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Editorial by XXX on pp. x–y of this issue

Prognostic Factors and Risk Groups in T1G3 Non–Muscle-invasive Bladder Cancer Patients Initially Treated with Bacillus Calmette-Guérin: Results of a Retrospective Multicenter Study of 2451 Patients

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Abstract

Background: The impact of prognostic factors in T1G3 non–muscle-invasive bladder cancer (BCa) patients is critical for proper treatment decision making.
Objective: To assess prognostic factors in patients who received bacillus Calmette-Guérin (BCG) as initial intravesical treatment of T1G3 tumors and to identify a subgroup of high-risk patients who should be considered for more aggressive treatment.

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Design, setting, and participants: Individual patient data were collected for 2451 T1G3 patients from 23 centers who received BCG between 1990 and 2011.
Outcome measurements and statistical analysis: Using Cox multivariable regression, the prognostic importance of several clinical variables was assessed for time to recurrence, progression, BCa-specific survival, and overall survival (OS).
Results and limitations: With a median follow-up of 5.2 yr, 465 patients (19%) progressed, 509 (21%) underwent cystectomy, and 221 (9%) died because of BCa. In multivariable analyses, the most important prognostic factors for progression were age, tumor size, and concomitant carcinoma in situ (CIS); the most important prognostic factors for BCa-specific survival and OS were age and tumor size. Patients were divided into four risk groups for progression according to the number of adverse factors among age ≥70 yr, size ≥3 cm, and presence of CIS. Progression rates at 10 yr ranged from 17% to 52%. BCa-specific death rates at 10 yr were 32% in patients ≥70 yr with tumor size ≥3 cm and 13% otherwise.
Conclusions: T1G3 patients ≥70 yr with tumors ≥3 cm and concomitant CIS should be treated more aggressively because of the high risk of progression.
Patient summary: Although the majority of T1G3 patients can be safely treated with intravesical bacillus Calmette-Guérin, there is a subgroup of T1G3 patients with age ≥70 yr, tumor size ≥3 cm, and concomitant CIS who have a high risk of progression and thus require aggressive treatment.

1. Introduction

T1G3 is considered to be a high-risk subgroup of non–muscle-invasive bladder cancer (NMIBC). Its natural history suggests an unfavorable long-term outcome, as documented by early untreated series reporting 27–65% disease progression rates [1] and a 34% cancer-specific death rate [2].

Bacillus Calmette-Guérin (BCG) is currently viewed as the gold standard conservative treatment option for T1G3 tumors [3,4]. This policy is based on several inconsistent retrospective series reporting a 5-yr disease-specific survival of up to 80% [5]. Meta-analyses including relatively small numbers of T1G3 patients have reached conflicting conclusions concerning the ability of BCG to reduce the risk of progression [6,7]. One-third of T1G3 patients will eventually progress under BCG [5] with a considerable risk of dying of their disease because of delaying radical surgery [8]. Early cystectomy, advocated by some authors as an alternative to BCG, has shown long-term survival rates not exceeding 80% [9], meaning that it does not guarantee cure for T1G3 tumors. The current understanding of T1G3 disease suggests that BCG is a feasible first-line treatment option, while cystectomy should be recommended in the presence of unfavorable prognostic factors [3,4,10,11]. Integrating prognostic factors to develop risk groups would be particularly helpful in clinical decision making for T1G3 patients. Current scoring systems that predict clinical outcomes in NMIBC [12,13] are inadequate for this purpose because of the low rate of T1G3 patients in these series.

The aim of the current study is to assess outcome-related prognostic factors in a large cohort of patients who received BCG as initial treatment of T1G3 tumors and to identify subgroups of high-risk patients who should be considered for more aggressive treatment.

2. Patients and methods

2.1. Study design

This is a multicenter retrospective study including patients from 23 different centers.

2.2. Inclusion criteria

Patients who have histologically confirmed T1G3 tumors (World Health Organization [WHO] 1973) or T1 high-grade tumors (International Society of Urological Pathology 1998/WHO 2004) on bladder biopsy or transurethral resection (TUR) and who received at least an induction course of BCG as their initial intravesical treatment for a T1G3/high-grade tumor from 1990 to 2011 were eligible. Patients with a previous NMIBC that was not T1G3/high grade were eligible as long as they did not receive BCG for that tumor.

