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Does neoadjuvant cisplatin-based chemotherapy improve the survival of patients with locally advanced bladder cancer: a meta-analysis of individual patient data from randomized clinical trials*

ADVANCED BLADDER CANCER OVERVIEW COLLABORATION: (COLLABORATORS: D. GHERSI, L.A. STEWART, M.K.B. PARMAR, C. COPPIN, J. MARTINEZ-PINEIRO, D. RAGHAVAN, M.A. WALLACE)
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Objectives To assess whether neoadjuvant or concurrent platinum-based chemotherapy improves the survival of patients with locally advanced bladder cancer, and to determine whether there is any evidence that chemotherapy is more or less effective within well-defined subgroups of patients.

Patients and methods A formal meta-analysis (overview) was carried out using updated individual data from 479 patients (301 deaths) from four randomized trials comparing local definitive treatment alone with neoadjuvant or concurrent single-agent cisplatin followed by local definitive treatment. Further summary data were available from a similar randomized trial of cisplatin and doxorubicin in 325 patients (127 deaths).

Results Combined analysis of the individual patient data gave an overall hazard ratio of 1.02 in favour of local therapy alone ($P=0.845$, 95% confidence interval = 0.81–1.26), representing a 2% increase in the relative risk of death with the use of chemotherapy. When this analysis was supplemented by data from the only trial for which individual patient information was not available, the hazard ratio was 0.91 in favour of chemotherapy ($P=0.328$, 95% confidence interval = 0.75–1.10), representing a 9% reduction in the relative risk of death. The only prognostic factor for which the evidence suggested a differential treatment effect (interaction) across groups was age (chi-square test for trend = 3.833, $P=0.05$), with younger age groups (< 60 years) exhibiting a possible effect in favour of chemotherapy.

Conclusions Despite a meta-analysis of all known randomized trials, there is still insufficient information to obtain a definitive answer to the question of whether neoadjuvant cisplatin-based chemotherapy improves the survival of patients with locally advanced bladder cancer. Such chemotherapy cannot therefore be currently recommended for routine use and any planned clinical trial should include a 'no chemotherapy' control arm.

Keywords Bladder cancer, chemotherapy, local treatment, survival, meta-analysis

Introduction

Bladder cancer is the second most common malignancy of the genito-urinary system. Worldwide, approximately 220 000 new cases are diagnosed each year, accounting for 3.5% of all new cancers [1]. Definitive treatment of locally advanced bladder cancer varies and may consist of cystectomy, radiotherapy or a combination of the two. Such local approaches to treatment give 5-year survival rates of around 30% with a median survival of about 2 years. However, approximately half of these patients are thought to present with unrecognized disseminated disease, and it has been suggested that systemic therapy may improve long-term survival [2].

During the past 15 years many phase II clinical trials have investigated the role of chemotherapy in patients with locally advanced bladder cancer. These studies have identified a number of active single-agent cytotoxic drugs, including cisplatin (C), methotrexate (M), doxorubicin (A) and vinblastine (V) [3,4]. Promising results have also been achieved with various combinations of drugs, in particular with the M-VAC and CMV [5] regimens. Although the response rates achieved in these phase II studies are encouraging, there is no conclusive evidence that chemotherapy improves survival [6], irrespective of whether it is given before (neoadjuvant or pre-emptive), with (concurrent) or after (adjuvant) local treatment. Despite this, many clinicians

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now use neoadjuvant chemotherapy in the routine treatment of locally advanced bladder cancer [2,3,7].

Five modestly sized randomized trials of neoadjuvant or concurrent cisplatin-based chemotherapy have been completed to date, the largest of which included 325 patients [9–13]. The problems of interpreting the results of such trials are not widely appreciated. For example, assuming a 2-year survival rate of 50% in the 'no chemotherapy' arm, 900 patients would be required to detect an absolute improvement in survival of 10% (from 50–60%) with reliability (90% power, 5% significance level) [14]. The largest of these trials had a sufficient number of patients to detect only absolute improvements in 2-year survival in the region of 15–20%. It is perhaps unrealistic to expect such relatively large improvements in survival, and it is more likely that any benefit of chemotherapy will be in the region of 5–10% [15]. None of the trials has had the statistical power to detect such moderate improvements in survival with reliability. Thus they are likely to produce results which would be conventionally regarded as 'negative', but would more appropriately be regarded as 'inconclusive' and potentially consistent with improvements in survival of the order of 5–10%. A meta-analysis or quantitative overview, combining the results from all completed randomized clinical trials, may include a sufficient number of patients to assess more reliably whether neoadjuvant chemotherapy is effective in the treatment of patients with locally advanced bladder cancer.

