Predicting Cancer Progression in Patients With Stage T1 Bladder Carcinoma

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Purpose: **A significant number of patients with stage T1 bladder carcinoma are at risk for cancer progression. We sought to identify factors associated with cancer progression in a series of patients with stage T1 bladder carcinoma treated with a contemporary therapeutic approach.**

Patients and Methods: **The study population consisted of 83 consecutive patients in whom stage T1 bladder carcinoma was diagnosed at the Mayo Clinic between 1987 and 1992. All patients underwent transurethral resection of the bladder (TURB) and had histologic confirmation of the diagnosis. The mean age was 71 years (range, 47 to 94 years). The male-to-female ratio was 3.9:1. The mean length of follow-up was 5.2 years (range, 1 day to 10.4 years). The depth of lamina propria invasion in the TURB specimens was measured with an ocular micrometer. Cancer progression was defined as the development of muscle-invasive or more advanced stage carcinoma, distant metastasis, or death from bladder cancer.**

Results: **The overall 5- and 7-year progression-free survival rates were 82% and 80%, respectively. The depth of invasion in the TURB specimens was associated with cancer progression (hazards ratio, 1.6 for doubling of depth of invasion; 95% confidence interval, 1.03 to 2.4; *P* = .037). The 5-year progression-free survival rate for patients with depth of invasion of ≥ 1.5 mm was 67%, compared with 93% for those with depth of invasion of less than 1.5 mm (*P* = .009). No other variable, including age, sex, tobacco use, alcohol use, the presence of carcinoma-in-situ, histologic grade, lymphocytic infiltration, or muscularis mucosae invasion, was associated with cancer progression.**

Conclusion: **The depth of invasion in the TURB specimens, measured with a micrometer, is predictive of cancer progression in patients with stage T1 bladder carcinoma.**

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THE BIOLOGIC BEHAVIOR of stage T1 bladder carcinoma is variable.[1-28] There is a need for an accurate, easy-to-use, reproducible prognostic system to identify patients at risk for cancer progression. In our previous study,[2] we found that the depth of invasion in specimens obtained by transurethral resection of the bladder (TURB) was strongly associated with final pathologic stage at cystectomy, and we established the optimal cut point (1.5 mm) of depth of invasion for predicting advanced-stage (stage T2 or higher) bladder carcinoma. However, our previous study[2] was limited because of the small number of patients treated with cystectomy before the bacille Calmette-Guérin (BCG) era. The prognostic significance of our proposed classification system, which is based on the depth of invasion measured with a micrometer, should be validated in a large series of patients treated by contemporary methods, with long-term follow-up. In this study, we sought to determine whether measurement of depth of invasion with a micrometer is useful in predicting clinical outcome in patients with stage T1 bladder carcinoma.

PATIENTS AND METHODS

The study population consisted of 83 consecutive patients who underwent TURB for urothelial carcinoma at the Mayo Clinic between December 1987 and November 1992. The 1997 tumor-node-metastasis staging system was used for pathologic staging. Stage T1 cancer is defined as cancer invading the subepithelial connective tissue, without invasion into the muscularis propria.[29] Pathologic stage was assigned after we reviewed the slides. All patients had stage T1 urothelial carcinoma, and none had lymph node or distant metastasis at the time of TURB. Clinical presentations were gross hematuria (54 patients), microhematuria (65), irritative symptoms (13), constitutional symptoms (one), abdominal pain (two), abdominal mass (one), and as an incidental finding (eight). Patients were treated primarily with TURB. One patient underwent complete cystectomy immediately after diagnosis. Within 3 months after diagnosis, eight patients received BCG, 12 received intravesical thiothepa, two received both intravesical chemotherapy (thiothepa and/or mitomycin) and BCG, one received chemotherapy and intravesical thiothepa, and one received intravesical thiotepa, BCG, and radiation therapy. Progression was defined as the development of muscle-invasive or more advanced stage carcinoma, distant metastasis, or death from bladder cancer.

