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Prognosis of Primary Papillary Ta Grade 3 Bladder Cancer in the Non–muscle-invasive Spectrum

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Abstract

Background: Ta grade 3 (G3) non–muscle-invasive bladder cancer (NMIBC) is a relatively rare diagnosis with an ambiguous character owing to the presence of an aggressive G3 component together with the lower malignant potential of the Ta component. The European Association of Urology (EAU) NMIBC guidelines recently changed the risk stratification for Ta G3 from high risk to intermediate, high, or very high risk. However, prognostic studies on Ta G3 carcinomas are limited and inconclusive.

Objective: To evaluate the prognostic value of categorizing Ta G3 compared to Ta G2 and T1 G3 carcinomas.

Design, setting, and participants: Individual patient data for 5170 primary Ta–T1 bladder tumors from 17 hospitals were analyzed. Transurethral resection of the tumor was performed between 1990 and 2018.

Outcome measurements and statistical analysis: Time to recurrence and time to progression were analyzed using cumulative incidence functions, log-rank tests, and multivariable Cox-regression models with interaction terms stratified by institution.

Results and limitations: Ta G3 represented 7.5% (387/5170) of Ta–T1 carcinomas of which 42% were classified as intermediate risk. Time to recurrence did not differ between Ta G3 and Ta G2 (p = 0.9) or T1 G3 (p = 0.4). Progression at 5 yr occurred for 3.6% (95% confidence interval [CI] 2.7–4.8%) of Ta G2, 13% (95% CI 9.3–17%) of Ta G3, and 20% (95% CI 17–23%) of T1 G3 carcinomas. Time to progression for Ta G3 was shorter than for Ta G2 (p < 0.001) and longer than for T1 G3 (p = 0.002). Patients with Ta G3 NMIBC with concomitant carcinoma in situ (CIS) had worse prognosis and a similar time to progression as for patients with T1 G3 NMIBC with CIS (p = 0.5). Multivariable analyses for recurrence and progression showed similar results.

Conclusions: The prognosis of Ta G3 tumors in terms of progression appears to be in between that of Ta G2 and T1 G3. However, patients with Ta G3 NMIBC with concomitant CIS have worse prognosis that is comparable to that of T1 G3 with CIS. Our results support the recent EAU NMIBC guideline changes for more refined risk stratification of Ta G3 tumors because many of these patients have better prognosis than previously thought.

Patient summary: We used data from 17 centers in Europe and Canada to assess the prognosis for patients with stage Ta grade 3 (G3) non–muscle-invasive bladder cancer (NMIBC). Time to cancer progression for Ta G3 cancer differed from both Ta G2 and T1 G3 tumors. Our results support the recent change in the European Association of Urology guidelines for more refined risk stratification of Ta G3 NMIBC because many patients with this tumor have better prognosis than previously thought.

1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) is a heterogeneous disease, which is reflected in differences in recurrence and progression [1,2]. To determine the optimal treatment and surveillance for each tumor, it is important to know where the tumor lies in the spectrum of recurrence and progression. Clinical and pathological information can help to predict the risks of recurrence and progression. The main prognosticators for recurrence are tumor multiplicity, tumor size, and prior recurrence [2]. Tumor stage and histological grade are important prognostic factors for progression [1,2]. As grade correlates with stage, the majority of Ta carcinomas are of lower grade, whereas the majority of T1 carcinomas are of higher grade. Therefore, Ta grade 3 (G3) tumors are relatively rare and estimated to represent approximately 7% of all Ta carcinomas [3]. Although the noninvasive character (Ta component) suggests limited aggressiveness, the G3 morphology might indicate high risk of progression. Therefore, the interpretation of G3 disease confined to the urothelium is ambiguous: should it be considered as a relatively indolent disease with lower risk of progression or as an aggressive undifferentiated carcinoma? Some studies suggest that Ta G3 carcinomas are potentially

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as lethal as T1 carcinomas, while others suggest that Ta G3 carcinomas should not be considered as aggressive as T1 G3 carcinomas [3–5]. Notably, guidelines have changed their recommendations on the management of Ta G3 carcinomas over the years. According to the previous 2020 European Association of Urology (EAU) NMIBC guidelines, all Ta G3 carcinomas were classified as high risk and should be managed as T1 carcinomas [6]. However, in the 2021 EAU NMIBC guidelines, Ta G3 tumors can either be intermediate, high, or very high risk, depending on the presence of carcinoma in situ (CIS), the patient's age, and tumor size and multiplicity [7].

