ORIGINAL ARTICLE

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The prognostic impact of tumor necrosis in non-muscle invasive bladder cancer

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SUMMARY

OBJECTIVE: We aimed to investigate the impact of tumor necrosis in non-muscle invasive bladder cancer on patients' recurrence and progression rates and survival outcomes.

METHODS: This study was conducted retrospectively in a single tertiary center in Turkey. Medical records of patients who underwent transurethral resection of the bladder tumor between January 2016 and January 2021 were reviewed. Patients with pTa and pT1 non-muscle invasive bladder cancer who had undergone complete resection were included in our study. All pathological specimens were reevaluated for the presence of tumor necrosis.

RESULTS: A total of 287 patients (244 males and 43 females) were included in our study. Of them, 33 (11.5%) patients had tumor necrosis. The rates of multiple and large tumors (>3 cm) were higher in patients with tumor necrosis (p=0.002 and p<0.001, respectively). Tumor necrosis was associated with higher rates of pT1 diseases (p<0.001), high-grade tumors (p<0.001), and the presence of lymphovascular invasion (p=0.007). The mean recurrence-free survival of patients with tumor necrosis was 42.3 (4.6) months, and the recurrence-free survival of patients without tumor necrosis was 43.5 (1.8) months (p=0.720). The mean progression-free survival of patients with tumor necrosis was 43.1 (4.6) months, and the progression-free survival of patients without tumor necrosis was 58.4 (0.9) months. In log-rank analysis, there was a statistically significant difference between patients with and without tumor necrosis in terms of progression-free survival (p<0.001).

CONCLUSION: In this study, we demonstrated that patients with non-muscle invasive bladder cancer and tumor necrosis in pathological specimens have shorter progression-free survival and more adverse pathological features.

KEYWORDS: Urinary bladder neoplasms. Necrosis. Prognosis. Disease progression. Recurrence.

INTRODUCTION

Bladder cancer is the fourth most frequent malignancy in men and the eighth leading cause of cancer death[1]. Localized bladder cancers are classified according to muscle invasion status, and muscle-invasive bladder cancers (MIBCs) require more aggressive treatments such as radical cystectomy and urinary diversion. Despite more favorable oncological outcomes, non-muscle invasive bladder cancers (NMIBC) have up to 40% progression rates after transurethral resection of bladder tumor (TUR-BT) at 5 years[2]. Several predictive factors for progression were identified, such as age, the number of tumors, tumor size, T stage, concomitant carcinoma in situ (CIS), and histological grade[3].

Several studies reported that tumor necrosis had adverse oncological outcomes in some malignant epithelial tumors such as breast, kidney, or lung[4-6]. In 2010, Zigeuner et al. investigated the oncological impact of tumor necrosis in patients with upper urinary tract urothelial carcinoma (UTUC) and concluded that tumor necrosis is significantly associated with adverse pathological features, disease recurrence, and survival[7]. To date, few studies have investigated the oncological effect of tumor necrosis in bladder cancer. Therefore, the clinical significance of tumor necrosis in NMIBC remains an issue that should be investigated.

Accurately forecasting the clinical outcomes of patients with NMIBC is critical to providing counseling and making decisions about adjuvant intravesical therapies, possible early cystectomy, and follow-up appointments. Tumor necrosis is a potentially relevant prognostic factor that has gotten less attention thus far. To the best of our knowledge, only one study has investigated the clinical significance of tumor necrosis in TUR-BT specimens. This previous study demonstrated that tumor necrosis in TUR-BT specimens without muscle invasion was a significant predictor of upstaging at subsequent radical cystectomy[8].

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In this study, we aimed to investigate the impact of tumor necrosis in NMIBC on patients' recurrence and progression rates and survival outcomes.

METHODS

This study was conducted retrospectively in a single tertiary center in Turkey after receiving approval from the institutional review board (decision no.: 2021/0720, date: January 12, 2022). The medical records of patients who underwent TUR-BT for bladder cancer between January 2016 and January 2021 were reviewed retrospectively. Patients with pTa and pT1 NMIBC who had undergone complete resection were included in our study. Patients with incomplete resection (n=36), MIBC at second TUR (n=5), early cystectomy (within 6 months) (n=37), concomitant UTUC (n=2), and without at least 6 months of follow-up (n=43) were excluded from the study. Patients' demographics such as age, gender, and clinical tumor characteristics such as recurrence status, tumor number, and size were noted.

