

The impact of tumor invasion to muscularis mucosae-vascular plexus on patient outcome in pT1 bladder urothelial carcinoma

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Summary *Objectives: T1 bladder cancer has a wide range of tumor behavior and lamina propria invasion depth has a high potential risk of disease progression. To evaluate the patient outcome according to the tumor invasion to the muscularis mucosae-vascular plexus (MM-VP) in pT1 bladder urothelial carcinoma (BUC).*

Materials and methods: This study is a retrospective analysis of patients consecutively recorded from 2007 to 2013. A total of 93 patients with a history of primary pT1 BUC and complete follow-up were included. We used a pathological sub-staging system according to the tumor invasion regarding the MM-VP: pT1a (invasion above MM-VP) and pT1b (MM-VP invasion). We evaluated recurrence-free survival (RFS), progression-free survival (PFS), disease-specific-survival (DSS) based on this sub-staging system.

Results: Pathological evaluation regarding the MM-VP invasion revealed 53 patients (57%) as pT1a BUC and 40 patients (43%) as pT1b BUC. The mean follow-up was 78.8 months. During the follow-up period; 60 patients (64.5%) had tumor recurrences, 32 patients (34.4%) had progression to invasive disease, 18 patients (19.4 %) died during follow-up related to the BUC. In 29 (54.7%) of pT1a and in 31(77.5%) of pT1b tumors, the recurrent disease was recorded during the follow-up period ($p = 0.023$). DSS rates at 5 years for pT1a and pT1b were 80.2% and 60.8%, respectively. PFS, RFS, and DSS rates were similar for pT1a/pT1b and did not reach statistical significance ($p > 0.05$).

Conclusions: Sub-staging of pT1 BUC according to the MM-VP invasion showed a limited impact on the outcome in our patient cohort. However, the presence of pT1b disease caused a significantly higher rate of recurrence.

KEY WORDS: T1 bladder cancer; Survival; Sub staging; Muscularis mucosae; Lamina propria depth.

Submitted 2 March 2020; Accepted 15 March 2020

INTRODUCTION

Bladder urothelial carcinoma (BUC) with pathological T1 stage represents a complex clinical dilemma due to its high rate of recurrence and progression. In fact, T1 BUC comprises a wide spectrum of different cases causing a huge clinical variability. At presentation, 75% of cases are non-muscle invasive bladder cancer (NMIBC), and approximately 70 % of patients present as pTa, 20 % as pT1, and 10 % with carcinoma in situ (CIS) lesions (1).

In T1 high-grade tumors, 1 and 5 years of disease-progression rates are 11.4% and 19.8%, respectively, and recurrence rates are between 21% to 53% despite intravesical treatments (2-7). This wide range in the recurrence and progression rates indicates the immense clinical variation of pT1 patients. Therefore, the overall management of T1 tumors is a challenge for urologists. How to differentiate the clinically aggressive pT1 tumors and how to provide the appropriate treatment strategy i.e. early cystectomy remains a difficult issue.

Tumor grade, stage, size of the tumor, multiplicity, and presence of CIS are known risk factors for recurrence and progression (1). Pathologic features like tumor growth pattern (papillary vs solid), tumor invasion pattern (broad vs trabecular vs infiltrative vs nested), and lymphovascular invasion were investigated to identify the variability of tumor behavior (3, 8, 9). Factors dependent on surgery i.e. re-TUR has shown the benefit of recurrence and progression-free survival (10). However, no strict criteria to predict prognosis in pT1 BUC have not been defined.

Due to a wide range of tumor behavior, there were many studies related to subclassification/sub-staging of T1 BUC since 1990 (11). These sub-staging systems were made according to the invasion of the muscularis mucosae-vascular plexus and invasion depth to lamina propria (11-13). Sub-staging according to MM-VP has been reported to be more superior than the invasion depth to lamina propria (14). However, the World Health Organization (WHO) (2004)/International Society of Urological Pathology (ISUP) and clinical guidelines do not recommend the sub-staging of T1 bladder cancer for the current daily practice (15, 16). Some reports showed that sub-staging is useful and predictive for progression of pT1 BUC (2, 12, 17, 18).

On the other hand, sub-staging is technically difficult and so far does not yield a clear prognostically significant separation on T1 bladder tumor (19, 20).

