Tumor profiling of liver metastases (LM) from CRC, NSCLC, pancreatic (PC), breast (BC) and gastroesophageal (GE) tumors reveals differences versus primary tumors including in cMET, CDK4, Her2, β-catenin and PD1

\[ \text{IHC-TUBB3} \]

In addition to cMET alterations previously reported to be important in LM, low expression of EGFR, caveolin, TOPO1 and EGFR gene copy number variation (CNV) increase significantly in NSCLC, EGFR and HER2 ISH (5%, 2%, 3%), cMET IHC (56%, 51%, 48%) and APC (71%, 48%, 65%) expression were higher in liver and lung than in other sites.

**Methods:**

Tumors from LD or metastatic sites submitted to Caris Life Sciences for IHC (protein expression), ISH (gene amplification) and NGS sequencing (Molecular Profiling) were included. Tumors for IHC (protein expression), ISH (gene amplification) and NGS sequencing (Molecular Profiling) were included. Tumors for IHC (protein expression), ISH (gene amplification) and NGS sequencing

**Results:**

**Background:**
Liver is the most common metastatic site for various tumors and metastatic sites. A. CRC, B. NSCLC, C. Pancreatic, D. Breast, E. GE cancers

**Figure 1:** Patient characteristics. The table shows patient age and gender distribution, pie charts indicate the composition of local disease (LD), other metastases (OM) or metastases to organs other than liver (LM) studied, labeled with N numbers of each cohort.

**Figure 2:** Selected biomarker frequencies in primary disease (LD), other metastases (OM) and liver metastases (LM) in the five cancer types. Markers included below show a similar change when LM is compared to OM and OM in all or some of the five cancer types investigated.

**Figure 3:** Additional selected biomarker alterations observed in individual cancer types. A. CRC, B. NSCLC, C. Pancreatic, D. Breast, E. GE cancers (An arrow indicates statistically significant difference p<0.05 between LD and LM.)

**Conclusions:**
We investigated a large cohort of more than 38,000 unpaired tumor samples from 5 cancer types and compared the molecular profiles of metastatic sites including liver and the local disease.

In CRC, pancreatic and GE cancers, male prevalence is significantly higher in LM than in LD.

In addition to cMET alterations previously reported to be important in LM, we report here a universal increase of TOPO1 expression in liver and breast, a similar trend for other markers indicative of proliferative and mitotic activity, i.e., TOP2A and TLES, in various cancer types.

PD-1 expression on tumor-infiltrating lymphocytes is significantly decreased in LM, suggesting a change in the microenvironment in LM compared to the local disease.

Targetable molecular alterations seen in LM in individual tumor types warrant investigation in clinical trials. Examples include cMET and BET inhibitors in NSCLC LM, Her2-targeted therapies in CRC LM, CDK4/6 and FGFR inhibitors in breast LM and Wnt pathway inhibitors in GE cancer LM.

While confirmation in patient tumors is needed, the observations made in this large cohort of unpaired samples point to tumor heterogeneity and variation in the tumor microenvironment, which may impact on tumor growth at metastatic sites and direct therapy. The enrichment of potentially actionable targets in LM supports use of fresh biopsies from dominant metastatic site for molecular profiling in order to direct therapy.

**References**