Introduction: Colorectal cancer (CRC) is a common cancer and cause of cancer death in the world. There is a need for biomarkers that can accurately predict outcomes after the surgical and medical treatment of CRC. Epigenetic clocks are based on methylated CpG dinucleotides that measure tissue-specific epigenetic age (EA) and associate with the biologic age of tissues. Elevated EA has been associated with various adverse clinical outcomes and age-related disease but has not yet been evaluated as a measure of the risk of CRC surgical complications. Consequently, we assessed whether the EA of colon tissue could be used as a biomarker of short-term surgical risk, and whether other environmental factors (smoking, DM, neoadjuvant chemotherapy, etc.) may affect EA of CRC patients.

Methods: Normal colon tissue was collected (N=75 patients), subjected to DNA extraction, and assessed using EPIC and HM450K methylation arrays (Illumina). Using the array results, the EA of the tissues was determined using four distinct epigenetic clocks (EpiTOC, Horvath, Hannum, PhenoAge). Epigenetic age acceleration (EAA) was also assessed to account for any potentially confounding effects of individual patient ages. Surgical complications were measured by the Clavien-Dindo classification system in 43 patients, calculated as Minor (n=19, Stage I-II), Major (n=6, Stage III-IV), or None (n=18). Epigenetic data were compared with demographic and perioperative information from the medical record and questionnaires.

Results: Based on EAA, we did not observe significant differences in perioperative outcomes and length of hospital stay. There was a trend for EAA to be associated with CEA levels and BMI. There were significant relationships between pack-years and epigenetic age acceleration with most epigenetic clocks (p=0.29, 0.01, 0.03, 0.01), pack-years and Clavien classification (p=0.02), as well as with epigenetic age acceleration and neoadjuvant chemotherapy (n=4) (p= 0.86, 0.01, 0.003, 0.01).

Conclusions: While our preliminary data do not provide evidence for a relationship between EA and perioperative events, there is a possibility that our study was underpowered to detect statistically significant associations. Further analysis of EA in relation to surgical outcomes is needed. We observed associations between pack-years and chemotherapy with the EA of the colon, and pack-years with worse surgical outcomes as measured by Clavien classifications. In light of the small sample size, further confirmatory studies are needed. Thus, we have identified an association of epigenetic age of the colon with tobacco and adjuvant chemotherapy but not with surgical complications.
Clavien Association with Pack Years (Smokers)

Clavien Classification

Age Acceleration

Epigenetic Age Test

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