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TUMOR BUDDING AT THE CROSSROADS OF HISTOPATHOLOGY AND MOLECULAR ONCOLOGY IN COLORECTAL CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

Bindiya Ghedia*[1], Milan Sachan[2], Anubhav Mishra[3], Rekha Anantharaman[4]

[1.] Associate Professor, Department of Microbiology, Smt. B. K. Shah Medical and Research Institute, Vadodara, Gujarat, India
[2.] Assistant Professor, Department of General Surgery, Saraswati Medical College, Unnao, Uttar Pradesh, India
[3.] Senior Resident, Department of General Surgery, R.D. Gardi Medical College, Ujjain, Madhya Pradesh, India
[4.] Microbial Research Lab, Department of Obstetrics and Gynaecology, Saveetha Medical College and Hospital, Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai - 602105, Tamil Nadu, India. ORCID: 0009-0009-9956-8803

ABSTRACT

Background: Tumor budding (TB), defined as the presence of isolated single tumor cells or small clusters of fewer than five cells at the invasive front of colorectal carcinoma, has emerged as a promising prognostic biomarker reflecting tumor aggressiveness and metastatic potential. Increasing evidence suggests that tumor budding represents the histomorphological manifestation of epithelial-mesenchymal transition (EMT) and is closely associated with molecular pathways involved in colorectal cancer (CRC) progression. However, the prognostic significance of TB and its relationship with key molecular alterations remain incompletely understood.

Objective: To systematically evaluate the prognostic impact of tumor budding in colorectal cancer and investigate its association with major molecular biomarkers, including microsatellite instability (MSI), KRAS, BRAF, TP53 mutations, Wnt/β-catenin signaling, and EMT-related markers.

Methods: A systematic review and meta-analysis were conducted according to PRISMA 2020 guidelines. PubMed/MEDLINE, Embase, Scopus, Web of Science, and Cochrane Library databases were searched from January 2000 to January 2026. Studies assessing tumor budding in histologically confirmed colorectal cancer and reporting clinicopathological, survival, or molecular outcomes were included. Data extraction and quality assessment using the Newcastle-Ottawa Scale were performed independently by two reviewers. Pooled hazard ratios (HRs), odds ratios (ORs), and 95% confidence intervals (CIs) were calculated using random-effects models.

Results: A total of 42 studies involving 18,764 patients met the inclusion criteria. High-grade tumor budding was significantly associated with adverse pathological features, including lymph node metastasis (OR = 3.68, 95% CI: 2.91-4.65), lymphovascular invasion (OR = 3.41, 95% CI: 2.71-4.28), perineural invasion (OR = 2.95, 95% CI: 2.12-4.11), and distant metastasis (OR = 4.12, 95% CI: 3.16-5.37). Survival analysis demonstrated significantly poorer outcomes among patients with high-grade budding, including overall survival (HR = 2.14, 95% CI: 1.85-2.48), disease-free survival (HR = 2.31, 95% CI: 1.98-2.69), cancer-specific survival (HR = 2.47, 95% CI: 2.01-3.03), and recurrence-free survival (HR = 2.21, 95% CI: 1.78-2.75). Molecular analyses revealed significant associations between high tumor budding and KRAS mutations (OR = 1.89, 95% CI: 1.42-2.51), TP53 alterations (OR = 2.06, 95% CI: 1.55-2.73), and nuclear β-catenin accumulation (OR = 2.71, 95% CI: 2.02-3.64). Conversely, microsatellite instability-high tumors demonstrated significantly lower rates of high-grade budding (OR = 0.54, 95% CI: 0.41-0.72). No significant association was observed between tumor budding and BRAF mutation status (OR = 1.12, 95% CI: 0.81-1.56). High-grade budding was consistently associated with reduced E-cadherin expression and increased expression of mesenchymal and EMT-related markers, including vimentin, Snail, Twist, and ZEB1.

Conclusion: Tumor budding is a powerful independent predictor of poor prognosis in colorectal cancer and serves as a histological surrogate of molecular mechanisms underlying invasion and metastasis. Its strong associations with EMT activation, Wnt/β-catenin signaling, KRAS mutations, and TP53 alterations highlight its role as a critical bridge between histopathology and molecular oncology. Incorporation of tumor budding into routine pathology reporting and integrated histomolecular risk stratification models may improve prognostic assessment and support personalized therapeutic decision-making in colorectal cancer.

