

Phase III Study of Molecularly Targeted Adjuvant Therapy in Locally Advanced Urothelial Cancer of the Bladder Based on p53 Status

Walter M. Stadler, Seth P. Lerner, Susan Groshen, John P. Stein,† Shan-Rong Shi, Derek Raghavan, David Esrig, Gary Steinberg, David Wood, Laurence Klotz, Craig Hall, Donald G. Skinner, and Richard J. Cote

Walter M. Stadler and Gary Steinberg, University of Chicago, Chicago, IL; Seth P. Lerner, Baylor College of Medicine, Houston, TX; Susan Groshen, University of Southern California; John P. Stein, Shan-Rong Shi, and Donald G. Skinner, University of Southern California Keck School of Medicine, Los Angeles, CA; Derek Raghavan, Levine Cancer Institute, Carolinas HealthCare System, Charlotte; Craig Hall, Piedmont Urologic Associates, High Point, NC; David Esrig, Oregon Urology Institute, Springfield, OR; David Wood, University of Michigan, Ann Arbor, MI; Laurence Klotz, Sunnybrook Hospital, University of Toronto, Toronto, Ontario, Canada; and Richard J. Cote, University of Miami Miller School of Medicine, Miami, FL.

†Deceased.

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W.M.S., S.P.L., and S.G. contributed equally to this work.

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Corresponding author: Richard J. Cote, MD, FRCPath, FCAP, Department of Pathology, University of Miami Miller School of Medicine, 1120 NW 14 St, Suite 1416, Miami, FL 33136; e-mail: rcote@med.miami.edu.

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A B S T R A C T

Introduction

Retrospective studies suggest that p53 alteration is prognostic for recurrence in patients with urothelial bladder cancer and predictive for benefit from combination methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) adjuvant chemotherapy.

Patients and Methods

Patients with pT1/T2N0M0 disease whose tumors demonstrated $\geq 10\%$ nuclear reactivity on centrally performed immunohistochemistry for p53 were offered random assignment to three cycles of adjuvant MVAC versus observation; p53-negative patients were observed. By using a log-rank test with one-sided $\alpha = .05$ and $\beta = .10$, 190 p53-positive patients were planned to be randomly assigned to detect an absolute improvement in probability of recurring by 3 years from 0.50 to 0.30.

Results

A total of 521 patients were registered, 499 underwent p53 assessment, 272 (55%) were positive, and 114 (42%) were randomly assigned. Accrual was halted on the basis of the data and safety monitoring board review of a futility analysis. Overall 5-year probability of recurring was 0.20 (95% CI, 0.16 to 0.24) with no difference on the basis of p53 status. Only 67% of patients randomly assigned to MVAC received all three cycles with 12 patients receiving no treatment. There was no difference in recurrence in the randomly assigned patients (hazard ratio, 0.78; 95% CI, 0.29 to 2.08; $P = .62$).

Conclusion

Neither the prognostic value of p53 nor the benefit of MVAC chemotherapy in patients with p53-positive tumors was confirmed, but the high patient refusal rate, lower than expected event rate, and failures to receive assigned therapy severely compromised study power.

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INTRODUCTION

Significant advances in surgical care of patients with locally advanced urothelial cancer of the bladder have led to marked decreases in perioperative morbidity and mortality, greater options for urinary diversion, and high degrees of patient satisfaction.¹ Nevertheless, long-term outcome continues to be compromised by the high risk of systemic recurrence with 40% to 50% of patients with pathologic stage III disease suffering recurrent incurable cancer. Several trials have addressed perioperative systemic treatment for patients with locally advanced disease, and a benefit from neoadjuvant cisplatin-based chemotherapy has been demonstrated.^{2,3} However, it has been difficult to demonstrate a significant benefit from adjuvant therapy, in large

part because the available prospective trials have all been severely underpowered.⁴

Outcome for patients with urothelial bladder cancer is determined not only by clinical stage, surgical quality, and use of perioperative chemotherapy but also by molecular markers associated with bladder carcinogenesis. Several biomarkers have been investigated for their prognostic value, including the tumor suppressor proteins p53 and retinoblastoma (pRb), and their downstream effectors. Several studies have suggested that dysregulated p53 is prognostic, with the greatest effect seen in early-stage (pT1/T2N0) disease, which has a historical recurrence rate of about 30%.⁵⁻⁷ Many studies, however, have been hampered by the various technologies for assessing p53 dysregulation. The most common methodology is based on the finding that mutant

p53 is stabilized and detectable by standard immunohistochemical (IHC) methods, but that normal p53 tends to be rapidly degraded and thus is not detectable by these methods.⁸ This assay depends on details of which IHC assay was used, is not sensitive to p53 mutations that lead to lack of protein expression, and correlates imperfectly with mutational status.

