

ORIGINAL ARTICLE

## Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

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### ABSTRACT

#### BACKGROUND

Despite aggressive local therapy, patients with locally advanced bladder cancer are at significant risk for metastases. We evaluated the ability of neoadjuvant chemotherapy to improve the outcome in patients with locally advanced bladder cancer who were treated with radical cystectomy.

#### METHODS

Patients were enrolled if they had muscle-invasive bladder cancer (stage T2 to T4a) and were to be treated with radical cystectomy. They were stratified according to age (less than 65 years vs. 65 years or older) and stage (superficial muscle invasion vs. more extensive disease) and were randomly assigned to radical cystectomy alone or three cycles of methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy.

#### RESULTS

We enrolled 317 patients over an 11-year period, 10 of whom were found to be ineligible; thus, 154 were assigned to receive surgery alone and 153 to receive combination therapy. According to an intention-to-treat analysis, the median survival among patients assigned to surgery alone was 46 months, as compared with 77 months among patients assigned to combination therapy ( $P=0.06$  by a two-sided stratified log-rank test). In both groups, improved survival was associated with the absence of residual cancer in the cystectomy specimen. Significantly more patients in the combination-therapy group had no residual disease than patients in the cystectomy group (38 percent vs. 15 percent,  $P<0.001$ ).

#### CONCLUSIONS

As compared with radical cystectomy alone, the use of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin followed by radical cystectomy increases the likelihood of eliminating residual cancer in the cystectomy specimen and is associated with improved survival among patients with locally advanced bladder cancer.

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**B**LADDER CANCER, THE FOURTH MOST common cancer in men and the eighth in women in the United States,<sup>1</sup> is a worldwide problem.<sup>2</sup> Tumors superficial to the muscularis propria are effectively treated with transurethral resection and intravesical therapy.<sup>3</sup> After radical cystectomy for locally advanced bladder cancer, there is a significant rate of recurrence (56 percent among patients with pathological stage T3, in which there is invasion of perivesical tissue), most commonly as distant metastases.<sup>4</sup> A previous Southwest Oncology Group (SWOG) study demonstrated that radiation therapy before radical cystectomy did not improve the outcome.<sup>5</sup> For these reasons, systemic chemotherapy has been explored in both neoadjuvant (preoperative) and adjuvant (postoperative) settings.

In 1985, a clinical trial suggested that a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) had substantially more activity than single drugs.<sup>6</sup> Subsequent trials found high rates of response to M-VAC among patients with local–regional or metastatic bladder cancer.<sup>7,8</sup> Randomized trials confirmed that M-VAC is more active than cisplatin alone<sup>9</sup> or in combination with cyclophosphamide and doxorubicin.<sup>10</sup> Neoadjuvant M-VAC has allowed some patients with muscle-invasive bladder cancer to retain their bladders and remain free of disease for more than 10 years.<sup>8</sup>

In 1987, SWOG initiated a trial to determine whether neoadjuvant M-VAC improves the survival of patients with locally advanced bladder cancer. This trial subsequently became an intergroup study. Participants were randomly assigned to receive three cycles of preoperative M-VAC followed by radical cystectomy or to undergo immediate cystectomy. Here, we present the results of this study.

## METHODS

### PATIENTS

Between August 1987 and July 1998, 317 patients with transitional-cell carcinoma of the bladder were enrolled in an intergroup study at 126 institutions affiliated with SWOG, the Eastern Cooperative Oncology Group, or Cancer and Leukemia Group B. Ten patients were subsequently found to be ineligible and were excluded. Patients with clinical tumor–node–metastases (TNM) stage T2N0M0 to T4aN0M0 bladder cancer who were candidates for radical cystectomy were eligible. Prior pelvic irradiation was not allowed. Patients were required to have

adequate renal, hepatic, and hematologic function and a SWOG performance status of 0 or 1. Tumors were staged according to the criteria in the fourth edition of the American Joint Committee on Cancer staging manual.<sup>11</sup> Patients had tumors invading the superficial muscle and beyond, to the level of the surrounding viscera (but not to the side wall of the pelvis). Patients were stratified according to age (younger than 65 years vs. 65 years or older) and stage (T2 vs. T3 or T4a; T2 represents invasion of superficial muscle and T3 invasion of deep muscle or perivesical fat). They were randomly assigned, with the use of dynamic balancing for stratification,<sup>12</sup> by a central computer at the SWOG Statistical Center to undergo radical cystectomy or to receive three cycles of chemotherapy with M-VAC followed by radical cystectomy. All patients provided written informed consent, and the study was approved by the ethics committees of participating institutions.