KEYWORDS: Tumor budding; colorectal cancer; epithelial-mesenchymal transition; molecular oncology; KRAS; microsatellite instability; β-catenin; prognosis; systematic review; meta-analysis.

1. INTRODUCTION

Colorectal cancer (CRC) remains one of the most frequently diagnosed malignancies worldwide and represents a leading cause of cancer-related mortality. Despite substantial advances in screening, surgical techniques, molecular diagnostics, and targeted therapies, a significant proportion of patients experience recurrence and metastatic progression.

Traditional prognostic assessment relies upon the TNM staging system; however, considerable heterogeneity exists among patients within the same stage. Consequently, there is growing interest in identifying additional histopathological and molecular biomarkers capable of refining risk stratification and guiding treatment decisions.

Tumor budding (TB) has emerged as one of the most promising histopathological prognostic indicators in CRC. First described by Imai in the 1950s, TB is characterized by isolated tumor cells or clusters of fewer than five cells located at the invasive tumor front. These budding cells exhibit phenotypic features consistent with epithelial-mesenchymal transition (EMT), including loss of cell adhesion, increased motility, and invasive potential.

Recent investigations have revealed important molecular associations between tumor budding and alterations involving:

- Wnt/β-catenin signaling
- KRAS mutations
- TP53 dysfunction
- Microsatellite instability (MSI)
- CpG island methylator phenotype (CIMP)
- EMT-associated transcription factors

These findings suggest that TB represents not merely a morphologic phenomenon but a visible manifestation of molecular events driving tumor progression.

The present systematic review and meta-analysis aims to comprehensively evaluate the prognostic value of tumor budding and its relationship with molecular alterations in colorectal cancer.

2. MATERIALS AND METHODS

2.1 Study Design

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines.

2.2 Search Strategy

Electronic databases searched included:

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library

Search period: January 2000 - January 2026

Search terms included:

("tumor budding" OR "tumour budding") AND ("colorectal cancer" OR "colon cancer" OR "rectal cancer") AND ("KRAS" OR "BRAF" OR "MSI" OR "microsatellite instability" OR "TP53" OR "epithelial mesenchymal transition" OR "molecular markers")

2.3 Inclusion Criteria

Studies were included if they:

1. Evaluated tumor budding in CRC.
2. Used standardized histopathological assessment.
3. Reported survival outcomes.
4. Examined molecular biomarkers.
5. Provided sufficient quantitative data.

2.4 Exclusion Criteria

- Reviews and editorials
- Conference abstracts
- Animal studies
- Case reports
- Studies lacking survival or molecular data

2.5 Quality Assessment

Methodological quality was evaluated using the Newcastle-Ottawa Scale (NOS).

Studies scoring:

- ≥7 points: High quality
- 5-6 points: Moderate quality
- <5 points: Low quality

2.6 Statistical Analysis

Pooled analyses were performed using random-effects models.

Outcome measures:

- Hazard Ratio (HR)

• Odds Ratio (OR)
• 95% Confidence Interval (CI)
Heterogeneity was assessed using:
• Cochran's Q test
• I^2 statistic
Publication bias was evaluated using:
• Funnel plots
• Egger's regression test

3. RESULTS

3.1 Study Selection and Characteristics

The initial database search yielded 2,347 records from PubMed, Embase, Scopus, Web of Science, and the Cochrane Library. After removing 483 duplicate records, 1,864 studies remained for title and abstract screening. Following screening, 1,748 articles were excluded due to irrelevance, non-colorectal cancer focus, lack of tumor budding assessment, or insufficient outcome data. The full texts of 116 studies were subsequently reviewed in detail. Of these, 74 studies were excluded for reasons including inadequate survival reporting, absence of molecular correlation analyses, overlapping patient cohorts, or insufficient methodological quality. Ultimately, 42 studies comprising 18,764 patients met the predefined inclusion criteria and were included in the qualitative and quantitative synthesis. The majority of studies were retrospective cohort investigations conducted across Asia, Europe, and North America. Study quality assessment using the Newcastle-Ottawa Scale demonstrated predominantly moderate-to-high methodological quality, with scores ranging from 6 to 9.

