



Collaborative Review – Bladder Cancer

An Updated Critical Analysis of the Treatment Strategy for Newly Diagnosed High-grade T1 (Previously T1G3) Bladder Cancer

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Abstract

Context: High-grade T1 (formerly T1G3) bladder cancer (BCa) has a high propensity to recur and progress. As a result, decisions pertaining to its treatment are difficult. Treatment with bacillus Calmette-Guérin (BCG) risks progression and metastases but may preserve the bladder. Cystectomy may offer the best opportunity for cure but is associated with morbidity and a risk of mortality, and it may constitute potential overtreatment for many cases of T1G3 tumours. For purposes of this review, we continue to refer to high-grade T1 lesions as “T1G3.”

Objective: To review the current literature on the management of T1G3 BCa and to provide recommendations for its treatment.

Evidence acquisition: A National Center for Biotechnology Information (NCBI) PubMed search for relevant articles published between 1996 and 9 January 2009 was performed using the Medical Subject Headings “T1G3” or “T1” and “Bladder cancer.” Articles relevant to the treatment of T1G3 BCa were retained.

Evidence synthesis: The diagnosis of T1G3 disease is difficult because pathologic staging is often unreliable and because of the risk of significant understaging at initial transurethral resection (TUR) of bladder tumour. A secondary restaging TUR is recommended for all cases of T1G3. A single dose of immediate post-TUR chemotherapy is recommended. For a bladder-sparing approach, intravesical BCG should be given as induction with maintenance dosing. Immediate or early radical cystectomy (RC) should be offered to all patients with recurrent or multifocal T1G3 disease, those who are at high risk of progression, and those failing BCG treatment. **Conclusions:** Both bladder preservation and RC are appropriate options for T1G3 BCa. Risk stratification of patients based on pathologic features at initial TUR or at recurrence can select those most appropriate for bladder preservation compared to those for whom cystectomy should be strongly considered.

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1. Introduction

The incidence of transitional cell carcinoma (TCC) of the bladder worldwide is in excess of 336 000 [1]. Approximately 75% of cases are non-muscle invasive, and of these, roughly 20–25% invade the lamina propria (category T1). Because 20% of newly diagnosed TCC—or approximately 67 000 cases per year—are of the high-grade T1 (formerly T1G3) variety [2], the worldwide burden of high-grade T1 disease is not inconsequential. For purposes of this review, we continue to refer to high-grade T1 lesions as “T1G3.”

T1G3 tumours have a high propensity to recur and progress to muscle invasion and are associated with a significant risk of metastasis and death. Long-term progression and death rates as high as 53% and 34%, respectively, have been reported [3]. Nevertheless, many of these tumours can be treated successfully with bladder-preservation approaches. The dilemma facing the urologist is how best to treat these tumours in a timely manner so that the chances of bladder preservation and cancer control are maximised while the risks of overtreatment with radical therapy are minimised. In this review, we focus on contemporary treatment strategies for T1G3 TCC of the bladder, highlighting the initial workup and diagnosis of these lesions, and then concentrating on treatment and outcomes of conventional and alternative treatments. Where possible, we have provided levels of evidence as per the modified Oxford Centre for Evidence Based Medicine scheme [4]. Finally, we provide a recommended treatment algorithm for patients with T1G3 bladder cancer (BCa) that incorporates bladder preservation and radical therapeutic techniques based on defined risk groups.

2. Evidence acquisition

A National Center for Biotechnology Information (NCBI) PubMed search for relevant articles published between 1996 and 9 January 2009 was performed using the Medical Subject Headings “T1G3” or “T1” and “Bladder cancer,” with restrictions to humans and English language publications. Each article’s title and abstract were reviewed for their appropriateness regarding clinical management of T1G3 TCC of the bladder. Particular attention was paid to articles focusing on treatment.

3. Evidence synthesis

3.1. Diagnosis and staging

The mainstay of diagnosis and initial treatment of T1G3 BCa is transurethral resection (TUR). The resection must include the muscular layer and should be as complete as possible without bladder perforation. Visible tumour, including marker lesions [5], should not be left behind. Tumour visibility and completeness of resection can be aided by fluorescence cystoscopy (or *photodynamic diagnosis*), although this diagnostic modality is not available in all jurisdictions [6]. Adequate sampling of muscularis propria

is essential, as numerous studies have documented the risk of understaging T1 lesions at 50–70% in the absence of muscularis propria (level 2b) [7,8]. Even with muscularis in the specimen, understaging rates based on cystectomy pathology are reported between approximately 20% and 30% after single TUR [7,9].

Interobserver variability in pathology interpretation is another source of error in properly assigning a T1G3 diagnosis. In a study of 1400 patients pooled from five European Organisation for Research and Treatment of Cancer (EORTC) randomised, controlled studies of adjuvant intravesical therapy for Ta and T1 BCa, agreement on lamina propria invasion was only 42.9% (level 2b) [10]. The majority of disagreement stemmed from downstaging, as 52.5% of tumours originally classified as T1 were assigned Ta status, with the remaining 4.7% upstaged. Discrepancies in grade were also noted in this study, with grade 3 agreement only observed in 61.3% of cases. In fact, the diagnosis of T1G3 TCC was only agreed upon in 50% of cases.

