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Review—Bladder Cancer

Adjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data

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Abstract

Objectives: To evaluate the effect of adjuvant chemotherapy in invasive bladder cancer.

Methods: We conducted a systematic review and meta-analysis of updated individual patient data from all available randomised controlled trials comparing local treatment plus adjuvant chemotherapy versus the same local treatment alone.

Results: Analyses were based on 491 patients from six trials, representing 90% of all patients randomised in cisplatin-based combination chemotherapy trials and 66% of patients from all eligible trials. The power of this meta-analysis is clearly limited. The overall hazard ratio for survival of 0.75 (95% CI 0.60–0.96, $p = 0.019$) suggests a 25% relative reduction in the risk of death for chemotherapy compared to that on control. Cox regression suggests that small imbalances in patient characteristics do not bias the results in favour of chemotherapy. However, the impact of trials that stopped early, of patients not receiving allocated treatments or not receiving salvage chemotherapy is less clear.

Conclusions: This IPD meta-analysis provides the best evidence currently available on the role of adjuvant chemotherapy for invasive bladder cancer. However, at present there is insufficient evidence on which to reliably base treatment decisions. These results highlight the urgent need for further research into the use of adjuvant chemotherapy. The results of appropriately sized randomised trials, such as the ongoing EORTC-30994 trial are needed before any definitive conclusions can be drawn.

Keywords: Systematic review; Meta-analysis; Randomised controlled trials; Cancer; Bladder; Chemotherapy

1. Introduction

Bladder cancer is the second most common cancer of the genito-urinary system. Worldwide, more than 100,000 cases of muscle invasive or advanced disease are diagnosed per year [1], with around 80% occurring in men.

Over the last 25 years a number of randomised controlled trials (RCTs) have compared local treatment plus adjuvant chemotherapy with local treatment alone ([2–9] and Otto et al., unpublished; Omura et al., unpublished and Allen et al., unpublished). Unfortunately, these trials have been small and lacked the statistical power to be able to reliably assess any effect of chemotherapy.

A previous systematic review of published trials [10] concluded that there was no good evidence to suggest that adjuvant chemotherapy improved the survival of patients with invasive bladder cancer. Furthermore, the reviewers noted a number of flaws in the design and reporting of the trials. A subsequent review of four trials that used cisplatin-based combination

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chemotherapy [4,6–8] concluded that the trials provided insufficient evidence to support the routine use of this type of adjuvant chemotherapy in invasive bladder cancer [11]. Criticisms raised by these reviewers related to the design, analysis and reporting of the trials. Firstly, all of the individual trials were underpowered to detect moderate differences between the two arms. Some of the methods used to analyse the individual trials were questionable, for example; not using conventional log rank tests to compare treatment and control arms; including non-randomised patients and excluding randomised patients, thereby not conducting an intention-to-treat analysis. Furthermore, some trials did not clearly define endpoints or report sufficient details of the survival analyses, focussing instead on subgroup analyses based on very small numbers of patients.

Therefore in June 2001, we initiated a systematic review and meta-analysis of individual patient data (IPD), which involves the central collection, validation and re-analysis of all randomised patients from all relevant trials. This meta-analysis was initiated and coordinated by the Medical Research Council (UK) Clinical Trials Unit and was part of a larger project encompassing neoadjuvant chemotherapy and concurrent chemotherapy, the results of which have already been published [12]. Use of data from individual patients has many advantages [13] that are particularly pertinent in this comparison. With IPD, the ability to carry out detailed data checking and conduct intention-to-treat analysis using appropriate statistical methodology may overcome problems relating to the quality of the original analyses and combining the results of all trials in a meta-analysis will increase the power to detect realistic treatment differences. Therefore, using this methodology, we aimed to provide a better evidence base with which to judge the effect of adjuvant chemotherapy on invasive bladder cancer.

2. Methods

We aimed to assess the effect of adjuvant chemotherapy plus standard local treatment (radical cystectomy, radical radiotherapy or preoperative radiotherapy and cystectomy) versus the same local treatment alone. A detailed, pre-specified protocol was followed which set out the objectives, inclusion criteria for trials, data to be collected, and analyses to be done. A copy of the protocol is available on request.

2.1. Trial Inclusion Criteria

To be included in the meta-analysis, trials had to be properly randomised. They should also have aimed to randomise patients with biopsy proven, invasive (i.e. clinical stage T2–T4a) transitional cell carcinoma of the bladder to receive local definitive treatment with or without adjuvant chemotherapy. The comparison had to be unconfounded by additional agents or interventions. The same local treatment should have been used on each arm, i.e. control and experimental arms had to differ only by the addition of chemotherapy. Trials should be closed to patient accrual, with the aim of including all trials that had completed patient recruitment at the time of the final data collation.

2.2. Identification of trials

To limit publication bias, published and unpublished trials were included. Computerised bibliographic searches of Medline and CancerLit were done using a version of the Cochrane Collaboration optimal search strategy [14]. These were supplemented by a search of the Cochrane Central Register of Controlled Trials and by hand searches of the reference lists of identified trials, bibliographies of relevant books and review articles. The National Cancer Institute PDQ (Physicians Data Query) Clinical Protocols, United Kingdom Coordinating Committee for Cancer Research trials register and the Current Controlled Trials metaRegister of trials were also searched to identify unpublished and ongoing trials. All trialists who took part in the meta-analysis were asked to help to identify additional trials. Initial searches were completed for the period up to and including January 1st, 2001. These were revised regularly to identify any additional new material that had appeared by our final analyses in September 2004. Two reviewers independently assessed all titles identified by search strategies for relevance and full papers were obtained for all potentially relevant titles. Where there was uncertainty about the eligibility of a trial or particular treatment arms within a trial, this was discussed and resolved by consensus within the project Secretariat, the international Advisory Group and the members of the ABC Collaborators' Group.

