# Esophagogastric

Getting esophagogastric patients on the right treatment, faster.

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*The incidence of esophagogastric cancer is rapidly rising, but only a minority of patients derive durable benefit from current therapies.* CIRCULOGENE'S *comprehensive ctDNA panel is a noninvasive technique that can be combined with traditional tissue biopsy to track cell-free DNA and detect disease biomarkers in blood faster and more accurately.*

## Cancer Discov.

2018 Jan;8(1):49-58. DOI: 10.1158/2159-8290.CD-17-0787.

### Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer

**Patients with microsatellite instability-high tumors were intrinsically resistant to chemotherapy but more likely to achieve durable response to immunotherapy.** In total, 53% of patients had at least one potentially actionable alteration…Patients with MSI-H tumors suffered rapid disease progression on standard cytotoxic therapy, with a significantly shorter PFS on first-line chemotherapy when compared to non-MSI-H tumors. **Overall, higher tumor mutational burden was associated with better outcome on immunotherapy.**

The data presented here suggest that **immunotherapy should be considered in patients with MSI-H esophagogastric cancer early in their disease course**, as such patients are unlikely to respond to cytotoxic chemotherapy. Given the limited material available for genomic profiling and the high degree of genomic heterogeneity present in esophagogastric tumors, a multiplex approach to the detection of multiple known biomarkers of response—possibly using tumor-derived, cell-free DNA as input—will be needed to realize the promise of precision medicine in patients with this aggressive and often fatal disease.

## Cancer Discov.

2019;9:1656–72. DOI: 10.1158/2159-8290.CD-19-0487

### Genomics and Targeted Therapies in Gastroesophageal Adenocarcinoma

The breadth of interlesion tumor heterogeneity within an individual patient means that biopsy of a single lesion incompletely represents the clinically relevant genomic composition of a patient's cancer burden.

To bypass the impracticality of taking multiple tissue biopsies, including synchronous primary and metastatic biopsies, emerging data suggest the clear potential of minimally invasive liquid biopsies for the isolation and sequencing of cell-free circulating tumor DNA (ctDNA) in peripheral blood.

- Biomarker concordance between metastases and ctDNA surpasses correlation between metastases and primary tumor
- ctDNA may complement traditional tissue-based genomic profiling to guide treatment in the metastatic setting
- ctDNA may be sampled longitudinally during the course of treatment to trace the evolution of clonal heterogeneity, including identifying drivers of intrinsic and acquired resistance.
- "Single target, single drug" rationale has proved too simplistic for gastroesophageal adenocarcinoma (GEA) because of intrinsic genomic instability and heterogeneity of this disease
- Comprehensive and repeated molecular profiling will be integral to patient and treatment selection

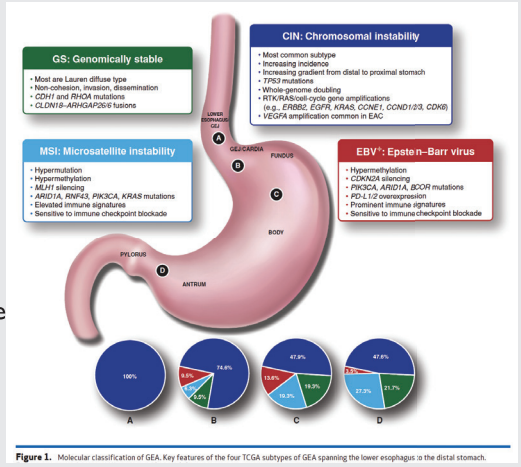



**Figure 1.** Molecular classification of GEA. Key features of the four TCGA subtypes of GEA spanning the lower esophagus to the distal stomach.

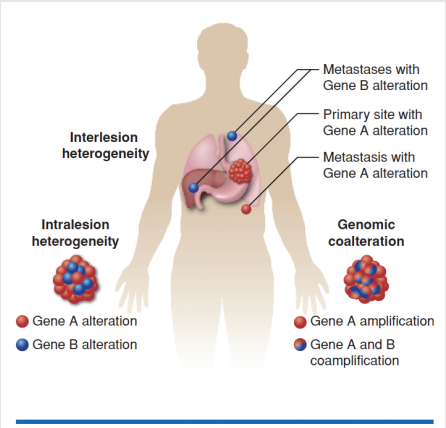



**Figure 2.** Types of genomic heterogeneity in GEA.

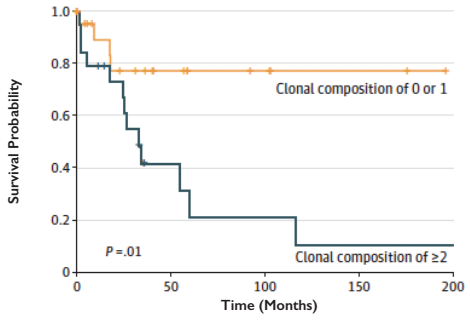
## JAMA Netw Open

2020;3(4):e203652. DOI:10.1001/jamanetworkopen.2020.3652

### Association Between Spatial Heterogeneity Within Nonmetastatic Gastroesophageal Adenocarcinomas and Survival

Precision medicine efforts in GEA have been hampered by the recognition that intratumoral heterogeneity confounds results of genomic testing yielded from limited sampling of the tumor. Pancancer TCGA studies have also deciphered intratumoral heterogeneity from whole-exome sequencing data, with worse survival observed in patients with higher heterogeneity.

