

## Surgical Factors Influence Bladder Cancer Outcomes: A Cooperative Group Report

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### A B S T R A C T

#### Purpose

A randomized, cooperative group trial (Southwest Oncology Group 8710, Intergroup 0080) reported that neoadjuvant chemotherapy improved the survival of patients with locally advanced bladder cancer who were treated with radical cystectomy. We evaluated whether surgical factors from patients enrolled onto the study predicted bladder cancer outcomes.

#### Patients and Methods

Surgical and tumor factors were recorded from surgical and pathologic reports from 268 patients with muscle-invasive bladder cancer who received radical cystectomy. Cystectomies were performed by 106 surgeons in 109 institutions. Half of the patients received neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy. Variables were tested in univariate and multivariate analyses for associations with postcystectomy survival (PCS) and local recurrence (LR) in all patients receiving cystectomy.

#### Results

Five-year PCS and LR rates were 54% and 15%, respectively. A multivariate model adjusted for MVAC ( $P = .97$ ), age ( $P = .03$ ), pathologic stage ( $P = .0002$ ), and node status ( $P = .04$ ) showed that surgical variables associated with longer PCS were negative margins ( $v$  positive; hazard ratio [HR], 0.37;  $P = .0007$ ), and  $\geq 10$  nodes removed ( $v < 10$ ; HR, 0.51;  $P = .0001$ ). These associations did not differ by treatment arms ( $P > .21$  for all tests of interactions between treatment and surgical variables). Predictors of LR in a multivariate model adjusted for MVAC ( $P = .16$ ), pathologic stage ( $P = .02$ ), and node status ( $P = .37$ ) were positive margins ( $v$  negative; odds ratio [OR], 11.2;  $P = .0001$ ) and fewer than 10 nodes removed ( $v \geq 10$ ; OR, 5.1;  $P = .002$ ).

#### Conclusion

Surgical factors influence bladder cancer outcomes after cystectomy, after adjustment for pathologic factors and neoadjuvant chemotherapy usage.

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### INTRODUCTION

Radical cystectomy (RC) with a pelvic lymphadenectomy provides excellent local control and long-term survival of muscle-invasive bladder cancer. The curative intent of radical surgery is to remove all cancer in the bladder, pelvis, and regional lymph nodes. Contemporary cystectomy series with 10-year follow-up show that surgery cures the majority of patients with muscle-invasive tumors that are confined to the bladder (pathologic [P] stage pT2), about half with extravesical disease (stage pT3-4),

and a significant minority with positive (N+) pelvic lymph nodes.<sup>1,2</sup> Surgery also provides important pathologic information to identify patients who are likely to develop recurrent disease. A large proportion of patients eventually die of bladder cancer owing to unrecognized and untreated nodal or distant metastasis present at the time of surgery. This has led to attempts to improve the survival of patients with locally advanced bladder cancer by integrating systemic chemotherapy with RC.

A randomized Intergroup trial conducted by the Southwest Oncology Group

(SWOG 8710, INT-0080) reported that neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy improved the survival of patients with muscle-invasive bladder cancer treated by cystectomy.<sup>3</sup> Half of the patients were randomly assigned to receive three cycles of the standardized MVAC regimen. All patients enrolled onto the study agreed to undergo an RC and a bilateral pelvic lymph node dissection (PLND). Surgery was performed by many different surgeons in multiple institutions located throughout the United States. Although the techniques of RC and PLND are well described, there are no currently accepted standards measuring the quality of surgery performed. Given that the quality of RC and extent of PLND might vary among surgeons, we evaluated the impact of surgical variables on bladder cancer outcomes among all patients enrolled onto this randomized, cooperative group trial who underwent a cystectomy. Our aim was to investigate associations of surgical factors with postcystectomy survival and local recurrence in patients receiving cystectomy on the SWOG 8710 trial, and to assess whether these associations depend on the assigned treatment received.

