Adjuvant Chemotherapy for Invasive Bladder Cancer: A 2013 Updated Systematic Review and Meta-Analysis of Randomized Trials


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Abstract

Context: The role of adjuvant chemotherapy remains poorly defined for the management of muscle-invasive bladder cancer (MIBC). The last meta-analysis evaluating adjuvant chemotherapy, conducted in 2005, had limited power to fully support its use.

Objective: To update the current evidence of the benefit of postoperative adjuvant cisplatin-based chemotherapy compared with control (ie, surgery alone) in patients with MIBC.

Evidence acquisition: A comprehensive literature review was performed to identify all randomized controlled trials (RCTs) comparing adjuvant cisplatin-based chemotherapy with control for patients with MIBC. The search included the Medline, Embase, Cochrane Central Register of Controlled Trials databases, and abstracts from the American Society of Clinical Oncology meetings up to May 2013. An updated systematic review and meta-analysis was performed.

Evidence synthesis: A total of 945 patients included in nine RCTs (five previously analyzed, one updated, and three new) were examined. For overall survival, the pooled hazard ratio (HR) across all nine trials was 0.77 (95% confidence interval [CI], 0.59–0.99; p = 0.049). For disease-free survival, the pooled HR across seven trials reporting this outcome was 0.66 (95% CI, 0.45–0.91; p = 0.014). This disease-free survival benefit was more apparent among those with positive nodal involvement (p = 0.010).

Conclusions: This updated and improved meta-analysis of randomized trials provides further evidence of an overall survival and disease-free survival benefit in patients with MIBC receiving adjuvant cisplatin-based chemotherapy after radical cystectomy.

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1. Introduction

More than 50,000 patients die from bladder cancer in the United States and European Union annually [1]. Most of the cases (70\%–75\%) are diagnosed as non–muscle-invasive disease; the remaining 25\% present as muscle-invasive bladder cancer (MIBC) [2]. Additionally, 10\%–15\% of patients in stage I develop invasive recurrent disease within 1 yr of treatment [3].

The current National Comprehensive Cancer Network (NCCN) guideline recommends radical cystectomy as the standard of care for all patients with muscle-invasive nonmetastatic disease and sufficient performance status. Neoadjuvant cisplatin-based chemotherapy is strongly recommended based on level I evidence showing a survival benefit [4,5]. Recent studies, however, demonstrate underutilization of this treatment strategy. A multi-institutional study of 4541 patients across 14 academic centers in the United States from 2003 to 2008 found that only 12\% of patients received neoadjuvant and 22\% received adjuvant chemotherapy [6]. Similar findings were revealed by Burger et al. using a feasibility questionnaire in 133 institutions from 17 European countries [7].

Due to the low rates of adoption of neoadjuvant chemotherapy, clinicians are often faced with the decision of whether or not to recommend adjuvant chemotherapy for many moderate- to high-risk patients who have not been exposed to neoadjuvant chemotherapy. Despite multiple randomized clinical trials (RCTs), the role of adjuvant chemotherapy in bladder cancer has remained controversial. NCCN recommendations for adjuvant chemotherapy are currently under consideration based on “pathologic risk (T3–4, positive nodes, positive margin, high-grade)” [8]. The Advanced Bladder Cancer Meta-Analysis Collaboration conducted a meta-analysis in 2005 [9], subsequently published as a Cochrane review [10]. Individual patient data were obtained for 491 patients from six trials. Ultimately, 66\% of patients from eligible trials (90\% randomized to cisplatin-based combination chemotherapy) were included in the Cochrane study. Table 1 summarizes the excluded trials. This meta-analysis found an overall 25\% relative reduction in risk of death for patients on chemotherapy. Issues cited included four of six trials stopping early, few deaths (283 of 491), and the failure of patients assigned to the control arm to receive standard of care at relapse [9].

Since this meta-analysis, several trials have been conducted to evaluate adjuvant cisplatin-based regimens for MIBC. Four phase 3 cooperative studies have recruited patients: the Italian Multicentric Study [11], the European Organization for Research and Treatment of Cancer (EORTC) study [12], the Spanish Oncologic Genito-Urinary Group (SOGUG) Study [13], and the US p53 Intergroup study [14]. Additionally, Lehmann et al. published an update of the 1994 Stockle trial [15] in 2006 with 10 yr of follow-up [16]. The EORTC trial has not yet been reported at the time of this paper. An Association of Urogenital Oncology phase 3 trial examining time to tumor progression in cystectomized MIBC patients who were unfit for cisplatin-based chemotherapy and treated with gemcitabine monotherapy was not included [17].

Given the existence of new data since the Cochrane paper almost a decade ago [10], and the availability of the most up-to-date statistical meta-analysis techniques such as random-effects and meta-regression models, the need for an updated meta-analysis is clear. These factors prompted us to embark on an updated systematic review and meta-analysis. In this study, in addition to an extended analysis examining if adjuvant cisplatin-based chemotherapy after radical cystectomy for patients with MIBC confers a benefit for overall survival (OS) and disease-free survival (DFS), the impact of other baseline covariates such as lymph node status is addressed.

2. Evidence acquisition

The present analysis builds on the 2005 Cochrane meta-analysis [10] and incorporates additional RCTs published after 2005. A prespecified protocol was followed that detailed trial inclusion criteria (Table 2), methods for trial identification, data extraction, and statistical analysis.

2.1. Search strategy

Both published and unpublished English-language trials were considered for study inclusion. To identify eligible trials, computerized bibliographic searches of PubMed/Medline and Embase were conducted in March 2013. Search terms used for PubMed/Medline and Embase are listed in the Supplement. Searches resulted in 4534 possible articles.

