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A practical approach to the recognition and management of superficial bladder cancer is based on risk assessment for tumor recurrence and progression.

Contemporary Management of Superficial Bladder Cancer

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Background: Bladder cancer is the second most common urologic malignancy after prostate cancer. Superficial bladder cancer presents as a heterogeneous group of tumors with variable biological potential. A significant percentage of patients diagnosed with superficial cancer will have multiple recurrences, and some will progress to invasive disease.

Methods: Patients are stratified into low- or high-risk for recurrence and progression. We review the most recent literature regarding intravesical therapy for superficial bladder cancer, and we summarize indications for the use of intravesical agents as well as their efficacy, toxicity, and cost.

Results: Several intravesical agents are available for the treatment of superficial bladder cancer. Patients may be identified as low- or high-risk for recurrence and progression. High-risk patients benefit from intravesical therapy.

Conclusions: Superficial bladder cancer is a heterogeneous group of diseases. Treatment is effective in preventing recurrences and progression in the high-risk group.

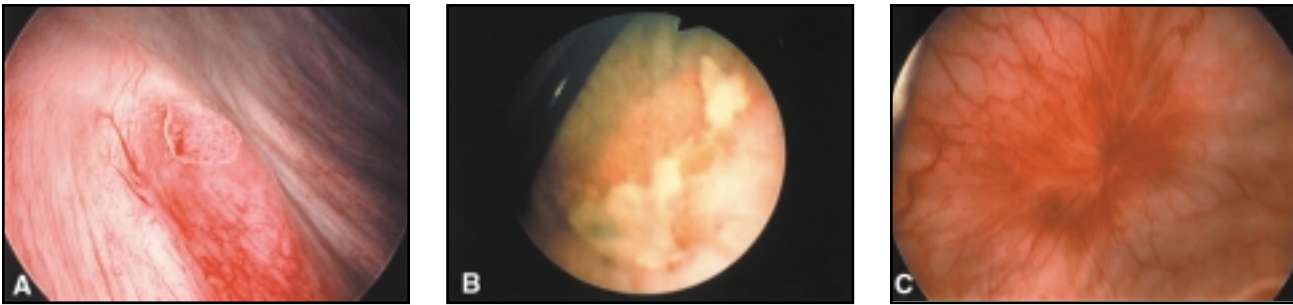
Introduction

Bladder cancer is the second most common urologic malignancy after prostate cancer. On histopathology, 93% of bladder cancers are transitional cell carcinomas, 5% are squamous cell carcinomas, and 2% are adenocarcinomas. The majority of bladder cancers present as superficial (80%), with only 15% presenting as invasive cancer and 5% as metastatic disease. Superficial bladder cancers are a heterogeneous group of cancers with variable biologic potentials. Three "substages" are defined (Table 1): Ta — papillary

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Figs 1A-C. — Superficial bladder cancers with variable cancer potentials. (A) Papillary, low-grade, low-stage tumor, (B) papillary/sessile, grade 3, T1 tumor, and (C) carcinoma in situ.

tumor confined to the urothelium (Fig 1A), T1 — papillary tumor invading the underlying lamina propria (Fig 1B), and Tcis (carcinoma in situ) — flat, reddened lesions on cystoscopic appearance with high-grade histologic features (ie, changes throughout the whole thickness of the urothelium, marked loss of polarity, and easily found mitotic figures) but with changes confined to the urothelium only (Fig 1C).

Diagnosis and Initial Management

The most common clinical presentation is asymptomatic gross or microscopic hematuria. Occasionally, patients present with irritative voiding symptoms: dysuria, frequency, and urgency. This symptom complex is highly suggestive of carcinoma in situ. The presence of hematuria is suggestive of cancer in the urinary tract until proven otherwise. Whenever the presence of transitional cell carcinoma is suspected, a full urologic evaluation consisting of cystoscopy, urinary cytology, and intravenous pyelogram is mandatory. This evaluation allows for assessment of the whole urinary tract since tumor lesions may be located anywhere along the upper urinary tract (calyces, renal pelvis, ureters) or lower urinary tract (bladder and proximal urethra). When a lesion is noted on cystoscopy, the configuration (flat, sessile, or papillary), location (trigone, base, right lateral wall, left lateral wall, dome), size (in centimeters), and number should be noted.

