Background: Elevated microsatellite alterations at selected tetranucleotide repeats (EMAST) is a different type of genomic instability in colon cancer (CRC) in contrast to mono-, and dinucleotide based instability microsatellite instability (MSI). In this study, we performed comprehensive genomic profiling (CGP) of CRC patients with different EMAST and MSI status to understand their genomic structure, which may help match them with relevant therapies.

Methods: 99 formalin-fixed, paraffin-embedded (FFPE) CRC tissues consisting of four subtypes based on their EMAST and MSI status, namely (1) EMAST+ and MSI-H; (2) EMAST+ and microsatellite-stable (MSS); (3) EMAST- and MSI-H, and (4) EMAST- and MSS, were subjected to next-generation sequencing (NGS) with a 440-gene panel to identify mutations and copy number variants (CNVs). Tumor mutational burden (TMB) was determined using mutations detected on exonic regions sequenced while CNV index was calculated to infer genome instability.

Results: In line with previous studies, the prevalence of TP53 (17.6%; n = 3) and APC (25.5%; n = 4) mutations was much lower whereas BRAF V600 mutation (41.2%; n = 7) was much higher in the subtype (1) CRCs which had both MSI-H and EMAST signatures. Interestingly, these dual positive tumors had a significant higher TMB and lower CNV index than other subtypes (TMB: (1) vs (2), (3) and (4): 54 vs 19, 25; and 16; p < 0.0001; CNV index: (1) vs (2), (3), and (4): 3.9 vs 13.7, 9.9, and 17.8; p < 0.0114, 0.006, and 0.0003), suggesting there are more likely to benefit from immune checkpoint inhibitors. Notably, ATM and ARID1A genes mutated in a mutually exclusive way in up to 13/17 (76.5%) of tumors with MSI-H and EMAST signatures, which may predict treatment benefit from the PARP inhibitors.

Conclusions: MSI-H and EMAST+ CRCs show distinctive genomic features that give them the potential opportunity for checkpoint inhibitors in combination with PARP inhibitors.

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