Table 1 – Excluded trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allen (unpublished)</td>
<td>Trial failed to recruit any patients</td>
</tr>
<tr>
<td>Einstein [39]</td>
<td>Data not available</td>
</tr>
<tr>
<td>Omura (unpublished)</td>
<td>Data not available</td>
</tr>
<tr>
<td>Richards [40]</td>
<td>Non–platinum-based chemotherapy regimen used.</td>
</tr>
<tr>
<td>Shearer [41]</td>
<td>Chemotherapy was administered before and after local treatment.</td>
</tr>
</tbody>
</table>

Table 2 – Trial inclusion criteria

To be eligible for inclusion, all publications had to meet the following criteria:
1. Study design: Randomized controlled trial
2. Population: Patients with biopsy-proven, muscle-invasive (clinical stage T2–T4a) transitional cell carcinoma of the bladder. Trials that also included a minority of pT1 patients were also included.
3. Intervention: Experimental group received local definitive treatment (resection) with adjuvant cisplatin-based chemotherapy. The same local treatment used as in control arm.
4. Comparator: Control group received local treatment (same as experimental group) without adjuvant chemotherapy. Controls must not have received any neoadjuvant chemotherapy.
5. Outcomes: Overall survival (time from study initiation until death/censoring). Disease-free survival (time from initiation until first recurrence or progression or death). Death is defined as death by any cause.

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Given the existence of new data since the Cochrane paper almost a decade ago [10], and the availability of the most up-to-date statistical meta-analysis techniques such as random-effects and meta-regression models, the need for an updated meta-analysis is clear. These factors prompted us to embark on an updated systematic review and meta-analysis. In this study, in addition to an extended analysis examining if adjuvant cisplatin-based chemotherapy after radical cystectomy for patients with MIBC confers a benefit for overall survival (OS) and disease-free survival (DFS), the impact of other baseline covariates such as lymph node status is addressed.
which were distributed evenly among six of the study authors, who were divided into three pairs. Within each pair, researchers completed independent reviews of assigned abstracts and identified articles for possible inclusion based on review of titles and abstracts in consideration of the inclusion criteria. In cases of pair disagreement, study pairs reached a consensus on whether to include the article. From the final list of candidate abstracts, full articles were retrieved for further review and evaluated for whether inclusion criteria were met.

In addition to a review of the literature search results, we conducted a search of abstracts presented at meetings of the American Society of Clinical Oncology (ASCO) from January 2007 to May 2013. Finally, the Cochrane Central Register of Controlled Trials (CENTRAL) was queried for pertinent ongoing or unpublished studies.

2.2. Data extraction

For data extraction of the nine resulting studies, the three pairs of authors responsible for the initial literature search reviewed full studies and extracted data independently for assigned trials. Data were extracted at the trial level and not the individual patient data level due to lack of availability. Any differences in extracted data were resolved via within-pair consensus. If a consensus could not be reached within study pairs, the entire group was consulted to achieve consensus on the most accurate results. Extracted data included details on study design, inclusion and exclusion criteria, randomization, participant demographic and oncologic characteristics, interventions, outcomes measured (OS and DFS), and results (number of events, hazard ratios [HRs], 95% confidence intervals [CIs], and \( p \) values).

2.3. Statistical analysis

Effect measures for the outcomes of OS and DFS are HRs. Study-specific HR point estimates and CIs were extracted from published studies, abstracts, and the 2005 Cochrane meta-analysis, with standard errors of log-hazard ratios estimated from published CIs. For trials with Kaplan-Meier log-rank or Wilcoxon \( p \) values available but either no published HRs or 95% CIs, we used a widely used method to estimate HRs and 95% CIs [18]. A random-effects model using inverse-variance weighting was used to pool estimates from the selected studies and previous meta-analysis [19]. The significant advantage of a random-effects model over a fixed-effects model (used in previous meta-analyses) is its ability to account for heterogeneity between trials [20]. Our random-effects model assumes a random variation of the underlying effect of chemotherapy across studies; therefore the CIs around the HR are wider than under an alternative fixed-effects model, as used in the last Cochrane meta-analysis [10]. We believe this assumption is more valid because of the heterogeneous nature of the chemotherapeutic regimens administered between trials. Chi-square (Cochran Q statistic) heterogeneity tests were performed to test statistical heterogeneity across studies. The \( I^2 \) statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance, was also calculated to measure inconsistencies between trials [21]. A \( p \) value < 0.05 for the Cochran Q statistic or an \( I^2 \) statistic > 50% indicated the presence of significant heterogeneity between studies [21]. To evaluate for publication bias, we used the Egger linear regression approach and funnel plots. Sensitivity analyses were also performed, investigating the effect on the composite HR under the following scenarios: cumulative addition of studies by year of publication, removal of studies from the analysis one at a time, removal of studies prior to the Cochrane meta-analysis, removal of abstracts that were not published in a peer-reviewed journal, removal of trials using a cisplatin single-agent chemotherapy regimen, and evaluation of studies using only cisplatin-gemcitabine-based chemotherapy regimens. Using meta-regression models, we also evaluated the effect of covariates such as gender and lymph node status on the outcome as information on these was available at the trial level [22].

2.4. Assessment of risk of bias and trial quality

Risk of bias in individual studies was assessed using a tool recommended by recent meta-analysis guidelines that evaluates aspects of RCT design and execution [23,24]. Risk of bias was assessed on the presence or absence of random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, and selective reporting.

