Management of Superficial Transitional Cell Carcinoma of the Bladder

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INTRODUCTION

Bladder cancer is the fourth most common cancer in men in the United States and the eighth most common cancer in women. An estimated 56,500 patients will be diagnosed with the disease in 2002, and 12,600 will die of the disease. Transitional cell carcinoma (TCC) accounts for 90% to 95% of cases, and adenocarcinoma and squamous cell carcinoma comprise the remaining cases. The occurrence of incidentally discovered bladder cancer at autopsy is virtually zero, indicating that most bladder cancers come to clinical detection during the patient’s lifetime. A majority of tumors are superficial (stage Ta, T1, or Tis) at the time of initial diagnosis. This review considers issues related to the diagnosis and management of superficial TCC of the bladder.

INITIAL EVALUATION OF BLADDER TUMORS

CASE 1 PRESENTATION

Patient 1 is a 67-year-old man with a history of recurrent TCC of the bladder who presents for routine surveillance cystoscopy. He has previously undergone treatment with intravesical thiotepa, doxorubicin, and bacillus Calmette-Guérin (BCG). His last tumor recurrence was more than 6 months ago. At the current examination, his urine cytology is positive for the presence of malignant cells, and cystoscopy reveals a sessile bladder tumor. Upon resection, the tumor is found to be high grade with invasion into the lamina propria (Figure 1, page 7). There are some slips of muscle present in the lamina propria. The patient’s three prior bladder tumors have been stage Ta high grade, stage Ta high grade, and—most recently—stage T1 high grade. The most recent prior tumor was multifocal, with one tumor located at the bladder neck.

• What is the clinical stage of patient 1’s current bladder tumor?
• What procedures should be performed at this point to further assess patient 1’s disease?

STAGE AND GRADE CONSIDERATIONS

Staging of TCC

Accurate determination of the stage and histologic grade of bladder tumors is a critical aspect of evaluation because these factors have a significant impact on management and prognosis. The normal bladder epithelium consists of 2 to 6 layers of transitional cells. The lamina propria, which underlies the basement membrane of the epithelium, is a connective tissue layer that also has slips of smooth muscle within it, called muscularis mucosae, which is different from the muscularis propria of the bladder wall, which lies below the lamina propria (Figure 2).

Staging of bladder cancer is based on the extent of penetration of the tumor into the wall of the bladder (Table 1). Pathologic staging performed on a specimen obtained by transurethral resection of bladder tumor (TURBT) can underestimate the true histologic extent of disease by 30% to 35% as demonstrated by repeat TURBT. Understaging by TURBT is more likely in higher grade tumors, as evidenced by the stronger association between higher histologic grade and infiltration of detrusor muscle in specimens examined at cystectomy compared to the assessment at TURBT. Previous studies have demonstrated that repeat TURBT can alter treatment decisions in up to 33% of patients owing to reassignment of stage. Repeat TURBT would be particularly useful in precise staging of patients with no muscle found in the specimen from the initial resection.

Histologic Grade of TCC

Histologic grade of TCC is assigned based on cellular morphologic characteristics, including nuclear-cytoplasmic ratio, presence of nucleoli, and cellular
pleomorphism. The World Health Organization (WHO) formerly classified tumors as grade I, II, or III. More recently, however, better understanding of the biology of these tumors has led to a redefinition of the grading system (Table 2). The WHO grading system now classifies tumors as low grade (previously grade I or I-II and some grade II) or high grade (previously grades II, II-III, and III).9

Papillary urothelial neoplasms of low malignant potential (PUNLMPs) are benign and very closely resemble normal epithelium. Most tumors of stage T1 or greater tend to be high grade. Stage Tis tumors, which are carcinoma in situ (CIS), are by definition high grade tumors. CIS occurs in the absence of other tumors in only 1% to 2% of cases.10 If left untreated, CIS can progress to invasive disease in more than 50% of cases.11

### Predictors of Recurrence

Approximately 15% to 25% of patients presenting with superficial bladder cancer develop progressive disease during follow-up.12,13 Tumor stage, grade, presence of concomitant dysplasia or CIS, multifocality, tumor size (> 3 cm), and tumor configuration (papillary or solid) are all predictors of recurrence and progression. Approximately 70% of superficial bladder tumors are solitary at presentation. The remaining 30% tend to be multifocal.14,15 Most (70%) superficial bladder tumors are confined to the urothelium (Ta or CIS) and the other 30% are staged as T1 (extending into the lamina propria).16

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Ta</td>
<td>Non-invasive papillary carcinoma</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: “flat tumor”</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades subepithelial connective tissue</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscle</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor invades superficial muscle (inner half)</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor invades deep muscle (outer half)</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades perivesical fat</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor invades fat microscopically</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor invades fat macroscopically (extravesical mass)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades prostate, uterus, vagina</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades pelvic wall, abdominal wall</td>
</tr>
<tr>
<td>Lymph nodes (N)</td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>Regional lymph nodes not involved</td>
</tr>
<tr>
<td>N1</td>
<td>Metastases in a single lymph node ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single lymph node &gt; 2 cm but ≤ 5 cm in greatest dimension; or multiple lymph nodes, none &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a single lymph node &gt; 5 cm in greatest dimension</td>
</tr>
<tr>
<td>Distant metastasis (M)</td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
</tr>
</tbody>
</table>

