Demographics and Epidemiologic Considerations

The American Cancer Society projects that bladder cancer will be diagnosed in 54,400 Americans this year (39,500 men and 14,900 women) and will account for 12,500 deaths (8,400 in men and 4,100 in women).1 As such, bladder cancer ranks as the fourth leading cause of cancer and seventh leading cause of cancer death in men in the United States. It is the eighth leading cause of cancer and tenth leading cause of cancer death in women. Internationally, bladder cancer accounts for approximately 200,000 to 250,000 new diagnoses annually and approximately 120,000 cancer deaths (Professor G. Steinbeck, Karolinska Hospital, Stockholm, Sweden, unpublished data).

Bladder cancer may be even more of a public health issue when one considers its true prevalence and issues of survival. Most bladder cancers present as “superficial” disease and are likely to recur in 50% to 75% of instances.2 Thus, the ongoing prevalence of bladder cancer far exceeds its primary incidence.

Moreover, although only 15% to 25% of these cases are likely to progress, an additional 25% of cases are “invasive” at initial presentation.3 Because at least 50% of these patients apparently already have occult metastases and will die of their disease,4 the physical, emotional, and economic costs of bladder cancer, both superficial and invasive, are substantial.

Epidemiologically, bladder cancer was one of the earliest cancers in which carcinogens were found to play a role in causing the disease. As early as 1895, Rehn observed an association between exposure to aromatic amines and bladder cancer in factory workers.5 Similar associations were subsequently identified in both experimental animal models6 and humans working in industries that permitted exposure to aromatic amines.7

Over the years, many studies have described an association between cigarette smoking and bladder cancer.8 Some reports have suggested that 50% of bladder cancers in men would not occur if the men did not smoke cigarettes, describing an increased risk among smokers of at least two- to fourfold.9 The number of cigarettes smoked, degree of inhalation, type of tobacco used (blond versus black), use of cigarette filters, and cessation of smoking each has been shown to have a relationship with development of bladder cancer.9,10

Traditional associations between the development of bladder cancer and exposure to artificial sweeteners or coffee have not been well founded. These agents currently are considered less likely to have a relationship.11 Moreover, the actual incidence of transitional cell cancer resulting from exposure to aromatic amines is probably relatively small and therefore more important from a historical and epidemiologic standpoint than from a soci-
etal standpoint. In contrast, the association between transitional cell cancer and cigarette smoking is highly important.

Several host factors have been suggested to play a role in the development of bladder cancer. These associations are based upon the ability to detoxify substances that may otherwise act as carcinogens. For example, the acetylation of aromatic amines may prevent their carcinogenic action. Thus, “slow” acetylators may have a higher incidence of bladder cancer than do “rapid” acetylators. Similarly, individuals with defects in the P450 cytochrome oxidase system may not detoxify carcinogens so that they remain active in the induction of neoplastic transformation. Unfortunately, the clinical application of these observations in identification of patients who might be at increased risk if exposed to environmental carcinogens has not received widespread attention.

Diagnosis of Bladder Cancer

Signs and Symptoms

The most common sign of the possible presence of bladder cancer is hematuria. This may be either visible grossly or apparent only on microscopic urinalysis. The degree of hematuria is not related to the volume of tumor or its stage.

Hematuria does not necessarily indicate that a cancer is present; inflammatory conditions, stone disease, and other conditions also may produce bleeding in the urinary tract. The microscopic appearance of some red blood cells in the urine (generally less than 3 to 5 per high-power field) may be considered normal in many individuals. In addition, instances may occur in which a urinalysis positive for blood may be sporadic even in patients with bladder cancer.

Some have therefore suggested that only patients who have persistently more than 3 to 5 red blood cells per high-power field on microscopic examination, or on at least two microscopic examinations, be evaluated for the possibility of bladder cancer. Others, however, consider this a matter of judgment and may proceed with noninvasive approaches in assessing their patients for bladder cancer although the yield in a screening mode may be low.

The appearance of gross hematuria or persistent microscopic hematuria should prompt an evaluation of the entire urinary tract, which should include radiologic imaging (ultrasonography or intravenous pyelography, or both), urinary cytologic studies, and cystoscopy.

Bladder cancer is usually asymptomatic. When gross hematuria occurs, it is usually referred to as “painless.” Occasionally, however, a patient may complain of severe irritability (a strong sense of urgency or severe burning on urination), which may reflect the presence of a form of bladder cancer known as carcinoma in situ. Generally, however, exophytic transitional cell cancer, even if invasive of the bladder wall, does not produce voiding symptoms.

Evaluation

Imaging Studies

The initial evaluation of individuals with either gross or microscopic hematuria is imaging of the urinary tract. Ultrasonography is useful in detecting the presence of a renal mass and in distinguishing between solid and cystic renal masses. Although ultrasound does not detect urothelial cancers in the renal pelvis, it is useful in distinguishing between soft tissue filling defects and stones. Moreover, it also may identify the presence of dilation of the upper urinary tract. This may reflect an obstructive transitional cell cancer either in the ureter or in the bladder as a muscle-invasive cancer at the vesicoureteral junction.

Intravenous pyelography is more useful than ultrasound in visualizing the profile of the urinary tract and in identifying the presence of any radiolucent filling defect in the calyces, renal pelvis, ureter, or bladder. Intravenous pyelogra-
phy is more sensitive in detecting such filling defects in the upper tract than it is in the bladder. For the latter, both filling and emptying aspects in the cystogram phase of the intravenous pyelogram may help in the identification of such radiolucent filling defects. However, the apparent absence of such defects in these images does not exclude the presence of a bladder cancer.

