Gastric Cancer:
Biology, Genetics, & Surgery

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Outline

- What is gastric cancer
- Risk factors
- Diagnosis & Pathology
- Treatment
- Hereditary causes

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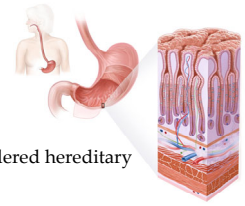
Gastric Cancer

- Gastric Cancer → Adenocarcinoma
  - Arises from the epithelial lining of the stomach
- 1 million cases/yr, worldwide
  - 4th leading cause of cancer death
- 27,000 cases per year in the U.S.
  - Overall, 5-year survival is 32%
- 1-3% of gastric cancers are considered hereditary



seer.cancer.gov

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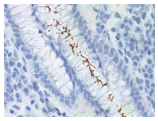
Risk Factors for Gastric Cancer

- Environmental risk factors
  - Helicobacter pylori infection
  - Diets rich in nitrites
    - preserved foods; cured meats high in salt content
  - Tobacco use
  - Radiation – *such as radiation therapy for a lymphoma*



- Other risk factors
  - Intestinal metaplasia due to chronic gastritis
  - Pernicious anemia (autoimmune)

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Symptoms of Gastric Cancer

- Symptoms are often vague
  - Epigastric pain (dull stomachache)
  - Fullness after eating (early satiety)
  - Anemia
- Concerning (late) symptoms
  - Unintentional weight loss
  - Difficulty swallowing
  - Vomiting after meals

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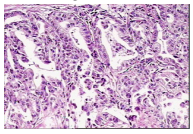
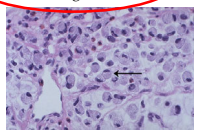
Histopathology of Gastric Cancer

Intestinal type	**Diffuse type**
Usually mass-forming, fungating	Diffuse thickening, signet ring cells
Distal stomach	Proximal stomach
H. Pylori, atrophic gastritis	Genetic predisposition
Older age	Younger age
Decreasing incidence	Increasing incidence





Laurén P. *Acta Pathol Microbiol Scand* 1965;64:31-49

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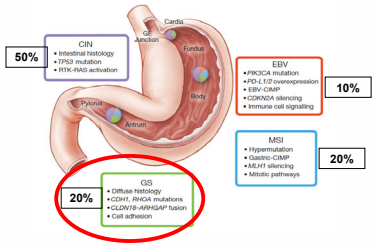
Gastric Cancer

Molecular Subtypes of Gastric Cancer



Cancer Genome Atlas Research Network. *Nature* 2014;513(7517):202-9

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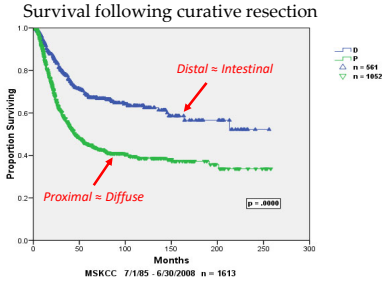
Gastric Cancer

Outcomes based on Histology

Survival following curative resection



Courtesy, Prof Sir Murray Brennan, MD FACS

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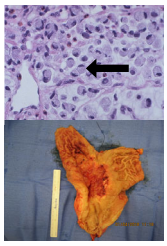
Gastric Cancer

Diffuse-type Gastric Cancer

- Diffuse stomach involvement
- Signet ring cells
- Increasing incidence
- Younger age of onset
- Rarely overexpresses HER2 *(~6%)*
- Infrequently MSI-hi, PDL1+
- Common genetic changes:
  - ✓cell adhesion pathways (e.g. *CDH1)*



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Clinical Scenario

60 year old man with family history of colon cancer

- Anemia on routine blood tests

- Colonoscopy – no polyps or cancer
- EGD - mass with mucosal erosions in the stomach
- Biopsy = poorly differentiated adenocarcinoma

What's next:

- CT scan shows no evidence of metastatic disease
- PET scan shows no evidence of distant metastasis
- Shows prominent lymph nodes just around the stomach
- Is clinical staging complete?