Patients with a prior history of recurrent tumors (especially within 3 months) have a greater propensity for recurrence and progression. Patients with CIS have a high likelihood of progression with an overall progression rate to muscle invasive disease of 54%.\(^{17}\) Patients with stage T1 disease are at particularly high risk for disease recurrence and progression, with only 30% of these patients being recurrence-free at 3 years if treated with TURBT alone.\(^{18,19}\) With regard to T1 tumors, a 15% to 20% death rate from bladder cancer and a significant risk of disease progression can be expected even with additional intravesical BCG therapy.\(^{20}\)

For low grade tumors, the likelihood of recurrence is high, but the likelihood of disease progression is not. While 50% to 60% of low grade tumors recur, only 2% to 11% of these tumors progress, as compared to high grade tumors, of which 50% progress in 3 years.\(^{21}\) Within each stage, lower grade tumors have a lower likelihood of progression compared to higher grade tumors. In a study of 219 patients with superficial bladder cancer,\(^{18}\) the progression rates for TaG1, TaG2, and TaG3 tumors were 2%, 6%, and 25%, respectively. For T1G1, T1G2, and T1G3 tumors, the progression rate was reported to be 0%, 21%, and 48%, respectively.\(^{18}\)

### Use of Urine-Based Bladder Tumor Markers

Voided urine cytology has traditionally been used to aid in the diagnosis and monitoring of patients with bladder TCC. Although the sensitivity of cytology for high grade tumors and CIS is excellent, its sensitivity is substantially lower for detecting lower grade tumors, which form the bulk of superficial cancers. The specificity of cytology is high, and hence there are very few false-positive urine cytology results. In order to improve the accuracy of cytology, barbotage cytology, flow cytometry and staining for antigens such as Lewis X and ABH blood group antigens have been pursued.\(^{22}\) Several urine-based markers are currently being evaluated for their ability to detect bladder cancer and to predict prognosis. Assays are commercially available for several of these markers, including nuclear matrix protein 22 (NMP22), bladder tumor antigen, and fibrinogen degradation product (Table 3).\(^{22}\) While many of these markers have a greater sensitivity than voided urine cytology for detecting low grade tumors, their specificity is lower than cytology, resulting in a high number of false-positive test results, which may prompt unnecessary cystoscopies. Overall, specificity for common tumor markers is 73% to 90% and sensitivity is 49% to 77%.\(^{23}\) The marker NMP22 may be able to detect recurrent bladder tumors prior to their being visible on cystoscopy.\(^{24}\)

### EVALUATION AND MANAGEMENT OF PATIENT 1

In patient 1, it is important to ascertain the precise histologic stage and grade of the bladder tumor. This requires rigid cystoscopy and random bladder biopsies to rule out the presence of CIS in the bladder. It also requires a repeat biopsy of the previous resection bed to obtain adequate muscle to determine if there is extension of tumor into the muscularis propria (indicating stage T2 disease). If repeat resection demonstrates T2 disease, the patient should undergo radical cystoprostatectomy.

In addition, biopsies of the prostatic urethra are required to rule out the presence of TCC in that area. This is particularly important as at least one previous recurrent bladder cancer, it may be cost-effective to alternate between tumor marker assays and cystoscopy with cytology every 3 months.\(^{23}\) Further studies are needed to evaluate the best marker for detection of primary or recurrent bladder cancer.
tumor was located at the bladder neck, which places the patient at higher risk for prostatic urethral involvement. Wash cytologies of the upper tracts and retrograde pyelograms or intravenous pyelograms are necessary to rule out the presence of upper tract disease. Patients who fail intravesical therapy are at higher risk for recurrence of TCC at extravesical sites such as the upper tracts or prostatic urethra (Figure 3, page 7), which can be as high as 25%, compared to an incidence of 2% in TCC patients generally.25,26

The presence of slips of muscle in the lamina propria on a TURBT specimen can sometimes be misleading as they usually represent muscularis mucosae and not muscularis propria. Some investigators have argued that extension of tumor beyond the level of the muscularis mucosae but not into muscularis propria still has a worse prognosis and have proposed subclassification of T1 tumors into T1a (into lamina propria up to the level of muscularis mucosae) and T1b (into lamina propria beyond the level of muscularis mucosae) on this basis.27 If this patient indeed has high grade T1 disease, treatment alternatives include a repeat course of intravesical therapy or proceeding to radical cystoprostatectomy.

RESECTION AND BIOPSY CONSIDERATIONS

CASE 2 PRESENTATION

Patient 2 is an 84-year-old frail woman who presents with recurrent low grade stage Ta TCC of the bladder (Figure 4, page 7). She has had 3 prior occurrences of bladder tumor, which were treated with intravesical thiotepa, BCG, and BCG, respectively. She has multiple comorbid conditions, including coronary artery disease, chronic obstructive pulmonary disease, and diabetes mellitus. Random bladder biopsies performed at prior TURBTs have all been negative. She has not had any documented occurrences of CIS. Her current tumor is solitary, situated on the trigone, and is less than 1 cm in diameter. Voided urine cytology is negative for tumor cells.

