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Review article

Tumor Budding: A Prognostic Marker of Aggressiveness and Metastatic Potential in Epithelial Cancers, with a Focus on Colorectal and Urothelial Carcinomas

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Abstract
A hallmark of malignancy is the ability of a tumor to disseminate and metastasize, a process that requires specific cellular adaptations. The American Joint Committee on Cancer developed the TNM staging system to classify malignancies and guide treatment strategies, reflecting the biological behavior and clinical outcomes of cancers. Despite its usefulness, ongoing efforts aim to identify additional diagnostic and prognostic parameters to improve accuracy and treatment outcomes. One such parameter is tumor budding, a distinctive morphological feature observed in epithelial cancers. tumor budding is characterized by single tumor cells or small clusters of up to four cells that detach from the invasive front and invade the surrounding stroma. First described in colorectal cancer, tumor budding has since been widely investigated and recognized as a predictor of adverse outcomes, including lymph node invasion, local and distant metastasis, lymphovascular invasion, and poor survival rates across multiple cancer types. Independent of pathological stage, tumor budding correlates with aggressive tumor behavior, highlighting its prognostic significance. In urothelial cancers, tumor budding has been linked to stage progression, distant metastasis, and survival outcomes, particularly in non-muscle invasive bladder cancer and muscle-invasive bladder cancer. This review examines the mechanisms underlying tumor budding, its clinical significance across various tumor types, and its prognostic implications in epithelial cancers. Understanding these factors could provide valuable insights into integrating tumor budding into routine pathological assessments and improving cancer management strategies.
Keywords. Tumor Budding, Cancer Invasion, Prognostic Biomarker.

Introduction

A defining characteristic of malignancy is the ability of tumors to spread and form metastases, a process that requires the development of distinct cellular properties. Tumor tissue comprises both cancer cells and various stromal cells, including endothelial cells, macrophages, and fibroblasts. The interactions and communication between these cellular components create a tumor-specific microenvironment that facilitates invasion and metastasis [1].

Building on this understanding, the tumor-node-metastasis (TNM) staging system, developed by the American Joint Committee on Cancer, provides a standardized classification of patients based on tumor grade. This system reflects the biological behavior of the disease and serves as a critical tool for clinicians in treatment planning. However, ongoing research aims to identify additional diagnostic and therapeutic parameters to further enhance prognostic accuracy and improve patient outcomes.

Intratumoral morphological heterogeneity, such as diverse patterns of tumor cell invasion, has emerged as a significant factor, particularly in breast cancer [2]. Among these factors, tumor budding (TB) is a key morphological marker. Tumor budding refers to a histological phenomenon observed in epithelial malignancies, where individual tumor cells or small clusters detach from the invasive tumor front and infiltrate the surrounding stroma [3]. Tumor budding has also been linked to increased invasiveness, metastatic potential, cancer progression, and treatment resistance, underscoring its importance as a biomarker for aggressive tumor phenotypes [4].

By providing insights into the dynamic interaction between tumor cells and the tumor microenvironment, tumor budding serves as a valuable prognostic and predictive factor across multiple cancer types. Ongoing research aims to uncover its molecular underpinnings, further enhancing its utility in clinical practice.

Tumor Budding (TB) Definition

Tumor budding (TB) refers to a histological phenomenon observed primarily at the invasive margin of tumors, where it is considered a key pathological feature [1]. This phenomenon occurs in a variety of epithelial malignancies, signifying the detachment and migration of cancer cells from the primary tumor mass into adjacent tissue. TB is often regarded as an indicator of tumor aggressiveness, as it reflects the ability of cancer cells to invade surrounding tissue and is associated with poorer prognosis across various cancers.

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Tumor Budding (TB) Terminology and History:

Depending on the researchers' background, several terms have been used to describe tumor budding in vitro or in experimental studies, including tumor cell dissociation, localized dedifferentiation, and epithelial-mesenchymal transition (EMT). However, the term "tumor budding" was first introduced by Morodomi et al. in 1989 [5]. It was later formally defined by Ueno and his colorectal cancer research group in 2002. They defined tumor budding (TB) as the detachment of single cancer cells or small groups of up to four cells from the invasive front of a tumor, which then invade the surrounding stroma. Ueno's group evaluated the prognostic significance of tumor budding as a histological feature of the invasive margin and worked to establish its optimal parameters. They concluded that tumor budding would serve as a reliable index for measuring the aggressiveness of rectal cancer, due to its reproducibility and effectiveness as a prognostic predictor [6].

