Grading and Staging of Bladder Carcinoma in Transurethral Resection Specimens

Correlation With 105 Matched Cystectomy Specimens

Liang Cheng, MD,1 Roxann M. Neumann, RN,2 Amy L. Weaver, MS,3 John C. Cheville, MD,2 Bradley C. Leibovich, MD,4 Dharamdas M. Ramnani, MD,2 Beth G. Scherer, MS,3 Ajay Nehra, MD,4 Horst Zincke, MD, PhD,4 and David G. Bostwick, MD3,4*

Key Words: Bladder; Carcinoma; Staging; Muscle invasion; Cystectomy; Grading; Transurethral resection

Abstract

We compared the grading and staging of transurethral resection of the bladder (TURB) and cystectomy specimens for 105 patients who underwent radical cystectomy for urothelial carcinoma between 1980 and 1984. Of 105 patients, 96% underwent cystectomy within 100 days of TURB (median interval, 10 days). Grading was performed according to the 1998 World Health Organization/International Society of Urologic Pathology grading system and staging according to the 1997 TNM classification. Histologic grade was low-grade, 13; high-grade, 92 in TURB specimens; low-grade, 17; high-grade, 88 in cystectomy specimens. Pathologic stage was Ta, 15; T1, 55; and T2, 35 in TURB specimens; Ta, 5; T1, 19; T2, 19; T3, 46; and T4, 16 in cystectomy specimens. Histologic grade at TURB was associated with pathologic stage at cystectomy (P < .001). When all advanced-stage (muscle-invasive) carcinomas (pT2 or more) were considered together, 55 patients were understaged by TURB, 4 had higher stage in TURB than in cystectomy, and 46 were the same stage as by cystectomy. Forty-three of 55 patients with stage T1 carcinoma at TURB had advanced-stage carcinoma at cystectomy, including 34 who had extravesicular extension (pT3 or more). We found pathologic understaging by TURB occurs in a significant number of patients with bladder cancer; the newly proposed grading system predicted final pathologic stage.

Carcinoma of the urinary bladder is a significant cause of morbidity and mortality in North American men, accounting for an estimated 54,200 new cases and 12,100 deaths in 1999.1 A reliable grading and staging system is needed to stratify patients into prognostically distinct groups and allow for comparison of treatment results among institutions. Accurate examination of specimens obtained by transurethral resection of the bladder (TURB) is critical for predicting patient outcome and selecting appropriate therapy. Comparison of TURB stage with final pathologic stage at cystectomy in previous studies was limited by small numbers of cases, reliance on review of pathologic reports for grading and staging, heterogeneity of natural history of bladder carcinoma with long intervals between biopsy and cystectomy, and variation in the grading and staging systems used among different institutions.2-16 The influence of the proposed World Health Organization and International Society of Urologic Pathology (WHO/ISUP) grading system17,18 on predicting the final pathologic stage is largely unknown. To our knowledge, there are no previous reports of the current grading system for predicting pathologic stage and correlation of grading between biopsy and cystectomy specimens. In the present study, we sought to determine the accuracy of staging by TURB and the usefulness of the current grading system by comparing the results of TURB with the final pathologic stage among 105 patients who underwent cystectomy for bladder carcinoma in the pre–bacille Calmette-Guérin (BCG) era.

Materials and Methods

The study population consisted of 105 patients treated by cystectomy at the Mayo Clinic, Rochester, MN, between
January 1980 and December 1984, the era preceding introduction of BCG therapy. This study period was chosen to allow for direct comparison of findings at transurethral resection with findings at cystectomy, since more recent cystectomy series tended to have long intervals between cystectomy and initial diagnosis. More aggressive treatment (radical cystectomy) was offered to patients in the pre-BCG era. All patients underwent TURB at a single institution before cystectomy. Cases in which histologic slides from TURB specimens were not available for review were excluded. We reviewed all histologic slides of TURB and cystectomy specimens retrospectively without knowledge of clinical outcome. Grading was performed by 2 pathologists (L.C. and D.G.B.) under the multihead microscope according to the 1998 WHO/ISUP classification (Boston, MA, 1998).17,18 The 1997 TNM (tumor, lymph nodes, and metastasis) system was used for pathologic staging.19 The cystectomy specimens were examined by frozen section at surgery and subsequently by permanent sections. The number of cancer sections submitted for frozen section examination from the cystectomy specimens varied from 6 to 42, depending on cancer volume and the preference of the pathologist. An average of 12 slides were examined per case, and the method of sampling remained constant during the study period.

The association between histologic grade and pathologic stage was assessed with the Wilcoxon rank sum test. The agreement between TURB and cystectomy specimens for grade and stage was assessed based on calculating kappa statistics. For the ordinal stage variables (Ta, T1, T2 or more), a weighted kappa statistic was calculated that ascribed more weight to smaller degrees of disagreement. The kappa statistic is a chance-corrected measure of agreement that represents the proportion of agreement beyond that expected due to chance alone and is scaled to vary from –1.0 to 1.0; a value less than 0.4 signifies poor or marginal agreement, and values between 0.4 and 0.75 denote fair to good agreement. A significant P value indicates that the kappa value is significantly greater than zero. All calculated P values were 2-sided, and a P value of less than .05 was considered statistically significant.

