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PILOT TESTING
Projects In Knowledge thanks Thomas P. Alderson, MD, for pilot testing this activity.

LEARNING OBJECTIVES
After participating in this activity, physicians will be better able to:
• Describe the epidemiology, risk factors, grading/staging, and natural history of superficial bladder cancer
• Evaluate patients with hematuria for bladder cancer using cystoscopy, cytology, and other urine-based tests, and radiologic imaging
• Formulate appropriate treatment strategies for superficial bladder cancer using surgical approaches and intravesical chemotherapy or immunotherapy
• Consider the latest data regarding bacillus Calmette-Guérin (BCG) and interferon combination therapy when formulating treatment plans for patients with superficial bladder cancer
• Select appropriate candidates for BCG/interferon combination therapy and BCG monotherapy
• Select appropriate doses and treatment intervals for intravesical immunotherapy regimens
• Prevent and manage toxicities associated with BCG and interferon
• Diagnose and treat recurrences of superficial bladder cancer following initial therapy

Estimated Time for Completion: 1.5 hours

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Diagnostic and Treatment Issues in Superficial Bladder Cancer
Monograph
A CME monograph designed for urologists who treat patients with superficial bladder cancer

Release Date: October 1, 2002. This independent CME activity is planned and produced in accordance with the ACCME Essential Areas and Policies. This enduring activity will be reviewed within 1 year of this date and rereleased or its designation for CME credit will become invalid.

Projects In Knowledge gratefully acknowledges the unrestricted educational grant from

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For more information about BCG/interferon in superficial bladder cancer, download the four-part Tx Reporter series, FAQs on Intravesical Immunotherapy for Superficial Bladder Cancer at www.projectsinknowledge.com. This series provides personal insights from Michael A. O'Donnell, MD, principal investigator of BCG/interferon trials, as he answers real questions from physicians like you.
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**Chair**

Ihor S. Sawczuk, MD  
Chairman, Department of Urology  
Hackensack University Medical Center  
Hackensack, New Jersey  
Professor of Urology  
College of Physicians and Surgeons, Columbia University  
New York, New York

**Faculty**

Muhammad S. Choudhury, MD  
Professor and Chairman  
Department of Urology  
New York Medical College  
Valhalla, New York

Cary N. Robertson, MD  
Associate Professor  
Division of Urology  
Department of Surgery  
Duke University Medical Center  
Durham, North Carolina

Craig D. Zippe, MD  
Co-Director, Prostate Center  
Urological Institute  
Cleveland Clinic Foundation  
Cleveland, Ohio

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Ihor S. Sawczuk, MD, is on the speakers bureau of Schering Oncology/Biotech.

Craig D. Zippe, MD, is on the speakers bureau of AstraZeneca Pharmaceuticals LP, Pfizer Inc, and TAP Pharmaceuticals Inc.
Overview of Superficial Bladder Cancer

Ihor S. Sawczuk, MD

Epidemiology and Risk Factors

Bladder cancer is the fourth most common malignancy in men and the tenth most common in women.1,2 The American Cancer Society estimates that in 2002, there will be 56,500 new cases of bladder cancer, of which 73% (41,500) will be in men. In addition, bladder cancer will cause an estimated 12,600 deaths in the United States in 2002.1 Lifetime risk varies by gender and race, with white men having the highest risk (2.8%) and black women the lowest (0.6%). Incidence is higher in the Northeast United States than in the West, which is not accounted for by differences in smoking, diet, or other lifestyle factors.4

Cigarette smoking is currently the single most important risk factor contributing to the development of bladder cancer. Risk of bladder cancer increases two- to fourfold among smokers, and declines, but does not return to baseline, on smoking cessation. Other risk factors include exposure to environmental carcinogens (e.g., aromatic amines), chemotherapy with cyclophosphamide, and pelvic radiation. Occupations with the greatest risk of exposure include textile workers, dye workers, tire and rubber workers, leather workers, bootblacks, painters, truck drivers, drill press operators, chemical workers, petroleum workers, and hairdressers. Fluid consumption may be an important modifiable risk factor, as one report found that men who drink at least six cups of water a day cut their risk of bladder cancer in half, compared with men who drink less than one cup a day.5

Pathology

In the United States, transitional cell carcinoma (TCC) accounts for over 90% of bladder cancer. Of these, 70% are “superficial” (non-muscle-invasive) cancers. Superficial TCC has a high rate of recurrence (50%–70%) and may progress to invasive disease, which is then associated with higher rates of morbidity and mortality.3

Squamous cell carcinoma (SCC) accounts for only 5% of bladder cancer cases in the United States, and it is usually associated with chronic cystitis resulting from urinary calculi, long-term indwelling catheters, or bladder diverticula. Adenocarcinoma of the bladder accounts for only 0.5% to 2% of bladder cancers and is usually of urachal origin.6

Grading and Staging of Bladder Cancer

The American Joint Committee on Cancer TNM staging of bladder cancer, as of 1998,7 is shown in Figure 1. The focus of this monograph is superficial bladder cancer, including:

- Ta lesions: papillary tumors confined to the mucosa, which account for about 70% of superficial TCCs. They are usually low grade, with low rates of progressive disease.4

- Carcinoma in situ (CIS or Tis): nonexophytic or “flat” lesions confined to the urothelium. These lesions, which are frequently multifocal, are often not visible by cystoscopy, and can occur alone or in conjunction with papillary lesions. Tis lesions are, by definition, high grade, and are associated with high recurrence rates, a high likelihood of invasion, and a substantial risk of cause-specific death.8

- T1 lesions: papillary or nodular tumors that have invaded the lamina propria. These tumors are more aggressive, with a greater likelihood of progression than Ta tumors. T1 tumors can be further subdivided into T1a (tumors not involving the muscularis mucosa) and T1b/T1c (tumors with deeper invasion to the muscularis mucosa or beyond).6

A number of different systems have been proposed for grading papillary tumors.6–11 Under the most recent grading system, developed by the WHO and the International Society of Urological Pathology,9 urothelial neoplasms are grouped into the following four categories:

- Urothelial papillomas: discrete papillary growth with a central fibrovascular core lined by urothelium of normal thickness and cytology; no architectural or cytologic atypia