- What is the next step in the evaluation of patient 2?

TRANSURETHRAL RESECTION OF BLADDER TUMOR

This patient will first require resection of her tumor. Resection of superficial TCCs can be performed using one of several methods. Standard TURBT can be accomplished using a 24F or 26F resectoscope with resection of the stalk of a papillary lesion. The base of the lesion is then separately biopsied with a cold-cut biopsy forceps or a resectoscope loop to obtain an adequate sample of the muscular wall. If a tumor appears papillary and low grade, every effort should be made to resect all tumor tissue because this may constitute adequate therapy for certain low grade stage Ta tumors.

If the lesion is broad-based, it may be easier to resect the surface of the tumor and then approach the base of the lesion. In tumors that are extensive and appear obviously invasive, it may be reasonable to obtain adequate tumor and muscle samples to assess pathologic stage and forego an attempt to resect the tumor completely, because such patients are likely to require radical cystectomy for definitive treatment of their tumor.

Resection of tumors on the lateral wall of the bladder should be performed with care because this may cause
stimulation of the obturator nerve with spasms of the adductor muscles and inadvertent bladder wall perforation. Prior administration of a muscle relaxant can prevent this complication. Resection of tumors near the ureteric orifices must be performed with care and using pure cutting current only to avoid the risk of scarring the orifices. On occasion, a ureteral stent may have to be placed prior to resecting tumors adjacent to the orifices. Additional random bladder biopsies should be obtained to determine the presence of CIS, which can be present concomitantly in 30% to 70% of patients with invasive tumors. This recommendation is somewhat controversial as the theoretical possibility exists that denudation of the mucosa caused by the biopsies may encourage implantation of floating tumor cells.

TCC of the prostatic urethra occurs in 10% to 51% of men with bladder cancer. Presence of tumor at the bladder neck, multifocal tumors, and extensive CIS are associated with a higher likelihood of prostatic urethral involvement. In men, therefore, an additional biopsy of the prostatic urethra should be obtained, particularly in those with multifocal tumors and tumors at the bladder neck. The presence and extent of prostatic urethral involvement can help predict the likelihood of the distal urethral margin being positive for TCC. Involvement of only the prostatic urethral mucosa by TCC does not increase the likelihood of distal urethral TCC, whereas involvement of the prostatic ducts and stroma can significantly increase the chances of distal urethral TCC.

Complications of Transurethral Resection

Complications of standard TURBT are rare, with perforation being the most frequent. Perforation is usually treated with prolonged Foley catheter drainage (7–10 days). Though there is a theoretical risk of extravesical spread of cancer from the perforation, this has not been frequently reported. Other complications that can occur include bleeding with clot retention, mechanical urethral injury from the resectoscope leading to urethral strictures, and injury to the obturator nerve.

LASER FULGURATION OF PAPILLARY TUMORS

Nd:YAG, KTP, and holmium:YAG lasers have been used for fulguration of papillary tumors. The advantages of using a laser are the absence of bleeding and decreased irritative voiding symptoms. Laser treatment can often be performed through a flexible cystoscope in an office setting, with local anesthesia. Complications include the possibility of bladder perforation, especially with the Nd:YAG lasers, which have a greater depth of penetration. Perforation of adjacent small bowel (without concomitant bladder perforation) caused by forward scatter of the laser energy is very rare but has been described, resulting in peritonitis and necessitating exploratory laparotomy and repair.

TREATMENT OPTIONS FOR PATIENT 2

Given patient 2’s advanced age and comorbid diseases, as well as the low grade and stage of her cancer, further attempts at conservative therapy may be justified. A fourth course of intravesical therapy, with an alternative agent such as mitomycin C, can be administered. A reasonable proportion of patients who fail initial treatment with BCG or mitomycin C can respond to treatment with the other agent. Trials of sequential chemoimmunotherapy with 4 cycles of mitomycin C followed by 6 cycles of BCG, or regimens that alternate between the two treatments, have not demonstrated differences in efficacy; in addition, in comparison to standard BCG therapy, adverse effects were somewhat reduced with the newer treatment regimens.

A treatment option that seems counterintuitive in a patient such as this, who has been treated with TURBT and intravesical therapy in the past, is the option of fulguration with no additional therapy. Patients with a well-documented, recurrent low grade papillary bladder tumor can often be managed in this manner. In a tumor such as this, with none of the features associated with progression (ie, multifocality, CIS, high grade, large size) it is reasonable to closely monitor the patient with periodic cystoscopy, and perform fulguration of the recurrent tumors as they appear. This can even be accomplished in the office setting using a flexible cystoscope and Nd:Yag laser. Cystectomy would be overly aggressive in this patient.

CHEMOTHERAPEUTIC AGENTS

CASE 3 PRESENTATION

Patient 3 is a 72-year-old man who presents with microscopic hematuria of 1 month’s duration, detected during a routine annual physical examination. Results of further work-up, including intravenous pyelogram and renal ultrasonography, are negative. Cystoscopy reveals a single 1-cm, papillary tumor on the left lateral wall of the bladder, which on resection is found to be stage Ta, low grade TCC (Figure 5, page 7).

• Is this patient a candidate for intravesical therapy?
• What options are available for intravesical therapy for superficial TCC?

