

Long-Term Survival Results of a Randomized Trial Comparing Gemcitabine Plus Cisplatin, With Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin in Patients With Bladder Cancer

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ABSTRACT

Purpose

To compare long-term survival in patients with locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium treated with gemcitabine/cisplatin (GC) or methotrexate/vinblastine/doxorubicin/cisplatin (MVAC).

Patients and Methods

Efficacy data from a large randomized phase III study of GC versus MVAC were updated. Time-to-event analyses were performed on the observed distributions of overall and progression-free survival.

Results

A total of 405 patients were randomly assigned: 203 to the GC arm and 202 to the MVAC arm. At the time of analysis, 347 patients had died (GC arm, 176 patients; MVAC arm, 171 patients). Overall survival was similar in both arms (hazard ratio [HR], 1.09; 95% CI, 0.88 to 1.34; $P = .66$) with a median survival of 14.0 months for GC and 15.2 months for MVAC. The 5-year overall survival rates were 13.0% and 15.3%, respectively ($P = .53$). The median progression-free survival was 7.7 months for GC and 8.3 months for MVAC, with an HR of 1.09. The 5-year progression-free survival rates were 9.8% and 11.3%, respectively ($P = .63$). Significant prognostic factors favoring overall survival included performance score (> 70), TNM staging (M0 v M1), low/normal alkaline phosphatase level, number of disease sites ($\leq$ three), and the absence of visceral metastases. By adjusting for these prognostic factors, the HR was 0.99 for overall survival and 1.01 for progression-free survival. The 5-year overall survival rates for patients with and without visceral metastases were 6.8% and 20.9%, respectively.

Conclusion

Long-term overall and progression-free survival after treatment with GC or MVAC are similar. These results strengthen the role of GC as a standard of care in patients with locally advanced or metastatic TCC.

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INTRODUCTION

Combination chemotherapy is the treatment of choice for patients with inoperable locally advanced or metastatic bladder cancer. On the basis of superior efficacy in phase III studies, the methotrexate/vinblastine/doxorubicin/cisplatin (MVAC) regimen be-

came frequently used.¹⁻⁴ However, MVAC treatment is associated with substantial toxicities and a toxic death rate of approximately 3% to 4%.^{2,3} Thus, a need for alternative therapies that can provide a better survival outcome or a similar survival benefit without the inherent toxicity of the MVAC regimen was identified.

On the basis of encouraging results with gemcitabine and cisplatin (GC) in several phase II bladder cancer studies,⁵ an international, multicenter, randomized phase III study in 405 patients was performed to compare overall survival between GC- and MVAC-treated patients with locally advanced or metastatic transitional cell carcinoma (TCC) of the urothelium.⁶ This study showed similar efficacy with regard to overall survival (GC, 13.8 months; MVAC, 14.8 months), time to progressive disease (GC, 7.4 months; MVAC, 7.4 months), and response rate (GC, 49.4%; MVAC, 45.7%); however, a better safety profile was observed with GC, resulting in significantly less febrile neutropenia, neutropenic sepsis, and mucositis than with MVAC. In addition, a recent cost-utility analysis of the GC versus MVAC regimens based on data from the United Kingdom concluded that GC offered reasonable value in this disease setting.⁷ The detailed results of the GC versus MVAC study have been reported in this journal⁶ and led to the widespread use and approval of the GC combination in more than 60 countries throughout the world.

The median length of follow-up of the patients in this study at the time of the initial report was 19 months, and uncertainties remained regarding the long-term efficacy of the GC combination, especially compared with MVAC. We therefore performed an updated analysis of overall survival and other time-to-event end points 5 years after the last patient was enrolled onto the study. In addition, as in the initial publication, prespecified patient characteristics were investigated for their importance as prognostic factors. An update on the safety results was not performed, given that

all patients had already completed their chemotherapy at the time of the first survival analysis, and therefore, no changes were to be expected from a new analysis.

