

## Liquid Biopsy From Bile-circulating Tumor DNA In Patients With Biliary Tract Cancer

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**Background** : Although Liquid biopsy of blood is useful for cancer diagnosis and prediction of prognosis, diagnostic and prognostic value of ctDNA in bile fluid for BTCs are not clear yet. We evaluate determine whether liquid biopsy for circulating tumor DNA (ctDNA) can replace tissue biopsy when assessing somatic mutations in biliary tract cancers (BTCs).

**Methods** : Bile samples were obtained from 42 patients with BTC. Matched formalin-fixed paraffin-embedded (FFPE) samples were obtained from 20 of these patients and matched plasma samples from 16 of them. Droplet digital PCR (ddPCR) was used for detection KRAS somatic mutation.

**Results** : KRAS mutations were identified in the bile ctDNA of 20 of 42 (48%) patients. Patients with mutant KRAS showed significantly worse survival than those with wild-type KRAS (2-year survival rates: 0% vs 55.5%, respectively;  $P = 0.018$ ). There was 80.0% mutational concordance between the paired bile ctDNA and FFPE samples, and 42.9% between the plasma and FFPE samples. On transcriptomic sequencing of one set of paired bile and FFPE samples, expression level of KRAS-associated signaling oncogenes in the bile and tissue samples showed a strong positive correlation ( $r = 0.991$ ,  $P < 0.001$ ).

**Conclusions** : Liquid biopsy of bile reliably detect mutational variants within the bile ctDNA of BTC patients. These results suggest that bile is an effective biopsy fluid for ctDNA analysis and can replace tissue biopsy in BTC patients.

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