## PATIENTS AND METHODS

Eligibility criteria for the SWOG 8710 trial was a muscle-invasive (clinical stage T2-T4a, N0, M0) bladder cancer and a candidate for RC; no prior pelvic radiation; adequate renal, hepatic, and hematologic function; and a SWOG performance status of 0 or 1. Patients were randomly assigned to receive either RC alone or three cycles of MVAC followed by RC. A total of 317 patients were accrued over an 11-year period (1987 to 1998). Of these, 307 patients (97%) had complete records available for review. Thirty-nine patients (13%) with available records did not have a cystectomy (13 refused, 22 had RC aborted because of unresectable tumor or positive nodes, and four experienced tumor progression while receiving MVAC). Of the 268 patients who had a cystectomy, nine had surgery performed outside of protocol. All patients that received cystectomy and had available records ( $n = 268$ ) were used in the following supplemental analysis. All patients were to be observed until death. Median follow-up time postcystectomy for those patients alive at last contact was 8.9 years, and 96% of all patients had known survival status at 5 years.

Biologic and surgical variables were retrieved from the original operative and pathology reports and reviewed by the first author. Patient, tumor, and surgical variables analyzed included age at surgery ( $< 65$  v  $\geq 65$  years), sex, pathologic stage (pT), node status (negative v positive), total number of nodes examined ( $< 10$  v  $\geq 10$ , where 10 was the median; and by quartiles), soft tissue margins (negative v positive), extent of PLND (none v limited v standard), surgeon type (urologist v urologic oncologist, defined as having received specialized training in urologic oncology), institution (academic, community, or Veterans Affairs [VA]/military), type of urinary diversion (ileal conduit v continent or orthotopic diversion), and treatment received (cystectomy with or without MVAC chemotherapy). Five patients switched treatment arm after randomization, four of whom were randomized to the MVAC arm. Pathologic stage was assigned according to the 1997

version of the tumor-node-metastasis staging system as organ-confined (pT0-2) versus extravesical (pT3-4) disease.

Prescribed surgery consisted of an RC (removal of the bladder and adjacent organs with a margin of perivesical adipose tissue within the muscular-skeletal boundaries of the pelvis) and a bilateral PLND. The extent of PLND was recorded directly from the operative report, independent from the number of nodes examined. A standard PLND included the distal common iliac, external iliac, obturator, and hypogastric nodes. A limited PLND included only nodes sampled medial to the external iliac vein and obturator nodes. If no lymph node dissection was dictated by the surgeon and no nodes were found in the specimen by the pathologist, the patient was recorded as having received no PLND and was classified as node-negative. This occurred in 18 patients (7%). We also recorded node counts according to how the surgeon submitted the nodes to pathology (separate or en bloc with the cystectomy specimen).

## Statistical Analysis

The end points of our study were survival and local recurrence. Survival was defined as the time from cystectomy until death as a result of any cause. Local recurrence was defined as appearance of a pelvic mass on computed tomography scan at any time during follow-up and confirmed by histologic biopsy.

Our aim was to identify variables univariately associated with the outcomes and then test whether the variables related to surgery were important predictors of outcome after adjusting for other patient, disease, and treatment-related variables. Cox proportional hazards regression was used to test for surgical predictors of postcystectomy survival. Multivariate proportional hazards models were adjusted for treatment, age, pathologic stage, and node status. Logistic regression was used to test for surgical predictors of local recurrence. Multivariate logistic regression models for local recurrence were adjusted for treatment, pathologic stage, and node status. All proportional hazards models and logistic regression models were fit with the use of the PHREG and LOGISTIC procedures, respectively, in the SAS software package (SAS/STAT User's Guide, version 8, 1999; SAS Institute Inc, Cary, NC). The Wald  $\chi^2$  statistic was used to evaluate the contribution of each individual covariate in both the univariate and multivariate proportional hazards and logistic regression models. We used interactions to test whether the effects of the surgical variables depended on the treatment received. Interactions between treatment and the surgical variables were tested by assessing the Wald  $\chi^2$  statistic for each individual interaction in the covariate-adjusted models.

All variables had complete records except margin status, which was missing for 26 patients. Any model including margin status used only the 242 patients with complete records. Survival curves and point estimates were based on Kaplan-Meier estimates generated using the LIFETEST procedure in SAS software. All statistical tests were two sided and  $P$  values were considered significant if less than .05. Analysis of the data was performed by the SWOG Statistical Center and approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center (New York, NY).