- Papillary urothelial neoplasm of low malignant potential (equivalent to WHO grade I): orderly arrangement of cells within papillae, with minimal architectural or nuclear atypia, irrespective of cell thickness; lesions are generally thick with enlarged nuclei; mitoses are infrequent and limited to basal layer

- Papillary urothelial carcinoma, low grade (equivalent to WHO grade I): overall orderly appearance with moderately altered architectural/cytologic features; definite cytologic atypia; mitoses are infrequent, usually occur in lower half, and may be observed at any level of urothelium

- Papillary urothelial carcinoma, high grade (equivalent to WHO grades II and III): totally disorderly appearance at low magnification; marked architectural and cytologic abnormalities; mitoses frequently seen at all levels of urothelium

Natural History

Important endpoints in the natural history of bladder cancer include recurrence, progression, and survival. Recurrence is defined as appearance of tumors of the same stage and grade as the primary tumor. Recurrence is common (60%–90%), and while not life threatening, impacts on quality of life as a result of the need for frequent surveillance and cystoscopy, as well as intravesical therapy. Progression is defined as the development of higher grade tumors with muscle invasion or...
metastatic disease, and is associated with an increased risk of death. Survival, both progression-free and overall, is the most important endpoint to consider in the natural history and in clinical trials of various interventions for bladder cancer.6

Superficial bladder cancer comprises a heterogeneous group of tumors with varying natural histories. Prognostic factors that predict recurrence or progression include stage, grade, presence of CIS, tumor size >5 cm, multiple (>3) tumors, tumor structure (papillary or sessile), age >50 years, and male gender. Of these, the most important are disease stage, grade, and number of tumors, which have been used to stratify patients into low-, intermediate-, and high-risk groups with defined risks of progression, mortality, and recurrence (Table 1).12 Stratification of patients into risk groups can potentially influence the development of risk-group based treatment.13

The accumulation of multiple genetic defects over time is related to the severity of disease. Loss of chromosome 5q is associated with dysplasia and often precedes invasion of the lamina propria. Subsequent loss of chromosomes 11p and 17p, as well as mutations in p53, are associated with muscular and lymphatic invasion, which can lead to systemic metastasis. Positive p53 staining following BCG may also be predictive of poor outcome.14 The number of genetic defects is more relevant in terms of progression to metastasis than is the order in which these defects appear.

Conclusion
Urinary bladder cancer is a common malignancy in the United States, accounting for considerable morbidity and mortality, particularly among men. Cigarette smoking is the most common risk factor. TCC accounts for over 90% of bladder cancer cases, of which 70% are superficial. Superficial TCC has a high rate of recurrence (50%–70%) and may progress to invasive disease, which is associated with higher rates of morbidity and mortality. Patients at greatest risk for recurrence, progression, and mortality include those with T1 tumors (especially if high-grade or multiple tumors), high-grade Ta tumors, or CIS.

Table 1. Primary Superficial Bladder Cancer Risk Groups.12

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Grade</th>
<th>Stage</th>
<th>Recurrence</th>
<th>Progression</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>I</td>
<td>Ta</td>
<td>37%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>T1</td>
<td>3%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>II</td>
<td>Ta</td>
<td>45%</td>
<td>15%</td>
<td>9.5%</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>T1</td>
<td>15%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>High Risk</td>
<td>II</td>
<td>Ta</td>
<td>60%</td>
<td>30%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>Ta</td>
<td>54%</td>
<td>30%</td>
<td>9.5%</td>
</tr>
</tbody>
</table>

References

Diagnosis of Superficial Bladder Cancer

Craig D. Zippe, MD

Hematuria is the most common sign of bladder cancer, with about 80% of transitional cell carcinomas (TCCs) being diagnosed with either gross or microscopic hematuria. Some patients, particularly those with carcinoma in situ (CIS), will have symptoms of bladder irritability, including urinary frequency, urgency, and dysuria.7 Patients with hematuria and those with persistent symptoms should receive a thorough evaluation for bladder cancer.

Determining the Clinical Significance of Hematuria

Although the majority of patients with bladder cancer have hematuria, most patients with hematuria will not have bladder cancer. About 15% with gross painless hematuria will have bladder cancer,7 and 2% to 22% with microscopic hematuria will have a malignancy.3 Hematuria is a common sign of many benign conditions, including urinary tract stones and inflammatory disorders. Hematuria may also be a predictor of bladder cancer, preceding diagnosis by as much as 5 to 6 years.4 Evaluation for bladder cancer is warranted if more than three to five red blood cells per high-power field is a
persistent finding on microscopic evaluation. A bladder cancer workup is indicated for any hematuria, unless an alternate cause of hematuria is clearly present (eg, cystitis in a young woman, known glomerulopathy). In evaluating patients with hematuria, it is necessary to assess the entire urinary tract. Because no single imaging technique reliably detects most bladder cancers, multiple diagnostic techniques are needed (eg, upper tract imaging, cystoscopy, cytology). Figure 1 summarizes the American Urological Association’s Best Practice Policy Recommendations regarding evaluation of asymptomatic microscopic hematuria.

Cystoscopy

Cystoscopy is the gold standard for diagnosis of bladder cancer since it allows complete visualization of the urethral and bladder mucosa. Lesions visualized during cystoscopy are biopsied and/or resected. Disadvantages of rigid cystoscopy include its invasiveness, requirement for anesthesia, and postoperative discomfort. With fiberoptic flexible instruments, outpatient cystoscopy with minimal patient discomfort using topical intrarethral anesthesia can be performed. The standard schedule for cystoscopic surveillance (ie, every 3–4 months) has not been clinically validated.

Cystoscopy is 73% sensitive and 51% specific in diagnosing bladder cancer. Investigational studies have suggested that sensitivity can be improved to 97% with intravesical instillation of 5-aminoolevulinic acid, which induces porphyrin fluorescence, prior to cystoscopy, and use of a violet light from a krypton laser (wavelength 406.7 nm).

Voided urine cytology has a sensitivity of 35% to 40% and a specificity of 90% to 95%. Sensitivity can be improved when three voided specimens are obtained on 3 separate days. Urine cytology is most accurate in high-grade tumors, but has poor sensitivity in detecting low-grade tumors, the cells of which more closely resemble normal urothelium. It is most helpful in diagnosis and follow-up of CIS or high-grade T1 or Ta tumors.

