Bladder Cancer

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Incidence and Epidemiology

The incidence of bladder cancer varies throughout the world. In the United States, the age-adjusted death rate for bladder cancer in males has remained more or less constant at five/100,000 for the past 45 years, with approximately 30,000 new cases and 10,000 deaths projected for 1977, somewhat more than two-thirds of which will occur in males.1

The worldwide nature of bladder cancer does not gainsay the possibility, indeed probability, that it is a disease with multiple etiologies, acting either alone or in concert, and including physical, chemical and possibly viral carcinogens, which may vary in etiologic role from place to place or even in the same place at different times.2-4 The ultimate goal of prevention is not yet in view and is logically dependent upon a much greater knowledge of causes than is currently available. For the present then, early diagnosis and appropriate therapy remain the principal determinants of successful management.

Diagnosis

Most patients with bladder cancer manifest gross hematuria as a presenting symptom. However, symptoms of vesical irritation—frequency, urgency, burning—are not uncommon, especially in patients with diffuse in situ cancer, infiltrating tumors, or tumors in which secondary infection has developed. There are no early physical signs of bladder cancer and a high index of suspicion with implementation of specialized investigations in suspected patients is essential for early diagnosis.

Urine cytology is highly useful in the diagnosis and follow-up of patients with bladder cancer, but its value as a screening device awaits the appropriate definition of high-risk groups and/or the development of automated techniques that will make routine mass screening more feasible.5-7

Cystoscopy and biopsy are critical not only to diagnosis but also to treatment decisions. Intravenous urography is a necessary step in evaluation since it may provide circumstantial evidence regarding tumor stage, as well as demonstrate the integrity of the upper tracts, important in light of the potential multicentricity of urothelial tumors.

Other procedures, such as cystography, lymphangiography and arteriography, have supplemental usefulness in the clinical staging of bladder tumors but are not employed routinely by most clinicians. Cost-benefit considerations will almost certainly limit their use.

Formal diagnosis and staging of bladder tumors therefore ultimately rests on cystoscopy, biopsy and bimanual examination of the patient under anesthesia.

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Classification

The vast majority of bladder cancers in this hemisphere are transitional cell tumors, with adenocarcinoma and squamous carcinoma comprising less than five percent of the total. In Egypt, on the other hand, where bilharziasis is endemic and where its association with bladder cancer is so striking, squamous cancers comprise most bladder tumors. (See "Parasites in the Etiology of Cancer—Bilharziasis and Bladder Cancer" in the March/April, 1977 issue of Ca-A Cancer Journal for Clinicians.)

Bladder cancer may be characterized on the basis of such histologic features as cell type, grade, lymphatic invasion, vascular invasion, type and extent of infiltration and karyotype; by such gross features as morphology (papillary or solid), site, size and number; by cytogenetic characteristics, for example, DNA mass and rate of incorporation of tritiated thymidine and cytidine into DNA and RNA, respectively; and by the immunologic feature of retention or loss of blood group (A,B,O) antigens by the tumor cells. Nevertheless, in terms of simplicity, reproducibility, availability, therapeutic relevance and prognostic significance, the pathologic features of grade, stage and multicentricity (in space and time) are the most useful parameters of classification.8,9 Although both pathologists and clinicians have more or less sensed the potential significance of grading and staging since Virchow's time, systems for grading and staging are a relatively recent event in medical history and, in fact, formalization of the concept of multicentricity has yet to take place.

In 1922, Broders first developed a system of grading bladder tumors, primarily on the basis of the degree of cellular anaplasia, ranging from Grade I carcinoma (papilloma) to Grade IV carcinoma (anaplastic carcinoma).10 Some pathologists prefer to recognize a histologically benign tumor (papilloma) as distinct from the various grades of carcinoma; others do not. Since papilloma (Grade I carcinoma) does not invade and does not metastasize (except possibly from iatrogenic influence), its inclusion in a "carcinoma" series improves end results, a factor that must be considered in the analysis of published data on bladder tumors.

In 1946, Jewett and Strong related the
depth of infiltration into the bladder wall to the incidence of local fixation, perivesical lymphatic invasion and metastases in an autopsy series and established a basis for staging that has undergone little modification over the ensuing years. 11

There is as yet no universal agreement on systems for grading and staging bladder tumors but efforts to achieve such agreement are well underway. A comparison of the Jewett-Marshall and the current U.I.C.C. staging systems is shown in Figure 1.

No system for classifying bladder tumors according to multicentricity has yet been proposed although the number of bladder tumors present at any one observation (multiplicity in space), the number of new tumors (multiplicity in time) as distinguished from the number of recurrent tumors, and the rate at which new tumors develop, are each practical considerations in treatment decisions.