Therefore, new clinical series are required to evaluate the clinical utility of sub-staging in pT1 BUC.

In the present study, we evaluated the impact of the invasion of the muscularis mucosae-vascular plexus (MM-VP) on the clinical outcome of T1 BUC.

PATIENTS AND METHODS

We evaluated a total of 140 patients, who were referred to our center or diagnosed in our center with primary and pathologically reported pT1 BUC between 2007 to 2013. Data of the patients were recorded prospectively in our electronic database and reviewed retrospectively for the study. The study protocol was approved by the local ethics committee (Number: 27-2014). Due to the retrospective nature of the study, only written consent was obtained from the patients.

The original pathology slides of all pT1 bladder tumors were re-evaluated by two uropathologists (EB/FG) for stage and grade. We used the *World Health Organization 2004* classifications to review grade. After this re-evaluation, initial pathological staging was confirmed in 82% of patients. We further excluded patients with a history of previous bladder cancer diagnosis, an absence of muscular layer, an absence of a *repeated transurethral resection (Re-TUR)* after 3 to 6 weeks, the presence of concomitant CIS and with upstaged/downstaged tumors based on this pathological re-evaluation. A total of 14 patients were lost to follow-up and as a result, 93 patients were eligible for final analysis. All patients received intravesical BCG treatment with at least 1 year duration. The follow-up cystoscopies and imaging of the upper urinary tract are planned according to the recommendation of EAU 15. Recurrences were defined as pTa, pT1 and CIS tumors and progression was defined as pT2 or higher stage and/or development of metastasis. We used a pathological sub-staging system

Figure 1.
Microscopic apperance.

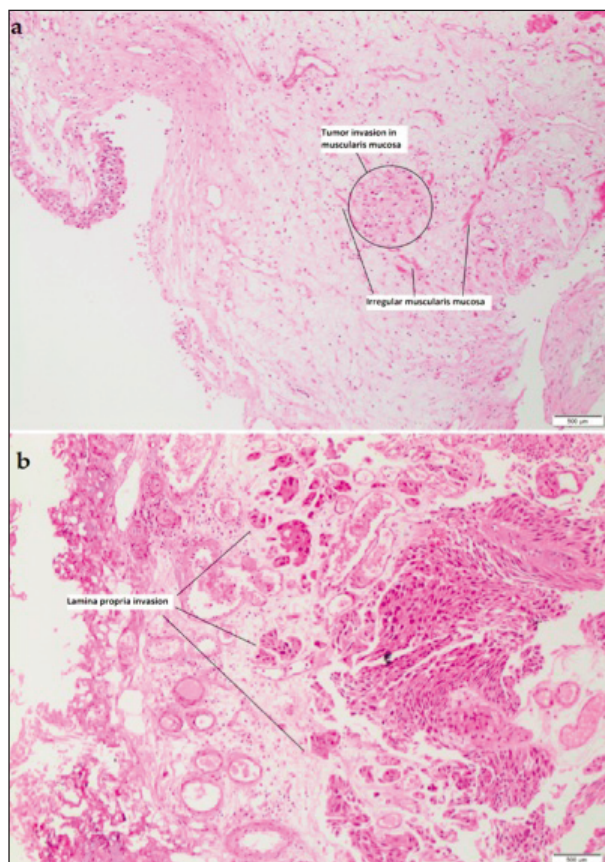


Table 1.
Characteristics of the patients based on the two sub-staging systems.

	T1a (n: 53)	T1b (n: 40)	P value
Gender (M/F)	42/11	31/9	0.839
Age (year)	64.8 (10.7)	64.3 (12.1)	0.834
Tumor size (< 3 cm/> 3 cm)	< 3 cm	28 (70%)	0.556
	> 3 cm	13 (25%)	
Tumor number	Solitary	25 (62%)	0.351
	Multiple	15 (37%)	
Grade (Low/high)	Low	15 (37%)	0.029
	High	25 (62%)	
Follow up time (month)	83.4 (61.7)	72.7 (46.7)	0.359
Recurrence (n)	29 (55%)	31 (77%)	0.023
Progression (n)	8 (15%)	10 (25%)	0.231
Time to recurrence(month)	17.3 (29.1)	13.2 (14.2)	0.491
Time to progression(month)	42.9 (49.8)	30.5 (38.4)	0.440

according to the tumor invasion regarding the MM-VP: T1a (invasion above MM-VP), T1b (MM-VP invasion) bladder cancer 12. Whenever muscularis mucosae-vascular plexus were not identified the presence of large blood vessels in the upper one-half of the lamina propria coursing parallel to the mucosa was used as a morphologic landmark of the level of the MM (Figure 1) (12). Statistical analyses were performed using the SPSS software version 20. The *Chi-square* test and Student t-test were used to compare in two groups. A p value of less than 0.05 was considered to show statistically significant results. For the multivariate analyses, the possible factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictor of tumor recurrence.