3. Evidence synthesis

After reviewing abstracts of potential studies and applying inclusion criteria, the final set of included studies comprised the five studies from the 2005 Cochrane meta-analysis [25–29], one updated analysis [16], and three new studies [11,13,14]. Our meta-analysis includes data from nine trials published from 1991 to 2012, with a total of 945 patients in the intention-to-treat population. There were 475 patients assigned to treatment arms and 470 to control arms. The median follow-up ranged from approximately 30 mo to 69 mo. Table 3 summarizes the included studies.

3.1. Systematic review process

Our search identified 5200 articles, 1648 abstracts, and 55 clinical trial records. All abstracts were screened, and 6813 studies were excluded. This resulted in 35 articles assessed for eligibility, of which 18 articles required qualitative synthesis. Although some studies included high-risk pT1 patients, in these trials patients with pT1 disease were a minority compared with those with \( \geq \) pT2 stage disease, so these trials were included. A total of nine trials were included in the final analysis. Table 3 summarizes the final studies included in the present analyses. Figure 1 presents a visual flowchart encapsulating the data according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis format.
| Study                  | Country          | Academic center/hospital                                                                 | Eligibility criteria                                                                                                                                                                                                                                                                                                                                                     | ACT regimen                                                                 | Duration of ACT | Total patients (ITT population) | Accrual period      | Pathologic tumor (pT) categories                                                                 |
|-----------------------|------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|---------------------------------|-----------------|---------------------------------------------------------------------------------------------|
| Bono et al. [25]      | Italy            | Nine unspecified institutions                                                            | 1. Histologically proven muscle-infiltrating transitional cell carcinoma of the bladder at least 3 cm in diameter (T2–T4a; any G)  
2. No clinical evidence of lymph node or distant metastases  
3. Absence of other histologic subtypes of tumor  
4. No tumors other than in the bladder  
5. Serum creatinine <1.6 mg/dl  
6. No severe cardiovascular disease  
7. Normal hepatic and respiratory function  
8. Absence of important anemia, uncontrollable diabetes, or active uncontrollable infections | Cisplatin 70 mg/m²  
MTX 40 mg/m²  
Vinblasitine 4 mg/m² | Four 21-d cycles | 43 47 | December 1984–December 1987 | For 1st 6 trials below:  
T0–1: 10  
T2: 25  
T3: 144  
T4: 70  
Unknown: 30 | T0–1: 8  
T2: 35  
T3: 291  
T4: 70  
Unknown: 52 |  |
| Freiha et al. [26]    | USA              | Stanford University Medical Center                                                        | 1. Stage p3b and p4 TCC (N0 or N+) of the bladder  
2. No evidence of metastasis (M0) | Cisplatin 100 mg/m²  
MTX 30 mg/m²  
Vinblasitine 4 mg/m² | Four 21-d cycles | 27 28 | April 1986–April 1993 |  |
| Otto et al. [27]      | Germany          | Department of Urology, Essen, Germany                                                    | 1. Stage T3  
2. No evidence of metastasis (M0) | MTX 30 mg/m²  
Vinblasitine 3 mg/m²  
Epirubicin 45 mg/m²  
Cisplatin 70 mg/m² | Three 28-d cycles | 55 53 | January 1993–June 1999 |  |
| Skinner et al. [28]   | USA              | University of Southern California/Kenneth Norris, Jr. Cancer Hospital/Hospital of the Good Samaritan, Los Angeles, CA | 1. Surgically confirmed invasive carcinoma of bladder (either pure transitional cell carcinoma or transitional cell carcinoma associated with squamous or glandular differentiation with or without in situ carcinoma)  
2. Stage P3, P4, or N+/M0  
3. No involved lymph nodes above aortic bifurcation  
4. Age 9–75 yr with signed informed consent | Cisplatin, doxorubicin, cyclophosphamide, 5-fluorouracil, vinblasitine, and bleomycin Patients 18–91: PAC (cisplatin 100 mg/m²; doxorubicin 60 mg/m²; cyclophosphamide 600 mg/m²) | Four 28-d cycles | 50 52 | July 1980–December 1988 |  |
| Lehmann et al. [16]   | Germany          | Saarland University, Mainz University, CIMH Mannheim/University of Heidelberg            | 1. Radical cystectomy patients with histologically confirmed locally advanced bladder cancer  
2. Tumor stages pT3, pT4a, and/or pN+ using 2002 TNM system | MVAC or MVEC (one patient received carboplatin instead of cisplatin) | Three cycles | 26 23 | May 1987–December 1990 |  |
| Studer et al. [29]    | Switzerland      | Berne, Basel, St. Gallen, Zurich, and Swiss Group for Clinical Cancer Research            | 1. Radical cystectomy for multifocal recurrent superficial stage T1 urothelial bladder cancer or recurrent or newly diagnosed muscle-invasive T2–T4a urothelial cancer  
2. Preoperative chest x-ray, bone scan, liver ultrasound all negative for metastases | Cisplatin | Three cycles | 46 45 | April 1984–May 1989 |  |
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Academic center/hospital</th>
<th>Eligibility criteria</th>
<th>ACT regimen</th>
<th>Duration of ACT</th>
<th>Total patients (ITT population)</th>
<th>Accrual period</th>
<th>Pathologic tumor (pT) categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1. Stage pT1/T2 N0M0 urothelial cancer who had undergone a radical cystectomy and bilateral pelvic lymphadenectomy within the prior 9 wk&lt;br&gt;2. Total of ≥15 lymph nodes removed or a normal computed tomography if fewer nodes were identified&lt;br&gt;3. Patients with Pa, P0, or Pis disease were included if T1, T2a, or T2b disease was present on the pre cystectomy transurethral resection specimen&lt;br&gt;4. Performance status of 0 or 1, a chest x-ray free from metastatic disease within 6 wk of cystectomy&lt;br&gt;5. Normal organ function, including a WBC count ≥4000/μl; platelet count ≥150,000/μl; creatinine ≤1.8 mg/dl; ALT, AST, and alkaline phosphatase ≤2 time upper limit of normal; and normal total bilirubin</td>
<td>MTX&lt;br&gt; Vinblastine&lt;br&gt; Doxorubicin&lt;br&gt; Cisplatin</td>
<td>Three cycles</td>
<td>58</td>
<td>56</td>
<td>August 1997–January 2006</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>Regina Elena Cancer Institute, Belcolle Hospital, Viterbo, San Giovanni Bosco Hospital, Torino, Policlinico Universitario, Cagliari, NCI, Genova</td>
<td>1. Histologically proven TCC&lt;br&gt;2. pT2 G3 (N0–2), or pT3–4 (N0–2) any G, or pN1–2, any T; any G&lt;br&gt;3. Radical cystectomy performed with no residual disease and minimum of 10 lymph nodes dissected&lt;br&gt;4. Randomization within 10 wk after surgery&lt;br&gt;5. ECOG PS ≤2&lt;br&gt;6. Age ≤75 yr&lt;br&gt;7. Adequate bone marrow reserve&lt;br&gt;8. Creatinine clearance ≥60 ml/min&lt;br&gt;9. Good liver function</td>
<td>Gemcitabine&lt;br&gt; 1000 mg/m²&lt;br&gt; Cisplatin 70 mg/m²</td>
<td>Four&lt;br&gt; 28-d cycles</td>
<td>102</td>
<td>92</td>
<td>September 2001–July 2007</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>SOGUG and GIJO-AEU Spanish (24 centers)</td>
<td>1. Resected high-risk muscle invasive bladder carcinoma (pT3–4 and/or pN+)&lt;br&gt;2. ECOG PS 0–1&lt;br&gt;3. Adequate renal function (CrCl &gt;50 ml/min)&lt;br&gt;4. ≤8 wk post cystectomy&lt;br&gt;5. No relevant comorbidities&lt;br&gt;6. Signed informed consent&lt;br&gt;7. No prior chemo/radiotherapy&lt;br&gt;8. No other malignancies in previous 5 yr</td>
<td>Paclitaxel 80 mg/m²&lt;br&gt; Gemcitabine 1000 mg/m²&lt;br&gt; Cisplatin 70 mg/m²</td>
<td>Four&lt;br&gt; 21-d cycles</td>
<td>68</td>
<td>74</td>
<td>July 2000–July 2007</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>European Union and USA</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>475</td>
<td>470</td>
<td>April 1984–July 2007</td>
</tr>
</tbody>
</table>