All patients had undergone a complete initial TUR-BT, and an experienced uropathologist performed pathological examinations. All TUR-BT procedures were performed with standard techniques and a monopolar or bipolar cauterization system. The en bloc resection technique was not used. The pathological T stage was determined according to the 2017 tumor, node, and metastasis classification of urinary bladder cancer. The World Health Organization 2004/2016 histological grading system was used to determine the histological grade. Concurrent carcinoma in situ (CIS), variant histology, and lymphovascular invasion were recorded. All pathological specimens were reevaluated by the same experienced uropathologist to determine the presence of tumor necrosis. The occurrence of microscopic granular necrosis without inflammation or fibrosis was evaluated as tumor necrosis. Tumor necrosis was characterized by well-defined necrotic foci being sharply demarcated from adjacent viable tumors. A constant feature was the loss of architecture, resulting in an amorphous necrotic mass containing granular nuclear and cytoplasmic debris without an associated neutrophilic infiltrate. These foci were often microscopic, but many ranged up to several millimeters or larger[9].

After initial TUR-BT and pathological examinations, patients with pT1 tumors underwent a second TUR-BT. Afterward, all patients with high-grade or pT1 tumors were recommended to receive adjuvant intravesical Bacillus Calmette-Guerin (BCG) treatment. Adjuvant intravesical mitomycin C (MMC) treatment was recommended for patients with intermediate-risk NMIBC according to the European Urological Association (EAU) guidelines. Postoperative single-dose MMC was administered to patients with tumors who appeared to be low risk. Patients with low-risk NMIBC confirmed by the pathology report were followed without any further adjuvant intravesical therapy. Cystoscopy and urine cytology were used for patients' follow-ups, and the schedule was determined according to risk stratification and EAU guidelines. High- and intermediate-risk patients underwent cystoscopy every 3 months for the first 2 years, every 6 months for the subsequent 3 years, and every year after 5 years. Patients with low-risk diseases underwent follow-up cystoscopies 3 and 12 months after the initial TUR-BT and then yearly for 5 years. Tumor recurrence was defined as the detection of pathologically confirmed urothelial carcinoma, and progression was defined as the detection of pT2 urothelial carcinoma at tumor recurrence during patients' follow-up.

Statistical analysis

Statistical Package for the Social Sciences version 26.0 (SPSS Inc., IBM, NY, USA) was used to perform statistical analyses. Evaluation of distributions was performed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics (frequency, percentage, mean, standard deviation, median, etc.) were used to evaluate the data. Pearson's chi-square and Fisher's exact tests were used to analyze categorical variables. Cox regression analyses were used to determine the predictive factors for recurrence and progression. Cumulative survival rates were analyzed using the Kaplan-Meier method, and the significance of differences in the survival rates was analyzed using the log-rank test. A $p<0.05$ was accepted for statistical significance.

RESULTS

After the exclusions, a total of 287 patients, 244 (85%) males and 43 females (15%), were included in our study. The mean (SD) age was 66.2 (10.3) years, and 93 (32.4%) of the patients had recurrent NMIBC. Patients' clinicopathologic characteristics are presented in Table 1. A total of 33 (11.5%) patients had tumor necrosis. Patients' clinical and pathological characteristics were compared between the two groups with or without tumor necrosis. The rates of multiple and large tumors (>3 cm) were higher in patients with tumor necrosis ($p=0.002$ and $p<0.001$, respectively). Tumor necrosis was associated with higher rates of pT1 diseases ($p<0.001$), high-grade tumors ($p<0.001$), and the presence of lymphovascular invasion (LVI) ($p=0.007$) (Table 1).

During the mean (SD) 27.9 (13.6) months of follow-up, 85 (29.6%) patients had tumor recurrence and 23 (8%) patients had tumor progression. Tumor necrosis was significantly associated with tumor progression ($p=0.001$), but not with tumor recurrence ($p=0.927$). In multivariate Cox regression analysis,

Table 1. Patients' clinicopathologic variables and comparisons according to presence of tumor necrosis.