Since pathological diagnosis of a Ta G3 tumor is rather unusual, evaluation of the prognosis for patients with Ta G3 tumors is complicated. Moreover, assessment of the risk of progression in patients with Ta G3 is not straightforward because of differences in the presence of concomitant CIS, adjuvant treatment modalities, and follow-up duration. In the current study, we aimed to evaluate the prognosis of primary Ta G3 carcinomas, with or without CIS and/or Bacillus Calmette-Guérin (BCG) treatment, in comparison to primary Ta G2 and primary T1 G3 carcinomas within a large cohort of patients with Ta–T1 disease.

2. Patients and methods

2.1. Patients, treatment, and follow-up

In this multicenter study, we retrospectively identified 5295 patients with primary Ta–T1 NMIBC from 17 hospitals with their first diagnosis between 1990 and 2018. During quality control, we excluded 125 cases (2%) because of duplicate entries, <3 months of follow-up, missing grade or stage, CIS-only, muscle-invasive tumor at repeat transurethral resection of bladder tumor (TURBT), or death, progression, or cystectomy within 3 months [8]. Decisions on treatment, such as re-TURBT and/or adjuvant bladder instillations, and follow-up were made by the treating clinician. Patients were followed for both their first recurrence and progression. Tumor recurrence was defined as a pathologically confirmed Ta–T1 bladder tumor during follow-up [1,2]. Tumor progression was defined as the development of muscle-invasive and/or metastatic disease [1,2].

2.2. Statistical analysis

Descriptive statistics were summarized as the frequency and percentage for categorical data with 95% confidence intervals (CIs) and as the median and interquartile range (IQR) for continuous data. With the date of the primary TURBT as the starting point, time to recurrence and time to progression were estimated using cumulative incidence functions with death prior to an event as a competing risk. Patients with no events were censored at their date of last follow-up. Times to recurrence and progression were compared using a log-rank test stratified by institution. The curves were curtailed at 15 yr of follow-up.

Multivariable Cox proportional-hazard models for recurrence and progression stratified by institution were used to compare the prognosis between World Health Organization (WHO) 1973 grade categories in combination with stage, adjusting for sex (female vs male), age ($\leq$70 yr vs >70 yr), tumor multiplicity (solitary vs multiple), tumor size (<3 cm vs $\geq$3 cm), presence of CIS (no vs yes), single instillation of intravesical chemotherapy (no vs yes), intravesical chemotherapy induction (no vs yes), BCG induction (no vs yes), and re-TURBT (no vs yes). Terms were added to the Cox model to assess interaction between stage/grade categories and CIS. The heterogeneity of prognosis according to the presence of CIS was tested using Cochran's Q statistic and illustrated in a forest plot. Statistical analyses were performed using SPSS v26.0 (IBM, Armonk, NY, USA) and Stata v14.1 (StataCorp, College Station, TX, USA). Tests were two-sided and p values <0.05 were considered statistically significant.

Table 1 – Patient and tumor characteristics and treatment for every stage and grade combination among the 5170 patients with Ta–T1 primary bladder cancer included in the study

