

Bladder Cancer, 1996

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Introduction

Bladder cancer, one of the first cancers associated with industrialization,¹ is not unexpectedly increasing in incidence in the modern world. In the United States, it is projected that 52,900 new cases will be diagnosed and 11,700 people will die of the disease in 1996.² Despite efforts to decrease cigarette smoking, the most common cause of bladder cancer, there has been a steady increase in the incidence of bladder cancer.^{1,3}

Though the medical community has not yet succeeded in significantly lowering the incidence of this largely preventable cancer, we have succeeded in improving the treatment of the disease. The survival of bladder cancer in the past decade has increased by eight percent despite an increase of 36 percent in incidence.³ Fewer patients are requiring radical cystectomy as the primary treatment, and those who do often can receive bladder replacement and enjoy a better quality of life. A decade ago bladder cancer was considered to be resistant to chemotherapy, but with the advent and increased use of cis-

platin/methotrexate-based combination chemotherapy, complete response and long-term disease-free survival occur in as many as 23 percent of patients with metastatic disease.⁴ While considerable progress has been made in the treatment of bladder cancer, the increase in mortality projected for 1996 emphasizes the need to further improve prevention, detection, and treatment.

Epidemiology and Etiology

In the United States, the most common histologic cell type in bladder cancer is transitional cell carcinoma, occurring in over 90 percent of patients. Other histologic cell types, in decreasing order of frequency, are squamous cell carcinoma (often associated with chronic inflammation); adenocarcinoma (occasionally associated with urachal remnants); undifferentiated carcinoma; rhabdomyosarcoma; and rare histologic types such as sarcomatoid carcinoma, small-cell carcinoma, and lymphoepithelioma.⁵ Squamous cell carcinoma and adenocarcinoma of the bladder generally present at higher stages than transitional cell carcinoma, are less responsive to chemotherapy, and have a less-favorable prognosis.

Transitional cell carcinoma was first associated with aniline dye exposure in the German dye industry.¹ Since then multiple chemical and environmental exposures, as listed in Table 1, have been associated with transitional cell carcinoma of the bladder.⁶ The listed chemicals

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Table 1
Chemicals and Occupations Associated with Bladder Cancer

Chemicals	Occupations
α - and β -Naphthylamine	Textile workers
4-Aminobiphenyl	Dye workers
Benzidine	Tire and rubber workers
Chlornaphazine	Leather workers
4-Chloro-o-toluidine	Bootblacks
o-Toluidine	Painters
4,4'-Methylene bis (2-chloroaniline)	Truck drivers
Methylene dianiline	Drill press operators
Benzidine-derived azo dyes	Chemical workers
Phenacetin-containing compounds	Petroleum workers Hairdressers

are highly carcinogenic, but fortunately exposure to these chemicals is limited. Cigarette smoking carries a relative risk of developing bladder cancer of only three to one in most studies, but it is estimated that as many as 60 percent of bladder cancers may result from smoking.⁷

The increasing incidence of bladder cancer despite the reduction in smoking in the United States suggests that other environmental factors may be playing an increasing role in the development of bladder cancer. Several reports of increased risk of bladder cancer associated with increased water intake are of concern. While bladder cancer occurs most frequently in highly industrialized regions, increased risk associated with exposure to drinking water in rural areas with high pesticide use has been reported.⁶ The specific carcinogens in water and our industrial environment have for the most part not been defined. Identification and removal of these chemicals could reverse the trend of increasing incidence of bladder and other cancers.

Multiple genetic changes are associated with bladder cancer, including expression of *RAS* and *MYC* protooncogenes and oncogenes related to the epidermal growth factor receptor.⁸ Studies of X chromosome inactivation suggest that bladder tumors typically descend from a single cell.⁸ Genetic changes may confer a growth advantage on the cell, resulting in an expanding layer of urothelium with a proclivity for tumor formation. Genetic studies may explain the well-known clinical dichotomy between low-grade papillary tumors that frequently recur but rarely progress and high-grade in situ or flat tumors that commonly invade and spread aggressively. Mutation of the retinoblastoma (*RB*) gene, common in many tumors, is frequent in bladder cancer and confers a proliferative advantage on tumor cells.⁹ Bladder tumors exhibiting decreased expression of RB protein are found to have significant increased risk for muscle invasion.¹⁰ Mutation of the well-known tumor suppressor gene *p53*, located on

