JOURNAL OF CLINICAL ONCOLOGY

International Phase III Trial Assessing Neoadjuvant Cisplatin, Methotrexate, and Vinblastine Chemotherapy for Muscle-Invasive Bladder Cancer: Long-Term Results of the BA06 30894 Trial

International Collaboration of Trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group

ABSTRACT

Purpose
This article presents the long-term results of the international multicenter randomized trial that investigated the use of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy in patients with muscle-invasive urothelial cancer of the bladder treated by cystectomy and/or radiotherapy. Nine hundred seventy-six patients were recruited between 1989 and 1995, and median follow-up is now 8.0 years.

Patients and Methods
This was a randomized phase III trial of either no neoadjuvant chemotherapy or three cycles of CMV.

Results
The previously reported possible survival advantage of CMV is now statistically significant at the 5% level. Results show a statistically significant 16% reduction in the risk of death (hazard ratio, 0.84; 95% CI, 0.72 to 0.99; $P = .037$, corresponding to an increase in 10-year survival from 30% to 36%) after CMV.

Conclusion
We conclude that CMV chemotherapy improves outcome as first-line adjunctive treatment for invasive bladder cancer. Two large randomized trials (by the Medical Research Council/European Organisation for Research and Treatment of Cancer and Southwest Oncology Group) have confirmed a statistically significant and clinically relevant survival benefit, and neoadjuvant chemotherapy followed by definitive local therapy should be viewed as state of the art, as compared with cystectomy or radiotherapy alone, for deeply invasive bladder cancer.

J Clin Oncol 29:2171-2177. © 2011 by American Society of Clinical Oncology

INTRODUCTION

In 1999, we published the first results of the largest ever randomized trial of neoadjuvant chemotherapy in muscle-invasive bladder cancer.[1] This was an international multicenter study comparing local radical treatment alone with local radical treatment preceded by three cycles of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy. The trial was open to patient entry between 1989 and 1995 and recruited 976 patients. The first analysis showed a conventionally nonsignificant 15% reduction in the risk of death after neoadjuvant chemotherapy (hazard ratio [HR], 0.85; 95% CI, 0.71 to 1.02; $P = .075$), which translated into an

absolute difference in 3-year survival of 5.5% (95% CI, −0.5% to 11%), with 3-year survival rates of 50% in patients who did not receive CMV and 55.5% in patients who did receive CMV.

At that time, the median length of follow-up for those patients still alive was 4 years. Also at that time, the survival benefit from neoadjuvant chemotherapy did not meet our prespecified clinical trial goal, and the study was reported as such. The study has now further matured, with a median length of follow-up for patients still alive of more than 8 years. Data for this analysis were locked in 2005. For a number of practical and institutional reasons (eg, centers closing down the trial to further follow-up), only a small amount of more recent data has been
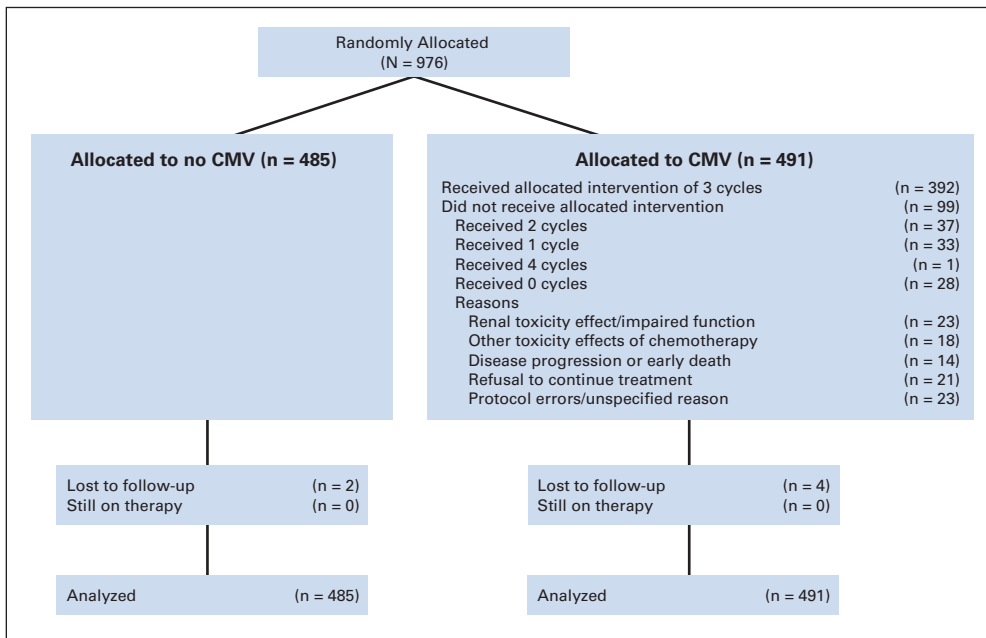
Fig 1. CONSORT diagram. CMV, cisplatin, methotrexate, and vinblastine.

forthcoming, and further analysis with longer follow-up is considered impracticable. The following updated results are presented as the definitive and final outcome of this important study.

