological procedures and is associated with significant complications and morbidity [2,3]. Survival after radical cystectomy has been shown to be associated with the pathological stage of the cystectomy specimen, with 5-year overall survival (OS) ranging from 81- 93% for patients with pT0 disease and 46- 48% for patients with pT3 disease [4-7]. Risk of recurrence, however, is >50% [7] and is not improved with the use of preoperative radiation therapy [8]. It is believed that the high recurrence rate is the result of micro-metastasis at the time of local treatment (cystectomy and/or radiotherapy), and this has been addressed with adjuvant or neoadjuvant chemotherapy (NAC) [9].

Although the definitive data to support cisplatin-based adjuvant chemotherapy are not available, cisplatin-based NAC has been shown to improve survival in patients with MIBC who underwent radical cystectomy as compared with patients who underwent surgery alone [10-13]. The currently accepted standard of care in surgically-fit patients with MIBC is the use of cisplatin-based NAC prior to radical cystectomy [14]. In addition to potentially eliminating micro-metastasis, NAC can result in down-staging of the cancer [1].

Interestingly, a meta-analysis reported by Advanced Bladder Cancer Meta-analysis Collaboration in 2011 suggested that there is currently insufficient information to obtain a definitive answer to the question of whether cisplatin-based NAC improves the survival of patients with locally-advanced bladder cancer [10]. Though available evidence supports the use of NAC, the benefits of different cisplatin-based NAC regimes, preoperative timing for NAC and dose schedule remain unclear [15].

The objective of the present study was to perform an updated meta-analysis to assess the effect of cisplatin-based NAC followed by local treatment on survival in patients with bladder cancer with an emphasis on different cisplatin-based combinations and different local treatments.

Materials and Methods

Literature search strategy and data extraction

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines [16]. PubMed, CENTRAL and Embase were searched using the following search terms: (neoadjuvant chemotherapy) AND (bladder cancer) AND (randomized OR prospective); (bladder cancer AND neoadjuvant) AND (chemotherapy OR radiotherapy OR surgery) from inception until November 22, 2016. Inclusion criteria were as follows: (1) two-arm randomized controlled trials that compared cisplatin-based neoadjuvant chemotherapy plus local treatment *versus* the same local treatment without neoadjuvant chemotherapy; (2) patients had histologically-confirmed bladder cancer (adenocarcinoma, transitional or squamous-cell carcinoma); and, (3) survival data (overall survival [OS] and/or progress-free survival [PFS]) were reported. Local treatment included radical cystectomy or radiotherapy. Studies that compared cisplatin-based neoadjuvant chemotherapy with other types of chemotherapy were excluded. Single-arm studies, letters, comments, editorials, case reports, proceedings and personal communications were excluded, as were studies that did not report outcomes quantitatively. Searches were conducted by two independent reviewers, and a third was consulted to resolve any disagreements.

Data extracted from eligible studies included the first authors and year of publication, number of patients and demographic information, tumor stage and detail protocol of NAC and local treatments. Data of OS (primary outcome) and PFS (secondary outcome) were extracted and summarized. Two independent reviewers extracted the data, and a third reviewer was consulted to resolve any uncertainties.

Data analysis

The primary outcome for this meta-analysis was the hazard ratio (HR) for OS and secondary outcome was the HR for PFS. Hazard ratios with 95% confidence intervals (CIs) for survival outcomes were extracted for each individual study. If the HR and 95% CI were not available, the HR and its variance were estimated as described in Parmar *et al.* and Williamson *et al.* [16,17]. Subgroup analyses were performed based on both NAC therapies and local treatments. A χ^2 -based test of homogeneity was performed, and the inconsistency index (I^2) and Q statistics were determined. If the I^2 statistic indicated significant heterogeneity ($I^2 > 50\%$), a random-effects model of analysis was used. Otherwise, a fixed-effect model was employed. Pooled effects were

calculated, and a two-sided P value < 0.05 was considered to indicate statistical significance. Sensitivity analysis was carried out using the leave-one-out approach. Publication bias was assessed by constructing funnel plots and Egger's test. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution, and a one-tailed significance level $P > 0.05$ (Egger's test). All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ, USA).

