



Commentary

The battle for prognosis at the invasive front of colorectal cancer

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Outcome of patients with colorectal cancer (CRC) is highly dependent on the essential and additional prognostic factors from the TNM staging system proposed by the UICC and AJCC. Additionally, novel and promising prognostic biomarkers are listed in the WHO classification 2019. At the invasive front of CRC, there are two such factors within the tumour microenvironment (TME) which battle for prognosis: tumour budding [1] and the immune cell infiltration [2].

Tumour budding defined as single cells or clusters up to four tumour cells is found at the invasion front of CRC [1]. It is associated with local and distant metastases and is therefore a histomorphological biomarker of tumour progression and worse prognosis [1]. According to the International Tumour Budding Consensus Conference (ITBCC) 2016, tumour budding is graded based on bud number into BD1 (0–4 buds/hotspot 0.785mm²), BD2 (5–9 buds/hotspot 0.785mm²) and BD3 (≥ 10 buds/hotspot 0.785 mm²), and may potentially support patient management in three clinical scenarios: first, in pT1 CRC, high grade tumour budding is associated with presence of local lymph node metastases and is therefore an indicator for a radical oncologic resection [3]; second, in stage II CRC, high grade tumour budding is an independent prognostic factor and may select stage II CRC patients for adjuvant treatment [4]; third, intratumoural budding (ITB) defined as tumour buds within the main tumour body can be assessed in preoperative biopsies and be a potential indicator for neo-adjuvant therapy [5].

In allegory to history, tumour buds can be seen as the heavy cavalry of CRC, but they need the ideal battleground. In the case of the invasive cancer front, this ideal battleground corresponds to a tumour microenvironment with a pronounced desmoplastic stroma reaction. Not surprisingly, tumour budding is highly associated with the mesenchymal Consensus Molecular Subtype (CMS) 4 [6]. The dynamic of tumour buds is dependent on the interaction with other cell types of the TME such as stromal and inflammatory cells [7]. Tumour buds undergo complete or partial epithelial-mesenchymal transition (EMT) and their immunohistochemical profile clearly

differs from the neoplastic cell population of the main tumour body [7]. Often found in tumour buds are overexpression of EpCam, nuclear β -catenin, CXCL12, TrkB, Pontin, CK7, NF κ B, Laminin5, CathepsinB, L1 and MMP9, whereas membranous E-Cadherin, Ki-67, RKIP, Cdx2, MUC2 and Caspase3 are under-expressed or lost [7]. This profile reflects the involvement of tumour budding in lymphovascular invasion and further development of local and distant metastases.

Now the question arises: what opposes the heavy cavalry at the invasive front of CRC? Already in 1986, Jass proposed lymphocytic infiltration as a prognostic factor in rectal cancer [8]. In the last two decades, the role of the immune infiltration was systematically investigated and implemented as the Immunoscore [2]. The Immunoscore was recently validated by an international consortium supported by the Society for Immunotherapy of Cancer (SITC) for its clinical use as a strong prognostic factor in stage I-III colon cancer patients. The consensus immunescore includes the intratumoral and peritumoral density of CD3+ and CD8+ T-cell effectors using a digital image analysis approach, which is intended to help increase the reproducibility of the immunescore and its promising and selective role for immunotherapy [2].

Nevertheless, patient outcome in CRC is strongly influenced by the result at the end of the battle between tumour-related and host-related factors. A combined scoring system including tumour budding and immune cells is therefore a very promising approach to better assess prognosis, especially if its evaluation and validation is based on automated digital methods. Indeed, several studies have shown a combined tumour buds-lymphocyte index to be a more accurate prognostic factor than tumour budding or immune cells alone [9].

In this research article of EBioMedicine, Fujiyoshi et al. provided new evidence supporting this “attacker-defender” model based on tumour budding and adaptive anti-tumour immunity using multiplex immunofluorescence, machine learning algorithms and image analysis [10]. The study’s strength is based on large and molecularly well characterized cohorts and a digital pathology approach highlighting two important aspects: first, the density of CD3+CD8+ and CD3+CD8+CD45+ was inversely associated with tumour budding count which underlines the role for cytotoxic anti-tumour immunity in suppressing microinvasion and second, the prognostic value of tumour

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budding based on the ITBCC proposal, independent of molecular and immune parameters.

Tumour budding represents an aggressive morphologic feature at the invasive tumour front and is responsible for adverse outcome in all stages of CRC. Hypothesis-driven research into an anti-budding therapy would be a novel and important avenue for further investigation.

Declaration of Competing Interest

The authors have nothing to disclose.

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