Molecular abnormalities of 17 types of gastrointestinal cancer in an international cohort of 14,207 patients

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ABSTRACT #11053

Background: Gastrointestinal cancers (GICs) are classified based on both organ and tissue of origin, but might be better classified based on their molecular profile. We performed a multiplatform biomarker analysis of the main 17 types of GICs to identify molecular abnormalities and their associations.
Methods: We analyzed 14,207 cases of GIC (96% from USA) using gene sequencing (up to 44 different genes, Sanger, NGS), protein expression by immunohistochemistry (up to 28 gene products) and gene amplification by CISH or FISH (up to 8 genes). We performed heat map analysis on a select list of molecular anomalies in 17 GIC sites.
Results: Steroid receptor (ER, PR) expression was distinctively high in neuroendocrine cancers (CA) (10-40%) while AR expression was elevated in hepatocellular carcinoma (HCC) (20%). HER2 overexpression and amplification was distinctively elevated in gastric, GEJ, esophageal and gall bladder CA (up to 20%). Overexpression of TOP2a was noted in most of the GICs, reflecting their highly proliferative and aggressive nature. Overexpression of cMET (up to 82%) and EGFR amplification (up to 32%) was noted in a majority of GICs suggesting benefit from cMET and EGFR targeted therapies. HCC had a high frequency of CTNNB1 (19%, 11/58) and low frequency of ABL1 mutation (3%, 2/59). Distribution of APC mutations in GIC ranged from 10-73%. PIK3CA mutation and PTEN loss were frequent events (up to 15% and 89% respectively) in a majority of GIC, suggesting potential benefit of targeting the PI3K pathway. KRAS mutations were more frequent in the lower GI tract. Based on 2 dimensional hierarchical clustering, biomarkers clustered in 2 distinct clusters and tumor types clustered in 3 distinct clusters.
Conclusion: Molecular profiling of GICs might allow us to reconsider clinical trial design and disease management based on individual cancer molecular abnormalities. Protein expression and copy number alterations should be considered together with mutational analysis to refine cancer treatment in GI tract malignancies.

Background

Gastrointestinal cancers are among the most common tumors and represent the leading cause of cancer-related death worldwide (Jemal A, Bray F, Center MM, et al: Global cancer statistics. CA Cancer J Clin 61:69-90, 2011). Better understanding of the molecular determinants of cancer have led to improved therapeutic interventions. However, the fundamental biology of gastric, pancreatic, and biliary tract cancers is unclear and although many of the molecular pathways of colorectal cancer have now been elucidated, few effective targeted agents are available in clinical practice for these diseases. The goal of this study was to determine the molecular aberrations and gene signatures in gastrointestinal cancers in order to identify available treatment options.

Methods

All 14,207 cases referred to Caris Life Sciences between 2009 through April 2014 from 50 states and 59 countries were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing on cancer associated genes was performed per physician request and included a combination of sequencing (Sanger, NGS or pyrosequencing), protein expression (immunohistochemistry), and gene amplification (CISH or FISH). Hierarchical cluster analysis was done using gplots library and the R software (Comprehensive R Archive Network).