Computed tomography (CT) scanning and magnetic resonance (MR) imaging are not usually used as initial studies for the diagnosis of transitional cell cancer of either the upper tracts or the bladder. Occasionally, they may help to assess whether a particular upper tract or bladder tumor may be invasive of the kidney, ureter, or bladder wall, respectively. These studies lack sufficient accuracy, however, for reliable staging of these lesions.

Cytologic Study

Cytologic study of urine is an important adjunct in the diagnosis of transitional cell cancer. Voided urine specimens should be obtained for cytologic evaluation in patients with hematuria. Cytologic study of urine is important in the diagnosis of transitional cell cancer in patients who have irritative voiding symptoms and negative results of urine cultures. Unfortunately, urinary cytologic study has poor sensitivity for low-grade transitional cell cancers and cannot be used to exclude the presence of a malignancy. A positive finding in a urinary cytologic study, however, is highly predictive of the presence of a high-grade transitional cell cancer.

Tumor Markers

Recent reports have proposed the presence of “markers” in voided urine that may help in the detection of transitional cell cancer. Interest in the use of such markers has been based on a desire to avoid the need for cystoscopy for surveillance and the fact that cytologic study of urine is not sensitive enough to detect low-grade transitional cell cancer.

An assay that has attracted attention recently is the bladder tumor antigen (BTA) test and its BTA stat and BTA TRAK derivatives. The BTA test strip detects substances released from the extracellular matrix in the presence of bladder cancer. The BTA stat and BTA TRAK tests detect a protein called human complement-related H factor, possibly produced by malignant urothelial cells and thought to be involved in the prevention of cell lysis by a complement-mediated pathway.

Unfortunately, these BTA tests do not appear to have sufficient sensitivity to detect most low-grade malignancies and appear to be inferior to urinary cytologic evaluation in detecting high-grade malignancies and carcinoma in situ. Moreover, their specificity may be affected substantially by urinary infections, stone disease, nephritis, inflammatory conditions, and instrumentation of the urinary tract, suggesting that their clinical application in detecting bladder cancer may be unreliable.

Another test that has engendered strong interest is an assay for nuclear matrix protein (NMP) 22, which is derived from nuclear matrix protein mitotic apparatus. The sensitivity of NMP22 for low-grade disease appears to be far better than that of either the BTA test or urinary cytology (approximately 70% versus 50% or 30% to 40%, respectively). However, 25% to 30% of low-grade tumors are not detected by this assay.

Telomerase is another substance currently being assessed for its potential usefulness in diagnosing transitional cell cancer and in monitoring for recurrence. Telomerase is a ribonucleoprotein enzyme responsible for production of telomeres, which are DNA sequences that occupy the ends of chromosomes and protect their integrity during DNA replication and may be involved in the immortalization of a cancer cell.
Determination of telomerase level in voided urine has been found to have an overall sensitivity of more than 80% for the detection of urothelial malignancies (79% sensitivity for low-grade disease and 87.5% sensitivity for high-grade cancer) and an overall specificity of 70%. Telomerase testing may have more promise for clinical application than does the BTA test and its derivatives based on both sensitivity and specificity. It also may have more clinical promise than does NMP22 testing because it does not rely on the interpretation of a test point that falls within a broad distribution of overlapping data with a movable threshold level.

Recent studies have suggested that the assessment of urine for fibrin or fibrinogen degradation products by immunoassay may be useful in indicating the presence of bladder cancer. The sensitivity of this test in detecting low-stage (Ta, T1) disease was 62%, and that for low-grade disease (G1 or G2 on a scale of G1 to G4, with G4 being the most poorly differentiated) was 61% to 64%. Detection of muscle-invasive disease was 100% (but in only 12 patients, in only 75% of whom cytologic study detected disease), and that of high-grade (G3, G4) disease was 86%.

Although fibrin or fibrinogen testing has been suggested to be better than urinary cytologic study, it failed to detect one-third of cases of carcinoma in situ and approximately 15% of cases of high-grade disease, instances in which it is important that the sensitivity of detecting bladder cancer approach 100%. In addition, conditions other than cancer affected the specificity of this assay.

Assays for hyaluronidase and hyaluronic acid, which are associated with induction of angiogenesis, and assessment of selected tumor antigens are other means proposed to serve as markers for detection of bladder cancer. Each of these has shown enhanced sensitivity in detecting urothelial cancers, but each still requires further testing to identify guidelines by which it most effectively may be applied clinically and validation to determine its applicability in individual patients.

Direct Visualization and Pathologic Evaluation

Direct visualization is important in characterizing the appearance of radiolucent filling defects identified on imaging studies. Ureteroscopy of the upper tracts and cystoscopy of the bladder can be used to diagnose the presence of a papillary or a solid transitional cell cancer, establish whether more than one focus of disease is present, identify location, and visualize any additional abnormal mucosal areas. When a ureteroscope cannot be passed, sonography may be useful in distinguishing a soft tissue filling defect from calculus disease. A brush biopsy of such lesions may then help in confirming the diagnosis of an upper urinary tract urothelial malignancy.

After each of these maneuvers, the sine qua non of diagnosis of transitional cell cancer is the evaluation of the pathology of the resected tissue specimen. Therefore, any exophytic tumor should be resected both for treatment and for establishment of diagnosis and prognosis. Assessment of the grade and the depth to which the tumor has penetrated the bladder wall allows classification and staging of the tumor, estimation of its prognosis, and determination of the type of therapy (other than the transurethral resection already done) that may be needed.

