PATHOHISTOLOGIC PROGNOSTIC AND PREDICTIVE PARAMETERS IN COLORECTAL CANCER – TUMOR BUDDING

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Summary

The failure of the AJCC/UICC staging system in predicting prognosis in intermediate-stage of colorectal cancers (CRCs) may be overcome by adding tumor budding (TB) in pathology report as the presence of high-grade TB has been consistently associated with negative clinicopathologic parameters in gastrointestinal tumors, especially in CRCs. Over the past few decades, numerous methods of assessing TB in CRC have been proposed, with variations in the area of assessment, cut-off values, and use of standard hematoxylin and eosin (H&E) stained slides vs. cytokeratin immunohistochemistry. This review summarizes previous studies in this scientific area and resulting guidelines. The concept of whether peritumoral budding (PTB) vs. intratumoral budding (ITB), or both, should be assesed is still under discussion. The original studies on TB utilized PTB, or assesment of budding at the invasive front of the CRC, and current guidelines pertain to that. Budding category and tumor grade are not the same and TB has an independent prognostic value and should be taken into account along with other clinicopathological factors in a multidisciplinary setting. TB should be routinely reported in stage II CRC, next to other high-risk factors, in order to aid the decision for adjuvant therapy.

Keywords: colorectal cancer; tumor budding; pathology report; peritumoral budding; intratumoral budding.

INTRODUCTION

Adenocarcinoma of the colon represents 98% of colonic cancers and is the most common primary colon carcinoma (1). Globally, and for high sociodemographic index (SDI) countries, colon and rectal cancer ranked third for cancer incidence and second for cancer death in 2015. Colon and rectum cancer incidence ranked lowest in low SDI countries as the eighth most common cancer and was the sixth leading cause for cancer mortality. Between 2005 and 2015, incidence increased by 37% and is of special concern (2). Stage is the most important prognostic factor (1). With the rise of personalized medicine, accurate pathology reporting of colorectal cancer (CRC) resection specimen is crucial because it gives essential information that helps plan the treatment of individual patients and contains some key prognostic parameters (3,4).

Tumor staging according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) system is currently regarded as the standard for staging of CRC. The TNM classification provides the strongest prognostic information for patients with early stage disease and those with advanced disease. It is less efficient in predicting disease outcome for patients with intermediate levels of disease (5,6).

The failure of the AJCC/UICC staging system in predicting prognosis in intermediate-stage tumors may be overcome by adding additional factors, either morphological, molecular or treatment-related, which could stratify patients more precisely into different risk categories (7-9). Among morphological tumor-related factors, tumor budding has been shown to be a strong prognostic factor in CRC (10). The first description of what we now call tumor budding (TB) was by Imai in the article from 1954, as "sprouting" at the invasive edge of carcinomas (11,12).

TUMOR BUDDING - NEW STANDARD ELEMENT IN COLORECTAL CANCER PATHOLOGY REPORT?

Tumor buds are thought to result from the process known as epithelial-mesenchymal transition (EMT), (13). The EMT process, by allowing a polarized cell to assume a more mesenchymal phenotype with increased migratory capacity, invasiveness, and resistance to apoptosis, seems to play a major role in the development of tumor buds. In fact, TB reflects a process of dedifferentiation, and represents the histologic hallmark of EMT (14).

EMT is a process of cellular plasticity first discovered in embryonic development and reflects a reversible embryonic program and was later recognized to play an important role in cancer propagation (15-18). EMT is recognized as a driving force of cancer cell metastasis and drug resistance, two leading causes of cancer recurrence and cancer-related death (19). Induction of EMT has been shown to contribute significantly to chemoresistance in CRC (20). Cells undergoing EMT loose the apical-basal polarity of epithelial cells, downregulate cell adhesion molecule expression and induce the expression of vimentin filaments, fibronectin and N-cadherin. In EMT there is loss of E-cadherin, a homophilic calcium dependent cell adhesion molecule located in the adherents junctions of epithelia. Loss of E-cadherin expression is correlated with increased invasiveness of cancer cells. Reduced E-cadherin expression occurs when the zinc finger containing proteins Slug, Snail and SIP1 or the basic helix-loop-helix gene called Twist downregulate the E-cadherin promoter by binding to a series of inhibitory E-box sites (21).

Tumor buds in colorectal carcinoma show downregulation of adhesion protein E-cadherin, accompanying nuclear translocation of beta-catenin, and loss of cell polarity with acquisition of fibroblastoid morphology as demonstrated by Brabletz et al. in 2001 (22).

Tumor budding is defined as single cells or clusters of up to four cells at the invasive margin of CRC and can be stratified into peritumoral budding (PTB, tumor buds at the tumor front) and intratumoral budding (ITB, tumor buds in the tumor center) (23,24). The presence of high-grade TB has been consistently associated with negative clinicopathologic parameters in gastrointestinal tumors, especially in CRCs (10,23,25-27).