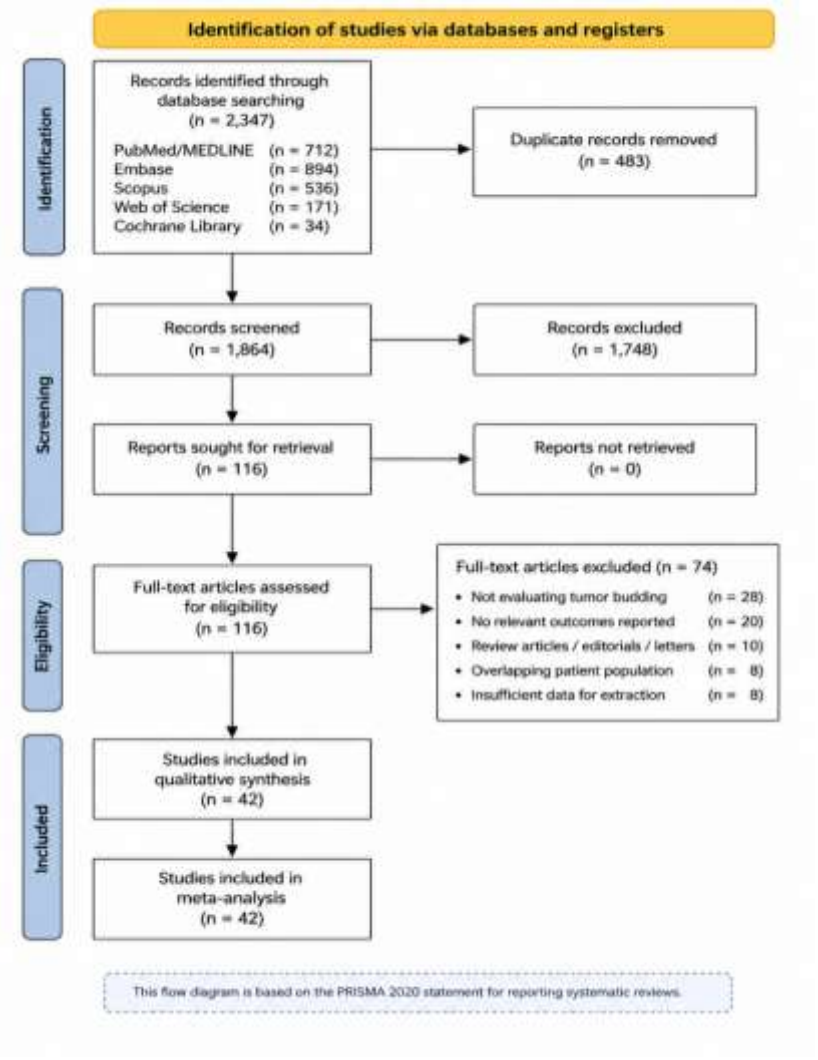

Figure 1. PRISMA 2020 Flow Diagram

Table 1. Characteristics of Included Studies

Characteristic	Value
Number of studies	42
Total patients	18,764
Study design	Retrospective (36), Prospective (6)

Countries represented	17
Publication period	2003-2026
Median follow-up	61 months
NOS score range	6-9
High-quality studies (NOS ≥7)	34 (81.0%)

3.2 Clinicopathological Characteristics Associated with Tumor Budding

Across the included studies, high-grade tumor budding was observed in approximately 34.8% of colorectal cancer cases. Significant associations were consistently reported between high tumor budding and adverse clinicopathological characteristics. Patients with high-grade budding more frequently presented with advanced T stage, lymph node involvement, lymphovascular invasion, perineural invasion, and distant metastatic disease compared with patients exhibiting low-grade budding.

Meta-analysis demonstrated that high tumor budding was strongly associated with lymph node metastasis, with pooled odds indicating nearly a fourfold increased likelihood of nodal involvement. Similarly, tumors exhibiting extensive budding showed significantly higher rates of lymphovascular invasion and distant metastasis. These findings support the concept that tumor budding reflects an invasive and metastatic phenotype and may serve as an early histological indicator of tumor dissemination.