2.3. Exclusion criteria

Patients with a history of muscle-invasive disease (T2 or higher) or upper tract urothelial cancer, patients with nonurothelial carcinoma, patients who previously received BCG for a tumor that was not T1G3/high grade, or patients who did not receive BCG as initial intravesical treatment for a T1G3/high-grade tumor were ineligible.

2.4. Database construction, prognostic factors, and outcome variables

Based on an updated literature search on NMIBC and T1G3 conducted in 2010, potential prognostic factors were identified. Individual patient data were requested for the following patient and tumor characteristics and were included in the database: age, gender, smoking history and intensity, exposure to chemical compounds, tumor status (primary or recurrent), previous intravesical chemotherapy, tumor size (<3 cm vs ≥3 cm), tumor focality (solitary vs multiple), presence of carcinoma in situ (CIS), urethral involvement with or without stromal invasion, presence of muscle in the tissue specimen, restaging TUR, and results of pathology at restaging.

Information on BCG dose, total number of instillations, toxicity, dose reduction for toxicity, and reasons for stopping BCG was also recorded. Any instillations beyond six were defined as maintenance BCG.

The following end points were assessed: time to first recurrence, progression to muscle-invasive disease, and the duration of cancer-specific survival (CSS) and overall survival (OS).

Individual patient data were transferred to the secretariat in electronic format. Data quality control was carried out, and queries for inconsistent and missing data were sent back to the participating centers for resolution. All patients from centers with insufficient data quality were excluded.

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2.5. Statistical analysis

Times to events were calculated taking the date of starting BCG as time zero. OS was estimated using the Kaplan-Meier technique. To take into account patients who died before observing the event of interest (competing risk), times to the other events were estimated using cumulative incidence functions. Patients without an event or death prior to the event were censored at the last date of follow-up.

Univariable and step-down multivariable Cox proportional hazards regression models using a significance level of 0.01 were used to identify prognostic factors related to the end points of interest. Risk groups were formed based on the factors found to be of prognostic significance for progression and bladder cancer (BCa)–specific survival in the multivariable models.

3. Results

In November 2010, 25 centers agreed to take part in the study. Individual patient data from each center were checked electronically, and queries were sent back to investigators to provide missing data and correct inconsistencies. All patients from two centers were excluded for quality control reasons. Patients from 23 centers were retained for the study, with between 9 and 396 patients per center, for a total of 2451 patients who met the eligibility criteria (Supplemental Table 1).

3.1. Baseline characteristics and treatment

Baseline patient information is reported in Table 1. Median age of patients was 68 yr, 82% were male, 89% were primary T1G3, 56% had multifocal disease, 46% had tumors <3 cm, 24% had concomitant CIS, and 38% had a restaging TUR.

Table 2 provides information on the number of BCG instillations, the dose, and reasons for stopping treatment. Thirty-eight percent of the cohort received some sort of maintenance.

3.2. Clinical outcome

Clinical outcome is reported in Table 3. At a median follow-up of 5.2 yr and a maximum follow-up of 18.7 yr (interquartile range: 2.6–8.5), 1244 patients (51%) had a recurrence, and 465 patients (19%) progressed to muscle-invasive disease. Progression to extravesical, locoregional, and/or systemic disease was documented in 221 patients (9%). Five hundred and nine patients (21%) eventually underwent cystectomy, 205 (40%) for non–muscle-invasive recurrence and 288 (57%)

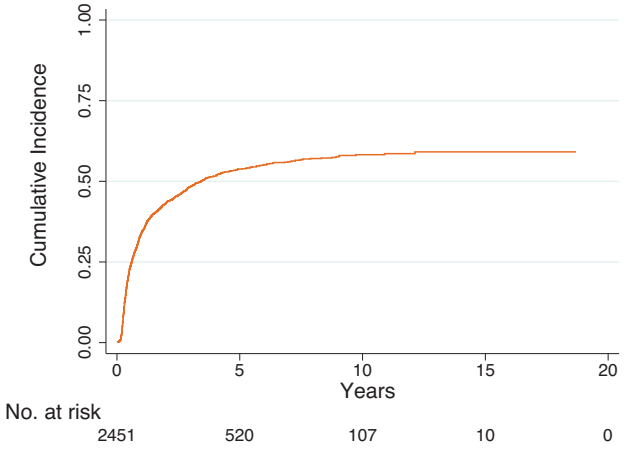

Fig. 1 – Cumulative incidence curve for time to recurrence.

