Approximately 54,400 new cases of transitional cell carcinoma of the bladder were reported in the United States in 1999, with an estimated 12,500 deaths attributable to this cancer. Close to 75% of all bladder tumors are confined to the mucosa (epithelium) or submucosa (lamina propria) only (stage Ta, T1, or Tis).

The majority of transitional cell carcinomas are papillary in morphology and are derived from the urothelium. At initial presentation, 70% of these tumors are superficial, defined as involving the mucosa (epithelium) or submucosa (lamina propria) only (stage Ta, T1, or Tis).

The natural history of superficial transitional cell carcinoma is still largely unpredictable because of tumor heterogeneity, as well as the multifocal nature of the disease. Tumors recur in 40% to 80% of patients and progress in 5% to 30%, despite complete resection. In general, superficial transitional cell carcinoma, when it does recur, remains stable with regard to stage and grade. Yet, in selected cases, the risk of progression to a muscle-invasive tumor is as high as 50% to 80%. The two basic categories of risk factors are tumor burden and dedifferentiation.

Transitional cell carcinoma in situ (Tis) histologically consists of poorly differentiated transitional cell carcinoma confined to the urothelium. Frequently associated with high-grade yet superficial papillary tumors, Tis portends a poor prognosis. Patients with carcinoma in situ have the highest recurrence rate. When treated with endoscopic resection alone, between 40% and 80% of these patients will progress to high-stage, muscle-invasive transitional cell carcinoma.

The time to progression to muscle-invasive disease remains unpredictable; however, patients with marked voiding symptoms, which implies increased tumor burden, clearly have a shorter interval preceding the development of invasive tumor. As many as 20% of patients with diffuse Tis are found to have evidence of muscle invasion on final pathologic examination when ultimately treated with radical cystectomy. Furthermore, as many as 10% of those patients with only focal Tis are found to have occult regional metastases at the time of radical surgery.

**Treatment Approach**

Transurethral resection of all visible transitional cell carcinoma (when possible) remains the ultimate method of pathologic staging and primary treatment. Pathologic review and appropriate additional clinical staging are required to identify patients at risk for recurrence and those for whom intravesical treatment is appropriate.

In patients with low-grade, low-stage, small-volume disease, careful surveillance endoscopy and intermittent resection or fulguration alone may be sufficient. In patients with higher-grade tumors, large-volume, and/or multifocal disease, adjuvant therapies should be considered.

Adjuvant intravesical therapy, whether in the form of chemotherapeutic or immunologic agents, is indicated in patients at high risk for tumor recurrence. High-risk patients include those with multiple or large tumors at initial resection, tumor recurrence(s), high-grade tumors, or papillary tumors associated with carcinoma in situ, as well as those with carcinoma in situ without papillary invasion.
transitional cell carcinoma.

When intravesical agents are used to destroy residual transitional cell carcinoma following incomplete resection, the treatment is considered to be therapeutic in nature. However, when the agents are selected after complete resection of all visible tumor, treatment is defined as prophylactic.

Chemotherapeutic agents that have historically been used for treating superficial transitional cell carcinoma of the bladder include thiotepa (triethyl-enethiophosphoramide [Thioplex]), mitomycin (Mutamycin), doxorubicin, epirubicin (4′-epidoxorubicin [Ellence]), and, most recently, valrubicin (N-tri-fluoracetyladriamycin-14-valerate [Valstar]). Biological therapies employing immunologically active agents include bacillus Calmette-Guérin (BCG), bropiramine (2-amino-5-bromo-6-phenyl-4-[3H]-pyrimidinone), recombinant interferon-alfa-2b (Intron A), and photosensitizers combined with laser therapy.

It remains a peculiarity of urologic practice that many agents commonly used to treat bladder cancer have never actually been approved by the Food and Drug Administration (FDA) for that specific use. This is especially relevant when discussing the management of intravesical treatment of superficial transitional cell carcinoma of the bladder. The only agents approved by the FDA for use in patients with transitional cell carcinoma are thiotepa, BCG, and valrubicin. Thiotepa was approved only for the treatment of low-grade, low-stage papillary transitional cell carcinoma, whereas bacillus Calmette-Guérin was approved only for patients with Tis. Valrubicin recently received FDA approval only for the treatment of refractory Tis.