PATIENTS AND METHODS

Eligibility Criteria

The details of the study have been reported in detail in this journal.⁶ In summary, eligible patients had measurable or assessable, histologically proven, locally advanced (T4b, N2, or N3) or metastatic (M1) TCC of the urothelium. Prior immunotherapy or chemotherapy was not allowed. Prior local intravesical therapy, radiation, or immunotherapy was permitted if it was completed at least 4 weeks before enrollment. Eligible patients were required to have Karnofsky performance score (PS) of 70 or more, adequate bone marrow reserve (WBC count $\geq 3.5 \times 10^9/L$, platelets $\geq 100 \times 10^9/L$, and hemoglobin ≥ 10 g/dL) and renal function (creatinine clearance ≥ 60 mL/min), and an estimated life expectancy of at least 12 weeks. This study was conducted according to the ethical principles of the Declaration of Helsinki, the applicable guidelines for Good Clinical Practice, or the applicable laws and regulations of the countries where the study was conducted, whichever represented the greater protection of the individual. Written informed consent was obtained from all patients before random assignment.

Patient Characteristics

Patient characteristics were generally well balanced across treatment arms (Table 1). A total of 137 patients had locally advanced disease (34%) and 268 patients had metastatic disease (66%), respectively. Visceral metastases were present in a total of 132 patients (33%).

Table 1. Baseline Patient Characteristics

Parameter	GC Arm (n = 203)		MVAC Arm (n = 202)	
	No. of Patients	%	No. of Patients	%
No. of patients randomly assigned to treatment	203		202	
Male	160	78.8	160	79.2
Median age, years	63.0		63.0	
White	197	97.0	197	97.5
Karnofsky performance score $\geq 80^*$	165	82.5	159	81.1
TNM stage				
Any T, any N, M0	60	29.6	72	35.6
Any T, any N, M1	141	69.5	127	62.9
Any T, any N, Mx	2	1.0	3	1.5
Visceral metastases	99	48.8	93	46.0
4 or more sites of disease	42	20.7	35	17.3
High alkaline phosphatase†	56	28.6	51	26.0
Patients with measurable disease	182	89.7	181	89.6
Prior treatment				
Intravesical therapy	28	13.8	23	11.4
Cystectomy	77	37.9	79	39.1
Radiation	27	13.3	23	11.4

Abbreviations: GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin.

*Baseline n = 200 for GC, n = 196 for MVAC.

†Baseline n = 196 for GC, n = 196 for MVAC.

Study Design and Treatment Evaluation

Patients were randomly assigned to receive either GC or MVAC in this phase III, active controlled, open-label, randomized study. The Pocock and Simon minimization method was used to perform treatment allocation by the Netherlands Cancer Institute.⁸ Before random assignment, patients were stratified according to the following criteria: PS, stage, visceral metastases, alkaline phosphatase level, prior radiotherapy, measurable disease, and investigator site. Patients in the GC arm were randomly assigned to receive gemcitabine 1,000 mg/m² during 30 to 60 minutes on days 1, 8, and 15, plus cisplatin 70 mg/m² on day 2. Patients in the MVAC arm were randomly assigned to receive methotrexate 30 mg/m² on days 1, 15, and 22; vinblastine 3 mg/m² on days 2, 15, and 22; doxorubicin 30 mg/m² on day 2; and cisplatin 70 mg/m² as a 1- to 8-hour infusion on day 2. Cycles were repeated every 28 days.

In both arms, cycles were not initiated unless WBC was $\geq 3.0 \times 10^9/L$ and platelets were $\geq 100 \times 10^9/L$. If a cycle was delayed for more than 4 weeks, patients were taken off the study. In the GC arm, gemcitabine doses on day 8 or 15 were omitted for WBC $\leq 1.99 \times 10^9/L$ and platelets $\leq 49 \times 10^9/L$. In the MVAC arm, methotrexate or vinblastine doses on day 15 or 22 were delayed for WBC $\leq 2.9 \times 10^9/L$ and platelets $\leq 74 \times 10^9/L$. Doses were adjusted for nonhematologic toxicity, including mucositis, in both study arms. Patients received a maximum of six cycles of treatment unless they experienced disease progression, developed unacceptable toxicity, or the patient, attending physician, or sponsor requested discontinuation.

