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Tumour Budding as Independent Predictor for Clinical Staging of Colorectal Cancer: A Single Center Study

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ABSTRACT

Background: Colorectal cancer is a major global health issue, ranking third in incidence and second in mortality. Tumour budding has emerged as a significant independent prognostic factor, aiding in the prediction of recurrence and survival in colorectal cancer patients. This study aims to investigate its role in the clinical stage of colorectal cancer. ***Methods:*** This study was an observational analytic study with a cross-sectional design. The study sample was all colorectal cancer patients who underwent definitive surgery without neoadjuvant chemotherapy or radiotherapy at Prof. I.G.N.G Ngoerah Hospital, Denpasar, Indonesia. ***Results:*** Age in this study was found to have a mean of 59.56 ± 13.00. The most common gender is male, and the most common tumour location is the rectum, with as many as 17 (28.8%). The most histopathological grade was low grade, 48 (81.4%) subjects with the most histomorphology was moderately diff 33 (55.95). LVI result was negative 33 (55.9%), clinical stage III-IV 43 (72.9%), depth of invasion T3-T4 43 (72.9%), positive nodal status 40 (67.8%), and without metastasis 39 (66.1%). Budding tumours were found to be mostly low-grade with 23 (39%). High tumour budding was associated with the high clinical stage (III-IV) with RR 5.209 (95% CI 0.744-36.464; P=0.039), associated with depth of invasion T3-T4 with RR 5.209 (95% CI 0.744-36.464; P=0.039) and weakly correlated (r=0.283; p=0.030), also associated with positive nodal status with RR 6.650 (95% CI 0.942-46.922; P=0.014) and weakly correlated (r=0.386; p-0.003). ***Conclusions:*** High tumour budding is associated with a high clinical stage, high depth of invasion, and positive nodal status.

Keywords: colorectal cancer; depth of invasion; clinicopathology; clinical stage; Budding tumour; nodal status.

INTRODUCTION

Colorectal cancer is a significant global health issue. It ranks as the third most common cancer and has the second highest mortality rate. In Indonesia, as of 2020, colorectal cancer ranked fourth with an incidence of 34,189 cases (8.6%), following breast cancer, cervical cancer, and lung cancer. The mortality rate for colorectal cancer also ranked fourth in Indonesia, with 9,444 deaths (4.0%) [1].

Colorectal cancer is classified using the TNM system, which assesses the degree of cancer cell invasion into the colon wall, lymph node involvement, and metastasis. The prognosis of colorectal cancer varies depending on the cancer stage; for instance, stage I cancer has a 5-year survival rate of approximately 90%, whereas advanced-stage colorectal cancer has a 5-year survival rate of only 11%. This staging system is also useful in determining patient management. This highlights the importance of early detection in managing colorectal cancer to achieve the best prognosis [2].

However, there is heterogeneity in survival and recurrence rates even among colorectal cancers of the same stage. Studies have been conducted to identify other factors influencing colorectal cancer prognosis, such as tumour grade, histological subtype, vascular invasion, perineural invasion, and marginal status. One newly identified prognostic factor is tumour budding. Tumour budding consists of clusters of 1-4 undifferentiated tumour cells located at the invasive front of the tumour. It is considered a representation of the epithelial-mesenchymal transition process due to the loss of cell membrane stability. Tumour budding indicates the aggressiveness of a tumour and its ability to resist apoptosis. Studies have been conducted to understand the formation process of tumour budding [3,4].

According to the International Tumor Budding Consensus Conference (ITBCC) in 2016, tumour budding is established as an independent prognostic factor and can predict recurrence and survival in colorectal cancer [4]. Tumour budding also has clinical implications for determining the management of certain stages of colorectal cancer therapy [5].

Research on tumour budding is expected to aid in determining therapy management and predicting colorectal cancer prognosis more specifically, thereby reducing recurrence and mortality rates in colorectal cancer. Based on the theory and findings from several studies, the clinicopathology and presence of tumour budding in colorectal cancer are intriguing topics for further exploration.

