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Building epigenetic clocks for estimating accelerating aging in patients with testicular cancer treated with cisplatin-based chemotherapy.

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Background: DNA methylation is highly correlated with chronological age. This is essential for constructing epigenetic clocks. Epigenetic clocks can shade light not only about the biological age, but also describe the functional state of the body after chemotherapy (CT). Patients with testicular cancer (TC) treated with CT are prone to develop metabolic syndrome (MetS) later in life, that may be also mediated through epigenetic changes (Bucher, Clin Epigenetics. 2019; 11:179). If age acceleration is also a mediator in the CT~MetS relationship remains unknown. We developed an epigenetic clock, and then analyzed differences in biological age acceleration between groups of TC patients 16 years after CT. TC patients had undergone one of two treatments: either surgery or a combination of CT or surgery only. Half of the patients in both treatment-groups had developed MetS. **Methods:** First, we used an elastic net to develop epigenetic clocks based on DNA methylation from publicly available data sets (EPIC array). We tested the differences in age accelerations (residual and intrinsic age acceleration) between groups of TC patients that received CT and orchiectomy with those TC patients with orchiectomy only. Also, the linear regression used treatment type and MetS diagnosis as independent variables. **Results:** Five epigenetic clocks were developed, of which one, performing best, was chosen to be used in further analyses. This clock, the Aurora's clock, had a root mean square error of 3.1/3.8 and R2 of 0.95/0.9 shown in two different test sets. In addition to Aurora's clock, eABEC and Levine DNAm PhenoAge were used (Lee, BMC Genomics. 2020, 21, 747; Levine, Aging. 2018, 2018,10:573-591). The linear regressions indicated a lower age acceleration for the group treated with both CT and surgery, compared to the group treated with surgery only. The significance level varied between the clocks, with a p-value ranging from 0.03 to 0.17. All three clocks estimated a higher age acceleration for patients diagnosed with MetS, but this was only significant when applying Levine DNAm PhenoAge ($p = 0.03$ for residual age acceleration, and $p = 0.045$ for intrinsic age acceleration). **Conclusions:** These findings indicate that CT does not lead to increased age acceleration 16 years after treatment. However, individuals diagnosed with MetS can have an elevated age acceleration. These findings can have clinical implications for managing patients' after TC diagnosis (i.e. MetS can be predicted from age acceleration). Testing the clocks in an independent cohort of TC is needed for validation of our results.
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