Supportive care, including blood transfusions, antiemetics, and analgesics, was permitted as appropriate. In the absence of disease progression, palliative radiotherapy was allowed for pre-existing, painful bony lesions. Prophylactic use of growth factors such as filgrastim was not recommended in either arm. No other antineoplastic therapy was permitted during the study.

Blood counts and serum chemistries were performed weekly, and creatinine clearance was calculated before chemotherapy administration. PS was assessed before each cycle, and weight was measured weekly. Tumors were assessed using WHO criteria, and were performed radiologically and by physical examination. Tumors were reassessed every two cycles, and responses were confirmed after at least 4 weeks.

Overall survival was measured from the date of random assignment until death. Patients who had not died or who were lost to follow-up were censored for overall survival when they were last known to be alive. Progression-free survival was measured from the date of random assignment until death or progression. Patients who were alive and who had not experienced disease progression, or who were lost to follow-up, were censored for progression-free survival at the date that they were last known to be alive and progression free.

Statistical Considerations

The Kaplan-Meier method was used to calculate time-to-event end points, which were compared using the log-rank and Wilcoxon tests. For both end points, the 5-year survival rate was computed for each treatment arm using the Kaplan-Meier method and compared based on a normal approximation for the difference between the rates. The Cox proportional hazards model was used to examine the effects of prespecified baseline prognostic factors, including PS, TNM stage, presence of visceral metastases, alkaline phosphatase level, number of disease sites, prior radiotherapy, disease measurability, age, sex, and time to diagnosis. The

Wald test was used to calculate *P* values. Factors that showed individual prognostic value in univariate models were used to examine their joint prognostic value in a multivariate model. A final model was developed using a backward selection strategy. This strategy involved eliminating the factor with the largest non-significant *P* value in a sequential fashion until all factors remaining were statistically significant. Treatment was added to the final model to assess its effect when adjusted for the presence of important prognostic factors.

RESULTS

Between November 1996 and September 1998, 426 patients were entered onto the study. From this group, 405 patients were randomly assigned: 203 to the GC arm and 202 to the MVAC arm. Nineteen patients did not meet protocol entry criteria, one patient died as a result of bladder cancer before random assignment, and one patient did not continue because of personal reasons. For this analysis, the database was locked in April 2004 (ie, more than 5 years after the last patient had been enrolled onto the study).

Long-Term Overall Survival

At the time of our initial analysis,⁶ 274 patients had died (GC, 139 patients; MVAC, 135 patients), producing a censoring rate of 32%. In this survival update, 347 patients had died (GC, 176 patients; MVAC, 171 patients), producing a censoring rate of 14%. As of April 2004, 58 patients were still alive (GC, 27 patients; MVAC, 31 patients); 16 patients in the GC arm and 21 patients in the MVAC arm were still in complete remission. Overall survival was similar on both arms (hazard ratio [HR], 1.09; 95% CI, 0.88 to 1.34; *P* = .66; Fig 1; Table 2). Median survival was 14.0 months (95% CI, 12.3 to 15.5 months) with GC, and 15.2 months (95% CI, 13.2 to 17.3 months) with MVAC. The differences in survival rates at 24 months (GC, 25.0%; MVAC, 31.0%), 48 months (GC, 16.4%; MVAC, 17.3%), and 60 months (GC, 13.0%; MVAC, 15.3%) were not significant (Table 2).