PATIENTS AND METHODS

Full details of the trial design, patient eligibility, and treatment were published previously.[1] In summary, eligible patients had to have histologically proven muscle-invasive urothelial cell carcinoma of the bladder (T2 grade 3, T3, or T4a and N0/X, M0) and be considered suitable for curative treatment. Glomerular filtration rate had to be more than 50 mL/min, and informed consent of the patient needed to have been obtained. Figure 1 shows the trial design.

Chemotherapy

The CMV regimen used in this trial was as follows: day 1: methotrexate 30 mg/m^2 intravenous (IV) bolus and vinblastine 4 mg/m^2 IV bolus; day 2 before hydration: cisplatin 100 mg/m^2 IV infusion; day 2 after hydration: folinic acid 15 mg (oral or IV) every 6 hours for four doses commencing 24 hours after methotrexate on day 1; day 8: methotrexate 30 mg/m^2 IV bolus and vinblastine 4 mg/m^2 IV bolus; and day 9: folinic acid 15 mg (oral) every 6 hours for four doses after methotrexate on day 8. This schedule was repeated every 21 days for a total of three cycles. The protocol contained detailed dose reduction schedules, available on request.

Study Design, Outcome Measures, and Statistical Analysis

Random assignment was performed by a telephone call, facsimile, or computer connection to the Medical Research Council (MRC) Cancer Trials Office (now the MRC Clinical Trials Unit), European Organisation for Research and Treatment of Cancer Headquarters, National Cancer Institute of Canada Clinical Trials Group Central Office, or Australian National Health and Medical Research Council Clinical Trials Centre. A minimization method for randomly assigning patients was used, and patients were stratified by institution, choice of definitive treatment (cystectomy, radiotherapy, or radiotherapy plus cystectomy) and tumor stage. Each institution selected its preferred local treatment option (radiotherapy/cystectomy) to reduce individual bias in selection of treatments for specific patients.

Kaplan-Meier curves of overall and disease-specific survival, metastases-free survival, locoregional disease-free survival, overall disease-free survival, and locoregional control were compared using the two-sided log-rank test. All analyses were by intention to treat. To calculate the absolute difference in survival time and the other outcome measures between CMV and no CMV at fixed time points, the HR was applied to the event rate for the no CMV group.[2]

Overall survival was defined as the time from random assignment to death from any cause. Patients still alive were censored at the time of last follow-up. For disease-specific survival, only deaths caused by bladder cancer where considered events. Metastasis-free survival was defined as the

	3-Year Rate (%)				5-Year Rate (%)		10-Year Rate (%)				
End Point	No CMV	CMV	Difference	95% CI	No CMV	CMV	No CMV	CMV	HR	95% CI	P
Overall survival	50	56	6	0 to 11	43	49	30	36	0.84	0.72 to 0.99	.037
Metastasis-free survival	44	53	9	4 to 14	38	47	23	33	0.77	0.66 to 0.90	.001
Locoregional disease-free survival	41	46	5	0 to 10	34	39	22	27	0.87	0.75 to 1.01	.067
Disease-free survival	38	45	7	2 to 13	32	39	20	27	0.82	0.70 to 0.95	.008
Locoregional control	55	56	1	−5 to 7	50	51	39	40	0.96	0.80 to 1.15	.632

Table 1. End Points

Abbreviations: CMV, cisplatin, methotrexate, and vinblastine; HR, hazard ratio.

time from random assignment to first recognition of metastases or death. Patients who were alive and free from metastases were censored at the time of last follow-up. Locoregional disease-free survival was defined as the time from random assignment to reappearance of locoregional disease (invasive tumor within the bladder or pelvis) or death. Patients who were alive and free from locoregional disease were censored at the time of last follow-up. Disease-free survival was defined as the time from random assignment to reappearance of locoregional disease, metastases, or death. Patients who were alive and disease free were censored at the time of last follow-up. Locoregional control was defined as the time from random assignment to reappearance of locoregional disease (invasive tumor within the bladder or pelvis). Patients who were free from locoregional disease were censored at the time of last follow-up.

