

# Quality of Pathologic Response and Surgery Correlate With Survival for Patients With Completely Resected Bladder Cancer After Neoadjuvant Chemotherapy

Guru Sonpavde, MD<sup>1</sup>; Bryan H. Goldman, MD<sup>2</sup>; V. O. Speights, MD<sup>3</sup>; Seth P. Lerner, MD<sup>1</sup>; David P. Wood, MD<sup>4</sup>; Nicholas J. Vogelzang, MD<sup>5</sup>; Donald L. Trump, MD<sup>6</sup>; Ronald B. Natale, MD<sup>7</sup>; H. Barton Grossman, MD<sup>8</sup>; and E. David Crawford, MD<sup>9</sup>

**BACKGROUND:** In a retrospective study of Southwestern Oncology Group (SWOG)-S8710/INT-0080 (radical cystectomy [RC] alone vs 3 cycles of neoadjuvant chemotherapy [NC] with methotrexate, vinblastine, doxorubicin, and cisplatin before RC for bladder cancer), factors found to be associated with improved overall survival (OS) included pathologic complete response, defined as P0; treatment with NC; completion of RC with negative surgical margins; and  $\geq 10$  pelvic lymph nodes (LNs) removed. **METHODS:** The authors used stratified Cox regression to retrospectively study the association of quality of pathologic response after RC with OS in the subset of S8710 patients who received NC and RC with negative surgical margins. **RESULTS:** Of 154 patients who received NC, 68 (44.2%) were  $<P2$  (P0, Pa, P1, or carcinoma in situ [CIS]) at RC, 46 (29.9%) were P0, and the remainder had P2+ disease or did not undergo RC. In 115 patients who had RC with negative surgical margins, compared with P0 patients, those with residual Pa, P1, or CIS appeared to have worse OS ( $P = .054$ ); OS was significantly worse for patients with residual P2+ disease ( $P = .0006$ ). LN-positive (LN+) disease was found to be associated with worse OS than LN-negative (LN-) disease ( $P = .0005$ ). Patients with LN- disease (ie, those with  $<10$  LNs removed) appeared to have inferior OS compared with those with 10+ LNs removed ( $P = .079$ ). The combination of pre-NC clinical stage and post-RC pathologic stage was found to be predictive of OS ( $P < .0001$ ). **CONCLUSIONS:** NC and RC with negative surgical margins for bladder cancer followed by pathologic P0 and LN- disease were found to correlate with improved OS. A combination of baseline clinical stage and post-RC pathologic stage may better predict OS. **Cancer 2009;115:4104-9. © 2009 American Cancer Society.**

**KEY WORDS:** neoadjuvant chemotherapy, bladder cancer, pathologic complete response, overall survival.

**Corresponding author:** Guru Sonpavde, MD, Departments of Medicine and Urology, Baylor College of Medicine, 501 Medical Center Boulevard, Webster, TX 77598; Fax: (281) 332-8429; gurus@bcm.edu

<sup>1</sup>Department of Medicine, Section of Medical Oncology, Baylor College of Medicine, Houston, Texas; <sup>2</sup>Southwest Oncology Group Statistical Center, Seattle, Washington; <sup>3</sup>Department of Medicine, Section of Medical Oncology, Scott and White Clinic, Temple, Texas; <sup>4</sup>Department of Urology, University of Michigan, Ann Arbor, Michigan; <sup>5</sup>Department of Medicine, Section of Medical Oncology, Nevada Cancer Institute, Las Vegas, Nevada; <sup>6</sup>Department of Medicine, Section of Medical Oncology, Roswell Park Cancer Institute, Buffalo, New York; <sup>7</sup>Department of Medicine, Section of Medical Oncology, Cedars-Sinai Comprehensive Cancer Center, Los Angeles, California; <sup>8</sup>Department of Urology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; <sup>9</sup>Department of Urology, University of Colorado, Aurora, Colorado

From the Southwest Oncology Group, Eastern Cooperative Oncology Group, and Cancer and Leukemia Group B.