	Total	Necrosis (-)	Necrosis (+)	p-value
Age				
≤70 years	187 (65.2%)	168 (66.1%)	19 (57.6%)	0.331[a]
>70 years	100 (34.8%)	86 (33.9%)	14 (42.4%)	
Sex				
Female	43 (15.0%)	38 (15.0%)	5 (15.2%)	1.000[b]
Male	244 (85.0%)	216 (85.0%)	28 (84.8%)	
Recurrence status				
Primary	194 (67.6%)	170 (66.9%)	24 (72.7%)	0.503[a]
Recurrent	93 (32.4%)	84 (33.1%)	9 (27.3%)	
Tumor number				
Single	144 (50.2%)	136 (53.5%)	8 (24.2%)	**0.002[a]**
Multiple	143 (49.8%)	118 (46.5%)	25 (75.8%)	
Tumor size				
≤3 cm	171 (59.6%)	164 (64.6%)	7 (21.2%)	**<0.001[a]**
>3 cm	116 (40.4%)	90 (35.4%)	26 (78.8%)	
T stage				
pTa	209 (72.8%)	204 (80.3%)	5 (15.2%)	**<0.001[a]**
pT1	78 (27.2%)	50 (19.7%)	28 (84.8%)	
Tumor grade				
Low	135 (47.0%)	135 (53.1%)	0 (0.0%)	**<0.001[a]**
High	152 (53.0%)	119 (46.9%)	33 (100.0%)	
Concurrent CIS				
No	265 (92.3%)	237 (93.3%)	28 (84.4%)	0.153[b]
Yes	22 (7.7%)	17 (6.7%)	5 (15.2%)	
Variant histology				
No	273 (95.1%)	243 (95.7%)	30 (90.9%)	0.209[b]
Yes	14 (4.9%)	11 (4.3%)	3 (9.1%)	
Lymphovascular invasion				
Negative	270 (94.1%)	243 (95.7%)	27 (81.8%)	**0.007[b]**
Positive	17 (5.9%)	11 (4.3%)	6 (18.2%)	
Single-dose intravesical chemotherapy				
No	223 (77.7%)	192 (75.6%)	31 (93.9%)	**0.017[a]**
Yes	64 (22.3%)	62 (24.4%)	2 (6.1%)	
Adjuvant treatment				
None	99 (34.5%)	93 (36.6%)	6 (18.2%)	**0.000[a]**
Mitomycin	58 (20.2%)	57 (22.4%)	1 (3.0%)	
BCG	130 (45.3%)	104 (40.9%)	26 (78.8%)	
Recurrence				
No	202 (70.4%)	179 (70.5%)	23 (69.7%)	0.927[a]
Yes	85 (29.6%)	75 (29.5%)	10 (30.3%)	
Progression				
No	264 (92.0%)	240 (94.5%)	24 (72.7%)	**<0.001[b]**
Yes	23 (8.0%)	14 (5.5%)	9 (27.3%)	

[a]Pearson's chi-square. [b]Fisher's exact test. BCG: Bacillus Calmette-Guerin; CIS: carcinoma in situ. Bold indicates statistically significant value.

T stage (pT1 vs. pTa) (HR: 2.479, 95%CI 1.362–4.513, p=0.003) and adjuvant BCG treatment (HR: 0.343, 95%CI 0.193–0.609, p<0.001) were significant predictive factors for tumor recurrence. However, the only significant predictive factor for progression was the T stage (pT1 vs. pTa) (HR: 18.494, 95%CI 3.153–108.476) in multivariate analysis (Table 2).

In Kaplan-Meier analyses, the overall mean (SD) estimated recurrence-free survival (RFS) was 43.7 (1.7) months. The RFS of patients with tumor necrosis was 42.3 (4.6) months, and the RFS of patients without tumor necrosis was 43.5 (1.8) months. RFS was similar between the two groups (p=0.720) (Figure 1). The progression-free survival (PFS) was 57.0 (1.0) months in the overall population. The PFS of patients with tumor necrosis was 43.1 (4.6) months, and the PFS of patients without tumor necrosis was 58.4 (0.9) months. In log-rank analysis, patients with tumor necrosis exhibited a considerably shorter PFS than those without (p<0.001) (Figure 1).