Exploratory interaction analyses were planned to assess whether CMV was more effective or less effective over no CMV (in terms of overall survival) in subgroups defined by all initial patient characteristics collected at random assignment and the chosen definitive treatment. To test for consistencies in the size of any effect of CMV, a χ^2 test for interaction was performed, or when appropriate, a χ^2 test for trend was performed. Kaplan-Meier curves of overall survival and locoregional disease-free survival were produced in subgroups of patients who actually received cystec-

tomy only and patients who actually received radiotherapy only, and the difference between CMV and no CMV in each subgroup was compared using the two-sided log-rank test.

The trial was originally powered to detect an absolute improvement in 2-year survival of 10% (50% increased to 60%; with a power approaching 90%, a two-sided significance level of 5% required 374 events). There was no correction of the P value to adjust for the previous analysis.

RESULTS

Between November 1989 and July 1995, 976 patients were recruited from 106 institutions in 20 countries by seven different national or international clinical groups; 491 patients were randomly assigned to receive CMV, and 485 patients were assigned to not receive CMV. The initial patient characteristics and choice of local radical treatment have been published previously[1] and were balanced between arms. In summary, 34% (n = 334), 58% (n = 567), and 8% (n = 75) of patients had T2, T3, and T4a disease, respectively; 88% (n = 854) had
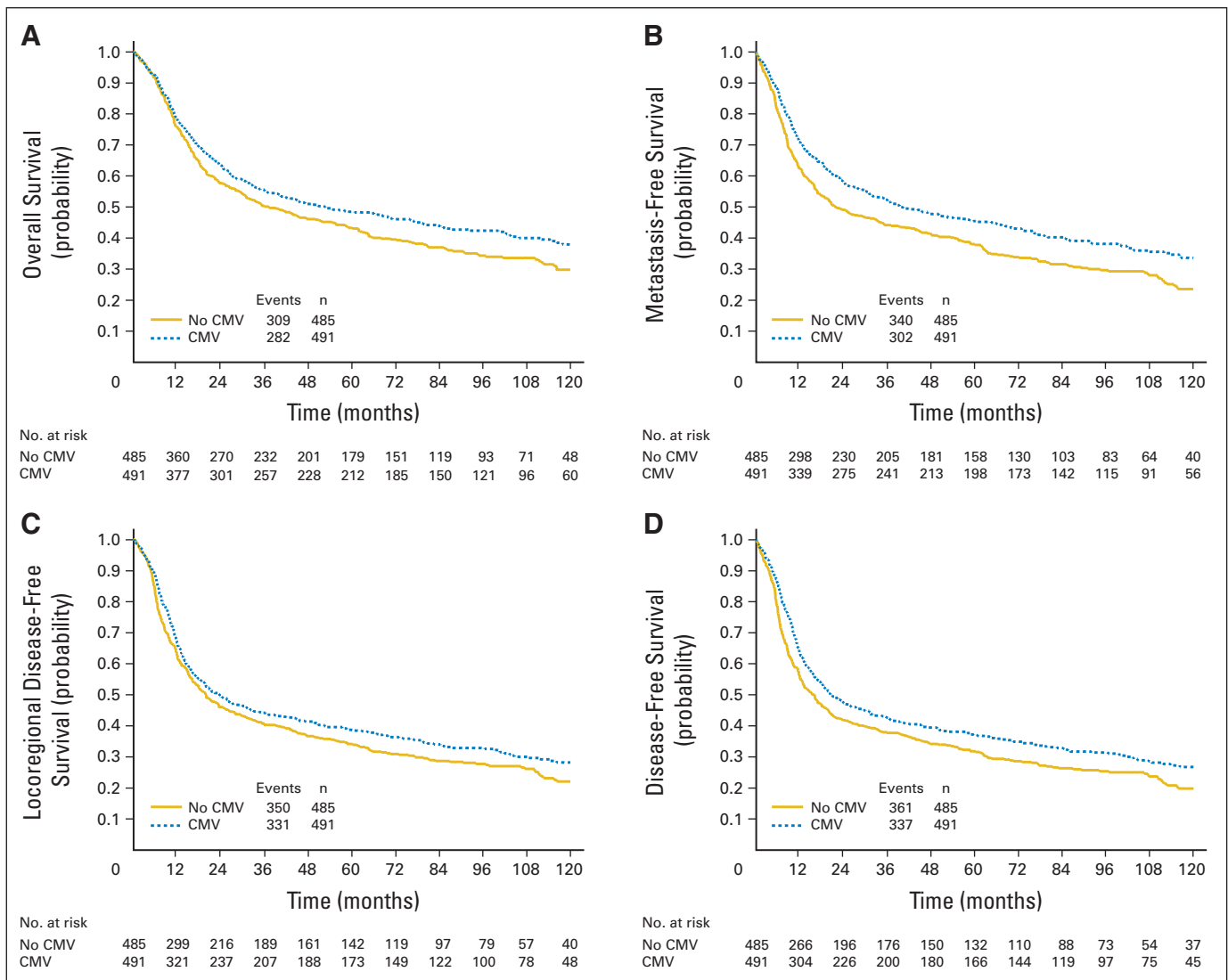