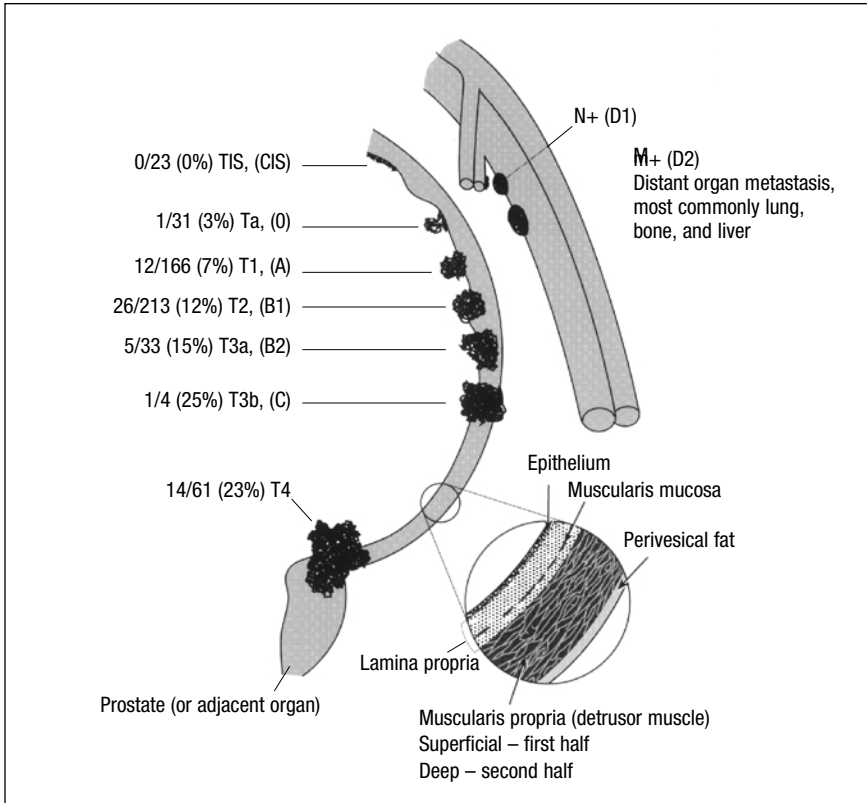


Fig. 1. Illustrated is the TNM and Jewett-Marshall (in parentheses) staging systems for bladder cancer. Stage Ta (0) tumors are limited to the epithelial layer. Invasion begins with stage T1 (A) tumors that extend to the lamina propria and progresses to T2 (B1), less than halfway through the detrusor muscle; T3a (B2), more than halfway through the detrusor muscle; T3b (C), into perivesical fat; and T4, into adjacent organs. Metastasis typically begins with pelvic lymph nodes [N+ or (D1)] prior to spreading systemically [M+ or (D2)]. The percentages listed to the left represent typical incidences of nodal metastases according to primary tumor stage.

chromosome 17p, confers genetic instability. Nuclear overexpression of p53 protein is correlated with a significantly increased risk of disease progression.¹¹

Clinical Features

The most frequent presenting feature of bladder cancer is gross or microscopic hematuria, which occurs in 80 percent of

patients.¹² Delay in referring patients with hematuria for cystoscopic examination remains a too-common problem in the management of bladder cancer, and we must guard against increasing this problem as the “gatekeeper” philosophy is applied to reduce the cost of medical care. Hematuria in bladder cancer is typically intermittent, making it easy to be deceived into believing that an interven-

tion for benign disease, most commonly antibiotics for presumed urinary tract infection, has been effective.

Twenty percent or more of patients complain of irritative voiding symptoms, such as frequency, urgency, or dysuria, which can further obscure the true diagnosis.¹³ Irritative symptoms are more frequently associated with aggressive bladder tumors, such as grade III carcinoma or carcinoma in situ. Fortunately, urinary cytology is positive in more than 80 percent of patients with high-grade transitional cell carcinoma.¹⁴ Urinary cytology is helpful when positive, but more than one quarter of patients with bladder cancer may have a negative urinary cytology. Immunocytology is under investigation and has been reported to increase the sensitivity of cytology from 70 to 90 percent.¹⁵ Flow cytometry may improve the sensitivity of urinary cytology to as high as 93 percent,¹⁶ but the mainstay of diagnosis in bladder cancer continues to be cystoscopic examination.

Diagnosis

Cystoscopic examination is done with a high index of suspicion in patients with abnormal cytology or hematuria, and raised, roughened, or reddened areas are readily biopsied with cupped forceps. Bladder wash cytology done at the time of cystoscopy will further increase the detection of transitional cell carcinoma. Visible tumors are resected transurethraly, and tissue is submitted for pathologic examination, thereby accomplishing the most important therapeutic and diagnostic steps simultaneously. Transurethral resection done under anesthesia permits deep resection for muscle biopsy as well as thorough bimanual examination, important clinical staging procedures.

Random bladder biopsies, taken from the margin of the tumor; suspicious remote areas; and preselected sites, such as the lateral walls, dome, posterior wall, trigone, and, most important, the prostat-

ic urethra in men, provide important prognostic information. Atypia or carcinoma in situ in such biopsies markedly increases the risk of tumor recurrence and stage progression.

Review of cystoprostatectomy specimens reveals that the prostatic urethra will harbor transitional cell carcinoma in up to 40 percent of patients.¹⁷ Invasive transitional cell carcinoma within the prostatic urethra is associated with poor prognosis, and the detection of noninvasive carcinoma within the prostatic urethra significantly influences treatment planning because intravesical chemotherapy is generally ineffective in the prostatic urethra and orthotopic bladder replacement carries the risk of urethral recurrence.

Only two to three percent of patients with bladder cancer will develop upper tract transitional cell carcinoma,¹⁸ but intravenous urography is considered an important baseline study, particularly in patients with hematuria. Carcinoma in situ of the bladder frequently extends to the distal ureters,¹⁹ and intravenous urography, retrograde pyelography with ureteral wash cytology, or even ureteroscopy may be required to exclude upper tract carcinoma. For tumors not invading the detrusor muscle, additional imaging studies such as cystography, computed axial tomography, magnetic resonance imaging, ultrasonography, and bone or liver scans are neither necessary nor cost effective.

Treatment of Superficial Bladder Cancer

The primary treatment for papillary bladder tumors that do not invade the detrusor muscle, that is, stage Ta or T1 transitional cell carcinoma (Fig. 1), is transurethral resection. Small, low-grade, noninvasive tumors can be fulgurated or lasered. These procedures can be done without anesthesia and have minimal morbidity, but pathologic examination may be

compromised. While it has been suggested that laser surgery would reduce tumor recurrence, this has not been demonstrated in appropriate controlled studies.²⁰

Despite complete tumor resection, two thirds of patients, on average, will develop tumor recurrence within five years. By 15 years 88 percent of patients will develop tumor recurrence.²¹ The high rate of bladder tumor recurrence provides opportunity to institute chemoprevention or prophylactic therapy.

INTRAVESICAL THERAPY

The primary approach to prevention of recurrence of superficial bladder cancer and the attendant risk of tumor progression and cancer death has been intravesical therapy, initially intravesical chemotherapy and, in this decade, intravesical immunotherapy with bacillus Calmette-Guèrin (BCG). The natural history of bladder cancer, however, shows that only four percent of patients with stage Ta and two percent of patients with grade I tumors developed progression to muscle invasion in 39 months.²² Because these patients are also at lower risk of recurrence, adjunctive intravesical therapy is generally not necessary. Because of the high risk of tumor recurrence and progression for patients with multiple primary tumors, recurrent tumors, grade III or stage T1 tumors, positive postresection cytology, or dysplasia or carcinoma in situ on random biopsy, these patients are considered candidates for intravesical therapy.

The goals of intravesical therapy are the prevention or postponement of tumor recurrence, eradication of residual visible or microscopic transitional cell carcinoma, prevention of disease progression, reduction in the need for radical cystectomy, and maintenance and prolongation of a good quality of life. While reduction of tumor recurrence is a significant achievement, prevention of tumor progression is clearly the most important goal of therapy.

