An Evolving Approach to the Surgical Management of Superficial Bladder Carcinoma

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Malignant epithelial tumors of the urinary bladder are the fourth most common cancer among men, excluding squamous cell cancer of the skin, and are diagnosed in over 50,000 patients each year.[1] Although the ratio is decreasing somewhat, bladder cancer is three times as common in males than in females and is responsible for over 10,000 deaths annually. White males may have an increased risk compared to Afro-American males though this appears to be true for superficial disease only.[2] Well-documented risk factors for the disease include cigarette smoking, chemical carcinogens, schistosomiasis and chronic urinary tract infections, and a wide variety of occupations concentrated in the chemical, dye, rubber, and textile industries. Occupational exposure appears to be a contributory factor for the disease in nearly 25% of the male population in the United States with bladder carcinoma.[3]

Epithelial tumors account for between 95% and 99% of all primary bladder tumors. About 90% of the epithelial bladder tumors in the Western Hemisphere are classified as transitional cell type and appear primarily as papillary lesions. Other cell types include squamous cell (7%) and adenocarcinoma (2%) while approximately 1% are undifferentiated. However, about one-fourth of transitional cell carcinomas show areas of glandular or squamous differentiation or both.[4] Those patients presenting with flat or sessile lesions have a greater chance of other cellular composition.[5] Transitional cell epithelial tumors are less predominant in certain areas of the world where epidemic schistosomal infection contributes to the development of squamous tumors. Nonepithelial tumors, which comprise 1% to 5% of primary bladder malignancies, can arise from connective, adipose, muscular, neurological, vascular, hematopoietic, or endocrine tissue.

The bladder is also a site for metastasis from nearly any other primary site by either direct extension or distant spread. The most common tumors reported to spread to the bladder arise from the prostate, uterus, ovary, lung, breast, and stomach.[5] Melanoma, leukemia, and lymphoma are also

known to metastasize to the bladder. Endometriosis, an entity that shares some characteristics with neoplasia, can also rarely present in the urinary bladder.

BIOLOGICAL BEHAVIOR

Cancer of the bladder is generally categorized into superficial and invasive disease because the natural history and management of these two entities differ. Normally, the bladder is lined by transitional epithelium which varies in thickness from five to seven cell layers in the collapsed state to two to three cell layers when the bladder is distended (Fig. 1).[4] The lamina propria is a thin, loose, fibrovascular sheet of tissue which separates the deeper muscular layers from the superficial epithelial layer. Invasion through the lamina propria has prognostic significance and is important for proper tumor staging in addition to determination of cell type and grade. Several studies document that approximately 75% of tumors will be superficially confined to the epithelium or lamina propria at presentation.[1,6]

The biological behavior of transitional cell bladder carcinoma is also correlated with other factors besides the depth of invasion. Risk of recurrence and progression both increase significantly with increasing histological tumor grade, penetration of the lamina propria, multiplicity of tumors, and size greater than 5 cm.[7] Time to recurrence can also indicate the aggressiveness of transitional cell carcinoma. For example, low-grade, low-stage tumors (stage Ta, grade I-II) followed for 10 years have an 80% chance of no recurrence during that time if there is no recurrence during the first three months after diagnosis, but will recur 70% of the time if a recurrence is noted in that three-month interval.[8] Appropriate management requires proper diagnosis and staging because superficial tumors generally pose only a local management problem but progression to invasion requires more extensive treatment. However, when superficial malignancy becomes resistant to intravesical therapy, there are few options left for the surgeon short of surgical removal of the bladder. The need to identify patients with refractive disease or those in the earliest stages of invasion is underscored by the results of cystectomy in patients with invasive bladder carcinoma.[9] It is alarming that even superficial invasion is associated with only a 75% five-year survival rate which drops significantly to between 31% to 63% for the more deeply invasive tumors. Non-transitional cell carcinomas of the bladder have a more dismal outcome because they are often invasive at first presentation, have a high rate of recurrence, and have a five-year survival rate of less than 20% in most series.[10-12]

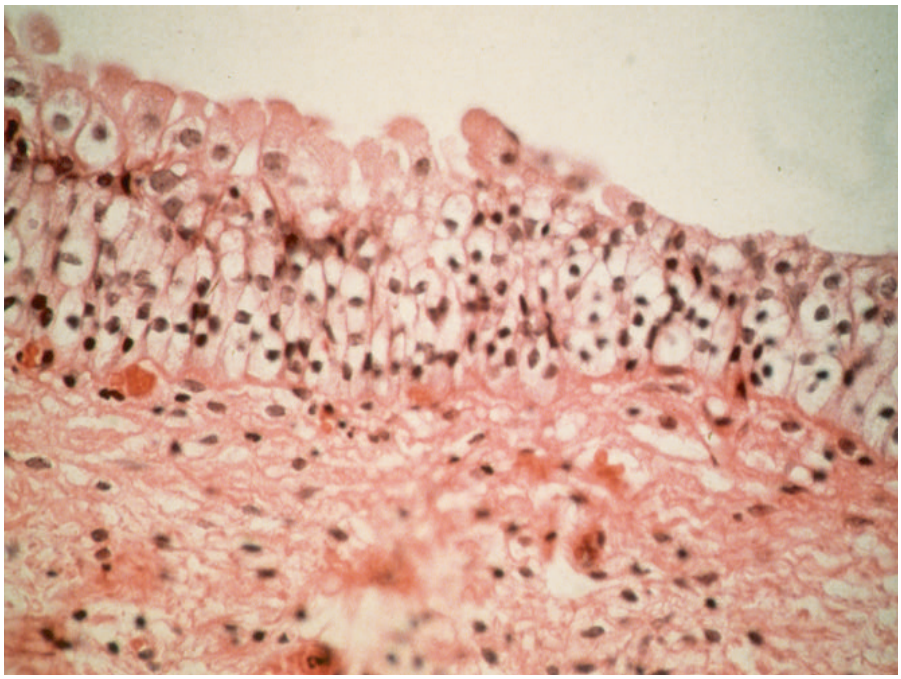

Figure 1. Normal transitional epithelium separated from underlying muscle by lamina propria. Note small, uniformly stained nuclei.

Special note must be made of transitional cell carcinoma in situ (CIS) which is an insidious, generally diffuse, high-grade, intraepithelial malignancy with a rather innocuous appearance that can belie an aggressive natural history (Fig. 2). Although the exact incidence of this entity is not clear, 10% of patients in a large series of newly diagnosed bladder carcinoma had CIS.[13] Carcinoma in situ of the bladder differs from similar lesions in other organs because it is a definite malignancy rather than precancerous lesion.[14] CIS frequently appears as a velvety or erythematous patch of mucosa and may occur alone or in association with either low-grade superficial or high-grade invasive disease. Appearance alone can be deceptive, however, because dysplasia or frank CIS has been found in biopsies of normal appearing bladder epithelium in 18% of patients with a papillary tumor.[15] Aggressive treatment of this disorder is indicated because it has been estimated that 30% to 35% of patients with CIS will progress to invasive disease.[4] Furthermore, patients with urinary tract symptoms associated with carcinoma in situ have a shorter interval to development of invasive disease.

