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Neo-adjuvant chemotherapy for invasive bladder cancer (Review)

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[Intervention Review]

Neo-adjuvant chemotherapy for invasive bladder cancer

Advanced Bladder Cancer Meta-analysis Collaboration¹

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ABSTRACT

Background

Controversy exists as to whether neoadjuvant chemotherapy improves survival in patients with invasive bladder cancer, despite randomised controlled trials (RCTs) involving over 3000 patients.

Objectives

To conduct a systematic review and meta-analysis of individual patient data to evaluate the effect of neoadjuvant chemotherapy on survival in patients with this invasive bladder cancer.

Search methods

MEDLINE and Cancerlit searches were supplemented with information from registers and by hand searching meeting proceedings and also by discussion with relevant trialists and organisations. These have been regularly updated until June 2003.

Selection criteria

Trials that aimed to randomise patients with biopsy proven invasive (i.e. clinical stage T2 to T4a) transitional cell carcinoma of the bladder to receive local definitive treatment with or without neoadjuvant chemotherapy were eligible for inclusion.

Data collection and analysis

We collected, validated and re-analysed updated data on all randomised patients from all available randomised trials, including 3005 patients from 11 RCTs. For all outcomes, we obtained overall pooled hazard ratios using the fixed effects model. To explore the potential impact of trial design we pre-planned analyses that grouped trials by important aspects of their design that might influence the treatment effect. To investigate any differences in effect by pre-defined patient subgroups we used a stratified logrank analysis on the primary endpoint of survival.

Main results

These results include data from one extra trial and so update those in the original publication ABC 2003. Platinum based combination chemotherapy showed a significant benefit on overall survival with a combined hazard ratio (HR) 0.86 (95% CI 0.77 to 0.95, $P = 0.003$); 14% reduction in the risk of death; 5% absolute benefit at 5 years (95% CI 1% to 7%); overall survival increased from 45% to 50%. This effect was observed irrespective of the type of local treatment and did not vary between subgroups of patients. The HR for all trials, including those that used single-agent cisplatin, tended to favour neoadjuvant chemotherapy (HR= 0.89, 95% CI 0.81 to 0.98, $P = 0.022$). Although platinum based combination chemotherapy was beneficial, there was no clear evidence to support the use of single-agent platinum, indeed there was significant difference in the effect between these groups of trials ($P = 0.029$).

Neo-adjuvant chemotherapy for invasive bladder cancer (Review)

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Authors' conclusions

This improvement in survival encourages the use of platinum based combination chemotherapy for patients with invasive bladder cancer.

PLAIN LANGUAGE SUMMARY

Adding chemotherapy before surgery and/or radiotherapy in patients with invasive bladder cancer.

The standard treatment for invasive bladder cancer is surgery (to remove the bladder and surrounding tissues), and/or radiotherapy (to kill the cancer cells). This review suggests that 50 out of 100 patients will be alive at five years, when they are given chemotherapy using a platinum drug in combination with other drugs, before having surgery and/or radiotherapy. This is compared to 45 out of every 100 patients who were given surgery and/or radiotherapy without chemotherapy. This benefit of platinum-based combination chemotherapy was seen in all types of patients and encourages its use for the treatment of invasive bladder cancer. However, chemotherapy based on a single platinum drug did not help patients live longer, and is not recommended.

BACKGROUND

Bladder cancer is the second most common cancer of the genitourinary system; 80% of all cases are in men. Worldwide estimates suggest that the frequency of bladder cancer is about 336,000 new cases per year (Parkin 1999), of which about a third are likely to be invasive or metastatic disease.

Neoadjuvant chemotherapy, given before local treatment, may reduce primary tumour volume and could be effective in the control of metastatic disease when the volume of micrometastases is likely to be small (Soloway 1981; Fagg 1984; Raghavan 1984). This could be important since about half of the patients who present with invasive disease are likely to have occult metastases. Furthermore, patients may best tolerate chemotherapy before they have received potentially debilitating local treatment with either surgery or radiotherapy. Local treatments may also affect drug delivery by altering blood supply especially to the tissues affected by the tumour (Martinez 1998). Therefore, neoadjuvant chemotherapy has the potential to deliver the drugs more efficiently and at higher doses than in the adjuvant setting and provides an opportunity to prospectively assess the response to chemotherapy.

Several randomised trials, most of which have included platinum-based regimens (Abol-Enein 1997; MRC/EORTC 1999; Bassi 1999; Cortesi (unpub); Malmstrom 1996; Martinez 1995; Raghavan 1991; Sengelov 2002; Shearer 1988; Sherif 2002; Grossman 2003) have been done to investigate the use of neoadjuvant chemotherapy. These trials, which have been undertaken over almost twenty years, have mostly been of modest size and shown inconclusive results. However, combining the results of all of the relevant randomised trials in a meta-analysis could provide

sufficient evidence and increase the statistical power to reliably assess the value of neoadjuvant chemotherapy in the treatment of invasive bladder cancer. In 1991, we initiated and coordinated a systematic review and meta-analysis of individual patient data from all of the existing trials that compared local definitive treatment with or without neoadjuvant systemic chemotherapy (ABCOC 1995). At that time, only four trials, including less than 500 patients, were available. The results showed no clear evidence of either benefit or harm from the treatment and it was concluded that further large-scale randomised evidence was necessary. Subsequent systematic reviews and meta-analyses based on summary data extracted from trial reports have been of limited value, because of their methodological limitations and because only a subset of the trials were published at the time (Parmar 1999; Sternberg 2001). No good evidence existed to suggest that neoadjuvant chemotherapy, with either cisplatin alone, or in combination with other agents, improved survival in this group of patients.

We therefore initiated a new systematic review and meta-analysis of individual patient data to build on the previous project and to collect, validate and re-analyse trial data on all randomised patients from all relevant trials. Use of data from individual patients has many advantages in such a meta-analysis (Stewart 1995). In particular, such data permit time-to-event analyses, which are extremely important in diseases where prolongation of survival, rather than cure, is anticipated for most patients. They also allow analyses to assess whether chemotherapy is more or less effective in different subgroups of patients. Importantly, there is evidence from the cancer field that meta-analyses based on data extracted from published reports can give different results from those based on updated individual patient data (AOCTG 1991; Stewart 1993;

Clarke 1998). Our meta-analysis was initiated and coordinated by the Medical Research Council (UK) Clinical Trials Unit.

OBJECTIVES

This meta-analysis forms the main part of a broader project looking at the effect of chemotherapy given in three different ways in invasive bladder cancer: (1) before local treatment (neoadjuvant); (2) during local treatment (concurrent) and (3) after local treatment (adjuvant). We followed a detailed prespecified protocol, which defines the objectives, inclusion criteria for trials, data to be obtained, and analyses to be done. A copy of the trial protocol is available on request. In the first part of the project we aimed to assess the effect of neoadjuvant chemotherapy plus standard local treatment (radical cystectomy, radical radiotherapy or preoperative radiotherapy plus cystectomy) versus the same local treatment alone. We also aimed to compare the effect of concurrent chemoradiotherapy plus local treatment with that of the same local treatment alone. Work is continuing on the separate question of adjuvant chemotherapy and results will be presented in due course.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the meta-analysis, trials had to be properly randomised and should have been closed to patient accrual at the time of the final data collation.

Types of participants

Trials should have aimed to randomise patients with biopsy proven invasive (i.e. clinical stage T2 to T4a) transitional cell carcinoma of the bladder.

Types of interventions

Patients should have been randomised to receive local definitive treatment with or without neoadjuvant 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.

