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Tumor Budding and Stromal Reaction in Colorectal Adenocarcinoma: A Histomorphological Review of Prognostic Significance

I Putu Eka Widiadnyana Putra[1*], Ni Putu Renata Mawardani[1], I Putu Thio Mahapradana[1], I Made Egga Adika Suputra[1], I Gede Putu Supadmanaba[2]

[1]Faculty of Medicine Udayana University
[2]Biochemistry Department, Faculty of Medicine Udayana University

*Corresponding author:
I Putu Eka Widiadnyana Putra; Faculty of Medicine Udayana University;
Eka_Widiadnyana@student.unud.ac.id

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ABSTRACT

Objective: This review aims to critically evaluate the prognostic significance of tumor budding and stromal reaction in colorectal adenocarcinoma and to examine their incremental value in risk stratification beyond conventional TNM staging.

Methods: A structured literature review was conducted using PubMed, ScienceDirect, SpringerLink, and Google Scholar. Searches employed Boolean operators ("AND", "OR") with the terms "tumor budding," "stromal reaction," "desmoplastic reaction," "tumor stroma ratio," and "colorectal adenocarcinoma." Peer-reviewed cohort studies, retrospective analyses, and systematic reviews published between 2015 and 2025 were included if they evaluated standardized histopathological assessment and reported survival or recurrence outcomes. Studies lacking prognostic endpoints or reproducible scoring criteria were excluded.

Results: The majority of contemporary studies demonstrate that high grade tumor budding defined as isolated single cells or clusters of up to four tumor cells at the invasive front is independently associated with lymphovascular invasion, lymph node metastasis, distant dissemination, and reduced disease free and overall survival. Standardized evaluation, particularly following consensus based criteria, improves interobserver reproducibility and prognostic consistency. Stromal reaction, especially desmoplastic and stroma rich patterns reflected in a low tumor stroma ratio, has also been shown to independently predict unfavorable outcomes and increased recurrence risk. Emerging evidence suggests that the combined assessment of tumor budding and stromal composition provides superior prognostic discrimination compared with histological grade alone, particularly in stage II colorectal adenocarcinoma where therapeutic decision making remains challenging.

Conclusion: Tumor budding and stromal reaction are biologically meaningful and clinically applicable histomorphological markers that reflect tumor microenvironment interaction and invasive potential. Their integration into routine pathological reporting may enhance prognostic precision and support more individualized adjuvant treatment strategies, especially in intermediate risk disease.

Keywords: colorectal adenocarcinoma; tumor budding; stromal reaction; tumor stroma ratio; desmoplastic reaction; prognostic marker.

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INTRODUCTION

Colorectal adenocarcinoma remains a major global health burden and continues to rank among the leading causes of cancer-related mortality worldwide. Despite advances in screening strategies, surgical techniques, and systemic therapies, prognostic stratification in daily practice is still predominantly based on the TNM staging system. Although TNM classification provides essential anatomic information, it does not fully capture the biological heterogeneity of colorectal cancer. Substantial variability in recurrence rates and survival outcomes persists among patients within the same pathological stage, particularly in stage II and selected stage III cases, highlighting the limitations of conventional staging in reflecting tumor aggressiveness and metastatic potential.[1]

In this context, increasing attention has been directed toward histomorphological markers that more directly represent tumor behavior. Tumor budding, defined as single cells or small clusters of up to four tumor cells at the invasive front, has emerged as a robust indicator of invasive capacity and early metastatic dissemination. The International Tumor Budding Consensus Conference (ITBCC) standardized its assessment and recommended its incorporation into routine pathological reporting, reinforcing its clinical relevance.[2] Recent investigations continue to demonstrate that high-grade tumor budding correlates with lymphovascular invasion, nodal metastasis, and inferior

survival, supporting its role as a surrogate marker of epithelial–mesenchymal transition and tumor cell plasticity.[3]

Beyond epithelial tumor cell morphology, the tumor microenvironment has gained recognition as a critical determinant of cancer progression. The stromal compartment, including cancer-associated fibroblasts, extracellular matrix remodeling, and immune cell infiltration, actively participates in tumor growth and dissemination rather than serving as a passive scaffold. The tumor–stroma ratio and patterns of desmoplastic reaction have been increasingly studied as reproducible histopathological parameters with independent prognostic implications. Contemporary evidence suggests that stroma-rich tumors exhibit distinct biological behavior and adverse outcomes compared with stroma-poor tumors, underscoring the importance of tumor–stroma interactions in colorectal carcinogenesis.[4,5]