A study by Hase et al. in 1993 first adopted the phrase "tumor budding", and showed a dramatic decrease in survival with increased budding in colorectal carcinoma (5-year survival of 22 vs. 71%, p<0.001). This first definition of budding was subjective, with budding defined as small clusters of cells at the invasive front, and budding classified into none or mild (BD-1) and moderate or severe (BD-2), (28).

Over the past few decades, numerous methods of assessing TB in CRC have been proposed, with variations in the area of assessment, cut-off values, and use of standard hematoxylin and eosin (H&E) stained slides vs. cytokeratin immunohistochemistry (12). Puppa et al. demonstrated that in a multicentre, multinational study in 2012 where they assessed the diagnostic reproducibility of five methods (10,14,23,26-29). We updated and modified the table represented

in the respective article (14) and included some other results reported by other authors (10,14,23,26-31), (*Table 1*). They also concluded that cytokeratin immuno-histochemistry (IHC) with CK AE1/AE3 antibody detected a higher percentage of TB-positive cases with all methods compared to H&E-stained slides, but did not influence agreement levels.

The Ueno method was elaborated again in 2008 (32), introducing the grading system for colorectal carcinoma based upon quantification of „areas of poorly differentiated components", and again further in 2012 (31), introducing the grading system based upon quantification of „poorly differentiated clusters", which are morphologically closely related to TB (the nests are slightly larger) and also the micropapillary variant of colorectal carcinoma. Future studies are needed to prove the originality of poorly differentiated clusters as a histological feature as well as a prognostic variable (5).

The concept of whether PTB vs. ITB, or both, should be assesed is still under discussion (12). The original studies on TB in pT1 colorectal carcinoma utilized PTB, or assesment of budding at the invasive front of the carcinoma (23,28). The idea of ITB was introduced in 2011 in the context of preoperative biopsies of colorectal carcinoma (33), however, it was first reported in 1989 in a series of rectal cancer biopsies and found to be associated with lymph node metastases (34).

In 2017 Lugli et al. reached an agreement that gave way to the latest recommendations for tumor reporting in CRC based on the International tumor budding consensus conference (ITBCC) that was held in 2016 (35). Basically, it is the Ueno method, with some modifications. They emphasized the value of both ITB and PTB – both are morphologic manifestations of EMT. But while PTB can only be assessed in surgical resection specimens, ITB can be assessed in both CRC biopsies and resection specimens. In recent studies, ITB present in preoperative biopsies has shown a correlation with high-grade PTB, lymph node metastases and tumor regression grade in the corresponding colorectal cancer resection specimens (33,36,37). However, the ITBCC group agrees that the quality of evidence relating ITB in colorectal cancer to lymph node metastasis remains low. Although ITB may prove to be a promising biomarker in the preoperative management of CRC-patients, there is insufficient evidence to support its routine reporting at this time. The ITBCC group therefore recommends further research in this area before reporting of ITB is implemented in routine practice.

Table 1. Updated and modified table from the interobserver study article by Puppa et al. (14)

First author, year of publication	Definition of tumor budding	Assessed tumor field	Specimen area surface size	Grading and interpretation of tumor budding	Stage(s) of CRC assessed
Hase 1993 (28)	Small clusters of undifferentiated cancer cells (implying at the invasive tumor front/frontal region margins)	Overall tumor	Same as assessed tumor field	1. None or mild (BD-1) 2. Moderate or severe (BD-2)	Early and advanced (method conceived for stages A-D of the Duke classification)
Nakamura 2005 (26)		Entire advancing edge - entire invasive margin involved by tumor budding selected	Same as assessed tumor field	1. Low grade (none or mild: 1/3*)2. 2. High-grade (moderate: 1/3-2/3* or marked: >2/3*) *Proportion of the entire invasive margin involved by tumor budding	Advanced (2005)
Nakamura 2008 (30)					Stage II (2008)
Ueno 2002/2004 (23,27)	Isolated single cancer cell or a cluster composed of <5 cancer cells (implying at the invasive tumor front/frontal region/margins)	Area with maximum tumor budding (magnification 250x)	0.385 mm²	1. Low grade: <10 buds 2. High grade: ≥10 buds	Advanced
Ueno 2004 (29)			0.785 mm²	1. Negative: <5 buds 2. Positive: ≥5 buds	Early invasive (I)
Ueno 2012 (31)		Area with maximum tumor budding (magnification 200x)	Microscopic field of a 20x objective lens (field with a major axis of 1 mm)	1. G1: <5 buds 2. G2: 5-9 buds 3. G3: ≥10 buds	Stage II or III
Wang 2009 (10)		Entire tumor (all tumor slides) scanned at low magnification - area with maximum tumor budding selected (magnification 200x) For cases with no identifiable budding, bud counts were generated in 5 random areas at 200x per case)	0.94985 mm²	1. High budding; positive area if ≥1 bud present 2. Low budding; negative area if no buds present For cases with no identifiable budding: 1. High budding; if at least 50% of areas were positive) 2. Low budding; <50% of areas were positive)	T3N0M0 (IIA)

