European Review for Medical and Pharmacological Sciences 2022; 26: 7649-7655

Side specific differences of tumor budding on non-metastatic colon cancer

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Abstract. – OBJECTIVE: Recent literature suggests that tumor budding (TB) may have a significant clinical impact on colorectal cancers. Our study aims to reveal the effect of TB on the long-term outcomes of patients and to reveal whether there is a difference in tumor location and TB in colonic cancer.

PATIENTS AND METHODS: A cohort of 100 patients with non-metastatic colon cancer was included in the study. The clinicopathological information of the patients was reviewed. Patients' preparations were re-evaluated to identify TB as: low, medium, and high and represent 0-4 buds, 5-9 buds, and 10 or more buds per 0.785 mm², respectively. Long-term oncological outcomes of patients were analyzed. The recurrence, metastasis, and final status of the patients were determined during the follow-up period.

RESULTS: Low TN was associated with <65 year (p = 0.048), absence of lymphatic metastasis (p = 0.003), and absence of perineural invasion (p = 0.023). High TB was associated with higher pT stage (p = 0.017) and tumor stage (p = 0.005). Additionally, right-sided tumors had a high TB score than left side (82.3% *vs*. 23.6%, p = 0.011). Patients with high TB had lower overall survival, but these were not statically significant. According to multiple regression analysis, mortality risk was associated with age (p = 0.046), pN status (p = 0.003) and TB (p = 0.040).

CONCLUSIONS: High TB is associated with mortality in colon cancer and is more common in right colonic carcinoma.

Key Words:
Colon cancer, Cancer localization, Tumor budding.

Introduction

In the last three decades, colon cancer is considered as the proximal (right) colon and distal (left) colon according to the tumor location[1]. Increasing evidence[2] suggests that molecular changes can differ between these tumor sites. Some scholars[3] show that colon cancers in the proximal and distal colon regions can show differences in survival. In particular, proximal colon cancer has been associated with worse survival than distal colon cancer in many studies, although not all studies. Some of the reasons are thought to be various genetic and epigenetic changes[3].

Tumor budding (TB) is the presence of small discrete clusters of tumor cells on the tumor's invasive margin. The migration of these tumor cells is thought to be a step towards the metastatic process[4]. Many studies[5] in recent years have shown that TB may be an independent prognostic factor in colorectal cancer. However, studies investigating the difference in TB amount according to the tumor's distal and proximal localization are limited. In this study, we aimed at investigating TB's effect on colon cancer patients' outcomes, whether TB differs in the right and left colon cancers and its effect on survival.

Patients and Methods

Case Selection

For the study, patients who were operated on for colorectal cancer in Diyarbakır Gazi Yaşargil Training and Research Hospital between January 2012 and December 2018 were retrospectively analyzed. Ethical approval for this study was obtained from the Ethics Committee of Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital (IRB number: 711/05.03.2021).

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Exclusion Criteria

Appendix tumors (n=36), familial adenomatous coli syndromes (n=39), rectal cancers (n=126), anal canal cancers (n=24), synchronous or metachronous colon cancers (n=19), and all metastatic colon cancers (n=35) at the time of diagnosis were excluded from the study. All patients who received preoperative chemotherapy (126 rectal and 18 colon cancer) were excluded to eliminate the effect of neoadjuvant therapy on TB[6,7]. Also, patients who underwent R1 resection (n=13), patients with less than 12 lymph nodes removed (n=11), and patients with early postoperative mortality (within the first 30 days) (n=19) were excluded from the study. Besides, pathology preparations of 24 patients were not available so they were excluded.

Evaluation of Tumor Budding

A pathologist, blinded to the oncological results of the patients re-evaluated the pathology preparations. Immunohistochemical examination was performed on preparations stained with hematoxylin and eosin (H&E) and, if necessary, stained with pan-cytokeratin (IHC) (Figure 1).

