Clinical Observations on Sixty-nine Cases of in Situ Carcinoma of the Urinary Bladder

George M. Farrow, David C. Utz, Charles C. Rife, and Laurence F. Greene

Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55901

Summary

In the course of screening 35,000 urological outpatients with urine cytological examinations, cytological indication of cancer was found in 106 patients in the absence of a cystoscopically visible bladder tumor. Sixty-nine of the 106 patients have biopsy-proven in situ carcinoma of the bladder, all transitional in type and anaplastic. Follow-up data on effects of therapy are available on 58 patients treated by various means, including total cystectomy, partial cystectomy, transurethral fulguration, intravesical thiotepa, and external radiation. The duration of symptoms before diagnosis was remarkably long, and the prolonged course of the in situ lesion was also noteworthy. Differences in the observed behavior of in situ bladder carcinoma may be due, in addition to differences in host resistance, to the existence of two pathogenetic forms of bladder cancer, one arising in an extensive field of abnormal epithelium and the other developing in a focal area of abnormality.

Materials and Methods

All subjects who had cytological screening are outpatients mainly from the urological service, and they comprise a broad cross-section of urological practice. We have not further characterized this population and have not collected data on such factors in the history as smoking or occupational or environmental exposure. Each has had a cystoscopic examination. Cytological and cystoscopic results are compared, and divergent results are reported promptly to the responsible physician. In nearly every case, follow-up has been maintained by periodic patient evaluation by the urology staff, and this has included cystoscopic and cytological examination. For patients who have not returned regularly for follow-up examination, correspondence is maintained, usually with the home physician.

Findings and Clinical Features

Of 69 patients with proven in situ bladder cancer, 63 were men and 6 were women. They ranged in age at the time of diagnosis from 31 to 87 years, with an average of 63.1 years (62.7 years for the men and 66.1 years for the women). Symptoms brought 61 patients to the physician; of the 8 who were asymptomatic, all had microhematuria as a cause for the urological consultation. By far the most common symptoms were those of bladder irritation (dysuria, urgency, and frequency) in 54 patients. Six other patients complained of gross hematuria, and 1 had penile pain. The average duration of symptoms among the symptomatic group before the first cytological abnormality was detected was 32.2 months. Cystoscopic examination revealed no overt neoplasm in any patient. The most frequently noted cystoscopic abnormalities were increased vascularity of the mucosa and erythematous granular zones without clearly defined margins.

Pathological Features

All the carcinomas were transitional, and in none was squamous (epidermoid) metaplasia noted. All showed moderate to severe degrees of anaplasia, Grades 3 and 4 on Broders’ scale. Urine cytological findings generally consisted of large, anaplastic, mostly single cells. Decreased intercellular cohesiveness was evident in the sections of altered mucosa and accounts for both the abundant shedding of cells into the urine and the pronounced fragility of the mucosal surface, which often produced the artifact of mucosa missing from portions of the biopsy specimens. Characteristically, in these neoplasms, each individual cell of the epithelial surface shows malignant cytomorphological features, but there is no overt architectural alteration of...
the epithelium. The cell layers of the mucosa may be increased numerically and exist in a disorderly array, but there are no papillary structures supported on a stroma and there is no extension beyond the basement membrane into the submucosa (Fig. 1).