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Laparoscopy

- Detects peritoneal metastases too small to be seen on CT
  - Approximately 1 in 5 patients will have carcinomatosis
- Peritoneal lavage can detect microscopic peritoneal cancer
  - 10-14% of patients undergoing laparoscopy will have microscopic metastasis
- Laparoscopy avoids unnecessary surgery in ⅓ of patients
  - Accurate staging (> 90%)
  - Appropriately select patients for systemic therapy

Burke et al. *Ann Surg* 1997;225:262-7.
Lowy et al. *Surgery* 1996;119:611-4.
Bentrem et al. *Ann Surg Oncol* 2005;12(5):1-7.
Ikoma et al. Ann Surg Oncol 2016;23:4332-37.

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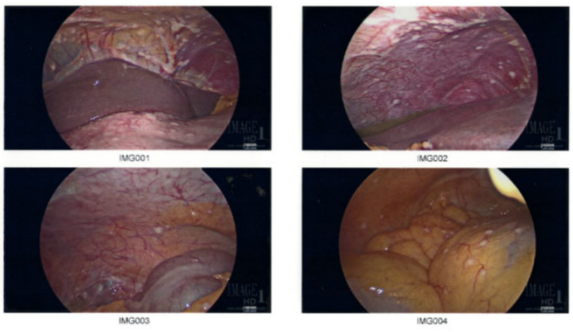
Laparoscopy for Gastric Cancer



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Treatment of Gastric Cancer

Treatment based on clinical stage

- **Early stage** (Stage I)
- **Middle stage** (Stage II – III)
- **Late stage** (Stage IV)

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Treatment of Gastric Cancer

Treatment based on clinical stage

- **Early stage** (Stage I) – often treated with surgery only
- **Middle stage** (Stage II – III)
  – combination chemotherapy, surgery, +/- radiation
- **Late stage** (Stage IV)
  – systemic therapy
  - surgery may be used for palliation of bleeding/obstruction

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Clinical Scenario

60 year old man with gastric cancer

- Clinical stage is T3N+
- Staging laparoscopy negative; peritoneal cytology negative
- Neoadjuvant chemotherapy with FLOT regimen

- Surgery: Subtotal gastrectomy → ypT3N3b
- HER2 negative *(IHC)*
- PDL1 negative
- Molecular path: *ARID1A, TSC2, MSH6* (VAF 46%)
  - MSH6 germline mutation → Lynch Syndrome
- Follow up: peritoneal tumor recurrence at 9 months after operation

Al-Batran et al. Lancet 2019

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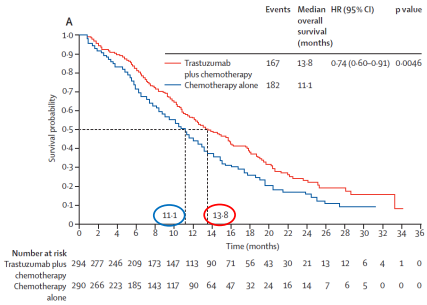
HER2 targeted therapy



Bang et al. *Lancet* 2010;376:687-697.

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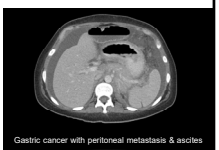
Challenges in Gastric Cancer

Clinical dilemmas:

- Diagnosis at an advanced stage is common
- Frequent metastasis to peritoneal cavity
- Treatment of advanced cancer is not curative



Barriers to studying gastric cancer:

- Gastric cancer is not common in U.S.
  - Especially early-stage gastric cancer
- Access to patients and biospecimens for research are scarce

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Challenges in Gastric Cancer

Clinical dilemmas:

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Gastric cancer with peritoneal metastasis & ascites

Barriers to studying gastric cancer:

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Gastric Cancer

Peritoneal Carcinomatosis

- Peritoneal metastasis present in ~ 30% of patients at diagnosis
- Peritoneal recurrence rate is ~40% after curative surgery
- Targeted therapy for metastatic gastric cancer is limited
  - ~22% of gastric adenocarcinomas overexpress HER2* (ToGA trial)
    … ***only*** 6% of diffuse type gastric cancers are HER2+
  - **Rare** PD-L1 expression in diffuse-type cancers**

*HER2 → *trastuzumab*
**PD-L1 → *pembrolizumab*

Bang et al. *Lancet* 2010;376:687-97.