Types of outcome measures

The primary endpoint of overall survival was defined as the time from randomisation until death. Living patients were censored on 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 happened first. Loco-regional disease-free survival was defined as the time from randomisation to first local recurrence or progression (after randomisation) or death. Metastases-free survival was defined as the time from randomisation to first metastases (after randomisation) or death. Patients alive without disease were censored on the date of last follow up. For all endpoints, death was defined as death by any cause.

Search methods for identification of studies

To limit publication bias, both published and unpublished trials were included. We searched MEDLINE and CancerLit databases using a version of the Cochrane Collaboration optimal search strategy (Dickersin 1994). These searches were supplemented 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. Trials that had not been published in the English language were not excluded. 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 June 2004. Two reviewers independently assessed all titles identified by search strategies for relevance. Abstracts were downloaded for all titles of potential relevance, and full papers obtained for all abstracts judged potentially relevant. In cases of uncertainty about the eligibility of a trial or particular treatment arms within a trial, the matter was discussed and resolved by consensus within the project secretariat and the international advisory group.

1. PT=RANDOMIZED-CONTROLLED-TRIAL
2. RANDOMIZED-CONTROLLED-TRIAL.DE.
3. RANDOM-ALLOCATION.DE.
4. DOUBLE-BLIND-METHOD.DE.
5. SINGLE-BLIND-METHOD.DE.
6. 1 OR 2 OR 3 OR 4 OR 5
7. PT=CLINICAL-TRIAL
8. CLINICAL-TRIAL#.DE.
9. (CLIN\$ WITH TRIAL\$.AB, TI.
10. ((SINGL\$ OR DOUBL\$ OR TREBL\$ OR TRIPL\$) WITH (BLIND\$ OR MASK\$)).AB, TI.
11. PLACEBO\$.DE.
12. PLACEBO\$.AB, TI.

13. RANDOM\$.AB, TI.
14. RESEARCH-DESIGN.DE
15. 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
16. CARCINOMA#.DE.
17. BLADDER-NEOPLASMS.DE.
18. BLADDER ADJ CARCINOMA\$.AB, TI.
19. BLADDER ADJ CANCER\$.AB, TI
20. BLADDER ADJ NEOPLASM\$.AB, TI.
21. (CANCER WITH BALDDER).AB, TI.
22. (CARCINOMA WITH BLADDER).AB, TI.
23. 16 AND 17
24. 18 OR 19 OR 20 OR 21 OR 22
25. 23 OR 24
26. DRUG-THERAPY#.DE
27. QS NEOPLASMS# WITH DT
28. 26 OR 27
29. RADIOTHERAPY#.DE
30. QS NEOPLASMS# WITH RT
31. 29 OR 30
32. SURGERY#.DE
33. QS NEOPLASMS# WITH SU
34. 32 OR 33
35. 28 OR 31 OR 34
36. SUPERFICIAL
37. 6 OR 15
38. 37 AND 25 AND 35
39. 38 NOT 36

Data collection and analysis

We sought up-to-date individual patient information on date of randomisation, survival status, local recurrence status, metastases status and date of last follow up. Details of treatment allocated, age, sex, TNM category, grade, performance status, tumour diameter, renal function and pre-treatment haemoglobin were also obtained. To reduce potential bias, we requested information for all randomised patients including those who had been excluded from the investigators' original analyses. All data were thoroughly checked (Stewart 1995) for consistency, plausibility and integrity of randomisation and follow up. Any queries were resolved and the final database entries verified by the responsible trial investigator or statistician.

Analyses of all endpoints, subsets and subgroups were pre-specified in the protocol and carried out on an intention-to-treat basis. Analyses of all of the 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) using the fixed-effect model (Yusuf 1985). [NB. Hazard Ratios calculated are labelled as Peto ORs in all of the forest plots.] 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 neoadjuvant 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, we calculated a pooled HR for each group of trials and for all trials together. A chi-square test for quantitative interaction was used to find out whether the effect of neoadjuvant chemotherapy differed substantially between the trial groups. These analyses focused on the primary endpoint of overall survival, however they were conducted for the other endpoints to help to support or to refute any patterns found. The effects of chemotherapy within subgroups of patients were investigated using similar stratified 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.

We also calculated absolute differences at five years, using the overall HRs and event rate on the control arm (Parmar 1995). Confidence intervals for absolute differences were calculated from the baseline event rate and the HR at the 95% confidence interval boundary values. Chi² heterogeneity tests (Stewart 1995) were used to test for statistical heterogeneity across trials. The power of this test is however acknowledged to be low and thus only gross statistical heterogeneity is likely to be detected. We used Chi-square tests for interaction or trend 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 (Kaplan 1958). All P values quoted are two-sided.

RESULTS

Description of studies

(1) Neoadjuvant Chemotherapy trials

We identified 14 randomised trials using neoadjuvant chemotherapy that were potentially eligible for inclusion. Three of these were subsequently found to be ineligible; one because it was confounded by the use of additional treatments in both arms (Ozono 1991), a second because chemoradiotherapy was used as the local treatment (Shipley 1998) and the third compared neoadjuvant with adjuvant chemotherapy (Millikan 2001). There were therefore 11 remaining trials eligible for inclusion and data were obtained for all of these. In our original publication (ABC 2003), one of these trials, including a total of 317 patients, was not available because the investigators felt unable to supply data for inclusion in the

meta-analysis prior to publication. This trial has now been published (Grossman 2003) and the investigators have supplied data for inclusion in this update of the original meta-analysis.

Individual patient data were supplied on 3005 patients from 11 randomised controlled trials (Abol-Enein 1997; MRC/EORTC 1999; Cortesi (unpub); Malmstrom 1996; Martinez 1995; Raghavan 1991; Sengelov 2002; Sherif 2002; Wallace 1991; Grossman 2003) representing 98% of individuals from all known, eligible randomised trials. Data were collected for 18 of the 51 randomised patients who had been excluded from the investigators' analyses of these ten trials and were reinstated in the meta-analysis. For the available trials, patient accrual ranged from 96 to 976. In six trials (Martinez 1995; Cortesi (unpub); Abol-Enein 1997; Bassi 1999; Sherif 2002; Grossman 2003) the planned local treatment was radical cystectomy, two used radical radiotherapy (Wallace 1991; Raghavan 1991) and one used pre-operative radiotherapy and cystectomy (Malmstrom 1996). Two trials used a combination of one or more of these local treatments (MRC/EORTC 1999; Sengelov 2002). All of the trials used platinum-based chemotherapy. Ten trials used cisplatin, either as a single agent (Martinez 1995; Raghavan 1991; Wallace 1991 (3 trials)) or in combination with one or more of doxorubicin / epirubicin, methotrexate and vinblastine (MRC/EORTC 1999; Bassi 1999; Cortesi (unpub); Malmstrom 1996; Sengelov 2002; Sherif 2002; Grossman 2003 (7 trials)). Cisplatin doses ranged from 70 mg/m² per cycle for 2 to 4 cycles to 100 mg/m² per cycle given in 2 to 3 cycles, every 2 to 4 weeks. One further trial used carboplatin in combination with methotrexate and vinblastine (Abol-Enein 1997). The carboplatin dose per cycle was 300 mg/m² given in 2 cycles at 3-week intervals.