Biopsy samples also may be taken either of any endoscopically abnormal area of the urothelium or at random both in the bladder and in the prostatic urethra to determine whether more diffuse involvement of the mucosa by malignant cells is present. The presence of “flat” carcinoma in situ may substantially influence the course of therapy and the prognosis.
Traditionally, bladder cancer has been characterized as either superficial or invasive (Fig. 1). \(^{27}\) Superficial cancers are papillary tumors confined to the mucosa (Ta), papillary (and occasionally nodular) tumors that infiltrate the lamina propria (T1), and nonexophytic diatheses known as carcinoma in situ that replace or undermine the normal mucosa and involve focal or diffuse areas of the urothelium (Tis) (see Fig. 4, p. 277).

Recent reports have suggested prognostic distinctions among tumors that penetrate the lamina propria only microscopically (stage T1a), those that penetrate more extensively up to the layer of the muscularis mucosae (stage T1b), and those that penetrate through the muscularis propria into the perivesical soft tissue either microscopically (stage T3a) or extensively (stage T3b). These distinctions are a recent change in the World Health Organization (WHO) classification system, which now combines all muscle-invasive tumors into one category (stage T2) rather than maintaining the separation that formerly had characterized the staging system (stage T2 for superficial invasion and stage T3a for deep muscle invasion). The involvement of lymph nodes is designated by the N category, and involvement of adjacent structures is categorized as stage T4. This format implies a simple pattern of sequential development according to which early cancers appear as lower stages, then progress to higher stages in sequence. However, this is not necessarily what characterizes the different forms of bladder cancer seen clinically. Rather, a variety of pathways that do not necessarily occur in sequence but that are possibly interrelated may more accurately reflect the biology of the different forms of bladder cancer.

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### Biology and Staging of Bladder Cancer

Traditionally, bladder cancer has been characterized as either superficial or invasive (Fig. 1). \(^{27}\) Superficial cancers are papillary tumors confined to the mucosa (Ta), papillary (and occasionally nodular) tumors that infiltrate the lamina propria (T1), and nonexophytic diatheses known as carcinoma in situ that replace or undermine the normal mucosa and involve focal or diffuse areas of the urothelium (Tis) (see Fig. 4, p. 277).

Recent reports have suggested prognostic distinctions among tumors that penetrate the lamina propria only microscopically (stage T1a), those that penetrate more extensively up to the layer of the muscularis mucosae (stage T1b), and those that penetrate through
the muscularis mucosae to involve extensively the deeper portions of the lamina propria (stage T1c). These distinctions have not been incorporated into the commonly accepted staging system.

Invasive cancers include generally nodular tumors that infiltrate the muscularis propria or the serosa (T2 to T3).
with a corresponding increased likelihood of the development of metastatic disease (see Fig. 5, p. 279).

Prognostic distinctions have been observed among tumors involving the prostate that have remained mucosally confined in the prostatic urethra versus those that have extended into the ducts but remain confined to the mucosa versus those that have penetrated into the stroma. It has been suggested that distinctions be made in staging these cancers, but such distinctions have not yet been incorporated into the formal staging system.

Although other factors, such as tumor grade, configuration, architecture of infiltration (papillary or solid, broad front
or tentacular), abnormalities at sites other than the primary tumor (e.g., carcinoma in situ), vascular/lymphatic involvement, and various chromosomal abnormalities (e.g., p53 expression, RB deletions, epidermal growth factor receptor expression, E-cadherin expression, high level of Ki-67), also affect prognosis, they have not been incorporated into the standard staging schema.

A staging schema based on the progressive depth of involvement of the bladder wall by the tumor has been used to assign treatment and to assess outcomes and prognosis. The portrayal of this schema has implied a sequence of stages in cancer development (Fig. 1). Analysis of the prognosis of various forms of bladder cancer suggests, however, that this staging schema may not adequately reflect the true biologic nature of different forms of the disease.

Conceivably, a more accurate representation of the biology of bladder cancer might show a variety of distinct but interrelated pathways by which different forms of bladder cancer might develop and progress (Fig. 2). This concept is supported not only by clinical observations but also by recent findings of molecular distinctions between various types of bladder cancer that coincide with the hypothesis of separate pathways to account for the development of distinct tumor diatheses (Fig. 3). Ultimately, molecular profiles may be used to complement the standard histopathologic staging system traditionally used to characterize bladder cancers and assess their prognosis.

**SUPERFICIAL BLADDER CANCER**

The category of superficial transitional cell cancers includes papillary tumors confined to the urothelium (stage Ta), papillary and papillonodular tumors that have penetrated the basement membrane and infiltrated into the submucosal lamina propria (stage T1), and tumor diatheses that replace normal urothelium but remain in the plane of the mucosa (flat carcinoma in situ; stage Tis) (Fig. 4).

The likelihood of recurrence of each of the papillary types of tumor ranges from 50% to 75% and increases with multiplicity of disease and size of the presenting tumors. This pattern of behavior may reflect one or a combination of the following factors: incomplete resection of the initial tumor(s), implantation of tumor cells as a result of resection, or the presence of cancer cells at more diffuse mucosal sites, reflecting either the presence of stem cells or the existence of a neoplastic field effect in which urothelial involvement was not visible at the time of resection.

Prognostic distinctions between the two forms of papillary bladder cancer are based upon the likelihood of their progression. Mucosally confined tumors (stage Ta) have only a 2% to 4% likelihood of progression. In tumors that have penetrated the lamina propria (stage T1), however, the likelihood of progression is 20% to 30%. In each case, the likelihood of progression is greater the higher the grade of the disease. Stage Ta tumors are high grade in only 1% to 3% of cases. Most often, they are low to moderate grade. In contrast, stage T1 tumors may be high grade in 30% to 50% of cases and are rarely low grade.