2.3. Data collected

Up-to-date individual patient information on date of randomisation, survival, local recurrence, metastases and date of last follow-up was sought. Details of treatment allocated, age, sex, TNM category, grade, performance status, tumour diameter, renal function and pre-treatment haemoglobin were also collected. To reduce potential bias [15], information was requested for all randomised patients including those who had been excluded from the investigators' original analyses.

2.4. Data checking

A number of standard checks were applied to all incoming trials, including checks for missing values, data validity and consistency across variables. To assess the randomisation integrity, we looked for unusual patterns in the sequencing of allocation or imbalances in baseline characteristics between treatment arms. Follow-up of patients still alive was also assessed to ensure that it was balanced by treatment arm and as up-to-date as possible. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician.

2.5. Definition of Endpoints

The primary endpoint of overall survival was defined as the time from randomisation until death. Patients still alive were censored at the date of last follow-up. Overall disease-free survival was defined as the time from randomisation until first recurrence or progression (after randomisation) or death, whichever occurred first. Loco-regional disease-free survival was defined as the time from randomisation to first loco-regional recurrence or progression (after randomisation) or death. Metastases-free survival was defined as

the time from randomisation to first metastases (after randomisation) or death. In each case, patients alive without disease were censored on the date of last follow-up. For all endpoints, death was defined as death by any cause.

2.6. Analysis and statistics

Analyses of all endpoints, subsets and subgroups were pre-specified in the protocol and carried out on an intention-to-treat basis; that is, patients were analysed according to their allocated treatment, irrespective of whether they received that treatment. Analyses of all endpoints were stratified by trial, and the log rank expected number of deaths and variance used to calculate individual trial hazard ratios and overall pooled hazard ratios (HR) based on the fixed effect model [16]. Thus, the times to event (recurrence, progression or death) for individual patients were used within trials to calculate the HR, representing the overall risk of an event for those patients allocated to adjuvant chemotherapy compared with those allocated to no chemotherapy.

To examine the potential impact of trial design and the treatments used, we prospectively planned analyses that grouped trials by important aspects that might influence the effect of chemotherapy. Groups were defined according to the type of the chemotherapy regimen and also by the local treatment. For each of these analyses, a pooled HR was calculated for each group of trials and for all trials together. A chi-square test for interaction was used to test whether there were any substantial differences in the effect of adjuvant chemotherapy between the trial groups. The effects of chemotherapy within subgroups of patients were investigated using similar analyses. Analyses were performed for each pre-specified subgroup, for example, comparing treatment and control for males and for females within each individual trial. These results were then combined to give overall HRs for males and for females. These analyses focused on the primary endpoint of overall survival. However they were conducted for the other endpoints to help support or refute any patterns found.

Results are also presented as absolute differences at three years, calculated using the overall HRs and the control arm event rate [17]. Confidence intervals for absolute differences were calculated from the baseline event rate and the HR at the 95% confidence interval boundary values. Chi-square heterogeneity tests were used to test for statistical heterogeneity across trials. We also calculated the I^2 statistic [18] to measure any inconsistency between the trials. Chi-square tests for interaction or trend were used to test for differences in outcome between subsets of trials or between subgroups of patients. Survival curves are presented as simple (non-stratified) Kaplan-Meier curves [19]. All p-values quoted are two-sided.

2.7. Exploratory analyses of survival

In addition to the planned analyses described, we conducted supplementary analyses to investigate some of the previous criticisms of these trials in more detail. To assess whether modest imbalances impact on (a) the results of individual trials and (b) the pooled results over all trials, we performed Cox regression analyses, stratified by trial, including in the model terms for age, sex, grade, pT and pN categories. Because data on every variable were not available for all patients from each trial, a proportion of patients were necessarily lost from these analyses. Therefore, we conducted a second, unadjusted Cox regression analysis stratified by trial based on the same subset of patients, so that direct comparisons could be made.

To investigate whether the collection and analysis of updated follow-up was able to counter any potential effects of early stopping in these trials, we estimated HRs from the trial publications using the reported statistics or from the survival curves [20] and compared these with HRs obtained from updated IPD.

3. Results

We identified 11 RCTs that had used adjuvant chemotherapy, all of which were potentially eligible for inclusion. We understand that one trial (Allen TD, unpublished) failed to recruit any patients and was therefore considered ineligible. One further trial had given chemotherapy both before and after local treatment [9] and was therefore considered separately [12]. This left 9 trials that were eligible for inclusion (Table 1). We were unable to locate data for two trials; one of 129 patients [2], and one of 80 patients [3]. A third trial (Omura, unpublished) closed early due to a lack of funding after randomising 42 patients. No data were available for this trial.

We therefore included 6 trials (Otto et al., unpublished and [4–8]) that randomised 498 patients (Table 1). IPD were supplied for 493 of these patients because data on 5/43 patients, who had been excluded from the investigators' own analyses, could not be obtained. The 493 patients include 90% (402 patients) of all patients randomised in adjuvant cisplatin-based combination chemotherapy trials and represent 66% of individuals from all known randomised trials.

Patient accrual for the individual trials ranged from 49 to 108. Design features of these trials are summarised in Table 1. For all of these trials, the planned local treatment was cystectomy and all trials used cisplatin-based chemotherapy; one as a single agent [5] and five in combination with one or more of methotrexate, vinblastine, cyclophosphamide and either doxorubicin or epirubicin. The planned cisplatin doses ranged from 90 mg/m^2 per cycle for 2 cycles to 100 mg/m^2 per cycle for 4 cycles, every 3–4 weeks.

