Abstract 536 : Molecular Differences with Therapeutic Implications in Early-onset Compared to Average-onset Cholangiocarcinoma

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Background

- Cholangiocarcinoma (CCA) has one of the fastest rising incidence rates (8% APR) among early-onset (eo) cancers.
- Real-world age-stratified multi-omic characterization of eoCCA could reveal molecular features with prognostic and therapeutic implications.
- We sought to compare the molecular characteristics of eoCCA with average-onset CCA (aoCCA) utilizing a real-world multi-omics dataset.

Methods

- The study comprised patients whose tumors underwent molecular analysis at Caris Life Sciences (Phoenix, AZ) using whole exome and whole transcriptome analyses.
- Patients were categorized by age as eoCCA defined as <50 years and aoCCA ≥50 years.
- *P* values were adjusted for multiple testing and considered significant at Q<0.05 for molecular comparisons and Q<0.25 for Gene Set Enrichment Analysis (GSEA).
- Insurance claims data was used for survival comparison using Kaplan-Meier estimates.

Results

The baseline characteristics listed below:

Table 1. Baseline Characteristics

Characteristic	eoCCA (n=453)	aoCCA (n=5134)
Median Age (years)	44	68
Sex: Female	60.70%	54.60%
Sex: Male	39.30%	45.40%
Primary Tumor Site		
Intrahepatic	57%	53%
Extrahepatic	14%	16%
Gallbladder	21%	23%
Others	8%	8%

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Targetable Molecular Alterations

- Differences in the prevalences of targetable alterations were observed (Figure 1).
- FGFR2 fusion was significantly more prevalent in eoCCA (15.7% vs 5.9% in aoCCA, Q<0.001)

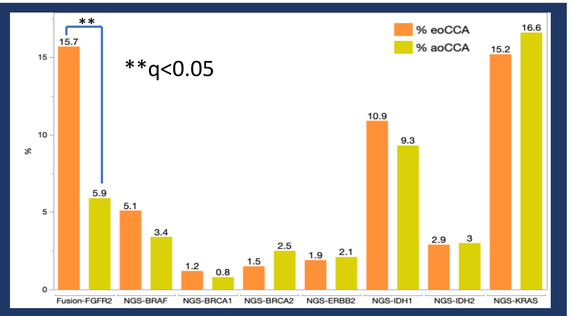

Figure 1. Prevalence of Targetable Molecular Alterations

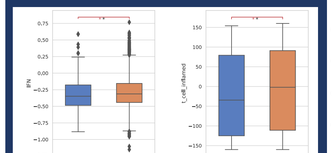

Figure 2. IFN & TIS Signatures

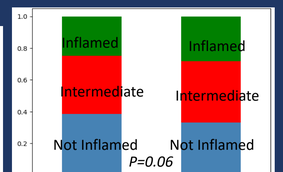

Figure 3. Distribution of Inflamed Tumors

Immune Oncology Relevant Markers

- MSI-H tumors (4.1% eoCCA vs 2.4% aoCCA), and high- TMB (6.1% vs 5.1%) were numerically higher in eoCCA (Q=1).
- The Interferon Gamma - IFG Score (Fold Change FC: 1.1, Q=0.01) and T-Cell Inflammation Score TIS (FC:17.3, Q=0.03) were higher in aoCCA (Figure 2).
- The distribution of inflamed tumors were not significantly different, *P*=0.06 (Figure 3).
- On GSEA, angiogenesis was enriched in eoCCA (normalized enrichment score NES=1.51, Q=0.16) while IFG (NES= -1.58, Q =0.06) and inflammatory response (NES= -1.46, FDR-p=0.18) were enriched in aoCCA.

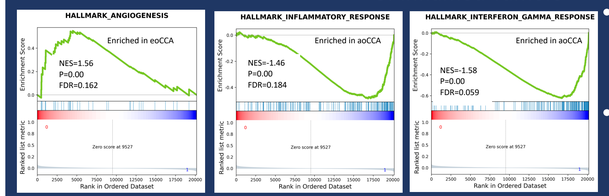

Figure 4. Results of GSEA for a) Angiogenesis, b) Interferon gamma response and c) Inflammatory response

Conclusions

- In the largest age-stratified analysis of molecular characteristics of CCA, we identified crucial differences, including higher prevalence of FGFR2 fusions and significant differences in immunotherapy-related markers.
- Patients with eoCCA experienced better outcomes that was impacted by the FGFR2 fusion status.
- Our findings, especially higher FGFR2 fusion prevalence in eoCCA, underscore the need for NGS testing

Survival Analysis

- Median OS was longer in eoCCA (16.5 vs 13.3 mo), HR 0.86, 95%CI 0.78-0.95, *P*=0.004.
- Among patients exposed to immunotherapy, median OS was longer in patients with eoCCA (19.2 vs 8.1 mo) - HR 0.54, 95%CI 0.30-0.98, p=0.04 (Figure 5).
- No survival difference was identified in patients on chemotherapy (HR 0.91, 95%CI 0.76-1.08, *P*=0.28).

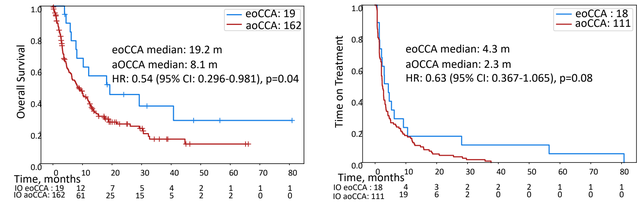

Figure 5. Survival Analysis Results (Left) and Time on Treatment (Right) for Patients Exposed to Immunotherapy

Survival by FGFR2 Fusion Status

- Median OS was highest for patients with FGFR2 Fusion- eoCCA 21.7 vs aoCCA 18.6mo, followed by FGFR2 Fusion negative – eoCCA 15.0 vs aoCCA 12.2mo, *P*=0.002 (Figure 6).
- Figure 7 Shows differentially expressed molecular alterations (Q<0.05).

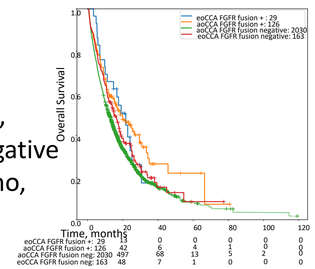

Figure 6. FGFR2 Fusion Status and Survival Outcomes

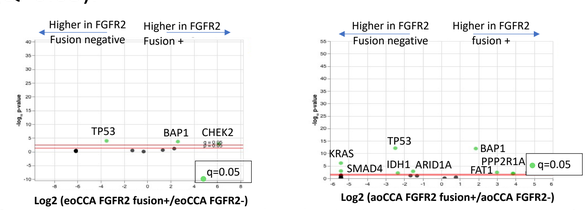

Figure 7. Volcano Plot of Molecular Differences in FGFR2 Fusion Positive vs Negative eoCCA (left) and aoCCA (right)

References:

1. Koh et al. Patterns in Cancer Incidence Among People Younger Than 50 Years in the US, 2010 to 2019. *JAMA Network Open*. 2023
2. Ogobuiro et al. Multiomic characterization to reveal a distinct molecular landscape in young-onset pancreatic cancer. JCO. 2022