	Ta G1 (n = 1121)	Ta G2 (n = 1803)	Ta G3 (n = 387)	T1 G1 (n = 99)	T1 G2 (n = 734)	T1 G3 (n = 1026)
Median age, yr (IQR)	66 (58–75)	68 (61–76)	71 (63–78)	68 (61–75)	69 (61–77)	70 (63–78)
Multiple tumors, n (%)	284 (25)	569 (32)	178 (46)	35 (35)	273 (37)	431 (42)
Data missing	6	12	4	0	4	7
Tumor size $\geq$3 cm, n (%)	223 (20)	419 (23)	128 (33)	30 (30)	334 (46)	451 (44)
Data missing	47	114	39	2	40	56
Concomitant CIS, n (%)	10 (0.9)	63 (3.5)	79 (20)	1 (1.0)	57 (7.7)	265 (26)
Single instillation, n (%)	502 (45)	742 (41)	127 (33)	56 (57)	228 (31)	232 (23)
Data missing	105	153	54	1	57	142
Induction CTx, n (%)	136 (12)	315 (17)	57 (15)	11 (11)	121 (16)	78 (7.6)
Data missing	8	11	1	1	3	6
BCG induction, n (%)	26 (2.3)	238 (13)	220 (57)	2 (2.0)	302 (41)	748 (73)
Data missing	8	21	2	0	2	6
Re-TURBT, n (%)	64 (5.7)	235 (13)	137 (35)	9 (0.9)	266 (36)	624 (61)
Data missing	82	73	8	0	71	80
Prognostic risk group, n (%)[a]						
Low risk	893 (80)	0 (0)	0 (0)	31 (31)	0 (0)	0 (0)
Intermediate risk	218 (19)	1677 (93)	164 (42)	59 (60)	133 (18)	0 (0)
High risk	10 (0.9)	126 (7)	209 (54)	9 (9.1)	581 (79)	723 (70)
Very high risk	0 (0)	0 (0)	14 (3.6)	0 (0)	20 (2.7)	303 (30)

G = tumor grade according to the World Health Organization 1973 grading system; IQR = interquartile range; CIS = carcinoma in situ; CTx = chemotherapy; BCG = Bacillus Calmette-Guérin; Re-TURBT = repeat transurethral resection of bladder tumor.

[a] European Association of Urology 2021 prognostic risk factor groups for non–muscle-invasive bladder cancer [1,7].

3. Results

Baseline patient and tumor characteristics and treatment data for 5170 patients with primary Ta–T1 bladder cancer from 17 hospitals are presented in Table 1. Median follow-up for patients without recurrence or progression was 46.9 mo (IQR 23.2–84.9). A total of 387 patients with Ta G3 carcinomas were identified, corresponding to 7.5% of Ta–T1 tumors and 12% of Ta tumors. All 17 participating hospitals diagnosed Ta G3 tumor(s) during the study period. Recurrence was observed in 2239 patients and stage progression in 387 patients.

3.1. Prognosis of Ta G3 compared to Ta G2 and T1 G3 carcinomas

3.1.1. Time to recurrence

The recurrence risk at 1 yr was 23% (95% CI 18–27%) for Ta G3, 19% (95% CI 17–20%) for Ta G2, and 28% (95% CI 25–31%) for T1 G3 carcinomas. Recurrence at 5 yr was 47% (95% CI 41–52%) for Ta G3, 48% (95% CI 45–51%) for Ta G2, and 48% (95% CI 44–51%) for T1 G3 carcinomas.

Time to recurrence did not significantly differ between Ta G3 and Ta G2 (p = 0.9) or Ta G3 and T1 G3 (p = 0.4). Figure 1 shows the cumulative risk of recurrence for Ta G2, Ta G3, and T1 G3 carcinomas over time. On multivariable analysis, time to recurrence did not significantly differ between Ta G3 and Ta G2 carcinomas (hazard ratio [HR] 0.98, 95% CI 0.78–1.23; p = 0.9) or between Ta G3 and T1 G3 carcinomas (HR 1.06, 95% CI 0.85–1.34; p = 0.6; Table 2).

3.1.2. Time to progression

The risk of progression at 1 yr of follow-up was 0.4% (95% CI 0.2–0.8%) for Ta G2, 2.5% (95% CI 1.2–4.5%) for Ta G3, and 7.2% (95% CI 5.7–8.9%) for T1 G3. At 5 yr, the risk of progression was 3.6% (95% CI 2.7–4.8%) for Ta G2, 13% (95% CI 9.3–17%) for Ta G3, and 20% (95% CI 17–23%) for T1 G3 tumors.

Time to progression significantly differed between Ta G2 and Ta G3 (p < 0.001) and between Ta G3 and T1 G3 (p = 0.002). Figure 2 shows the cumulative risk of progression for Ta G2, Ta G3 and T1 G3 carcinomas over time. On multivariable analysis, time to progression was significantly shorter for Ta G3 versus Ta G2 (HR 0.31, 95% CI 0.18–0.52; p < 0.001) and longer for Ta G3 versus T1 G3 (HR 1.69, 95% CI 1.09–2.6; p = 0.018; Table 3).