METHOD

This study employs an observational analytic design with a cross-sectional approach to evaluate the relationship between tumour budding and the clinicopathological characteristics of colorectal cancer. The research was conducted at Prof. I.G.N.G. Ngoerah Central General Hospital, Denpasar, Indonesia from October to December 2023. The target population includes all colorectal cancer patients undergoing definitive surgery without neoadjuvant therapy, while the accessible population consists of patients at the hospital from 2019 to 2021. The study sample comprises patients meeting the inclusion and exclusion criteria, selected consecutively.

Inclusion criteria include patients with known clinical and histopathological stages who have undergone definitive surgery without neoadjuvant therapy. Exclusion criteria include patients with infectious diseases, autoimmune conditions, or other cancers, as well as those with incomplete clinical and histopathological data. The sample size was determined using the formula for cross-sectional studies with a significance level of $\alpha = 0.05$ and 80% power, resulting in a minimum sample requirement of 41, which was increased to 45 to anticipate potential dropouts.

A consecutive sampling technique was used, recruiting samples sequentially from medical records until the minimum number was reached. Primary data were obtained from clinical observations and histopathological examinations.

The dependent variable in this study is the clinicopathological parameters, including age, gender, tumour location, histopathological grade, depth of invasion, nodal status, and metastasis. The independent variable is the tumour budding observed in histopathological specimens. Tumour budding is defined as small clusters of malignant cells at the invasive tumour front, assessed based on grade. Clinicopathological characteristics include age, gender, tumour location, clinical stage, histopathological grade, depth of invasion, nodal status, and metastasis, categorised according to clinical standards.

Data collection was conducted using data collection sheets and computers for analysis. The research procedure began with obtaining ethical approval, followed by data collection from medical records, data selection, and extraction, and data analysis using SPSS version 26 software. Analysis was performed using the chi-square test with a 95% confidence level. Univariate analysis was used to describe the sample characteristics, while bivariate analysis and Spearman correlation were used to evaluate the relationship between variables.

RESULTS

This study involved 59 subjects, with characteristics summarised in Table 1. The average age of the subjects was 59.56 ± 13.00 years, with the majority being aged 50 or older (67.8%). Most subjects were male (81.3%). The most common tumour location was the rectum (28.8%), followed by the rectosigmoid region (27.1%). The majority of subjects had low-grade histopathology (81.4%) and moderately differentiated histomorphology (55.9%). A total of 55.9% of subjects tested negative for lymphovascular invasion (LVI), and the majority were in clinical stages III-IV (72.9%). The most common depth of invasion was T3-T4 (72.9%), with positive nodal status in 67.8% of subjects. Most subjects did not show metastasis (66.1%). Tumour budding was most frequently found at a low grade (39%).

TABLE 1: The Characteristics of the Research Data.

Characteristic	Category	Frequency	Percentage
Age	≥50 years	40	67.8%
	<50 years	19	32.2%
	Mean age ± SD	59.56 ± 13.00	
Gender	Male	49	81.3%
	Female	10	16.9%
Tumour Location	Rectum	17	28.8%
	Rectosigmoid	16	27.1%
	Ascending Colon	7	11.9%
	Transverse Colon	7	11.9%
	Sigmoid Colon	7	11.9%
	Caecum	4	6.8%
	Descending Colon	1	1.7%
Histopathological Grade	Low-grade	48	81.4%
	High-grade	11	18.6%

Characteristic	Category	Frequency	Percentage
Histomorphology	Moderately Differentiated	33	55.9%
	Well Differentiated	12	20.3%
	Poorly Differentiated	9	15.3%
	Mucinous Adenocarcinoma	5	8.5%
Lymphovascular Invasion (LVI)	Negative	33	55.9%
	Positive	26	44.1%
Clinical Stage	III-IV	43	72.9%
	I-II	16	27.1%
Depth of Invasion	T3-T4	43	72.9%
	T1-T2	16	27.1%
Nodal Status	Positive	40	67.8%
	Negative	19	32.2%
Metastasis	M0	39	66.1%
	M1	20	33.9%
Tumour Budding Grade	Low	23	39.0%
	Intermediate	21	35.6%
	High	15	25.4%

The correlation analysis between tumour budding and colorectal cancer clinicopathology is shown in Table 2. It was found that tumour budding has a weak but statistically significant correlation with tumour invasion depth and nodal status.