Yet, in most urologic practices, the off-label use of these agents frequently benefits the patient. For example, BCG is used as a first-line therapy for both papillary transitional cell carcinoma and Tis despite the fact that it has been approved only for the management of Tis. In addition, a number of other options are available for patients who do not respond to or cannot tolerate intravesical BCG.

Immunologic Agents

BCG

Although not yet completely understood, the mechanism of BCG, and, indeed, of all biologically active agents, is immunomodulation. It appears that the mycobacteria of BCG attach to the surface epithelium of the bladder tumor and normal bladder; this attachment is facilitated by fibronectin. The mycobacteria are subsequently internalized and form complexes with various glycoproteins; the mycobacteria-glycoprotein complexes presumably stimulate a T-cell-mediated immune response. In addition, BCG directly activates macrophages, T and B lymphocytes, and natural killer cells, as well as antibody-dependent killer cells. These factors then activate lymphokine and interferon production. Bacillus Calmette-Guérin should not be administered to immunocompromised hosts, patients receiving therapeutic (rather than replacement) exogenous steroids, those who have had a traumatic catheterization, or those with persistent gross hematuria following bladder tumor resection. Patients with gross hematuria at the time of catheterization are at greatest risk for the development of systemic BCG-induced infection and possibly death.[7]

Interferon

Since interferon is clearly one of the end products of successful BCG treatment of superficial transitional cell carcinoma, it would seem logical that direct instillation of interferon into the bladder should also control this cancer. Various subtypes of interferon have, in fact, been used, unfortunately with only limited effect.

Recombinant interferon-alfa-2b has demonstrated some efficacy in the treatment of Tis in clinical trials. The appropriate intravesical dosage seems to be in the range of 50 to 100 million units administered weekly for 6 weeks. Durable responses to interferon, however, are clearly less impressive than with BCG, possibly indicating that some other factor or combination of factors, such as the cell-mediated cascade, is necessary for a maximal beneficial effect. Also, intravesical interferon-alfa-2b seems to be more effective when used as initial treatment, rather than as a salvage regimen in patients who have not responded to BCG.[8]

In an earlier study looking at doses of interferon-alfa-2b, patients treated with a high dose (100 million units) had clearly superior responses than those given a low dose (10 million units). Interestingly, however, six of the nine patients in this study had proved unresponsive to prior intravesical BCG therapy, and maximum follow-up was only 12 months.[9]

Greenberg is currently conducting a phase II trial to determine whether the combination of BCG plus interferon-alfa-2b is more effective than either agent alone. Other investigators are attempting to define the best possible dose of BCG and interferon-alfa-2b when used in combination. There is
ample clinical as well as laboratory evidence that, with biologically active agents, more is not always better, and lower-dose combinations may not only keep the cost of these treatments down but also yield superior results.[9,10]

**Other Immunomodulators**

Other immunomodulators that have been evaluated in the management of transitional cell carcinoma include bropiramine and TP-40.

**Bropiramine** is an oral inducer of interferon and other cytokines that can activate several related immunologic defense mechanisms.[11,12] Initial reports indicated exceptional response rates, especially in patients with stage Tis disease. Among this latter group, biopsies and bladder wash cytologies became negative in 61% of patients, including complete responses in 50% to 60% patients who had received prior BCG treatment. Complete responses occurred in 60% to 70% of patients who had not received prior BCG treatment and 80% of patients with primary Tis cancers (de novo tumors not associated with papillary disease).[11]

Subsequent, careful monitoring failed to demonstrate sufficient efficacy of bropiramine to win FDA approval, however. In addition, significant cardiac-related toxicity was associated with this treatment, and it is currently no longer in clinical trials or available for general use.

TP-40, a *Pseudomonas exotoxin*, was used in phase I research studies and found to have excellent response in patients with stage Tis bladder tumors, although little or no activity against superficial papillary transitional cell carcinoma. Since no apparent toxicity was uncovered in this phase I study, the maximum tolerated dose was not determined.[13] Unfortunately, despite the promise of TP-40 in patients with BCG-refractory Tis, phase II studies of this agent have not been initiated.

**Photodynamic Therapy**

A number of recent reports have demonstrated a possible role for photodynamic therapy (PDT) in the treatment of recurrent Ta, T1, and Tis transitional cell carcinoma. Photodynamic therapy is a form of cancer treatment based on the destruction of cells by the interaction of light (400 to 760 nm) with a photosensitizing dye and oxygen. When administered systemically, these substances accumulate in both tumor and normal tissues. Upon exposure to light of an appropriate wavelength, based on the nature of the specific photosensitizing agent, an in situ chemical reaction ensues. The ultimate effect is the local production of reactive oxygen radicals that are cytotoxic.