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Gastric cancer

HIPEC & Gastrectomy for Cancer

Phase II study to determine the efficacy of gastrectomy and heated intraperitoneal chemotherapy (HIPEC) for gastric cancer with limited peritoneal metastasis **[17C0070]**

- **Eligibility**
  - Adenocarcinoma of the stomach
  - + Cytology and/or limited peritoneal metastasis (PCI ≤ 10)
- **Primary endpoint:** Overall Survival
- **Secondary endpoints:**
  - Intra-peritoneal PFS
  - Distant disease-free survival
  - Treatment-related morbidity

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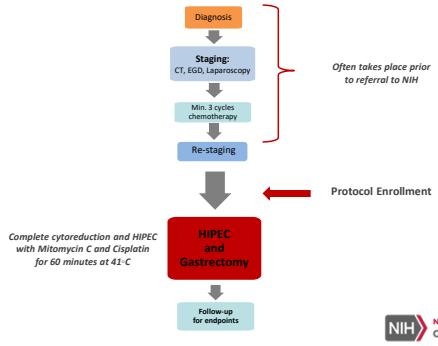
HIPEC & Gastrectomy for Cancer



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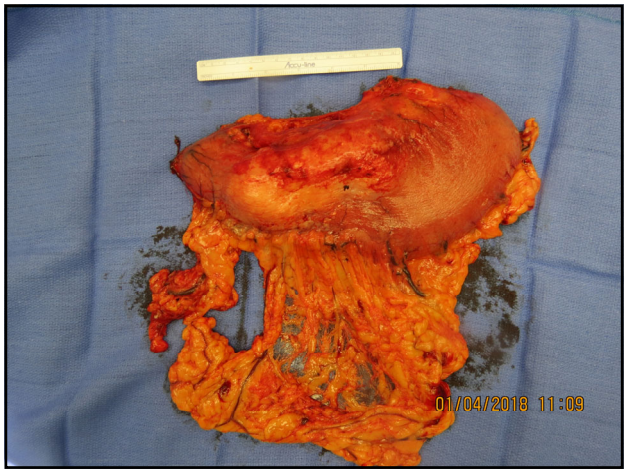

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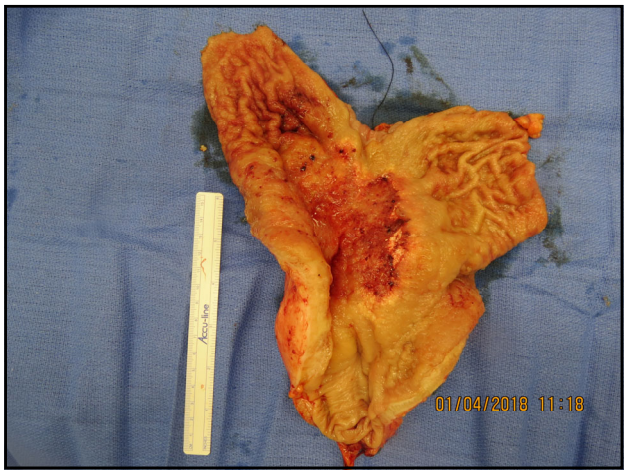