Molecular analysis of p53 alterations could provide a theoretical advantage, but until recently, technologies for mutational analysis of the large p53 gene were not applicable to large clinical cohorts. Subsequent studies have demonstrated that both mutations and IHC-detected expression are independent prognostic variables, suggesting that nonmutational p53 stabilization may have functional consequences as well.⁹ Downstream signaling partners of the p53 DNA damage response pathway, such as p21 expression, have thus also been investigated as clinical biomarkers. High expression of p21, reflecting an intact p53 pathway, has been associated with good prognosis in bladder cancer even in the context of apparent dysregulated p53 expression.¹⁰

In addition to p53 being prognostic, several studies have suggested that p53 inactivation may be predictive of benefit from DNA-damaging therapy. The literature regarding these effects is controversial and complex not only because of the aforementioned challenges with assessing p53 status but also because the effects may be dependent on the type of DNA damage that is induced. Nevertheless, several studies¹¹ have demonstrated that normal p53 is necessary for successful response to DNA damage that leads to G₂-M arrest and that lack of a normal p53 pathway leads to increased death when cancer cells are exposed to such agents. There have been few clinical studies assessing the potential for p53 to be a predictive biomarker for benefit from DNA-damaging therapy. However, in a retrospective analysis of patients with bladder cancer who were treated in a prospective adjuvant trial, the benefit from a cisplatin-based regimen was confined to patients with p53 inactivation.¹² To further assess the hypothesis that in the setting of p53 inactivation there is clinical benefit from cisplatin-based therapy, a phase III trial of adjuvant combination methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) was conducted in