Hosmer-Lemeshow goodness of fit statistics was used to access model fit. Survival rate was analyzed using the Kaplan-Meier method and compared between the 2 groups with the log-rank test.

RESULTS

In total 73 male and 20 female patients were included in the study. Mean age at initial diagnosis was 64.6 (+/-11.3) years and mean follow up time was 78.8 (+/-58.4) months. Overall, radical cystectomy was performed in 14 patients (15.0%), and a total of 4 patients (4.3%) refused radical cystectomy due to surgical and/or risks of the anesthesia. These patients received radiotherapy plus chemotherapy due to the progression to muscle-invasive disease during this follow-up. Mean recurrence time was 15.2 ± 22.5 months and mean pro-

Table 2.
Logistic regression analysis to determine the independent predictors of recurrence.

Risk factors	Sig.	Exp (B)	95% C.I. for EXP (B)	
			Lower	Upper
Tumor number (solitary vs multiple)	0.068	3.117	0.918	10.585
Tumor grade (Low vs high)	0.000	12.643	3.680	43.432
Substage (T1a vs T1b)	0.026	4.219	1.191	14.947
Tumor size (< 3 cm vs > 3 cm)	0.006	7.325	1.758	30.525

gression time was 37.1 ± 44.5 months considering the all pT1 cases.

The results of the comparison of the sub-staging system are shown in Table 1. There were no statistically significant differences between the two groups according to age, gender, size, multiplicity, follow up time. The MM-VP invasion was not detected in 53 tumors (56.9%) and patients were classified as pT1a. The MM-VP invasion was present in 40 patients (43.0%) that we classified as pT1b. 25 (47.1%) for T1a vs. 15(37.5%) for T1b had multiple tumors ($p = 0.351$) (Table-1). 40% and 62% of patients were high grade BUC in T1a and T1b, respectively. There was a statistically significant difference between sub-staging according to pT1a/pT1b and the WHO 2004 grade system ($p = 0.003$).

In 29 (54.7%) of pT1a and in 31(77.5%) of pT1b tumors, the recurrent disease was recorded during the follow-up period. This difference was statistically significant ($p = 0.023$). In total, 18 patients (19.3%) progressed to further stages, and 12 patients (14%) died of BUC. There was no statistically significant difference between the two groups based on progression ($p: 0.231$). Stepwise multivariate regression analysis revealed that

the grade of bladder cancer, the pathological sub-staging system according to the tumor invasion regarding the MM-VP, and tumor size were the prominent factors affecting the recurrence of bladder cancer (Table 2). Mean recurrence and progression time based on pT1a/pT1b was $17.3 \pm 29.1/42.9 \pm 49.8$ months and $13.25 \pm 14.2/30.5 \pm 38.4$ months, respectively. Although mean recurrence time and progression time longer in pT1a group than pT1b group, it did not reach statistically significant differences between groups because of the small sample size ($p > 0.05$). Disease-specific survival (DSS) rates at 5 year for pT1a and pT1b were 80.2% and 60.8%, respectively. Progression free survival (PFS), recurrence free survival (RFS) and DSS rates were similar for pT1a/pT1b and did not reached statistically significance ($p > 0.05$) (Figures 2-3).

Figure 2. Kaplan-Meier estimates of disease specific survival according to invasion of MM-VP in primary T1 transitional cell carcinoma (TCC) of the bladder.