Quality assessment

The methodological quality of the included studies was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) by two reviewers [19]. Six domains are examined: random sequence generation; allocation concealment; blinding of patients and personnel; blinding of outcome assessment; incomplete outcome data; and, selective reporting risk.

Results

Literature search and study characteristics

A flow diagram of study selection is shown in Figure 1. After identifying 292 articles in the database searches, 239 non-relevant studies were excluded and 53 full text articles were assessed. Subsequently, 39 studies were excluded, including 16 single-arm studies, eight studies with irrelevant study design, five articles with irrelevant outcome, four articles with duplicated study population and six articles without full-text. Fourteen studies were included in the meta-analysis [20-33].

The 14 studies included a total of 3,302 patients with bladder cancer, and the number of participant ranged from 33 to 949 (Table 1). The mean age of patients ranged from 49 to 68 years. A total of 1,662 patients received NAC followed by local treatment and 1,640 received local treatment only. For local treatment, 865 patients underwent cystectomy, 317 received radiotherapy and 458 patients received both cystectomy and radiotherapy. The regimens and treatment dosage are summarized in Table 2. For patients treated with cystectomy, three studies used methotrexate plus vinblastine,

Figure 1

FIGURE 1. . PRISMA flow diagram of study selection

TABLE 1. Characteristics of included studies

First author (publication year)	Treatment		Number of patients		Mean Age (y)		Male (%)		Tumor stage (T1/T2/T3/T4)	
	neoadjuvant chemotherapy	Local treatment	NAC	Control	NAC	Control	NAC	Control	NAC	Control
Kitamura (2014) [20]	M-VAC	Cystectomy	64	66	63	63	89%	90%	0/35/27/2	0/35/28/3
Khaled (2014) [32]	GC	Radical cystectomy	59	55	54	57	76%	82%	0/1/45/13	0/1/37/17
Osman (2014) [33]	GC	Radical cystectomy	30	30	49	53	93%	97	0/6/18/6	0/8/18/4
International Collaboration of trialists (2011) [21]	MVC-folinic acid	Radiotherapy + cystectomy	491	485	64*		88%		0/334/567/75	
Grossman (2003) [20]	M-VAC	Cystectomy	153	154	63	63	83%	81%	0/61/92 _(T3+T4a) /0	0/61/93 _(T3+T4a) /0
Sherif (2002) [23]	MC-leucovorin (folinic acid)	Cystectomy	155	154	65	65	75%	86%	0/64/80/10	0/65/76/13
Sengelov (2002)-Cystectomy* [24]	MC-leucovorin (folinic acid)	Cystectomy	17	16	66*		79%		2/7/19/4	
Sengelov (2002)-Radiotherapy* [24]	MC leucovorin (folinic acid)	Radiotherapy	61	59	63*		82%		0/16/66/37	
Millikan (2001) [25]	M-VAC	Cystectomy	70	70	66*	67*	79%	64%	0/0/63/7	0/0/62/8
Shipley (1998) [26]	CMV	Radiotherapy	61	62	NA	NA	77%	85%	0/23/38 _(T3+T4a) /0	0/24/38 _(T3+T4a) /0
Coppin (1996) [27]	C	Radiotherapy	51	48	65*	65*	67%	81%	0/19 _(T2+T3A) /25 _{(T3B+T4A)/7} _(T4B)	0/17 _(T2+T3A) /27 _{(T3B+T4A)/4} _(T4B)
Malmstrom (1996) [28]	CA	Cystectomy	151	160	64		82%	76%	27/52/72 _(T3+T4A) /0	31/64/65 _(T3+T4A) /0
Martinez-Piñero (1995) [29]	C	Cystectomy	62	60	60	63	90%	83%	0/17/39/6	0/17/33/4
Ozono (1991) [30]	CA--CPM	Radiation	18	18	63	60	100%	94%	1/5/8/1	3/2/10/1
Wallace (1991)-West* [30] Midlands	C	Radiotherapy	83	76	65	65	77%	80%	0/26/44/13	0/24/41/11
Wallace (1991)-Australia* [31]	C	Radiotherapy	42	54	68	65	76%	83%	0/3/34/5	0/14/27/13