Four of the six trials (293/493 patients) stopped early; three because the results of interim analyses favoured chemotherapy [4,6,7] and the fourth because interim results showed less benefit of chemotherapy than had been anticipated [5]. Updated follow-up was supplied for all surviving patients for two of these four trials [4,7] and for a proportion of the surviving patients from one further trial [5]. Further details are provided in Table 2. We found no good evidence that important patient characteristics such as age, grade or stage were imbalanced by arm for individual trials. For all trials

Table 1
Characteristics of eligible trials

Trial	Comparison	Stage	Adjuvant CT	Duration of CT	Local Treatment	No. patients randomised (excluded from investigators analyses)
Included trials						
Skinner et al.	S vs. S + CT	T3-T4, N+, M0	Cisplatin 100 mg/m^2 Cyclophosphamide 600 mg/m^2 Doxorubicin 60 mg/m^2	4 × 4-weekly cycles	Cystectomy	102 (12)
Bono et al.	S vs. S + CT	T2-T4a, N0, M0	Cisplatin 70 mg/m^2 Methotrexate 40 mg/m^2	4 cycles	Cystectomy	93 (12)
Studer et al.	S vs. S + CT	T1 (grade2) – T4	Cisplatin 90 mg/m^2	2 × 4-weekly cycles	Cystectomy	91 (14)
Freiha et al.	S vs. S + CT	T3b-T4, any N, M0	Cisplatin 100 mg/m^2 Methotrexate 30 mg/m^2 Vinblastine 4 mg/m^2	4 × 3-weekly cycles	Cystectomy	55 (5)
Stockle et al.	S vs. S + CT	T3b-T4a	Cisplatin Methotrexate Vinblastine Doxorubicin	3 cycles	Cystectomy	49 (0)
Otto et al.	S vs. S + CT	T3, N1-2, M0	Cisplatin 70 mg/ m^2 Methotrexate 30 mg/m^2 Vinblastine 3 mg/m^2 Epirubicin 45 mg/m^2	3 × 4-weekly cycles	Cystectomy	108 (0)
Subtotal						498 (43)
Unavailable trials						
Richards	RT vs. RT + CT	T3, Nx, M0	Doxorubicin 50 mg/m^2 5-FU 500 mg/m^2	At least 4 × 3-weekly cycles	Radiotherapy	129
Einstein	RT + S vs. RT + S +CT	T2-T4a, N0-3, M0	Cisplatin 70 mg/m^2	8 × 3-weekly cycles	Radiotherapy + Cystectomy	80
Omura	RT + S vs. RT + S + CT	Unknown	Cisplatin 60 mg/m^2 Doxorubicin 40 mg/m^2 Cyclophosphamide 400 mg/m^2	6 × 4-weekly cycles	Radiotherapy + Cystectomy	42
Total (all trials)						749

together, there was a slight imbalance by age group, although the median age was comparable in both arms (Table 3).

Data on allocated treatment were missing for two patients from one trial [8] and therefore these patients are excluded from the analyses. Patients' characteristics for the remaining 491 patients across all trials are shown in Table 3. Data for age and sex were provided for all trials. Pathological T and N categories and grade were supplied for five trials. Performance status, tumour diameter and renal function could only be supplied in full for one trial, although two others were able to provide some data on renal function. Pre-treatment haemoglobin was not supplied in full for any of the trials. Based on these available data, patients were mostly male with a median age of 62 years (range 23–85 years). They had tumours that were predominantly pT3, grade 3. The median follow-up for all surviving patients was 5.2 years (range 0.1–14.8 years).

3.1. Overall Survival

Survival analyses were based on 283 events and 491 patients from 6 trials. Fig. 1 shows that the confidence intervals around the estimated HR for these trials are wide and so the individual results are inconclusive. There was no clear evidence of statistical heterogeneity or inconsistency between the trials ($\chi^2 = 2.25$, $p = 0.814$; $I^2 = 0\%$). The overall hazard ratio of 0.75 (95% CI 0.60–0.96) represents a 25% relative decrease in the risk of death on chemotherapy compared with that on control. This is conventionally significant ($p = 0.019$), and is equivalent to an absolute improvement in survival of 9% (95% CI 1%–16%) at 3 years. With this number of patients, it is possible to reliably detect an absolute effect in the order of 15% (80% power, 5% significance). The survival curve for these results is shown in Fig. 2.

Pre-planned analyses grouping trials according to whether cisplatin was used or not, or by the type of local treatment employed were not possible, as all trials

Table 2
Summary of trial details (included trials only)

	Bono	Freiha	Skinner	Studer	Stockle	Otto
Randomisation/allocation method	Central; blocked in groups of 10	Simple randomisation: sealed envelope	Central telephone; minimisation	Stratified by nodal status	Locked randomisation list	Central telephone; permuted blocks
Patients randomised	93	55	102	91	49	108
Patients excluded by investigator	12	5	11	14	0	0
No. excluded patients reinstated in the meta-analysis	9	1	11	14	N/A	N/A
Stopped early	No	Yes (planned accrual 40 pts per arm)	Yes	Yes	Yes	No
Reason for early stopping	N/A	Patients in control arm performed better than anticipated therefore many more patients (≫80 planned) would have been needed to show difference in survival	Planned analysis after 75 pts showed benefit of CT ($p = 0.05$). Decision was to continue trial for further 2 years	Interim analysis of 80 patients showed smaller difference than expected. Accrual rate too low therefore stopped trial	Significant advantage in favour of CT for RFS ($p = 0.0015$)	N/A
Accrual period	Aug 1983–Oct 1987	Mar 1986–Oct 1991	Jul 1980–May 1989	Jan 1984–May 1989	May 1987–Aug 1990	Jan 1993–Jun 1999
Follow-up updated	20 patients (8.76–18.44 years)	No	28 patients (11.51–20.25 years)	6 patients (12.76–17.29 years)	10 patients (13.83–16.13 years)	Not necessary follow-up up-to-date
Follow-up not updated	24 patients (0.57–3.62 years)	21 patients (2.17–7.75 years)	N/A	30 patients (3.06–8.20 years)	N/A	51 patients (0.65–7.18 years)
Median follow up	3.45 years	5.08 years	14.54 years	6.09 years	14.83 years	3.62 years
No. lost to follow-up	3	0	0	10	0	0
Follow-up balanced by arm	Yes	Yes	Yes	Yes	Yes	Yes

