MOLECULAR CHARACTERIZATION OF EARLY VS. LATE ONSET GASTROESOPHAGEAL CANCER

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Introduction

- Gastroesophageal cancer is thought to be the result of both environmental exposures and an accumulation of molecular changes over time, causing genetic instability.[1]
- The majority of gastroesophageal cancer patients are over the age of 45 Over the past several decades, however, an increasing number of cases are being diagnosed in younger individuals. [2,3,4,5,6]
- In patients with early onset gastroesophageal cancer, the relative influence of genetics on the development of gastroesophageal cancer is presumed to be greater than that of the environment. Therefore, this set of patients is considered unique from those who develop sporadic cancer at a later age. [1]
- If this is the case, early onset gastroesophageal cancer may pave the path toward a better understanding of the molecular genetic pathways involved in gastroesophageal carcinogenesis.

Objective

- To investigate whether early onset gastroesophageal adenocarcinoma is a distinct molecular entity from sporadic gastroesophageal adenocarcinoma occurring in the older population.
- To identify the tumor molecular variations that may define individual differences in age of onset of gastroesophageal adenocarcinoma.

Methods

- Molecular profiles of 1,154 tumors from patients <45 yrs old (n=197) and patients >60 yrs old (n=957) were compared to each other.
- Protein expression (Immunohistochemistry), gene amplification (In Situ Hybridization), and next generation sequencing were tested on gastric and esophageal tumors.
- Chi-square test was used for comparative analysis
- Gastroesophageal, gastric, and esophageal tumors were analyzed separately, with analysis of primary and metastatic tumor subgroups.

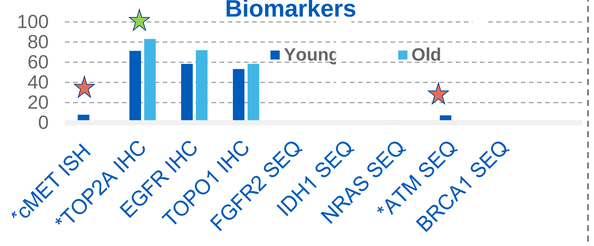
Results: Gastroesophageal

A

Biomarker	Young	Old	P-value
cMET ISH	6	2	**0.048**
TOPO2A IHC	72	82	**0.003**
EGFR IHC	56	74	**0.015**
TOPO1 IHC	56	60	ns
FGFR2 SEQ	1.4	0	**0.02**
IDH1 SEQ	1.4	0	**0.026**
NRAS SEQ	1.4	1.4	ns
ATM SEQ	4.3	1.4	ns
BRCA1 SEQ	3	1	ns

- Percent of biomarker aberrations in young and old. TOPO2A and EGFR are more common in old. cMET, FGFR2, and IDH1 are more common in young

B



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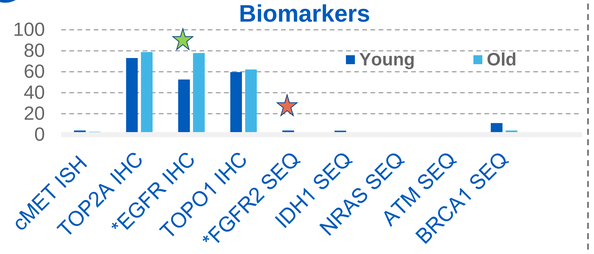


- cMET amplification is more frequent in the young than in the old in combined gastroesophageal, primary gastroesophageal, and primary esophageal tumors.
- Overexpression of TOPO2A is more frequent in the old than in the young in combined gastroesophageal, primary gastroesophageal, and combined gastric tumors.
- EGFR expression is also more frequent in the old than in the young for combined gastroesophageal, metastatic gastroesophageal, and combined esophageal tumors.