NAC, Neoadjuvant chemotherapy; RCT, randomized controlled trial; M, methotrexate; V, vinblastine; A, doxorubicin; C, cisplatin; CPM, cyclophosphamide.

* The studies by Sengel and Wallace each reported on two groups of patients; and the groups are presented separately in this table.

TABLE 2. Summary of regimens stratified by the type of local treatment and neoadjuvant chemotherapy

	Neoadjuvant chemotherapy	Regimen	Median follow-up
<i>Cystectomy</i>			
Kitamura (2014) [20]	M-VAC	Methotrexate 30 mg/m ² i.v. on days 1, 15, and 22; vinblastine 3 mg/m ² i.v. on days 2, 15, and 22; doxorubicin 30 mg/m ² i.v. on day 2, and cisplatin 70 mg/m ² i.v. on day 2. Repeat every 28 days.	55 months
Khaled (2014) [32]	GC	Gemcitabine 1250 mg/m ² on days 1 and 8 and Cisplatin 70 mg/m ² on day 2 every 21 days (3 cycles)	3 years
Osman (2014) [33]	GC	Cisplatin (70 mg/m ² Day 1), Gemcitabine (1250 mg/m ² Day 1,8) Q 3 weeks for 3 Cycles	5 years
Grossman (2003) [22]	M-VAC	Methotrexate (30 mg/m ²) on days 1, 15, and 22; vinblastine (3 mg/m ²) on days 2, 15, and 22 for three 28-day cycles; and doxorubicin (30 mg/m ²) and cisplatin (70 mg/m ²) on day 2. Doses adjusted if toxic effects occurred.	8.4 years / 8.7 years
Millikan (2001) [25]	M-VAC	Each 28-day cycle patients received methotrexate (30 mg/m ²) on day 1 and vinblastine (3 mg/m ²), doxorubicin (30 mg/m ²), and cisplatin (70 mg/m ²) on day 2. On day 15 and day 22, patients were treated with methotrexate (30 mg/m ²) and vinblastine (3 mg/m ²) as a brief outpatient infusion.	6.8 years
Sherif (2002) [23]	MC-leucovorin (folinic acid)	Cisplatin 100 mg/m ² i.v. and methotrexate 250 mg/m ² i.v. Leucovorin 15 mg administered orally 24 hours after initiation of methotrexate infusion, and then 15 mg every 6 hours for a total of 8 doses.	5.3 years
Sengelov (2002)-Cystectomy* [24]	MC-leucovorin (folinic acid)	Three cycles of cisplatin 100 mg/m ² and methotrexate 250 mg/m ² with leucovorin rescue at 3-week intervals. Leucovorin was started 24 hours after methotrexate at a dose of 15 mg orally every 6 hours for a total of 8 doses.	42 months
Malmstrom (1996) [28]	CA	Two cycles of 70 mg/m ² cisplatin and 30 mg/m ² doxorubicin with a 3-week interval between the cycles.	5 years
Martinez-Piñero (1995) [29]	C	100 mg/m ² cisplatin in 1 day by i.v. infusion. Cycle repeated at 3 weekly intervals for 3 times. Dosage adjusted if signs of renal or hematological toxicity.	78 months
<i>Radiotherapy</i>			
Coppin (1996) [27]	C	Cisplatin 100 mg/m ² within 3 days of beginning radiotherapy and repeated every 2 weeks for a total of 3 cycles.	6.5 years
Wallace (1991)-West* [31] Midlands	C	Cisplatin 100 mg/m ² repeated at 3 weekly intervals for 3 courses.	16 months
Wallace (1991)-Australia* [31]	C	Cisplatin 100 mg/m ² repeated at 3 weekly intervals for 2 courses.	16 months
Sengelov (2002)-Radiotherapy* [24]	MC-leucovorin (folinic acid)	Three cycles of cisplatin 100 mg/m ² and methotrexate 250 mg/m ² with leucovorin rescue at 3-week intervals. Leucovorin was started 24 hours after methotrexate at a dose of 15 mg orally every 6 hours for a total of 8 doses.	42 months
Shipley (1998) [26]	CMV	Methotrexate 30 mg/m ² administered i.v. on days 0,14, and 21 of each 28-day cycle; cisplatin 70 mg/m ² day 1; and vinblastine 3 mg/m ² days 1, 14, and 21. Cisplatin 100 mg/m ² days 1 and 22 of induction chemoradiotherapy.	60 months
Ozono (1991) [30]	CA--CPM	500 mg/m ² cyclophosphamide on day 1, 50 mg/m ² of doxorubicin and 30-70 mg/m ² cisplatin on day 2 (CAP therapy) + 14-20 Gy of radiation over 7-10 days preoperative days.	
<i>Radiotherapy and/or Cystectomy</i>			
International Collaboration of trialists (2011) [21]	MVC-folinic acid	Day 1: methotrexate 30 mg/m ² i.v. and vinblastine 4 mg/m ² i.v. bolus; day 2 before hydration: cisplatin 100 mg/m ² IV infusion; day 2 after hydration: folinic acid 15 mg (oral or i.v.) every 6 hours for 4 doses commencing 24 hours after methotrexate on day 1; day 8: methotrexate 30 mg/m ² i.v. bolus and vinblastine 4 mg/m ² i.v. bolus; day 9: folinic acid 15 mg(oral) every 6 hours for 4 doses after methotrexate on day 8. Repeat every 21 days for a total of 3 cycles.	13.9 years