Patients who have high grade Ta, Tis, or T1 disease are candidates for intravesical chemotherapy or
immunotherapy in addition to resection. Patients with a history of recurrent low grade Ta disease also may be candidates for intravesical therapy to prevent or delay recurrences. Recurrence rates following different types of intravesical therapy in patients with superficial TCC are shown in Table 4.

THIOTEPA

This was the first agent to be used for intravesical chemotherapy. The overall efficacy of thiotepa is about 38%.39,40 However due to its relatively low molecular weight (189 kD), it is more likely to be systemically absorbed than other agents. Myelosuppression occurs in 9% to 54% of patients.41,42 In a large randomized trial, thiotepa as a single intravesical instillation following TURBT was not shown to yield any benefit in terms of preventing recurrence or disease progression.43 Many large studies have demonstrated a delay in interval to recurrence and a decrease in the recurrence rate in patients receiving a full 4-week course of intravesical thiotepa compared to those who undergo TURBT alone; however, these differences are not always statistically significant.44,45 The combination of lower efficacy, higher toxicity, and the availability of better alternatives has led to a severe decline in the use of this agent.

DOXORUBICIN

Doxorubicin is an anthracycline antibiotic with a molecular weight of 580 kD. Because of its higher molecular weight, the risk of systemic absorption is low. The major toxicity of doxorubicin is chemical cystitis, which occurs in approximately 25% of patients. There is almost no systemic toxicity. Results of intravesical administration of doxorubicin have been comparable to those obtained with thiotepa, with an average response rate of 38%.40 Studies using short courses of intravesical doxorubicin and maintenance regimens for as long as 2 years have shown no significant decrease in recurrence rates.46 Due to relatively low response rates, doxorubicin is not widely used for the treatment of superficial bladder cancer.

EPIRUBICIN

Epirubicin has a similar mechanism of action to doxorubicin but appears to have better response rates. Toxicity is limited to a chemical cystitis, which occurs in approximately 15% of patients. A single instillation of epirubicin after TURBT can significantly reduce recurrence rates except in low grade Ta tumors. A complete ablation of 56% of visible lesions was observed in one trial of intravesical epirubicin.40 Maintenance therapy for 2 years or longer can delay time to recurrence but may not decrease the number of recurrences per patient.47 However, it is not clear whether prolonged maintenance therapy with epirubicin is more effective than a standard 6-dose induction treatment. This agent is not available for intravesical use in the United States.

MITOMYCIN C

Mitomycin C is an alkylating agent with a molecular weight of 329 kD. It can be administered intravesically at doses ranging from 20 mg to 60 mg. A single instillation of mitomycin C immediately following TURBT has been shown to decrease the incidence of recurrence within the 2 years following resection.48 In a multicenter study of 502 patients who underwent resection for newly diagnosed superficial bladder cancer,48 patients were randomized into 3 treatment arms: no mitomycin C, a single postresection dose, and a postresection dose followed by 1 dose of mitomycin C every 3 months for 1 year. Patients receiving either of the two dosing schedules of mitomycin C had lower recurrence rates and longer recurrence-free intervals compared to the control group. A review of multiple studies revealed a 15% decrease in recurrence rates when mitomycin C is given prophylactically following TURBT.49 Although the administration of immediate post-TURBT intravesical mitomycin C reduces recurrences for up to 2 years after therapy, the effect is lost beyond that time point. In addition, mitomycin C does not significantly affect progression of disease to a higher stage (ie, T2 or muscle invasion).45 It may prevent such disease progression in only 5% to 15% of patients.40,50

Table 4. Comparison of Recurrence Rates Following Different Types of Intravesical Therapy for Superficial Transitional Cell Carcinoma of the Bladder

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Median Difference (confidence interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TURBT + thiotepa vs TURBT alone</td>
<td>19 (9–28)</td>
</tr>
<tr>
<td>TURBT + BCG vs TURBT alone</td>
<td>30 (19–39)</td>
</tr>
<tr>
<td>TURBT + mitomycin C vs TURBT alone</td>
<td>15 (7–22)</td>
</tr>
<tr>
<td>TURBT + doxorubicin vs TURBT alone</td>
<td>10 (2–17)</td>
</tr>
<tr>
<td>TURBT + BCG vs TURBT + doxorubicin</td>
<td>23 (13–32)</td>
</tr>
<tr>
<td>TURBT + BCG vs TURBT + thiotepa</td>
<td>30 (10–47)</td>
</tr>
</tbody>
</table>

BCG = bacillus Calmette-Guérin, TURBT = transurethral resection of bladder tumor.

*Difference indicates an advantage for the treatment listed first in order.

Figure 1. Cystoscopic photograph of stage T1 high grade bladder tumor.

Figure 3. High grade muscle-invasive bladder tumor extending into the prostatic urethra.

Figure 4. Cystoscopic photograph of a low grade papilloma of the bladder.

Figure 5. Cystoscopic photograph of a low grade stage Ta bladder tumor.

