The Pathologist’s Role in Multidisciplinary Management of Bladder Cancer*

JENÖ E. SZAKACS, M.D., and JULIO POW-SANG, M.D.

Departments of Pathology† and Urology,‡
H. Lee Moffitt Cancer Center
University of South Florida Health Sciences Center,
Tampa, FL 33612

ABSTRACT

The pathologist plays an important role in management of bladder cancer, as a member of the multidisciplinary team of urologists, radiation therapists, and medical oncologists. The therapeutic goal is saving the bladder function as long as possible. The pathologic determinants utilized for selection of therapeutic modalities are described in 172 consecutively treated patients with transitional cell carcinoma and 20 patients with other forms of bladder tumors during a five year period. Based on histologic type, pathologic stage, and status of the urothelium, 100 patients were treated by resection and intravesical instillation of cytostatic drugs or bacille Calmette-Guérin (BCG). Seventy patients underwent radical cystectomy and bladder substitution by continent urinary diversion. Serial transurethral resection (TUR) biopsies and cytologic evaluations were found adequate in evaluating pathologic determinants for progression and for survival except in cases of Grade 2 papillary transitional carcinomas where additional experimental studies need to be further developed, such as nuclear ploidy and molecular genetic studies, to identify patients at high risk for progression. Of the 70 patients with radical cystectomy and 5 with partial cystectomy, 49 are living, a median of 36.8 months since surgery. There was one intraoperative death and one post-operative death within 30 days post-operatively.

Introduction

Modern approach to control urologic cancer requires a multidisciplinary participation of urologic surgeons, radiation therapists, medical oncologists, radiologists, and pathologists. The pathologist’s role is to evaluate cytologic, bioptic, and resection specimens of bladder tumors that will allow classification of patients into either a high risk or a low risk group for progression of the disease. The therapeutic approach varies according to the extent of the disease, if it is superficial or invasive, and if it falls into the high or
low risk categories. At Moffitt Cancer Center, during a five-year period, 192 patients were treated with bladder cancer, 172 with transitional cell carcinomas; the other 18 patients presented with squamous cell carcinoma, adenocarcinoma or undifferentiated carcinoma, and two patients with sarcomas (table 1). This presentation will emphasize the surgical pathology and biological behavior of transitional cell carcinomas, the major group forming more than 90% of bladder tumors.\textsuperscript{1} The other histologic types are high risk, invasive malignancies differing in biological behavior from transitional cell carcinomas.

Bladder cancer has its peak incidence in the seventh decade, and it affects males three times more than females. The annual incidence in the US is about 46,000 with 10,000 deaths per year. The overall five-year survival of patients with bladder cancer is about 52%, but interestingly, no further excess cancer specific mortality is noted six years after diagnosis.\textsuperscript{2} At the time of diagnosis, 70% of the tumors are localized to the bladder, 25% are invasive carcinomas, and 5% present with distant metastases without necessarily having localizing bladder symptoms.

### TABLE I

<table>
<thead>
<tr>
<th>Cystectomy All Cases</th>
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<tbody>
<tr>
<td>Transitional cell carcinoma</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Undifferentiated (small cell)</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
<tr>
<td>Total</td>
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The superficial carcinomas of low risk for recurrence and progression can be treated and even cured by bladder preserving procedures\textsuperscript{3} while the muscle invasive tumors require radical intervention, cystectomy and/or radiation therapy.

Transitional cell tumors in our material are classified according to Mostofi and are staged by the TNM system.\textsuperscript{1,4} Urothelial carcinomas are heterogeneous with markedly different outcomes that necessitate discussion separately of superficial bladder cancer (Tis, Ta and T1) from that of muscle invasive disease (T2-T3).

Seventy-five percent of the superficial urothelial tumors are papillary transitional cell carcinomas. The papillary carcinomas are lined by urothelial cells of increasing anaplasia from grade I to grade III as described by Koss.\textsuperscript{5} Grade I papillary carcinoma represents 75% of superficial urothelial tumors and grade II about 20%. Grade III papillary tumors are rare. All forms of papillary tumors tend to recur up to as high as 70% after transurethral resection. Progression to infiltrating tumors is relatively rare, occurring in only approximately 20% of the cases.\textsuperscript{6} Another form of superficial urothelial tumor is that of the non-papillary non-infiltrating carcinoma referred to as carcinoma in-situ (flat) generally accepted as a grade III intraepithelial carcinoma.

Muscle invasive bladder carcinoma is at high risk for progression, the invasion of muscularis propria indicates need for aggressive management such as radical surgery and radiation therapy or both.\textsuperscript{7} Tumor staging is dependent on the extent or depth of invasion and in advanced stages the presence of nodal or distant metastases. The following are illustrative examples from our material.