Table 3
Characteristics of 491analysed patients

Subgroup	Adjuvant chemotherapy (246 patients)	No adjuvant chemotherapy (245 patients)	Total (491 patients)
Age*			
Median age (interquartile range)	61.5 (55–67)	62.0 (57–68)	62.0 (56–67)
Range	23–76	30–85	23–85
<55	60 (24%)	43 (18%)	103 (21%)
55–64	92 (37%)	105 (43%)	197 (40%)
≥65	94 (38%)	97 (40%)	191 (39%)
Unknown	0	0	0 (0%)
Sex*			
Male	205 (83%)	196 (80%)	401 (82%)
Female	41 (17%)	49 (20%)	90 (18%)
Unknown	0	0	0
pT category†			
T0–1	10 (5%)	8 (3%)	18 (4%)
T2	25 (10%)	35 (14%)	60 (12%)
T3	144 (59%)	147 (60%)	291 (59%)
T4	37 (15%)	33 (13%)	70 (14%)
Unknown	30 (12%)	22 (9%)	52 (11%)
pN category‡			
N0	149 (61%)	156 (64%)	305 (62%)
N1/N2	85 (35%)	81 (33%)	166 (34%)
NX/unknown	12 (5%)	8 (3%)	20 (4%)
Grade[a]			
G0–G1	7 (3%)	9 (4%)	16 (3%)
G2	30 (12%)	30 (12%)	60 (12%)
G3	155 (63%)	155 (63%)	310 (63%)
G4	40 (16%)	40 (16%)	80 (16%)
Unknown	14 (6%)	11 (4%)	25 (5%)

NB Unknowns are largely as a result of trials not collecting all of the data items requested.
* Data supplied for all trials.
† Data supplied for all trials but with a large proportion of missing data for two trials [5,6].
‡ Data supplied for all trials but with a large proportion of missing data for one trial [5].
[a] Data supplied for all trials but with a large proportion of missing data for two trials [5,7].

used cystectomy as the local treatment and used a cisplatin-based chemotherapy regimen. However, an analysis of trials grouped according to whether they had used single-agent cisplatin or cisplatin-based combination chemotherapy was possible, although it was limited by small numbers and the fact that only one trial used single agent cisplatin therapy. The hazard ratio (HR) for the one trial that gave cisplatin as a single agent was 1.02 (95% CI 0.57–1.84, $p = 0.945$, Fig. 1). For the group of five trials (400 patients) that used cisplatin-based combination chemotherapy the pooled HR of 0.71 (95% CI 0.55–0.92, $p = 0.010$) represents a 29% relative decrease in the risk of death on chemotherapy compared to that on control (Fig. 1). There was no evidence of a difference in the effect of chemotherapy between these two groups of trials (interaction $\chi^2 = 1.20$, $p = 0.237$).

3.2. Disease-free survival

Data on overall disease-free survival was supplied for five trials including 383 patients and 239 events. One trial could not provide data on recurrence or metastases and so could only be included in the analysis of overall survival (Otto et al., unpublished). The overall HR of 0.68 (95% CI 0.53–0.89) represents a 32% relative decrease in the risk of recurrence or death on chemotherapy compared to that on control ($p = 0.004$). There was no clear evidence of statistical heterogeneity or inconsistency between the trials ($\chi^2 = 4.80$, $p = 0.308$; $I^2 = 0\%$). This is equivalent to an absolute improvement in disease-free survival of 12% (95% CI 4%–19%) at 3 years. For the group of four trials (292 patients) that used cisplatin-based combination chemotherapy the combined HR of 0.62 (95% CI 0.46–0.83, $p = 0.001$) represents a 38% relative decrease in the risk of recurrence or death on chemotherapy compared to that on control.

Data on locoregional disease-free survival and metastases-free survival were only available for 2 trials that included 192 patients, with 113 events (locoregional disease-free survival) and 115 events (metastases-free survival). These analyses were therefore extremely limited due to the low numbers of patients and are not presented here. Further details are available on request.

3.3. Subgroup analyses

Predefined patient subgroups analyses were extremely limited due to the low numbers of patients and are therefore, exploratory in nature. Nevertheless, we found no evidence to suggest that chemotherapy was any more (or less) effective in any of the patient subgroups based on age, sex, grade, pT and pN category. Further pre-planned analyses of performance status, pre-treatment haemoglobin and tumour diameter were not possible because sufficient data were not available.

3.4. Exploratory analyses of survival

3.4.1. Cox regression analyses

Although based on fewer patients and events than the log rank tests, the results for the unadjusted Cox model were broadly similar to those from the log rank test, both for all trials and for the combination chemotherapy trials together (Table 4). Overall, there was a slight imbalance by age across all trials, with a slightly higher proportion of younger patients in the chemotherapy arm than the in the control arm. This