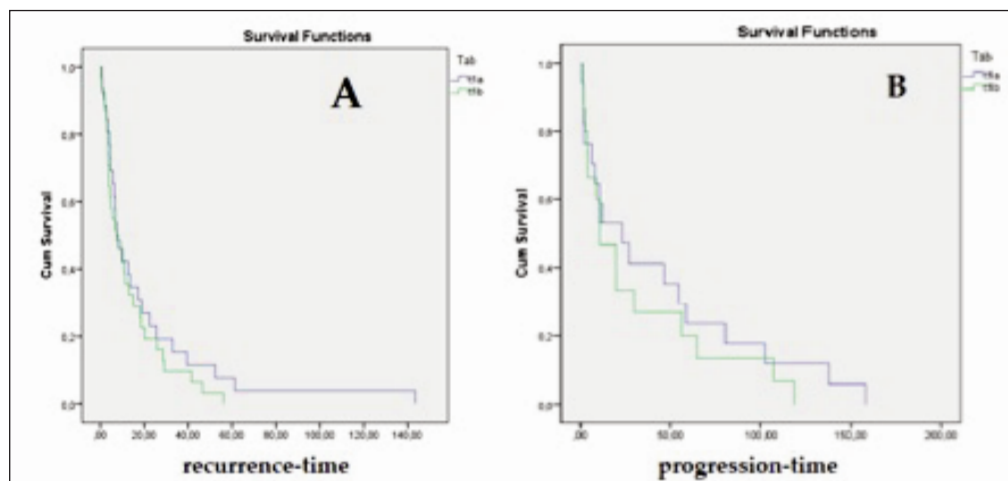
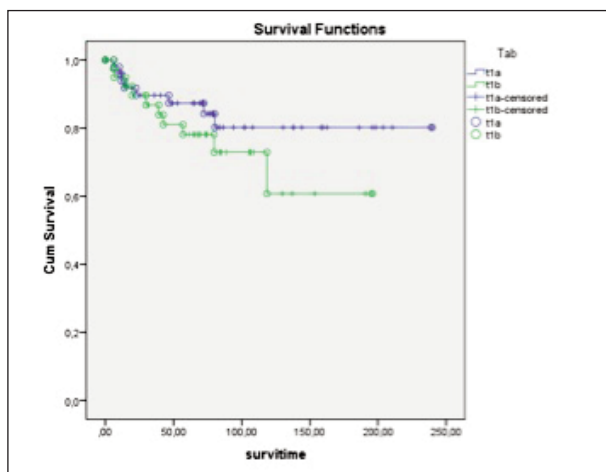


Figure 3. Kaplan-Meier estimates of recurrence-free (A) and progression-free (B) survival according to invasion of MM-VP in primary T1 transitional cell carcinoma (TCC) of the bladder. Whereas the recurrence-free interval and progression-free were similar for both groups.

DISCUSSION

In this study, sub-staging based on the invasion of MM-VP has no effect on progression and recurrence-free survival rates in patients with pT1 BUC. However, patients with pT1b have experienced a higher rate of recurrence during follow-up compared to pT1a group. Disease-specific survival was relatively longer in T1a however there was no statistically significant difference in Kaplan-Meier survival estimate analyses.

The management of T1 bladder cancer is a great challenge for urologists because of its wide and unpredictable range of clinical behavior. Therefore, pT1 disease represents a spectrum of different patients with different tumor behavior. Because of that, investigations have been focused on how to classify and predict the prognosis. Tumor grade, size, multiplicity, the presence of CIS, Re-TUR, lymphovascular invasion, BCG treatment, age, histotype and histological variants, tumor growth pattern, 3rd-month cystoscopy results, time to relapse are known parameters that affect prognosis (16). According to TNM classification, pT1 tumors recurrence and progression are not homogeneous some of them very aggressive that require early radical cystectomy. Remaining cases should need to follow up with cystoscopies after intravesical therapy. In the contrary, some patients who are treated more aggressively, in fact, may receive overtreatment. However, some

pT1 cases may progress to the inoperable stage under the conservative approach. So any improvement to the treatment strategy for the management of pT1 BUC is significant. This study proposes that invasion of MM-VP (pT1b) may be associated with a higher and earlier recurrence, although a statistical difference was not shown. Larger series with longer follow-up may show a remarkable distinction for pT1b sub-staging.

Different sub-staging systems have been studied in the literature recently (11, 13, 18). WHO (2004)/ISUP and clinical guidelines do not recommend the sub-staging of T1 bladder cancer yet (15, 16). Invasion of muscularis mucosae-vascular plexus invasion and depth and area to lamina propria invasion were most commonly applied sub-classification (12, 13). Orsola *et al.* substaged according to invasion superficial to, into or beyond the muscularis mucosae (13, 18). Holmang *et al.* substaged based on the absent or presence of MM-VP invasion (T1a/T1b) as in our study (21). Van Rhijn *et al.* investigated two sub-staging systems based on the extent of lamina propria involvement [T1-microinvasive (T1m) versus T1-extensive-invasive (T1e)] and invasion to MM-VP (12).