## RESULTS

Table 1 lists characteristics and surgical and pathologic variables for all patients. Half of the patients received

**Table 1.** Distribution of Patient, Treatment, Pathologic, and Surgical Factors Among the 268 Patients Who Had a Cystectomy

Variable	No. of Patients	%	Variable	No. of Patients	%
Age, years			PLND		
< 65	148	55	None	24	9
≥ 65	120	45	Limited	98	37
			Standard	146	54
Sex			Margins		
Male	216	81	Negative	217	81*
Female	52	19	Positive	25	9
			Not reported	26	10
Treatment received			Surgeon		
RC	133	50	Urologist	153	57
MVAC + RC	135	50	Urologic oncologist	115	43
Pathologic stage (pT)			Institution type		
pT0-2	184	69	Academic	137	51
pT3-4	84	31	Community	84	31
			VA/military	47	18
Node status			Urinary diversion		
Negative	213	79	Ileal conduit	191	71
Positive	55	21	Orthotopic	77	29
Nodes removed (quartiles)			Local recurrence		
0-4	63	24	No	227	85
5-9	67	25	Yes	41	15
10-15	67	25			
> 15	71	26			

Abbreviations: PLND, pelvic lymph node dissection; RC, radical cystectomy; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; VA, Veterans Affairs.  
\*Of patients with margins reported, 90% were negative and 10% positive.

MVAC chemotherapy before cystectomy. The patients were well balanced between treatment arms of the study relative to the variables shown in Table 1, except for pathologic stage and node status. Patients receiving neoadjuvant MVAC had more organ-confined tumors (tumor downstaging;  $P = .001$  from  $\chi^2$  test) and fewer positive nodes ( $P = .04$ ) than patients who had surgery alone.

Twenty-four patients (9%) had no node dissection, 98 patients (37%) had a limited node sampling, and 146 patients (54%) had a standard bilateral PLND. The median number of nodes removed from all patients was 10 (range, zero to 54 nodes). Twenty-four percent of the patients had zero to four nodes removed, 25% had five to nine nodes, 25% had 10 to 15 nodes, and 26% had more than 15 nodes removed. The median number of nodes after none, limited, or standard PLND was zero, seven (range, zero to 16), and 15 (range, one to 54), respectively. Node status was positive for 55 patients (21%). Of the 242 patients with status of surgical margins reported, 25 (10%) had positive margins. Local recurrence occurred in 41 (15%) of the 268 patients after cystectomy and was balanced between treatment arms.

Study patients were operated on by 106 different surgeons in 109 institutions. Fourteen surgeons performed five or more cystectomies on this study and 92 did fewer than five operations. All but one of the high-volume surgeons were urologic oncologists. Of the 109 institutions represented, 50 were community hospitals ( $n = 84$  patients), 36 were academic medical

centers ( $n = 137$  patients), and 23 were VA/military hospitals ( $n = 47$  patients), of which half had academic affiliations. Of the 268 cystectomies, 115 were performed by urologic oncologists and 153 were performed by general urologists. The type of surgeons handling patients was dependent on the type of institution. Ninety percent of patients who had surgery at academic institutions were operated on by urologic oncologists, whereas urologic oncologists were only responsible for 9% of patients who received surgery at VA/military and community institutions combined.

### Urinary Diversion

One hundred ninety-one patients received an ileal conduit urinary diversion and 77 had a continent stoma or orthotopic diversion. The type of urinary diversion was associated with the type of surgeon, type of institution, and the age of the patient. Eighty-four percent of patients treated by urologists received ileal conduits compared with 55% of patients treated by urologic oncologists. Likewise, 60% of patients treated at academic institutions received ileal conduits, compared with 90% at community and 72% at VA/military institutions. Eighty percent of patients 65 years or older received ileal conduits, compared with 65% of those younger than 65 years.

