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Impact of pT1a–pT1b Substaging on Recurrence and Progression in High-Grade T1 Bladder Cancer

Yüksek Dereceli T1 Mesane Kanserinde pT1a–pT1b Alt Evrelemenin Nüks ve Progresyon Üzerine Etkisi

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ABSTRACT

Objective: To evaluate the prognostic impact of pT1a–pT1b substaging on recurrence and progression in patients with high-grade T1 bladder cancer and to determine whether substaging serves as an independent predictor when assessed alongside established clinical and pathological risk factors.

Materials and Methods: This retrospective, single-center cohort study included patients diagnosed with high-grade pT1 urothelial carcinoma who underwent transurethral resection of a bladder tumor (TURBT) between January 2017 and March 2025. Cases with ≥pT2 disease, other malignancies, the Bacillus Calmette-Guérin (BCG) contraindications, treatment non-compliance, incomplete follow-up, or trigonal tumors with unreliable muscularis mucosa assessment were excluded. Demographic, clinical, pathological, and follow-up data were extracted from institutional records. Recurrence and progression were defined according to standard criteria. Substaging was performed by experienced uropathologists. Survival outcomes were analyzed using the Kaplan–Meier method, and independent predictors were identified by multivariate Cox regression.

Results: Of 152 patients, 110 (72.4%) were classified as pT1a and 42 (27.6%) as pT1b. Carcinoma in situ (CIS) and tumor size ≥3 cm were significantly more frequent in pT1b cases. In multivariate analysis, CIS and tumor size ≥3 cm were independent predictors of both recurrence and progression. Although pT1b substaging was associated with worse recurrence-free survival on Kaplan–Meier analysis, it was not an independent predictor of recurrence in the Cox model; however, it independently predicted progression (HR=3.38). Kaplan–Meier analyses also demonstrated significantly worse progression-free survival in the pT1b group.

Conclusion: pT1 substaging, particularly the identification of pT1b disease, provides meaningful prognostic information for progression in high-grade T1 bladder cancer. Integrating substaging with key pathological factors such as CIS and tumor size may improve individualized risk stratification and support early risk-adapted treatment decisions.

Keywords: bladder cancer, carcinoma in situ, progression, pT1 substaging, recurrence

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ÖZET

Amaç: Yüksek dereceli pT1 mesane kanserinde pT1a–pT1b alt evrelemenin nüks ve progresyon üzerindeki etkisini değerlendirmek ve alt evrelemenin bilinen klinik ve patolojik risk faktörleriyle birlikte bağımsız bir prognostik belirteç olarak değerini belirlemek.

Gereç ve Yöntemler: Bu retrospektif ve tek merkezli kohort çalışmasına Ocak 2017–Mart 2025 arasında transüretral mesane tümörü rezeksiyonu (TURBT) uygulanarak yüksek dereceli pT1 ürotelyal karsinom tanısı alan hastalar dâhil edildi. ≥pT2 evresi, ek malignite, Bacillus Calmette-Guérin (BCG) kontrendikasyonu, tedavi uyumsuzluğu, eksik takip verisi veya muskularis mukozanın güvenilir değerlendirilemediği trigon tümörleri dışlandı. Demografik, klinik, patolojik ve takip verileri kaydedildi. Nüks ve progresyon standart kriterlere göre tanımlandı. Alt evreleme deneyimli üropatologlar tarafından yapıldı. Sağkalım analizlerinde Kaplan–Meier yöntemi, bağımsız prediktörlerin belirlenmesinde çok değişkenli Cox regresyonu kullanıldı.

Bulgular: Toplam 152 hastanın 110'u (%72.4) pT1a, 42'si (%27.6) pT1b idi. pT1b olgularda eşlik eden karsinoma in situ (CIS) ve tümör boyutu ≥3 cm daha sık saptandı. Çok değişkenli analizde CIS ve tümör boyutu ≥3 cm hem nüks hem progresyon için bağımsız risk faktörleri olarak belirlendi. pT1b alt evresi yalnızca progresyon için bağımsız öngördürücüydü (HR=3.38); nüks için bağımsız anlamlılık göstermedi. Kaplan–Meier analizlerinde ise pT1b grubunda rekürrenssiz ve progresyonsuz sağkalım daha kötü bulundu.

