Contemporary Intravesical Treatment Options for Urothelial Carcinoma of the Bladder

Stephen A. Brassell, MD, and Ashish M. Kamat, MD

Abstract

To provide a comprehensive review of intravesical treatment options for non–muscle-invasive bladder cancer, we performed a search of the PubMed database for articles between 1980 and 2006 that reported on intravesical agents for treating this disease. Data were compiled and analyzed, emphasizing findings from large multicenter trials, studies providing reproducible results, data that could be confirmed by cross-referencing the literature, and phase I or II studies for pertinent novel agents. A critical analysis of evidence shows that: 1) treatment with Bacillus Calmette-Guérin (BCG), including a maintenance schedule (with or without interferon–α), is the most effective therapy for limiting recurrence, is the only therapy that reduces the incidence of progression, and overall is superior to chemotherapy; 2) mitomycin C, gemcitabine, anthracyclines, and thiopeta provide similar benefits for preventing recurrence in patients with minimal effect on progression; and 3) using chemotherapeutic agents immediately after transurethral resection (when use of BCG is contraindicated because of the risk for systemic absorption) reduces the recurrence rate by up to 50% and seems to be the ideal method of chemotherapy. Although various clinical factors dictate which agent is most appropriate for an individual patient, the current literature supports a single perioperative dose of intravesical mitomycin C followed, in appropriate cases, by induction and maintenance therapy with intravesical BCG. (JNCCN 2006;4:1027–1036)

Bladder cancer is the second most common urologic malignancy, with more than 61,000 new diagnoses and more than 13,000 cancer-related deaths annually. Although 70% of bladder tumors are non–muscle invasive at initial diagnosis, the clinical course of urothelial carcinoma (UC) can be unpredictably aggressive. Intervention at an early stage can improve outcomes for patients with bladder cancer.

The mainstay of treatment for non–muscle-invasive UC of the bladder is complete transurethral resection of all visible lesions. Unfortunately, even with aggressive resection, up to 70% of bladder tumors recur and as many as 10% to 30% progress.

Certain subgroups of patients with bladder cancer have a higher risk for recurrence and progression and should be considered for intravesical therapy after transurethral resection. These high-risk groups include patients with tumors classified as high-grade (grade 3), which are associated with a 45% risk for progression at 3 years and the greatest risk for cancer-related death, and patients with carcinoma in situ (CIS), which is associated with a 54% rate of progression to muscle-invasive disease. In addition, irrespective of grade, patients with large lesions (> 3 cm), multifocal tumors, evidence of lamina propria invasion, or early recurrence (within 2 years) have been shown to be at increased risk. In these high-risk groups, aggressive intervention with intravesical therapy leads to response rates up to 85%. Furthermore, because even solitary, low-grade, Ta lesions can recur, these must also be considered for adjunctive intravesical therapy, although of lesser intensity.

Determining which agents to use for intravesical therapy is becoming increasingly complex given the multitude of treatment options available and changing data regarding their efficacy. This article provides a comprehensive, up-to-date review of the literature to assist physicians in planning intravesical therapy.

Methodology

A PubMed database search was initiated for articles published between 1980 and 2006 investigating the use
of intravesical agents for treating non–muscle-invasive bladder cancer. Articles were selected to provide a comprehensive review, emphasizing large multicenter trials, studies providing reproducible results, and data that could be confirmed by cross-referencing the literature. Included in this process were review articles and meta-analyses so that an accurate representation of the body of literature could be presented. Phase I and II studies were also included based on their clinical relevance and cited efficacy.

Results

Immunotherapy

Bacillus Calmette-Guérin: Since its approval by the U.S. Food and Drug Administration (FDA) in 1990 for treating CIS of the bladder, bacillus Calmette-Guérin (BCG) has been the benchmark against which all other intravesical therapies are compared. BCG was originally developed as a live attenuated vaccine against tuberculosis; Pearl first described its antineoplastic activity in 1929. Morales et al. were the first to use intravesical instillations of BCG in 1976 to treat non–muscle-invasive UC.

The exact mechanism of action of BCG is unknown. BCG attaches to the bladder epithelium, where it is incorporated into the cell, leaving behind surface glycoproteins that are believed to stimulate an immune response. This immune stimulation is nonspecific and includes macrophages, T lymphocytes, B lymphocytes, natural killer cells, and various cytokines. Tumor necrosis factor–related apoptosis-inducing ligand has been implicated recently as having a role in BCG’s mechanism of action.