Tumor Budding (TB) Description

Tumor budding (TB), as described by Hase et al. [7], refers to small clusters of undifferentiated cancer cells located at the invasive tumor front. These clusters, or "buds," are classified into intratumoral buds (ITB), located within the tumor core, and peritumoral buds (PTB), situated at the invasive margin. Studies suggest a higher density of TB in the PTB region, particularly at the invasive front, compared to the tumor core [8], underscoring its role in tumor invasiveness.

TB quantification, as outlined by [9], involves counting 10 or more buds within a single "hot spot" at the invasive margin, assessed using a 20x objective lens over a 0.785 mm^2 area. TB is also closely linked to epithelial-mesenchymal transition (EMT), a process enabling epithelial cancer cells to acquire mesenchymal traits, enhancing their migration and invasion into surrounding stroma [10]. EMT is critical in tumor progression and metastasis. Thus, TB serves as a key histological marker for cancer prognosis, reflecting tumor aggressiveness and metastatic potential.

Pathogenesis of Tumor Budding (TB)

Lugli and colleagues have significantly advanced the understanding of tumor budding as a histological phenomenon observed in various cancers, where individual malignant cells or small clusters of malignant cells are found at the invasive front of tumors. This phenomenon is considered a manifestation of epithelial-mesenchymal transition (EMT), as tumor buds often exhibit a loss of epithelial markers and a gain of mesenchymal traits, which facilitate invasion and metastasis [11].

Tumor budding (TB) is a hallmark of cancer invasion and metastasis, characterized by the formation of finger-like projections or "buds" extending from the primary tumor into the surrounding stroma. The International Tumor Budding Consensus Conference (ITBCC) defines these buds in colorectal cancer as single cancer cells or clusters of fewer than four cells that detach from the main tumor mass, forming the histological basis for invasion and dissemination [12,13]. Tumor budding is associated with increased motility, invasiveness, and epithelial-mesenchymal transition (EMT), a process critical to metastatic progression [9,10].

At the tumor invasion front, malignant cells penetrate the stroma either individually or in small groups, a phenomenon accompanied by cellular dedifferentiation and architectural disarray. This includes the loss of glandular and trabecular patterns in differentiated and undifferentiated carcinomas, respectively [2,12]. Invasive tumor cells often exhibit cytoplasmic microfilaments, pseudopodia, and a loss of cell polarity, cell-to-cell adhesion, and cell-basal membrane connections, reflecting a transition to a mesenchymal phenotype [1]. During epithelial-mesenchymal transition (EMT), epithelial cells undergo morphological changes, acquiring mesenchymal characteristics such as enhanced migratory ability, invasiveness, apoptosis resistance, and extracellular matrix (ECM) production. These changes further promote the detachment of tumor buds [14,15].

Lugli et al. [11], explored the significance of intratumoral budding in colorectal cancer and its association with peritumoral budding and mismatch repair status. They found that intratumoral budding correlates strongly with peritumoral budding and is associated with features indicative of epithelial–mesenchymal transition (EMT). EMT involves the downregulation of adhesion molecules such as E-cadherin, disrupting intercellular epithelial junctions and facilitating cellular migration [16]. This loss of adhesion, coupled with decreased membrane localization of E-cadherin, is consistently observed in tumor budding across malignancies, including colorectal cancer [1].

The molecular mechanisms driving tumor budding (TB) and EMT remain under intense investigation. Studies suggest that EMT allows neoplastic epithelial cells to acquire a mesenchymal phenotype, enhancing their ability to invade, migrate, and resist apoptotic signals [17,18]. Analyzing the molecular composition of invasive cancer cell structures and their microenvironments may yield critical insights into the processes underlying tumor budding and identify novel therapeutic targets for combating cancer progression.

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Importance of Tumor Budding (TB)

Tumor budding (TB) refers to the presence of clusters of undifferentiated malignant cells in the tumor stroma, primarily (but not exclusively) near the invasive front of a tumor [12]. The infiltrative border configuration of tumors enhances their progression and dissemination, facilitating invasion of the vascular and lymphatic systems [19]. Both TB and tumor border configuration have emerged as significant prognostic factors, gaining substantial recognition from the International Union Against Cancer (UICC) [20]. Extensive research has established TB as a strong predictor of adverse clinical outcomes, particularly due to its association with lymph node involvement, lymphatic invasion, metastasis, and local recurrence, all contributing to poor disease-free survival [21].

