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ASSOCIATION OF TUMOUR BUDDING WITH LYMPHOVASCULAR INVASION AND HISTOLOGICAL GRADE IN COLORECTAL ADENOCARCINOMA: A PROSPECTIVE OBSERVATIONAL STUDY

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ARTICLE HISTORY	ABSTRACT
Received on: 22-08-2026 Revised on: 09-09-2026 Accepted on: 15-10-2026	Background: Tumour budding is increasingly recognized as a marker of aggressive behaviour in colorectal carcinoma. This study aimed to evaluate its association with lymphovascular invasion (LVI), histological grade, and other adverse pathological features.
Keywords: Colorectal adenocarcinoma; Tumour budding; Lymphovascular invasion; Histological grade; Nodal metastasis.	Methods: This prospective observational study included 120 colorectal adenocarcinoma resection specimens. Tumour budding was assessed according to the ITBCC criteria and classified as Bd1, Bd2, or Bd3. Associations with LVI, histological grade, pT stage, nodal status, tumour deposits, and pathological stage were analysed.
Corresponding Author Enoch Raju Kanikella	Results: Bd1, Bd2, and Bd3 were identified in 46.7%, 30.0%, and 23.3% of cases, respectively. The incidence of LVI increased from 19.6% in Bd1 to 60.7% in Bd3, while the proportion of high-grade tumours increased from 7.1% to 50.0% (both $p < 0.001$). Higher tumour budding grades were also associated with nodal positivity, advanced pT stage, tumour deposits, and higher pathological stage. On multivariable analysis, LVI, high histological grade, and nodal positivity remained independently associated with intermediate-to-high tumour budding.
	Conclusion: Tumour budding closely reflects adverse pathological features in colorectal adenocarcinoma and may serve as a valuable histopathological marker of aggressive tumour behaviour.

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INTRODUCTION

There is significant biological heterogeneity in colorectal adenocarcinoma, with tumours of similar anatomical stage having very different invasive behaviour and clinical outcomes. In addition to traditional parameters like depth of invasion, lymph-node status, lymphovascular invasion (LVI) and histological grade, the morphology of the invasive tumour front has been gaining more attention. One such feature is called tumour budding, and is defined as isolated malignant cells or very small clusters that have broken away from the bulk of the tumour, a pattern believed to be associated with higher invasive and metastatic potential. In colorectal cancer, prominent budding was shown to be significantly associated with increased recurrence and reduced long-term survival, in early studies by Hase et al. [1]. This was later validated by Ueno et al. who demonstrated that budding was a negative prognostic factor in rectal carcinoma and retained prognostic information in addition to the other pathological factors [2].

The importance of tumour budding is even more pronounced in early disease, where conventional staging alone may not be sufficient to identify biologically aggressive tumours. High budding in stage I–II colorectal carcinoma was strongly associated with an adverse clinical course, and was shown to be an indicator of occult invasive potential in apparently localized disease by Prall et al. [3]. This has been supported by a wider body of pooled evidence. Rogers et al. conducted a meta-analysis of 34 studies involving 7,821 patients, which revealed that tumour budding is linked to lymph-node metastasis, recurrence and colorectal cancer-related mortality, thus reflecting multiple aspects of tumour aggressiveness [4].

Previous studies have been difficult to compare with each other because there was significant variation in the definition, counting, and grading of buds. The International Tumor Budding Consensus Conference solved this issue by proposing that a bud should be considered a single tumour cell or a cluster of up to four cells, measured in a standardised 0.785 mm² hotspot at the invasive front. The three-tier system that resulted assigns budding to Bd1 (0–4

buds), Bd2 (5–9 buds), and Bd3 (10 or more buds) [5]. In stage I–IV colorectal cancer, the ITBCC system was reproducible, and budding category was correlated with more advanced pT, pN, and overall TNM stage, as shown by subsequent validation by Dawson et al. [6].

Tumour budding is also found to be closely related to other unfavourable histological features.