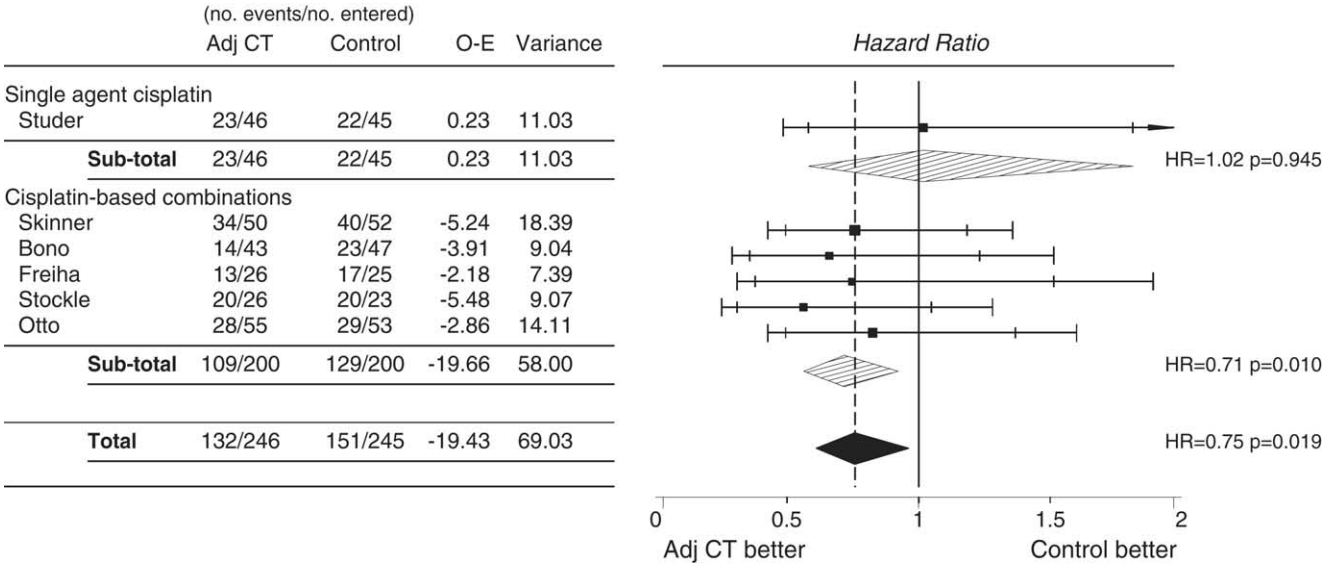

Fig. 1. Hazard ratio plot for survival. Each individual trial is represented by a square, the centre of which denotes hazard ratio for that trial; extremities of horizontal bars denote 99% CI and inner bars mark 95% CI. Size of square is directly proportional to amount of information in the trial. The black diamond gives the overall hazard ratio for combined results of all trials; the centre denotes hazard ratio and the extremities the 95% CI. The shaded diamonds represent hazard ratios for the trial groups; the centre denotes the hazard ratio and the extremities the 95% CI. Trials are ordered chronologically by date of start of trial (oldest first).

meant that when the model was adjusted for age alone, the estimate of effect moved towards equivalence compared with the unadjusted analysis. However, when all of the baseline characteristics (age, sex, grade, pT and pN) were taken into account, the Cox regression survival analysis tended more in favour of adjuvant chemotherapy, suggesting that overall, the proportion of poor prognosis patients was greater in the chemotherapy arm.

3.4.2. Comparison with published results

For the three trials that stopped early and provided updated follow-up [4,5,7] HRs based on the original reported analyses were estimated using data presented in the publications of the individual trials. These were compared with HRs calculated from updated IPD. For each of the three trials, the HRs estimated at the time of the original analysis were more strongly in favour of adjuvant chemotherapy than those obtained from the updated IPD (Table 5).

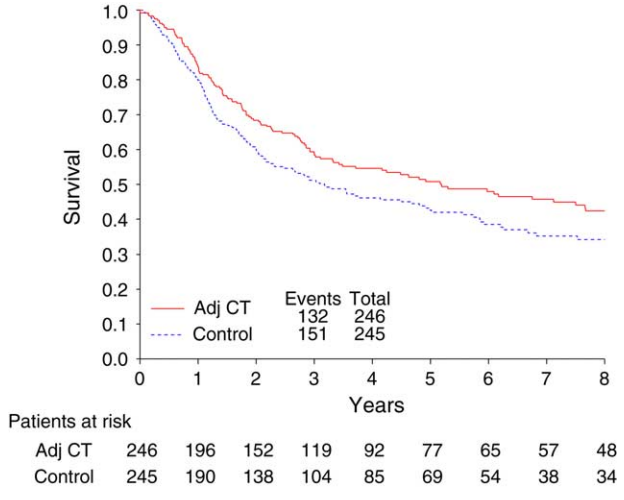

Fig. 2. Kaplan-Meier curve for survival (All trials).

4. Discussion

This meta-analysis aimed to address the question of whether adjuvant chemotherapy improves survival of patients with invasive bladder cancer. We obtained IPD for six trials, including 90% of the total patients randomised in adjuvant cisplatin-based combination chemotherapy trials (66% of the total randomised patients in all adjuvant chemotherapy trials). However, in spite of combining data from all of these trials, this meta-analysis was limited by small numbers, with only 491 patients and 283 deaths. The overall hazard ratio for all trials of 0.75 suggests an absolute improvement in survival of 9% (95% CI 1% to 16%) at 3 years; 11% (95% CI 3% to 18%) for those trials that used cisplatin-based combination chemotherapy. However, this analysis was further limited, to only 400 patients and 238 deaths and we are therefore unable to provide a definitive comment on the true effect of this therapy.

Because we have analysed IPD, we have been able to address some of the prior criticisms of these trials. For example, use of inappropriate or non-standard statistical tests, not reporting overall survival results

Table 4
Overall survival results from the Logrank test and Cox regression model

	Events	Patients	HR	95% CI	*p*-value
All trials					
Log rank test, stratified by trial	283	491	0.75	0.60–0.96	0.019
Unadjusted Cox model, stratified by trial	238	418	0.71	0.55–0.92	0.009
Cox model, stratified by trial (including arm and age only)	238	418	0.73	0.56–0.95	0.017
Cox model, stratified by trial (including arm, age, sex, grade, pathological T category and pathological N category)	238	418	0.69	0.53–0.89	0.005
Combination chemotherapy trials only					
Log rank test, stratified by trial	238	400	0.71	0.55–0.92	0.010
Unadjusted Cox model, stratified by trial	202	347	0.67	0.51–0.89	0.006
Cox model, stratified by trial (including arm and age only)	202	347	0.70	0.53–0.93	0.014
Cox model, stratified by trial (including arm, age, sex, grade, pathological T category and pathological N category)	202	347	0.65	0.49–0.86	0.003