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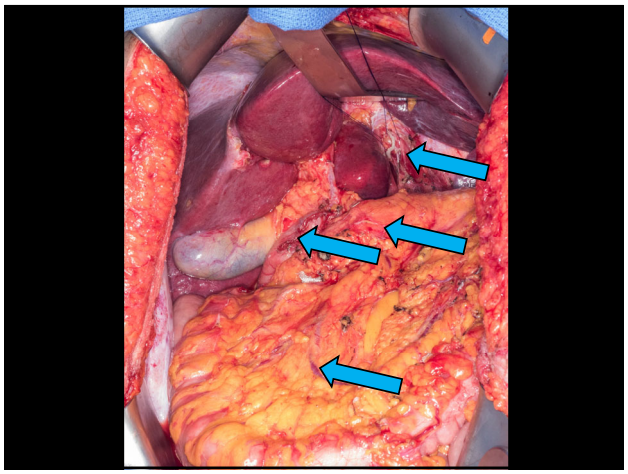

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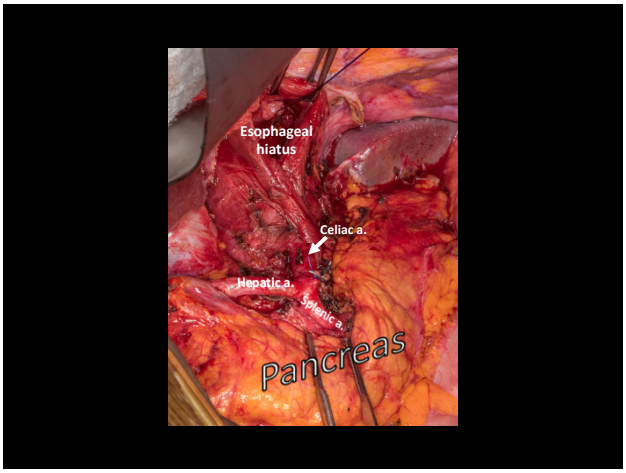

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Gastric Cancer

Summary Part I

Gastric cancer is particularly aggressive and difficult to treat, especially diffuse-type

Some gastric cancers have hereditary causes

Gastric cancer frequently spreads to the peritoneal cavity

Staging laparoscopy is integral to diagnosis and staging

Peritoneal-directed therapy is not standard, but is being investigated

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Gastric cancer

Gastric Cancer Syndromes

Syndrome	Associated gene mutations	Lifetime gastric cancer risk	Notes
Hereditary Diffuse Gastric Cancer (HDGC)	*CDH1* (~40%)	25-42%	Breast cancer risk 42-55%
Gastric Adenocarcinoma & Proximal Polyposis (GAPPS)	*APC* promoter 1B	-	Intestinal type
Familial intestinal gastric cancer	Unknown	-	Intestinal type cancer in absence of polyposis
Familial adenomatous polyposis	*APC*	≤ 2%	
Juvenile polyposis syndrome	*SMAD4, BMPR1A*	-	
Lynch syndrome	*MLH1, MSH2*	5% - *MLH1* 9% - *MSH2*	Intestinal type
Li-Fraumeni syndrome	*TP53*	5%	
Peutz-Jeghers syndrome	*STK11*	2-3%	

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Hereditary Gastric Cancer

GAPPS

- Autosomal dominant polyposis syndrome
- Pathogenic mutation in *APC* gene promoter
- Carpeting of fundic gland polyps in proximal stomach with antral sparing
  - >100 polyps carpeting the proximal stomach
  - Predominantly fundic gland polyps with associated dysplasia
  - May also have infrequent colon polyps
- Polyposis observed in patients as young as 12 years old

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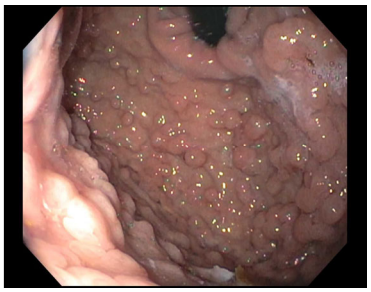
Hereditary Gastric Cancer