DISCUSSION

Tumor necrosis is a pathophysiological manifestation of ischemia and hypoxia-induced by inadequate neovascularization, which is seen in rapidly growing tumors[10]. Ischemia or reduced oxygen causes the hypoxia-inducible factor (HIF) transcription factor to stabilize and activate, causing gene transcription to stimulate angiogenesis and restore oxygen and nutritional balance[11]. Hypoxia and HIF regulate the transcription of genes encoding processes like angiogenesis, invasion, and apoptosis. Some previous studies demonstrated that HIF-1 alpha overexpression was significantly correlated with worse prognosis in urothelial bladder cancer or upper urinary tract cancer[12,13].

The potential prognostic significance of tumor necrosis in urothelial cancers was investigated by Langner et al. in 2006. They included 268 patients with UTUC in this study and reported that 133 (42.2%) patients had tumor necrosis. In this

Table 2. Univariate and multivariate Cox regression analysis for recurrence and progression.

	Recurrence				Progression			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age (>70 vs. ≤70*) (years)	1.048 (0.668–1.644)	0.839	–	–	1.362 (0.587–3.156)	0.472	–	–
Sex (male vs. female*)	0.787 (0.450–1.377)	0.402	–	–	1.264 (0.375–4.266)	0.706	–	–
Recurrence status (recurrent vs. primary*)	2.009 (1.306–3.089)	<0.001	–	–	1.710 (0.749–3.908)	0.203	–	–
Tumor number (multiple vs. single*)	1.651 (1.071–2.545)	0.023	–	–	2.100 (0.889–4.960)	0.091	–	–
Tumor size (>3 cm vs. ≤3 cm*)	1.518 (0.990–2.326)	0.055	–	–	2.562 (1.107–5.932)	0.028	–	–
T stage (pT1 vs. pTa*)	1.554 (0.991–2.436)	0.055	2.479 (1.362–4.513)	0.003	22.988 (6.699–78.886)	<0.001	18.494 (3.153–108.476)	<0.001
Tumor grade (high vs. low*)	1.037 (0.677–1.587)	0.869	–	–	10.625 (2.487–45.387)	<0.001	–	–
Concurrent CIS (yes vs. no*)	1.411 (0.680–2.925)	0.355	–	–	3.100 (1.045–9.192)	0.041	–	–
Variant histology (yes vs. no*)	0.477 (0.110–1.819)	0.261	–	–	1.006 (0.135–7.485)	0.995	–	–
Lymphovascular invasion (yes vs. no*)	0.608 (0.192–1.925)	0.397	–	–	1.773 (0.414–7.597)	0.440	–	–
Tumor necrosis (yes vs. no*)	1.127 (0.581–2.184)	0.724	–	–	5.828 (2.513–13.515)	<0.001	–	–
Single-dose intravesical chemotherapy (yes vs. no*)	0.604 (0.379–0.962)	0.034	–	–	0.968 (0.358–2.616)	0.949	–	–
Adjuvant treatment		0.123		<0.001		0.150		
Mitomycin vs. none*	1.114 (0.646–1.921)	0.697	1.052 (0.599–1.847)	0.860	0.206 (0.026–1.646)	0.136		
BCG vs. none*	0.660 (0.404–1.079)	0.098	0.343 (0.193–0.609)	<0.001	1.439 (0.602–3.441)	0.413	–	–

*Reference.

