Current State of Classification and Staging of Bladder Cancer

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Summary

The most important determinant for treatment as well as prognosis is the presence or absence of muscle invasion as determined by the histopathological material obtained by a properly performed biopsy. Histological grade of the tumor is also important inasmuch as high-grade tumors are usually always associated with invasion, whereas low-grade tumors are usually superficial. The presence or absence of carcinoma in situ is also an important histological feature and may be diagnosed with increasing accuracy by improved cytopathological techniques.

The TNM system, although useful in the accurate staging of definitive cystectomy specimens, offers little to clinical management. The inherent and significant problems of clinical staging and difficulties in attempting to correlate presenting pathology with correct management persist. What is needed, in my opinion, is simplification of clinical staging, elimination of stages that cannot be accurately determined by existing methods, and better identification of criteria for treatment planning.

In 1922, Broders (2) noted that malignant tumors of the bladder epithelium varied in behavior and prognosis according to their cellular activity, and he subsequently formulated a method of grading based on the percentage of undifferentiated epithelium. Since Broders' initial observation, a considerable volume of information and knowledge has accumulated concerning various histological features and their relationship to prognosis. Nevertheless, there has been little effort to formulate a clinical plan of management on the basis of these histological features in attempting to alter the natural history of bladder cancer.

Various histological criteria such as cell types, patterns, and grades have been well described in previous studies (4, 6, 13, 17). Jewett and Strong (9) were the first to emphasize the significance of pathological stage relating to prognosis. From an autopsy study they noted that, when tumors of the bladder were confined to the mucosa (Stage A), there was little likelihood of concomitant lymph node or disseminated blood-borne metastatic disease. However, 74% of bladder tumors that had penetrated the muscularis (Stage C) were associated with lymph node or disseminated blood-borne metastases. In the group of tumors infiltrating but confined to the muscularis (Stage B), metastases were present in 12% (9). In a later publication, based on 80 cases, Jewett (8) suggested the clinical segregation of the Stage B category into superficial (Stage B1) and deep (Stage B2), stating that "regardless of histologic pattern and degree of malignancy, [tumors] which have infiltrated less than half way through the muscularis usually are still confined to the bladder wall and tumors which have infiltrated more deeply usually have spread beyond" (8). This basic premise has resulted in a division of the initial staging system of Jewett and Strong, further modified by Marshall in 1952 to include Stage 0, indicating those tumors not infiltrating the lamina propria as well as including in situ or intraepithelial carcinoma. In addition, Marshall included "those cancers in which, although there [had] been biopsy proof of the existence of the tumor within 30 days of surgical removal of the definitive specimen, no tumor can be found microscopically in that specimen" (10). Chart 1 illustrates the current version of the Marshall modification of the staging system used extensively in the United States, that of Jewett and Strong. Although the initial staging system was based on pathological material, its main use is in clinical staging with its relation to prognosis and indication for treatment alternatives.

In 1950, the Union Internationale Contre le Cancer (UICC) appointed a Committee on Tumor Nomenclature and Statistics to develop general definitions of local extension of malignant tumors and, in 1954, established a special Committee on Clinical Stage Classification and Applied Statistics under the chairmanship of Dr. P. Denoix of France. The charge of this committee was to "pursue studies in the field and to extend the general techniques of classification to cancer at all sites" (24). Between 1954 and 1967 this committee developed and outlined the general rules of the TNM system and proposed a classification system of cancer at 23 sites, none involving the genitourinary system. The TNM system is based on the assessment of: (a) the extent of the primary tumor (T), (b) the condition of the regional nodes (N), and (c) the absence or presence of distant metastases (M).