### SUPERFICIAL UROTHELIAL TUMORS

The first is a non-invasive transitional cell carcinoma of the bladder in a
35-year-old male who underwent transurethral resection and three monthly cystoscopic follow-up for a period of three years. Tumor cells were well differentiated grade I and, as shown in the flow diagram (figure 1), recurrences were found both in the right and anterior wall as well as in the base. No invasion developed, and the histologic grade did not change. During the third year, cystoscopic examinations found only negative biopsies after treatment with BCG. In addition to transurethral resections, cytologic examinations were performed and ploidy studies were done.

One other patient with similar history was followed for 20 years by transurethral resections before he developed muscle invasive carcinoma and underwent cystectomy. Patients with superficial carcinoma are considered at high risk when they present in stage T1 or TIS and with high histologic grade III or IV.

Predictors of recurrence and of progression of superficial transitional cell carcinoma are listed in Table II.8

![Figure 1. Flow chart of diagnostic procedures and treatment of one patient with stage Ta bladder cancer. Cystoscopy and cytologic follow-up every 3 months for a 3-year period. TUR = transurethral resection of tumor; Ta stage; Grade GI-II of III; BCG = Bacillus Calmette-Guerin.]

<table>
<thead>
<tr>
<th>TABLE II</th>
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</thead>
<tbody>
<tr>
<td>Predictors of Recurrence and of Progression of Superficial Transitional Cell Carcinoma</td>
</tr>
</tbody>
</table>

| Multiplicity of tumors |
| Large size (> 3 cm) |
| Depth of invasion |
| Histologic grade |
| Coexistent carcinoma in situ dysplasia |
| Epithelial growth factor positivity |
| Loss of surface blood group antigens |
| Aneuploidy |
later with carcinoma invading the inner half of muscularis propria (stage T2). A partial cystectomy was performed and, as of March 1994, the patient is free of tumor.

The presence of coexistent carcinoma in situ with superficial transitional cell carcinoma places the patient again into the high risk category.\textsuperscript{10} Carcinoma in situ with high grade nuclear anaplasia and a peculiar phenomenon of carcinoma in situ, the pagetoid spread, is illustrated in figure 4. Tumor cells are seen within the epithelium. Loss of cohesion of these cells may lead to massive denudation (figure 5) of the surface. Extensive desquamation allows cytologic detection of the tumor, but the pathologist must be alert not to accept denuded mucosal surfaces as evidence of lack of carcinoma. In the case illustrated, one-half of the specimen is denuded, the other half is with carcinoma in situ. Progression of carcinoma in situ to both papillary and invasive carcinoma is well documented. Progression, however, is slower than it was presumed. Normig\textsuperscript{11} and colleagues found that progression could be predicted based on ploidy studies of biopsies and bladder washings. Progression-

\textbf{Figure 2.} Bladder biopsy, 1-8-90, male, 46-years-old. Papillary transitional cell carcinoma, grade II, limited to mucosa, stage Ta (hematoxylin & eosin $\times$250).

\textbf{Figure 3.} Same patient as in Fig. 2. Bladder biopsy, April 12, 1991. Transitional cell carcinoma, grade III, invading inner half of muscularis propria, stage T2 (hematoxylin & eosin $\times$400).
free survival decreased with appearance of increasing number of aneuploid cell populations. Development of multiple aneuploid populations is a strong predictor of clinical progression that it precedes by up to 20 months.

**MUSCLE INVASIVE UROTHELIAL CARCINOMA**

The histologic prognostic factors as to survival are listed in table III in cases of muscle invasive transitional cell carcinoma. These are the tumor size, histologic grade, pattern of invasion, lymphatic invasion, and nodal status.

It is generally accepted that muscle invasive tumors are derived from the clonal evolution of superficial tumors. Studies have shown that solid invasive tumors arise from preexisting low grade papillary tumors or from carcinoma in situ. Twenty percent of invasive bladder carcinomas are infiltrating from the start. Grossly, the tumors are sessile, nodular, and bulky, infiltrating the blad-
TABLE III
Histologic Prognostic Factors (Survival)
Muscle Invasive Transitional Cell Carcinoma

<table>
<thead>
<tr>
<th>Tumor size</th>
<th>Histologic grade</th>
<th>Pattern of invasion</th>
<th>Lymphatic invasion</th>
<th>Nodal status</th>
</tr>
</thead>
</table>

Muscle invasive transitional cell carcinomas have several histologic features that influence survival. Tumor size, histologic grade, pattern of invasion, lymphatic invasion, and nodal status all play a role in determining prognosis.

Infiltrating tumors are mostly of high grade, Grade III, and rarely Grade II or Grade I. With increasing depth of infiltration, invasion of vessels and lymphatics is increasingly more frequent. Invasive tumors have a high rate of recurrence and extend by intravesical spread, and induce death either from renal failure or owing to extensive local neoplastic involvement and widespread metastases. The prognosis is reportedly poorer for undifferentiated carcinomas, squamous cell carcinomas, and adenocarcinomas. A number of patients present at the time of diagnosis with metastatic disease, metastases to bone, lungs, and liver without urinary symptoms requiring therapy.