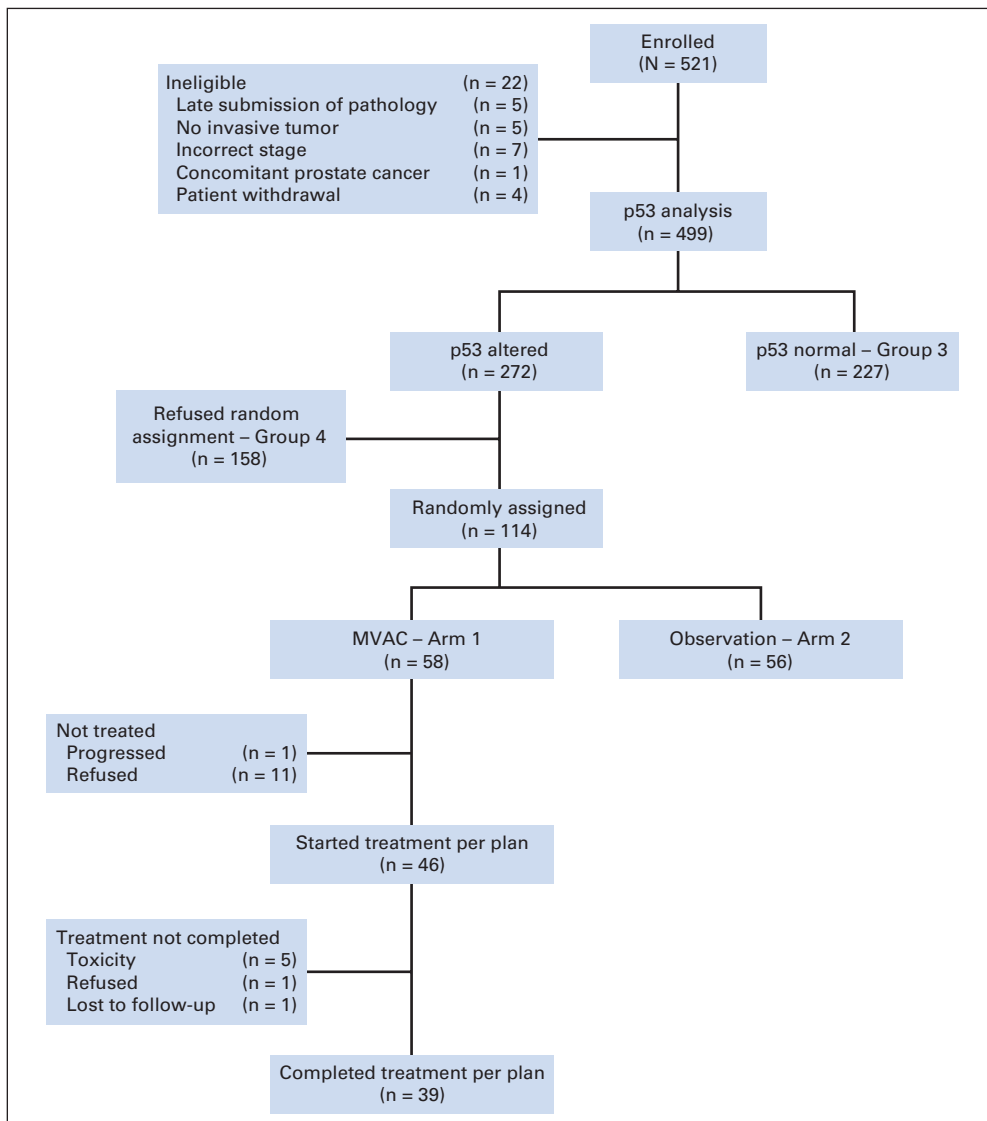


Fig 1. CONSORT diagram describing cohort, p53 analysis, randomization, and treatment. MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

patients with p53-altered T1/T2N0 urothelial cancer of the bladder. This trial also sought to prospectively compare the recurrence and overall survival of patients with and without tumors demonstrating p53 alterations.

PATIENTS AND METHODS

All patients provided written informed consent, and the protocol was approved by the local institutional review board or ethics review panel at all participating institutions.

Patients

Patients with stage pT1/T2N0M0 urothelial cancer who had undergone a radical cystectomy and bilateral pelvic lymphadenectomy within the prior 9 weeks were eligible. Patients were required to have ≥ 15 lymph nodes removed or a normal computed tomography if fewer nodes were identified. Patients with Pa, P0, or Pis disease were included if T1, T2a, or T2b disease was present on the precystectomy transurethral resection specimen. Pathology and operative reports were centrally reviewed. Patients were also required to have a performance status of 0 or 1, a chest x-ray free from metastatic disease within 6 weeks of cystectomy, and normal organ function, including a WBC count $\geq 4,000/\mu\text{L}$; platelet count $\geq 150,000/\mu\text{L}$; creatinine ≤ 1.8 mg/dL; AST, ALT, and alkaline phosphatase $\leq 2\times$ the upper limit of normal; and normal total bilirubin. Patients with serious arrhythmias or congestive heart failure or who had received prior systemic chemotherapy or local pelvic radiotherapy were not eligible. Patients with previous or concomitant malignancies were also excluded with the exception of pT2 (Gleason score ≤ 7) prostate cancer, basal or squamous cell carcinoma of the skin, in situ cervical cancer, or other malignancies definitively treated more than 5 years before registration without any evidence of recurrence.

p53 Analysis and Randomization

Pathology specimens were centrally assessed for p53 and p21 expression by a single pathologist (R.J.C.). The formalin-fixed, paraffin-embedded tissue was sectioned at 5- μm intervals, deparaffinized, rehydrated through graded alcohols, and subject to antigen retrieval in heated citrate buffer. Following blocking with horse serum, the primary monoclonal antibody was applied (1:200 for oncogene PAb1801 p53 antibody and 1:40 for oncogene p21 antibody). Following incubation and wash, a biotinylated secondary antibody was applied and visualized with an avidin-biotin complex immunoperoxidase system (Vector Laboratories, Burlingame, CA) that used 0.03% diaminobenzidine (DAB) as the chromagen and hematoxylin as the counterstain. Both external and internal controls were used to assess the quality of the IHC reaction. Patients with $\geq 10\%$ nuclear immunoreactivity were considered altered for p53 (p53 positive) and patients with less than 10% nuclear immunoreactivity were considered altered for p21.

