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肿瘤出芽在恶性肿瘤中的研究进展

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摘 要:肿瘤出芽(tumor budding,TB)是恶性肿瘤浸润前沿的微观形态特征,已被证实具有明确的预后预测价值。本文系统综述了TB在不同类型实体瘤中的评估标准、分子机制及临床意义,重点探讨TB与上皮-间质转化(epithelial-mesenchymal transition,EMT)及肿瘤微环境(tumor microenvironment,TME)的关联,及其在个体化治疗决策中的潜在作用。近年来,人工智能(artificial intelligence,AI)技术在TB的自动化识别与空间定量分析中展现出显著优势,为克服传统病理评估中标准不统一和主观性强等局限提供了新的解决方案。未来应通过多中心合作建立跨癌种的统一评估体系,并推动其在临床预后分层与个体化治疗中的转化应用。

关键词:肿瘤出芽;预后;人工智能;标准化;上皮-间质转化;肿瘤微环境
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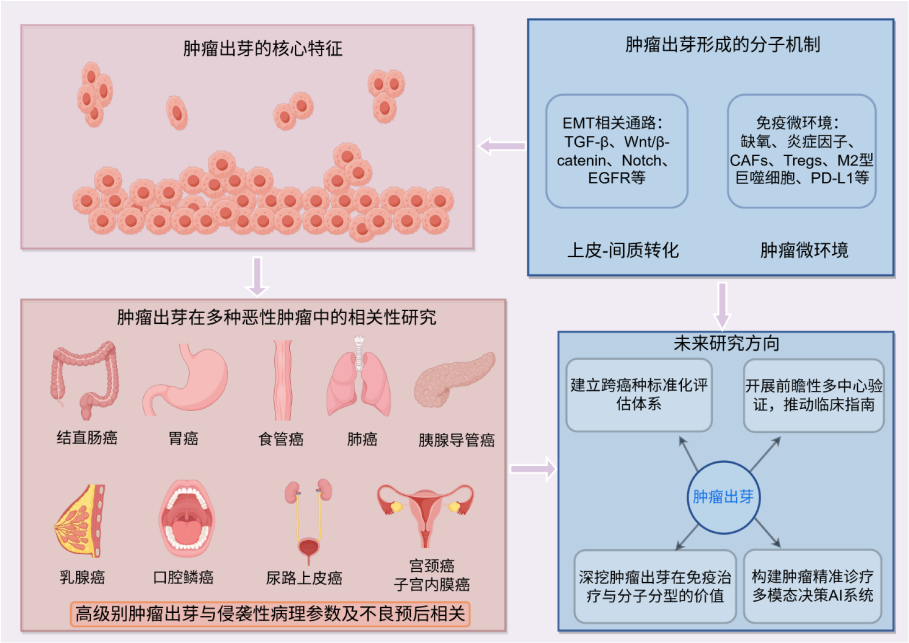
Research advances in tumor budding in malignant tumors

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Abstract: Tumor budding (TB), defined as the presence of discrete single tumor cells or small clusters of up to four cells at the invasive front, is a key histopathological hallmark of aggressive tumor behavior and a robust, independent prognostic factor across numerous cancer types. This review synthesizes current knowledge on TB, with a focus on its assessment methodologies, biological underpinnings, and clinical relevance. Standardized evaluation is crucial for its application. The International Tumor Budding Consensus Conference (ITBCC) criteria provide a foundational three-tier grading system, and now are widely adopted in colorectal cancer. However, its application to other malignancies such as gastric or lung carcinoma requires adaptation due to histological heterogeneity. While hematoxylin and eosin (HE) staining is routinely used, immunohistochemistry (IHC) enhances diagnostic accuracy by facilitating the precise identification of epithelial tumor buds. Biologically, TB is closely associated with the epithelial-mesenchymal transition (EMT), a process driven by tumor microenvironment (TME) signals including hypoxia and crosstalk with cancer-associated fibroblasts. This triggers key pathways such as TGF-β and Wnt/β-catenin, resulting in the loss of epithelial markers and acquisition of mesenchymal markers, thereby promoting cellular invasion. Furthermore, TB is linked to an immunosuppressive TME, characterized by a reduction in cytotoxic lymphocytes and an increase in regulatory immune cells and programmed death-ligand 1(PD-L1) expression, suggesting its role in facilitating immune evasion. Clinically, high-grade TB consistently correlates with adverse clinic-pathological features including lymph node metastasis and advanced stage, and predicts worse survival outcomes in cancers such as colorectal, gastric, pancreatic, and breast carcinoma. Despite its prognostic strength, the integration of TB into routine clinical practice faces several challenges: a lack of uniform standards beyond colorectal cancer, significant inter-observer variability, an urgent need for prospective validation, and the integration of artificial intelligence (AI) technologies into diagnostic workflows. AI offers promising solutions by enabling automated, quantitative, and reproducible TB

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assessment. Future priorities should include establishing cancer-specific guidelines through multicenter collaborations, validating the predictive value of TB for therapies such as immunotherapy, and developing AI-driven tools for practical clinical integration. Ultimately, TB holds significant potential to evolve into a precise biomarker for risk stratification and personalized treatment strategies in oncology.



Key words: tumor budding; prognosis; artificial intelligence; standardization; epithelial-mesenchymal transition; tumor microenvironment

肿瘤出芽(tumor budding,TB)是一种通过常规苏木精-伊红(hematoxylin-Eosin staining,HE)染色即可识别的组织病理学特征,特指在肿瘤浸润前沿存在的单个肿瘤细胞或由<5个肿瘤细胞组成的细胞簇脱离原发灶、呈芽状浸润周围间质的现象,这一特征动态体现了肿瘤的侵袭与转移潜能,已被证实是多种癌症类型独立的不良预后因子[1]。TB最初在结直肠癌中被详尽描述,但随着研究的深入,其在胃癌、口腔鳞癌、乳腺癌、宫颈癌等众多实体瘤中的普遍存在和重要临床意义不断被揭示[2-6]。

随着国际肿瘤出芽共识会议(International Tumor Budding Consensus Conference,ITBCC)标准的推出与推广,TB的评估正逐步走向规范化,使其在临床病理诊断和预后评估中的价值日益凸显[1]。TB并非一个简单的形态学特征,它直观反映了肿瘤的侵袭性生物学行为,并与上皮-间质转化(epithelial-mesenchymal transition,EMT)、细胞迁移、免疫逃逸及治疗抵抗等关键过程密切相关[2,7-9]。鉴于TB在基础研究与临床实践中的桥梁作用日益凸显,系统梳理其评估标准、分子机制及跨癌种的预后价值显得尤为重要。

基于上述重要进展,本文旨在系统梳理TB研究的关键进展。为全面展现该领域的研究全貌,本文将依次从以下几个方面展开论述:(1)TB的评估标准;(2)TB发生发展的核心分子机制,特别是其与EMT及肿瘤微环境(tumor microenvironment,TME)的相关性;(3)TB在多种癌症中的临床预后价值及其对治疗决策的潜在指导意义;(4)当前TB检测评估方法的演进、标准化挑战及人工智能(artificial intelligence,AI)等新技术带来的解决方案;(5)展望TB作为治疗靶点的转化医学前景及未来研究方向。通过对这些方面的综合评述,本文旨在为推动TB的深入基础研究和临床转化应用提供清晰的参考框架,不仅系统梳理TB在不同实体瘤中的研究全景,还将结合本团队在尿路上皮癌中的研究分析当前挑战,并展望AI等技术驱动的未来发展方向。

1 TB的评估标准

1.1 TB的观察

目前,最常用于观察TB的方法是HE染色,在光学显微镜下,TB通常表现为单个或<5个细胞组成的

细胞簇,呈现明显的异型性,胞质呈嗜酸,细胞核多形性、深染,核仁增大,并可见异常有丝分裂象[10]。然而,当肿瘤浸润前沿伴有显著炎症反应或存在大量组织碎片时,HE染色中TB与退变或撕裂的组织碎片在形态上易发生重叠,从而导致识别困难。在此情况下,免疫组织化学(immunohistochemistry,IHC)染色因能特异性标记上皮来源的肿瘤细胞,有助于清晰区分TB与非肿瘤性结构,常被推荐作为辅助或首选手段[11]。相比于HE染色,IHC具有更高的特异性和准确性,是一种优越的检测方法,能最大程度减少观察TB时的误差[12,13]。尽管目前国内观察TB使用HE染色占主导地位,但结合HE与IHC两种方法进行综合评价,有望提升TB检测的可靠性,减少误判[9]。