The area where the tumor was the most invasive was first scanned at low magnification, and the densest TB area was determined. The densest TB area was then examined under higher magnification (field of view 0.785 mm^2), and the number

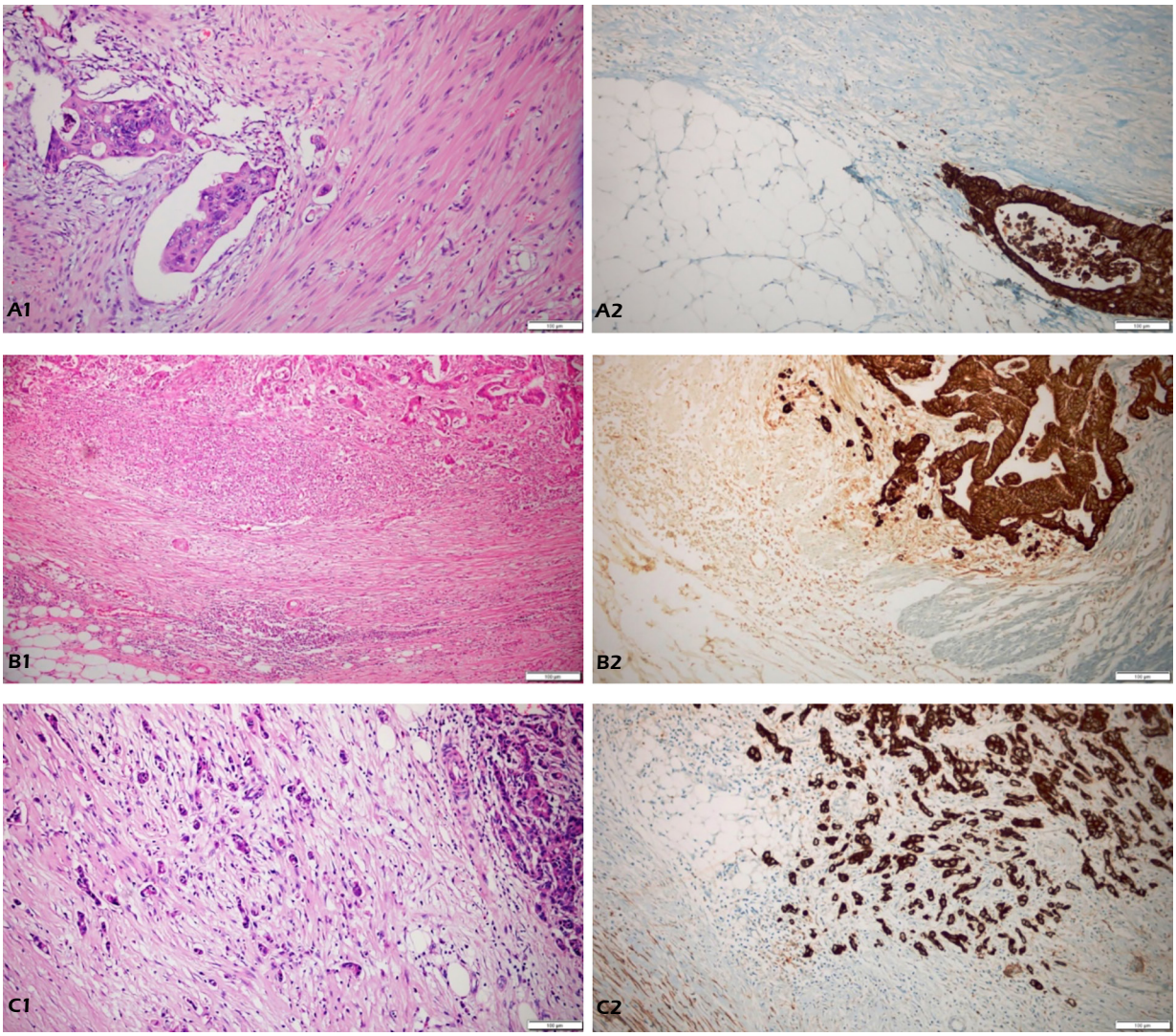

Figure 1. This composite image shows tumor budding with H&E staining and IHC staining with Pan-cytokeratin (×200). **A,** Low TB has seen in H&E staining (**A1**), and Pan-cytokeratin staining (**A2**). **B,** Intermediate TB has seen in H&E staining (**B1**), and Pan-cytokeratin staining (**B2**). **C,** High TB has seen in H&E staining (**C1**), seen on Pan-cytokeratin staining (**C2**).