GENETIC ABNORMALITIES IN BLADDER CARCINOMA

Cytogenetic and molecular genetic studies have been directed almost exclusively to transitional cell malignancies with very little known about the molecular biology and cytogenetics of the uncommon bladder carcinoma types.[16] The well-known multifocal nature of transitional cell carcinoma has suggested the role of a chemical carcinogen which initiates simultaneous proliferation of many clones resulting in either synchronous or metachronous tumor formation. However, several findings support a monoclonal theory of bladder carcinogenesis with intraepithelial or intravesical spread of viable tumor cells possibly abetted by growth factors and cytokines.[17] For example, patients with the uncommon presentation of an upper tract transitional cell tumor have about a 40% risk of developing a bladder carcinoma but only a 2% risk of a contralateral upper tract transitional cell tumor. Because patients with bladder tumors only develop an upper tract tumor about 1% of the time, monoclonal tumorigenesis with a

downstream implantation or intraepithelial spread of viable cells is suggested. Support for this theory is seen in cytogenetic and molecular genetic studies of multiple bladder tumors which have shown within each patient the exact inactivation of the same chromosome in the tumor cells but random inactivations in the normal cells.[18] The monoclonal origin for transitional cell carcinoma is strongly suggested in a recent study of one patient with an invasive renal transitional cell tumor, an ipsilateral ureteral tumor, and a concurrent bladder tumor with identical amplification of c-*erb* B-2 and p53 mutations in all tumors.[19]

CYTOGENETIC STUDIES

Cytogenetic studies have revealed a large number of structural and numerical chromosomal changes associated with bladder cancers which may account for their biological variability.[17] Bladder tumors nearly always have multiple cytogenetic changes with no one particular marker chromosome or genetic change associated with bladder carcinogenesis. An increase in chromosome number (hyperploidy) is associated with aggressive phenotypes and tumor invasion and may be a predictor of progression. Low-grade, low-stage tumors are nearly always diploid with less propensity for progression especially in the absence of an abnormal chromosome.

Structural changes are relatively common in bladder carcinoma with deletion of part or all of chromosome 9 reported in greater than 50% of tumors regardless of stage and grade and associated with a loss of a tumor suppressor gene in some cases.[17] Other frequent structural changes include aberrations of chromosomes 1, 5, 7, and 11. Loss of portions of chromosomes 17 and 18 are associated with invasive malignancies and may be a relatively late event in the tumor biological progression. Over 25% of bladder tumors present with translocations, often with other genomic abnormalities.

Numerical chromosomal changes also occur in bladder carcinoma with deletion of chromosome 9 the most common in all stages and grades. Trisomy of chromosome 7 is also a common change and can be the only anomaly in these epithelial tumors.[17] Loss of chromosome Y unrelated to aging has been reported in up to 50% of male patients with bladder cancer and is associated with more complex karyotypes and poorer clinical prognosis.

Few cytogenetic studies of carcinoma in situ exist, but in the absence of karyotypic changes or loss of sex chromosomes, CIS does not usually become invasive, though it is recurrent.[20] CIS associated with structural abnormalities of chromosomes 1, 5, 8, and 11, however, recurred and was often invasive. The prognostic value of these genetic characteristics awaits further evaluation.

ONCOGENES AND GROWTH FACTORS

Some of the earliest work on oncogenes occurred in human bladder carcinoma cell lines, and urothelial malignancies consequently have been some of the most extensively studied human neoplasms.[16] Approximately 10% of the transitional cell tumors studied

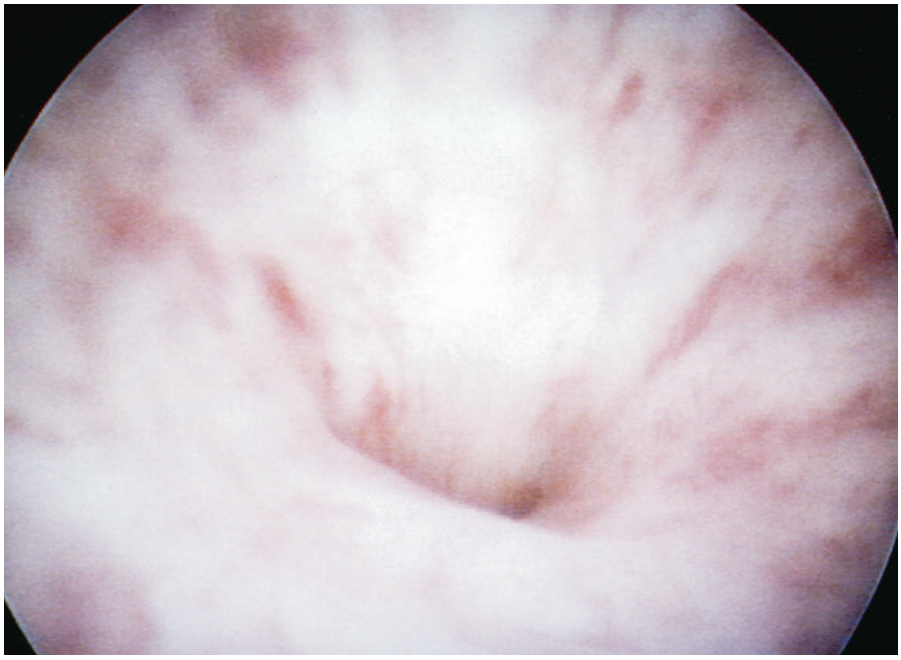

Figure 2a. Typical innocuous appearance of carcinoma in situ around a ureteral orifice.

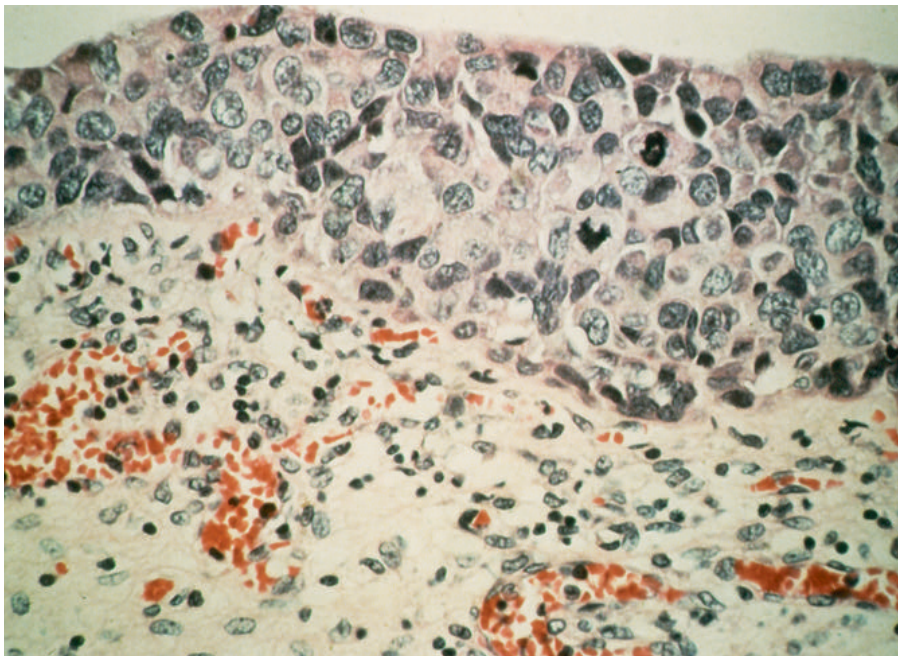

Figure 2b. Marked cellular anaplasia with variable nuclear size, shape, and stain intensity of high-grade intraepithelial neoplasia are characteristic of carcinoma in situ.

contain an abnormal *ras* proto-oncogene with at least 4 different mechanisms by which the *ras* family of genes can manifest. Expression of the *ras* product, p55, has been detected in the urine of more than 50% of bladder cancer patients in one study with inconclusive association with tumor grade and stage.[21] Interestingly, one report has related tumor progression in schistosomal-related squamous cell carcinoma to the increased expression of either normal or mutant c-H-*ras*.[22] Less is known about the role of other proto-oncogenes and growth factors in bladder carcinogenesis.

