Results: Of the 58 rectal cancer patient samples included, 13 had a TRS of 0-1; 33 had a TRS of 2 and 12 had a TRS of 3. Chromatin texture of lymphocytes in the tumor microenvironment were found to show significant heterogeneity differences between TRS 0-1 (luminance kurtosis: -0.47) vs TRS 2 (kurtosis: -0.4) vs 3 (kurtosis: -0.4), with $p < 0.03$. Similarly, chromatin texture in fibroblasts was significantly different between TRS 0-1 (luminance kurtosis: -0.57) vs TRS 2 (kurtosis: -0.52) vs 3 (kurtosis: -0.43), with $p < 0.03$.A linear discriminant machine classifier trained using chromatin texture features yielded a cross-validated AUC of 0.76 ± 0.06 in distinguishing between TRS 0-1 vs 3.

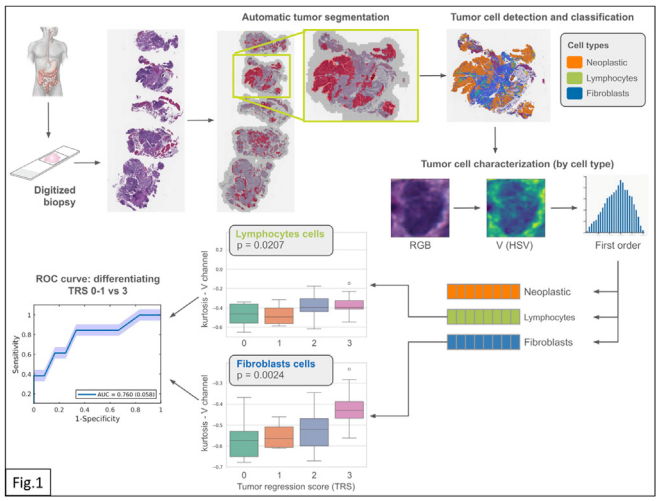

Figure 1 - 551.

Conclusions: Computational analysis of digitized rectal biopsies revealed predictive nuclear chromatin texture features associated with responses to chemoradiation in rectal cancers. After further validation, this AI signature could personalize treatment options in RAD patients, especially for patients who will not benefit from standard CRT.

Lab Invest 105 (2025) 102782

https://doi.org/10.1016/j.labinv.2024.102782

552 | Epstein-Barr Virus Associated Gastric Cancer: a Histopathologic Study with Comprehensive Molecular Profiling

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Disclosures: Valentina Angerilli: None; Jessica Gasparello: None; Antonio Collesei: None; Carlotta Ceccon: None; Marianna Sabbadin: None; Paola Parente: None; Alessandro Vanoli: None; Monia Niero: None; Claudio Luchini: None; Roberta Gafa': None; Angelo Dei Tos: None; Federica Grillo: None; Luca Mastracci: None; Matteo Fassan: None

Background: A subset of gastric cancers (GCs) is linked to Epstein-Barr virus (EBV) infection. This study aims to characterize the histopathological and molecular features of EBV-associated GCs (EBV-GCs), focusing on predictive biomarkers and genomic and transcriptomic analysis.

Design: A total of 38 EBV-GCs were collected from five institutions. The presence of EBV was confirmed with *in-situ hybridization*. Immunohistochemistry for HER2, PD-L1, CLDN18 and MMR proteins were performed. Genomic and transcriptomic profile was assessed using AmoyDX Master panel that at the DNA level can identify SNV, InDels, and CNV on 571 hot genes, microsatellite status, TMB, and HRD, while on the RNA level, in addition to fusions on 45 hot genes, it also quantifies the expression of 2396 cancer-related transcripts.

Results: Most EBV-GCs were diagnosed as pT3/pT4 (69%), were located in the corpus/fundus (50%) and were associated with intestinal metaplasia (63%). Six EBV-GCs (16%) were associated with dysplasia. The following histotypes were identified: carcinoma with lymphoid stroma (CLS; 63%), tubular high-grade (16%), mixed (13%) and tubular low-grade (8%). MMR deficiency and HER2 positivity were each observed in 5% of cases, while all tumors had a PD-L1 Combined Positive Score ≥ 10. CLDN18 moderate/strong expression in $\geq$75% of cancer cells was detected in 67% of cases, though no clinicopathological or molecular associations were identified. The most frequently altered genes were *PIK3CA* (35%), *AIRD1A* (15%), *APC* (9%), *CTNNB1*(9%), *KTM2C* (9%) and *KTM2D* (9%). TMB-high status was found in 20.5% of cases. A preliminary transcriptomic analysis revealed a differential expression between CLS and the other histotypes. A total of 99 transcripts were found to be deregulated (Log2FC>1.5; Log2FC<-1) among the two subgroups, including EBV-related transcripts, transcripts coding for oncoproteins, tumor suppressor proteins, cytokines and chemokines, transcripts coding for anti-cancer immune response regulators already druggable and novel regulators.

Conclusions: EBV-GCs are a discrete pathologic and molecular entity. EBV-GCs are located mainly in the corpus/fundus, with common histotypes like CLS. Key molecular features include CLDN18 and PD-L1 positivity, frequent *PIK3CA* mutations, and TMB-high. Transcriptomic findings offer a foundation for further exploration into the molecular underpinnings of CLS and its distinctiveness from other histotypes, which may lead to improved therapeutic strategies.

Lab Invest 105 (2025) 102783

https://doi.org/10.1016/j.labinv.2024.102783