Amin *et al.* commented that the efficacy of the sub-staging of T1 bladder tumors is still controversial since lack of consensus to define the depth of invasion criteria and established clinical significance (22). The main problem may be the detection of MM-VP since it is not a constant layer, 6% to 75% of pathology specimen were not identified (23). Main studies of interest of MM invasion in T1 NMIBC with staging system and assessment rate were changes between 63% to 100% (22). In our study we planned to reclassify the T1 tumors based on presence or absence of MM-VP invasion and depth invasion to lamina propria: T1a (the tumor does not infiltrate the MM-VP) and T1b (the tumor infiltrates and/or invades the [MM-VP]), and T1m (micro-invasive- a single focus of lamina propria invasion with a maximum diameter of 0.5 mm) and T1e (extensive-invasive, > 0.5 mm). If the MM-VP was not seen at the invasion front, we classify pT1a or pT1b according to the depth of invasion into the lamina propria by looking at the MM-VP in tumor-free areas in the same or other TUR slides (12). We classified as T1a/b all the patients and classification according to lamina propria invasion depth (T1m/e) < 0.5 mm or > 0.5 mm was not feasible result in our study. Since only 6 of the patients classified as T1m BCa and all the others reported as T1eBCa so we could not analyze only the presence or absence of MM-VP invasion (T1a/T1b).

In literature the largest study was reported by Rouprêt *et al.* with 587 patients, that pT1a/b sub-staging based on the MM-VP invasion was very predictive of T1 NMIBC behavior as recurrence-free ($p = 0.03$) progression-free ($p < 0.001$) and cancer-specific survival ($p = 0.02$) in 35 months median follow up time (24). In our study, pT1a BUC a was a higher recurrence rate of 29(54.7%) than T1b 31(77.5%) ($p: 0.023$) but there were no statistically significant differences between two groups with Kaplan Meier analyses (log rank, p -value > 0.05) in 78.8 (58.4) months mean follow-up time.

Skoup *et al.* reported that T1 sub-staging was the independent prognostic factors for tumour progression ($p < 0.0001$), cancer-specific survival ($p = 0.0001$) and over-

all survival ($p = 0.0002$) (25). De-Marko *et al.* analyzed two sub-staging systems for T1 bladder cancers based on MM-VP invasion (T1a/b/c) and lamina propria invasion depth (T1m/e) two sub-staging system were not reached prognostic significance level for progression-free survival and disease-specific survival after 9.5 years of follow-up 20. Van Rhijn *et al.* evaluated MM-VP invasion depth as T1a/T1b/T1c and lamina propria invasion above or below to 0.5 mm (T1m/T1e), which show a higher predictive value for disease progression and disease-specific survival (12). Orsola *et al.* reported that sub-staging using depth of lamina propria invasion was significant for progression (13). In our study, there were no statistically significant differences between disease progression, recurrence and cancer-specific survival between the T1a/b sub-staging systems.

Patriarca *et al.* report that 1 mm invasion system predicted progression ($p < 0.04$) and Re-TUR increase the survival rate (26). They reclassified 1 mm sub-staging system in 100% of cases, the T1m/e in 100%, and the anatomy-based method (T1 a/b) in 72.3% of cases (26). In our study, we detected only 6 cases with T1m groups based on 0.5 mm threshold, so 1 mm of invasion threshold might be more useful results clinically. Finally, although the EORTC and CUETO risk scores improve risk stratification by quantifying recurrence and progression possibilities, their performance remains imperfect. These scoring systems may further improve with using this sub-staging system (27).

Our study has some limitations such as reporting the retrospective data of a relatively small patient group. Our results could not show statistically significant differences according to disease-specific survival and progression-free survival because of the small sample size.

CONCLUSIONS

Based on the findings presented in this study, sub-staging of T1 BUC according to the muscularis mucosae-vascular plexus invasion showed a limited impact on the outcome in our patient cohort. However, the presence of pT1b disease was found to be associated with significantly higher of recurrence.

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