Mutational analysis of *KRAS* and *BRAF* in synchronous and multiple colorectal lesions in the same patient.

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BACKGROUND: Colorectal cancer is the third leading cause of cancer deaths in women and the fourth in men, in Brazil. Understanding the malignant transformation has profound translation implications and has been the focus of several studies. Specifically, the monoclonaty of synchronic tumors has been claimed, but still controversial.

HYPOTHESIS: To investigate if simultaneously multiple precursor lesions and colorectal adenocarcinoma (adenomas, serrated polyps and adenocarcinomas) in the same patient harbored the same molecular alterations. METHODS: We analyzed the *KRAS* and *BRAF* mutations in multiple and synchronous colorectal lesions in 13 patients (mean age 69±9.7, 8 males and 5 females) presenting at least one mutated lesion, previously analyzed (7 *KRAS* mutated and 6 *BRAF* mutated patients). Mutational analysis was performed using Sanger sequencing and COBAS platform. Furthermore, we correlated mutation status with endoscopic, histopathological and demographic characteristics.

RESULTS: Thirty-eight synchronous colorectal lesions (mean, 3±0.8 per patient) were analyzed, being 36 (94.7%) precursor lesions and 2 (5.3%) adenocarcinomas. Adenomas were the main precursor lesion (63.9%; tubular adenoma, 91.3%) followed by serrated polyps (26.1%; hyperplastic polyps, 76.9%; sessile serrated adenoma, 15.4%; traditional serrated adenoma, 7.7%). Advanced adenoma represented 21.7% of all adenomas. Among patients analyzed for *KRAS* mutation, 5 of 7 patients presented lesions in the same localization, proximal or distal colon, and 5 of 7 patients in the same pathway (adenoma-carcinoma or serrated pathways). Among these patients, 1 of 7 patients presented the same *KRAS* mutation type (Gly12Val) in two lesions (adenocarcinoma and early adenoma) of three simultaneous lesions (plus hyperplastic polyp). Among patients analyzed for *BRAF* mutation, 1 of 6 patients presented synchronous lesions in the same colonic localization (distal or proximal colon), and 2 of 6 patients in the same pathway (adenoma-carcinoma or serrated pathway). One out of 6 patients presented the same mutational status, mutated for BRAF (V600E) in all three lesions (all hyperplastic polyps). In conclusion, apparently synchronous lesions in the same pathway of carcinogenesis are homogenous for *BRAF* mutation but heterogeneous for *KRAS* mutation.