### OBJECTIVES OF THE STUDY

The primary objective of the study was to compare the survival among patients treated with cystectomy alone with survival among those treated with M-VAC followed by cystectomy in a randomized phase 3 trial. A secondary objective was to quantify the effect of neoadjuvant M-VAC on the stage of the tumor (“tumor down-staging”). Down-staging can occur without chemotherapy when the tumor is removed by the diagnostic transurethral resection.

### PATHOLOGICAL EXAMINATION

Two pathological reviews were performed. The biopsy specimen obtained before registration was assessed to document eligibility (invasion of the muscularis propria), and the cystectomy specimens were reviewed to assess the pathological stage and to determine the rate of down-staging. An initial pathological review was not possible in the case of 46 patients (20 in the combination-therapy group and 26 in the group assigned to undergo cystectomy alone) because slides were not submitted or were lost in shipment. We assumed that this was a random occurrence, and these patients are included in all of the reported analyses. Central pathological review could not confirm the occurrence of muscle invasion in 17 patients (11 in the combination-therapy group and 6 in the cystectomy group). These patients were classified as having clinical stage T2 to T4a at the institutions that enrolled them in the study, and they underwent randomization. These patients are probably representative of patients who

are treated for muscle-invasive bladder cancer, so they were also included in all of the analyses. Of the six patients assigned to the cystectomy group, one had insufficient cystectomy data for analysis. The other five had pathological stage pT2 disease or a higher stage at cystectomy, supporting our decision to include them in the analyses.

#### TREATMENT

##### Radical Cystectomy

All patients were to be treated with radical cystectomy either initially or after three cycles of M-VAC. Radical cystectomy included a bilateral pelvic lymphadenectomy. A variety of urinary diversions were performed, including the creation of ileal conduits, continent cutaneous reservoirs, and orthotopic reservoirs (neobladders).

##### Chemotherapy

Patients assigned to neoadjuvant chemotherapy were to be given three 28-day cycles of M-VAC, as follows: methotrexate (30 mg per square meter of body-surface area) on days 1, 15, and 22; vinblastine (3 mg per square meter) on days 2, 15, and 22; and doxorubicin (30 mg per square meter) and cisplatin (70 mg per square meter) on day 2. The doses were adjusted if toxic effects occurred.

#### STATISTICAL ANALYSIS

The accrual goal of 298 eligible, randomized patients was based on a statistical power of 80 percent to detect a 50 percent or greater improvement in median survival between the combination-therapy group and the cystectomy group. The probability of a type I error was specified at 0.05 with use of a stratified log-rank test. The study design called for one-sided testing, since the standard of medical practice would be affected only if combination therapy proved to be superior to cystectomy alone. If the outcome of combination therapy was the same as or inferior to the outcome of cystectomy alone, radical cystectomy would remain standard medical practice. Furthermore, on the basis of previous experience, neoadjuvant chemotherapy with M-VAC was unlikely to result in a higher mortality rate than cystectomy alone. In accordance with the policy of the Journal, however, only two-sided P values are reported.

The prespecified primary means of analysis was the stratified log-rank test. Survival was measured from the time of randomization. Proportional-hazards models were used to adjust for covariates and

to evaluate interaction terms in which overall survival was the end point. After the inclusion of indicators for the main effects of age group, tumor stage, and treatment group in the proportional-hazards model, interactions between treatment group and age group and tumor stage were evaluated with the Score chi-square test.

