Original Article

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Prognostic Values of Inflammatory Markers in Patients with High-grade Lamina Propria-invasive Bladder Cancer

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Abstract

Objective: In this study, we investigated the prognostic values of various pathological and inflammatory parameters in patients with high-grade lamina propria-invasive (T1G3) bladder cancer (BC).

Materials and Methods: Between 2006 and 2018, patients with pathological evaluation of T1G3 bladder urothelial carcinoma in our institution who did not meet the exclusion criteria were included in the study. Parameters such as gender, tumor diameter, tumor number, lamina propria invasion depth, presence of carcinoma *in situ*, presence of lymphovascular invasion (LVI), presence of variant histology, lymphocyte monocyte ratio (LMR), platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), and systemic inflammatory markers (SIM) were statistically analyzed.

Results: After the exclusion criteria were evaluated, 76 patients were included in the study from 157 patients. Recurrence was observed in 37 (48.68%) patients, and progression was observed in 21 (27.63%) patients. A significant relationship was discovered between LMR (p<0,001), PLR (p<0.004), NLR (p<0.002), tumor diameter (p<0.002), number of tumors (p<0,007), and SIM score (p<0,001) with the probability of recurrence. The probability of progression was associated with NLR (p<0.023), LVI (p<0.005), tumor diameter (p<0.012) and tumor number (p<0.001). A significant relationship was found between SIM (p<0.041) and recurrence-free survival. We found a significant relationship between LVI (p<0.022) and progression-free survival.

Conclusions: In this study, we found positive correlations between some inflammatory markers and recurrence/progression in patients with T1G3 BC. According to our study, inflammatory parameters such as NLR, PLR, LMR, and SIM score should be evaluated while investigating the possibility of recurrence/progression in patients with T1G3 BC.

Keywords: Non-muscle invasive bladder cancer, high-risk bladder cancer, neutrophil-lymphocyte ratio, platelet-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, progression, recurrence-free survival

Introduction

Bladder cancer (BC) is the tenth most frequent cancer in the world and the seventh most prevalent cancer among men. The global incidence for men is 9.5 per 100,000 population/year, whereas for women it is 2.4 (1). At the time of diagnosis, 75% of BCs are non-muscle invasive (NMIBC) (2). Progression occurs in approximately 1 in every 5 individuals with lamina propria-invasive high-grade (T1G3) BC (3,4). The European Organization for Research on Treatment of Cancer (EORTC) and the Spanish Urology Association for Oncological Treatment (CUETO) nomograms use a variety of clinical and pathological variables to predict recurrence and progression in NMIBC patients (5,6). Individuals with diverse pathologic data were classified as very high-risk according to the European Association of Urology (EAU) CIOMC 2014 recommendation. For patients in the very high-risk group, the guidelines suggest an early cystectomy (7). In BCG-refractory tumors, early cystectomy is also advised. Delayed early cystectomy is associated with lower cancer-specific survival (8). However, the presence of lymphovascular invasion (LVI) and the presence of some variant histology (VH), which are suggested for early cystectomy in the EAU NMIBC guidelines, were not validated in the nomograms. Among the inflammatory parameters in the literature, neutrophil lymphocyte ratio (NLR) (9), platelet lymphocyte ratio (PLR) (10) and systemic inflammatory markers (SIM) score (11) were associated with recurrence, and NLR (9), lymphocyte monocyte ratio (LMR) (12) and SIM score (11) were associated with progression.

Therefore, in this study, the prognostic value of pathological parameters such as depth of lamina propria invasion, VH, and

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LVI, as well as inflammatory parameters such as NLR, PLR, LMR, and SIM score were evaluated in patients with T1G3 BC.

Materials and Methods

Before starting the study, the approval of the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 77, date: 04.05.2023) was obtained.

Inclusion and Exclusion Criteria

This study included patients with T1G3 bladder urothelial carcinoma who underwent pathologic examinations at our institution department of pathology between 2006 and 2018. The patients' data were reviewed retrospectively. Patients who met any of the following criteria were excluded:

- Patients with a history of upper urinary tract urothelial carcinoma before bladder transurethral resection (TURB).

- Patients who underwent incomplete TURB due to tumor load, followed by an early cystectomy and/or chemotherapy and/or radiation.

- Patients with any clinical, pathologic, or prognostic data that were unknown.

- Patients with recurrent T1G3 BC whose included specimens were not the first T1G3 specimens.