High tumour budding shows a weak correlation (r=0.283; p=0.030) with T3-T4 invasion depth and a weak correlation (r=0.386; p=0.003) with positive nodal status.

TABLE 2: Correlation of Tumour Budding with Colorectal Cancer Clinicopathology.

Variable	Tumour Budding Grade (n=59)			r	p-value
	Low (n=23)	Intermediate (n=21)	High (n=15)		
Age				***0,073***	***0,584***
≥50 years	14 (60,9%)	16 (76,2%)	10 (66,7%)		
<50 years	9 (39,1%)	5 (23,8%)	5 (33,3%)		
Mean ± SD	57,04±11,73	62,14±12,43	59,80±15,59	0,107	0,421
Gender				***0,045***	***0,734***
Male	18 (78,3%)	19 (90,5%)	12 (80,0%)		
Female	5 (21,7%)	2 (9,5%)	3 (20,0%)		
Location				***0,078***	***0,555***
Left Colon	18 (78,3%)	12 (57,1%)	11 (73,3%)		
Right Colon	5 (21,7%)	9 (42,9%)	4 (26,7%)		
Histopathological Grade				***0,245***	***0,061***
High Grade	2 (8,7%)	4 (19,0%)	5 (33,3%)		
Low Grade	21 (91,3%)	17 (81,0%)	10 (66,7%)		
Histomorphology				***0,020***	***0,881***
Well + Moderate	16 (69,6%)	19 (90,5%)	10 (66,7%)		
Poor + Mucinous	7 (30,4%)	2 (9,5%)	5 (33,3%)		
Lymphovascular Invasion (LVI)				***0,239***	***0,068***
Positive	7 (30,4%)	10 (47,6%)	9 (60,0%)		
Negative	16 (69,6%)	11 (52,4%)	6 (40,0%)		
Clinical Stage				***0,224***	***0,088***
Stage III-IV	15 (65,2%)	14 (66,7%)	14 (93,3%)		
Stage I-II	8 (34,8%)	7 (11,9%)	1 (6,7%)		
Depth of Invasion				***0,283***	***0,030****
T3-T4	15 (65,2%)	14 (66,7%)	14 (93,3%)		
T1-T2	8 (34,8%)	7 (33,3%)	1 (6,7%)		
Nodal Status				***0,386***	***0,003****
Positive	11 (47,8%)	15 (71,4%)	14 (93,3%)		
Negative	12 (52,2%)	6 (28,6%)	1 (6,7%)		
Metastasis				***0,166***	***0,209***
M1	6 (26,1%)	7 (33,3%)	7 (46,7%)		
M0	17 (73,9%)	14 (66,7%)	8 (53,3%)		

Note: *Significant.

The results of the bivariate analysis using the Chi-square test between tumour budding groups and colorectal cancer clinicopathology are presented in Table 3. There is a significant relationship between high tumour budding and clinical stage, depth of invasion, and nodal status. High tumour budding is associated with higher clinical stages (III-IV) with a relative risk (RR) of 5.209 (95% CI: 0.744-36.464; p=0.039), indicating that high tumour budding increases the risk of clinical stages III-IV by 5.2 times compared to stages I-II. Additionally, high tumour budding is associated with tumour invasion depth T3-T4 with an RR of 5.209 (95% CI: 0.744-36.464; p=0.039), and positive nodal status with an RR of 6.650 (95% CI: 0.942-46.922; p=0.014), indicating a 6.6-fold increased risk compared to negative nodal status.

TABLE 3: Relationship of Tumour Budding with Colorectal Cancer Clinicopathology.

