Molecular Profile and Mutational Signatures of Micro-Satellite Stable Early Onset Colorectal Cancer in a Multi-Ethnic Cohort

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Abstract:

Background: Colorectal cancer (CRC) incidence in those aged 50 years and above has decreased over the last 2 decades. However, there is a rising incidence in CRC among individuals under 50 years of age, termed early-onset colorectal cancer (EOCRC). EOCRC patients are more advanced stage with poor histopathological characteristics compared to late-onset colorectal cancer (LOCRC) patients. This study aimed to compare the genomic profiles between microsatellite stable (MSS) EOCRC and LOCRC.

Methods: Fresh frozen tissue of 218 MSS, POLE wild-type (wt) CRCs identified from the Singapore General Hospital and National Cancer Centre Singapore Tissue Repositories were extracted as a discovery cohort and whole-exome sequencing were performed. Genomic profiles of 446 MSS, POLE-wt CRCs from The Cancer Genome Atlas (TCGA) were analyzed as a validation cohort.

Results: Lower tumor mutational burden was seen in EOCRC compared to LOCRC for both the local (1.96 vs 2.31 mut/MB, p = 0.005) and TCGA (2.73 vs 3.33 mut/MB, p = 0.004) cohorts. APC mutations were lower among EOCRC compared to LOCRC in both the local [38 (67.6%) vs 137 (84.6%), p = 0.011] and TCGA [33 (57.9%) vs 295 (75.9%), p = 0.007] cohorts. There was a lower mean proportion of clock-like SBS1 signature in EOCRC compared to LOCRC in both local (20.2% vs 23.7%, p = 0.08) and TCGA cohorts (24.3% vs 28.4%, p = 0.05).

Conclusion: MSS-EOCRC may be associated with APC wild-type CRC and less clock-like signatures. Further studies to identify biomarkers in EOCRC can tailor treatment strategies and improve outcomes.

Keywords:

Early onset colorectal cancer, mutational profile, molecular signatures.