Intravesical Chemotherapy

Intravesical chemotherapy became popular in the early 1960s, when thiotepa was demonstrated by many investigators to reduce tumor recurrence and eradicate about one third of papillary tumors.²¹ Because most papillary tumors can be readily resected transurethraly, prophylaxis against tumor recurrence has been the most common use of intravesical chemotherapy. Controlled trials demonstrate that intravesical chemotherapy does significantly reduce tumor recurrence, but unfortunately, evidence suggests that neither long-term recurrence nor progression is reduced with current intravesical chemotherapy protocols.²³

Unlike systemic chemotherapy, response to topical intravesical chemotherapy is proportional to the concentration rather than the dose of drug.²⁴ Response is also related to the duration of exposure, which is generally short and limited by bladder capacity. Due to the short contact time in the bladder, cytotoxic drugs that have been found to be useful intravesically are, as expected, cell-cycle independent. Currently used drugs include thiotepa, doxorubicin, and mitomycin C.

The alkylating agent thiotepa has been extensively studied.²³ In 10 controlled prophylaxis trials, six found that thiotepa significantly reduced tumor recurrence compared with surgical resection alone. Reduction in tumor recurrence ranged from zero to 41 percent and averaged 12 percent. Surprisingly, optimal reduction in tumor recurrence occurred when thiotepa was given as a single, early postoperative instillation. Early postoperative instillation has been postulated to prevent seeding of tumor cells in the bladder. Long-term follow-up studies have shown no reduction in the incidence of tumor recurrence at five years, and no study has reported a statistically significant reduction in the incidence of tumor progression resulting from thiotepa instillation.²¹

The anthracycline antibiotic doxorubicin is an intercalating agent and inhibitor of topoisomerase II that has been used since the 1970s in the treatment and prophylaxis of bladder cancer. In the treatment of papillary tumors, a complete-response rate of 38 percent has been reported in 712 patients worldwide.²⁵ Three of five controlled trials of doxorubicin prophylaxis have demonstrated statistically significant reduction in tumor recurrence, with benefits relative to surgery alone ranging from five to 39 percent and averaging 13 percent.²³ As noted with thiotepa administration, a single, postoperative instillation resulted in the greatest reduction in tumor recurrence. No study has yet demonstrated a significant reduction of tumor recurrence beyond three years of follow-up, and controlled trials attempting to extend the benefit of doxorubicin with maintenance chemotherapy demonstrate no advantage of continued administration.²⁶ Three studies have compared disease progression in controlled doxorubicin trials. In each study disease progression was higher in treated patients than in controls, though not significantly so.²⁷⁻²⁹

The alkylating agent mitomycin, like doxorubicin, belongs to the class of antibiotic chemotherapeutic agents. Mitomycin has been widely used in Europe and the United States for the treatment and prophylaxis of bladder cancer due to its favorable toxicity profile and presumed, though not proved, greater efficacy. In the treatment of papillary tumors, complete response has been reported in 43 percent of 627 patients worldwide.²⁵ Only two of six controlled prophylaxis trials found mitomycin to significantly reduce tumor recurrence compared with surgery alone.²³ In those studies the benefit of mitomycin ranged from one to 43 percent and averaged 15 percent. In contrast with other agents, the study showing the greatest advantage (43 percent) of mitomycin chemotherapy used a maintenance schedule, but controlled compar-

isons of long- and short-term administration, as with other agents, show no advantage for maintenance mitomycin chemotherapy.²⁷ Three controlled studies have focused on tumor progression with mitomycin treatment, and none found significant reduction in stage progression.²³ As with other chemotherapy studied to date, mitomycin has not been reported to reduce the incidence of tumor recurrence beyond three years.

The complete response rate of mitomycin in the treatment of carcinoma in situ is 53 percent and compares favorably with the complete response rates of thiotepa (38 percent) and doxorubicin (48 percent).³⁰ While some have considered mitomycin to be more effective than previous intravesical chemotherapies, controlled comparisons of mitomycin with thiotepa and doxorubicin fail to show any significant therapeutic advantage for mitomycin over the less-expensive alternative drugs.³¹⁻³⁴

Intravesical Immunotherapy

Despite the checkered past of BCG immunotherapy in other cancers, intravesical BCG immunotherapy is now recognized to be the treatment of choice for carcinoma in situ of the bladder and is considered by most to be the best prophylactic treatment for patients with aggressive superficial transitional cell carcinoma. While the mechanism of action of BCG is incompletely defined, it is recognized as a potent nonspecific immune stimulant. Intravesical BCG induces infiltration of a broad range of inflammatory and immune cells in the lamina propria of the bladder and activates macrophages, T and B lymphocytes, natural killer cells, and a variety of other immune surveillance mechanisms including lymphokine and interferon production.

Multiple studies, as illustrated in Table 2, have demonstrated that BCG prophylaxis markedly reduces tumor recurrence when compared with surgical

Table 2
Tumor Recurrence and Progression in Controlled Studies*

Agent	Number of Patients/Series/ Significant Results	Recurrence (percent)			Progression (percent)		
		Control	Treated	Benefit	Control	Treated	Probability
Thiotepa	1,007/10/6	56	44	12	6	4	Not significant
Doxorubicin	1,241/5/3	47	34	13	8	9	Not significant
Mitomycin	1,157/6/2	50	35	15	7	4	Not significant
Bacillus Calmette-Guérin	496/5/4	72	32	40	23	13	0.03

*Comparison of relative benefits of intravesical chemotherapy or immunotherapy with respect to reduction in tumor recurrence and progression versus surgery alone.