Radiologic Imaging

Intravenous pyelography (IVP) with or without concomitant retrograde pyelography outlines the upper urinary tract. It is less sensitive in the bladder. Malignant disease should be suspected if radiolucent filling defects are observed in the calyces, renal pelvis, ureter, or bladder, or if unexplained hydronephrosis or nonfunction is present.

Ultrasoundography detects and determines the nature of a renal mass, and identifies upper urinary tract stones or hydronephrosis, but is inadequate for detecting filling defects consistent with TCC in the urothelium.

CT may be useful in the initial evaluation of hematuria, being more sensitive than IVP for detecting small renal masses, small urinary calculi (on noncontrast images), and nonurologic disease processes. The main disadvantage of CT is the inability to visualize small (<1 cm) urothelial lesions.

Tumor Markers

Cystoscopy, cytology, and urinalysis together do not detect 100% of all bladder cancers. This, coupled with a desire to avoid the need for frequent cystoscopy to detect recurrences, has led to the investigation of new
Surgical Modalities in the Treatment of Bladder Cancer

Craig D. Zippe, MD

Transurethral resection (TUR) of all visible lesions is the standard initial treatment of superficial bladder cancer. TUR removes the tumor and allows for pathologic analysis of the resected specimen, establishing the diagnosis and providing important information about the tumor grade and depth of bladder invasion. Other surgical/nonpharmacologic treatment approaches include laser treatment and photodynamic therapy, which are therapeutic but less commonly used as initial therapy because they do not supply grading and staging information. High risk for progressive disease, or failure of conservative approaches (in conjunction with intravesical pharmacologic therapy) should prompt consideration of cystectomy.

Transurethral Resection

During TUR, the primary lesion is completely resected with an electrosurgical loop and sent for pathologic analysis. A separate sampling of the tumor base determines whether the tumor has been completely removed and whether there is invasive disease. During TUR, areas of mucosa away from the primary lesion should be biopsied and examined for carcinoma in situ (CIS). Transurethral prostatic sampling should be performed to rule out CIS of the prostatic urethra or ducts, particularly for patients who may be candidates for orthotopic urinary diversion.

Laser and Photodynamic Therapy

Laser therapy, most commonly with the neodymium: yttrium-aluminum-garnet laser with an end-fire noncontact fiber, can be used for tumor ablation, but does not allow for pathologic analysis. Thus, it is more commonly reserved for treatment of recurrences so that pathologic analysis can be performed on the initial tumor. Advantages compared with TUR include minimal bleeding, use of flexible cystoscopes, and less postoperative bladder irritation.

Photodynamic therapy uses a photosensitizer (a hematoporphyrin preparation) to enhance the photosensitization of cancerous cells to subsequent administration of light therapy. The photosensitizing drug can be instilled intravesically before light administration. The whole bladder is illuminated for 12 to 20 minutes via laser light with an optical fiber passed through a standard cystoscope, with the patient under general or modified local anesthesia. Photodynamic therapy’s most common use is for patients who do not respond to intravesical therapy. It is more effective for small than for large tumors.
Is TUR Enough?

Recurrence of bladder cancer following TUR is extremely common (60%–70%), and 20% to 30% of recurrent tumors progress to higher stage or grade disease. As a result, use of induction and maintenance intravesical therapies following TUR is now common clinical practice for many patients. The goals of intravesical therapy are to eradicate existing disease and to prevent recurrence and sometimes progression, while sparing the bladder.

Patients with small, solitary, well-differentiated Ta tumors have a low risk of recurrence following TUR. Thus, intravesical therapy may be unnecessary in this population. However, superficial bladder cancer patients with multiple tumor recurrences or a recurrence within 3 to 6 months of resection, lamina propria invasion, multifocal or high-grade disease, T1 tumor of any grade, a large (>5 cm) solid tumor, CIS, or a positive cytology after TUR (in the presence of a negative complete work-up for upper urinary tract disease) are all candidates for induction and maintenance intravesical therapy. Intravesical therapies will be discussed in detail in subsequent sections of this monograph.

Cystectomy

Although bladder preservation is clearly preferable to cystectomy, this should not override patient survival and curative potential. Cystectomy is associated with excellent recurrence-free overall survival rates (median 10.2 years in those with accurate preoperative staging). Following treatment with intravesical immunotherapy, cystectomy should be recommended for patients with increasing grade and/or stage, abnormal p53, high-grade disease, CIS, or lamina propria-invasive transitional cell carcinoma.

In patients who are at high risk of progression, metastases, and death (eg, those with muscle-invasive disease), radical cystectomy may be an option as initial therapy. Concerns about clinical understaging provide another rationale for early cystectomy. Clinical understaging occurs in 34% to 62% of cases and is associated with worse cancer-specific survival rates.

Historically, urinary tract reconstruction after radical cystectomy entailed use of the ileum as a urinary conduit and urostomy, which required an external urine-collecting device. The social impact and effects on quality of life made this an unappealing option for many patients. Subsequent options allowed for use of the small intestine to make a continent cutaneous reservoir, which could be drained using intermittent catheterization. The newest surgical technique (orthotopic neobladder) allows connection of the small bowel pouch to the urethra, eliminating the need for external appliances. Orthotopic diversion is associated with complications rates similar to those of standard ileal conduit urinary diversion. These options have been met with greater patient satisfaction, and lessened the social impact and reduced the negative effects of cystectomy on quality of life.

Conclusion

TUR remains the standard initial treatment for bladder cancer, usually in conjunction with intravesical pharmacologic therapy in all but the lowest-risk patients. TUR has the advantage of providing grading and staging as well as pathologic information. Laser and phototherapy are usually reserved for treatment of recurrences or for patients who have failed intravesical therapy. Cystectomy is recommended as initial therapy for high-risk patients and for those with a high risk of progressive disease after failure of more conservative options.

References


Intravesical Chemotherapy

Muhammad S. Choudhury, MD

Commonly used intravesical chemotherapy agents include thiotepa, mitomycin C, and doxorubicin (Table 1). However, use of intravesical chemotherapy following transurethral resection (TUR) is controversial, with conflicting data regarding net effect on the rate of recurrence or risk of progression in patients with superficial bladder cancer. The one exception may be immediate post-TUR administration of mitomycin C, which was recently found to significantly reduce recurrence compared with later administration.

