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T1 Substaging of Nonmuscle Invasive Bladder Cancer is Associated with bacillus Calmette-Guérin Failure and Improves Patient Stratification at Diagnosis

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Purpose: Currently, markers are lacking that can identify patients with high risk nonmuscle invasive bladder cancer who will fail bacillus Calmette-Guérin treatment. Therefore, we evaluated the prognostic value of T1 substaging in patients with primary high risk nonmuscle invasive bladder cancer.

Materials and Methods: Patients with primary high risk nonmuscle invasive bladder cancer who received ≥5 bacillus Calmette-Guérin induction instillations were included. All tumors were centrally reviewed, which included T1 substaging (microinvasion vs extensive invasion of the lamina propria). T1 patients were stratified into high risk or highest risk subgroups according to major urology guidelines. Primary end point was bacillus Calmette-Guérin failure, defined as development of a high grade recurrence. Secondary end points were high grade recurrence-free survival, defined as time from primary diagnosis to biopsy-proven high grade recurrence and progression-free survival. Time-to-event analyses were used to predict survival.

Results: A total of 264 patients with high risk nonmuscle invasive bladder cancer had tumor invasion of the lamina propria, of which 73% were classified as extensive invasion and 27% as microinvasion. Median followup was 68 months (IQR 43–98) and bacillus Calmette-Guérin failure was more common among patients with extensive vs microinvasive tumors (41% vs 21%, p=0.002). The 3-year high grade recurrence-free survival (defined as bacillus Calmette-Guerin failure) for patients with extensive vs microinvasive tumors was 64% vs 83% (p=0.004). In multivariate analysis, T1 substaging was an independent predictor of high grade recurrence-free survival (HR 3.2, p=0.005) and progression-free survival (HR 3.0, p=0.009). Patients with highest risk/microinvasive disease have an improved progression-free survival as compared to highest risk/T1e disease (p.adj=0.038).

Conclusions: T1 substaging provides important prognostic information on patients with primary high risk nonmuscle invasive bladder cancer treated with

Abbreviations and Acronyms

BCG = bacillus Calmette-Guérin
CIS = carcinoma in situ
DSS = disease-specific survival
HG = high grade
HG-RFS = high grade recurrence-free survival defined as BCG failure
HPF = (microscopic) high-powered field (objective 40×)
HR-NMIBC = high risk nonmuscle invasive bladder cancer
LVI = lymphovascular invasion
MIBC = muscle invasive bladder cancer
MM-VP = muscularis mucosae-vascular plexus
p.adj = adjusted p value
PFS = progression-free survival
RC = radical cystectomy
re-TURBT = repeated transurethral resection of bladder tumor
T1e = T1 extensive invasion of the lamina propria
T1m = T1 microinvasion of the lamina propria
TaHG = pTa high grade
TILs = tumor infiltrating lymphocytes
VH = variant histology

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bacillus Calmette-Guérin. The risk of bacillus Calmette-Guérin failure is higher in extensive vs microinvasive tumors. Substaging of T1 high risk nonmuscle invasive bladder cancer has the potential to guide treatment decisions on bacillus Calmette-Guérin vs alternative strategies at diagnosis.

Key Words: BCG vaccine; urinary bladder neoplasms; prognosis; carcinoma, transitional cell; neoplasm staging

NONMUSCLE invasive bladder cancer accounts for ~75% of newly diagnosed bladder cancer cases.[1] In case of lamina propria (T1) invasion, patients are at high risk for recurrent and progressive disease.[2,3] Patients with T1 high risk nonmuscle invasive bladder cancer are treated with transurethral resection of the bladder tumor and adjuvant intravesical bacillus Calmette-Guérin induction instillations.[4] In 30%-50% of patients with HR-NMIBC, BCG therapy fails and these patients develop high grade recurrences or progression to muscle invasive bladder cancer. In case of progression, neoadjuvant chemotherapy followed by radical cystectomy is the standard of care.[4] Despite treatment, 50%-70% of progressed patients die within 5 years after diagnosis.[5]