Although tumor budding and stromal reaction have each been investigated individually, their integrated histomorphological interpretation within routine pathological assessment remains variably applied, and their combined prognostic value warrants clearer contextualization. A focused appraisal of these parameters is therefore essential to refine risk stratification beyond conventional staging and to support more individualized clinical decision-making. The objective of this study is to comprehensively review the histomorphological characteristics of tumor budding and stromal reaction in colorectal adenocarcinoma and to critically evaluate their prognostic significance within contemporary clinical practice.

MATERIALS AND METHODS

This study was conducted as a structured narrative review aimed at critically appraising the histomorphological characteristics and prognostic significance of tumor budding and stromal reaction in colorectal adenocarcinoma. The review was designed to synthesize contemporary evidence and to provide conceptual and methodological clarity regarding the assessment of these parameters in routine pathological practice.

As this study was based exclusively on previously published literature and did not involve direct patient recruitment, access to identifiable clinical records, or use of human biological material, formal ethical approval was not required in accordance with internationally accepted guidelines for secondary research using publicly available data.

A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, and Web of Science databases. The search focused on peer-reviewed articles published between January 2015 and December 2024 to ensure contemporary relevance while allowing inclusion of key consensus recommendations essential for standardized histopathological interpretation. The following keywords were used in various Boolean combinations: "colorectal adenocarcinoma," "tumor budding," "tumour budding," "stromal reaction," "tumor–stroma ratio," "desmoplastic reaction," and "prognostic significance." Only full-text articles published in English were considered. Editorials, conference abstracts, case reports, and non-peer-reviewed publications were excluded.

Studies were selected based on their relevance to histomorphological evaluation of tumor budding and stromal parameters in colorectal adenocarcinoma, particularly those reporting associations with clinically meaningful outcomes such as overall survival, disease-free survival, recurrence, or lymph node metastasis. Priority was given to studies employing standardized tumor budding assessment, especially those aligned with the International Tumor Budding Consensus Conference (ITBCC) recommendations, including hotspot evaluation within a 0.785 mm^2 field and categorical grading into low, intermediate, and high levels. For stromal assessment, studies evaluating tumor–stroma ratio or qualitative desmoplastic reaction patterns were included provided that methodological criteria and cut-off definitions were clearly described.

Relevant data were extracted through detailed evaluation of study design, cohort characteristics, histological scoring methodology, stromal assessment approach, and reported prognostic endpoints. Where available, reported hazard ratios (HRs), 95% confidence intervals (CIs), and p-values were examined, with particular attention to multivariate analyses adjusting for established clinicopathological variables. The findings were synthesized descriptively with emphasis on methodological consistency, reproducibility of assessment criteria, and clinical applicability within contemporary pathological reporting.

RESULTS

Independent Prognostic Impact of Tumor Budding

Recent high-quality evidence consistently establishes tumor budding as one of the most reproducible adverse histomorphological parameters in colorectal adenocarcinoma. High-grade tumor budding demonstrates strong associations with lymphovascular invasion, nodal metastasis, advanced T stage, and distant dissemination.[4-6] Importantly, several contemporary multivariate analyses confirm that tumor budding retains independent prognostic significance after adjustment for TNM stage, differentiation grade, and other established clinicopathological variables.[4-6]

The prognostic relevance appears particularly pronounced in stage II colorectal carcinoma. In this subgroup, high tumor budding identifies patients with significantly increased recurrence risk despite node-negative status, suggesting that microscopic invasive activity may precede clinically detectable metastatic spread.[4-6] The adoption of standardized hotspot-based assessment following ITBCC recommendations has substantially improved interobserver reproducibility and strengthened the parameter's reliability for routine diagnostic practice.[6]