TUMOR SUPPRESSOR GENES

As with nearly all other tumors, mutation of p53 which resides in chromosome 17 has been evaluated for its role in bladder malignancies. Abnormalities of p53 have been associated with high-grade malignancies, higher recurrence rates, and poorer survival rates, though this association is not absolute. One interesting study which compared p53 mutations in smokers and nonsmokers concluded that cigarette smoke exposure may not alter the types of p53 mutations that occur but may increase the extent of the damage sustained by the DNA.[23] Alteration of the retinoblastoma *RB* gene may be more important as a prognosticator in patients who present with muscle invasive disease because of a relatively high incidence compared to superficial tumors and a poorer prognosis than in patients who retained *RB* expression. The frequency and variety of chromosomal aberrations found in transitional cell carcinomas suggests that there are many candidates for tumor suppressor genes and that their description may allow subclassification of urothelial malignancies.

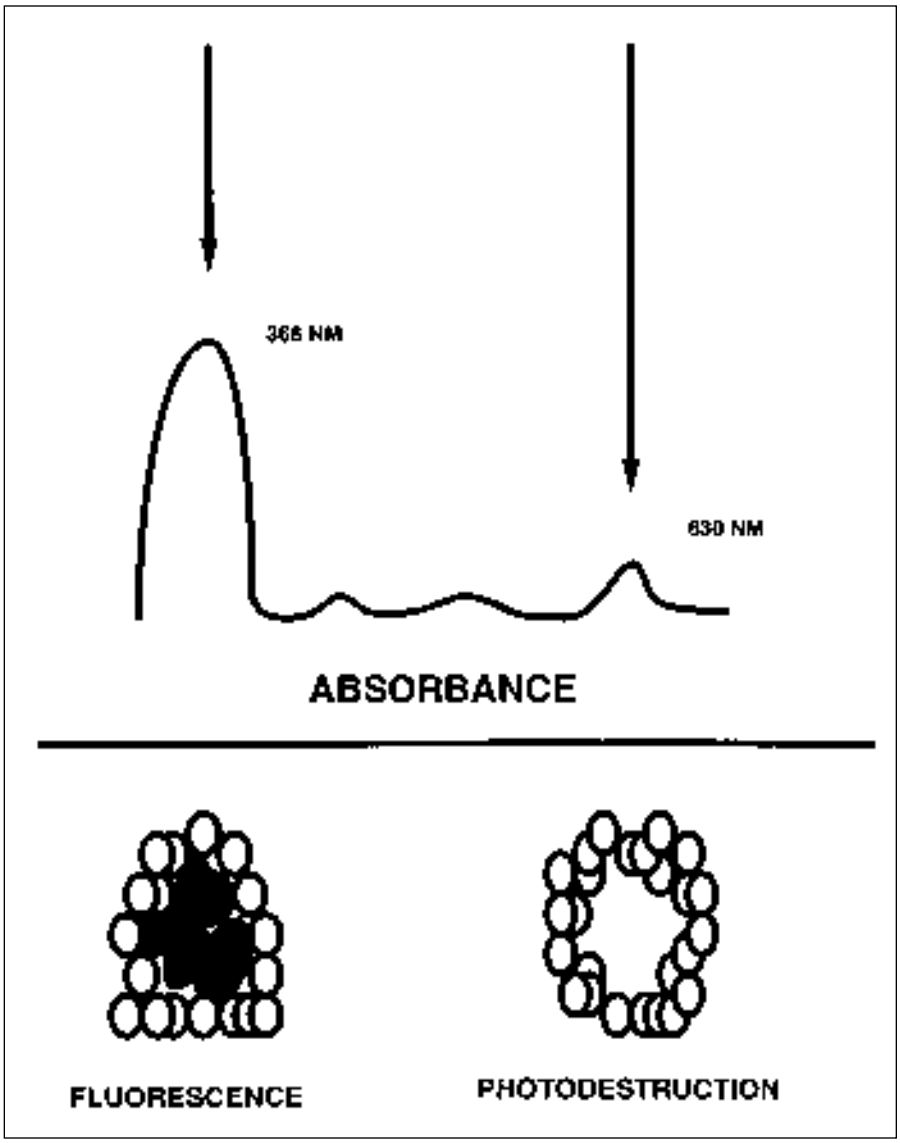

Figure 3. Schematic representation of a typical porphyrin photosensitizer absorption spectrum and its clinical manifestations.

DIAGNOSIS OF SUPERFICIAL BLADDER CANCER

Eighty percent of all patients with bladder carcinoma initially present with painless microscopic or gross hematuria.[24] Occasionally, irritative symptoms such as frequency, urgency, and dysuria are associated with bladder carcinoma, especially carcinoma in situ. Because only slightly more than half of bladder tumors can be seen on radiographic studies, the definitive diagnosis for bladder cancer is established with cystoscopy and biopsy. Diagnostic cystoscopy can be carried out with either rigid or flexible instruments in the office, though retrieving cytological or tissue specimens is more difficult with flexible instruments. Flexible cystoscopy is not the procedure of choice with gross hematuria because of poor visibility. Although cystoscopy alone may provide the diagnosis of bladder cancer, it is imperative to obtain proper tissue specimens, including underlying muscle, to gauge properly the grade and extent of the disease.

CYTOLOGICAL EVALUATION

A urinary cytological examination is often obtained during diagnostic cystoscopy in a patient with a history suggestive of bladder cancer. The mechanical action of barbotage provides better specimens for cytological examinations.[25] Cytological preparations are more sensitive for detection of higher-grade lesions, though up to 20% false negative cytology is reported for high-grade lesions.[26] Flow cytometry performed on specimens from barbotage have been reported to be superior to cytology in recent studies, but cytology is superior to flow cytometry in the presence of inflammation. Flow cytometry may be helpful in identification of patients likely to progress to invasive disease, though the high cost of its use may not justify routine application of this assay.[27]

FLUORESCENCE

Fluorescence is the emission of light from an excited molecule as it returns to its ground state. Enhancement of the ability to detect bladder neoplasia is

being evaluated with various photosensitizing agents which fluoresce when exposed to specific wavelengths of light. Absorbance of light by the sensitizer can result in visible fluorescence when the most commonly used porphyrin sensitizers are administered. Depending on the sensitizer used, there is a variable period of time when concentration of the agent is greater in tumor or dysplastic tissue than in normal epithelium. It is during this window of opportunity that fluorescence can be used to identify suspicious areas for biopsy and therapy (Fig. 3). Once identified, the photosensitizer can be activated by a different wavelength of light with sufficient energy to destroy those cells in a form of treatment called photodynamic therapy.[28] The addition of an optical multichannel analyzer has improved fluorescent detection from earlier reports by digital subtraction of autofluorescence.[29] More importantly, the diagnostic application of photosensitization also may be more practical now because the more rapidly metabolized sensitizers currently in clinical trials lack the prolonged skin photosensitivity that has limited this method for diagnostic purposes. These newer sensitizers also have properties that make them amenable to monoclonal antibody attachment which may enhance selectivity.