Patients and methods

Formal quantitative methodology was used to combine the results from completed randomized clinical trials, both published and unpublished, which compared neoadjuvant or concurrent chemotherapy plus local definitive treatment with local treatment alone. The methodology used was similar to that used in the Advanced Ovarian Cancer Overview [16].

Trials were eligible for inclusion in the overview if they included patients with biopsy-proven transitional cell carcinoma of the bladder and were randomized in such a way that did not allow prior knowledge of the treatment allocated. All trials included in this meta-analysis were identified by participants in the workshop on 'Upfront chemotherapy in invasive bladder cancer' held in San Francisco in May 1989 [17]. Bibliographic searches using MEDLINE, Cancerlit and reference lists of related papers and meeting abstracts did not lead to the identification of any additional trials, nor did the Physician Data Query database of ongoing trials. None of the studies included in the meta-analysis had been published at the time that they were identified.

Seven eligible studies were identified, two of which are currently ongoing and have not therefore been included in this meta-analysis (Table 1). The original investigators of the remaining five studies were asked to provide basic identifying, prognostic and survival data for each patient randomized. All trial data were checked thoroughly before entry into the meta-analysis database, and then were verified by the investigator responsible.

All analyses were carried out on intention to treat, that is patients were analysed according to their allocated treatment, irrespective of whether or not they actually received that treatment. Analyses were stratified by trial and the logrank expected and observed numbers of deaths were used to calculate individual and an overall pooled hazard ratio (HR) using the fixed effects model [18]. Thus the time to death for individual patients was used within trials to generate the HR, which represents the overall relative risk of a patient dying on treatment compared with those in the control. A HR of 1 indicates no difference between treatment and control. A HR of <1 favours the treatment group, for example a HR of 0.8 represents a 20% relative reduction in the hazard, or relative risk of death, in the treatment group. A HR of >1.0 favours the control group, for example a HR of 1.3 indicates a 30% relative benefit for the control group. As the absolute difference between treatments depends on both the HR and the underlying baseline survival, and the way that these inter-relate is not intuitive, the results are presented as both HRs and absolute differences.

The absolute survival difference was calculated by applying the HR to the control arm survival at a particular point in time, using the expression:

$$S = PC^{HR} - PC \text{ [19]}$$

where S = survival benefit and PC = survival on control. Results are presented graphically as HR plots and as simple (non-stratified) Kaplan–Meier survival curves to give a visual summary of the survival experience.

Chi-square tests were used to test for gross statistical heterogeneity in the results of the various trials, and a chi-square test for trend was used to assess whether treatment was differentially effective in different groups within a prognostic variable [20]. All *P*-values are 2-sided and the chi-square values are calculated on 1 degree of freedom (d.f.) unless otherwise specified.

Individual patient data were available from four of the five eligible trials. Despite the potentially serious problems of using trial information from the published analysis [21] for which individual data were not available, it was thought important to consider how the results of this trial may influence the meta-analysis. Thus estimated results (HR and standard error) from this trial were used to supplement the information from the four trials which provided individual patient information.

Table 1 Trials comparing neoadjuvant chemotherapy plus local definitive treatment with local definitive treatment alone in patients with locally advanced bladder cancer

Trial reference	*Chemotherapy dose and schedule*	*Local treatment*	*Opened*	*Closed*	*Patients* (n)
Canada [8]	C 100 mg/m^2 q 2 wks × 3(W)	Radiotherapy ± cystectomy	May 85	Mar 89	102
Australia [9]	C 100 mg/m^2 q 2 3wks × 2	Radiotherapy	Feb 85	Feb 88	137
England [9]	C 100 mg/m^2 q 3wks × 3	Radiotherapy	Jun 84	Jun 88	159
Spain [10]	C 100 mg/m^2 q 3wks × 3	Cystectomy	Oct 84	Aug 89	122
Norway [11]	C 100 mg/m^2 d1 A 30 mg/m^2 d2, q 3wks × 2	Radiotherapy ± cystectomy	Dec 85	May 89	325
Ongoing trials					
MRC/EORTC [12]	C 100 mg/m^{2}d2 M 30 mg/m^2 d1, d8 V 4 mg/m^2 d1, d8, q 3wks × 3	Radiotherapy ± cystectomy	Nov 89	N/A	Target accrual 915
SWOG [13]	M 30 mg/m^2 d1, d15, d22 V 3 mg/m^2 d2, d15, d22 A 30 mg/m^2 d2 C 70 mg/m^2 d2, q 4wks × 3	Cystectomy	Aug 87	N/A	Target accrual 298