High-grade intratumoural budding in stage II colorectal cancer was found to be associated with LVI and unfavourable outcome, indicating that budding and vascular invasion may be related aspects of an aggressive invasive phenotype [7]. In an Indian series, Deb and Jacob identified significant associations between intratumoural and peritumoural budding and both lymphovascular emboli and lymph-node metastasis, but not tumour grade [8]. These variable results highlight the need to consider budding along with other pathological parameters such as LVI, differentiation, and nodal status in each population.

The present prospective observational study, therefore, assessed the involvement of tumour budding in colorectal adenocarcinoma (CRC) using the standardized ITBCC approach and correlated it with the presence of LVI and histological grade. Secondary analyses were carried out to determine the association of increasing budding category with depth of invasion, lymph-node metastasis, perineural invasion, tumour deposits, and pathological stage.

METHODS

Study design and case selection

The study was a prospective observational histopathology study of 120 consecutive colorectal adenocarcinoma resection specimens received at a tertiary care centre from January to December 2025. The cases included were primary colorectal adenocarcinomas with a sufficient invasive tumour front and complete essential histopathological data. Biopsy-only specimens, recurrent tumours, metastatic tumours to the colorectum, non-adenocarcinoma malignancies, specimens with insufficient invasive front, specimens with major tissue artefact, and rectal cancers treated with neoadjuvant chemotherapy and/or radiotherapy were excluded.

Histopathological assessment

Tumour site, size, histological subtype, histological grade, depth of invasion, lymph-node status, lymphovascular invasion (LVI), perineural invasion (PNI), tumour deposits, resection-margin status, distant metastasis, and pathological stage were evaluated in resection specimens. Histological grade was recorded as well, moderately or poorly differentiated, and further classified as low grade (well/moderately differentiated) or high grade (poorly differentiated). Overall LVI was deemed to be present if either lymphatic invasion or venous invasion was seen.

Tumour budding was evaluated at the invasive front based on the International Tumor Budding Consensus Conference (ITBCC) method. A tumour bud was described as a single tumour cell or a cluster of up to four tumour cells. Buds were counted in a 0.785-mm² hotspot and classified as Bd1 (0–4 buds), Bd2 (5–9 buds), or Bd3 (≥10 buds). Bd2 and Bd3 were pooled together as intermediate/high budding and compared to Bd1 for regression analyses. Pathological pT and pN categories and overall stage groups were determined according to AJCC criteria. Node positivity was determined by the presence of metastatic tumour in the regional lymph nodes, whereas

pN1c was only given when there were no positive lymph nodes but there were tumour deposits.

Study outcomes

The primary outcomes were the correlations between the tumour-budding category and LVI, and between the tumour-budding category and histological grade. Secondary analyses were performed to assess the associations between tumour budding and pT stage, nodal metastasis, PNI, tumour deposits and pathological stage.

Statistical analysis

Data for continuous variables were presented as mean ± SD and for categorical variables as n (%). The chi-square test or Fisher exact test was used to assess the association between budding categories and categorical pathological variables (where applicable), while the Kruskal–Wallis test was used to assess the association between budding categories and ordinal variables (where applicable). Cramér's V was used for the principal categorical associations. To identify the factors associated with intermediate/high budding (Bd2/Bd3 vs. Bd1), binary logistic regression was used. Univariable analysis was performed on age, sex, tumour size, tumour location, histological grade, LVI, PNI, advanced pT stage, nodal positivity and tumour deposits. A multivariable model was created that was parsimonious and included clinically relevant adverse pathological features; results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) and p values. Variance inflation factors were used to check for multicollinearity. The overall performance of the model was assessed by the likelihood-ratio test, Hosmer–Lemeshow goodness-of-fit test, and area under the receiver-operating-characteristic curve. All tests were two-tailed and p<0.05 was deemed statistically significant.