The method of TB reporting in CRC by ITBCC group is as follows (35):

1. The field (specimen) area for the 20x objective lens of your microscope based on the eyepiece field number (FN) diameter should be defined with the conversion table (35).
2. H&E-stained slide with greatest degree of budding at the invasive front should be selected
3. Scan 10 individual fields at medium power (10x objective) to identify the "hotspot" at the invasive front (for pT1 endoscopic resections all fields should be scanned - usually <10 fields available)
4. Count tumor buds in the selected "hotspot" (20x objective)
5. Divide the bud count by the normalization factor for your microscope to determine the tumor bud count per $0.785mm^2$
6. The budding (Bd) category based on bud count and indicate the absolute count per $0.785mm^2$ should be selected: Bd1 (low) – 1-4 buds, Bd2 (intermediate) – 5-9 buds, Bd3 (high) – ≥10 buds.

Although the final tumor bud count is performed on H&E, the ITBCC group claims that IHC can be helpful in challenging cases (ie, glandular fragmentation, strong peritumoral inflammation, reactive stromal cells) to confirm that the cells being counted are indeed tumor buds, although IHC may also stain apoptotic bodies and cellular debris, which should not be counted as buds. H&E recommendations might change as more data on IHC assessment become available (*Figure 1*).

The ITBCC group agrees that TB category and tumor grade are not the same, that TB has an independent prognostic value and should be taken into account along with other clinicopathological factors in a multidisciplinary setting (TNM classification, prognostic factors such as tumor grade, histological subtype, vascular invasion, perineural invasion, margin status, molecular biomarkers such as microsatellite, KRAS mutation and BRAF mutation status). The ITBCC group considers the prognostic value of TB category to be at least equivalent to that of vascular invasion, tumor grade and perineural invasion status, and therefore recommends that TB should be taken into account along with these and other clinicopathologic factors in the risk assessment of CRC and be included in guidelines/protocols for CRC reporting.
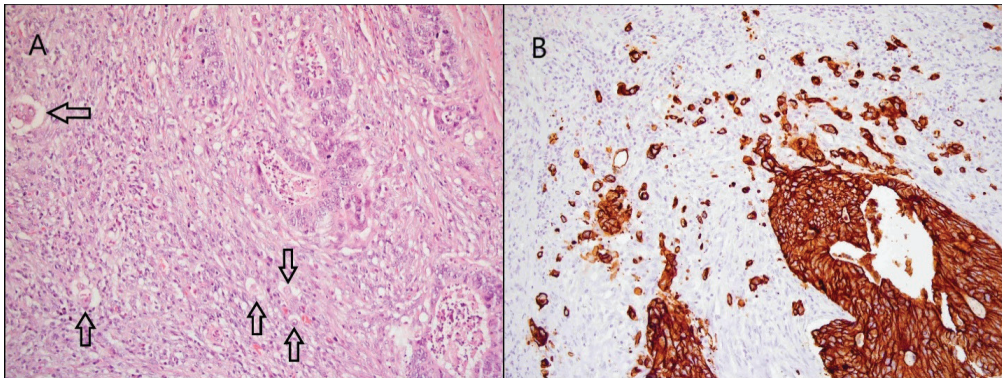
Figure 1. Tumor budding at the invasive front of the adenocarcinoma of the colon. (A) H&E stain, magnification 200x, vertical arrows show tumor buds which are hardly seen in strong peritumoral inflammation of the adenocarcinoma of the colon, horizontal arrow shows cluster of at least 5 cells which exceeds the size of tumor bud; (B) Immunohistochemical analysis (CK AE1/AE3 stain) in the same tumor, magnification 200x.

TUMOR BUDDING AS A COLORECTAL CANCER PROGNOSTIC FACTOR

TB is also of interest in distinct subgroups of CRC as a prognostic factor (5,12,35). It is associated with a higher TNM stage, high tumor grade, the presence of lymphovascular invasion and consequently with lymph node and distant metastases (38-42). Berg and Schaeffer presented a summary of key studies on TB in pT1 and stage II colorectal carcinoma in a review article that recently appeared on Modern Pathology web site (12).