### Postcystectomy Survival

The 5-year postcystectomy survival rate for all patients was 54%. Table 2 lists univariate associations between the

**Table 2.** Bladder Cancer Outcomes by Surgical and Pathologic Variables for the 268 Patients Undergoing Cystectomy

Variable	Survival				Local Recurrence		
	At Risk	Deaths	5-Year Survival* (%)	<i>P</i> †	No. of Patients	%	<i>P</i> ‡
Age, years							
< 65	148	75	61	.005	19	13	.22
≥ 65	120	84	42		22	18	
Sex							
Male	216	133	51	.22	32	15	.66
Female	52	26	58		9	17	
Pathologic stage (pT)							
pT0-2	184	90	67	< .0001	14	8	< .0001
pT3-4	84	69	22		27	32	
Node status							
Negative	213	114	60	< .0001	25	12	.002
Positive	55	45	22		16	29	
Margins§							
Negative	217	114	61		15	7	
Positive	25	25	0	< .0001	17	68	< .0001
Nodes removed							
< 10	130	90	44	.0007	33	25	< .0001
≥ 10	138	69	61		8	6	
Nodes removed (quartiles)							
0-4	63	43	44		19	30	
5-9	67	47	44	.008	14	21	< .0001
10-15	67	35	61		4	6	
> 15	71	34	62		4	6	
PLND							
None	24	17	33		12	50	
Limited	98	63	46	.01	22	22	< .0001
Standard	146	79	60		7	5	
Surgeon							
Urologist	153	98	48	.053	33	23	.06
Urologic oncologist	115	61	58		8	6	
Institution type							
Academic	137	72	57		14	10	
Community	84	52	54	.053¶	18	21	.02¶
VA/military	47	35	40		9	19	
Urinary diversion							
Ileal conduit	191	126	48	.006	29	15	.93
Continent stoma or orthotopic	77	33	63		12	16	
Local recurrence							
No	227	120	60	< .0001	—	—	—
Yes	41	39	9				

Abbreviations: PLND, pelvic lymph node dissection; VA, Veterans Affairs.

\*Survival at 5 years is Kaplan-Meier estimate.

†*P* values are from univariate proportion-hazards regressions and are two sided.

‡*P* values are from univariate logistic regressions and are two sided.

§Margin status only available for 242 patients.

||For test of standard v other.

¶For test of academic v other.

patient variables and the outcomes of survival and local recurrence. Univariate predictors of longer postcystectomy survival ( $P < .05$ ) were age younger than 65 years, pathologically organ-confined tumors (stage pT0-2), negative node status, negative soft tissue margins,  $\geq 10$  nodes removed, standard PLND (v none to limited), and continent urinary diversions. Type of surgeon (urologic oncologist) and type of institution (academic v other) were suggestive ( $P = .053$  for both tests).

As shown in Table 2, the 5-year survival rate after RC and no node dissection was 33% (median, 2.4 years), 46% after a limited dissection (median, 4.2 years), and 60% with a standard dissection (median, 7.2 years). Figure 1 shows survival curves by fewer than versus greater than or equal to the median number of 10 nodes removed for patients receiving cystectomy. Among 138 patients who had 10 or more nodes removed, the probability of survival 5 years after cystectomy was 61% (median survival time, 7.7 years),

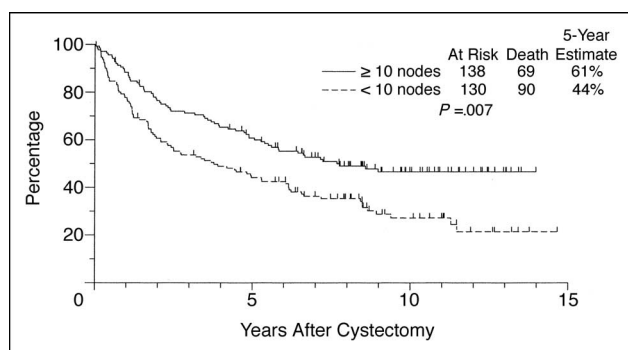


Fig 1. Postcystectomy survival by number of lymph nodes removed.

compared with 44% for the 130 patients (median survival time, 3.8 years) having fewer than 10 nodes removed ( $P = .0007$ ). Figure 2 suggests that the survival advantage conferred by removing 10 or more nodes was retained in both node-negative and node-positive patients. Among 213 node-negative patients, 5-year survival for the group with  $\geq 10$  versus fewer than 10 nodes removed was 69% and 52%, respectively (median survival not reached and 5.3 years, respectively). Among the 42 node-positive patients, 5-year survival for those with  $\geq 10$  versus fewer than 10 nodes removed was 34% and 9%, respectively (median, 2.3 and 1.2 years, respectively). The comparisons of survival among node groups in Figures 1 and 2 are mainly for visualization purposes and do not provide an adequate assessment because other potentially confounding covariates such as disease status cannot be adjusted for using this type of univariate analysis.

