Prediction of response to neoadjuvant chemotherapy in carcinomas of the upper gastrointestinal tract.

Abstract:
Multimodal treatment protocols are increasingly employed to improve the survival of patients with locally advanced adenocarcinomas of the upper gastrointestinal tract, however, only 30-40% per year of the patients respond to 5-FU and cisplatin-based neoadjuvant chemotherapy. The goal of our studies is the identification of reliable genetic markers, on the genomic DNA-level, mRNA, or protein level that could predict response of upper gastrointestinal carcinomas prior to neoadjuvant chemotherapy. In esophageal carcinomas, a higher gene expression of methylenetetrahydrofolate reductase (MTHFR), an enzyme involved in folate metabolism, was more frequently found in responding patients. In addition high gene expression of caldesmon and of the two drug carrier proteins, MRP1 and MDR1 was associated with response to therapy. By performing a genome-wide profiling on the protein level in a small group of patients, new potential markers were identified, which have to be validated in ongoing studies. In gastric carcinomas, mutations of the p53 gene revealed no association with response or survival, but tumors with a high rate of loss of heterozygosity (LOH), determined by microsatellite analysis, showed a better response to a cisplatin-based chemotherapy. Analysis of expression of 5-FU-(e.g., TS, DPD, and TP) and cisplatin-(e.g., ERCC1, ERCC4, GADD45A, and KU80) related genes, demonstrated an association of DPD expression with response and
survival. The combined consideration of TP and GADD45 gene expression, showed the most obvious association with therapy response in this tumor. Our studies point to promising markers with potential use for chemotherapy response prediction of adenocarcinomas of the upper gastrointestinal tract, but prospective studies for validation are necessary.