Initial Localization of Lesions

Tissue confirmation by cystoscopic localization and biopsy of the neoplastic mucosa was not always promptly achieved after the initial cytological abnormality had been detected. In many patients multiple cystoscopic procedures were required, often under anesthesia, and systematic biopsy of normal-appearing mucosa was sometimes required to yield a positive tissue diagnosis. Among 38 patients who were treated by modalities other than total cystectomy, cystoscopic observations and selective biopsies were compiled. The initial lesions appeared to have been in the following sites in the bladder (a single case might have more than 1 site, but where more than 3 exist the case is listed as “diffuse”): urethra, 0; right trigone, 5; left trigone, 2; base, 0; posterior wall, 10; dome, 4; anterior wall, 0; right lateral wall, 5; left lateral wall, 6; vesical neck, 1; diffuse, 9. Although total cystectomy patients were generally more symptomatic and their bladders showed more extensive mucosal alteration, in virtually every case after step-sectioning and total mapping of the resected bladders, the neoplastic change in the mucosa was far more extensive than had been documented preoperatively. The results of this mapping in 21 cases have been the subject of a previous report (2) and will be briefly summarized. Four cases showed microscopic foci of submucosal invasion, 3 in solitary zones and 1 multifocal. No lymph node metastases were detected. The inferior half of the bladder was a distinct zone of predilection for the lesions. More than 50% of the bladder mucosa was involved in most cases. Extension into the prostatic ducts had occurred in 7 of 19 male patients, and extension into the mucosal lining of 1 or both distal ureters was observed in 12 of the 21 cases. Since the earlier publication (2), an additional 8 cases have been mapped. Findings have been essentially the same, and 1 case showed a solitary focus of microinvasion.

Therapy

Table 1 lists the various forms of therapy used. In several cases more than 1 modality was used at some time in the patient’s course. To each of the 69 cases, a primary therapy has been assigned. In those cases in which only 1 form of therapy was used, the selection was clear, but in a number of cases the category assignment was to some extent arbitrary and was based on what appeared to be the dominant form of therapy.

Cystectomy Group

There were 31 patients in this group. Two were treated elsewhere, and follow-up data are not available.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Total</th>
<th>Definitive therapy</th>
<th>Cases with follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cystectomy</td>
<td>31</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>Segmental resection</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Transurethral fulguration</td>
<td>24</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>20</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Radiation</td>
<td>6</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>No therapy</td>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>69</td>
<td>58</td>
</tr>
</tbody>
</table>

* Cases distributed elsewhere in the table.
Symptoms ranged in duration from 4 to 96 months, with an average of 35.9 months. Cystectomy from the time of the 1st positive cytology was delayed a minimum of 3 months to a maximum of 84 months, with an average of 26 months. Thirteen of these men had radical cystectomy, including the prostate, bladder, seminal vesicles, and vasa deferentia. One had a simple total cystectomy in which the prostate was left.

Table 2 lists the forms of therapy employed before cystectomy, except for 2 patients who had no therapy before this operation. Findings at the time of total bladder mapping with respect to results of these various forms of therapy will be presented under each primary therapy category (Table 1). Two of these bladders contained solitary foci of microinvasion. None of these patients has died of bladder cancer, and in none has evidence of recurrent urothelial cancer developed. There were 2 immediate postoperative deaths, and 1 death occurred 24 months after cystectomy from unrelated causes. The remaining patients are living, up to 61 months after cystectomy.

Noncystectomy Group

There are 38 patients in this group. Four received no therapy at our institution and are lost to follow-up, and 5 others who were treated by us are also not currently under our supervision. Of the remaining 29 patients being followed, 2 have died from causes unrelated to bladder cancer and 3 have invasive bladder cancer. Among the 24 surviving patients still at risk for the development of invasive cancer, the period since the 1st positive cytological study is 6 to 84 months, with an average of 33.5 months. Among the 3 invasive cases, the duration of proven in situ carcinoma ranged from 23 to 58 months and averaged 40.7 months (see Chart 6).

Transurethral Fulguration. Twenty-four patients were treated with periodic transurethral electrofulguration of visible mucosal abnormalities, and in 15 of these it was the primary form of therapy. Adequate follow-up data are available on 12 patients (Table 1). Nine of these patients were symptomatic, and the duration of symptoms ranged from 2 to 96 months, with an average of 31 months (Chart 3). The course from the 1st positive cytological finding in these patients was often prolonged; in those patients still living and without evidence of invasion, this period has ranged up to 84 months and averages 39.7 months. One patient died from unrelated causes. Two have invasive bladder cancer.
In 1 of these patients, after 23 months a cystoscopically visible invasive tumor developed, and the patient underwent radical cystectomy; regional lymph node metastases were found. In the other patient, after 58 months a cystoscopically visible tumor developed, which on biopsy showed submucosal invasion; this patient has received radiation therapy.