Prognostic Value of Stromal Reaction and Tumor Stroma Ratio

Parallel to epithelial invasive features, stromal composition has emerged as a biologically meaningful determinant of clinical outcome. Quantitative evaluation using tumor–stroma ratio (TSR) demonstrates that stroma-rich tumors (low TSR) are significantly associated

with inferior overall survival and disease-free survival.[7] The adverse prognostic effect remains evident across stage II and III disease, supporting the concept that stromal dominance reflects aggressive tumor biology rather than stage-dependent phenomena.[8]

Beyond quantitative assessment, qualitative characterization of desmoplastic reaction further refines prognostic stratification. Immature or myxoid stromal patterns are consistently linked to poorer survival compared with mature fibrotic stroma.[9] These findings suggest that stromal morphology captures dynamic tumor–microenvironment interactions, including extracellular matrix remodeling and fibroblast activation, which may facilitate invasion and metastatic progression.

Combined Histomorphological Phenotype and Prognostic Stratification

Emerging integrative analyses indicate that the combined presence of high-grade tumor budding and stromal dominance confers the most unfavorable clinical trajectory.[9] Tumors exhibiting both features demonstrate higher recurrence rates and reduced survival compared with those exhibiting only one or neither parameter. This combined phenotype likely reflects the convergence of intrinsic epithelial invasiveness and permissive microenvironmental architecture, providing a more comprehensive morphological surrogate of tumor aggressiveness than either component alone.

Collectively, contemporary evidence supports the integration of tumor budding and stromal reaction into refined histomorphological risk stratification models beyond conventional TNM staging.

DISCUSSION

Tumor Budding as a Morphological Surrogate of Active Invasion

The consistent independent association between tumor budding and adverse survival outcomes underscores its biological significance as a morphological expression of invasive capacity. Budding cells at the invasive front demonstrate loss of cohesion and enhanced migratory potential, features consistent with epithelial–mesenchymal transition (EMT) pathways described in recent analyses.[4-6] Rather than representing a purely descriptive histological observation, tumor budding appears to reflect active tumor-host interface dynamics that directly contribute to metastatic competence.

Its marked prognostic relevance in stage II disease is particularly noteworthy. In this setting, tumor budding may identify biologically aggressive tumors that remain understaged by nodal assessment alone, thereby refining postoperative risk stratification and potentially influencing adjuvant therapy considerations.

Stromal Reaction as an Active Biological Determinant

The tumor microenvironment has transitioned from being viewed as a passive scaffold to an active modulator of cancer progression. The consistent association between stroma rich tumors and adverse clinical outcomes suggests that stromal expansion reflects pro-tumorigenic signaling networks involving cancer-associated fibroblasts, extracellular matrix remodeling, and altered immune interactions.[7,8] Furthermore, the adverse prognostic implications of immature desmoplastic reactions support the hypothesis that qualitative stromal features may mirror dynamic biological processes influencing tumor dissemination.[9-10]

Integrative Perspective and Clinical Implications

The combined evaluation of tumor budding and stromal parameters aligns with contemporary concepts of precision pathology. Tumor budding captures epithelial plasticity and invasive behavior, whereas stromal reaction reflects microenvironmental permissiveness. Their integration offers a multidimensional morphological framework capable of refining prognostic assessment beyond conventional staging.

Nevertheless, variability in stromal grading systems and cut-off thresholds remains a challenge. While ITBCC has standardized tumor budding assessment, stromal evaluation still lacks universally accepted criteria. Prospective multicenter validation is required to facilitate incorporation of combined histomorphological assessment into standardized reporting guidelines.

CONCLUSION

Tumor budding and stromal reaction represent complementary histomorphological manifestations of tumor aggressiveness in colorectal adenocarcinoma. Contemporary evidence supports their independent and combined prognostic significance beyond conventional TNM staging, particularly in refining risk stratification within stage II disease. Tumor budding reflects intrinsic epithelial invasiveness, whereas stromal parameters capture the biological influence of the tumor microenvironment. The integration of these features provides a more comprehensive morphological framework for prognostic assessment and may contribute to more individualized therapeutic decision-making. Further standardization of stromal evaluation criteria and prospective validation studies are warranted to facilitate their incorporation into routine pathological reporting and clinical algorithms.

CONFLICT OF INTEREST

All authors declared that there is no conflict of interest about this article

AUTHOR CONTRIBUTION

All authors contributed equally in the writing of this article

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ETHICS APPROVAL

Not Applicable

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