Table 1 – Baseline characteristics of the 2451 T1G3 patients

Variable	No. (%)
Age, yr	
<70	1390 (56.7)
≥70	1061 (43.3)
68	Median
60–74	Interquartile range
Sex	
Male	2012 (82.1)
Female	439 (17.9)
Smoking history	
Never smoked	469 (19.1)
Stopped smoking	618 (25.2)
Current smoker	465 (19.0)
Missing/unknown	899 (36.7)
Exposure to chemical compounds	
No	968 (39.5)
Yes	86 (3.5)
Missing/unknown	1397 (57.0)
Tumor status	
Primary T1G3	2179 (88.9)
Recurrent after non-T1G3	272 (11.1)
Previous intravesical chemotherapy	
No	2320 (94.7)
Yes	131 (5.3)
Muscle in TUR specimen	
No	416 (17.0)
Yes	1768 (72.1)
Missing/unknown	267 (10.9)
Tumor grade	
WHO 1973 grade 3	1703 (69.5)
WHO 2004 high grade	1780 (72.6)
Grade 3 and/or high grade	2451 (100)
Tumor focality	
Solitary	964 (39.3)
Multiple	1365 (55.7)
Missing/unknown	122 (5.0)
Largest tumor diameter, cm	
<3	1137 (46.4)
≥3	560 (22.9)
Missing/unknown	754 (30.8)
Concomitant CIS	
No	1852 (75.6)
Yes	599 (24.4)
Invasion of prostatic urethra	
No	1337 (54.6)
Yes, without stromal invasion	44 (1.8)
Yes, with stromal invasion	5 (0.2)
Missing/unknown	1065 (43.4)
Restaging TUR before BCG	
No	1342 (54.8)
Yes	935 (38.2)
Missing/unknown	174 (7.1)
Pathology at restaging TUR*	
No residual tumor	267 (28.6)
Ta	378 (40.4)
T1	289 (30.9)
Missing/unknown	1 (0.1)

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; TUR = transurethral resection; WHO = World Health Organization.
* Information on patients with muscle invasion at restaging TUR was not available, as muscle invasion before starting BCG was an exclusion criterion.

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Table 2 – Bacillus Calmette-Guérin treatment schedule and tolerability

Variable	No. (%)
Number of BCG instillations	
6 (induction only)	1515 (61.8)
7–15	618 (25.2)
16–21	226 (9.2)
≥22	92 (3.8)
BCG dose	
Full	2337 (97.0)
One-third	49 (2.0)
One-fourth	17 (0.7)
Missing/unknown	8 (0.3)
Reasons for stopping BCG	
Planned treatment completed	1875 (76.5)
Local toxicity	84 (3.4)
Systemic toxicity	32 (1.3)
Local and systemic toxicity	21 (0.9)
Patient refusal	25 (1.0)
Patient lost to follow-up	15 (0.6)
Recurrence	141 (5.8)
Death	8 (0.3)
Other	48 (2.0)
Missing/unknown	202 (8.2)

BCG = bacillus Calmette-Guérin.

for muscle-invasive disease. Pathology at cystectomy revealed CIS in 206 patients (40%) and nodal disease in 72 of cases (14%). A total of 596 patients (24%) died, 221 (9%) because of BCa. Of the 221 BCa-specific deaths, 113 (51%) occurred in patients who received cystectomy. As shown in Figures 1–4, the 10-yr recurrence, progression, overall death, and BCa-specific death rates were 58.3% (95% confidence interval, 55.7–60.9), 23.3% (95% CI, 21.0–25.6), 41.5% (95% CI, 38.3–44.9), and 14.8% (95% CI, 12.2–17.4), respectively.