C, Cisplatin. A, Adriamycin (doxorubicin). M, Methotrexate. V, Vinblastine. q, Every. d, Day. W, Concurrent

Results

Analysis of trials providing individual patient data

Individual patient data from 479 patients were available for analysis, with a median follow-up for surviving patients of approximately 3 years. A total of 301 deaths was observed. Table 1 describes each of the trials in terms of the chemotherapy and local treatments used. Three trials [9,10] completed chemotherapy before starting local treatment, and the remaining trial [8] gave chemotherapy concurrently with radiotherapy, or radiotherapy plus cystectomy. All trials were well balanced between treatments for age, sex, stage and grade.

The estimated treatment effect from two trials tended to favour chemotherapy, while the other two tended to favour local treatment alone (Fig. 1). The confidence intervals for all four trials cross unity indicating that no individual trial provides a statistically convincing result. There was no evidence of gross statistical heterogeneity between the trials ($\chi^2 = 3.096$, d.f. $= 3$, $P = 0.377$). The overall HR of 1.02 (95% CI 0.81 to 1.26) similarly provides an inconclusive result. This is reflected in the overall survival curve (Fig. 2), which shows no evidence of a difference between treatments ($\chi^2 = 0.038$, $P = 0.845$).

Analysis supplemented with published data

The only trial for which individual patient information was not available [11] was also the only one to investigate cisplatin in combination with doxorubicin. A total of 325 patients were randomized to this trial of whom 14 were considered by the original investigators to be ineligible for analysis. One-hundred and twenty-seven deaths were reported. As shown in Fig. 3, the results of this trial tended to favour chemotherapy ($P = 0.034$). The inclusion of this trial in a supplementary analysis increases the total number of patients to 790 and the total number of deaths to 428. The corresponding HR was 0.91, now in favour of chemotherapy (95% CI 0.75–1.10) (Fig. 3). The result remained conventionally non-significant ($\chi^2 = 0.956$, $P = 0.33$).

Treatment by prognostic factor interaction

Age, sex, stage and grade were investigated to assess whether there was any evidence that chemotherapy was more or less effective within well-defined groups for each of these prognostic variables. For example, stage was investigated to assess whether chemotherapy was either more or less effective in the sub-groups defined by T2, T3 and T4.

Grade was available from only two trials, leading to reduced numbers of patients in this particular investigation. The results presented in Figs 4 and 5 indicate that age was the only factor for which there was any evidence suggesting a differential effect for different groups (test for trend: $\chi^2 = 3.833$, $P = 0.05$), with a larger effect being observed in younger age groups. There was no evidence of a differential effect by sex ($\chi^2 = 2.102$, $P = 0.15$), grade ($\chi^2 = 0.078$, $P = 0.78$) or stage ($\chi^2 = 1.562$, $P = 0.21$).

