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DO VASCULAR, LYMPHATIC, AND PERINEURAL INVASION HAVE PROGNOSTIC IMPLICATIONS FOR BLADDER CANCER AFTER RADICAL CYSTECTOMY?

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ABSTRACT

Objectives. To elucidate the respective prognostic implications of vascular, lymphatic, and perineural invasion noted on the pathologic analyses of radical cystectomy specimens. Controversy still exists on whether the pathologic features of vascular, lymphatic, and perineural invasion have any role as prognostic indicators for bladder cancer.

Methods. A retrospective review of 125 patients with bladder cancer treated with radical cystectomy was conducted. Patients who received either preoperative or postoperative chemotherapy, those with lymph node metastasis confirmed on postoperative pathologic analysis, those who did not undergo standard bilateral pelvic lymph node dissection, and those receiving palliative treatment were excluded from the study.

Results. The mean patient age was 62.5 years (range 39 to 84), and the median follow-up duration was 41.0 months (range 1 to 146). Vascular, lymphatic, and perineural invasion was present in 8.8%, 20.8%, and 8.8% of specimens, respectively, and 28% of patients had at least one of the three pathologic features in the specimen. Univariate analysis revealed that vascular invasion, lymphatic invasion, and perineural invasion were significant prognostic predictors of overall survival. However, only the tumor stage and vascular invasion proved to be independent prognostic predictors of disease-specific survival on multivariate analysis.

Conclusions. The results of the present study have shown that the pathologic tumor stage and the pathologic presence of vascular invasion are independent prognostic predictors for disease-specific survival in patients who have undergone radical cystectomy for bladder cancer. Additional study should be performed on the prognostic implications of lymphatic and perineural invasion. UROLOGY **65:** 697–702, 2005. © 2005 Elsevier Inc.

Today, radical cystectomy is still the standard treatment for patients with muscle-invasive bladder cancer. However, invasive bladder cancer has a predilection for early and occult metastasis. Despite effective local treatment by radical cystectomy, about one half of the patients with locally invasive bladder cancer ultimately die of the disease.

In an effort to improve the fate of patients with muscle-invasive and locally advanced bladder cancer, many institutions are providing additional therapy, such as adjuvant systemic chemotherapy, to these patients after radical cystectomy. Even though published series have been unable to establish a definite benefit from adjuvant chemotherapy, the results from administration of postoperative adjuvant chemotherapy may be improved soon with the development of various new chemotherapeutic agents.[1] Furthermore, reports have indicated that adequate patient selection may augment the efficacy of adjuvant chemotherapy.[2] Therefore, identifying patients who may actually benefit from immediate or delayed postoperative treatment would be essential, as well as developing effective adjuvant treatment modalities.

Patients with invasive bladder cancer are at significant risk of tumor progression after radical cystectomy. Also, bladder cancer cases of similar stage

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and grade have often demonstrated variable clinical outcomes after radical cystectomy. Thus, many have tried to determine reliable prognostic indicators that can be used in planning the optimal treatment and follow-up after radical cystectomy. To date, tumor stage, tumor grade, the presence of lymph node metastasis, and ureteral obstruction have been reported to be associated with the prognosis of bladder cancer. However, controversy still exists on whether the pathologic features of vascular, lymphatic, and perineural invasion have any role as prognostic indicators for bladder cancer.[3–6] Thus, we tried to elucidate the respective prognostic implications of vascular, lymphatic, and perineural invasion noted on the pathologic analysis of radical cystectomy specimens. We compared the survival rates of patients with and without positive findings regarding these three aforementioned pathologic features.

MATERIAL AND METHODS

From January 1991 to March 2002, a total of 181 patients underwent radical cystectomy for transitional cell carcinoma of the bladder at our institution. Excluding patients who also received either preoperative or postoperative chemotherapy, those with lymph node metastasis confirmed on postoperative pathologic analysis, those who did not undergo standard bilateral pelvic lymph node dissection, and those who received palliative treatment, we performed a retrospective study of 125 patients by reviewing their records. In reviewing the patients' records, we assessed the pathologic findings from the radical cystectomy specimens, which were reviewed by a single pathologist, along with the results of the postoperative follow-up evaluations, including the clinical and radiologic findings. If necessary, patient survival was confirmed by telephone or mail.

Bladder cancer was staged according to the TNM classification devised by the International Union Against Cancer in 1997 and graded according to the 1999 classification from the World Health Organization.[7,8] Pathologic vascular invasion was defined as tumor present in vessels with a vascular wall and red blood cells in the lumen. Only when tumor had invaded vessels with a definite endothelial lining was it considered lymphatic invasion. Additional serial sections were made in difficult cases. If doubt persisted even with additional sections, the specimen was not categorized as demonstrating the feature of vascular invasion. Perineural invasion was defined as tumor invading the perineural sheath or endoneurium.

The mean age of the subjects (100 men and 25 women) was 62.5 years (range 39 to 84). The mean follow-up duration (from the time of cystectomy to death or last known follow-up visit) was 41.0 months (range 1 to 146; Table I). The patients were initially seen 2 months after surgery, then every 4 months for 1 year, and every 6 months until disease progression or death.

The chi-square test was used to determine correlations among the variables. The Kaplan-Meier probability of survival analysis was used to determine the prognostic effects of vascular, lymphatic, and perineural invasion, and differences among the pathologic features were assessed by log-rank tests. Statistical significance was conferred by $P \leq 0.05$. Multivariate analysis was performed according to the Cox proportional hazards regression model with the Statistical Package for Social Sciences to identify significant prognostic factors. All dependent variables were entered as categorical ones. Only the variables found to be significant on univariate analyses ($P \leq 0.05$) were entered into the multivariate analysis. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS, Chicago, Ill) programs.

TABLE I. *Patient characteristics*

Demographics	
Patients (n)	125
Men	100 (80.0)
Women	25 (20.0)
Age (yr)	
Median	62.5
Range	39–84
Follow-up (mo)	
Median	41.0
Range	1–146
T stage (n)	
T0–T1	37 (29.6)
T2	58 (46.4)
T3	22 (17.6)
T4	8 (6.4)
Grade (n)	
1	1 (0.8)
2	31 (24.8)
3	92 (73.6)

Data in parentheses are percentages.

RESULTS

Of the 125 subjects included in our study, 4 (3.2%) had only vascular invasion, 16 (12.8%) had only lymphatic invasion, and 1 (0.8%) had only perineural invasion and 2 (1.6%) had both vascular and lymphatic invasion, 2 (1.6%) had both vascular and perineural invasion, and 5 (4.0%) had both lymphatic and perineural invasion. Three patients (2.4%) had all three pathologic characteristics.

When comparing the respective proportions of the 125 total subjects with vascular, lymphatic, and perineural invasion by stratifying them according to tumor stage and grade, significant associations between the tumor stage and each of the three pathologic factors were observed ($P < 0.05$, chi-square test). However, tumor grade proved to have no definite association with these pathologic features ($P > 0.05$).

Of the 125 subjects, significant differences in overall survival ($P = 0.0007$, log-rank test; Fig. 1A) and progression-free survival ($P = 0.0345$, log-rank test; Fig. 1B) were observed between those with no invasion and those with at least one type of invasion. Also, when analyzed similarly, but in three separate subject groups with each invasion type, the group with vascular invasion demonstrated significant differences in both overall survival ($P = 0.0001$, log-rank test; Fig. 2A) and progression-free survival ($P = 0.0002$; Fig. 2B)