No markers are available to predict which patients will benefit from BCG treatment.[6] Repeated BCG instillations in nonresponders cause a delay in RC and a recent study showed that progression to MIBC is associated with worse overall survival compared to patients with primary MIBC at diagnosis.[5] Furthermore, the ongoing global BCG shortage demands selective use of limited resources. Thus, there is a clinical need for markers to identify patients who will benefit from BCG and patients who should receive other treatments.[7] To improve patient stratification, guidelines use the presence of aggressive clinicopathological features to identify a subgroup of HR-NMIBC patients at the highest risk of progression.[4,8] For these patients, both American and European guidelines strongly recommend to consider an immediate RC.[4,8] Despite this substratification of HR-NMIBC patients at the highest risk of progression, performing immediate RC in all of these patients results in overtreatment.[2,3]

Over the years, T1 substaging has been investigated as a prognostic tool in HR-NMIBC. Several methods have been described to assess depth and extent of tumor invasion into the lamina propria, which was associated with an increased risk of progression and death.[9–15] Some evidence showed that deeper invasion was also associated with recurrent disease.[16,17] T1 substaging is recommended for pathologists since the 2016 WHO classification.[18] However, the most optimal T1 substaging system remains to be defined.[19,20] T1 substaging by evaluation of muscularis mucosae-vascular plexus (T1a/b MM-VP) invasion is challenging due to difficult assessment of the MM-VP and T1 metric substaging by (optical) micrometers is impractical and time-consuming.[12,16] T1 microinvasive vs extensive substaging, in which tumor invasion should not exceed 1 HPF, is easy to use and proved more accurate than MM-VP substaging in earlier studies.[9,21]

Currently, it is unknown if T1 substaging is associated with treatment response in HR-NMIBC. Furthermore, it is unclear if T1 substaging has the potential to guide treatment decisions. Here, we investigated whether T1 HPF substaging was associated with BCG failure and if this substaging method can be used to improve patient stratification at diagnosis.

MATERIALS AND METHODS

Patients and Pathology

All patients with a primary diagnosis of HR-NMIBC (Tis or Ta/T1HG urothelial carcinoma), who underwent transurethral resection of the bladder tumor with or without re-TURBT and who received ≥5/6 BCG induction instillations were retrospectively included at 3 Dutch (Erasmus MC; Franciscus Gasthuis & Vlietland and Amphia) and 1 Norwegian hospital (Stavanger University Hospital) from 2000–2017. Additional information on patient inclusion can be found in the supplementary methods (https://www.jurology.com). The study was approved by the Erasmus MC Medical Ethics Committee (MEC-2018-1097). Hematoxylin and eosin (HE) slides from all primary tumors, re-TURBTs and recurrent tumors were centrally reviewed by a uropathologist who was blinded for clinical information. Assessment included T stage, tumor grade (WHO 1973/2016), presence of concomitant carcinoma in situ, T1 HPF substaging, lymphovascular invasion, variant histology, tumor infiltrating lymphocytes (TILs) and tumor necrosis (TN). T stage, tumor grade, CIS, LVI, VH and TN were scored according to standard WHO criteria.[18] T1 HPF substaging was performed as described previously (in this manuscript referred to as T1 substaging).[9] Briefly, if a single focus of lamina propria invasion with a maximum diameter of 0.5mm (ie 1 HPF, objective 40×) was observed, the tumor was defined as T1m. If tumor invasion was >0.5 mm or when more than 1 invasive focus was observed, the tumor was defined as T1e. TILs were scored as either absent/sparse vs marked within the tumor area.[22] Patients for whom T1 disease was confirmed in either the primary or re-TURBT specimen, and with identifiable detrusor, were included in the

Table 1. *Baseline study characteristics of 264 patients with primary T1 high risk nonmuscle invasive bladder cancer*