First-generation photosensitizers caused prolonged phototoxicity and had inferior tumor specificity, resulting in accumulation within the detrusor muscle with subsequent permanent loss of bladder capacity and acute post-PDT syndrome, characterized by frequency, urgency, nocturia, and bladder spasms.[14] Since the tumor cells preferentially take up the newer photosensitizing agents, these drugs appear to have a more specific cytotoxic effect against the malignant cells and, thus, less toxicity. A newer agent, 5-aminolaevulinic acid (ALA), generates a photosensitizer called protoporphyrin IX (PpIX), which has fewer side effects and a much shorter period of systemic phototoxicity than previous photosensitizing agents.

Patients with resistant superficial bladder cancer who were treated with prophylactic whole-bladder PDT demonstrated complete response rates at 3 months of 84% and 75% for residual-resistant papillary transitional cell carcinoma and refractory Tis, respectively. At a median of 50 months, 59% of responding patients were alive, and 31 of 34 responders remained disease free.[15]

In a similar study, 36 patients with BCG-refractory Tis demonstrated a complete response rate of 58% at 3 months with a durable response rate (no tumor recurrence at 12 months) of 31%.[16] At 12 months, 14 patients subsequently underwent cystectomy, 12 for persistent disease and 2 for a recurrence. Most patients initially diagnosed with Tis who subsequently developed a recurrence following whole-bladder PDT were easily managed with trans-urethral resection for superficial recurrence only.

Thus, it seems obvious that, in some patients, altering the expected natural history of the transitional cell carcinoma represents a beneficial outcome.

**Chemotherapeutic Agents**

The mechanism of action of chemotherapeutic agents used in the management of transitional cell carcinoma of the bladder is clearly quite different from that of the biological immunomodulators.

**Thiotepa**

Thiotepa, the first intravesical chemotherapeutic compound, was initially used in the 1960s. This alkylating agent works by cross-linking nucleic acids and proteins. It has moderate activity against superficial, low-grade papillary transitional cell carcinoma but has minimal efficacy against Tis and higher-grade tumors. Because of its relatively low molecular weight (189 daltons), thiotepa is readily
absorbed from the urothelium. Toxicity in the form of myelosuppression is the limiting factor of thiotepa therapy and mandates careful monitoring of the patient’s white blood cell and platelet counts prior to each intravesical instillation. With the availability of other intravesical agents, few clinicians currently recommend thiotepa as a first-line alternative to BCG. Clearly, few, if any, data support the use of thiotepa in patients with refractory transitional cell carcinoma.[17]

**Doxorubicin and Epirubicin**

Doxorubicin is an antibiotic chemotherapeutic agent with a high relative molecular weight (580 daltons). It appears to work equally well in both high-grade and low-grade bladder tumors. However, doxorubicin is inferior in efficacy to BCG regardless of tumor grade or stage. In addition, a small but significant and unpredictable number of patients treated with intravesical doxorubicin developed serious toxicity from chemotherapy-induced cystitis, resulting in permanent bladder contracture.[18]

Again, this drug, although never approved for the treatment of transitional cell carcinoma, was used in many clinical trials and remains currently available to be used, off label, as an intravesical agent for superficial bladder cancer.

Many studies of intravesical doxorubicin therapy have originated outside of the United States; in these studies, intravesical doxorubicin has yielded response rates between 31% and 74%. Similarly, in the United States, complete remissions have been described in approximately 65% of patients treated with this agent. Unfortunately, attempts to improve these response rates with sequential combination prophylactic regimens resulted in no difference between randomized groups.

Epirubicin is an anthracycline derivative of doxorubicin and, as such, has similar antitumor activity. Adverse effects of epirubicin are usually limited to chemical cystitis. Systemic effects of epirubicin occur only in the rarest of cases, and are commonly associated with higher concentrations (80 mg in 50 mL of saline) of the drug and administration in the immediate post-resection period.