All histologic slides were reviewed at a two-person microscope by two pathologists (L.C. and D.G.B.) who were unaware of patient outcome. The depth of invasion in the TURB specimens was measured with a micrometer, as previously described.[2] Briefly, the depth of invasion was measured from the basement membrane of the bladder mucosa to the deepest invasive cancer cells. When TURB tissue fragments contained cancer without intervening stroma or the speci-

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mens were not oriented, the depth of invasion was measured from the shortest distance, to avoid overestimation of the depth of invasion (Fig 1). The depth of invasion was also measured according to the level of the muscularis mucosae and was classified as invasion above the muscularis mucosae, invasion into or deeper than the muscularis mucosae, or not assessable because of an absence of muscularis mucosae.[2,14,17,30-34] Histologic grading was performed using the newly proposed World Health Organization and International Society of Urologic Pathology grading system[35] and based on the worst grade of invasive urothelial carcinoma. The presence or absence of lymphocytic infiltration adjacent to the cancer was recorded.

The time from bladder cancer diagnosis to progression or the date of last follow-up was calculated, and progression-free survival estimates were obtained using the Kaplan-Meier method. The association between clinical and pathologic characteristics and time to progression was evaluated using Cox proportional hazards models. Because depth of invasion measured with a micrometer was positively skewed, the log base-2 transformation was used and the reported hazards ratio is for doubling of depth of invasion. The depth of invasion was analyzed as a continuous variable. In addition, depths of invasion were dichotomized for illustrative purposes. All P values were two-sided, and $P < .05$ was considered statistically significant.

RESULTS

Table 1 summarizes the patient characteristics and pathologic findings. The mean age was 71 years (range, 47 to 94 years; median, 72 years). The male-to-female ratio was 3.9:1. The mean length of follow-up was 5.2 years (range, 1 day to 10.4 years; median, 5.4 years). Thirty-nine patients had cancer recurrence. Sixteen patients developed progression (Fig 2), including stage T2 (10 patients), T3 (two), and T4 (one) cancer. Of these 16 patients, one had lymph node metastasis and two died from bladder cancer, with progression discovered at the time of death. Six of the 39 patients with cancer recurrence died from bladder cancer and 33 died from other causes. The mean interval from diagnosis to progression was 2.3 years (range, 2 days to 7.3 years). Twenty-five patients underwent complete cystectomy, and pathologic stages were T0 (four patients), Tis (carcinoma-in-situ) (five), T1 (eight), T2a (one), T2b (three), T3 (two), and T4 (two). Vascular invasion was identified in eight patients; two of these patients had cancer progression, including one who died from bladder cancer. Because of the limited number of patients with vascular invasion, no further analysis was performed.

Five- and 7-year progression-free survival rates were 82% and 80%, respectively. The depth of invasion in the TURB specimens, measured with a micrometer, was predictive of cancer progression. The relative risk of progression for doubling of depth of invasion was 1.6 (95% confidence interval, 1.03 to 2.4; $P = .037$) when the depth of invasion was analyzed as a continuous variable. The mean depth of invasion for the entire study group was 1.5 mm (range, 0.5 to 5.0 mm; median, 1.0 mm). Among the 16 patients whose disease progressed, the mean depth of invasion was 1.9 mm (range, 0.5 to 4.0 mm; median, 1.5 mm). The 5-year progression-free survival rate for patients with median depth of invasion of ≥ 1.0 mm was 76%, compared with 95% for those with depth of invasion of less than 1.0 mm ($P = .01$, Fig 2A). The 5-year progression-free survival rate for patients with depth of invasion of ≥ 1.5 mm was 67%, compared with 93% for those with depth of invasion of less than 1.5 mm ($P = .009$, Fig 2B).

When depth of invasion was entered into a multiple Cox regression model in which a stepwise variable selection method was used, none of the other variables, including age, sex, tobacco use, alcohol use, the presence of carcinoma-in-situ, histologic grade, lymphocytic infiltration, or muscularis mucosae invasion, were identified as being significantly associated with cancer progression. Muscularis mucosae was not present in 39 patients (47%); therefore, the level of muscularis mucosae invasion could not be determined in these patients.