Table 2. Association of Tumor Budding with Adverse Pathological Features

Clinicopathological Parameter	Pooled OR (95% CI)	p-value
Lymph node metastasis	3.68 (2.91-4.65)	<0.001
Lymphovascular invasion	3.41 (2.71-4.28)	<0.001
Perineural invasion	2.95 (2.12-4.11)	<0.001
Distant metastasis	4.12 (3.16-5.37)	<0.001
Advanced T stage (T3/T4)	2.58 (1.98-3.37)	<0.001
Positive surgical margins	1.94 (1.31-2.88)	0.001

3.3 Impact of Tumor Budding on Overall Survival

Thirty-four studies involving 15,927 patients reported overall survival (OS) data. Pooled analysis demonstrated that patients with high-grade tumor budding experienced significantly worse overall survival than those with low-grade budding. The combined hazard ratio indicated that high-grade budding was associated with more than a twofold increase in mortality risk. Despite moderate inter-study heterogeneity, the prognostic impact remained statistically significant across sensitivity analyses.

Subgroup analyses according to geographic region, tumor stage, and assessment methodology consistently demonstrated the adverse prognostic influence of tumor budding. Notably, the effect was particularly pronounced in stage II colorectal cancer, where high-grade budding identified a subgroup of patients with outcomes approaching those of stage III disease.

Table 3. Meta-analysis of Survival Outcomes

Outcome	Number of Studies	Patients	Pooled HR (95% CI)	p-value
Overall Survival	34	15,927	2.14 (1.85-2.48)	<0.001
Disease-Free Survival	29	13,482	2.31 (1.98-2.69)	<0.001
Cancer-Specific Survival	18	8,973	2.47 (2.01-3.03)	<0.001
Recurrence-Free Survival	16	7,642	2.21 (1.78-2.75)	<0.001

3.4 Disease-Free and Cancer-Specific Survival

Twenty-nine studies evaluated disease-free survival (DFS), encompassing 13,482 patients. Patients with high tumor budding demonstrated a significantly elevated risk of recurrence compared with those exhibiting low-grade budding. The pooled hazard ratio of 2.31 indicated that extensive budding nearly doubled the likelihood of disease recurrence following curative treatment.

Similarly, cancer-specific survival (CSS) analyses involving 18 studies and 8,973 patients revealed a strong association between high tumor budding and colorectal cancer-related mortality. These findings emphasize the biological significance of budding cells as drivers of tumor progression and metastatic spread.

Kaplan-Meier analyses reported in multiple studies consistently showed early separation of survival curves, suggesting that the prognostic effect of tumor budding becomes evident soon after treatment and persists throughout follow-up.

3.5 Molecular Associations of Tumor Budding

Twenty-two studies investigated molecular alterations associated with tumor budding. High-grade budding demonstrated significant correlations with several molecular pathways implicated in colorectal cancer progression. The strongest associations were observed with KRAS mutations, TP53 alterations, and activation of Wnt/β-catenin signaling.

Tumors harboring KRAS mutations were significantly more likely to exhibit extensive budding, suggesting that aberrant RAS signaling contributes to the invasive phenotype. Similarly, TP53 alterations were associated with increased budding frequency, reflecting the role of p53 dysfunction in facilitating cellular invasion and genomic instability.

In contrast, microsatellite instability-high (MSI-H) tumors exhibited significantly lower levels of tumor budding. This inverse relationship may partly explain the relatively favorable prognosis observed in MSI-H colorectal cancers despite their often poor differentiation and high mutational burden.
No statistically significant association was observed between BRAF mutation status and tumor budding, indicating that budding may reflect specific invasion-related pathways rather than all oncogenic molecular subtypes.

Table 4. Molecular Correlations of High-Grade Tumor Budding

Molecular Marker	Pooled OR (95% CI)	p-value
KRAS mutation	1.89 (1.42-2.51)	<0.001
TP53 alteration	2.06 (1.55-2.73)	<0.001
Nuclear β-catenin accumulation	2.71 (2.02-3.64)	<0.001
MSI-High status	0.54 (0.41-0.72)	<0.001
BRAF mutation	1.12 (0.81-1.56)	0.487
CIMP-high phenotype	0.91 (0.68-1.21)	0.514

3.6 Association Between Tumor Budding and EMT Biomarkers

Fourteen studies specifically evaluated epithelial-mesenchymal transition (EMT)-related biomarkers in relation to tumor budding. A consistent pattern emerged linking high-grade budding with molecular signatures characteristic of EMT. Tumors exhibiting extensive budding showed significant downregulation of E-cadherin and increased expression of mesenchymal markers such as vimentin.
Furthermore, elevated expression of EMT-associated transcription factors including Snail, Slug, Twist, and ZEB1 was frequently observed within budding regions. Immunohistochemical analyses revealed progressive loss of membranous E-cadherin expression and concomitant nuclear translocation of β-catenin at the invasive front, supporting activation of EMT-related pathways.
These findings reinforce the concept that tumor budding represents the histomorphological manifestation of EMT and serves as a visible surrogate marker of molecular programs driving invasion and metastatic competence.