3.3. *Prognostic factors*

Tables 4–7 report the results of the univariable and multivariable analyses of prognostic factors for recurrence, progression, OS, and BCa-specific survival, respectively. Gender was found to be significantly associated with

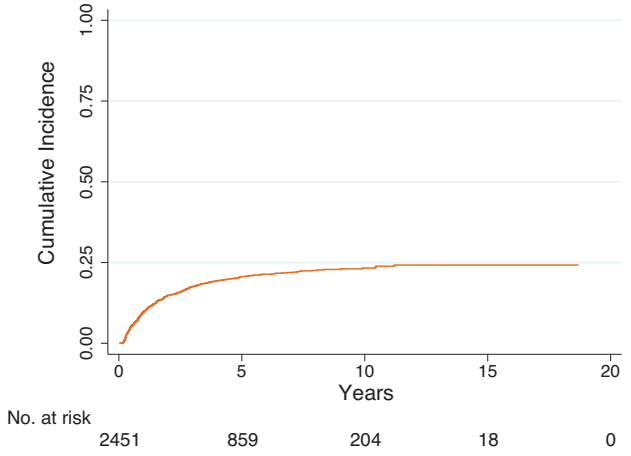

Fig. 2 – Cumulative incidence curve for time to progression.

Table 3 – Clinical outcome of T1G3 patients treated with bacillus Calmette-Guérin

Variable	No. (%)
Recurrence	
No	1207 (49.2)
Yes	1244 (50.8)
Stage at first recurrence	
Ta	450 (36.2)
T1	455 (36.6)
T2	229 (18.4)
T3	30 (2.4)
T4	18 (1.4)
CIS alone	27 (2.2)
Extravesical	15 (1.2)
Missing/unknown	20 (1.6)
Grade at first recurrence	
G1–G2/low grade	379 (30.5)
G3/high grade	804 (64.6)
CIS alone	27 (2.2)
Extravesical	15 (1.2)
Missing/unknown	19 (1.5)
CIS at first recurrence	
No	798 (64.2)
Yes	418 (33.6)
Missing/unknown	28 (2.2)
CIS recurrence	
No	1956 (79.8)
Yes	495 (20.2)
Progression to muscle invasion (≥pT2)	
No	1986 (81.0)
Yes	465 (19.0)
Stage at first progression	
T2	347 (74.6)
T3	54 (11.6)
T4	23 (5.0)
Missing/unknown	41 (8.8)
Extravesical recurrence	
No	1857 (75.8)
Locoregional	73 (3.0)
Systemic	87 (3.6)
Locoregional and systemic	61 (2.5)
Missing/unknown	373 (15.2)
Radical cystectomy	
No	1942 (79.2)
Yes	509 (20.8)
Age at cystectomy, yr	
20–49	38 (7.47)
50–59	79 (15.52)
60–69	193 (37.92)
70–79	164 (32.22)
80–89	34 (6.68)
≥90	1 (0.20)
Pathologic stage at cystectomy	
T0	103 (20.2)
T1	92 (18.1)
T2	135 (26.5)
T3	116 (22.8)
T4	37 (7.3)
CIS alone	10 (2.0)
Missing/unknown	16 (3.1)
Timing of cystectomy (clinical tumor status at cystectomy)	
No recurrence	9 (1.8)
TaT1	76 (14.9)
<T1G3	30 (5.9)
T1G3	33 (6.5)
Unknown	13 (2.6)
CIS	87 (17.1)
Progression	337 (66.2)
Before cystectomy	226 (44.4)
At cystectomy	111 (21.8)
CIS at cystectomy	
No	284 (55.8)

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Table 3 (*Continued*)

Variable	No. (%)
Yes	206 (40.5)
Missing/unknown	19 (3.7)
Nodal status at cystectomy	
N0	254 (49.9)
N+	72 (14.1)
Missing/unknown	183 (36.0)
Survival status	
Alive	1855 (75.7)
Dead (all causes)	596 (24.3)
Dead (bladder cancer)	221 (9.0)
Cause of death	
Bladder cancer	221 (37.1)
Other neoplasms	81 (13.6)
Treatment related	14 (2.4)
Chronic disease	126 (21.1)
Missing/unknown	154 (25.8)