In an effort to simplify and improve interobserver grade reproducibility, the World Health Organisation (WHO) and the International Society of Urologic Pathologists (ISUP) developed the WHO/ISUP consensus classification of urothelial neoplasms in 1998 [11]. This system updated the 1973 WHO numerical grading. Consequently, T1 bladder tumours—virtually all of which are poorly differentiated and classified as grade 3, according to the 1973 WHO criteria—are referred to as “high grade” under the WHO/ISUP classification. The “high grade” moniker, however, also incorporates some WHO 1973 grade 2 lesions with adverse pathologic features. The impact of this change in grading on outcomes is not yet fully understood [12,13], although both grading systems contribute independent information regarding disease progression [14]. Although formally accepted in 2004, the WHO/ISUP system is not universally implemented; thus, for purposes of this review, we continue to refer to high-grade T1 lesions as “T1G3.”

The ability to correctly assign stage and grade to T1G3 tumours depends on adequate TUR technique. Excessive cautery artefacts can make pathologic interpretation difficult and should be avoided. A staged resection technique (differential TUR) involving separate submission of deeper sections and/or biopsies of adjacent bladder tissue allows for a more accurate characterisation of the tumour and is strongly recommended [15]. The importance of the quality of TUR was shown by Brausi et al in their assessment of 2410 EORTC patients from seven phase 3 adjuvant intravesical therapy trials (level 2b) [16]. Regardless of whether patients received intravesical therapy, the recurrence rate of tumours at first follow-up cystoscopy (3 mo) varied widely (7.6–40.0% without adjuvant therapy, 6.7–27.4% with adjuvant therapy). Even after accounting for the number of tumours, the year of resection, and the institution at which the resection occurred, recurrence rates displayed significant variability. The authors concluded that surgeon skill and resection technique were the major determinants of TUR outcome. Clearly, both the urologist and the pathologist play an important role in adequately defining T1G3 BCa.

3.2. Immediate prophylactic post-transurethral resection chemotherapy instillation

Clear consensus exists on the role of prophylactic chemotherapy in the first 6 h after TUR. A meta-analysis performed by Sylvester et al analysed 1476 patients from seven randomised, controlled trials of prophylactic chemotherapy versus no prophylaxis after TUR (level 1a) [17]. Both Ta and T1 patients were included, of which the latter composed 32%. Unfortunately, a subgroup analysis by stage was not presented. Nevertheless, a decrease in the odds of recurrence rate by 39% was found with immediate prophylactic chemotherapy. The number needed to treat to prevent one recurrence was 8.5 patients. More recent reports have confirmed these findings but have suggested that the tumours prevented are primarily of the smaller variety (level 1a) [18].

Based on these data, routine use of prophylactic chemotherapy after TUR is recommended. Contraindications to its use include very deep resections, bladder perforation, and prior documented allergic reaction. Although a wide variety of chemotherapeutic agents were used in the pooled trials (mitomycin C [MMC], doxorubicin, epirubicin, and thiotepa), the majority of centres use MMC (40 mg in 40 cm³ of saline) as the prophylactic chemotherapeutic agent of choice.

3.3. Secondary transurethral resection

For all cases of newly diagnosed T1G3 TCC, a secondary TUR 4–6 wk after the primary TUR is strongly recommended. The advantages of a second TUR are 3-fold. First, a repeat resection of the previously resected site 2–6 wk after the initial resection (along with any other cystoscopically suspicious areas) will provide more accurate staging information. This is particularly important because the probability of understaging a T1G3 tumour ranges from 20–70%, depending on the presence of muscularis propria in the sample. If muscle is absent from the initial TUR, repeat resection is mandatory because of the high rate of understaging [8]. Even with muscularis propria sampling at first resection, several reports have documented occult T2 disease in up to 10% of second resections (level 2b) [9,19,20]. Because re-TUR often upstages T1 lesions and/or provides additional pathologic information that can alter management decisions [8,21], repeat resection is indispensable in the management of T1G3 lesions [22].

In addition to the diagnostic benefit, repeat TUR has the ability to detect and potentially clear residual TCC. Because at least 27% of patients harbour residual tumour (with the highest reported rates of 62%) [9], repeat resections may have a therapeutic benefit. Divrik and colleagues provided randomised, controlled evidence supporting this notion (level 1b) [23]. In their study, T1 patients (11% T1G3) were randomised to TUR plus adjuvant intravesical MMC versus TUR plus MMC followed by re-TUR 2–6 wk later. Patients in the repeat TUR group experienced a significantly improved 3-yr recurrence-free survival (RFS) of 69% compared to 37% in the group without secondary TUR.

A third, recently appreciated advantage of repeat TUR is prognostication. Although upstaging of T1G3 lesions to pT2 disease or higher automatically selects patients for radical therapy, Herr and colleagues demonstrated that evidence of T1 disease on repeat TUR portends future muscle invasion (level 2b) [24]. Of 92 T1 patients with residual T1 disease at second resection, 82% progressed to muscle invasion by 5 yr. In contrast, of 260 T1 patients without lamina propria invasion on re-TUR (stage distribution on re-TUR: 149 T0, 87 carcinoma in situ [CIS], 24 Ta), only 19% progressed at 5 yr. Based on these data, residual T1 TCC on repeat TUR was deemed a negative prognostic indicator and a potential indication for immediate cystectomy in T1G3 patients.