Sonuç: pT1 alt evrelemesi, özellikle pT1b hastaların belirlenmesi, yüksek dereceli T1 mesane kanserinde progresyon riskinin öngörülmesinde değerli bir prognostik belirteçtir. Alt evrelemenin CIS ve tümör boyutu gibi güçlü patolojik parametrelerle birlikte değerlendirilmesi, bireyselleştirilmiş risk sınıflandırmasını geliştirebilir ve erken dönemde risk uyarlanmış tedavi kararlarını destekleyebilir.

Anahtar Kelimeler: karsinoma in situ, mesane kanseri, progresyon, pT1 substaging, rekürrens

INTRODUCTION

Bladder cancer is one of the predominant malignant diseases encountered in urological practice, and a considerable share of cases are detected while still confined to the non-muscle-invasive spectrum at initial presentation (1). Within this group, high-grade pT1 tumors hold particular importance in terms of their biological behavior and clinical course. These neoplasms, which show lamina propria invasion, have higher recurrence and progression rates compared to low-grade superficial tumors and therefore require a more aggressive follow-up and treatment approach (2). However, the heterogeneous nature of the pT1 stage has increasingly highlighted the need for additional parameters in risk classification in the current literature.

One of the most important approaches to improving the prognostic predictive power in pT1 tumors is the substaging system according to the extent to which the tumor infiltrates the lamina propria. Tumors showing more superficial invasion that do not reach the muscularis mucosa layer are defined as pT1a; tumors reaching this structure or showing deeper invasion are defined as pT1b (3). Since its introduction, the concept of substaging has been evaluated in numerous studies, and it has been suggested that tumors categorized as pT1b demonstrate a markedly higher likelihood of advancing to more invasive stages (4, 5). However, for these findings to be systematically reflected in clinical practice, clearer, reproducible data based on large patient series are required.

Studies investigating the prognostic value of the pT1a–pT1b distinction in the literature exhibit significant methodological heterogeneity. In particular, the variable histological detectability of the muscularis mucosa, differences in interpretation between pathology laboratories, and insufficient sample size in some series are the main factors limiting the generalizability of substaging results (6,7). Furthermore, the inability to clearly establish the relationship between substaging and strong prognostic indicators such as tumor size, multifocality, and accompanying carcinoma in situ (CIS) complicates the understanding of the biological diversity within the pT1 class (8).

Although intravesical the Bacillus Calmette-Guérin (BCG) therapy is the standard approach in guidelines for high-grade pT1 tumors, the clinical response shows significant heterogeneity (9). While early progression is observed in some pT1b patients, longer-term tumor control can be achieved in pT1a cases (10). This situation raises the question of the potential contribution of substaging, particularly in determining the timing of radical cystectomy. The objective of this investigation is to clarify the prognostic relevance of the pT1a–pT1b subdivision by assessing its association with recurrence and progression in high-grade pT1 disease, and to explore how this stratification interacts with established clinical and pathological risk determinants.

MATERIALS AND METHODS

The present study was designed as a retrospective observational study conducted at a single tertiary institution. The institutional ethics board of Gaziosmanpasa Training and Research Hospital reviewed and authorized the study protocol (Approval no.: 2025/167, Date: 2025-11-26), and all steps adhered to the ethical standards outlined in the Declaration of Helsinki. Participants provided written consent permitting the de-identified use of their clinical information for research purposes. A total of 152 consecutive patients who received transurethral resection of a bladder lesion (TUR-BT) at our institution between January 2017 and March 2025 and were subsequently confirmed to have high-grade pT1 urothelial carcinoma were identified and included in the final analysis. Patients with muscle-invasive bladder cancer (≥pT2), those with concomitant malignancies, those contraindicated for BCG therapy or non-compliant with treatment, and those followed up at other centers or with incomplete follow-up data were excluded from the study. Additionally, tumors located in the trigone, where the musculomucosal anatomy was not suitable for evaluation and substaging was not considered reliable, were not included in the analysis. Patients with adequate tissue sampling, evaluable lamina propria invasion depth, and at least one year of cystoscopic follow-up data after TUR-BT were included in the study.