CIS = carcinoma in situ.

progression in the univariable analysis but not in the multivariable one. Similarly, T1G3 progressing from an NMIBC of lower stage and/or lower grade significantly affected both CSS and OS solely in the univariable analysis. In the multivariable models, tumor size was the only variable that independently predicted all four outcome measures. Tumor multiplicity predicted only recurrence and concomitant CIS predicted only tumor progression, while age ≥70 yr had an independent negative impact on progression and both overall and BCa-specific survival. When BCG was administered with maintenance, an independent protective effect on all outcome measures was observed.

3.4. Risk groups

Patients were divided into four risk groups for progression according to the number of adverse prognostic factors among age ≥70 yr, tumor size ≥3 cm, and presence of CIS. Progression rates at 10 yr were 17.3% (95% CI, 13.0–21.6), 25.3% (95% CI, 20.9–29.7), 32.2% (95% CI, 26.5–37.9), and 52.0% (95% CI, 37.7–66.3) for patients with zero, one, two, and three adverse factors, respectively (Fig. 5). Dividing patients into two risk groups for BCa-specific survival according to the presence of both age ≥70 yr and tumor

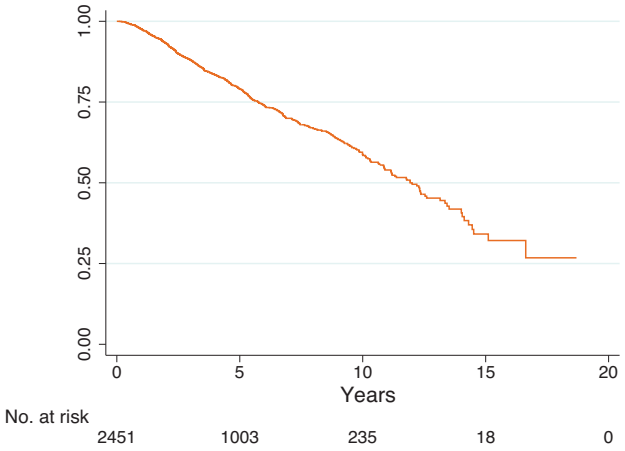

Fig. 3 – Kaplan-Meier curve for duration of overall survival.

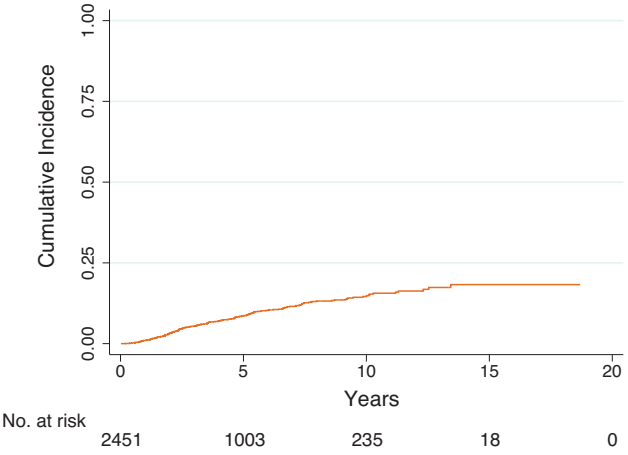

Fig. 4 – Cumulative incidence curve for time to bladder cancer death.

Table 4 – Univariable and multivariable analyses of time to recurrence

	Univariable		Multivariable	
Factor	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				NS
<70, ≥70	1.12 (1.00–1.25)	0.047		
Sex				NS
Male, female	1.07 (0.93–1.24)	0.32		
Tumor status				NS
Primary, recurrent	1.02 (0.85–1.22)	0.82		
No. of tumors				
Single, multiple	1.38 (1.23–1.56)	<0.001	1.28 (1.12–1.47)	<0.001
Tumor size, cm				
<3, ≥3	1.37 (1.19–1.58)	<0.001	1.33 (1.15–1.53)	<0.001
Concomitant CIS				NS
No, yes	1.24 (1.09–1.40)	0.001		
Maintenance BCG				
No, yes	0.60 (0.53–0.67)	<0.001	0.61 (0.53–0.70)	<0.001

