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The Relationship of Tumor Budding with TNM Stage, Histopathological Parameters, and Survival in Colorectal Cancer

Kolorektal Kanserlerde Tümör Tomurcuklanmasının TNM Evresi, Histopatolojik Parametreler ve Sağkalım ile İlişkisi

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Abstract

Objectives: Tumor budding is a well-recognized histopathological feature linked to aggressive tumor behavior in colorectal cancer. This study aimed to investigate the association between tumor budding and TNM stage, histopathological parameters, and survival outcomes in patients undergoing surgical treatment for colorectal cancer.

Material and Methods: A retrospective analysis was conducted of 481 patients who underwent surgery for colorectal cancer between January 2015 and February 2021. Demographic data, clinical characteristics, pathological findings, and survival outcomes were evaluated. Patients were categorized according to the presence or absence of tumor budding. Comparative analyses were performed to assess differences in TNM stage, histopathological features, and survival between the two groups. Statistical evaluation was carried out using appropriate parametric and non-parametric methods.

Results: Tumor budding was detected in 22 patients (4.6%). No significant associations were identified between tumor budding and sex, emergency surgery, tumor localization, surgical procedure type, or CA 19-9 levels ($p>0.05$). Conversely, tumor budding was significantly associated with ASA score ($p=0.006$) and with preoperative CEA levels ($p=0.015$). Pathological assessment demonstrated correlations between tumor budding and advanced T stage ($p<0.001$), and between tumor budding and the presence of distant metastasis (M stage) ($p=0.004$). No statistically significant relationship was observed between tumor budding and N stage, lymphovascular invasion, or perineural invasion. Survival analysis showed no significant differences between patients with and without tumor budding in terms of local recurrence, distant recurrence, or mean overall survival.

Conclusion: Tumor budding is associated with advanced T stage and distant metastasis in colorectal cancer and may serve as a marker of aggressive tumor biology. However, its influence on recurrence and long-term survival was not clearly demonstrated. These findings support the consideration of tumor budding as an additional prognostic parameter alongside TNM staging.

Keywords: Colorectal cancer, tumor budding, TNM stage, metastasis, survival

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Öz

Giriş / Amaç: Tümör tomurcuklanması, kolorektal kanserlerde agresif tümör davranışı ile ilişkilendirilen önemli bir histopatolojik bulgudur. Bu çalışmada, kolorektal kanser nedeniyle opere edilen hastalarda tümör tomurcuklanmasının TNM evresi, histopatolojik parametreler ve sağkalım üzerindeki etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Ocak 2015-Şubat 2021 yılları arasında kolorektal kanser tanısı ile opere edilen 481 hasta retrospektif olarak incelendi. Hastaların demografik özellikleri, klinik verileri, patolojik bulguları ve sağkalım verileri değerlendirildi. Hastalar, tümör tomurcuklanması varlığına göre iki gruba ayrıldı. Tümör tomurcuklanması olan ve olmayan gruplar; TNM evresi, histopatolojik parametreler ve sağkalım açısından karşılaştırıldı. İstatistiksel analizler uygun parametrik ve non-parametrik testler kullanılarak yapıldı.

Bulgular: Hastaların 22'sinde (%4,6) tümör tomurcuklanması saptandı. Tümör tomurcuklanması ile cinsiyet, acil cerrahi, tümör yerleşimi, cerrahi türü ve CA 19-9 düzeyleri arasında anlamlı ilişki izlenmedi ($p>0,05$). Buna karşın, ASA skoru ($p=0,006$) ve preoperatif CEA düzeyi ($p=0,015$) tümör tomurcuklanması ile anlamlı ilişkili bulundu. Patolojik incelemede tümör tomurcuklanması, ileri T evresi ($p<0,001$) ve uzak metastaz varlığı (M evresi) ile anlamlı ilişki gösterirken ($p=0,004$), N evresi, lenfovasküler invazyon ve perinöral invazyon ile anlamlı ilişki saptanmadı. Sağkalım analizlerinde tümör tomurcuklanması ile lokal nüks, uzak nüks ve ortalama sağkalım arasında istatistiksel olarak anlamlı fark bulunmadı.

Tartışma / Sonuç: Tümör tomurcuklanması, kolorektal kanserde ileri T evresi ve uzak metastaz ile ilişkili olup agresif tümör biyolojisinin bir göstergesi olarak değerlendirilebilir. Ancak uzun dönem takiplerde nüks ve sağkalım üzerine etkisi net olarak gösterilememiştir. Bu bulgular, tümör tomurcuklanmasının TNM evrelemesine ek prognostik bir biyobelirteç olarak değerlendirilmesi gerektiğini düşündürmektedir.