of tumor buds counted. Tumor buddings were classified as low (0-4), intermediate (between 5 and 9), and high (10 or more) as recommended by the International Tumor Budding Consensus Conference (ITBCC) in 2016[8,9].

Examined Parameters

According to cancer location, right colon cancer was defined as location of the tumor, including the cecum/appendix, ascending colon, hepatic flexure, and proximal transverse colon (proximal two-thirds of the transverse colon). Left colon cancer was defined as location of the tumor, including the distal transverse colon (distal one-third of the transverse colon), splenic flexure, descending colon, and sigmoid colon.

Histopathological features of all patients were examined, and factors affecting mortality were determined. The final status of the patients was determined during the follow-up period. The overall survival was analyzed. The relationship between TB and tumor sites was investigated.

Statistical Analysis

SPSS 23.0 (SPSS Corp., Armonk, NY, USA) package program was used for statistical analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean deviation and minimum-maximum. The variables' compatibility to normal distribution was examined using one of the analytical methods, the Shapiro-Wilk test. Chi-square test and Fischer's Precision Test were used for comparisons of categorical variables. Logistic regression analysis was used to determine the independent variables affecting the mortality findings of the patients. Kaplan-Meier analysis and Log Rank tests were used for survival analysis. A p-value of <0.05 was considered statistically significant.

Results

During the study period, 464 colorectal cancer patients were operated on in our hospital; however, only 100 patients who met the inclusion criteria were analyzed. Forty-one percent of the patients were women, and 59% were men. The average age was 58.8±15.5 years (range: 19-90 years). Tumor localization was in the left colon in 72% of the cases and in the right colon in 28%. Thirteen percent of the patients had stage 1, 49% had stage 2, and 38% had stage 3 cancer. Histopathological examination revealed high TB in 30% of the cases, intermediate TB in 30%, and low TB in 40%. During the mean follow-up period of 32.8±19.7 months, 71% of the patients had received adjuvant chemotherapy (5-Fluorouracil-based), metastasis occurred in 6 patients, and 27 were dead. There was a statistically significant relationship between tumor budding and age, pT stage, lymph node metastasis, tumor stage, and perineural invasion (Table I).

Low TN was associated with <65 year (p = 0.048), absence of lymphatic metastasis (p = 0.003), absence of perineural invasion (p = 0.023). High TB was associated with higher pT stage (p = 0.017) and tumor stage (p = 0.005) (Table II). While 82.3% of right colon tumors were high TB, this rate was 23.6 in left colon tumors (p = 0.011) (Table III).

The median overall survival time of the cohort was 39.73 months (95% CI, 35.252-44.2071). Overall survival of 1, 3, and 5 years was shorter in patients with high TB, but this was not statistically significant (p = 0.605) (Table IV). Also, no statistical difference was found between right and left colon cancers in terms of overall survival.

The multiple regression analysis is shown in Table V. The variables of age, gender, tumor location, pT, pN, TB, histopathologic type, histological grade, vascular invasion, perineural invasion, and receiving adjuvant chemotherapy were added to the model. Age, pN, receiving adjuvant chemotherapy, and tumor budding variables were determined to be risk factors associated with mortality (p < 0.05).

