Potential clinical scenarios of tumour budding in colorectal cancer

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Abstract

Tumour budding, defined as single tumour cells or clusters of 4 tumour cells or less detached from the main tumour body, is a well-established indicator of aggressive tumour biology in colorectal cancer. As a marker of tumour dissemination, evidence points towards tumour budding as a morphological correlate of epithelial-mesenchymal type changes in the tumour microenvironment. Despite many studies in the literature going back decades, tumour budding has not been systematically integrated in colorectal cancer reporting protocols. The recently published proceedings of the International Tumour Budding Consensus Conference (ITBCC) have sparked the systematic implementation of tumour budding in routine reporting of colorectal cancer. Tumour budding may be particularly relevant to patient management in endoscopically resected pT1 colorectal cancer, stage II tumour and pre-operative biopsies. The present review focuses mainly on these three potential clinical scenarios with the aim to provide a concise and updated overview on tumour budding in CRC. (Acta gastroenterol. belg., **2019**, 82, **515-518**).

Key words : Colorectal cancer, biomarker, tumour budding, clinical scenarios.

Key Points

– Tumour budding is a robust independent prognostic indicator in colorectal cancer.

– From a biological point of view, evidence points towards tumour budding as a morphological correlate of epithelial-mesenchymal transition-type changes in the tumour microenvironment

– In 2016, the ITBCC established evidence-based guidelines on scoring and reporting tumour budding in colorectal cancer.

– According to the ITBCC recommendations, tumour budding can be used together with other clinico-pathological risk factors to guide patient management in endoscopically resected pT1 and stage II colorectal cancer

– The role of tumour budding in pre-operative biopsies as a marker of tumour progression and as a potential predictor of response to neoadjuvant therapy is promising but needs to be further clarified

Background

Tumour budding, defined as a single cell or cluster up to four cells at the invasive front of colorectal cancer (CRC) (1), is proposed as an additional prognostic factor in the 8th edition of the TNM classification published by the UICC (2). The association of tumour budding with tumour progression and hence with presence of local and distant metastases is supported by the biological features and pathogenetic aspects of tumour buds. Indeed, tumour buds are part of the tumour microenvironment (TME) and involved in epithelial-mesenchymal transition (EMT)-type changes although such changes may be partial and result in double-positive phenotype in only a subset of buds (3-6). Tumour buds are typically characterized by upregulation and expression of biomarkers of migration, invasion and survival (3). In contrast, WNT signalling pathway proteins are mostly deregulated resulting in E-Cadherin under-expression (7).

The implementation of tumour budding in daily practice was mainly due to a lack of an international standardized scoring system. The aim of the International

Table 1. — **Statements of the International Tumour Budding Consensus Conference (adapted from (8))**

Statement	
	1. Tumour budding is defined as a single tumour cell or a cell cluster of up to 4 tumour cells.
	2. Tumour budding is an independent predictor of lymph node metastasis in pT1 colorectal cancer.
	3. Tumour budding is an independent predictor of survival in stage II colorectal cancer.
	4. Tumour budding should be taken into account along with other clinicopathological factors in a multidisciplinary setting.
	5. Tumour budding is counted on H&E.
	6. Intratumoural budding in colorectal cancer has been shown to be related to lymph node metastasis.
	7. Tumour budding is assessed in one hotspot (in a field measuring 0.785 mm²) at the invasive front.
	8. For tumour budding assessment in colorectal cancer, the hotspot method is recommended.
	9. A three-tier system should be used along with the budding count in order to facilitate risk stratification in colorectal cancer.
	10. Tumour budding should be included in guidelines and protocols for colorectal cancer reporting.
	11. Tumour budding and tumour grade are not the same.

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Tumour Budding Consensus Conference (ITBCC) held in Bern in 2016 was to propose a solid, simple and cost-effective scoring system for tumour budding in CRC. Based on the available data in the literature, 23 experts in GI Pathology from all over the world agreed on the statements as listed in Table 1 (8).

In summary, tumour budding includes 3 budding grades, namely BD 1 (0-4 buds/hotspot, area 0.785mm^2), BD 2 (5-9 buds/hotspot, area 0.785mm^2) and BD 3 (≥10 buds/hotspot, area 0.785mm^2). Since published in Modern Pathology in 2017 the ITBCC guidelines have been incorporated in guidelines and protocols, most notably the updated CRC reporting checklist of the College of American Pathologists (CAP) (9-12) and used in several studies (4,13-15). Tumour budding can be used to guide clinical management in colorectal cancer patients in the three potential clinical scenarios presented below.