Table 3 lists results of a proportional hazards regression analysis used to test for surgical predictors of postcystectomy survival after adjusting for other covariates. In this multivariate model adjusted for treatment, age, pathologic stage, and node status, surgical predictors of longer postcystectomy survival were negative surgical margins ( $P = .0007$ ) and  $\geq 10$  nodes removed ( $P = .0001$ ). The adjusted hazard

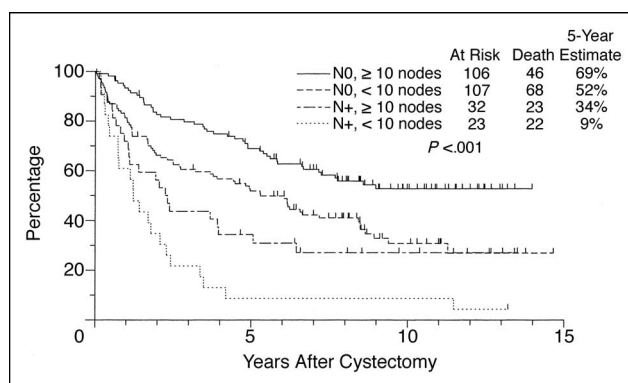


Fig 2. Postcystectomy survival by node status and number of nodes removed.

Table 3. Multivariate Proportional Hazards Regression Model for Postcystectomy Survival

Variable	HR*	95% CI	$P^{\dagger}$
Treatment RC v MVAC + RC	1.0	0.7 to 1.4	.97 $\ddagger$
Age $\geq 65$ v < 65 years	1.5	1.0 to 3.6	.03
pT stage 3-4 v 0-2	2.3	1.5 to 3.6	.0002
Node status positive v negative	1.6	1.0 to 2.5	.04
Margins Positive v negative	2.7	1.5 to 4.9	.0007
Nodes removed < 10 v $\geq 10$	2.0	1.4 to 2.8	.0001

Abbreviations: HR, hazard ratio; RC, radical cystectomy; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

\*Each HR and  $P$  is adjusted for all other covariates in the model.

$\dagger P$  values are two sided and based on the Wald  $\chi^2$  test.

$\ddagger$ Treatment was insignificant because pT stage explains much of the treatment effect.

ratio for death for patients with positive surgical margins relative to negative was 2.7 (95% CI, 1.5 to 4.9), and that for patients with fewer than 10 relative to  $\geq 10$  nodes removed was 2.0 (95% CI, 1.4 to 2.8). Type of surgeon and type of institution (academic v other) were not significant ( $P > .05$ ) and were removed from the model. Tests for interactions between treatment and margin status, and treatment and nodes removed in the multivariate model were not significant ( $P > .21$  for each test), suggesting that the associations of margins and nodes examined with survival did not depend on whether MVAC was received.

The PLND variable was not significant ( $P = .15$ ) when substituted for the node count variable in the model shown in Table 3. PLND and the number of nodes (by quartiles) were closely correlated (data not shown), although there was overlap among PLND categories. Type of PLND was a coarse categorization of the actual number of nodes removed, suggesting that node counts are a more accurate measure of the extent of the lymph node dissection.

### Local Recurrence

Of the 268 patients, 41 (15%) had a local recurrence after cystectomy. As listed in Table 2, predictors of local recurrence ( $P < .05$ ) were pT3-4, negative nodes, less than 10 nodes removed, no or limited PLND, and positive surgical margins. Type of surgeon was suggestive ( $P = .06$ ), where 23% of the patients operated on by general urologists had a local recurrence, compared with 6% of patients operated on by urologic oncologists. Table 4 indicates that surgical predictors of a local recurrence in a multivariate logistic regression model adjusted for treatment, pathologic stage, and node status were positive margins ( $P = .0001$ ) and less than 10 nodes removed ( $P = .002$ ). The adjusted odds of a patient with positive surgical margins having a local recurrence were 11.2 times greater than that for negative margins (95% CI, 3.3 to 37.8), whereas the adjusted odds were 5.1 times greater for less than 10 relative to  $\geq 10$  nodes removed (95% CI, 1.8 to 14.7). Tests for interactions