Impact on Recurrence and Progression Rates

Table 2 shows the minimal net benefit of intravesical chemotherapy on recurrence and progression rates, as determined by a review of 22 prospective, randomized, controlled trials involving nearly 4000 patients.

Prophylactic adjuvant chemotherapy reduced the rate of recurrence by only 14% overall. Although 13 trials reported a statistically significant decrease in tumor recurrence with varying durations of follow-up, long-term studies have shown that adjuvant intravesical chemotherapy does not decrease the risk of recurrence compared with TUR alone. Among nine prospective, randomized, controlled trials that reported progression data, none demonstrated a significant decrease in the rate of progression among patients treated with adjuvant intravesical chemotherapy.

Among 1039 patients treated with thiotepa, mitomycin C, or doxorubicin, there was no net improvement in the rate of progression. Overall, among 2011 randomized patients, progression occurred in 7.5% of patients treated with intravesical chemotherapy versus 6.9% of patients treated with surgery alone.

Similar results were reported from a meta-analysis of four European Organization for the Research and Treatment of Cancer (EORTC) and two Medical Research
Council (MRC) phase III randomized trials that enrolled patients with primary or recurrent stage Ta or T1 transitional cell carcinoma. The majority of patients enrolled in these trials were previously untreated and had solitary primary tumors. Only a small proportion of patients had high-grade disease (12% grade 3), multifocal disease (28%), or recurrent tumors (18%). Thus, the risk of recurrence was fairly low. Among 1629 patients treated with intravesical chemotherapy, 53% remained disease free at 10 years compared with 47% of 906 patients treated with TUR only. These results support the conclusion that prophylactic adjuvant intravesical chemotherapy produces only a marginal improvement in the rate of recurrence in patients with superficial bladder cancer.

In contrast to these reports, a recent meta-analysis by Huncharek et al found that intravesical chemotherapy has “a major impact on decreasing the chance of recurrence of recurrent superficial bladder cancer.” This review of eight randomized trials concluded that the odds ratios for recurrence were 0.62, 0.46, and 0.35 with adjuvant chemotherapy versus TUR alone at years 1, 2, and 3, respectively, representing a 38% reduction at 1 year and up to a 70% reduction at 3 years. The 2- and 3-year data were found to be heterogeneous according to drug type, with doxorubicin having the least impact on rate of recurrence.

### Mitomycin C

Immediate administration of mitomycin C in the perioperative period following TUR may reduce recurrence rates. In an analysis of 205 patients with frequently recurrent stage Ta or T1 tumors from the Finnbladder IV study, rates of recurrence-free survival at 2 years were significantly improved when mitomycin C was administered the day of surgery: 63% versus 44% for patients who received the first dose 1 or more days after surgery (P = .0006). Mitomycin should be administered immediately, or within 2 hours of completion of TUR, as long as there is no significant bleeding or suspicion of bladder perforation. It is given via a three-way Foley catheter, which is clamped for 1 hour while the patient’s intravenous fluids are reduced. Thereafter, the bladder is allowed to drain by gravity and is flushed with 1 L of briskly flowing sterile water or saline. The Foley catheter may then be removed. Variables such as low urine pH, high urine output, and incomplete emptying may impact on mitomycin response rates.

### Table 1. Intravesical Chemotherapy Agents

<table>
<thead>
<tr>
<th>Chemotherapy Agent</th>
<th>Recommended Dose*</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiota</td>
<td>30 mg diluted in 30 mL water, given weekly x 6 weeks, then monthly for up to 1 year</td>
<td>Leukopenia/thrombocytopenia, irritative voiding symptoms; treatment-related deaths have been reported</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>30–100 mg at a concentration of 1 mg/mL. Instillation schedules vary from weekly to every 3 weeks; maintenance therapy common but no demonstrated benefit</td>
<td>Chemical cystitis, allergic reactions, GI side effects, irritative bladder symptoms, fever, malaise</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>20–60 mg at a concentration of 0.5 to 2 mg/mL, given weekly x 8 weeks, then monthly for up to 1 year</td>
<td>Leukopenia/thrombocytopenia, chemical cystitis, allergic reactions/delayed hypersensitivity reaction</td>
</tr>
<tr>
<td>Valrubicin (for BCG-refractory CIS)</td>
<td>800 mg (20 mL) in 55 mL saline given weekly x 6 weeks</td>
<td>Irritative bladder symptoms</td>
</tr>
</tbody>
</table>

*Following intravesical administration, these agents should be retained in the bladder for 1–2 hours.

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ.

### Table 2. Intravesical Chemotherapy After TUR: Net Effect on Recurrence and Progression Rates

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Studies</th>
<th>Patients</th>
<th>Recurrence Rate (%)</th>
<th>Net Benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiota</td>
<td>9</td>
<td>1130</td>
<td>61</td>
<td>49</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>6</td>
<td>1157</td>
<td>53</td>
<td>44</td>
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<tr>
<td>Doxorubicin</td>
<td>5</td>
<td>1389</td>
<td>53</td>
<td>38</td>
</tr>
<tr>
<td>Overall</td>
<td>22</td>
<td>3899</td>
<td>54</td>
<td>40</td>
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</table>

**Effect on Progression Rates**

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Studies</th>
<th>Patients</th>
<th>Recurrence Rate (%)</th>
<th>Net Benefit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiota</td>
<td>3</td>
<td>314</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>3</td>
<td>336</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>3</td>
<td>389</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Overall</td>
<td>9</td>
<td>1039</td>
<td>9</td>
<td>8</td>
</tr>
</tbody>
</table>

*Includes 2 additional trials on ethoglucid and epirubicin, not shown.


### Conclusion

Overall net benefit of intravesical chemotherapy is small, and these agents are associated with considerable toxicity. Thus, use of intravesical chemotherapy is usually reserved for patients who are not candidates for immunotherapy, or in whom immunotherapy has failed. Perioperative mitomycin C is a novel option in reducing recurrences.

### References


Bacillus Calmette-Guérin (BCG) is considered the gold standard for initial treatment of superficial bladder cancer following transurethral resection (TUR). In contrast to the modest benefits of chemotherapy, BCG is highly effective. However, it is associated with dose-limiting toxicity, and the majority of patients treated with BCG eventually experience disease recurrence or progression. Recent evidence suggests that combining BCG with intravesical interferon may produce synergistic efficacy without increasing toxicity. Moreover, combination therapy may allow lower doses of BCG to be used in BCG-sensitized patients without compromising overall response.