The likelihood of progression of these cancer diatheses is also greater in the setting of concomitant flat carcinoma in situ either next to or at sites distant from the exophytic lesions. In addition, although superficial tumors appear to have papillary architecture, those that may have penetrated the lamina propria may occasionally assume a more papillonodular configuration. This, too, may be associated with a greater likelihood for the development of progressive disease and is more commonly seen in high-grade cancers and in association with carcinoma in situ.
The distinctive courses the various types or stages of superficial cancer may follow suggest that a pattern of different pathways rather than a schema of sequential changes (stages) may more accurately characterize the development of these tumors and more precisely represent their varying biologic potentials.29

Thus, low-grade papillary tumors confined to the mucosa appear to have only an increased risk of recurrence and almost no risk of progression. These tumors may therefore reflect primarily a proliferative diathesis. Although transurethral resection theoretically restores the epithelium to normal as visualized endoscopically, field changes may occur that represent either multiple areas of neoplastic transformation or seeding by stem cells, all of which share the same neoplastic characteristics.40

High-grade tumors are more common among those that have penetrated the lamina propria and are also commonly seen in association with flat carcinoma in situ.35 This suggests a different pathway of development, in which neoplastic transformation has resulted not only in a proliferative diathesis but also in the appearance of cells with higher nuclear:cytoplasmic ratios, irregular nuclear shape, clumped chromatin, and a greater invasive capability, to which the term dysplasia may be applied.29

Fig. 4. Superficial bladder cancer. This category includes tumors that remain confined to the mucosa and extend in papillary form into the lumen of the bladder (A), those that have penetrated the lamina propria and may assume a papillary form or occasionally a more papillonodular form (B), and those that maintain the normal plane of the urothelium while replacing the urothelium or undermining it in the form of carcinoma in situ (C). Recent reports suggest that the extent of lamina propria infiltration may be associated with a specific prognosis of disease. Thus, only slight microscopic penetration, as shown here, may represent a less aggressive diathesis than that of disease that has penetrated to the muscularis mucosae, both of which may be less aggressive than those forms of disease that have penetrated the lamina propria deeply up to the level of the muscularis propria.
Dysplasia is used to imply a process whereby a more aggressive cancer diathesis has occurred, as reflected in the genesis morphologically of higher grade cells with the biochemical ability to invade and metastasize. The high-grade cells produced in this putative pathway of cancer development may proliferate to generate either a papillary higher grade tumor that infiltrates the lamina propria or a flat carcinoma in situ with cells that both undermine the normal urothelium and penetrate the bladder wall microscopically, ultimately assuming a more nodular configuration.

Recent studies have identified distinct genetic changes in association with these neoplastic diatheses (Fig. 3), thereby supporting the concept of disparate but interrelated pathways of tumor development. For example, tumors with changes in chromosome 9 appear to manifest a proliferative diathesis with little likelihood of progression. In contrast, tumors with changes in chromosome 17p (with enhanced expression of p53) generally appear as high-grade lesions and as flat carcinoma in situ. Such tumors may reflect a more dysplastic diathesis with a greater likelihood for invasion and progression. Moreover, within each of these categories, expression of p53 appears to indicate a more aggressive biologic behavior within each stage of disease.

Invasive Bladder Cancer

Transitional cell cancer that has penetrated into the muscularis propria is categorized as invasive. Although tumors that penetrate only the superficial portion of the muscularis appear to have a better prognosis than do those that penetrate more deeply, it is difficult to distinguish these clinically. Such distinctions usually are made retrospectively on analysis of partial or total cystectomy specimens.

Characteristics occasionally found in tumors that infiltrate more superficially are a more papillary configuration, penetration of the bladder wall in a “broad front” pattern, and involvement of the bladder wall lymphatics and vasculature in one-third of cases. In contrast, tumors that penetrate the muscularis more deeply usually have a solid or nodular configuration, often appear to invade in tentacular fashion, and involve the bladder wall lymphatics and vasculature in two-thirds of instances. These two types of tumor have not yet been distinguished molecularly. Possibly, those that penetrate only superficially may arise from high-grade superficially invasive papillary tumors whereas those that penetrate more deeply and have a nodular configuration arise from flat carcinoma in situ.

Tumors that penetrate the muscularis only superficially may be associated with a lower incidence of metastases than are those that penetrate more deeply. Whether this results from the detection of cancer early as opposed to late in its history or reflects the intrinsic biologic capabilities of the cancer is unknown.

Most tumors that penetrate more deeply are at this stage of disease at the initial diagnosis. At least 50% of these may have occult metastatic disease at initial diagnosis, and these present with gross metastases, often within 2 years of diagnosis despite prompt aggressive regional intervention. This suggests a symptomatically “silent” history of these cancers at the onset of their development and during their early course; it may also reflect a more aggressive intrinsic biology from the outset that predicts progression.

Flat carcinoma in situ is an entity that may be considered more appropriately in conjunction with invasive bladder cancer. Indeed, it was first identified in association with muscle-invasive cancers in cystectomy specimens. Since then, carcinoma in situ has been associated biologically with a potentially more aggressive cancer diathesis.

Some have suggested that solid, deeply invasive cancers originate in foci
of flat carcinoma in situ. Others have observed abnormalities in chromosome 17p, with increased expression of p53, in both flat carcinoma in situ and more aggressive forms of muscle-invasive cancers, suggesting a possible relationship between these entities in the generation of nodular, deeply invasive, more aggressive disease.

