Digitally assessed features of the tumor microenvironment as a predictor of lymph node metastasis and distant recurrence in patients with T1 colorectal cancer

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Introduction: Colorectal cancer (CRC) is the third most common cancer worldwide with an increasing number of patients being detected in an early stage. The choice of completion resection or follow-up by endoscopy highly depends on histopathological risk factors. However, the current selection of patients for completion resection leads to substantial overtreatment as most patients do not have locoregional lymph node metastases (LNMs).
The aim of this study was to investigate associations between digital features of the tumor microenvironment and risk of LNMs and distant recurrence in patients with T1 CRC.

Material and Methods: In total 466 patients were included during an 11-year period starting January 2001. The patients were divided into 2 subgroups consisting of 273 patients who received an endoscopic resection alone and 193 patients where the endoscopic resection was followed by a completion resection. Histopathological slides stained for H&E, cytokeratin, CD3 and CD8, were scanned and digitized. AI-based algorithms were developed using Visiopharm Quantitative Digital software to determine tumor-stroma ratio (TSR), tumor buds (TBs), and tumor-infiltrating lymphocytes (TILs).

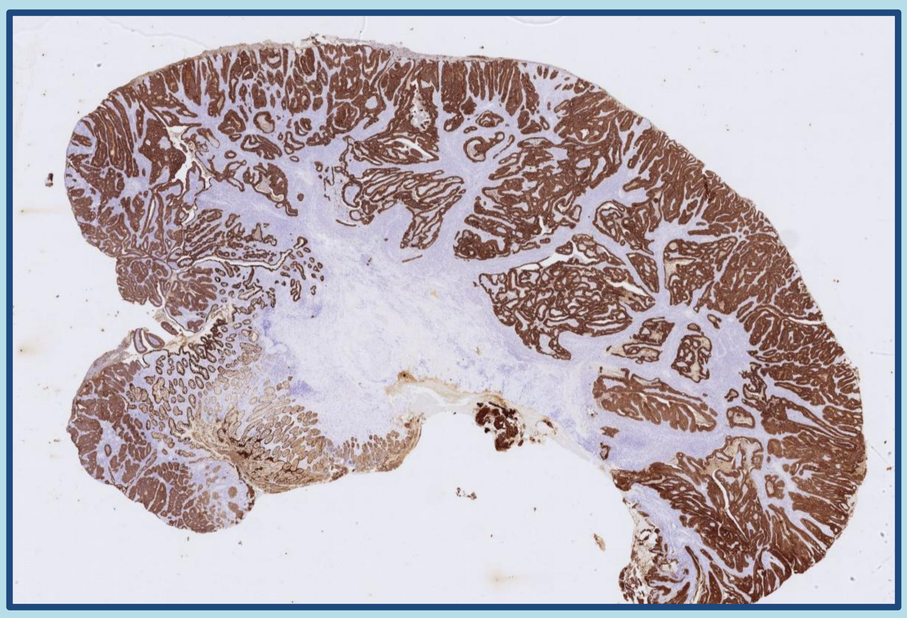

Fig. 1a: Polyp with pT1 adenocarcinoma, cytokeratin stain

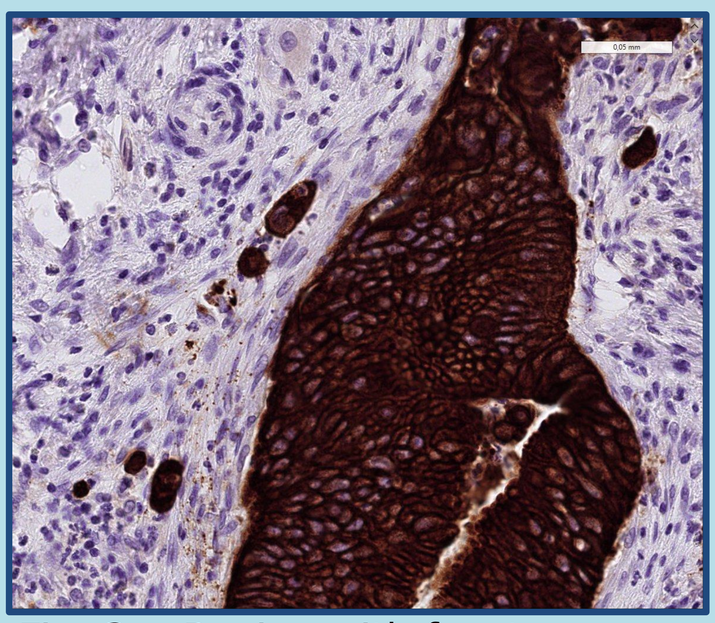

Fig. 2a: Region with few tumor buds, cytokeratin stain

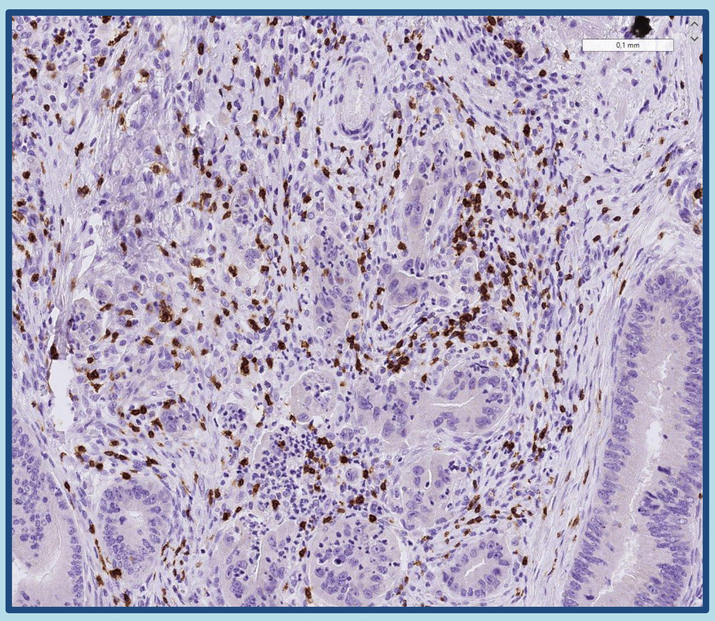

Fig. 3a: TILs, CD3 stain

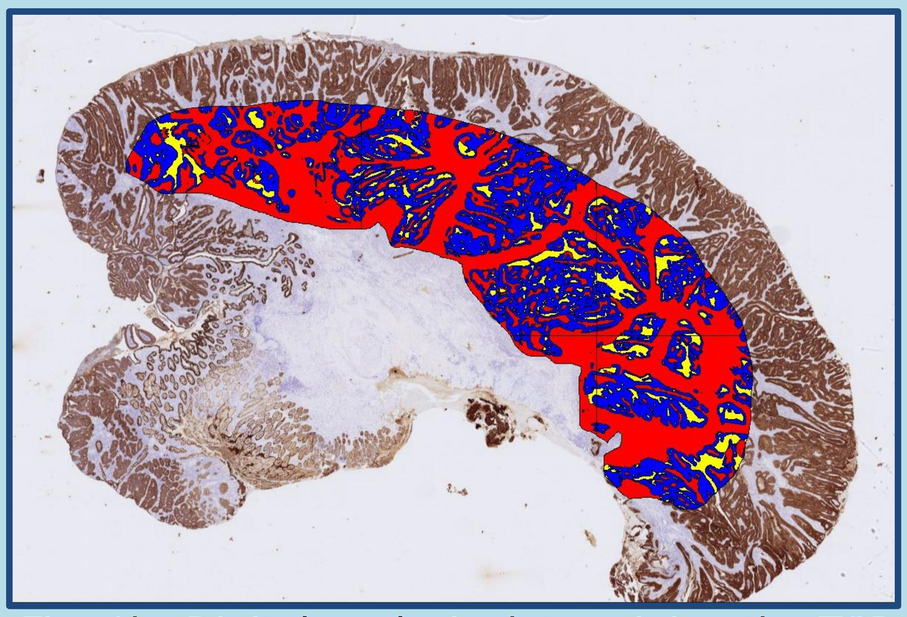

Fig. 1b: Digital analysis determining the TSR

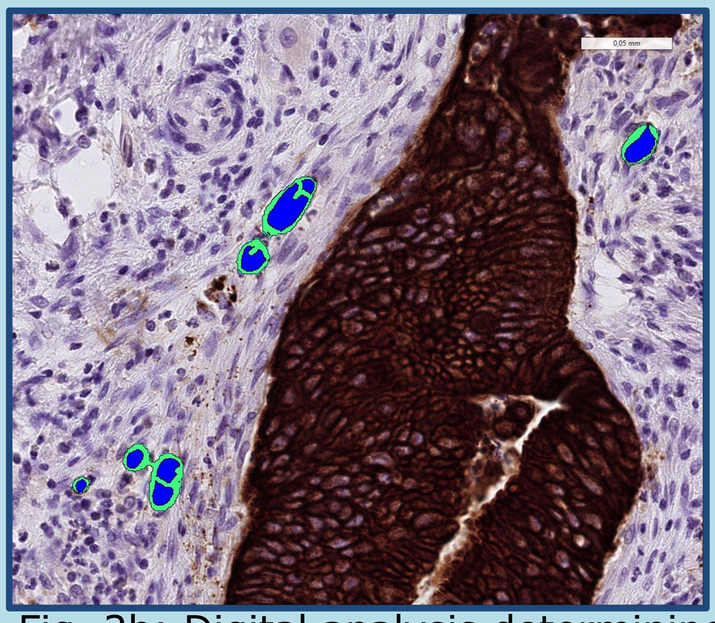

Fig. 2b: Digital analysis determining number of tumor buds/mm^2

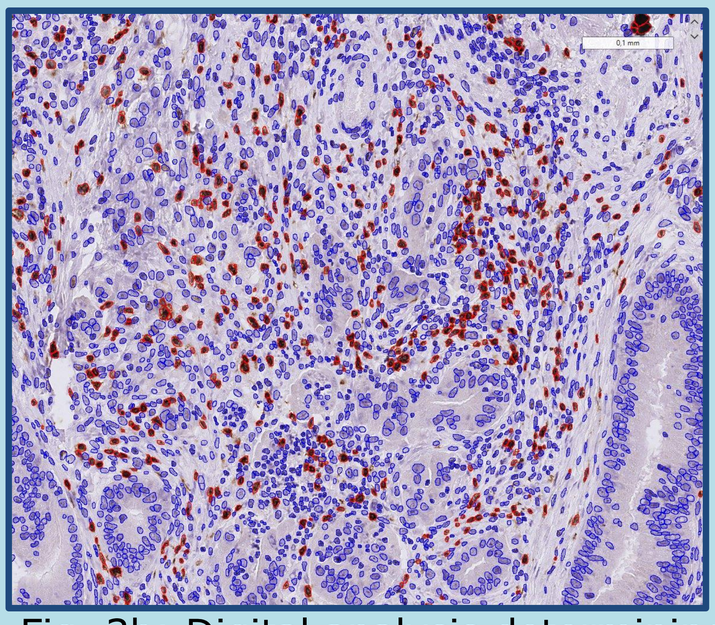

Fig. 3b: Digital analysis determining count of CD3+ TILs/mm^2

Results: The group of patients receiving a completion resection were significantly younger, included a higher number of females and more often had a non-radical resection margin in the endoscopic resection. LNMs were detected in 22 out of the 193 patients (11.4%) with surgical resection. Univariate analysis revealed that a high number of TBs were associated with LNM ($p < 0.05$) while no significant difference was found in TSR and TILs. Information concerning distant recurrence for patients with T1 cancer was available for 449 patients. Distant metastases occurred in 22 patients (4.9%). Low numbers of CD3+ TILs and CD8+ TILs were associated with an increased risk of distant recurrence ($p<0.05$), while no significant difference was found for TSR and TBs.

Conclusions : Digitally assessed TBs were associated with an increased frequency of LNMs, while digitally assessed TILs were associated with distant recurrence in T1 CRC. Adding these factors to the traditionally assessed histological risk factors might add to the development of a more precise prediction model with the potential to reduce the number of patients in need of completion resection.

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