DISCUSSION

Histologic examination of specimens obtained by TURB is an integral part of clinical staging. In this study, we found that the depth of invasion, measured with a micrometer, was significantly associated with cancer progression in patients with stage T1 bladder carcinoma. The 5-year progression-free survival rate for patients with depth of invasion of less than 1.5 mm was 93%, compared with 67% for those with depth of invasion of ≥ 1.5 mm. In contrast, stratification of patients according to the level of muscularis mucosae invasion was indeterminate. Further, approximately half of the patients (47%) did not have assessable muscularis mucosae for substaging, a percentage similar to that in our previous study (45%).[2] These findings indicate that the newly proposed classification of stage T1 bladder carcinoma is useful in stratifying patients into different prognostic groups. Given these data and our previous observation,[2] we recommend stratifying patients on the basis of micrometer measurement of depth of invasion.

The current study has several limitations. We describe here a new classification system for bladder carcinoma that is based on micrometer measurement of depth of invasion in TURB specimens, and we recognize the difficulty involved in making an unequivocal diagnosis of invasive carcinoma in poorly oriented specimens. The treatments were not randomized, and the number of outcome events in this study were also limited; therefore, one should be cautious in interpreting our data. Some variables that were inconclusive may become significant if the sample size and the number of outcome events are increased. The lack of prognostic significance of histologic grade in this study may be attributed to the small sample size, limited number of