	No. (%)
Age at diagnosis (yrs):	
Median (IQR)	71 (66—77)
Gender:	
Male	215 (81)
Female	49 (19)
Substaging:	
T1 microinvasion	72 (27)
T1 extended invasion	192 (73)
Tumor grade (WHO 1973):	
2	6 (2)
3	258 (98)
Smoking:	
No	85 (32)
Yes/stopped	165 (63)
Missing	14 (5)
Concomitant CIS:	
No	205 (78)
Yes	59 (22)
Tumor focality:	
Unifocal	129 (49)
Multifocal	132 (50)
Missing	3 (1)
Tumor size (cm):	
<3	51 (19)
≥3	43 (16)
Missing	170 (65)
Tumor infiltrating lymphocytes:	
No	74 (28)
Yes	190 (72)
Tumor necrosis:	
No	244 (92)
Yes	20 (8)
Lymphovascular invasion:	
No	249 (94)
Yes	15 (6)
Variant histology:	
No	216 (82)
Diffuse	21 (8)
Micropapillary	12 (4)
Glandular	8 (3)
Squamous	4 (1.5)
Neuroendocrine	1 (0.5)
Sarcamatoid	1 (0.5)
Other	1 (0.5)
Re-TURBT performed:	
No	51 (19)
Yes	213 (81)
Risk classification at start of BCG:	
High risk	90 (34)
Highest risk	174 (66)
Adequate BCG:*	
No	27 (10)
Yes	237 (90)
Median BCG maintenance instillations (IQR)	12 (6—18)
BCG maintenance completed:	
1 Yr (≥3 cycles)	173 (66)
3 Yrs (≥9 cycles)	52 (20)
Median total BCG instillations (IQR)	18 (12—24)
BCG failure:†	
No	171 (65)
Yes	93 (35)
BCG failure (characteristics):	
1. MIBC as first recurrence	20 (8)
2. T1, grade 3/HG after BCG induction	19 (7)
3. HG recurrence after adequate BCG	54 (20)
Progression (MIBC, lymph node disease and metastases):	
No	201 (76)
Yes	63 (24)
Median time to progression (IQR)	18 (10—48)
Lymph node metastases:	
N0	247 (93)
N1-3	17 (6)
Distant metastases:	
M0	240 (91)
M1	24 (9)
Death from bladder cancer at last followup	41 (15)
Death of other cause:	67 (26)
Unknown	6 (2)
Alive	150 (57)
Median total mos followup (IQR)	68 (43—98)
Median followup BCG responders (IQR)	71 (55—99)
Median mos time to BCG failure (IQR)	7 (5—16)

Data in table 1 are also summarized in table 2, stratified by T1 substaging.
* Defined as ≥5/6 inductions + ≥2/3 maintenance instillations.
† Specified by major urology guidelines, which include patients with muscle invasive recurrences, T1HG after BCG induction and high grade recurrences after adequate BCG therapy.

analyses. After review, patients were stratified into a high risk or highest risk subgroup, according to the AUA/SUO nonmuscle invasive bladder cancer algorithm and EAU risk stratification.[4,8] Highest risk clinicopathological features were: T1G3/HG with concomitant CIS, lymphovascular invasion or VH, T1G3/HG with prostatic urethra involvement or multifocal and/or large (≥3 cm) T1G3/HG.[4,8]

Definitions, End Points and Statistics

Primary end point was BCG failure. BCG failure was defined as biopsy proven T1HG disease after ≥5 BCG induction instillations, HG disease after adequate BCG therapy or recurring muscle invasive disease.[4,8] Adequate BCG consists of ≥5/6 BCG induction instillations plus ≥2/3 BCG maintenance instillations.[23] Secondary end points were 3-year HG recurrence-free survival, progression-free survival and disease-specific survival. Time-to-recurrence was defined as the moment from primary T1 diagnosis until a biopsy-proven HG recurrence occurred (BCG failure). Three-year HG-RFS was selected because duration of the BCG regimen is 3 years.[4] Patients with only HG cytology or low grade (LG) biopsy recurrences were not considered BCG failures.[4,23] Further details on definitions and statistical analyses can be found in the supplementary methods (https://www.jurology.com).