Patients with altered p53 were asked to re consent to random assignment. Allocation was based on a minimization/randomization method stratified by age (< 65 v ≥ 65 years), stage (pT1 v pT2), grade (1 and 2 v 3 and 4), and p21 status.¹³ Patients assigned to receive MVAC were to begin chemotherapy within 2 weeks of random assignment and within 12 weeks of cystectomy.

Treatment and Monitoring

MVAC was administered for three cycles.¹⁴ Growth factor support was not routinely administered, and toxicity was reported by using Common Terminology Criteria for Adverse Events (CTCAE) v2.0 criteria. All patients were followed every 3 months for the first year, every 6 months for the following 4 years, and annually thereafter. Clinical follow-up required a physical examination, routine laboratory tests, and a chest x-ray; computed tomography scans were at the discretion of the treating physician.

Statistical Plan

The primary objective was to compare recurrence in patients with p53-positive tumors randomly assigned to MVAC (arm 1) versus observation (arm 2); the secondary objective was to compare recurrence in patients with p53-positive (arms 1 and 2, and group 4) versus p53-negative tumors (group 3).

For the latter groups, survival was calculated as the time from registration to time of death due to any cause, and time to recurrence (TTR) was calculated as the time from registration to the first observation of disease recurrence, censoring patients who died of unrelated causes. When comparing patients randomly assigned to MVAC versus those randomly assigned to observation, the times were calculated from the date of random assignment. The statistical design specified a 0.20 absolute reduction in probability of recurrence at 3 years (from an estimated 0.50 to 0.30), corresponding to a hazard ratio of 0.52. Under the assumption of an exponential TTR distribution, 3 years of accrual, a 2.0-year minimum follow-up, a one-sided α error of .05, and using a log-rank statistic, 190 patients were planned to be randomly assigned to provide a power of 0.90. All primary analyses were specified to be on an intent-to-treat basis. The probabilities of survival plots, estimates, and 95% CIs were based on the Kaplan-Meier product-limit method; the probabilities of recurring plots, estimates, and 95% CIs were based on cumulative incidence curves, with death from non-bladder cancer as a competing cause of treatment failure.¹⁵ An interim analysis was planned after 100 patients had been randomly assigned and followed for 1 year. At the time of the interim analysis, the independent Data and Safety Monitoring Board reviewed the results of the first 110 randomly assigned patients and recommended study closure. Four patients who

Table 1. Comparison of Patients With p53-Positive and p53-Negative Tumors According to Baseline Characteristics

Characteristic	Total		p53 Negative		p53 Positive		P*
	No.	%	No.	%	No.	%	
Total patients	499		227	100	272	55	
Age, years							.59
< 65	286	57	127	56	159	58	
≥ 65	213	43	100	44	113	42	
Sex							.43
Female	99	20	49	22	50	18	
Male	400	80	178	78	222	82	
Race/ethnicity							.24
White	454	91	203	89	251	92	
Black	22	4	13	6	9	3	
Asian	9	2	6	3	3	1	
Hispanic	11	2	3	1	8	3	
Other	3	1	2	1	1	1	
Stage							.64
pT1	185	37	87	38	98	36	
pT2 and pT2a	314	63	140	62	174	64	
Grade							.037
1 or 2	24	5	16	7	8	3	
3 or 4	473	95	210	93	263	97	
Missing	2		1		1		
No. of nodes identified							.11
< 15	168	34	68	30	100	37	
≥ 15	331	66	159	70	172	63	
p21 status							< .001
Absent	145	29	35	16	110	41	
Present	350	71	190	84	160	59	
Missing	4		2		2		
Lymphovascular invasion							.97
No	259	52	117	52	142	52	
Yes	102	20	46	20	56	21	
Unknown	138	28	64	28	74	27	
Bladder carcinoma in situ							.66
No	124	25	60	26	64	24	
Yes	302	61	137	60	165	61	
Unknown	73	14	30	13	43	16	

*P value based on Pearson χ^2 test.

were randomly assigned after the time of the data lock for the interim analysis but before the Board recommendation are included in the final analysis.

have neither recurred nor died, 198 (54%) have more than 5 years and 305 (84%) have more than 3 years of follow-up.

