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Titel des Beitrags: Genetic heterogeneity in synchronous colorectal cancers impacts genotyping approaches and therapeutic strategies.

Abstract: Synchronous colorectal carcinomas (sCRC) are clinically challenging neoplasms. Although the epidemiological characteristics are quite well established, their biological basis is still poorly understood. Hence, we performed comprehensive molecular profiling of 23 sCRC cases comprising 50 synchronous primary tumors, 5 metastases, and corresponding normal tissue by targeted deep sequencing of 30 CRC-related genes, microsatellite analysis and analysis for methylated MLH1. We identified a striking inter- and intratumoral genetic heterogeneity of sCRC. Twenty (87%) cases showed genetic heterogeneity leaving only three cases with tumors that had an identical genetic make-up. Intertumoral heterogeneity was frequently observed for clinically actionable genes, including KRAS. Specifically, 44% of the cases harbored tumors of which at least one was KRAS mutated and the other KRAS wildtype. Moreover, 48% of the cases had at least double, sometimes even triple or quadruple mutations in KRAS, APC, TP53, PIK3CA, and TGFBR2, most of them being subclonal events. Lastly, we detected four cases (17%) with microsatellite instable (MSI) tumors with one case harboring one MSI- and a distinct microsatellite stable carcinoma. Our
data demonstrate a striking genetic heterogeneity not only between different sCRC of a single case but also within a single tumor. These results contribute to the biological understanding of sCRC and directly impact genotyping strategies and oncological decision making. Testing one tumor or a single metastasis may not suffice in the sCRC setting as clinically relevant and tumor-specific genetic information may be left undetected compromising optimal oncological therapy. © 2015 Wiley Periodicals, Inc.