Anahtar Kelimeler: Kolorektal kanser, tümör tomurcuklanması, TNM evresi, metastaz, sağkalım

Introduction

Tumor budding refers to the presence of isolated tumor cells or small clusters of tumor cells that detach from neoplastic glandular structures at the invasive margin of adenocarcinomas. Neoplasms demonstrating tumor budding are associated with a significantly more aggressive clinical behavior (1). In colorectal cancer (CRC), tumor budding has been recognized as an independent prognostic indicator and may facilitate patient stratification into risk groups that are more clinically informative than those based solely on TNM staging. Furthermore, it holds potential value in therapeutic decision-making, particularly in patients with T1 and T3 N0 (stage II, Dukes B) disease. However, despite its prognostic relevance, widespread implementation in routine pathological reporting has been limited by the absence of a standardized definition, especially concerning its qualitative criteria and quantitative assessment (2).

Tumor budding has been shown to enhance the metastatic potential of cancer cells by increasing their invasive properties, and numerous studies have demonstrated the impact of this phenomenon on clinical outcomes (3). In recent years, growing evidence has emerged regarding the effects of tumor budding, particularly on lymph node metastasis and overall survival (4). The histological characterization of tumor budding and its interaction with immune responses are important for a better understanding of cancer biology, and research in this field continues to expand (5). Several studies have reported that specific characteristics of tumor buds, such as their number and size, exert a significant prognostic impact on disease progression (2). As in many other malignancies, tumor budding in CRC is associated with an aggressive disease course, influencing treatment strategies and becoming an important criterion in patient management (6).

The present study was designed to explore the association of tumor budding with TNM stage, histopathological characteristics, and survival outcomes in patients who underwent surgical treatment for CRC.

Materials and Methods

The study was conducted as a single-center retrospective investigation at Çukurova University Faculty of Medicine Balcalı Hospital, in accordance with ethical and scientific approval granted by the Çukurova University Research Ethics Committee at its meeting (approval no: 162, date: 09.01.2026). A total of 481 patients who underwent surgery between January 2015 and February 2021 were evaluated. Demographic data (age and sex), ASA score, emergency surgery status, tumor location, surgical procedure, preoperative CEA and CA 19-9 levels, pathological findings (tumor type, TNM stage, lymphovascular invasion, number of retrieved lymph nodes, number of malignant lymph nodes, and presence of perineural invasion), and survival data (local recurrence, peritoneal recurrence, liver recurrence, para-aortic recurrence, and mean survival) were evaluated.

Patients were categorized into two groups according to whether tumor budding was present or absent. The study cohort comprised 22 patients with tumor budding and 459 without evidence of tumor budding.

Statistical Analysis

All study data were entered and analyzed using the SPSS for Windows, version 10.0 (IBM Corp., Armonk, NY, USA). Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Continuous variables were compared between groups using the two-sided Student's t-test for normally distributed variables, while the Mann-Whitney U test was used for variables that did not meet the normality assumption. A p-value of <0.05 was considered statistically significant.

Results

Comparative analysis between patients with and without tumor budding revealed no statistically significant associations with sex (p=0.098), emergency surgical intervention (p=0.604), tumor localization (p=0.301), surgical procedure type (p=0.096), or preoperative CA 19-9 levels (p=0.128). None of these variables showed a statistically significant association with the presence of tumor budding.

In contrast, tumor budding showed a statistically significant association with the ASA score (p=0.006) and preoperative CEA levels (p=0.015) (Table 1).

A comparison of pathological variables revealed no significant associations of tumor budding with tumor type (p=0.999), lymphovascular invasion (p=0.639), number of retrieved lymph nodes (p=0.437), number of metastatic lymph nodes (p=0.827), or presence of perineural invasion (p=0.642). However, when TNM staging was evaluated, significant associations were identified between tumor budding and T stage (p<0.001) and M stage (p=0.004). No significant association was found between tumor budding and N stage (p=0.740) (Table 2).

Survival outcomes were also compared. No statistically significant associations were observed between tumor budding and local recurrence (p=0.463), peritoneal recurrence (p=0.406), liver recurrence (p=0.531), para-aortic recurrence (p=0.623), or mean overall survival (months) (p=0.078) (Table 3, Figure 1).