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

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Table 5 – Univariable and multivariable analyses of time to progression

Factor	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				
<70, ≥70	1.44 (1.20–1.73)	<0.001	1.36 (1.11–1.67)	0.003
Sex				NS
Male, female	1.31 (1.05–1.64)	0.015		
Tumor status				NS
Primary, recurrent	1.15 (0.87–1.53)	0.32		
No. of tumors				NS
Single, multiple	1.04 (0.86–1.26)	0.66		
Tumor size, cm				
<3, ≥3	1.91 (1.55–2.34)	<0.001	1.85 (1.51–2.28)	<0.001
Concomitant CIS				
No, yes	1.41 (1.16–1.71)	0.001	1.46 (1.17–1.82)	0.001
Maintenance BCG				
No, yes	0.78 (0.64–0.94)	0.01	0.73 (0.59–0.90)	0.004

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

Table 6 – Univariable and multivariable analyses of duration of survival

Factor	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				
<70, ≥70	2.75 (2.33–3.24)	<0.001	2.45 (2.03–2.97)	<0.001
Sex				NS
Male, female	0.91 (0.74–1.13)	0.40		
Tumor status				NS
Primary, recurrent	1.46 (1.16–1.85)	0.002		
No. of tumors				NS
Single, multiple	1.04 (0.88–1.23)	0.65		
Tumor size, cm				
<3, ≥3	1.61 (1.34–1.94)	<0.001	1.52 (1.26–1.83)	<0.001
Concomitant CIS				NS
No, yes	1.08 (0.91–1.29)	0.38		
Maintenance BCG				
No, yes	0.76 (0.64–0.90)	0.001	0.74 (0.61–0.90)	0.002

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

Table 7 – Univariable and multivariable analyses of duration of bladder cancer–specific survival

Factor	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, yr				
<70, ≥70	2.03 (1.56–2.66)	<0.001	1.84 (1.36–2.49)	<0.001
Sex				NS
Male, female	1.10 (0.79–1.53)	0.56		
Tumor status				NS
Primary, recurrent	1.52 (1.04–2.22)	0.03		
No. of tumors				NS
Single, multiple	1.30 (0.98–1.73)	0.07		
Tumor size, cm				
<3, ≥3	2.34 (1.74–3.15)	<0.001	2.22 (1.65–2.99)	<0.001
Concomitant CIS				NS
No, yes	1.16 (0.87–1.55)	0.32		
Maintenance BCG				
No, yes	0.72 (0.54–0.96)	0.023	0.68 (0.50–0.93)	0.015

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma in situ; HR = hazard ratio; NS = excluded from final model because not statistically significant.

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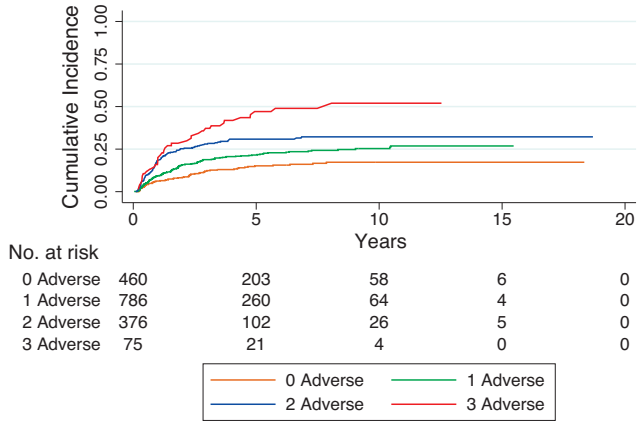

Fig. 5 – Cumulative incidence curves for time to progression according to the number of adverse prognostic factors for progression among patients ≥70 yr, tumor size ≥3 cm, and presence of carcinoma in situ.

