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

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Background: Liver is the most common metastatic site for various tumors and associates with poor prognosis. To understand LM as distinct molecularly from other origins such as CRC, NSCLC, BC and GE, we compared a large cohort of LM with local disease (LD) and other metastases (OM).

Methods: Tumors from LD or metastatic sites submitted to Caris Life Sciences for IHC (protein expression), ISH (gene amplification) and NGS sequencing (mutation, MT, CNV) between 2009 and 2015 were studied. A total of 9818 NSCLC (6289 LD, 420 LM, 3109 OM), 3486 PC (1453 LD, 1111 LM, 922 OM), 9739 BC (4413 LD, 1232 LM, 4094 OM), 1656 GE (1456 LD, 200 LM, 3937 OM) and 6368 CRC (4842 LD, 1526 LM, 3069 OM) were included. Tumors (metastases and primary) were not paired. Chi-square tests were used for statistics.

Results: TOPO1 expression (Table) was highest in LM vs OM and LD, $p < 0.01$, suggesting a difference in DNA replication activity. Similar observations were made for TOP2A and TLE3. PD-L1 varied, and PD-1 on TILs was consistently the lowest in LM, and highest in LD ($p < 0.02$). Additionally, in CRC LM, OM and LD, Her2 ISH (5%, 2%, 3%), cMET IHC (56%, 51%, 48%) and APC (71%, 48%, 65%) MT were the highest in LM. In NSCLC, cMET ISH was higher in LM than LD (6.1% vs. 2.2%). MYC mutation was 6% in LM, 0 in OM and LD. In PC, cMET IHC was highest in LM (64%), followed by OM (57%) and LD (48%). In BC, CDK4 CNV was seen in 15% of LM, but not in OM or LD. In GE, CTNNB1 mutation was seen in 8% of LM, 2% in OM and 1% in LD. ($p < 0.05$).

Conclusions: Molecular alterations shared by LM in 5 tumor types may warrant investigation in clinical trials of cMETi, BETi, CDKi, Her2, b-catenin and immune checkpoint inhibitors. Further research into alterations seen in LM may identify molecular drivers responsible for liver metastases. Differences between LM, OM, and LD support use of fresh biopsies from dominant metastatic site for molecular profiling.

%		TOPO1	TOP2A	TLE3	PD-L1	PD-1
NSCLC	LM	76	78	40	19	40
	OM	55	77	40	30	56
	LD	49	61	39	22	63
PC	LM	70	69	42	11	32
	OM	56	53	31	7	29
	LD	35	37	30	5	41
GE	LM	78	91	49	13	43
	OM	59	74	31	8	45
	LD	61	82	34	9	63
CRC	LM	60	86	30	2	35
	OM	53	74	25	3	38
	LD	39	85	26	2	48
BC	LM	79	67	64	4	30
	OM	65	64	53	9	47
	LD	55	57	54	10	52

Results

		Local Diseases (LD)	Other Mets (OM) (Mets to organs other than liver)	Liver Mets (LM)
Average Age	CRC	60.6	58.1	59.3
	NSCLC	67	63.6	64.9
	Pancreatic	63.6	62.5	61
	Breast Cancer	55.4	56.9	56.1
	GE cancers	60.9	59	61
Gender (male %)	CRC	**55%**	**47%**	**58%**
	NSCLC	48%	49%	50%
	Pancreatic	**53%**	**50%**	**59%**
	Breast Cancer	0.86%	1%	0.65%
	GE cancers	**59%**	**67%**	**84%**

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) and liver mets (LM) studied, labeled with N numbers of each cohort.

- In CRC, pancreatic and GE cancers, male prevalence is significantly higher in LM than OM (all p <0.0001)

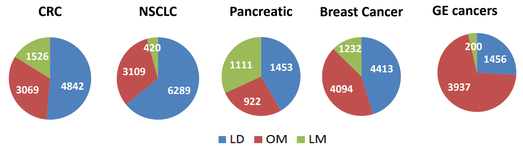
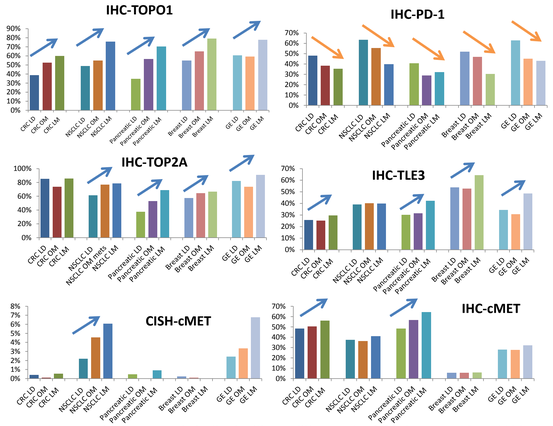


Figure 2: Selected biomarker frequency in local disease (LD), other metastases (OM) and liver metastases (LM) in the five cancer types. Markers included below show a similar change when LM is compared to LD and OM in all or some of the five cancer types investigated.