Table 1. Demographic data

Variable	Tumor budding present (n=22)	Tumor budding absent (n=459)	p-value
Age (years), mean ± SD	64.13±11.42	60.84±12.48	0.226
Sex			0.098
Male	10 (45.5%)	289 (63.0%)	
Female	12 (54.5%)	170 (37.0%)	
ASA score			0.006
I	2 (10.5%)	191 (41.9%)	
II	15 (78.9%)	194 (42.5%)	
III	2 (10.5%)	71 (15.6%)	
Emergency surgery	2 (9.1%)	59 (12.9%)	0.604
Tumor location			0.301
Right colon	8 (36.4%)	112 (24.4%)	
Transverse colon	0	18 (3.9%)	
Left colon	1 (4.5%)	41 (8.9%)	
Sigmoid colon	5 (22.7%)	62 (13.5%)	
Rectosigmoid	1 (4.5%)	45 (9.8%)	
Rectum	5 (22.7%)	165 (35.9%)	
Multiple	2 (9.1%)	16 (3.5%)	
Type of surgery			0.096
Open	8 (36.4%)	250 (54.5%)	
Laparoscopic	14 (63.6%)	209 (45.5%)	
Preoperative CEA, median (range)	5.7 (0.5-70.30)	2.81 (0-6620)	0.015
Preoperative CA 19-9, median (range)	17.9 (0-325)	11.6 (0-8040)	0.128

SD: Standard deviation, ASA: American Society of Anesthesiologists, CEA: Carcinoembryonic antigen, CA: Cancer antigen

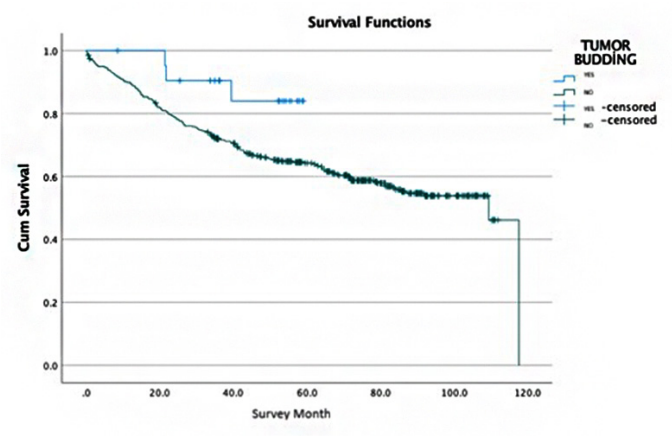

Figure 1. Kaplan-Meier survival curve

Table 2. Pathological characteristics

Variable	Present	Absent	p-value
Tumor type			0.999
Adenocarcinoma	22 (100%)	438 (95.4%)	
Other	0	21 (4.6%)	
T stage			<0.001
T0	0	30 (6.5%)	
T1	0	31 (6.8%)	
T2	1 (4.5%)	67 (14.6%)	
T3*	11 (50.0%)	71 (15.5%)	
T4	10 (45.5%)	260 (56.6%)	
N stage			0.740
N0	13 (59.1%)	255 (55.6%)	
N1	7 (31.8%)	121 (26.4%)	
N2	2 (9.1%)	82 (17.9%)	
M stage			0.004
M0	15 (68.2%)	407 (88.7%)	
M1	7 (31.8%)	52 (11.3%)	
Lymphovascular invasion	18 (81.8%)	356 (77.6%)	0.639
Number of lymph nodes, median (range)	17 (5-64)	15 (0-75)	0.437
Number of metastatic lymph nodes, median (range)	0 (0-6)	0 (0-46)	0.827
Perineural invasion	13 (59.1%)	248 (54.0%)	0.642

*: Statistically significant

Table 3. Survival data

Outcome	Present	Absent	p-value
Local recurrence	0	11 (2.4%)	0.463
Peritoneal recurrence	0	14 (3.1%)	0.406
Liver recurrence	1 (4.5%)	38 (8.3%)	0.531
Para-aortic recurrence	0	5 (1.1%)	0.623
Mean survival (months)	54.139	78.403	0.078

Discussion

In this study, which assessed the prognostic implications of tumor budding in CRC, tumor budding was significantly associated with advanced T stage and distant metastasis. Nevertheless, long-term follow-up analysis did not reveal a meaningful association between tumor budding and recurrence or overall survival outcomes.

The emergence of tumor budding is characterized by the detachment of individual tumor cells or small cellular clusters from the main tumor mass. These budding cells are regarded as precursors of metastatic spread, given their ability to infiltrate the extracellular matrix, enter lymphatic and vascular channels, and subsequently establish metastases in regional lymph nodes and distant organs. Histopathologically, tumor budding is widely considered a morphological correlate of epithelial-mesenchymal transitio (5,7-9).

Although initially established as a prognostic indicator in CRC, accumulating evidence has demonstrated its prognostic value in malignancies of other anatomical origins, including pancreatic, ampullary, gastroesophageal, pulmonary, and anal squamous cell carcinomas (3,6,10,11).

In 2016, the International Tumor Budding Consensus Conference established uniform criteria for the assessment and reporting of tumor budding and provided evidence-based guidance in line with the grading of recommendations assessment, development and evaluation framework (Table 4) (12).