STAGING

Patients with a suspicious lesion found at cystoscopy or those with previous positive cytology or flow cytometry require a biopsy. Patients with recurrent irritative voiding symptoms of dysuria, frequency, and urgency also should undergo biopsies in the course of their evaluation to eliminate the possibility of carcinoma in situ. Areas of excessive vascularity not explained by clinical circumstances (such as a recent urinary tract infection) may signify dysplasia or transitional cell carcinoma in situ and should be considered for biopsy. Location, number, and size of lesions should be noted and may be recorded by video-endoscopic photography before tissue is removed. Multiple cold cup biopsies are performed after careful visual examination of the bladder. Specimens are typically taken from tissue adjacent to any obvious tumor and from areas lateral to each ureteral orifice, the posterior bladder wall, and the bladder dome. Multiple biopsies are important because even the normal appearing urothelium can contain dysplasia or frank carcinoma in up to 18% of patients.[15] In patients suspected to harbor carcinoma in situ, a biopsy of the prostatic urethra should be taken because approximately one-fourth of men with CIS will have prostatic urethral involvement.[30]

Biopsy forceps obtain tissue by sharp amputation created by two opposing cups moving with scissor-like action which allows minimal crushing of the tissue and avoids electrocoagulation artifact. Small papillary tumors may be completely removed by the biopsy forceps. The rigid biopsy instruments can reach most areas in the bladder, though the dome and anterior bladder walls pose a more difficult problem for tissue acquisition. The 6-mm diameter specimen can adequately sample the underlying muscle to determine neoplastic invasion. Flexible biopsy instruments may allow sampling of tumors in otherwise inaccessible areas such as the anterior bladder wall or dome but provide a smaller (2-mm) diameter sample and frequently do not obtain underlying muscle with the specimen.[31]

Bladder biopsies can also be obtained by using a resectoscope. The resectoscope consists of a mobile thin wire loop placed through a rigid working sheath. Tissue is cut or coagulated through two types of current supplied by an electrosurgical unit connected to the endoscopic instrument. Cutting occurs through activation of an unmodulated high-frequency continuous wave current of approximately 2500 kilocycles per second. Cauterization occurs by modulation of the high frequency to create intermittent oscillations of progressively decreasing amplitude, usually about 500 kilocycles per second. Because the cutting current does not provide much hemostasis, most tissue is resected using a blend of the two types of current. Coagulation artifact increases proportional to the cutting current setting and the percentage of coagulation in the blend and can obscure very important information about the degree of disease involvement in the underlying muscle. Therefore, for bladder biopsies obtained by electroresection, it is important to obtain an adequate sample of the base of the lesion and the adjacent muscle with non-thermal biopsy instruments.

ENDOSCOPIC TREATMENT OF BLADDER CANCER

The primary method for intravesical treatment of superficial transitional cell carcinoma of the bladder is endoscopic removal of the malignant tissue. Endoscopic management of bladder malignancies can range from a short, simple procedure to a complicated process that challenges the manual dexterity and imagination of the seasoned endoscopist. The presence or extent of disease is not often appreciated before cystoscopic evaluation, and it is pru-

Figure 4. A flat-end optical laser fiber (far right) is offset from the tumor for exposure, while the contact-tipped optical fibers have various configurations for fine or broad-based direct vaporization of tissue.

dent, therefore, to have a variety of instruments available for both diagnosis and treatment. Once the diagnosis is made, intravesical management of high-grade superficial transitional cell carcinoma includes adjuvant chemo- or immunotherapy in addition to surgical resection of papillary tumors. The presence of dysplasia or CIS also warrants intravesical therapy.

TRANSURETHRAL RESECTION

Transurethral resection is the primary method used for endoscopic treatment of papillary bladder malignancies. Because of the diffuse nature of CIS, transurethral resection is not often curative for that entity and is reserved for obtaining biopsy specimens before institution of adjuvant intravesical therapy. Occasionally an endoscopic snare may be used to loop around a papillary tumor with a narrow stalk but transurethral resection is the mainstay for tumor removal. Transurethral resection is generally reserved for superficial disease, but this approach is also an option for definitive therapy in selected cases of relatively small, low-grade lesions with superficial muscle invasion where five-year survival rates have been reported as high as 40%.[32] Patients with localized invasive disease who are a poor risk for major operative intervention may also benefit from transurethral resection alone.

Most superficial papillary tumors are less than 3 cm in diameter and occur on the posterior or lateral bladder wall making them accessible for transurethral resection. Many urologists prefer to send the entire specimen with a sample of the underlying muscle, though some advocate resection of the superficial portion of the tumor with a second specimen sent as deeper resection which includes bladder muscle. Others prefer a cold cup biopsy of the tumor base after resection of the superficial papillary portion. Regardless of the method of resection, fulguration of the tumor base is performed for hemostasis and is felt to destroy any remaining undetected tumor cells. However, a contrary view suggests that resection into the muscle may not be wise for superficial disease because it may promote tumor cell implantation in the uncovered muscle.[26]

Transurethral resection is possible in most cases of superficial disease, but the surgical technique occasionally must be modified. For example, complete resection may not be possible or desirable in patients with an extensive tumor or a lesion in an inaccessible location. In these cases, it is important to obtain enough tissue to assess tumor grade and stage accurately without bladder perforation. Minimal use of electrocautery is advised around the ureteral orifice, but tumors that encroach on the ureteral orifice can be difficult to eradicate without risk of damage. It is important to remember that resection of tumors on the lateral bladder wall may stimulate an obturator nerve reflex for adduction which could result in a bladder perforation. Care must also be taken with tumors in a diverticulum where biopsy alone is recommended for these lesions that are best managed by partial or total cystectomy.[26]

FULGURATION

Small papillary lesions a few millimeters in diameter can be eradicated by use of an electrode attached to an electrocautery unit. This technique can be useful for patients with recently biopsied small papillary lesions or with small recurrences of low-grade papillary lesions.[33] It is important to have proper muscle tissue samples to determine tumor grade and stage because fulguration destroys cellular morphology and the ability to detect invasion.

LASER THERMAL DESTRUCTION

Thermal ablation of malignant tissue has long been an accepted and successful method of tumor destruction. A laser is a light source which provides controlled thermal energy and has gained increasing acceptance as an alternative to electrocautery resection. Lasers are identified by the medium used to generate light with different wavelengths emitted by a wide variety of solid, liquid, and gas laser media. Lasers are capable of producing light of extreme brightness and singularity of color which can be directed unlike the disorganized light from an incandescent source. Despite the ability to produce thermal tissue destruction from a variety of laser types, only a few lasers are routinely used at this time as surgical tools for the ablation or coagulation of tissue.

The effects of laser energy on tissues are a function of the laser wavelength, tissue absorption characteristics, power delivered, and time of exposure. Tissue destruction can be accomplished by either coagulation or vaporization. As tissue temperature increases from 50° to 100°C, tissue effects progress from protein denaturation to DNA destruction and changes in membrane permeability. Capillary coagulation occurs around 60° to 65°C. If the tissue temperature exceeds 100°C, the fluid content of the tissue will vaporize in a plume containing fluid vapor and charred tissue components. A zone of coagulation necrosis surrounds the surgical defect created in the tissue.

By adjusting the method of light delivery, power density, or time of exposure, the degree of thermal conduction and local tissue repair mechanisms can be controlled. The desired depth of light penetration in the treatment of bladder carcinoma depends on the thickness of the tissue and whether the malignancy is diffuse or focal. Several local tissue factors contribute to the scatter and absorption of the energy. Generally, a longer wavelength will correspond to greater depth of light penetration. Consequently, short-wavelength ultraviolet light will only penetrate in fractions of a millimeter, while argon and potassium titanyl phosphate (KTP) lasers will penetrate 1 to 3 mm and the longer wavelength laser neodymium: yttrium-aluminum-garnet (Nd:YAG) will penetrate approximately 4 to 7 mm.[34] Despite a longer wavelength, however, the carbon dioxide (CO_2) laser only penetrates a fraction of a millimeter because its energy is absorbed by water in the cell. These penetration characteristics frequently dictate the type of laser to be used for thermal ablation of tissue. Although other lasers are under investigation for use in the bladder, the most commonly used laser for thermal ablation of tumors is the Nd:YAG followed by the argon or KTP laser. Most hospitals currently have one or more types of lasers available which have characteristics appropriate for use in the bladder.