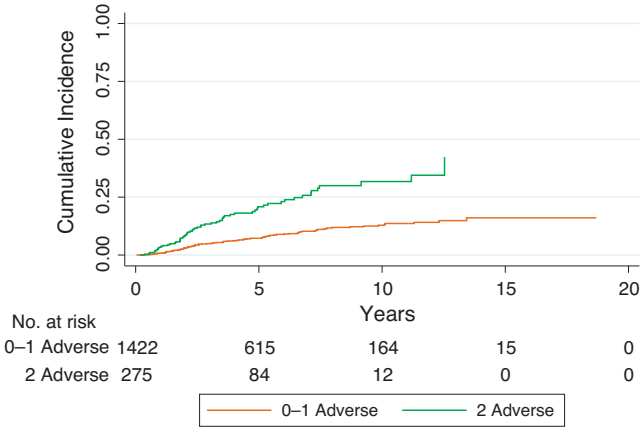

Fig. 6 – Cumulative incidence curves for bladder cancer death according to the presence of both age ≥70 yr and tumor size ≥3 cm.

≥3 cm, the BCa-specific death rates at 10 yr were 31.7% (95% CI, 21.0–42.4) for patients with both factors present, as opposed to 12.9% (95% CI, 10.0–15.8) for patients without both of these factors. Patients with none of these factors and those with one factor had similar CSS (Fig. 6).

4. Discussion

In the largest-ever reported series of T1G3 patients receiving BCG as primary intravesical treatment, with a median follow-up of 5.2 yr and a maximum follow-up of 18.7 yr, 19% of patients progressed and 9% died because of BCa, with 37% of progressing patients dying because of malignant disease or its treatment. Seventy-nine percent of patients retained their bladders. These favorable outcomes are comparable to recent smaller series of conservatively managed T1G3 patients [5,11,14] and confirm that most T1G3 tumors can be safely treated with first-line BCG. Maintenance BCG, documented in 38% of our patients, appeared to have a significant positive impact on all outcome measures. Recently, induction-only BCG was found to have high treatment success rates in a series of patients with high-risk NMIBC that was restaged with a second TUR [15]. Our results are the first in a large series of T1G3 patients to suggest that when BCG is chosen, it should be given with maintenance. This is not a randomized comparison, however, so definitive conclusions cannot be drawn.

Since NMIBC progressing to muscle-invasive disease is known to have an unfavorable prognosis even when treated with cystectomy [8], early identification of T1G3 patients who are destined to progress becomes of utmost importance. Apart from the benefit of BCG, a number of clinical and pathologic variables beyond grade and stage have long been recognized to affect the prognosis of NMIBC [16]. Concerning the T1G3 subcategory, treatment decision making has usually been based on a number of prognostic factors that have been assessed in small series or subgroups of this disease category [10–12,17]. Defining the impact of the most common clinicopathologic variables associated with T1G3 constituted the primary objective of this study.

The most striking finding was the independent prognostic value of tumor size on all outcome measures. The role of tumor size has been a matter of controversy in the recent literature. Some reports have recognized a tumor size >3 cm to be predictive of both recurrence and progression [12] or of recurrence only [18], while other reports have failed to show any clinical value [11,17]. Notably, in all the reported series, T1G3 patients were largely underrepresented and considerably fewer in number compared with the present series. In our analysis, age affected not only OS but also progression and BCa-specific death. This finding is in line with that of a large series of NMIBC patients treated with BCG that also included T1G3 [14], suggesting that BCG may be less effective in elderly patients [18].

Concomitant CIS, another important prognostic factor in this study, is a common finding in T1G3 tumors; however, its prevalence has been shown to vary considerably, from 10% in early series [12] up to 50% in more recent reports in which multiple biopsies [11] or restaging TUR [15] were routinely adopted. This situation may account for the changing view on the role of CIS, traditionally considered a major determinant of unfavorable outcomes [12,19], as a factor with little [15] or no [11] prognostic importance in T1G3 patients. In our series, the rate of concomitant CIS (24%) was in line with that of a subgroup of T1G3 patients from a recent prospective series [14]. In contrast to this latter series that included a large number of intermediate- to high-risk NMIBC patients in whom CIS was linked to only disease recurrence, we confirmed the role of CIS as an independent predictor of tumor progression in this cohort of high-grade T1 tumors. Similar to previous findings [15], tumor multiplicity predicted only disease recurrence. We failed to confirm that female gender has a negative impact on outcomes [11]. Recently, high-risk NMIBC progressing from lower-risk categories was found to be associated with significantly worse outcomes than primary high-risk NMIBC [20]. We were unable to show that T1G3 recurring from an NMIBC of lower stage and/or grade had an independent prognostic impact on outcomes as compared with primary T1G3.