Variable	Tumour Budding Grade (n=59)		RR	95% CI	p-value
	High (n=15)	Low-Intermediate (n=44)			
Age					
≥50 years	10 (66,7%)	30 (68,2%)	0,950	0,377-2,394	0,914
<50 years	5 (33,3%)	14 (31,8%)			
Gender					
Male	12 (80,0%	37 (84,1%)	0,816	0,281-2,372	0,715
Female	3 (20,0%)	7 (15,9%)			
Location					
Left Colon	11 (73,3%)	30 (68,2%)	0,828	0,304-2,254	0,708
Right Colon	4 (26,7%)	14 (31,8%)			
Histopathological Grade					
High Grade	5 (33,3%)	6 (13,6%)	2,182	0,932-5,107	0,091
Low Grade	10 (66,7%)	38 (86,4%)			
Histomorphology					
Well + Moderate	10 (66,7%)	35 (79,5%)	0,622	0,255-1,516	0,311
Poor + Mucinous	5 (33,3%)	9 (20,5%)			
Lymphovascular Invasion (LVI)					
Positive	9 (60,0%)	17 (38,6%)	1,904	0,777-4,664	0,150
Negative	6 (40,0%)	27 (61,4%)			
Clinical Stage					
Stage III-IV	14 (93,3%)	29 (65,9%)	5,209	0,744-36,464	0,039*
Stage I-II	1 (6,7%)	15 (34,1%)			
Depth of Invasion					
T3-T4	14 (93,3%)	29 (65,9%)	5,209	0,744-36,464	0,039*
T1-T2	1 (6,7%)	15 (34,1%)			
Nodal Status					
Positive	14 (93,3%)	26 (59,1%)	6,650	0,942-46,922	0,014*
Negative	1 (6,7%)	18 (40,9%)			
Metastasis					
M1	7 (46,7%)	13 (29,5%)	1,706	0,723-4,029	0,226
M0	8 (53,3%)	31 (70,5%)			

Note: *Significant.

DISCUSSION

Tumour budding is a histopathological phenomenon characterised by the presence of individual tumour cells or small clusters of cells (fewer than five) that are detached from the main tumour mass and found in the surrounding stroma or at the invasive front of the tumour. This is often observed in various types of cancer, including colorectal cancer, pancreatic cancer, and breast cancer. Tumour budding is frequently associated with Epithelial-Mesenchymal Transition (EMT), a process where epithelial cells lose their epithelial characteristics and acquire mesenchymal traits. This allows tumour cells to become more mobile and invasive, facilitating their spread from the primary tumour to surrounding tissues. Tumour-budding cells can penetrate the basement membrane and enter the surrounding stroma. This process indicates an early stage of metastasis, where tumour cells begin to spread from the primary tumour site.

Budding tumour cells interact with the stromal microenvironment, including fibroblasts, immune cells, and the extracellular matrix. These interactions can support the survival and growth of budding tumour cells and help them evade the body's immune response. Several molecular markers have been identified in budding tumour cells, including high expression of proteins such as vimentin (a mesenchymal marker) and N-cadherin, along with decreased expression of E-cadherin (an epithelial marker).

These markers indicate phenotypic changes associated with EMT and a higher invasive potential.

The presence of tumour budding is often associated with a poorer prognosis in cancer patients. This is because budding cells are more likely to cause metastasis, a major factor in cancer malignancy. Tumour budding is often used as a prognostic parameter in cancer assessment. Overall, tumour budding reflects the ability of tumour cells to change shape and adapt to their microenvironment, allowing them to spread and establish in new locations. This phenomenon is a focus of research due to its significant role in cancer invasion and metastasis and its potential as a therapeutic target in cancer treatment.

The average age in this study was 59.56 ± 13.00 years, with the majority being aged ≥50 years, accounting for 40 (67.8%) subjects. This result is consistent with Mulia et al. at Prof. I.G.N.G. Ngoerah Central General Hospital, Denpasar, Indonesia, where 144 colorectal cancer patients had an average age of 53.6 ± 12.2 years, and those aged >50 years were the majority, with 92 respondents (63.9%) [6]. Similar findings were reported by Maker & Sriwidyani, where most of the 82 colorectal cancer patients were aged ≥50 years (84.0%) [5]. However, this differs from Pestana et Martin, where colorectal cancer is often found in the elderly, occurring more frequently in the sixth and seventh decades of life, although there has been an observed increase in incidence among younger individuals in recent decades [7].