The initial management consists of complete transurethral resection of any visible tumors and selected biopsies of the bladder mucosa including the prostatic urethra. At the time of resection, an examination under anesthesia is performed prior to and following resection. The presence of a palpable mass suggests muscle invasion by tumor.

With cystoscopic and pathologic findings, the clinician can determine if further treatment with intravesical therapy is required. Additional treatment decisions

are based on the estimates of risk of recurrence and progression. Patients can be stratified in two groups: low risk and high risk for recurrence and progression (Table 2).

Low-Risk Group

In most cases, patients present either with a bladder tumor for the first time or with a long interval of time without recurrence. On cystoscopy, there may be up to 3 lesions, they could be up to 3 cm in size, and they have a papillary configuration. On histopathology, the lesions do not invade the lamina propria (stage Ta) and are well or moderately differentiated (grade I or II).

High-Risk Group

Patients in this group may present with a bladder tumor for the first time, or they may have had multiple recurrences in a short period of time. On cystoscopy, there may be more than 3 lesions, they may be larger than 3 cm, and they may appear to be less papillary (sessile) in configuration. Unfavorable findings include incomplete resection due to technical problems (such as location of the tumor in an area that is difficult to resect) or diffuse bladder involvement. Pathologically, tumors are high grade and/or invade the lamina propria (T1 lesions). The presence of carcinoma in situ alone or associated with papillary tumors is also an adverse prognostic sign.

Newer molecular markers are being evaluated to more precisely define poor risk. These markers include immunostaining for mutated p53, the presence of aneu-

Table 1. — Substages of Superficial Bladder Cancer

Ta	Papillary tumor confined to the urothelium
T1	Papillary tumor invading the underlying lamina propria
Tcis	Flat, reddened lesion on cystoscopic appearance; high-grade histologic features confined to the urothelium

ploidy, and a high proliferation rate (Ki-67 immunostain-positive tumors).

Management

Patients with tumors with low-risk characteristics for recurrence and progression are managed by transurethral resection (TUR) alone. Patients are followed with periodic cystoscopies and urine cytologies. These examinations are performed every 6 months for the first 2 years and then yearly for at least 5 years. Newer assays for the presence of the bladder tumor antigen (BTA) and nuclear matrix protein (NMP-22) in voided urine have recently been introduced in clinical practice to supplement the cystoscopic and cytologic evaluation. However, the true role of these newer tumor assays in the routine management of bladder cancer has yet to be defined due to their poor specificity.¹

Tumors at high risk of recurrence and progression are treated with intravesical therapy after complete resection of all visible tumors. Agents commonly used in the United States are thiotepa, mitomycin C, bacillus Calmette-Guérin (BCG), and interferon. Valrubicin was recently approved for the treatment of BCG refractory carcinoma in situ. Characteristics of these agents are summarized in Table 3.

The first-line intravesical agents for superficial bladder cancer are either BCG or mitomycin C. For carcinoma in situ, BCG is the first agent of choice. The optimal dose and treatment schedules for any of the intravesical agents are unknown. A 6- to 8-week course is usually recommended. Patients who fail primary treatment may be treated with a different agent. In the case of BCG, a second course with the same agent may be considered. A recent Southwest Oncology Group study suggests continuing intravesical BCG for up to 3 years to decrease recurrence and progres-

Table 2. — Superficial Bladder Cancer Risk Groups

	Low	High
Multiple, frequent recurrences	No	Yes
Appearance	Papillary, fine stalk	Papillary, thick stalk, or sessile
Size	≤3 cm	>3 cm
Number of lesions	≤3	>3
Transurethral resection	Complete	Incomplete
Stage	Ta	T1, Tcis
Grade	I-II	III

sion.¹³ Cystectomy is recommended for patients who fail a second BCG course due to the high risk (30%-60%) of progression.²² INF- α and valrubicin may be used to salvage patients who decline cystectomy or are not candidates for surgery.^{17,20}