More common in YOUNG More common in OLD

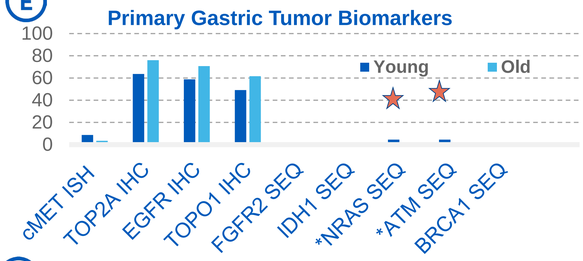
Results: Gastric

D

Biomarker	Young	Old	P-value
cMET ISH	7	2	ns
TOPO2A IHC	65	78	**0.009**
EGFR IHC	61	73	ns
TOPO1 IHC	52	63	**0.04**
FGFR2 SEQ	2.3	0	**0.048**
IDH1 SEQ	2.3	0	**0.049**
NRAS SEQ	2.3	0	**0.047**
ATM SEQ	2.3	1.8	ns
BRCA1 SEQ	0	2	ns

- Percent of biomarker aberrations in young and old. TOPO2A and TOPO1 are more common in old. FGFR2, IDH1, and NRAS are more common in young

E



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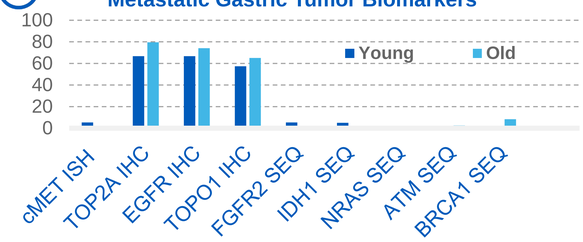


Results: Esophageal

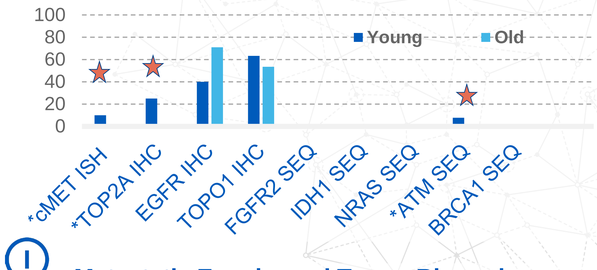
G

Biomarker	Young	Old	P-value
cMET ISH	6	1	**0.06**
TOPO2A IHC	88	86	ns
EGFR IHC	39	75	**0.007**
TOPO1 IHC	63	56	ns
FGFR2 SEQ	0	0	ns
IDH1 SEQ	0	0	ns
NRAS SEQ	0	2.8	ns
ATM SEQ	5	0	**0.009**
BRCA1 SEQ	17	0	**0.02**

- Percent of biomarker aberrations in young and old. EGFR is more common in old. cMET, ATM, and BRCA1 are more common in young.

- FGR2 and IDH1 mutations are more frequent in the young in combined gastroesophageal and combined gastric tumors.
- ATM is more frequent in the young in combined esophageal and primary gastroesophageal tumors.
- BRCA1 mutation is more frequent in the young in combined esophageal tumors.

H



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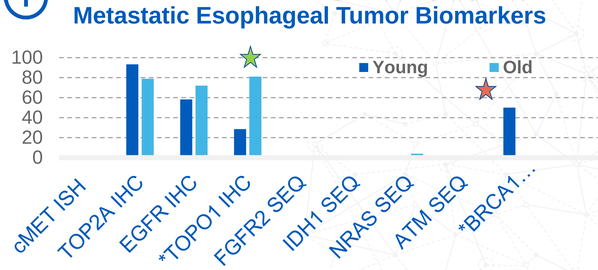

Conclusion

- The molecular profile of gastroesophageal cancer in young patients is unique from that of older patients, suggesting that it may represent a distinct entity in gastroesophageal carcinogenesis.
- The prevalence of aberrations in the young like cMET amplification, FGFR2, IDH1 and BRCA1 mutations may indicate therapeutic targets in young patients.

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