At our center, intravesical BCG administration is the standard treatment protocol for high-risk pT1 bladder cancer. In routine practice, eligible patients are treated with BCG following TUR-BT, generally with an induction course and maintenance therapy when clinically appropriate and feasible. However, as this study is retrospective in nature, details of individual BCG induction or maintenance therapy were not included in the analysis; nevertheless, patients with BCG contraindications or those who did not adhere to treatment were excluded from the study population to ensure that all analyses were performed on a homogeneous group in terms of treatment. The demographic characteristics of the included patients (age, gender, body mass index), tumor-related clinical and pathological variables (tumor size, tumor number, presence of accompanying carcinoma in situ [CIS]), TUR-BT dates, and cystoscopy, urinary cytology, and radiological examination results during follow-up were obtained from the electronic data archive. Recurrence was defined as the reappearance of any Ta, T1, or CIS lesion during follow-up; progression was defined as advancement to muscle-invasive bladder cancer (≥pT2), development of metastatic disease, or death due to bladder cancer.

Tumors showing limited invasion that do not reach the muscularis mucosae fibers in the superficial zone of the lamina propria were classified as pT1a, whereas tumors with invasion reaching or exceeding the muscularis mucosae were classified as pT1b. All pathological specimens were reviewed by the same institutional pathology team experienced in uropathology, and difficult or equivocal cases were assessed by consensus within the team. In specimens where the muscularis mucosa could not be histologically identified, large submucosal vessels were used as anatomical reference points in accordance with the literature (11). All cases were followed up in accordance with international guidelines; cystoscopy was performed every three months for the first two years, every six months between the third and fifth years, and annually thereafter.

All statistical procedures were conducted using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as means accompanied by standard deviations, whereas categorical data were summarized as absolute frequencies and corresponding percentages. Comparisons between study groups were performed with the Chi-square test or Fisher's exact test for categorical variables. In contrast, continuous variables were evaluated using the Mann–Whitney U test due to non-parametric distribution characteristics. Recurrence-free survival (RFS) and progression-free survival (PFS) were defined as the time from the first TUR-BT to the first detected recurrence or progression event, respectively. For RFS analysis, recurrence (Ta, T1, or CIS) was considered an event, and patients without recurrence at the last follow-up were censored. For PFS analysis, progression to muscle-invasive disease (≥pT2), development of metastatic disease, or bladder cancer-specific death were defined as events, and patients without progression at last follow-up were censored. Censoring rates were calculated and reported for both survival outcomes. The mean recurrence-free and progression-free survival times were estimated using the Kaplan-Meier method and presented in a separate table. Recurrence-free and progression-free intervals were estimated through the Kaplan–Meier method, and survival distributions for the pT1a and pT1b groups were contrasted using the log-rank test. In addition to Kaplan–Meier survival analyses, cumulative hazard functions were estimated using the Nelson–Aalen method. Independent predictors of recurrence and progression were evaluated using multivariable Cox proportional hazards regression models including age, tumor size, concomitant carcinoma in situ, and pT1 substaging. All variables were entered simultaneously using the enter method, and results were reported as regression coefficients, hazard ratios with 95% confidence intervals, and p values. The proportional hazards assumption was assessed and no violation was observed. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

A total of 152 patients with pT1 bladder tumors were included in the study; 110 (72.4%) were classified as pT1a and 42 (27.6%) as pT1b. According to the baseline characteristics summarized in Table 1, the age of patients in the pT1b group was significantly higher than that in the pT1a group (72.5 ± 6.9 vs. 68.8 ± 8.8 years, p = 0.008). Body mass index distribution was similar between the two groups (26.6 ± 2.6 vs. 26.3 ± 3.3 kg/m^2, p = 0.485). No significant difference was found in gender distribution; males constituted the majority of patients in both groups (p = 0.592). Tumor size (≥3 cm rate) and multifocality frequency were similar between the pT1a and pT1b groups (27.3% vs 33.3%, p = 0.549; 23.6% vs 28.6%, p = 0.536, respectively). However, the presence of concomitant CIS was significantly higher in pT1b cases (28.6% vs. 9.1%, p = 0.004). Although the recurrence rate during follow-up was higher in pT1b patients (35.7% vs. 20.0%), this difference was borderline statistically significant (p = 0.057). The progression rate was significantly higher in the pT1b group (28.5% vs. 9.1%, p = 0.004) (Table 1).