and over-emphasing subgroup analyses based on very small numbers of patients. Furthermore, we found no clear imbalances in known prognostic factors such as age, pathological stage or grade between the arms of individual trials. Minor imbalances did not seem to bias the results in favour of adjuvant chemotherapy. However, even with the collection and re-analysis of IPD, there are some issues that we have not been able to address. In two trials [4,7] around a quarter of patients randomised to receive chemotherapy did not receive it; many received no chemotherapy at all and others received regimens other than those described in the trial protocol. The most likely influence of this on our results would be to dilute the apparent effect of chemotherapy. In contrast, four trials [4,6–8] did not specify salvage chemotherapy for patients on the control arm whose disease progressed or recurred, with a likely consequence of exaggerating the estimate in favour of chemotherapy. It should be noted though, that where such data were available, we found that many patients did in fact receive additional salvage treatments, including chemotherapy (Fig. 3). It is difficult therefore to assess the extent to which these conflicting factors could be influencing the results of this meta-analysis. Systematic removal of any of these patients could introduce other biases into the analysis.

Trials that stop early following favourable interim analyses can unduly influence the results of a meta-analysis, although obtaining updated follow-up may go some way to redressing the effects of trials that stopped on a 'random high', even without additional accrual into the trial [21]. However, if early treatment effects reflect differences between patients in the two treatment arms or some other type of selection bias, then extended follow-up is unlikely to make a difference. Any inflated benefits seen in early analyses are likely to persist. In this meta-analysis, three trials stopped early because of favourable interim results. The underlying reasons why the results of these trials led to their being stopped earlier than planned remain unclear. We have been able to show that in all of the individual trials, the arms are balanced at least in terms of known prognostic factors, such as age, sex, grade and pT category. However, other subtle imbalances in the known or perhaps more importantly, in unknown prognostic factors could exist. For those trials with extended follow-up a comparison of the results estimated from the trial reports [20] with the results obtained from updated IPD showed that the latter tended more towards equivalence with the estimate of treatment effect being reduced.

In interpreting these results, we should also consider that IPD for three further eligible trials (251

Table 5
Estimates of treatment effect from publications and from IPD with updated follow-up

Trial	Skinner[a]	Studer[b]	Stockle
Endpoint analysed	Survival	Survival	Disease-free survival[*]
% Patients with updated follow up since published analysis[**]	100	22	100
HR derived from published statistics or survival curves [20]	0.65	0.86	0.39
HR from IPD	0.75	1.02	0.45

[*] Disease free survival shown as overall survival was not presented in trial publication.
[**] Where date of analysis is not reported, it has been estimated as 12 months prior to date of report.
[a] Skinner trial HR derived from published survival curve.
[b] Studer trial only trial to have used single agent cisplatin chemotherapy.