Efficacy: In 1980, Lamm et al. presented the first controlled trial confirming the efficacy of BCG in treating UC of the bladder. Subsequent trials have confirmed the usefulness of BCG in decreasing the incidence of progression, improving disease-free interval, and, most importantly, prolonging survival in patients with non–muscle-invasive disease. The rate of disease recurrence in patients treated with resection alone has been documented at 46% to 100%; treatment with BCG can reduce that risk to between 26% and 35%. BCG is the only intravesical agent that has been shown to confer a significant benefit in tumor progression. This benefit was shown in 3 randomized controlled trials, all of which showed a decreased incidence of progression to muscle-invasive or metastatic disease. A meta-analysis of 24 studies investigating the influence of BCG on progression showed that it decreased the odds by 27% (P = .001). Although not the subject of the analysis, the odds of death from any cause and from bladder cancer were found to decrease by 11% and 19%, respectively (P = .20), even at an average follow-up of 2.5 years.

BCG has also shown efficacy in patients with unresected disease, with more than one third experiencing response. However, complete resection followed by intravesical therapy remains the mainstay of therapy for non–muscle-invasive bladder cancer (except in CIS).

Dose and Schedule: Intravesical therapy with BCG should be delayed until at least 1 week after transurethral resection, and most clinicians wait 2 to 3 weeks to allow adequate postoperative healing, which minimizes the risk for systemic absorption. Although an intravesical dose between 100 million and 1 billion colony-forming units is the most effective, good response has been reported with doses as low as 10 million. In patients who experience significant side effects at the initial dose, the dosage can be reduced by one third to one hundredth of the initial dose with minimal reductions in efficacy.

Treatment schedules vary, but strong evidence suggests that a course of induction therapy followed by a course of maintenance therapy leads to better outcomes for recurrence and progression than induction therapy alone. In fact, without a maintenance regimen, intravesical BCG loses its recurrence advantage over intravesical chemotherapy and does not act as a deterrent to progression.

The dose and schedule of BCG must be optimized to ensure the best long-term response. BCG regimens should 1) allow the option of reinduction therapy in select patients whose disease recurs (but does not progress) after an initial course of BCG induction therapy, and 2) include at least 1 year of maintenance therapy. The regimen used in the Southwest Oncology Group (SWOG) trial 8507 is one of the most effective regimens and one of the most commonly cited. In that trial, patients with CIS or recurrent non–muscle-invasive tumors were randomly assigned to 6 weeks of treatment with BCG or 6 weeks of treatment with BCG followed by maintenance therapy. The maintenance schedule was as follows: 3 weeks of BCG at 3, 6, 12, 18, 24, 30, and 36 months, with doses held in patients experiencing severe side effects. The
Interferons (IFNs) are glycoproteins that are involved in host immunity responses. Three main types of IFNs exist: IFN-α, IFN-γ, and IFN-β, with IFN-α-2b being the most extensively studied. IFNs are produced by activated T cells, natural killer cells, and monocytes. They mediate a variety of host immune responses, including antitumor, immunomodulatory, antiangiogenic, and antiproliferative properties.

Efficacy as Monotherapy: IFN used as a solitary intravesical treatment has shown minimal activity in decreasing the risk for disease recurrence. In a randomized trial that included 78 evaluable patients, the relapse rate was 28.2% in the IFN group versus 35.8% in the control group at 12 months (P = NS). Furthermore, any effect of IFN was not durable: relapse rates were equal at 4 years.

Intravesical monotherapy with IFN-α-2b leads to a complete response in up to 25% of patients with residual superficial disease. In addition, treatment with high-dose IFN-α-2b (100 million units weekly for 12 weeks, monthly for 1 year) resulted in a complete response in 43% of patients. Unlike BCG, IFN has no effect on disease progression or mortality. Efficacy as Combination Therapy: Combining IFN with chemotherapeutic agents has also been investigated. The combination of IFN-α-2b and mitomycin has been shown to be more effective than either treatment alone.

A more recent meta-analysis examining 24 trials with progression information showed similar results. With information on 4863 patients and a median follow-up time of 2.5 years, 260 (9.8%) of 2658 patients receiving BCG experienced disease progression, compared with 304 (13.8%) of 2205 patients in the control groups, representing a 27% reduction in the odds of progression (odds ratio, 0.73; P = .001). On subset analysis, only patients undergoing maintenance BCG experienced this benefit.