Patient characteristics, which reflect the eligibility criteria of the included trials, are given in Table 1. Age, sex and clinical T stage data were provided for all trials. Grade and performance status were supplied for eight trials, and clinical N category for seven trials. Tumour diameter and renal function (recorded as glomerular filtration rate) were supplied in full for only one trial. Pre-treatment haemoglobin data could not be supplied in full for any of the trials. Based on the available data, patients were mostly male with a median age across all trials of 63 years (range 30 to 90 years) with good performance status and tumours that were predominantly T2 to T3. The median follow up for surviving patients across all trials is 6.4 years. For one trial (Wallace 1991), follow up could not be updated, however survival data for this trial had been included in the 1995 IPD meta-analysis conducted by the ABCOC 1995. These data were therefore included in our survival analysis. Two trials had only recorded survival and overall disease-free survival and so could not be included in the analyses of locoregional disease-free survival or metastases-free survival (Cortesi (unpub); Grossman 2003). One trial (Abol-Enein 1997) had only recorded overall disease-free survival and so could only be included in the analysis of this endpoint.

(2) Concurrent Chemoradiotherapy trials

Searches identified only one moderately sized eligible trial (Coppin 1996) for this comparison. One hundred two patients were randomised and patient characteristics are similar to those for the neoadjuvant trials, most were male with a median age of 64 years (range 39 to 75 years), good performance status and with tumours that were predominantly T2 to T3. Cisplatin was given at 100 mg/m² per cycle in 3 cycles every 2 weeks. The median follow up for living patients was just over 13 years.

(3) Neoadjuvant plus adjuvant chemotherapy trials

One trial compared chemotherapy both before and after local treatment with local treatment alone (Shearer 1988) and its results are presented alongside those of the neoadjuvant chemotherapy trials. The 398 patients in this trial were mostly male with a median age of 67 years (range 41 to 87 years) and all had T3 tumours. Methotrexate was given at 100 mg/m² per cycle for six cycles every 2 weeks. Patients in the chemotherapy arm also received a further 9 cycles of adjuvant methotrexate at 100 mg/m² per cycle every four weeks. The median follow up for living patients was slightly under 9 years. Data for 25 patients who had been excluded from the original analysis were unavailable.

Risk of bias in included studies

All data were thoroughly checked for validity, consistency, plausibility and integrity of randomisation and follow-up. Any queries were resolved and the final database entries verified by the responsible investigator, data manager or statistician.

Effects of interventions

Survival

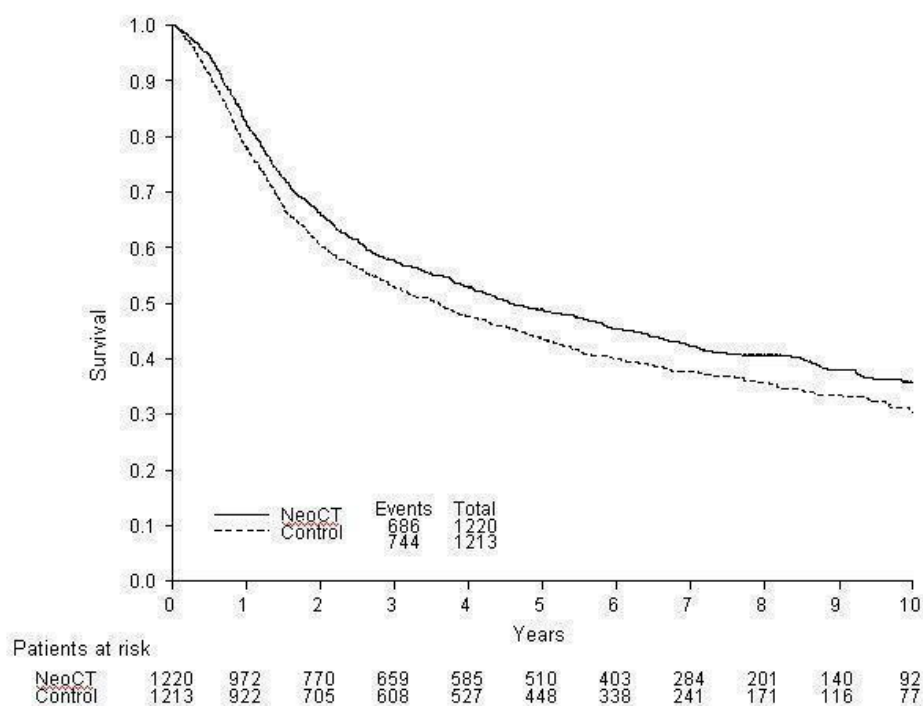
(1) Neoadjuvant chemotherapy trials

Survival data were supplied for 10 of the 11 trials with 2809 patients included. A total of 1691 deaths have been recorded. The confidence intervals for individual trial results are wide and the results of most individual trials are inconclusive. There is no clear evidence of statistical heterogeneity ($P = 0.47$) or inconsistency ($I^2 = 0\%$) between trials. The overall hazard ratio (HR) of 0.89 (95% CI 0.81 to 0.98) for these trials represents an 11% relative reduction in the risk of death associated with neoadjuvant chemotherapy which is conventionally significant ($P = 0.022$). This is equivalent to an absolute improvement of 4% at five years (95% CI 0% to 7%) increasing overall survival from 45% to 49%.

When we grouped the trials according to whether they used single agent platinum or platinum-based combination chemotherapy as pre-specified in the protocol (Outcome 1.01- Survival by chemotherapy type), we noted a difference in the effect of chemotherapy between the groups (interaction $P = 0.029$). The HR of 1.15 (95% CI 0.90 to 1.47) for those trials using single-agent chemotherapy is in favour of local treatment alone. This translates to an absolute benefit of -5% at 5 years (95% CI -14% to 4%). How-

ever, few trials and patients were included in this comparison, the confidence intervals are wide and the result is not conventionally significant ($P = 0.264$). By contrast, the combined HR for those trials using combination chemotherapy was 0.86 (95% CI 0.77 to 0.95, $P = 0.003$), equivalent to a 14% relative reduction in the risk of death; an absolute benefit of 5% at 5 years (95% CI 2% to 9%) improving survival from 45% to 50%. The survival curves for the combination chemotherapy trials, which separate by six months and remain apart thereafter, illustrate this benefit (Figure 1). [NB. Hazard Ratios calculated are labelled as Peto ORs in all of the forest plots.]

Figure 1. Overall survival in the cisplatin-based combination chemotherapy trials



The other pre-specified subset grouping was by planned local treatment: cystectomy alone, radical radiotherapy alone or combined radiotherapy and cystectomy. Since we had noted evidence of a difference in the effect between the single agent and combination chemotherapy group, this analysis was restricted to trials that had used combination chemotherapy (Outcome 1.02 - Survival by lo-

cal treatment). We noted no evidence of a difference in the effect of chemotherapy in the three local treatment groups (interaction $P = 0.656$).

Other Endpoints

Data on overall disease-free survival were available from 10 trials that included 2846 patients and 1847 events, of which 1606 (87%) were recurrences and 241 (13%) were deaths. Further information is given in Table 2. As for overall survival, in the pre-specified analysis according to whether trials had used single agent platinum or platinum-based combination chemotherapy, we noted a difference in the effect of chemotherapy between the group (interaction $P=0.024$) (Outcome 1.03 - Overall disease-free survival by chemotherapy type). For the combination chemotherapy trials, the combined HR of 0.78 (95% CI 0.71 to 0.86, $P = 0.0000005$) is equivalent to a 22% relative reduction in the risk of locoregional recurrence, metastases or death; an absolute disease-free survival benefit of 9% at 5 years (95% CI 5% to 12%).

For loco-regional disease-free survival and metastases-free survival, data were available for 7 trials that included 2180 patients with 1398 events (loco-regional disease-free survival) and 1345 events (metastases-free survival). For both endpoints approximately half of the events were deaths. Further information is given in Table 2. Again, the results for these endpoints show a similar pattern to survival, both in terms of chemotherapy type (Table 3) and local treatment (Table 4) with a significant benefit of platinum-based combination chemotherapy.