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**Neoadjuvant** treatment with methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy was evaluated for patients with locally advanced bladder cancer (clinical T2 to T4a) treated with radical cystectomy (RC) in a phase 3 trial (S8710) conducted by the Southwest Oncology Group.<sup>1</sup> A total of 317 patients were randomized to RC or 3 cycles of MVAC followed by RC. The median survival among patients assigned to surgery alone was 46 months, compared with 77 months with MVAC ( $P = .06$ ). Significantly more patients in the MVAC group had no residual disease (P0) than patients in the cystectomy group (38% vs 15%;  $P < .001$ ). In both groups, improved survival was associated with P0 disease, with the 5-year survival rate for all patients with P0 disease being an impressive 85%. The International Collaboration of Trialists trial and a meta-analysis have confirmed the value of neoadjuvant cisplatin-based combination chemotherapy.<sup>2-4</sup> Retrospective analyses of S8710 revealed that survival was associated with neoadjuvant MVAC, completion of RC, and  $\geq 10$  pelvic lymph nodes (LNs) removed.<sup>5,6</sup> Five-year survival was 81% in patients treated with neoadjuvant MVAC and RC with  $\geq 10$  LNs removed ( $n = 66$ ), 66% in patients treated with RC alone with  $\geq 10$  LNs removed ( $n = 60$ ), 55% for those treated with MVAC and RC with  $< 10$  LNs removed ( $n = 49$ ), and 39% for those treated with RC alone with  $< 10$  LNs removed ( $n = 44$ ). Pooled across treatment arms, the 5-year survival of patients with positive surgical margins ( $n = 25$ ) and those who did not undergo RC ( $n = 39$ ) was dismal at 0% and 11%, respectively. Therefore, both the quality of surgery and neoadjuvant chemotherapy (NC) appeared to impact favorably and independently on outcomes.

Pathologic complete remission (pCR) with neoadjuvant therapy for breast cancer is also highly correlated with survival. However, the optimal definition of pCR is unsettled.<sup>7-12</sup> When there is no residual invasive cancer in the breast, the number of involved axillary LNs is inversely related to survival. Conversely, patients who convert to LN-negative (LN-) status after treatment have excellent survival, even with residual disease in the breast. To our knowledge, there is no evidence that residual in situ carcinoma increases risk of distant disease recurrence.<sup>13,14</sup> In a recent retrospective analysis, residual cancer burden calculated after NC for breast cancer as a continuous index combining primary tumor (size and cellularity) and

lymph node (number and size) characteristics for the prediction of distant recurrence-free survival was found to be independently prognostic in a multivariate model.<sup>15</sup> In another retrospective analysis of women who received NC, risk stratification of patients was facilitated by the combination of pretreatment clinical stage and post-therapy pathologic stage.<sup>16</sup> S8710 defined pCR as the absence of all residual bladder cancer (P0). However, residual non-muscle invasive cancer including carcinoma in situ (CIS), Pa, and P1 disease may correlate with outcomes similar to P0 and may differentially impact prognosis compared with P2+ disease. Similar to breast cancer, outcomes after NC are likely associated with pretherapy clinical staging and post-therapy pathologic staging and tumor burden. Therefore, we planned a retrospective study of the S8710 trial to evaluate the correlation of the quality of pathologic response with neoadjuvant MVAC and surgical resection with overall survival (OS).

## MATERIALS AND METHODS

### *Retrospective Cohort Study of a Prospective Trial*

We retrospectively studied patients in S8710 who received neoadjuvant MVAC chemotherapy and completed RC with negative surgical margins. The primary goals were to determine the association between pathologic response (P0 vs Pa, P1, CIS vs P2+), pathologic lymph node involvement, and quality of pelvic lymph node dissection and OS. In addition, the correlation between a combination of baseline clinical stage and RC pathologic stage and OS was analyzed.

### *Statistical Analysis*

Associations between various pathologic and clinical features in the subset of S8710 patients who received NC and RC with negative surgical margins and OS were evaluated using stratified proportional hazards regression. Baseline clinical T classification (T2 vs T3-4), pathologic stage at cystectomy (P0 vs Pa/P1/CIS vs P2+), and number of LNs removed ( $< 10$  vs  $10+$ ) were explored as potential prognostic factors. Because all patients included in the analysis were treated with RC, Day 0 in these survival models was defined as the date of cystectomy.