Table 2 – Multivariable analysis of factors affecting time to recurrence for Ta G2, Ta G3, and T1 G3 carcinomas stratified by institution[a]

	HR (95% CI)	p value
Age (≤70 yr vs >70 yr)	**1.18 (1.05–1.35)**	**0.008**
Sex (female vs male)	0.96 (0.82–1.13)	0.6
Tumor multiplicity (solitary vs multiple)	**1.72 (1.51–1.96)**	**<0.001**
Tumor size (<3 cm vs ≥3 cm)	**1.35 (1.18–1.56)**	**<0.001**
Presence of CIS (no vs yes)	1.18 (0.95–1.46)	0.1
Single instillation (no vs yes)	**0.76 (0.63–0.91)**	**0.003**
Induction chemotherapy (no vs yes)	**0.76 (0.62–0.92)**	**0.006**
Induction BCG (no vs yes)	**0.65 (0.55–0.78)**	**<0.001**
Re-TURBT (no vs yes)	0.98 (0.82–1.18)	0.9
Ta G3 versus Ta G2	0.98 (0.78–1.23)	0.9
Ta G3 versus T1 G3	1.06 (0.85–1.34)	0.6

HR = hazard ratio; CI = confidence interval; CIS = carcinoma in situ; Re-TURBT = repeat transurethral resection of bladder tumor; BCG = Bacillus Calmette-Guérin; G = tumor grade according to the World Health Organization 1973 grading system.

[a] Recurrence did not significantly differ for Ta G3 versus Ta G2 or Ta G3 versus T1 G3 carcinomas.

3.1.2.1. Time to progression for patients with or without concomitant CIS.

In total, 63/1803 (3.5%) of patients with Ta G2 had concomitant CIS versus 79/387 (20%) patients with Ta G3 and 265/1026 (26%) patients with T1 G3 (Table 1). The risk of progression at 5 yr was 5.9% (95% CI 1.5–15%) for Ta G2 with CIS, 20% (95% CI 11–30%) for Ta G3 with CIS, and 22% (95% CI 16–28%) for T1 G3 with CIS. Time to progression significantly differed for Ta G2 and Ta G3 patients with concomitant CIS (p = 0.004) but not for Ta G3 and T1 G3 patients with concomitant CIS (p = 0.8). Similar results were found on multivariable analysis, with a significant difference for Ta G3 versus Ta G2 (HR 0.10, 95% CI 0.01–0.76; p = 0.027) but not between Ta G3 and T1 G3 (HR 1.29, 95% CI 0.58–2.90; p = 0.5).

The risk of progression at 5 yr was 3.5% (95% CI 2.6–4.7%) for Ta G2 without CIS, 11% (95% CI 7.2–16%) for Ta G3 with-

