Adjuvant chemotherapy in patients with locally advanced bladder cancer after neoadjuvant chemotherapy and radical cystectomy: a systematic review and pooled analysis

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Background: Neoadjuvant chemotherapy (NAC) could ameliorate the stage of locally advanced bladder cancer (LABC) which is defined in pT3/T4 and/or pN+, improve overall survival (OS) before radical cystectomy (RC). However, for LABC, the decision to use adjuvant chemotherapy (AC) after NAC and RC is still controversial.

Methods: We performed a comprehensive search of the PubMed, Embase, and Cochrane Library databases for literature that reported prognosis after using AC following NAC and RC. Cumulative analyses of hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were performed. We performed all analyses by Review Manager software, version 5.3, and Stata 15.0.

Results: Six retrospective cohort studies were included, involving 4,346 patients. Pooled analysis results showed that using AC after NAC and RC can improve OS (HR =0.83, 95% CI: 0.74–0.94, P=0.002; I^2 =0%) and cancer-specific survival (CSS) (HR =0.56, 95% CI: 0.32–0.99, P=0.04; I^2 =0%) but cannot extend recurrence-free survival (RFS) (HR =0.52, 95% CI: 0.27–1.01, P=0.05; I^2 =53%) for LABC patients.

Conclusions: This pooled analysis shows that AC after NAC and RC can improve the prognosis for patients with LABC.

Keywords: Urinary bladder neoplasms; meta-analysis; adjuvant chemotherapy; neoadjuvant chemotherapy (NAC)

Introduction

Bladder cancer (BCa) is a prevailing, invasive, malignant tumor in the urinary system (1). In 2019, there were 80,470 bladder cancer, with 17,670 deaths, occurred in America (2). Radical cystectomy (RC) is regard as the standard surgery of muscle-invasive bladder cancer (3). With the development of neoadjuvant chemotherapy (NAC), NAC combined with RC have been increasingly proved effective in BCa, which can improve patients' survival and quality of life. However, most patients will still relapse and develop metastasis (4).

In addition, bladder cancer patients need to monitor tumor recurrence throughout their lives, and full-course treatment of locally advanced bladder cancer (LABC) is so expensive that few patients could afford (5).

Current NAC and radical cystectomy (RC) are recommended by U.S. guidelines as the treatment of choice for LABC (6). NAC can reduce the stage of invasive bladder cancer and improve overall survival (OS) before RC (7). However, for patients with LABC (pT3–T4 or pN+, there is little existing evidence to guide treatment (8). Matthew

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D. Galsky (9) conducted a study involving 5,396 patients with LABC and concluded that there is a significant improvement in overall survival (HR 0.70; 95% CI: 0.64 to 0.76) for those who had adjuvant chemotherapy(AC) after RC. However, the current research on the efficacy of AC after NAC and RC is controversial. Some clinical studies suggest that the use of AC can prolong the survival of patients who received NAC and RC, but some researchers believed that using adjuvant chemotherapy is not beneficial to prognosis (7,8,10-13).

Here, a pooled-analysis was systematically performed to explore whether the prognosis of patients receiving AC after NAC and RC significantly improved.

Methods

This research was finished in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) reporting checklist (available at http://dx.doi.org/10.21037/tau-20-571) (14). Because of the nature of the study design, no ethical standards approval or informed consent was required.

Search strategy

A comprehensive review of the literatures was performed in accordance with the PRISMA statement in January 2020 in PubMed (ncbi.nlm.nih.gov/pubmed), Embase (embase.com), and the Cochrane Central Search Library (cochranelibrary.com). We used following Search terms to search literature: "Neoadjuvant Therapy"[Mesh] OR (neoadjuvant chemotherapy OR Preoperative Chemotherapy)) AND (neoplasms OR cancer OR carcinoma) AND ("Urinary Bladder Neoplasms"[Mesh] OR (bladder OR urinary bladder)) AND ("Cystectomy"[Mesh] OR Radical Cystectomy) AND ("Chemotherapy, Adjuvant"[Mesh] OR Adjuvant Chemotherapy). We reviewed all abstracts and review studies about this topic and identified manually the references of original studies.