Figure 6. Cystoscopic photograph of areas of multifocal carcinoma in situ on posterior bladder wall.
When used for standard intravesical chemotherapy, mitomycin C is administered weekly for 4 weeks. It has been used in maintenance regimens for up to 1 year. Overall response rates vary from 39% to 77%. The response rates tend to be higher for CIS than for papillary lesions. The value of prolonged maintenance therapy with mitomycin C is controversial, with studies yielding mixed results. Some larger studies have demonstrated a benefit from maintenance therapy administered over a period of 2 to 3 years compared to no therapy. However, other studies comparing short duration maintenance therapy to induction therapy have not been able to demonstrate similar benefits.

Overall, intravesical chemotherapy does not appear to yield any advantage in terms of preventing disease progression, appearance of distant metastasis, or survival. Tumor recurrence during a follow-up period of 5 years or more is high and is particularly worse for those with CIS. However, intravesical chemotherapy does increase the disease-free interval in patients with superficial bladder cancer.

Side effects of mitomycin C include chemical cystitis and allergic skin reactions, which can manifest as contact dermatitis. The skin reactions are due to delayed hypersensitivity and tend to occur after the second dose but are self-limiting. It can also rarely cause myelosuppression and aplastic anemia. It can be more expensive on a dose-by-dose basis compared to BCG.

TREATMENT OF PATIENT 3

Patient 3 has a single, small, low grade, stage Ta TCC of the bladder. He has none of the commonly recognized factors that would place him at a higher risk for recurrence or progression. He would require no further treatment at this time and can be monitored on a strict surveillance program. In older individuals with recurrent low grade Ta lesions, periodic cystoscopy with fulguration or cautery of the lesion is also a reasonable option. The risk of progression in these tumors is extremely low. Another option for patient 3 would be instillation of a single dose of intravesical mitomycin C immediately following TURBT to reduce the risk of recurrence and delay the time to recurrence.

IMMUNOTHERAPY WITH BCG

CASE 4 PRESENTATION

Patient 4 is a 60-year-old man with a history of smoking who is referred to a urologist because of microscopic hematuria identified on routine examination. Results of voided urine cytology are positive for malignant cells. Further work-up, including an intravenous pyelogram, renal ultrasound, and flexible cystoscopy, suggests the etiology to be a bladder tumor arising from the posterior wall which, on TURBT, is found to be a high grade Ta lesion. Several foci of CIS (Figure 6, page 7) are also identified in the bladder.

• What is the next step in the management of patient 4?

PRINCIPLES OF THERAPY WITH BCG

BCG was developed as a vaccine against tuberculosis. It was first found to be effective against superficial bladder cancer by Morales in 1976. The current indications for intravesical BCG administration include the presence of CIS, recurrent Ta tumors, high grade Ta tumors, and T1 tumors.

A number of randomized trials have demonstrated the benefit of intravesical BCG therapy compared to TURBT alone. Tumor-free response rates vary from 66% for those treated with BCG to 17% for those treated with TURBT alone. Higher cancer progression rates and cancer-specific death rates are also reported in patients who receive TURBT alone compared to those who receive TURBT plus intravesical BCG. This has been borne out by studies with follow-up periods of as long as 10 years. However, in patients with high grade T1 disease, the risk of progression to metastatic disease persists, and ultimately, as many as 35% of these patients may die of bladder cancer. Intravesical BCG may also eradicate residual tumor in the bladder, although it is most effective if administered after complete resection of all visible tumor. Eradication of residual tumor has been observed in 35% of patients after one 6-week course of BCG and another 36% of patients after a second course.

BCG is most effective in treating CIS, with response rates as high as 70% to 80%. It is estimated that the use of intravesical BCG has reduced the need for cystectomy in this group of people by 75%. The use of maintenance BCG is still somewhat controversial, though there appears to be a significant decrease in recurrence rates and time to disease progression with a 3-week maintenance regimen (1 instillation/week) administered at 3 months after start of induction and every 6 months thereafter for 3 years. The tumor-free rate in patients with CIS receiving 27 months of maintenance BCG was 84%, compared to 68% for those receiving only the induction course.

The response to BCG appears to be durable, particularly in cases of CIS. Among patients who demonstrate a complete response to the treatment, 64% are likely to
remain tumor-free at 5 years after therapy. However, many of these patients subsequently develop recurrent disease by 10 years of follow-up. At 10 years, 31% of patients were found to be free of recurrence. Intra-vesical BCG may also be used for TCC involving the prostatic urethra, as long as the tumor is not invading the stroma.

Comparisons of the efficacy of BCG and mitomycin C have yielded equivocal results. Some studies suggest that BCG therapy is superior, leading to lower recurrence rates (40% vs 58%). The recurrence-free interval also appears to be longer following BCG therapy. None of the studies comparing BCG and mitomycin C have been able to demonstrate any relative benefit for either agent in terms of preventing disease progression. Initially, it was surmised that these differences were a result of variation in dosing schedule of BCG and mitomycin C in the different trials as well as due to the different strains of BCG being used. However, a prospective randomized trial comparing 2 different strains of BCG (Tice BCG and RIVM-BCG) and mitomycin C failed to show a similar difference between the two strains of BCG and actually demonstrated that mitomycin C therapy resulted in lower recurrence rates. There is also some indication that recurrence after BCG therapy may be more frequent in patients with tumors other than CIS. Additionally, patients receiving BCG therapy experienced a greater number of adverse effects.