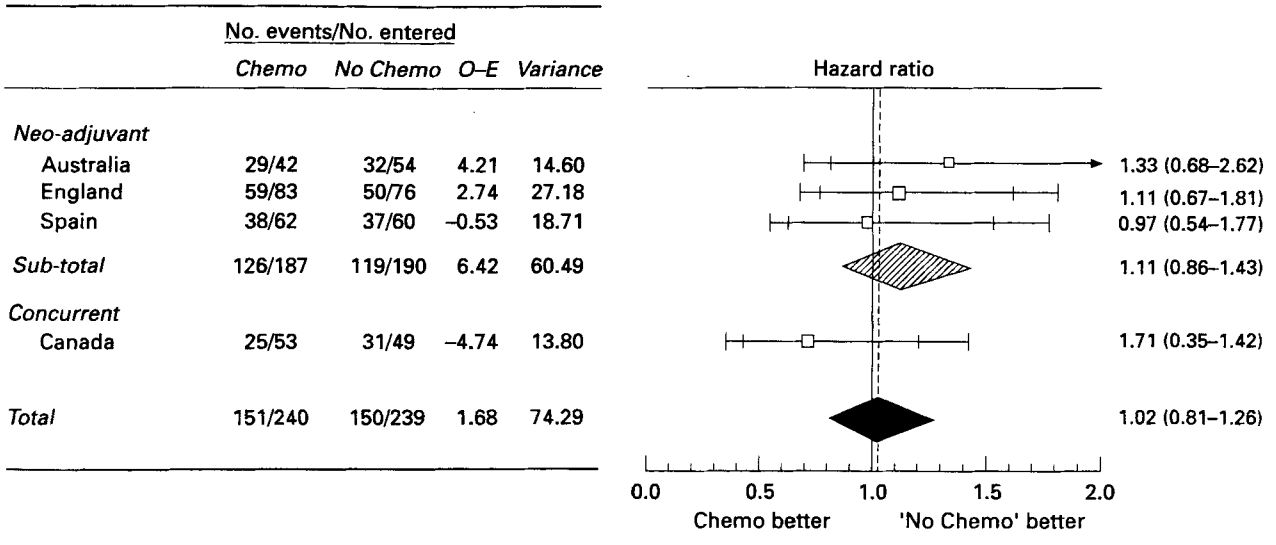

Fig. 1 Hazard ratio plot for trials with individual patient data. HR, 1.02, 95% CI 0.81–1.26. Treatment effect: $\chi^2=0.038$, $P=0.845$. Test for heterogeneity: $\chi^2=3.096$, d.f. = 3, $P=0.377$.