Inclusion/exclusion criteria

The following selection criteria needed to be met in qualified studies: studies appraising the effect of using AC after neoadjuvant chemotherapy and RC; reports containing important information about AC use and bladder cancer susceptibility, overall survival (OS), cancer-specific survival (CSS), recurrence-free survival (RFS); sufficient information was provided for a hazard ratio (HR) including a 95% confidence interval (95% CI); cohort studies having a controlled group; study's language is English. The following are the exclusion criteria: reviews, case series, case reports, letters, and editorials; studies cannot estimate HR with a 95% CI; animal-related studies.

Data extraction

Two independent researchers (ZYC and JH) extracted the data of eligible studies. Argument was solved by discussing with a third researcher (HJ). We extracted individually the data from the literature and demographics. The following information were contained: author, ethnicity, area of study, study type, publication year, tumor stage, sample size, age, survival analysis, exposure or intervention definition, adjusted variables, Newcastle-Ottawa Scale (NOS) score, duration and median follow-up. An HR with a 95% CI was used to assess the association between adjuvant chemotherapy use and OS, CSS, and RFS after neoadjuvant chemotherapy and radical cystectomy. If the HRs, their 95% CIs and P values were available, they were obtained from the original articles. If not, we computed the HRs and 95% CIs according to the methods (15).

Statistical analysis

We took the HRs and 95% CIs together to survey the effect of using AC after NAC and radical cystectomy for outcomes. The HRs and 95% CIs directly were collected in the article if they were available. To avoid calculation errors, two independent researchers completed this process. We tested Statistical heterogeneity in studies by a formal Q-statistic and the chi-squared (I^2) test. The degree of heterogeneity was investigated through the value of I^2 (no heterogeneity: $I^2 <25\%$; moderate heterogeneity: $I^2 =25–50\%$; substantial heterogeneity: $I^2 >50\%$). The random-effects model was utilized when we found substantial heterogeneity. When we found moderate or no heterogeneity, the fixed-effects model was utilized. The level of statistical significance was set at 0.05 (16).We could not assess publication bias (17,18) because the amount of the included studies is small, so to appraise the stability of the pooled-analysis results, a sensitivity analysis was done using the leave-one-out cross validation. Review Manager (RevMan) v5.3 was used to perform this meta-analysis.
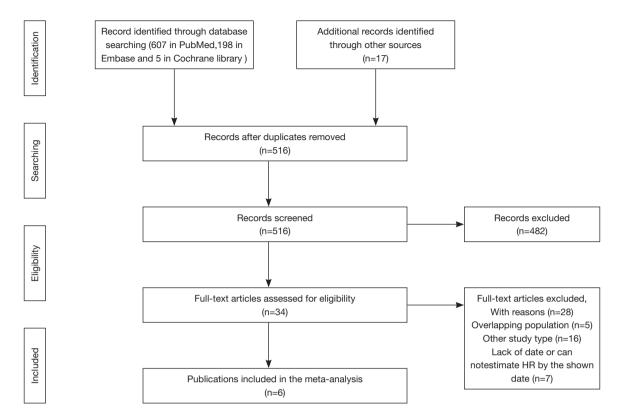
Figure 1 Flow chart of studies selection.

Results

Study selection and characteristics

Eventually, we got 607 records through databases. Our present meta-analysis included six studies (7,8,10-13) in accordance with the inclusion and exclusion criteria, which completely investigated the effects of using AC after neoadjuvant chemotherapy and RC and their outcomes (*Figure 1*). Especially, data were available from four researches on the effects of using adjuvant chemotherapy on the OS of patients with LABC, three studies about RFS, and two studies about CSS. Three thousand ninety-six patients with pT3/T4 and/or pN+ were included; 76% (n=2,355) of them were in the exposure group and 24% (n=741) were in the control group. We summarized the main characteristics of the qualified studies in *Table 1*. The results are summarized in *Table 2*. To assess the quality, the Newcastle-Ottawa Scale (NOS) scores (Table S1) of the including studies ranged from 7 to 8.

