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Clinical And Molecular Characteristics Of Pathologic Subtype In Cholangiocarcinoma

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Background : Pathologically, cholangiocarcinoma (CCA) can be divided as two pathological subtype; large duct type and small duct type. It represents different origin and carcinogenesis of CCA. However, its clinical impact and molecular characteristics are not well known yet, and we evaluated clinical and molecular features according to pathological subtype.

Methods : On 3 different cohort (Korea ; Keimyung University Dongsan Hospital, USA ; Mayo clinic, TCGA), 107 cases of CCA were included which had available clinical and molecular data (RNA sequencing with mutation). For Korea and USA data, we performed next generation RNA sequencing and RNA expression, variants and fusions were analyzed. For TCGA data, we downloaded clinical and genetic information from TCGA serve. We analyzed clinical and molecular features for them.

Results : On large duct type, frequency of extrahepatic CCA (Klatskin and distal bile duct ca), periductal infiltrating type, history of cholangitis or IHD stone, and N1 stage were significantly high compared to small duct type. In addition, level of serum CEA and CA 19-9 were significantly high in large duct type. In small duct type, history of hepatitis was significantly frequent than large duct type. In both type, frequency of mass forming type was similar. Patients with large duct type showed significant poor disease-free and overall survival than those with small duct type. On multivariate analysis, large duct type, lymph node metastasis and vascular invasion were independent poor prognostic factors. On mutation analysis, KRAS, PIK3CA gene mutation was common in large duct type, whether IDH1/2 mutation and FGFR2 fusion were common in small duct type. On pathway analysis, inflammation related, AKT, Wnt and KRAS related signalling were enriched in large duct type, while metabolism and EMT related pathways were enriched in small duct type.

Conclusions : Two pathological subtypes of intrahepatic CCA with distinct clinical, biological and prognostic differences were identified. Therefore, molecular characteristic of CCA can be predicted based on pathological subtype, and it may lead to more rational targeted approaches to treatment.

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