RESULTS

Study Population

The study population consisted of 535 primary HR-NMIBC patients who received ≥5 BCG induction instillations. After pathology review, 26 cases were excluded because of the following reasons: up staging to muscle invasion in 4, downgrading to G2/LG in 5, and 17 cases had degraded hematoxylin and eosin slides and tissue blocks. Of the remaining 509 HR-NMIBC patients, 264 were included based on the presence of lamina propria invasion (T1) in the primary and/or re-TURBT specimen. Clinicopathological

Table 2. *Main study variables and outcome parameters stratified for T1 substaging in 72 patients with T1m vs 192 with T1e disease*

	T1m		T1e	
Median yrs age at diagnosis (IQR)	73 (64–80)		70 (63–75)	
No. female gender (%)	21	(29)	28	(15)
No. active smoker (%)	15	(20)	62	(33)
No. re-TURBT (%)	57	(79)	156	(81)
No. WHO grade 3 (%)	69	(96)	189	(98)
No. CIS (%)	11	(15)	48	(25)
No. multifocal (%)	34	(47)	98	(51)
No. variant histology (%)	3	(4)	45	(23)
No. TILs (%)	30	(42)	160	(83)
No. LVI (%)	2	(3)	13	(7)
No. tumor necrosis (%)	4	(6)	16	(8)
No. BCG failure (%)	15	(21)	78	(41)
No. progression (%)	9	(13)	54	(28)
No. death from BC (%)	6	(8)	35	(18)

characteristics of patients with T1 disease at diagnosis is depicted in table 1. Median age was 67 years (IQR 62–71), 81% of patients were male, and the median time from T1 diagnosis to BCG induction was 8 weeks. Median followup for the entire cohort was 70 months (IQR 48–90).

T1 Substaging is Associated with BCG Failure

T1 substaging was assessed in all tumors; T1m was present in 72 (27%) and T1e in 192 (73%). An overview of main study variables and outcome parameters according to T1 substaging is included in table 2. Patients with T1m vs T1e disease underwent the same number of re-TURBTs (79% vs 81%, p=0.731). Adequate BCG was administered in 237/264 (90%) patients. Reasons for not having received adequate BCG were incorrect planning/BCG intolerance in 7/264 (3%) and discontinuation of BCG treatment due to persistent ≥T1 disease following BCG induction in 20/264 (8%). Of the patients 93/321 developed BCG failure; 20 had a muscle invasive recurrence, 19 had recurrent T1HG disease after BCG induction and 54 patients had a HG recurrence after adequate BCG. The median time to BCG failure was 7 months (IQR 5–16 months). BCG failure occurred more often in patients with T1e HR-NMIBC than in patients with T1m disease: 41% vs 21%, p=0.002. Furthermore, patients with T1e disease had significantly worse 3-year HG-RFS than patients with T1m tumors: 64% vs 83% (p=0.004), worse PFS (p=0.014), but not DSS (p=0.08) (fig. 1, *A* to *C*). In multivariate analysis, T1 substaging was an independent predictor of HG-RFS (HR 3.2, p=0.005), PFS (HR 3.0, p=0.009) and DSS (HR 3.1, p=0.031) (HG-RFS in table 3; PFS and DSS in supplementary table 1, https://www.jurology.com).

Understaging of T1 HR-NMIBC may occur in case a re-TURBT is not performed. Hence, to exclude the possibility that understaging of T1 disease could have caused our observed association between T1e substaging and poor clinical outcome, the analyses were repeated in 213/264 patients who also received a re-TURBT. BCG failure occurred more often in patients with T1e vs T1m disease (39% vs 18%, p=0.005). In addition, the 3-year HG-RFS (p=0.011) and PFS (p=0.028) remained worse in patients with T1e tumors, in contrast to the DSS (p=0.12) (supplementary fig. 1, *A* to *C*, https://www.jurology.com). In multivariate analysis, T1 substaging remained an independent predictor of HG-RFS (HR 3.2, p=0.016) and PFS (HR 2.9, p=0.025), yet not for