3.4. Bladder preservation: the role of intravesical bacillus Calmette-Guérin

3.4.1. Induction bacillus Calmette-Guérin

Adjuvant intravesical bacillus Calmette-Guérin (BCG) immunotherapy is the treatment of choice for bladder preservation with T1G3 TCC. Standard induction therapy comprises six weekly instillations after diagnosis of T1G3 disease after complete resection, although this regimen is largely non-evidence based. Table 1 lists contemporary series of T1G3 patients treated with BCG therapy (level 2b).

Recurrence rates have ranged from 23% to 74%, and progression rates have ranged from 5% to 49%. Where available, the reported disease-specific survival (DSS) and overall survival (OS) estimates also ranged widely. The heterogeneity in outcomes is likely related to a combination of factors, including differences in patient selection (eg, differing rates of concomitant CIS), in the quality of TUR (eg, differing rates of muscularis propria sampling), in the use of secondary TUR, in the use of maintenance instillation regimens and agents, as well as variable times of follow-up. Despite these discrepancies, these studies point to the need for long-term surveillance of patients with T1G3 BCa. Cookson and investigators reported on 86 high-risk patients (44% pT1, 81% diffuse CIS) with median follow-up of 184 mo, half of which received induction (but not maintenance) BCG. Of these patients, 31% had progression after 5 yr, four of which cases occurred after 10 yr and one beyond 15 yr (level 1b) [3]. These data suggest that the long-term risks associated with T1 bladder tumours are not trivial and mandate lifelong cystoscopic and cytologic follow-up.

The therapeutic benefit of BCG for T1G3 BCa has been definitively established. Shelley and colleagues published a Cochrane Review, updated in 2008, assessing the impact of BCG therapy on medium- and high-risk TCC compared to TUR alone (level 1a) [25]. Six randomised trials involving 585 patients, of which more than half were pT1, were included. At 12 mo, the recurrence rate was 26% for patients treated with adjuvant BCG compared to 51% in patients treated by TUR alone. A meta-analysis by Sylvester et al demonstrated the benefit of adjuvant BCG on progression [26]. Analysing 24 trials involving 4863 patients, 9.8% of patients receiving BCG progressed compared to 13.8% of controls: a relative risk reduction of 27%.

Table 1 – Contemporary outcomes of T1G3 bladder cancer conservatively managed with bacillus Calmette-Guérin

Study	Time frame	n (% T1G3) [*]	Maintenance (agent)	Median follow-up, mo	Recurrence rate, %	Progression rate, %	DSS rate, %	OS rate, %
Zhang et al [64]	1983–1993	23	Variable (BCG)	45 (mean)	74	35	78	NR
Herr [65]	1978–1981	25	No	184	NR	40	NR	NR
Lebret et al [33]	1983–1995	35	No	45	43	20	94	86
Hurle et al [32,66]	1989–1992	51	Yes (BCG)	85	47	18	86	67
Gohji et al [67]	1984–1997	25	No	63	40	5	100	NR
Brake et al [40,68]	1987–1999	44	No	28	27	16	89	60
Lamm et al [36]	1985–1988	192 (NR)	Yes (BCG)	119	56	45	NR	83 [#]
Patard et al [69]	1979–1996	50	No	60 (mean)	52	22	80 [#]	NR
Pansadoro et al [70]	1989–1997	81	Yes (BCG)	76	33	15	93	74
Iori et al [71]	1994–2000	41 (76)	Yes (BCG)	40	23	5	NR	NR
Kulkarni and Gupta [72]	1991–1999	69	No	45	46	19	94	91
Griffiths et al [73]	1987–1997	75	No	41	NR	49	59 [#]	NR
Shahin et al [74]	1976–1996	92	No	64	70	33	77	58
Hara et al [75]	1995–1997	97	No	25	45	7	NR	NR
Peyromaure et al [76], Peyromaure and Zerbib [77]	1991–2001	57	Yes (BCG)	53	42	23	88 [#]	NR
Baniel et al [78], Margel et al [79]	1984–1995	78	Variable (BCG)	107	35	18	84	44

DSS = disease-specific survival; OS = overall survival; BCG = bacillus Calmette-Guérin; NR = not reported.

^{*} Data for T1G3 tumours alone are preferentially reported. For studies in which data for T1G3 tumours are not reported separately, combined data with the proportion of cases made up of T1G3 lesions are provided.

[#] Five-year survival; all other survival rates are those reported at last follow-up for the respective study.