**Table 4.** Multivariate Logistic Regression Model for Probability of a Local Recurrence

Variable	OR*	95% CI	P†
Treatment RC v MVAC + RC	0.5	0.2 to 1.3	.16
pT stage 3-4 v 0-2	3.8	1.2 to 12.2	.02
Node status positive v negative	1.7	0.5 to 5.2	.37
Margins positive v negative	11.2	3.3 to 37.8	.0001
Nodes removed < 10 v ≥ 10	5.1	1.8 to 14.7	.002

Abbreviations: OR, odd ratio; RC, radical cystectomy; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin.

\*Each OR and P value is adjusted for all other covariates in the model. †P values are two sided and based on the Wald  $\chi^2$  test.

between treatment and margin status, and treatment and nodes removed in the multivariate model were not significant ( $P > .6$  for each test), suggesting that the associations of margins and nodes examined with local recurrence did not depend on whether MVAC was given.

### Associations Among Surgical Factors and Other Covariates

Surgical margins and number of nodes removed were the strongest surgical predictors of survival and local recurrence. These two surgical factors also were associated with

each other. Positive surgical margins were associated with fewer nodes removed ( $P = .01$  from  $\chi^2$  test); 17 (68%) of the 25 patients with positive margins had less than 10 nodes removed. These two surgical factors were also correlated with other variables. Table 5 lists univariate associations of number of nodes removed and surgical margin status with the other patient variables. Univariate predictors ( $P < .05$ ) of less than 10 nodes removed were urologists and nonacademic institutions. Predictors of no or limited PLND (v standard) were the same as those for less than 10 nodes removed (data not shown). Univariate predictors of positive margins were older patients, more advanced pT stages, positive node status, surgery by urologists, and surgery at nonacademic institutions.

It was of interest to investigate whether the type of surgeon or type of institution (academic v other) was an important predictor of margin status or nodes removed after adjusting for patient characteristics and extent of disease. Although these are crude representations, one would expect the institution and surgeon variables to provide some surrogate measure of the knowledge base of the surgeons and the practice standards held by institutions. The high correlation between these two variables makes separating the individual importance of either difficult, so separate

**Table 5.** Associations of Number of Nodes Removed and Status of Surgical Margins With Other Patient Variables

Variable	Total No. of Patients	Nodes Removed			Surgical Margins			
		< 10 Nodes Removed		P*	Total No. of Patients§	Positive Margins†		P*
No. of Patients	%	No. of Patients	%					
Age, years								
< 65	148	68	46	.35	134	7	5	.004
≥ 65	120	62	52		108	18	17	
Sex								
Male	216	104	48	.81	194	21	11	.61
Female	52	26	50		48	4	8	
Treatment								
RC	133	66	50	.72	117	16	14	.10
MVAC + RC	135	64	47		125	9	7	
Pathologic stage (pT)								
pT0-2	184	90	49	.84	169	1	1	< .0001
pT3-4	84	40	48		73	24	33	
Node status								
Negative	213	107	50	.27	194	13	7	.0002
Positive	55	23	42		48	12	25	
Surgeon								
Urologist	153	96	63	< .0001	131	21	16	.002
Urologic oncologist	115	34	30		111	4	4	
Institution type								
Academic	137	50	37		134	7	5	
Community	84	55	65	< .0001‡	71	14	20	.006‡
VA/military	47	25	53		37	4	11	

Abbreviations: RC, radical cystectomy; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; VA, Veterans Affairs.

\*P values are from univariate logistic regressions and are two sided.

†Margin status only available for 242 patients.

‡For test of academic v other.

adjusted models were fit for each. A multivariate logistic regression model using margin status as the response and adjusting for treatment, pT stage, node status, and age found type of surgeon (general urologist) to be an important predictor of positive margin status ( $P = .0004$ ). The same model found that type of institution (nonacademic) predicted positive margins ( $P = .009$ ) when substituted for type of surgeon. Likewise, a multivariate logistic regression using number of nodes removed ( $< 10$  v  $\geq 10$ ) as the response and adjusting for treatment, pT stage, node status, and age found that type of surgeon (general urologist) predicted removal of less than 10 nodes ( $P < .0001$ ). Type of institution (nonacademic) predicted removal of less than 10 nodes ( $P = .0001$ ) when substituted for type of surgeon in that model. These investigations are purely exploratory and causal relationships should not be drawn, but they do suggest that much of the variability in quality of surgery can be explained by characteristics of the surgeon or institution, even after patient characteristics and extent of disease are accounted for.