The existence of in situ carcinoma of the bladder has been recognized since 1952. 12,13 To what extent this is a new entity and to what extent an old but previously unknown entity may never be fully defined. However, its recognition has added a new dimension to the concept of bladder tumor multicentricity. On the one hand, conceptually, every epithelial cancer must have an in situ stage; on the other hand, the diffuse in situ cancer, clinically characterized by increasing frequency and urgency of urination with progressively diminishing bladder capacity, is currently treated by nothing short of cystectomy. How the finding of in situ cancer should dictate a specific approach in therapy will remain uncertain until the occurrence and behavior of this type of lesion are more fully understood.

Clinical utilization of the pathologic features of grade, stage and multicentricity clearly depends on the reliability of the pathologist and the clinician in assessing these parameters accurately. There are considerable differences among pathologists in the grading of tumors, in part, a consequence of the persistent element of subjectivity in interpretation and, in part, a consequence of the lack of universal agreement on grading criteria and on terminology. Guidelines for identification and designation of tumor stage are also uncertain, not so much from the pathologist's standpoint, because here criteria are more or less well-defined, but rather because of practical errors in clinical staging. Assessment of multicentricity is made difficult by lack of any established system for recording this parameter, by the frequent failure of clinicians to distinguish between new tumors and "recurrent" tumors, and by the lack of accepted and standardized policies for the "random" biopsies that may prove essential to adequate characterization of multicentricity.

Staging

Clinical staging provides the basis for therapeutic recommendations and primarily depends on cystoscopy, biopsy (with efforts to obtain histologic evidence of the relationship of tumor to bladder muscle) and bimanual examination under anesthesia. 14 Intravenous pyelography, cystography, lymphangiography and arteriography also play an adjunctive role in determining the depth of infiltration and/or regional extension of tumor, but the former are the most used and useful parameters. The error between the clinically estimated stage and the pathologically determined stage is illustrated in a series of patients treated by radical cystectomy with pelvic lymph node dissection without prior irradiation in whom clinical staging was based on cystoscopy, biopsy, bimanual examination under anesthesia and intravenous pyelography. 15 (Fig. 2.) There is an obvious tendency to understage tumors. This clinical error is of greatest practical significance in patients with tumors judged to be superficial, since treatment decisions are usually vastly different for patients with superficial versus deeply infiltrating tumors. In any event, errors in clinical staging may lead to erroneous treatment decisions, which muddy the evaluation of therapy and the causes of treatment failure.

Treatment and Results

The treatment of bladder cancer may in-
volve irradiation, surgery, chemotherapy and, not uncommonly, various combinations of these three modalities. Furthermore, a variety of observations point to immunologic relationships between host and bladder tumor, which may ultimately prove useful in defining programs of immunotherapy. At the present time, however, the immunotherapy of bladder cancer is an unproved and experimental procedure.

Papilloma

For the patient with papilloma (Grade I papillary carcinoma), endoscopic resection and/or fulguration is the procedure of choice. This effectively removes the existing tumor or tumors, but offers no assurance regarding new lesions; the latter develop in roughly one-third of patients with a solitary tumor and two-thirds of those with initially multiple lesions. Although the five-year life expectancy of patients with papilloma so managed is the same as that of individuals of comparable age without papilloma, follow-up cystoscopy at three-six month intervals is advised indefinitely, not only because of the varying and unpredictable development of new lesions, but because of a 10-20 percent risk of developing frank bladder cancer.

Intravesical chemotherapy with a variety of substances, especially the alkylating agents, thiotepa or epodyl, has had an apparently salutary effect on existing papillomas and/or the prevention of new lesions, although satisfactory controlled studies of these and other agents have yet to be conducted.

In rare instances, the papilloma formation is so diffuse or so rapid that endoscopic treatment is impractical if not impossible. Suprapubic excision and fulguration, definitive irradiation (external or intracavitary) or total cystectomy have been variously employed but have proved less than optimal solutions.

Low-Grade Superficial Cancer

For patients with low-grade cancers of the O and A category, endoscopic treatment is preferably utilized. Such treatment has a high probability of controlling existing lesions, a low morbidity and mortality, and preserves urinary and sexual

| Clinical Stage | No. of Patients | Pathological Stage |
|----------------|----------------|-------------------|
| IS             | 7              | A                 |
| A              | 17             | B_1               |
| B_1            | 42             | B_2               |
| B_2            | 39             | C                 |
| C              | 26             | D_1               |
| D_1            | 6              |                   |
| **Total**      | 137            |                   |

**Table:** Comparison of the preoperative clinical estimate of tumor stage and the postoperative pathologic definition of tumor stage in 137 patients with bladder cancer treated by radical cystectomy, with bilateral pelvic lymph node dissection, and without irradiation.
functions. Unfortunately it offers no prophylaxis against new lesions and not inconceivably might augment them, although evidence is lacking.