Direction of the laser beam to the desired target is generally accomplished with an optical fiber composed of quartz and silica which internally reflects the laser beam along the long axis of the fiber to its exit at the end. In this "free beam" method, the laser beam is offset from the tissue for exposure. In cases where penetration is a concern, the deeper penetration characteristics

of a Nd:YAG laser can be altered by the use of a contact laser optical fiber. The non-contact fiber tip does not alter the thermal damage expected from the type of laser used. A contact optical fiber, on the other hand, focuses the thermal energy from the laser at the surface in contact with tissue and confines penetration to less than 1 mm (Fig. 4).[35] The contact optical fiber can vaporize or coagulate tissue depending on the amount of energy used.

Laser therapy should be preceded by appropriate staging biopsies because destruction of bladder malignancies by laser thermal treatment does not provide tissue for histological evaluation. Laser therapy was initially restricted to patients with recurrent tumors where the pathological diagnosis was determined; it is now reasonable to treat the first occurrence with a laser if the tumor appears as a well-pedunculated, low-grade papillary tumor and a biopsy of the tumor base is obtained. Thermal laser treatment is not particularly effective for carcinoma in situ because of its extent and multifocal nature.

The laser thermal energy is applied to superficial bladder tumors through either rigid or flexible endoscopic equipment with the capability to deflect the optical fiber. Continuous-flow irrigation used with rigid instruments can control bladder distention. A flat-end optical fiber which provides an oval laser beam spot is usually used, but fibers with 90° deflection of the beam may be employed for lesions in positions difficult to reach. Once the tumor is identified, the fiber is extended to within a few millimeters of the tissue, and the laser is activated by a foot pedal. For the Nd:YAG laser, 25 to 40 W of continuous power is applied until blanching of the tumor occurs (Fig. 5). For larger tumors, systematic application of the laser energy proceeds until the entire tumor undergoes white discoloration. It is important to discontinue treatment once the visual effect is noted because the 20% to 30% forward scatter of the Nd:YAG laser energy may lead to an undesired complication such as perforation or damage to an adjacent organ. When a larger tumor is involved, it may be necessary to abrade the treated area to repeat the laser exposure for the deeper portion of the tumor. The tumor usually will slough in 7 to 10 days after treatment making it unnecessary to remove the tumor tissue directly. Posttreatment evaluation is recommended at the standard time interval used for other intravesical therapies.

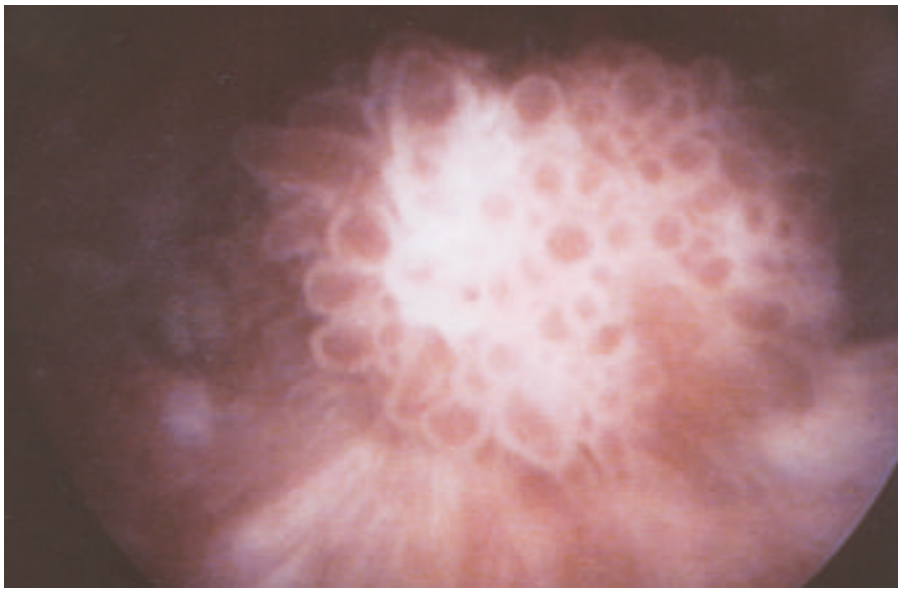

Figure 5a (above). Low-grade papillary transitional cell lesion before exposure to Nd:YAG laser energy. The tumor is exposed to 25 to 40 W of continuous power until blanching (Fig. 5b below) occurs. Overexposure can lead to excessive damage and perforation.

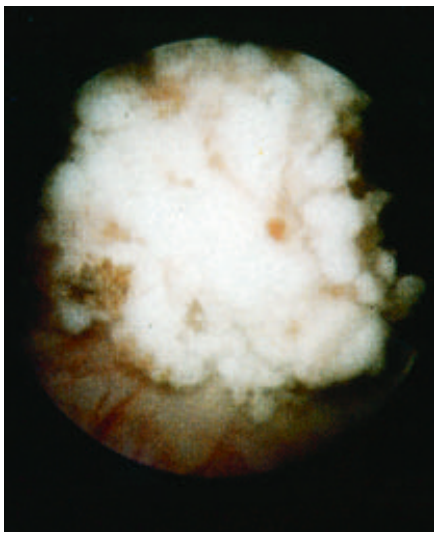

Figure 5b.

Long-term studies have demonstrated effective treatment of superficial bladder cancer by the Nd:YAG laser.[36] Laser therapy does not appear to decrease recurrences of superficial bladder tumors appreciably, as most investigators report about equal numbers compared to recurrences after transurethral electroresection.[37] However, availability of a laser suitable for intravesical procedures allows the endoscopist more flexibility and can be advantageous in different clinical situations. For instance, use of the Nd:YAG laser is not associated with bleeding because of vascular coagulation. This more effective hemostasis prevents catheterization solely for bleeding and clot retention and affords the patient the opportunity to resume mobility very soon after the procedure. Patients ordinarily require less anesthesia for laser procedures, and stimulation of the obturator reflex does not occur. Flexible endoscopic instruments can be used with the small diameter optical fibers which makes this treatment less painful for the patient and allows treatment of lesions in locations otherwise inaccessible to rigid instruments. Safety of laser ablation of bladder tumors is evidenced by the extremely low risk of bladder perforation.[36]

Surgical use of lasers does have some unique requirements because of their characteristics. Proper training is imperative for both physicians and operating room personnel to ensure the safety of both patient and personnel. Precautions unnecessary for other modalities include protective eyewear appropriate to filter the wavelength in use, telescopic lens covers for endoscopic use, and proper draping techniques to prevent fire. Intravesical use of lasers causes less concern for some of these precautions, but it is important that all personnel involved with the procedures understand the potential for complications related to laser use. Most hospitals currently have trained personnel and standard safety protocols.

Figure 6. Diffusion medium can provide isotropic light distribution to irregular surfaces in viscus organs like the bladder. The flat-end optical fiber transmits 630 nm red visible light nearly straight through the saline-filled cannister (a) while a 0.02% soybean emulsion scatters light uniformly throughout the container (b). The surface area ordinarily shielded by the indentations of the container in (a) receive light exposure when diffusion medium is added in this simulation of an irregular mucosal surface.

