#111P - The concordance between circulating tumor DNA and tissue genomic profiling in patients with advanced biliary tract cancer

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INTRODUCTION

- **Backgrounds**: Recent advances in molecular profiling have revealed potential therapeutic targets for biliary tract cancer (BTC), but **difficulties in obtaining an adequate sample could hamper molecular evaluations** in patients with BTC.
- Circulating tumor DNA (ctDNA) can thus help address any challenges associated with the limited use of tissue-based analysis in BTC.
- **Objectives**: We aimed **to evaluate the concordance between ctDNA and tissue genomic profiling** in patients with advanced BTC and evaluate **the feasibility of liquid biopsy** in the treatment of patients with BTC.

METHODS

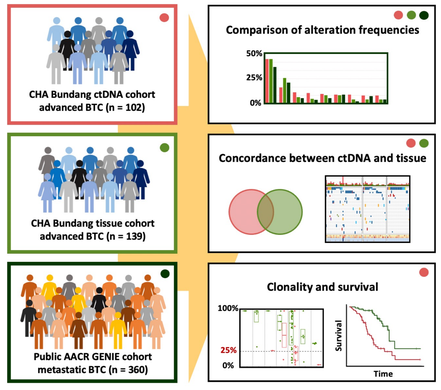

Figure 1. The study cohort and workflow

Cohorts and public data

- Patients before systemic therapy at CHA Bundang Medical Center from Jan 2019 to Dec 2022.
- ctDNA-based genomic data were generated using AlphaLiquid®100 from IMB Dx.
- Genomic data of 360 patients with metastatic BTC were downloaded from AACR GENIE v13.0.

Treatment

- Gemcitabine & cisplatin (Gem/Cis) chemotherapy (100%, 139/139)

RESULTS

Table 1. The baseline characteristics of CHA Bundang patients with BTC

Characteristics	Tissue cohort (n = 139)	ctDNA cohort (n = 102)	P value
Midian age (IQR)	66 (59-71)	66 (58-71)	0.96
Gender			0.36
Male	82 (59.0%)	54 (52.9%)	
Female	57 (41.0%)	48 (47.1%)	
Primary site			0.29
Intrahepatic	61 (43.9%)	50 (49.0%)	
Extrahepatic	50 (36.0%)	27 (26.5%)	
Gallbladder	28 (20.1%)	25 (24.5%)	
Extent of disease			0.45
Metastatic or recurred	103 (74.1%)	80 (78.4%)	
Locally advanced	36 (25.9%)	22 (21.6%)	
Baseline CA19-9 (U/mL)			0.68
Normal (0~37 U/mL)	52 (37.4%)	35 (34.3%)	
Abnormal (>37 U/mL)	87 (62.6%)	67 (65.7%)	

ctDNA cohort

- 102 patients with cell free DNA greater than 5ng extracted from blood samples were included.

Detection of alterations in ctDNA

- 99% (101/102 patients)

Variants in 15 key genes

- *ATM*, *BRCA1*, *BRCA2*, *BRAF*, ***ERBB2***, ***FGFR2***, ***IDH1***, *IDH2*, *KRAS*, *MAP2K1*, *MET*, *NF1*, *NRAS*, *PIK3CA* and *TP53*

CONCLUSION

ctDNA-based genotyping using liquid biopsy demonstrated ① **clinically acceptable concordance** with tissue genomic profiling in patients with advanced BTC and ② **could complement the limitation** of tissue-based genomic analysis in BTC.

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Almost no significant difference in frequency between ctDNA and tissue

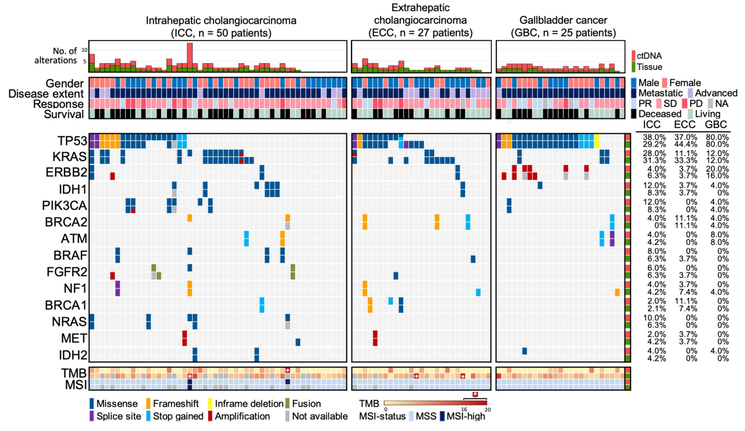

Figure 2. Intra-patient genetic landscape of BTC in ctDNA and tissue (n = 102 patients)

- Only clinically actionable variants (Tier 1 or 2 based on AMP/ASCO/CAP guideline) in key genes were analyzed.

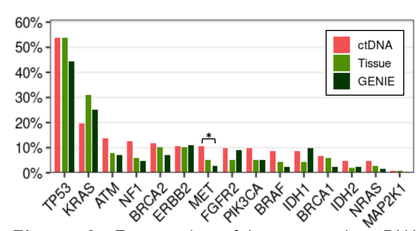

Figure 3. Frequencies of key genes in ctDNA, tissue and public GENIE cohorts

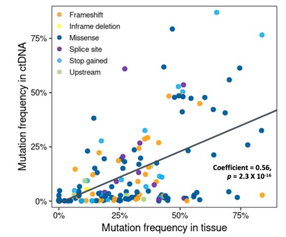

Figure 4. The correlation of mutation frequencies between ctDNA and tissue

Table 2. Intra-patient concordance of actionable targets between ctDNA and tissue

Actionable target	Sensitivity
IDH1 mutation	100%
FGFR2 fusion	66.7%
PIK3CA mutation	100%
ERBB2 amplification	40%
BRCA1/2 mutations	100%
MET amplification	100%
MSI-high	100%

Concordance of Tier 1 or 2 mutations

- Sensitivity: 84.8%
- Positive predictive value: 79.4%

Detection of actionable targets

- 34.3% (35/102 patients)

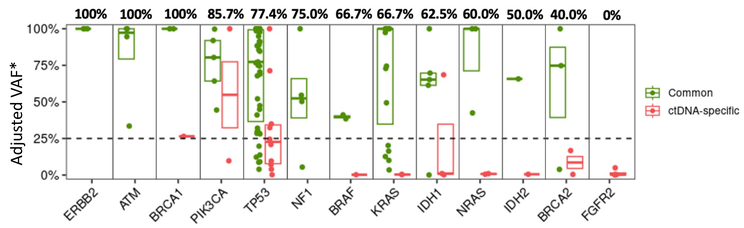

Figure 5. The distribution of clonality of ctDNA mutations in key genes.
* Adjusted VAF(Variant allele frequency) = VAF/max VAF

Patients with high ctDNA VAF showed poor prognosis in Gem/Cis chemotherapy

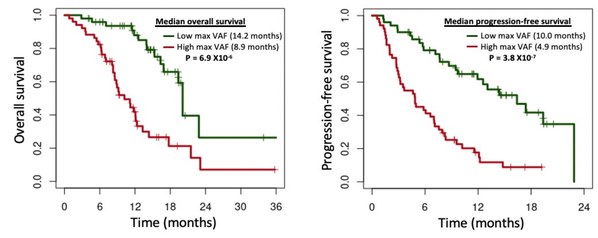

Figure 6. Overall and progression free survival with max VAF of somatic ctDNA variants