RESULTS

Accrual and Follow-Up

Study conduct is summarized in Figure 1. Between August 1997 and January 2006, 521 patients from 39 institutions were enrolled and 499 were eligible. Reasons for exclusion included late submission of tumor block (n = 5), no invasive tumor in submitted specimen (n = 5), incorrect staging or histology on central review (n = 7), presence of clinically significant prostate cancer (n = 1), and patient decision to withdraw (n = 4). Forty-five percent of eligible patients were p53 negative and were observed. Of 272 patients with p53-positive tumors, 114 (42%) agreed to random assignment. Twelve of 58 patients randomly assigned to chemotherapy never received treatment because of rapid disease recurrence in one patient and refusal in the other 11. None of the patients with p53-negative tumors and none of the patients randomly assigned to observation received adjuvant therapy. Median follow-up at the time of final analysis for the entire cohort was 5.4 years (95% CI, 5.1 to 5.9 years). Of 365 patients who

Prognostic Value of p53 Positivity

Table 1 provides baseline characteristics for p53-positive versus p53-negative patients. There were no major differences in age, sex, race/ethnicity, or stage, but patients with p53-positive tumors had a minimally higher rate of grade 3 to 4 tumors. There was also no difference in clinical prognostic factors, including the number of lymph nodes identified, lymphovascular invasion, or associated carcinoma in situ. As expected, patients with p53-altered tumors had a lower rate of p21 expression. A total of 95 patients progressed and 98 patients died with 63% of the deaths due to bladder cancer. Overall 5-year probability of recurring for all 499 eligible patients was 0.20 (95% CI, 0.16 to 0.24). Figure 2 shows that there was no difference in TTR or overall survival between patients with p53-positive versus those with p53-negative tumors.

MVAC Compliance

Only 46 of 58 patients assigned to MVAC therapy received any treatment. Of these, eight began chemotherapy later than the specified