Treatment of Bladder Cancer

SUPERFICIAL BLADDER CANCER

The same transurethral resection done to obtain tissue for the diagnosis of superficial bladder cancer is generally sufficient in treating mucosally confined disease, whether only one tumor exists or several tumors are present. The standard approach in the management of patients who have been diagnosed with stage Ta superficial disease is surveillance. Generally, urinary cytologic study is done and cystoscopy is performed every 3 months. Recurrence, which may be expected in 50% to 75% of cases but is usually of the same grade and stage, can then again be successfully treated by repeat transurethral resection.

In addition, intravesical instillation of substances such as thioteca, mitomycin-C, and doxorubicin may be used to prolong the interval to recurrence or eliminate recurrences altogether. Although approximately 40% to 50% of these cases appear to respond to such intravesical treatments, the maximum benefit of these agents in preventing recurrence during long-term follow-up is less than 10% compared with those who receive no adjunctive intravesical therapy.

Superficial tumors that are high grade and have infiltrated the lamina propria (stage T1) or are accompanied by flat carcinoma in situ are at particular risk not only for recurrence but also for progression. Moreover, when stage T1 disease is diagnosed, additional resection may uncover residual disease in 30% to 35% of cases. It is equally important to evaluate urinary cytology after resection of these lesions to assess the possibility of residual disease at the primary tumor site or the presence of carcinoma in situ elsewhere in the bladder.

In these instances, and in those in which flat carcinoma in situ is the only form of malignancy present, treatment with intravesical bacille Calmette-Guérin (BCG) may be valuable. Various re-
ports have described a 70% response rate. Although irritative symptoms, hematuria, and occasional BCGosis (and death, but only in the setting of traumatic catheterization or active bleeding) have been reported, these may occur only in a few patients, and treatment is generally well tolerated. In each instance, long-term surveillance needs to be done not only because of the risk of recurrence but also, more importantly, because of the risk of progression.

Whether BCG treatment prevents ultimate progression is controversial. Recent reports have suggested that this may not be the case. However, the overall short-term benefit may be worthwhile because some suppression or elimination of cells not endoscopically apparent may prolong the clinically disease-free interval in the individual patient. Therefore, the standard of practice has been to use intravesical BCG therapy, especially because such treatment may have benefit and is generally well tolerated. Patients who have persistently positive findings of cytologic study despite intravesical treatment can be considered for cystectomy to cure the disease at a stage at which the cancer is still contained within the bladder.

MUSCLE-INVASIVE BLADDER CANCER

Radical cystectomy remains the standard treatment for muscle-infiltrative bladder cancer. Once considered a procedure that seriously affected the patient’s quality of life, it is now a far more acceptable option because of the major advances made in urinary diversion. The creation of orthotopic continent reservoirs makes it possible for patients to recover near-normal voiding function if the urethra is not removed. If the entire lower urinary tract must be excised, the construction of similar reservoirs that can be catheterized improves appearance by avoiding the need for an external appliance.

Unfortunately, cystectomy is most effective in patients whose cancers have penetrated only superficially into the muscularis. Because at least 50% of patients with deep muscle invasion are likely to have metastases within 2 years of surgery, cystectomy will fail in at least this many patients. Failure occurs in up to 70% to 80% of patients with deeply invasive disease.

The same transurethral resection done to obtain tissue for the diagnosis of superficial bladder cancer is often sufficient for treating mucosally confined disease whether the patient has one tumor or several.

Because most patients with muscle-invasive disease are diagnosed with this form of disease at initial clinical presentation, two major objectives remain in approaching this form of bladder cancer. One is to identify a means by which bladder cancer may be diagnosed earlier, presumably before it metastasizes, and the other is to discover systemic regimens that may help in the cure of metastatic disease. Neither objective has been realized yet.

Some have suggested that screening individuals at risk for the development of bladder cancer by routine testing for microscopic hematuria may detect at an early stage those who might develop invasive bladder cancer. Evidence for the efficacy of this approach, however, and the cost savings that might be anticipated have not been convincing.

Although many regimens using combinations of chemotherapeutic agents have been studied, none has been shown ultimately to prolong survival. The initial results of three regimens—MVAC
methotrexate, vinblastine, doxorubicin, and cisplatin), CMV (cisplatin, methotrexate, and vincristine), and CISCA (cisplatin, cyclophosphamide, and doxorubicin)—have been promising, showing a prolonged interval of disease-free survival. The regimens have been used as both neoadjuvant and adjuvant therapy with the possibility that disease-free survival and cancer-specific survival might be enhanced.

Difficulties have been encountered in their use, however, because of toxicity, deleterious effects on quality of existence, inadequate patient compliance, delivery of insufficient intensity of drug doses, and failure ultimately to decrease cancer-specific death. Several new agents such as gemcitabine and paclitaxel may have promise in the treatment of metastatic bladder cancer. Trials to explore the use of these and other agents in combination with already established regimens are needed to show their efficacy.

Several protocols have been designed to incorporate the presence or absence of markers of potential aggressiveness of disease to determine the course of treatment. In one study, the expression of p53 (which indicates a defect in chromosome 17p and has been associated within each stage with more aggressive behavior by the cancer that expresses it) will be used to determine whether adjunctive chemotherapy should be administered after cystectomy in patients with muscle-infiltrative disease. The expression of p53 (which indicates a defect in chromosome 17p and has been associated within each stage with more aggressive behavior by the cancer that expresses it) will be used to determine whether adjunctive chemotherapy should be administered after cystectomy in patients with muscle-infiltrative disease. (J.P. Stein, MD, Norris Comprehensive Cancer Center, Los Angeles, CA; S. Lerner, MD, Baylor College of Medicine, Houston, TX; D.G. Skinner, PhD, Norris Comprehensive Cancer Center, Los Angeles, CA; unpublished data).