The stated objectives are to: (a) aid the clinician in the planning of treatment, (b) give more indication of prognosis, (c) assist in an evaluation of treatment results, (d) facilitate the exchange of information between treatment centers, and (d) contribute to the continuing investigation of human cancer (24). Essentially, it is a universal system designed to provide a method of conveying one's experience to others without ambiguity. In 1974, the UICC and its committee on TNM Classification, chaired by Dr. Bridget Van der Werf-Messing of the Netherlands, classified cancer of the blad-

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1 Presented at the National Bladder Cancer Conference, November 28 to December 1, 1976, Miami Beach, Fla.
der, prostate, kidney, and testis according to the TNM system (24). As in other sites, this classification proposal will be subjected to a trial of 5 years, 1975 to 1979. Therefore, the classifications of these tumors of urological sites are not definitive and may be adjusted by further experience and input by groups of urological oncologists acting through the United States representative to the UICC, Dr. F. K. Mostofi. Nevertheless, the classification represents the 1st potentially workable classification of cancer of the various genitourinary sites acceptable to an international group (see "Appendix").

Chart 2 compares the original system of Jewett and Strong with Marshall's modification and the TNM system. Several obvious advantages of this TNM system are apparent. (a) Clinical (T) and histopathological (P) criteria use different letter symbols for comparable stages, thus avoiding confusion in interpretation of results of therapy. (b) TIS has been introduced as a specific entity for carcinoma in situ, and it defines the lesion as "anaplasia of surface epithelium without the formation of papillary structures and without infiltration" (24). This definition and classification is an important contribution to bladder staging and should help alleviate much of the current confusion over definition of this lesion.

In Marshall's modification, carcinoma in situ was grouped with papillary tumors that did not involve the lamina propria as well as the definitive surgical specimen in which there was no microscopic tumor, even though there had been biopsy-proven tissue present during the previous 30 days (10, 11). (c) Stage T1, or histopathological stage P1, represents all papillary tumors not involving muscle, thus relegating the Stages 0 and P0 to no microscopic evidence of tumor in the definitive specimen and T0, being a clinical stage, to no residual tumor on biopsy.

The TNM system also adds N and M groups for classification of those tumors associated with metastases, to either regional nodes (N) or distant sites (M). These distinctions are of little practical importance because of serious limitations in our ability to detect early metastases as well as our inability to influence prognosis once gross metastases are apparent.

The disadvantages of the TNM system are that it perpetuates the apparent bad features of the Marshall modification of the Jewett-Strong classification, simply substitutes different letters for similar stages, and does not meet its 1st stated objective, to "aid the clinician in the planning of treatment." The primary weakness of the Marshall-Jewett-Strong system was Jewett's segregation of muscle invasion into superficial (less than half way) (B1), and deep (more than half way) (B2). This modification, recommended by Jewett in 1952, was based on 80 patients and has been adopted by others, including the TNM system (9). In the 1956 Symposium on Bladder Cancer, Whitmore and Marshall (23) attempted to further group patients into superficial (0AB1) and deep (B2C) in an effort to improve accuracy of staging, initiation of treatment, and prevention of progression.

This grouping was based on Jewett's report in 1952 that superficial and deep tumors could be segregated by means...
of a properly performed bimanual pelvic examination and biopsy specimen (9). A palpable mass or induration with histological evidence of tumor in the muscle almost always indicated deep penetration unless the induration disappeared following transurethral resection of the tumor growth. If no induration could be felt, it was most probable that the tumor was superficial. Subsequent reports by Marshall (11), Marshall and Whitmore (12), and Whitmore and Marshall (23) demonstrated that the preoperative estimation for this 1 criterion was 81% accurate by this method. The simple consideration of these observations was the ability to determine whether or not the tumor was deeply infiltrating, and these investigators demonstrated a direct relation to prognosis, inasmuch as approximately 50% of patients with superficial tumors survived 5 years after cystectomy compared to a 5-year survival of only 15% for those with deeply infiltrating tumors. Marshall further demonstrated a clinical relationship between the histological grade of the malignancy and its depth of invasion (10). He noted that, in general, low-grade tumors were encountered in superficial stages and high-grade tumors were associated with deep invasion, and that deviation from this observation was observed in only 7 of 104 consecutive cystectomy specimens (10). Thus the grade of the tumor became an important consideration in the classification of bladder carcinoma according to stage.