RESULTS

Clinicopathological characteristics

A total of 120 colorectal adenocarcinoma resection specimens were evaluated. The mean age was 62.2 ± 9.0 years, and 63 (52.5%) patients were male. Conventional adenocarcinoma was the predominant histological subtype, while most tumours were moderately differentiated and pT3. Lymphovascular invasion (LVI) was identified in 45 (37.5%) cases, perineural invasion (PNI) in 26 (21.7%), and tumour deposits in 15 (12.5%). The overall clinicopathological profile is summarized in Table 01.

Table 01: Clinicopathological characteristics of the study population

Characteristic	Overall (N=120)
Age, years	62.2 ± 9.0
Male sex	63 (52.5%)
Tumour size, cm	4.5 ± 1.4
Tumour location	
Right colon	45 (37.5%)
Left colon	37 (30.8%)
Rectum/rectosigmoid	38 (31.7%)
Histological subtype	
Conventional adenocarcinoma	95 (79.2%)
Mucinous adenocarcinoma	9 (7.5%)
Signet-ring cell carcinoma	2 (1.7%)
Medullary carcinoma	2 (1.7%)
Other adenocarcinoma subtype	12 (10.0%)
Histological grade	
Well differentiated	25 (20.8%)

Moderately differentiated	69 (57.5%)
Poorly differentiated	26 (21.7%)
pT stage	
pT1	5 (4.2%)
pT2	24 (20.0%)
pT3	63 (52.5%)
pT4a	15 (12.5%)
pT4b	13 (10.8%)
pN stage	
pN0	58 (48.3%)
pN1a	20 (16.7%)
pN1b	19 (15.8%)
pN1c	6 (5.0%)
pN2a	9 (7.5%)
pN2b	8 (6.7%)
Lymphovascular invasion	45 (37.5%)
Perineural invasion	26 (21.7%)
Tumour deposits	15 (12.5%)
Distant metastasis at resection	20 (16.7%)
AJCC pathological stage	
Stage I	16 (13.3%)
Stage II	31 (25.8%)
Stage III	53 (44.2%)
Stage IV	20 (16.7%)

Data are mean $\pm$ SD or n (%).

Distribution of tumour budding

According to the ITBCC classification, 56 (46.7%) tumours were classified as Bd1, 36 (30.0%) as Bd2, and 28 (23.3%) as Bd3. Increasing budding category was associated with several adverse pathological features, particularly higher histological grade, LVI, advanced pT stage, nodal metastasis, tumour deposits, and higher pathological stage (Table 02).

Table 02: Clinicopathological characteristics according to tumour-budding category

Characteristic	Bd1 (n=56)	Bd2 (n=36)	Bd3 (n=28)	Test statistic	p value
Histological grade				$\chi^2=22.59$	<0.001
Well differentiated	17 (30.4%)	5 (13.9%)	3 (10.7%)		
Moderately differentiated	35 (62.5%)	23 (63.9%)	11 (39.3%)		
Poorly differentiated	4 (7.1%)	8 (22.2%)	14 (50.0%)		
Lymphovascular invasion				$\chi^2=15.51$	<0.001
Absent	45 (80.4%)	19 (52.8%)	11 (39.3%)		
Present	11 (19.6%)	17 (47.2%)	17 (60.7%)		
Perineural invasion				$\chi^2=5.38$	0.068
Absent	49 (87.5%)	26 (72.2%)	19 (67.9%)		
Present	7 (12.5%)	10 (27.8%)	9 (32.1%)		
pT stage				H=13.28	0.001
pT1	2 (3.6%)	3 (8.3%)	0 (0.0%)		
pT2	18 (32.1%)	4 (11.1%)	2 (7.1%)		
pT3	30 (53.6%)	17 (47.2%)	16 (57.1%)		
pT4a	4 (7.1%)	7 (19.4%)	4 (14.3%)		
pT4b	2 (3.6%)	5 (13.9%)	6 (21.4%)		
Node positivity				$\chi^2=23.21$	<0.001
Absent	41 (73.2%)	18 (50.0%)	5 (17.9%)		
Present	15 (26.8%)	18 (50.0%)	23 (82.1%)		
Tumour deposits				Exact test	0.014
Absent	53 (94.6%)	32 (88.9%)	20 (71.4%)		
Present	3 (5.4%)	4 (11.1%)	8 (28.6%)		
Pathological stage				H=19.71	<0.001
Stage I	13 (23.2%)	3 (8.3%)	0 (0.0%)		
Stage II	21 (37.5%)	7 (19.4%)	3 (10.7%)		
Stage III	16 (28.6%)	19 (52.8%)	18 (64.3%)		
Stage IV	6 (10.7%)	7 (19.4%)	7 (25.0%)		