M, methotrexate; V, vinblastine; A, doxorubicin; C, cisplatin; CPM, cyclophosphamide.

* The studies by Sengel and Wallace each reported on two groups of patients, and the groups are presented and analyzed separately in this study.

doxorubicin and cisplatin (M-VAC), two studies used gemcitabine plus cisplatin (GC), two studies used methotrexate, cisplatin plus leucovorin (folinic acid) (MC-leucovorin), one study used cisplatin plus doxorubicin (CA) and one study used cisplatin only as NAC. For patients treated with radiotherapy, three studies used cisplatin only, one study used methotrexate, MC-leucovorin, one study used cisplatin plus methotrexate, vinblastine (CMV), and one study used cisplatin, doxorubicin plus cyclophosphamide (CA-CPM) as NAC. The study reported by International Collaboration of Trialists (2011) included patients treated with methotrexate, vinblastine and MVC-leucovorin followed by either cystectomy and/or radiotherapy [21].

Overall survival

All 14 studies were included in the meta-analysis OS (Figure 2). No evidence of significant heterogeneity was observed across the data (Q statistic=15.786, $I^2 = 4.98\%$); therefore, a fixed-effects model was used. Pooled analysis found that patients who received cisplatin-based NAC had similar OS than those who received local treatment alone (pooled HR = 0.92, 95% CI: 0.84 to 1.00, $P = 0.056$) (Figure 2).

Sensitivity analysis and publication bias for OS

According to sensitivity analyses for OS, the removal of the studies by Grossman (2003), Millikan (2001) and Wallace (1991) resulted in the pooled HR becoming significant (Supplemental Table 1), indicating OS findings may have been overly influenced by each of these studies. No evidence of publication bias was noted (Egger's $t = 0.421$, 1-tailed $P = 0.340$, Supplemental Figure 1).