**BCG Monotherapy**

BCG is a live, attenuated mycobacteria. Therefore, certain measures and precautions must be taken to maximize efficacy and minimize complications. BCG should not be administered within 10 to 14 days of any invasive procedure (including TUR and biopsy), which potentially provides a means for BCG entry into the bloodstream. Patients should be instructed to avoid fluid intake for 4 hours prior to instillation and to empty their bladder before the instillation. A urethral catheter is used to drain the bladder, and treatment should be aborted if traumatic catheterization occurs. The constituted BCG suspension is instilled slowly by gravity (not forced). Patients should be instructed to retain the solution for 2 hours, if possible, during which time they may be ambulatory. Patients should void in a seated position to avoid splashing. For the next 6 hours, patients should disinfect voided urine with household bleach, delaying 15 minutes before flushing. Excessive fluid intake is not necessary after BCG treatment. If prophylactic antibiotics are medically indicated in a BCG patient, it is important to avoid fluoroquinolones, macrolides, tetracyclines, and aminoglycosides because they are capable of rendering BCG nonviable and ineffective. (However, they can be used to treat BCG toxicity.) Condoms are recommended during sex to decrease the theoretical risk of BCG infection of the partner, since BCG is shed from the urethra for at least 48 hours and for up to 1 week after treatment.

**Efficacy**

Intravesical BCG is substantially more effective than intravesical chemotherapy in reducing the rate of recurrence and progression (Table 1). In a retrospective comparative review of 3405 patients treated with chemotherapy versus 496 BCG patients, intravesical BCG produced a 40% decrease in the rate of recurrence and a 10% decrease in the rate of progression ($P = .003$). In contrast, intravesical chemotherapy produced only a 13% decrease in the rate of recurrence and no benefit in terms of the rate of progression.

A study of long-term outcomes further supported the use of intravesical BCG as an initial bladder-sparing strategy. In this study, 98 patients with grade I to III Ta or T1 cancer (20 of whom also had CIS) were treated with TUR and at least one course of BCG between 1981 and 1989. After a minimum of 10 years of follow-up, 25% had progressed to grade III T2 disease after a median 19.1 months (range 1.2–143.7 months).

Table 1. **BCG is More Effective Than Chemotherapy for Reducing Rate of Recurrence and Progression.**

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<th>Ctrl Rx Net Benefit</th>
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<td>496</td>
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**Safety**

Cystitis (91%), hematuria (43%), and mild flu-like symptoms, including low-grade fever (29%), malaise (24%), and nausea (5%) are the most common adverse events associated with bladder instillation of BCG. These symptoms can usually be managed symptomatically (eg, with oxybutynin, phenazopyridine, and nonsteroidal anti-inflammatory drugs [NSAIDs], particularly COX-2 inhibitors) and clear within 12 to 24 hours of treatment. Cystitis usually responds to fluoroquinolone antibiotics and/or isoniazid or rifampin, and prednisone (note that the antibiotics must be continued throughout and for 2 weeks after the prednisone therapy). Severe local symptoms lasting more than 48 hours and not responding to usual symptomatic management may be prevented/alleviated with isoniazid 300 mg/d for 3 days starting the day before the next dose of BCG. BCG sepsis (high fever/shaking chills with hemodynamic collapse [hypotension]) may be life threatening! BCG sepsis should be treated immediately with intravenous fluid plus isoniazid 300 mg, rifampin 600 mg, ethambutol 1200 mg, and prednisolone 40 mg, and no additional BCG courses should be given. Fluoroquinolones should be added to the regimen if there are severe...
complications, one of the standard antituberculosis drugs is not tolerated, or gram-negative sepsis is a concern. BCG is now known to be resistant to cycloserine, which should no longer be used to treat BCG sepsis.

Other serious adverse events, which may be dose-limiting or require treatment discontinuation, include high uncontrollable fever (3%), granulomatous prostatitis (1%), major hematuria (1%), hepatitis/pneumonitis (0.7%), arthritis (0.5%), epididymo-orchitis (0.4%), ureteral obstruction (0.3%), and contracted bladder (0.2%). Patients with prolonged temperature 101.5°F should be treated with isoniazid 300 mg/d for 3 months. As a general rule, additional BCG doses should be deferred until the patient is asymptomatic.

Since reduced doses of BCG are associated with less toxicity, several studies have investigated the efficacy and safety of lower doses. Most of these studies—with the exception of one—have shown that reduced doses (one half to one third of the standard dose) appear to be as effective as, and less toxic than, standard-dose BCG. An optimal dose has not been identified.

Three strains of BCG are available: Connaught strain (Theracys®), Pasteur strain (Tice®), and Armand-Frappier strain (Pacis®). Bioequivalence is measured in colony-forming units (CFUs). Gram weights differ in various strains (eg, Tice 50 mg is equivalent to Theracys 81 mg). All commercially available strains are thought to be essentially identical in terms of their intrinsic biologic activity, but there may be differences in processing and packaging that affect stability in solution, shelf life, and the total CFU count.

**Interferon Monotherapy**

**Efficacy**

Several trials have investigated intravesical interferon alfa-2b in patients with residual papillary transitional cell carcinoma (pTCC) or carcinoma in situ (CIS) or following TUR.20-23 Response rates (complete response [CR] plus partial response [PR]) ranging from 25% to 75% have been reported in patients with residual pTCC treated with ≥50 million units (mIU) of interferon alfa-2b. Response rates up to 66% have been reported in patients with CIS. In CIS patients, Glashan observed a 43% CR rate to 100 mIU interferon alfa-2b, with a median duration of CR >12 months, and a lower response rate (5%) with a dose of only 10 mIU, hinting at a possible dose-response relationship.

The efficacy of intravesical interferon alfa in preventing recurrence and progression of superficial bladder cancer following complete TUR has been evaluated in several studies.18-19 Recurrence rates ranged from 21% to 60%, which are somewhat higher than the recurrence rates observed with BCG. However, observations that intravesical interferon alfa-2b therapy has substantial activity in up to 20% of patients who failed BCG therapy24,25 are extremely encouraging and suggest that one important application of interferon alfa-2b is in the treatment of BCG failures.