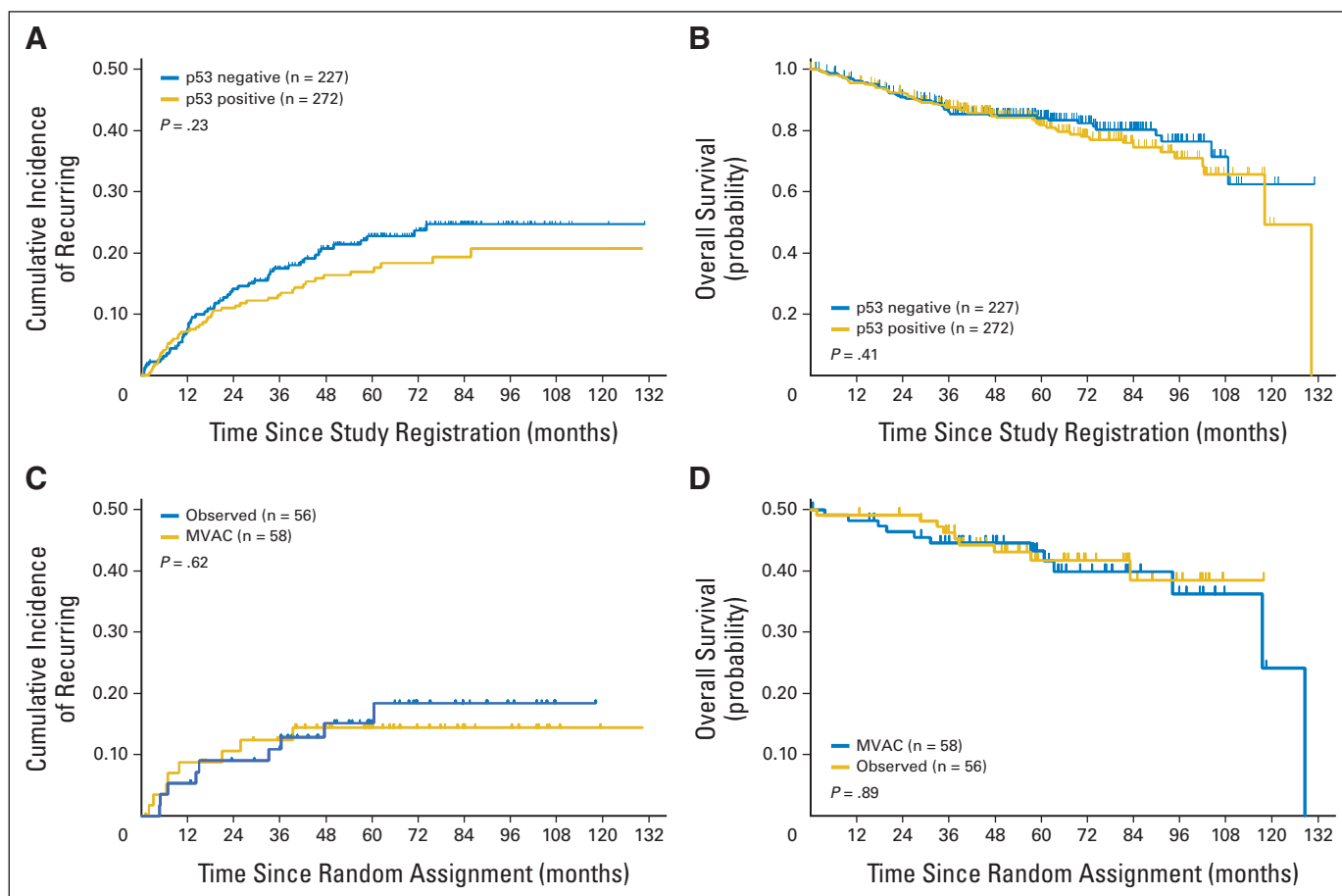


Fig 2. Effect of p53 immunohistochemistry on recurrence and survival. (A) Estimated cumulative incidence curves for time to recurrence and (B) Kaplan-Meier curves for overall survival, based on p53 nuclear immunoreactivity (negative is wild type and positive is altered). (C) Estimated cumulative incidence curves for time to recurrence and (D) Kaplan-Meier curves for overall survival among patients with p53-altered tumors in patients randomly assigned to observation versus chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC; intent-to-treat analysis). Two-sided *P* values are based on the log-rank test for (A) and (B) and on the stratified log-rank test (stratified by age (< 65 v ≥ 65 years), stage (pT1 v pT2), grade (1 to 2 v 3 to 4), and p21 status for (C) and (D).

12 weeks post cystectomy (seven at 13 weeks and one at 14 weeks); 41 patients began cycle 2 and 39 began cycle 3. Reasons for not beginning a subsequent cycle of chemotherapy included toxicity (n = 5), patient refusal (n = 1), and loss to follow-up (n = 1). Of the 39 patients who started all three cycles of therapy, the median percent of total planned drug doses administered for methotrexate, vinblastine, doxorubicin, and cisplatin were 71%, 71%, 86%, and 100%, respectively. No unexpected or fatal toxicities were observed.

Outcome in p53-Positive Randomly Assigned Arms

Table 2 provides baseline characteristics for randomly assigned p53-positive patients. There was no major difference in baseline age, sex, stage, or grade, the number of lymph nodes removed, presence of lymphovascular invasion, associated carcinoma in situ, or p21 expression. Overall probability of recurring by 5 years for all randomly assigned patients was 0.15 (95% CI, 0.09 to 0.23), and the overall probability of surviving 5 years was 0.85 (95% CI, 0.78 to 0.92). No difference in TTR or survival could be detected (Figs 2C and 2D).

Because the 21% noncompliance with assignment to MVAC therapy had the potential for diluting the power of the prespecified intent-to-treat analysis, four additional exploratory/sensitivity analyses were performed. We analyzed TTR, excluding all noncompliant patients, by the treatment received instead of as assigned, and by using a landmark analysis that analyzed only those patients in each arm as

Table 2. Comparison of Patients Randomly Assigned to MVAC (arm 1) and Control/Observation (arm 2) According to Baseline Characteristics