In another study, expression of p53 will be used to determine whether bladder-conservative approaches (extensive transurethral resection, radiation, and chemotherapy) can be used instead of cystectomy in treating muscle-infiltrative disease on the premise that cancers that do not express p53 may be less aggressive and therefore more amenable to more preservative treatments.

Each study may have some potentially considerable pitfalls. For example, the regimens of chemotherapy chosen may be ineffective in themselves but also specifically in those cancers that express p53; the full chemotherapeutic regimen may be difficult to deliver in compliance with protocol design; the p53 marker has not been fully validated as indicative of potential failure and may provide a misleading guidepost; controls may not be adequate to permit rigorous interpretation of results; and crossover treatments built into the protocol’s design may interfere with interpretation of effects on cancer-specific survival.

Each of these considerations individually and in the aggregate could compromise ultimate interpretation of results. These studies may, however, identify advantages of such marker-driven approaches.

The failure of cystectomy to cure so many patients with muscle-infiltrative disease has prompted some to assert that bladder-conserving approaches are equally efficacious. These protocols incorporate extensive transurethral resection, radiation therapy, and systemic chemotherapy. The use of extensive transurethral resection has been most effective in selected patients who have only superficial involvement of the muscularis. However, this group of patients also appears to have the greatest advantage with cystectomy, possibly because the intrinsic biologic potential of this form of the disease is less aggressive. Because the risk of recurrence and further progression may be high with transurethral resection, continued surveillance with consideration of the need for salvage cystectomy is critical in these patients.

Those who do not respond to this approach and then undergo salvage cys-
tectomy may be at no greater disadvan-
tage than those who undergo cystectomy
initially and are cured or ultimately fail
with metastatic disease. What would be
most important in this setting is the abili-
ty to identify those patients at risk for
progression who might still be at a cur-
able stage of disease. These patients
might be considered for aggressive treat-
ment initially.

**Conclusion**

Bladder cancer constitutes a variety of
diseases. Although most patients with su-
perficial cancers do not face a life-threat-
ening situation, many patients with mus-
cle-invasive disease unfortunately do.

Advances need to be made in both
categories. In the former, finding a means
of controlling disease, preventing recur-
rence, and preventing progression in the
small proportion of patients at risk is criti-
cal. Markers need to be developed that
are sufficiently sensitive and specific to be
used both for diagnosing cancer in popu-
lations at risk and in monitoring patients
for recurrence or for possible progression.

In invasive disease, the challenge is
to identify patients earlier, when disease
might be less advanced and more amenable
to regional cure. Identifying
systemic regimens that will effectively
treat patients with more advanced dis-
ease and permit approaches that may
preserve bladder function and avoid the
need for extensive surgery is equally im-
portant.

Advances in our understanding of
the biology of the various forms of blad-
ner cancer, the pathways that various
forms of bladder cancer may follow, the
role of specific chromosomal abnormali-
ties in determining these pathways, and
the means by which various treatments
based on these understandings may be
applied are important areas for further
investigation.