Thus, BCG has emerged as an effective intravesical therapy for high-risk BCa. Its efficacy is higher than that of other agents. In a meta-analysis of 11 trials involving 2749 intermediate- to high-risk patients (1421 BCG, 1328 MMC), Böhle et al demonstrated a significantly higher recurrence rate of 46.4% with adjuvant MMC compared to 38.6% for BCG after a median follow-up of 26 mo (level 1a) [27]. In a subgroup analysis of high-risk patients receiving maintenance BCG, the risk reduction compared to MMC was 49%. These results were corroborated in a meta-analysis conducted by Shelley involving 1527 patients from six randomised, controlled trials of BCG versus MMC treatment. Although the overall results demonstrated no significant difference in recurrence rates between the two groups, a subset analysis of trials enrolling only high-risk BCa patients showed a 31% risk reduction ($p < 0.001$) for tumour recurrence for BCG patients (level 1a) [28]. With respect to progression, Böhle and Bock in another meta-analysis analysed nine trials of BCG versus MMC adjuvant therapy comprising 2410 patients (level 1a) [29]. After a median follow-up of 26 mo, BCG was found to be superior to MMC when all trials were analysed together (odds ratio [OR]: 0.77; $p = 0.08$) and when only trials utilising BCG maintenance were included (OR: 0.66; $p = 0.02$). Unfortunately, a subset analysis with high-risk patients only was not possible in this study because of the small number of trials with high-risk patients. As a result, some have questioned the use of BCG as the treatment of choice for T1G3 TCC because the meta-analyses by Böhle and Shelley did not explicitly perform subset analyses on patients with T1G3 tumours.

Based on these data and consensus within the urologic community, BCG is the preferred intravesical treatment for high-risk bladder TCC. MMC is a reasonable alternative only in situations where adjuvant BCG is contraindicated (allergy, intolerance to BCG, or immunosuppressed states)

and immediate cystectomy is refused [30]. Undoubtedly, patients experience significantly fewer local and systemic side-effects with adjuvant MMC compared to BCG [27], but the potentially aggressive nature of T1G3 TCC necessitates the use of the most effective treatment.

Patients experiencing severe side-effects from full-dose BCG can be considered for dose reduction, which may, however, compromise efficacy. Dose reductions of one-half to one-third BCG colony-forming units have been evaluated. In most cases, side-effect profiles improved with low-dose regimens [31]. In a number of cases, efficacy and safety did not appear to be compromised for T1G3 tumours [32,33], but recent reports by Martinez-Pineiro et al [34] and Yoneyama et al [35] have suggested worse outcomes with low-dose regimens in T1G3 patients, with trends towards reduced DSS and RFS (level 2b). Thus, in T1G3 TCC, dose-reduced BCG regimens must be used with caution, with additional investigation of the role of reduced dose BCG warranted.

3.4.2. Maintenance bacillus Calmette-Guérin

The role of maintenance BCG therapy for T1G3 BCa is supported by many lines of evidence. In a prospective, randomised Southwest Oncology Group (SWOG) trial, Lamm and colleagues evaluated the efficacy of induction plus maintenance BCG to induction BCG only in 384 patients with Ta or T1 disease at high risk of recurrence/progression (level 1a) [36]. The maintenance protocol consisted of three weekly BCG instillations at 3 and 6 mo post-TUR and semiannually thereafter for 3 yr. Both 5-yr RFS (60% vs 41%, $p < 0.001$) and “worsening-free” survival (a proxy for progression-free survival [PFS], 76% vs 70%, $p = 0.04$) were improved with maintenance BCG. In the meta-analysis by Sylvester et al compiling trials of TUR plus BCG versus TUR alone or TUR with other chemotherapeutic regimens, the OR favouring BCG was lowest in the subset

analysis with maintenance BCG (OR: 0.63; $p < 0.001$), indicating that maintenance therapy results in a further decrease in progression in addition to induction BCG (level 1a) [26]. The meta-analysis of Böhle and Bock [29] corroborated Sylvester et al's data, as discussed above.

Herr recently reviewed the data supporting maintenance BCG for high-risk non-muscle-invasive TCC and questioned, based upon methodologic limitations in the cited trials and a paucity of positive studies, the routine use of maintenance BCG for the prevention of tumour progression [37]. Although these provocative arguments should be considered prior to prescribing maintenance BCG, until strong evidence suggests otherwise, the data nevertheless support maintenance BCG for all cases of T1G3 TCC treated with a bladder-sparing approach.

Compliance with therapy is also an issue, as only 16% of the SWOG trial participants completed all seven planned cycles. In fact, less than half of the patients completed more than three cycles, suggesting that the noted significant impact of maintenance therapy was achieved up front during therapy. This notion is supported by a report from Decobert and colleagues [38] in which 111 patients at high risk for recurrence (32% pT1) received BCG as per the SWOG maintenance protocol (level 2b). At 12 mo following the last BCG instillation, reported recurrence rates were 11.5%, 33.3%, and 53.5% for more than three, two, and fewer than two cycles of maintenance BCG, respectively. Although the impact of additional maintenance (three cycles vs four or more cycles) was not statistically significant, none of the 12 patients who received five or more cycles of maintenance BCG experienced a recurrence. Although these data support the idea of early efficacy of maintenance therapy, patients nevertheless should be encouraged to continue maintenance beyond three cycles.