Data are n (%). χ^2 , Pearson chi-square statistic; H, Kruskal–Wallis statistic. An exact Fisher–Freeman–Halton test was used for tumour deposits because of sparse cell counts.

Association of tumour budding with lymphovascular invasion

LVI showed a clear graded relationship with increasing tumour budding. LVI was present in 11 (19.6%) Bd1 tumours, compared with 17 (47.2%) Bd2 and 17 (60.7%) Bd3 tumours (Figure 01). The association was statistically significant and of moderate magnitude ($\chi^2=15.51$, $p<0.001$; Cramér's $V=0.360$).

When Bd2 and Bd3 were combined, the presence of LVI was associated with approximately 4.6-fold higher odds of intermediate/high tumour budding compared with Bd1 (OR 4.64, 95% CI 2.04–10.55; $z=3.66$, $p<0.001$) (Table 03).

Association of tumour budding with histological grade

High-grade morphology also increased progressively across budding categories. High-grade tumours constituted 4 (7.1%) of Bd1, 8 (22.2%) of Bd2, and 14 (50.0%) of Bd3 cases (Figure 02). The association between tumour budding and two-tier histological grade was significant ($\chi^2=20.21$, $p<0.001$; Cramér's $V=0.410$), with a significant increasing trend in high-grade morphology across Bd1 to Bd3 ($z=4.07$, $p<0.001$) (Table 03).

Table 03: Primary associations of tumour budding with lymphovascular invasion and histological grade

Pathological feature	Bd1 (n=56)	Bd2 (n=36)	Bd3 (n=28)	Test statistic	p value	Cramér's V
LVI present	11 (19.6%)	17 (47.2%)	17 (60.7%)	$\chi^2=15.51$	<0.001	0.360
High histological grade	4 (7.1%)	8 (22.2%)	14 (50.0%)	$\chi^2=20.21$	<0.001	0.410

For LVI, comparison of Bd2/Bd3 versus Bd1 yielded OR 4.64 (95% CI 2.04–10.55), $z=3.66$, $p<0.001$. For histological grade, the logistic trend across Bd1–Bd3 was significant ($z=4.07$, $p<0.001$). LVI, lymphovascular invasion.

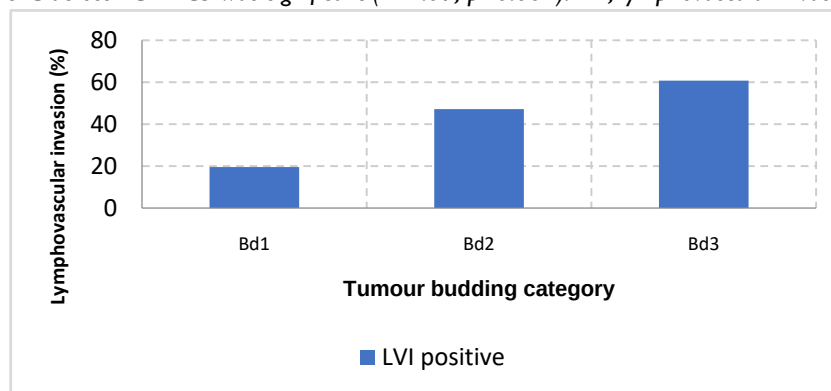


Figure 01: Frequency of lymphovascular invasion according to tumour-budding category. Lymphovascular invasion increased progressively from Bd1 to Bd3 ($\chi^2=15.51$, $p<0.001$).