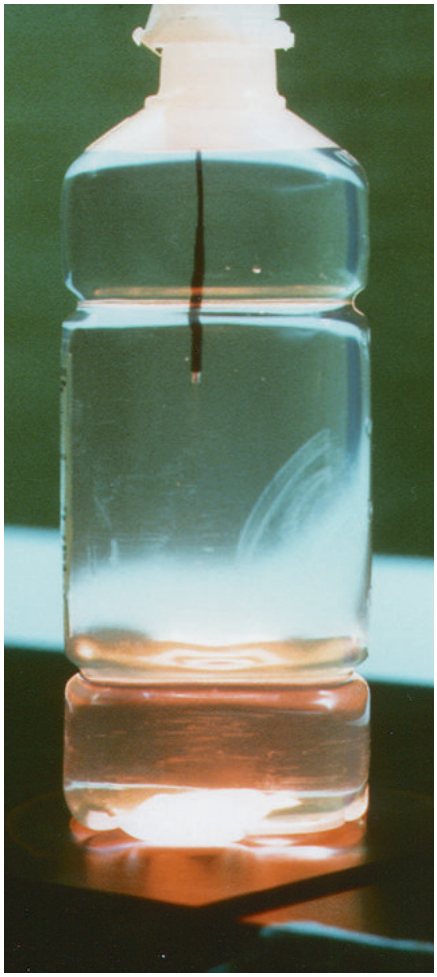

Figure 6a.

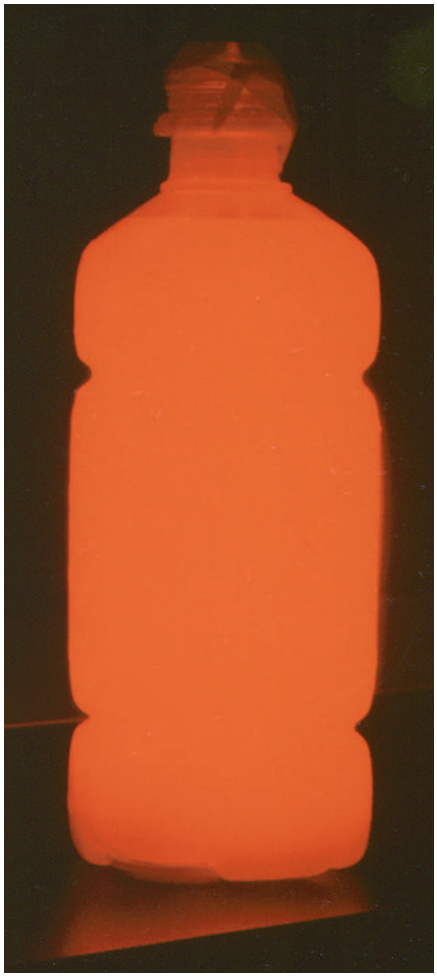

Figure 6b.

PHOTODYNAMIC THERAPY

Direct resection or laser thermal ablation of carcinoma in situ is difficult because of the often diffuse extent of the disease. Endoscopic management of this form of bladder malignancy usually entails proper diagnosis and staging, though transurethral resection with fulguration of adjacent transitional epithelium will occasionally provide long-term control of focal carcinoma in situ associated with small-volume papillary tumors. The primary therapy for CIS, however, continues to be immunotherapy from intravesical instillation of bacillus Calmette-Guerin (BCG) resulting in a durable complete response rate of about 65%.[38] Other intravesical agents may also be used with less effectiveness. Regardless of repeat and maintenance therapy strategies, about one-fourth of the patients with CIS will fail intravesical therapy. There is a reluctance to perform radical cystectomy for superficial disease, but there are few alternatives to this management dilemma because of the aggressive natural history of CIS. Photodynamic therapy (PDT), however, is one alternative to radical surgery that has shown an effect on this disease.

The phenomenon of photosensitization has been known for nearly a century but began to get attention for clinical use after the invention of lasers as a light source which could provide sufficient energy of specific light wavelengths to activate the sensitizers.[28] Photodynamic therapy causes tissue destruction when light absorbed by a photosensitizer in the oxygenated target tissue stimulates a photo-oxidative process that interrupts cell functions.[39] This relatively selective treatment for neoplasia relies on a window of opportunity when a gradient of sensitizer retention exists between tumor and adjacent normal tissue. The mechanism for selective retention in tumors is poorly understood but relates to photosensitizer chemical properties and physiologic and anatomic differences between neoplasia and normal tissue. Increased endocytosis in neoplastic cells mediated by low density lipoprotein (LDL) receptors may also play a role in selective sensitizer retention.

The two-step process of PDT first requires the delivery of a sensitizer to the target tissue followed by its activation with a light source. Hematoporphyrin derivative (HPD) was the initial photosensitizer used but most recent clinical treatments have used a porphyrin derivative known as Photofrin II® (P II). Several other compounds which share structural similarities with the more well-known porphyrin photosensitizers P II and HPD have advanced to clinical trials.[40] Biosynthesis of an endogenous sensitizer, protoporphyrin IX, by the topical or oral administration of its precursor 5-aminolevulinic acid (ALA) is also under evaluation.[41]

The light delivery system most frequently used for PDT is a tunable dye laser with an interchangeable dye module to coincide with the absorbance spectrum of different sensitizers. It is expected that inexpensive and reliable laser sources with solid state technology will be available in the future.

Photodynamic cytotoxicity is suspected to result from singlet oxygen production from direct energy transfer following light absorption. Other photochemical products such as superoxide ion may also contribute to cell death, but the evidence suggests that singlet oxygen is the major phototoxic agent at the cellular level.[42] The cytotoxic mechanisms in PDT have been attributed to both direct cellular effects and the effect of PDT on the tumor vascularity. The primary cellular targets of photochemically induced singlet oxygen damage appear to be mitochondrial and cytoplasmic membranes, with inactivation of membrane transport systems probably one of the initial effects of PDT. Several types of microvascular damage occur during or shortly after PDT.[43] Many investigators currently feel that in vivo tumor death is due to a combination of both direct cytotoxicity

and disruption of tumor vasculature.

Transitional cell carcinoma of the bladder is responsive to PDT with better responses generally noted for treatment of carcinoma in situ.[44] Treatment of papillary lesions less than 2 cm in diameter with energy densities ranging from 100 J/cm^2 to 250 J/cm^2 has resulted in 46% to 80% complete response rates at an interval of three months after focal PDT.[41] The higher response rates were seen in reports with small numbers of patients, and only one report has longer than a three-month follow-up. Papillary tumors greater than 2 cm in diameter have shown only partial response to PDT.

The treatment of transitional cell CIS appears more effective than PDT of papillary lesions. Because CIS is diffuse, uniform light distribution throughout the bladder is required instead of focal irradiation of tumors. PDT for carcinoma in situ usually has been performed with exposure of the entire bladder epithelium simultaneously to energy densities ranging from 25 J/cm^2 to 45 J/cm^2 after placement of a spherical-tipped optical fiber in the center of the saline-distended bladder. The standard sensitizer dose used in most studies of human PDT with P II is 2.0 to 2.5 mg/kg, and treatment occurs 48 to 72 hours after intravenous injection. The few studies reported show complete response rates from 60% to 80%.[41] Most of these patients had not been treated by intravesical BCG prior to PDT. There is only one report of PDT for bladder carcinoma with long-term results in which there were 9 sustained complete responses in 15 patients evaluated with resistant carcinoma in situ 24 to 54 months after whole-bladder PDT.[45] Two more patients were rendered disease-free after retreatment with PDT, and two other patients had eradication of their tumors with transurethral resection or Nd:YAG laser fulguration.

Dosimetry is a critical element for accurate determination of energy delivery within the bladder and remains relatively crude. Proper dosimetry requires accurate surface area calculation which is difficult for the distensible topography of the bladder surface. Light irradiance varies with the square of the distance, and both unequal light distribution from commercially available optical fibers and inaccurate optical fiber position may have contributed to treatment failures and side effects such as bladder volume loss. We have modified light distribution through use of a soybean emulsion solution to scatter light uniformly throughout the bladder in patients with BCG-resistant carcinoma in situ (Fig. 6).[46] Transabdominal sonography is used in three planes for calculation of bladder surface area and for more accurate optical fiber placement (Fig. 7). This initial report has now been expanded to 27 patients using a decreased dose of 1.5 mg/kg of P II with complete responses in 8 (31%) and partial responses in 14 (52%). The average time to recurrence is 12.5 months but many patients with partial response and with recurrence after complete response have now become responsive again to more conventional intravesical therapeutic agents.