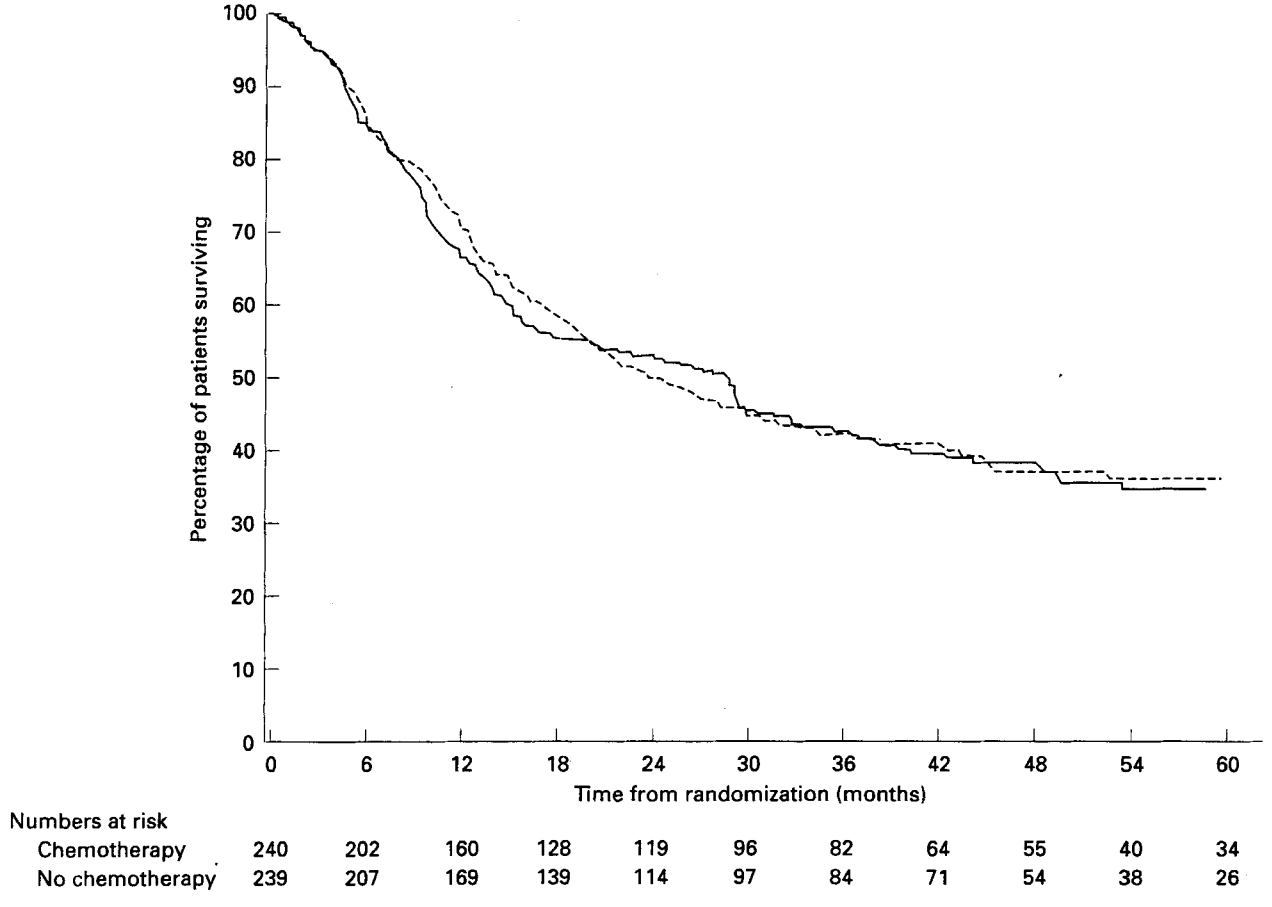

Fig. 2. Survival curve for the four trials with individual patient data. (Neoadjuvant chemotherapy followed by local definitive treatment versus local definitive treatment alone.) —, Chemotherapy. – – –, No chemotherapy.

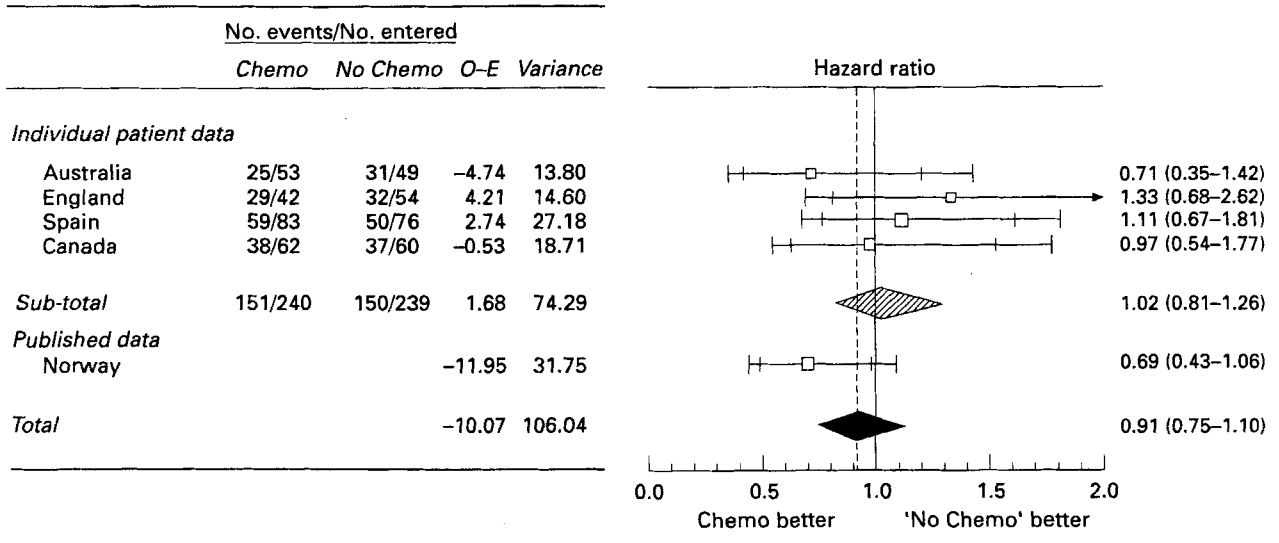

Fig. 3. Hazard ratio plot for trials with individual patient data supplemented with published data. HR = 0.91, 95% CI 0.75–1.10.