- Patients who underwent early cystectomy for various reasons.

- Patients who underwent part of their diagnosis and treatment at an outside facility and did not fulfill any of the study exclusion criteria were included in the trial.

Patient Follow-up

Every three months, cystoscopy and urine cytology were performed in accordance with the EAU NMIBC guidelines (7). The same urologist conducted a re-TURB within 2 to 6 weeks of the original TURB (5). The re-TURB treatment involved removal of the bladder's hyperemic patch-like lesions and the tumor scar and baseline. According to the EAU guidelines, each patient underwent adjuvant and 1-3 years of maintenance intravesical BCG treatment (7).

Pathological Evaluation

All specimens were analyzed using standard pathologic methods and staged using the tumor, node, metastasis classification from 2009. Tumor grade was determined using the World Health Organization's 1973 methodology. The presence of tumor cells in an endothelium-covered area without a submuscular layer is termed as LVI (13). If micropapillary, neuroendocrine, sarcomatoid, nested, microcystic, or plasmacytoid variants were found, the histology was marked as VH (14).

The pathology materials of the patients included in the study were re-examined by a single uropathologist, and the depth of lamina-propria, existence of concurrent LVI, presence of concurrent carcinoma *in situ* (CIS), and presence of VH were all re-examined and included in the study.

The depth of the lamina-propria was evaluated by the invasion of the muscularis mucosa (MM) and vascular plexus (VP). Patients without MM-VP invasion were focally invaded, whereas those who did have MM-VP invasion were termed diffusely invaded.

Laboratory Evaluation

Blood samples taken one month before TURB were used to determine the patients' inflammatory parameters. Because the receiver operating characteristic (ROC) analysis was not significant, the NLR, PLR, and LMR threshold values in the reference publications were used. NLR, PLR, and LMR were divided into 2.5, 150, and 3.41, respectively, based on previously used thresholds in the literature (10,15,16). The SIM score was determined based on positive responses to these thresholds, with 1 point awarded for any value over the set threshold, and these values were then combined to yield a final score between 0 and 3.

Prognose Definition

The emergence of tumors at any time after TURB was classified as recurrence, and advancement was defined as the development of invasion to the muscle layer or clinical T3,4 and/or clinical N1,2 and/or clinical M1 disease in TURB performed after TURB.

The statistical impact of pathologic and clinical factors on the probability of recurrence, probability of progression, recurrence-free survival (RFS), and progression-free survival (PFS) were investigated. RFS was determined as the time to recurrence, whereas PFS was determined as the time to progression.

Statistical Analysis

SPSS version 17.0 software was used for statistical analysis. Histogram plots and the Kolmogorov-Smirnov test were used to assess the variables' conformance to the normal distribution. Descriptive analyses are presented using mean, standard deviation, and median values. The Pearson chi-square test was used to compare categorical variables. The Mann-Whitney U test was used to compare two groups of variables that were not normally distributed (non-parametric). Because the ROC analysis for LMR, PLR, and NLR cut off values were not significant, meta-analysis cut-off values were used as a basis (11). The variables influencing recurrence and progression were determined using Kaplan-Meier analysis, and the effect coefficients were discovered using Cox regression analysis for significant variables. P-values less than 0.05 were considered statistically significant.

Results

Seventy-six patients with T1G3 BC were included in the study between 2006 and 2018. Eleven (14.47%) patients were female and 65 (85.53%) were male. The mean age of patients was 66.28±9.58. The median duration of follow-up was 43.89±31.54 months, the median RFS was 10.16±14.18 months, and the median PFS was 16.10±12.28 months. Recurrence occurred in 37 individuals (48.68%) and progression occurred in 21 patients (27.63%) (Table 1).

A significant relationship was discovered between LMR ($p<0.001$), PLR ($p<0.004$), NLR ($p<0.002$), tumor diameter ($p<0.002$), number of tumors ($p<0.007$), and SIM score ($p<0.001$) with the probability of recurrence. Patients with LMR <3.41, PLR ≥150, NLR ≥2.5, tumor diameter ≥3, tumor number

≥8, and SIM score 3 had a greater recurrence rate (Table 2). When the probability of progression was compared, NLR (p<0.023), LVI (p<0.005), tumor diameter (p<0.012), and tumor number (p<0.001) were all substantially linked with progression. Patients with NLR ≥2.5, presence of LVI, tumor diameter ≥3, and tumor number ≥8 had a greater rate of progression (Table 2). Factors influencing PFS were investigated. Accordingly, a significant relationship was found between the SIM score (p<0.041) and RFS. The recurrence rate was also found to be high in patients with high SIM scores (Table 3). The factors that influence PFS were investigated, and a significant relationship between LVI (p<0.041) and PFS was found (Table 3). It was determined that the presence of LVI adversely affected progression. The presence of LVI increased progression by 0.288 times (95% confidence interval: 0.090-0.915).