The standard dose of BCG is 1 ampule of Tice or 3 vials of Connaught strain, dissolved in 50 cc of normal saline solution. Instillations are usually commenced 2 to 3 weeks following a TURBT to allow healing of the epithelium. If the patient has gross hematuria, BCG instillation should be suspended until the hematuria resolves. BCG is contraindicated in immunosuppressed individuals. A dwell time of 2 hours is recommended after instillation. Intercourse is avoided for 48 hours after instillation. The presence of vesicoureteric reflux is not a contraindication to BCG therapy.

The mechanism of action of BCG is thought to be through the induction of cytokine production. Animal experiments indicate that a variety of cytokines, including interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor, and interferon γ are released in response to BCG. Uptake and presentation of the BCG antigens by tumor cells can induce a T-cell response as well as promote an antibody- and cell-mediated immune response.

**INITIAL MANAGEMENT OF PATIENT 4**

The high grade of patient 4’s tumor and the presence of CIS make him a candidate for induction BCG therapy. He receives treatment with intravesical BCG administered as a 6-week induction course. Surveillance cystoscopy at 6 months reveals multiple areas of patchy erythema with no papillary tumor. Biopsy confirms the presence of CIS.

- Is patient 4 a candidate for a second course of BCG therapy?
- Is patient 4 a candidate for cystectomy at this point?

**MANAGEMENT FOLLOWING FAILURE OF BCG THERAPY**

Approximately 30% of patients experience failure of induction BCG therapy, and an additional 30% to 40% experience recurrence within 5 years of follow-up. A small proportion of these patients, especially those with CIS, can be salvaged with a second induction course of BCG therapy.

The risk of disease progression is very high in patients who fail BCG therapy, particularly if they have recurrent CIS. Thus, the histology of the recurrent tumor is important in deciding further management. For those who recur with high grade T1 tumors or CIS, radical cystectomy should be considered the standard of care. Treatment with newer agents such as valrubicin or BCG combined with interferon alpha may be alternatives in selected patients with recurrent superficial bladder cancer, particularly if they are not considered to be surgical candidates.

**Treatment Options for Patient 4**

Patient 4 had high grade Ta tumor along with multifocal CIS, which has recurred after BCG therapy. Administration of a second 6-week induction course of BCG can salvage approximately 20% of patients with CIS who fail their first course of intravesical BCG. If he fails a second course of BCG, he should be counseled regarding a radical cystoprostatectomy. If he demonstrates an initial response to the second course of BCG, additional maintenance BCG can be administered at 6-month intervals for up to 3 years.

**COMPLICATIONS OF BCG IMMUNOTHERAPY**

**CASE 5 PRESENTATION**

Patient 5 is a 66-year-old woman found to have recurrent, high-grade stage Ta TCC during follow-up for bladder cancer. She has had 2 prior occurrences of bladder tumor, which have been high grade Ta and high grade T1 disease, treated after TURBT with thiotepa and BCG, respectively. She is started on her second course of
induction BCG. After the second weekly instillation, she develops a fever to 39.5°C, chills, sweats, and rigors. The fever does not resolve with oral acetaminophen. Her leukocyte count is mildly elevated, and the results of liver function tests are normal. Results of urine culture are negative.

• What is the next step in the management of patient 5?

This patient appears to have a complication related to the BCG therapy. Most complications result from a vigorous host response to the BCG, and can be local and/or systemic (Table 5). Local manifestations of such a response include cystitis with dysuria and other voiding symptoms. Severe complications include contracted bladder, ureteral obstruction, prostatitis, epididymitis, miliary tuberculosis, and BCG sepsis. A higher likelihood of adverse effects exists in patients previously exposed to or immunized with BCG. Adverse effects typically require prior sensitization to BCG and tend to manifest after the second instillation or during a repeat course of BCG. Management of the most frequently encountered complications from intravesical BCG administration are listed in Table 6.

BCG CYSTITIS

Symptoms of BCG cystitis typically start a few hours after instillation and worsen with each successive instillation. In the presence of severe cystitis symptoms, additional instillations can be delayed to allow the symptoms to abate. Routine prophylactic use of isoniazid (INH) for preventing local or systemic side effects has not proven to be of much benefit in randomized trials.79 Instillation should not be performed in the presence of gross hematuria.

Cystitis symptoms also could reflect a bacterial cystitis caused by contamination during catheterization. Treatment for a presumed bacterial cystitis can be with cephalosporins, amoxicillin, or trimethoprim.80 There is some concern that the use of fluoroquinolones and tetracyclines can destroy the BCG, leading to a mitigation of the tumor response to BCG, so these antibiotics are not recommended in this situation.