**Figure 1. Kaplan-Meier Analysis of Survival in the Study Patient Population**




No. at risk

| | | | | | |
|---|---|---|---|---|---|
| Clonal composition of 0 or 1 | 22 | 8 | 4 | 2 | 0 |
| Clonal composition of ≥ 2 | 19 | 4 | 2 | 1 | 1 |

**Data are stratified based on clonal composition count.**

Esophagogastric Case Study

# CIRCULOGENE Molecular Tumor Board—Esophageal Ca MSI-H

## 75-Year-Old Male

## LOCALLY ADVANCED EUS T3N1/STAGE III MSI-H GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMA

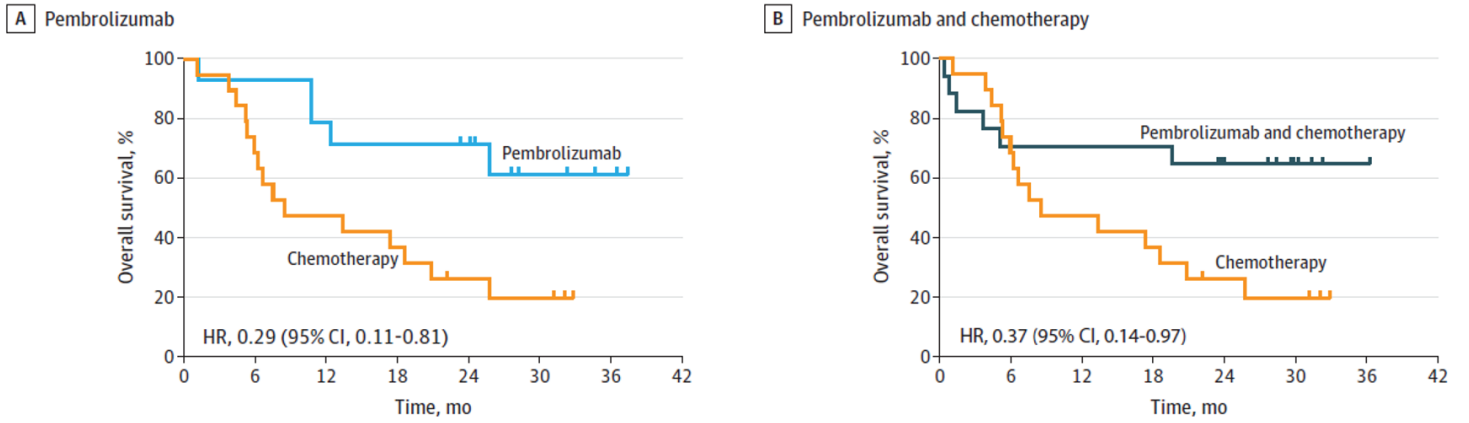
**So many tests we order in oncology guide us to what we should do. Sometimes the same results guide us to what not to do. The liquid biopsy MSI-H finding in this case is exactly that. A simple result, but forcing complexity in the therapeutic decision making.**

In this disease presentation, there will be insufficient tumor and normal tissue for MSI testing. Without that information, the standard treatment would be concurrent chemo-radiation therapy (CRT) and then a considered post-CRT surgical resection. However, MSI-H cancers need to be known because they need to be treated differently.

Knowing the MSI-H tumor biology is knowing how the tumor biology should best be treated. In the MAGIC trial of perioperative chemotherapy, patients with MSI-H GEJ cancers had no benefit and in fact had a marked detriment in outcome with cytotoxic chemotherapy. Surgery alone achieved a 70% 2-year OS, whereas if perioperative chemotherapy was given, that 2-year OS was under 20%! The approach of perioperative chemotherapy alone is a clear signal of a wrong therapeutic multi-modality approach. Immune checkpoint blockade is superior to chemotherapy in up-front metastatic colorectal cancers and all MSI-H cancers. Even in KEYNOTE-062, the addition of chemotherapy to first-line pembrolizumab/anti-PD-1 therapy in the metastatic MSI-H GEJ/gastric subset of patients resulted in an early 20% drop in OS that did not occur with pembrolizumab alone. The three-year OS was far superior in the anti-PD-1-treated MSI-H patients than chemotherapy. There is, however, a preserved therapeutic benefit of RT in MSI-H cancers. Studies are ongoing of immune checkpoint blockade concurrent with radiation therapy in MSI-H GEJ cancers but with no definitive data yet.

| IMMUNOTHERAPY TEST RESULTS | FDA GUIDANCE |
|---|---|
| PD-L1 EXPRESSION | Negative |
| MSI-H | Detected |

Figure 3. Overall Survival in Patients With MSI-H Tumors and PD-L1 CPS of 1 or Greater




The best curative outcomes in GEJ cancers occur with multi-modality therapy. An important treatment distinction is the needed compartmental treatments. Given what data we have, a standard neoadjuvant concurrent CRT approach is reasonable. However, the chemotherapy would only be for maximal radiation sensitization. Systemic therapy would still be a compartmental need not achieved by chemotherapy. Immune checkpoint blockade is the best survival outcome treatment in MSI-H GEJ cancers and would be the best systemic compartment treatment. If surgery after CRT is not undertaken or if there is any residual cancer after surgery, immune checkpoint blockade should be given to optimally treat this MSI-H immune responsive cancer. The option of neoadjuvant immune-radiation therapy is still unknown therapeutic territory at this time but is very intriguing.

Knowing the tumor biology illuminates how the tumor biology can best be treated to change the destiny of the tumor biology. A liquid biopsy for plasma NGS and MSI testing makes sure the tumor biology is not missed. This represents precision oncology guiding personalized cancer treatment for patients.

Case Study Prepared by Doctor Paul Walker
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Sources:
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- JAMA Oncol. 2020;6(10):1571-1580., DOI:10.1001/jamaoncol.2020.3370
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