Discussion

The causes of molecular changes and differences in tumor regions in colon cancer are unknown. However, differences in environmental risk factors or differences in colon microbiota may affect carcinogenesis in a site-specific manner. Tumor budding, which has been increasingly discussed in recent years, may be one of these regional differences. Our study aimed at investigating the differences in TB scores between tumor regions in the consecutively resected colonic adenocarcinoma cohort. The results of our analysis show that high TB is usually detected in the right colonic adenocarcinoma. Additionally, our study confirmed that high TB is also an influencing factor in mortality.

Table I. Clinicopathologic features of patients.

Variables		(N)	(%)
Gender	Male	59	59.0%
	Female	41	41.0%
Age	< 65 year	54	54.0%
	> 65 year	46	46.0%
Tumor localization	Right	28	28.0%
	Left	72	72.0%
pT	1	1	1.0%
	2	12	12.0%
	3	42	42.0%
	4	45	45.0%
pN	0	62	62.0%
	1	20	20.0%
	2	18	18.0%
Tumor stage	1	13	13.0%
	2	49	49.0%
	3	38	38.0%
Tumor budding	High	30	30.0%
	Intermediate	30	30.0%
	Low	40	40.0%
Histological grade	Poor differentiated	3	3.0%
	Moderated differentiated	47	47.0%
	Well-differentiated	41	41.0%
	NA	9	9.0%
Vascular invasion	Absent	72	72.0%
	Present	28	28.0%
Perineural invasion	Absent	67	67.0%
	Present	33	33.0%
Adjuvant chemotherapy	No	29	29.0%
	Yes	71	71.0%
Last status	Dead	27	27.0%
	Alive	73	73.0%

Imai[9] first described tumor budding in the 1950s. For a long time, how many tumor buds are significant and how they shall be enumerated were important questions to be answered concerns. A reproducible method with a definite cut point must be used to be relevant in clinical practice for prognostication and therapeutic decision-making[10]. Over the time since TB was identified, there has been confusion in its assessment and quantification. Although in 2016, at the ITBCC, it was classified as low TB (numbers 0-4), intermediate TB (numbers between 5 and 9), and high TB (10 or more)[8]. We would like to state that this classification was made with maximum attention to ITBCC consensus in our study.

The ITBCC group suggests that tumor budding should be evaluated in H&E, as the vast majority of outcome data are based on H&E assessment. However, the data regarding the evaluation by IHC staining were not sufficient. They pointed out that tumor buds can be hidden by a peritumoral inflammatory infiltration, making it difficult to identify it in H&E. Therefore, they emphasized that, from time to time, when tumor buds are difficult to distinguish from reactive stromal cells, the tumor buds will be better visualized with pan-cytokeratin immunohistochemical staining[8]. In our study, we used pan-cytokeratin immunohistochemical staining in cases where evaluation of tumor buds is difficult.

Today, TB has the potential to affect clinical decision-making under two main headings. First, in patients with pT1 colorectal cancer, intermediate or high TB is an independent predictor of lymphatic metastasis, and the need for radical surgery (rather than local excision of the tumor) is increasingly being taken into account (with other clinicopathological factors). Second, in patients with stage II colon cancer, high TB is a strong adverse prognostic factor (high-risk characteristic) that should warrant systemic therapy[8]. Supporting this information, a statistically significant relationship between TB and pT stage, lymphatic and perineural invasion, and tumor stage was re-

Table II. Association of tumor budding and clinicopathologic features.