Progression-free survival

PFS data were available in six articles. Forest plot for meta-analysis of PFS is shown in Figure 3. There was evidence of significant heterogeneity (Q statistic=21.632, $I^2 = 76.89\%$); therefore, a random-effects model of analysis was used. The pooled analysis revealed no significant difference in PFS between patients who received cisplatin-based NAC or local treatment alone (pooled HR = 0.95, 95% CI: 0.69 to 1.29, $P = 0.725$).

Subgroup analyses

Due to the limited number of suitable articles available, only four subgroups of cisplatin-based NAC were analyzed (Figure 4). No difference in OS in patients treated with cisplatin alone

before radiotherapy (pooled HR = 0.95, 95% CI: 0.76 to 1.19, $P = 0.686$) [25,29], GC before cystectomy (pooled HR=0.75, 95%CI: 0.50 to 1.12), MC-folinic acid before cystectomy (pooled HR = 0.84, 95% CI: 0.64 to 1.10, $P = 0.210$) [21,22], and MVAC before cystectomy (pooled HR = 1.22, 95% CI: 0.98 to 1.52, $P = 0.076$) [18,20,23].

Subgroup analysis of cystectomy or radiotherapy after NAC showed no significant difference in OS between patients who received NAC followed by cystectomy and those who received cystectomy alone (pooled HR = 0.96, 95% CI: 0.84 to 1.09, $P = 0.527$; Figure 5). Similarly, no significant difference in OS was observed between patients who received NAC followed by radiotherapy and those treated with radiotherapy alone (pooled HR = 0.95, 95% CI: 0.80 to 1.12, $P = 0.539$; Figure 5).

Quality assessment

Results of the quality assessment are summarized in Supplemental Table 2. Only five studies reported allocation concealment (selection bias), and no study provided blinding information (performance bias and detection bias). Attrition bias was low in every included study, and all of the pre-specified outcomes were reported in all studies (reporting bias).

Discussion

The overall pooled results of the 14 included studies indicated that cisplatin-based NAC and local treatment improved survival in patients with advanced/invasive bladder cancer similarly, regardless the combination of regimens. Subgroups analysis of the three different cisplatin-based NAC regimens did not find a difference in efficacy among the NAC regimens and also failed to show that NAC followed by local treatment (cystectomy or radiotherapy) improved survival compared with local treatment alone suggesting the benefit of adding cisplatin-based NAC to local treatment is still undefined.

Various large-scale trials have provided varying results with respect to the survival benefit of NAC in patients with bladder cancer. The Southwest Oncology Group 8710 phase III trial randomized 317 men with cT2-T4aN0M0 operative MIBC to receive methotrexate/vinblastine, doxorubicin/cisplatin NAC followed by surgery or surgery alone. [22] This randomized controlled trial reported that 38% of surgical specimens were pathologically free of cancer in the NAC group as compared with only 15% in the group that did not receive NAC and a survival benefit in the NAC group was seen. [22] The International Collaboration of Trialists

FIGURE 2. Forest plot for meta-analysis of overall survival for all articles relating to neoadjuvant therapy.

FIGURE 3. Forest plot for meta-analysis of progress-free survival for articles relating to neoadjuvant therapy.

randomized 976 patients with MIBC to receive three cycles of cisplatin/methotrexate/vinblastine NAC followed by local treatment or local treatment alone (cystectomy and/or radiotherapy). [21] While the initial results of the trial did not demonstrate a survival benefit with NAC, an update of long-term results indicated a 5-year OS in the NAC group of 36% vs. 30% in the local treatment alone group (hazard ratio [HR] = 0.84, $P=0.037$) [21]. Both large scale trials demonstrate a survival benefit with NAC; however, in the Nordic I trial, 311 patients were randomized to receive two

cycles of cisplatin/doxorubicin or no NAC followed by radical cystectomy [28]. The results showed no OS or cancer-specific survival benefit of NAC at 5 years (59% vs. 51%) [28]. The Nordic II trial, which randomized 309 patients to three cycles of cisplatin/methotrexate NAC followed by radical cystectomy or radical cystectomy alone, also found no difference in 5-year survival (53% vs. 46%) [23]. Interestingly however, a combined analysis of the data from both Nordic trials showed that NAC was associated with improved 5-year OS (56% vs. 48%, $P=0.049$) with a 20% reduction in the relative hazard in