## DISCUSSION

The primary question asked by the SWOG-Intergroup study was whether neoadjuvant MVAC chemotherapy improves the survival of patients with locally advanced bladder cancer. Although MVAC improved survival compared with cystectomy alone, the primary aim of the trial focused on the chemotherapy question. The surgeon and surgical variability were not considered as risk factors predictive of bladder cancer outcomes. The cooperative group mechanism ensures a large participation of diverse community and academic hospitals and surgeons, including possible variations in the quality of RC as it is currently practiced in the United States. We sought to evaluate whether surgery influences bladder cancer outcomes among all patients receiving RC on the SWOG trial. We found substantial variability in how cystectomy was performed, especially in the extent of PLND, and that surgical factors play a significant role in determining the outcome of patients with locally advanced bladder cancer who are treated by RC, whether or not they receive neoadjuvant chemotherapy.

Patients who underwent an RC and a standard template PLND, achieved a negative surgical margin, and had more lymph nodes removed had superior postcystectomy survival than patients who had less favorable surgical features. Urologic oncologists achieved better long-term survival and fewer local recurrences among their patients than did general urologists. A positive surgical margin, regardless of node status or total number of nodes removed, was associated with a local recurrence and death as a result of bladder cancer. The 5-year survival rate for patients having RC and no, limited, or standard lymph node dissection was

33%, 46%, and 60%, respectively. The 5-year survival rate for patients with fewer than 10 nodes removed was 44% compared with 61% for patients with more than 10 nodes examined. Local recurrences occurred in only 6% of patients after RC and a standard pelvic node dissection removing more than 10 nodes, compared with 25% after a limited node dissection with fewer than 10 nodes. Half the patients who had no node dissection had a local recurrence. The importance of locoregional control is emphasized by the fact that 91% of the 41 patients who had a local recurrence died as a result of bladder cancer, including all 25 patients who had positive surgical margins. The fact that both surgical margins and number of nodes were independent predictors of postcystectomy survival and local recurrence in multivariate models suggests that the quality of surgery significantly influences bladder cancer outcomes.

Single-institution cystectomy series have shown for both node-negative and node-positive patients with invasive bladder cancer that overall survival improves with an increasing number of lymph nodes examined.<sup>4,5</sup> A recent analysis of 1,923 patients obtained from the Surveillance, Epidemiology, and End Results program cancer registry showed improved postcystectomy survival with a more comprehensive lymph node dissection.<sup>6</sup> The extent of lymphadenectomy also was relevant to survival in patients with locally advanced disease who received chemotherapy, suggesting that maximum surgical debulking of the primary tumor and regional lymph nodes is an essential part of combined therapy. The Surveillance, Epidemiology, and End Results data suggest that excision of a predetermined minimum number of nodes (10 to 14) should be used as a surrogate measure of the quality of lymphadenectomy or pathologic examination on which to base accurate staging of node status and to optimize therapeutic benefit of RC.

Our study has limitations. It represents a secondary analysis of a prospective trial. The associations we found could be considered suggestive but no causal inferences should be drawn. Other variables that were not measured might have contributed to the observed associations between surgical variables and bladder cancer outcomes. The patients were operated on over a decade, and it is possible that unmeasured surgical practices have improved over time. However, it is unlikely that patient selection, surgical techniques, or the surrogate markers (surgical margins and number of nodes) defining surgical variability changed significantly during the years of the study.

Why some surgeons elected to do no or a limited node sampling rather than a complete PLND was not clear from the operative records. One reason might be that the protocol did not mandate specific limits of the pelvic node dissection. Patient age and assigned treatment group were not contributing factors given that equal numbers of older patients in each arm had no or a limited node dissection. The most likely reason was experience of the individual surgeon.

Sixty-two percent of general urologists performed a limited or no node dissection compared with 23% of urologic oncologists ( $P < .001$ ).