Heat map showing % biomarker alterations (sample size range)	ABL1	ALK	APC	ATM	TP53	ERCC1	PDGFRA	c-KIT	CDH1	cMET	cMET	cMET	CSF1R	CTNNB1	FBXW7	FGFR1	FGFR2	FLT3	GNAS	HNF1A	IDH1	JAK2	JAK3	KDR	EGFR	ERBB4	Her2	Her2	Her2	KRAS	NRAS	HRAS	PIK3CA	AKT1	PTEN	PTEN	BRAF	SMAD4	SMARCB1	SMO	STK11	VHL	PTPN11	RB1	RET	MLH1	MPL	NOTCH1	NPM1	RRM1	TOPO1	TS
	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	IHC	ISH	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	IHC	ISH	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	IHC	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	SEQ	IHC	IHC	IHC
Esophageal (120-628)	1	0	13	5	66	33	1	0	0	39	4	1	0	2	2	0	0	0	0	0	0	0	1	1	0	1	12	20	2	3	1	0	3	1	2	33	1	8	0	0	3	0	0	1	0	0	0	0	0	40	64	28
GEJ (10-42)	0	0	12	4	77	30	0	0	0	46	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	4	12	18	0	6	0	0	0	0	0	46	0	0	0	0	0	0	0	0	0	0	0	0	0	39	63	47
Gastric (105-672)	1	0	7	2	44	34	0	0	2	30	2	2	0	2	3	0	2	0	3	2	1	0	3	1	1	0	4	9	1	8	1	0	8	0	3	31	2	3	2	1	2	0	0	1	1	2	0	0	0	35	68	19
Peritoneum (17-169)	0	0	5	0	14	25	0	0	5	56	0	0	0	0	0	0	0	0	5	0	0	0	5	0	0	0	0	0	0	4	0	0	0	0	0	56	0	0	0	0	0	0	0	0	0	0	0	0	0	27	70	12
Biliary, bile (85-486)	0	0	5	0	25	27	0	0	0	49	0	3	0	1	0	0	0	0	0	0	13	0	4	0	1	1	2	5	0	21	3	0	4	0	3	34	3	4	0	0	3	0	0	0	0	1	0	0	0	17	58	12
Gallbladder (27-173)	0	0	11	3	50	30	0	0	0	53	2	3	0	0	0	0	0	0	0	0	0	0	3	3	2	0	8	14	0	12	2	0	3	0	3	33	1	12	0	0	3	0	0	0	0	0	0	0	0	34	57	26
GIST (37-166)	2	0	7	0	0	56	5	72	0	5	0	2	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0	0	0	0	0	0	2	0	0	79	2	0	0	0	0	2	0	4	0	0	0	0	0	24	45	23
HCC (53-287)	3	0	0	3	24	35	0	0	0	27	3	1	0	19	1	0	0	0	0	0	3	0	1	0	0	0	0	3	1	2	1	0	3	0	1	25	0	0	0	2	3	0	1	4	0	0	0	0	0	20	51	12
NET (96-570)	1	0	9	3	9	21	0	1	0	5	2	2	0	0	1	0	1	1	1	0	0	0	1	3	0	0	0	0	0	7	0	0	1	0	1	76	1	0	0	2	1	0	0	3	0	0	0	0	0	12	42	7
Neuro pancreatic (34-191)	0	0	5	0	7	29	0	0	2	4	0	2	0	0	0	0	0	0	0	3	0	0	2	0	0	2	0	0	2	5	2	0	0	2	0	72	1	2	0	0	3	2	0	0	0	0	0	0	0	15	55	9
Pancreatic adeno(383-2349)	0	0	6	3	60	29	0	1	0	59	1	4	0	1	0	0	0	0	2	1	0	0	2	0	1	0	1	5	1	80	0	1	3	0	1	32	1	12	0	0	2	1	0	1	0	1	0	0	0	20	57	11
Duodenum (14-75)	6	0	33	21	39	37	0	0	0	49	0	6	0	6	6	0	0	0	6	0	0	0	0	6	6	0	0	3	11	47	0	0	6	0	11	39	3	33	0	0	6	0	0	0	0	0	0	0	0	31	56	24
Small intestine (24-111)	0	0	10	0	52	30	0	0	0	56	0	0	0	3	6	0	0	0	0	0	3	0	0	0	3	0	0	2	0	47	6	0	5	0	0	33	8	3	0	0	0	0	0	0	0	0	0	0	0	41	52	22
Appendix (75-438)	0	0	12	6	20	46	0	1	0	51	0	2	0	0	6	0	0	0	26	0	0	0	2	0	0	0	0	0	1	52	0	0	6	1	1	38	2	18	0	1	0	0	0	0	0	2	0	0	0	25	64	12
Colon (691-4895)	1	0	60	5	60	26	1	1	0	52	2	2	1	2	6	0	0	0	1	3	1	0	2	1	2	1	2	6	1	45	4	0	15	2	3	26	11	13	0	0	1	0	0	1	0	1	0	0	0	43	57	14
Rectal cancer (139-892)	0	0	61	3	68	29	1	0	1	51	2	3	0	1	6	0	0	0	0	0	2	0	1	1	1	1	2	7	1	44	5	0	11	1	1	22	3	8	0	0	3	0	0	0	0	1	0	0	0	41	59	16
Anal cancer (32-179)	2	0	5	0	7	50	0	0	0	19	0	2	0	0	6	0	0	0	0	0	0	0	7	0	0	2	0	2	2	3	0	0	30	2	3	46	0	2	0	0	0	2	0	0	0	0	0	0	0	59	66	34

Figure 1: Heat map of % biomarker alterations across 17 gastrointestinal cancer types. The color coding scheme goes from gray representing no alteration to shades of red representing increasing biomarker alterations.