**References**

1. Landis SH, Murray T, Bolden S, et al: Cancer sta-
tistics, 1998. CA Cancer J Clin 1998;48:6-29.
2. Heney NM, Ahmed S, Flanagan MJ, et al: Superficial bladder cancer: Progression and recur-
rence. J Urol 1983;130:1083-1086.
3. Kaye KW, Lange PH: Mode of presentation of
invasive bladder cancer: Reassessment of the prob-
lem. J Urol 1982;128:31-33.
4. Prout GR Jr, Griffin PP, Shipley WU: Bladder
 carcino ma as a systemic disease. Cancer
1979;43:2532-2539.
5. Rehm L: Blasengeschwulste bei Fuchsin-
Arbeitern. Arch Klin Chir 1895;50:588.
6. Hueper WC, Wiley FH, Wolfe HD: Experimental production of bladder tumors in dogs
by administration of beta-naphthylamine. Hyg Tox
1938;20:46.
7. Case RAM, Hosker ME, McDonald DB, et al: Tumours of the urinary bladder in workmen
engaged in the British chemical industry. Role of
aryl benzidine, alpha-naphthylamine, and beta-
naphthylamine. Br J Intern Med 1954;11:75.
8. Morrison AS, Buring JE, Verhoeck WG, et al: An international study of smoking and bladder can-
cer. J Urol 1984;131:650-654.
9. Clavel J, Cordier S, Boccon-Gibod L, et al: Tobacco and bladder cancer in males: Increased
risk for inhalers and smokers of black tobacco. Int J Cancer 1989;44:605-610.
10. Vineis P, Esteve J, Hartge P, et al: Effects of
timing and type of tobacco in cigarette-induced
bladder cancer. Cancer Res 1998;48:3849-3852.
11. Ellwein LB, Cohen SM: The health risks of sac-
charin revisited. Crit Rev Toxicol 1990;20:311-326.
12. Cartwright RA, Glashan RW, Rogers HJ, et al: The role of N-acetyltransferase in bladder carci-
genesis: A pharmacogenetic epidemiological
approach to bladder cancer. Lancet 1982;2:842-845.
13. Mommsen S, Barfod NM, Aagaard J: N-acetyl-
transferase phenotypes in the urinary bladder car-
cinogenesis of a low-risk population. Carcino-
genesis 1985;6:199-201.
14. Bartsch H, Caporaso N, Coda M, et al: Carcinogen hemoglobin adducts, urinary muta-
genicity, and metabolic phenotype in active and
passive cigarette smokers. J Natl Cancer Inst
1990;82:1826-1831.
15. Varkarakis MJ, Gaeta J, Moore RH, et al: Superficial bladder tumor: Aspects of clinical pro-
gression. Urology 1974;4:414-420.
16. Badalament RA, Fair WR, Whitmore WF Jr, et al: The relative value of cytometry and cytology in
the management of bladder cancer: The Memorial
Sloan-Kettering Cancer Center experience. Semin
17. Sarosdy MF, deVere White RW, Soloway MS, et al: Results of a multicenter trial using the BTA test to monitor for and diagnose recurrent bladder cancer. J Urol 1995;154:379-383.
18. Sarosdy MF, Hudson MA, Ellis WJ, et al: Improved detection of recurrent bladder cancer using the Bard BTA stat Test. Urology 1997;50:349-353.
19. Droller MJ: Commentary on Sarosdy MF et al: Improved detection of recurrent bladder cancer using the Bard BTA test. J Urol 1998;159:601.
20. Soloway MS, Briggman V, Carpinito GA, et al: Use of a new tumor marker, urinary NMP22, in the detection of occult or rapidly recurring transitional cell carcinoma of the urinary tract following surgical treatment. J Urol 1996;156:363-367.
21. Stamper DS, Carpinito GA, Rodriguez-Villanueva J, et al: Evaluation of NMP22 in the detection of transitional cell carcinoma of the bladder. J Urol 1998;159:394.
22. Lin Y, Miyamoto H, Fujinami K, et al: Telomerase activity in human bladder cancer. Clin Cancer Res 1996;2:929-932.
23. Kavaler E, Landman J, Chang Y, et al: Detecting human bladder carcinoma cells in voided urine samples by assaying for the presence of telomerase activity. Cancer 1998;82:708-714.
24. Schmetter BS, Habicht KK, Lamm DL, et al: A multicenter trial evaluation of the fibrin/fibrinogen degradation products test for detection and monitoring of bladder cancer. J Urol 1997;158:801-805.
25. Lokeshwar V, Phan H, Obeck C, et al: HA-HAase urine test for detecting bladder cancer and evaluating its grade. J Urol 1997;157(Suppl):341.
26. Huland E, Huland H, Meier T, et al: Comparison of 15 monoclonal antibodies against tumor-associated antigens of transitional cell carcinoma of the human bladder. J Urol 1991;146:1631-1636.
27. Hall RR, Beynon LL, Horwitz A, et al: Urology and the TNM classification. Lancet 1988;1:1145-1146.
28. Hermanek P, Sobin LH: UICC-International Union Against Cancer TNM Classification of Malignant Tumors. Heidelberg, Germany, Springer Verlag, 1987, p 133.
29. Droller MJ: Bladder cancer. Curr Probl Surg 1981;18:205-279.
30. Jones PA, Droller MJ: Pathways of development and progression in bladder cancer: New correlations between clinical observations and molecular mechanisms. Semin Urol 1993;11:177-192.
31. Fitzpatrick JM: Superficial Bladder Cancer: Natural History, Evaluation, and Management. Houston, American Urological Association, Inc., 1992, p 9.
32. Jakse G, Loidl W, Seeber G, et al: Stage T1, grade 3 transitional cell carcinoma of the bladder: An unfavorable tumor? J Urol 1987;137:39-43.
33. Abel PD: Follow-up of patients with ‘superficial’ transitional cell carcinoma of the bladder: The case for a change in policy. Br J Urol 1993;72:135-142.
34. Prout GR Jr, Barton BA, Griffin PP, et al: Treated history of noninvasive grade 1 transitional cell carcinoma: The National Bladder Cancer Group. J Urol 1992;148:1413-1419.
35. Birch BR, Harland SJ: The pT1 G3 bladder tumour. Br J Urol 1986;64:109-116.
36. Bostwick DG: Natural history of early bladder cancer. J Cell Biochem Suppl 1992;16:31-38.
37. Kakizoe T, Tobisu K, Takai K, et al: Relationship between papillary and nodular transitional cell carcinoma in the human urinary bladder. Cancer Res 1988;48:2299-2303.
38. Pomerance A: Pathology and prognosis following total cystectomy for carcinoma of the bladder. Br J Urol 1972;44:451-458.
39. Kakizoe T, Matumoto K, Nishio Y, et al: Significance of carcinoma in situ and dysplasia in association with bladder cancer. J Urol 1985;133:395-398.
40. Aprikian AG, Sarkis AS, Reuter VE, et al: Biological markers of prognosis in transitional cell carcinoma of the bladder: Current concepts. Semin Urol 1993;11:137-144.