AC after neoadjuvant chemotherapy and RC improves OS for LABC

Four studies reported the effects of using AC after neoadjuvant chemotherapy and RC on the OS of patients with LABC, which involved 2,887 patients with pT3/T4 and/or pN+ {NAC+RC [2198] *vs.* NAC+RC+AC [689]}. A fixed-effects model was utilized because no significant heterogeneity was found between these studies (I^2 =0%; P=0.50). Mainly, using AC after neoadjuvant chemotherapy and RC was conducive to the OS of patients with LABC (HR =0.83, 95% CI: 0.74–0.94; P=0.002) (*Figure 2*).

Adjuvant chemotherapy after NAC and RC improves CSS of LABC

Another two studies showed the association between using AC after neoadjuvant chemotherapy and RC and CSS of patients with bladder cancer, which involved 125 patients with pT3/T4 and/or pN+ {NAC+RC [75] *vs.* NAC+RC+AC

Table 1 Characteristics of included retrospective studies

Study (year), area	Ethnicity	Study type	Tumor stage	Exposure (event*)	Control (event*)	Definition of exposure and control	Chemotherapy regimen	Duration and median follow-up	Adjusted variables	Survival analysis	NOS score	Reference
Wilson Sui et al. (2017) USA	Caucasian	Cohort study	pT3/4 and/or pN+	168	537	Ex: NAC+RC+AC Co: NAC+RC	Not mentioned	2004–2013, 44 mo	Age, gender, race, Charlson/Deyo Score, type of facility, insurance status, year of diagnosis, tumor grade, cN stage, pT stage, pN stage, histology, number of LN examined, number of LN positive	OS	7	14
Thomas Seisen et al. (2017) USA	Caucasian	Cohort study	pT3/4 and/or pN+	184	604	Ex: NAC+RC+AC Co: NAC+RC	Not mentioned	2006–2012, 45.7 mo	Age, gender, race, CCI, insurance status, income level, educational level, county type, facility type, year of diagnosis, facility location, pathologic stage, surgical margins	OS	8	7
William P. Parker et al. (2017) USA	Caucasian	Cohort study	pT3/4 and/or pN1-3	326	1033	Ex: NAC+RC+AC Co: NAC+RC	Not mentioned	2006–2012, 3.7 y	Age, gender, race, Charlson-Deyo, insurance status, population of residence, facility type, pathologic classification, adjuvant RT	OS	8	6
Nieves Martinez Chanza et al. (2018) USA	Caucasian	Cohort study	pT3/4 and/or pN1-3	23	106	Ex: NAC+RC+AC Co: NAC+RC	NAC: GC or MVAC AC: GC or MVAC	1991–2013, 30 mo	Age, gender, smoking history, performance status, Charlson score, cT stage, cN+ stage, histology, pathological stage, NAC regimen, No. of NAC cycles, AC regimen, No. of AC cycles	RFS	8	15
Wassim Kassouf et al. (2009) USA	Caucasian	Cohort study	pN+	11	24	Ex: NAC+RC+AC Co: NAC+RC	Not mentioned	1993–2003, 50 mo	Age, sex, clinical N category, performance status, histologic type, pathologic stage, lymph node density (%), surgical margin status, adjuvant chemotherapy	OS, RFS, CSS	7	13
Kamran Zargar-Shoshtari et al. (2016) USA	Caucasian	Cohort study	pN+	29	51	Ex: NAC+RC+AC Co: NAC+RC	NAC: GC or MVAC AC: GC or MVAC	2001–2013, NR	Age, gender, Charlson comorbidity index, eGFR after cystectomy, neoadjuvant regimen, number of cycles, clinical T-stage, clinical N-stage, pathological T-stage, pathological N-stage, lymphovascular invasion, positive margin	RFS, CSS	7	1

Age, means median age; Bca, bladder cancer; Co, controlled group; CSS, cancer-specific survival; NOS, Newcastle-Ottawa Scale; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; Od, overall death; OS, overall survival; RFS, recurrence-free survival; GC, Gemcitabine + cisplatin; MVAC, Methotrexate + Vincristine + adriamycin + cisplatin. Event* means the bladder cancer incidence or oncologic outcomes such as recurrence, progression, cancer-specific death, and overall death.