There was insufficient data available to formally investigate toxicity or quality of life in these trials. However, where it was reported in the publications, the most common chemotherapy-related toxicities included nausea and vomiting haematological toxicities and impaired renal function.

Subsidiary Analyses of Survival in Patient Subgroups

Subgroup analyses across all trials would not have been appropriate because of the differences in effect noted for single agent and combination chemotherapy. We therefore restricted these analyses to those trials that had used combination chemotherapy and had been able to provide adequate baseline data (age, sex and T category available for all trials; performance status available for six trials; N category available in full for five trials and grade available in full for four trials; tumour diameter and renal function only available for one trial). The power of these analyses was inevitably limited. However we recorded no strong evidence to suggest that combination chemotherapy was differentially effective in groups of patients defined by age, sex, T category, N category, grade, performance status or renal function. There was some suggestion of a differential effect between groups of patients defined by tumour diameter (trend $P = 0.008$), however this analysis was based on data that was largely from one trial (MRC/EORTC 1999) and should therefore be interpreted with caution (Table 5).

(2) Concurrent Chemoradiotherapy Trials

The HR of 0.76 (95% CI 0.49 to 1.18) suggests a 24% reduction in the relative risk of death associated with concurrent chemoradiotherapy, although this was not conventionally significant ($P = 0.229$) (Outcome 2.01 - Survival).

(3) Neoadjuvant plus Adjuvant Chemotherapy Trials

The HR of 0.85 (95% CI 0.68 to 1.05) represents a 15% relative

reduction in the risk of death with neoadjuvant and adjuvant chemotherapy, compared with control, but this was not conventionally significant ($P = 0.136$) (Outcome 3.01 - Survival).

DISCUSSION

Our findings show a beneficial effect of neoadjuvant chemotherapy. This effect was most clear in those trials that used combination, platinum-based chemotherapy, with a 5% improvement in survival at five years. The results for disease-free survival, locoregional disease-free survival and metastases-free survival lend support to the evidence of survival benefits associated with combination chemotherapy. We had insufficient evidence to formally test whether any of the specific combinations of chemotherapy used in these trials is more or less active, however there is no evidence of statistical heterogeneity between the trials in the combination chemotherapy group. The effect of combination chemotherapy also appears independent of the local treatment used, with a similar benefit of chemotherapy seen whether cystectomy, radiotherapy or radiotherapy and cystectomy was used as local treatment. This analysis however cannot directly measure the underlying relative efficacy of the various local treatments.

The subgroup analyses are exploratory in nature and had fairly low power, these analyses should therefore be interpreted with caution. No strong evidence was seen that the effect of neoadjuvant combination chemotherapy varied across patient subgroups. However we found a suggestion of a trend in the effect of chemotherapy when patients were grouped according to tumour diameter. Although tumour diameter is difficult to measure accurately, this observation might warrant further investigation. The overall absolute benefit of 5% at 5 years therefore provides the best estimate of effect in all subgroups however the clinical interpretation of this benefit may vary due to the differing underlying prognoses of these patients. For example, at 5 years, neoadjuvant chemotherapy improves survival from 55% to 60% in patients with T1 to T2 disease, from 40% to 45% in T3 and from 25% to 30% in the group of patients with T4 disease.

Despite a significant difference in the effect of neoadjuvant chemotherapy between groups of trials using single agent chemotherapy and combination chemotherapy, we did not find sufficient evidence to reliably determine the effect of single agent cisplatin chemotherapy on survival. Indeed, only three small trials including a total of 376 patients used single-agent cisplatin and the combined HR of survival for this group is based on just 261 events. With such low power, the results are far less reliable than those for the combination chemotherapy group. Furthermore, these three trials are among the earliest trials of neoadjuvant chemotherapy and may be less relevant in today's context, where combination regimens are preferred.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings show a clear survival benefit associated with neoadjuvant combination chemotherapy for patients with invasive bladder cancer. However, few of the trials in this meta-analysis measured toxicity or quality of life in ways that would allow data to be combined in a meta-analysis and clearly these are major issues for patients and clinicians when considering their treatment options.

Implications for research

In light of these results, promising new drug regimens or treatment approaches should be compared in randomised trials against neoadjuvant platinum-based combination chemotherapy.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abol-Encin 1997

Methods	RCT Accrual 1984-1996	
Participants	196 T2-T4a, Nx, M0	
Interventions	Surgery alone vs. neoadjuvant chemotherapy + surgery Neoadjuvant CT: 2 cycles every 4 weeks of Carboplatin (300mg/m2), Methotrexate (50mg/m2) and Vinblastine (4mg/m2)	
Outcomes	Disease free survival	
Notes	No data on overall survival	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Bassi 1999

Methods	RCT Accrual 1989-01996	
Participants	206 T2-T4, N0, M0	
Interventions	Surgery alone vs. neoadjuvant chemotherapy + surgery Neoadjuvant CT: 4 cycles every 4 weeks of Cisplatin (70mg/m2), Methotrexate (30mg/m2), Vinblastine (3mg/m2) and Doxorubicin (30mg/m2)	
Outcomes	Survival Disease-free survival Locoregional disease-free survival Metastases-free survival	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Bassi 1999 (Continued)

Allocation concealment (selection bias)	Low risk	A - Adequate
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Coppin 1996

Methods	RCT Accrual 1985-1989
Participants	102 T2-T4b
Interventions	Radiotherapy or radiotherapy + surgery vs. concurrent chemoradiotherapy or concurrent chemoradiotherapy + surgery CT: 3 cycles every 2 weeks of Cisplatin (100mg/m2)
Outcomes	Survival Disease-free survival Locoregional disease-free survival Metastases-free survival
Notes	Concurrent chemotherapy and radiotherapy used therefore not included in main comparison of neoadjuvant chemotherapy +/- local treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Cortesi (unpub)

Methods	RCT Accrual 1988-1992
Participants	171 (18 missing) T2-T4, N0, M0
Interventions	Surgery alone vs. neoadjuvant chemotherapy + surgery Neoadjuvant CT: 3 cycles every 4 weeks of Cisplatin (70mg/m2), Methotrexate (30mg/m2), Vinblastine (3mg/m2) and Epirubicin (40mg/m2)
Outcomes	Survival Disease-free survival
Notes	

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Grossman 2003

Methods	RCT Accrual 1987-1998
Participants	317 T2-T4a, N0, M0
Interventions	Surgery alone vs. neoadjuvant chemotherapy + surgery Neoadjuvant CT: 3 cycles every 4 weeks of Cisplatin (70mg/m2), Methotrexate (30mg/m2), Vinblastine (3mg/m2) and Doxorubicin (30mg/m2)
Outcomes	Survival Overall disease free survival
Notes	Not included in original analyses published in the Lancet

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Malmstrom 1996

Methods	RCT Accrual 1985-1989
Participants	325 (14 missing) T1 (grade 3) - T4a, Nx, M0
Interventions	Radiotherapy + surgery vs. neoadjuvant chemotherapy + radiotherapy + surgery Neoadjuvant CT: 2 cycles every 3 weeks of Cisplatin (70mg/m2) and Doxorubicin (30mg/m2)
Outcomes	Survival Disease-free survival Locoregional disease-free survival Metastases free-survival

Malmstrom 1996 (Continued)

Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Martinez 1995

Methods	RCT Accrual 1984-1989	
Participants	122 (1 missing) T2-T4a, Nx-N2, M0	
Interventions	Surgery alone vs. neoadjuvant chemotherapy + surgery Neoadjuvant CT: 3 cycles every 3 weeks of Cisplatin (100mg/m2)	
Outcomes	Survival Disease free survival Locoregional disease-free survival Metastases free-survival	
Notes	Single agent cisplatin	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

MRC/EORTC 1999

Methods	RCT Accrual 1989-1995	
Participants	976 T2 (grade 3), T3, T4a, N0, M0	
Interventions	Cystectomy (+/- radiotherapy) or radiotherapy alone vs. Neoadjuvant chemotherapy plus cystectomy (+/- radiotherapy) or radiotherapy alone Neoadjuvant CT: 3 cycles every 3 weeks of Cisplatin (100mg/m2), Methotrexate (30mg/m2) and Vinblastine (4mg/m2)	

MRC/EORTC 1999 (Continued)

Outcomes	Survival Overall disease-free survival Locoregional disease-free survival Metastases-free survival	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Natale 2001

Methods	RCT	
Participants	317	
Interventions	Surgery alone vs. neoadjuvant chemotherapy + surgery Neoadjuvant CT: 3 cycles every 4 weeks of Cisplatin (70mg/m2), Methotrexate (30mg/m2), Vinblastine (3mg/m2) and Doxorubicin (30mg/m2)	
Outcomes	Survival	
Notes	Preliminary results of Grossman 2003 (presented at ASCO 2001)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Raghavan 1991

Methods	RCT Accrual 1985-1988	
Participants	96 T2-T4, Nx, M0	
Interventions	Radiotherapy alone vs. neoadjuvant chemotherapy + radiotherapy Neoadjuvant CT: 2 cycles every 3 weeks of Cisplatin (100mg/m2)	

Raghavan 1991 (Continued)

Outcomes	Survival Disease free survival Locoregional disease-free survival Metastases free-survival	
Notes	Single agent cisplatin	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sengelov 2002

Methods	RCT Accrual 1989-1995	
Participants	153 T2-T4b, Nx-N0, M0	
Interventions	Surgery alone or radiotherapy alone vs. neoadjuvant chemotherapy + surgery or radiotherapy Neoadjuvant CT: 3 cycles every 3 weeks of Cisplatin (100mg/m2) and Methotrexate (250mg/m2)	
Outcomes	Survival Disease free survival Locoregional disease-free survival Metastases free-survival	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Shearer 1988

Methods	RCT Accrual 1978-1986	
Participants	423 (25 missing) T3-T4a, Nx, M0	

Shearer 1988 (Continued)

Interventions	Radiotherapy alone or radiotherapy + surgery vs. Neoadjuvant chemotherapy + radiotherapy or radiotherapy and surgery + adjuvant chemotherapy Neoadjuvant CT: 6 cycles every 2 weeks of Methotrexate (100mg/m2) and Leucovorin (15mg) Adjuvant CT: 9 cycles every 4 weeks of Methotrexate (100mg/m2) a	
Outcomes	Survival Disease free survival Locoregional disease-free survival Metastases free-survival	
Notes	Trial used neoadjuvant and adjuvant chemotherapy therefore not included in the main comparison of neoadjuvant chemotherapy	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sherif 2002

Methods	RCT Accrual 1990-1997	
Participants	317 (8 missing) T2-T4a, Nx, M0	
Interventions	Surgery alone vs. Neoadjuvant chemotherapy + surgery Neoadjuvant CT: 3 cycles every 3 weeks of Cisplatin (100mg/m2) and Methotrexate (250mg/m2)	
Outcomes	Survival Disease free survival Locoregional disease-free survival Metastases free-survival	
Notes		
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Wallace 1991

Methods	RCT Accrual 1984-1988
Participants	159 T2-T4, Nx, M0
Interventions	Radiotherapy alone vs. Neoadjuvant chemotherapy + radiotherapy Neoadjuvant CT: 3 cycles every 3 weeks of Cisplatin (100mg/m ²)
Outcomes	Survival
Notes	Single-agent cisplatin

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Millikan 2001	Trial compared neoadjuvant chemotherapy + local treatment on one arm with local treatment + adjuvant chemotherapy on the other
Ozono 1991	Confounded by use of different treatments on both arms of the trial
Shipley 1998	Local treatment used was chemoradiotherapy and not surgery, radiotherapy or radiotherapy + surgery

DATA AND ANALYSES

Comparison 1. Neoadjuvant CT + Local treatment vs Local treatment alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival by chemotherapy type	10	2809	Peto Odds Ratio (95% CI)	0.89 [0.81, 0.98]
1.1 Single agent platinum	3	376	Peto Odds Ratio (95% CI)	1.15 [0.90, 1.47]
1.2 Platinum based combination chemotherapy	7	2433	Peto Odds Ratio (95% CI)	0.86 [0.77, 0.95]
2 Survival by local treatment type (combination CT trials only)	7	2421	Peto Odds Ratio (95% CI)	0.86 [0.77, 0.95]
2.1 Cystectomy	6	1508	Peto Odds Ratio (95% CI)	0.86 [0.75, 0.98]
2.2 Radiotherapy	2	526	Peto Odds Ratio (95% CI)	0.90 [0.74, 1.11]
2.3 Radiotherapy + cystectomy	2	387	Peto Odds Ratio (95% CI)	0.77 [0.58, 1.02]
3 Overall disease-free survival by chemotherapy type	10	2846	Peto Odds Ratio (95% CI)	0.81 [0.74, 0.89]
3.1 Single agent cisplatin trials	2	217	Peto Odds Ratio (95% CI)	1.14 [0.83, 1.55]
3.2 Platinum-based combination trials	8	2629	Peto Odds Ratio (95% CI)	0.78 [0.71, 0.86]

Comparison 2. Concurrent CRT + local treatment vs local treatment alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	1	102	Peto Odds Ratio (95% CI)	0.76 [0.49, 1.18]

Comparison 3. Neoadjuvant CT + Local Treatment + Adjuvant CT vs Local Treatment alone