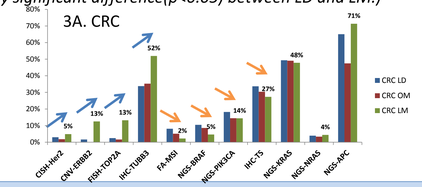


An arrow indicates statistically significant difference(p<0.05) between LD and LM.

Common observations in 5 cancer types:

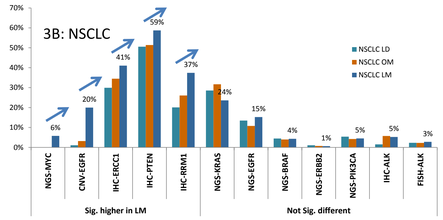
- While TOPO1, TOP2A and TLE3 expression increase significantly in all or most of LM compared to LD, PD-1 expression on TIL's are significantly lower in LM.
- cMET gene amplification (CISH) or protein expression (IHC) increase significantly in NSCLC, CRC and pancreatic cancer LMs, respectively.

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.)*



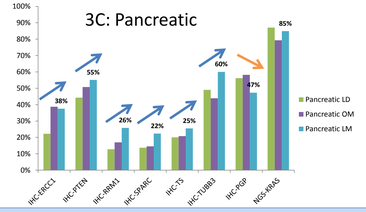
In CRC:

- Her2 amplification tested by CISH and NextGen (gene copy number variation or CNV) as well as TOPO2A amplification tested by FISH are significantly higher in LM compared to LD.
- BRAF and PIK3CA mutation rates and MSI frequency are lower in LM.



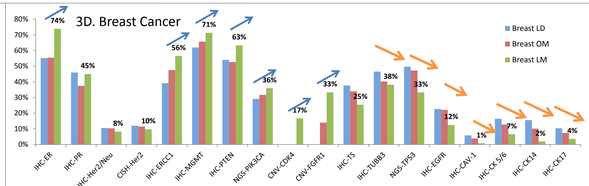
In NSCLC:

- Frequencies of key oncogenic drivers of NSCLC are not different in LM, OM and LD
- Protein expression ERCC1, PTEN and RRM1 expression are significantly higher in LM than LD.
- EGFR gene copy number variation (CNV) increase was seen in 2/10 LM; 2/63 OM and 1/95 LD tested. A MYC mutation (R450fs) was seen in 17 NSCLM LM tested while no MYC mutation was seen any of the 137 LD or 117 OM.



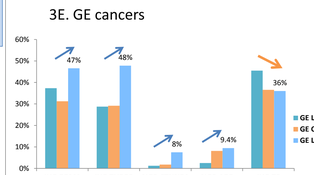
In Pancreatic Cancer:

- Significantly higher expression of IHC markers including ERCC1, RRM1, SPARC and TS are seen in LM while Pgp expression is lower in LM.
- KRAS mutation rate is not significantly different in LD, OM or LM.



In Breast Cancer:

- Mutate rate of PIK3CA and gene copy number increase (CNV) of CDK4 and FGFR1 are significantly higher in the LM than LD.
- Low expression of EGFR, caveolin-1 and cytokeratins are more frequent in the LM.



In GE Cancers:

- Protein expressions of RRM1 and TUBB3, as well as mutation rate of CTNNB1 and APC are significantly higher in the LM.
- Expression of TS is significantly lower in the 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 OM.
- In addition to cMET alterations previously reported to be important in LM development, we report here a universal increase of TOPO1 expression in liver mets, and a similar trend for other markers indicative of proliferative and mitotic activity, i.e., TOPO2A and TLE3, 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 cancer LM and Wnt pathway inhibitors in GE cancer LM.
- While confirmation in paired 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

Roessler., S., XW. Wang, et.al. (2015) "Integrative Genomic and Transcriptomic Characterization of Matched Primary and Metastatic Liver and Colorectal Carcinoma" Int J. Biol Sci 11 (1): 88-98