Fig 2. Kaplan-Meier curves for (A) overall survival, (B) metastasis-free survival, (C) locoregional disease-free survival, and (D) disease-free survival. CMV, cisplatin, methotrexate, and vinblastine.

2173

grade 3 disease; and 65% (n = 634) had N0. The median age was 64 years; 88% of patients (n = 863) were male; and 43% (n = 415), 50% (n = 485), and 8% (n = 76) of patients chose the local radical treatment of radiotherapy, cystectomy, and a combination of radiotherapy and cystectomy, respectively. In this updated analysis, the median follow-up time for patients still alive is 8.0 years (interquartile range, 5.7 to 10.2 years), and the maximum follow-up time is 13.9 years.

Primary End Points

The updated results for overall survival, metastases-free survival, locoregional disease-free survival, disease-free survival, and locoregional control are listed in Table 1 and shown in Figure 2. The results show a conventionally statistically significant 16% reduction in the risk of death (HR, 0.84; 95% CI, 0.72 to 0.99; $P = .037$), 23% reduction in the risk of metastases or death (HR, 0.77; 95% CI, 0.66 to 0.90; $P = .001$), 13% reduction in the risk of local disease or death (HR, 0.87; 95% CI, 0.75 to 1.01; $P = .067$), 18% reduction in the risk of disease or death (HR, 0.82; 95% CI, 0.70 to 0.95; $P = .008$), and 4% reduction in the risk of locoregional relapse (HR, 0.96; 95% CI, 0.80 to 1.15; $P = .632$) after CMV.

Cause of Death

A total of 591 patients have died (Table 2). The main cause of death was bladder cancer, which was attributed to 72% of deaths (223 of 309 deaths) in patients who did not receive CMV and 70% of deaths (198 of 282 deaths) in patient who received CMV. An exploratory analysis of disease-specific survival resulted in an HR of 0.83 (95% CI, 0.68 to 1.00; $P = .050$). Table 2 shows cause of death according to the type of definitive treatment actually received.

The addition of CMV to standard treatment resulted in a 16% reduction in the overall risk of death from all causes. Inevitably, the potential benefit of chemotherapy will have been compromised by any treatment-related deaths. Chemotherapy-related mortality was 1%, operative mortality after cystectomy was 3.7%, and one death was attributed to radiotherapy.

Treatment-Related Mortality

Trialists were concerned from the outset that the operative risks of cystectomy might be magnified by preoperative chemotherapy or that CMV itself might cause treatment-related deaths, including more

cardiovascular toxicity. Table 2 shows that neither treatment was risk free, but chemotherapy-related mortality was low (1%) and less than half that reported for methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in a subsequent international trial of MVAC versus gemcitabine plus cisplatin.[3]

Salvage Chemotherapy

Twenty-nine patients in the CMV arm and 84 patients in the no CMV arm received some form of salvage chemotherapy. Given the efficacy of chemotherapy observed in this trial and other studies, salvage chemotherapy is unlikely to have influenced overall survival, although it is recognized that the true impact of salvage chemotherapy given in this situation cannot be determined with certainty.

Interaction Analyses

As reported previously, there is a suggestion (for overall survival) that neoadjuvant CMV may have had a greater effect in the following three subgroups: patients with better renal function, larger tumor size, or poorly differentiated tumors (data not shown). There was no evidence that neoadjuvant CMV had a greater or lesser effect in subgroups of choice of definitive treatment (radiotherapy, cystectomy, or radiotherapy plus cystectomy; test of interaction χ^2 value [df] = 0.112 [2]; $P = .946$).