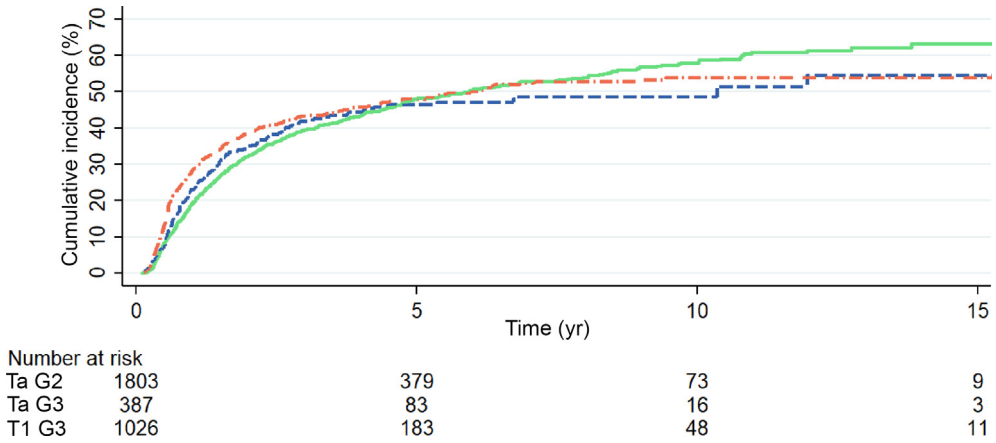

Fig. 1 – Cumulative incidence curves for recurrence of Ta G2 (solid green line), Ta G3 (dashed blue line) and T1 G3 (dashed red line) carcinomas. Time to recurrence did not significantly differ between Ta G2 and Ta G3 (p = 0.9) or T1 G3 (p = 0.4). G = tumor grade according to the World Health Organization 1973 grading system.

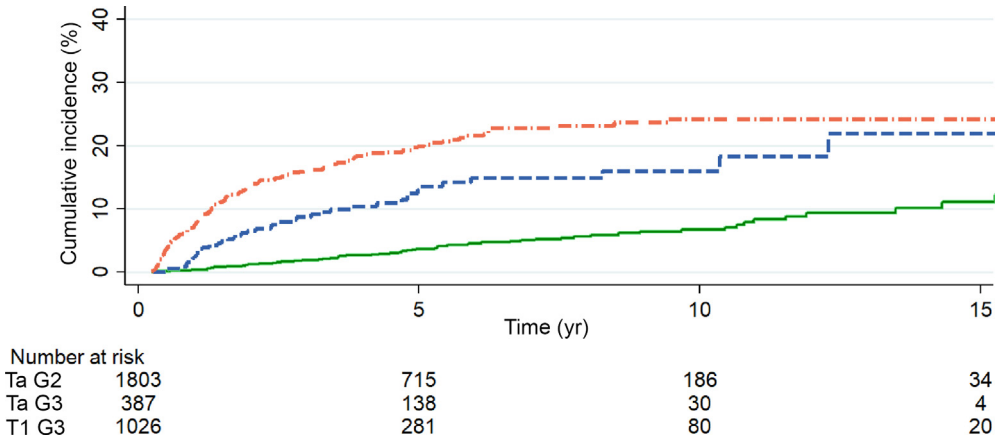

Fig. 2 – Cumulative incidence curves for progression of Ta G2 (solid green line), Ta G3 (dashed blue line), and T1 G3 (dashed red line) carcinomas. Time to progression was significantly shorter for Ta G3 in comparison to Ta G2 ($p < 0.001$) and longer in comparison to T1 G3 ($p = 0.002$). G = tumor grade according to the World Health Organization 1973 grading system.

Table 3 – Multivariable analysis of factors affecting time to progression for Ta G2, Ta G3, and T1 G3 carcinomas stratified by institution[a]

	HR (95% CI)	*p* value
Age (≤70 yr vs >70 yr)	**1.37 (1.01–1.86)**	**0.043**
Sex (female vs male)	0.92 (0.63–1.34)	0.7
Tumor multiplicity (solitary vs multiple)	**1.62 (1.19–2.19)**	**0.002**
Tumor size (<3 cm vs ≥3 cm)	**1.48 (1.08–2.02)**	**0.013**
Presence of CIS (no vs yes)	1.44 (0.98–2.13)	0.06
Single instillation (no vs yes)	0.70 (0.47–1.04)	0.08
Induction chemotherapy (no vs yes)	**0.53 (0.31–0.92)**	**0.02**
Induction BCG (no vs yes)	**0.59 (0.41–0.86)**	**0.006**
Re-TURBT (no vs yes)	1.07 (0.74–1.55)	0.7
Ta G3 versus Ta G2	**0.31 (0.18–0.52)**	**<0.001**
Ta G3 versus T1 G3	**1.69 (1.09–2.60)**	**0.018**

HR = hazard ratio; CI = confidence interval; CIS = carcinoma in situ; Re-TURBT = repeat transurethral resection of bladder tumor; BCG = bacillus Calmette-Guérin; G = tumor grade according to the World Health Organization 1973 grading system.

[a] Time to progression differed significantly for Ta G3 versus Ta G2 and Ta G3 versus T1 G3 carcinomas.

out CIS, and 19% (95% CI 16–23%) for T1 G3 without CIS. Among patients without concomitant CIS, time to progression was significantly shorter for Ta G3 than for Ta G2 ($p = 0.007$) and longer for Ta G3 than for T1 G3 ($p < 0.001$) carcinomas.