Age in this study did not correlate with or relate to tumour budding. Similar results were found in previous studies [8,9]. In a study by Huh et al., involving 3707 colorectal cancer patients with a median age of 60 years (range 16-90 years), the majority aged ≥60 years, no association was found between age and tumour budding (p=0.202) [10]. Similar results were reported by Maker & Sriwidyani with a p-value of 0.288 [5].

The majority of subjects were male. According to WHO data from 2019, 60% of cases occurred in males. There is geographical variation in incidence worldwide, with the highest incidence estimated in Australia and New Zealand, with an Age Standardised Rate (ASR) of 44.8 per 100,000 men and 32.2 per 100,000 women [1]. In Indonesia, colorectal cancer is the third most common malignancy, having risen from the sixth position [11]. At Prof. I.G.N.G. Ngoerah Central General Hospital, Denpasar, Indonesia from 2016-2017, there were 137 colorectal cancer patients, with more males than females in the case group. The male sample group consisted of 73 individuals (53.3%), while there were 64 females (46.7%) [12]. Similar results were reported by Mulia, where colorectal cancer patients at Prof. I.G.N.G. Ngoerah Central General Hospital, Denpasar, Indonesia from 2018-2022 included 77 males (53.5%) and 67 females (46.5%) [6]. Maker & Sriwidyani also found similar results, with 51 (62.2%) males [5].

Gender was not found to correlate with or relate to tumour budding, consistent with previous studies [4,9]. In the study by Huh et al., involving 3707 colorectal cancer patients, 2,227 (60%) were male, and no association was found with tumour budding (p=0.496) [10]. Similar results were reported by Maker & Sriwidyani with a p-value of 0.077 [5].

The most common tumour location was the rectum, with 17 (28.8%) cases, and overall, the left colon was the most common site, with 41 subjects (69.4%). This is consistent with Mulia, where the rectum was the most frequent location, with 91 (63.2%) cases [6]. Similar findings were reported by Maker & Sriwidyani, who found the left colon to be the most common site, with 55 (67.1%) cases [5]. At the Anatomical Pathology Department of RS Al-Islam Bandung from January 2012 to December 2017, the most common site of colorectal cancer was the rectum, with 37 cases (60.66%). This study's results align with previous research conducted at Immanuel Hospital Bandung from January 2009 to December 2011, which stated that the highest predilection site for colorectal cancer was the rectum (68.2%). Factors influencing this include diet. Certain types of food, such as low-fibre, high-protein, and high-fat diets, can prolong faecal transit time. This can trigger colorectal cancer, particularly in the rectal area, due to the rectum's function as a transit and defecation site [13].

The study contrasts with the findings of Fernanda, where the most common location was the ascending colon at 12 (36.4%) [14], aligning with research by Myers et al., which indicated that the right colon, including the ascending colon, is the most frequent site for colon tumours [15], with a percentage of 19%. Huh et al. found that out of 3,707 colon cancer patients, 2,692 (72.6%) had colon cancer compared to rectal cancer [10].

Bivariate analysis and correlation tests found no significant association between high tumour budding and tumour location. This result is consistent with systematic reviews, which stated that there is no relationship between tumour location and tumour budding [2,16]. A study by Huh et al. also found no association between location and high tumour budding (p=0.343) [10]. Similar results were reported by Maker & Sriwidyani with a p-value of 0.494 [5].

The most common histopathological grade was low grade, with 48 (81.4%) subjects, and the most common histomorphology was moderately differentiated, with 33 (55.95%) subjects. Similar results were found by Maker & Sriwidyani, who reported a predominance of low-grade cases, 74 (90.1%) [5]. A study by Mulia found that the most common histopathological feature in colon cancer patients was moderately differentiated, with 59 (41%) [6]. This study aligns with Utara, which showed well-differentiated adenocarcinoma in 69 respondents (49%) [17]. Research conducted at the Digestive Surgery Clinic of Hasan Sadikin Central General Hospital, Bandung, Indonesia from January

2005 to December 2008 also found that well-differentiated adenocarcinoma was the most common histopathological finding, at 57.1% [13].