1.2 TB计数和分级

根据2016年ITBCC推荐的标准,TB的评估应采用三级分级系统:在20倍物镜视野下(面积0.785 mm^2),计数肿瘤浸润前沿"热点区"内的TB数量:0~4个为低级别TB(Bd1),5~9个为中级别TB(Bd2),≥10个为高级别TB(Bd3)。这一标准不仅是结直肠癌的评估规范,也是其他癌种的重要参考,但需根据不同癌种进行验证和调整[1]。不同TB分级之间具有显著的临床预后差异,例如在III期结直肠癌患者中,与低级别的Bd1相比,Bd2和Bd3类别均与接受以奥沙利铂为基础的标准辅助化疗后较差的5年总生存率(overall survival,OS)和3年无病生存率(disease free survival,DFS)密切相关[1]。TB主要分布在肿瘤与间质交界处,高级别TB与淋巴结转移显著相关[2];类似的现象也在子宫内膜癌中被观察到,高级别TB与肿瘤高级别、晚期分期和淋巴结转移显著相关[14]。2023年,中国临床肿瘤学会(Chinese Society of Clinical Oncology,CSCO)结直肠癌诊疗指南及《中国结直肠癌诊疗规范(2023版)》均明确建议采用ITBCC标准进行TB分级和病理报告[15]。尽管ITBCC标准在结直肠癌中适用,但在胃癌、肺癌等恶性肿瘤中,TB分级评估仍需确定癌种特异性阈值,目前仍缺乏统一标准。

2 TB形成的相关分子机制

2.1 TB与EMT

统一的评估标准是临床应用TB的前提,而对其背后分子机制的深入理解,则是揭示TB生物学本质、开发靶向策略的关键。TB是EMT动态过程在肿瘤侵袭前沿的组织学体现,连接了微观分子事件与宏观侵袭形态[16]。EMT是上皮细胞逐渐向间质细胞转化的过程,在肿瘤进展中,该过程受到TME中多种信号的高度调控,从而增强细胞迁移能力[17]。其典型分子特征包括上皮标志物(如Ecadherin)表达下降,以及间质标志物(如Ncadherin、Vimentin)的上调,同时细胞形态由规则上皮样向多边形或鹅卵石状转变[9]。TB区域的细胞同样呈现Ecadherin丢失、Ncadherin及Vimentin获得,并且高表达ZEB1、ZEB2、β-catenin等EMT核心转录因子[18,19],从分子层面证实TB是活跃EMT程序在组织形态上的直接反映。

EMT的发生依赖TME中多种细胞外信号的精密调控,这些信号(如缺氧、炎症因子)通过激活细胞表面受体,进而启动胞内信号转导通路,包括TGF-β、Wnt/β-catenin、Notch、EGFR等,进而促使信号分子入核,调节EMT核心转录因子,驱动上皮细胞向完全或部分间质表型转变,从而增强其迁移和侵袭能力[20-22]。不同上游信号通路通过激活EMT核心转录因子(如Snail、ZEB、Twist),构成驱动TB形成的共同分子枢纽。例如,TGF-β通路可通过Smad或非Smad(如MAPK)途径上调Snail、ZEB1促进EMT[21],其持续激活与TB形成及不良预后相关。Wnt/β-catenin通路的异常激活可驱动EMT与肿瘤侵袭,例如,蛋白质精氨酸甲基转移酶6(Protein arginine methyltransferase 6,PRMT6)可通过转录上调YTH结构域家族蛋白2(YTH domain family member 2,YTHDF2)等方式激活该通路[23],且该通路核心蛋白β-catenin核积累是TB区域的标志性特征。EGFR信号异常则可通过促进上皮细胞黏附分子(epithelial cell adhesion molecule,EpCAM)裂解,影响β-catenin/淋巴样增强因子1(lymphoid enhancer-binding factor 1,LEF1)核转位,上调ZEB2、Twist等转录因子,交叉调节EMT程序[22,24]。

在不同癌种中,驱动TB形成的上游信号存在异质性,但均通过这一核心枢纽发挥作用。例如,在结直肠癌中,ERM结合磷酸蛋白50(ERM-binding phosphoprotein-50,EBP50)耗竭通过稳定β-catenin驱动Slug表达,启动EMT并促进TB形成[25]。在胃腺癌中,肿瘤前缘中较高的含锌指和BTB结构域蛋白7A(zinc finger and BTB domain-containing protein

7A,ZBTB7A)表达通过EGFR-MEK-ERK和PI3K-AKT-mTOR途径启动EMT,从而形成TB[26]。

这些研究从时空动态的角度,将局部微环境信号、EMT程序与TB的形态学表现紧密关联起来[18]。因此,TB可视为局部微环境诱导下EMT程序在组织学上的具体体现。

2.2 TB与TME

TME是驱动TB形成与演进的关键基础,其作用主要体现在直接诱导EMT和重塑免疫微环境两个方面。一方面,TME关键组分直接激活EMT程序驱动TB形成[18]。例如,缺氧通过激活Yes相关蛋白(Yes-associated protein,YAP)进而与缺氧诱导因子(hypoxia-inducible factor,HIF)-1α这一核心转录因子结合,促进EMT及TB的形成[18]。癌症相关成纤维细胞(cancer-associated fibroblasts,CAFs)则可通过分泌细胞因子(如CCL5),稳定HIF-1α或上调ZEB1并诱导EMT,促进TB形成[27]。另一方面,TB的形成与免疫微环境的重塑构成恶性循环。高级别TB通常伴随肿瘤浸润淋巴细胞密度下降[28],而免疫抑制性细胞浸润增加,如效应免疫细胞$CD3^+$、$CD4^+$、$CD8^+$ T细胞和成熟树突状细胞数量下降,而免疫抑制细胞$CD163^+$ M2型巨噬细胞与$FOXP3^+$ Treg则增多[29,30]。此外,肿瘤相关中性粒细胞(tumor-associated neutrophils,TANs)在TB区域的浸润也增加[31]。机制上,Fcγ受体IIIb(Fc region γ receptor III-B,FCGR3B)的高表达通过抑制自然杀伤细胞(natural killer cells,NK细胞)介导的细胞毒性来促进TB进展;同时,核受体亚家族4A组成员2(nuclear receptor subfamily 4 group A member 2,NR4A2) 作为下调基因之一,能够反式激活FOXP3,后者参与调节性T细胞的分化、维持与功能,在肿瘤细胞的发展与存活中扮演重要角色,这些改变共同塑造了免疫抑制微环境,促进TB形成[32]。尤为重要的是,在缺氧等TME条件下,TB细胞及周围的免疫细胞可上调免疫检查点分子程序性死亡配体1(programmed death-ligand 1,PD-L1)的表达,直接介导适应性免疫抑制[33,34]。

这种独特的免疫微环境赋予了TB重要的临床意义。TB相关的免疫抑制表型与患者的不良预后显著相关[35]。同时,TB区域PD-L1的上调提示其可作为预测免疫检查点抑制剂(如抗PD-1/PD-L1疗法)疗效的潜在生物标志物[34]。因此,TB的评估不仅有助于预后分层,更为了解免疫治疗耐药机制和制定联合策略(如靶向TB相关通路以逆转免疫抑制)提供了线索[29,32,36]。TB形成的机制及其与TME的相互作用见图1。

3 TB与各恶性肿瘤的相关性及预后价值

上述分子机制构成了TB形成的共性基础,然而其临床意义的具体呈现则因癌种而异。本节系统梳理TB在结直肠癌、胃癌等十种恶性肿瘤中的研究现状,重点对比分析各癌种的异同。

3.1 结直肠癌

结直肠癌中TB研究历史最久,体系最为成熟。随着科研进展,结直肠癌的TB分级有了国际共识,2016年ITBCC推荐的标准将TB分为三级分级系统[1],并且该标准已写入临床指南,评估最为规范,其模式是其他癌种的标杆。研究证实TB与结直肠癌不良预后参数密切相关,如高TNM分期、淋巴结转移等,并且高级别TB是患者OS和DFS缩短的明确危险因素[37,38]。微卫星高度不稳定(microsatellite instability-high,MSI-H)状态通常与TB呈负相关[39],但在早发性结肠癌中此关联不显著,提示年轻患者可能存在独特生物学行为[40]。TB已被建议作为早期结直肠癌术后病理常规评估项目,用于指导高风险患者的监测或辅助治疗决策[9]。

然而,其应用仍存在局限性。首先,对肿瘤内异质性及原发灶与转移灶间的评估差异缺乏深入分析[37];其次,TB的预后价值尚未与分子特征(如MSI-H状态)充分整合,这限制了对患者进行更精准风险分层的能力[38]。未来需在前瞻性研究中验证TB在分子亚型中的价值,并探索其在个体化治疗决策中的作用[39]。

3.2 胃癌

与评估体系相对成熟的结直肠癌相比,TB在胃癌中的应用面临组织学异质性带来的挑战。在胃癌中,TB同样被证实是重要的不良预后标志物,其与胃癌的不良病理特征呈显著正相关,如淋巴结转移、淋巴血管浸润(lymphovascular invasion,LVI)及临床分期较晚等[41-43],并且高级别TB不仅影响患者的OS和DFS,还可作为独立的预后预测因子[42,44]。然而,胃癌TB评估面临比结直肠癌更为复杂的挑战,其核心在于显著的形态学异质性和组织学分型的依赖性。目前广泛采用的是ITBCC所提出的三级