Five-year survival rates are approximately 70 percent for patients with low-grade Stage A tumors and 30-40 percent for patients with low-grade Stage B tumors treated by transurethral resection; thus, such treatment seems to have a favorable influence on survival, although the patient has a significantly lower life expectancy as a consequence of the neoplasm.15,16 However, whether diminished survival is due to the failure of the treatment to control the original tumor or to the development of new lesions (multicentricity in time) is undefined.

Although transurethral resection clearly has the capacity to control focal low-grade, low-stage tumors, the prospects of success diminish as tumor grade and tumor stage increase. This fact and the feature of multicentricity in time, space or both, provide the basis for what may loosely be termed, the "aggressive" treatment of the disease. The term as used in this discussion includes full-course radiation therapy, or total or partial cystectomy, or combined cystectomy and irradiation. Partial cystectomy (segmental resection) in highly selected patients seems to control a solitary high-stage bladder cancer as well as total cystectomy. Its weaknesses—namely the possibility of tumor spillage and new tumor formation in the residual bladder — are offset by reduced operative mortality, greater functional preservation and the meticulous case selection. Selecting patients for earlier "aggressive" treatment, that is, those with low-grade, low-stage tumors destined to do poorly with transurethral resection, is a principal persisting problem in the conservative treatment of this disease. Some of the significant selection factors appear to be (1) the appearance of new lesions of higher grade, (2) the concurrence of in situ carcinoma, (3) the existence or appearance of certain karyotype changes, (4) host immunologic responses, (5) the loss of A, B, O antigens from tumor cells and, (6) evidence of more than minimal muscle invasion.20-22,27,31

Lymphatic and blood vessel invasion with the sequelae of regional lymph node and distant metastases seem to go hand-in-hand with muscle invasion—an observation not inconsistent with the fact that the size and number of bladder wall lymphatics increase progressively as the tumor extends from lamina propria more and more deeply into the muscle. An obvious weakness of focal treatment is the technical uncertainty of accomplishing adequate local excision of muscle infiltrating tumors. However, even the most aggressive of regional treatments may not control tumors that have demonstrably invaded either lymphatics or blood vessels.

In Situ Carcinoma

In situ carcinoma is a special problem for a variety of reasons. Whether it is a new entity or a newly recognized entity is, from the treatment standpoint, academic. Of importance to therapy is the fact that the lesion may easily be overlooked during cystoscopy and that its natural history is still largely uncertain.5 To what extent papillary and/or solid carcinomas of varying grades have their origins in these clinically recognized in situ carcinomas and the length of the natural period of evolution are largely unknown. Furthermore, if all clinical cancers have such a clinically recognizable in situ phase, are such phases identical or do they have features that anticipate the "end product"?

A working approach to such questions is to treat in situ cancer as one does low-stage cancer, which it indeed is, applying focal treatment to focal lesions and radical treatment to the diffuse or multifocal ones, especially if the latter are rapidly or repeatedly recurrent and associated with in situ cancer in the prostatic urethra. There is justifiably wide divergence of opinion in this area but, at the least, the presence of identifiable carcinoma in situ indicates the need for increased vigilance to detect new lesions (i.e., multicentricity in time) and unrecognized infiltration.

High-Grade and/or High-Stage Tumors

Although successes with the transurethral treatment of high-grade or deeply infil-
trating tumors (B2, C) have been recorded, they are more or less anecdotal and fortuitous, providing little practical argument against the aggressive treatment of such lesions. Over the past 20 years, experience with radiation therapy alone, cystectomy alone, and preoperative irradiation with cystectomy has established the overall superiority of the latter in the management of these lesions. 9, 14, 15, 32 The available data suggest that combination treatment has reduced the rate of local (pelvic) recurrences without appreciably reducing the rate of distant metastases. Furthermore, the favorable impact of combined treatment has been greatest in patients with high-stage but low-grade lesions and especially in those whose tumors have been down-staged as a result of preoperative irradiation.

In sum, preoperative irradiation with cystectomy has raised the five-year survival rate of patients with Stage B2 and C cancers to the 40-50 percent range, from a level of about 20 percent with either irradiation alone or cystectomy alone. This has been accompanied by a 50 percent reduction in pelvic recurrences to about 15 percent. Of the patients who die within the first five years postcystectomy, 60-70 percent die with distant metastases, principally to bone, lung and liver. 32 Interesting, and by no means fully explained, is the observation that preoperative irradiation has not improved the survival rate of patients with low-stage tumors in whom multicentricity in space or time or both has provided the indication for cystectomy. For these patients, the five-year survival rate postcystectomy, with or without preoperative irradiation, remains in the 50-60 percent range.