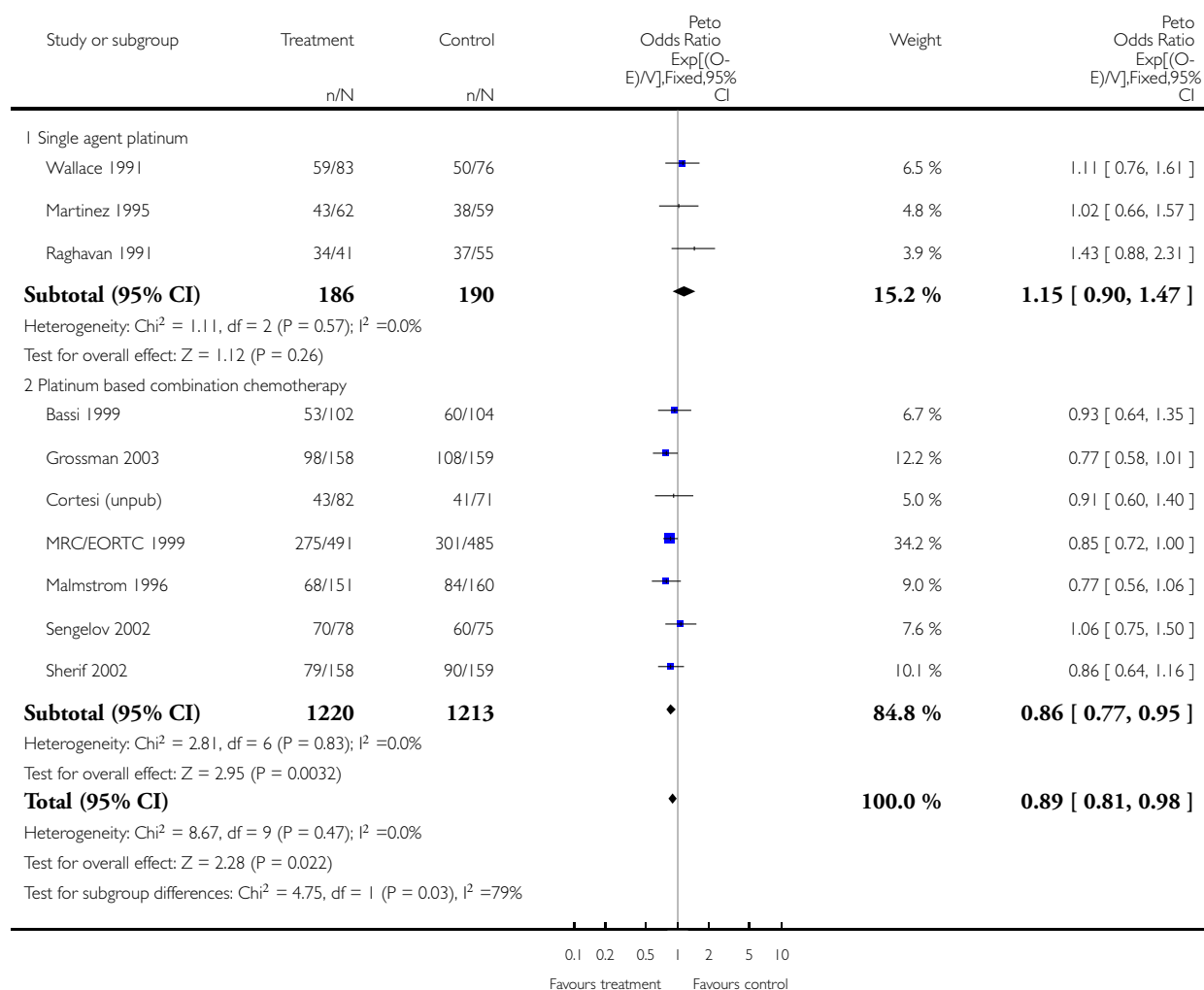
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival	1	398	Peto Odds Ratio (95% CI)	0.85 [0.68, 1.05]

Analysis 1.1. Comparison 1 Neoadjuvant CT + Local treatment vs Local treatment alone, Outcome 1 Survival by chemotherapy type.

Review: Neo-adjuvant chemotherapy for invasive bladder cancer

Comparison: 1 Neoadjuvant CT + Local treatment vs Local treatment alone

Outcome: 1 Survival by chemotherapy type

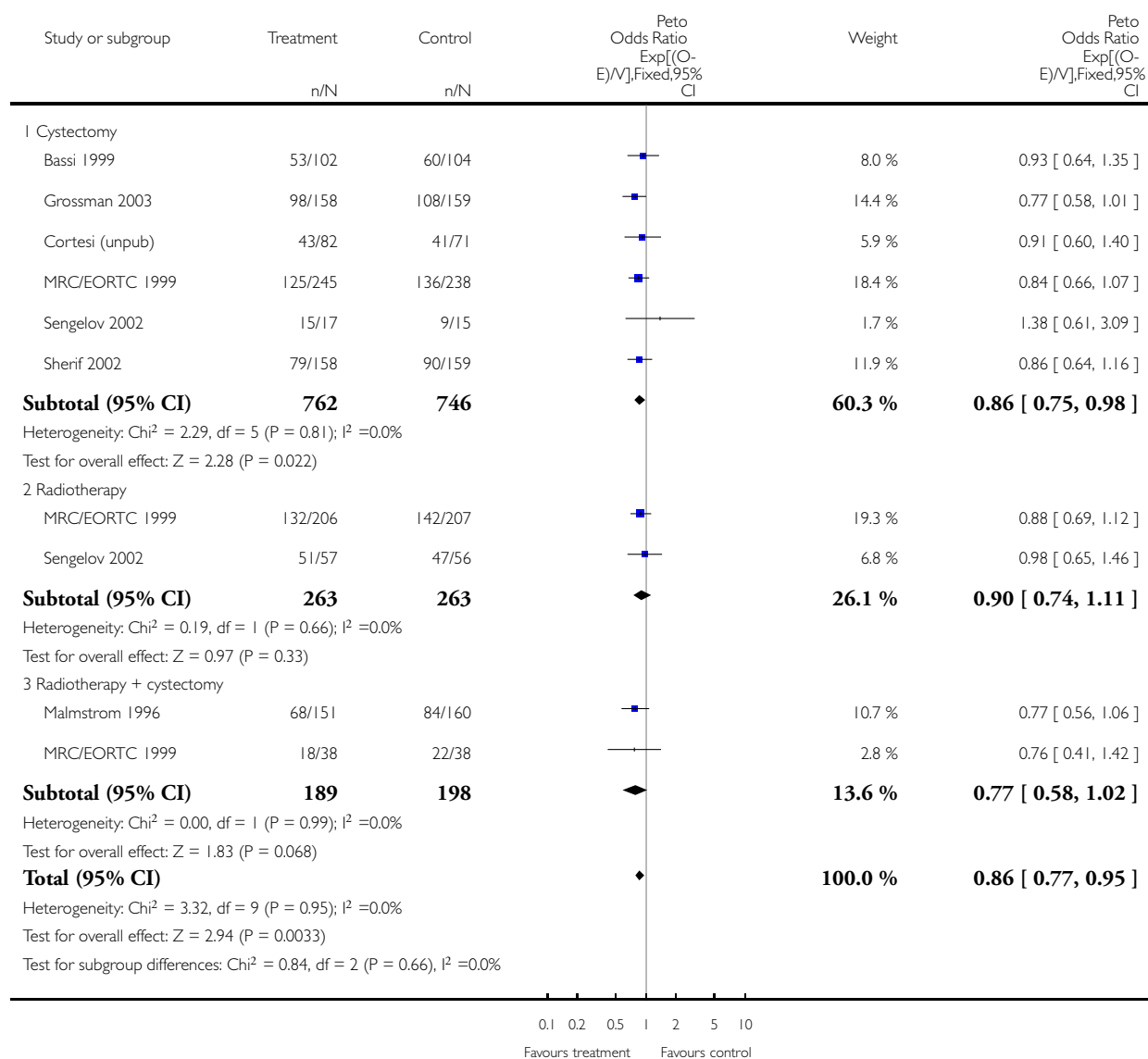


Analysis 1.2. Comparison 1 Neoadjuvant CT + Local treatment vs Local treatment alone, Outcome 2 Survival by local treatment type (combination CT trials only).