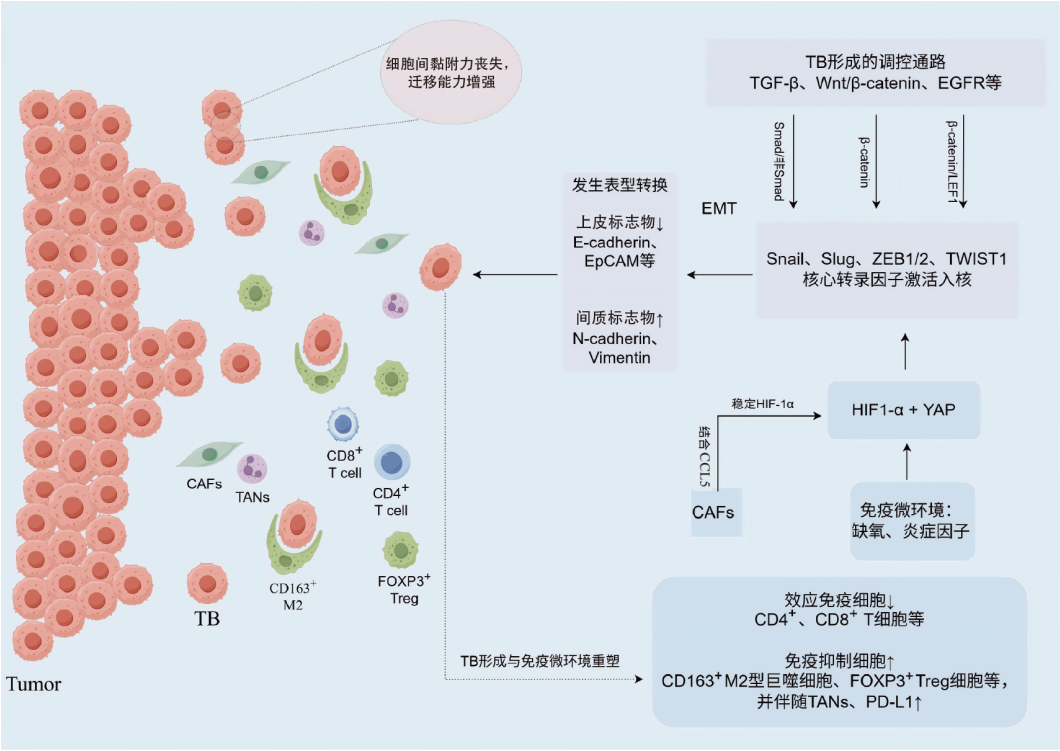


图1　TB形成的相关分子机制示意图

本图概括了TB形成的多因素调控网络。其核心机制在于：TME中的关键信号（如缺氧、炎症因子）及细胞组分（CAFs）通过HIF-1α/YAP轴激活Snail、Slug、ZEB1等核心转录因子，促进多条EMT相关信号通路，如TGF-β、Wnt/β-catenin、EGFR等激活，最终使得肿瘤细胞发生表型转换：上皮标志物（如E-cadherin、EpCAM）下调，间质标志物（如N-cadherin、Vimentin）上调，细胞获得迁移与侵袭能力，最终在组织学上外化为侵袭前沿的TB。TB的形成与特定的免疫微环境重塑密切相关，常伴随抗肿瘤的$CD4^+$、$CD8^+$ T细胞等数量下降，而$CD163^+$ M2型巨噬细胞、$FOXP3^+$ Treg等免疫抑制细胞浸润增加及PD-L1表达上调，共同构成免疫抑制生态，促进肿瘤进展。该模型揭示了TB作为连接促侵袭微环境、EMT可塑性及免疫逃逸的整合性生物学标志的价值。本图由Figdraw提供素材绘制。

Figure 1　Molecular mechanisms involved in TB formation

This diagram summarizes the multifactorial regulatory network underlying tumor budding (TB) formation. The core mechanism centers on key signals (e.g., hypoxia, inflammatory cytokines) and cellular components (e.g., CAFs) within the TME. These elements activate core transcription factors such as Snail, Slug, and ZEB1 via the HIF-1α/YAP axis, thereby driving the activation of multiple EMT-related pathways (e.g., TGF-β, Wnt/β-catenin, EGFR) and ultimately triggering epithelial-mesenchymal transition. This, in turn, activates multiple EMT-related pathways, including TGF-β, Wnt/β-catenin, and EGFR, ultimately driving a phenotypic shift in tumor cells: downregulation of epithelial markers (e.g., E-cadherin, EpCAM) and upregulation of mesenchymal markers (e.g., N-cadherin, Vimentin). Consequently, cells acquire migratory and invasive capabilities, histologically manifested as TB at the invasive front. This figure was created with materials from Figdraw.

分级系统[41,43,44]，也有研究沿用二级分类、四级TB分类[42,45]，这种标准不统一本身就反映了评估的复杂性，但更深层的原因在于肠型胃癌与弥漫型胃癌的形态学差异。关键分歧在于弥漫型胃癌的应用：由于弥漫型胃癌本身缺乏明确的腺体结构，病理上难以有效区分弥漫型胃癌与TB的形态特征，这使得ITBCC分级系统主要应用于肠型胃癌，而在弥漫型胃癌中的应用仍受限[46]。然而，部分弥漫型胃癌可表现为局限性膨胀性生长模式，其侵袭前沿与间质分界清晰，此类病例被归类为瘤内出芽进行评估[45]。TB与分子特征的关系尚存争议：TB与特定基因型（如HER2阳性及MSI-H）的负相关性已被报道[43]，与之矛盾的是，少数MSI-H胃癌亦可表现为高级别TB并与不良预后相关[44]，这种MSI-H背景下TB预后意义的异质性，在结直肠癌中亦存在。

相较于评估体系成熟的结直肠癌，胃癌TB研究面临更根本的挑战：首先，由于肠型与弥漫型胃癌在组织学上的固有差异，基于腺体结构的ITBCC标准在弥漫型癌中的应用存在理论困境，评估标准难以统一[46]；其次，现有研究缺乏与分子分型的系统整

合,因而难以界定TB在不同分子背景下的精准预后价值[43,44,46]。

3.3 食管癌

作为一种常见的消化道肿瘤,食管癌的TB研究显示其具有与胃癌相似的预后价值,但也存在组织学类型间的差异。在食管癌中,TB同样被证实具有显著的预后指示作用,尤其在食管鳞状细胞癌中的证据较为充分:高级别TB与食管鳞状细胞癌的淋巴结转移、结缔组织增生反应及高TNM分期显著相关[47],是患者OS和DFS不良的独立危险因素[47,48]。然而,TB在腺癌中的生存分析出现分歧,既有研究认为其与生存结局无关[49],亦有研究支持其具有显著的预后意义[50]。这种差异可能与腺癌的异质性、样本量、评估标准不一以及新辅助治疗的应用有关[47,51,52]。值得注意的是,由于食管腺癌与胃食管结合部腺癌在生物学行为上的连续性,其TB评估常参考胃癌或结直肠癌的标准[49]。目前,食管癌的TB评估多借鉴ITBCC为结直肠癌设立的三级系统[47-50],但标准尚未统一。例如,有研究通过IHC与ROC曲线分析,建立了另一套阈值不同的三级分级系统,将TB分为低级别(0~4个)、中级别(5~15个)和高级别(≥16个)[52]。这再次表明,简单套用结直肠癌阈值可能不适用于所有食管癌亚型。

当前研究主要为排除新辅助治疗患者的单中心回顾性分析,其结论的普适性受限[47,51,52]。未来需开展前瞻性研究以建立并验证标准化的评估体系,并深入探索TB在不同组织学类型、治疗背景及分子分型下的动态变化与临床意义。

3.4 肺癌

消化道肿瘤的研究提示,TB的评估高度依赖其组织学背景,而在同样具有多样组织学亚型的肺癌中,TB的评估标准与预后意义面临更复杂的界定。在肺癌领域,TB作为一种新兴且有希望的预后因素被广泛研究,但其评估标准的适用性仍存在争议[53]。在评估标准上,虽多数参照ITBCC[54,55],但也有研究采用二级分级(如0~9个出芽为低级别,≥10个为高级别)[56],这直接反映了领域内缺乏共识。一个显著特点是TB与侵袭性特征的关联因组织学亚型而异,无论是肺鳞状细胞癌还是肺腺癌,TB与多种侵袭性病理特征存在显著关联,包括肿瘤坏死、胸膜浸润、神经周围浸润、气腔扩散(spread through air spaces,STAS)、LVI等[53-55,57]。特殊的是,TB与病理特征之间的关联性在组织学亚型间存在差异:在肺鳞状细胞癌中TB与最小细胞巢尺寸(minimum cell nest size,MCNS)相关[55],而肺腺癌中TB则更多与间质纤维化及PET-CT影像中的高SUVmax值具有相关性[57]。此外,临床病理特征亦随TB分级而异:高级别TB常见于年龄较大的患者,且神经周围浸润比例更高;低级别TB则多见于肺腺癌,而高级别TB则更多表现为角化或基底样表型[55]。在预后价值方面,高级别TB是肺鳞状细胞癌患者OS缩短的独立预测因素[55]。