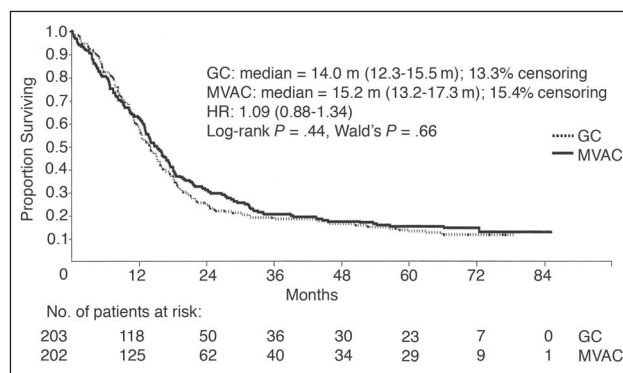


Fig 1. Kaplan-Meier curves for overall survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

Table 2. Overall Survival Summary

Parameter	GC Arm (n = 203)		MVAC Arm (n = 202)		Comparison <i>P</i>
	No.	95% CI	No.	95% CI	
Patients censored	27		31		
%	13.3		15.3		
No. of events (death)	176		171		
Minimum, months	0.23		0.26		
25th percentile	8.3	7.3 to 10.3	7.4	6.2 to 9.2	
Median, months	14.0	12.3 to 15.5	15.2	13.2 to 17.3	
75th percentile	24.1	19.3 to 31.7	30.8	23.8 to 39.5	
Maximum, months	> 78.8		> 85.1		
Log-rank <i>P</i>	.4431				
Hazard ratio	1.09	0.88 to 1.34			
12-month survival rate	58.4	51.6 to 65.2	62.6	55.9 to 69.3	.3963
24-month survival rate	25.0	19.0 to 31.0	31.0	24.6 to 37.4	.1795
36-month survival rate	19.0	13.6 to 24.4	20.4	14.8 to 26.0	.7307
48-month survival rate	16.4	11.2 to 21.5	17.3	12.0 to 22.6	.7996
60-month survival rate	13.0	8.3 to 17.8	15.3	10.3 to 20.3	.5260

Abbreviations: GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin.

Univariate analyses were performed on prognostic groups based on several prespecified factors, including PS and visceral metastases (Table 3). A multivariate analysis of all significant prognostic factors was conducted using backward selection to determine the final model. Independent prognostic factors adversely affecting overall survival included PS (> 70), TNM staging (M0 *v* M1), low/normal alkaline phosphatase expression, number of sites of disease (< 3), and the absence of visceral metastasis. When treatment was added to this final model of significant prognostic factors, there was no treatment effect for overall survival. Again, there was a similar survival between the two

arms. The adjusted HR for overall survival was 0.99 (95% CI, 0.79 to 1.23; Wald $P = .93$).

Long-Term Progression-Free Survival

At the time of our initial analysis,⁶ 334 patients had experienced disease progression or died (GC, 171 patients; MVAC, 163 patients), producing a censoring rate of 17.5%. In this updated report, 362 patients had experienced disease progression or died (GC, 184 patients; MVAC, 178 patients), producing a censoring rate of 10.6%. Progression-free survival was similar in the two arms (HR, 1.09; 95% CI, 0.89 to 1.34; $P = .63$) as shown in Figure 2. The median