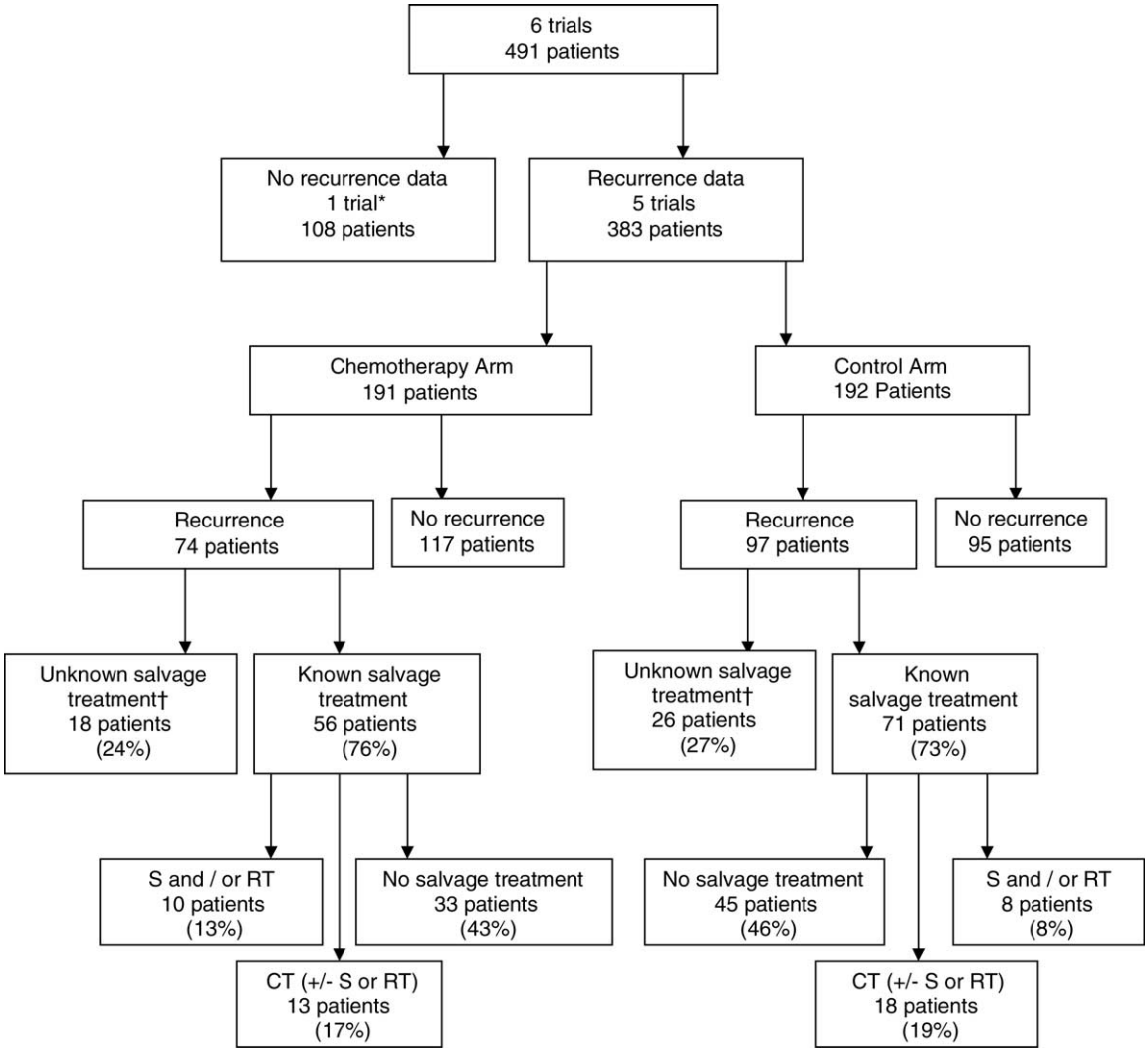

Fig. 3. Recurrence and treatment for recurrence flow diagram; * Otto et al (unpublished) supplied overall survival data only. Patients who recurred on the control arm received 2 cycles of MVEC (PJ Goebell, pers comm.). † Treatment on recurrence data not available for 3 trials [4–6]. However, for one trial [6] patients randomised to control were treated with standard CMV on first evidence of recurrence and for another trial [5] there was no restriction on patients randomised to control arm receiving chemotherapy on recurrence/progression. For the final trial [4] patients randomised to the control arm were not recommended to receive chemotherapy on recurrence. S—surgery; RT—radiotherapy; CT—chemotherapy.

patients) were unavailable. Despite the potential problems of using information from published analyses when IPD is not available, we thought it important to consider how the results of the unavailable trials might impact on these findings. However, one trial was never published [Omura et al., unpublished] and another did not publish survival data [3]. Therefore, we were only able to estimate a HR [20] for one trial of 129 patients [2]. The inclusion of this estimate (HR = 0.97) in a sensitivity analysis had little impact on the pooled HR estimate for the meta-analysis, changing it from 0.75 to 0.77. It should be acknowledged that this trial used a different local treatment (radiotherapy) to all of the other trials and was also unique in using a non-cisplatin based regimen. It is also worth noting that even if IPD had been available from all of the unavailable trials, we would have still fallen short of the 900 events needed to reliably detect a 9% absolute survival benefit with 80% power (5% significance).

Despite being limited by small numbers and by the caveats described, this IPD meta-analysis of all available data, using gold standard methodology, provides the best information currently available on the role of adjuvant chemotherapy for invasive bladder cancer. We conclude that the current evidence is clearly limited with too few trials and too few patients on which to base reliable treatment decisions. It is clear that the results of additional appropriately sized RCTs are required before a definitive answer can be obtained. Ongoing studies such as the EORTC-30994 trial and the USC p53 trial are therefore of particular impor-

tance. If these reach their recruitment targets, around 2000 additional patients will have taken part in relevant RCTs, and will provide the power needed to detect realistic treatment effects reliably. However, we recognise that adjuvant chemotherapy is already being used in the treatment of patients with invasive bladder cancer. The results presented here should encourage this only in the context of ongoing trials. We hope that the results draw the attention of the urological oncology community to consider the need for extensive participation in such ongoing and future randomised trials on this subject.

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Contributors: All aspects of the meta-analysis were carried out under the auspices of the ABC group. A.V. Bono, P.J. Goebell, S. Groshen, J. Lehmann, U. Studer, F.M. Torti, collated and supplied the individual patients data, contributed to the discussions of the results and commented on the drafts of the report. H. Abol-Enein, P. Bassi, M. Boyer, C.M.L. Coppin, E. Cortesi, R.R. Hall, A. Horwich, P.-U. Malmström, J.A. Martinez-Piñeiro, L. Sengeløv, A. Sherif, D.M.A. Wallace, contributed to the discussions of the results and commented on the drafts of the report. The project was organised by the Advisory Group, N.W. Clarke, J.T. Roberts, R. Sylvester and the Secretariat, M.K.B. Parmar, L.A. Stewart, J.F. Tierney, C.L. Vale, who were responsible for formulating the questions, developing the protocol and discussing the preliminary results. The secretariat, M.K.B. Parmar, L.A. Stewart, J.F. Tierney, C.L. Vale, were responsible for receiving, checking and analysing data. C.L. Vale, managed the project and drafted the report, with detailed input from J.F. Tierney, L.A. Stewart, M.K.B. Parmar. None of these authors have declared any conflict of interest in connection with this research.

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Editorial Comment

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The last published meta-analysis of neoadjuvant randomised trials [1] has demonstated for cisplatin based combination chemotherapy in invasive bladder cancer an absolute benefit overall survival of 6.5%. The principal advantages in the adjuvant setting are the absence of delay for surgery and the pathological evaluation allowing a more accurate selection of patients for systemic treatment. When the treatment effect is modest, the limited use of adjuvant chemotherapy to patients at the highest risk of relapse may produce the largest absolute benefits and avoid toxic but useless treatment to patients at low risk. The current data have been unable to reliably support the use of adjuvant therapy into standard oncology practice because of the lack of appropriate randomised studies. The first meta-analysis based on individual patient data published in the current issue [2] suggests an absolute improvement in survival of 9% at 3 years for chemotherapy compared to control, but its impact is clearly too limited and insufficient to be conclusive to support the routine use of adjuvant cisplatin-chemotherapy because of the low number of patients (491 patients). To clearly answer the question of its role, it is essential to include patients in the ongoing EORTC-30994 trial comparing after cystectomy immediate versus delayed chemotherapy (1300 patients planned).