In early lesions (pT1), it appears to be one of the strongest parameters associated with the presence of regional lymph node spread (5,43,44). In fact, high-grade TB has been well established as one of the pathologic prognostic criteria that carry increased risk for lymph node metastases, and therefore, need for surgery post polypectomy (12,23,28,29,45,46). TB carried a relative risk of 5.1 for lymph node metastasis, in addition to lymphatic invasion, submucosal invasion depth of >1 mm and poor histological differentiation (12,44). By the ITBCC group, in pT1 CRC, Bd2 and Bd3 are associated with an increased risk of lymph node metastasis (35). The Japanese Society for Cancer of the Colon and Rectum (JSCCR) has incorporated TB into „JSCCR Guidelines 2016" (47), for which pT1 carcinoma patients require subsequent surgery (along with vascular invasion,

high grade and submucosal depth of invasion >1000 μm), using their consensus method for assessment of budding, and applying a cut-off of 5 or more buds (intermediate and high-grade categories – G2/3) as an independent predictor of lymph node metastasis. „Japanese method" for TB assessment is the same as the ITBCC group's, with Ueno and Ajioka being the same authors in both articles (35,47).

In patients with AJCC/UICC stage II disease (which encompasses a group of patients with T3-T4 tumors and no lymph node metastases), the extent of TB could be used to select patients with node-negative cancers for adjuvant therapy (5,28,12,38,48,49). Although some of these patients are cured with surgery, a subset of these patients have a substantial risk of recurrence (50). TB has been well established as a poor prognostic factor in stage II colorectal carcinoma (12,48,51). A systematic review by Petrelli et al. in 2015 (52) showed high-grade budding to be a significant poor prognostic factor with an odds ratio of 6.25 for mortality. The ITBCC group agrees that TB grade is an independent predictor of survival in stage II CRC and that Bd3 is associated with an increased risk of recurrence and mortality (35). Patients with stage III CRC are generally offered adjuvant chemotherapy, whereas those with stage II are not, unless other high-risk features are present (ie, tumor perforation, lymphovascular invasion, serosal involvement – pT4a, poor tumor differentiation in microsatellite stable tumors, close/indeterminate/positive margins, perineural invasion and low lymph node yield). However, some stage II CRC patients show worse survival than stage III patients who receive adjuvant chemotherapy (53-55). Numerous studies have shown TB to be an independent predictor of recurrence and survival in stage II CRC with outcomes similar to stage III colorectar cancer (35).

High-grade TB has also been reported to predict non-responders to anti-EGFR therapies, along with K-Ras mutation status. Of interest in that study, low-grade TB was 100% predictive of response to EGFR therapy, with all low-grade budding having at least partial response, and no progressive or even stable disease (12,56).

CONCLUSION

We conclude that tumor budding should be routinely reported in stage II CRC, next to other high-risk factors, in order to aid the decision for adjuvant therapy, along with ITBCC group recommendation that in addition to the Bd

category the absolute bud count should also be provided, as this avoids loss of information that may occur when applying a cut-off to borderline cases.

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Sažetak

Tumorsko pupanje u karcinomu debelog crijeva i rektuma

Neuspjeh AJCC/UICC staging sustava u predviđanju prognoze u srednjem stadiju karcinoma debelog crijeva i rektuma (KDCR) može se prevladati dodavanjem tumorskog pupanja (TP) u nalaz patologa jer je prisutnost visokog gradusa TP dosljedno povezivana s negativnim klinikopatološkim parametrima u gastrointestinalnih tumora, posebno u KDCR. Tijekom proteklih nekoliko desetljeća predložene su brojne metode procjene TP u KDCR, s varijacijama područja procjene, graničnim vrijednostima i korištenjem standardnih hematoksilin-eozinom obojenih preparata nasuprot imunohistokemiji citokeratinom. Ovaj pregledni članak sažima dosadašnja istraživanja u ovom znanstvenom području i proizašle smjernice. Još uvijek se razmatra koncept treba li se procjenjivati peritumorsko pupanje (PTP) ili intratumorsko pupanje (ITP), ili oboje. Izvorne studije o TP-u koristile su PTP ili procjenu pupanja na invazivnom rubu KDCR, a trenutne se smjernice odnose na to. Kategorija pupanja i stupanj tumora nisu isti, a TP ima nezavisnu prognostičku vrijednost te ga treba uzeti u obzir zajedno s drugim kliničkopatološkim čimbenicima u multidisciplinarnom okruženju. TP bi trebalo rutinski izvijestiti u stadiju II KDCR, pored drugih visokorizičnih čimbenika, kako bi se pomogla odluka o adjuvantnoj terapiji.

Ključne riječi: karcinom debelog crijeva i rektuma; tumorsko pupanje; izvještaj patologa; peritumorsko pupanje; intratumorsko pupanje.

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