Largely ignored in our analysis is the influence of the pathologist, whose technique and diligence in examining the cystectomy specimen and searching for nodes may vary. Although practice guidelines for examining and reporting of cystectomy and lymph node specimens are available,<sup>7,8</sup> quality assurance of recommended pathology protocols has not been verified and none has been standardized or validated. For example, the minimum number of nodes required to label a patient as node-negative has not been determined reliably. This fact alone is critical to the medical oncologist who must decide which patients are at high risk for tumor recurrence, which patients to treat with chemotherapy, and how to evaluate the results of treatment.

We found that although all pathology reports described the pathologic stage of cancer, in some cases other variables were poorly documented in the records. Margin status was not mentioned in 26 patients (10%), and number of nodes was not reported in another 18 patients (7%). Only 1% to 2% of pathology reports from academic medical centers failed to report margins or nodes compared with 15% and 21% from community or VA/military hospitals, respectively. The surgeon can aid the pathologist by submitting nodes separately rather than en bloc with the bladder. We found that the median number of nodes recovered in separate node packets was 12 (range, one to 54) compared with only four (range, zero to 12) in en bloc specimens.

When improved survival correlates with increasing numbers of lymph nodes reported by the pathologist, three factors are potentially involved: a diminished risk of local and regional recurrence may result from a complete pelvic lymphadenectomy, which yields more lymph nodes in the specimen; the surgeon who performs a more complete node dissection may secure wider margins around the bladder and adjacent organs; or a more thorough examination of the specimen by the pathologist may result in more accurate staging. Although we cannot assign a mechanism for the improved outcome with increased node count, other studies suggest that variations in the number of nodes identified per specimen are not related specifically to pathologic examination but to variations in the extent of the lymphadenectomy.<sup>4,9</sup> Our data show that reduced local recurrence and better survival were associated with negative surgical margins and higher node counts. These two significant surgical variables are interrelated and depend on the experience of the surgeon and thoroughness of the PLND. The data emerging from collective studies is that the quality of RC is critical to outcome.

Our findings raise larger questions worthy of additional investigation, especially in an era of combined-

modality therapy for invasive bladder cancer. We demonstrate substantial variability in the type of surgical resection performed and hence the number of lymph nodes removed. The technique and the diligence of the pathologist also may vary. The result is that tumors may be understaged or overtreated, directly influencing a patient's duration and quality of survival. Does removing more nodes influence survival or is it merely better staging and a way of identifying candidates for chemotherapy? The fact that patients who had limited sampling of nodes fared worse than similarly staged patients who had more complete clearing of regional nodes suggests (but does not prove) that lymphadenectomy might have therapeutic benefit. If RC and pelvic node dissection are based on anatomic guidelines, why is there substantial variability among individual surgeons regarding margin status and number of lymph nodes retrieved? Is there adequate communication between the surgeon and the pathologist? Is the retrieval of a small number of lymph nodes an indication for adjuvant chemotherapy? These and other questions can be answered by prospective trials in which surgical resection of invasive bladder cancer is founded on accepted anatomic boundaries, well-defined margins, and verifiably complete lymph node templates of dissection.

The need to secure and retain local and regional control of invasive bladder cancers, even extravesical tumors with positive nodes, will assume increasing importance as systemic therapy improves and reduces deaths from distant metastases. Accepted surgical standards for RC with PLND and pathologic assessment of cystectomy specimens should be established and prospectively validated. Given that nodes are related to both margins and outcome, a minimum number should be agreed on as a proxy measure of the quality of surgery. This is important not only for individual patient management but also for the design and evaluation of adjuvant and neoadjuvant chemotherapy studies in bladder cancer. Improving the general quality of surgery may even prove to be as important as or more important than anticipated improvements in chemotherapy regimens.

Our study shows that improved postcystectomy survival and reduced local recurrence are associated with negative surgical margins and more lymph nodes removed. Surgical variables influence bladder cancer outcomes, with or without neoadjuvant chemotherapy, emphasizing that quality assurance of RC and pelvic lymphadenectomy should be factored in combined-modality clinical trials of invasive bladder cancer.

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### **Authors' Disclosures of Potential Conflicts of Interest**

The authors indicated no potential conflicts of interest.

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