The results of the subgroup analysis were confirmed by a significant interaction in the Cox model between time to progression for Ta G3 and T1 G3 according to the presence of concomitant CIS ($p = 0.037$ for Cochran's *Q*; Supplementary Fig. 1).

3.1.2.2. Time to progression for patients with or without BCG induction. BCG induction therapy was given to 238/1803 (13%) patients with Ta G2 carcinomas, in comparison to 220/387 (57%) patients with Ta G3 and 748/1026 (73%) patients with T1 G3 carcinomas (Table 1). Stratified by the 2021 EAU NMIBC risk groups, 79/164 (48%) patients with intermediate-risk Ta G3 received BCG, versus 141/223 (63%) patients with high-/very high-risk Ta G3. In the group receiving BCG induction, the risk of progression at 5 yr was 7.4% (95% CI 4.0–12%) for Ta G2, 15% (95% CI 9.8–21%) for Ta G3, and 19% (95% CI 16–22%) for T1 G3. There was a significant difference in time to progression for patients who received BCG induction between Ta G2 and Ta G3 ($p = 0.002$). However, time to progression was not significantly different between Ta G3 and T1 G3 ($p = 0.17$). Similar results were found on multivariable analysis, with a significant difference between Ta G3 and Ta G2 (HR 0.24, 95% CI 0.09–0.61; $p = 0.003$) but not between Ta G3 and T1 G3 carcinomas (HR 1.50, 95% CI 0.89–2.53; $p = 0.13$).

In the group that did not receive BCG induction, the risk of progression at 5 yr was 3.0% (95% CI 2.1–4.2%) for Ta G2, 10% (95% CI 5.8–17%) for Ta G3, and 22% (95% CI 17–28%) for T1 G3. Time to progression for patients without BCG induction was significantly shorter for Ta G3 than for Ta G2 ($p = 0.007$) and longer than for T1 G3 ($p < 0.001$).

3.1.3. Time to progression for Ta G3 carcinomas by EAU NMIBC risk group

According to the risk groups in the 2021 EAU NMIBC guideline, 42% of Ta G3 tumors in the present study were considered intermediate risk, 54% were high risk, and 3.6% very high risk (Table 1), as opposed to the previous EAU NMIBC guideline, according to which all Ta G3 tumors were high risk by definition. Time to progression (Fig. 3) significantly differed between intermediate-risk Ta G3and high-risk/very high-risk Ta G3 ($p = 0.023$).

4. Discussion

Patients with Ta G3 carcinomas represent a small group within the NMIBC spectrum. The literature on oncological outcomes and prognostic factors for these patients is sparse and results are inconclusive or contradictory, probably because of the rarity of Ta G3 carcinomas, as well as differences in patient and/or tumor characteristics, treatment modalities, and follow-up duration. In our study we retrospectively identified 387 Ta G3 tumors, corresponding to 7.5% of 5170 Ta–T1 carcinomas, which is in line with a previous report [3]. From a clinical point of view, time to recurrence was similar between Ta G3 and Ta G2 and T1 G3 carcinomas. Furthermore, patients with Ta G3 carcinoma