PDT remains experimental at this stage in the United States, but approval for general use of PDT for bladder carcinoma has recently been granted in Canada. Filing with regulatory agencies in both the United States and Europe is underway. PDT may be more efficient in the near future with several photosensitizers in preliminary trials which do not possess the long-term dermal photosensitivity seen with P II. With closer attention to dosimetry and lack of skin photosensitivity leading to improved photosensitization, an increased understanding of photobiology may allow widespread clinical use of PDT for both diagnostic and therapeutic purposes.

FUTURE APPROACHES TO MANAGEMENT OF SUPERFICIAL BLADDER CARCINOMA

The treatment for superficial bladder carcinoma continues to evolve with refinement of existing approaches and exploration of new avenues for therapy. Surgical excision or thermal ablation for low-grade superficial papillary tumors will continue to play a major role because of its effectiveness for diagnosis and simultaneous definitive treatment. Despite the reasonable success of intravesical immunotherapy with BCG, investigation continues for more effective or better tolerated methods to control high-grade or diffuse superficial disease.[38] These include intravesical instillation of various cytokines, such as interferon and tumor necrosis factor, or other compounds like keyhole-limpet hemocyanin, the blood pigment of a marine invertebrate which has shown to have an effect on transitional cell carcinoma with few side effects.[47] Other biological response modifiers like the α-interferon inducer bropirimine may be administered orally.[48]

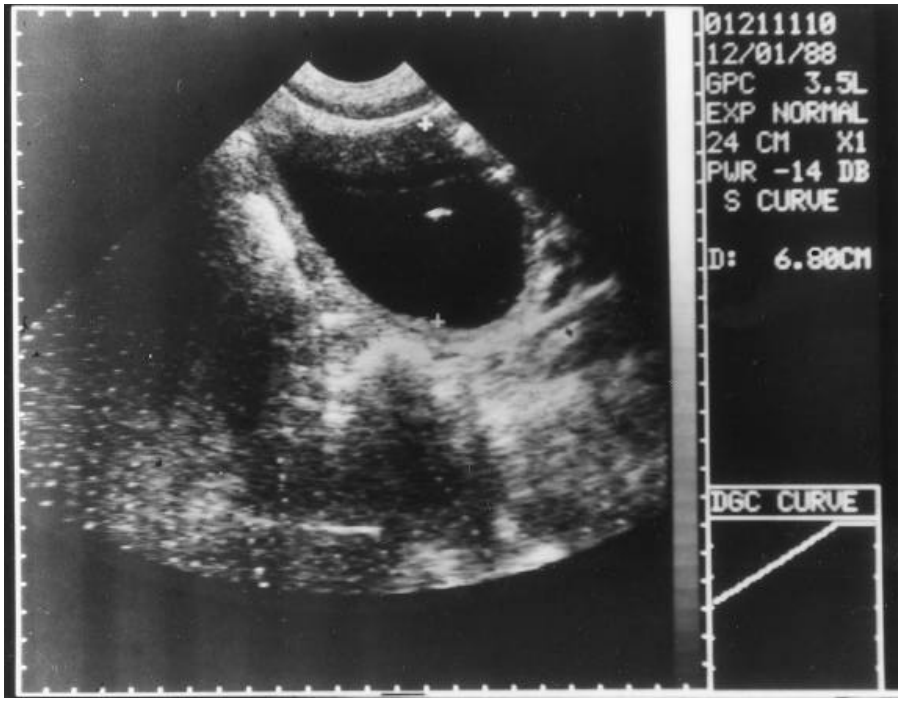

Figure 7. Transabdominal ultrasound demonstrating spherical-tipped laser optical fiber placement in bladder during photodynamic therapy. Surface area for dosimetry calculation is determined by real-time ultrasound measurements.

The possibility of gene therapy has captured the imagination of both scientists and the general public and may represent one of the largest potential rewards for the investment in molecular biological research over the past several years.[49] Since the first patient was treated with gene therapy in 1990, at least 5 of the approximately 60 protocols of human gene therapy approved by the National Institutes of Health Recombinant DNA Advisory Committee are for urologic malignancies.[50] Although to date expectations have decidedly outweighed results, the rapid acquisition of molecular genetic information and increasingly sophisticated technology have improved this labor-intensive and expensive approach.

The two general approaches that have been employed for clinical application of gene therapy involve selective destruction of cells or replacement of defective genes.[50] Cytoreductive gene therapy selectively targets malignant cells for destruction usually by boosting the host's immune response against the tumor through vaccination with genetically altered tumor cells. In this method, tumor cells are removed from the patient, stimulated to produce an immunogenic cytokine, and reinjected into the patient.[51] This method has been limited by the relatively small tumor burden destroyed in the preclinical models. Another promising cytoreductive approach transfers genes of drug susceptibility into patients.

The other broad molecular genetic approach involves correction of a defective or deleted gene by introduction of the normal wild-type gene. Identification of both oncogenes and tumor suppressor genes provides targets for this method of gene-directed therapy. Recent development of somewhat efficient engineered portions of DNA or RNA which serve as vehicles capable of receiving the therapeutic gene has allowed direct transfer of recombinant genetic material into patients. All vectors currently available use either retroviruses or DNA viruses genetically altered to prevent replication within human cells for transduction but have limitations to their attractiveness.[50,52]

The rapid evolution of molecular genetic techniques and accumulation of knowledge suggest that molecular biological therapy will play a role in management of several diseases which pose management problems. Gene therapy may not yet be ready for general use, but some very clear urological targets such as high-grade bladder carcinoma are under evaluation. If advances continue at the present pace, gene therapy may well indeed become part of the surgical armamentarium. STI

