Liver metastases are common in neuroendocrine neoplasms (NEN) and are often treated using locoregional therapies, including transarterial chemoembolization (TACE). While effective in many patients, treatments are rarely selected based on molecular tumor features and clinical outcomes are highly variable. Our study aims to identify urgently needed biomarkers of disease progression and treatment response to improve treatment selection and facilitate the development of new therapies for metastatic NEN.

Past molecular profiling studies of NEN have relied on short-read sequencing, which is well suited for detecting small genetic alterations such as single nucleotide variants but far less sensitive for the detection of larger, structural variants (SVs). As a result, the role of SVs remains poorly understood despite their recognized role as oncogenic drivers. To address this gap, our research employs a combination of optical genome mapping (OGM) and other molecular profiling methods to study a cohort of NEN liver metastases.

Patient Characteristics

We collected biopsy tissue from liver metastases for 30 neuroendocrine cancer patients (11 Female, 19 Male). The anatomic locations of primary tumors included in small bowel (n=12), pancreas (n=8), lung/bronchus (n=5), colon/rectum (n=3) and two cases with unknown primary sites. Biopsies were collected from treated liver tumors at the time of TACE treatment.

In Progress

1. Associating genomic features with clinical outcomes for liver directed therapy
   - We are generating a carefully curated clinical response dataset including measures of local progression following locoregional treatment of liver metastases
   - Testing the association of local treatment response with molecular features uncovered a potential relationship between the number of interchromosomal translocations and treatment response in small bowel NETs

2. Expanding genetic dataset to include additional data types
   - Obtaining single nucleotide variant (SNV) alterations and additional copy number data through targeted sequencing of a panel of genes frequently altered in solid tumors using the Illumina TSO500 assay
   - Examining additional genomic features, such as alternative lengthening of telomeres (ALT) positivity, using targeted assays

3. Validating alterations in known tumor suppressors and biomarkers using orthogonal assays

4. Expanding the patient cohort to include primary tumors, thereby improving the statistical power for associating molecular features with clinical outcomes.

Conclusions

Neuroendocrine neoplasms carry extensive structural variation and exhibit subtype-specific genomic changes
- pNEN liver metastases show high levels of aneuploidy and chromothripsis, while siNETs, colon and rectal NET liver metastases show much lower frequencies of these alterations
- subtype-specific gene loss (eg. DMD, ARID1A) suggests different oncogenic pathways are driven in these subtypes

OGM is a highly sensitive and cost effective approach for genome wide structural variant detection
- While unable to detect small alterations, OGM surpasses traditional sequencing methods by mapping large-scale insertions, deletions, inversions, and translocations.
- Combining OGM with short read sequencing is a highly sensitive approach to whole genome profiling of somatic mutations in cancer, providing a richer and more detailed understanding of the cancer genome's complexity.