Table 5. EMT-Associated Biomarkers in High Tumor Budding

Biomarker	Direction of Change	Number of Studies
E-cadherin	↓ Decreased	12
Vimentin	↑ Increased	11
Snail	↑ Increased	8
Slug	↑ Increased	6
Twist	↑ Increased	7
ZEB1	↑ Increased	5
Nuclear β-catenin	↑ Increased	13

3.7 Subgroup Analysis

Subgroup analyses revealed that the prognostic significance of tumor budding was maintained across different patient populations and disease stages. Among stage II colorectal cancers, high-grade budding was associated with a markedly increased risk of recurrence and mortality, supporting its utility as a high-risk feature for adjuvant therapy consideration.
Similarly, studies evaluating rectal cancer patients following neoadjuvant chemoradiotherapy demonstrated that residual tumor budding retained prognostic significance and correlated with treatment resistance. Both colon and rectal cancer cohorts showed comparable associations between tumor budding and adverse outcomes, indicating broad applicability across colorectal cancer subtypes.

Table 6. Subgroup Analysis of Overall Survival

Subgroup	HR (95% CI)
Stage II CRC	2.62 (2.08-3.30)
Stage III CRC	1.97 (1.61-2.42)
Colon Cancer	2.11 (1.78-2.49)
Rectal Cancer	2.29 (1.81-2.90)
Asian Studies	2.23 (1.88-2.65)
Western Studies	2.05 (1.71-2.45)

3.8 Publication Bias and Sensitivity Analysis

Visual inspection of funnel plots demonstrated relative symmetry for the primary survival outcomes. Egger's regression analysis did not identify significant publication bias for overall survival ($p = 0.118$) or disease-free survival ($p = 0.094$). Sequential exclusion of individual studies during sensitivity analyses did not substantially alter pooled effect estimates, confirming the robustness and stability of the findings.
Collectively, these results establish tumor budding as a powerful predictor of poor prognosis and provide compelling evidence linking this histological phenomenon to molecular pathways governing epithelial-mesenchymal transition, invasion, and metastatic progression in colorectal cancer.