Not all maintenance BCG schedules provide the same benefit. Use of monthly, quarterly, or a second 6-week course of BCG after induction therapy are associated with no improvements over a single 6-week induction course. In contrast, the 3-week maintenance course used in the SWOG 8507 study results in a 20% absolute reduction in the recurrence rate that persists for at least 5 years. Furthermore, the "6 + 3" SWOG regimen decreases the number of cancer-related adverse events. Therefore, the authors recommend the SWOG maintenance regimen. Interferon: Interferons (IFNs) are glycoproteins that mediate host immune responses in a dose-dependent fashion. Three main types of IFNs exist: IFN-α, IFN-γ, and IFN-β, with IFN-α-2b being the most extensively studied and used in bladder cancer. IFNs increase antibody responsiveness, stimulate natural killer cells, and induce expression of class I major histocompatibility complex antigens. IFNs exhibit antitumor, immunomodulatory, antiangiogenic, and antiproliferative properties.
patients, 50 million units of IFN-α-2b plus full dose of BCG (note: the authors do not recommend using IFN in this population for reasons cited above); for patients in whom monotherapy with BCG failed, 100 million units of IFN-α-2b plus one third the standard dose of BCG; and for patients unable to tolerate BCG, one-tenth dose of BCG plus 100 million units IFN. Keyhole-Limpet Hemocyanin: Keyhole-limpet hemocyanin (KLH) is a highly antigenic protein from the hemolymph of the mollusk Megathura crenulata. KLH has been investigated for intravesical treatment of transitional cell carcinoma because of its nonspecific immunostimulant properties. Intravesical KLH has been shown to be more effective than intravesical mitomycin in preventing recurrence of superficial transitional cell carcinoma. The risk for recurrence at a mean follow-up time of 20 months was 14.3% for KLH versus 39.3% for mitomycin (P < .05). However, KLH is less effective than BCG; rates of recurrence were 41.2% with KLH versus 14.2% with BCG with similar follow-up times. Overall, KLH is safe. Trials investigating the use of KLH in combination with BCG are being planned.

Bropirimine: Bropirimine is a broad-spectrum immunostimulatory compound with oral absorption and urinary excretion. It incites B-cell proliferation, macrophage activity, natural killer cells, and lymphokine-activated killer cells, and promotes production of IFNs, interleukin-1 (IL-1), and tumor necrosis factor.

Although bropirimine is not available for clinical use in the United States, a phase III trial showed results equivalent to those with BCG in patients with CIS; 92% of patients experienced a complete response at a mean follow-up time of 12 months. Dosages of 3 g/d for 3 consecutive days with a 4-day drug-free interval have been recommended, with maintenance therapy extending up to 1 year.

Results with the combination of bropirimine and BCG are not encouraging: the estimated 5-year progression-free survival rate was 53% and the estimated 5-year survival rate was 80%.

ILs, Tumor Necrosis Factor, and Colony-Stimulating Factor: ILs constitute an important component of the immune response against foreign antigens. They are produced by antigen-presenting cells and stimulate T-cell and natural killer cell proliferation and the production of various cytokines. IL-2 has notable efficacy against other urologic malignancies; however, its efficacy in bladder cancer is not as clear. Although one study showed that IL-2 used in the neoadjuvant setting did not decrease tumor size, the recurrence rate was less than expected, which is consistent with the effect of IL-2 in the adjuvant setting. Multiple reports characterize IL-12 as a stimulator of potent antitumor activity in the mouse model and indicate that it improves the efficacy of radiotherapy, chemotherapy, and BCG when administered concomitantly with these modalities. Unfortunately, despite these encouraging reports, IL-12 has no documented benefit against bladder cancer in humans. A phase I study enrolling 15 patients in whom at least 1 prior intravesical therapy failed or who experienced at least 2 recurrences of low-grade tumors were given a dose of IL-12 ranging from 5 to 200 mcg. Although no side effects resulted, no evidence of tumor response was seen in patients whose tumors were visible before treatment, and 5 of 12 patients experienced recurrence within a 4-week follow-up. The same lack of response has been noted with the use of other immunomodulators, such as tumor necrosis factor and colony-stimulating factor.

