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Therapy stratification of rectal cancer patients by epigenetic testing

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Considerable progresses have been made in the development of neoadjuvant colorectal cancer (CRC) therapeutics and many patients respond to neoadjuvant chemo-radiotherapy resulting in tumor down staging. In up to 20% a complete pathological response is observed, characterized by absence of residual primary tumor in the pathological specimen that translates into excellent disease-free survival of more than 90%. For such patients, an observational watch-and-wait approach, may replace surgical intervention. However, therapeutics are still away from optimal and the main obstacles in patient treatment are moderate efficacy and intrinsic resistance. In addition, a complete response to neoadjuvant chemo-radiotherapy can currently be determined only by a pathological evaluation following surgery. This highlights the need for predictive biomarkers allowing stratification of patients according to their response to neoadjuvant chemo-radiotherapy. Epigenetic marks, like DNA methylation have been identified as potential candidate biomarkers for the prediction of treatment efficacy. Therefore, we investigated the role of DNA methylation in therapy response to identify a DNA methylation signature, able to stratify CRC patients in therapy responders and non-responders to advice clinicians whether one can stick to a wait-and-watch approach, or to surgery. A retrospective epigenome-wide-DNA-methylation study using 48 FFPE CRC samples was conducted using Illumina's Human Methylation EPIC Bead Chip. Biostatistics confirmed distinct DNA methylation profiles for patients in accordance to their response to neoadjuvant therapy with an almost perfect discrimination between the groups. The most striking observation to emerge from the data was the gradual character (either increasing or decreasing) of the methylation status from non-responder, via partial responder towards full responder to neoadjuvant therapy. Consequently, the identified DNA methylation signature has predictive potential to shed light on patient's individual response status to neoadjuvant chemo-radiotherapy and can be used for therapy decisions whether a watch-and-wait approach or operative intervention is the more appropriate strategy.