In a large, cooperative group trial with extended follow-up, it is difficult to collect accurate information on the cause of death in all cases; we therefore tried to approximate it as an exploratory analysis. Death from bladder cancer was defined as a death within 180 days after randomization (to account for treatment-related deaths) or after documented disease progression. Data on deaths from other causes were censored at the time of death for the cause-specific analysis.

#### RESULTS

A total of 317 patients were enrolled and underwent randomization over an 11-year period, 10 of whom (5 in each group) were found to be ineligible as a result of either an incorrect histologic diagnosis (8 patients) or evidence of metastatic disease at the time of randomization (2 patients). Thus, 307 were eligible: 153 in the group assigned to M-VAC followed by cystectomy and 154 in the group assigned to cystectomy alone. The median age was 63 years (range, 39 to 84), and the ratio of male to female patients was 4:1. The two groups were balanced

Table 1. Base-Line Characteristics of the Patients.\*

Characteristic	Total (N=307)	Cystectomy Alone (N=154)	M-VAC and Cystectomy (N=153)
Age—yr			
Median	63	63	63
Range	39–84	39–84	36–79
Sex—no. (%)			
Male	251 (82)	124 (81)	127 (83)
Female	56 (18)	30 (19)	26 (17)
Age and tumor stage—no. (%)			
<65 yr and T2	61 (20)	35 (23)	26 (17)
<65 yr and T3 or T4a	111 (36)	52 (34)	59 (39)
≥65 yr and T2	61 (20)	26 (17)	35 (23)
≥65 yr and T3 or T4a	74 (24)	41 (27)	33 (22)

\* Of the 317 patients who underwent randomization, 10 (5 in each group) were found to be ineligible and were excluded from the analysis. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

**Table 2. Adverse Effects among 150 Patients Who Received Any Methotrexate, Vinblastine, Doxorubicin, and Cisplatin.\***

Adverse Effect	Grade 3	Grade 4	Grade 5
	number of patients		
Granulocytopenia	35	50	0
Thrombocytopenia	7	0	0
Anemia	9	1	0
Nausea or vomiting	9	0	0
Stomatitis	15	0	0
Diarrhea or constipation	6	0	0
Renal effects	1	0	0
Neuropathy	3	0	0
Fatigue, lethargy, and malaise	5	0	0
Maximal grade of any adverse effect	53	55	0

\* Grade 3 was defined as a moderate adverse effect, grade 4 as a severe effect, and grade 5 as a life-threatening effect.

**Table 3. Postoperative Complications among Patients Who Underwent Cystectomy.\***

Complication	Cystectomy Alone (N=124)			M-VAC and Cystectomy (N=126)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
	number of patients					
Anemia	0	0	0	3	0	0
Cardiac effects	0	2	1	2	2	0
Gastrointestinal effects	5	5	0	2	6	0
Genitourinary effects	7	1	0	5	2	1
Hemorrhage	0	0	0	3	0	0
Infection	3	0	1	2	1	0
Neurologic effects	0	0	0	3	0	0
Pulmonary effects	1	0	0	3	0	0
Thrombosis or embolism	0	1	0	0	0	0
Delayed wound healing or wound infection	2	1	0	2	0	0
Other	2	0	0	1	1	0
Maximal grade of any adverse effect	15	10	1	15	11	1

\* Grade 3 was defined as a moderate adverse effect, grade 4 as a severe effect, and grade 5 as a life-threatening effect. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

with respect to all stratification categories (Table 1). The planned radical cystectomy was performed in 82 percent of the patients in the combination-therapy group and 81 percent of the patients in the cystectomy group. In the combination-therapy group, 16 patients did not undergo cystectomy for medical reasons, 10 did not undergo surgery for other reasons, and the status of 1 is unknown. In the cystectomy group, 20 patients did not undergo cystectomy for medical reasons and 10 for other reasons. Nine patients (two in the combination-therapy group and seven in the cystectomy group) underwent cystectomy outside the study. For patients who underwent cystectomy according to the protocol, the mean time to surgery in the cystectomy group was 17 days (median, 16; range, 1 to 55). Patients in the combination-therapy group underwent cystectomy a mean of 115 days (median, 113; range, 11 to 169) after randomization.