Epirubicin has recently demonstrated an ability to alter the natural history of primary superficial bladder cancer. Instillation of a single dose (100 mg in 100 mL of physiologic saline) of epirubicin immediately following transurethral resection in patients with primary superficial bladder cancer produced a statistically significant recurrence-free rate of 66% after 2 years. In contrast, patients treated with tumor resection plus immediate instillation of interferon-alpha-2b (50 million units in 100 mL of physiologic saline) had a 37% recurrence-free rate, which did not differ significantly from the 40% recurrence-free rate seen in patients treated with resection only.[19]

These results support previous studies demonstrating similar decreases in the rates of recurrence in patients treated with a single instillation of epirubicin, doxorubicin, or thiotepa following tumor resection.[20,21] Epirubicin recently won FDA approval for the adjuvant treatment (in combination regimens) of patients with early, node-positive breast cancer; unfortunately, however it is unlikely to be approved in the United States in the near future for the management of primary or recurrent transitional cell carcinoma of the bladder. Currently, there are no active studies in the United States using epirubicin against bladder transitional cell carcinoma.

**Mitomycin**

Mitomycin, albeit smaller in molecular weight (329 daltons) than doxorubicin, also demonstrates little systemic absorption (approximately 1%) because of its relative size. Mitomycin is also an antibiotic chemotherapeutic agent that acts by inhibiting DNA synthesis. It may actually have greater efficacy in higher-grade bladder tumors and is a therapeutic as well as a prophylactic agent.

Mitomycin is effective in treating incompletely resected papillary transitional cell carcinoma. It is used more frequently for this purpose in Europe, where [marker] studies are commonly employed to evaluate intravesical agents. After BCG, mitomycin is probably the next most commonly used drug in the management of transitional cell carcinoma.

Overall results with mitomycin and other adjuvant intravesical chemotherapy remain inferior to those with BCG, especially in patients at high risk of tumor recurrence.[22-25] However, mitomycin can be used effectively in patients with superficial transitional cell carcinoma who are poor candidates for BCG immunotherapy, are unable to tolerate BCG due to toxicity, or who have disease refractory to BCG.

Local irritative chemical cystitis is noted quite frequently in patients treated with mitomycin. A marked necroinflammatory process follows mitomycin instillation, with a histiocytic response that extends into the detrusor wall[26] and can lead to bladder mucosal changes. These mucosal changes are described pathologically as dystrophic calcifications and, when viewed for the first time, can appear quite abnormal and suggestive of aggressive tumor recurrence. Fortunately, mitomycin has fewer long-term sequelae than does doxorubicin.[27,28]
Valrubicin

Valrubicin, the newest clinically available agent for the management of transitional cell carcinoma, is a novel anthracycline. This semisynthetic analog of doxorubicin is characterized by two crucial substitutions on the doxorubicin molecule: (1) A 5-carbon, straight-chain valerate ester replaces the hydroxyl group of doxorubicin on the C-14 chain, and (2) an additional tri-fluoroacetyl group is present on the 3′-amino group of the carbohydrate ring. These changes render valrubicin highly lipophilic and poorly water soluble characteristics that make this agent more suitable clinically for intravesical chemotherapy.

Valrubicin has a more rapid uptake into cancer cells and lacks the high level of preferential negative ion binding in cell membranes thought to be responsible for both the cardiac and mucosal and skin contact toxicity associated with doxorubicin. Valrubicin inhibits the incorporation of nucleosides into nucleic acids, causing extensive chromosomal damage and cell-cycle arrest in the G2 phase. Its principal metabolites inhibit topoisomerase II, thus arresting DNA synthesis.

The toxicity of valrubicin appears to be limited to local cystitis. To date, there have been no cases of progressive bladder contracture, as has been seen with the other chemotherapeutic agents used intravesically. In addition, valrubicin is a macromolecule, which significantly limits its systemic absorption and accounts for its lack of systemic toxicity.[29]

Currently, valrubicin is undergoing additional phase II intergroup studies, despite the fact that the FDA, based on the outcomes of earlier studies, has already approved the drug for the treatment of stage Tis transitional cell carcinoma in patients who do not respond to BCG and who refuse to undergo or are unable to medically tolerate radical cystectomy and urinary diversion. The pivotal studies have clearly shown that patients who develop progressive disease after intravesical valrubicin therapy, do so early within 6 months of starting therapy. This minimal delay in the actual surgical exenteration and urinary diversion may, indeed, warrant a trial of valrubicin prior to cystectomy in selected cases. This is true even in cases when the surgical risk is acceptable.