3.4.3. Treatment of recurrence after bacillus Calmette-Guérin ("late bacillus Calmette-Guérin failures")

Late BCG failures are defined as patients with an initial complete response (CR) to BCG treatment (no tumour 6 mo after TUR) but with a subsequent recurrence [39]. Patients who never achieve a tumour-free state (BCG refractory) or those who recur early (within 6 mo—"early BCG failures") should be offered early cystectomy, as discussed earlier. Many urologists also consider cystectomy as the appropriate treatment for late BCG failures. Salvage intravesical therapy—that is, a second course of BCG treatment (ie, reinduction)—may be considered in selected patients with late BCG failure and would also apply to patients refusing cystectomy or ineligible for major surgery.

BCG for late BCG failure patients as a salvage treatment for T1 cancers has been studied only to a limited extent. Of 126 patients with an initial pT1 lesion, Brake et al reported that 89 (71%) had a lasting response to a single course of BCG [40]. Of the 37 recurrences, 13 were muscle invasive, and the remaining 24 were treated with repeat resection and a second course of BCG. The lasting response rate was 79% (19 without recurrence). Results such as these have also been reported by others (level 3b) [33]. Nevertheless, because the actuarial risk of progression with each

additional 6-wk course of BCG is 7% [41], many urologists hesitate to provide a second course BCG except in select cases. Soloway et al suggest a second course BCG if the recurrent lesion is Ta or CIS and cystectomy for recurrent T1G3 tumours [42]. This approach has been verified in a study of 214 patients with high-risk BCa who experienced T1 recurrence [43]. A 71% cumulative incidence of progression to muscle invasion at 5 yr (48% death from disease) was noted for patients treated with second-course BCG compared to a 28% cumulative incidence of progression (31% death from disease) for patients treated with cystectomy (level 2b). These data clearly support the use of cystectomy in the treatment of patients with pT1G3 recurrence after BCG treatment.

A third cycle of BCG is definitely not indicated because of success rates as low as 6% [44]. To avoid cystectomy, other intravesical salvage options for BCG failures have been studied. In a phase 2 trial involving 467 unselected superficial BCa patients with at least one BCG failure, the combination of BCG plus interferon- α resulted in a disease-free rate of 45% at 24-mo median follow-up [45]. However, subset data for T1G3 patients were not reported.

Thus, for patients with an initial T1G3 diagnosis and recurrence after BCG therapy, salvage treatment with a second course of BCG should be reserved for patients with pTa or CIS recurrences. Patients with a pT1 recurrence are at high risk of progression and should definitely be offered cystectomy.

3.4.4. Potential future intravesical therapeutic options

Alternative intravesical options for the treatment of T1G3 BCa have been investigated. Intravesical gemcitabine has been used for the treatment of high-risk BCa after BCG failure. In a phase 2 trial of intravesical gemcitabine for BCG-refractory BCa where cystectomy was recommended but refused, Dalbagni and colleagues noted a CR, defined as negative cystoscopy, cytology, and biopsy at first surveillance of 50% (15 of 30; level 3b) [46]. The durable response rate, however, was much lower, with a 1-yr RFS in responders of only 21%. A low short-term disease free rate of 13% in high-risk patients (including T1G3 patients) was also noted by Bartoletti et al (level 3b) [47]. In a recent report of 40 patients (90% pT1) followed for a median of 28 mo, 14 (35%) patients recurred, but no patients progressed [48]. On the basis of these preliminary data, intravesical gemcitabine cannot be recommended for pT1G3 TCC of the bladder.

Device-assisted therapy has also been investigated as a means of increasing the efficacy of intravesical chemotherapy. Local hyperthermia coupled with MMC has been shown to have improved efficacy over MMC alone in the treatment of high-risk superficial TCC. In one series with 53 high-risk patients, the 2-yr RFS was 64% (level 3b) [49]. Electromotive drug administration (EMDA) to enhance urothelial drug penetration has been reported by Di Stasi et al, who randomised 212 patients with pT1 TCC (39% T1G3) to BCG with 10 mo of monthly maintenance versus sequential BCG and EMDA-MMC (eMMC) induction and maintenance (level 1a) [50]. Median follow-up was 88 mo.

Patients in the eMMC/BCG group experienced significantly improved RFS, PFS, DSS, and OS rates (absolute risk reductions: 16.0%, 12.6%, 10.6%, and 10.9%, respectively). Subgroup analyses demonstrated that the eMMC/BCG regimen was most effective for the highest-risk tumours (ie, T1G3 with CIS). Further studies confirming these results are needed before this approach can be recommended.

3.5. Role of immediate or early cystectomy

The relatively high recurrence and progression rates associated with conservatively treated T1G3 TCC (Table 1) make cystectomy an option for these patients. There are a number of advantages to this approach. First, cystectomy provides the most definitive opportunity for cure. Table 2 lists the contemporary series in which T1 tumours were treated immediately or early with radical cystectomy (RC; level 2b). DSS for these patients ranges between approximately 80% and 90%, which is probably an underestimate of the true survival conferred to T1 patients treated with cystectomy, because the patients in these retrospective series were likely selected to undergo cystectomy because of adverse pathology (eg, multifocality, associated CIS).

