Optimal Management of the T1G3 Bladder Cancer

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Management decisions for a patient with a high-grade T1 urothelial cancer of the bladder are both critical and controversial. In the authors' view, if one uses a grading scale of 0 to 10 for difficulty in decision making (10 being the most difficult), the patient with T1G3 tumor rates a 10.

By definition, these high-grade bladder tumors invade the lamina propria without involving the muscularis propria [1]. They have high propensity for recurrence and progression. Following transurethral resection (TURBT) of the initial T1G3 tumor with no additional therapy, there is a recurrence rate of 50% to 70% and a progression rate of 25% to 50% [2,3].

The optimal management of these tumors requires an accurate diagnosis including the stage and grade, and careful assessment of prognostic factors. The wide range of available treatment options includes TURBT alone, adding intravesical therapy, radical cystectomy, and even possibly chemoradiation. Despite advances in the understanding of the biologic behavior of these tumors, both the choice and timing of treatment remain controversial [3].

Diagnosis, evaluation, and initial management

The initial critical step is to establish an accurate diagnosis. An inaccurate diagnosis, particularly understaging, can adversely impact the survival of the patient. Overtreatment affects the quality of life and possibly leads to unnecessary morbidity. This is precisely why the decision making is so difficult.

Thorough endoscopic evaluation of the bladder followed by complete excision of all visible tumors should be performed. To avoid staging errors, cautery artifact should be minimized. It is imperative to have muscle from the muscularis propria in the specimen and some advocate cold cup biopsies of the tumor base [4]. Tumor resection is improved by using a videoendoscope with continuous flow. Some advocate the use of fluorescence endoscopy using 5-alpha aminolevulinic acid to facilitate complete resection and identification of carcinoma in situ [5]. The authors have not used this.

Herr [6] retrospectively evaluated the concordance of the pathologic diagnoses between an initial resection and a second TURBT in 150 patients. The results of the second resection changed the treatment in 33% of these patients. He emphasized the importance of obtaining muscle in the resected specimen. Of 23 patients with a T1 lesion without muscle in the first resection, 11 (49%) were upstaged to T2 after obtaining information from the second TURBT. A caveat of this study is that not only did different urologists perform the first and second TURBTs, but different pathologists read the first and second bladder tumor specimens. Dutta et al [7] similarly reported a 64% risk of understaging T1 lesions when muscle was absent compared with only 30% when muscle was present in the TURBT specimen.

Can the urologist be confident that the TURBT removed the entire tumor? Clearly the experience of the urologist is critical but there are many variables. Zurkirchen et al [8] retrospectively reviewed those patients who underwent follow-up TURBTs within 6 weeks of the initial resection. A total of 37% had persistent tumor on the second resection. Grimm et al [9] similarly retrospectively

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reviewed 83 patients who underwent a repeat TURBT a mean of 7 weeks after the initial TURBT. Residual tumor was found in 33%. On univariate analysis, tumor stage and grade were identified as predictive for residual tumor on restaging TURBT. Furthermore, there was a significant decrease in 5-year disease-free survival between those who underwent a second TURBT and those who did not (63% and 40%, respectively). Both multifocality and tumor grade increased the risk of finding residual tumor on a second TURBT. There are no studies available at present regarding the optimal timing of the second resection. The consensus is, however, that this should be performed within 1 to 4 weeks following the initial resection. May et al [10] and Sanchez-Oritz et al [11] reported that a delay of more than 12 weeks in muscle-invasive bladder cancer leads to significant upstaging. Undue delay in second resection should be avoided.

Abnormal-looking urothelium should be biopsied. The role of random bladder biopsy is controversial, however, and there is no strong evidence currently to support this [12–15]. Whenever cold cup biopsies are performed it is advisable to fulgurate the biopsy sites to prevent bleeding [16]. Bladder wash cytology is an integral part of the second endoscopic session because it provides a representative mini biopsy from the entire bladder urothelium and may be particularly helpful if there is no visible tumor yet there are cancer cells in the cytology.

These studies show that the risk of upstaging on second TURBT is at least 30% if muscle is present in the specimen and even higher if muscle is not present. Further, the risk of residual tumor on second TURBT is also significant. Even for solitary, papillary-appearing tumors, the risk is 24% to 27% and it is higher for multifocal, nonpapillary lesions. The authors recommend that a second TURBT be considered in patients with a T1G3 tumor. The authors do not always perform a second resection. Most patients who present to the authors with a high-grade T1 tumor have had the initial resection elsewhere and a second resection (the authors' first) is performed. If the authors perform a first resection and the tumor is small, has a minimal lamina propria invasion, and muscle is clearly present and uninvolved, they do not perform a second TUR. Nonetheless, most of the time, they perform a second TURBT.