当前研究的局限性在于大多聚焦鳞癌,且简单套用其他癌种的阈值可能不适用于肺腺癌[56]。因此,未来研究的关键在于建立肺癌亚型特异性的评估标准,并通过前瞻性队列研究和多组学技术明确其临床价值[55]。

3.5 胰腺导管腺癌

胰腺导管腺癌的TB研究不仅关注其预后价值,更开始探索其与特定分子靶点及免疫治疗反应的关联,展现了超越单纯预后分层的转化潜力。在胰腺导管腺癌中,TB通常依据ITBCC标准被分为三级[29,58,59]。高级别TB被确认为不良预后的独立预测因子,与是否术前接受新辅助治疗无关,且与LVI、神经侵犯、淋巴结转移及低分化等侵袭性病理特征显著相关[58,59],并且高级别TB与患者OS和DFS缩短独立相关[29,58-60]。研究亮点在于开始超越单纯的预后关联,探索TB的分子机制及治疗关联。例如,研究发现胰腺导管腺癌中凝血酶阳性表达、蛋白酶激活受体1(protease-activated receptor 1,PAR-1)阴性表达与高级别TB相关,提示更强的侵袭性行为,因此凝血酶和PAR-1可能成为新型抗癌治疗策略的潜在靶点[61]。此外,高级别TB合并PD-L1阳性患者常对应更高WHO分级、黏液缺失及更高PD-L1表达水平,提示免疫逃逸参与疾病进展及治疗耐受,这也印证了上述高级别TB患者可以从PD-1/PD-L1免疫治疗中获益的可能性[60],为TB作为治疗反应预测标志物提供了初步探索。

然而该领域研究同样受限于单中心、小样本的回顾性设计,推动TB成为可靠的生物标志物,必须解决国际统一评分标准缺失的问题[60,61],并加强与分子分型、治疗反应的关联研究。

3.6 乳腺癌

与结直肠癌相比,TB在乳腺癌中的研究起步较

晚,且评估标准尚未统一。除了采用ITBCC三级分级系统外[36,62,63],不同研究采用了多样的阈值,如4个或8个/高倍视野(high power field,HPF)定义为高级别TB[64,65]。这种阈值的多样性反映了乳腺癌的异质性,也增加了不同研究间的比较难度。与其他癌种相似,在乳腺癌中TB也与多种高侵袭性临床病理特征相关,包括高龄、绝经后状态、低分化、LVI、淋巴结转移及神经周围浸润等,TB也是患者OS和DFS的独立危险因素[62,63]。其预后价值具有分子亚型特异性,在HER2过表达型、管腔A型及三阴性乳腺癌中意义更显著,而在管腔B型中未见明显关联[65]。此外,研究识别出*NOL4*、*STAR*、*C8G*和*NEIL1*等七个基因在高级别TB中过表达,可作为潜在的生物标志物与治疗靶点[36]。

当前该领域的核心挑战是病理评估者间观察差异大,可重复性低[63,66],且证据基础多为小样本回顾性研究[62,63,65]。因此,未来关键在于建立统一的评估标准,开展基于分子亚型的大规模前瞻性研究,并通过多中心研究和公共数据库,如肿瘤基因组图谱(The Cancer Genome Atlas,TCGA),共享数据以确定最佳阈值,明确其临床应用价值。

3.7 口腔鳞状细胞癌

从腺上皮来源的乳腺癌转向探讨体表及上消化-呼吸道鳞状上皮来源的肿瘤,口腔鳞状细胞癌为研究TB提供了另一个经典模型。口腔鳞状细胞癌是最常见的头颈部恶性肿瘤,TB已被确定为其独立预后因素[67]。然而,其评估体系尚未统一,除采用ITBCC三级系统外[68,69],不同研究使用的二级分级阈值(如4、5或10个/HPF)各异[6,67,70,71],影响了结果的可比性。

在临床病理特征方面,TB与口腔鳞状细胞癌的多种侵袭性行为密切相关,包括淋巴结转移、神经周围侵犯、血管侵犯以及包膜外侵犯(extranodal extension,ENE)等[69,70]。值得注意的是,高级别TB被证实是导致ENE的独立风险因素,而ENE本身是口腔鳞状细胞癌预后不良的重要指标,进一步凸显了TB在疾病进展中的关键作用[71]。此外,TB与微血管密度和淋巴管密度呈正相关,提示TB可能在促进血管和淋巴管生成方面发挥重要作用[6,67]。从预后角度看,高级别TB与淋巴结转移、肿瘤复发及肿瘤相关死亡率显著相关[72],同时也与患者OS和无远处转移生存期(distant metastasis-free survival,DMFS)的降低密切相关[68,69]。

现有证据多源于回顾性研究,难以确立因果关系,且受临床治疗异质性、样本分析能力与技术方法差异的限制[6,67,69,73]。因此,未来需通过前瞻性研究和标准化评估进一步验证其预后价值,并探索其在辅助治疗决策中的潜在作用。

3.8 尿路上皮癌

与体表黏膜的口腔鳞癌不同,尿路上皮癌作为覆盖于泌尿系统内壁的特殊上皮来源肿瘤,其TB的评估与意义具有独特背景。在尿路上皮癌中,TB已被广泛证实是一个重要的预后指标。高级别TB与更晚的病理分期、淋巴结转移、LVI、神经侵犯及远处转移等侵袭性临床病理特征显著相关,并可作为OS、无复发生存期(recurrence-free survival,RFS)及疾病特异性生存期(disease-specific survival,DSS)的独立预测因子[74,75]。

本团队在尿路上皮癌TB的评估中采用ITBCC三级分级系统[31],但有研究为更精准地进行风险分层,将TB整合进一个包含生长模式、间质淋巴细胞浸润等参数的新型四级组织学分级系统。该研究对TB分级采用客观分级标准(Bd1: <5个/HPF;Bd2: 5~12个/HPF;Bd3: ≥13个/HPF),发现高级别TB与更高的组织学分级、增强的EMT活性、细胞外基质(extracellular matrix,ECM)重塑以及免疫浸润减少有关,且该综合分级系统的预后价值优于传统WHO分级[75],提示TB作为组合标志物的一部分可能更具价值。此外,TB在膀胱、肾盂、输尿管等不同解剖部位的尿路上皮癌中均显示出预后价值,但也提示需关注部位间的潜在差异[76]。

当前研究主要受限于回顾性单中心设计,存在样本量不足、观察者间差异以及对淋巴结转移可能低估等问题[74,77]。未来需通过多中心前瞻性研究,采用标准化评估流程来验证这些发现,并深入探索TB在不同解剖部位及分子亚型中的特异性。

3.9 宫颈癌

宫颈癌作为与HPV感染密切相关的代表性恶性肿瘤,其TB的研究呈现出独特的病因关联性。TB在宫颈鳞癌与宫颈腺癌中的预后意义已得到多项研究证实,但目前主要采用的两级分级系统,尚未形成统一阈值,例如,有研究将10 HPF下<3个肿瘤芽定义为低级别TB,≥4个定义为高级别TB[78],也有研究采用<2个与≥3个作为分界标准[79]。这种阈值的不

统一,反映了宫颈癌TB研究对标准化的迫切需求。

高级别TB与宫旁浸润、LVI、淋巴结转移、深间质浸润等不良病理特征相关,是患者OS和DFS缩短的独立危险因素[79,80]。在组织学亚型中,高级别TB更多见于宫颈鳞癌[79]。对于宫颈腺癌,高级别TB更多见于HPV非依赖性腺癌和Silva C型肿瘤,并且在基于TB的新型分级系统上能够有效对HPV相关腺癌和胃型腺癌患者的OS进行分层,并预测肿瘤复发[81]。相较于仅与HPV相关腺癌复发有关的Silva分型,以及在此背景下与预后无显著关联的传统FIGO分期,TB可能提供一种更精细且实用的预后评估工具[80,81]。在分子机制方面,有研究通过Mclust算法发现VI型胶原蛋白与TB密切相关,如VI型胶原蛋白α2链(collagen type VI alpha 2 chain, COL6A2),提示其作为宫颈癌预后标志物及TB相关预测因子的潜力[78]。