Review: Neo-adjuvant chemotherapy for invasive bladder cancer

Comparison: 1 Neoadjuvant CT + Local treatment vs Local treatment alone

Outcome: 2 Survival by local treatment type (combination CT trials only)

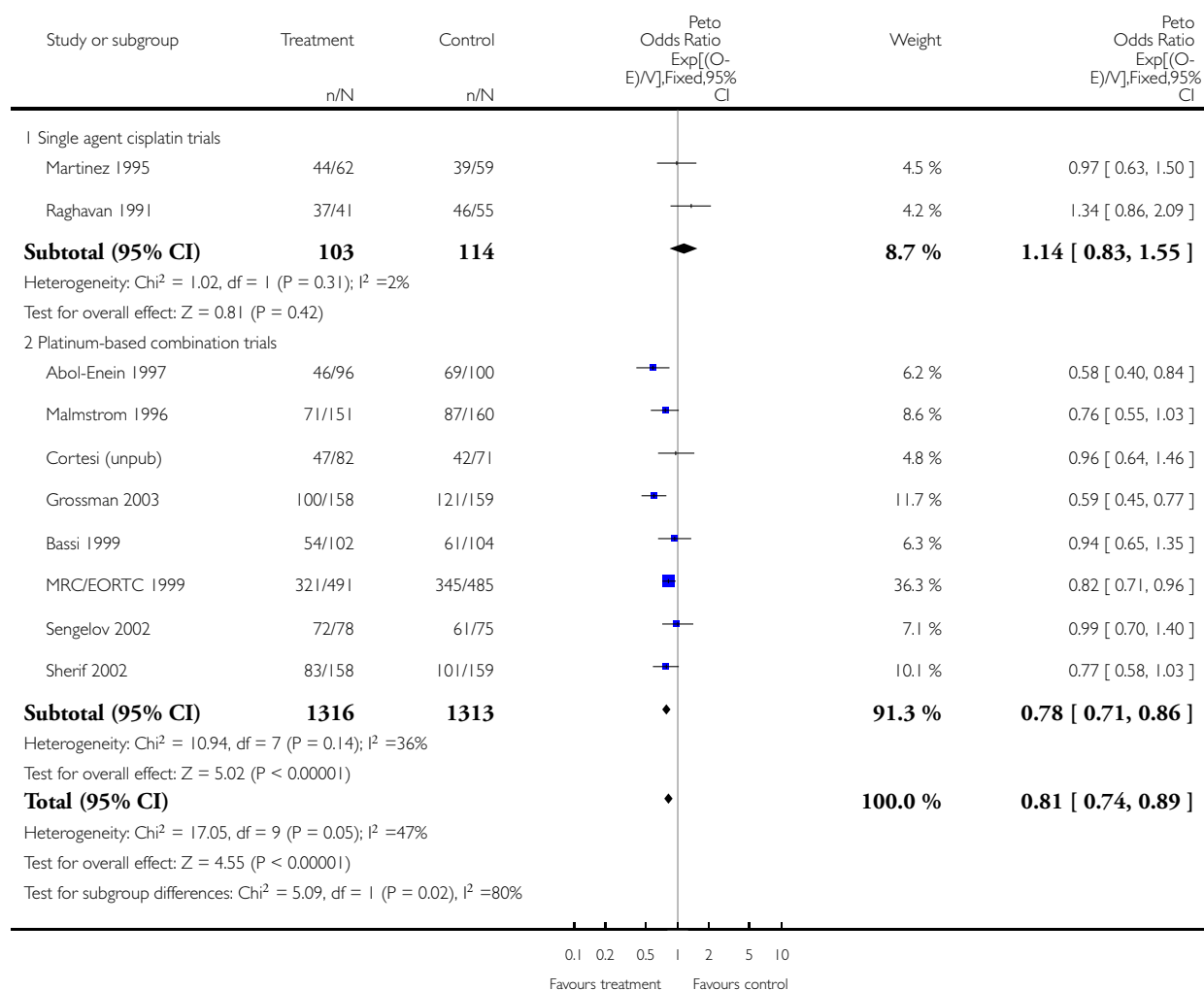


Analysis 1.3. Comparison 1 Neoadjuvant CT + Local treatment vs Local treatment alone, Outcome 3 Overall disease-free survival by chemotherapy type.

Review: Neo-adjuvant chemotherapy for invasive bladder cancer

Comparison: 1 Neoadjuvant CT + Local treatment vs Local treatment alone

Outcome: 3 Overall disease-free survival by chemotherapy type

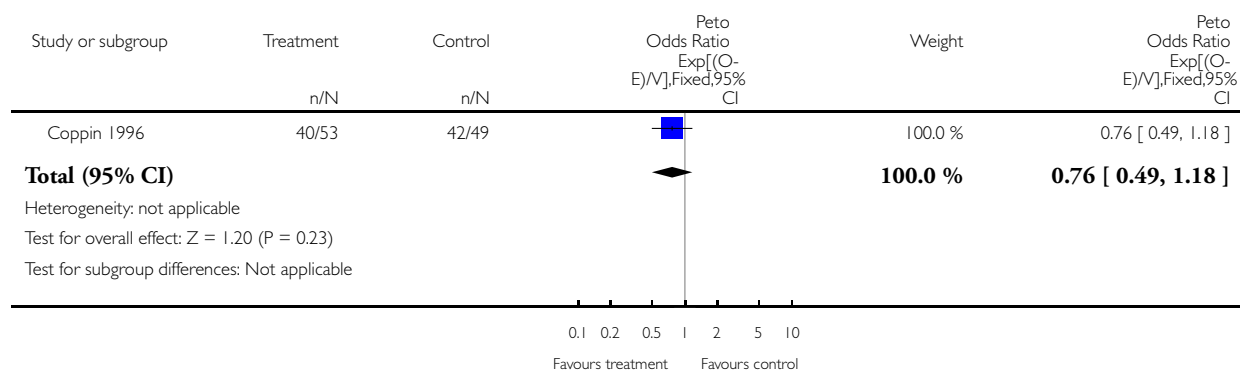


Analysis 2.1. Comparison 2 Concurrent CTRT + local treatment vs local treatment alone, Outcome 1 Survival.

Review: Neo-adjuvant chemotherapy for invasive bladder cancer

Comparison: 2 Concurrent CTRT + local treatment vs local treatment alone

Outcome: 1 Survival

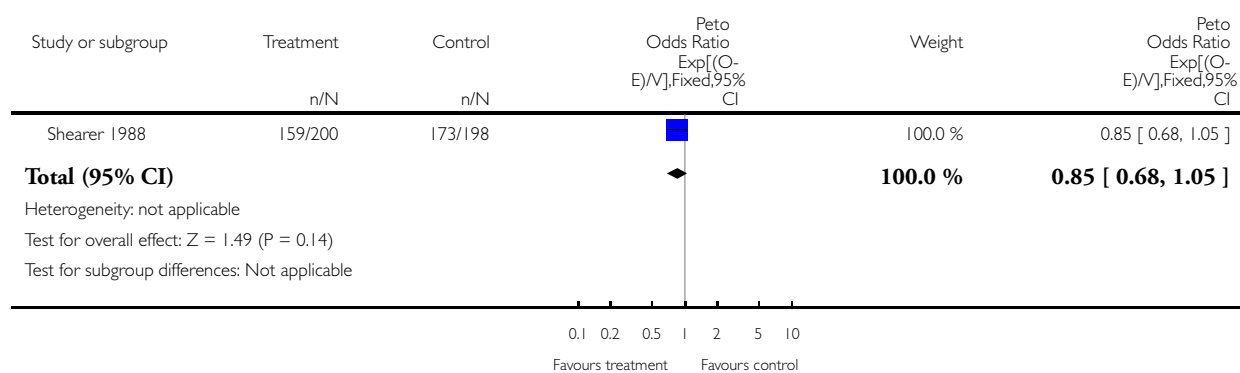


Analysis 3.1. Comparison 3 Neoadjuvant CT + Local Treatment + Adjuvant CT vs Local Treatment alone, Outcome 1 Survival.