Several studies have demonstrated that TB functions as an independent prognostic marker, irrespective of pathological stage [22]. TB has been identified as an independent risk factor for colorectal cancer due to its high biological activity and prognostic significance. Regardless of Dukes stage, patients exhibiting prominent tumor budding may benefit from intensified monitoring and adjuvant treatment strategies [9,7].

Fukumoto et al. [10], identified a strong correlation between TB, lymphovascular invasion, and reduced progression-free survival, reinforcing its association with cancer recurrence. Furthermore, TB has been consistently linked to higher tumor grade, advanced TNM staging, and both local and distant metastasis [3].

Beyond colorectal cancer, TB has emerged as a critical pathological indicator in other malignancies. For example, in T1 non-muscle-invasive bladder cancer (NMIBC), TB predicts advanced-stage progression and shows high interobserver agreement, without the need for costly or time-consuming immunohistochemical staining, making it a practical tool for clinical use [10]. To improve therapeutic outcomes and overcome resistance, a deeper understanding of the molecular pathways driving TB is essential. Such insights could guide the development of targeted therapies, ultimately enhancing patient prognosis [1].

How to Count Tumor Budding (TB)?

The assessment of tumor budding (TB) follows the standardized guidelines established by the International Tumor Budding Consensus Conference (ITBCC) in 2016 [9]. According to these guidelines, TB is evaluated on hematoxylin-eosin (H&E)-stained sections using a 10x objective lens to identify the area with the highest density of tumor buds at the invasive front. Tumor buds are then counted within a single "hot spot" using a 20x objective lens, and the count is adjusted with a correction factor to correspond to a standardized field area of 0.785 mm^2. Tumor budding must be independently scored by two pathologists, blinded to clinical data [23].

While H&E-stained sections are the recommended primary method for analyzing tumor budding, cytokeratin immunostaining can be employed in challenging cases, such as those with dense inflammatory reactions at the invasive front, to enhance accuracy [24,9,20]. The consensus conference held in Bern in 2016 reinforced this methodology and introduced a three-tier grading system for tumor budding (TB) based on the number of tumor buds observed in the selected field: Bd1 (low): 0–4 buds, Bd2 (intermediate): 5–9 buds, and Bd3 (high): ≥10 buds. High-grade tumor budding (Bd3), as shown in “Figure 1”, is characterized by a large number of tumor buds and is associated with a worse prognosis [9]. This standardized approach provides a reproducible and clinically relevant framework for evaluating tumor budding, ensuring consistent prognostic assessment in routine pathology practice.

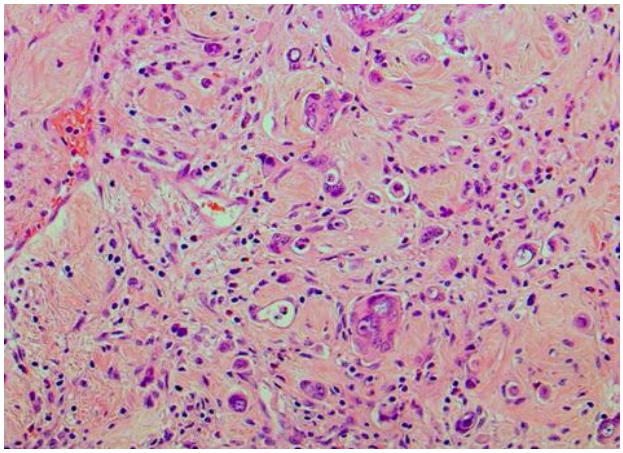
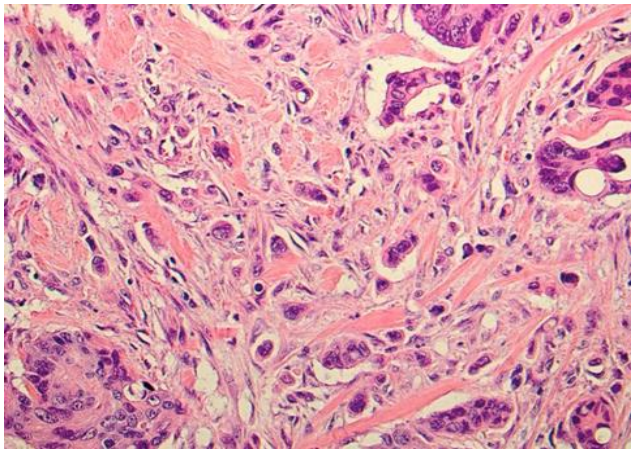
a  b 

Figure1 (a & b). Examples of TB high grade (hotspot, 0.785 mm2) at the invasive front as a poor histopathological feature in stage II colorectal cancer.