BCG SEPSIS

BCG sepsis can be fatal. It is heralded by chills, hypotension, and fever, which may be observed within a few

### Table 5. Incidence of Complications Following Intravesical BCG Therapy for Superficial Bladder Cancer

<table>
<thead>
<tr>
<th>Complication</th>
<th>Lamm et al75 N = 2602</th>
<th>Steg et al74 N = 220</th>
<th>Ali-El-Dien et al77 N = 58</th>
<th>Paterson et al78 N = 200</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystitis</td>
<td>198 (90%)</td>
<td>36 (62%)</td>
<td>200 (100%)</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>24 (1%)</td>
<td>22 (10%)</td>
<td>4 (6.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Granulomatous prostatitis</td>
<td>23 (0.9%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epididymo-orchitis</td>
<td>10 (0.4%)</td>
<td>2 (1%)</td>
<td>1 (1.7%)</td>
<td></td>
</tr>
<tr>
<td>Ureteral obstruction</td>
<td>8 (0.3%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contracted bladder</td>
<td>6 (0.2%)</td>
<td>4 (2%)</td>
<td>1 (1.7%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Renal abscess</td>
<td>2 (0.1%)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>8 (4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Systemic complications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>75 (2.9%)</td>
<td>12 (5%)</td>
<td>3 (5.2%)</td>
<td>7 (3.5%)</td>
</tr>
<tr>
<td>Pneumonitis/hepatitis</td>
<td>18 (0.7%)</td>
<td>5 (2.2%)</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12 (0.5%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8 (0.3%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Cytopenia</td>
<td>2 (0.1%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>10 (0.4%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Approximately 10 deaths directly attributable to BCG sepsis have been reported.

BCG = bacillus Calmette-Guérin.

* A dash indicates data were not reported.

hours after instillation. Hemodynamic resuscitation is carried out as required, and a combination of antituberculous medications, including INH, rifampicin, pyridoxine, and/or ethambutol, is administered. In addition, intravenous steroids may also be required.

Fever can occur in the absence of sepsis after BCG instillation due to the release of cytokines in response to BCG. This fever usually resolves within 48 hours and responds to antipyretics. Patients with fever lasting more than 48 hours or with temperature elevation higher than 39.5°C should be treated with a 3-month course of INH and pyridoxine. BCG therapy should be avoided in immunosuppressed individuals.

**TREATMENT OF PATIENT 5**

This patient has BCG bacteremia and sepsis. She should be treated emergently with intravenous hydration and antituberculous therapy with INH, rifampicin, and ethambutol. She should receive no further instillations of BCG. If there is no resolution of symptoms within 24 hours, intravenous steroids can be added to the regimen. An alternative treatment regimen such as intravesical mitomycin can be considered for her TCC.

**THERAPEUTIC OPTIONS FOR REFRACTORY SUPERFICIAL TCC**

**CASE 6 PRESENTATION**

Patient 6 is a 79-year-old man who presents with a recurrent bladder tumor detected during surveillance cystoscopy. His first tumor occurred when he was 60 years old, and he has had multiple recurrent stage Ta tumors since that time. He has previously been treated with intravesical thiotepa and BCG. His last tumor (stage Ta, low grade, with CIS) was 1 year ago, and was treated with TURBT and intravesical BCG. His current solitary tumor is stage Ta high grade. Random bladder biopsies reveal the presence of CIS. Results of upper tract studies and prostatic urethral biopsies are negative. His past medical history is significant for diabetes mellitus, coronary artery disease, hypertension, and Parkinson’s disease. He has previously undergone 2 coronary artery bypass graft procedures.

- **What are the treatment options for patient 6?**
- **Should cystectomy be recommended for patient 6?**

Treatment of patients who have failed prior intravesical therapy with standard agents is problematic. In patients without severe comorbidities cystectomy may be an option. If additional intravesical therapy is contemplated, there are some options that have become available in recent years.

**INTERFERON ALFA-2B**

Interferon alpha-2b is one of a group of interferons produced by lymphocytes and macrophages. The interferons can stimulate cytokine production, antigen presentation, natural killer (NK) cell activity, and activation of T and B lymphocytes. All of these actions are thought to be responsible for the activity of interferon alfa-2b against TCC of the bladder. Initial studies of interferon alfa revealed inferior efficacy when compared to BCG. However subsequent trials using intravesical administration of interferon alfa-2b resulted in complete responses in patients with stages Ta, T1, and Tis disease. Many of these patients had failed prior BCG therapy. Randomized studies indicate that up to 67% of prior

<p>| Table 6. Most Frequent Complications of Intravesical BCG Therapy and Their Management |
|-----------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Complication</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local complications</strong></td>
<td></td>
</tr>
<tr>
<td>Cystitis, hematuria</td>
<td>Stop BCG, provide symptomatic therapy.</td>
</tr>
<tr>
<td>Symptomatic prostatitis/epididymo-orchitis, ureteral obstruction</td>
<td>Stop BCG. Isoniazid (300 mg/day) and rifampicin (600 mg/day) for 3 months.</td>
</tr>
<tr>
<td>Bladder contracture</td>
<td>Stop BCG. Perform hydrodistension/augmentation. Can administer isoniazid (300 mg/instillation) for prophylaxis.</td>
</tr>
<tr>
<td><strong>Systemic complications</strong></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>Hold BCG and resume when afebrile; administer antipyretics.</td>
</tr>
<tr>
<td>Fever &gt; 38.5°C for more than 24 h</td>
<td>Isoniazid (300 mg/day) for 3 months. Hold BCG and resume when afebrile.</td>
</tr>
<tr>
<td>Rash, arthralgia, arthritis</td>
<td>Isoniazid (300 mg/day) for 3 months. Continue BCG only if absolutely necessary.</td>
</tr>
<tr>
<td>Sepsis, pneumonia, hepatitis</td>
<td>No further BCG. Isoniazid (300 mg/day), rifampicin (600 mg/day), and ethambutol (1200 mg/day) for 6 months. Also consider prednisone 40 mg/day.</td>
</tr>
</tbody>
</table>

BCG = bacillus Calmette-Guérin.
BCG failures may respond to intravesical interferon alfa-2b, with responses lasting as long as 10 years. Some responses may last only a year, however.