Attempts have been made further to substage T1 tumors. Holmang et al [17] retrospectively reviewed 121 patients with T1G3 bladder cancers and evaluated whether the tumors invaded above the level of the muscularis mucosae (stage T1a) or invaded into and beyond it (stage T1b). A total of 54% of patients were categorized as T1a and 40% as T1b; only 6% of patients could not be substaged. Stage T1b tumors were more likely to progress following the initial TUR; 58% of those with grade 3 T1b tumors progressed to muscle-invasive disease compared with only 36% with grade 3 T1a tumors. The 5-year overall survival for T1a and T1b tumors was 54% and 42%, respectively. Hasui et al [18] similarly reported a worse prognosis if the T1 tumor invaded the muscularis mucosae. With a mean follow-up of 78 months, the progression rates for T1a and T1b cancers were 7% and 54%, respectively. Moreover, the increase risk of progression was seen regardless of the grade, size, or multifocality of the tumor. Smits et al [19] categorized T1 tumors into T1a, T1b, and T1c (up to, into, and beyond the muscularis mucosae, respectively) and retrospectively evaluated the risk of recurrence and progression among the three groups. There was no difference in the 3-year risk of recurrence between the three groups; however, the risk of progression was 6%, 33%, and 55%, respectively. Furthermore, if the pathology was T1c and associated carcinoma in situ the risk of progression was 27 times compared with those without T1c and carcinoma in situ. Despite these reports, this substaging system has not been widely adopted because muscularis mucosae are often absent or difficult to identify. The authors' pathologists usually provide this information.

Cheng et al [20] measured the depth of invasion to substage T1 tumors, to obviate the difficulty in identifying the muscularis mucosae. They retrospectively reviewed 55 patients with T1 bladder cancer. TURBT specimens were evaluated for depth of stromal invasion, as measured with a micrometer from the basement membrane to the deepest tumor cells. There was a significant correlation between the depth of invasion in the TURBT specimen and the stage at cystectomy. Using a cutoff of greater than 1.5 mm depth of invasion, the sensitivity, specificity, and positive and negative predictive values for predicting advanced stage disease (>T2) were 81%, 83%, 95%, and 56%, respectively.

Prognostic factors

Various prognostic factors associated with T1G3 tumors should be carefully identified and

evaluated. These greatly assist the physician in the decision-making process. The most accepted predictors of progression in patients with T1G3 bladder tumors are clinical and pathologic. The response to intravesical therapy is a reliable predictor of progression that can be assessed at 3 to 9 months [21–23]. After analyzing the outcome in 191 patients with stage T1 disease with or without carcinoma in situ, Solsona et al [23] reported that 80% who were not free of cancer at 3 months had progression. They also indicated that high grade, association of carcinoma in situ, and prostate mucosa or duct involvement represent significant pathologic predictors of progression. Tumor size, multiplicity, and vascular invasion are other important prognostic factors [24].

A variety of biologic markers have been studied as a prognostic marker for T1 disease. It seems that T1G3 tumors behave as bacillus Calmette-Guérin (BCG) sensitive, responding to treatment after initial therapy, or BCG refractory, continuing to recur or progress despite BCG. Efforts have been made to define predictors for the response to BCG or patients at high risk for progression. The p53 tumor suppresser gene is a commonly altered gene in human malignancies. In a series of 60 patients with bladder cancer Pfister et al [25] observed mutant p53 in 66% of stage T1 grade 3 but in no stage Ta grade 1 tumor. Tumors with mutant p53 inactivate transcription of p21 and the Bax gene. Alterations of p53 were associated with BCG failure. Others have not found that p53 expression correlates with BCG failure [26–28]. Controversial results have also been reported in regard to p53 expression as an independent predictor of progression. In a case-control study Llopis et al [29] showed that p53 expression analyzed at a cutoff of 20% positivity is a significant predictor of progression. Others have also reported this finding [30,31]. Steiner et al [32] did not note that p53 status was helpful for selecting candidates for radical cystectomy. Lopez-Beltran et al [33] reported a number of cell cycle regulators, such as p27kip1, cyclin D1, and cyclin D3, which are independent predictors. None of these factors can accurately predict the biologic behavior of a T1G3 tumor and hence the search for more reliable prognostic indicators continues.