**Table 1.** Correlation Between Clinicopathologic Features and Overall Survival Among Patients Treated With Neoadjuvant MVAC and RC

Characteristic	No.	Median OS, y	HR (95% CI)
<b>Pathologic stage</b>			
P0	46	13.6	1.0
P1/CIS/Pa	22	10.6	2.05 (0.99-4.24)
P2+	47	3.7	2.75 (1.54-4.89)*
<b>Lymph node status†</b>			
LN-	93	10.6	1.0
LN+	17	2.4	2.90 (1.59-5.28)*
<b>Lymph nodes removed (LN- only)</b>			
10+	50	13.7	1.0
<10	43	7.2	1.66 (0.94-2.90)
<b>Clinical T classification/pathology</b>			
cT2→<P2	35	NR	1.0
cT3-4→<P2	33	8.9	1.87 (0.96-3.63)
cT2→P2+	13	1.8	7.64 (3.51-16.61)*
cT3-4→P2+	34	5.1	2.82 (1.48-5.38)*

MVAC indicates methotrexate, vinblastine, doxorubicin, and cisplatin; RC, radical cystectomy; OS, overall survival; HR, hazard ratio, relative to the reference of 1.0; 95% CI, 95% confidence interval; CIS, carcinoma in situ; LN, lymph node; -, negative; +, positive; NR, not reported.

\* $P < .005$ .

†Lymph node status was missing for 5 patients.

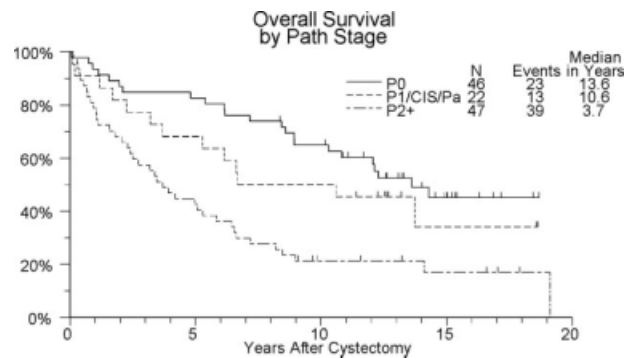
## RESULTS

### Quality of Pathologic Response With Neoadjuvant MVAC Appears to Be a Function of Baseline Stage

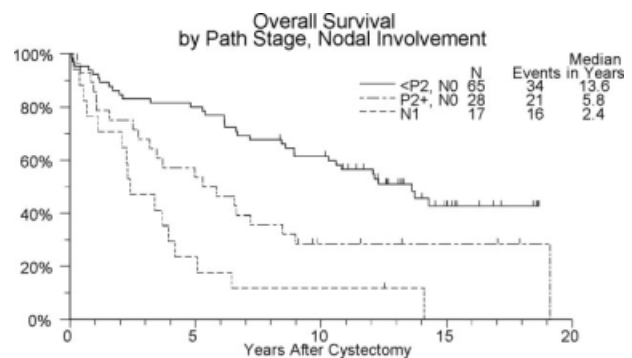
Of all 154 patients who received neoadjuvant MVAC, 68 (44%) had <P2 disease (P0, Pa, P1, or CIS) at RC, and 46 (30%) had P0 disease. The remainder of patients exhibited residual  $\geq$ P2 disease or did not undergo RC for a variety of reasons. Among the 62 (40%) with clinical T2 disease at baseline, 34 (55%) and 24 (39%) were classified as having <P2 and P0 disease, respectively. Among the 92 (60%) patients with T3 through T4 disease, 32 (35%) were classified with <P2, and 22 (24%) with P0 disease.

### Pathologic Stage at Cystectomy Confers Prognostic Impact

In the 115 of these 154 patients who underwent RC with negative surgical margins, several pathologic features were found to be associated with OS (Table 1). Pathologic response defined as either P0 or <P2 was predictive of enhanced OS. The hazard ratio (HR) of OS for >P0 ver-



**FIGURE 1.** Postcystectomy survival by pathologic (Path) stage after therapy with the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) is shown. CIS indicates carcinoma in situ.