On the other hand, has the test of time borne out the importance of distinguishing between superficial muscle invasion and deep invasion, or has this segregation increased the clinical or histopathological staging error? In 1975, Richie et al. (21) pointed out in a group of 140 patients that any degree of muscle infiltration significantly influenced survival compared to tumors without muscle infiltration or those penetrating into the perivesical fat (Table 1). Similar findings can be found in the published reports of other investigators (Table 2). The depth of muscle infiltration thus becomes far less important than the significance of any degree of muscle infiltration, and the latter can be determined with far greater accuracy than our efforts to assess depth. If the major goals of a classification system are to aid the clinician in the planning of treatment as well as to give indication of prognosis, current evidence would support the contention that a properly performed biopsy indicating the presence or absence of muscle invasion as well as the grade of the tumor remains the most important determinant of clinical staging, and that further efforts to assess depth of penetration or extension of the primary tumor have resulted in increasing error and confusion over management.

For example, any classification system is only as good as the existing methodology in determining extent of the local tumor. Numerous techniques, including i.v. pyelography, pelvic arteriography, triple-contrast cystography, and ultrasound, have been used to assess clinical stage before therapy. Results of the National Cooperative Bladder Cancer Study, however, indicate that accuracy of clinical staging according to the Marshall modification of the Jewett-Strong system approaches only 50% and that the main error was in assessing depth of infiltration (Table 3). It is unlikely that computerized axial tomography will significantly alter this error, although it may improve our ability to detect early soft tissue metastases.

Recently, considerable enthusiasm has been expressed for the use of bilateral pedal lymphangiography in detecting the early presence of pelvic or retroperitoneal nodal metastases from bladder and prostatic cancer. Unfortunately, even under the best of circumstances this examination has such a margin of error that its use has only increased the error of clinical staging vis-à-vis pathological staging and further confused the clinician attempting to plan management. J. Schmidt (personal communication) has recently reported a prospective study of 40 consecutive patients undergoing bilateral pedal lymphangiography followed by surgical staging and has documented a 50% error in the ability of lymphangiography to predict either the presence or absence of nodal metastases in patients with prostatic carcinoma. It would appear, therefore, that this test should be relegated to history in the management of bladder cancer, and patients should be spared the burden of the expense associated with its use.

Therefore the TNM system, although clarifying some of the ambiguous portions of the Jewett-Strong system, perpetuates the problems. Basically, except for TIS and T1, the TNM system defines stage according to the A, B, C, D method of Jewett and Strong, simply changing the letters and clearly identifying the clinical from the histopathological staging.

Although accurate pathological staging is important in assessing the results of therapy, the accuracy of clinical staging is probably not as important to the patient as the ability of the clinician to group those tumors requiring aggressive therapy vis-à-vis those satisfactorily managed by more conservative methods. In this area there has been progress, and we hope the cytopathologist will offer further advances.

The presence and natural history of carcinoma in situ have become an extremely important contribution to our understanding of bladder cancer (14, 15, 22, 25). Current evidence suggests that the presence of carcinoma in situ in association with overt bladder cancer is ominous and should encourage the clinician to aggressive therapy. Carcinoma in situ is usually associated with a high-grade overt tumor or may precede high-grade bladder cancer, and evidence suggests that any degree of invasion associated with a high-grade tumor signifies an ominous prognosis unless aggressive therapy is initiated (22).

Thus it would appear that the clinician needs simplification of staging rather than further confusion and fragmenta-

<table>
<thead>
<tr>
<th>Stage</th>
<th>5-yr survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-A</td>
<td>78.6</td>
</tr>
<tr>
<td>B1</td>
<td>39.9 All B, 40.0</td>
</tr>
<tr>
<td>B2</td>
<td>40.4</td>
</tr>
<tr>
<td>C</td>
<td>19.7</td>
</tr>
<tr>
<td>D</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Table 1
Pathological stage and 5-year survival for 140 patients treated by cystectomy

Note the nearly identical survival for Stage B1 and Stage B2 and the statistical significance between survival of those patients with tumor confined to the mucosa compared to those with muscle invasion ($p < 0.01$) [Data from Richie et al. (21)].
Classification of Bladder Cancer