Table 3
Recurrence in Controlled Comparison Trials

Reference (year)	Recurrence (percent)				Probability Level
	BCG	Thiotepa	Doxorubicin	Mitomycin C	
Brosman ³⁵ (1982)	0	47	—	—	<0.01
Netto et al ³⁶ (1983)	7	43	—	—	<0.01
Martinez et al ³⁷ (1990)	13	36	43	—	<0.01
BCG /thiotepa average*:	7	42	—	—	—
Lamm et al ³⁸ (1991)	63	—	83	—	<0.02
BCG/doxorubicin average*:	38	—	63	—	—
DeBruyne et al ³⁹ (1988)	30	—	—	25	NS
Finnblad ⁴⁰ (1990)	28	—	—	62	<0.01
Rubben ⁴¹ (1990)	35	—	—	35	NS
Witjes ⁴² (1995)	29 (RIVM)	—	—	26	NS
	34 (Tice)	—	—	—	NS
Lamm et al ⁴³ (1993)	20	—	—	33	<0.01
BCG/mitomycin average*:	29	—	—	36	—
BCG/ chemotherapy average†:	25	—	43	—	—

*For all studies comparing both.

†For all studies.

BCG = bacillus Calmette-Guérin; NS = not significant

resection alone, and several studies suggest that, unlike chemotherapy, protection from tumor recurrence lasts for at least five years.²³ Importantly, long-term reduction in tumor recurrence appears to be associated with a reduction in tumor progression in patients treated with BCG. As illustrated in Table 2, statistically significant reduction in tumor progression occurred in BCG-treated patients, and overall progression was reduced from 23 percent in patients treated with surgery alone to 13 percent in those treated with adjuvant BCG ($P<0.03$).

Controlled, randomized studies of BCG immunotherapy and intravesical chemotherapy, as illustrated in Table 3, have shown that BCG provides superior protection from tumor recurrence when compared with thiotepa, doxorubicin, and mitomycin.³⁵⁻⁴³ In these nine randomized comparison studies, BCG was found to result in significantly fewer recurrences in all comparisons with thiotepa and doxorubicin and two of five comparisons with mitomycin. Overall, tumor recurrence was reduced from an average of 43 percent with chemotherapy to 25 percent with BCG.

BCG immunotherapy is particularly effective in transitional cell carcinoma in situ. As illustrated in Table 4, complete response to intravesical chemotherapy in carcinoma in situ ranges from 38 percent for thiotepa to 53 percent for mitomycin. Despite these significant response rates, intravesical chemotherapy has not been demonstrated to alter the long-term aggressive natural history of carcinoma in situ, and in general fewer than 20 percent of patients remain disease free for five years. The overall complete-response rate of carcinoma in situ to BCG is now over 70 percent.

The Southwest Oncology Group comparison of Connaught BCG and doxorubicin is representative of the excellent long-term result of BCG in the treatment of carcinoma in situ.³⁰ In that study of 112 patients with carcinoma in situ random-

ized to doxorubicin chemotherapy or BCG immunotherapy, complete response was documented in 34 percent of patients in the doxorubicin arm and 70 percent in the BCG arm. By five years only 18 percent in the doxorubicin arm remained disease free, compared with 45 percent in the BCG arm ($P<0.001$). Of the patients who had a complete response to BCG, 64 percent maintained that complete response for five years. Compared with the historical natural history showing that 54 percent of patients with carcinoma in situ progress to invasive disease within five years,³⁰ these are remarkable results.

Recent data suggest that improved treatment schedules can further improve the results of BCG immunotherapy. The Southwest Oncology Group registered 660 patients in a randomized comparison of the standard six-week BCG induction treatment and a maintenance regimen. In 218 patients with carcinoma in situ, three additional induction BCG treatments at 12 weeks increased the complete response from the expected 73 percent to 87 percent ($P<0.04$).⁴⁴ In patients with carcinoma in situ who had complete response at three months, maintenance BCG treatments at 12 weeks, six months, and every six months to three years increased the long-term complete response from the expected 65 percent to 83 percent ($P<0.04$). In disease-free patients with rapidly recurring or aggressive stage Ta or T1 transitional cell carcinoma, the advantage of maintenance BCG was even more dramatic, increasing the long-term disease-free status from the expected 50 percent to 83 percent ($P<0.000001$).

ALTERNATIVE THERAPIES FOR SUPERFICIAL BLADDER CANCER

The success of BCG immunotherapy has prompted the search for more-effective and less-toxic immunotherapies. At present, two alternative immunotherapies are commercially available for the treat-

Table 4
Complete Response Rates of Intravesical Therapy*

Agent	No. of Cases Stage Ta or T1 / No. of Cases Carcinoma in Situ	Number of Complete Responses	
		Stage Ta or T1	Carcinoma in Situ
Thiotepa	231/89	88 (38%)	34 (38%)
Doxorubicin	712/212	273 (38%)	101 (48%)
Mitomycin	627/147	270 (43%)	78 (53%)
Interferon alfa	16/62	4 (25%)	29 (47%)
Bacillus Calmette-Guérin	188/718	115 (61%)	500 (70%)

*Complete responses are reported for superficial stage Ta or T1 transitional cell carcinoma and carcinoma in situ of the bladder (data from Bouffieux et al²⁵ and Lamm³⁰).

ment of cancer, interferon alfa and interleukin-2. Both agents appear to have activity in bladder cancer. As illustrated in Table 4, intravesical interferon alfa has resulted in a complete-response rate of 25 percent in 16 patients with stage Ta or T1 transitional cell carcinoma. Overall complete response in patients with carcinoma in situ treated with effective doses is 47 percent, and a controlled multicenter trial has demonstrated statistically significant improvement in complete response with 100 million units compared with 10 million units of intravesical interferon alfa 2B.⁴⁵

Preliminary studies have suggested that both intravesical and intravesical interleukin-2 can induce complete regression of transitional cell carcinoma, but data are insufficient for anything other than continued clinical investigation.

In Europe intravesical immunotherapy with keyhole-limpet hemocyanin has been studied in several randomized trials and found to be at least as good as mitomycin and ethoglucid chemotherapy.^{46,47} Keyhole-limpet hemocyanin has the advantage of appearing to be without signif-

icant local or systemic toxicity.

Oral agents also appear to have promise. The interferon inducer bropridine has been successfully used in the treatment of carcinoma in situ.⁴⁸ In Japan *Lactobacillus casei* has reduced tumor recurrence,⁴⁹ and we have recently observed a reduction of 40 percent in long-term recurrence with high-dose vitamins A, B₆, C, and E.⁴⁴

Photodynamic therapy using intravesical laser light and intravenous administration of the photosensitizer Photofrin II has a high response rate in carcinoma in situ and is being investigated as an alternative treatment modality.⁵⁰ Photodynamic therapy may be particularly useful in patients who have failed first-line intravesical therapies, especially those who are poor surgical risks for cystectomy.