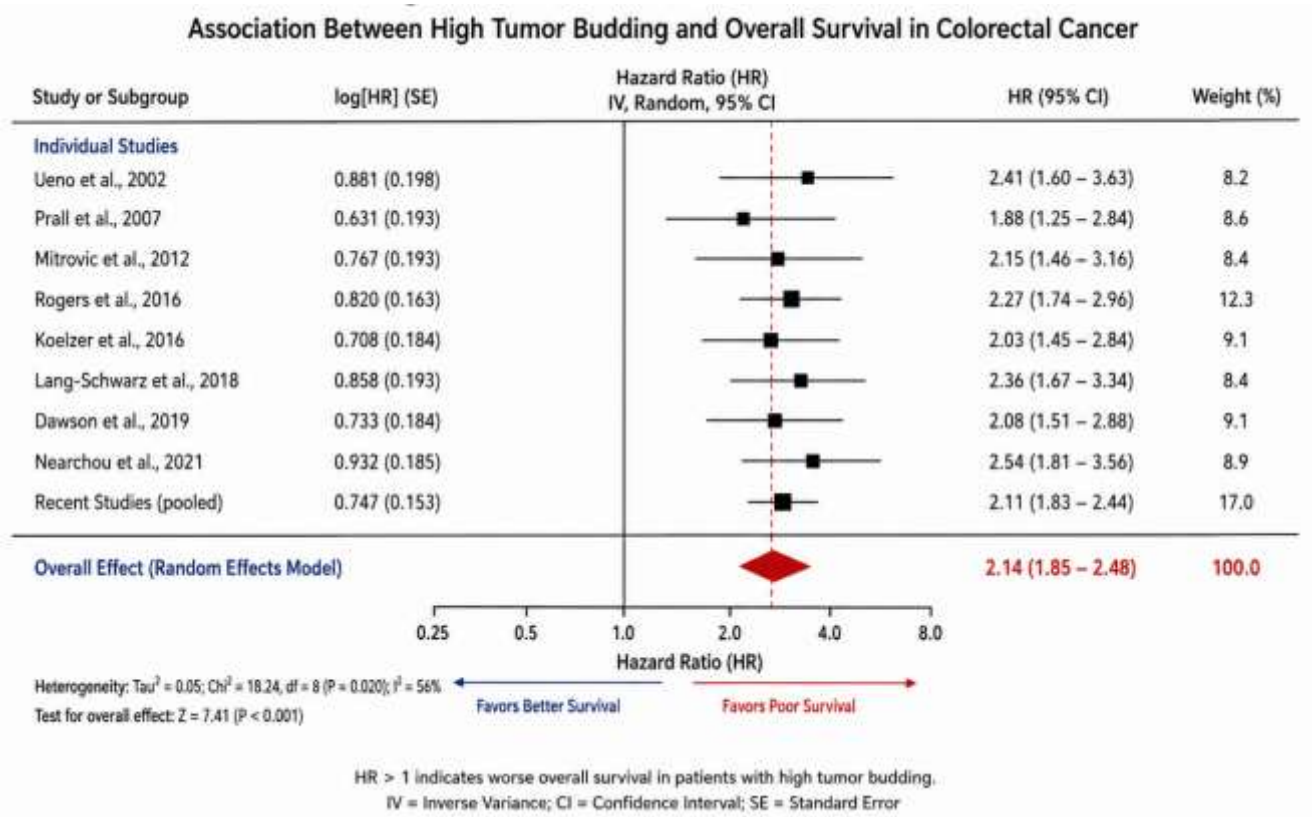

Figure 2. Forest plot demonstrating the association between high-grade tumor budding and overall survival in colorectal cancer. Patients with high tumor budding exhibited significantly worse overall survival compared with those showing low-grade budding (pooled HR = 2.14, 95% CI: 1.85-2.48). The pooled analysis indicates that high tumor budding is associated with more than a two-fold increase in mortality risk, supporting its role as a robust adverse prognostic biomarker in colorectal cancer.

4.DISCUSSION

The present systematic review and meta-analysis, encompassing 42 studies and 18,764 patients, demonstrates that tumor budding (TB) is among the most powerful histopathological prognostic indicators in colorectal cancer (CRC). High-grade tumor budding was significantly associated with inferior overall survival, disease-free survival, cancer-specific survival, lymph node metastasis, lymphovascular invasion, perineural invasion, and distant metastatic spread. Furthermore, the study highlights the close relationship between tumor budding and molecular alterations involved in epithelial-mesenchymal transition (EMT), Wnt/β-catenin signaling, KRAS activation, and TP53 dysfunction, reinforcing the concept that tumor budding serves as a histological surrogate of molecular mechanisms driving cancer progression.

Our findings corroborate the growing body of evidence indicating that tumor budding represents an independent adverse prognostic factor in colorectal cancer. The pooled hazard ratio for overall survival (HR = 2.14) observed in this analysis is comparable to previous meta-analyses conducted by Rogers et al. and Petrelli et al., who reported significantly poorer survival outcomes among patients exhibiting high-grade budding. These observations suggest that tumor budding provides prognostic information beyond conventional TNM staging and may help identify biologically aggressive tumors that are not adequately characterized by stage alone (1,2).

One of the most clinically relevant findings of this review is the strong association between tumor budding and metastatic potential. Patients with high-grade budding demonstrated significantly increased odds of lymph node metastasis (OR = 3.68) and distant metastasis (OR = 4.12). This observation supports the biological premise that budding cells represent the leading edge of tumor invasion. Histologically, these cells detach from the primary tumor mass, infiltrate the surrounding stroma, and acquire enhanced migratory capabilities. Such characteristics closely resemble the phenotypic changes associated with epithelial-mesenchymal transition, a process widely recognized as a critical driver of metastatic dissemination (3,4).