Tumor Budding in Malignancies

Tumor budding (TB) is a histopathological feature characterized by the presence of single cancer cells or small clusters (<4 cells) at the invasive tumor front. Initially described by Imai in 1949 in gastric cancer,

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subsequent studies have linked TB to poor clinical outcomes across multiple malignancies, including colorectal (CRC), esophageal, pancreatic, lung, and breast cancers [1,12].
Among these, Colorectal cancer (CRC) remains the most extensively studied. Tumor buds are classified as either peritumoral budding (PTB), located at the tumor margin, or intratumoral budding (ITB), found within the tumor core [9]. PTB assessment is limited to resection specimens, while ITB can be evaluated in both biopsies and resections. Both forms have demonstrated prognostic significance, aiding clinical decision-making and predicting tumor regression in CRC patients [3,25].
Beyond CRC, TB is increasingly recognized as a prognostic marker in other malignancies. For instance, TB in oral squamous cell carcinoma is associated with advanced disease stage and poor survival [10].
In esophageal, lung, and cervical cancers, the recently proposed three-tier tumor budding and nest size (TBNS) grading system has shown high predictive value, enabling refined prognostic stratification [13]. Future studies should focus on standardizing TB evaluation across tumor types and exploring its molecular underpinnings to enhance its utility as a universal prognostic biomarker.

Tumor Budding in Colorectal Cancer (CRC)

Tumor budding (TB) is a key histopathological feature in colorectal cancer (CRC), characterized by single malignant cells or clusters of fewer than five cells at the invasive tumor front, dispersed within the stromal tissue, these cells exhibit features of locomotion, including cytoplasmic flaps and lamellipodia-like projections, reflecting their invasive potential [12].
In T1 CRC, TB is a robust predictor of lymph node metastasis, underscoring its clinical utility in early-stage disease management [10, 26]. The presence of high-grade TB in biopsy or resection specimens may guide decisions on lymphadenectomy or adjuvant therapy, even in seemingly localized disease. Additionally, the morphology of the invasive tumor margin, closely linked to TB, provides valuable prognostic information. Tumors with infiltrative margins and prominent budding are associated with higher rates of recurrence, metastasis, and reduced survival [27,19]. These findings reinforce the role of TB as an independent prognostic factor in CRC, supporting its integration into routine pathological evaluation and risk stratification frameworks.

Tumor Budding and Urothelial Cancers

The classification of malignant tumors using the TNM staging system remains a cornerstone for predicting prognosis and guiding treatment decisions. In urothelial carcinoma of the bladder (UCB), stage is the most critical prognostic factor, as outlined in the 8th edition of the American Joint Committee on Cancer (AJCC) TNM classification [13]. Tumor budding (TB), a histopathological phenomenon linked to aggressive cancer behavior, has been explored as a potential prognostic marker in UCB.
Jimenez et al. [28], were the first to describe pathological growth patterns at the invasive front of urothelial carcinoma of the bladder (UCB), categorizing them into nodular, trabecular, and infiltrative types. The infiltrative growth pattern shares similarities with tumor budding, a concept originally described in colorectal adenocarcinomas [26]. High-grade tumor budding in UCB is associated with increased metastatic potential, particularly in non-muscle invasive urothelial carcinomas (NMIBC), and may serve as a valuable predictor of distant metastasis [29].
Tumor budding (TB) in urothelial carcinoma of the bladder (UCB) is characterized by the presence of single cells or small clusters of tumor cells at the invasive front, which penetrate the surrounding stromal area [1]. This phenomenon is associated with poor clinical outcomes, including stage progression in T1 non-muscle invasive bladder cancer (NMIBC) and distant metastasis in both NMIBC and muscle-invasive bladder cancer (MIBC) [10,8]. Survival analyses indicate that combining TB quantification with traditional clinicopathological parameters enhances prognostic accuracy, surpassing the predictive power of TNM staging alone [8].
Histological variations in urothelial carcinomas, now categorized into 13 subtypes by the World Health Organization (WHO), are frequently observed in metastatic disease and are associated with poor clinical outcomes [29]. Tumor budding (TB) has been recognized as a significant poor prognostic marker across these subtypes, especially in cases of micropapillary or plasmacytoid variants. These aggressive subtypes may warrant early radical cystectomy due to their more aggressive clinical course [29].
In resected urothelial carcinoma of the bladder (UCB), a novel tumor budding and cell nest size (TBNS) grading system has shown promising prognostic value. However, its application in biopsy samples and within the context of neoadjuvant therapy still requires further exploration [13]. Additionally, practical challenges, such as the selection of optimal slides, staining techniques (H&E vs. immunohistochemistry), and scoring methods (cut-off vs. continuous scale), need to be standardized to ensure reproducibility across studies [9]. Despite these obstacles, tumor budding remains a reliable biomarker, maintaining its prognostic significance regardless of the scoring system used.