Patients with grade I or II, stage Ta tumors typically remain at low risk for stage progression despite multiple recurrences and, therefore, can receive multiple trials of intravesical or alternative therapies without significant risk of cancer death. Patients with grade III, stage

T1 tumors, in contrast, are at high risk for muscle invasion and subsequent metastatic disease. In these patients failure to respond to conservative therapy should be considered a relative indication for proceeding with cystectomy to prevent disease extension beyond the bounds of resectability.

Treatment of Muscle-Invasive Bladder Cancer

The prognosis and treatment of bladder cancer change radically once invasion of the detrusor muscle occurs because as few as half of patients will survive five years despite aggressive treatment. Unfortunately, up to 84 percent of patients with muscle-invasive bladder cancer are diagnosed with this locally advanced stage at initial presentation.⁵¹ Therefore, improvement in the management of superficial bladder cancer will improve survival in only a minority of patients at risk of dying of the disease. Further improvement in survival will require earlier detection or improved treatment of advanced disease. There is some evidence that both may be possible.

A recent study suggests that simple home screening for microhematuria can identify patients at high risk of having bladder cancer and significantly reduce the stage at which tumors are diagnosed. Messing et al⁵² screened 1,575 men older than 50 years with serial home reagent strip tests for hematuria. Urologic evaluation of patients with microhematuria resulted in 1.3 percent of patients being diagnosed with bladder cancer. The proportion of patients with muscle-invasive cancers was significantly lower in the screened population, 4.8 percent, compared with the unscreened population, 24 percent ($P<0.007$). Importantly, no screened case died of bladder cancer during the three- to nine-year follow-up while 16 percent of the unscreened cases died of bladder cancer within two years ($P<0.025$).

Advances in the treatment of invasive and metastatic bladder cancer include improvement in the quality of life and the duration of life. This has been accomplished through advances in surgical technique with the advent of continent urinary diversion and orthotopic bladder substitution, bladder sparing with combined radiation therapy and chemotherapy, and cisplatin-based combination chemotherapy.

In the United States, cystoprostatectomy is the treatment of choice for most patients with stage T2 to T4 bladder cancer, but in Great Britain and Canada, cystectomy is generally reserved for patients who fail to respond to radiation therapy. Improvement in intravesical therapy, particularly BCG immunotherapy, and the advent of effective systemic chemotherapy have also increased interest in and success of bladder-sparing techniques, including repeat transurethral resection in patients with stage T2 disease, partial cystectomy in patients without diffuse urothelial disease, and radiation therapy.

As reviewed by Whitmore,⁵³ historical series of selected patients fail to show any remarkable difference in survival in patients with superficial muscle invasion (stage T2) when treatments are compared. Five-year survival rates range from 57 to 70 percent for transurethral resection, 43 to 60 percent for partial cystectomy, 54 to 62 percent for simple cystectomy, 19 to 57 percent for radiation therapy, and 45 to 92 percent for neoadjuvant chemotherapy and cystectomy. Historical comparisons are limited by selection and other biases and are of limited value in comparing treatment efficacies. In patients with higher-stage tumors, radical cystectomy and more recently radical cystectomy plus adjuvant or neoadjuvant chemotherapy appear to provide improved survival. The role of adjuvant chemotherapy, however, remains controversial.

Bladder preservation using chemotherapy and radiation therapy has been

evaluated and appears to result in a higher complete-response rate than radiation therapy alone. 5-Fluorouracil and cisplatin are considered to enhance the effect of radiation therapy. Two studies of 5-fluorouracil plus radiation therapy have found complete local-response rates in the range of 60 percent.^{54,55} In a controlled, randomized comparison of chemotherapy and radiation therapy with radiation therapy alone, the addition of cisplatin increased the two-year freedom-from-local-recurrence rate from 45 percent to 67 percent ($P=0.023$).⁵⁶

Encouraging results have recently been reported with the treatment of muscle-invasive bladder cancer with a bladder-sparing approach.⁵⁷ After transurethral resection of the bladder, the combination of cisplatin, methotrexate, and vinblastine (CMV) was administered for two cycles followed by 4,000 Gy of irradiation over five weeks with concomitant cisplatin at 70 mg/m² on day one and 21. Repeat urologic evaluation was then undertaken. Of the 53 patients entered, 28 had a clinical complete response (53 percent) and underwent an additional 2,480 cGy and one additional cycle of cisplatin. Those with incomplete responses underwent radical cystectomy. Of the 28 patients who completed the bladder-sparing protocol, 25 are alive and disease free, although three required cystectomy. The authors highlight the need for a randomized trial that includes a simultaneous comparison group before definitive recommendations for this bladder-sparing approach can be made. These results demonstrate the feasibility of a bladder-sparing approach, and therefore patients who are not candidates for radical cystectomy or who decline surgery may have an option that appears superior to radiation therapy alone.

A major advance in the surgical management of invasive bladder cancer occurred with the development and popularization of continent urinary diversion and orthotopic bladder substitution.

These procedures make cystectomy a more acceptable treatment for many patients. The popularization of these approaches began with the Kock continent ileal reservoir⁵⁸ and the Camey⁵⁹ ileal bladder, but these procedures have now largely been replaced by more successful operations.

Continent urinary diversions allow patients to avoid external collection devices and permit minimal change in body image with only a small stoma on the lower abdomen or at the umbilicus. Intermitent catheterization is required. The most commonly used continent diversion is the Indiana pouch.⁶⁰ As illustrated in Figure 2, the Indiana pouch uses the detubularized right colon and the narrowed terminal 10 cm of ileum. The ileocecal valve, which is intussuscepted surgically, provides the primary continence mechanism for the pouch. Overdistension will result in leakage and protect the pouch from rupture. The colon is more susceptible to malignant transformation, but the risk of cancer formation in the Indiana pouch is far less than that of ureterosigmoidostomy because the fecal and urinary systems remain separated. Removal of the distal ileum raises the risk of vitamin B₁₂ deficiency, but the long-term results of continent diversion appear to be at least as good as those of the standard Bricker diversion.