Table 2 Analysis of the effect of using adjuvant chemotherapy after neoadjuvant chemotherapy and radical cystectomy

Outcomes	No. of studies	No. of patients (events*)		Pooled HR (95% CI)	P	I^2 (%)	Effects model
		NAC+RC	NAC+RC+AC				
OS	4	2198	689	0.83 [0.74, 0.94]	0.002	0	Fixed
RFS	3	181	63	0.52 [0.27, 1.01]	0.05	53	Random
CSS	2	75	40	0.56 [0.32, 0.99]	0.04	0	Fixed

CI, confidence interval; CSS, cancer-specific survival; HR, hazard ratio; NA, it means that we cannot extract directly or estimate indirectly the number of events from the original article; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival. Event* means the bladder cancer incidence or oncologic outcomes such as recurrence, progression, cancer-specific death, and overall death.
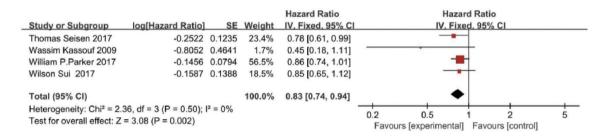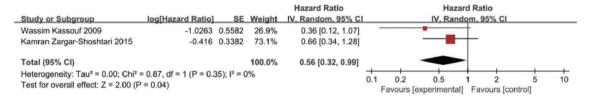

Figure 2 Forest plot of HR for overall survival. Association between using AC after NAC and +RC and overall survival; The diamond indicates the pooled HR value. HR, hazard ratio; CI, confidence interval; SE, standard error.

Figure 3 Forest plot of HR for cancer-specific survival. Association between using AC after NAC and +RC and cancer-specific survival; The diamond indicates the pooled HR value. HR, hazard ratio; CI, confidence interval; SE, standard error.

[40]}. No significant heterogeneity between these studies was found (I^2 =0%; P=0.35). Overall, using adjuvant chemotherapy after NAC and RC led to increased CSS of the LABC patients (HR =0.56, 95% CI: 0.32–0.99; P=0.04) (*Figure 3*).

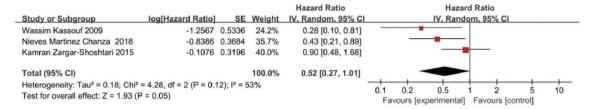### Adjuvant chemotherapy after NAC and RC marginally affected RFS in LABC

Three studies recorded the effects of using AC after neoadjuvant chemotherapy and RC on the RFS of bladder cancer patients; 244 patients with pT3/T4 and/or pN+ were included {NAC+RC [181] *vs.* NAC+RC+AC [63]}. A random-effects model was utilized in the analysis because

a substantial heterogeneity between the trials was found (I^2 =53%; P=0.12). Mainly, we found no significant relationship between the use of adjuvant chemotherapy after NAC and RC and the RFS of patients with LABC (HR =0.52, 95% CI: 0.27–1.01; P=0.05) (*Figure 4*).

Sensitivity analysis and quality of studies

We performed a sensitivity analysis to evaluate the stability of the pooled-analysis results. Because the overall HR did not change significantly after removing the studies related to heterogeneity, the pooled-analysis was convincing and adequately stable (*Figure 5*). Two independent researchers assessed the quality of these studies through the NOS