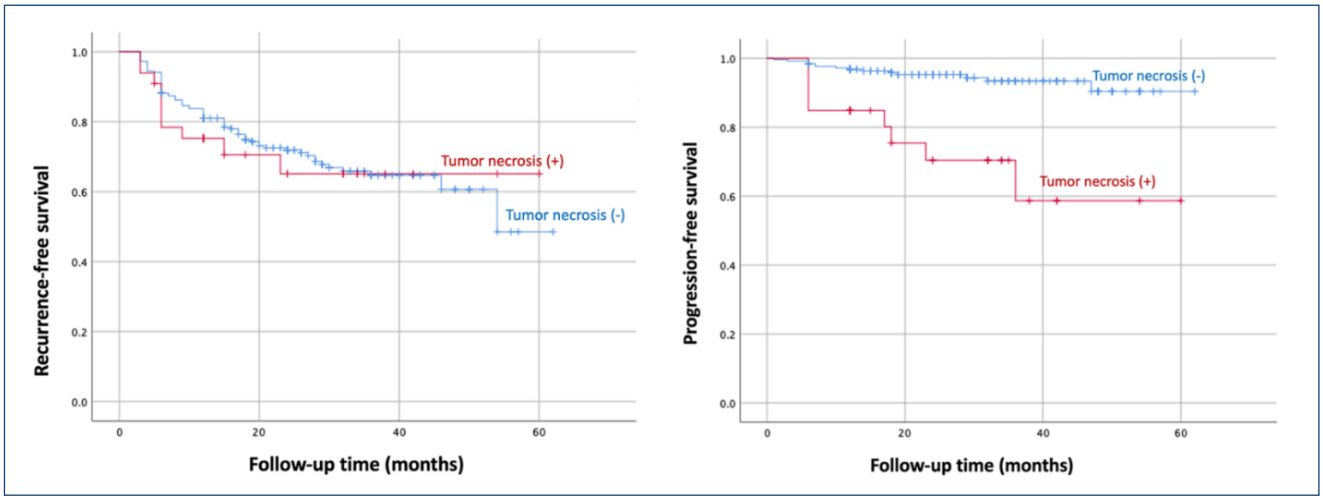

Figure 1. Kaplan-Meier survival curves for recurrence-free survival and progression-free survival.

study, the authors stated that higher tumor stage (p<0.001) and grade (p<0.001) were significantly associated with tumor necrosis. In addition to these findings, extensive tumor necrosis was an independent predictor of worse metastasis-free survival[14]. After this study, several studies were conducted to investigate the prognostic influence of tumor necrosis in UTUC. In summary, these studies reported that tumor necrosis was an independent prognostic variable of disease-specific survival, metastasis-free survival, and overall survival[15-19].

Only a limited number of papers in the literature investigate the prognostic effect of tumor necrosis in urothelial bladder cancer. In 2007, Ord et al. investigated the prognostic significance of hypoxia and necrosis in radical cystectomy specimens. They reported that the prevalence of tumor necrosis increased with a higher T stage. Tumor necrosis was an independent prognostic factor of cancer-specific survival (CSS) besides the T stage[20]. Then, Soave et al. conducted a study investigating the impact of tumor diameter and necrosis on disease recurrence and CSS. They included 517 patients who had undergone radical cystectomy and reported that tumor necrosis was present in 30.2% of the patients. This study demonstrated that tumor necrosis was significantly associated with adverse tumor features such as higher T stage and grade, lymph node invasion, positive surgical margin, and lymphovascular invasion[21]. Finally, Hodgson et al. also examined patients who had undergone radical cystectomy in their study and found that the presence of tumor necrosis was associated with a poor prognosis[22].

Our study has some limitations. First, patients' clinical and follow-up variables were noted retrospectively. However, despite the retrospective design, we reevaluated the pathological specimens for tumor necrosis. Second, this study was a single-center study with a limited number of patients. We could not evaluate CSS because of the small number of events (cancer-related death). Despite these limitations, to the best of our knowledge, no other study in English-written literature has investigated the prognostic impact of tumor necrosis in NMIBC. The only study that studied NMIBC pathological specimens included patients who had undergone early cystectomy, unlike ours[8]. In our study, we excluded patients with early cystectomy (within the first 6 months after initial TUR-BT).

CONCLUSION

This study demonstrated that patients with NMIBC and tumor necrosis in pathological specimens have shorter PFS and more adverse pathological features. Our results support that the presence of tumor necrosis should be reported regularly to help better understand patients' prognoses. Prospective and multicenter studies are required for more robust evidence-based recommendations.

ETHICAL APPROVAL

The protocol for this research has been approved by a suitably constituted ethics committee of the institution, and it conforms to the provisions of the Declaration of Helsinki. Committee of Istanbul Medeniyet University, approval no.: 2021/0720.

AUTHORS' CONTRIBUTIONS

MC: Conceptualization (lead), Formal Analysis (lead), Investigation (equal), Methodology (equal), Project administration (lead), Resources (equal), Writing – original draft (lead). **AI:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal). **GK:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal). **GEC:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal). **GA:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal), Supervision (equal). **AY:** Data curation (equal), Investigation (equal), Methodology (equal), Resources (equal), Supervision (equal), Writing – review & editing (lead).

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