Variables		All n: 100 (%)	Low n: 40 (%)	Intermediate n: 30 (%)	High n: 30 (%)	p
Age	< 65 year	54 (54%)	30 (75%)	20 (66.7%)	14 (46.7%)	**0.048**
	> 65 year	46 (46%)	10 (25%)	10 (33.3%)	16 (53.3%)	
Gender	Female	41 (41%)	17 (42.5%)	10 (33.3%)	14 (46.7%)	0.562
	Male	59 (59%)	23 (57.5%)	20 (66.7%)	16 (53.3%)	
T stage	1	1 (1%)	1 (2.5%)	0 (0%)	0 (0%)	**0.017**
	2	12 (12%)	8 (20%)	4 (13.3%)	0 (0%)	
	3	45 (45%)	24 (60%)	14 (46.7%)	7 (23.3%)	
	4	42 (42%)	7 (17.5%)	12 (40%)	23 (76.7%)	
N stage	0	62 (62%)	31 (77.5%)	14 (46.7%)	17 (56.7%)	0.069
	1	20 (20%)	4 (10.0%)	10 (33.3%)	6 (20.0%)	
	2	18 (18%)	5 (12.5%)	6 (20.0%)	7 (23.3%)	
Lymphatic metastasis	Absent	62 (62%)	31 (77.5%)	14 (46.7%)	17 (56.7%)	**0.003**
	Present	38 (38%)	9 (22.5%)	16 (53.3%)	13 (43.3%)	
Tumor stage	1	13 (13%)	9 (22.5%)	4 (13.3%)	0 (0%)	**0.005**
	2	49 (49%)	22 (55.0%)	10 (33.3%)	17 (56.7%)	
	3	38 (38%)	9 (22.5%)	16 (53.3%)	13 (43.3%)	
Histopathologic type	Adenocancer	91 (91%)	36 (90%)	27 (90%)	28 (93.3%)	0.914
	Mucinous adenocancer	9 (9%)	4 (10%)	3 (10%)	2 (6.7%)	
Perineural invasion	Absent	67 (67%)	33 (82.5%)	18 (60%)	16 (53.3%)	**0.023**
	Present	33 (33%)	7 (17.5%)	12 (40%)	14 (46.7%)	
Histological grade	Well	41 (41%)	14 (50.0%)	11 (40.7%)	16 (44.4%)	0.511
	Moderate	47 (47%)	12 (42.9%)	15 (55.6%)	20 (55.6%)	
	Poor	3 (3%)	2 (7.1%)	1 (3.7%)	0 (0%)	
Vasculer invasion	Absent	72 (72%)	33 (82.5%)	19 (63.3%)	20 (66.7%)	0.149
	Present	28 (28%)	7 (17.5%)	11 (36.7%)	10 (33.3%)	
Tumor side	Right colon	28 (28%)	5 (17.8%)	10 (35.7%)	13 (82.3%)	**0.011**
	Left colon	72 (72%)	35 (48.6%)	20 (27.8%)	17 (23.6%)	
Adjuvant chemotheraphy	No	29 (29%)	12 (30%)	6 (20%)	11 (36.7%)	0.367
	Yes	71 (71%)	28 (70%)	24 (80%)	19 (63.3%)	
Mortality	Dead	27 (27%)	7 (17.5%)	8 (26.7%)	12 (40%)	0.117
	Alive	73 (73%)	33 (82.5%)	22 (73.3%)	18 (60%)	

Table III. Association of tumor side with tumor budding and stage.

Variables		Right colon n, (%)	Left colon n, (%)	p
Tumor stage	1	6 (21.4%)	7 (9.7%)	0.218
	2	14 (50%)	35 (48.6%)	
	3	8 (28.6%)	30 (41.6%)	
Tumor budding	Low	5 (17.85%)	35 (48.6%)	**0.011**
	Intermediate	10 (35.7%)	20 (27.8%)	
	High	13 (82.3%)	17 (23.6%)	

Table IV. Comparison of overall survival of colonic adenocarcinomas.

	Median	95% CI Lower	95% CI Upper	p	1 year overall survival	3 years overall survival	5 years overall survival
TB group							
Low TB	74.64	59.07	90.21	0.605	95.0%	86.2%	56.6%
Intermediate TB	64.59	52.665	76.525		86.7%	73.0%	73.0%
High TB	54.16	43.158	65.170		83.3%	65.2%	48.9%
Tumor side							
Right colon	43.17	34.113	52.229	0.469	85.7%	67.9%	50.9%
Left colon	38.40	33.271	43.546		91.7%	75.5%	62.9%
Overall survival (month)	39.73	35.252	44.207	–	89.0%	72.4%	65.0%

Table V. Multivariate analysis of factors affecting mortality in colonic adenocarcinomas.