Table 1. Demographics and characteristics of the study population

		n	%
LMR	<3.41	35	(46.05)
	≥3.41	41	(53.95)
PLR	<150	51	(67.11)
	≥150	25	(32.89)
NLR	<2.5	34	(44.74)
	≥2.5	42	(55.26)
Focal/deep submucosal invasion	Focal	31	(40.79)
	Deep	45	(59.21)
Presence of the CIS	Yes	37	(48.68)
	No	39	(51.32)
Presence of lymphovascular invasion	Yes	9	(11.84)
	No	67	(88.16)
Gender	Man	65	(85.53)
	Woman	11	(14.47)
Age	<60	15	(19.74)
	60-70	32	(42.11)
	>70	29	(38.16)
Tumour diameter (cm)	<3	43	(56.58)
	≥3	33	(43.42)
Tumour number	1	34	(44.74)
	2-7	31	(40.79)
	≥8	11	(14.47)
SIM score	0.00	26	(34.21)
	1.00	15	(19.74)
	2.00	18	(23.68)
	3.00	17	(22.37)
Presence of variant histology	Yes	9	(11.84)
	No	67	(88.16)
Relapse	Yes	37	(48.68)
	No	39	(51.32)
Progression	Yes	21	(27.63)
	No	55	(72.37)
Follow-up time (month)		43.89±31.54	36.00 (3.00-150.00)
Recurrence time (month)		10.16±14.18	6.00 (1.00-84.00)
Progression time (month)		16.10±12.28	12.00 (2.00-45.00)

LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, CIS: Carcinoma *in situ*, SIM: Systemic inflammatory markers

Discussion

In contrast to the meta-analysis of data from 15,123 T1G3 patients (17), T1 subgrouping was performed using the T1 a, b, c system, and prognostic factors in NMIBC patients were investigated. Deep lamina propria invasion was found to be ineffective on progression probability and PFS. T1 subgrouping was performed in the present study based on MM-VP invasion. In one study, T1 subgrouping was performed based on T1a, b, c, and MM-VP invasion, and diffuse invasion was found to be associated with progression in the T1a, b, c system, whereas extensive invasion was found to be unrelated to progression in MM-VP invasion subgrouping (18). If the patient group of the present study had been subdivided according to the T1a, b, and c system, a relationship between the possibility of progression with deep invasion and PFS may have been uncovered.

LVI was found to be a risk factor for progression in a meta-analysis of 3,905 patients in 2014 (19). Similar to this meta-analysis, LVI was found to be effective on PFS in both univariate and multivariate analyses. In the current research, as in a previous study involving 1,289 T1G3 patients, no correlation was found between the presence of LVI and relapse (20). The EAU Guideline emphasizes that patients with LVI have a very high-risk of developing the disease and that early cystectomy should be performed in these patients (7). From this perspective, the presence of LVI in the patient group of the current study is associated with PFS, which is also consistent with the guidelines.

According to the CUETO study, 34% of T1G3 patients had CIS (5). In the current study, CIS ratio was 48.68% (37 patients) of T1G3 patients. The probability of progression was higher in the T1G3 + CIS group than in the T1G3 group, the probability of relapse was similar in the EORTC study, and the probability of both relapse and progression was higher in the T1G3 + CIS group than in the T1G3 group in the CUETO study (4-6). Unlike the EORTC and CUETO studies, the presence of CIS in T1G3 disease had no effect on the likelihood of relapse, progression, RFS, or PFS. This could be because of the small number of patients included in the study.

The presence of VH was found to be effective on both relapse and progression in a study involving 1,289 T1G3 patients (20). Furthermore, the EAU Guideline emphasizes that the presence of VH indicates very high-risk disease and that early cystectomy should be performed in these patients (7). There are only 9 patients with VH in our data. The lack of association between VH and progression may be due to the small number of patients with VH.