**Safety**

Intravesical interferon alfa is associated with minimal local toxicity. The most common adverse events are mild fever and flulike symptoms, which occur in <30% of treated patients.26 No dose-limiting toxicity has been observed up to a dose of 1000 mIU per instillation. The side effects of intravesical interferon alfa therapy can be controlled with NSAIDs.

**BCG/Interferon Combination Therapy**

The biologic activities of interferon alfa and BCG are complementary,27-29 and there is evidence of synergistic activity. BCG and interferon alfa are biocompatible and can be instilled simultaneously into the bladder.30

**Mechanisms of Action**

BCG antigens are taken up by macrophages and other antigen-presenting cells and presented to T cells, which stimulate a cellular immune response. The BCG-activated macrophages produce cytokines, including interleukin (IL)-12 and tumor necrosis factor alpha (TNF-α). IL-12 plays a dominant role in the induction of interferon gamma (IFN-γ) production,29 whereas TNF-α has direct antitumor activity. Activated T helper type 1 (Th1) cells produce IL-2 and IFN-γ, both of which correlate with clinical response.30,31 Exogenous intravesical interferon alfa augments the production of IFN-γ by Th1 cells, which in turn enhances BCG antigen presentation and further amplifies the cellular immune response. Intravesical interferon alfa also upregulates human leukocyte antigen and Fas expression on the bladder cancer cells, which increases presentation of BCG antigens by tumor cells and enhances tumor cell lysis by activated cytotoxic T lymphocytes.32 The end result is an effective anticancer immune response.

In addition to these synergistic immunomodulatory activities, in vitro studies have shown that BCG and interferon alfa-2b also have synergistic antiproliferative effects. In these experiments, two different bladder cancer cell lines (UCRU-BL-28 and J82) were incubated with either BCG alone at two doses (5 and 50 µg/mL), interferon alfa-2b alone at three doses (1, 100, and 1000 U/mL), or interferon alfa-2b plus BCG.30 Both BCG and interferon alfa-2b alone had dose-dependent antiproliferative effects on the UCRU-BL-28 cell line; however, the combination had dramatically greater dose-dependent effects on proliferation. Likewise, although the J82 cell line did not appear to be sensitive to either BCG or interferon alfa-2b alone, the combination of BCG plus interferon alfa-2b had an antiproliferative effect.

**Efficacy**

Based on the clinical rationale for combining BCG and interferon alfa-2b, a number of centers have investigated this combination in patients with superficial bladder cancer. These studies suggest that BCG/interferon alfa-2b may be superior to either agent alone and may allow BCG dose reduction without compromising antitumor efficacy.

Stricker et al33 combined 60 mg (1/2 dose) BCG (Pasteur strain) with 10 to 100 mIU interferon alfa-2b. This regimen was well tolerated and produced favorable response rates in patients with papillary tumors (60% no evidence of disease [NED], 40% PR), and CIS (86% CR) at a median of 1 year of follow-up. A randomized trial reported by Bercovich et al34 demonstrated that combination therapy with interferon alfa-2b (10 mIU) plus 1/2-dose BCG (Pasteur strain) yielded a lower rate of recurrence compared with full-dose BCG (22% versus 28%) and was associated with fewer BCG-related adverse events.
O'Donnell et al. treated 40 patients who failed one or more courses of BCG therapy with 1/3-dose BCG plus 50 mIU interferon alfa-2b for 6 to 8 weeks as induction therapy, followed by three 3-week maintenance treatments with 1/100 to 1/10-dose BCG plus 50 mIU interferon (titrated to symptoms) as maintenance therapy at months 5, 11, and 17. Patients in this study were at high risk of recurrence or progression; nearly all (98%) had multifocal disease and 85% had failed prior therapy within 6 months of treatment. More than three quarters had aggressive histology (CIS or grade III, stage T1 disease). More than half had multirecurrent disease, and 52% failed more than one course of BCG therapy. One third of the population had a disease duration of more than 4 years. Cystectomy had already been offered as a treatment option to 22 of the 40 patients.

After a median follow-up of 30 months, 63% were disease free at 12 months and 53% were disease free at 24 months (Fig. 1). There were no differences in response according to stage, grade, presence of CIS, number of previous recurrences, or number of prior BCG treatments. This low rate of recurrence is encouraging among this group of high-risk patients. Moreover, the 55% NED rate at 2 years compares favorably with that reported in historical series for either agent alone or for intravesical chemotherapy.

The majority of treatment failures occurred within the first 4 months (78% at first cystoscopy), thus permitting early radical cystectomy. None of the patients with early failure had metastasis or subsequently died of bladder cancer. Among four late recurrences (at 8, 21, 22, and 24 months), two were low-grade, low-stage tumors treated with TUR and two were extravesical disease. There were no recurrences after 24 months, and no patients who received all three planned maintenance therapy cycles had recurrence. Of the 22 patients for whom cystectomy had been recommended, 12 (55%) were disease free with a normally functioning bladder at the end of the study.

Researchers at the University of Florida investigated 1/3-dose BCG plus 50 mIU interferon alfa-2b combination therapy versus valrubicin (800 mg QW x 6 weeks) in 24 high-risk TCC patients. All had previously been treated with at least one course of BCG, and 11 had also received courses of chemotherapy. Patients who responded to BCG plus interferon induction therapy were given maintenance therapy with three weekly instillations every 3 months. Among the 15 patients treated with BCG/interferon, there were nine CRs, four after one course, four more after a second course, and an additional one after TUR was performed after the first course. Despite the delay in cystectomy while these patients underwent intravesical therapy, no patients died of bladder cancer, and no muscle-invasive disease was found among the nine patients who ultimately underwent cystectomy after failing one or more of the investigational regimens (BCG plus interferon or valrubicin).

Current, prospective, randomized trials are comparing the efficacy of combination therapy with that of single-agent (full- or reduced-dose) BCG. A randomized, phase IIIB trial in Singapore found the combination of interferon alfa-2b (10 mIU) plus 1/3-dose BCG (27 mg Connaught strain) produced a lower recurrence rate (10%) at a median follow-up of 19 months than either 1/3-dose (30%) or full-dose (50%) BCG alone. Moreover, the incidence of BCG-associated adverse events (local and systemic) was significantly reduced (P<0.01) in patients who received either reduced-dose BCG alone or the combination regimen. This study suggests a positive synergistic effect between BCG and interferon alfa-2b; however, a much larger, multicenter, randomized study is needed to confirm this.