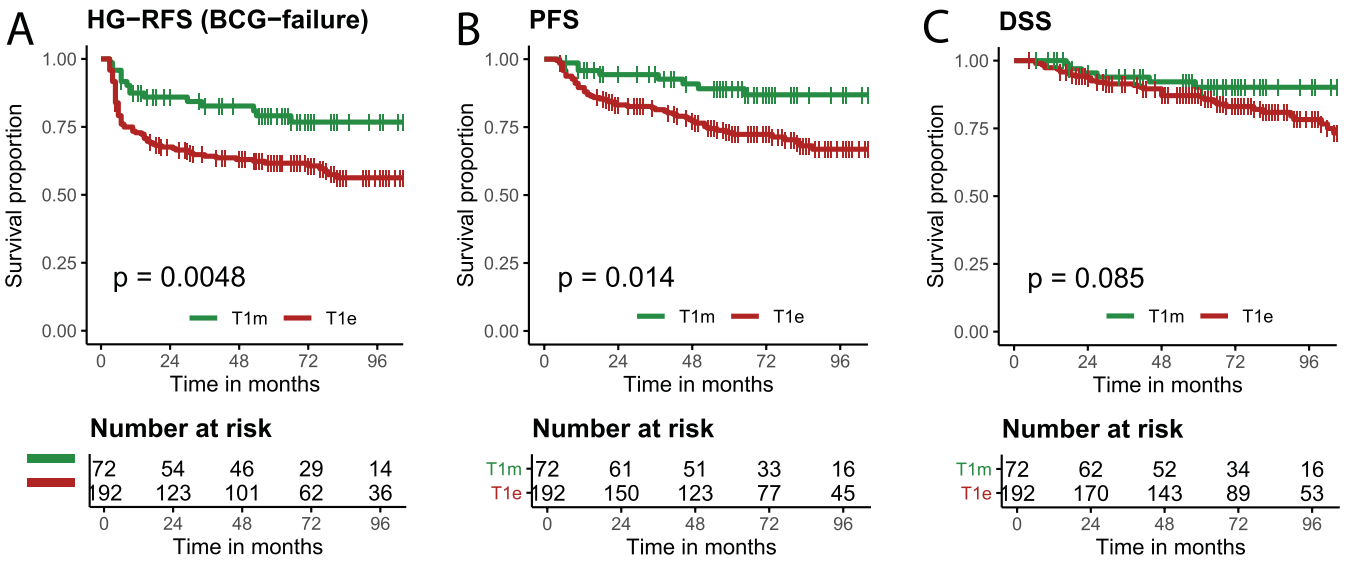

Figure 1. Kaplan-Meier estimates of clinical outcome in 264 patients with primary T1 high risk nonmuscle invasive bladder cancer stratified by T1 high-powered field substaging and with visible detrusor in specimen. *A*, HG-RFS (BCG failure). *B*, PFS. *C*, DSS. p Value is determined by log-rank test.

Table 3. *Univariate and multivariate Cox proportional hazard analyses of high grade recurrence-free survival in 264 primary T1 high risk nonmuscle invasive bladder cancer patients*

	HG-RFS Univariate		HG-RFS Multivariate	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age at diagnosis	1.0 (0.99–1.0)	0.255	1.0 (1.0–1.1)	0.047
Female gender	0.7 (0.4–1.3)	0.229	0.7 (0.3–1.6)	0.401
Smoking (active)	1.1 (0.7–1.7)	0.645	0.6 (0.3–1.1)	0.095
Pos re-TURBT	0.7 (0.4–1.0)	0.074	1.0 (0.5–2.1)	0.977
Substage T1e	2.2 (1.3–3.8)	0.006	3.2 (1.4–7.3)	0.005
Grade 3	2.3 (0.3–16)	0.409	0.7 (0.1–5.9)	0.803
Pos CIS	1.7 (1.1–2.7)	0.015	1.8 (0.96–3.4)	0.068
Size ≥3 cm	1.2 (0.6–2.4)	0.608	-	-
Multifocal	1.9 (1.3–2.9)	0.003	1.8 (0.98–3.3)	0.060
Pos variant histology	1.1 (0.7–1.9)	0.728	0.5 (0.2–1.2)	0.110
Pos TILs	1.1 (0.7–1.7)	0.727	0.8 (0.4–1.5)	0.438
Pos LVI	2.5 (1.3–4.9)	0.006	4.4 (2.1–9.4)	<0.001
Pos tumor necrosis	1.0 (0.5–2.2)	0.951	1.8 (0.7–4.5)	0.223