REFERENCES

1. Boring CS, Squires TS, Tong T, et al. Cancer statistics, 1994. CA 1994;44:7-26.
2. Schairer C, Hartge P, Hoover RN, et al. Racial differences in bladder cancer risk: a case-control study. Am J Epidemiol 1988;128:1027-37.
3. Silverman DT, Levin LI, Hoover RN, et al. Occupational risks of bladder cancer in the United States I: white men. JNCI 1989;81:1472-6.
4. Mostofi FK, Davis CJ Jr, Sesterhenn IA. Pathology of tumors of the urinary tract. In: Skinner DG, Lieskovsky G, eds. Diagnosis and management of genitourinary cancer. Philadelphia: W B Saunders; 1988. p 83-117.
5. Koss LG. Tumors of the urinary bladder. In: Firminger HI, ed. Atlas of tumor pathology. Washington, DC: Armed Forces Institute of Pathology; 1983. 2nd Series, Fascicle 11; p 1-115.
6. Ro JY, Staerkel GA, Ayala AG. Cytologic and histologic features of superficial bladder cancer. Urol Clin N Amer 1992;19:435-53.
7. Heney NM, Ahmed S, Flanagan MJ, et al. Superficial bladder cancer: progression and recurrence. J Urol 1983;130:1083-86.
8. Fitzpatrick JM, West AB, Butler MR, et al. Superficial bladder tumors: the importance of recurrence pattern following initial resection. J Urol 1986;135:920-6.
9. Pagano F, Bassi P, Galetti TP, et al. Results of contemporary radical cystectomy for invasive bladder cancer: A clinicopathological study with an emphasis on the inadequacy of TNM classification. J Urol 1991;145:45-50.
10. Bessette P, Abell M, Herwig K. Clinicopathologic study of squamous cell carcinoma of the bladder. J Urol 1974;112:66-71.
11. Jacobo E, Loening S, Schmidt JD, et al. Primary adenocarcinoma of the bladder: a retrospective study of 20 patients. J Urol 1977;117:54-60.
12. Kramer SA, Bredael J, Croker BP, et al. Primary non-urachal adenocarcinoma of the bladder. J Urol 1978;121:278-83.
13. Utz DC, Farrow DM. Carcinoma in situ of the urinary tract. Urol Clin North Am 1984;11:735-40.
14. Melicow MM, Hollowell JW. Intraurothelial cancer: carcinoma in situ, Bowen's disease of the urinary system: discussion of 30 cases. J Urol 1952;68:763-8.
15. Wallace DMA, Hindmarsh JR, Webb JN, et al. The role of multiple biopsies in the management of patients with bladder cancer. Br J Urol 1979;51:535-7.
16. Manyak MJ. The genetic basis of urologic malignancy. In: Crawford ED, Das S, eds. Current genitourinary cancer surgery. 2nd ed. Philadelphia: Lea and Febiger; 1995. In press.
17. Sandberg AA, Berger CS. Review of chromosome studies in urological tumors. II. Cytogenetics and molecular genetics of bladder cancer. J Urol 1994;151:545-60.
18. Sidransky D, Frost P, Von Eschenbach A, et al. Clonal origin of bladder cancer. N Engl J Med 1992;319:737-40.
19. Lunec J, Challen C, Wright C, et al. C-*erb* B-2 amplification and identical p53 mutations in concommitant transitional carcinomas of renal pelvis and urinary bladder [Letter to the Editor]. Lancet 1992;339:439.
20. Tyrkus M, Powell I, Fakr W. Cytogenetic studies of carcinoma in situ of the bladder: prognostic implications. J Urol 1992;148:44-6.
21. Stock LM, Brosman SA, Fahey JL, et al. *Ras*-related oncogene protein as a tumor marker in transitional cell carcinoma of the bladder. J Urol 1987;137:784-89.
22. Fujita J, Nakayama H, Onoue H, et al. Frequency of active *ras* oncogenes in human bladder cancers associated with schistosomiasis. Jpn J Cancer Res 1987;78:915-21.
23. Spruck CH III, Rideout WM III, Olumi AF, et al. Distinct pattern of p53 mutations in bladder cancer: relationship to tobacco usage. Cancer Res 1993;53:1162-64.
24. Varkarakis MJ, Gaeta J, Moore RH, et al. Superficial bladder tumor: aspects of clinical progression. Urology 1974;4:414-9.
25. Trott PA, Edwards L. Comparison of bladder washings and urine cytology in the diagnosis of bladder cancer. J Urol 1973;110:664-6.
26. Catalona WJ. Bladder cancer. In: Gillenwater JY, Grayhack JT, Howards SS, et al, eds. Adult and pediatric urology. St. Louis: Mosby-Year Book; 1991. Vol 1; p 1135-83.
27. Norming U, Tribukait B, Gustafson H, et al. Deoxyribonucleic acid profile and tumor progression in promary carcinoma in situ of the bladder: a study of 63 patients with grade 3 lesions. J Urol 1992;147:11-15.
28. Manyak MJ, Russo A, Smith PD, et al. Photodynamic therapy. J Clin Oncol 1988;6:380-91.
29. Baert L, Johansson J, Berg R, et al. Clinical fluorescence diagnosis of human bladder carcinoma following low-dose photofrin injection. Urology 1993;41:322-30.
30. Cummings KB, Barone JG, Ward WS. Diagnosis and staging of bladder cancer. Urol Clin N Amer 1992;19:455-71.
31. Manyak MJ, Nochomovitz LE. Cystourethroscopy, biopsy, and tissue preparation. In: Nochomovitz LE, ed. Bladder biopsy interpretation. New York: Raven Press; 1992. p 1-9.
32. Barnes RW, Bergman RT, Hadley HT, et al. Control of bladder tumors by endoscopic surgery. J Urol 1967;97:864-8.
33. Mebust WK. Transurethral resection of bladder tumors. In: Crawford ED, Das S, eds. Current genitourinary cancer surgery. Philadelphia: Lea and Febiger; 1990.
34. Stein BS. Laser-tissue interaction. In: Smith JA Jr, Stein BS, Benson RC Jr, eds. Lasers in urologic surgery. 3rd ed. St. Louis: Mosby-Year Book; 1994. p 10-25.

35. Manyak MJ, Aulisi GP. Free-beam and contact laser ablation of benign prostatic hyperplasia with the KTP/Nd: YAG laser: efficacy and versatility. World J Urol 1995;13:104-8.
36. Beer M, Jocham D, Beer A, et al. Adjuvant laser treatment of bladder cancer: 8 years' experience with the Nd-YAG laser 1064 nm. Br J Urol 1989;63:476-8.
37. Smith JA Jr. Laser surgery for transitional-cell carcinoma. Urol Clin N Amer 1992;19:473-83.
38. Lamm DL, Blumenstein BA, Crawford ED, et al. A randomized trial of intravesical doxorubicin and immunotherapy with Bacille Calmette-Guerin for transitional-cell carcinoma of the bladder. N Engl J Med 1991;325:1205-9.
39. Henderson B A, Dougherty TJ. How does photodynamic therapy work? Photochem Photobiol 1992;55:145-57.
40. Gomer CJ. Yearly review: preclinical examination of first and second generation photosensitizers used in photodynamic therapy. Photochem Photobiol 1991;54:1093-1107.
41. Manyak MJ. Photodynamic therapy: principles and practices in urology. Problems in Urology 1992;6:399-413.
42. Athar M, Elmets CA, Bickers DR, et al. A novel mechanism for the generation of superoxide anions in hematoporphyrin derivative-mediated cutaneous photosensitization. Activation of the xanthine oxidase pathway. J Clin Invest 1989;83:1137-43.
43. Star WM, Marijnissen HPA, Berg-Blok A, et al. Destruction of rat mammary tumor and normal tissue microcirculation by hematoporphyrin derivative observed in vivo in sandwich observation chambers. Cancer Res 1986;46:2532-40.
44. Benson RC Jr. Treatment of diffuse transitional cell carcinoma in situ by whole bladder hematoporphyrin derivative photodynamic therapy. J Urol 1985;134:675-8.
45. Jocham D, Beer M, Baumgartner R, et al. Long-term experience with integral photodynamic therapy of Tis bladder carcinoma. Ciba Found Symp 1989;146:198-205.
46. Manyak MJ. Photodynamic therapy: principles and urological applications. Sem Urol 1991;9:192-202.
47. Jurincic CD, Engelman U, Gasch J, et al. Immunotherapy in bladder cancer with keyhole-limpet hemocyanin: a randomized study. J Urol 1988;139:723-8.
48. Sarosdy MF, Lamm DL, Williams RD, et al. Phase I trial of oral bropirimine in superficial bladder cancer. J Urol 1992;147:31-33.
49. Manyak MJ. The clinical relevance of gene therapy. J Urol 1994;152:292-3.
50. Sanda MG, Simons JW. Gene therapy for urologic cancer. Urology 1994;44:617-24.
51. Dranoff G, Jaffee E, Lazenby A, et al. Vaccination with irradiated tumor cells engineered to secrete murine granulocyte-macrophage colony-stimulating factor stimulates potent, specific, and long-lasting antitumor immunity. Proc Nat Acad Sci USA 1993;90:3539-43.
52. Benchimol S. Viruses and cancer. In: Tannock IF, Hill RP, eds. The basic science of oncology. 2nd ed. New York: McGraw-Hill; 1992. p 88-101.