当前研究的局限包括新型分级系统随访时间短、罕见亚型样本量不足,以及主要基于切除标本进行分析[81]。未来需通过更大规模的多机构前瞻性研究,并纳入活检标本进行验证[81]。

3.10 子宫内膜癌

与HPV驱动的宫颈癌不同,子宫内膜癌的发生发展与内源性雌激素密切相关,这使其TB的形成可能受到独特的激素相关信号轴调控。关于TB在子宫内膜癌中的研究尚不及结直肠癌深入,且缺乏统一的分级标准,多数研究采用两级系统(常以5个/10 HPF为界)[4,82]。

在子宫内膜癌中TB与患者高龄、绝经后状态、肿瘤分级较高、FIGO分期较晚、深肌层浸润(≥1/2)、淋巴结转移、MELF(microcystic, elongated and fragmented,微囊、拉长和碎片状)浸润模式以及OS缩短等相关[83-85]。在分子机制方面,可能存在一个特殊的“激素-EMT轴”,即雌激素受体下调→E-cadherin缺失→EMT激活→TB形成[86-88]。这为内分泌治疗及靶向EMT的策略提供了潜在的理论依据。

目前证据主要来自单中心回顾性研究,存在选择偏倚,且对POLE突变型(POLE mutation, POLEmut)等关键分子亚型的分析因样本量不足而受限[4,14]。未来需要通过大规模、前瞻性的多中心研究,来进一步验证TB的预后价值及其在临床决策中的作用。

通过对十大恶性肿瘤的系统梳理可见,TB作为一种跨癌种的侵袭性标志物,其生物学特性、病理学意义及评估方法均存在显著的癌种异同性。生物学上,其发生虽普遍与EMT相关,但上游驱动信号具有多样性,例如在结直肠癌中主要由Wnt/β-catenin通路驱动[25],而在子宫内膜癌中则可能受独特的“雌激素-EMT轴”调控[86-88]。病理学上,TB的形态评估受组织学类型影响。例如,在胃癌中,ITBCC标准对弥漫型癌的适用性有限[46];而肺癌中的鳞癌与腺癌可能需要不同的判定阈值[56]。技术评估上,各癌种面临的挑战也各不相同:结直肠癌存在肿瘤内异质性干扰[37];乳腺癌因形态多样性和观察者差异而导致标准化困难[63,66];而胰腺癌等则缺乏前瞻性验证数据[60]。这种“共性机制、个性表现”的特征,既是TB作为通用生物标志物的潜力所在,也是其实现跨癌种标准化必须应对的核心挑战。未来需借助多组学与空间病理学技术,从分子到组织层面深化对TB癌种特异性的理解,以推动其向精准医疗工具转化(各癌种TB分级系统及临界值的比较分析见表1)。

4 挑战与未来展望

4.1 标准化挑战与共识的推广

ITBCC为结直肠癌建立的标准化评估方案是TB研究的重要里程碑[1]。值得肯定的是,这一框架在输尿管癌等其他实体瘤中也显示出良好的适用性,本团队的研究即证实了ITBCC标准能有效识别输尿管癌中的高危患者群体[76]。然而,该标准在不同癌种中的普适性仍面临考验。例如在肺癌中,虽参考ITBCC方案,却可能采用不同的计数阈值(如10个/0.785 mm^2作为低级别与高级别的界限),这反映了不同器官肿瘤生物学特性的内在差异[56]。此外,观察者间与观察者内的变异仍是实现标准化评估的核心障碍,即便经过系统培训,病理医师在热点区域选择和芽计数上的主观差异仍会影响结果的可重复性[63,66]。

4.2 数字病理与AI辅助诊断

面对标准化挑战,数字病理与AI技术正成为解决这些问题的关键手段。传统人工评估存在主观性强和定量困难等局限,这正推动评估技术向标准化、精准化的新方向发展。当前进展主要体现在以下4方面。(1)在基础识别层面,已从基于传统图像处理的半自动化方法,演进至基于深度学习的全自动分

表1　不同恶性肿瘤TB评估分级系统与临界值比较

Table 1　Comparison of TB assessment grading systems and cut-off values in various malignancies

癌种	常用分级系统	分级标准与临界值(个/10HPF)	参考文献
结直肠癌	ITBCC三级	低:0~4;中:5~9;高:≥10	[1]
胃癌	ITBCC三级	低:0~4;中:5~9;高:≥10	[41, 43, 44]
	二级	低:0~9;高:≥10	[42]
	四级	极低:0~3;低:4~5;中:6~10;高:>10	[45]
食管癌	ITBCC三级系统	低:0~4;中:5~9;高:≥10	[47-50]
	三级	低:0~4;中:5~15;高:≥16	[52]
肺癌	ITBCC三级系统	低:0~4;中:5~9;高:≥10	[54, 55]
	二级	低:0~9;高:≥10	[56]
胰腺导管癌	ITBCC三级系统	低:0~4;中:5~9;高:≥10	[29, 58, 59]
乳腺癌	ITBCC三级系统	低:0~4;中:5~9;高:≥10	[36, 62, 63]
	二级	低:0~4或0~8;高:>4或>8	[64, 65]
口腔鳞细胞癌	ITBCC三级系统	低:0~4;中:5~9;高:≥10	[68, 69]
	二级	低:0~4或0~8或0~10;高:>4或>8或>10	[6, 67, 70, 71]
尿路上皮癌	ITBCC三级系统	低:0~4;中:5~9;高:≥10	[31]
	三级	低:0~4;中:5~12;高:≥13	[75]
宫颈癌	二级	低:0~2或0~3;高:≥3或≥4	[78, 79]
子宫内膜癌	二级	低:0~5;高:≥5	[4, 82]

注:ITBCC指国际肿瘤出芽共识会议(International Tumor Budding Consensus Conference, ITBCC)所推荐的三级评估系统。

Note: ITBCC refers to the three-tier assessment system recommended by the International Tumor Budding Consensus Conference.

析。一方面,QuPath等开源平台可通过颜色去卷积与形态学过滤技术半自动识别TB,其定量结果与传统方法高度一致且已被证明具有预后价值[89]。另一方面,基于深度学习的卷积神经网络(convolutional neural network,CNN),能够直接对HE染色图像中的TB进行自动化区域分割与定量分析,其算法通过大量标注数据训练后,在多个平台验证中与病理学家评估具有高度一致性,并在风险预测中显示出优于人工计数的潜力[90]。(2)在空间分析层面,AI能够通过多重荧光技术解析TB与TME中免疫细胞、癌症干细胞等的空间关系,构建如"$CD8^+$ T细胞/TB比值""TLS/TB指数"等复合指标,通过R统计软件构建预后预测模型,并生成列线图进行可视化,通过ROC曲线、校准曲线和决策曲线分析对模型效能进行全面评估。该方法在胰腺导管腺癌[91]、三阴性乳腺癌[92]中的验证表明,其提供的预后信息优于或独立于传统的TNM分期系统。(3)在技术优化层面,创新的多模型AI框架,如结合掩码区域卷积神经网络(mask region-based convolutional neural network,Mask R-CNN)与生成对抗网络(generative adversarial network,GAN)实现了从HE切片到虚拟panCK染色的高精度转换,将染色流程从数小时缩短至分钟级,并且该方法已分别经病理医师评估与QuPath软件分析得到了验证,提升了TB评估效率[93]。(4)术前无创预测:以病理结果为金标准,AI可通过三种主要路径从CT、MRI等术前影像中预测肿瘤特征,主要包括:特征融合,即从CT影像衍生的参数图中提取手工影像组学特征与预训练CNN深度特征,经筛选后融合输入机器学习模型预测TB[94];网络迁移学习,将多期相增强CT与肿瘤区域信息直接输入预训练CNN,通过网络迁移学习实现从图像到TB分级的自动分类[8],以及多模态融合,联合CT、MRI等多模态影像,利用CNN提取深层特征并构建TB分级预测模型[95],最终形成综合预测系统。这些方法均以病理为金标准,通过多中心外部验证证实了其预测效能,共同推动了肿瘤评估从术后诊断向术前精准预测的关键跨越。

AI辅助的TB评估不仅与经验丰富的病理医师评估结果具有良好的一致性[90],而且能高效处理大量图像,并揭示人眼难以识别的细微特征,从而提供更多预后信息。尽管AI在TB识别与量化中潜力显著,但存在一定局限性:其一,模型训练依赖大量人工标注,耗时且存在主观性[90];其二,算法在不同染色与扫描条件下的泛化能力仍需多中心大样本验证[89,90,92];其三,现有方法多依赖于特定技术流程,难以阐明生物学机制,所产出的复杂指标在临床转化中也存在整合困难[91];最后是影像组学特征重复性未验证、影像采集与参数计算(如CT相位)缺