As a result of these data, BCG/interferon combination therapy is increasingly being evaluated as an intravesical immunotherapy in the treatment of bladder cancer failing to respond to BCG therapy alone. BCG/interferon is also being investigated in BCG-naive patients. O'Donnell reported preliminary findings indicating a disease-free rate of 68% at 2 years among 22 high-risk BCG-naive patients treated with full-dose BCG/interferon.

Safety

Combination therapy with interferon alfa-2b plus BCG (full or reduced dose) was safe and well tolerated in the study by O'Donnell et al. Adverse events of combination therapy were generally no worse than with BCG alone, with the most common side effects being local cystitis, transient hematuria, flu-like symptoms, and fever. There were no treatment discontinuations during the first maintenance cycle, but three patients discontinued during cycle 2 and another six during cycle 3, when side effects tended to peak. Ultimately, 40% of patients terminated maintenance therapy due to adverse events. There was only one serious adverse event: BCG-osis with granulomatous hepatitis, which responded well to antituberculosis therapy with isoniazid and rifampin.

A recent evaluation by O'Donnell et al. of 1100 patients recruited into a multicenter phase II study of BCG/interferon detected 10 cardiac events (ischemia, congestive heart failure, and arrhythmia), eight of which were not drug-related, and six reversible neurologic events (confusion, transient ischemic attack/cerebrovascular accident, weakness). Conversely, BCG/interferon is associated with fewer episodes of BCG sepsis than BCG alone (0.1% versus 0.4%, respectively), due not only to the lower BCG doses but also to a protective effect of interferon alfa, which enhances BCG clearance.
Clinical Recommendations

Currently, BCG/interferon therapy is considered investigational. It appears that the most appropriate candidates for first-line BCG/interferon therapy may be patients with high-risk bladder cancer (eg, T1 grade III or multifocal CIS), who are likely to receive only a single course of intravesical therapy prior to cystectomy. Combination therapy may also be indicated for patients with CIS or multifocal stage Ta grade II-III TCC who have failed a course of BCG. In addition, BCG/interferon may be appropriate for patients who fail two courses of BCG induction therapy but are not yet considered appropriate candidates for cystectomy.

Optimal doses of BCG and interferon have not yet been determined. Table 2 provides the dosing protocol used by O’Donnell et al in their studies of BCG/interferon. For BCG/interferon combination therapy, only the powder formulation of interferon should be used, since the solvent in the pre-mixed form contains bacteriostatic preservatives that could render BCG inactive. The interferon powder should be reconstituted in accordance with the manufacturer’s instructions. BCG and interferon should then be combined and administered together at the doses described in Figure 2.

Cystoscopic evaluation should be staggered with the induction and maintenance cycles of BCG/interferon so that 4 to 6 weeks elapse after each treatment before cystoscopy is performed.

The precautions and patient instructions necessary in administering BCG/interferon are similar to those described for BCG monotherapy. The strategies for managing BCG side effects are also applicable.

Conclusion

Preclinical and clinical data suggest that BCG and interferon alfa have complementary and potentially synergistic immunomodulatory and antitumor activity. Both enhance the T<sub>h</sub>1 cellular immune response and potentiate interferon-γ production. Open-label trials have demonstrated combination therapy to be well tolerated and to allow BCG dose reduction without compromising antitumor efficacy in patients with superficial bladder cancer. Moreover, BCG/interferon alfa appears safe and effective in patients with prior BCG failure, even in those who are considered “BCG refractory” (ie, those who had recurrence within 6 months of treatment) and those who have already failed at least two courses of BCG. Current investigations are focused on BCG-naïve patients.

References

Bladder cancer is a major health concern, resulting in considerable morbidity and mortality, particularly in men. This common malignancy is caused primarily by cigarette smoking and exposure to environmental carcinogens. Superficial (non–muscle-invasive) bladder cancer comprises a heterogeneous group of tumors with varying prognoses. Tumors with the greatest risk of recurrence, progression, and mortality include stage T1 tumors, carcinoma in situ, and high-grade Ta tumors. Hematuria (micro- or macroscopic) is the most common sign and should prompt an evaluation with cystoscopy, cytology, urinalysis, and radiologic imaging. Bladder cancer biomarkers may provide additional information.

Initial treatment for superficial bladder cancer consists of transurethral resection of the bladder tumor, followed in most cases by intravesical immunotherapy. Perioperative administration of mitomycin C is a recent approach that may also improve outcomes. Bacillus Calmette-Guérin (BCG) induction and maintenance therapy is considered the gold standard for intravesical immunotherapy, but its toxicity and high rates of recurrence indicate the need for alternative treatments. Recent investigations have shown that when BCG and interferon are combined, they have potentially synergistic activity and increased efficacy. This combination has been well tolerated and may allow for lower doses of BCG to be used, particularly in patients with previous BCG exposure who are at the greatest risk for toxicity. Randomized phase III trials comparing BCG/interferon with BCG monotherapy are underway, and reports from phase II studies of BCG/interferon are promising.
CME INFORMATION
Projects In Knowledge is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.
Projects In Knowledge designates this educational activity for up to 1.5 hours in Category 1 credit toward the AMA Physician’s Recognition Award. Each physician should claim only those hours of credit that were actually spent on the educational activity.

PILOT TESTING
Projects In Knowledge thanks Thomas P. Alderson, MD, for pilot testing this activity.

LEARNING OBJECTIVES
After participating in this activity, physicians will be better able to:
• Describe the epidemiology, risk factors, grading/staging, and natural history of superficial bladder cancer
• Evaluate patients with hematuria for bladder cancer using cystoscopy, cytology, and other urine-based tests, and radiologic imaging
• Formulate appropriate treatment strategies for superficial bladder cancer using surgical approaches and intravesical chemotherapy or immunotherapy
• Consider the latest data regarding bacillus Calmette-Guérin (BCG) and interferon combination therapy when formulating treatment plans for patients with superficial bladder cancer
• Select appropriate candidates for BCG/interferon combination therapy and BCG monotherapy
• Select appropriate doses and treatment intervals for intravesical immunotherapy regimens
• Prevent and manage toxicities associated with BCG and interferon
• Diagnose and treat recurrences of superficial bladder cancer following initial therapy

Estimated Time for Completion: 1.5 hours

FOR CME CREDIT
To receive documentation of your participation, complete the following steps:
1. Read this publication carefully.
2. Complete the Posttest, selecting the most appropriate choice for each question.
3. Complete the Evaluation.
4. Send photocopies of the Posttest and Evaluation to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094, or fax to (201) 617-7333 before October 1, 2003.

