Comprehensive analyses of rectal cancer genomes to reveal copy number variations as potential predictor of induction therapy efficacy.

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Abstract Disclosures

Background:
Genetic aberrations such as SNPs and structural aberrations are associated with malignancies and cancer is regarded as a disease of the genome. Genome profiling of individual tumors is provided by high-throughput sequencing and is about to enter routine clinical practice with impact on treatment decisions and tumor classification (NIH [2014] The Cancer Genome Atlas). Rectal tumors show a great variation in response to preoperative chemoradiotherapy and, therefore, robust and easy to obtain individual biomarkers are needed in order to adjust treatment strategies for each patient.

Methods:
Copy-number profiles were generated for 13 rectal tumors (pre CRT; Stage II or higher) using shotgun sequencing (HiSeq). For a subset of the tumors (n=10) the 20 genes most commonly mutated in colon cancer were screened for mutations using the commercially available GeneRead DNAseq Colon Cancer Gene Panel (QIAGEN) with subsequent sequencing using an Illumina MySeq.

Results:
The copy-number profiles of the 13 tumors revealed frequent gains of chromosomes 8q(54%), 13q(69%) and 20q(62%) and frequent losses of 1p(62%), 8p(77%), 14q(54%), 17p(62%) and 18(77%). Exon sequencing of only 20 genes most commonly mutated in colon cancer revealed at least one SNP with high or moderate clinical impact for each tumor (median=3.5 (range: 1-7)). Six of the ten tumors carried mutations in TP53 and APC, respectively, and five tumors have KRASmutations. The number of somatic amplifications in the
individual tumor genome correlated significantly with the regression in tumor mass by CRT (r=0.7, p=0.008).

Conclusions:
The detected copy-number aberrations of these rectal carcinomas are in agreement with former studies of colorectal tumors (Xie T, G DA, Lamb JR, et al. 2012. A comprehensive characterization of genome-wide copy number aberrations in colorectal cancer reveals novel oncogenes and patterns of alterations. PLoS One 7: e42001.) and all of the analyzed tumors carry several regions of abnormal copy-number state. The detected number of amplification may serve as predictor for a successful preoperative CRT.