ACT = adjuvant chemotherapy; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intention to treat; MTX = methotrexate; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; MVEC = methotrexate, vinblastine, epirubicin, and cisplatinum; SOGUG = Spanish Oncologic Genito-Urinary Group; WBC = white blood cell; TCC = transitional cell carcinoma.
3.2. Effects of interventions on primary outcome of overall survival

The primary outcome measured in this meta-analysis was OS, defined across studies as the time from radical cystectomy or randomization until death from any cause. Table 4 provides summary data on OS for each trial. In our first analysis, because individual patient data (including time to event) was available to the Cochrane authors for the first six trials, we used these Cochrane recalculated HRs and 95% CIs. Using a random-effects model, based on study-specific HRs and 95% CIs, the pooled HR across all nine studies was 0.78 (95% CI, 0.61–0.99; p = 0.044). This represents a 22% relative decrease in the risk of death when treated with adjuvant chemotherapy compared with control. Next, we used the Cochrane authors’ recalculated univariate HRs and 95% CIs for the first five trials only [25–29]. The Stockle 1995 trial was updated in 2006 by Lehmann et al., so we used the updated published HRs and 95% CIs. Although the Spanish SOGUG trial is currently unpublished, it was presented at a peer-reviewed ASCO meeting in 2010 with the full data presented being available [13]; we used multivariate HRs and