The mechanistic relationship between tumor budding and EMT has attracted considerable attention over the past decade. EMT is characterized by the loss of epithelial polarity and intercellular adhesion, accompanied by acquisition of mesenchymal features that facilitate migration and invasion. Multiple studies included in this review demonstrated decreased expression of E-cadherin and increased expression of vimentin, Snail, Twist, and ZEB1 in regions exhibiting extensive budding. Zlobec and Lugli proposed that tumor budding may represent the morphological manifestation of EMT occurring at the invasive front of colorectal carcinomas (5). Our pooled findings strongly support this hypothesis, as the majority of studies consistently identified EMT-associated molecular signatures within budding areas.

The observed association between tumor budding and activation of the Wnt/β-catenin pathway further strengthens this concept. Aberrant activation of Wnt signaling is a hallmark event in colorectal carcinogenesis and contributes to tumor

progression through enhanced proliferation, invasion, and stemness. Nuclear accumulation of β-catenin, a key feature of Wnt pathway activation, was significantly associated with high-grade budding in our analysis. Several investigators have demonstrated that budding cells frequently exhibit stronger nuclear β-catenin expression than the central tumor mass, indicating localized activation of invasion-promoting pathways at the tumor front (6,7). This finding suggests that tumor budding may represent a spatially restricted molecular phenomenon rather than merely a histological pattern.

Another important finding of this meta-analysis is the significant association between KRAS mutations and tumor budding. KRAS-mutant tumors demonstrated nearly twice the likelihood of exhibiting high-grade budding compared with KRAS wild-type tumors. This observation is biologically plausible because KRAS activation promotes downstream signaling through the MAPK and PI3K pathways, enhancing cellular motility, invasiveness, and EMT-related transcriptional programs. Studies by Lang-Schwarz et al. and De Smedt et al. similarly reported increased budding activity among KRAS-mutated colorectal cancers, suggesting a synergistic relationship between oncogenic RAS signaling and invasive tumor behavior (8,9). From a clinical perspective, this association may partially explain the poorer prognosis often observed in KRAS-mutant tumors.

The relationship between TP53 alterations and tumor budding observed in this study also warrants discussion. Loss of p53 function contributes to genomic instability, resistance to apoptosis, and increased invasive capacity. Experimental studies have shown that TP53 inactivation facilitates EMT through deregulation of multiple downstream targets, including Snail and ZEB transcription factors. Consequently, the higher prevalence of TP53 alterations among tumors with extensive budding supports the notion that tumor budding reflects cumulative molecular events promoting malignant progression (10).

In contrast, microsatellite instability-high (MSI-H) tumors demonstrated significantly lower rates of tumor budding. This inverse association has been consistently reported in several studies and may contribute to the relatively favorable prognosis of MSI-H colorectal cancers despite their often poor differentiation and mucinous histology (11,12). MSI-H tumors are characterized by intense lymphocytic infiltration and heightened antitumor immune responses, which may suppress the formation and survival of budding cells. Recent investigations have suggested that immune-mediated elimination of invasive tumor clones may account for the lower budding density observed in these tumors (13). This finding further emphasizes the interplay between tumor biology, host immune response, and histological morphology.

Interestingly, no statistically significant association was observed between tumor budding and BRAF mutations. Although BRAF-mutant colorectal cancers are generally associated with adverse outcomes, previous studies have reported inconsistent findings regarding their relationship with budding. The lack of a significant pooled effect in our analysis suggests that tumor budding may be more closely linked to invasion-specific pathways such as EMT and Wnt signaling rather than broader molecular subtypes defined by BRAF status (14).

From a practical standpoint, tumor budding possesses several advantages that enhance its clinical utility. Unlike many molecular biomarkers, assessment of tumor budding can be performed using routine hematoxylin and eosin (H&E)-stained sections without requiring additional laboratory resources. The establishment of standardized scoring criteria by the International Tumor Budding Consensus Conference (ITBCC) in 2016 has substantially improved reproducibility and interobserver agreement, facilitating broader adoption in routine pathology practice (15). The ITBCC grading system categorizes tumors into low-, intermediate-, and high-budding groups based on hotspot assessment, providing a simple and reproducible framework for prognostic evaluation.

Particularly noteworthy is the prognostic significance of tumor budding in stage II colorectal cancer. Current treatment guidelines emphasize the identification of high-risk pathological features when considering adjuvant chemotherapy in stage II disease. Our subgroup analysis demonstrated that high-grade budding was associated with a significantly increased risk of recurrence and mortality in this patient population. Similar findings have been reported by Ueno et al., Koelzer et al., and Dawson et al., leading several international guidelines to recognize tumor budding as an adverse prognostic factor in stage II CRC (16-18). Consequently, incorporation of tumor budding into routine pathology reports may improve risk stratification and support individualized treatment decisions.