Intravesical therapy

Following TUR of a high-grade T1 tumor, the risk of recurrence approaches 80% and the risk of progression is 50% to 65% [2,3]. The goals of adjuvant intravesical therapy are to decrease the rate of recurrence and ultimately decrease the chance of progression. Although low-grade tumors recur frequently but rarely progress, high-grade tumors or tumors that invade the lamina propria are potentially lethal. Intravesical therapy with chemotherapeutic or immunologic agents in an adjuvant fashion after endoscopic resection has been shown to decrease the recurrence rate of stages Ta and T1 transitional cell carcinoma of the bladder.

Immunotherapy

BCG is believed by many groups to be the most effective agent for treating carcinoma in situ and high-grade stage Ta or T1 transitional cell carcinoma [34–36]. To the authors' knowledge, the precise mechanism remains unclear. It seems that BCG must be in contact with tumor cells through novel receptors [37]. This contact results in a local immunologic host response, generating a T-helper cell response and immunocompetent cytotoxic T-cell activation. Data also suggest that during this process cytokines, such as interleukins, are released and exert antineoplastic activity [38–41]. In contemporary series of T1G3 tumors, the recurrence rate after TUR and intravesical BCG is 23% to 74% [41–43]. After analyzing the outcome of a series of 51 patients with stage T1G3 tumors treated with adjuvant BCG, Hurle et al [44] reported a recurrence rate of 25% at a median follow-up of 85 months. A higher recurrence rate of 44% was reported by Cookson and Sarosdy [41], who followed 86 patients with T1 tumors (mean = 59 months). In a series of 44 patients with T1G3 tumors and a mean follow-up of 28 months Brake et al [42] reported a 27% recurrence rate after TUR and adjuvant BCG. Controlled studies comparing TUR alone versus TUR and BCG indicate an almost 40% decrease in tumor recurrence with adjuvant therapy [41,44]. Most controlled studies enrolled patients with both Ta and T1 tumors [45–49]. In an analysis of more than 30 randomized controlled trials, the American Urological Association Bladder Cancer Clinical Guidelines Panel noted that intravesical BCG after TUR decreases the recurrence rate by 30% compared with TUR alone [50]. Furthermore, the guidelines panel stated that BCG and mitomycin C are superior to doxorubicin and thiotepa. In a randomized prospective study comparing mitomycin C with BCG, Malmström et al [35] noted

that BCG was superior to mitomycin C for prophylaxis. This finding was more evident in the group of patients with nonpapillary tumors or carcinoma in situ. No difference was observed in progression or survival. This study validated the previous results of Lundholm et al [51], who reported significantly longer time to treatment failure for BCG than for mitomycin C. To the authors' knowledge, the optimal dose and schedule of intravesical BCG have not been established. The most commonly used regimen of 6 weekly doses is arbitrary. The induction phase required for an efficient immune response may occur with fewer doses, although some patients may require more than 6 weekly doses. There is a suggestion that a lower dose of BCG is not as effective for high-grade cancer [52,53].

Maintenance bacillus Calmette-Guérin therapy

The Southwest Oncology Group reported promising results in a combined series of patients with stages Ta and T1 bladder tumors at high risk, using a maintenance protocol consisting of a 6-week induction course of BCG followed by three weekly instillations at 3 and 6 months, and every 6 months thereafter for 3 years. The limited number of patients (16%) who tolerated the maintenance BCG therapy to complete the 3-year program represents a significant drawback of this regimen [54,55]. This regimen seems promising, however, and at the present time most urologists believe that some maintenance BCG therapy is advisable.

Intravesical chemotherapy

Mitomycin C seems to be the most effective initial adjuvant intravesical chemotherapeutic agent for stages Ta and T1 bladder cancer [41,56]. Mitomycin C is an alkylating agent that binds to DNA, resulting in synthesis inhibition and strand breakage [57,58]. To the authors' knowledge there is no standard regimen for instilling mitomycin C and there has never been a proper dose-response study. When used to treat residual tumor, the drug is usually administered weekly for 6 to 8 weeks. The dose is 20 to 40 mg [59]. Substantial evidence suggests that tumor cell implantation is a cause of early tumor recurrence and may be influenced by a single dose of mitomycin C within 24 hours after TUR [60,61]. Other intravesical chemotherapeutic agents that have been shown to be beneficial for the prophylaxis of recurrence are thiotepa, doxorubicin, and epirubicin. Although intravesical treatment