Of the 153 patients who were randomly assigned to neoadjuvant M-VAC, 3 declined chemotherapy. The mean duration of chemotherapy (including treatment delays) was 103 days (median, 104; range, 1 to 478). Eighty-seven percent of the patients received at least one full cycle of M-VAC. Of the 150 patients who could be evaluated, 50 (33 percent) had grade 4 (severe) granulocytopenia (Table 2). Gastrointestinal toxicity in the form of grade 3 (moderate) nausea or vomiting, stomatitis, or diarrhea or constipation occurred in 26 patients (17 percent). There were no deaths attributable to M-VAC and no significant differences between the two groups in the rates or severity of postoperative complications (Table 3). One patient in each group died in the postoperative period.

Ninety deaths had occurred in the combination-therapy group after a median follow-up of 8.7 years (range, 3.1 to 13.0), and 100 deaths had occurred in the cystectomy group after a median follow-up of 8.4 years (range, 0.7 to 13.7). According to an intention-to-treat analysis, the median survival was 46 months (95 percent confidence interval, 25 to 60) among patients in the cystectomy group and 77 months (95 percent confidence interval, 55 to 104) among patients in the combination-therapy group (Fig. 1). At five years, 57 percent of the patients in the combination-therapy group were alive, as compared with 43 percent of those in the cystectomy group (P=0.06 by a stratified log-rank test).

Table 4 shows the results of log-rank tests and median survival estimates. Stage T2 bladder cancer was found in 35 percent of patients under the age

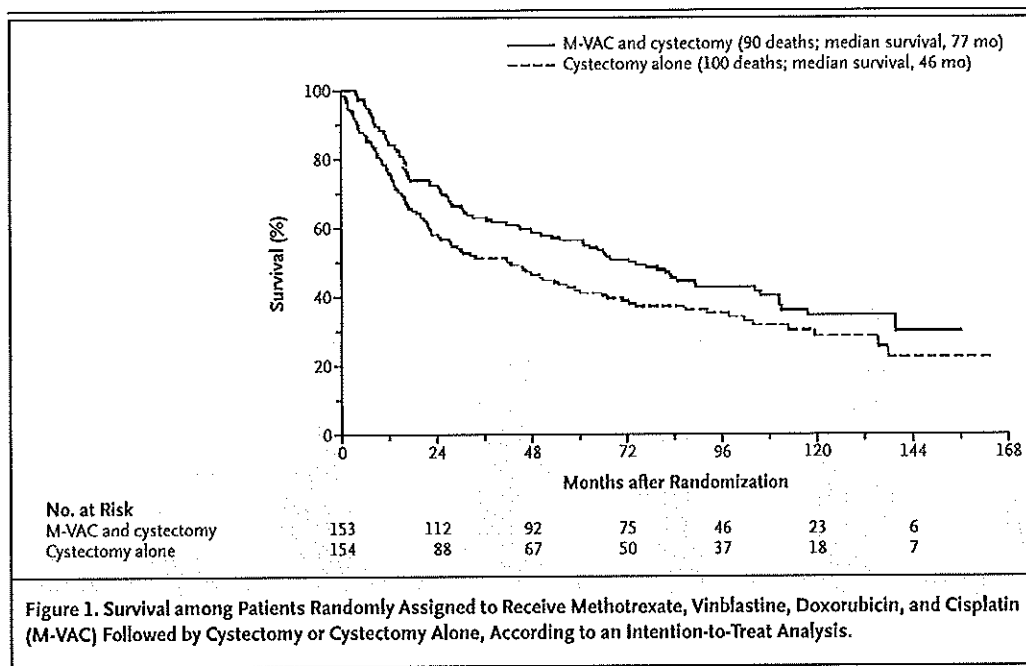


Figure 1. Survival among Patients Randomly Assigned to Receive Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (M-VAC) Followed by Cystectomy or Cystectomy Alone, According to an Intention-to-Treat Analysis.