Radiotherapy Versus Cystectomy

The choice of definitive treatment used in this trial was based on patient or physician choice and was not randomly assigned, and the trial was designed explicitly not to compare various definitive local treatments. Thus, no conclusions should be drawn from the data presented concerning the relative merit of cystectomy compared with radiotherapy. In Norway, preoperative radiotherapy was carried out, but there were insufficient numbers to analyze separately.

The importance of this caution is endorsed by the finding that although some patient and tumor characteristics were well balanced in the two groups (Table 3), fewer patients receiving radiotherapy, compared with patients who underwent cystectomy, had a WHO performance status of 0 (55% [223 of 403 patients] v 82% [353 of 428 patients], respectively), fewer patients had T2 tumors (31% [124 of 403 patients] v 38% [162 of 428 patients], respectively), fewer patients were N0 (62% [248 of 403 patients] v 75% [319 of 428 patients],

	No CMV (No. of patients)					**CMV (No. of patients)**					**Total Patients**	
	Definitive Treatment Received					**Definitive Treatment Received**						
Cause of Death	RT	Preoperative RT + Cystectomy	Cystectomy	Missing	Total	RT	Preoperative RT + Cystectomy	Cystectomy	Missing	Total	No.	%
Total patients	210	33	212	30	485	193	33	216	49	491	976	
Patients who died	144	18	126	21	309	120	14	107	41	282	591	
Cause of death												
Disease related (TCC)	116	9	80	18	223	93	12	75	18	198	421	71
Treatment related	0	1	15	0	16	1	0	8	7	16	32	5
Other malignancy	8	2	9	0	19	6	0	5	1	12	31	5
Cardiovascular	9	0	11	1	21	9	0	10	9	28	49	8
Other cause	10	5	8	1	24	10	2	6	5	23	47	8
Missing	1	1	3	1	6	1	0	3	1	5	11	2

Table 2. Cause of Death According to the Type of Definitive Treatment Actually Received

Abbreviations: CMV, cisplatin, methotrexate, and vinblastine; RT, radiotherapy; TCC, transitional cell carcinoma.

	RT (n = 403)		Preoperative RT + Cystectomy (n = 66)		Cystectomy (n = 428)	
Characteristic	No. of Patients	%	No. of Patients	%	No. of Patients	%
Tumor stage						
T2	124	31	24	36	162	38
T3	256	64	37	56	230	54
T4a	23	6	5	8	36	8
Histologic grade (local pathologist)						
1/2	59	15	8	12	45	11
3	344	85	58	88	382	89
Missing	0		0		1	
Nodal status						
N0	248	62	10	15	319	75
NX	155	38	56	85	109	25
Age, years						
< 55	55	14	13	20	87	20
55-65	151	37	33	50	195	46
> 65	197	49	20	30	146	34
Sex						
Male	348	86	57	86	389	91
Female	55	14	9	14	39	9
WHO performance status						
0	223	55	48	73	353	82
1	153	38	18	27	66	15
2/3	27	7	0	0	9	2
Tumor size, cm						
≤ 2.5	75	19	20	33	66	16
2.6-5.0	247	62	35	53	291	69
> 5	77	19	11	17	66	16
Missing	4		0		5	
Calculated GFR, mL/min						
< 50	38	9	2	3	33	8
50-59	113	28	17	26	99	23
60-69	251	62	47	71	292	69
Missing	1		0		4	

Table 3. Patient Demographics and Clinical Characteristics by Radiotherapy and Cystectomy Groups

Abbreviations: RT, radiotherapy; GFR, glomerular filtration rate.

respectively), and more patients were older than age 65 years (49% [197 of 403 patients] *v* 34% [146 of 428 patients], respectively). It seems that there was an element of selection when choosing definitive treatment so that survival after these two different forms of treatment should not be compared.

The interaction analysis (previous section) and Figures 3A and 3B show an important finding, namely, that for overall survival, there was no evidence that neoadjuvant CMV was more or less effective when combined with either radiotherapy or cystectomy. A total of 403 patients received radiotherapy alone, and 428 patients received cystectomy alone. The reductions in the risk of death with CMV were 20% and 26% for the radiotherapy alone and cystectomy alone groups, respectively (radiotherapy alone: HR, 0.80; 95% CI, 0.63 to 1.02; $P = .070$; cystectomy alone: HR, 0.74; 95% CI, 0.57 to 0.96; $P = .022$).