has been beneficial for decreasing the recurrence rate, this treatment has not decreased the chance of progression [57,58]. Others have suggested combining two chemotherapeutic agents. Isaka et al [61] treated 40 patients with stage T2 or less bladder cancer with a combination of mitomycin and doxorubicin. They achieved a 45% complete response in 20 patients treated for multiple recurrences. The tumor-free recurrence rate in 20 patients treated for prophylaxis after TUR was 66% at a mean follow-up of 14 months. Using the same intravesical combination in two regimens (with and without 1 year of maintenance) Fukui et al [62] observed that the maintenance regimen was beneficial for carcinoma in situ only. Despite a slightly better outcome, especially in patients with carcinoma in situ, combination chemotherapy resulted in a modest outcome improvement with increased local side effects.

Randomized, prospective trials demonstrate that the risk of recurrence can be reduced by 50% at 2 years and at least by 15% at 5 years with a single dose of immediate instillation of mitomycin following TUR [63–65]. It is also recommended that the single-dose mitomycin should be given within 6 hours but no more than 24 hours following TUR. If mitomycin is given within 24 hours following TUR, maintenance intravesical chemotherapy does not significantly reduce the recurrence further [66].

Following a TUR for a T1G3 tumor the authors recommend instilling a single dose of mitomycin within 24 hours. They instill this in the recovery room following the TUR. The catheter is clamped for 1 hour. This cannot be done if there is bleeding or perforation. This should be followed by a standard 6-week course of BCG. Maintenance BCG therapy (Southwest Oncology Group regimen) seems to be useful. Three months following the TUR and intravesical therapy, the authors perform a flexible cystoscopy and bladder wash cytology. Presence of tumor or positive cytology requires further careful evaluation including resection of the tumor, biopsies of the bladder mucosa, and prostatic urethra depending on the findings.

Treatment options after bacillus Calmette-Guérin failure

Although BCG is an effective adjuvant treatment for T1G3 bladder cancer, approximately 50% of patients recur and 15% to 50% of patients

progress within the first 5 years following BCG therapy (Table 1) [67–74]. Interpreting the results from many of the studies is difficult because of differences in the definition of BCG failure.

Herr and Dalbagni [75] define the "BCG re-fractory state" as the failure to achieve a disease-free state by 6 months after initial BCG therapy with either maintenance or retreatment at 3 months because of either persistence or recurrent disease. "BCG relapse" refers to recurrence after achieving disease-free status at 6 months. The "BCG in-tolerance" refers to discontinuation of the therapy because of side effects and should be considered as true BCG failures.

Radical cystectomy is the most appropriate option for patients who recur with high-grade or high-stage disease. A patient's personal preference and comorbidity, however, may require an alter-native treatment strategy. The treatment for BCG failure starts with a complete repeat resection of all visible tumors. The options following resection include the following.

Repeat bacillus Calmette-Guérin therapy

There are insufficient data in the literature on the effectiveness of repeat BCG therapy. Cookson and Sarosdy [41] reported excellent results with a response rate of 64% in patients with T1 re-currence following TUR and repeat BCG. Brake et al [69] reported a 51% response rate in BCG-refractory patients, but 30% of patients in this group progressed to muscle-invasive disease. Pan-sadoro et al [76] report an inferior response rate of 27% following TUR and a second 6-week course of BCG and even poorer response rate of 6% follow-ing a third cycle of BCG. The authors reserve repeat BCG therapy for selected patients who recur with low-grade or low-stage transitional cell

carcinoma and these patients need aggressive surveillance.

Intravesical chemotherapy

Although intravesical treatment with chemo-therapeutic agents, such as mitomycin C, is an option, there are little data regarding its role in recurrent T1G3 tumors following BCG failure. Response rates of 19% and 21% with mitomycin and valrubicin are among the few reports [77,78]. These results are poor and the authors do not recommend intravesical salvage chemotherapy especially for patients with T1G3 following BCG.