DSS (HR 2.8, p=0.08) (supplementary table 2, *A* and *B*, https://www.jurology.com). To confirm that the difference between T1m and T1e disease is not due to up staging of Ta to T1m disease at central review, we analyzed T1m/T1e vs TaHG disease. In total, 37 patients were down staged (T1 >Ta) and 12 patients were up staged (Ta >T1). Patients with Ta disease had a similar HG-RFS (p=0.592), PFS (p=0.828) and DSS (p=0.798) as patients with T1m disease (supplementary fig. 2, *A* to *C*, https://www.jurology.com). Importantly, patients with Ta disease had a favorable HG-RFS and PFS as compared to patients with T1e disease (both p <0.01). Lastly, we investigated whether T1e disease correlated with other characteristics. Patients with T1e tumors had more TILs (OR: 6.9, p <0.001) and VH (OR: 5.0, p=0.012) (supplementary table 3, https://www.jurology.com). Interestingly, all 12 patients with clinically unfavorable micropapillary VH had T1e disease.

T1 Substaging Improves Stratification of HR-NMIBC Patients

We determined if T1 substaging could improve accuracy of the current HR-NMIBC risk stratification for PFS. To this end, patients were stratified into the high risk (90, 34%) or highest risk (174, 66%) subgroup. Highest risk patients had a higher risk of developing progression than high risk patients (HR 2.1, p=0.001) and a worse PFS (fig. 2, *A*, p=0.017). Patients were stratified by T1 substaging and no difference was found in PFS within the high risk group (T1m vs T1e) (fig. 2, *B*, p.adj=0.754). Importantly, patients with highest risk/T1m disease had a comparable PFS to high risk patients (T1m/T1e)

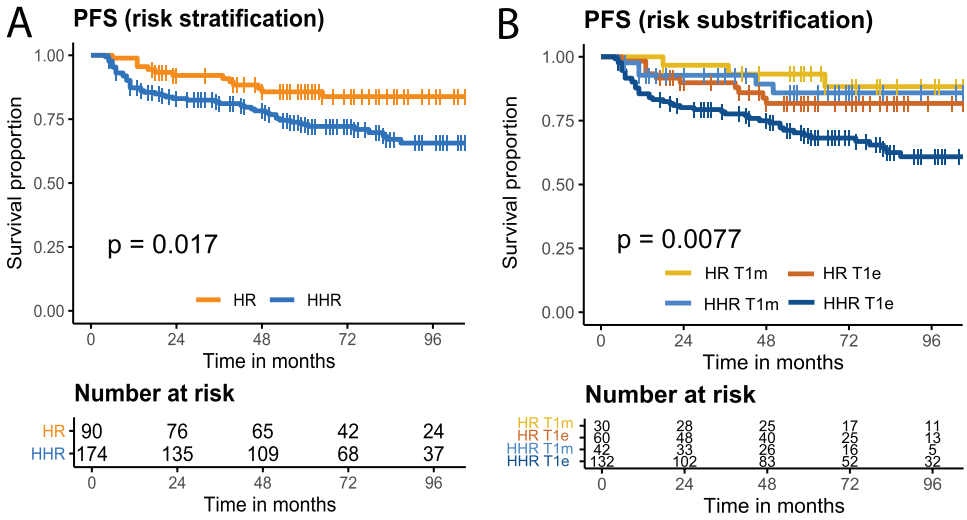

Figure 2. Kaplan-Meier estimates of progression-free survival according to substratification of T1 disease and T1 high-powered field substaging in 264 patients with primary T1 high risk nonmuscle invasive bladder cancer and with visible detrusor in specimen. *A*, PFS high risk vs highest risk subgroup. *B*, PFS high risk vs highest risk subgroups according to T1 substaging. *HR*, high risk patients. *HHR*, highest risk patients. p Value is determined by (pooled) log-rank test.