Table 2

Recorded 5-year survival (percentage) according to stage

<table>
<thead>
<tr>
<th>Treatment Series</th>
<th>Year of series</th>
<th>Stage 0-A</th>
<th>B1</th>
<th>B2</th>
<th>All B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transurethral resection Flocks (7)</td>
<td>1951</td>
<td>130/168 (77)</td>
<td>6/142 (47)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transurethral resection Barnes (1)</td>
<td>1967</td>
<td>146/233 (63)</td>
<td>46/114 (40)</td>
<td>3/57 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segmental resection Riches (20)</td>
<td>1960</td>
<td>7/12 (58)</td>
<td>16/44 (36)</td>
<td>0/6 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystectomy Cordonnier (3)</td>
<td>1974</td>
<td>31/67 (46)</td>
<td>24/46 (52)</td>
<td>12/30 (40)</td>
<td>36/76 (47)</td>
<td>11/36 (31)</td>
</tr>
<tr>
<td>Cystectomy Richie et al. (21)</td>
<td>1975</td>
<td>43/54 (79)</td>
<td>14/36 (40)</td>
<td>9/22 (40)</td>
<td>23/58 (40)</td>
<td>4/21 (20)</td>
</tr>
<tr>
<td>Cystectomy Pearse et al. (17)</td>
<td>1976</td>
<td>7/14 (50)</td>
<td>5/12 (42)</td>
<td>12/26 (42)</td>
<td>1/15 (13)</td>
<td></td>
</tr>
<tr>
<td>Cystectomy Prout (19)</td>
<td>1976</td>
<td>16/51 (32)</td>
<td>19/61 (31)</td>
<td>35/112 (31)</td>
<td>5/24 (21)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>357/534 (67)</td>
<td>71/186 (38)</td>
<td>57/165 (35)</td>
<td>258/651 (40)</td>
<td>30/191 (16)</td>
</tr>
</tbody>
</table>

Table 3

Bladder cancer staging error (percentage): clinical (T) versus pathological (P)

<table>
<thead>
<tr>
<th>Preoperative stage</th>
<th>Understage T &lt; P</th>
<th>Overstage T &gt; P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery only</td>
<td>Surgery only</td>
</tr>
<tr>
<td></td>
<td>Preoperative radiotherapy</td>
<td>Preoperative radiotherapy</td>
</tr>
<tr>
<td>B1</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td>B2</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>All B</td>
<td>46</td>
<td>20</td>
</tr>
<tr>
<td>C</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>B2-C</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Total error</td>
<td>42</td>
<td>21</td>
</tr>
</tbody>
</table>

Note the similarity in survival between Stages B1 and B2, both substantially different from Stage 0-A and C.

The important points that should be emphasized include the following. Staging of localized bladder cancer should depend primarily on the histopathological material obtained by biopsy. Important observations are grade, presence or absence of muscle invasion, and presence or absence of carcinoma in situ. Carcinoma in situ is determined by random biopsies as well as by assessment of the mucosa immediately adjacent to the primary tumor. If muscle invasion is obvious at the time of biopsy, on the basis of endoscopic appearance and/or bimanual examination, sufficient biopsy to document invasion and determine grade may be all that is required to indicate aggressive therapy, and complete resection is not necessary and may be detrimental. Dretler et al. (4) reported that survival of those patients with extensive localized lesions was better if only a biopsy was made for diagnosis rather than an attempt at resection, suggesting that resection may play a detrimental role by causing tumor dissemination.

Once the diagnosis of a high-grade or muscle-invading tumor has been established, efforts should be made to rule out metastatic disease. Appropriate studies should include chest X-ray, bone scan with correlated bone X-rays of any suspicious areas, and biochemical liver function studies with radioisotope liver scan performed only if the liver function studies are abnormal. If there is no evidence of metastatic disease, definitive therapy should be entertained. Other diagnostic efforts to stage the localized primary tumor, including pelvic arteriography, bilateral pedal lymphangiography, and triple-contrast cystography, offer little in the way of significant changes in treatment plan and burden the patient with expensive tests of primarily academic interest.