Interferon therapy

The long-term efficacy with interferon-α mono-therapy is less than 15% [79] and hence this therapy is unlikely to benefit BCG failure patients particularly with a T1G3 cancer. There are several reports, however, which confirm the substantial synergistic benefit of BCG plus interferon combi-nation therapy in BCG failure cases. The disease-free rates range from 50% to 60% and more importantly no one had unresectable or metastatic disease at cystectomy following BCG-interferon combination therapy [80,81]. In a multi-institu-tional study, O'Donnell et al [82] showed a re-sponse rate of 42% at a median follow-up of 24 months. The authors have used this combina-tion for some patients who have recurred after BCG and it is well tolerated.

Radiation therapy and photodynamic therapy

The role of radiation as a salvage option for BCG failure is unknown. The reported 5-year disease-free survival rate is 50%, however, in patients with high-grade T1 urothelial cancer

Table 1
Results of TUR plus BCG for T1G3 tumors

Series/year	No. patients	Follow-up (mo)	Recurrence (%)	Progression (%)
Pfister (1995)	26	54	50	27
Lebret (1998)	35	45	43	20
Brake (2000)	44	43	27	16
Patard (2001)	50	65	52	22
Kulkarni (2002)	69	48	46	12
Bogdanovic (2002)	43	53	28	16
Peyromaure (2003)	57	53	42	23
Shanin (2003)	92	64	70	33

Abbreviations: BCG, bacille Calmette-Guérin; TUR, transurethral resection.

treated with external beam radiation [83]. More-over, for T1 disease, the local recurrence and progression rates are approximately 50% [84]. These results are inferior to radical cystectomy and the authors do not recommend radiation ther-apy if the subsequent tumor is high-grade Ta or T1. Photodynamic therapy with 5-aminolevulinic acid may have a role in carcinoma in situ but there are no studies confirming its benefit in BCG failure with T1 disease [85].

Role of cystectomy: early versus deferred

The timing of cystectomy is a most debated issue in the management of T1G3 tumors. Despite intravesical adjuvant therapies, there is a substan-tial group of patients with initial high-grade stage T1 tumor who have progression and are at risk of dying from urothelial cancer [86].

Several groups recommend immediate or early cystectomy without a trial of adjuvant intravesical therapy with or without repeat TUR. Supporters of this approach argue that the 5-year survival rate of 90% may decrease to 50% to 60% if radical cystectomy is delayed until progression [87]. Apart from this, there are several valid arguments that support both early and deferred cystectomy.

Conservative management with TUR and intravesical treatment is associated with continu-ous decline in survival with lifelong risk of re-currence, progression, and metastasis [88]. Shahin et al [74] reported that in a series of 153 patients, following TUR and BCG for a T1G3 tumor the recurrence rate was 75% after 10 years. Further-more, their analysis indicated a continuous decline in survival with an estimated 30% of patients dead at 10 years. Herr [89], in is his editorial, stressed the fact that this is a high figure for a newly diagnosed non–muscle invasive bladder cancer. Currently, there are not reliable markers that can differentiate patients who recur from those who do not. On the basis of modern molecular techniques including comparative ge-nomic hybridization, fluorescence in situ hybrid-ization, and microarray expression, both T1 and T2 disease share the same gene alteration (chro-mosome 17) that specifies the invasive ability of the tumor [90].

The initial diagnosis of T1 disease is associated with significant understaging errors of as much as 25% to 40%. Delay in offering the correct treatment, such as cystectomy, affects the survival. In a series of 189 patients who underwent

cystectomy within 3 months of diagnosis of muscle-invasive disease, there was a significantly better 5-year progression-free survival than if cystectomy was performed more than 3 months following diagnosis (55% and 34%, respectively) [10].

Herr and Sogani [91] retrospectively evaluated 90 patients with high-risk superficial bladder cancer who ultimately underwent cystectomy. They demonstrated improved 15-year disease-specific survival for those who underwent cystec-tomy within 2 years after initial BCG treatment. Those who underwent cystectomy for recurrent superficial disease had better outcome than those who underwent surgery for progression. They concluded that deferring cystectomy until pro-gression to muscle-invasive disease may decrease the overall disease-specific survival. A total of 217 patients from their original cohort of 307 with high-risk superficial disease never required cystec-tomy, however, and were spared the morbidity of cystectomy.

Conservative management has a disadvantage of rigorous lifelong follow-up with cystoscopy and imaging studies apart from need for further adjuvant therapy for recurrences. The social im-plications and financial burden on the health system should be considered. Advancement in urinary diversion techniques has improved the quality of life. Hart et al [92] studied the quality of life following cystectomy and reported excellent overall quality of life; minimal emotional distress; and no significant problems with social, physical, and functional activities. Recently, Henningsohn et al [93] studied the quality of life in a series of 101 patients (patients who are recurrence free after cystectomy and orthotopic neobladder sub-stitution) and compared it with a matched control group. This study highlighted that the quality of life issues including sexual function and urinary leakage were similar. As a whole, the contempo-rary cystectomy in both genders has adapted several techniques to preserve quality of life [88].