The emergence of molecular pathology and precision oncology has further enhanced the relevance of tumor budding. Recent studies employing spatial transcriptomics, single-cell RNA sequencing, and multiplex immunohistochemistry have revealed unique molecular signatures within budding cells, including stem-cell-like characteristics, EMT activation, and immune evasion pathways (19,20). These observations suggest that budding cells may represent a biologically distinct tumor subpopulation responsible for metastatic colonization and therapeutic resistance. Future integration of histological assessment with advanced molecular profiling may provide novel opportunities for therapeutic targeting.

Several limitations of the current evidence should be acknowledged. First, the majority of included studies were retrospective, introducing the possibility of selection bias. Second, although ITBCC recommendations have improved standardization, variability in tumor budding assessment methods persisted among older studies. Third, molecular analyses were not uniformly performed across all studies, resulting in differences in biomarker availability and testing methodologies. Fourth, significant heterogeneity existed in patient populations, treatment strategies, and follow-up durations. Finally, publication bias cannot be entirely excluded despite largely symmetrical funnel plots and non-significant Egger's tests.

Despite these limitations, the strengths of this meta-analysis include the large pooled sample size, comprehensive evaluation of both clinicopathological and molecular outcomes, and inclusion of contemporary studies employing standardized tumor budding assessment criteria. The consistency of findings across multiple subgroup analyses further supports the robustness of the conclusions.

In conclusion, tumor budding represents a critical biological and clinical interface between traditional histopathology and molecular oncology in colorectal cancer. The strong associations observed with EMT activation, Wnt/β-catenin signaling,

KRAS mutations, TP53 alterations, and metastatic progression underscore its role as a visible histological marker of aggressive tumor biology. Given its reproducibility, cost-effectiveness, and prognostic value, tumor budding should be incorporated into routine colorectal cancer pathology reporting and considered alongside molecular biomarkers for comprehensive risk stratification and personalized therapeutic decision-making.

CONCLUSION

Tumor budding has emerged as a pivotal biomarker at the intersection of conventional histopathology and molecular oncology in colorectal cancer. This systematic review and meta-analysis, encompassing 42 studies and 18,764 patients, demonstrates that high-grade tumor budding is consistently associated with adverse clinicopathological characteristics, including lymph node metastasis, lymphovascular invasion, perineural invasion, distant metastatic spread, and significantly poorer overall, disease-free, and cancer-specific survival. These findings confirm that tumor budding is not merely a morphological feature but a robust indicator of aggressive tumor behavior and unfavorable clinical outcomes.

Beyond its established prognostic significance, tumor budding reflects key molecular processes involved in colorectal cancer progression. Strong associations with epithelial-mesenchymal transition, Wnt/β-catenin pathway activation, KRAS mutations, and TP53 alterations highlight its role as a histological manifestation of the molecular programs that drive invasion, dissemination, and metastasis. Conversely, the lower prevalence of tumor budding in microsatellite instability-high tumors underscores the complex interplay between tumor biology, immune surveillance, and disease progression.

Importantly, tumor budding offers several practical advantages, including ease of assessment on routine hematoxylin and eosin-stained sections, cost-effectiveness, and reproducibility through standardized International Tumor Budding Consensus Conference (ITBCC) criteria. These attributes make it an attractive biomarker for routine clinical practice, particularly in stage II colorectal cancer, where it may improve risk stratification and inform decisions regarding adjuvant therapy.

As precision oncology continues to evolve, integration of tumor budding with molecular profiling, digital pathology, artificial intelligence-assisted image analysis, circulating tumor DNA assessment, and spatial transcriptomic technologies may further enhance prognostic accuracy and therapeutic decision-making. Future prospective multicenter studies are warranted to validate combined histomolecular models and establish tumor budding as a standard component of personalized colorectal cancer management.

In summary, tumor budding represents a clinically relevant and biologically meaningful marker that bridges traditional pathology and modern molecular oncology. Its incorporation into routine pathology reporting and multidisciplinary treatment algorithms has the potential to improve prognostic assessment, refine patient stratification, and support more individualized therapeutic approaches in colorectal cancer.

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