For locoregional disease-free survival (Figs 3C and 3D), there was some evidence of a greater impact with CMV over no CMV given before cystectomy (a 26% reduction in risk; HR, 0.74; 95% CI, 0.58 to 0.95; $P = .019$) than the same chemotherapy given before radiotherapy (a 9% reduction in risk; HR, 0.91; 95% CI, 0.73 to 1.14; $P = .417$). However, this may be explained by the different patient and tumor characteristics discussed earlier.

DISCUSSION

This analysis of mature data shows that the previously reported possible survival advantage of CMV observed in the first analysis is now statistically significant at the 5% level and, although the estimates of HRs have remained relatively unchanged, the increase in the number of events has resulted in a narrowing of the 95% CIs. Three cycles of CMV before cystectomy or radiotherapy results in a 16% reduction in the risk of death, corresponding to an increase in 3-year survival from 50% to 56%, 10-year survival from 30% to 36%, and median survival time of 7 months (from 37 to 44 months).

CMV did not result in more cardiovascular deaths. Some might consider the number of cystectomy-related deaths (3.7%) to be high,[4] but this operative mortality rate was lower than that reported in one of the largest reviews of cystectomies performed in the United States[5] during the years covered by the trial. Thus, there is no evidence to suggest that the addition of neoadjuvant CMV made cystectomy (or radiotherapy) more dangerous in this trial.

At both the outset (1989) and the conclusion (1995) of the trial, more than 70% of participating clinicians were of the opinion that an
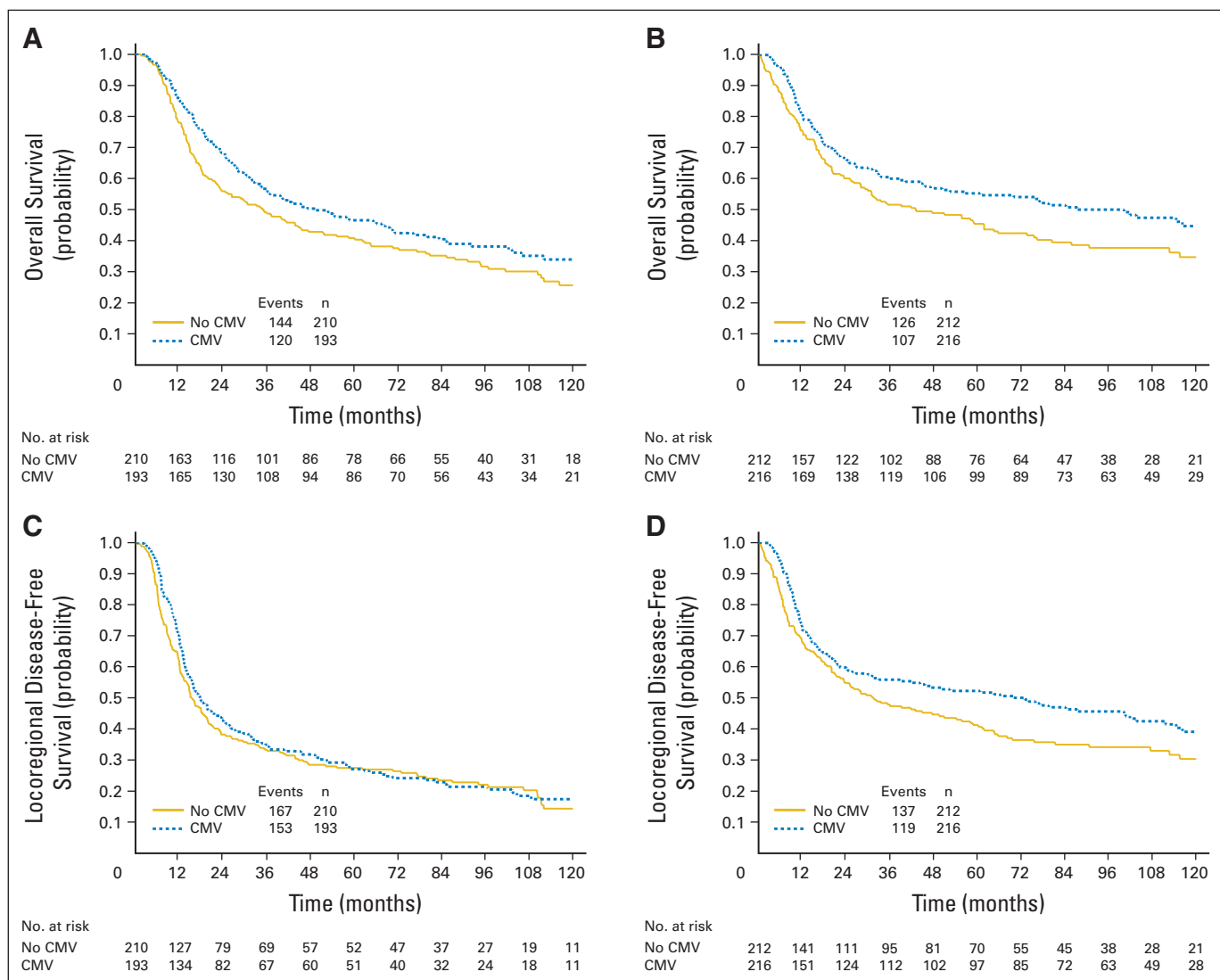
Fig 3. Overall survival in patients who received (A) radiotherapy only and (B) cystectomy only. Locoregional disease-free survival in patients who received (C) radiotherapy only and (D) cystectomy only. CMV, cisplatin, methotrexate, and vinblastine.