Intravesical Therapy Agents

Thiotepa

Thiotepa was the first intravesical agent used for the management of superficial bladder cancer. It is seldom used in the United States as most of the reported studies show marginal or no benefit when compared with controls. In addition, the toxicity profile associated with thiotepa is higher than with other intravesical agents. Myelosuppression, leukopenia, and thrombocytopenia occur in 9%-54% of patients treated with this agent.²⁻⁴

Mitomycin C

Mitomycin C, an alkylating agent, is used in doses ranging from 20-60 mg diluted in water at concentrations ranging from 0.5-2.0 mg/mL. Mitomycin C is administered weekly for 6 to 8 weeks as induction with or without maintenance for 1 year. In one study, the overall response rate was 43% for papillary lesions and 58% for carcinoma in situ.⁵ Tolley et al⁶ reported on

Table 3. — Intravesical Agents for Tumors at High Risk of Recurrence and Progression

	Dose	Induction Scheme	Most Common Toxicities	Cost Per Dose (AWP \$)
Mitomycin C	20 - 60 mg	Weekly \times 6 - 8 weeks	Chemical cystitis, allergic skin reactions	312.00
Bacillus Calmette-Guérin	80 mg	Weekly \times 6 weeks	Cystitis, hematuria	157.00
Interferon	10 - 100 million units	Weekly \times 6 weeks	Flu-like symptoms	1,210.00
Valrubicin	80 mg	Weekly \times 6 weeks	Bladder irritation	1,782.00

AWP = average wholesale price

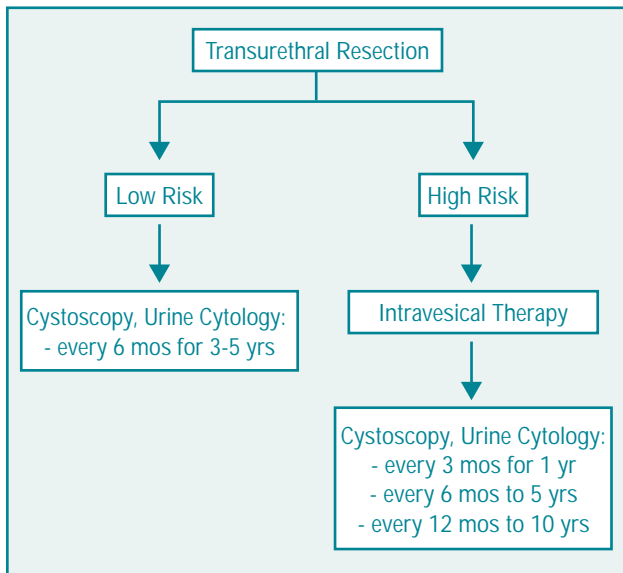


Fig 2. — Guidelines for frequency of examination for patients with superficial bladder cancer according to risk.

502 patients following complete resection. Patients were randomized among three treatment arms: no further treatment, a single instillation at resection, and immediate instillation of mitomycin C within 24 hours of resection followed by 1 year maintenance. A benefit was observed for the immediate instillation group with or without maintenance in recurrence-free survival in the first 2 years of a median follow-up of 7 years. A study by Solsona et al⁷ confirmed the beneficial effect of a single instillation of mitomycin C after TUR. The most common side effects from the intravesical use of mitomycin C are chemical cystitis and allergic skin reactions.^{4,8}

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) is a live attenuated form of mycobacterium bovis. The exact mechanism by which BCG produces its antitumor effect is unknown. BCG is considered the most active agent in the treatment of superficial bladder cancer, especially for carcinoma in situ. Morales and associates⁹ first reported on the use of BCG for the treatment of superficial bladder cancer in 1976. Since then, multiple studies have confirmed the efficacy of BCG in decreasing tumor recurrences from 83% to 44% and tumor progression from 35% to 7% when compared to TUR alone.^{10,11} A recent study by Herr¹² also demonstrated an improved long-term progression-free survival at a minimum follow-up of 15 years with the use of BCG in high-risk patients. Of concern was the finding that 35% of treated patients eventually died of bladder cancer when followed for many years. A recent Southwest Oncology Group study¹³ addressed the use of maintenance BCG. Standard induction therapy alone (6 week-