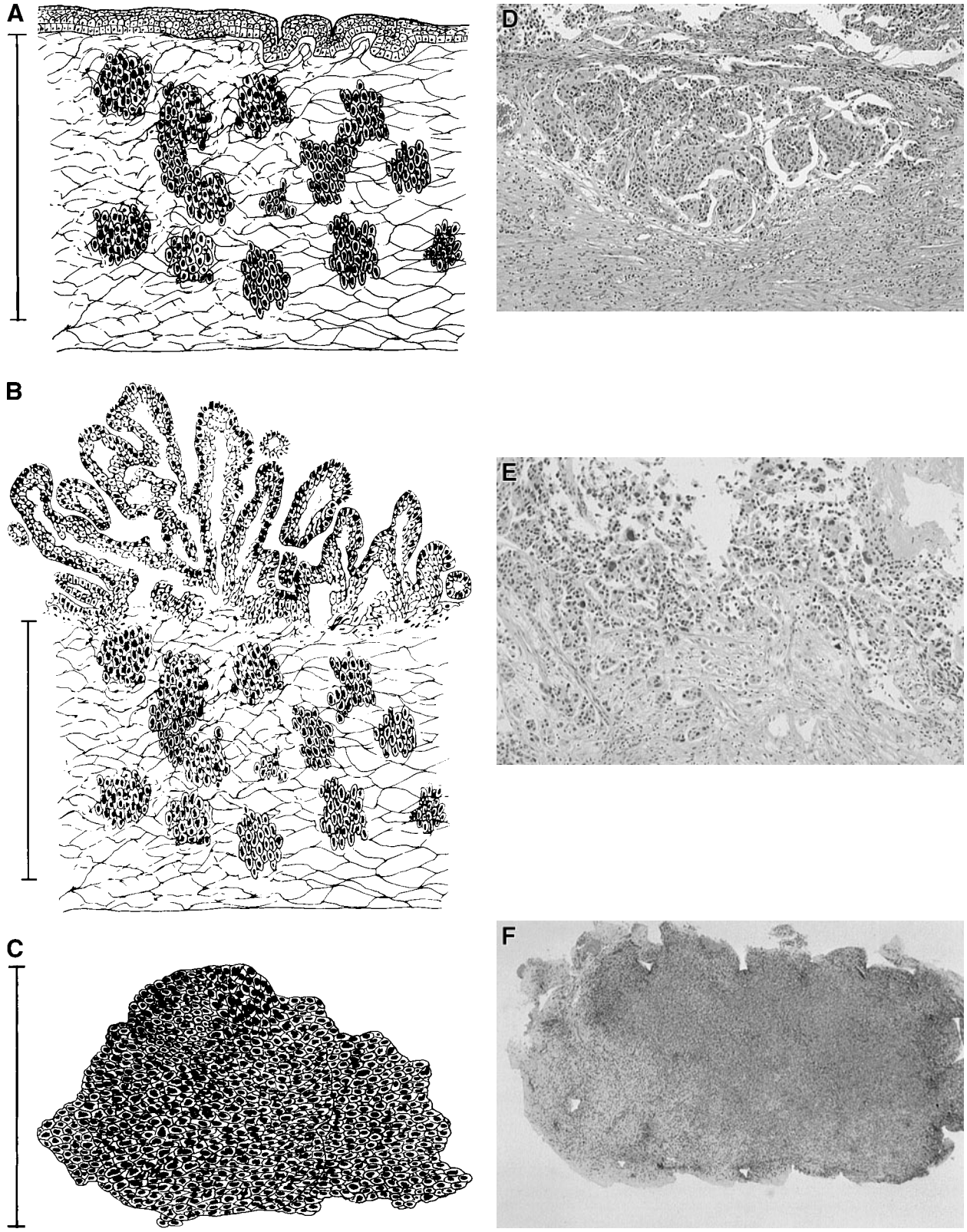

Fig 1. (A through C) Schematic illustrations for micrometer measurement of depth of invasion in TURB specimens; (D through F) histologic appearance of stage T1 urothelial carcinoma.

Table 1. Association Between Clinical and Pathologic Variables and Progression in Stage T1 Bladder Carcinoma

Variable	No. of Patients	%	5-Year Progression-Free Survival Rate (%)*	P†
Age				.57
< 72 years	39	47	86 ± 6	
≥ 72 years	44	53	77 ± 7	
Sex				.52
Male	66	80	85 ± 5	
Female	17	20	75 ± 11	
Tobacco use‡				.22
Never	24	30	70 ± 11	
Past	38	47	86 ± 6	
Current	19	23	87 ± 9	
Alcohol use‡				.52
Never	27	34	79 ± 9	
Past	7	9	83 ± 15	
Current	46	57	83 ± 6	
Carcinoma-in-situ				.65
Absent	65	78	83 ± 5	
Present	18	22	77 ± 10	
Histologic grade				.31
Low	28	34	88 ± 7	
High	55	66	79 ± 6	
Lymphocytic infiltration				.29
Absent	54	65	84 ± 6	
Present	29	35	78 ± 8	
Depth of invasion§				.38
Above muscularis mucosae	23	52	89 ± 7	
Into or below muscularis mucosae	21	48	68 ± 11	
Depth of invasion				.014
< 1.0 mm	27	33	95 ± 5	
≥ 1.0 mm	56	67	76 ± 6	
Depth of invasion				.009
< 1.5 mm	47	57	93 ± 4	
≥ 1.5 mm	36	43	67 ± 9	

*Rate ± SE.

†Based on the univariate Cox models. Age was analyzed as a continuous factor, and both tobacco and alcohol use were analyzed using two dummy variables to code for the three response categories.

‡Data on tobacco use and alcohol use were not available for two and three patients, respectively.

§Muscularis mucosae invasion could not be evaluated in 39 patients.

outcome events, and short-term follow-up, although patients with high-grade cancer tended to have a worse prognosis. Further, the impact of depth of invasion on cancer-specific survival should be tested in prospective studies. In addition, the choice of 1.5 mm as an optimal cut point for stratification of patients into different prognostic groups needs to be validated independently in a larger cohort with long-term follow-up. Despite these limitations, we found that measurement of depth of invasion provides significant prognostic information that may be useful in patient management and evaluation of treatment results.