As mentioned above, the FDA has approved valrubicin for intravesical use in patients who are unresponsive to standard BCG intravesical therapy but who are not candidates for cystectomy and urinary diversion. By doing so, the FDA created the potential for much broader use of this new intravesical medication. In fact, the drug has been used experimentally in a number of different and innovative trials. A small depth of penetration study, conducted in six patients prior to cystectomy, demonstrated that the measurable therapeutic anthracycline level exceeded 1,250 µm, which is beyond the level of T1 tumors.

Valrubicin has also been studied in a phase II setting as a peri-transurethral resection of bladder tumor treatment in 22 patients. The purpose of this study was to define the possible use of valrubicin to prevent tumor implantation at the time of transurethral resection in newly diagnosed patients with Ta or T1 papillary transitional cell carcinoma. The data demonstrated a 60% tumor-free response rate at 3 months; however, only 21% of patients remained recurrence free with a median follow-up of 18 months.[personal communication, Robert Bahnson, MD, Ohio State University, July, 1999]

Since the patient selection criteria differ from study to study, it is obviously important to define the patient population studied when reviewing outcomes. One must also look at the definition of response. Clearly, from the FDA’s point of view, the preferred end point of these studies of the management of transitional cell carcinoma is the presence or absence of tumor after therapeutic intervention. In our opinion, a better end point may be maintenance of a functional bladder that is free of disease progression.

Anecdotally, many practicing urologists can recall patients in whom initial treatment was considered ineffective because of the presence of minimal residual transitional cell carcinoma after induction therapy. Yet, years after the initial treatment, these same patients continued to have functional bladders, and, although the occasional development of superficial papillary tumors required management with resection and fulguration, the patients remained grateful for the partial response to initial therapy.

Management of Refractory Tis Disease

Clearly, one must define the term refractory Tis disease. The importance of this distinction relates to the high rate of progression and metastasis in patients who do not respond to initial treatment with BCG still the primary first therapy used in patients with Tis tumors. Studies indicate that patients who do not respond to their first induction course (six weekly intravesical instillations) of BCG or who exhibit an endoscopic recurrence within 6 months of initial intravesical treatment are at
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greatest risk for disease progression. Some experts believe that a second induction course of BCG is warranted before proceeding to “salvage” therapy, whether alternative intravesical agents or radical surgery. Personally, we have had little success administering a second course of BCG therapy in patients in whom there is an obvious lack of clinical response to initial BCG treatment upon endoscopic restaging. However, there is an interesting clinical entity that is not recognized in reviews of experimental protocols for the management of transitional cell carcinoma or Tis; namely, partial response. In the “black and white” world of clinical trials, if there is any evidence of even a small recurrence, treatment is considered to have failed. Yet, in the “real” world of patient management, one can readily identify patients who exhibit a beneficial partial clinical response. It is in these patients that we can attempt to manage recurrent disease conservatively. Whether this involves the use of a second induction course of BCG, initiation of a maintenance protocol before a second induction regimen, or a switch to a successive intravesical agent depends on the experience of the clinician. For the purpose of the rest of this discussion, we will define “refractory Tis” as recurrent disease following two courses of BCG or one course of BCG plus one additional course of another appropriate agent. Alternatively, in patients who cannot tolerate BCG due to toxicity or who have a contraindication to its primary use, failure to respond to any alternative intravesical agent would indicate refractory disease.

Treatment Options
Intravesical treatment options in patients with refractory Tis are actually quite limited. Certainly, at some point, the urologist may determine that it is in the best interests of the patient to discontinue conservative intravesical management and proceed with a cystectomy and urinary diversion. In clinical practice, the ease of this decision-making process obviously relates not only to the overall clinical condition of the patient but also to the symptoms associated with the refractory Tis, as well as the extent of the disease within the bladder. Multiple resections over many years in conjunction with recurrent tumor may severely impair normal bladder function. Specifically, it may be possible to manage patients with minimal symptoms and minimal disease with continued biopsy and fulguration. In contrast, patients with diffuse disease, severe irritative voiding symptoms, and, most importantly, small bladder capacity associated with urgency and urge-related incontinence, clearly benefit from earlier consideration of radical surgery. Valrubicin is the only intravesical agent that has been approved by the FDA for the management of refractory Tis. Despite the approval of valrubicin for this specific indication, its use has yet to be established in the urologic community at large. This is due primarily to urologists’ lack of familiarity with this new agent, which, in turn, relates to the fact that valrubicin has been studied primarily in phase I and limited phase II trials. With the obvious benefits and lack of notable systemic toxicity of valrubicin demonstrated in these smaller studies, large national and cooperative studies are currently underway. It is likely that, with this additional experience, the indications for this novel drug may broaden considerably. However, other agents should be considered in addition to valrubicin in this small, but difficult-to-manage patient population.
The options for intravesical treatment of refractory Tis are either biological or chemotherapeutic in nature. As mentioned above, BCG is the primary biological agent used in patients with transitional cell carcinoma, both for prophylaxis and for the treatment of unresectable disease. Because significant data also have indicated that BCG is the most useful agent for the primary treatment of Tis, it remains the overwhelming first choice of most urologists in the management of transitional cell carcinoma in general and Tis in particular. In addition, even when there is associated disease progression, BCG has been shown to delay the progression of tumor to muscle-invasive disease. Studies have shown that early BCG treatment significantly improves both the progression-free rate and disease-specific survival rate.[30,31] What seems somewhat surprising, at least in our view, is the lack of any significant progress in the successful development of intravesical agents for the treatment of transitional cell carcinoma since the mid-1980s. Indeed, only in the last several years has there been any headway in the development of new agents for this purpose.