FIGURE 4. Forest plot for meta-analysis of overall survival for the subgroups (cisplatin followed by radiotherapy, gemcitabine/cisplatin followed by cyctectomy, MC-folinic acid followed by cystectomy and M-VAC followed by cystectomy).

FIGURE 5. Forest plot for meta-analysis of overall survival for different local treatments.

probability of death [34]. It is important when interpreting the findings of these studies to consider that the three studies used fundamentally different NAC dosing regimens, which likely influenced the results.

A number of meta-analysis and systematic reviews have attempted to examine the usefulness of NAC in patients with bladder cancer. A 2003 meta-analysis performed by the Advanced Bladder Cancer (ABC) Meta-analysis Collaboration that included 10 randomized trials found a 9% overall relative reduction in the risk with the administration of NAC, and a 13% relative reduction with platinum-based NAC [12]. An update by the same organization published in 2011 included one additional trial (11 randomized trials in total) and was comprised of 3,005 patients (98% of patients from all eligible randomized trials) [10]. The results showed a significant benefit on overall survival in platinum-based combination chemotherapy (HR, 0.86 (95% CI 0.77 to 0.95, $P=0.003$). This effect was observed irrespective of the type of local treatment and did not vary between subgroups of patients. The HR for all trials, including those that used single-agent cisplatin, also showed benefit with NAC in OS (HR= 0.89, 95% CI 0.81 to 0.98, $P=0.022$) [10].

Yin *et al.* (2016) performed a systematic review and meta-analysis that compared NAC plus local treatment with the same local treatment alone [31]. The analysis included 15 randomized trials and prospective studies with a total of 5,051 patients. In contrast to our results, using data only from the randomized trials they found a significant overall OS benefit associated with cisplatin-based NAC (HR, 0.87; 95% CI, 0.79 to 0.96). Yin *et al.* found no significant difference between MVAC compared with GC in pathological complete response, but did find GC was associated with significantly lower OS (HR, 1.26; 95% CI, 1.01 to 1.57). The difference in results between our study and that of Yin *et al.* may, in part, reflect differences in the studies included in the analyses. A systematic review of the literature by Meeks *et al.* [13] published in 2012, analyzed prospective trials and preclinical data relating to cisplatin-based neoadjuvant chemotherapy in MIBC and concluded that cisplatin-based NAC improves OS in patients with MIBC [13].

Gemcitabine has been considered to be included in NAC regimens because gemcitabine plus cisplatin has a better safety profile than MVAC [36]. A phase III trial comparing GC and MVAC in patients with transitional cell carcinoma of the urothelium demonstrated that both groups had similar efficacy with respect to response, time-to-progression and OS, whereas GC was associated with less toxicity than MVAC [37]. Recent studies that compared neoadjuvant GC and MVAC also

found no difference between the two regimes in response rates and pathological and survival outcomes [11,38]. A meta-analysis that compared the relationship between NAC GC and MVAC regimens and pathologic complete response rates in patients with MIBC has recently been published [39]. Based on the retrospective data, patients receiving GC had similar pathologic complete response rate as those administered MVAC. We did not include GC in our study since the number of RCTs designed for comparing GC regimens plus local treatment and local treatment alone was limited and the findings were inconsistent. Khaled *et al.* found that neoadjuvant GC did not improve survival in locally advanced bladder cancer over radical cystectomy alone, but Osman *et al.* reported a beneficial effect of GC NAC in survival when compared with radical cystectomy alone [32,33].