Predicting the risk of disease progression or the probability of dying of disease in T1G3 patients based on

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their individual profile of prognostic factors remains a clinical challenge. Two previous studies have attempted to do so in large series of NMIBC patients mostly naive to intravesical therapies [12] or treated with BCG [13] in which clinical and pathologic variables were attributed a score that reflected their weight in predicting recurrence and progression. As for T1G3, the small number of T1G3 patients represents a significant limitation to the clinical value of both scoring systems. By dividing our cohort into risk groups based on the number of prognostic variables that were found to independently predict clinical outcomes ("adverse prognostic factors"), a progressive worsening of the most critical outcome measure (disease progression) was observed as the number of adverse factors that were simultaneously present in a patient increased. More specifically, the probability of progression at 10 yr increased from <17% in T1G3 patients with no adverse prognostic factors for progression to 25%, 32%, and 52% in T1G3 patients with one, two, or all three adverse prognostic factors, respectively. Age and size, but not CIS, were retained as independent predictors of CSS. The corresponding survival curves showed that patients ≥70 yr having a primary T1G3 tumor ≥3 cm are at significant risk of dying of BCa at 10 yr (31.7%), as opposed to the more promising 12.9% BCa-specific death rate in patients with either smaller tumors (<3 cm) or aged <70 yr.

This novel approach to predicting the prognosis of T1G3 tumors has significant clinical implications to guide clinicians in choosing the most appropriate treatment. The strength of our findings is supported by the fact that they are derived from a large, homogeneous series of T1G3 patients who were exposed to at least an induction course of BCG as their initial intravesical treatment. One criticism of the current study is related to the fact that our series is a retrospectively selected sample of favorable-prognosis T1G3 patients in whom BCG was more likely to be successful. Because of the retrospective design, the accuracy in reporting prognostic factors such as tumor size and CIS suffers from missing data and a lack of standardized assessment, there was no central pathology review, a second TUR was carried out in only 38% of the patients, and the assessment of BCG maintenance was not based on randomization. The validation of these findings in a prospective setting is therefore advisable.

5. Conclusions

T1G3 patients treated with at least an induction course of BCG show excellent long-term CSS, with 79% of patients retaining their bladders. The simultaneous presence of three adverse prognostic factors—age ≥70 yr, tumor size ≥3 cm, and concomitant CIS—identifies a subgroup of patients with an unfavorable outcome who should be considered for more aggressive treatment.

Author contributions: Paolo Gontero had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Gontero, Sylvester, Pisano, Joniau, Vander Eeckt, Serretta, Larré, Di Stasi, Van Rhijn, Witjes, Grotenhuis, Kiemeney, Colombo, Briganti, Babjuk, Malmström, Oderda, Irani, Malats, Baniel, Mano, Cai, Cha, Ardelt, Varkarakis, Bartoletti, Spahn, Johansson, Frea, Soukup, Xylinas, Dalbagni, Karnes, Shariat, Palou.
Analysis and interpretation of data: Gontero, Sylvester.
Drafting of the manuscript: Gontero.
Critical revision of the manuscript for important intellectual content: Sylvester, Joniau, Serretta, Di Stasi, Van Rhijn, Witjes, Grotenhuis, Kiemeney, Colombo, Briganti, Babjuk, Malmström, Irani, Malats, Baniel, Mano, Cai, Cha, Ardelt, Varkarakis, Bartoletti, Spahn, Johansson, Frea, Soukup, Xylinas, Dalbagni, Karnes, Shariat, Palou.
Statistical analysis: Sylvester.
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Supervision: Palou.
Other (specify): None.

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Appendix A. Supplementary data

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