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Figure 4 Forest plot of HR for recurrence-specific survival. Association between using AC after NAC and +RC and recurrence-specific survival; The diamond indicates the pooled HR value. HR, hazard ratio; CI, confidence interval; SE, standard error.
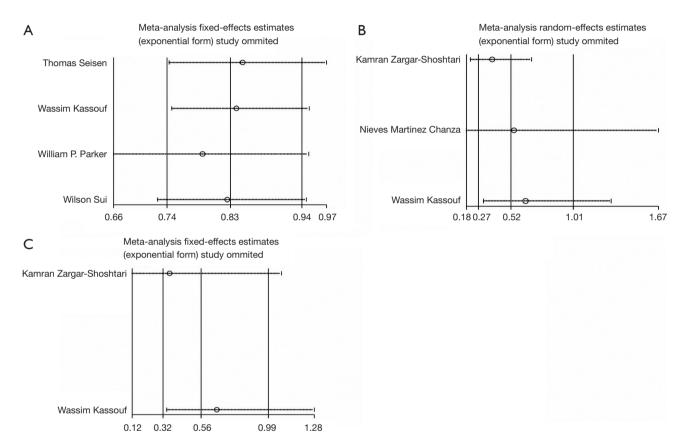

Figure 5 Sensitivity analysis for (A) overall survival, (B) recurrence-free survival, (C) cancer-specific survival.

(Newcastle-Ottawa Scale) (16). High-quality studies: scores of 7 to 9; low-quality study: score of <7.

Discussion

Patients with LABC after RC has a poor five-year OS of 25–38% (19-21). Despite treatment with NAC, patients having pathologic lymph node involvement also have a poor median OS of 13–26 months (22-24). These patients are limited to utilizing additional chemotherapy for treatment.

Bryan M. Burt (25) reported that AC after neoadjuvant chemotherapy and esophagectomy provided a benefit to the OS of patients with esophageal cancer. In addition, Haiying Sun *et al.* (26) had the same result for cervical cancer, so we wanted to know whether the same regimen was effective for patients with LABC and whether it could improve their prognosis. Thomas Seisen *et al.* reported that AC after neoadjuvant chemotherapy and RC was related to an OS benefit for patients with pT3/T4 and/or pN+ bladder cancer (12), but whether patients with LABC after NAC

and RC benefited from further adjuvant chemotherapy was unclear, although many scholars support additional chemotherapy (27).

Six retrospective cohort studies investigated the effects of using additional adjuvant chemotherapy after NAC and RC on the OS, RFS, and CSS of LABC. In the study by Wilson Sui (13), the AC group had a longer median OS compared with the observation group (23 *vs.* 20 months), but the result was not statistically significant, and AC was not related to the risk of death in a multivariate analysis. This conclusion was also supported by W.P. Parker (8) and W. Kassouf (10) Conversely, Seison (12) reported that the AC group had a significantly longer OS than the observation group. There was also a disagreement about the CSS of the AC group between K. Zargar-Shoshtari (7), who concluded that AC was not associated with obvious improvement in CSS, and W. Kassouf (10), whose study presented a positive result, proposing that LABC patients receiving AC after NAC and RC could realize an improved CSS. W. Kassouf (10) and N. Martinez Chanza (11) supported the view that AC could improve the RFS of the patients, and K. Zargar-Shoshtari (7) reported that RFS which was not statistically significant appeared longer in the experimental group. The current pooled-analysis showed a significant association between using additional adjuvant chemotherapy after NAC and RC and the CSS and OS of patients with bladder carcinoma, but no effect on the RFS. Because the data provided by these six studies was not very comprehensive, larger prospective studies need to verify the outcomes.

Actually, this present study represents the first meta-analysis of an effectiveness evaluation of AC after neoadjuvant chemotherapy and RC. Indeed, 3096 patients were included in these six studies with pT3/T4 and/or pN+ disease after NAC and RC. 741 of them further used AC that was independently related to overall survival and CSS. The results concluded that using additional AC after neoadjuvant chemotherapy and RC could extend the OS and CSS of patients with pT3/T4 and/or pN+ BCa but added no obvious benefit to their RFS.