of 65 years (61 of 172) and 45 percent of patients 65 years of age and older (61 of 135). A stratified proportional-hazards model showed that patients in the cystectomy group had a 33 percent greater risk of death than those in the combination-therapy group (hazard ratio, 1.33; 95 percent confidence interval, 1.00 to 1.76). Excluding the 17 patients without confirmed evidence of muscle invasion at entry yielded a nearly identical hazard ratio (1.32). Most of the patients in this 14-year study were enrolled in the early years. As a result, the survival curves are stable out to six years, with vital status known at that time for 92 percent of patients.

The other objective of our study was to quantify the effect of neoadjuvant M-VAC on the tumor stage. Of the 126 patients in the M-VAC group who underwent cystectomy, 48 (38 percent) of the surgical specimens were pathologically free of cancer (pT0) at the time of surgery. This group included 26 (50 percent) of the patients who initially had stage T2 disease and 22 (30 percent) of the patients who initially had stage T3 or T4a disease. By contrast, 15 percent of the 121 patients in the cystectomy group were pathologically free of cancer at cystectomy ( $P < 0.001$ ). At five years, 85 percent of the patients with a pT0 surgical specimen were alive (Fig. 2).

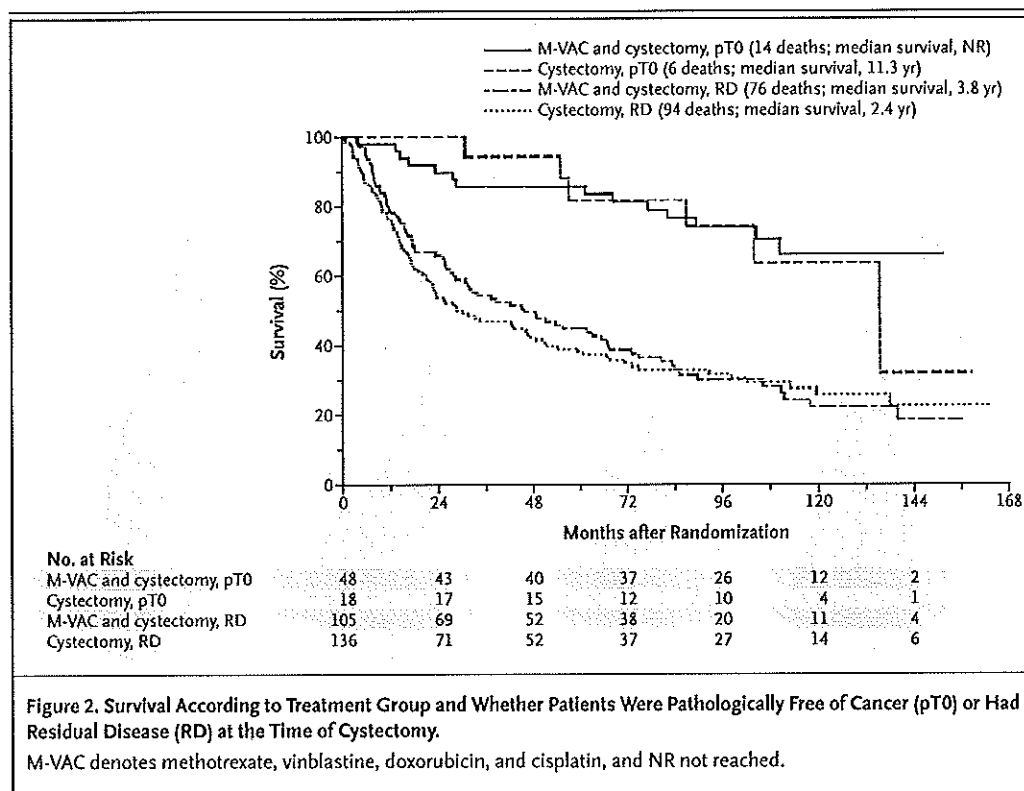
In exploratory analyses, we evaluated the effect of M-VAC on disease-specific survival. There were