Furthermore, a variety of specific programs of preoperative irradiation have been employed in conjunction with radical cystectomy, with or without lymph node dissection, showing more or less similar results. Does this mean that lymph node dissection does not materially affect survival, or does it indicate that appropriate programs of preoperative irradiation may sterilize small metastatic deposits in the regional lymph nodes? Although uncertain, there is circumstantial evidence to support the latter possibility. It is clear that lymph node dissection has the capacity to control minimal nodal metastases in some 10-20 percent of patients and that this figure has not been altered by any of the preoperative irradiation regimens explored thus far. It is safe to conclude that the optimal program of preoperative irradiation with cystectomy has yet to be established.

At the present time, the indications for aggressive treatment — i.e., cystectomy with adjunctive irradiation — may be summarized as follows:

1. Low-stage tumors (O, A, B) that are:
   a. multicentric in time and/or space at a rate making conservative treatment impossible or impractical,
   b. high-grade tumors,
   c. diffuse in situ cancers.

2. High-stage tumors (B2, C) not suitable for segmental resection because of multicentricity in time and/or space or because of proximity to bladder neck.

3. Selected metastatic tumors — i.e., those so staged because of adjacent organ invasion (prostate, vagina) or because of limited lymph node metastases.

Chemotherapy may ultimately play an important role in the management of patients with bladder cancer. As previously mentioned, there is already some evidence of its therapeutic as well as prophylactic value in the intracavitary use of alkylating agents in patients with bladder papilloma.

In patients with multicentric low-grade and/or low-stage tumors, intracavitary therapy with alkylating agents (adriamycin, bleomycin, mitomycin C) and others is under clinical exploration.

In patients with deeply infiltrating tumors subjected to “aggressive” treatment programs, the evidence is already clear that distant metastases unrecognized at the time of treatment are the principal cause of treatment failure. Systematic, disease-oriented, Phase II clinical trials have demonstrated the significant activity of cis-diammine dichloride platinum and or adriamycin; the incorporation of these and other agents into adjunct chemotherapy programs for high-risk patients
is another logical area for clinical exploration.17,18

Tumor multicentricity in space and/or time is a well-known feature of urothelial tumors, and a well-recognized, although poorly quantitated, cause of treatment failure. It is poorly quantitated in part because the term "recurrent bladder tumor" is used to encompass both the failures of original treatment and the failures due to new tumor formation. Approximately five percent of patients undergoing cystectomy for bladder cancer ultimately develop a urothelial lesion in one or both upper urinary tracts. Close to 10 percent of patients undergoing cystectomy for bladder cancer have in situ carcinoma in the distal ends of one or both ureters at the time of cystectomy. Between five and 10 percent of male patients undergoing cystectomy for bladder cancer have or will develop an independent carcinoma of the urethra.31 All of these risks of multicentricity are demonstrably greater in patients with multicentric bladder tumors, as might logically be anticipated. There is no established prophylaxis for urothelial tumors. Retinoids are logical candidates for clinical exploration in this regard.34 Urethrectomy in males undergoing cystectomy for bladder cancer is a logical prophylaxis. Frozen section of the ends of the ureters prior to intestinal diversion is also a useful precaution. For the rest, careful follow-up is the best that we can currently advise.

Future Prospects

Prospects for improvement in the bladder tumor problem rest with the following:

(1) Improved prophylaxis as the causes of bladder tumors are defined and either eliminated or circumvented.

(2) Earlier diagnosis through continued efforts at public and professional education and application of existing (e.g., cytology) and yet to be defined (e.g., tumor markers) diagnostic tests to appropriately selected high-risk populations.

(3) Improved treatment selection based on refinements in clinical staging, which will reduce clinical staging errors, and on the development of methods for tumor anticipation, which will justify earlier aggressive treatment of the high-risk patient.

(4) The further development and optimal use of multimodality therapy — surgery, irradiation, chemotherapy and immunotherapy — to reduce or eliminate the adverse impact of iatrogenic factors or of pre-existing metastases on treatment results.

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CORRECTION

Due to an editorial oversight, an unrevised version of “Differential Diagnosis of Upper Gastrointestinal Bleeding in Patients with Cancer,” by Paul Sherlock, M.D., and Sidney J. Winawer, M.D., containing a number of errors, was inadvertently printed in the January/February 1978 issue of Ca (Vol. 28, No. 1).

Reprints of Dr. Sherlock’s article, with the necessary corrections made, will be available soon as a Professional Education Publication of the American Cancer Society. Our apologies.

The Editor