There are limitations to this study that should be considered. The number of studies examining each NAC combination was small. We did not analyze other outcomes, such as adverse events, toxicity and quality of life, because most of studies did not report these outcomes in detail; therefore, the overall benefits (cost-benefits/effectiveness effects) of cisplatin-based NAC could not be fully assessed. Due to lack of data, it was not possible to perform subgroup analysis for OS in patients treated with both RT and cystectomy with or without NAC. Subgroup analysis of prognostic factors, such as lymphovascular invasion, micropapillary histology and p53 nuclear accumulation [40], and patient factors, such as age, race, performance status, obesity and smoking status [9], would also be helpful to further understand the benefits of NAC. This meta-analysis is not based on individual patient-level data since as these data were not available.

In conclusion, our analysis supported that platinum-based adjunctive chemotherapy followed by radiotherapy or cystectomy was associated with similar survival as patients undergoing cystectomy and/or radiotherapy alone. Future studies are required to evaluate the benefit of NAC in treating patients with bladder cancer.

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Supplemental Figure and Tables

SUPPLEMENTAL FIGURE 1. Funnel plot for publication bias of overall survival.

SUPPLEMENTAL TABLE 1. Sensitivity analysis of the pooled estimates of overall survival

First author (year)	Statistics with study removed				
	Points	Lower limit	Upper limit	Z-Value	P-Value
Kitamura (2014)	0.92	0.84	1.01	-1.83	0.067
Khaled (2014)	0.92	0.85	1.01	-1.74	0.081
Osman (2014)	0.92	0.84	1.01	-1.81	0.070
International collaboration of trialists (2011)	0.95	0.86	1.06	-0.88	0.381
Grossman (2003)	0.88	0.81	0.97	-2.65	0.008
Sherif (2002)	0.93	0.85	1.02	-1.55	0.122
Sengel (2002)-Cystectomy	0.92	0.84	1.00	-1.96	0.051
Sengel (2002)-Radiotherapy	0.92	0.84	1.00	-1.91	0.056
Millikan (2001)	0.91	0.83	0.99	-2.15	0.031
Shipley (1998)	0.92	0.84	1.00	-1.86	0.063
Coppin (1996)	0.93	0.85	1.01	-1.65	0.100
Malmstrom (1996)	0.93	0.85	1.02	-1.59	0.113
Martinez-Piñeiro (1995)	0.92	0.84	1.00	-1.93	0.054
Ozono (1991)	0.92	0.84	1.00	-1.91	0.057
Wallace (1991)-West Midlands	0.91	0.83	1.00	-2.01	0.044
Wallace (1991)-Australia	0.91	0.83	1.00	-2.07	0.039

SUPPLEMENTAL TABLE 2. Quality assessment

First author (publication year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessors (detection bias)	Incomplete outcome (attrition bias)	Selective outcome reporting (reporting bias)	Did the analysis include an intention-to-tr eat analysis?
Kitamura (2014)	low	low	unclear	unclear	low	low	unclear
Khaled (2014)	low	low	high	low	low	low	low
Osman (2014)	low	unclear	unclear	unclear	low	low	low
International Collaboration of Trialists (2011)	low	low	unclear	unclear	low	low	unclear
Grossman (2003)	low	unclear	unclear	unclear	low	low	low
Sengelov (2002)	low	low	unclear	unclear	low	low	low
Sherif (2002)	low	unclear	unclear	unclear	low	low	low
Millikan (2001)	low	unclear	unclear	unclear	low	low	low
Shipley (1998)	low	unclear	unclear	unclear	low	low	unclear
Coppin (1996)	low	unclear	unclear	unclear	low	low	unclear
Malmstrom (1996)	low	unclear	unclear	unclear	low	low	low
Martinez-Piñero (1995)	low	low	unclear	unclear	low	low	unclear
Ozono (1991)	low	unclear	unclear	unclear	low	low	unclear
Wallace (1991)	low	low	unclear	unclear	low	low	unclear