Because the progression rate is approximately 25% with TUR plus BCG and 50% with TUR alone, it seems that with early cystectomy at least 50% of patients are overtreated. Furthermore, the morbidity and mortality associated with radical cystectomy are 20% and 1% to 4%, respectively [94]. Despite techniques of orthotopic bladder replacement the quality of life is altered to a certain extent. It is reasonable, however, to offer immediate cystectomy to young patients with deep T1 tumors (>1.5 mm in depth) with at least

one additional bad prognostic factor (Box 1) including multifocality, carcinoma in situ, involvement of the prostate, and anatomic difficulties in TUR [88].

The most important issue is how to restrict radical cystectomy to selective patients at high risk and to choose an initial bladder-sparing approach in others without affecting survival. In most cases this goal can be achieved by combining complete TUR with BCG adjuvant therapy, while being prepared to recognize the appropriate time for radical cystectomy.

Recent advances in treatment options

Several studies are underway at various stages that are likely to impact in future the treatment options available to treat T1G3 tumor.

Sequential Intravesical therapy

To improve the efficacy of the intravesical therapy, several alternative approaches combining BCG with chemotherapeutic agents are being investigated. The rationale for giving immediate post–tumor resection chemotherapy before BCG is to reduce tumor implantation and to induce sloughing of the urothelium, allowing BCG to interact better with fibronectin and initiating an immune response. Soloway et al [95] suggested that complete resection of the tumor followed by immediate mitomycin C instillation and six weekly BGG instillations results in an acceptably low recurrence and progression rate.

Sequential regimen using drugs with different mechanism of action may be beneficial because of synergistic effect and may be well tolerated. In a randomized study of 188 patients with rapidly recurrent stages Ta and T1 transitional cell carcinoma, Rintala et al [96] compared mitomycin C alone with mitomycin C and BCG. At a mean follow-up of 34 months no difference was observed in terms of tumor recurrence and disease-free interval. A similar comparison was performed in the randomized phase III protocol of Witjes et al [97]. In this study patients were randomized to 10 instillations of mitomycin C or 4 instillations of mitomycin C followed by 6 weeks of BCG. No significant difference was observed in the two regimens in regard to recurrence, progression, or systemic toxicity. Randomized prospective studies show that sequential BCG and epirubicin is not more effective than BCG alone [98–100]. Serretta et al [101] reported using adjuvant sequential mitomycin C and epirubicin in 91 of 137 patients with T1G3 bladder cancer after initial TUR. With close to 20 years of follow-up overall recurrence rate was less in the sequential chemotherapy protocol but the overall progression rate was similar (9.5%). The cystectomy rate was 7% and the disease-specific death rate was 7%. Despite various studies it is still not proved that the sequential chemotherapy is superior to BCG monotherapy.

Newer intravesical agents

Gemcitabine and paclitaxel are promising intravesical chemotherapeutic agents currently at different stages of investigation. In a phase I study, Dalbagni et al [102] reported that intravesical gemcitabine was well tolerated with minimal bladder irritation and acceptable myelosuppression. Serum levels of gemcitabine were undetectable at concentrations of 5, 10, and 15 mg/mL. Serum gemcitabine was detected, however, at a concentration of 20 mg/mL. A complete response (negative posttreatment cystoscopy including a biopsy of the urothelium and a negative cytology) was achieved in 7 (39%) of 18 patients. In a phase II study of patients with BCG-refractory transitional cell carcinoma to determine the efficacy of gemcitabine as an intravesical agent, 28 patients completed therapy, and 16 achieved a complete response [103]. All the recent studies confirm that gemcitabine is an effective intravesical agent, with low systemic absorption and little systemic and local toxicity [104,105].

Paclitaxel is in the early stages of testing. In vitro studies showed that a 2-hour exposure to cancer cells has significant anticancer potency [106]. The intravesical delivery is difficult, however, because of its lipid-soluble properties. Chemical modification of this drug may negate this property and allow better intravesical delivery [107].