乏统一标准,均可能引入误差并影响模型的稳定性与可比性[94,95]。

4.3 当前研究的局限性与未来焦点

综合前文对各癌种TB研究可见,尽管TB的预后价值得到广泛证实,但其从基础研究到临床实践的转化仍面临一系列跨癌种的共性挑战,构成了该领域深化的主要瓶颈,具体体现在以下几个方面。(1)评估标准不统一:不同癌种甚至同一癌种内分级标准与计数阈值多样[6,42,45,67],缺乏基于多癌种大数据的生物学统一定义体系,导致结果难以比较整合。(2)研究证据有限:该领域绝大多数证据来源于回顾性、单中心、小样本研究[60,61,74,77],存在选择偏倚,且缺乏前瞻性验证数据,限制了其被临床指南采纳[39]。(3)评估主观性强: TB的识别与计数高度依赖病理医师经验,观察者间差异显著,影响了结果的可重复性与实验室间可比性[63,66]。(4)机制研究与临床表型脱节:TB形成的关键驱动信号、时空动态演变规律及其与治疗反应(如化疗、免疫治疗)的具体关联机制尚未明确[7,96]。(5)技术创新与临床整合之间的核心挑战:AI等新技术虽具潜力,但其临床应用仍受限于标注数据质量、算法泛化能力、可解释性及与现有工作流程整合等多重障碍[89,90,92]。这些共性挑战共同阻碍了TB从一项有潜力的形态学指标,转化为可常规用于临床决策的可靠工具。上述局限性反映了当前TB研究在标准化、可靠性、可推广性和综合性方面面临的挑战,需要通过未来的研究加以解决。

针对上述挑战,未来努力应聚焦于以下方向。(1)建立跨癌种的标准化体系:在ITBCC框架基础上推动适用于不同实体瘤的评估指南,建立以绝对值为核心的数字化病理标准,并鼓励报告绝对计数值以保留完整信息[2]。(2)开展前瞻性多中心验证:通过精心设计的队列研究确证TB的预后与辅助治疗指导价值,如直接验证TB在特定癌种(如晚期胃癌)中作为辅助化疗决策标志物的临床效用,这是推动其进入临床指南的关键[96]。(3)挖掘TB在免疫治疗与分子分型中的价值:鉴于高级别TB与免疫抑制微环境(如PD-L1表达上调、特定免疫细胞浸润)密切相关,未来需重点探索TB作为免疫检查点抑制剂疗效预测标志物的潜力[34];同时,需要阐明其在各癌种特定分子亚型(如HER2过表达型乳腺癌、HPV非依赖性宫颈癌等)中的预后异质性,使其成为超越传统病理分期的精细化分层工具[65]。(4)构建肿瘤精准诊疗多模态决策AI系统:聚焦于开发可解释、强泛化的新一代AI算法,构建标准化、高质量的多中心数据生态,并通过前瞻性临床验证推动AI工具与诊疗工作流的深度整合。最终目标是实现影像、病理、分子与临床信息的跨模态融合,建立具有明确临床价值的智能辅助决策系统,推动肿瘤评估向术前预测、定量分析和个体化诊疗的根本转变[91,95]。通过融合标准化、前瞻性验证与智能化技术,TB有望在精准医疗中发挥更重要的临床决策支持作用。

5 总结与展望

TB作为一个动态体现肿瘤侵袭转移能力的形态学标志物,在结直肠癌、胃癌、输尿管癌等众多实体瘤中已被证实具有明确的独立预后价值。尽管ITBCC共识为结直肠癌提供了标准化框架,但TB的广泛应用仍面临多重挑战,包括跨癌种标准缺失、评估者间变异以及高级别循证医学证据不足等。

展望未来,TB研究的突破需依赖标准化、技术驱动与临床转化的深度融合。数字病理与AI技术有望通过自动化、定量化分析提升评估一致性,并揭示TB与EMT及TME的相互作用。重点是开发可整合多模态数据的可解释AI模型,实现基于TB表型的患者分型,从而指导个体化治疗。最终,通过建立跨癌种统一标准,开展前瞻性研究并深入解析其分子机制,TB这一重要的生物标志物必将在精准医疗时代,为肿瘤患者的风险分层、预后判断及个体化治疗决策提供更强大的支持。

参考文献

[1] Lugli A, Kirsch R, Ajioka Y, et al. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. Mod Pathol, 2017, 30: 1299–311.

[2] Lugli A, Zlobec I, Berger MD, et al. Tumour budding in solid cancers. Nat Rev Clin Oncol, 2021, 18: 101–15.

[3] 王佩, 接玉, 姚林, 等. 肿瘤出芽在结直肠癌异时性远处转移中的临床意义. 中华实验外科杂志, 2023, 40: 985.
Wang P, Jie Y, Yao L, et al. Clinical significance of tumor budding in heterochronous distant metastases in colorectal cancer. Chinese Journal of Experimental Surgery, 2023, 40: 985.

[4] Rau TT, Bettschen E, Büchi C, et al. Prognostic impact

of tumor budding in endometrial carcinoma within distinct molecular subgroups. Mod Pathol, 2021, 34: 222–32.

[5] Zheng S, Luo J, Xie S, et al. Tumor budding of cervical squamous cell carcinoma: epithelial-mesenchymal transition-like cancer stem cells? PeerJ, 2022, 10: e13745.

[6] Assis EM, Rodrigues M, Vieira JC, et al. Microvascular density and tumor budding in oral squamous cell carcinoma. Med Oral Patol Oral Cir Bucal, 2023, 28: e174–82.

[7] Huang T, Bao H, Meng YH, et al. Tumour budding is a novel marker in breast cancer: the clinical application and future prospects. Ann Med, 2022, 54: 1303–12.

[8] Li X, Zou C, Wang C, et al. Non-invasive tumor budding evaluation and correlation with treatment response in bladder cancer: a multi-center cohort study. Adv Sci (Weinh), 2025, 12: e2416161.

[9] Zhang H, Meng X, Gou D, et al. Tumour budding in gastric and colorectal cancers: a review. Medicine (Baltimore), 2025, 104: e42215.

[10] 郑羽佳, 陈东来, 王文佳, 等. 食管癌肿瘤出芽的研究进展. 中华胸部外科电子杂志, 2021, 8: 51–5.
Zheng YJ, Chen DL, Wang WJ, et al. Research progress of tumor budding in esophageal cancer. Chinese Journal of Thoracic Surgery (Electronic Edition), 2021, 8: 51–5.

[11] 黄宇, 于溯洋, 刘雅婷, 等. 结直肠肿瘤中肿瘤出芽现象的研究进展. 肿瘤学杂志, 2022, 28: 99–104.
Huang Y, Yu SY, Liu YT, et al. Research progress of tumor budding in colorectal cancer. Journal of Chinese Oncology, 2022, 28: 99–104.

[12] Max N, Harbaum L, Pollheimer MJ, et al. Tumour budding with and without admixed inflammation: two different sides of the same coin? Br J Cancer, 2016, 114: 368–71.

[13] Leão PLR, Marangon Junior H, Melo VVM, et al. Reproducibility, repeatability, and level of difficulty of two methods for tumor budding evaluation in oral squamous cell carcinoma. J Oral Pathol Med, 2017, 46: 949–55.

[14] James E, Ravikumar G, Michael Raj AJ, et al. Prognostic significance of ″high″ tumor budding and ″high″ poorly differentiated clusters in endometrial carcinomas: independent predictors of lymphovascular space invasion and lymph node metastasis. Int J Gynecol Pathol, 2025, 44: 222–9.

[15] 中华医学会肿瘤学分会, 国家卫生健康委员会医政司. 中国结直肠癌诊疗规范(2023版). 协和医学杂志, 2023, 14: 706–33.
Chinese Society of Clinical Oncology, Medical Administration Bureau of National Health Commission.Chineseprotocol of diagnosis and treatment of colorectal cancer (2023 edition). Medical Journal of Peking Union Medical College Hospital, 2023, 14: 706–33.

[16] Ling Z, Cheng B, Tao X. Epithelial-to-mesenchymal transition in oral squamous cell carcinoma: challenges and opportunities. Int J Cancer, 2021, 148: 1548–61.

[17] Yang J, Antin P, Berx G, et al. Guidelines and definitions for research on epithelial-mesenchymal transition. Nat Rev Mol Cell Biol, 2020, 21: 341–52.

[18] Okuyama K, Suzuki K, Yanamoto S. Relationship between tumor budding and partial epithelial-mesenchymal transition in head and neck cancer. Cancers (Basel), 2023, 15: 1111.

[19] Lin LH, Zamuco RD, Shukla PS. Ovarian clear cell carcinoma and markers of epithelial-mesenchymal transition (EMT): immunohistochemical character-ization of tumor budding. Int J Gynecol Pathol, 2023, 42: 602–12.