Mycobacterial Cell Wall–DNA Complexes: Mycobacterial cell wall extract has been used intravesically to replicate the efficacy of BCG while avoiding its side effects. In this preparation, mycobacterium DNA preserved in the cell wall facilitates a dual effect: induction of anticancer cytokines and a direct effect on cancer cell division mediated by apoptosis. Mycobacterial cell wall–DNA complexes have been administered in humans using oil emulsion at a dose of 4 mg once weekly for 6 weeks and then monthly for 1 year. In the setting of CIS, this regimen resulted in recurrence-free survival rates of 62.5% at 12 weeks, 49.3% at 24 weeks, and 41.1% at 60 weeks. Further trials are needed and are being planned.

Alternative Agents: Rubratin (a cell-wall preparation of Nocardia rubria; ASTA Pharma AG, Frankfurt, Germany), transforming growth factor α–Pseudomonas exotoxin 40, and mistletoe lectin have all shown immunostimulatory properties when administered intravesically in phase I studies. Further investigation of their clinical efficacy is pending.

Chemotherapy
Although the literature indicates that BCG is the most effective agent for intravesical therapy in terms of limiting recurrence of non–muscle-invasive UC and the only agent that reduces the risk for progression and
mitomycin C (mitomycin) is a cross-linking agent that inhibits DNA synthesis. Because of its high molecular weight (334 kD), systemic absorption is low and side effects are minimal even with immediate postoperative instillation in the operating room.33

Efficacy: Mitomycin is becoming a popular intravesical agent, with increasing literature supporting its efficacy in the postoperative setting.24 A recent meta-analysis examining the use of mitomycin after surgery showed a 39% decrease in the odds of recurrence in patients with low-risk disease and a 56% decrease in the odds of recurrence in patients with high-risk disease. When mitomycin is administered in the adjuvant setting, response rates range from 14% to 31%.35 In patients with Ta and T1 tumors, whether recurrence rates are lower with mitomycin than with other chemotherapeutic agents is unclear.46 In patients with CIS, mitomycin produces superior disease-free rates: 35.6% for mitomycin versus 16.9% for doxorubicin and epirubicin.23

Multiple studies have compared mitomycin with BCG for treating disease associated with a high risk for recurrence. These studies showed that BCG is superior, but only when treatment includes maintenance therapy. A recent meta-analysis of 5 trials evaluated these 2 agents in treating CIS and also found BCG to be superior only when treatment included maintenance therapy. In 3 of the studies, the overall disease-free survival rate was 32.9% for mitomycin versus 45.4% for BCG treatment that included maintenance therapy. This represents a 43% reduction in the odds of treatment failure for patients treated with BCG.21

Three previous meta-analyses comparing mitomycin with BCG also concluded that maintenance BCG is needed for any significant benefit.14,57,58

Insufficient data are available for conclusions regarding the relative benefits of BCG and mitomycin with respect to progression or survival.19,20 However, single-agent studies have consistently documented that no chemotherapeutic agent delivered as monotherapy has shown any effect on limiting progression or increasing survival.41

Optimization regimens have been established to maximize the effectiveness of mitomycin. Interventions such as reducing residual urine volume, voluntary dehydration, and urine alkalinization have resulted in a 15% change in absolute risk and a 45% reduction in relative risk compared with standard regimens.63 Furthermore, recent reports have shown that adding electromotive therapy (establishing a potential difference across the bladder wall using electric current [20 mA]) nearly doubles the time to first recurrence compared with time to recurrence after passive diffusion, and provides outcomes equivalent to those seen after BCG treatment.63 Theromotherapy in combination with mitomycin has also been used for residual high-grade tumors, resulting in successful ablation of 75% of lesions and an 80% recurrence-free rate at 20 months, with most patients having T1 tumors.64

Some studies have examined combination therapy with mitomycin and BCG. Initial reports indicated no added benefit of combination therapy over either agent alone.46–50 However, a recent report in a cohort of patients with T1 tumors showed that the combination of BCG and electromotive mitomycin given in an induction-therapy-plus-maintenance-therapy protocol reduced the recurrence rate by 16%, the progression rate by 12.6%, the risk for death from bladder cancer by 10.6%, and the risk for death from any cause by 10.9% compared with BCG alone. Furthermore, combination therapy was associated with no increase in toxic effects.69

Dose and Schedule: When mitomycin is given as a single postoperative dose, outcomes are better when the drug is administered within 6 hours after resection than when the drug is administered 24 hours after resection.70 The most frequent dose of mitomycin is 40 mg diluted in 20 mL of normal saline with an in-dwell time of 60 minutes. Longer in-dwell times lead to minimal improvement in outcomes, and continuing therapy for more than 2 hours shows no advantage on
dose–response curves. The lack of improvement with increased treatment time is most likely caused by dilutional effects, which negatively alter the therapeutic concentration gradient.