Tumour budding is not directly related to histological grading because they evaluate different aspects of tumour characteristics. Tumour budding assesses the presence and distribution of single tumour cells or small clusters of tumour cells at the tumour margin, reflecting the potential for invasion and migration into surrounding tissues. In contrast, histological grading evaluates the degree of differentiation of tumour cells based on their microscopic structure, indicating how similar the tumour cells are to normal tissue cells.

Tumour budding is considered an independent prognostic factor associated with the risk of metastasis and poorer clinical outcomes. It focuses more on the invasive behaviour of tumour cells, while histological grading relates to tumour aggressiveness based on the degree of cell differentiation. High-grade tumours (less differentiated) tend to be more aggressive compared to low-grade tumours (more differentiated). Tumour budding is assessed by counting the number of budding foci at the tumour edge under specific microscopic magnification, typically done at the tumour invasion area. In contrast, histological grading is evaluated based on the overall microscopic appearance of the tumour, including cellular structure, growth patterns, and other morphological features. Tumour budding is often used as a marker to predict the risk of local invasion and metastasis spread, while histological grading is used to assess general prognosis and determine the aggressiveness of the required therapy. Tumour budding is related to the ability of tumour cells to detach from the main mass, migrate, and invade surrounding tissues, whereas histological grading is related to the maturity and differentiation of tumour cells, indicating how closely tumour cells resemble normal tissue cells.

Therefore, although both provide important information about tumour characteristics, tumour budding, and histological grading evaluate different aspects of tumour biology and have different prognostic values, so they are not directly related to each other. Bivariate analysis and correlation tests found no significant association between high tumour budding and histopathological grade and histomorphological features. This study aligns with Rusche et al., who found no association between histopathological grade and histomorphological features with tumour budding [18]. Similar results were reported by Maker & Sriwidyani, who found no association between histopathological grade and tumour budding, with a p-value of 0.089 [5]. A study by Huh et al. found that the most common histomorphology was well-moderate, 3,394 (91.5%), which was significantly associated with tumour budding with a p-value <0.001. However, after multivariate testing, no significant difference in the risk of differentiation (poor-mucinous) with tumour budding was found, with an OR of 1.222 (0.834–1.790; P=0.304) [10].

The most common LVI result was negative, with 33 (55.9%) cases, and bivariate analysis and correlation tests found no significant association between high tumour budding and LVI. The distribution of negative LVI data aligns with research conducted by Gunasekaran et al. at Prof. I.G.N.G. Ngoerah Central General Hospital, Denpasar, Indonesia from 2013-2017, with 72 cases (59.5%) of negative LVI. Huh et al. (2019) also found a majority of negative LVI cases, at 2,235 (60.3%) [19]. Previous studies found no association between LVI and tumour budding [2,16].

Lymphovascular invasion (LVI) is defined as the presence of cancer cell invasion into blood and lymphatic vessels. LVI is one of the prognostic factors in colorectal cancer. The presence of positive LVI is associated with a poorer prognosis in colorectal cancer. Like tumour budding, LVI reflects the aggressiveness of colorectal cancer. Although both have similar clinical implications, they are independent prognostic factors and thus are not related to each other.

The most common metastasis result was without metastasis, with 39 (66.1%) subjects, and bivariate analysis and correlation tests found no significant association between high tumour budding and metastasis. This study's findings differ from those of Nakamura et al., who found that metastasis to the liver and lungs in colorectal cancer was associated with high tumour budding, with an odds ratio of 0.1291, P<0.0001, although the increase in incidence did not reach 1. The difference in findings with Nakamura may be due to the small number of subjects with metastasis in this study, necessitating specific examination in metastasis cases to provide more representative results [20].