Variable	Median Survival		P Value†
	M-VAC and Cystectomy	Cystectomy Alone	
	<i>months</i>		
Unstratified	77	46	0.05
Primary analysis, stratified according to age and tumor stage			0.06
Stratified according to age			0.05
Age <65 yr	104	67	
Age ≥65 yr	61	30	
Stratified according to tumor stage			0.05
T2	105	75	
T3 or T4a	65	24	

\* There were 90 deaths in the combination-therapy group after a median follow-up of 8.7 years. There were 100 deaths in the cystectomy group after a median follow-up of 8.4 years. M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin.

† The log-rank test was used to calculate P values.

77 deaths from bladder cancer in the cystectomy group and 54 deaths in the combination-therapy group, for a disease-specific hazard ratio of 1.66 (95 percent confidence interval, 1.22 to 2.45;  $P = 0.002$ ). We also looked for potential interactions between the treatment group and the stratification factors — tumor stage (T2 vs. T3 or T4a) and age



(younger than 65 years vs. 65 years or older), with respect to overall survival. Neither tumor stage ( $P=0.45$ ) nor age ( $P=0.74$ ) had a significant interaction with treatment. Figure 3 shows the Kaplan–Meier survival estimates for each tumor stage group according to treatment.

### DISCUSSION

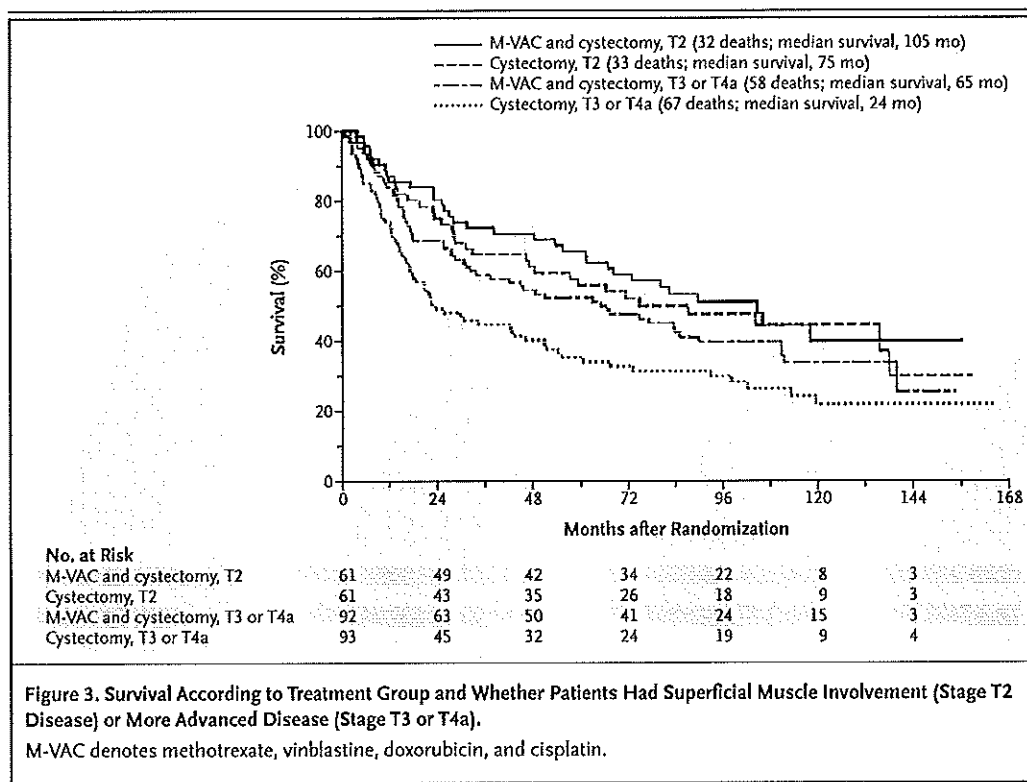
The risk of recurrence after radical cystectomy for clinically localized bladder cancer is high and stage-dependent.<sup>13</sup> Study of the pattern of recurrence at distant sites indicates that the predominant cause is occult micrometastases present at the time of cystectomy. For this reason, there is interest in combining definitive surgical or radiotherapeutic treatment for localized disease with systemic chemotherapy for occult metastases.