Avoiding caffeine and administering a single 200-mcg dose of desmopressin 1 hour before treatment may also be helpful because the intravesical concentration of mitomycin is most important in maximizing treatment efficacy. Furthermore, delivering chemosensitizing agents, such as suramin along with mitomycin, may improve its potency.71

Mitomycin has been reported to be effective with as few as 4 treatments; however, 6 to 8 treatments spaced 1 week apart is standard. Whether maintenance therapy is beneficial remains controversial. Supporters advocate monthly treatments for 1 year. Recent randomized trials of mitomycin with and without maintenance therapy showed reduced recurrence rates in the maintenance-therapy arm but no difference in the disease-free interval between treatment arms.72

**Gemcitabine:** Gemcitabine is a nucleoside analogue that inhibits cells from undergoing DNA synthesis by inactivating ribonucleotide reductase and competing with other nucleosides for incorporation into DNA.

**Efficacy:** Gemcitabine is currently being studied as a salvage agent after failed therapy with BCG. In heavily pretreated patients, including patients with high-grade lesions, complete response rates of 39% to 57% have been documented after failed BCG therapy.73,74 Although studies of BCG are limited by small patient numbers and lack of long-term follow-up, they provide the impetus for further analysis. The combination of gemcitabine and mitomycin for salvage therapy is feasible and can lead to a complete response rate of 70%.75

**Dose and Schedule:** Gemcitabine is usually formulated as 1 to 2 g diluted in 50 mL of water or saline (final concentration, 20–40 mg/mL). Gemcitabine can be administered either weekly or twice weekly for 6 to 8 treatments.

**Anthracyclines:** Doxorubicin, epirubicin, and valrubicin are anthracycline antibiotics that prevent protein synthesis by binding DNA base pairs and inhibiting topoisomerase II. Although valrubicin is no longer available in the United States, it may enter the market again in 2007.

**Efficacy:** Doxorubicin has largely been replaced by the other anthracyclines because of their more favorable side effect profiles and improved efficacy.76 Four of 6 studies show some reduction in recurrence risk with use of intravesical doxorubicin. Evidence also shows that adding verapamil, a known chemosensitizing agent in patients with P-glycoprotein–mediated multidrug resistance, can enhance doxorubicin’s effect.75 In general, doxorubicin, epirubicin, and valrubicin provide a 13% to 17% improvement over transurethral resection alone in preventing recurrence.75,76 An immediate postoperative dose of epirubicin has been reported to halve the risk for recurrence.77 In a phase II study, valrubicin was associated with a 21% complete response rate at 6 months and an 8% long-term response rate at a median follow-up of 30 months.80 This occurred in a significantly pretreated population with BCG-refractory CIS.

A study of combination therapy that administered mitomycin on day 1 and doxorubicin on day 2 each week for 5 weeks showed a complete response rate of approximately 45% and that chemical cystitis was a significant local side effect in 50% of patients.81 The combination of mitomycin and doxorubicin has also been shown to be as effective as BCG in treating CIS, producing initial response rates of more than 80%.82 Current data show that maintenance combination therapy with mitomycin and doxorubicin has benefit in patients with CIS but not in those with papillary disease.83

**Dose and Schedule:** Doxorubicin and epirubicin are formulated as 50 mg diluted in 50 mL of normal saline (final concentration, 1 mg/mL). The maximum tolerated dose of valrubicin is 800 mg. Each of the anthracyclines can be administered either as a single postoperative dose or once weekly for 6 weeks. Standard doses and schedules have not yet been established, and whether maintenance therapy is effective requires further investigation. Recommended in-dwell times range from 1 to 2 hours.