ly treatments) was compared with induction plus maintenance over a period of 3 years. Median recurrence-free survival time was twice as long and progression-free survival was significantly longer in the maintenance arm. Local toxicity secondary to BCG therapy is common but self-limited. Cystitis occurs in 90% of patients and hematuria in one third of patients.¹⁴ Severe complications such as fever, allergic reactions, and sepsis are rare and usually are associated to traumatic catheterization at the time of the BCG instillation.¹⁵ Prompt antituberculosis therapy can be life-saving if a patient develops a severe reaction to BCG.

Interferon

Interferon alpha (IFN- α) is the most commonly studied interferon in the treatment of superficial bladder cancer. An initial study¹⁶ with IFN- α reported a 38% complete response in 8 patients at a dose of 50 million units. A randomized control study¹⁷ compared 10 and 100 million units of IFN- α 2b given weekly for 12 weeks and then monthly for 1 year in the treatment of carcinoma in situ. High-dose and low-dose groups achieved complete response rates of 43% and 5%, respectively. Six of 9 patients (67%) who has failed prior BCG therapy had a complete response to interferon. Toxicity was low, and only 17% of patients had flu-like symptoms at the higher interferon dose. A recent study¹⁸ evaluated the combined use of low-dose BCG and IFN- α 2b. Twelve patients were treated with 60 mg of weekly BCG combined with IFN- α 2b. Four groups of 3 patients each received interferon in doses of 10, 30, 60, or 100 million units. There were no tumor progressions 12 months after treatment. Two patients had solitary recurrences. The treatment was safe and well tolerated.

Valrubicin

Valrubicin is an anthracycline related to doxorubicin. In animals, valrubicin is less toxic on contact with the bladder urothelium and does not cause cardiotoxicity when given systemically. The main toxicity is bladder irritation with frequency, dysuria, and urgency.¹⁹ An initial study²⁰ reported a complete response in 2 of 7 patients with BCG-refractory carcinoma in situ. Steinberg et al²¹ reported on 90 patients with recurrent carcinoma in situ who failed multiple prior courses of intravesical therapy including at least 1 course of BCG. Nineteen patients (21%) had a complete response (no evidence of disease recurrence for 6 months or longer). Median time to failure and/or last follow-up for complete responders was greater than 18 months. Of 79 patients who had recurrence after treatment, 44 (56%) underwent cystectomy. Valrubicin is recommended for patients with carcinoma in situ who have failed BCG and in whom immediate cystectomy is contraindicated.

Treatment Outcomes and Follow-up

In patients with superficial bladder cancer, 70% will respond to intravesical therapy while 30% will fail and develop a recurrence or progress to invasive disease. Surveillance of all patients with a diagnosis of bladder cancer is mandatory. Evaluation consists of cystoscopy and urine cytology. The roles of NMP-22 and the BTA test are currently controversial.¹ The frequency of examinations is dependent on risk. For low-risk patients, cystoscopy at 6-month intervals for the ensuing 3 to 5 years is adequate. For high-risk patients, cystoscopy is recommended every 3 months for the first year, every 6 months for 5 years, and yearly for 10 years (Fig 2). Patients with low-grade and low-stage tumors who fail BCG are candidates for a subsequent treatment with other intravesical agents. These patients have a low risk of progression with multiple recurrences being the major clinical challenge. Of the patients with high-grade tumors and carcinoma in situ who fail a first course of BCG, 50% will respond to a second course of BCG. Patients who fail this second course of treatment should undergo cystectomy as they are at a high likelihood (30%-60%) of developing invasive or metastatic disease.²²

Conclusions

The combination of cystoscopy findings and pathology characteristics of the tumor allows for the stratification of patients into a high-risk or low-risk group for cancer recurrence and progression. This assists decisions on intravesical therapy. Newer molecular markers promise the possibility of further refining risk assessment. For high-risk patients, several intravesical agents are available. Their use has proved beneficial in reducing recurrence and progression.

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