Table 4 – Hazard ratios for overall survival

<table>
<thead>
<tr>
<th>Study</th>
<th>Hazard ratio</th>
<th>Low 95% CI</th>
<th>High 95% CI</th>
<th>Randomized to treatment</th>
<th>Randomized to control</th>
<th>Events in treatment arm</th>
<th>Events in control arm</th>
<th>Male</th>
<th>Female</th>
<th>pN0</th>
<th>pN+</th>
<th>% pN+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bono et al. [25]</td>
<td>0.65</td>
<td>0.34</td>
<td>1.25</td>
<td>43</td>
<td>47</td>
<td>14</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>83</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Freiha et al. [26]</td>
<td>0.74</td>
<td>0.36</td>
<td>1.53</td>
<td>27</td>
<td>28</td>
<td>13</td>
<td>17</td>
<td>45</td>
<td>5</td>
<td>15</td>
<td>35</td>
<td>70.0</td>
</tr>
<tr>
<td>Otto et al. [27]</td>
<td>0.82</td>
<td>0.48</td>
<td>1.38</td>
<td>55</td>
<td>53</td>
<td>28</td>
<td>29</td>
<td>86</td>
<td>22</td>
<td>50</td>
<td>58</td>
<td>53.7</td>
</tr>
<tr>
<td>Skinner et al. [28]</td>
<td>0.75</td>
<td>0.48</td>
<td>1.19</td>
<td>50</td>
<td>52</td>
<td>34</td>
<td>40</td>
<td>69</td>
<td>22</td>
<td>58</td>
<td>33</td>
<td>36.3</td>
</tr>
<tr>
<td>Lehmann et al. [16]</td>
<td>0.57</td>
<td>0.31</td>
<td>1.05</td>
<td>26</td>
<td>23</td>
<td>20</td>
<td>20</td>
<td>41</td>
<td>8</td>
<td>20</td>
<td>29</td>
<td>59.2</td>
</tr>
<tr>
<td>Studer et al. [28]</td>
<td>1.02</td>
<td>0.57</td>
<td>1.84</td>
<td>46</td>
<td>45</td>
<td>23</td>
<td>32</td>
<td>57</td>
<td>20</td>
<td>70</td>
<td>7</td>
<td>9.1</td>
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<td>Italian [11]</td>
<td>1.29</td>
<td>0.84</td>
<td>1.99</td>
<td>102</td>
<td>92</td>
<td>46</td>
<td>38</td>
<td>165</td>
<td>18</td>
<td>96</td>
<td>87</td>
<td>47.5</td>
</tr>
<tr>
<td>Spanish [13]</td>
<td>0.38</td>
<td>0.22</td>
<td>0.65</td>
<td>68</td>
<td>74</td>
<td>24</td>
<td>45</td>
<td>126</td>
<td>16</td>
<td>62</td>
<td>80</td>
<td>56.3</td>
</tr>
<tr>
<td>Stadler et al. [14]</td>
<td>1.11</td>
<td>0.45</td>
<td>2.72</td>
<td>58</td>
<td>56</td>
<td>12</td>
<td>9</td>
<td>98</td>
<td>16</td>
<td>114</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
95% CIs provided to us by the authors. Using these updated numbers (Table 5), the pooled HR across all nine studies was 0.77 (95% CI, 0.59–0.99; p = 0.049) (Fig. 2). This translates to a 23% relative decrease in the risk of death when treated with adjuvant chemotherapy compared with control.

There was no heterogeneity in outcomes observed based on the Cochran Q statistic (p = 0.06) and an I² statistic of 46.5% (95% CI, 0–75). However, because there was a trend toward significance, we attempted to identify potential causes through meta-regression models to evaluate differences in outcome based on year of publication, total number of events, gender, and nodal status because this information was reported at the trial level in most of the trials included.

Meta-regression for gender was conducted on the absolute number of women reported in each trial and on the binary outcome of the ratio of women to men as greater or less.

### Table 5 – Sensitivity analyses for overall survival and disease-free survival

<table>
<thead>
<tr>
<th>Sensitivity analysis for overall survival</th>
<th>Pooled results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influence analysis: exclusion of each study to identify which one had the largest impact on the effect estimate</td>
<td></td>
</tr>
<tr>
<td>Original trials from Cochrane meta-analysis [35] and Spanish univariate HR [13] and Stadler et al. [14] and Italian [11] trials</td>
<td>HR: 0.777; p = 0.044; 95% CI, 0.607–0.994</td>
</tr>
<tr>
<td>Original trials from Cochrane meta-analysis [35] and Spanish multivariate HR [13] and Stadler et al. [14] and Italian [11] trials</td>
<td>HR: 0.766; p = 0.050; 95% CI, 0.587–0.999</td>
</tr>
<tr>
<td>Updated Stockle et al. [15] with Lehmann et al. [16] follow-up data</td>
<td>HR: 0.768; p = 0.049; 95% CI, 0.590–0.999</td>
</tr>
<tr>
<td>Exclusion of Studer et al. [29]: single-agent cisplatin</td>
<td>HR: 0.740; p = 0.042; 95% CI, 0.554–0.989</td>
</tr>
<tr>
<td>Inclusion of only Spanish [13] and Italian [11] studies: gemcitabine-based cisplatin chemotherapy regimens (differing from MVAC in most of the other trials)</td>
<td>HR: 0.706; p = 0.571; 95% CI, 0.212–2.351</td>
</tr>
<tr>
<td>Inclusion of only updated trials since prior Cochrane analysis: Lehmann et al. [16], Spanish [13], Stadler et al. [14], Italian [11]</td>
<td>HR: 0.736; p = 0.343; 95% CI, 0.391–1.386</td>
</tr>
<tr>
<td>Excluded Otto et al. [27] and Spanish trial</td>
<td>HR: 0.864; p = 0.227; 95% CI, 0.682–1.095</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity analysis for disease-free survival</th>
<th>Pooled results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influence analysis: exclusion of each study to identify which one had the largest impact on the effect estimate</td>
<td></td>
</tr>
<tr>
<td>Exclusion of Studer et al. [29]: single-agent cisplatin</td>
<td>HR: 0.63; p = 0.009; 95% CI, 0.44–0.89</td>
</tr>
<tr>
<td>Inclusion of only Spanish (2010) and Italian (2012) studies: gemcitabine-based cisplatin chemotherapy regimens (differing from MVAC in most of the other trials)</td>
<td>HR: 0.64; p = 0.393; 95% CI, 0.23–1.782</td>
</tr>
<tr>
<td>Exclusion of Spanish (2010) trial: unpublished, most positive results</td>
<td>HR: 0.77; p = 0.05; 95% CI, 0.55–0.999</td>
</tr>
</tbody>
</table>

CI = confidence interval; DFS = disease-free survival; HR = hazard ratio; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; OS = overall survival.