improvement in survival of 10% would be needed to justify the use of neoadjuvant CMV in routine practice. This magnitude of benefit has not been achieved with this trial, which shows, along with the meta-analysis published in 2005 by the Advanced Bladder Cancer Collaboration,[6,7] a clear benefit in overall survival of only 5% to 6% at 3 years.

As is common practice, the end point of locoregional disease-free survival has been defined to include the presence of tumor in the pelvis, distant metastases, and death. This is not helpful from the clinical perspective because the inclusion of distant metastases and death in the definition may overshadow the serious clinical problem of bladder cancer persisting or recurring in the pelvis after completion of definitive treatment. Thus, in Table 2, we have added data for locoregional control (HR, 0.96; 95% CI, 0.80 to 11.5; $P = .632$). These show no significant benefit from the addition of CMV to either radiotherapy or cystectomy, a finding that may be surprising but is important given the high local relapse rate in this situation and its symptomatic consequences for the patient.

Another measure of local control is the number of patients who underwent salvage cystectomy for tumor relapse in the bladder after

radiotherapy. It was hoped that the addition of CMV to radiotherapy would improve eradication of primary tumor, but we observed no evidence to support any benefit.

Overall, 49% of patients (240 of 491 patients) who received CMV were reported to have developed locoregional relapse compared with 48% of patients (231 of 485 patients) who did not receive CMV. In patients who received radiotherapy as definite treatment, 57% of patients (120 of 210 patients) who received CMV were reported to have developed locoregional relapse compared with 62% of patients (120 of 193 patients) who did not receive CMV. In patients who received cystectomy as definite treatment, 40% of patients (84 of 212 patients) who received CMV were reported to have developed locoregional relapse compared with 39% of patients (84 of 216 patients) who did not receive CMV.

The Southwest Oncology Group (SWOG) study published in 2003[8] enrolled 317 patients onto a study of neoadjuvant MVAC before cystectomy versus cystectomy alone and showed a 25% reduction in the risk of death with the addition of MVAC (HR, 0.75; 95% CI, 0.57 to 1.00; $P = .06$). In our study, although we have observed a smaller

reduction in risk of death with CMV (ie, 16%), this was statistically significant at the 5% level and included both cystectomy and radiotherapy patients. When analyzing patients in our trial who only had cystectomy (n = 428), a similar population to that of the SWOG study, we found a similar effect size (HR, 0.74; 95% CI, 0.57 to 0.96; P = .022), although these results should be interpreted with caution because in our trial the choice of whether to give patients cystectomy or radiotherapy was based on patient or physician choice and was not randomly assigned and there is some evidence to suggest there was an element of patient selection. In the SWOG trial, 33% of evaluable patients (n = 50) had grade 4 (severe) granulocytopenia, with 17% of patients (n = 26) experiencing grade 3 GI toxicity (nausea, vomiting, stomatitis, diarrhea, or constipation). In our study, as reported in the initial analysis,[1] although serious adverse effects from CMV chemotherapy were not common, five patients assigned to chemotherapy died from toxic effects during treatment (mortality rate, 1%). Data on nausea and vomiting were not collected, but anecdotal reports suggest that they were common despite the recommended use of antiemetics according to institutional practice. WHO grade 3 or 4 leukopenia, thrombocytopenia, and neutropenic fever occurred in 16%, 6.5%, and 10% of patients, respectively. No grade 3 or 4 renal toxic effects occurred, but 26% of patients required dose decreases or delay (according to protocol) because of impaired renal function.

