Intratumor heterogeneity in hepatocellular carcinoma.

Morphologic intratumor heterogeneity is well known to exist in hepatocellular carcinoma (HCC), but very few systematic analyses of this phenomenon have been performed. The aim of this study was to comprehensively characterize morphologic intratumor heterogeneity in HCC. Also, taken into account were well-known immunohistochemical markers and molecular changes in liver cells that are considered in proposed classifications of liver cell neoplasms or discussed as molecular therapeutic targets. In HCC of 23 patients without medical pretreatment, a total of 120 tumor areas were defined. Analyzed were cell and tissue morphology, expression of the liver cell markers cytokeratin (CK)7, CD44, ?-fetoprotein (AFP), epithelial cell adhesion molecule (EpCAM), and glutamine synthetase (GS) along with mutations of TP53 and CTNNB1, assayed by both Sanger and next-generation sequencing. Overall, intratumor heterogeneity was detectable in the majority of HCC cases (20 of 23, 87%). Heterogeneity solely on the level of morphology was found in 6 of 23 cases (26%), morphologic heterogeneity combined with immunohistochemical heterogeneity in 9 of 23 cases (39%), and heterogeneity with respect to morphologic, immunohistochemical, and mutational status of TP53 and CTNNB1 in 5 of 23 cases (22%). Our findings demonstrate that intratumor
heterogeneity represents a challenge for the establishment of a robust HCC classification and may contribute to treatment failure and drug resistance in many cases of HCC.