Table 3. Prespecified Prognostic Factors

Prognostic Factor	GC Arm (n = 203)		MVAC Arm (n = 202)		Effect on OS			Effect on PFS		
	No.	%	No.	%	HR*	95% CI	Wald <i>P</i>	HR*	95% CI	Wald <i>P</i>
KPS: good (> 70) <i>v</i> poor (70)	165 <i>v</i> 34	81.3 <i>v</i> 16.7	159 <i>v</i> 34	78.7 <i>v</i> 16.8	2.11	1.60 to 2.77	< .0001†	2.01	1.53 to 2.64	< .0001†
Missing	4	2.0	9	4.5						
TNM staging: M0 <i>v</i> M1	60 <i>v</i> 141	29.6 <i>v</i> 69.5	72 <i>v</i> 127	35.6 <i>v</i> 62.9	1.88	1.49 to 2.38	< .0001†	1.58	1.26 to 1.99	< .0001†
Missing	2	1.0	3	1.5						
Prior radiotherapy: yes <i>v</i> no	27 <i>v</i> 176	13.3 <i>v</i> 86.7	23 <i>v</i> 179	11.4 <i>v</i> 88.6	1.34	0.98 to 1.83	.0708	1.28	0.94 to 1.75	.1239
Age group: ≤ 70 <i>v</i> > 70 years	160 <i>v</i> 43	78.8 <i>v</i> 21.2	159 <i>v</i> 43	78.7 <i>v</i> 21.3	1.05	0.81 to 1.36	.6924	1.05	0.81 to 1.35	.7266
Sex: female <i>v</i> male	43 <i>v</i> 160	21.2 <i>v</i> 78.8	42 <i>v</i> 160	20.8 <i>v</i> 79.2	1.17	0.90 to 1.53	.2526	1.14	0.88 to 1.48	.3149
Time to diagnosis: ≤ 12 <i>v</i> > 12 months	134 <i>v</i> 69	66.0 <i>v</i> 34.0	131 <i>v</i> 71	64.9 <i>v</i> 35.1	1.04	0.84 to 1.30	.7182	0.99	0.80 to 1.23	.9526
Alk. phos. group: normal <i>v</i> high	140 <i>v</i> 56	69.0 <i>v</i> 27.6	142 <i>v</i> 55	70.3 <i>v</i> 27.2	1.83	1.45 to 2.31	< .0001†	1.67	1.33 to 2.10	< .0001†
Missing	7	3.4	5	2.5						
Disease: measurable <i>v</i> nonmeasurable	182 <i>v</i> 21	89.7 <i>v</i> 10.3	181 <i>v</i> 21	89.6 <i>v</i> 10.4	0.77	0.54 to 1.11	.1620	0.70	0.49 to 0.99	.0435
Number of sites: ≤ 3 <i>v</i> > 3	161 <i>v</i> 42	79.3 <i>v</i> 20.7	167 <i>v</i> 35	82.7 <i>v</i> 17.3	1.42	1.09 to 1.85	.0096†	1.36	1.05 to 1.76	.0211†
Visceral metastasis: no <i>v</i> yes	99 <i>v</i> 104	48.8 <i>v</i> 51.2	93 <i>v</i> 109	46.0 <i>v</i> 54.0	2.08	1.68 to 2.57	< .0001†	1.92	1.55 to 2.36	< .0001†

Abbreviations: GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; KPS, Karnofsky performance score; Alk. phos., alkaline phosphatase.

*An HR > 1 indicates a better outcome for the first grouping within each prognostic factor.

†Statistically significant *P* values.

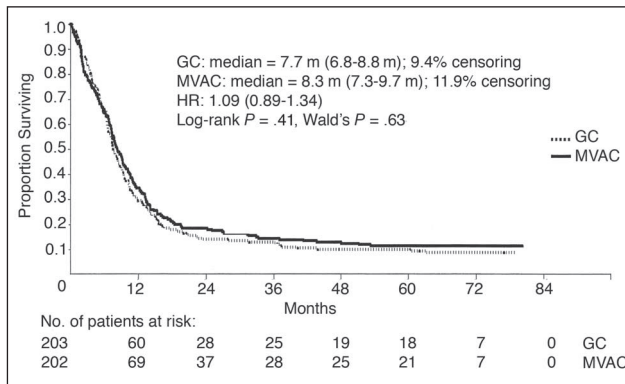


Fig 2. Kaplan-Meier curves for progression-free survival. GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; HR, hazard ratio; Pts, patients.

progression-free survival was 7.7 months with GC (95% CI, 6.8 to 8.8 months) and 8.3 months with MVAC (95% CI, 7.3 to 9.7 months). The differences in progression-free survival rates at 24 months (GC, 13.9%; MVAC, 18.4%), 48 months (GC, 9.8%; MVAC, 12.8%), and 60 months (GC, 9.8%; MVAC, 11.3%) were not significant (Table 4). A multivariate analysis of all significant prognostic factors was conducted using backward selection to determine the final model for progression-free survival. Independent prognostic factors adversely affecting progression-free survival were poor PS (70), high alkaline phosphatase, measurable disease, presence of visceral metastases, TNM staging (M1), and number of disease sites (> three; Table 3). When treatment was added to this final model of significant prognostic factors, there was no treatment effect for progression-free survival. Again, there was a similar progression-free survival in the two arms. The adjusted HR for

progression-free survival was 1.01 (95% CI, 0.81 to 1.25; Wald $P = .94$).