The significance of depth of invasion in predicting patient outcome was evaluated in several studies.[2,14,17,30-34,36] The concept of microinvasive urothelial carcinoma, based on measurement of depth of invasion, was first introduced by Farrow and Utz.[36] Using 5.0 mm as the cutoff, they found that the cancer death rate was higher among patients with microinvasion than among those with in-situ tumors. Several groups recently proposed substaging T1 bladder cancer on the basis of muscularis mucosae invasion.[14,17,30,32-34] However, muscularis mucosae can be identified in only 15% to 83% of biopsy specimens,[30-33,37-40] and 6% of patients do not have muscularis mucosae.[37] Further, adipose tissue was frequently identified in the lamina propria of the urinary bladder.[41] In the current study, patients with cancer invasion below muscularis mucosae tended to have a worse prognosis (5-year progression-free survival rate, 68%) compared with

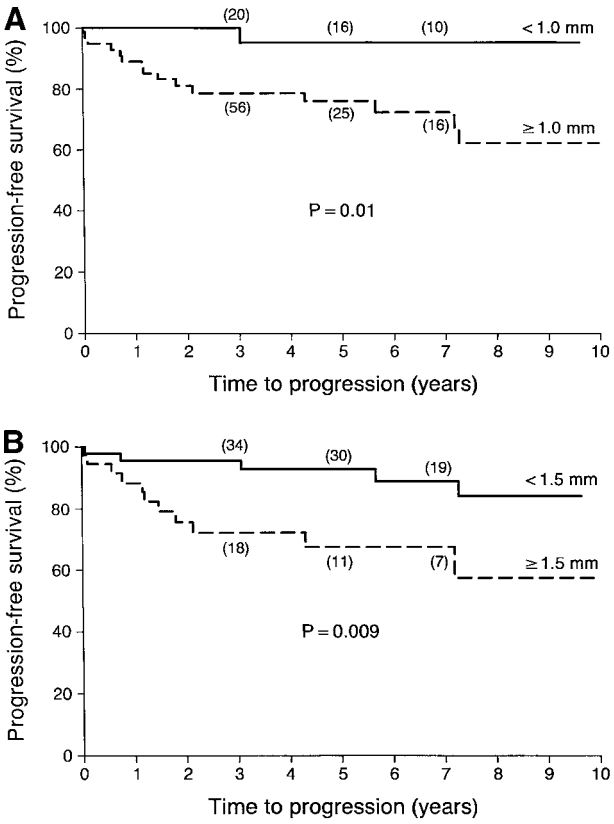

Fig 2. Progression-free survival rates according to the level of depth of invasion in the TURB specimens, using the median value (1.0 mm) (A) or the cut point of 1.5 mm (B). Numbers in parentheses represent numbers of patients under observation at 3, 5, and 7 years.

those patients with invasion above muscularis mucosae (89% 5-year progression-free survival) ($P = .38$). In their study involving 70 patients with stage T1 bladder cancer, Platz et al[31] found no difference in 10-year survival rates between patients with invasion above muscularis mucosae (65%) and patients with invasion below muscularis mucosae (60%). The 1998 Bladder Consensus Conference Committee stated that ''substage based on the relationship of tumor to muscularis mucosae should not be universally adopted or advocated to pathologist.''[35]

In our recent study of 64 radical cystectomy specimens removed because of bladder carcinoma,[42] we found that the mean thickness of the lamina propria in the bladder was 1.4 mm, which suggests that patients with depth of invasion of $\geq$ 1.5 mm may harbor more advanced bladder carcinoma that was simply not sampled. It can be difficult to demonstrate muscle wall invasion in a TURB specimen when the cancer is deeply invasive and extensively destroying adjacent normal tissues. The current tumor-node-metastasis staging system is based on examination of cystectomy specimens. Micrometer measurement of depth of invasion in TURB specimens may enable more accurate description of tumor extent at the time of diagnosis, and we have now incorporated this approach into routine practice.

In conclusion, we propose a new classification system for stage T1 bladder carcinoma that is useful for identifying patients at risk of cancer progression. Depth of invasion in TURB specimens, measured with a micrometer, should be reported.

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