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Conclusion

Tumor budding (TB) is a significant histopathological feature with strong prognostic implications across various epithelial malignancies, particularly colorectal and urothelial carcinoma. Its association with adverse clinical outcomes emphasizes its clinical relevance, though current challenges in assessment methodologies hinder its widespread implementation. Emerging research linking TB to epithelial-mesenchymal transition (EMT) highlights its potential as both a biomarker for identifying aggressive cancer phenotypes and a target for novel therapeutic interventions. Future studies should focus on the molecular characterization of TB to better understand its role in tumor evolution, paving the way for TB-specific treatments. Integrating TB as a routine component of pathological evaluation could transform personalized oncology by enabling more accurate prognostic stratification and individualized treatment strategies. Collaborative efforts to standardize scoring systems and incorporate technology-driven solutions will be essential in unlocking the full clinical potential of TB and enhancing cancer care outcomes globally.

Conflict of interest. Nil.

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المستخلص

تُعد قدرة الورم على الانتشار وتكوين النقائل السمة المميزة للأورام الخبيثة، وهي عملية تتطلب تكيفات خلوية محددة. وقد طورت اللجنة الأمريكية المشتركة للسرطان نظام تصنيف الأورام لتصنيف الأورام الخبيثة وتوجيه استراتيجيات العلاج، مما يعكس السلوك البيولوجي والنتائج السريرية للأورام. وعلى الرغم من فائدته، لا تزال الجهود مستمرة لتحديد معايير تشخيصية ومقاييس تنبؤية إضافية لتحسين دقة التصنيف ونتائج العلاج. يُعد تبرعم الورم أحد هذه المعايير، وهو ميزة مورفولوجية مميزة تُلاحظ في السرطانات الظهارية. يتميز تبرعم الورم بوجود خلايا خبيثة منفردة أو في تجمعات صغيرة تصل إلى أربع خلايا تنفصل عن جبهة الورم الغازية حيث تغزو النسيج المحيط. وقد تم وصف هذه الظاهرة لأول مرة في سرطان القولون والمستقيم، ومنذ ذلك الحين تم التحقيق فيها بشكل واسع والاعتراف بها كمؤشر لتوقع النتائج السلبية، بما في ذلك غزو العقد الليمفاوية، والانتشار الموضعي والنقائل البعيدة، والغزو لأوعية الدم واللمف، وكذلك مؤشر للمعدلات المنخفضة للبقاء على قيد الحياة ببالرغم من العلاج، وهذا في أنواع عديدة من السرطان. وبغض النظر عن المرحلة المرضية، يرتبط تبرعم الورم كعلامة على السلوك العنيف للورم السرطاني مما يبرز أهميته التنبؤية. وكمثال سرطانات الظهارة للمسالك البولية، ارتبط تبرعم الورم بتطور المرحلة المرضية، والإنتشار الورم، وغير لك لا سيما في سرطان المثانة. تستعرض هذه المراجعة للآليات الكامنة وراء تبرعم الورم، وأهميته السريرية في أنواع مختلفة من الأورام، وآثاره التنبؤية في سرطانات الظهارة البولية. إن فهم هذه العوامل يمكن أن يوفر رؤى محددة وقيمة لإدماج عامل تبرعم الورم في التشخيص والتقييم الباثولوجي للحالات المرضية بحيث يصبح روتيني ولابد منه ولما له من تأثير أيضاً في تحسن استراتيجيات التشخيص والعلاج في الأورام السرطانية.

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