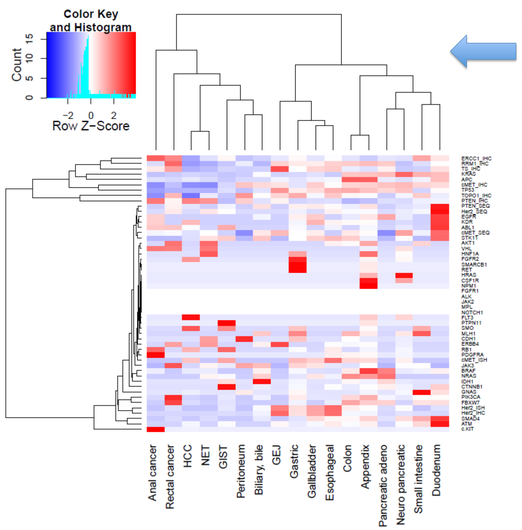
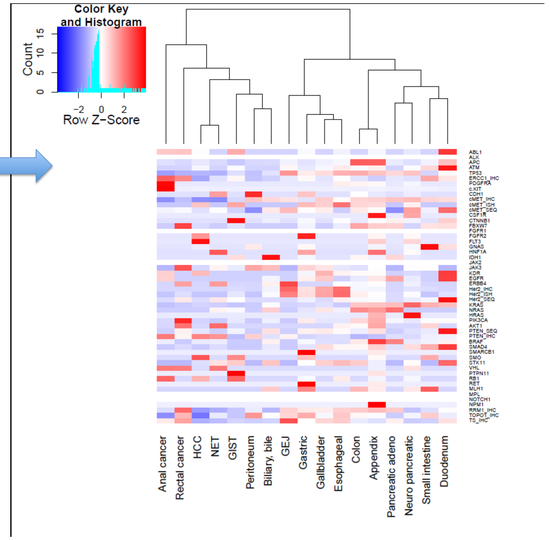


Figure 2a: 2-dimensional hierarchical clustering of biomarkers and lineages showing 3 clusters for tumor types and 2 clusters for biomarkers
Figure 2b: 1-dimensional hierarchical clustering showing 3 distinct clusters for tumor types.
Cluster 1. Anal, rectal, HCC, NET, GIST, peritoneal and biliary cancers
Cluster 2. GEJ, gastric, gallbladder and esophageal cancers
Cluster 3. Colon, appendix, pancreatic adenocarcinoma, pancreatic neuroendocrine tumor, small intestine and duodenal cancers



Conclusions

- Every tumor type in the gastrointestinal system has biomarker alterations that may predict sensitivity to conventional as well as targeted therapies
- Cluster analysis showed 3 distinct tumor type clusters based on biomarker distribution
- CMET over expression is present across all gastrointestinal tumors with lower expression in GIST, NET and pancreatic neuroendocrine tumors . This did not correlate with cMET amplification or gene mutation. cMET inhibitors may be beneficial in a majority of gastrointestinal tumors
- Presence of cKIT mutations are limited to GIST tumors and p53 mutations are absent in GIST
- Presence of CTNNB1 mutations are limited to HCC indicating potential benefit from Wnt pathway inhibitors
- Her2 overexpression and amplification are present in esophageal, GEJ, gastric and gallbladder cancers suggesting potential benefit from Her2 targeted therapies. These results did not correlate with Her2 mutation.
- The majority of KRAS mutations were found in lower GI tract cancers indicating lack of benefit from EGFR antibody therapy.
- Activation of PI3K pathway (PTEN loss of expression/ PIK3CA mutation) was found in a majority of gastrointestinal cancer types suggesting potential benefit with agents targeting this pathway.
- Expression pattern of ERCC1, RRM1, TOPO1 and TS could indicate cancer types which may benefit from platinum, gemcitabine, irinotecan/topotecan and fluoropyrimidines.

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