[20] Ang HL, Mohan CD, Shanmugam MK, et al. Mechanism of epithelial-mesenchymal transition in cancer and its regulation by natural compounds. Med Res Rev, 2023, 43: 1141–200.

[21] Zhang YE, Stuelten CH. Alternative splicing in EMT and TGF-β signaling during cancer progression. Semin Cancer Biol, 2024, 101: 1–11.

[22] Gires O, Pan M, Schinke H, et al. Expression and function of epithelial cell adhesion molecule EpCAM: where are we after 40 years? Cancer Metastasis Rev, 2020, 39: 969–87.

[23] Yu P, Xu T, Ma W, et al. PRMT6-mediated transcriptional activation of YTHDF2 promotes glioblastoma migration, invasion, and EMT via the Wnt-β-catenin pathway. J Exp Clin Cancer Res, 2024, 43: 116.

[24] Hsu YT, Osmulski P, Wang Y, et al. EpCAM-regulated transcription exerts influences on nanomechanical properties of endometrial cancer cells that promote epithelial-to-mesenchymal transition. Cancer Res, 2016, 76: 6171–82.

[25] Itou T, Ishibashi Y, Oguri Y, et al. EBP50 depletion and nuclear β-catenin accumulation engender aggressive behavior of colorectal carcinoma through induction of tumor budding. Cancers (Basel), 2023, 16: 183.

[26] Sun Y, He J, Shi DB, et al. Elevated ZBTB7A expression in the tumor invasive front correlates with more tumor budding formation in gastric adenocarcinoma. J Cancer Res Clin Oncol, 2021, 147: 105–15.

[27] Xu H, Zhao J, Li J, et al. Cancer associated fibroblast-

derived CCL5 promotes hepatocellular carcinomametastasis through activating HIF1α/ZEB1 axis. Cell Death Dis, 2022, 13: 478.

[28] Alpsoy A, Yavuz A, Simsek K, et al. Evaluation of tumor budding, desmoplastic reaction, and lymphocytic infiltration in predicting survival for pancreatic ductal adenocarcinoma. World J Gastrointest Oncol, 2025, 17: 107021.

[29] Sadozai H, Acharjee A, Gruber T, et al. Pancreatic cancers with high grade tumor budding exhibithallmarks of diminished anti-tumor immunity. Cancers (Basel), 2021, 13: 1090.

[30] Hori Y, Kubota A, Yokose T, et al. Prognostic role of tumor-infiltrating lymphocytes and tumor budding in early oral tongue carcinoma. Laryngoscope, 2021, 131: 2512–8.

[31] 李光影, 杨静. 上尿路上皮癌肿瘤出芽与肿瘤相关中性粒细胞及患者预后的相关性研究. 中国医学创新, 2022, 19: 157–62.
Li GY, Yang J. Study on the correlation between tumor budding and tumor-associated neutrophils and prognosis of patients with upper tract urothelial carcinoma. Medical Innovation of China, 2022, 19: 157–62.

[32] Le TM, Nguyen HDT, Lee E, et al. Transcriptomic immune profiles can represent the tumor immune microenvironment related to the tumor budding histology in uterine cervical cancer. Genes (Basel), 2022, 13: 1405.

[33] Wen Q, Han T, Wang Z, et al. Role and mechanism of programmed death-ligand 1 in hypoxia-induced liver cancer immune escape. Oncol Lett, 2020, 19: 2595–601.

[34] Secinti IE, Ozgur T, Dede I. PD-L1 expression in colorectal adenocarcinoma is associated with the tumor immune microenvironment and epithelial-mesenchymal transition. Am J Clin Pathol, 2022, 158: 506–15.

[35] Zhou QQ, Ren YM, Shi SM, et al. Microenvironmental code of pancreatic ductal adenocarcinoma: the prognostic symphony of budding, matrix and lymphocytes.World J Gastrointest Oncol, 2025, 17: 110523.

[36] Janyasupab P, Singhanat K, Warnnissorn M, et al. Identification of tumor budding-associated genes in breast cancer through transcriptomic profiling and network diffusion analysis. Biomolecules, 2024, 14: 896.

[37] Kang G, Pyo JS, Kim NY, et al. Clinicopathological significances and prognostic role of intratumoral budding in colorectal cancers. J Clin Med, 2022, 11: 5540.

[38] 吴勇金, 薛天慧, 颜兵. 肿瘤生长形式和肿瘤出芽对I-III期结直肠癌患者预后的判断价值. 解放军医学杂志, 2023, 48: 708–14.
Wu YJ, Xue TH, Yan B. Value of tumor growth pattern and tumor budding on judgment of patient's prognosis with stage I-III colorectal cancer. Medical Journal of Chinese People's Liberation Army, 2023, 48: 708–14.

[39] Hacking S, Sajjan S, Angert M, et al. Tumor budding in colorectal carcinoma showing a paradoxical mitotic index (via PHH3) with possible association to the tumor stromal microenvironment. Appl Immunohistochem Mol Morphol, 2020, 28: 627–34.

[40] Collaborative R. Impact of microsatellite status in early-onset colonic cancer. Br J Surg, 2022, 109: 632–6.

[41] Kucuk S. Prognostic value of tumour budding in stomach cancers. Int J Clin Pract, 2021, 75: e14922.

[42] Wang X, Yang X, Cai F, et al. The key role of tumor budding in predicting the status of lymph node involvement in early gastric cancer patients: a clinical multicenter validation in China. Ann Surg Oncol, 2024, 31: 4224–35.

[43] Ulase D, Heckl S, Behrens HM, et al. Prognostic significance of tumour budding assessed in gastric carcinoma according to the criteria of the International Tumour Budding Consensus Conference. Histopathology, 2020, 76: 433–46.

[44] Jesinghaus M, Herz AL, Kohlruss M, et al. Post-neoadjuvant assessment of tumour budding according to ITBCC subgroups delivers stage- and regression-grade independent prognostic information in intestinal-type gastric adenocarcinoma. J Pathol Clin Res, 2022, 8: 448–57.

[45] Lian J, Zhang W, Wang C, et al. Quantifying tumor budding: implications for prognosis in gastricadenocarcinoma. Am J Surg Pathol, 2025, 49: 363–71.

[46] Kemi N, Eskuri M, Ikäläinen J, et al. Tumor budding and prognosis in gastric adenocarcinoma. Am J Surg Pathol, 2019, 43: 229–34.

[47] Gunizi OC, Altunay B, Turgut SD, et al. The prognostic significance of desmoplastic reaction, tumor budding and tumor-infiltrating lymphocytes in esophageal squamouscell carcinomas. BMC Gastroenterol, 2025, 25: 476.

[48] Deng J, Zhang L, Wang Z, et al. Pathological features of the differentiation landscape in esophageal squamous cell cancer and their correlations with prognosis. Front Oncol, 2024, 14: 1442212.

[49] Jakab Á, Zarándy L, Kocsmár I, et al. Local invasion

patterns characterized by SARIFA and tumor budding differ and have distinct prognostic significance in esophageal adenocarcinoma and squamous cell carcinoma. Cancers (Basel), 2024, 16: 3144.

[50] Lohneis P, Hieggelke L, Gebauer F, et al. Tumor budding assessed according to the criteria of the International Tumor Budding Consensus Conference determines prognosis in resected esophageal adenocarcinoma. Virchows Arch, 2021, 478: 393–400.

[51] Li ZW, He L, Zheng Z, et al. Combined assessment of tumour cell nest size and desmoplastic reaction as an excellent prognostic predictor in oesophageal squamous cell carcinoma. Histopathology, 2022, 80: 1112–20.

[52] Li Z, Liu L, Wang B, et al. Tumor budding and tumor-infiltrating lymphocytes can predict prognosis in pT1b esophageal squamous cell carcinoma. Thorac Cancer, 2023, 14: 2608–17.

[53] Wankhede D, Hofman P, Grover S. Prognostic impact of tumour budding in squamous cell carcinoma of the lung: a systematic review and meta-analysis. Histopathology, 2023, 82: 521–30.

[54] Ciflik KB, Dogan HT, Dogan E, et al. Can tumour budding change the future of pulmonary adenocarcinoma? Pathol Res Pract, 2023, 250: 154808.

[55] Stögbauer F, Lautizi M, Kriegsmann M, et al. Tumour cell budding and spread through air spaces in squamous cell carcinoma of the lung - Determination and validation of optimal prognostic cut-offs. Lung Cancer, 2022, 169: 1–12.

[56] Volmonen KK, Rönty MJ, Sederholm A, et al. Evaluating tumour budding could improve the new grading system for lung adenocarcinoma. Lung Cancer, 2025, 199: 108067.

[57] Gürçay N, Acar LN, Ünal TDK, et al. High grade tumor budding is associated with poor survival in pathologic stage I lung adenocarcinoma. Ann Diagn Pathol, 2023, 66: 152188.