Impact of Prognostic Factors on Long-Term Survival

Baseline Karnofsky PS and the presence of visceral metastases had the highest prognostic value for survival, as indicated in Table 3. Plots of the survival curves for these two important prognostic factors are shown in Figures 3A and 3B. Patients without visceral metastases to bone, liver, or lung had a median overall survival of 18.4 months and a 5-year survival rate of 20.9% (95% CI, 15.3% to 26.5%), whereas patients with visceral metastases had a median overall survival of 10.3 months and 5-year survival rate of 6.8% (95% CI, 3.2% to 10.4%; Fig 3A). Patients with a baseline Karnofsky PS of 70 had a worse outcome, with a median overall survival of 8.3 months and a 5-year survival rate that was inestimable (due to the low number of patients meeting this criteria), whereas patients with a Karnofsky PS of 80 to 100 had a better outcome, with a median overall survival of 16.0 months and a 5-year survival probability of 16.5% (Fig 3B).

DISCUSSION

Long-term survival of patients with advanced bladder cancer is uncommon, although this disease remains amenable to chemotherapeutic intervention. We report herein on the 5-year survival of patients with locally advanced or metastatic bladder cancer comparing GC with MVAC treatment in a large, international, multicenter phase III study. This analysis confirms that some patients can achieve long-term

Table 4. Progression-Free Survival Summary

Parameter	GC Arm (n = 203)		MVAC Arm (n = 202)		Comparison <i>P</i>
	No.	95% CI	No.	95% CI	
Patients censored	19		24		
%	9.4		11.9		
No. of events (death)	184		178		
Minimum, months	0.20		0.26		
25th percentile	4.4	3.5 to 5.5	3.8	2.6 to 5.2	
Median, months	7.7	6.8 to 8.8	8.3	7.3 to 9.7	
75th percentile	14.1	11.3 to 16.4	15.4	13.2 to 19.6	
Maximum, months	> 78.8		> 80.3		
Log-rank <i>P</i>	0.4072				
Hazard ratio	1.09	0.89 to 1.34			
12-month PFS rate	29.7	23.4 to 36.0	34.4	27.8 to 40.9	.3179
24-month PFS rate	13.9	9.1 to 18.6	18.4	13.1 to 23.8	.2134
36-month PFS rate	12.9	8.3 to 17.5	14.3	9.5 to 19.2	.6691
48-month PFS rate	9.8	5.7 to 13.9	12.8	8.2 to 17.4	.3408
60-month PFS rate	9.8	5.7 to 13.9	11.3	6.9 to 15.7	.6302

Abbreviations: GC, gemcitabine/cisplatin; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; PFS, progression-free survival.