Table 1. Baseline demographic and clinicopathological characteristics of the study cohort stratified by pT1 substaging (pT1a vs pT1b)

Variable	pT1a (n = 110)	pT1b (n = 42)	p-value
Age (years)*	68.8 ± 8.8	72.5 ± 6.86	***0.008***
BMI (kg/m^2)*	26.3 ± 3.3	26.6 ± 2.59	0.485
Gender, n (%) Male Female	 95 (86.3 %) 15 (13.7 %)	 38 (90.4 %) 4 (9.6 %)	0.592
Tumor size ≥3 cm, n (%)	30 (27.3 %)	14 (33.3 %)	0.549
Multifocality, n (%)	26 (23.6 %)	12 (28.6 %)	0.536
Concomitant CIS, n (%)	10 (9.1 %)	12 (28.6 %)	***0.004***
Recurrence, n (%)	22 (20 %)	15 (35.7%)	0.057
Progression, n (%)	10 (9.1 %)	12 (28.5 %)	***0.004***

*mean ± standard deviation, BMI: body mass index, CIS: Carcinoma in Situ, Statistically significant results (p < 0.05) are presented in bold italics.

In the multivariate Cox regression analysis, age and pT1 substaging did not emerge as independent predictors for recurrence ($p = 0.995$ and $p = 0.374$, respectively). In contrast, concomitant CIS ($p < 0.001$) and tumor size ≥3 cm ($p < 0.001$) were identified as strong and independent risk factors for recurrence. In the multivariate analysis for progression, the effect of age was again insignificant ($p = 0.887$), while pT1b substaging ($p = 0.011$), concomitant CIS ($p < 0.001$), and tumor size ≥3 cm ($p < 0.001$) were determined as independent predictors for progression (Table 2).

In the Kaplan–Meier analysis, recurrence-free survival differed significantly according to pT1 substaging (Figure 1A). The mean recurrence-free survival was 69.15 months in the pT1a group and 41.93 months in the pT1b group, with the difference reaching statistical significance on log-rank testing (log-rank $\chi^2 = 5.152$, $p = 0.023$). During the recurrence-free survival analysis, 115 patients (75.7%) were censored, while recurrence events occurred in 37 patients (24.3%). The cumulative hazard analysis demonstrated a progressively higher risk of recurrence in patients with pT1b tumors over time, as illustrated in Figure 1B.

Similarly, progression-free survival showed a clear separation between pT1a and pT1b tumors (Figure 2A). The mean progression-free survival was 73.46 months for pT1a cases and 45.16 months for pT1b cases, and this difference was statistically significant according to the log-rank test (log-rank $\chi^2 = 7.891$, $p = 0.005$). In the progression-free survival analysis, 130 patients (85.5%) were censored, whereas progression events were observed in 22 patients (14.5%). Consistent with these findings, cumulative hazard curves indicated a higher risk of progression in the pT1b group throughout follow-up (Figure 2B). Mean recurrence-free and progression-free survival times according to pT1 substaging are summarized in Table 3.

Table 2. Multivariate Cox regression analysis for predictors of recurrence and progression

Variable	Beta	Wald	HR (Exp(B))	95% CI	p-value
Recurrence					
Age (years)	0.001	0.000	1.00	0.95–1.05	0.995
pT1b vs pT1a	−0.357	0.790	0.70	0.32–1.54	0.374
Concomitant CIS	2.605	33.286	13.53	5.59–32.75	***<0.001***
Tumor size ≥3 cm	3.463	45.846	31.94	11.71–87.14	***<0.001***
Progression					
Age (years)	0.001	0.020	1.00	0.94–1.05	0.887
pT1b vs pT1a	1.217	6.420	3.38	1.32–8.65	***0.011***
Concomitant CIS	3.084	21.710	21.84	5.97–79.96	***<0.001***
Tumor size ≥3 cm	2.563	22.954	12.98	4.55–37.03	***<0.001***

CI: Confidence Interval, CIS: Carcinoma in Situ, HR: Hazard Ratio. Statistically significant results ($p < 0.05$) are presented in bold italics.