95% CIs provided to us by the authors. Using these updated numbers (Table 5), the pooled HR across all nine studies was 0.77 (95% CI, 0.59–0.99; p = 0.049) (Fig. 2). This translates to a 23% relative decrease in the risk of death when treated with adjuvant chemotherapy compared with control.

There was no heterogeneity in outcomes observed based on the Cochran Q statistic (p = 0.06) and an I² statistic of 46.5% (95% CI, 0–75). However, because there was a trend toward significance, we attempted to identify potential causes through meta-regression models to evaluate differences in outcome based on year of publication, total number of events, gender, and nodal status because this information was reported at the trial level in most of the trials included. Meta-regression for gender was conducted on the absolute number of women reported in each trial and on the binary outcome of the ratio of women to men as greater or less.
than 1. Meta-regression for nodal status was conducted on the absolute number of patients reported in each trial as N0 versus N1+ and on the binary outcome of the ratio of N1+ to N0 patients reported by each trial as greater or less than 1. We did not find any effect modification in any of these covariates (all meta-regression p values >0.05 for OS end point; results not shown).

3.3. Effects of interventions on secondary outcome of disease-free survival

The secondary outcome measured in this meta-analysis was DFS, defined across studies as time from radical cystectomy or randomization until the earliest occurrence of relapse, progression, or death. Table 6 enumerates the specific definitions of DFS as provided by each trial.

Table 6 also provides summary data for DFS. Meta-analysis of included trials resulted in an overall HR of 0.66 for DFS with adjuvant cisplatin-based chemotherapy (p = 0.014; 95% CI, 0.48–0.92). This translates to a 34% relative decrease in the risk of disease recurrence when treated with adjuvant chemotherapy compared with control. A forest plot summarizing DFS for all studies by chemotherapy type is shown in Figure 3.

Between-trial heterogeneity in outcomes was observed based on the Cochran Q statistic (p = 0.007) and I² = 63.7% (95% CI, 22–83). Potential reasons for this heterogeneity were explored through the same meta-regressions as previously described. Effect modification was present by the ratio of N1+ patients to N0 patients as reported at the trial level being greater or less than 1 (p = 0.006); this is visualized using a L’Abbé plot (Fig. 4). After stratification of studies by nodal ratio (Fig. 5), no further heterogeneity was identified, with an I² within each group of 0% (indicating that all of the observed heterogeneity was corrected for after stratifying on nodal ratio; p values for heterogeneity were also nonsignificant). The HR for DFS associated with adjuvant cisplatin-based chemotherapy in studies with higher nodal involvement was 0.39 (95% CI, 0.28–0.54), compared with an HR of 0.89 (95% CI, 0.69–1.15) in studies with less nodal involvement.

3.4. Sensitivity analyses

Various sensitivity analyses for both OS and DFS result were conducted and are summarized in Table 5.

3.5. Publication bias (quantitative)

For both OS and DFS, statistical tests did not indicate significant publication bias (Supplemental Fig. 1–3).

3.6. Quality assessment and qualitative risk of bias

Results of the risk of bias assessment are presented and detailed in Supplemental Table 1 and Supplemental Figure 4. Two main sources of biases of included trials include (1) an unblinded design that can bias results in favor of adjuvant chemotherapy, and (2) the decision to terminate...
trials early, for benefit of adjuvant chemotherapy [16], for low accrual rate [11,13,29], or for lack of benefit of adjuvant chemotherapy [26,29].

3.7. Discussion

In this updated meta-analysis, we found a positive benefit on OS for cisplatin-based adjuvant chemotherapy compared with no adjuvant chemotherapy following radical cystectomy in patients with MIBC. These results confirm the findings from previous meta-analyses, with significantly greater statistical power due to the inclusion of three additional trials [11,13,14] as well as the latest follow-up data from the original 1994 Stockle study [16]. Although this meta-analysis did not have access to individual patient data, unlike prior investigations, we explored the effect of positive lymph nodes and used improved statistical methods including random effects [19] and meta-regression models [22] to account for heterogeneity between studies.

Most RCTs of MIBC have historically had a relatively low number of enrolled patients. Of the seven published studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
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<tbody>
<tr>
<td>Cisplatin-based combinations:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skinner</td>
<td>0.73 (0.46–1.15)</td>
<td>14.66</td>
</tr>
<tr>
<td>Freha</td>
<td>0.46 (0.23–0.91)</td>
<td>10.78</td>
</tr>
<tr>
<td>Bono</td>
<td>0.75 (0.40–1.40)</td>
<td>11.73</td>
</tr>
<tr>
<td>Lehmann</td>
<td>0.35 (0.18–0.71)</td>
<td>10.56</td>
</tr>
<tr>
<td>Stadler</td>
<td>0.98 (0.45–2.12)</td>
<td>9.55</td>
</tr>
<tr>
<td>Subtotal (I² = 26.7%, p = 0.244)</td>
<td>0.62 (0.45–0.87)</td>
<td>57.28</td>
</tr>
</tbody>
</table>

| Single agent cisplatin: | | |
| Studer | 1.02 (0.58–1.81) | 12.54 |
| Subtotal (I² = .%, p = .) | 1.02 (0.58–1.81) | 12.54 |

| Gemcitabine-cisplatin combinations: | | |
| Spanish | 0.38 (0.25–0.58) | 15.14 |
| Italian | 1.08 (0.70–1.66) | 15.04 |
| Subtotal (I² = 91.3%, p = 0.001) | 0.64 (0.23–1.78) | 30.18 |

| Overall (I² = 63.7%, p = 0.007) | 0.66 (0.48–0.92) | 100.00 |

NOTE: Weights are from random-effects analysis.