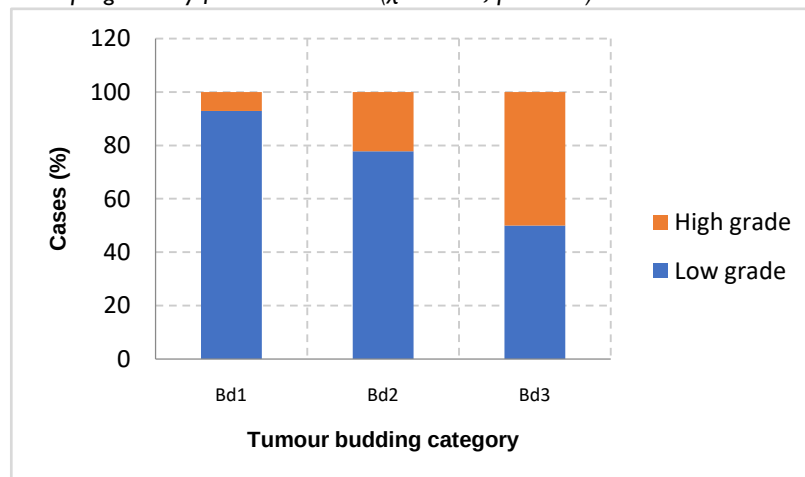


Figure 02: Histological grade according to tumour-budding category

Stacked distribution of low- and high-grade colorectal adenocarcinoma across Bd1, Bd2, and Bd3 categories. High-grade morphology became progressively more frequent with increasing tumour budding ($\chi^2=20.21$, $p<0.001$).

Relationship with depth of invasion and nodal status

Increasing tumour budding was associated with more advanced local invasion and nodal disease. Node positivity increased from 15 (26.8%) in Bd1 to 18 (50.0%) in Bd2 and 23 (82.1%) in Bd3 tumours ($\chi^2=23.21$, $p<0.001$). Higher budding categories were also associated with increasing pT stage ($H=13.28$, $p=0.001$) and a shift toward more advanced pathological stage ($H=19.71$, $p<0.001$) (Table 02).

Tumour deposits were more frequent with increasing budding, whereas the increase in PNI did not reach statistical significance.

Univariable analysis

On univariable logistic regression, tumour size, high histological grade, LVI, PNI, advanced pT stage, node positivity, and tumour deposits were associated with intermediate/high budding (Bd2/Bd3). Age, sex, and right-sided tumour location were not significantly associated (Table 04).

Table 04: Univariable predictors of intermediate/high tumour budding

Predictor	Crude OR (95% CI)	Wald z	p value
Age, per 10 years	0.90 (0.60–1.35)	–0.49	0.624
Male sex	0.81 (0.39–1.66)	–0.59	0.558
Tumour size, per cm	1.49 (1.11–1.99)	2.70	0.007
Right-colon location	1.15 (0.55–2.42)	0.38	0.706
High histological grade	6.81 (2.18–21.30)	3.30	<0.001
Lymphovascular invasion	4.64 (2.04–10.55)	3.66	<0.001
Perineural invasion	2.96 (1.14–7.69)	2.22	0.026
pT3/pT4 stage	3.40 (1.39–8.28)	2.69	0.007
Node positivity	4.87 (2.23–10.64)	3.97	<0.001
Tumour deposits	4.08 (1.09–15.29)	2.08	0.037

Outcome: Bd2/Bd3 versus Bd1. OR, odds ratio; CI, confidence interval.

Multivariable analysis

In multivariable logistic regression, LVI, high histological grade, and node positivity remained independently associated with intermediate/high tumour budding. High histological grade demonstrated the largest adjusted association. Advanced pT stage showed a borderline association after adjustment, while PNI was no longer independently associated (Table 05).