Table 3. Mean recurrence-free and progression-free survival times according to pT1 substaging

Survival outcome	pT1 substage	Mean survival (months)	Std. Error	95% Confidence Interval
Recurrence-free survival	pT1a	69.15	2.82	63.62–74.68
	pT1b	41.93	3.74	34.61–49.25
Progression-free survival	pT1a	73.46	3.22	67.14–79.77
	pT1b	45.16	3.51	38.28–52.04

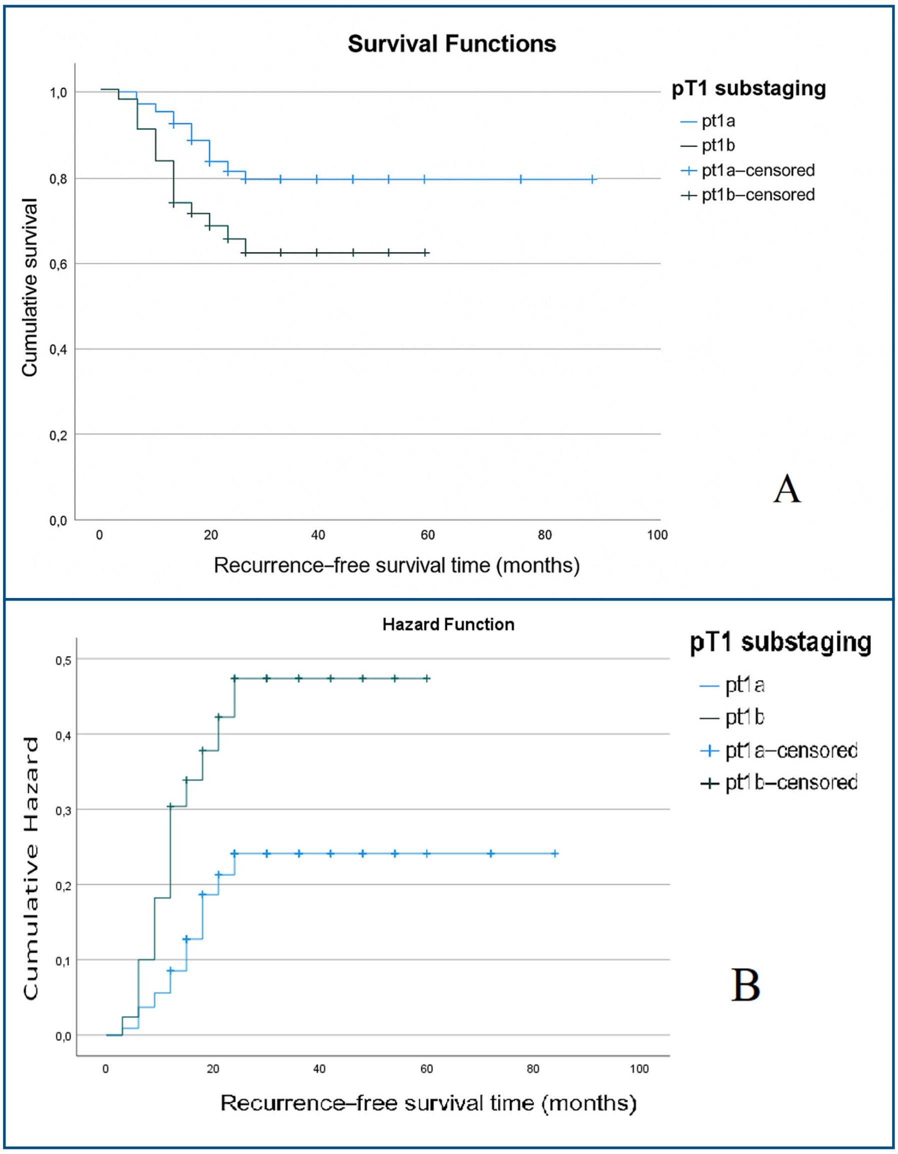


Figure 1A. Kaplan–Meier curves for recurrence-free survival stratified by pT1 substaging (pT1a vs pT1b).
1B. Cumulative hazard curves for recurrence according to pT1 substaging (Nelson–Aalen estimator).