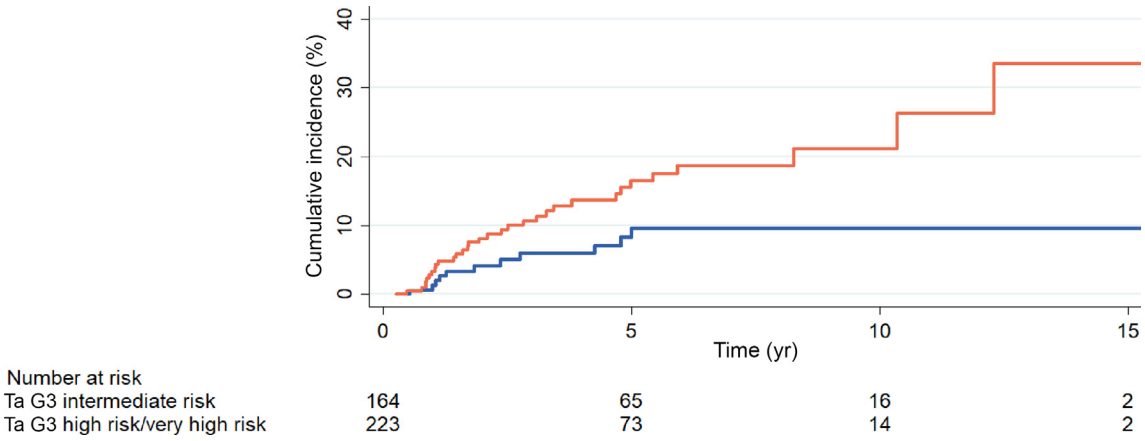

Fig. 3 – Cumulative incidence curves for progression of intermediate-risk Ta G3 (*n* = 164; blue line) and high-risk (*n* = 209)/very high-risk (*n* = 14) Ta G3 (red line) Ta G3 according to European Association of Urology risk groups for non–muscle-invasive bladder cancer. Time to progression significantly differed between the intermediate-risk and high-risk/very high-risk groups (*p* = 0.023). G = tumor grade according to the World Health Organization 1973 grading system.

had a longer time to progression in comparison to those with T1 G3 carcinoma, but a shorter time to progression in comparison to Ta G2. Subgroup analyses showed that patients with Ta G3 NMIBC with concomitant CIS had poorer prognosis and a similar time to progression to patients with T1 G3 with concomitant CIS. Finally, time to progression was significantly longer for intermediate-risk Ta G3 than for high-risk/very high-risk Ta G3.

The aim of grading and staging of bladder cancer is to provide the clinician with an indication of the clinical behavior to tailor treatment and follow-up strategies. Herr [4] reported that Ta G3 carcinomas are potentially as lethal as T1 carcinomas and suggested that aggressive treatment is warranted. However, the study comprised a select subgroup of patients with multiple and recurrent disease. Moreover, 72% had concurrent CIS lesions and all patients received BCG treatment [4]. A review by Sylvester et al. [3] of Ta G3 tumors using data from multiple studies with small numbers of patients found that the risk of progression to muscle-invasive disease was between 20% and 25%. The authors suggested treating and monitoring these patients as high-risk cases [3]. On the contrary, a contemporary larger study of 285 primary Ta G3 carcinomas suggested that Ta G3 without concomitant CIS should not be considered as aggressive as T1 G3 carcinoma [5]. The median follow-up was 44.5 mo and 70% of the patients received BCG induction therapy; no prognostic role for other tumor characteristics such as tumor size and multiplicity in patients with Ta G3 tumors was identified [5]. Our study showed that time to progression of Ta G3 significantly differed from both Ta G2 and T1 G3 carcinomas. Moreover, the distinction is clinically significant since the risk of progression at 5 yr was 3.6% for Ta G2, 13% for Ta G3, and 20% for T1 G3. However, for patients with concomitant CIS, which is regarded as a precursor lesion for the development for invasive disease, even though it is also a mucosa-confined lesion [9], Ta G3 was more like T1 G3 (risk of progression 20% vs 22% at 5 yr). For patients without CIS, Ta G3 had a longer time to progression than T1 G3 (risk of progression 11% vs 19% at 5 yr). It appears that prognosis in terms of progression is not solely based on the G3 or the Ta component and lies more or less in between the prognosis for each, with the exception of patients with concomitant CIS.