Clinical scenario 1 : role of tumour budding in pT1 CRC

Patient management of endoscopically resected pT1 colorectal cancer ('malignant polyps') can include segmental resection, which includes the assessment of lymph nodes to which the tumour may have spread or follow-up alone. The decision to perform a segmental resection rests mainly on the assessment of histopathological features associated with nodal metastases. If no risk factors are present, the probability of lymph node metastases is very low (<1%), rendering further treatment unnecessary, whereas if multiple risk factors are present, the probability of nodal metastases rises to 35-40% (1). Therefore, accurate assessment of these factors is essential for the correct identification of at-risk patients while avoiding over-treatment.

Traditionally, histological risk factors for nodal metastases include such as high tumour grade, the presence of lympho-vascular invasion and depth/level of invasion. However, tumour budding has been demonstrated to be at least as strong a predictor for lymph node metastases and is the best-studied clinical scenario for clinical implementation. Indeed, the odds ratio (OR) of tumour budding for lymph node metastases reported in meta-analyses ranges from 4.59-7.7(16-19). Although studies included in these meta-analyses vary considerably in terms of histologic assessment methods to detect tumour budding, inclusion/exclusion criteria and cohort size, they do provide strong support for a significant relationship between tumour budding and lymph node metastases in pT1 CRC. Therefore, it is highly recommended to report tumour budding along with the above-mentioned risk features in these tumours (8).

Clinical scenario 2 : Role of tumour budding in stage II CRC

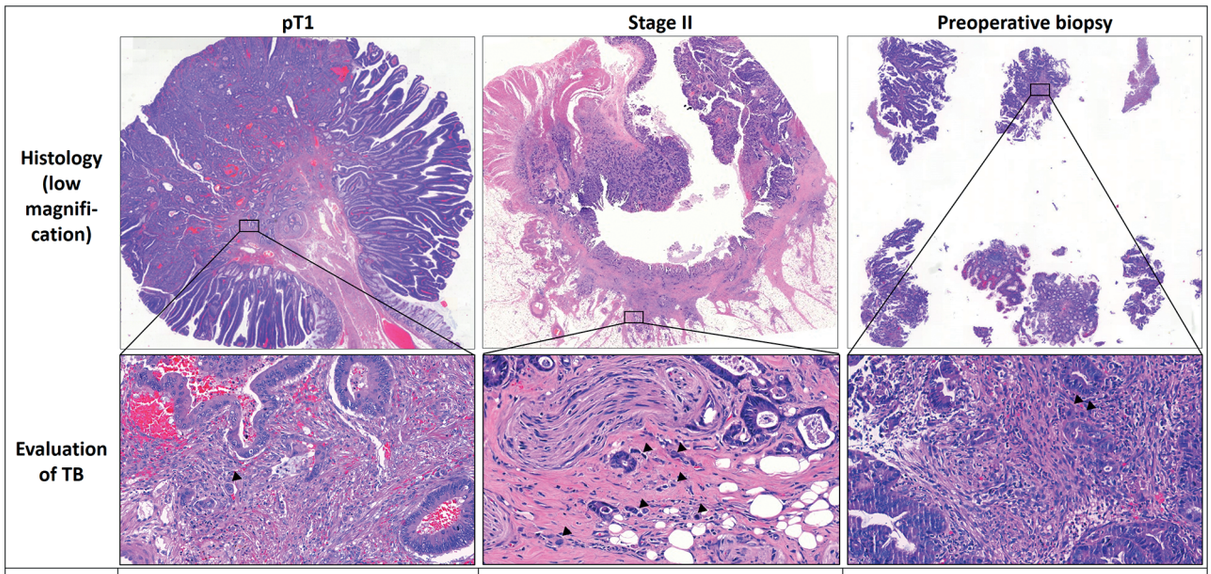
In stage II colorectal cancer, patients have considerably variable outcomes, partly due to differences in substage. However, the TNM classification system alone does not adequately reflect the biology of a certain tumour. In stage II CRC, the indication of adjuvant chemotherapy is unclear, and while such therapies may result in marginally increased survival in these patients, risks may outweigh the benefits if a generalized approach is taken (20). Hence, reliable biomarkers are highly sought after to identify patients with particularly aggressive CRC that may truly benefit from adjuvant therapy. According to the current NCCN guidelines, patients considered at high risk for recurrence may be offered adjuvant therapy if one or more of the following features are present : poorly differentiated histology (exclusive of MSI-high tumours, lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, localized perforation or close/indeterminate or positive margins (21).

Although the NCCN risk factors are certainly associated with decreased disease-free survival, tumour budding may also be considered an excellent indicator of adverse tumour biology in stage II CRC. High-grade tumour budding (BD 3 ; ≥10 buds/hotspot, area 0.785mm^2) identifies a subset of stage II patients with prognosis similar to stage III CRC (22, 23). A meta-analysis including 12 studies and 1652 patients demonstrated a 25% decrease in 5 year-overall survival in patients with high-grade tumour budding (24). Therefore, tumour budding should also be reported in stage II CRC and included in risk stratification of these tumours (8).