Characteristic	MVAC (arm 1)		Observation (arm 2)		Total
	No.	%	No.	%	
Total patients	58	51	56	49	114
Sex					
Female	7	12	9	16	16
Male	51	88	47	84	98
Age, years					
< 65	37	64	41	73	78
≥ 65	21	36	15	27	36
Stage					
pT1	21	36	16	29	37
pT2	37	64	40	71	77
Grade					
1 or 2	2	3	1	2	3
3 or 4	56	97	55	98	111
No. of nodes identified					
< 15	22	38	14	25	36
≥ 15	36	62	42	75	78
p21 status					
Absent	24	41	22	39	46
Present	34	59	34	61	68
Lymphovascular invasion					
No	33	57	25	45	58
Yes	13	22	14	25	27
Unknown	12	21	17	30	29
Bladder carcinoma in situ					
No	16	27	12	21	28
Yes	34	59	32	57	66
Unknown	8	14	12	21	20

Abbreviation: MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

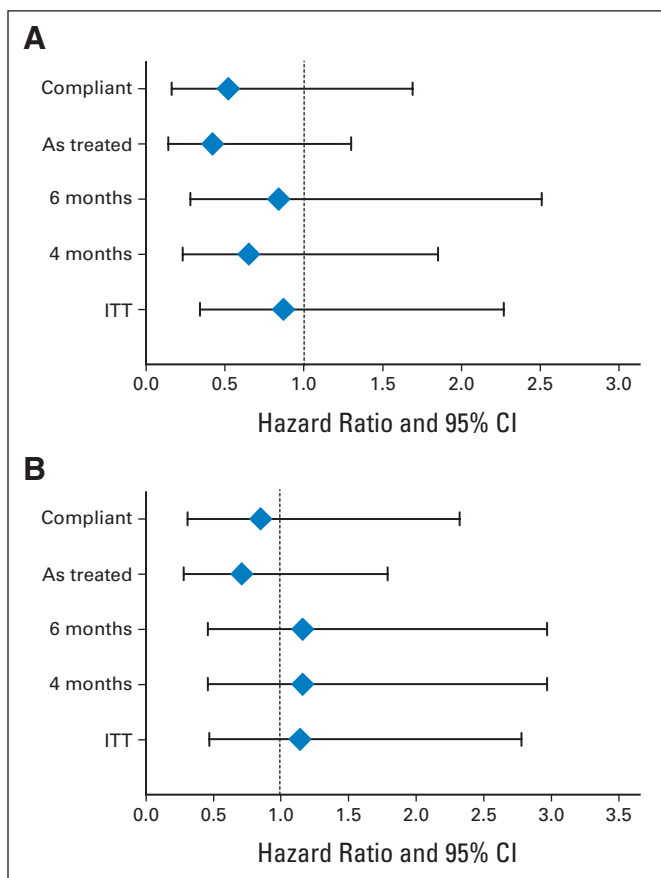


Fig 3. Post hoc analysis and forest plots of time to recurrence and overall survival hazard ratios with 95% CIs to assess the impact of noncompliance with assigned therapy in the arm treated with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC). Compliant excludes patients who refused assigned treatment; as treated includes all patients and analyzes them according to treatment received; 4-month and 6-month landmark analyses assessed only those patients in each arm as assigned who survived without recurrence to a 4- or 6-month landmark, respectively; and ITT represents protocol-specified intent-to-treat analysis.

assigned who survived without recurrence to a 4- or 6-month landmark (Fig 3). There was a numerical improvement in time to recurrence using the first two post hoc analyses, but this did not reach the usual criteria for statistical significance and was not apparent with the landmark analysis.

DISCUSSION

To the best of our knowledge, this was the first study in bladder cancer to base a treatment decision on a molecular alteration and was, at the time, the largest randomized study of adjuvant chemotherapy. The focus was on patients with T1/T2N0 disease, a group not usually treated with adjuvant therapy but for whom recurrence rates are historically high. This study demonstrated a 5-year probability of recurring of approximately 0.20, which is better than that observed in older surgical series but nevertheless emphasizes the highly malignant nature of the disease and the need to improve outcomes for these patients.

There are basically three ways to accomplish this goal. The first is to develop more effective systemic agents and regimens. Despite their inadequacies and multiple efforts to develop alternatives, the MVAC and gemcitabine-cisplatin regimens remain the best available for this disease. The second is to develop better prognostic biomarkers. Under the assumption that the relative benefit of treatment is equivalent across prognostic groups, a greater absolute benefit will be accomplished in patients with the worst prognosis. The last is to develop better predictive biomarkers for benefit from the available regimens.

