Gene Expression Profiles of HCC: Implications for Prognosis and Surgical treatment Options

Hee Jung Wang

Department of Surgery, Ajou University School of Medicine, Suwon, Korea

(Background) Hepatocellular carcinoma (HCC) is one of the most lethal cancers worldwide. Although recent advances in diagnosis and management of HCC, its prognosis remains poor because of the high incidence of recurrence and the absence of effective adjuvant drugs after surgical treatment. There are also some debates in surgical management of HCC: difficulty of early diagnosis in very early stage HCC, selection of treatment modality in early stage HCC, down staging in intermediate stage HCC, and a role of surgery as clinical trial for advanced stage HCC. Llovet et al. proposed that gene expression profiling can be useful to offer better tools to characterize small liver nodules, to further discriminate the best candidates for resection or liver transplantation, and to guide personalized medicine, although specific knowledge of the molecular diagnosis of HCC is preliminary, and further studies are required. . **(Methods)** Using six pairs of HCC and surrounding non-cancer liver tissue, comparative proteomic analysis by 2-dimensional electrophoresis was performed. We confirmed 188 proteins that were either up- or down-regulated in cancer tissue compared with background liver. 84 additional proteins were detected by data analysis and data mining using a software that meta-analyzes gene pathway and interaction. 272 candidate genes in total were selected. RNAs from cryopreserved HCC tissues of 128 patients (Training cohort) were extracted and quantitative real-time PCR was performed to determine gene expression. Through confirming significant up- or down-regulation of mRNA expression for 272 candidate genes, 57 genes were selected as the development group. **(Results)** From survival analysis (univariate Cox analysis, Kaplan-Meier analysis, combogene analysis and cross validation) in a training cohort of 128 HCC patients, four candidate genes (*CDH1*, *ID2*, *MMP9*, and *TCF3*) with significant prognostic values were selected to develop a risk score of patient survival. Patients with high risk scores calculated from the four-gene signature showed significantly shorter overall survival times. Subsequently, the 4-gene signature was validated in an independent cohort of 231 patients (P=0.00011). Moreover, the multivariate Cox analysis revealed that the 4-gene signature (P=0.0026) and tumor stage (P=0.0023) were independent prognostic factors for overall survival. **(Conclusion)** We suggest that the proposed 4-gene signature help predict the clinical outcome of HCC patients beyond traditional clinico-pathological parameters. I believe that the potentials of gene expression profiling should be continuously verified for the improvement of the outcome after surgical management of HCC patients and for solving various debates in HCC management.