There is no convincing evidence that either adjuvant or neoadjuvant treatment of localized bladder cancer improves survival.<sup>14</sup> Although the adjuvant approach allows the selection of patients with the highest risk of recurrence on the basis of the pathological stage to receive chemotherapy, chemo-

therapy may be difficult to administer after radical cystectomy. In a randomized trial comparing neoadjuvant with adjuvant chemotherapy, 97 percent of patients in the neoadjuvant group received at least two cycles of chemotherapy, whereas only 77 percent of the patients in the adjuvant group received at least two cycles.<sup>15</sup>

Our study demonstrates that the four-drug combination M-VAC can be given safely before radical cystectomy to patients with locally advanced bladder cancer. Although, overall, the adverse effects were moderate, with at least one third of patients having severe hematologic or gastrointestinal effects, all patients recovered, and there were no treatment-related deaths. Furthermore, M-VAC did not adversely affect a patient's chance of undergoing radical cystectomy, nor did it increase the risk of death or complications related to the surgery.

We found a significant and clinically meaningful improvement in survival among patients who received neoadjuvant chemotherapy. The estimated risk of death was reduced by 33 percent in the group assigned to receive M-VAC and cystectomy, as compared with the group assigned to undergo



cystectomy alone. The survival benefit of neoadjuvant M-VAC appears to be strongly related to downstaging of the tumor to pT0: 38 percent of the patients in this group had no evidence of cancer at cystectomy, as compared with 15 percent of the patients in the cystectomy group ( $P < 0.001$ ); the respective five-year survival rates were 85 and 82 percent. Chemotherapy-induced downstaging did not appear to introduce selection bias, because the median survival among patients in the combination-therapy group who had residual disease at cystectomy was also at least as good as that among patients in the cystectomy group who had residual disease at cystectomy.

Our results contrast with the negative results of seven other randomized trials. This difference may be due to the proven superiority of the chemotherapy regimen we used over those used in the other trials and to differences among the patients selected. The largest of the other trials randomly assigned 976 patients with stage T2, grade 3, or stage T3 or T4 bladder cancer either to immediate cystectomy or radiotherapy or to three cycles of neoadjuvant chemotherapy with cisplatin, methotrexate, and vin-

blastine followed by cystectomy or radiotherapy.<sup>16</sup> Median survival in the chemotherapy group was 44 months, as compared with 37.5 months in the immediate-cystectomy group. The three-year survival rate in the chemotherapy group was 56 percent, as compared with 50 percent in the group that did not receive chemotherapy. This trial differed from ours in terms of the type of chemotherapy used, the use of radiation, and the duration of follow-up. With longer follow-up in that study, a statistically significant survival advantage has emerged in the neoadjuvant-chemotherapy group.<sup>17</sup> The other six negative trials used single-agent cisplatin or a two-drug combination.

Although a single successful clinical trial should not necessarily change standard medical practice, we believe that neoadjuvant M-VAC can be offered to patients with locally advanced bladder cancer who are candidates for radical cystectomy. A safe and successful outcome with this four-drug regimen requires the selection of patients with adequate renal function, careful monitoring for chemotherapy-induced toxic effects, and appropriate intervention in the event of severe adverse effects.

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**CORRECTION**

**Neoadjuvant Chemotherapy plus Cystectomy  
Compared with Cystectomy Alone for Locally  
Advanced Bladder Cancer**

Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer . On page 864, lines 3 to 5 of the last partial paragraph should have read, "The estimated risk of death was reduced by 25 percent in the group assigned to receive M-VAC and cystectomy," rather than "The estimated risk of death was reduced by 33 percent," as printed.