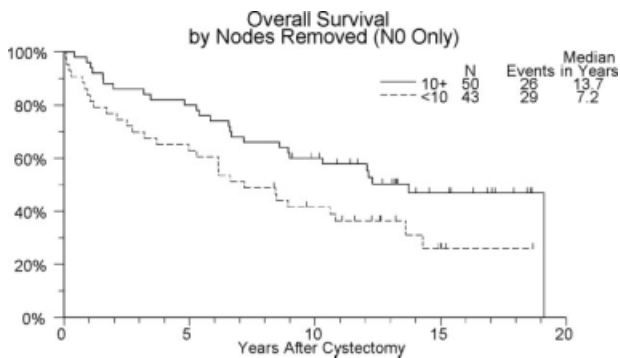


**FIGURE 2.** Survival based on pathologic (Path) lymph node disease at the time of cystectomy is shown.

sus P0 disease was 2.51 (95% confidence interval [95% CI], 1.47-4.27;  $P = .0008$ ), whereas the HR for P2+ versus <P2 disease was 2.24 (95% CI, 1.34-3.76;  $P = .0022$ ). Compared with P0 patients, those with residual Pa, P1, or CIS appeared to have worse OS (Fig. 1), but the difference did not quite achieve statistical significance (HR, 2.05; 95% CI, 0.99-4.24 [ $P = .054$ ]), whereas OS was found to be significantly worse for patients with residual P2+ disease (HR, 2.75; 95% CI, 1.54-4.89 [ $P = .0006$ ]). Pathologic LN-positive (LN+) disease was found to be associated with worse OS than LN- disease (HR, 2.90; 95% CI, 1.59-5.28 [ $P = .0005$ ]) (Fig. 2).

### Quality of LN Dissection Has Prognostic Value

Patients with LN- disease (ie, those with <10 LNs removed) appeared to have inferior OS compared with



**FIGURE 3.** Survival based on the number of lymph nodes removed for pathologic NO disease is shown.

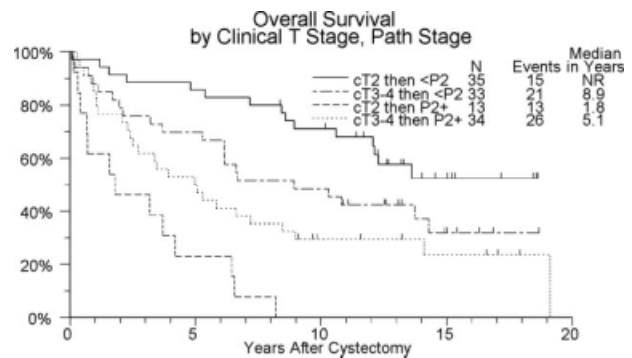
patients in whom 10+ LNs were removed, although this result was not statistically significant (HR, 1.66; 95% CI, 0.94-2.90 [ $P = .079$ ]) (Fig. 3). The median OS was 7.2 years for patients with <10 LNs removed versus 13.7 years for patients with  $\geq 10$  LNs removed.

### Combination of Baseline Clinical Stage and Post-MVAC Pathologic Stage as a Prognostic Factor

The combination of baseline clinical stage and post-RC pathologic stage (<P2 vs P2+) was found to be prognostic for OS (Fig. 4). Among patients with initial T2 disease, the presence of P2+ disease after RC was found to be associated with a >7-fold higher risk of death than <P2 disease (Table 1).

## DISCUSSION

Among patients treated with NC and RC with negative surgical margins for bladder cancer, pathologic P0 and LN- disease at RC was found to correlate with improved OS. Compared with patients with P0 disease, those with residual Pa, P1, or CIS appeared to have worse OS, and those with P2+ disease had a significantly worse OS. A combination of baseline clinical stage and post-RC pathologic stage may better predict OS. Because positive surgical margins and lack of RC were found to be correlated with dismal outcomes in a previous retrospective analysis of all patients enrolled in the S8710 trial, we conducted this analysis only in those patients who underwent a complete RC with negative surgical margins.<sup>5,6</sup> Although this retrospective analysis is limited because of the modest



**FIGURE 4.** Postcystectomy survival by baseline clinical stage and pathologic (Path) stage (<P2 vs P2+) after therapy with the combination of methotrexate, vinblastine, doxorubicin, and cisplatin is shown. NR indicates not reported.