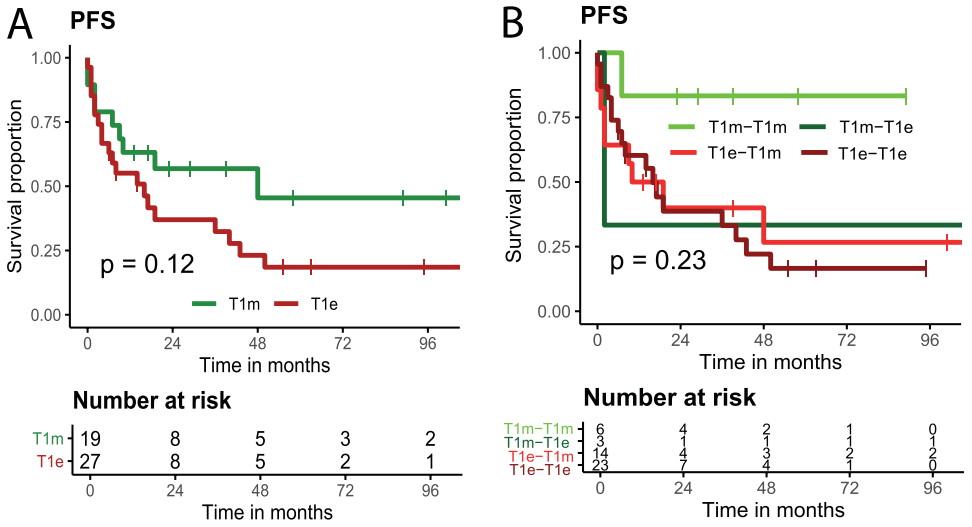

Figure 3. Kaplan-Meier estimates of progression-free survival in 46 patients with primary T1 high risk nonmuscle invasive bladder cancer who developed T1 recurrence, stratified by T1 high-powered field substaging and with visible detrusor in specimen. *A*, PFS of primary T1 patients with T1 recurrences stratified according to T1 substaging. *B*, PFS in primary-recurrent T1 combinations both stratified by T1 substaging. p Value is determined by (pooled) log-rank test.

(p.adj = 0.823). Patients with highest risk/T1e disease had a significantly worse PFS than highest risk/T1m disease (p.adj = 0.038).

Recurrent T1e Disease is Associated with a Very High Risk of Disease Progression

Lastly, we determined whether T1 substaging of recurrences was associated with PFS. Of 264 patients 84 developed nonmuscle invasive recurrences, ie Tis/Ta in 38 and T1 in 46. Patients with T1 recurrences had a worse PFS than patients with Ta/Tis recurrences (HR 4.1, p <0.001). Within the group of patients with T1 recurrences, 19/46 (41%) had T1m and 27/46 (59%) had T1e disease. Patients with a T1e recurrence had a nonsignificant increased risk of progression, compared to patients with a T1m recurrence (HR 1.8, p = 0.12, fig. 3, *A* and supplementary table 4, https://www.jurology.com). Patients with primary and recurrent T1e disease (T1e-T1e) had a worse PFS compared to patients with primary and recurrent T1m disease, but the difference was not statistically significant after multiple testing correction (T1m-T1m; p.adj = 0.19; fig. 3, *B*).

DISCUSSION

T1 substaging is easy to use and predictive of outcome in HR-NMIBC, but it is unknown whether T1 substaging improves patient stratification in the context of current guidelines.[4,8,17,21,24] Thus, we investigated if T1 substaging was associated with BCG failure and whether T1 substaging could be used as a tool to refine risk stratification in a cohort of BCG treated HR-NMIBC patients.

Patients with T1e HR-NMIBC were more likely to fail BCG, suggesting that they should be surveilled with vigilance. In a previous study (79 patients), T1e vs T1m was associated with a worse 5-year RFS (29% vs 64%), but treatment information was unavailable.[25] Rouprêt et al showed a worse RFS in T1b disease (ie below muscularis mucosae in T1 MM-VP substaging).[16] However, analysis did not include important predictive variables such as CIS, LVI and VH. Moreover, by selecting RFS as an end point, LG recurrences, which are not considered BCG failures, were included as events.[4] Therefore, we selected HG-RFS to define BCG failure as our primary end point, since a HG recurrence will affect therapeutic decision making.