The most common tumour budding was low-grade, with 23 (39%) subjects. This result is consistent with Huh et al., who found the majority to be low, at 1,671 (45.1) [10]. This differs from the findings of Maker & Sriwidyani, who found the majority to be high-grade, with 42 (51.2%) [5]. The most common clinical stage was III-IV, with 43 (72.9%) subjects, and it was found that high tumour budding is associated with high clinical stages (III-IV) in colorectal cancer, with an RR of 5.209 (95% CI 0.744-36.464; P=0.039). This is similar to the findings of Huh et al., who reported a p-value <0.001 [10].

The study found that the most common depth of invasion was T3-T4, with 43 (72.9%) subjects and high tumour budding was associated with a high degree of tumour invasion depth in colorectal cancer (T3-T4), with an RR of 5.209 (95% CI 0.744-36.464; P=0.039) and a weak correlation (r=0.283; p=0.030). Depth of invasion is one of the risk factors for metastasis to lymph nodes (nodal status). This result is similar to the findings of Huh et al. (2019),

who found a majority of the T3-T4 population, at 2,642 (71.3%), with a significant association with tumour budding, p<0.001, and RR 26.290 (8.283–83.444; <0.001). Similar results were also found in previous research at Prof. I.G.N.G. Ngoerah Central General Hospital, Denpasar, Indonesia. Systematic literature reviews also state that T3-T4 invasion depth is significantly associated with tumour budding [2,4,8,16].

The most common nodal status was positive, with 40 (67.8%) subjects, and high tumour budding was associated with positive nodal status in colorectal cancer, with an RR of 6.650 (95% CI 0.942-46.922; P=0.014) and a weak correlation (r=0.386; p=0.003). Similar results were reported by Maker & Sriwidyani, who found a significant association between nodal status and tumour budding with a p-value <0.001, although the majority of cases had negative nodal status, at 49 (61.2%) [5]. A study by Huh et al. found the majority of the nodal population to be negative, at 2,642 (71.3%), and high nodal status was significantly associated with tumour budding, p<0.001, RR 6.731 (4.669–9.703) [10]. Systematic literature reviews also state that nodal status is significantly associated with tumour budding [2,4,8,16].

Tumour budding is thought to reflect epithelial-mesenchymal transition (EMT), where cancer cells lose their epithelial characteristics, such as polarity and adhesion, during EMT. With mesenchymal characteristics, cancer cells have migratory capacity and become more resistant to apoptotic signals. Tumour cells with these properties begin to detach from the main tumour, either as individual cells or in small clusters. The loss of tumour cell adhesion from the main tumour is thought to be an initial step in the metastasis process [21]. The presence of tumour budding in colorectal cancer is significantly associated with poor prognosis. Therefore, the study results suggest that higher tumour budding will influence higher clinical stage, invasion depth, and positive nodal status, which are closely related to poor prognosis in patients, necessitating comprehensive management. This is consistent with previous research that found a significant association with lymph node metastasis, clinical stage, and pathological stage T [22].

Tumour budding has significant implications in the context of poor clinical outcomes for patients because it indicates the presence of single tumour cells or small clusters of tumour cells detaching from the main mass and spreading to surrounding tissues. This indicates the invasive nature of the tumour, often associated with aggressive behaviour and the ability to spread to other parts of the body. Tumour budding is often associated with an increased risk of metastasis, both to regional lymph nodes and distant organs. The presence of tumour budding may indicate that the tumour is more likely to spread from its original site, worsening the patient's prognosis. Patients with high tumour budding tend to have a poorer response to therapy, including surgery, chemotherapy, and radiotherapy. Tumour cells exhibiting tumour budding may be more resistant to conventional therapy, making disease control more difficult.

Tumour budding is associated with an increased risk of local recurrence after surgery. Patients with tumour budding may be more likely to experience cancer recurrence at the same site or elsewhere, even after seemingly successful treatment. Many studies indicate that tumour budding is a significant negative prognostic factor. Patients with high levels of tumour budding often have shorter survival compared to those without or with low levels of tumour budding. The presence of tumour budding can lead to categorising patients into higher-risk groups, which can influence treatment choices and overall patient management strategies [2,4,8,16].