Review: Neo-adjuvant chemotherapy for invasive bladder cancer

Comparison: 3 Neoadjuvant CT + Local Treatment + Adjuvant CT vs Local Treatment alone

Outcome: 1 Survival



ADDITIONAL TABLES

Table 1. Characteristics of included patients

		Neo CT (n=1502)	Control (n=1503)	Total (n=3005)
Age	<55	265 (18%)	287 (19%)	552
	55-64	599 (40%)	532 (35%)	1131
	≥65	638 (42%)	684 (46%)	1322
	Unknown	0	0	0
Sex	Male	1267 (84%)	1273 (85%)	2540
	Female	235 (16%)	230 (15%)	465
	Unknown	0	0	0
T category	T0-1	33 (2%)	31 (2%)	64
	T2	507 (34%)	541 (36%)	1048
	T3-T4a	927 (62%)	898 (60%)	1825
	T4b	11 (1%)	9 (1%)	20
	Unknown	24 (2%)	24 (2%)	48
N category	N0	797 (53%)	765 (51%)	1562
	N1/N2	55 (4%)	62 (4%)	117
	Nx/Unknown	650 (43%)	676 (45%)	1326
Grade	G0-1	155 (10%)	136 (9%)	291
	G2	179 (12%)	219 (15%)	398
	G3	805 (54%)	789 (52%)	1594
	G4	10 (1%)	28 (2%)	38
	Unknown	353 (24%)	331 (22%)	684
Performance Status	0	774 (52%)	756 (50%)	1530
	1	292 (19%)	312 (21%)	604

Table 1. Characteristics of included patients (Continued)

	2	49 (3%)	60 (4%)	109
	3	13 (1%)	8 (1%)	21
	Unknown	374 (25%)	367 (24%)	741
Tumour diameter (cm)	<2.5	96 (6%)	101 (7%)	197
	2.5-5.0	247 (16%)	284 (19%)	531
	>5.0	238 (16%)	205 (14%)	443
	Unknown	921 (61%)	913 (61%)	1834
Renal function (GFR)	≤59	40 (3%)	42 (3%)	82
	60-69	119 (8%)	134 (9%)	253
	>69	330 (22%)	305 (20%)	635
	Unknown	1013 (67%)	1022 (68%)	2035

Table 2. First events reported by treatment arm

First event	Neo CT (n =1502)	Control (n = 1503)
Alive (no recurrence)	451 (30%)	388 (26%)
Local recurrence	208 (14%)	213 (14%)
Metastasis	150 (10%)	196 (13%)
Local recurrence and metastases together	176 (12%)	200 (13%)
Death (No recurrence)	194 (13%)	306 (20%)
Unknown	323 (22%)	200 (13%)

Table 3. Results for all endpoints by chemotherapy type

Endpoint	CT Type	No patients / events	HR (95% CI)	Effect P value	Abs benefit (95% CI)	Interaction p-value
Overall survival	Single agent platinum	261/376	1.15 (0.90-1.47)	0.26	-5% (-14% to 4%)	
	Platinum based combinations	1430/2433	0.86 (0.77-0.95)	0.003	5% (2% to 9%)	0.029
	All trials	1691/2890	0.89 (0.81-0.98)	0.022	4% (0% to 7%)	
Disease-free survival	Single agent platinum	166/217	1.14 (0.83-1.55)	0.42	-5% (-16% to 7%)	
	Platinum based combinations	1681/2629	0.78 (0.71-0.86)	0.0000005	9% (5% to 12%)	0.024
	All trials	1847/2846	0.81 (0.74-0.89)	0.000005	8% (4% to 11%)	
Locoregional disease-free survival	Single agent platinum	166/217	1.12 (0.82-1.52)	0.49	-4% (-15% to 7%)	
	Platinum based combinations	1232/1963	0.87 (0.77-0.97)	0.012	5% (3% to 11%)	0.131
	All trials	1398/2180	0.89 (0.80-0.99)	0.032	4% (0% to 8%)	
Metastases-free survival	Single agent platinum	154/217	1.21 (0.88-1.67)	0.25	-7% (-18% to 5%)	
	Platinum based combinations	1181/1963	0.82 (0.73-0.92)	0.001	7% (3% to 11%)	0.025
	All trials	1335/2180	0.86 (0.77-0.95)	0.004	5% (2% to 9%)	

Table 4. Results for all endpoints by local treatment (combination CT trials only)

Endpoint	Local treatment type	HR (95% CI)	Interaction p-value
Overall survival	Cystectomy	0.86 (0.75-0.98)	
	Radiotherapy	0.90 (0.74-1.11)	
	Radiotherapy + cystectomy	0.77 (0.58-1.02)	0.656

Table 4. Results for all endpoints by local treatment (combination CT trials only) (Continued)

Disease-free survival	Cystectomy	0.75 (0.66-0.84)	
	Radiotherapy	0.92 (0.76-1.11)	
	Radiotherapy + cystectomy	0.71 (0.54-0.94)	0.158
Locoregional disease free survival	Cystectomy	0.86 (0.69-1.01)	
	Radiotherapy	0.96 (0.79-1.16)	
	Radiotherapy + cystectomy	0.73 (0.55-0.96)	0.286
Metastases free survival	Cystectomy	0.82 (0.70-0.96)	
	Radiotherapy	0.87 (0.71-1.06)	
	Radiotherapy + cystectomy	0.73 (0.56-0.97)	0.649

Table 5. Results of subgroup analyses (survival - combination CT trials only)

Subgroup	Categories	Interaction	Trend
Age	< 55, 55 to < 65, ≥ 65	1.572 (2 d.f.) P=0.456	0.482 (1 d.f.) P=0.488
Sex	Male, Female	0.266 (1d.f) P=0.606	-
T category	T1-2, T3, T4	0.324 (2 d.f.) P=0.850	0.108 (1 d.f.) P=0.742
N category	N0, N1/N2	0.080 (1d.f.) P=0.777	-
Grade	G1/G2, G3/G4	1.154 (1d.f.) P=0.283	-
Tumour diameter (cm)	< 2.5, 2.5 to 5.0, > 5.0	7.733 (2 d.f.) P=0.021	7.079 (1d.f.) P=0.008
Performance status	0, 1, 2 to 3	1.511 (2 d.f.) P=0.470	0.004 (1 d.f.) P=0.95
Renal function (GFR)	≤ 59, 60 to 69, > 69	3.573 (2 d.f.) P=0.168	3.564 (1d.f.) P=0.059
d.f. = degrees of freedom			

WHAT'S NEW

Last assessed as up-to-date: 3 November 2003.

Date	Event	Description
17 January 2012	Amended	Added grant info.

HISTORY

Review first published: Issue 2, 2005

Date	Event	Description
29 May 2008	Amended	Converted to new review format.
3 November 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All aspects of the meta-analysis were carried out under the auspices of the ABC group.

H Abol-Enein, P Bassi, M Boyer, C M L Coppin, E Cortesi, H.B Grossman, R R Hall, A Horwich, P-U Malmström, J A Martinez-Piñeiro, L Sengeløv, A Sherif and D M A Wallace collated and supplied the individual patients' data, contributed to the discussions of the results and commented on the drafts of the report. A V Bono, P J Goebell, S Groshen, F M Torti M Stöckle and U Studer 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, D Raghavan, J T Roberts and R Sylvester and the Secretariat, M K B Parmar, L A Stewart, J F Tierney and C L Vale, who were responsible for formulating the questions, developing the protocol and discussing the preliminary results. The secretariat, MKB Parmar, L A Stewart, J F Tierney and 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 and M K B Parmar.

DECLARATIONS OF INTEREST

None given.

SOURCES OF SUPPORT

Internal sources

- Medical Research Council, UK.

External sources

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INDEX TERMS

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MeSH check words

Humans