In conclusion, the most important determinant for treatment as well as prognosis is the presence or absence of muscle invasion as determined by the histopathological material obtained by a properly performed biopsy. Histological grade of the tumor is also important, inasmuch as high-grade tumors are usually associated with invasion, whereas low-grade tumors are usually superficial. The presence or absence of carcinoma in situ is also an important histological feature and may be diagnosed with increased accuracy by improved cytopathological techniques.

The TNM system, although useful in the accurate staging of definitive cystectomy specimens, offers little to clinical management. The inherent and significant problems of clinical staging and difficulties in attempting to correlate presenting pathology with correct management planning persist. What is needed, in my opinion, is simplification of clinical staging, elimination of stages that cannot be accurately determined by existing methods, and better identification of criteria for treatment planning.

Appendix

The TNM System for classification of bladder cancer follows (24).

1. The classification applies only to epithelial tumors. Papilloma is excluded.

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but such cases may be listed under the category $G_0$.

2. There must be histological or cytological verification of the disease.

3. The following are the minimum requirements for assessment of the $T$, $N$, and $M$ categories.

**T** categories: Clinical examination, urography, cystoscopy, bimanual examination under adequate anesthesia and biopsy or transurethral resection of the tumor (if indicated) before definitive treatment.

$T_0$ No residual induration after complete transurethral resection of the lesion and/or, microscopically, the tumor does not extend beyond the lamina propria.

$T_1$ Tumor fixed in the bladder wall that persists after transurethral resection of the exophytic portion of the lesion and/or there is microscopic invasion of deep muscle or extension through the bladder wall.

$T_2$ Invasion of deep muscle.

$T_3$ Extension through the bladder wall.

**P** categories: Clinical examination under adequate anesthesia and biopsy or transurethral resection of the tumor (if indicated) before definitive treatment when clinical suspicion warrants, radiographic or isotope studies should be done.

If these requirements cannot be met the symbols $T^*$, $N^*$, or $M^*$ will be used.

**TNM Classification**

- **$T$**: Primary tumor
  - The suffix (m) may be added to the appropriate $T$ category to indicate multiple tumors, thus $T_{nm}$.

- **$T_{is}$**: Carcinoma in situ. Definite anaplasia of surface epithelium without the formation of papillary structures and without infiltration.

- **$T_4$**: Tumor fixed or invading neighboring structures and/or there is microscopic evidence of such involvement.

- **$T_{nm}$**: Tumor invading prostate, uterus, or vagina.

- **$T_{nm}$**: Tumor fixed to the pelvic wall and/or infiltrating abdominal wall.

- **$N$** categories: Clinical examination, lymphography, and urography.

- **$N_0$**: No evidence of involvement of regional lymph nodes.

- **$N_1$**: Involvement of a single homolateral regional lymph node.

- **$N_2$**: Involvement of contralateral or bilateral or multiple regional lymph nodes.

- **$N_3$**: There is a fixed mass on the pelvic wall with a free space between this and the tumor.

- **$N_{nm}$**: No evidence of involvement of regional lymph nodes.

- **$N_{nm}$**: Involvement of a single homolateral regional lymph node.

- **$N_{nm}$**: Involvement of contralateral or bilateral or multiple regional lymph nodes.

- **$N_{nm}$**: There is a fixed mass on the pelvis wall with a free space between this and the tumor.

- **$N_{nm}$**: Involvement of juxtaregional lymph nodes.

**$P$** category: Histopathological grading.

- **$P$**: Tumor with infiltration of prostate or other extravesical structures.

**$G$**: Histopathological grading.

- **$G_0$**: No evidence of anaplasia (i.e., papilloma).

- **$G_1$**: Low-grade malignancy.

- **$G_2$**: Medium-grade malignancy.

- **$G_3$**: High-grade malignancy.

**$L$** categories: Clinical examination, chest radiography, and biochemical testing. In the more advanced primary tumors or when clinical suspicion warrants, radiographic or isotope studies should be done.

Note: The histopathological categories and grading conform to the recommendations of WHO. (See Histological Typing of Urinary Bladder Tumors, Geneva, WHO, 1973.)

**Stage grouping**

No stage grouping is at present recommended.

References


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