

Molecular profiles of malignant colorectal polyps within the European Polyp Surveillance Study (EPOS IV)

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Aims To assess the risk of recurrence and metastasis following endoscopic or surgical treatment of pT1 colorectal cancer (CRC), as well as the necessity for invasive surgical treatment, utilizing conventional and novel histological molecular markers.

Methods We analyzed patients who were treated for T1 CRC in a tertiary center and had follow up of at least 3 years or underwent surgical resection and whose resection specimens were available. Conventional histopathological biomarkers, including (1) grade of differentiation, (2) lymphovascular invasion (LVI), (3) tumor budding (TB), (4) neuroinvasion, (5) resection margin and novel histopathological biomarkers: (1) poorly differentiated clusters (PDCs), (2) desmoplastic response, (3) tumor infiltrating lymphocytes (CD8), (4) CDX2, (5) mesenchymal bcatenin expression, (6) aSMA, (7) TGFb, (8) SNAIL, (9) GREM. Clinical surveillance data post-treatment was retrieved, and the primary endpoint was oncological failure, defined as CRC recurrence, local, and regional metastases. Histopathological evaluation was blinded to previous histology results and clinical surveillance data.

Results The analysis included 75 patients with pT1 cancer. The mean age of patients was 65 years, with 66% being male. Primary surgery was performed in 35% of cases, while 65% underwent endoscopic resection. Lesions were distributed, with 24% in the rectum and 76% in the colon, with a mean lesion size of 24.2 mm, and 64% of pedunculated morphology. The distribution of other assessed histopathological risk factors is presented in Table 1. After the median follow-up time of 3.7 years 8 patients (10.6%) with recurrence, local or regional metastases were observed. Apart from conventional histological biomarkers, two novel biomarkers were identified: desmoplastic reaction at invasive front (present in 6 (75%) patients with an endpoint) and tumor infiltrating lymphocytes (CD8) at invasive front (absent in all patients with an endpoint). All patients with an endpoint exhibited at least one positive conventional or novel risk factor (sensitivity of 100%, specificity of 39%). Most patients (63%) with an endpoint had a combination of multiple positive histological risk factors of high tumor budding, high grade differentiation, lymphovascular invasion and desmoplastic reaction at invasive front.

Conclusions We identified two novel histological biomarkers which combined with conventional ones could optimize endoscopic treatment of T1 CRC.

1. Table 1. Distribution of the histopathological risk factors assessed in the cohort.
Differentiation Low grade (%) 70 (93.3%) High grade (%) 5 (6.7%) Invasion depth for pedunculated morphology (%) Haggitt 1 12 (25%) Haggitt 2 17 (35.4%) Haggitt 3 16 (33.3%) Haggitt 4 3 (6.3%) Angioinvasion HE staining*Positive (%) 10 (13.3%) Negative

(%) 65 (86.7%) Lymphovascular invasion, HE staining*Positive (%) 15 (20%) Negative (%) 60 (80%) Lymphovascular invasion, D2-40 Positive (%) 9 (12%) Negative (%) 66 (88%) Neuroinvasion Positive (%) 2 (2.7%) Negative (%) 73 (97.3%) Budding>10, high 26 (34.7%) Low or medium 49 (65.3%) PDC high,>10 2 (2.7%) low,<10 73 (97.3%) Desmoplastic response Positive (%) 39 (52%) Negative (%) 36 (48%) Inflammatory infiltrate, CD8 Positive (%) 9 (12%) Negative (%) 66 (88%) CDX2 invasive front 48 (64%) nuclear 27 (36%) Betacatenin mesenchymal None 55 (73.3%) Nuclear/Membranous 20 (26.7%) AlfaSMA None 30 (40%) Nuclear/Membranous 45 (60%) TGFB None 34 (45.3%) cytoplasmic/membranous 41 (54.7%) SNAIL Positive (%) 69 (92%) Negative (%) 6 (8%) GREM Positive (%) 72 (96%) Negative (%) 3 (4%)*hematoxylin and eosin

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Conflicts of interest

Authors do not have any conflict of interest to disclose.

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