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Editorial Comment

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The Advanced Bladder Cancer Meta-analysis Collaboration supported by the Medical Research Council Trial Unit has presented in this issue of European Urology an interesting meta-analysis of trials of adjuvant chemotherapy in infiltrating bladder cancer [1]. This study has clear limitations since the number of available trials was very limited: six randomised trials with 491 patients. It suggests a 25% decrease of the relative risk of death in the adjuvant chemotherapy patients population. This may translate in a 9% survival rate advantage at 3 years. However 900 events would be necessary to demonstrate this particular survival advantage with an α-risk of 5% and a power of 80%. Thus, in no case the conclusion of the study is that it demonstrates a survival advantage of adjuvant chemotherapy in localised bladder cancer. But conversely the conclusion of the study is that there are arguments to study adjuvant chemotherapy in localised bladder cancer. This may strongly encourage urologists and medical oncologists to include patients in prospective randomised trials in the USA and in Europe. In the South California University trial (4B-95-1 trial) patients with pN0 disease after radical cystectomy and who express p53 mutation in the tumour are randomised either to receive adjuvant chemotherapy (4 cycles of M-VAC (Methotrexate, Vinblastine, Adriamycine and Cisplatin)) or to have careful follow-up. In the EORTC 30994 trial, patients who have had radical cystectomy and who have pathological stages pT3-4a pN0-1 or pN1 (whatever was pT stage) are eligible for entry in the trial. Patients are randomised to receive either delayed chemotherapy after recurrence or immediate chemotherapy after cystectomy. The chemotherapy program is either four cycles of conventional M-VAC, accelerated (every two weeks) M-VAC or combination of Gemcitabine and Cisplatin.

There are two limitations to trial accrual. The first is the same limitation than in the neoadjuvant setting: namely creatinine clearance and less importantly age

and performance status [2]. In the past we have had the experience of feasibility of adjuvant chemotherapy after radical cystectomy: only 50% of patients who were proposed to receive chemotherapy, actually received it [3]. The causes which led to no administration of adjuvant chemotherapy were: low creatinine clearance, older age, poor performance status, major comorbidities and patients refusal. Even in the adjuvant chemotherapy randomised trials, the proportion of patients who actually received 3 or 4 cycles of chemotherapy was 50–70%: for example it is 52% in the University of South California trial [4]. Thus, patients who actually have participated to the randomised trials may be not representative of the overall patients population.

The second limitation to trial accrual is the routine administration of adjuvant chemotherapy in pN1 and even pT3 patients as it is done in the USA and often done in Europe. It is noteworthy that the US National Comprehensive Center Network recommends ''to consider adjuvant chemotherapy'' in these patients groups who are at high risk of recurrence after radical cystectomy [5]. Therefore, there is a great risk of not answering to the question on the actual role of adjuvant chemotherapy in localised bladder cancer. This is an important problem because not answering the question could lead to inappropriate use of adjuvant chemotherapy and unjustified over treatment, based on unproven results. However accrual in these trials is actually slow. This is a major concern. It could be proposed to all participating centres in these trials, to register all patients who had radical cystectomy, and then to prospectively register data on their evolution. This could allow to better manage the interpretation of these trials. Inclusion bias and representativeness of included patients may be known [6]. Moreover, if trials accrual is eventually to small to permit trials analyses, the results of chemotherapy and control patients groups who were treated outside the trials may help in the interpretation of treatments options results. This has been done in the past to demonstrate the activity of adjuvant chemotherapy in osteosarcoma [7]. It is noteworthy that osteosarcoma patients who received adjuvant chemotherapy both in the trial and in the routine settings had the same survival benefit when compared to the survival benefit of patients who had only local treatment without adjuvant chemotherapy. However, survival benefit was important (around 40% overall survival rate increase). Nonetheless, patients inclusion in prospective adjuvant chemotherapy trials is urgently needed and recommended in localised bladder cancer after cystectomy.

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Editorial Comment

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Careful study of this highly interesting paper confronts the reader with a difficult situation. On one side the overall hazard ratio for survival suggests an impressive 25% relative reduction in the risk of death for adjuvant chemotherapy compared to that of control; on the other side the authors conclude that there is insufficient evidence on which to reliably base treatment decisions. Why is that?

Criticism of previous trials:

There was major criticism raised against design, analysis and reporting of all previous trials: All of the individual trials were underpowered to detect moderate differences between the two arms. Some of these methods used to analyze the individual trials were questionable, for example: not using conventional log rank tests to compare treatment and control arms; including non-randomized patients and excluding randomized patients, thereby not conducting an intention-to-treat analysis. Furthermore, some trials did not clearly define endpoints or did not report sufficient details of the survival analyses, focussing on subgroup analyses instead based on very small numbers.

The authors conclude that the current evidence is clearly limited with too few trials and too few patients on which to base reliable treatment decisions.

Auxiliary measures:

The authors

(1) initiated a systematic review and meta-analysis of *individual patient data* (IPD), which involves the central collection, validation an re-analysis of all randomized patients from all relevant trials. Use of data from individual patients has many advantages that are particularly pertinent in this comparison. With IPD, the ability to carry out detailed data checking an conduct intention-to-treat analysis using appropriate statistical methodology may overcome problems relating to the quality of the original analyses and combining the results of all trials in a meta-analysis will increase the power to detect realistic treatment differences. Therefore, using this methodology, the authors aimed to provide a better evidence base with which to judge the effect of adjuvant chemotherapy on invasive bladder cancer.
(2) To reduce potential bias, information was requested for *all randomized patients including those who had been excluded* from the investigator's original analyses.
(3) *Follow-up of patients still alive* was also assessed to ensure that it was balanced by treatment arm and as up-to-date as possible.
(4) Analyses of all endpoints, subsets and subgroups were pre-specified in the protocol and carried out on an *intention-to-treat-basis*; that is, patients were analyzed according to their allocated treatment, irrespective of whether they received that treatment.
(5) To limit publication bias, published and *unpublished trials* were included.
(6) Four trials (4,6–8) did not specify salvage chemotherapy for patients on the control arm whose disease progressed or recurred, with a likely consequence of exaggerating the estimate in favour of chemotherapy.

Basic problem remains:

This meta-analysis would have still fallen short of the 900 events to reliably detect the 9% absolute survival benefit that was found in the metaanalysis with 80% power (5% significance), since the overall number of patients in the studies presented is too small to reach the needed power.

The authors final conclusion must be reiterated:

Extensive participation of urologists in ongoing and future randomized trials on this subject.