Various other new strategies include gene therapy [108]; immunostimulants, such as mycobacterium cell wall DNA extract prepared from the *Mycobacterium phlei* [109]; growth factor–related signaling pathway modifiers [110]; and intravesical delivery of activated tumoricidal macrophages [111]. Recent advances in the intravesical delivery system for chemotherapeutic drugs include electromotive intravesical mitomycin C and mitomycin C in conjunction with local microwave hyperthermia. Both these methods show better tissue concentration and a statistically superior reduction in recurrence. Further studies are awaited [112,113].

Summary

T1G3 transitional cell carcinoma of the bladder represents a highly malignant tumor with a variable and unpredictable biologic potential. The most critical aspect of management requires a detailed discussion with the patient regarding the treatment options. Both the physician and the

patient should be willing to reconsider the treatment options as the disease continues to evolve.

In most cases initial management involves complete resection of the tumor, accurate staging of the disease, and intravesical immunotherapy or chemotherapy. Rigorous surveillance with long-term follow-up is crucial for managing these cases. In selected cases with adverse prognostic factors immediate cystectomy should be considered. The choice and timing of the decision to abandon bladder preservation and proceed with cystectomy should be continuously reconsidered on an individual patient basis, in concordance with the evolution of the disease (Fig. 1). The goal is to spare the bladder when possible but not at the risk of death from metastatic disease. Radical cystectomy in high-grade stage T1 transitional cell carcinoma offers excellent results in regard to the prevention of recurrence and progression and survival. Improvements in urinary diversion and nerve-sparing techniques have decreased the magnitude of social implications related to cystectomy in most patients regardless of gender. The discovery of reliable
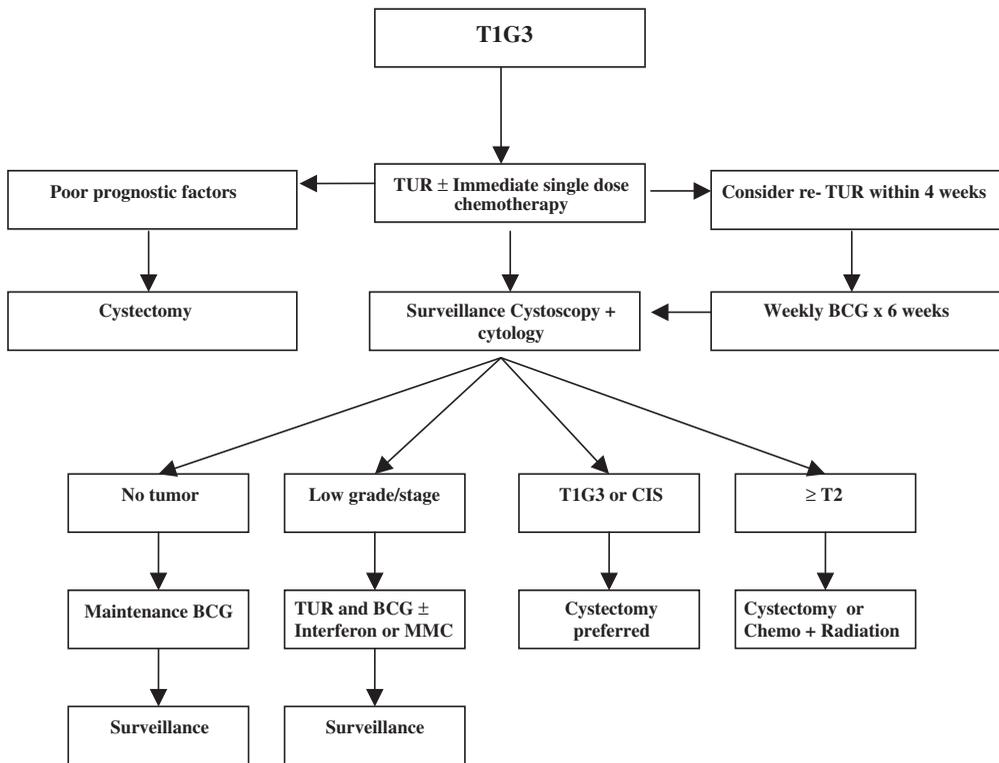

Fig. 1. Therapeutic flow chart for T1G3 tumors. BCG, bacille Calmette-Guérin; CIS, carcinoma in situ; MMC, mitomycin C; TUR, transurethral resection.

markers may contribute to better selection of patients for bladder sparing. Until then, the optimal treatment for the T1G3 tumor remains controversial.

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