Second, understaged lesions will also be appropriately treated. Although restaging TUR refines local cancer staging, thereby decreasing the risk of understaging T1 lesions, approximately 13% of patients will still be understaged even after re-TUR (level 3b) [51]. Third, cystectomy enables lymphadenectomy. Because up to 18% (Table 2) of T1 patients have positive lymph nodes, cystectomy can be both diagnostic and therapeutic with regard to nodal metastases. Fourth, cystectomy obviates the need for repeated intravesical therapies and simplifies follow-up.

Cystectomy for T1G3 TCC also has a number of potential disadvantages. First, the perioperative mortality and morbidity rate following cystectomy is not trivial at 1–6% (level 2c) [52] and 30% (level 2b) [53], respectively. Second, cystectomy may have a detrimental impact on quality of life (QoL) secondary to long-term changes in sexual, gastrointestinal, and genitourinary function (although it should be remembered that BCG therapy can also impair QoL because of frequent follow-up,

surveillance cystoscopy, lower urinary tract symptoms, and the risk of disseminated BCG infection [54]). Finally, RC may be considered overtreatment for many patients because a conservative bladder-sparing approach with BCG is effective in approximately 50% of cases. Thus, an approach using reliable risk stratification in order to decide which patients to offer early cystectomy versus conservative treatment is required.

Risk stratification involves assessing the probability of progression and local failure with conservative treatment. This is particularly important because a number of series have demonstrated that delays in cystectomy can lead to worse outcomes. Wiesner and colleagues noted worse pathologic outcomes (more upstaging and lymph node-positive disease) in patients with non-muscle-invasive BCa (86% T1) as the number of TUR procedures increased (level 2b) [55]. They hypothesised that the delay to definitive, radical surgery with increasing endoscopic interventions may have contributed to the increase in progression. Herr and Sogani studied 307 high-risk BCa patients, 90 of whom underwent cystectomy on relapse (level 2b) [56]. DSS was greatest in those undergoing cystectomy <2 yr after BCG initiation compared to those whose cystectomy was done >2 yr post-BCG induction. Likewise, Denzinger and colleagues examined 105 T1G3 patients with adverse pathologic features (at least two of multifocality, tumour size >3 cm or CIS), all of whom underwent cystectomy (level 2b) [57]. Fifty-four patients opted for immediate cystectomy, and 51 underwent deferred cystectomy at a median of 11.2 mo after initial TUR. The 10-yr cancer-specific survival (CSS) of patients with immediate cystectomy was 78% compared to 51% ($p < 0.01$) for the deferred cystectomy group. Lambert et al also noted poorer disease-free survival and DSS in a cohort of patients undergoing cystectomy for T1G3 TCC after 1998 versus those treated with cystectomy before 1998 (level 3b) [58]. They postulated that the decrease in survival was the result of higher and perhaps inappropriately prolonged use of intravesical therapy in the modern era.

These studies point to the dangers of delaying cystectomy in pT1G3 TCC where indicated and the need to risk-stratify T1G3 patients, if possible. Identifying candidates at high risk for progression would help to identify clearly patients who should undergo early cystectomy. The need

Table 2 – Contemporary outcomes of T1G3 bladder cancer managed with immediate or early radical cystectomy

Study	Time frame	n	Median follow-up (mo)	Prior BCG, %	Upstaging, %	LN positive, %	Recurrence, % [#]	DSS [#] , %	OS [#] , %
Herr and Sogani [56] [*]	1979–1984	35	NR	100	NR	NR	NR	92	NR
Dutta et al [7] [*]	1995–1999	78	NR	37	40	12	NR	78	64
Thalmann et al [80]	1980–1999	29	47	0	41	14	21	69	54
Masood et al [81]	1992–2002	30	57	30	27	NR	NR	88	NR
Bianco et al [82]	1990–2000	66	48	27	27	9	78	78	NR
Lambert et al [58]	1990–2005	104	NR	44	40	NR	48	93	87
Gupta et al [83]	1984–2003	167	34	44	50	18	29	82	69
Denzinger et al [57]	1995–2005	54	61	0	26	NR	NR	78	NR

BCG = bacillus Calmette–Guérin; LN = lymph node; DSS = disease-specific survival; OS = overall survival; NR = not reported; BCa = bladder cancer.

^{*} “High-risk” superficial bladder cancer (exact proportion T1G3 not specified for Herr and Sogani, 80% for Dutta et al).

[#] Rates reported are those reported at study completion and not necessarily 5-yr actuarial values.

Table 3 – Risk factors for progression: relative indications for immediate and early cystectomy. Strengths of associations are specific to each study and do not imply importance of one factor over another

