OBJECTIVES:: Individualized risk assessment in patients with UICC stage II colon cancer based on a panel of molecular genetic alterations.

BACKGROUND:: Risk assessment in patients with colon cancer and localized disease (UICC stage II) is not sufficiently reliable. Development of metachronous metastasis is assumed to be governed largely by individual tumor genetics.

METHODS:: Fresh frozen tissue from 232 patients (T3-4, N0, M0) with complete tumor resection and a median follow-up of 97 months was analyzed for microsatellite stability, KRAS exon 2, and BRAF exon 15 mutations. Gene expression of the WNT-pathway surrogate marker osteopontin and the metastasis-associated genes SASH1 and MACC1 was determined for 179 patients. The results were correlated with metachronous distant metastasis risk (n = 22 patients).

RESULTS:: Mutations of KRAS were detected in 30% patients, mutations of BRAF in 15% patients, and microsatellite instability in 26% patients. Risk of recurrence was associated with KRAS mutation (P = 0.033), microsatellite stable tumors (P = 0.015), decreased expression of SASH1 (P = 0.049), and increased expression of MACC1 (P < 0.001). MACC1 was the only independent parameter for recurrence prediction (hazard ratio: 6.2; 95% confidence interval: 2.4-16; P < 0.001).

Integrative 2-step cluster analysis allocated patients into 4 groups,
according to their tumor genetics. KRAS mutation, BRAF wild type, microsatellite stability, and high
MACC1 expression defined the group with the highest risk of recurrence (16%, 7 of 43), whereas
BRAF wild type, microsatellite instability, and low MACC1 expression defined the group with the
lowest risk (4%, 1 of 26). CONCLUSIONS: MACC1 expression predicts development of metastases,
outperforming microsatellite stability status, as well as KRAS/BRAF mutation status.