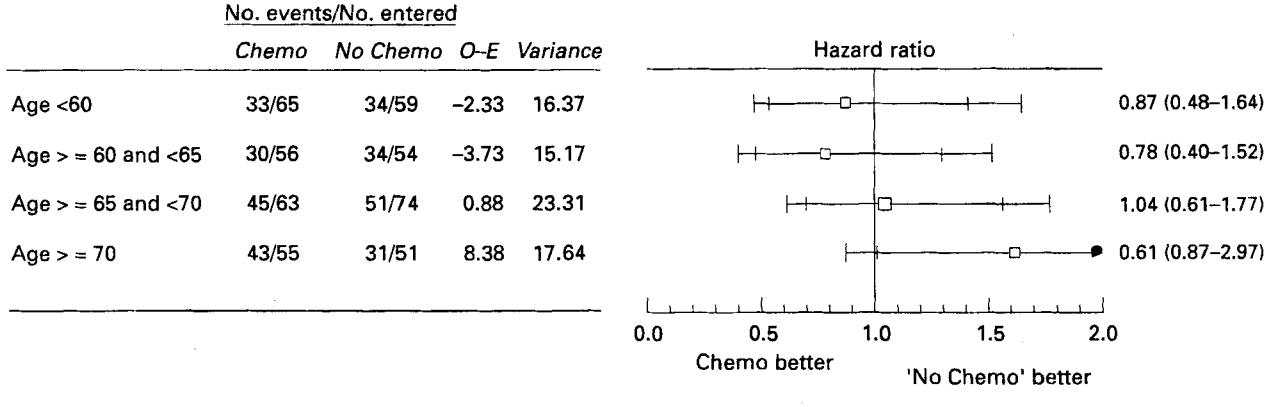

Fig. 4. Hazard ratio plot for the prognostic factor interaction: treatment × age. Test for trend $\chi^2 = 3.83$, d.f. = 3, $P = 0.05$.

Discussion

This overview has addressed the question of whether neoadjuvant chemotherapy in locally advanced bladder cancer improves survival. Despite combining the results of all relevant trials, there were still only 301 deaths on which conclusions could be based. Thus there is still insufficient information to answer this question reliably.

The results for each of the trials, and the overall results, are inconclusive. From the meta-analysis of individual patient data, the overall HR of 1.02 gives an estimated 1% detriment in absolute survival from the use of chemotherapy at 2 years (from 50 to 49%). However, the confidence intervals indicate that these overall results are consistent both with a possible absolute improvement in absolute survival of 7% (from 50 to 57%), and with a detriment of 8% (reducing 2-year survival from 50 to 42%).

When the individual patient-based analysis was supplemented with summary information from the published trial unavailable for inclusion in the meta-analysis, the overall HR of 0.91 gives an estimate of absolute improvement in 2-year survival of 3% (from 50 to 53%). However, the confidence intervals suggest that this result is consistent with an improvement at 2 years of 9% (from 50 to 59%) or, conversely, a possible reduction in survival of 3% (from 50 to 47%). It must be stressed that this result may not be reliable: individual patient data were not available from this trial and 14 patients were excluded from the published analysis — both of which could potentially bias the results.

A possible differential effect of treatment in different age groups is of particular interest. Although age has previously been identified as a prognostic factor in locally advanced bladder cancer [22], the results of this study *suggest* that chemotherapy may be more effective in younger patients (those under the age of 60 years), and appears to become less effective in, and possibly even

	No. events/No. entered			
	Chemo	*No Chemo*	*O–E*	*Variance*
Sex				
Male	114/188	126/196	−4.85	59.09
Female	37/52	24/43	4.93	14.30
Stage				
Stage 2	26/60	27/63	−1.71	12.08
Stage 3	99/145	90/138	5.54	46.71
Stage 4	26/34	33/38	−0.77	12.05
Grade				
Grade 2	15/25	9/14	−0.27	5.10
Grade 3	48/89	59/95	−5.02	26.61