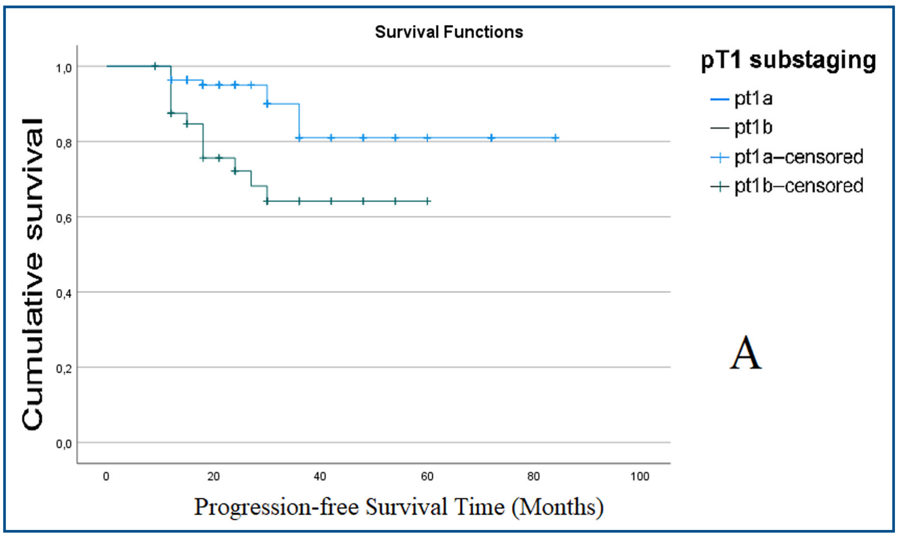
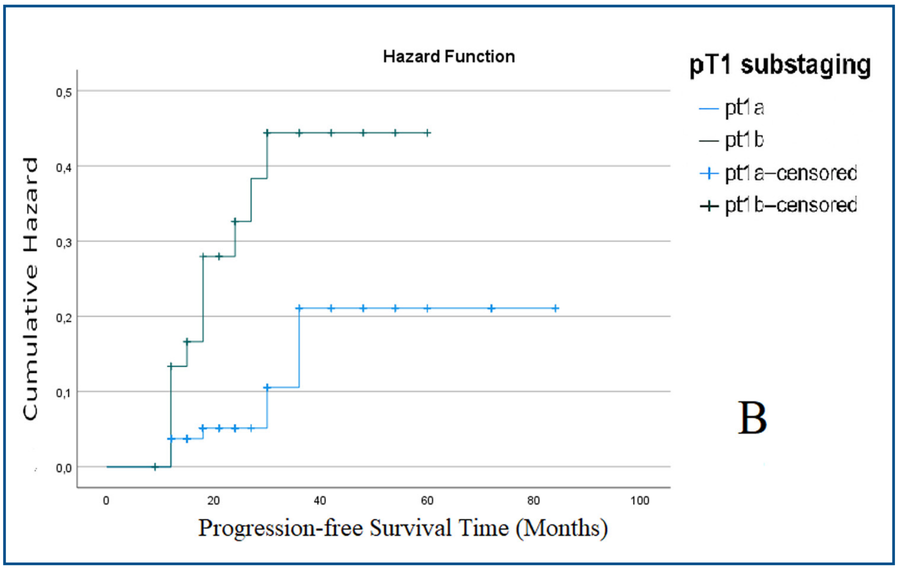


Figure 2A. Kaplan–Meier curves for progression-free survival stratified by pT1 substaging (pT1a vs pT1b).



2B. Cumulative hazard curves for progression according to pT1 substaging (Nelson–Aalen estimator).

DISCUSSION

This study demonstrated that dividing pT1 tumors into substages has a meaningful impact on predicting recurrence and progression, with pT1b lesions exhibiting a distinctly less favorable clinical trajectory. The results reinforce that substaging provides important prognostic insight in T1 bladder cancer. The markedly reduced progression-free survival observed in pT1b cases further suggests that the extent of lamina propria invasion serves as a key pathological marker of tumor aggressiveness.