Results

The median age of the patients was 65 years (range, 44-78 years) at TURB. The male/female ratio was 6:1. The median interval from TURB to cystectomy was 10 days (range, 2-293 days). Ninety-six percent of patients underwent cystectomy within 100 days after TURB. In TURB specimens, pathologic stages were as follows: Ta, 15 patients; T1, 55 patients; and T2, 35 patients; and in cystectomy specimens, Ta, 5 patients; T1, 19 patients; T2, 19 patients; T3, 46 patients; and T4, 16 patients. Nineteen patients (18.1%) had lymph node metastasis at cystectomy. The histologic grade was low-grade (13 patients) and high-grade (92 patients) in TURB specimens; and low-grade (17 patients) and high-grade (88 patients) in cystectomy specimens. Histologic grade at TURB was associated with pathologic stage at cystectomy (P < .001). Cancer invading into the muscle wall (pT2) could not be distinguished from that invading beyond the muscle wall (pT3 or more) by examination of TURB specimens. When considering all advanced-stage (muscle-invasive) carcinomas (pT2 or more) at cystectomy as a single group, 55 patients (52.3%) were understaged by TURB, 4 (3.8%) had lower stage carcinoma in cystectomy specimens, and 46 (43.8%) were staged the same (into the muscle wall) by cystectomy. Forty-three (78%) of 55 patients with stage T1 carcinoma at TURB had advanced stage carcinoma (pT2 or more), including 34 whose cancers were not organ-confined (pT3 or more) at cystectomy (Table 1). Muscularis propria was present in 19 patients (34%) with stage T1 carcinoma by TURB. There was marginal agreement between TURB and cystectomy for pathologic stage (44% agreement; kappa = 0.31; P < .001) and histologic grade (85% agreement; kappa = 0.38; P = .002) (Tables 1 and 2).

Discussion

We found understaging by TURB in 52.3% of patients. In a significant number (78%) of patients with stage T1 carcinoma at TURB, cancer invaded into or beyond the muscle wall at cystectomy. These findings indicate a need for an improved staging system for TURB specimens, especially for cancer invading the lamina propria without evidence of muscle invasion (T1). Histologic grade at TURB, based on the 1998 WHO/ISUP classification system, was associated with final pathologic stage and correlated with grade in cystectomy specimens. Thus, histologic grade, based on the newly proposed classification system,18 is an important prognostic determinant for patients with bladder carcinoma and should be reported.

There is a need for standardized terminology and classification that will allow for valid comparison of treatment results among institutions.2 Recent collaborative efforts by the WHO/ISUP led to a consensus classification of bladder neoplasms.17,18 It is largely unknown whether the new system can be applied consistently and uniformly, resulting in improved patient management. We found that the WHO/ISUP grading system was a significant prognostic determinant in TURB specimens for predicting final pathologic stage in cystectomy specimens. Cheng et al20 studied...
164 patients with noninvasive (Ta) papillary urothelial carcinoma and found that histologic grading based on the newly proposed WHO/ISUP grading system stratifies patients into prognostically different groups. Seven-year cancer (stage) progression-free survival for patients with Ta papillary urothelial neoplasm of low malignant potential, low-grade, and high-grade carcinoma was 93%, 82%, and 61%, respectively. The discordance in tumor grade between TURB and cystectomy specimens in the present study may be attributed to sampling variation, such as removal of most of the tumor by TURB and cancer heterogeneity.

Clinical understaging with TURB is a recognized problem in bladder cancer. Several studies have compared the clinical stage and final pathologic stage at cystectomy and found a substantial staging error (approximately 50%), similar to our results. In a review of 220 patients who underwent cystectomy for bladder carcinoma between 1969 and 1990, Amling et al found an overall staging error in 56% of the patients, including clinical understaging in 31%. In a study of 261 patients who were treated by cystectomy, Pagano et al found an overall staging error of 56%. The overall accuracy of staging by TURB was 46% in the report by Yaman et al of 65 patients who were treated by cystectomy. The rates of accurate staging by transrectal ultrasonography and computed tomography were 40% and 35%, respectively. Voges et al reviewed 164 patients who underwent preoperative staging for bladder cancer by computed tomography and found that only 32% of patients were staged correctly. In a retrospective study of 182 patients with clinical stage TIS, Ta, or T1 cancer, Freeman et al found understaging in 34% of patients. These understaged patients accounted for about one half (47%) of all bladder cancer deaths. Forty percent of patients with lamina propria invasion (T1) in the TURB specimens were upstaged to at least muscle invasion (T2 or more) in the final pathologic stage determined by radical cystectomy specimens. The different rates of staging error among studies likely is attributed to patient selection factors, treatment, and tissue sampling techniques. The strengths of the present study, compared with previous studies, include a large cohort with short interval between TURB and cystectomy (with less influence of natural history of bladder carcinoma), review of histologic