Orthotopic bladder replacement, when practicable, provides the optimal reconstruction of the urinary tract following cystectomy. Currently orthotopic bladder reconstruction is appropriate only for men who have low risk for recurrence of transitional cell carcinoma of the urethra. The short female urethra, like the prostatic urethra in the male, is generally removed at the time of cystectomy to provide an adequate surgical margin, so women are currently not considered to be candidates for orthotopic bladder substitution. Research is in progress to extend the benefit of this surgery to women. Using the normal male urethra allows

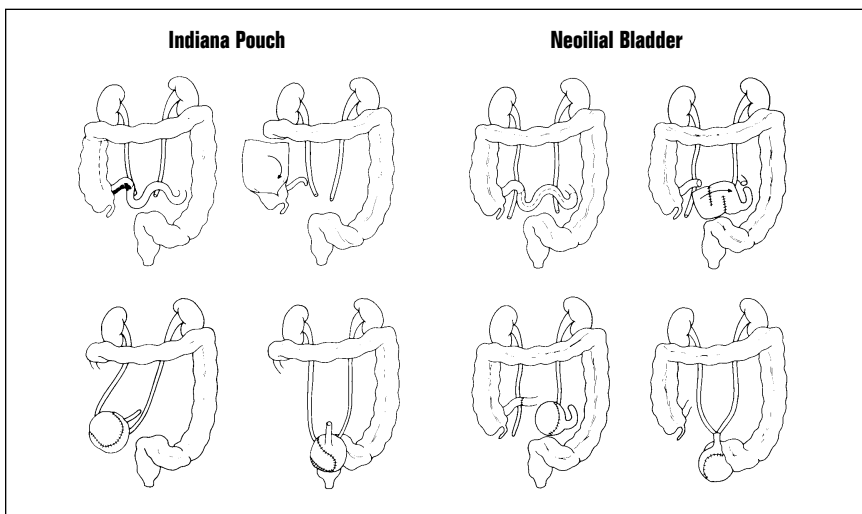


Fig. 2. Illustrations of the two most-common bladder substitutes. The "Indiana pouch" on the left uses the ascending colon as a reservoir, the ileocecal valve as a continence mechanism, and the terminal ileum as a catheterizable conduit that is generally brought to the umbilicus. The neoilial bladder on the right is constructed from ileum folded into a spherical reservoir. The reservoir is then sewn to the urethra, and the patient voids by increasing abdominal pressure.

preservation of body image, near normal voiding with the aid of Valsalva, and protection from urinary infection by avoiding instrumentation and direct contact of urine with the skin.

Various orthotopic bladder substitutions have been developed using colon and ileum. The cecum and terminal ileum have been successfully used,⁶¹ but this diversion suffers the same risk of vitamin B₁₂ deficiency and malignant degeneration as noted above with continent colon diversions. Perhaps the most frequently performed orthotopic substitution procedure performed is the Hautmann⁶² neoilial bladder, which uses a "W" shaped detubularized segment of distal ileum and antireflux uretero-ileal anastomoses. We have preferred a modification of the Studer⁶³ bladder, which uses an "S" shaped detubularized segment of ileum and a nonrefluxing intussuscepted ureter-

al anastomosis into a tubularized ileal segment (Fig. 2). Preserving a 10-cm segment of ileum allows generous resection of the distal ureters, which commonly develop carcinoma in situ, and ready conversion to a standard ileal diversion if removal of the neobladder and urethra is necessitated by the occurrence of transitional cell carcinoma of the urethra.

Treatment of Metastatic Disease: Patient Selection for Chemotherapy

One of the most difficult and challenging problems in oncology is the treatment of patients with metastatic transitional cell cancer of the bladder. About 30 percent of patients with transitional cell cancer of the bladder develop metastases during the course of their disease. These patients are roughly equally divided between those who present with regional or dis-