When integrated with existing literature, this study demonstrates the relationship between tumor budding and TNM stages and indicates that tumor budding should be considered not only a histological criterion but also a prognostic biomarker for clinical outcomes. These findings necessitate further investigation into the defining characteristics of tumor budding, particularly in advanced-stage CRC (13).

The association between the number of tumor buds, their morphological characteristics, invasive potential, and survival rates highlights the complexity of cancer biology. In this context, the role of the tumor microenvironment must be considered. Specific features of tumor budding are associated with immune cell infiltration, and this interaction may influence clinical prognosis (14).

The histopathological evaluation of tumor budding in CRC is essential for detecting the initial steps of metastatic dissemination and should be considered within a multidisciplinary context. Incorporating tumor budding assessment into surgical decision-

Table 4. Statements of the ITBCC 2016 according to the GRADE system

No	Statement	Recommendation	Evidence
1	Tumor budding is defined as a single tumor cell or a cluster composed of four or fewer tumor cells.	Strong (vote: 22/22, 100%)	High
2	Tumor budding is an independent predictor of lymph node metastasis in pT1-stage colorectal cancer.	Strong (vote: 23/23, 100%)	High
3	Tumor budding is an independent predictor of survival in stage II colorectal cancer.	Strong (vote: 23/23, 100%)	High
4	Tumor budding should be considered together with other clinicopathological features in a multidisciplinary setting.	Strong (vote: 23/23, 100%)	High
5	Tumor budding should be counted on hematoxylin and eosin-stained sections.	Strong (vote: 19/22, 86%)	Moderate
6	Intratumoral budding exists in colorectal cancer and has been shown to be associated with lymph node metastasis.	Strong (vote: 22/22, 100%)	Low
7	Tumor budding should be assessed in a single hot spot area measuring 0.785 mm2 at the invasive front.	Strong (vote: 22/22, 100%)	Moderate
8	The hot spot method is recommended for the assessment of tumor budding in colorectal cancer.	Strong (vote: 22/22, 100%)	Moderate
9	A three-tier grading system should be used in combination with bud counting to facilitate risk stratification in colorectal cancer.	Strong (vote: 23/23, 100%)	Moderate
10	Tumor budding should be included in colorectal cancer reporting guidelines/protocols.	Strong (vote: 23/23, 100%)	High
11	Tumor budding is not synonymous with tumor grade.	Strong (vote: 23/23, 100%)	High

ITBCC: International tumor budding consensus conference, GRADE: Grading of recommendations assessment, development and evaluation

making, oncologic treatment planning, and systematic follow-up strategies may enhance current therapeutic algorithms and promote personalized management approaches (15).

In a large-scale meta-analysis encompassing 1.503 patients, Qu et al. (16) reported that high-grade tumor budding was significantly associated with adverse clinical outcomes in metastatic CRC. Consistent with these findings, our results indicate that tumor budding is a negative prognostic factor and is significantly associated with advanced T and M stages.

A substantial body of literature has investigated the association between tumor budding, nodal metastasis, and recurrence. In a study by Zhang et al. (17) tumor budding was found to be significantly correlated with both local recurrence and lymph node metastasis in patients undergoing surgery for early-stage CRC. Similarly, Rueda-Lara et al. (18) identified tumor budding as an unfavorable prognostic parameter that was significantly linked to recurrence in patients with stage II and III CRC. In contrast to these reports, our findings did not demonstrate a statistically significant relationship between tumor budding and either lymph node metastasis or tumor recurrence.

Study Limitations

The retrospective, single-center design and the relatively small number of patients with tumor budding may limit the study's generalizability and statistical power.

Conclusion

In patients treated surgically for CRC, the presence of tumor budding may reflect a more advanced T classification and a greater propensity for metastatic spread. Accordingly, such patients may warrant closer surveillance and consideration of more aggressive therapeutic strategies. Incorporating tumor budding into postoperative risk assessment may also facilitate the implementation of more individualized treatment approaches tailored to disease severity and metastatic potential.

Ethics

Ethics Committee Approval: The study was conducted as a single-center retrospective investigation at Çukurova University Faculty of Medicine Balcalı Hospital, in accordance with ethical and scientific approval granted by the Çukurova University Research Ethics Committee at its meeting (approval no: 162, date: 09.01.2026).

Informed Consent: Retrospective analysis.

Footnotes

Authorship Contributions

Concept/Design: Z.Z., B.Y., Data Collection or Processing: Z.Z., Y.K., İ.A., O.Y., Analysis or Interpretation: Z.Z., Y.K., İ.A., B.Y., İ.C.E., C.K.P., Literature Review: V.D., O.Y., Writing, Reviewing and Editing: Z.Z., V.D., İ.C.E., C.K.P.

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