The overall model was statistically significant (likelihood-ratio $\chi^2=44.56$, $df=5$, $p<0.001$), demonstrated good discrimination (AUC=0.826), and showed no evidence of poor calibration (Hosmer–Lemeshow $\chi^2=1.34$, $df=8$, $p=0.995$). Variance inflation factors were low, indicating no important multicollinearity.

Table 05: Multivariable predictors of intermediate/high tumour budding

Predictor	Adjusted OR (95% CI)	Wald z	p value	VIF
Lymphovascular invasion	3.47 (1.33–9.01)	2.55	0.011	1.82
High histological grade	8.73 (2.30–33.10)	3.19	0.001	1.30
pT3/pT4 stage	2.81 (0.98–8.03)	1.93	0.054	2.14
Node positivity	3.78 (1.53–9.35)	2.88	0.004	2.05
Perineural invasion	2.28 (0.75–6.90)	1.45	0.146	1.35

Outcome: Bd2/Bd3 versus Bd1. Model likelihood-ratio $\chi^2=44.56$, $df=5$, $p<0.001$; AUC=0.826. OR, odds ratio; CI, confidence interval; VIF, variance inflation factor.

DISCUSSION

Tumour budding was clearly related to the histopathological adverse features in colorectal adenocarcinoma in the current dataset. Lymphovascular invasion was found to be 19.6% in Bd1, 47.2% in Bd2, and 60.7% in Bd3, and high-grade morphology was 7.1% in Bd1, 22.2% in Bd2, and 50.0% in Bd3. Budding was also associated with increasing depth of invasion, nodal metastasis, tumour deposits and pathological stage. LVI, high histological grade and node positivity were all independently associated with intermediate/high budding, suggesting that budding is a morphological marker for an aggressive invasive phenotype and not a mere microscopic feature.

These results are similar to population-based data. Graham et al. examined 553 colorectal carcinomas and found that 32% were high budding, 46% were low budding and 22% were no budding. High budding was linked to advanced pathological stage and, after multivariable adjustment, was a risk factor for colorectal cancer-specific mortality of 2.57-fold. Importantly, observer agreement was good, with weighted κ values of 0.70–0.72 which indicates the reproducibility of budding when a standardized approach is used [9].

The tight correlation between budding and LVI found in our analysis is also consistent with the analysis of the two invasive features together. Huh et al. analysed 3707 stage I to III colorectal cancer patients and classified them by the

presence of LVI, PNI and tumour budding. Of these, 1,495 had none of the three features, whereas 1,063, 861, and 288 had one, two, or all three adverse factors, respectively. The median follow-up was 52 months, and the increasing burden of risk groups was found to be significant in terms of 5-year disease-free survival between stages I, II, and III, and the combined pathological risk score was found to be independently prognostic [10]. This supports our observation that budding clusters with LVI and other aggressive histological features rather than acting independently of the invasive pathway.

This is further supported by the prospective multicentre SACURA analysis, which shows a graded nature of our Bd1–Bd3 findings. The authors Ueno et al. reviewed 991 stage II colon cancers centrally, and found 376 to be Bd1, 331 to be Bd2 and 284 to be Bd3. The 5-year relapse-free survival rate was 90.9% for Bd1, 85.1% for Bd2 and 74.4% for Bd3. Recurrence in liver, lung, lymph nodes and peritoneum was also correlated with budding grade, and budding grade was an independent prognostic factor along with T stage [11]. The step-wise increase in LVI, nodal positivity and pathological stage within budding categories in our study is therefore biologically consistent with the step-wise prognostic gradient shown in this large prospective cohort.