The risk of progression can be mitigated by differences in adjuvant treatment decisions, and it is known that adjuvant BCG treatment reduces the risk of progression [10]. Lebret et al. [11] suggested that the distinction between Ta and T1 tumors was irrelevant for patients with G3 disease treated with BCG because 25% (8/32) of patients in their series with Ta G3 tumors experienced progression. Comparable results were found in a more recent study with similar risks of progression for patients with primary high-grade (HG/G2–G3) Ta tumors (12/48, 25%) and T1 HG tumors (22/143, 23%) treated with BCG over median follow-up of 55.6 mo [12]. Concomitant CIS was observed in 14% of Ta HG tumors versus 19% of T1 HG tumors [12]. Our subgroup analyses also showed that if patients received BCG induction therapy, time to progression for Ta G3 was more similar to time to progression for T1 G3. The risk of progression at 5 yr was 15% for Ta G3 and 19% for T1 G3 after at least BCG induction. The higher proportion of patients with T1 G3 carcinomas who received BCG treatment (73% of T1 G3 vs 57% of Ta G3 cases) may explain these findings, as more T1 G3 carcinoma patients than Ta G3 patients may have a lower risk of progression. Another possible explanation is that patients with Ta G3 disease with more aggressive characteristics (such as concomitant CIS or larger tumors) were more likely to receive BCG, thereby inducing a selection bias. The likelihood of a selection bias when evaluating a BCG cohort—in ours and previous studies—is supported by the fact that 48% of patients with intermediate-risk Ta G3 received BCG induction, as opposed to 63% of patients with high-/very high-risk Ta G3. Among patients who did not receive BCG induction, Ta G3 was not as aggressive as T1 G3, since the risk of progression at 5 yr was 10% for Ta G3 and 22% for T1 G3.

According to the 2021 EAU NMIBC guideline changes, Ta G3 tumors can be intermediate, high, or very high risk, depending on the presence of CIS, age, and tumor size and multiplicity [7]. Our results support this more refined risk stratification of Ta G3 tumors because many of these patients were no longer classified as high risk but as inter-

mediate risk (42% of Ta G3 cases in our study) with significantly better prognosis than previously thought. In addition, we found that age as well as tumor size and multiplicity were significant prognosticators for progression. Interestingly, Bree et al. [13] advocated the opposite and suggested that all Ta HG tumors, regardless of the new EAU risk stratification, should be considered high risk because of similar risk of progression. However, they analyzed a subset of patients who received BCG, used only the WHO 2004 grading classification, excluded patients with concomitant CIS, and did not compare Ta HG with T1 HG.

Limitations of our study are the retrospective setting, in which differences in adjuvant treatment decisions could influence outcome. The criteria for BCG induction therapy were based on physician discretion and were probably not uniform, with changes in guidelines over the years another factor. Although we applied interaction terms in the Cox model, the subgroup analyses for CIS and induction BCG were still based on relatively small patient numbers. Moreover, while there is some evidence that re-TURBT in high-grade T1 disease may improve prognosis, its value for high-grade Ta disease is inconclusive [14–17]. In our study, re-TURBT was performed in 35% of Ta G3 and 61% of T1 G3 cases. Even though the benefit of re-TURBT is not crystal clear, it is possible that differences in the proportion of patients who underwent re-TURBT may have influenced the results. To overcome the above limitations, our results need prospective validation. Another limitation is the absence of central pathology review. Incorrect staging and grading can result in misclassification of Ta G3 tumors [18,19]. However, this is also true for daily clinical practice, since observer variability is a recognized and inevitable problem in the grading and staging of bladder tumors. A further limitation may be that the WHO 1973 grading system appears to be outdated and is used less frequently than the WHO 2004/2016 system. However, the EAU NMIBC guidelines still advise use of both the WHO 1973 and WHO 2004/2016 grading systems as they both provide prognostic value [1,7,8]. Moreover, we recently showed that the prognostic value of the WHO 1973 system was better for time to progression than the WHO 2004/2016 system and a multidisciplinary opinion paper by the International Society of Urological Pathology advocated the incorporation of WHO 1973 G3 in a future three-tier grading system [8,20]. A strength of our study is the large cohort of patients with primary NMIBC with individual patient data available.

5. Conclusions

Patients with Ta G3 carcinomas represent a small group within the NMIBC spectrum. Our study suggests that Ta G3 carcinomas should be considered as a separate group since time to progression of Ta G3 differed from both Ta G2 and T1 G3 and lay in between these two categories. However, patients with Ta G3 NMIBC with concomitant CIS have worse prognosis and a similar time to progression as for T1 G3 with CIS. Therefore, our results support the recent EAU NMIBC guideline changes on risk stratification, in which Ta G3 carcinomas may be classified as intermediate, high, or very high risk, since many of these patients have better prognosis than previously thought.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.01.004.

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