In the real-world situation, it may occur that a re-TURBT is not performed, especially when detrusor muscle was visible. Most studies investigating T1 substaging showed an association with PFS and DSS. None of the 36 studies included in a recent meta-analysis took into account the impact of I) adequate BCG treatment, II) a re-TURBT before BCG induction, III) detrusor muscle in the transurethral resection/re-TURBT specimen to prevent the risk of understaging of T1 disease and IV) a comparison of T1m vs TaHG disease.[9,17,20,21,24,26] Therefore, we also performed 2 subanalyses in patients who received a re-TURBT and compared T1m vs TaHG disease to investigate up staging at centralized review.

Guidelines recommend considering an immediate RC in HR-NMIBC patients with highest risk features, but this may lead to overtreatment by RC.[4,8] In line with previous studies, we observed a higher progression rate in patients with highest risk prognostic factors.[2,3,27] To our knowledge, we are the first to demonstrate that T1 substaging

improves stratification of highest risk patients. Interestingly, highest risk/T1m patients had a risk of progression comparable to patients with high risk disease, indicating that a bladder sparing approach is worthwhile investigating. Hence, prospective trials are needed to assess the safety of bladder-sparing approaches in highest risk/T1m patients. Patients with highest risk/T1e disease had the worst outcome and for these patients immediate RCs should be considered.

T1e disease was associated with the presence of VH and TILs. T1e disease is more invasive than T1m disease, which may clarify the association with VH that is frequently found in advanced disease.[28] In contrast to T1e tumors, T1m disease rarely shows inflammatory features such as TILs.[20] In line with recent findings, we found that TILs were not associated with clinical outcome, possibly because not the overall presence, but specific T cell subsets predict BCG failure.[29]

The main limitation of this study is its retrospective design, which led to missing data on tumor size and therefore we had to exclude this parameter from our analyses. Nonetheless, in a multivariate analysis of 110 patients for whom tumor size was available, T1 substaging was predictive of HG-RFS, PFS and DSS (data not shown). Moreover, it is unlikely that highest risk patients were misclassified as high risk due to missing tumor size, as 51/110 (46%) of the patients with a reported size had a large tumor ($\geq$3 cm), which far exceeds the expected 18% patients with large tumors in European Organization for Research and Treatment of Cancer (EORTC) studies (ie reporting bias in favor of large tumors).[3] The prevalence of LVI varies considerably in literature, yet our cohort showed a relatively low prevalence (5%).[30] LVI scoring was based on hematoxylin and eosin slides, without the use of endothelial markers to facilitate diagnosis.[30] VH pointed towards a nonsignificant favorable outcome, yet results should be treated with caution due to a low number of cases, heterogeneity in variant types and selection bias, as T1 tumors with aggressive VH may have been treated with immediate RC instead of BCG therapy.[4,8] We selected T1 HPF substaging as it was shown that T1 metric substaging (using micrometers) is time-consuming and T1 MM-VP substaging is more difficult and less predictive than T1 HPF substaging.[10,12,21] Additionally, a low interobserver variability has been reported for T1 HPF substaging.[10] T1 HPF substaging is easy to use, can be implemented in every clinical practice without additional costs, is reproducible with a proven prognostic value and has a 100% evaluation rate.[9,10,12,15,21]

CONCLUSIONS

T1 HR-NMIBC patients with T1e tumors were at higher risk of BCG failure compared to both T1m and TaHG tumors, while T1m and TaHG tumors have a similar risk of BCG failure. T1 substaging has potential to guide treatment decisions on BCG vs alternative treatments. A prospective trial is needed to investigate whether bladder-sparing approaches are safe in patients with highest risk/T1m disease. In contrast, for patients with the highest risk/T1e disease early RC should be considered.

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