### Table 1
Correlation of Pathologic Stage Between Transurethral Resection of the Bladder (TURB) and Cystectomy Specimens

<table>
<thead>
<tr>
<th>Cystectomy</th>
<th>TURB</th>
<th>Ta</th>
<th>T1</th>
<th>T2</th>
<th>T3a</th>
<th>T3b</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ta</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>315</td>
</tr>
<tr>
<td>T1</td>
<td>2</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1055</td>
</tr>
<tr>
<td>T2</td>
<td>0</td>
<td>2</td>
<td></td>
<td>9</td>
<td>13</td>
<td></td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>19</td>
<td></td>
<td>19</td>
<td>20</td>
<td>26</td>
<td></td>
<td>16105</td>
</tr>
</tbody>
</table>

* After combining cystectomy stage T3 and T4 with T2, there was marginal agreement between TURB and cystectomy specimens (kappa = 0.31; P < .001).

### Table 2
Correlation of Histologic Grade Between Transurethral Resection of the Bladder (TURB) and Cystectomy Specimens

<table>
<thead>
<tr>
<th>Cystectomy</th>
<th>TURB</th>
<th>Low-Grade</th>
<th>High-Grade</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade</td>
<td>7</td>
<td></td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>High-grade</td>
<td>10</td>
<td></td>
<td>82</td>
<td>92</td>
</tr>
</tbody>
</table>

* There was marginal agreement between TURB and cystectomy specimens (kappa = 0.38; P = .002).

### Table 3
Association Between Histologic Grade at Transurethral Resection of the Bladder (TURB) and Final Pathologic Stage at Cystectomy

<table>
<thead>
<tr>
<th>Cystectomy</th>
<th>TURB</th>
<th>Ta</th>
<th>T1</th>
<th>T2</th>
<th>T3a</th>
<th>T3b</th>
<th>T4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>High</td>
<td>1</td>
<td>14</td>
<td>16</td>
<td></td>
<td>18</td>
<td>23</td>
<td>16</td>
<td>88</td>
</tr>
</tbody>
</table>

* There was a significant association between histologic grade at TURB and final pathologic stage at cystectomy (Wilcoxon rank sum test, P < .001).
slides without reliance on pathologic reports, and use of the newly proposed grading system.

Clinical and pathologic staging of bladder cancer should reliably reflect the natural history of cancer and precisely describe the anatomic extent and cancer burden on the basis of the best available data. Current TNM staging is based on the examination of cystectomy specimens. Examination of TURB specimens may yield a significant level of staging error in comparison with pathologic examination of cystectomy specimens. Furthermore, examination of TURB specimens could not distinguish stage T2 cancer from those that were not organ-confined cancer (T3 or more). Muscularis propria may not always be identifiable in TURB specimens, even when the cancer is extensive.

Heterogeneity of patient populations defined by current stage groupings creates uncertainty about the comparative efficacy of different treatments and patient outcome.22 New substaging systems are being studied in an effort to improve clinical staging and to allow greater precision in predicting outcome for individual patients.23-28 All these staging systems relied on identification of muscularis mucosae, which is difficult to apply in routine practice and were not recommended in a recent consensus meeting organized by the WHO/ISUP.18 Pathologists should have a major role in the standardization of staging and development of guidelines for pathologic evaluation of specimens.2,17,18,24,29-37 A micrometer-based measurement of depth of invasion for substaging of T1 bladder carcinoma was proposed recently.38-40 Of 83 patients with stage T1 bladder carcinoma diagnosed in TURB specimens, with a median follow-up of 5.4 years, Cheng et al38 found that the 5-year cancer (stage) progression-free survival was 67% for patients with a depth of invasion of 1.5 mm or more, in comparison with a 93% 5-year progression-free survival for patients with a depth of invasion of less than 1.5 mm (P = .009).

Several limitations of our study should be considered. Our patient population differed in certain aspects from those of other studies. All patients were selected for cystectomy and treated before the introduction of BCG therapy. Most patients (96%) underwent cystectomy within 100 days of TURB. Caution is warranted in comparing our findings with recent studies in which patients received less aggressive surgical treatment, such as intravesical therapy or radiation therapy. Furthermore, our sample size was moderate. Assessment of TURB specimens in conjunction with imaging studies, such as transrectal ultrasonography, computed tomography, and magnetic resonance imaging, may improve the accuracy of predicting the final pathologic stage.41-44

Pathologic understaging by TURB occurred in a significant number of patients with bladder cancer. An improved staging system for TURB specimens is needed to stratify patients for optimal management.

References