A wide range of doses have been used—from 10 million units to a billion units—with minimal toxicity, which manifests primarily as mild flu-like symptoms. In an effort to exploit the synergies between BCG and interferon alfa-2b, especially for patients who are thought to have failed induction BCG from lack of a significant immune response, a combination of the 2 agents has been used intravesically. The combination allows a lower dose of BCG (one-third of the standard dose) to be used and is given as an induction followed by maintenance therapy (one instillation per week for 3 weeks) at 5, 11, and 17 months after start of induction. In a trial involving 40 patients on this regimen, after a follow-up period of 30 months, 55% of patients remained free of recurrence, with no recurrences being reported after the first 24 months. If supported by further, large-scale studies, this approach may be a viable option for patients with BCG-refractory superficial bladder cancer.

**VALRUBICIN**

Valrubicin is an anthracycline analogue of doxorubicin that is less toxic and more effective than doxorubicin in animal models. It has been used in the treatment of BCG-refractory CIS in a study of 90 patients at a dose of 800 mg administered as 6 weekly intravesical treatments. The complete response rate was 21% at 6 months after therapy. However, the response was not found to be durable, with 17% of patients being disease-free at 1 year and only 8% being disease-free at a median follow-up of 30 months. Valrubicin is currently approved by the US Food and Drug Administration for treatment of CIS that has failed BCG therapy. Absorption of valrubicin when given intravesically is minimal, but waiting at least 2 weeks after TURBT is recommended to prevent systemic absorption and consequent myelosuppression.

**EXPERIMENTAL AGENTS**

**Gemcitabine**

Intravesical administration of gemcitabine has shown some promise in phase I trials for the treatment of BCG-refractory recurrent superficial TCC. In the first reported study, 11 of 18 patients demonstrated response to twice-weekly administration of intravesical gemcitabine for 3 weeks. Seven of the patients had a complete response and 4 had a mixed response (defined as negative cystoscopy with positive cytology). The level of toxicity was acceptable, with 2 patients experiencing grade 3 toxicity and none experiencing grade 4 toxicity. Further trials are needed before this therapy can be FDA approved and routinely applied.

**Keyhole Limpet Hemocyanin**

Keyhole limpet hemocyanin (KLH) is a known inducer of hypersensitivity reactions and has been used to test immune competence. It has been found to reduce recurrence rates of bladder tumors when administered intradermally. In studies comparing KLH to chemotherapy agents such as mitomycin C and ethoglucid, lower recurrence rates have been observed after the intradermal and intravesical administration of KLH. However, KLH does not appear to be superior to BCG therapy. The main advantage of KLH is its lower toxicity, with fever being the most commonly reported adverse event. Further trials will help determine the true applicability of KLH for the treatment of superficial bladder cancer.

**Tumor Necrosis Factor**

Tumor necrosis factor (TNF) is produced by macrophages and is found at high levels in the bladder after BCG instillation. While the administration of TNF yielded encouraging results in animal models of bladder cancer, clinical trials demonstrated little efficacy and hence it has not found a use in the treatment of bladder cancer.

**Bropirimine**

Bropirimine is an orally absorbed interferon inducer that is excreted in the urine. It was found to be effective in limiting the growth of tumors in animals and showed efficacy in the treatment of both residual bladder and upper tract cancers. However, administration of bropirimine resulted in significant cardiac toxicity and deaths, which caused all further research involving this agent to be abandoned.

**TREATMENT OPTIONS FOR PATIENT 6**

Though radical cystoprostatectomy with urinary diversion would generally be appropriate for a patient with recurring CIS and high-grade superficial TCC, this patient’s severe comorbidities make him a poor candidate for surgery. A trial of further intravesical therapy with either valrubicin or BCG plus interferon alfa-2b may yield a response and would be a less risky alternative to surgery.

**CONCLUSION**

Management of superficial bladder cancer has evolved over the past 2 decades. With the advent of new
Management of Superficial TCC of the Bladder

Figure 7. Algorithm for management of superficial transitional cell carcinoma. BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; HG = high grade; LG = low grade; TURBT = transurethral resection of bladder tumor.
chemo- and immunotherapeutic agents, intravesical therapy has become the mainstay of treatment. This has resulted in a greater likelihood of bladder preservation, especially for patients with CIS, and has significantly improved the disease outcome in these patients. Therapeutic regimens and dosing schedules continue to be optimized and new agents are in development, further improving our ability to manage this disease. Although bladder preservation is much more likely with today’s treatment options, there still is a role for cystectomy—even in patients with disease that is not muscle invasive—to avert disease progression and improve survival. Figure 7 provides an algorithm that can serve as a general paradigm for the management of patients with superficial TCC. The specific therapeutic choices must be tailored to the individual patient.

REFERENCES