**Fig. 3 – Disease-free survival for all studies by chemotherapy type. CI = confidence interval; ES = effect size.**

**Fig. 4 – Visualization of effect modification by lymph node status using a L’Abbé plot.**
included in our analysis, six trended toward a benefit of cisplatin-based adjuvant chemotherapy, whereas one did not, but none of the results were statistically significant. Prior to the two most recent trials, all published RCTs each enrolled <100 patients. Only one of the nine trials we include in our analysis reported statistically significant results. The Spanish trial, as yet unpublished, enrolled 142 patients and was the only trial demonstrating a statistically significant benefit of adjuvant chemotherapy with an HR of 0.38 (95% CI, 0.22–0.65) in favor of adjuvant chemotherapy versus observation, although with limited statistical power, with the trial closing early due to slow accrual [13]. In contrast, the Italian trial accrued 183 patients and reported a nonsignificant HR of 1.29 (95% CI, 0.84–1.99) [11].

It is notable that these two most recent trial results with which we have updated previous analyses provide conflicting estimates of the effect of adjuvant chemotherapy on OS, with HRs ranging from 0.38 [13] to 1.29 [11], with nonoverlapping 95% CIs. This might be due to the different chemotherapy regimens used, with the Spanish centers adding paclitaxel to the gemcitabine/cisplatin regimen that has shown a trend to improved survival benefit when compared with the dual regimen in advanced disease [42]. Of note, in sensitivity analyses these two most recent trials also had the largest influence on the results, with exclusion of the Spanish trial resulting in the least favorable pooled effect estimate, and exclusion of the Italian trial resulting in the most positive pooled effect estimate.

With regard to the secondary outcome of DFS, we found stronger evidence supporting the benefit of cisplatin-based adjuvant chemotherapy. Most studies agreed on the definition of “progression-free” survival (time to relapse or disease-related death) but did not clarify the censoring of patients who died from alternative causes, suggesting a tentative but incompletely confirmed basis of comparison of results across studies. Additionally, across trials there were different starting points for the secondary outcome, with some defining it as time from radical cystectomy and others defining it as time from randomization until the earliest occurrence of relapse or death from any cause. The time at which patients were randomized also differed. These may lead to minor differences in the length of DFS. Interestingly, we found that the differences in DFS outcomes between trials may be explained by the more positive results for adjuvant chemotherapy observed in trials with a greater proportion of patients with positive lymph nodes. This may imply there was a greater absolute benefit in treating patients with nodal involvement, suggesting nodal involvement could be a relative indication for adjuvant chemotherapy. Unfortunately, this finding was not replicated in terms of OS, perhaps due to insufficient statistical power.

It was challenging to account for differences in chemotherapy regimens and adherence among patients in nine different trials. Thus because the current trend is to use cisplatin combination chemotherapy, we conducted a sensitivity analysis by excluding the trial with single-agent cisplatin (Table 5) [29] and found that the pooled HR for both OS and DFS decreased from 0.77 to 0.74 and 0.66 to 0.63 respectively, and hence may reflect and confirm the superior efficacy of the cisplatin combination over single-agent chemotherapy regimens that underlies current oncologic practice.

A substantial percentage of patients randomized to the adjuvant chemotherapy arm in many trials did not complete all prespecified chemotherapy cycles. One possible reason is that many patients diagnosed with bladder cancer are elderly and may not tolerate the recommended

<table>
<thead>
<tr>
<th>Study ID</th>
<th>ES (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skinner</td>
<td>0.73 (0.46–1.15)</td>
<td>16.12</td>
</tr>
<tr>
<td>Studer</td>
<td>1.02 (0.58–1.81)</td>
<td>13.90</td>
</tr>
<tr>
<td>Bono</td>
<td>0.75 (0.40–1.40)</td>
<td>13.04</td>
</tr>
<tr>
<td>Italian</td>
<td>1.08 (0.70–1.66)</td>
<td>16.50</td>
</tr>
<tr>
<td>Subtotal (I^2 = 0.0%, p = 0.567)</td>
<td>0.89 (0.69–1.15)</td>
<td>59.56</td>
</tr>
<tr>
<td>Freiha</td>
<td>0.46 (0.23–0.91)</td>
<td>12.03</td>
</tr>
<tr>
<td>Lehmann</td>
<td>0.35 (0.18–0.71)</td>
<td>11.79</td>
</tr>
<tr>
<td>Spanish</td>
<td>0.38 (0.25–0.58)</td>
<td>16.61</td>
</tr>
<tr>
<td>Subtotal (I^2 = 0.0%, p = 0.852)</td>
<td>0.39 (0.28–0.54)</td>
<td>40.44</td>
</tr>
<tr>
<td>Overall  (I^2 = 67.2%, p = 0.006)</td>
<td>0.64 (0.45–0.91)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Fig. 5 – Stratification of studies by nodal ratio. CI = confidence interval; ES = effect size.**
number of chemotherapy cycles well. In the six published trials for which we could evaluate the percentage of patients who received three or more cycles of chemotherapy, only two trials [25,26] had adjuvant chemotherapy adherence near 90%, with other trials having between 52% and 74% adherence [11,15,16,28,29]. We chose to base our results on an intention-to-treat analysis, and although effect estimates may be diluted using intention to treat given the substantial rates of nonadherence in these trials, intention-to-treat analysis is considered the gold standard in terms of minimizing potential biases [30].

Based on our assessment of risk of bias, we conducted a sensitivity analysis excluding two trials available only in abstract form [13,27]. Largely due to the important influence of the Spanish trial on the pooled effect estimate, the results of this sensitivity analysis showed nonsignificant results in regard to OS.