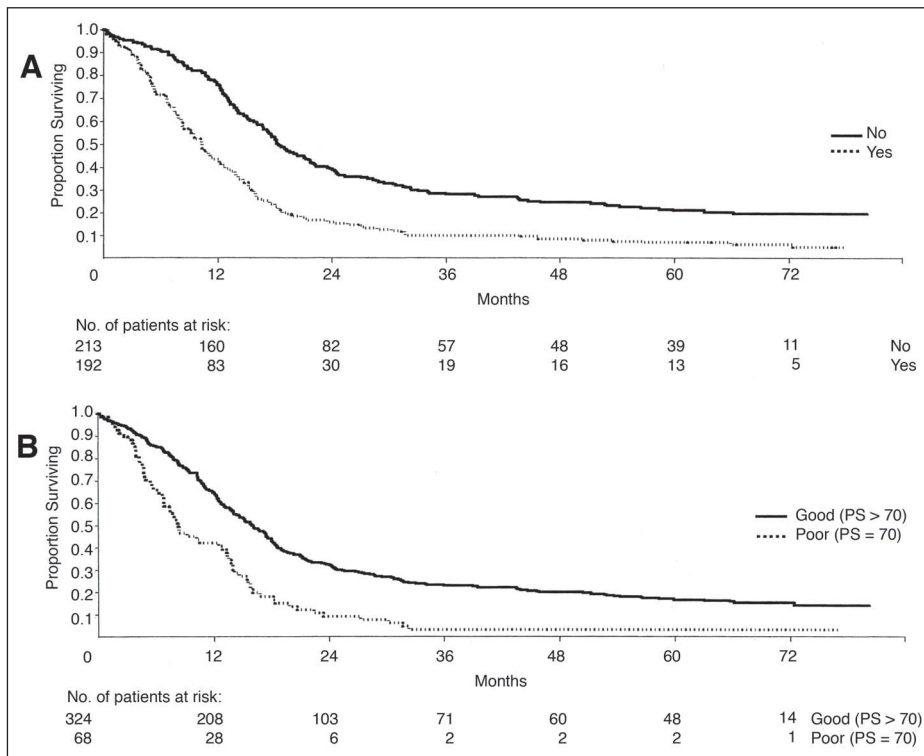


Fig 3. Kaplan-Meier curves showing effect of (A) visceral metastases and (B) Karnofsky performance score (PS) on overall survival.

disease control and possible cure with systemic chemotherapy. It also supports the earlier conclusions that GC provides similar efficacy in terms of overall survival and progression-free survival compared with MVAC in this patient population but does so with a superior safety profile.⁶ These long-term results provide additional support for GC as a standard of care in patients with locally advanced and metastatic bladder cancer. However, it should be emphasized that this conclusion cannot be translated to the adjuvant setting. Thus, administration of GC as neoadjuvant or adjuvant treatment should be explored further within the framework of clinical trials.

The data also corroborate findings by Stadler et al,⁹ who analyzed the long-term survival in the three initial and previously published phase II bladder cancer trials¹⁰⁻¹² in which patients were treated with GC. The overall median survival of 121 patients was 13.2 months, and the estimated 4-year survival was $13\% \pm 6\%$, comparable to those observed in this larger phase III study directly comparing GC and MVAC.

The results of our univariate analysis are in line with the findings by Bajorin et al,¹³ who defined Karnofsky PS and presence or absence of visceral metastases as important, independent prognostic variables.^{13,14} The final results of this phase III study, the largest study done so far in locally advanced and metastatic bladder cancer, confirm the prognostic value of these two pretreatment characteristics for overall survival. In addition, in our study, elevated alkaline phosphatase, in accordance with a study by Sengelov et al,¹⁵

as well as the number of disease sites ($> \text{three}$ v $\leq \text{three}$) also had prognostic value for survival.

When treatment was added in the final multiple regression model, the HR for overall survival (0.99) and progression-free survival (1.01) indicated identical efficacy of both treatment regimens. Although this phase III study was not designed as an equivalence trial, the long-term overall survival results demonstrate the similar efficacy of the GC and MVAC regimens in patients with locally advanced and metastatic bladder cancer. Subgroup analyses of relevant prognostic factors did not disclose any statistically significant differences between GC- and MVAC-treated patients.

In summary, the increasing acceptance and use of GC in patients with locally advanced and metastatic bladder cancer is supported by its similar clinical efficacy compared with MVAC. The 5-year survival data, along with the better tolerability and safety profile of the GC combination, continues to support and strengthen the conclusion⁶ that the GC regimen is a safe and effective alternative to MVAC therapy in this patient population. However, more efficacious treatment regimens need to be developed¹⁶ to increase the long-term survival probability of patients with inoperable locally advanced and metastatic urothelial cancer.

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Annamaria Zimmermann, Eli Lilly; Michael Arning, Eli Lilly. Consultant/Advisory Role: Malcolm Moore, Eli Lilly. Stock Own-

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