Tumour budding can relate to decisions regarding adjuvant therapy, such as chemotherapy, because it is associated with poorer prognosis, indicating a higher potential for invasion and metastasis. Patients with high levels of tumour budding may require more aggressive additional therapy to control cancer spread. Tumour budding indicates the ability of tumour cells to spread; its presence can be used to identify patients at higher risk of metastasis. This can be a factor in considering the use of adjuvant chemotherapy after surgery to reduce the risk of recurrence and cancer spread. Assessment of tumour budding can help stratify patients into different risk groups. Patients with high-level tumour budding may be placed in a high-risk group and therefore may be advised to undergo adjuvant chemotherapy. Information about tumour budding can be used alongside other prognostic factors (such as tumour size, lymph node involvement, and surgical margin status) to make more precise and individualised decisions regarding the need for additional therapy. Some cancer treatment guidelines have begun to consider tumour budding as a factor in determining treatment plans. In colorectal cancer, adjuvant chemotherapy is recommended for patients with significant tumour budding, even if their cancer stage is relatively early. Overall, tumour budding is an important indicator of cancer aggressiveness that can influence decisions regarding additional therapy, such as chemotherapy, to improve patient treatment outcomes.

Research on the relationship between tumour budding and clinicopathological features of colorectal cancer using medical record data has several limitations to consider, such as limitations in medical record data. Medical records are often incomplete or inconsistent. Some important information may be missing or not well-documented, which can affect the validity of the research results. Different medical records may use different terminology or recording formats, complicating the data analysis process. Sample selection from medical records can lead to selection bias, especially if data is only taken from patients receiving care at one specific hospital or clinic. This can affect the generalisability of the research results.

Additionally, other clinicopathological characteristics can differ between pathologists. Variability in interpretation can affect data reliability. Medical record data may not cover a long enough period to observe disease progression and the long-term effects of tumour budding on patient clinical outcomes. Research using medical record data is often retrospective, which has weaknesses compared to prospective studies. Uncontrolled or unrecorded factors in medical records can influence results.

Patients with colorectal cancer may receive various types of treatment based on doctor preference or specific patient conditions. This variability can affect the relationship between tumour budding and clinicopathological features. Medical record data may not always include the detailed information needed for in-depth analysis, such as molecular or genetic data that can help understand the mechanisms behind tumour budding. Medical records can contain information bias if data is not recorded objectively or if there are errors in data recording.

Research using data from a single institution may not be generalisable to a broader population with different characteristics. Addressing these limitations requires a careful approach in research design, including the use of data validation techniques, appropriate statistical analysis, and efforts to collect more comprehensive and standardised data.

Tumour budding is not yet a routine component in histopathological examinations. This leads to limitations in the amount of data available and potential bias, with many samples being excluded due to incomplete data. The quality and representation of tissue samples taken for histopathological analysis can affect tumour budding assessment. Unrepresentative or degraded samples can provide inaccurate information. Therefore, making tumour budding a routine examination component will improve the representation of the samples taken, providing more accurate research results.

Tumour budding is part of a complex and multifactorial tumour biology process. Understanding how tumour budding interacts with other factors, such as the tumour microenvironment, immune system, and genetic factors, is a significant challenge. The identification and validation of specific biomarkers related to tumour budding are still in development. The lack of reliable biomarkers limits the ability to perform more accurate diagnosis and prognosis. Variations in clinicopathological presentation between patients and different cancer types can affect the generalisation of research results. This requires studies with larger and more diverse populations to draw stronger conclusions.

External factors such as differences in treatment methods, variations in surgical techniques, and individual patient factors such as comorbidities can affect research results and make interpretation more complex. Despite facing many challenges, research on tumour budding remains important as it can provide valuable insights into the mechanisms of cancer invasion and metastasis, as well as the potential for developing new diagnostic and therapeutic strategies. Overcoming these challenges requires a multidisciplinary approach, collaboration between laboratories, and the use of advanced technology to enhance the accuracy and consistency of research results.

CONCLUSIONS

This study concludes that high tumour budding is an independent predictor for clinical stage of colorectal cancer. It associated with high clinical stage, high depth of invasion and positive nodal status.

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