In 3 patients among the delayed cystectomy group who were first treated by periodic fulguration, the bladder, on mapping, showed extensive residual in situ carcinoma. In 1 of these patients, there was a small focus of microinvasion.

**Intravesical Thiotepa.** In 20 patients thiotepa was applied topically to the bladder mucosa by intravesical instillation of 60 mg in 60 ml of solution for 60 min. In 16 patients it was the primary therapy, and in 14 of these adequate follow-up data are available (Chart 4). Details of the number of treatments are not available for all patients, but where they are known it ranged from 3 to 21. Eleven of these patients were symptomatic, and the duration before the 1st positive cytological examination ranged from 2 to 54 months, with an average of 26 months. None of these patients has died. Thirteen currently have no evidence of invasive tumor, and the duration of follow-up from the 1st positive cytological examination is up to 67 months, with an average of 27.9 months. In 1 patient followed for 40 months, during which there was no cystoscopic evidence of invasion in the bladder, a hard irregular prostate developed, which on biopsy showed in situ and invasive transitional cell carcinoma of the prostatic ducts. At the time of an abortive attempt at total cystectomy, retroperitoneal nodal and liver metastases were found.

Four patients among the delayed cystectomy group had received intravesical thiotepa. The number of treatments ranged from 6 to 20. Bladder mapping revealed residual viable in situ carcinoma in 3 of the bladders, and in 1 of these there was extensive perirethral prostatic ductal extension. One patient who had received approximately 10 treatments, the last of which was about 2 months before conservative cystectomy (prostate left in), had severe generalized cystitis, but no residual neoplasm was identified.

**Radiation.** Six patients received radiation therapy, 3 as a prelude to total cystectomy and 3 as primary therapy (Chart 5). Of the primary therapy group, 2 patients were symptomatic for 18 and 48 months. All 3 patients received radiation within 1 year of the diagnosis in doses of 5000, 4800, and 2500 rads externally. Two of these patients are alive at 24 and 60 months from the 1st positive cytological examination, and 1 patient died after 48 months from uremia but without evidence of invasion or metastasis.

Three patients received radiation therapy in doses of 3000, 4800, and 4800 rads externally as a prelude to total cystectomy. All had residual viable carcinoma at the time of cystectomy. In 2 cases this was entirely in situ, but in 1 the only residual neoplasm was a small focus of microinvasive carcinoma on the left posterior wall.

**Segmental Resection**

Five patients had segmental resection of portions of the bladder for what was thought cystoscopically to be localized carcinoma in situ. These cases have been included among other forms of primary therapy (Table 1): total cystectomy in 2 cases, periodic fulguration in 2 cases, and topical thiotepa in 1 case. Two of these patients remained asymptomatic for about 2 years after segmental resection; then symptoms recurred and urine cytological tests were again positive. The 3 others continued to have positive urine cytological tests and to experience symptoms from the immediate postoperative period onward. Two patients subsequently required treatment by total cystectomy, and extensive residual in situ carcinoma was found.

**Invasive Tumors**

Chart 6 illustrates the clinical courses in 8 cases in which invasion occurred. In 3 of these, total immediate cystectomy was the therapy and any conclusions concerning the duration of the disease can be based only on symptoms, which ranged from 33 to 60 months and averaged 43 months. Among the delayed cystectomy and noncystectomy cases, the symptoms among the 4 symptomatic patients ranged from 6 to 96 months and averaged 32.5 months. The period from the 1st positive cytological examination to the discovery of invasion in the 5 patients ranged from 20 to 58 months and averaged 41.2 months. Three of the 5 patients were found to have more than microinvasion after these intervals.
In situ carcinoma

The screening technique should detect all forms of bladder cancer by giant histological sections. They found that carcinoma in situ merged with invasive cancer in 33 cases, and neoplasia in these cases tended to be multifocal; in 10 cases there was no carcinoma in situ next to the invasive lesion and the cancer was unifocal. Thus, there may be 2 pathogenic forms of bladder cancer, 1 arising in an extensive field of abnormal epithelium, of which we believe our cases to be examples, and a 2nd form arising in a focal area of abnormality.