This trial attempted to confirm p53 IHC as a prognostic biomarker and to determine whether patients with pathologic pT1/T2N0 urothelial bladder cancer who also had p53-altered tumors would benefit from MVAC. The trial was based on extensive preliminary but retrospective data suggesting the value of p53 for these indications and was performed in a prospective manner with a standardized centrally performed biomarker assay. The trial was, however, unable to demonstrate either a prognostic or a predictive value for p53 overexpression. Notably, the better overall patient outcome than predicted limited the power of a single biomarker. In addition, and in retrospect, the data for the predictive value of p53 were somewhat limited by current clinical trial standards.¹² It is also important to note that the lack of random assignment to treatment in the p53-negative group means that a pure predictive value of p53 IHC could not be assessed even if a major difference in the p53-positive randomized arms were demonstrated.

Another possible factor for the observed results was the higher rate of p53 alterations observed compared with earlier studies, possibly because of changes in technique such as better antigen retrieval methods. Whether mutation analysis and/or more comprehensive p53 pathway analysis may be more useful is the subject of current research with the collected samples. Nevertheless, this is, to the best of our knowledge, the only prospective study of p53 as a prognostic or predictive biomarker that uses a centrally assessed standardized assay methodology.

Perhaps the most important factor in the failure of the trial to support the original hypothesis is that the number of patients randomly assigned and, more importantly, who received treatment as assigned, was much lower than anticipated. Under the original plan, patients were to agree to biomarker analysis, and the therapeutic aspects of the trial immediately postoperatively for the biomarker analysis was to be completed in a timely manner. To then address the ethical challenges of consenting to a potentially toxic therapy in the postoperative state, a re-consent process was put into place. It was anticipated that the majority of patients would re-consent, but in reality only 40% did, leading to a much larger trial than anticipated. Equally concerning is the fact that only 39 of 58 patients assigned to MVAC therapy actually received three cycles as planned. Legitimate toxicity and disease considerations contributed to this observation, but the vast majority of patients not receiving therapy simply declined. Although the challenges of randomizing between a toxic therapy and observation with deferred therapy at time of progression are well known and anticipated, it is

unclear whether the nature of the patient population or biases of treating physicians contributed to these observations.

These challenges limited the ability for the trial to evaluate the potential of p53 overexpression to define a group that might be sensitive to cisplatin-based chemotherapy. The low randomization rate and poor compliance with assigned treatment made the trial's power to detect any biologically plausible predictive value negligible. Post hoc analyses of time to recurrence on the basis of treatment as assigned or by elimination of patients who refused therapy give some hint that p53 expression may have modest predictive value. However, this was not apparent with landmark analyses, which are less susceptible to the well-known biases associated with these approaches. It must thus be concluded that the study was unable to determine whether p53 overexpression alone can define a subgroup of patients who benefit from adjuvant MVAC therapy.

Nevertheless, the extensive sample collection along with the well-annotated clinical and outcome data all obtained in a prospective manner will form the basis of further exploratory biomarker studies. The carefully controlled nature of this trial will make it much more likely that biomarkers identified in this effort will be clinically qualified in future prospective confirmatory studies.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

Conception and design: Seth P. Lerner, Susan Groshen, John P. Stein, Derek Raghavan, David Esrig, Donald G. Skinner

Administrative support: Susan Groshen

Provision of study materials or patients: Walter M. Stadler, Seth P. Lerner, Derek Raghavan, Gary Steinberg, David Wood, Laurence Klotz, Craig Hall, Donald G. Skinner

Collection and assembly of data: Walter M. Stadler, Seth P. Lerner, Susan Groshen, John P. Stein, Gary Steinberg, David Wood, Laurence Klotz, Craig Hall, Donald G. Skinner

Data analysis and interpretation: Walter M. Stadler, Seth P. Lerner, Susan Groshen, John P. Stein, Shan-Rong Shi, Derek Raghavan, Richard J. Cote

Manuscript writing: All authors

Final approval of manuscript: All authors

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