A comparison of particular relevance comes from Lee and Chan who analysed 135 stage II colon adenocarcinomas by budding assessment compatible with ITBCC. Bd3 tumours

represented 20% of their cohort and were significantly associated with pT4 disease and LVI. They also showed a significant survival gradient (5-year disease-specific survival of 89%, 73%, and 52% for Bd1, Bd2, and Bd3, respectively). The poorly differentiated clusters also correlated well with high-grade budding, and the two grading systems were within one category of each other in 95% of cases [12]. Their findings are similar to our finding of a strong correlation between budding and LVI and histological grade. Results from a tertiary-care facility in India are also consistent. Shah et al. analysed 100 primary colorectal carcinomas and concluded that tumour budding was significantly related to T stage, N stage, overall TNM stage, and LVI. Average budding and the highest budding area also demonstrated a significant relationship with cancer-specific survival. These observations are particularly relevant to our cohort, where the prevalence of nodal positivity rose from 26.8% in Bd1 to 82.1% in Bd3, and increasing pathological stage was a progressive occurrence with increasing budding [13].

This correlation with histological aggressiveness has also been shown in different geographic populations. El Agy et al. investigated 100 colon adenocarcinoma patients with the ITBCC three-tier system and observed that Bd3 was significantly correlated with PNI, vascular invasion, distant metastasis, and advanced TNM stage. High budding was also linked to increased death rate, and worse overall survival, and molecular analysis revealed more microsatellite-stable disease and KRAS mutations in high-budding tumours [14]. In our study, we did not perform molecular profiling or survival follow-up but the high adjusted association between high histological grade and intermediate/high budding is in line with the general idea that budding is a marker for biologically aggressive tumours.

The association of node positivity with budding is also confirmed by more advanced stage data. Using the ITBCC criteria, Luo et al. assessed 547 stage III–IV colorectal cancers and found significantly worse prognosis for Bd2–3 tumours. The 5-year progression-free survival rate was 45% in Bd2–3 versus 72% in Bd1, and the 5-year overall survival rate was 17% versus 49% respectively. Multivariable analysis showed that Bd2–3 was an independent prognostic factor together with stage IV disease and involvement of four or more regional lymph nodes [15]. These data support the association we found in our cohort between increasing budding category and progression of the nodal stage and overall stage.

The literature as a whole is consistent with a pathological pattern: the higher the degree of tumour budding, the more likely the tumour is to have lymphovascular invasion, the less differentiated the tumour is, the more likely the tumour has spread to the nodes, the deeper the tumour has grown into the host tissue, and the more advanced the disease. The association of high histological grade with Bd2/Bd3 was the strongest in our adjusted model, followed by positivity of node and LVI, while that with advanced pT stage was borderline, and that with PNI was attenuated. This attenuation is possible since many of these variables are overlapping expressions of the tumour invasiveness and metastatic capacity. The relatively small variance inflation factors indicate that the adjusted associations were not due to large statistical collinearity, but the small sample size may restrict precision.

The study features a number of methodological strengths such as consecutive resection cases, standardized ITBCC assessment in a hotspot of 0.785 mm², the retention of the Bd1/Bd2/Bd3 classification and simultaneous assessment of established pathological adverse features. Exclusion of neoadjuvantly treated rectal cancers also minimizes distortion of budding due to treatment-related regression. Some limitations are the single centre design, the relatively small number of patients and the lack of outcome follow up, which does not allow direct evaluation of recurrence or survival. The binary regression classification of Bd2 and Bd3 was helpful for the stability of the model, but it can also partially mask the step-wise biological gradient seen in the three-tier classification. Interobserver reproducibility was also not evaluated.

Overall, the findings support tumour budding as a readily assessable histomorphological marker that integrates with established indicators of colorectal cancer aggressiveness. Its strong associations with LVI, histological grade, and nodal metastasis suggest that routine standardized budding assessment may add useful information to conventional pathological evaluation and help refine risk stratification beyond TNM stage alone.

CONCLUSION

Tumour budding showed strong associations with lymphovascular invasion, high histological grade, and nodal metastasis in colorectal adenocarcinoma. Increasing budding category also paralleled more advanced local invasion and pathological stage, supporting its value as a practical histomorphological marker of aggressive tumour behaviour.

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AUTHOR CONTRIBUTION

All Authors are Contributed Equally.

CONFLICT OF INTEREST

Not Declared.

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