Node-positive bladder cancer was a type of LABC which means poor prognosis. As the limitation of pooled data, we could not conduct subgroup analysis on pN- or pN+ about OS or CSS for additional AC. Walz *et al.* considered that either MVAC or GC had no significant effect on CSS or OS after RC in high-risk patients which included positive node patients (28). However, Pak *et al.* argued that AC after RC was associated with improved OS in patients with node-positive bladder cancer (29). Consequently, the effect of

additional AC on the node-positive patients is still unclear.

In aspect of chemotherapy regimen of NAC and AC, not only merely two of six studies described the exact chemotherapy regimens of patients, but also all of them didn't mentioned whether same regimen used in NAC and AC. In EAU guideline, they strongly recommended to offer cisplatin-based combination chemotherapy to LABC in NAC and AC (30). However, we didn't find any studies to identify the same chemotherapy regimen in NAC and AC.

Furthermore, the results didn't show whether all of LABC patients need to have an additional AC. However, there have been some studies indicated patients with different biomarkers had different sensitivity on chemotherapy. Woonyoung Choi *et al.* found that p53-like MIBCs were consistently resistant to neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin chemotherapy (31). Van Allen *et al.* found that Somatic ERCC2 mutations correlate with complete response to cisplatin-based chemosensitivity in MIBC (32). Consequently, we should stratify patients with different biomarkers.

Different from chemotherapy only era, with the rise of immunotherapy, more and more immunotherapy agents such as PD-1 blockade and PD-L1 blockade have been applied in therapy of LABC. Necchi *et al.* found that Median OS for those continuing atezolizumab (PD-L1 blockade) treatment after the previous platinum-based chemotherapy was 12.8 months, compared to 3.6 months for those not treated with atezolizumab (33). In another clinical trail—Keynote045, comparing pembrolizumab (blockade interaction between PD-1 and PD-L1) to chemotherapy after previously platinum-based chemotherapy. The median OS was 10.3 *vs.* 7.4 months (34). These studies showed that application of immunotherapy agents followed by NAC and RC probably have a better prognosis.

Some limitations also exist in our meta-analysis. First, the type of chemotherapy was not available, because these six studies used different chemotherapies. Some studies used platinum-based regimens, but some used carboplatin-based regimens, which probably resulted in different effects for patients. Second, although we confirmed the positive effects of using additional AC after neoadjuvant chemotherapy and RC for patients with pT3/T4 and/or pN+, we do not know whether using additional AC after neoadjuvant chemotherapy and RC could extend the OS or CSS of patients with pT0-2 bladder cancer, because these six studies selected only patients with pT3/T4 and/or pN+ cancer. Third, English is the only language of these

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qualified studies, so increased publication bias might be found in the exclusion of studies in other languages.

Conclusions

Our meta-analysis supported a favorable clinical role for additional AC for patients with LABC after neoadjuvant chemotherapy and RC. We found that using additional AC after neoadjuvant chemotherapy and RC could extend the OS and CSS of patients with LABC. Large, prospective, multicenter, randomized controlled trials are still essential to confirm the role of AC for LABC.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tau-20-571

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau-20-571). Dr. XZ serves as an unpaid editorial board member of *Translational Andrology and Urology* from Mar 2015 to Feb 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table S1 The Newcastle-Ottawa Scale (NOS) for assessing the quality of cohort studies

Study (year)	Selection				Comparability		Assessment of outcome			Total quality score
	Representative-ness of the exposed cohort	Ascertainment of exposure	Selection of Controls	Demonstration that outcome of interest was not present at start of study	Study controls for the most important factors	Study controls for any additional factor	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohort	
Wilson Sui (2017)	*	*	*	–	*	*	*	*	–	7
Thomas Seisen (2017)	*	*	*	–	*	*	*	*	*	8
William P. Parker (2017)	*	*	*	–	*	*	*	*	*	8
Nieves Martinez Chanza (2018)	*	*	*	–	*	*	*	*	*	8
Wassim Kassouf (2009)	*	*	*	–	*	*	*	*	–	7
Kamran Zargar-Shoshtari (2016)	*	*	*	–	*	*	*	*	–	7