While all features of 'high-risk' stage II CRC including tumour budding are associated with more aggressive tumour behaviour, there is no clear data in the literature linking any of them to increased effectiveness of chemotherapy. However, the standardized consensus guidelines of the ITBCC provide the basis to include systematic and prospective inclusion of tumour budding in clinical trials.

Clinical scenario 3 : Potential role of intra-tumoural budding in CRC

In 1989, Morodomi et al described the presence of tumour buds in rectal cancer biopsies and their association with presence of lymph node metastases (25). This approach led to several studies analysing the phenomenon of tumour budding within the main tumour body. The term "intratumoural budding (ITB)" was first introduced in 2011 to better distinguish ITB from the classic tumour budding at the invasive front of CRC, namely peritumoural budding (PTB) (26). Based on several studies, ITB seems to be highly associated with PTB and hence also a strong predictor of tumour progression, local and distant metastases and worse prognosis (26). Since ITB can be detected on biopsy material, budding can also have a major impact on preoperative management of CRC patients. At the moment there are seven studies which published data on the impact of ITB in preoperative biopsies, five are based on rectal cancer and two on CRC cohorts (27). In



	Peritumoural Budding		Peritumoural Budding		Intratumoural Budding	
No. of TB	0-4	≥5	0-9	≥10	No cut-off defined	
Potential clinical implication	No further therapy if no additional risk factors	Resection should be considered along with other histopathological features	No adjuvant therapy if no additional risk factors	Adjuvant therapy should be considered along with other risk factors	No neo-adjuvant therapy (further studies needed before implementation in rountine diagnostics)	Neo-adjuvant therapy should be considered

Figure 1. — Assessment and potential clinical implications of tumour budding in CRC. Arrowheads point to selected tumor buds. TB : tumor buds.

rectal cancer, tumour budding in preoperative biopsies was associated with more advanced tumour and nodal stage, distal intratumoural spread, local recurrence, response to neoadjuvant chemoradiotherapy, disease-free survival (DFS) and a predictor of cancer-related deaths (25,28,29). In CRC, ITB was correlated with TNM stage, vascular invasion and tumour grade (30,31). In a recent study, microsatellite instability status associated with low budding was a predictor of complete pathological response after neo-adjuvant therapy in rectal cancer patients (32).

Although budding is promising in the preoperative management of CRC patients, the ITBCC recommended further research before its implementation in routine practice (8). Indeed, the tumour budding scoring system on pre-operative biopsies is not yet defined and questions such as number of biopsies needed, hotspot vs field number, area number and H&E staining vs immunohistochemistry are still open. The ITBCC scoring system may still be applicable in preoperative biopsies as the hotspot approach in the pre-defined area (0.785mm^2) allows a tumour bud count even in a few biopsies. Nevertheless, more data are definitely necessary for a solid and reproducible tumour budding scoring system in biopsies.

Conclusion and prospects for future research

The ITBCC proceedings based on a consensus conference are a solid basis for future multi-centric clinical retrospective and prospective trials. Indeed, more data are needed to validate the ITBCC scoring system, especially for the clinical scenarios including the pT1 and stage II CRC patients. The validation of the ITBCC scoring system is an important further step and bridge to a digital tumour budding scoring system. Despite the discussion about a standardized budding scoring system, one should keep in mind that the biologic rationale of tumour budding is actually simple – the more tumour buds detected in CRC resections and biopsies, the more aggressive the tumour. Also, it must considered that clinical endpoints differ for each of the scenarios discussed (Fig. 1). For instance, in pT1 CRC, nodal status is the endpoint of interest. Therefore, the number of buds to define tumour budding as a risk factor (≥ 5 buds/0.785mm^2 ; BD 2 and BD3) is different from budding as a risk factor in stage II CRC (≥ 10 buds/0.785mm^2 ; BD3), where disease-free and overall survival are relevant endpoints.

Despite the wealth of studies and data in the literature on tumour budding, tumour buds only constitute part of the tumour microenvironment. Other cell types, such as immune cells may counteract tumour buds and therefore the proposal of a Budding-T-cell scoring system (BTS) may be an approach which better reflects the biologic dynamic of tumour and host related factors. Also, the relationship between tumour budding in the primary tumour, metastatic sites and important parameters in colorectal liver metastases (CRLM), such as histological growth pattern and tumour regression grade, should

be further characterized (33). A crucial next step is the investigation on potentially predictive and prognostic molecular biomarkers of tumour budding which could be the basis for a future anti-budding therapy.

Conflict of interest

None of the authors have any potential conflict of interest including any financial activities, additional affiliations, personal or other relationships with other people or organizations that could influence, or be perceived to influence, their work, such as employment, consultancies, stock ownership, honoraria, patent applications/registrations, grants or other funding.

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