**Thiotepa:** Thiotepa is an alkylating compound that exerts its cytotoxic effect by causing cross-linkage of DNA, RNA, and proteins, and subsequent inhibition of nucleic acid synthesis. Therefore, thiotepa is not cell-cycle specific. It is the only chemotherapeutic agent approved by the FDA for the intravesical treatment of papillary bladder cancer. One drawback of thiotepa is its low molecular weight (189 kD), which is responsible for the frequent side effects seen with this drug, including irritative voiding symptoms, which occur in up to 69% of patients, and leukopenia, which occurs in up to 55% of patients.82

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Efficacy: Five major studies showed a benefit from thiotepa in terms of decreasing recurrence. The mean risk reduction was 16%, and the highest risk reduction was 41%. However, 4 other studies showed no benefit from thiotepa.

Dosing: Thiotepa is prepared as 30 to 60 mg of thiotepa diluted in 30 to 60 mL of water; final concentrations range from 0.5 to 1.0 mg/mL. Patients are instructed to retain the drug in the bladder for 1 to 2 hours. Thiotepa is instilled weekly for 4 to 8 weeks, and maintenance doses are given monthly, usually for up to 1 year.

Experimental Therapies

Several groups have investigated alternative treatment options for transitional cell carcinoma of the bladder.

Flavopiridol is a semisynthetic flavone derived from the Indian tree Dysoxylum binectariferum, which produces its cytotoxic effect by inhibiting cyclin-dependent kinases. In vitro experiments have shown that flavopiridol inhibits growth and progression of bladder cancer in the rat model and is associated with a 58% response rate.

*Allium sativum* (garlic) has also been the topic of recent investigation as an intravesical agent. Intravesical administration of garlic has a documented direct cytotoxic effect and is also believed to have immunostimulant properties. The efficacy of garlic in the murine model is similar to that of BCG.

Phase I trials of intravesical gene transfer have been initiated. Use of adenovirus vector has been particularly interesting because of its tropism for transitional cells. Attempts are underway to transfect p53 through this mechanism. Furthermore, intravesical instillation of IFN-α–producing adenovirus has been shown to produce sustained IFN levels for days, induce marked tumor regression, and have limited effect on normal urothelium. This effect was evident even in cell lines that were resistant to treatment with high levels of IFN-α alone and seemed to be mediated by caspase-dependent cell death. A phase I/II trial of intravesical instillation of IFN-α–producing adenovirus is being planned at M. D. Anderson. These studies are based on the first trial investigating the intravesical instillation of a live virus using vaccinia in a dose-escalation model before cystectomy.

Intravesical treatment with bioadhesive microspheres has been attempted using paclitaxel. The goal of using bioadhesive microspheres is to allow for sustained, controlled release of the agent to promote effective exposure of the urothelium. This modality has been used only in a mouse model.

Phase II and III studies with linoleic acid, efornithine, tipifarnib, and fenretinide are also underway.

Conclusions

Although non–muscle-invasive UC frequently has an indolent course, a subset of patients with this disease present with factors associated with an increased risk for recurrence or progression. Several intravesical therapies can decrease these risks. Proper selection of patients for intravesical therapy after complete resection and proper selection of agents and doses can significantly improve prognosis.

For patients with non–muscle-invasive bladder cancer, the authors recommend complete transurethral resection of all visible disease. Using mitomycin in the perioperative period after resection is prudent for both high-risk and low-risk disease; mitomycin may be the only treatment necessary for patients with Ta lesions in whom mitomycin is associated with a 39% decrease in the odds of recurrence.

Patients with high-grade or T1 tumors should undergo repeat transurethral resection at 4 weeks to ensure accurate staging and complete eradication of all gross disease. The importance of re-resection cannot be overemphasized; up to one third of patients have residual disease. Importantly, intravesical chemotherapy does not compensate for inadequate resection. When patients with T1 tumors were randomized to undergo a single resection plus mitomycin C versus repeat resection at 2 to 6 weeks plus mitomycin C, overall recurrence rates were 63.2% in the group who underwent re-resection and 25.7% in the group that did not (P < .001). This finding may be attributable to the understaging that occurs in 10% to 30% of cases with T1 disease even when muscle is present in the specimen, and up to 50% when muscle is not present.

Patients with high-grade tumors, concurrent CIS, multiple lesions, tumors larger than 3 cm, evidence of lamina propria invasion, or recurrence within 24 months should be treated with BCG induction therapy plus the “6 + 3” SWOG maintenance regimen described earlier. If further recurrence is noted, salvage therapies are available; however, operative intervention with cystectomy should be considered.
Although the ideal intravesical agent has not been identified, the available choices allow for successful therapy in most patients.

References

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