Metastatic Spread Emerging from Liver Metastases of Colorectal Cancer

Does the Seed Leave the Soil Again?

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Objective: To investigate whether liver metastases contribute to metastatic spread of colorectal cancer (CRC) by shedding intact tumor cells. Background: Metastases represent the primary cause of death in CRC. Understanding the metastatic activity of metastases and which patients are at high risk for tumor cell dissemination may, therefore, have significant influence on cancer care in the future.

Methods: Circulating tumor cells (CTCs) were detected in the hepatic inflow (portal venous blood [PVB]) and outflow compartment (hepatic venous blood [HVB]) of a training (n 1⁄4 55) and validation (n 1⁄4 50) set using the CellSearch system. Isolated CTC from the HVB were subjected to gene expression analyses by quantitative polymerase chain reaction.

Results: CTC detection rate (37.2% vs 19.6%; P 1⁄4 0.04) and count (mean: 12.7, SEM: 5.9 vs 1.9; 1.2; P 1⁄4 0.01) were significantly higher in HVB compared to PVB. The increased CTC detection rate (54% vs 11.4%; P<0.001) and CTC count (14.7 5.1 vs 1.1 0.6; P<0.001) in the HVB compared to the PVB compartment was confirmed in the validation cohort. Expression of epithelial markers and genes involved in cell-to-cell and cell-to- matrix adhesion was reduced in CTC compared to tumor cells in liver metastases. Metastasis size greater than 5cm was associated with CTC shedding from established liver metastases in the training and validation cohorts.

Conclusions: Colorectal liver metastases shed intact tumor cells with an invasive phenotype. Metastasis size serves as a surrogate marker for meta- static activity of colorectal liver metastases.