If you complete these steps and score 70% or higher, Projects In Knowledge will mail you an acknowledgment of your participation in this activity. Please note: If you score lower than 70%, you will be given another chance to take the Posttest.
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- Complete the CME Evaluation.
- Mail or fax the completed posttest and evaluation to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.

Projects In Knowledge will mail you an acknowledgment of your participation in this activity if your combined score on the posttest is 70% or better. If your combined score is lower than 70%, you will be notified by mail and will be given another opportunity to take the posttest.

Name

Degrees/Credentials

Mailing Address

City

State

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Phone

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E-mail

Please indicate your answers below (circle one).

1. Which of the following tumor stages accounts for about 70% of all superficial bladder cancers?
   a. Ta          b. T1          c. CIS

2. Which of the following groups has the highest risk of bladder cancer?

3. Which of the following would not be considered high-risk bladder cancer?
   a. Multiple grade II, stage T1 tumors   b. A single grade II, stage T1 tumor
   c. Grade III, stage Ta disease         d. CIS

4. The majority of patients with hematuria:
   a. Have bladder cancer    b. Do not have bladder cancer

5. Compared with cytology, most urine-based bladder cancer tests are:
   a. More sensitive and more specific   b. More sensitive but less specific
   c. Less sensitive but more specific   d. Less sensitive and less specific

6. Laser therapy:
   a. Is therapeutic in superficial bladder cancer
   b. Is rarely used as initial therapy because it does not allow pathologic analysis
   c. Is associated with less bleeding and postoperative bladder irritation than TUR
   d. All of the above
7. TUR alone is sufficient treatment in the majority of patients, resulting in low rates of recurrence and progression.
   a. True  b. False

8. With the newest surgical technique (orthotopic neobladder), external appliances are no longer necessary following cystectomy.
   a. True  b. False

9. Which of the following offers the greatest reduction in recurrence rates when given intravesically after a TUR?
   a. Chemotherapy (e.g., doxorubicin, thiotepa)
   b. Immunotherapy (BCG or BCG/interferon)
   c. Both produce equivalent reductions in recurrence rates

10. The effectiveness of mitomycin C appears to be greatest when given:
    a. 1 or more days after TUR  b. Perioperatively (within 2 hours of TUR)
    c. At any time (effectiveness is the same regardless of when it is given)

11. Following a TUR and biopsy, BCG administration:
    a. Can be performed immediately  b. Can be performed after 5 to 7 days
    c. Can be performed after 10 to 14 days  d. Should be delayed at least 1 month

12. Following treatment with BCG, patients:
    a. Should remain as still as possible in a prone position for 2 hours before voiding
    b. Drink at least 12 glasses of water over the next 24 hours to flush out BCG
    c. Disinfect voided urine with household bleach for 15 minutes during the 6 hours posttreatment
    d. Should avoid sexual intercourse for up to 1 month posttreatment

13. Which of the following should not be used in the treatment of BCG sepsis?
    a. Cycloserine  b. Isoniazid  c. Prednisolone
    d. Rifampin  e. All of the above are OK to use

14. In a study by O'Donnell et al, a 2-year recurrence-free survival rate of 53% was observed when BCG failures were re-treated with:
    a. Full-dose BCG monotherapy
    b. 1/3-dose BCG monotherapy
    c. 100 mIU interferon alfa-2b monotherapy
    d. 1/3-dose BCG + 50 mIU interferon alfa-2b
    e. 1/3-dose BCG + 100 mIU interferon alfa-2b
    f. Full-dose BCG + 50 mIU interferon alfa-2b

15. Which formulation of interferon alfa-2b should be used in combination with BCG?
    a. Powder  b. Solution  c. Either one is acceptable
CME Evaluation Survey
Diagnostic and Treatment Issues in Superficial Bladder Cancer

Instructions
Please complete this survey, along with the CME Posttest, and mail or fax (both sides) to Projects In Knowledge, One Harmon Plaza, Secaucus, NJ 07094; fax: 1-201-617-7333.

1. Please rate the extent to which you achieved the learning objectives:

   - Describe the epidemiology, risk factors, grading/staging, and natural history of superficial bladder cancer
   - Evaluate patients with hematuria for bladder cancer using cystoscopy, cytology, and other urine-based tests, and radiologic imaging
   - Formulate appropriate treatment strategies for superficial bladder cancer using surgical approaches and intravesical chemotherapy or immunotherapy
   - Consider the latest data regarding bacillus Calmette-Guérin (BCG) and interferon combination therapy when formulating treatment plans for patients with superficial bladder cancer
   - Select appropriate candidates for BCG/interferon combination therapy and BCG monotherapy
   - Select appropriate doses and treatment intervals for intravesical immunotherapy regimens
   - Prevent and manage toxicities associated with BCG and interferon
   - Diagnose and treat recurrences of superficial bladder cancer following initial therapy

2. Please rate the overall value of this enduring material:

   - Strongly Agree
   - Agree
   - Disagree
   - Strongly Disagree

3. Course was free from commercial bias:

   If you “Disagree” or “Strongly Disagree,” why?

   - Just Right
   - Too Advanced
   - Too Basic

4. Please rate the level of the material presented:

   - Just Right
   - Too Advanced
   - Too Basic

5. Please list any changes in your practice that you would consider making as a result of participating in this activity:

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6. Please rate your interest in self-directed or distance learning in the following formats:

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7. Please tell us how long it took you to complete this course:  

8. Please list topics and/or experts you would find interesting and professionally relevant for future CME activities:

9. Follow-up:
   As part of our ongoing continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our CME courses on professional practice. Please indicate your willingness to participate in such a survey:

   - ❑ Yes, I would be interested in participating in a follow-up survey.
   - ❑ No, I’m not interested in participating in a follow-up survey.

Additional comments about this activity:

Thank you for your participation.