In the present study, NLR was found to have an effect on the probability of relapse and progression, similar to a meta-analysis involving 1,046 T1G3 patients (9). In a study examining the factors that influence muscle invasion, the PLR cut-off value was determined to be 218 in TURB patients, and similar to the current

Table 2. Probability of recurrence and progression

		Recurrence				p-value	Exp (B) 95% CI	p-value	Progression				p-value	Exp (B) 95% CI	p-value
		Yes		No					Yes		No				
		n	%	n	%				n	%	n	%			
Age	<60	8	53.33	7	46.67	0.917			6	40	9	60	0.276		
	60-70	15	46.88	17	53.13				6	1,875	26	81.25			
	>70	14	48.28	15	51.72				9	31.03	20	68.97			
Gender	Man	30	46.15	35	53.85	0.283			17	26.15	48	73.85	0.484		
	Woman	7	63.64	4	36.36				4	36.36	7	63.64			
Tumour diameter (cm)	<3	16	37.21	27	62.79	0.002	0.392 (0.119-1,286)	0.122	7	16.28	36	83.72	0.012	2,373 (0.796-7,077)	0.121
	≥3	21	63.64	12	36.36				14	42.42	19	57.58			
Tumour number	1	16	47.06	18	52.94	0.007	1.938 (0.569-6,601)	0.140	8	23.53	26	76.47	0.001	0.596 (0.196-1,814)	0.240
	2-7	11	35.48	20	64.52				5	16.13	26	83.87			
	≥8	10	90.91	1	9.09				8	72.73	3	27.27			
Focal/deep Submucosal invasion	Focal	14	45.16	17	54.84	0.610			6	19.35	25	80.65	0.180		
	Deep	23	51.11	22	48.89				15	33.33	30	66.67			
Presence of the CIS	Yes	18	48.65	19	51.35	0.995			13	35.14	24	64.86	0.154		
	No	19	48.72	20	51.28				8	20.51	31	79.49			
Presence of lymphovascular invasion	Yes	7	77.78	2	22.22	0.063			6	66.67	3	33.33	0.005	0.351 (0.054-2,270)	0.271
	No	30	44.78	37	55.22				15	22.39	52	77.61			
Presence of variant histology	Yes	5	13.51	4	10.26	0.660			3	14.29	6	10.91	0.684		
	No	32	86.49	35	89.74				18	85.71	49	89.09			
LMR	<3.41	25	71.43	10	28.57	<0.001	4.636 (0.905-23,748)	0.066	12	34.29	23	65.71	0.231		
	≥3.41	12	29.27	29	70.73				9	21.95	32	78.05			
PLR	<150	19	37.25	32	62.75	0.004	0.399 (0.108-1,472)	0.168	13	25.49	38	74.51	0.551		
	≥150	18	72.00	7	28.00				8	32.00	17	68.00			
NLR	<2.5	10	29.41	24	70.59	0.002	1.251 (0.250-6,265)	0.786	5	14.71	29	85.29	0.023	2,846 (0.974-8,313)	0.056
	≥2.5	27	64.29	15	35.71				16	38.10	26	61.90			
SIM score	0	6	23.08	20	76.92	0.001	1.088 (0.256-4,628)	0.993	4	15.38	22	84.62	0.289		
	1	6	40.00	9	60.00				5	33.33	10	66.67			
	2	11	61.11	7	38.89				5	27.78	13	72.22			
	3	14	82.35	3	17.65				7	41.18	10	58.82			

Chi-square test binary logistic regression, CI: Confidence interval, LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, SIM: Systemic inflammatory markers, CIS: Carcinoma *in situ*