How patients and clinicians apply the findings from this trial will vary, and although improvements of this magnitude have resulted in the wide use of adjuvant treatment in a number of other cancers (including breast, colon, ovary, and stomach), the increase in survival will need to be balanced against the toxicity and other disadvantages of chemotherapy (eg, the cost to the patient in terms of treatment time and impact on quality of life). This is a decision each doctor has to make with each patient.

Although the combination of gemcitabine with cisplatin has shown comparable efficacy and lesser toxicity when compared with MVAC,[3] no new agent or combination has yet shown any evidence of being more active or effective than CMV or MVAC. Although reduced morbidity is welcome, it is significantly increased efficacy that is required. Also of importance, no randomized trial has shown that gemcitabine plus cisplatin confers an equivalent survival benefit in the neoadjuvant context.

Since completion of the trial in 1995, other chemotherapy regimens have been introduced for advanced urothelial cancer,[9-11] and some authors have suggested that they should be tested in new trials of adjuvant or neoadjuvant therapy. It would seem that although overall response rates of 50% to 60% and complete response rates of 20% may be encouraging indicators of activity in phase II studies, they may not predict a major increment in cure rate in phase III studies in the (neo)adjuvant setting, and it is likely that only modest improvements will be achieved. Therefore, to ultimately get considerable improvements for both individuals and populations, a series of modest improvements to be added together may be required, as opposed to one breakthrough treatment. We believe that future trials should consider new strategies for treatment development such as the development of new surrogate end points/biomarkers and targeted agents that may provide better evidence of treatment activity and individualized treatment strategies that may result in larger improvements in specific subpopulations.

We conclude that CMV chemotherapy improves outcome as first-line adjunctive treatment for invasive bladder cancer. Neoadjuvant CMV or MVAC chemotherapy followed by definitive local therapy should constitute the state of the art for fit patients with deeply invasive bladder cancer, as compared with cystectomy or radiotherapy alone.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Reginald Hall, Richard Sylvester, Derek Raghavan, Mahesh K.B. Parmar
Provision of study materials or patients: Reginald Hall
Collection and assembly of data: Richard Sylvester, Derek Raghavan, Mahesh K.B. Parmar
Data analysis and interpretation: Gareth Griffiths, Richard Sylvester, Derek Raghavan, Mahesh K.B. Parmar
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. International Collaboration of Trialists: Neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle-invasive bladder cancer: A randomised controlled trial. Lancet 354:533-540, 1999

2. Parmar MKB, Machin D: Survival Analysis: A Practical Approach. Chichester, United Kingdom, John Wiley & Sons, 1995

3. von der Maase H, Sengelov L, Roberts JT, et al: Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 23:4602-4608, 2005

4. Rosario DJ, Becker M, Anderson JB: The changing pattern of mortality and morbidity from radical cystectomy. BJU Int 85:427-430, 2000

5. Hollenbeck BK, Wei Y, Birkmeyer JD: Volume, process of care, and operative mortality for cystectomy for bladder cancer. Urology 69:871-875, 2007

6. Advanced Bladder Cancer Meta-Analysis Collaboration: Neoadjuvant chemotherapy in invasive bladder cancer: Update of a systematic review and meta-analysis of individual patient data. Eur Urol 48:202-206, 2005

7. Advanced Bladder Cancer Meta-Analysis Collaboration: Adjuvant chemotherapy in invasive bladder cancer: A systematic review and meta-analysis of individual patient data. Eur Urol 48:189-201, 2005

8. Grossman HB, Natale RB, Tangen CM, et al: Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 349:859-866, 2003

9. Stenzl A, Cowan NC, De Santis M, et al: The updated EAU guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 55:815-825, 2009

10. Pliarchopoulou K, Laschos K, Pectasides D: Current chemotherapeutic options for the treatment of advanced bladder cancer: A review. Urol Oncol [epub ahead of print on September 13, 2010]

11. Volpe A, Racioppi M, D'Agostino D, et al: Advanced bladder cancer: New agents and new approaches—A review. Urol Oncol [epub ahead of print on September 21, 2010]

■ ■ ■