[58] Argon A, Oz O, Kebat TA. Evaluation and prognostic significance of tumor budding in pancreatic ductal adenocarcinomas. Indian J Pathol Microbiol, 2023, 66: 38–43.

[59] Ibuki E, Kadota K, Kimura N, et al. Prognostic significance of tumor budding in patients with pancreatic invasive ductal carcinoma who received neoadjuvant therapy. Heliyon, 2024, 10: e23928.

[60] Pęksa R, Kunc M, Czapiewski P, et al. Tumor budding is an independent prognostic factor in pancreatic adenocarcinoma and it positively correlates with PD-L1 expression on tumor cells. Biomedicines, 2022, 10: 761.

[61] Krištić A, Franin I, Vodopić T, et al. Association of tumor budding grade with immunohistochemical expression of thrombin and PAR-1 in pancreatic ductal adenocarcinoma. Anticancer Res, 2025, 45: 5191–202.

[62] Ozer SP. Tumor budding in invasive breast carcinoma: correlation with clinicopathological parameters, hormone receptor status, and survival: an observational study. Rev Assoc Med Bras (1992), 2023, 69: e20230191.

[63] Silva DJ, Miranda G, Amaro T, et al. Prognostic value of tumor budding for early breast cancer. Biomedicines, 2023, 11: 2906.

[64] González LO, Eiro N, Fraile M, et al. Joint tumor bud-MMP/TIMP count at the invasive front improves the prognostic evaluation of invasive breast carcinoma. Biomedicines, 2021, 9: 196.

[65] Xiang Z, He Q, Huang L, et al. Breast cancer classification based on tumor budding and stem cell-related signatures facilitate prognosis evaluation. Front Oncol, 2021, 11: 818869.

[66] Ranaee M, Torabi H, Azhganzad N, et al. The relationship between tumor budding and patient′s survival in breast cancer. Clin Pathol, 2024, 17: 2632010x241235543.

[67] De Assis EM, Rodrigues M, Vieira JC, et al. Lymphatic vascular density, the expression of podoplanin and tumor budding in oral squamous cell carcinoma. Head Neck Pathol, 2023, 17: 371–82.

[68] Mneimneh WS, Xu B, Ghossein C, et al. Clinicopathologic characteristics of young patients with oral squamous cell carcinoma. Head Neck Pathol, 2021, 15: 1099–108.

[69] Cacchi C, Fischer HJ, Wermker K, et al. New tumor budding evaluation in head and neck squamous cell carcinomas. Cancers (Basel), 2024, 16: 587.

[70] Boščić D, Dragaš E, Košec A, et al. Combined model of tumor-stroma ratio and tumor budding are not associated with tumor recurrence or metastasis in oral squamous cell carcinoma patients. Diagnostics (Basel), 2025, 15: 1844.

[71] Noda Y, Ishida M, Ueno Y, et al. Novel pathological predictive factors for extranodal extension in oral squamous cell carcinoma: a retrospective cohort study based on tumor budding, desmoplastic reaction, tumor-infiltrating lymphocytes, and depth of invasion. BMC Cancer, 2022, 22: 402.

[72] Chang HY, Hang JF, Kuo YJ. New histopathologic risk model for early t-stage oral squamous cell carcinoma:

focusing on a modified worst pattern of invasion system and a new tumor budding score. Am J Surg Pathol, 2024, 48: 59–69.

[73] Stögbauer F, Wirth M, Lauterbach M, et al. Tumor budding and lymphovascular invasion as prognostic factors in p16-positive oropharyngeal squamous cell carcinomas. Br J Cancer, 2025, 132: 212–21.

[74] Kawamura K, Miyai K, Asakuma J, et al. Tumor budding in upper urinary tract urothelial carcinoma: a putative prognostic factor for extraurothelial recurrence and overall survival. Virchows Arch, 2021, 479: 45–55.

[75] Eckstein M, Matek C, Wagner P, et al. Proposal for a novel histological scoring system as a potential grading approach for muscle-invasive urothelial bladder cancer correlating with disease aggressiveness and patient outcomes. Eur Urol Oncol, 2024, 7: 128–38.

[76] 杨静, 李光影, 王远. 肿瘤出芽与输尿管癌临床病理特征及预后分析. 锦州医科大学学报, 2021, 42: 40–3.
Yang J, Li GY, Wang Y. Clinicopathological features and prognostic analysis of tumor budding and ureteral carcinoma. Journal of Jinzhou Medical University, 2021, 42: 40–3.

[77] Cin M, Akyıldız İğdem A, Bektaş S, et al. Is immunohistochemical galectin-3 expression associated with the epithelial-mesenchymal transition in high- and low-grade invasive urothelial carcinomas of the bladder? Diagnostics (Basel), 2024, 14: 2270

[78] Lee OE, Le TM, Chong GO, et al. The Mclust analysis of tumor budding unveils the role of the collagen family in cervical cancer progression. Life (Basel), 2024, 14: 1004.

[79] Chong GO, Park JY N, Han HS, et al. Intratumoral budding: a novel prognostic biomarker for tumor recurrence and a potential predictor of nodal metastasis in uterine cervical cancer. Eur J Surg Oncol, 2021, 47: 3182–7.

[80] Zhang W, Song Y, Shi H, et al. Further confirmation of a highly prognostic grading scheme based upon tumour budding and cell cluster size in cervical squamous cell carcinoma. Histopathology, 2025, 86: 967–78.

[81] Shi H, Ye L, Lu W, et al. Grading of endocervical adenocarcinoma: a novel prognostic system based on tumor budding and cell cluster size. Mod Pathol, 2022, 35: 524–32.

[82] Ocal I, Guzelis I. Tumor budding is a valuable prognostic parameter in endometrial carcinomas. Indian J Pathol Microbiol, 2022, 65: 851–5.

[83] Mateva S, Nikolova M, Yordanov A. Patterns of myometrial invasion in endometrial adenocarcinoma with emphasizing on microcystic, elongated and fragmented (MELF) glands pattern: a narrative review of the literature. Diagnostics (Basel), 2021, 11: 1707.

[84] Qi X, Zhu L, Zhang B. Clinicopathologic association and prognostic impact of microcystic, elongated and fragmented pattern invasion, combined with tumor budding in endometrioid endometrial cancer. J Obstet Gynaecol Res, 2022, 48: 2431–41.

[85] Zhen Y, Zhang X. Clinicopathological features, molecular mechanisms and prognosis of microcystic, elongated and fragmented (MELF) pattern in endometrial carcinoma: a review. Gynecol Obstet Clin Med, 2024, 4: 216–20.

[86] Gelissen JH, Huang GS. Intersections of endocrine pathways and the epithelial mesenchymal transition in endometrial cancer. Front Oncol, 2022, 12: 914405.

[87] Chiu HC, Li CJ, Yiang GT, et al. Epithelial to mesenchymal transition and cell biology of molecular regulation in endometrial carcinogenesis. J Clin Med, 2019, 8: 439.

[88] Senguttuvan RN, Cohen JG. Combining the prognostic role of age with molecular advances in the understanding of endometrial cancer. Lancet Oncol, 2024, 25: 688–90.

[89] Fisher NC, Loughrey MB, Coleman HG, et al. Development of a semi-automated method for tumour budding assessment in colorectal cancer and comparison with manual methods. Histopathology, 2022, 80: 485–500.

[90] Pai RK, Hartman D, Schaeffer DF, et al. Development and initial validation of a deep learning algorithm to quantify histological features in colorectal carcinoma including tumour budding/poorly differentiated clusters. Histopathology, 2021, 79: 391–405.

[91] Zhou T, Man Q, Li X, et al. Artificial intelligence-based comprehensive analysis of immune-stemness-tumor budding profile to predict survival of patients with pancreatic adenocarcinoma. Cancer Biol Med, 2023, 20: 196–217.

[92] Hou X, Li X, Han Y, et al. Triple-negative breast cancer survival prediction using artificial intelligence through integrated analysis of tertiary lymphoid structures and tumor budding. Cancer, 2024, 130: 1499–512.

[93] Hou X, Guan Z, Zhang X, et al. Evaluation of tumor budding with virtual panCK stains generated by novel multi-model CNN framework. Comput Methods Programs Biomed, 2024, 257: 108352.

[94] Tang X, Zhuang Z, Jiang L, et al. A preoperative CT-based multiparameter deep learning and radiomic model with extracellular volume parameter images can predict the tumor budding grade in rectal cancer patients. Acad Radiol, 2025, 32: 4002–12.

[95] Liu Z, Jia J, Bai F, et al. Predicting rectal cancer tumor budding grading based on MRI and CT with multimodal deep transfer learning: a dual-center study. Heliyon, 2024, 10: e28769.

[96] Xue C, Du Y, Li Y, et al. Tumor budding as a predictor for prognosis and therapeutic response in gastric cancer: a mini review. Front Oncol, 2022, 12: 1003959.