Table 3. Recurrence free survival and progression free survival statistics

		Recurrence free-survival						Progression free-survival					
		Estimate	95% CI		p-value	Exp (B) 95% CI	p-value	Estimate	95% CI		p-value	Exp (B) 95% CI	p-value
			Lower bound	Upper bound					Lower bound	Upper bound			
Age	<60	12,750	8,887	16,613	0.382			20,667	10,238	31,095	0.416		
	60-70	10,933	0,245	21,622				11,667	5,496	17,837			
	>70	7,857	4,177	11,538				16,000	6,691	25,309			
Gender	Man	11,433	5,883	16,984	0.071			15,765	9,852	21,677	0.994		
	Woman	4,714	3,890	5,539				17,500	4,487	30,513			
Tumour diameter (cm)	<3	7,250	4,853	9,647	0.276			17,429	7,318	27,540	0.536		
	≥3	12,381	4,586	20,176				15,429	9,133	21,724			
Tumour number	1	8,750	5,246	12,254	0.614			18,875	10,130	27,620	0.614		
	1-7	14,909	0,575	29,243				19,800	4,997	34,603			
	≥8	7,200	4,111	10,289				11,000	5,632	16,368			
Focal/deep submucosal invasion	Focal	14,786	3,736	25,835	0.149			15,000	9,297	20,703	0.829		
	Deep	7,348	4,627	10,069				16,533	9,441	23,626			
Presence of CIS	Yes	6,278	4,358	8,198	0.051			13,692	8,552	18,832	0.174		
	No	13,842	5,351	22,333				20,000	9,062	30,938			
Presence of lymphovascular invasion	Yes	5,286	2,730	7,842	0.153			8,833	4,867	12,799	0.022	0.288 (0.090-0.915)	0.035
	No	11,300	5,755	16,845				19,000	12,308	25,692			
Presence of variant histology	Yes	8,400	2,091	14,709	0.776			22,667	0.000	45,421	0.268		
	No	10,438	5,225	15,650				15,000	9,922	20,078			
LMR	<3.41	12,160	5,596	18,724	0.095			18,167	9,614	26,720	0.456		
	≥3.41	6,000	3,563	8,437				13,333	8,831	17,836			
PLR	<150	8,158	4,719	11,596	0.538			18,077	12,178	23,976	0.509		
	≥150	12,278	3,576	20,980				12,875	2,844	22,906			
NLR	<2.5	6,700	3,074	10,326	0.250			13,800	7,559	20,041	0.670		
	≥2.5	11,444	5,358	17,531				16,813	10,146	23,479			
SIM score	0	3,667	2,462	4,871	0.041	0.754 (0.527-1,080)	0.124	13,000	5,201	20,799	0.605		
	1	8,500	4,621	12,379				13,600	7,572	19,628			
	2	11,455	5,883	17,026				26,400	16,746	36,054			
	3	12,643	1,531	23,754				12,286	0.780	23,792			

Chi-square Test Binary Logistic Regression, CI: Confidence interval, CIS: Carcinoma *in situ*, LMR: Lymphocyte monocyte ratio, PLR: Platelet lymphocyte ratio, NLR: Neutrophil lymphocyte ratio, SIM: Systemic inflammatory markers

study, no correlation was found with PLR progression (12). PLR was found to be effective on the probability of recurrence, similar to a meta-analysis (10). There have been few studies in the literature examining the relationship between muscle invasion and LMR in T1G3 patients. Similar to study (12), LMR was not found to be effective on the probability of progression. One study of 1,151 high-risk patients with NMIBC discovered that a high SIM score correlated with recurrence and progression. We found a positive correlation between a high SIM score and the probability of recurrence, but in contrast to that study, the current study determined that a high SIM score was not associated with progression. The lack of a correlation between a high SIM score and progression in the current study could be attributed to the small sample size and the heterogeneity of the groups with and without progression (11).

Similar to the EORTC study, there was no correlation between the probability of relapse and progression in T1G3 patients or between gender or age, but there was a correlation between tumor size and tumor number (6).

Study Limitations

Small number of patients and retrospective nature are limitations of our study.

Conclusion

In the literature, there are studies investigating the prognostic values of inflammatory markers in T1G3 patients. We examined 4 parameters together in our study (NLR, PLR, LMR, SIM). All parameters were associated with the probability of recurrence. NLR was associated with the probability of progression. SIM was assessed with RFS. We found that inflammatory parameters must be considered when evaluating T1G3 patients. Despite having some patients, the prognostic significance of pathological and clinical parameters that were not included in the nomogram but had been shown to affect progression in other studies were investigated together. Clinical, pathological, and molecular data that have been shown to be accurate in multiple studies but are not included in nomograms should be evaluated with EORTC and CUETO-like studies, and significant data should be validated for nomograms.

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Ethics

Ethics Committee Approval: Before starting the study, the approval of the Çukurova University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (decision no: 77, date: 04.05.2023) was obtained.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: İ.Ö.Y., Design: İ.Ö.Y., Data Collection or Processing: İ.Ö.Y., Analysis or Interpretation: İ.Ö.Y., Literature Search: İ.Ö.Y., Writing: İ.Ö.Y., M.D., N.A., İ.A.A., Y.B., V.İ.

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