Discussion

It was the purpose of this study to gain some insight into the natural history of early bladder cancer and not to assess the effectiveness of various forms of therapy. Unfortunately, neither is clearly known, and it may be difficult to assess the results of this interaction in our cases. These are the only data available to us, and so we present them as we have them. The ideal design for such a study would include a large study population typical of the general population at risk for bladder cancer. These subjects should be asymptomatic and, by a universally accurate screening technique, be found to be free of malignant or premalignant findings. The screening technique should detect all forms of bladder neoplasia and not select the more malignant forms. Each subject should be periodically and regularly screened, and as tumors evolve no therapy should be introduced to alter the course of the disease. This ideal study is, of course, unrealistic.

The present study differs from the ideal in essentially every point. The study population has not been characterized and may not represent a typical population at risk for bladder cancer. Furthermore, all the tumor-bearing subjects when seen initially already had symptoms or findings of incipient neoplasia. The screening method utilized, urine cytology, more readily detects cytological abnormality on the more anaplastic portion of the neoplastic spectrum. Thus, no cases of early, well-differentiated transitional cell neoplasia are included in our series. Finally, all our tumor patients received some form of therapy, and, with the exception of the cystectomy cases, the effect of this therapy on the course of the disease is difficult to evaluate. Moreover, this study reflects the manner in which the patient presents himself to the physician, and observations on the course of the disease beginning at this juncture have some practical value.

The prolonged duration of symptoms and of the proven in situ lesion among our cases comes as a revelation to us. In our previous report on this subject (6), in which we presented data on 62 other patients, invasive cancer had developed in 37 within 5 years and most of these within 3 years. This retrospective study was made before the initiation of our urine cytology screening program. These cases may have been initially more advanced. Most showed pronounced cystoscopic abnormalities; in fact, 12 patients had previously been treated for a bladder tumor. In their 1964 study of a similar group of 25 patients, Melamed et al. (4) reported that invasion had developed in 9 patients after periods of 8 to 67 months. All but 1 of their patients, likewise, had harbored a previous bladder tumor. Kulatilake et al. (3), in 1970, reported on a series of 5 patients with carcinoma in situ, all of whom had deep radiation therapy; 2 died from unrelated causes, 1 had recurrent cancer at 2 years, and another died from metastases 2 years later. Yates-Bell (7), in 1971, reported on 5 cases—2 treated by cystectomy, 2 by radioactive gold grains, and 1 by transurethral resection. In the 3 noncystectomy patients, invasive carcinoma developed after 12 to 30 months, and there were 2 tumor-related deaths in 2 years. Barlebo et al. (1), in 1972, reported on 10 cases of carcinoma in situ followed cystoscopically for up to 72 months, in which there was no visible invasion. Several of these patients received radiation therapy.

If differences in observed behavior of in situ bladder carcinoma are real, they could be explained by differences either in host resistance or in tumor potential. Single-shot screening techniques, such as used in our study, detect cases of bladder cancer prevalent in the screened population irrespective of the presence of invasion. If those tumors found to be cystoscopically visible, more advanced, or even invasive are eliminated from study, as we have done, then less rapidly evolving tumors are selectively included. Thus, it is entirely conceivable that, during the interval observed for the evolution of an in situ tumor, another tumor may have begun, evolved more rapidly through the in situ stage, and presented initially as an advanced tumor. Some credence is given to this concept by the recent work of Soto et al. (5) in a study of cystectomy specimens in 45 cases of bladder cancer by giant histological sections. They found that carcinoma in situ merged with invasive cancer in 33 cases, and neoplasia in these cases tended to be multifocal; in 10 cases there was no carcinoma in situ next to the invasive lesion and the cancer was unifocal. Thus, there may be 2 pathogenic forms of bladder cancer, 1 arising in an extensive field of abnormal epithelium, of which we believe our cases to be examples, and a 2nd form arising in a focal area of abnormality.

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