The diagnostic work-up include cytologic examination of urine, cystoscopy, and transurethral biopsies. All visible lesions need to be biopsied deep enough to establish muscle invasion if present. Clinical staging in addition requires examination under anesthesia and radiologic evaluation. The tumor stage correlates with the likelihood of lymph node involvement and with survival. Median survival for patients with positive nodes above the aortic bifurcation is reported as 6 to 9 months and for patients with positive pelvic nodes, 18 months.

Several factors indicating poor prognosis may be found in some cases. In our series, the bladder of a 62-year-old man with Grade 3 muscle invasive carcinoma has invaded the prostate, and it contained multiple topographically separate nodules in the bladder wall. There was extensive carcinoma in situ change adjacent to the tumor masses. In addition, the left ureter was obstructed by tumor growth causing hydronephrosis. In spite of radical cystoprostatectomy, nephrectomy, and chemotherapy, this patient expired six months after radical surgery.

In table IV are illustrated post-cystectomy survival of our 75 patients at 12, 24, and 30 months. Our survival data is limited as the median follow-up is only 36 months, varying from 2 to 81 months (table V) for our cystectomy patients. The 26 patients who have expired so far are also listed by stage. Three of the 19 stage T2 cystectomy patients died, as did 10 of the 19 stage T3, and 6 of the seven stage T4. One patient died without carcinoma owing to intercurrent disease, and the second patient died of a lung carcinoma, a second primary. There were one intraoperative and one postoperative deaths within 30 days, both of stage T1 carcinoma.

Since the presentation of this report at the spring meeting of the Association of Clinical Scientists (1993), Frazier et al published their experience with a large series of patients treated by radical cystectomy for transitional cell carcinoma. These authors have analyzed the value of
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TABLE V
Transitional Cell Carcinoma
Postcystectomy Follow-up*

<table>
<thead>
<tr>
<th>Stage</th>
<th>No.</th>
<th>Deceased</th>
<th>Months of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>No.</td>
<td>Median</td>
</tr>
<tr>
<td>TIS &amp; Ta</td>
<td>6</td>
<td>0</td>
<td>49</td>
</tr>
<tr>
<td>T1b</td>
<td>14</td>
<td>2b</td>
<td>35</td>
</tr>
<tr>
<td>T2</td>
<td>19</td>
<td>3c</td>
<td>44</td>
</tr>
<tr>
<td>T3</td>
<td>19</td>
<td>10</td>
<td>29.5</td>
</tr>
<tr>
<td>T4</td>
<td>7</td>
<td>6</td>
<td>33.5</td>
</tr>
<tr>
<td>TX</td>
<td>10</td>
<td>5d</td>
<td>35</td>
</tr>
<tr>
<td>Totals</td>
<td>75</td>
<td>26</td>
<td>36.8</td>
</tr>
</tbody>
</table>


a2 cases of TIS and 4 cases of Ta.
b1 intraoperative and 1 postoperative death.
c1 death owing to second primary lung carcinoma.
d1 death owing to second primary lung carcinoma.

deficit cancer. Serial transurethral biopsies and cytologic examinations are evaluated for prognostic indicators of progression and in cases of invasive cancer cystectomy specimens are scrutinized for pathologic determinants of survival. The information obtained is presented by the pathologist to the multidisciplinary group of urologists, medical oncologists and radiation therapy oncologists. Newer methods of diagnosis are needed particularly in differentiating grade 2 superficial bladder tumors, one-half of which expected to progress while the other half remains non-invasive.\(^3,6,19\) Morphologic criteria for this differentiation is insufficient and more modern molecular genetic studies and flow cytometry of nuclear ploidy together with cytologic examination of urine has promise to identify patients at high risk for progression.

One of the therapeutic goals of our multidisciplinary team is to preserve bladder function in selected cases as part of a multi-institutional protocol evaluating systemic chemotherapy and radiation therapy. The histologic type, pathologic stage of bladder tumors and status of urothelium adjacent to tumor areas form an important basis for selection of therapeutic modality.

Local intravesical therapy with cytostatic drugs or BCG decrease recurrences and may achieve complete cure of superficial cancer. Serial transurethral biopsies and cytologic examinations are evaluated for prognostic indicators of progression and in cases of invasive cancer cystectomy specimens are scrutinized for pathologic determinants of survival. The information obtained is presented by the pathologist to the multidisciplinary group of urologists, medical oncologists and radiation therapy oncologists. Newer methods of diagnosis are needed particularly in differentiating grade 2 superficial bladder tumors, one-half of which expected to progress while the other half remains non-invasive.\(^3,6,19\) Morphologic criteria for this differentiation is insufficient and more modern molecular genetic studies and flow cytometry of nuclear ploidy together with cytologic examination of urine has promise to identify patients at high risk for progression.

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References