number of patients studied, it suggests that residual pathologic stage after neoadjuvant MVAC is associated with postcystectomy survival in patients who undergo RC with negative surgical margins. Progression-free survival could not be analyzed because of the inadequate capture of this endpoint in the prospective trial. Furthermore, because of the very long follow-up time now available for these patients, a large number of non-cancer-related deaths may have been captured in this analysis. Therefore, the hazard ratio estimates presented herein may represent conservative estimates of the true association between survival and pathologic and clinical stage. In addition, the original pathology slides and specimens were not available for a more detailed analysis of residual tumor volume. Central pathology review was performed for the initial tumor biopsy, but not for the cystectomy specimen. Among patients with LN- disease, those with more extensive LN dissection were found to have superior outcomes, although this result was not statistically significant. Similar findings have been reported elsewhere in RC patients who did not receive NC.<sup>17</sup> The prognostic impact of the number of LNs removed in patients with LN+ disease was not analyzed, because there were few patients in this category ( $n = 17$ ), and the dismal OS of patients with LN+ disease was already known.

Patients with lower baseline clinical stage (T2) achieved subsequent major pathologic response (<P2) more often (73%) than those with T3 through T4 disease (49%). Baseline T2 disease followed by <P2 at RC was associated with the best post-RC survival, whereas those with T2 disease and subsequent residual muscle-invasive

disease (P2+) were found to have the worst outcomes, and may represent patients with chemoresistant disease, although this result is based on a small subset ( $n = 13$ ) and therefore must be interpreted with caution. Tumor biology is most likely the underlying factor driving the chemoresponsiveness in addition to initial clinical stage, but tumor genomics and proteomics could not be evaluated on the current study. Because a proportion of patients with T2 disease may attain <P2 residual stage with the initial cystoscopic biopsy or transurethral resection of the bladder tumor (TURBT), an independent impact of optimal TURBT on OS may also be occurring in patients receiving MVAC. Therefore, all the benefit may not be attributable to NC. However, the extent of TURBT required or performed was not defined or available in the current study, which also hampers the evaluation of its impact. Urologists should most likely still perform an optimal TURBT in patients with T2 disease who may receive NC. Studies support some breast cancers being generally sensitive to different classes of chemotherapy, whereas others may be intrinsically resistant to different classes of chemotherapy.<sup>18,19</sup> This finding in the setting of breast cancer may be applicable to the bladder cancer setting. The data from the current study are hypothesis generating, and with further validation they may assist in optimally risk-stratifying patients enrolled in future trials of adjuvant therapy with potentially non-cross-resistant biologic agents based on pathologic stage of residual disease after NC.

Although adjuvant chemotherapy has been evaluated for muscle-invasive bladder cancer, to our knowledge definitive data from large randomized trials have not been available.<sup>20-23</sup> In addition, a recent retrospective study demonstrated that approximately 30% of patients who underwent radical cystectomy developed complications within 90 days that could contraindicate adjuvant chemotherapy.<sup>24</sup> Response to neoadjuvant MVAC may also be predicted by genomic and proteomic analysis of tumor tissue obtained at baseline biopsy. Fourteen genes were found to be predictive of pCR in a retrospective study of patients with bladder cancer who received neoadjuvant MVAC.<sup>25,26</sup> Among those genes, topoisomerase IIa (target of doxorubicin) was down-regulated in the nonresponder group. A correlation was found between low/intermediate *BRCA1* mRNA levels (which mediates DNA repair) and pCR as well as long-term outcomes

with neoadjuvant cisplatin-combination chemotherapy for bladder cancer in a retrospective study of 49 patients.<sup>27</sup> In the setting of neoadjuvant therapy of breast cancer, early modulation of pharmacodynamic biomarkers (eg, Ki-67) after brief neoadjuvant therapy appears to correlate with long-term clinical outcomes, and this paradigm needs to be evaluated in bladder cancer.<sup>28,29</sup> Thus, the neoadjuvant paradigm holds considerable promise in the development of tailored therapy for patients with locally advanced bladder cancer. In addition, this paradigm has the potential to enable the efficient use of resources and accelerate the pace of systemic therapy development because of the availability of pathologic response as an intermediate endpoint.

### Conflict of Interest Disclosures

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