3.8. Limitations

Given the significant heterogeneity among published results, we used a more conservative random-effects statistical analysis to pool results [19]. Another limitation is our lack of access to individual patient data, preventing us from performing additional survival analyses adjusting for similar covariates. Additionally, across trials there were different definitions of our secondary outcome, DFS, with some defining it as time from radical cystectomy while others defined it as time from randomization until the earliest occurrence of relapse or death from any cause. The time at which patients were randomized also differed. These may lead to minor differences in the length of DFS. Overall, the size of this pooled meta-analysis across nine trials is still relatively small at n = 945. It is unclear whether the additional 242 patients from the EORTC phase 3 trial [12] will change our conclusions about OS and DFS. It is also important to state some of the flaws of earlier trials that can affect results. For example, three trials stopped early due to favorable interim results [15,26,28], and this can unduly influence the final results of a later meta-analysis [9]. Each trial has been assessed for risk for bias, which is reported in detail (Supplemental Table 1 and Supplemental Fig. 4). One of the earlier trials conducted by Stockle et al. [15] also had serious methodological flaws; most patients in the control arm who progressed did not receive any chemotherapy on relapse. Also, 8 of 26 patients (31%) in the treatment arm did not end up receiving chemotherapy. Another limitation was the variation in the eligibility criteria in terms of baseline severity. For example the Spanish trial selected pT3 or N+ patients only, which could explain why this trial was able to show a significant benefit because the patients had by default more advanced disease. In contrast, the Italian trial, which did not show a benefit for cisplatin-based adjuvant chemotherapy, had nearly a third of patients with pT1–2 disease [11]. Finally, given the lack of sufficient information on T stage in the source publications for this meta-analysis, meta-regression could not be performed to examine the impact of T stage at time of radical cystectomy on the benefit from adjuvant chemotherapy.

Two ongoing studies are presently investigating adjuvant chemotherapy for MIBC patients. The MAGNOLIA study is a placebo-controlled phase 2 clinical trial to evaluate the safety and effects of reCMAGE-A3 plus AS15 cancer immunotherapeutic product in subjects with MAGE-A3–positive MIBC after radical cystectomy [31]. The Ad/HER2/Neu phase 1 trial tests a therapeutic cancer vaccine in the adjuvant setting (adjuvant bladder cancer patients) characterized by human HER2/Neu expression [32].

The implications of our updated meta-analysis on routine clinical practice of those who care for patients with bladder cancer are twofold. First, neoadjuvant chemotherapy for eligible patients should continue to be recommended for patients diagnosed with MIBC, due to the overwhelming level 1 evidence [4,33–35]. However, the reality is that neoadjuvant cisplatin-based chemotherapy remains underused even at high-volume academic centers [36,37]. Second, for cystectomized patients who have not yet received any chemotherapy, adjuvant cisplatin-based chemotherapy may be considered after accurate pathologic staging has been obtained, provided that postoperative complications do not preclude them. In a 10-yr review of cystectomies at Memorial Sloan-Kettering Cancer Center, 64% of patients (735 of 1142) experienced one or more complications within 90 d of surgery, with about 30% (347 of 1142) not able to receive adjuvant chemotherapy due to postoperative complications [38]. Nevertheless, it is important to note the advantage of adjuvant chemotherapy is its ability to direct systemic therapy based on complete pathologic staging. We believe that high-risk patients, such as those with extravesical and/or node-positive disease, will most likely benefit [33]. This might explain why adjuvant chemotherapy is more frequently administered in North America than neoadjuvant chemotherapy (22% vs 12% of T2–4a N0M0 bladder cancer patients) [6].

4. Conclusions

Our updated meta-analysis of nine randomized trials, which now includes 945 patients, has found a benefit for OS and DFS in MIBC patients who underwent adjuvant chemotherapy after radical cystectomy compared with those who underwent surgery alone. The positive findings of our analysis, which are consistent with previous results in terms of magnitude of benefit of adjuvant chemotherapy, provide greater confidence in the therapeutic benefit of cisplatin-based adjuvant chemotherapy, particularly given the conservative random-effects statistical analysis used, adding to the robustness of the findings. Additionally, updated statistical meta-analysis techniques allowed us to identify the new finding that lymph node–positive patients benefit more than lymph node–negative patients in terms of DFS. This present meta-analysis strengthens the evidence behind the beneficial role of cisplatin-based adjuvant chemotherapy in MIBC.

Author contributions: Joaquim Bellmunt had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition of data: Leow, Martin-Doyle, Rajagopal, Patel, Anderson, Rothman, Bellmunt.

Analysis and interpretation of data: Leow, Martin-Doyle, Rajagopal, Patel, Anderson, Rothman, Bellmunt.

Drafting of the manuscript: Leow, Martin-Doyle, Rajagopal, Patel, Anderson, Rothman, Bellmunt.

Critical revision of the manuscript for important intellectual content: Leow, Martin-Doyle, Rajagopal, Patel, Anderson, Rothman, Cote, Urun, Chang, Choueiri, Bellmunt.

Statistical analysis: Leow, Martin-Doyle, Rajagopal, Patel, Anderson, Rothman, Bellmunt.

Obtaining funding: Chang, Choueiri, Bellmunt.

Administrative, technical, or material support: Chang, Choueiri, Bellmunt.

Supervision: Chang, Choueiri, Bellmunt.

Other (specify): None.

Financial disclosures: Joaquim Bellmunt certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.eururo.2013.08.033.

References