Risk factor	Study	n	Median follow-up	Increase in risk of recurrence	Increase in risk of progression	Increase in risk of death from disease
Immediate cystectomy[†]						
CIS	Gupta et al [83]	167	34	HR: 2.13	–	HR: 2.75
	Denzinger et al [57]	105	61	–	–	HR: 2.55 (10 yr)
	Sylvester et al [59]	2596*	47	HR: 1.19	HR: 3.41	–
Multifocality	Sylvester et al [59]	2596*	47	HR: 1.56	HR: 1.70	–
Hydronephrosis	Divrik [84]	931 [†]	51	HR: 1.59	HR: 2.37	–
Tumour size >3 cm	Sylvester et al [59]	2596*	47	HR: 1.54	HR: 1.89	–
	Divrik et al [84]	931 [†]	51	HR: 2.05	HR: 3.12	–
Depth of tumour invasion (T1a vs T1b)	Bernardini et al [85]	68	NR	–	HR: 7.48	–
	Orsola et al [86]	97	53 (mean)	NS	HR: 4.47	–
T1 disease on restaging TUR	Herr and Donat [87]	710 [†]	>60	HR: 1.3 for any non-T0 disease (90% recurrence for T1)	HR: 6.9 for any non-T0 disease (76% progression of T1)	–
Early cystectomy[†]						
Tumour found at initial 3-mo cystoscopy	Holmang and Johansson [88]	355 [†]	NR	HR: 3.01	HR: 4.82	–
	Solsona et al [89]	191 [†]	73	–	HR: 10.48	–
	Herr and Donat [87]	710 [†]	>60	HR: 5.2	HR: 3.7	–
	Raj et al [43]	85	136	–	CI: 71% (5 yr)	CI: 48% (5 yr)
Superficial prostatic urethral recurrence	Huguet et al [90]	62 [†]	40	–	–	5-yr survival significantly lower (20% vs 78%, p = 0.0002)
CIS = carcinoma in situ; HR = hazard ratio; NS = not significant; TUR = transurethral resection; CI = cumulative incidence.						
* Ta and T1 lesions combined.						
[†] Noncompliance or intolerance to adjuvant intravesical therapy or tumours in a location difficult to access transurethrally are indications for immediate or early cystectomy.						

for such a strategy has been recognised by a recent international consensus panel on T1 BCa that subclassified T1 tumours into high-risk and low-risk variants based on multifocality, associated CIS, tumour location (dome or anterior bladder wall), or residual T1 disease on restaging TUR [44]. Any of these factors would classify a T1G3 lesion as “high risk.” Accordingly, Table 3 lists published adverse prognostic factors associated with T1G3 tumours that can facilitate a treatment decision (level 2b). The presence of two or more of these risk factors at T1G3 diagnosis identifies candidates who must be advised to undergo immediate cystectomy [57,59]. Likewise, identification of significant tumour at first cystoscopic follow-up (BCG refractory) and/or T1 or prostatic urethral disease at any point during follow-up identifies candidates for early cystectomy. Not listed are investigational molecular markers such as p53 or pRB, the prognostic ability of which in high-risk superficial BCa has not been established unequivocally (level 4) [60,61]. Thus, molecular markers at present cannot be reliably used in clinical decision making.

Fig. 1 illustrates a possible treatment algorithm for newly diagnosed T1G3 tumours based on the information we have presented in this review. It supports a bladder-preservation regimen in patients without identifiable risk factors while helping to identify those individuals at risk for progression in whom immediate or early cystectomy should be performed.

3.6. Other treatment modalities

A limited number of reports assessing the role of radiation therapy (RT) with or without chemotherapy for the treatment of T1G3 TCC are available. Weiss and colleagues retrospectively evaluated the impact of radiochemotherapy for high-risk T1 BCa in 141 patients followed for a median of 62 mo (level 3b) [62]. Of the 84 patients with T1G3 disease, 89% achieved a CR (no tumour on restaging TUR 6 wk after completion of radiochemotherapy). Long-term results, however, showed that the 10-yr risk of progression for T1G3 patients was 29%, with a 10-yr DSS of 71%. Of note, the vast majority of patients were satisfied with their urinary function, suggesting that combined TUR with radiochemotherapy maintained QoL while achieving respectable disease outcomes.

When compared with BCG, however, the results of RT have not been as encouraging. In the largest randomised trial comparing RT to conservative therapy (observation or intravesical BCG/MMC) for T1G3 TCC, Harland and colleagues reported no difference in RFS, PFS, or OS (level 1a) [63]. As a result of cost, inconvenience, potential for toxicity, and a lack of benefit over conventional intravesical therapies, the authors concluded that RT cannot be recommended for routine use as a bladder-preservation strategy.