41. Hopman AH, Moesker O, Smeets AW, et al: Numerical chromosome 1, 7, 9, and 11 alterations in bladder cancer detected by in situ hybridization. Cancer Res 1991;51:646-651.
42. Tsai YC, Nichols PW, Hiti AL, et al: Allelic losses of chromosomes 9, 11, and 17 in human bladder cancer. Cancer Res 1990;50:44-47.
43. Sidransky D, Messing E: Molecular genetics and biochemical mechanisms in bladder cancer: Oncogenes, tumor suppressor genes, and growth factors. Urol Clin North Am 1992;19:629-639.
44. Raghavan D, Shipley WU, Garnick MB, et al: Biology and management of bladder cancer. N Engl J Med 1990;322:1129-1138.
45. Soto EA, Friedell GH, Tiltman AJ: Bladder cancer as seen in giant histologic sections. Cancer 1977;39:447-455.
46. Prout GR Jr, Griffin PP, Shipley WU: Bladder carcinoma as a systemic disease. Cancer 1979;43:2532-2539.
47. Melchert MM: Histological study of vesical urothelium intervening between gross neoplasm in total cystectomy. J Urol 1952;68:261.
48. Hudson MA, Herr HW: Carcinoma in situ of the bladder. J Urol 1995;153:564-572.
49. Lamm DL: Long-term results of intravesical therapy for superficial bladder cancer. Urol Clin North Am 1992;19:573-580.
50. Lamm DL, van der Meijden AP, Akaza H, et al: Intravesical chemotherapy and immunotherapy: How do we assess their effectiveness and what are their limitations and uses? Int J Urol 1995;2(Suppl 2):23-35.
51. Ailhauzen AF, Prout GR Jr, Daly JF: Non-invasive papillary carcinoma of the bladder associated with carcinoma in situ. J Urol 1976;116:575-580.
52. Klán R, Loy V, Huland H: Residual tumor discovered in routine second transurethral resection in patients with stage T1 transitional cell carcinoma of the bladder. J Urol 1991;146:316-318.
53. Brosman SA, Lamm DL: The preparation, handling and use of intravesical bacillus Calmette-
Guérin for the management of stage Ta, T1, carcinoma in situ and transitional cell cancer. J Urol 1990;144:313-315.
54. Lamm DL: Carcinoma in situ. Urol Clin North Am 1992;19:499-508.
55. Lamm DL, Steg A, Boccon-Gibod L, et al: Complications of bacillus Calmette-Guérin immunotherapy: Review of 2602 patients and comparison of chemotherapy complications. Prog Clin Biol Res 1989;310:335-355.
56. Merz VW, Marth D, Kraft R, et al: Analysis of early failures after intravesical instillation therapy with bacille Calmette-Guérin for carcinoma in situ of the bladder. Br J Urol 1995;75:180-184.
57. Herr HW, Schwab DM, Zhang ZF, et al: Intravesical bacillus Calmette-Guérin therapy prevents tumor progression and death from superficial bladder cancer: Ten-year follow-up of a prospective randomized trial. J Clin Oncol 1995;13:1404-1408.
58. Sell A, Jakobsen A, Nerstrom B, et al: Treatment of advanced bladder cancer category T2, T3, and T4a: A randomized multicenter study of preoperative irradiation and cystectomy versus radical irradiation and early salvage cystectomy for residual tumor: DAVECA Protocol 8201: Danish Vesical Cancer Group. Scand J Urol Nephrol Suppl 1991;138:193-201.
59. Skinner DG, Lieszkovsky G: Contemporary cystectomy with pelvic node dissection compared to preoperative radiation therapy plus cystectomy in management of invasive bladder cancer. J Urol 1984;131:1069-1072.
60. Messing EM, Young TB, Hunt VB, et al: The significance of asymptomatic microhematuria in men 50 or more years old: Findings of a home screening study using urinary dipsticks. J Urol 1987;137:919-922.
61. Howard RS, Golin AL: Long-term follow-up of asymptomatic microhematuria. J Urol 1991;145:335-336.
62. Sternberg CN, Yagoda A, Scher HI, et al: MVAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 1988;139:461-469.
63. Harker WG, Meyers FJ, Freiha FS, et al: Cisplatin, methotrexate, and vinblastine (CMV): An effective chemotherapy regimen for metastatic transitional cell carcinoma of the urinary tract: A Northern California Oncology Group study. J Clin Oncol 1985;3:1463-1470.
64. Logothetis CJ, Dexeu FH, Finn L, et al: A prospective randomized trial comparing MVAC and CISCA chemotherapy for patients with metastatic urothelial tumors. J Clin Oncol 1990;8:1050-1055.
65. Martínez-Piñeiro JA, Gonzalez Martin M, Arocena F, et al: Neoadjuvant cisplatin chemotherapy before radical cystectomy in invasive transitional cell carcinoma of the bladder: A prospective randomized phase III study. J Urol 1995;153:964-973.
66. Hall RR: Bladder preserving treatment: The role of transurethral surgery alone and with combined modality therapy for muscle-invading bladder cancer, in Vogelzang NJ, Scardino PT, Shipley WU (eds): Comprehensive Textbook of Genitourinary Oncology. Baltimore, Williams & Wilkins, 1995, p 509.
67. Prout GR Jr, Shipley WU, Kaufman DS, et al: Interval report of a phase I-II study utilizing multiple modalities in the treatment of invasive bladder cancer: A bladder-sparing trial. Urol Clin North Am 1991;18:547-554.
68. Wajsman Z, Marino R, Parsons J, et al: Bladder-sparing approach in the treatment of invasive bladder cancer. Semin Urol 1990;8:210-215.
69. Herr HW: Conservative management of muscle-infiltrating bladder cancer: Prospective experience. J Urol 1987;138:1162-1163.
70. Solsona E, Iborra I, Ricos J, et al: Feasibility of transurethral resection for muscle-infiltrating carcinoma of the bladder: Prospective study. J Urol 1992;147:1513-1515.
71. Slack NH, Prout GR Jr: Heterogeneity of invasive bladder carcinoma and different responses to treatment, in Bonney WW, Prout GR (eds): Bladder Cancer. Baltimore, Williams & Wilkins, 1980, p 213. AUA Monographs, vol. 1.
72. Jewett HJ, Strong GH: Infiltrating carcinoma of the bladder: Relation of depth of penetration of the bladder wall to incidence of local extension and metastases. J Urol 1946;55:366.
73. Koss LG: Tumors of the Urinary Bladder. Washington, DC, Armed Forces Institute of Pathology, 1974. Atlas of Tumor Pathology, Second Series, Fascicle 11.