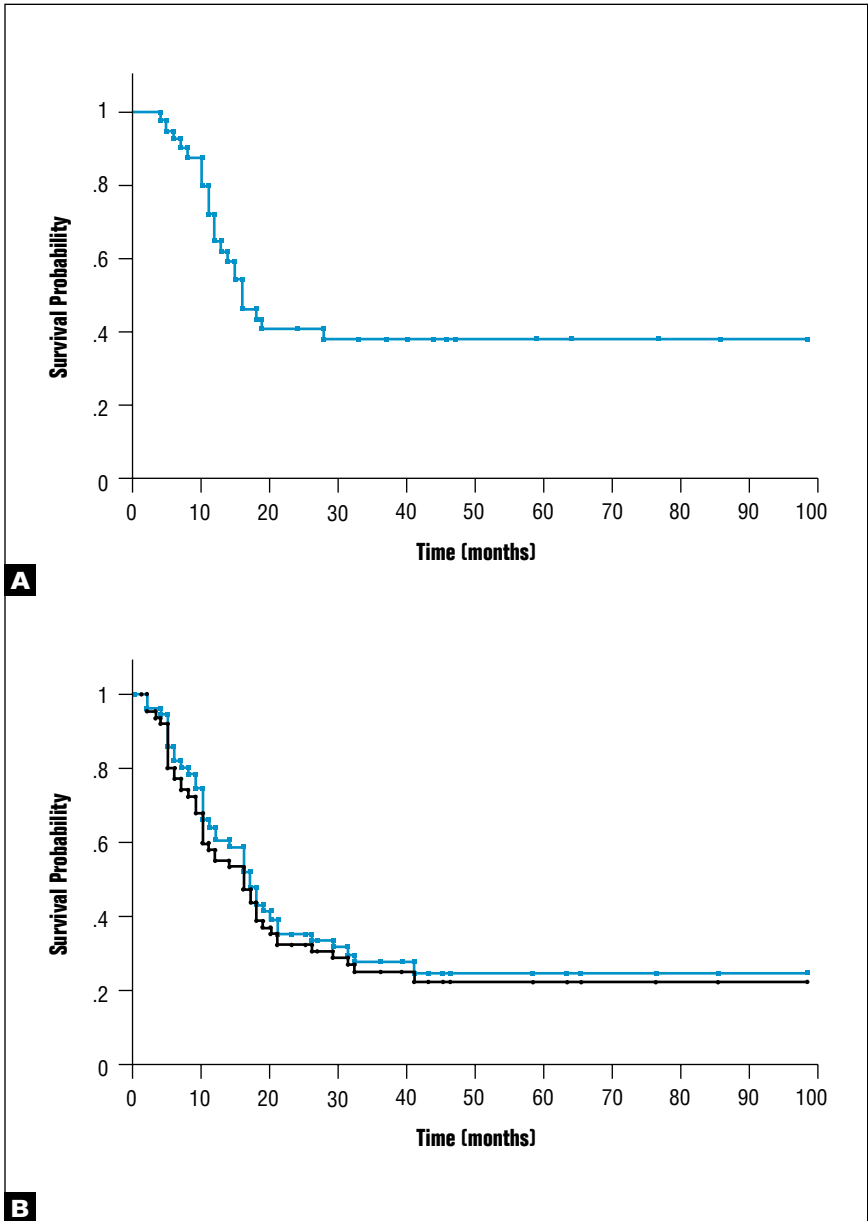


Fig. 3. Long-term survival for advanced transitional cell carcinoma of the urothelium treated with the combination of cisplatin, methotrexate, and vinblastine plus surgical debulking. (A) Progression-free survival, all patients. (B) Survival, all evaluable patients (blue), all entered on study (black). Adapted with permission of Miller and Torti.⁶⁶

tant metastases at diagnosis and those who relapse after local therapy for invasive transitional cancer.

Historically, patients with metastases have died rapidly. This has been thought to be due to the rapid growth of metastatic disease in lung, liver, and bone and the frequent and severe local and regional morbidity with frequent ureteral obstruction and infection. The clinical management of these patients is challenging and frequently involves close cooperation of medical oncologists, radiation therapists, and urologists.

Selecting patients for chemotherapy, particularly for more-aggressive regimens like CMV or the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC), requires a great deal of clinical judgment. Some patients with bladder cancer have impaired renal function, are frail, or have other comorbidity that makes aggressive chemotherapy problematic. For such patients, less aggressive chemotherapy or, where appropriate, irradiation directed to symptomatic sites of metastases may be the appropriate treatment. However, recent evidence confirms that age alone should not be used as a contraindication to aggressive therapy.⁶⁴

Metastatic Disease: Single-Agent Chemotherapy

With rare exceptions, such as Burkitt's lymphoma or choriocarcinoma in women, single-agent chemotherapy does not produce prolonged remission and is rarely curative. Nonetheless, single-agent chemotherapy trials generate response information upon which combination regimens can be designed and tested. Among single agents evaluated in transitional cell carcinoma of the bladder, the most effective are cisplatin and methotrexate. Cisplatin is probably the most active chemotherapeutic agent, producing responses in 15 to 40 percent of patients treated.⁶⁵⁻⁶⁷

Patients rarely achieve complete responses, however. Methotrexate has also been thoroughly studied, producing responses at both low doses (20 to 100 mg/m²) and intermediate doses (about 200 mg/m² with folinic acid rescue).⁶⁸⁻⁷⁰ Vinblastine, 5-fluorouracil, and doxorubicin are also useful agents.⁶⁶ Carboplatin as a single agent appears to have a lesser response rate at 400 mg/m² than cisplatin at 70 to 100 mg/m², although it has been successfully substituted for cisplatin in combination regimens; further controlled studies need to be performed to clarify

About 30 percent of patients with transitional cell cancer of the bladder develop metastases during the course of their disease.

the relative utility and toxicity of carboplatin and cisplatin.^{66,71} Recently, gallium nitrate has shown promise, although toxicity has been substantial.^{72,73}

Metastatic Disease: Combination Chemotherapy

A number of combinations of chemotherapeutic agents have been investigated in detail. The CMV combination consists of cisplatin 100mg/m² day one and vinblastine 4 mg/m² and methotrexate 30 mg/m² days one and eight repeated every 21 days.^{66,74} The M-VAC combination consists of methotrexate 30 mg/m² day one, vinblastine 3 mg/m² day three, doxorubicin 30 mg/m² day two, cisplatin 70 mg/m² day two, and vinblastine and methotrexate at the same doses day 14 and 21, in repeated cycles every 28 to 35 days.^{75,76} The CISCA combination consists of cyclophosphamide 650 mg/m², doxorubicin 50 mg/m², and cisplatin 100 mg/m².⁷⁷

In the last few years, certain observations have been made concerning patients treated with these regimens. These observations are listed below.

1. A combination of CMV and aggressive surgical resection of residual disease produces a cohort of patients (about 23 percent of all entered patients, 40 percent of all evaluable patients) who remain continuously disease free off treatment for many years. These patients are probably cured (Fig. 3).⁶⁶

2. The highest response rates in metastatic disease have been reported with cisplatin, methotrexate, and vinblastine +/- doxorubicin. A number of investigations using CMV and M-VAC have been reported to produce clinical complete responses in a substantial proportion of patients.^{66,76,78,79}

3. M-VAC appears superior to CISCA, as determined in a randomized trial demonstrating a higher overall response rate (65 percent versus 46 percent) and improved median survival (48 weeks versus 36 weeks, $p=.004$).⁸⁰

4. M-VAC is superior to single-agent cisplatin. In a randomized trial of 269 patients with advanced urothelial carcinoma, M-VAC compared favorably with cisplatin in response rate (39 percent versus 12 percent), progression-free survival (10.0 months versus 4.3 months), and survival (12.5 months versus 8.2 months). Toxicity was substantially greater for the combination treatment.⁸¹

5. CMV and M-VAC have resulted in the expression of heretofore clinically occult disease in certain sites. Isolated brain recurrences have been described in patients treated with these regimens; brain metastases had rarely been reported prior to the advent of chemotherapies capable of producing complete responses at peripheral metastatic sites.⁸²⁻⁸⁴

6. The toxicity of these regimens is substantial and sometimes life threatening. Toxicity can be partially ameliorated by the use of growth factors; growth factors allow conventional doses of

combination chemotherapy to be delivered closer to intended schedules.^{85,86} This is important because in one study of M-VAC, for example, about three quarters of patients treated required dose modifications.⁸¹