This study is consistent with the literature in showing that the presence of accompanying CIS and a tumor size ≥3 cm are independent risk factors for both recurrence and progression. The fact that CIS is more frequently seen with pT1b tumors suggests that this group has a more biologically aggressive phenotype. Similarly, large tumor size may contribute to an increased risk of progression by reflecting high proliferative capacity and the possibility of more extensive submucosal spread. When translated into clinical practice, these findings highlight the necessity of considering tumor size and the presence of CIS in determining treatment strategy, independent of substaging (12,13). Although the literature presents variable outcomes regarding the prognostic relevance of pT1 substaging, numerous reports indicate that pT1b tumors exhibit higher progression rates (4,14). In our analysis, pT1b status similarly emerged as an independent determinant of progression, further supporting its incorporation into clinical risk-stratification models. Conversely, substaging did not independently predict recurrence, suggesting that recurrence may depend more heavily on multifactorial influences—such as the intravesical microenvironment, host immunologic activity, and the therapeutic effectiveness of BCG—rather than on the biological extent of invasion alone (15,16). Therefore, while substaging contributes meaningfully to predicting progression, its capacity to forecast recurrence appears relatively limited.

In Kaplan–Meier analyses, the distinct divergence of both recurrence-free and progression-free survival curves in the pT1a and pT1b groups is a valuable finding in terms of the clinical significance of pT1 substaging. In particular, the early separation of progression-free survival curves suggests a more aggressive course in pT1b patients, which may warrant more careful clinical evaluation and may be taken into account when discussing treatment intensity, including radical cystectomy, in selected cases (17,18). This situation demonstrates that substaging is a practical and applicable tool that contributes to the individualization of treatment strategies.

This study has certain limitations. Foremost, its retrospective design may have introduced potential selection bias and may have affected the overall reliability of the collected data. Heterogeneity in follow-up duration and limited follow-up data in some patients may also have influenced the timing of recurrence and progression. Although trigonal tumors were excluded because substaging assessment was considered unreliable in this location, depth assessment may still be challenging in some specimens in which the muscularis mucosae cannot be clearly identified. Although the use of submucosal vessels as an anatomical reference is an accepted method in the literature, interobserver variability cannot be completely eliminated. Furthermore, detailed patient-level information regarding BCG treatment, including induction schedule, maintenance course, completion status, and protocol variations, was not available for analysis, which may have influenced recurrence and progression rates. In addition, because of the retrospective design and incomplete treatment-record granularity in some screened cases, the exact number of patients who discontinued BCG therapy before study inclusion could not be determined reliably. Therefore, the independent effect of BCG exposure and discontinuation on oncological outcomes could not be assessed separately. Multicenter, prospective studies with standardized pathology assessment and detailed recording of BCG treatment protocols would help clarify the true prognostic value of substaging.

Despite these constraints, the study delivers coherent and clinically relevant evidence underscoring the prognostic value of pT1 substaging in high-grade pT1 bladder cancer. The findings suggest that the pT1b subgroup may follow a more biologically aggressive course and could be considered a higher-risk subgroup during individualized decision-making regarding follow-up and treatment strategy. Furthermore, the fact that tumor size and the presence of CIS are strong predictors of both recurrence and progression highlights the importance of considering these variables alongside pT1 substaging in clinical decision algorithms. These results indicate that pT1 tumors require more detailed risk classification and that the inclusion of substaging in routine pathological reporting could provide meaningful contributions to clinical management.

CONCLUSION

This study demonstrates that pT1a–pT1b substaging in high-grade pT1 bladder cancer has significant prognostic value, particularly in terms of progression. The significantly increased risk of progression in pT1b patients necessitates closer monitoring of this subgroup and, when necessary, more aggressive treatment strategies. In terms of recurrence, tumor size and the presence of accompanying CIS emerge as independent risk factors, and it is important to integrate these parameters with substaging into treatment decision-making processes. Overall, the results indicate that incorporating pT1 substaging into current risk-stratification systems for high-risk T1 bladder cancer could enhance clinical decision-making; nevertheless, confirmation through larger, well-designed prospective studies remains necessary.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The authors declare that they have no relevant financial interests.

Ethical Approval: This study was approved by the Gaziosmanpasa Training and Research Hospital Ethics Committee (Approval No: 2025/167, Date:2025-11-26). Research involving human participants and/or animals All analysis performed involving human participants were in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent: An informed consent was obtained from all the patients.

Author Contributions: MG: Conceptualization, review of articles, and manuscript preparation. AA: Data collection, manuscript writing/editing. MO: Analysis and interpretation of data, manuscript editing. HC: Manuscript writing/

editing. KM: Analysis and interpretation of data, manuscript writing/editing. BA: Contribution to data interpretation and critical revision of the manuscript. SB: Supervision of the manuscript.

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