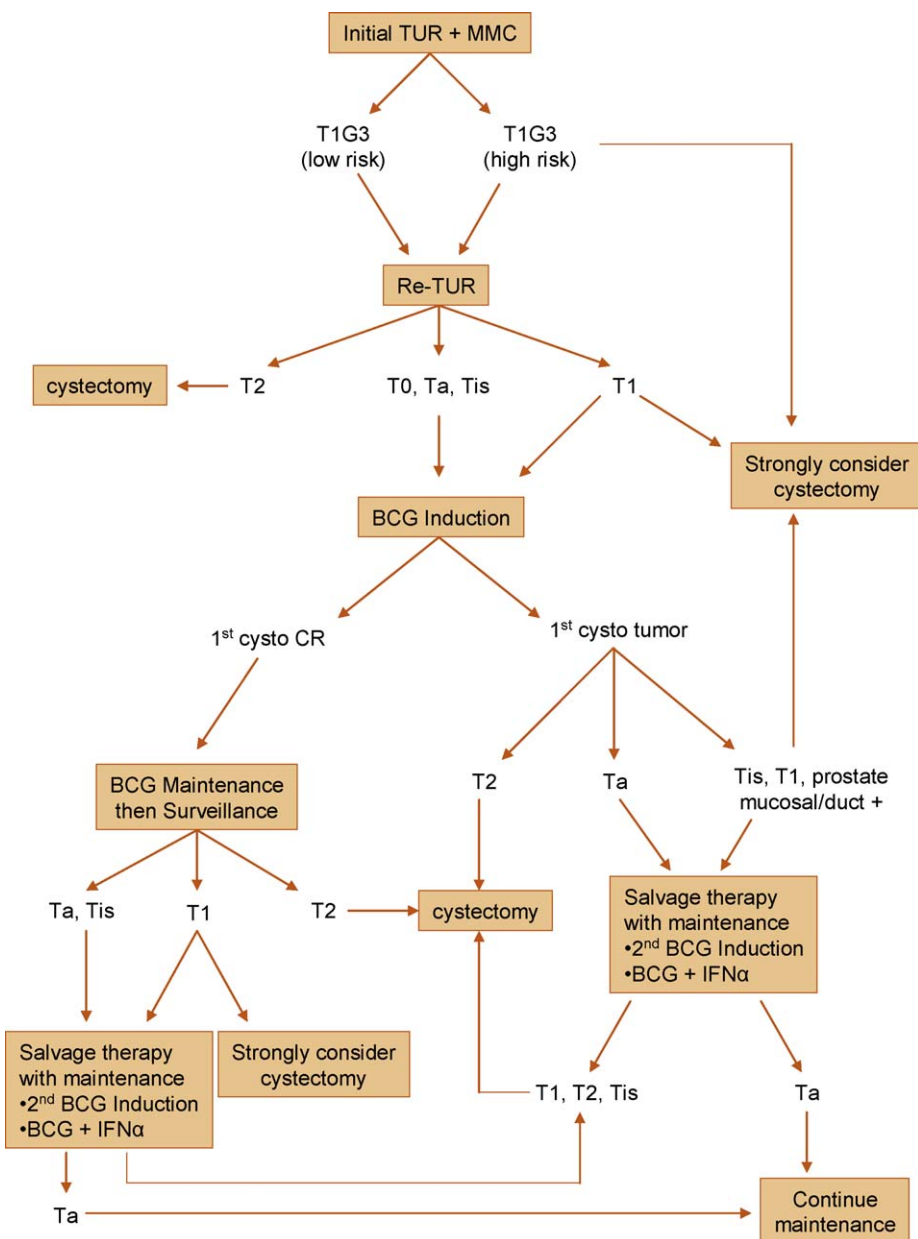


Fig. 1 – Proposed algorithm for treatment of T1G3 bladder cancer. Management decisions are outlined in boxes. High-risk T1G3 (first “decision node”) refers to tumours with associated risk factors for progression (Table 2), whereas low-risk T1G3 tumours lack any risk factors for progression. All pathology identified after the first cystoscopic assessment assumes adequate transurethral resection (ie, re-resection of T1 lesions). Although not explicitly stated, treatment decisions for non-muscle-invasive recurrences are also influenced by tumour grade (eg, Ta, grade 3 vs Ta, grade 1) and require clinical judgment based on the specific circumstances of each case. TUR = transurethral resection; MMC = mitomycin C; BCG = bacillus Calmette-Guérin; INF- α = interferon- α .

3.7. Quality of life

The excellent CSS and OS rates achieved with cystectomy for stage T1 TCC (Table 2) must be weighed against the understandable wish of the patient to preserve his or her own bladder along with the risks and morbidity of cystectomy. Intravesical treatment may result in bladder preservation but not without risk and morbidity. Although CSS remains of paramount importance, QoL considerations, which are difficult to assess, cannot be ignored.

Kulkarni et al performed decision analysis that enabled comparisons of cystectomy and BCG while accounting for detriments in QoL related to either treatment (level 2b) [54]. Not surprisingly, they found that the treatment associated with the highest gain in quality-adjusted life expectancy (QALE) was dependent on patient age and comorbidity. Younger, healthier patients had higher QALE when treated with cystectomy, but after age 65, a higher QALE was noted with BCG treatment. This suggests that one treatment modality may not be ideal for all patients. Rather, the type of tumour and its associated risk factors for progression along

with patient factors such as age, comorbidity, and preferences must all be considered when making a final treatment recommendation.

4. Conclusions

T1G3 tumours are heterogeneous in nature and thus difficult to treat. Bladder preservation with BCG and RC are the current standard treatment modalities of choice for these tumours. The decision to pursue bladder preservation versus cystectomy depends on a number of tumour factors, which can indicate the risk of progression. We present a risk-stratified approach for these lesions that should maximise the chances of safely identifying those patients in whom a bladder-preservation strategy can be pursued while also identifying those at high risk of progression for whom immediate or early cystectomy must be offered.

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Acquisition of data: Kulkarni.

Analysis and interpretation of data: Kulkarni, Hakenberg, Gschwend, Thalmann, Kamat, Kassouf, Zlotta.

Drafting of the manuscript: Kulkarni, Hakenberg, Gschwend, Thalmann, Kamat, Kassouf, Zlotta.

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