However, the use of growth factors to augment chemotherapy dosage and enhance response and survival has not been successful.⁸⁷⁻⁸⁹ Minimal to moderate dose escalation has been associated with substantial toxicity (nadir thrombocytopenia and mucositis and, in spite of growth factor support, neutropenia).⁹⁰ In a recent M-VAC dose-escalation evaluation, for example, severe or life-threatening mucositis occurred in 20 of 35 patients and eight toxic deaths occurred in the 35 patients studied, including three potentially related to cardiorespiratory toxicity (congestive heart failure, respiratory failure, and possible myocardial infarction).⁸⁹ Further, in the relatively small numbers of patients evaluated, modest dose escalation did not substantially enhance response rates. The overall response rate of dose-intensive M-VAC therapy was 60 percent compared with the previous intergroup experience with standard-dose M-VAC of 39 percent. The complete response rate in the dose-intensive treatment was 17 percent versus 13 percent in previous intergroup experience.⁸⁹ However, complete evaluation of dose intensity was hampered by the toxicities mentioned above.

Adjuvant or Neoadjuvant Chemotherapy

Use of adjuvant chemotherapy after surgical resection of muscle-invasive but clinically localized (T2, T3a, or T3B; N0 or N1) bladder cancer is not considered standard treatment. Neither is the use of chemotherapy prior to surgical resection (neoadjuvant therapy) or the use of chemotherapy as an adjunct to radiation therapy delivered with curative intent. The routine use of such approaches

should be discouraged. These patients should, whenever possible, be placed on clinical trials.

CHEMOTHERAPY ADJUVANT TO SURGICAL RESECTION

The use of chemotherapy in bladder cancer as adjuvant treatment after surgical resection has had limited investigation. Nonetheless, the trials reported thus far support the use of chemotherapy in this clinical setting. Skinner et al⁹¹ treated 91 patients with T3, T4, or N1,M0 transitional cell carcinoma or transitional cell carcinoma plus squamous or glandular elements with chemotherapy, primarily cisplatin, cyclophosphamide, and doxorubicin. They found increased disease-free survival for patients receiving chemotherapy compared with control patients (70 percent versus 46 percent at three years) and increased survival (4.3 years versus 2.4 years).

Stockle et al⁹² treated patients with methotrexate, vinblastine, cisplatin, and either doxorubicin or epirubicin. They found relapse in 18 of 23 patients who received local treatment alone but in only three of 18 who received adjuvant chemotherapy.

Logothetis et al^{93,94} compared the outcome of three groups of patients with transitional cell carcinoma: those who received chemotherapy with cyclophosphamide, doxorubicin, and cisplatin for local/regional bladder cancer at high risk of recurrence, those who received no chemotherapy but also were at high risk of recurrence, and those who received no chemotherapy. Survival rates at about three years for the high-risk patients equaled those of low-risk patients in this nonrandomized comparison (61 percent versus 73 percent). However, those who did not receive chemotherapy had a survival of 38 percent. Prospective, randomized trials of adjuvant chemotherapy are ongoing and will hopefully clarify the role, if any, of this treatment.

CHEMOTHERAPY PRIOR TO SURGICAL RESECTION (NEOADJUVANT CHEMOTHERAPY)

A substantial body of literature is accumulating on the use of chemotherapy prior to surgical resection of localized transitional cell carcinoma of the bladder. The basis and justification for neoadjuvant therapy is the substantial chemotherapeutic activity against the primary muscle-invasive bladder tumor. CMV and M-VAC are active against deeply muscle-invasive bladder cancers, causing significant downstaging.

Three cycles of CMV have recently been reported to produce a complete-response rate of 56 percent and a partial-response rate of 25 percent (81 percent overall) in 36 patients with muscle-invasive bladder cancer.⁹⁵ In another study, CMV produced a pathologic complete response in six of 24 (25 percent) patients who underwent cystectomy. At 48 months, 15 patients (58 percent) were alive without evidence of disease.⁹⁶

In an M-VAC series of 60 patients surgically staged, 14 (23 percent) were downstaged to T0.⁹⁷ A recent M-VAC neoadjuvant study reported a response rate of 78 percent, but there were no pathologic complete responders.⁹⁸ In another M-VAC study, clinical complete response was reported in 47 percent of patients.⁹⁹

In locally advanced T3 or T4, N0 patients, CMV produced an overall response rate of 57 percent, with four of 44 complete responses at six weeks and two more between six and 12 weeks.¹⁰⁰ In patients with metastatic disease whose bladders remained intact, CMV produced a complete response to muscle-invasive disease in 11 of 17 patients (65 percent).¹⁰¹

Summary

In superficial Ta or T1 tumors intravesical chemotherapy can eradicate existing carcinoma in one third to one half of patients

and reduce tumor recurrence by 12 to 15 percent, on average. Superficial bladder cancer is remarkably sensitive to immunotherapy, particularly BCG. The use of BCG eradicates about two thirds of papillary carcinoma and nearly 90 percent of carcinoma in situ and reduces tumor recurrence by an average of 40 percent. Data now suggest that BCG immunotherapy reduces long-term tumor recurrence, disease progression, and mortality. The proclivity for tumor recurrence makes superficial bladder cancer an ideal malignancy for the evaluation of chemoprevention, and preliminary data suggest that high doses of vitamins may also reduce tumor recurrence.

In locally advanced T2b to T4, N0 or N1, M0 bladder cancer, substantial clinical responses can be achieved if chemotherapy is used prior to surgical resection of muscle-invasive tumor (neoadjuvant

treatment). Controlled trials are necessary to ascertain whether neoadjuvant chemotherapy improves survival. The use of CMV prior to and concomitant with bladder irradiation is also encouraging, but will require randomized trials to clarify its role in the treatment of invasive, nonmetastatic cancer. Finally, trials suggest benefit for chemotherapy used adjuvantly (after cystectomy) for muscle-invasive bladder cancer. However, further investigation is necessary to clarify and confirm the role of chemotherapy in this setting before it can be recommended routinely for patients.

In metastatic disease, chemotherapy with CMV or M-VAC with surgical resection of residual masses can produce a cohort of long-term survivors with advanced bladder cancer. How to increase this small but important population of patients is a question for further research. **CA**

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