					95% CI		
	Beta	Se	Wald	Odd ratio	Lower	Upper	*p*
Age	-0.031	0.016	3.999	0.969	0.940	0.999	**0.046**
Gender	-0.227	0.464	0.240	0.797	0.321	1.977	0.624
Adjuvant chemotheraphy	1.196	0.478	6.267	3.308	1.297	8.440	**0.012**
Tumor localization	0.110	0.496	0.049	1.116	0.422	2.953	0.825
pT	-0.631	0.379	2.768	0.532	0.253	1.119	0.096
pN	-0.861	0.286	9.086	0.423	0.241	0.740	**0.003**
Tumor budding	0.574	0.279	4.215	1.775	1.026	3.069	**0.040**
Histopathologic type	-0.333	0.746	0.200	0.716	0.166	3.092	0.655
Histological grade	0.743	0.439	2.858	2.101	0.888	4.970	0.091
Vasculer invasion	-0.817	0.480	2.904	0.442	0.172	1.131	0.088
Perineural invasion	-0.466	0.467	0.994	0.627	0.251	1.568	0.319

vealed in our study. Besides, multiple regression analysis showed us that the mortality risk was associated with tumor budding (odds ratio: 1.775) ($p = 0.040$).

The right colon and left colon cancers may exhibit different biological behavior. Studies investigating the relationship between tumor localization and TB are pretty limited. In this study we aimed to analyze whether the right colon and the left colon exhibit different biological behavior in terms of TB. Side-specific differentiation of colorectal cancer has been discussed in previous studies, but most of the studies have limitations in patient selection. Van Wyk et al[11] found no difference in TB between the colon and rectum in their study of 952 colorectal cancer. Similarly, Fujiyoshi et al[12] compared 915 colorectal cancers in their research and did not find a statistical relationship between localization and TB. Graham et al[13] described equally frequent high TB in the proximal colon and distal colon tumors. However, these studies, unfortunately, include them in rectal cancers, but neoadjuvant chemotherapy protocols applied in rectal cancers may cause downregulation in TB[6,7,12-15]. Landau et al[1] excluded rectal cancers and detected higher TB levels in the right colon, especially in the cecum compared to the left colon. In our study, we excluded rectal cancer to not fall into this error, and we found that right colon cancers contained a higher proportion of high TB.

Several literature studies[16-18] using large population-based databases have reported higher mortality rates proximally compared to distal colon cancer; however, not all studies have confirmed the proximal tumor location negative prognostic effects. Some authors[19,20] suggest that the poor prognosis in proximal colon cancer may only be for stage 3 and 4 cancers not in stage 1 or 2 diseases. Our study did not find a statistically significant difference between location and overall survival. This may be because we excluded the stage 4 patients from the analysis.

Study Limitation

The limitation of our study is the cohort's small size, resulting from the comprehensive exclusion criteria to obtain standardized data in analyses. Another limitation is that the genetic profiles of these patients were not examined because we excluded metastatic cancers in our study. Currently, the genetic profile is used only for the selection of biological agents in the treatment of metastatic patients. Therefore, we did not look at the genetic profile of each of our patients in the past.

Conclusions

The results of this study showed that advanced age (> 65 years of age), lymphatic metastasis, and high TB affect colon cancer mortality. High TB is more common in right colon cancer. New studies are required to investigate whether the genetic changes that play a role in the etiology of colon cancer and show regional differences affect TB.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

We thank to Dr. Mehmet Ali Acikgoz for his help in collecting and analyzing the data.

Financial Disclosure
There is no financial support.

Ethical Approval
This study was obtained from the Ethics Committee of Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital (Date: 05.03.2021, No: 711).

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