Conclusions
Superficial transitional cell carcinoma of the bladder remains largely unpredictable because of tumor heterogeneity, as well as the multifocal nature of this process. Transurethral resection is the foundation of the diagnosis and initial treatment of superficial
transitional cell carcinoma.
If recurrence develops or pathologic assessment suggests that the patient is at high risk for progression to muscle-invasive disease or has a high likelihood of recurrence, adjuvant intravesical therapy is initiated. In the case of superficial papillary disease, this usually means prophylactic intravesical chemotherapy. When managing patients with Tis tumors, treatments are generally felt to be therapeutic in nature. The higher the grade of superficial transitional cell carcinoma, the higher the tumor volume at initial diagnosis, and the higher the stage, the more likely it is to recur. The three goals of intravesical therapy for superficial transitional cell carcinoma are destruction of all tumor, prophylaxis against recurrence, and prevention of progression. Patients with high-grade Ta or T1 tumors, with or without Tis, must be carefully followed endoscopically and treated with adjuvant intravesical therapy to avoid the development of life-threatening disease. Currently, BCG appears to have the greatest efficacy in preventing recurrence and progression. Because recurrence rates continue to be high despite intravesical therapy, albeit lower than rates in patients treated with transurethral resection only, the assessment of intravesical therapies is more appropriately measured against their ability to prevent disease progression (quantity-of-life issues) and preserve bladder function (quality-of-life issues). In addition, clinicians must keep in mind that low-grade papillary tumors have a low rate of progression. Therefore, we must endeavor to avoid overtreating patients with potentially toxic intravesical therapy, which may ultimately result in compromised bladder function and severe irritative voiding symptoms that can be remedied only by cystectomy and urinary diversion. When choosing an agent for intravesical therapy after transurethral resection, one must take into consideration the pathologic assessment of the lesion, the number of lesions, patient comorbidities, the toxicity of the therapy, and the patient’s likelihood of tolerating a full course of that therapy. With the availability of new agents that can be used either alone or in combination, we may be able to offer our patients the possibility of bladder salvage when clinically appropriate. Nevertheless, bladder removal continues to be the definitive therapeutic option for the potential cure of high-grade superficial bladder cancer. With the recent advances in the types of urinary diversion available and improvements in intraoperative patient management, properly selected patients should expect to enjoy long-term survival and improved quality of life. As clinicians, we must temper our enthusiasm for the next clinical trial and the promise of new miracle cures. When involved in these trials, we also need to be flexible with regard to response criteria. The assessment of patient success based on preservation of function and risk of subsequent progression, rather than the arbitrary end point necessitated by clinical research response criteria, is an integral part of the clinician’s responsibility. A marker that would allow us to predict which patients with aggressive superficial tumors require early exenterative surgical management would be most welcome. Currently, investigators have demonstrated the prognostic value of urinary cytokine levels at different points during a 6-week instillation protocol, indicating a possible role for an increased number of treatments during the induction phase of therapy. Rather than using BCG alone as the initial treatment option, employing a combination of BCG with an effective, locally active chemotherapeutic intravesical agent may improve expected response. Likewise, experimenting with doses and treatment scheduling may yield advances, particularly in patients with Tis tumors. Issues of treatment toxicity (Table 1) and cost (Table 2) may also have an impact on the eventual development of combination therapies. Despite our overall success with current protocol management, complacency is not an acceptable attitude.

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