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Copy-number Intratumor Heterogeneity Predicts Relapse in Early-stage Colon Cancer †

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Abstract: Genomic intratumor heterogeneity has been occasionally appointed as a prognostic predictor in solid malignancies. This is in part due to its ability to promote somatic evolutionary processes that can drive cancer progression and therapeutic failure. Many solid tumors are highly heterogeneous entities showing variable karyotypes because of elevated levels of ongoing chromosome instability. To what extent measuring levels of intratumor heterogeneity might provide valuable information to make clinical decisions remains elusive. In colon cancer, the selection of high-risk patients with stage II colon cancer is crucial to ensure the clinical benefit of adjuvant chemotherapy after surgery. We investigated the prognostic value of genomic intratumor heterogeneity and aneuploidy, aiming to generate a clinico-genomic model that aids patient stratification. By combining an array of genomic methodologies, we assessed levels of intratumor heterogeneity by measuring the proportion of subclonal copy-number alterations and mutations. Results indicated that tumor aneuploidy and copy-number heterogeneity are predictive of a poor outcome in early-stage colon cancer and improve the discriminative performance compared to solely clinicopathological data. Identifying the cellular consequences of such high levels of intratumor heterogeneity becomes of utmost importance to understanding genomic insults in cancer. Thus, we focused on the role of whole-genome doubling as a definitive feature of chromosome instability and assessed treatment resistance in *in vitro* models. Our findings provide further insight into how tetraploid karyotypes result in greater tolerance levels to chemo-radiotherapeutic agents.

Keywords: intratumor heterogeneity; colon cancer; disease prognosis;

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Conflicts of Interest

The authors declare no conflict of interest.