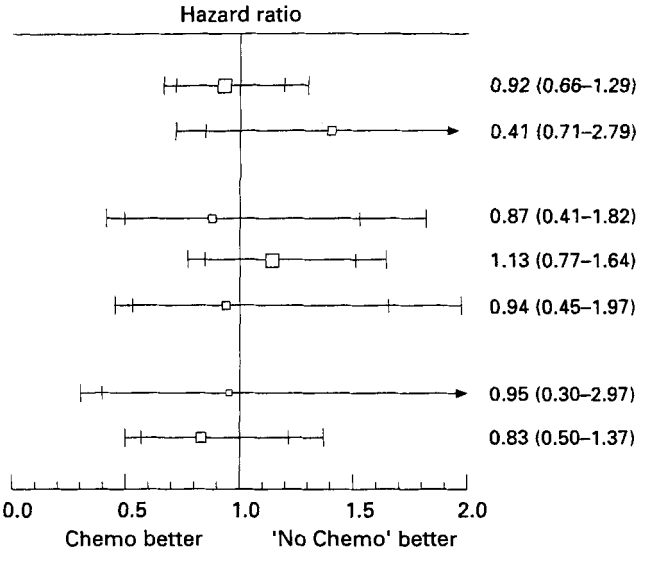

Fig. 5. Hazard ratio plot for the prognostic factor interactions: treatment × sex ($\chi^2 = 2.102$, $P = 0.15$), treatment × stage (trend $\chi^2 = 0.078$, $P = 0.78$) and treatment × grade, ($\chi^2 = 1.562$, $P = 0.21$).

detrimental to, patients over the age of 70 years. These results must be treated with caution as they are by no means conclusive, and this hypothesis was not specified in advance of the meta-analysis.

This result therefore awaits confirmation in further prospective randomized clinical trials. Of note was that these results are in contrast to those of two trials in patients with metastatic disease which suggested that older age groups fared better than younger age groups [23,24].

In general, it is believed that cisplatin in combination with other chemotherapeutic agents is more effective than cisplatin alone. As four of the five trials included in this overview used single-agent cisplatin, it could be argued that they did not use the best available chemotherapy. Indeed, the HR plots suggest that the largest treatment effect was observed in the single trial using combination chemotherapy, which may indicate some support for this hypothesis. However, because individual patient data were not available from this trial, it has not been possible to study in detail whether the patients differed in any way from the patients in the other four trials. This trial could, for example, have consisted of a predominantly younger group of patients. Furthermore, no randomized trial comparing single-agent cisplatin with cisplatin in combination, in the treatment of patients with locally advanced disease, has demonstrated statistically convincing differences in survival [25]. However, one randomized trial in patients with *metastatic* bladder cancer [25] has suggested that the M-VAC combination significantly increased the median survival of patients when compared with single-agent cisplatin.

Recently, there has been renewed interest in cisplatin-based *adjuvant* therapy, with the publication of two small randomized trials [27,28] which have indicated that survival may be improved using this form of chemotherapy. The editorial comments attached to these articles suggest that, because of the size and design of the trials, they must be regarded as encouraging, but inconclusive. When the results from more trials become available it may be that a meta-analysis of trials using adjuvant chemotherapy will provide a more reliable answer.

Implications for practice

From this meta-analysis it can be seen that if survival is the principal endpoint, neoadjuvant cisplatin-based chemotherapy cannot currently be recommended for routine use in patients with locally advanced bladder cancer. Although there is some evidence that chemotherapy sometimes has an important palliative effect in patients with more advanced disease [24], in the neoadjuvant setting it is relatively aggressive, and it is not clear whether any palliation would compensate for the toxicity of treatment. Unfortunately, there is little good comparative data available on this issue.

Implications for research

A reliable answer to the question posed in this meta-analysis will emerge only after more information from

appropriately sized randomized trials becomes available. Some information will result from an international randomized controlled trial co-ordinated by the British Medical Research Council and the European Organisation for Research and Treatment of Cancer, together with a number of other national groups [12], and from a South-West Oncology Group trial (SWOG). The international trial compares neoadjuvant CMV plus local definitive therapy with local definitive therapy alone, and aims to include at least 900 patients. As of 31 October 1994, 867 patients had been recruited. The SWOG trial compares cystectomy alone with neoadjuvant M-VAC followed by cystectomy, and aims to include 300 patients. Unfortunately, data from these trials will not be available for at least another 2–3 years. Until then it is likely that this question will remain unanswered. Thus any current randomized trial should still have a 'no chemotherapy' control arm.

Explanation of the hazard ratio plots

The HR is given along the horizontal axis, with the vertical line drawn through unity indicating equivalence or no difference between treatments. HR values to the right of this line favour the 'no chemotherapy' control group and those to the left favour the chemotherapy 'treatment' group. Each individual trial is represented by a square, the centre of which denotes the HR for that trial, with horizontal bars whose extremities denote the 99% CI and the inner tick marks the 95% CI. The size of the square is directly proportional to the amount of information in the trial. The black diamond at the foot of the plot gives the overall HR when the results of all trials are combined, the centre of which denotes the HR and the extremities the 95% CI. Similarly, the hatched diamonds represent the HR for sub-totalled results.

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