GAPPS



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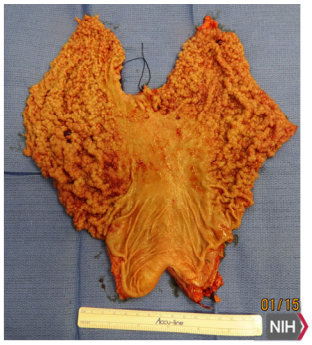
GAPPS



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Familial adenomatous polyposis	*APC*	≤ 2%	
Juvenile polyposis syndrome	*SMAD4, BMPR1A*	-	
Lynch syndrome	*MLH1, MSH2*	8% - *MLH1* 9% - *MSH2*	Intestinal type
Li-Fraumeni syndrome	*TP53*	5%	
Peutz-Jeghers syndrome	*STK11*	2-3%	

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Hereditary Diffuse Gastric Cancer (HDGC)

HDGC – syndrome linked to ↑ gastric and lobular breast cancer risk
- Lifetime risk of gastric cancer = 25-42%

Variants (mutations) in the ***CDH1*** gene are common cause
- Autosomal dominant pattern of inheritance
- 150+ different pathogenic *CDH1* variants reported

The risk of stomach cancer is high, and gastric cancer screening is not considered effective
- Therefore, removal of the entire stomach (total gastrectomy) is recommended

Blair et al. *Lancet Oncol* 2020
Roberts et al. *JAMA Oncol* 2019
Benusiglio et al. *Gastric Cancer* 2019
Xicola et al. *J Med Genet* 2019

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Guidelines for Genetic Testing

***CDH1* testing** is recommended when one of the following criteria have been met (and cancer diagnoses are confirmed):

Family criteria
- ≥2 cases of gastric cancer in family (any age); at least one is DGC
- ≥1 case of DGC in family (any age) and ≥1 case of LBC < 70 years
- ≥2 cases of LBC in family < 50 years

Individual criteria
- DGC at age <50 years
- DGC at any age in patient with cleft lip/palate (or in a 1st degree relative)
- Personal history of DGC and LBC at age <70 years
- Personal history of bilateral LBC at age <70 years

*Intestinal-type gastric cancers and non-lobular breast cancers should **not** be used to fulfill these genetic testing criteria

Blair VR et al. *Lancet Oncol* 2020;21(8):e386-397.

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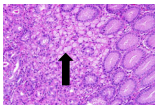
Hereditary Gastric Cancer Cohort

Observations from our natural history study *(est. 2017)*
- 500+ patients, 130+ kindreds

Data from prophylactic surgery and surveillance endoscopy

125+ prophylactic total gastrectomies for *CDH1*
- All asymptomatic patients, normal pre-op EGD
- 95% have early-stage gastric cancer (signet ring cells, SRCs)
- Most common are microscopic cancer cell clusters



Surveillance: endoscopy with random gastric biopsies
- SRCs found in patients ranging in age from 18 to 75
- Many patients under surveillance for several years

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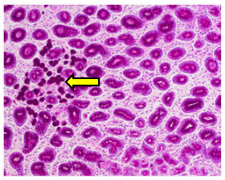
Is Surveillance a Viable Option?

Existing belief: cancer surveillance in HDGC is *not* safe or reliable
- Infiltrative tumors (not mass-forming), subtle endoscopic findings

Nearly all *CDH1* mutation carriers have early cancers in their stomachs

Therefore, we believe that cancer surveillance is less about detection, and more about prognosis

That is:
- **Will these cancer cells ever progress?**



Cancer cells not visible on EGD because they lay beneath the epithelium

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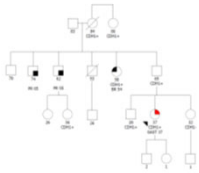
Gastric Cancer

Clinical Scenario #2

37 yr-old woman with family history of breast cancer

- Cancer gene panel testing ➔ pathogenic variant in CDH1 (c.1137+2T>C)
- No family history of gastric cancer



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Gastric Cancer

Uniqueness of Gastric Cancers due to CDH1

Things we know to be true

- Patients carry the *CDH1* mutation from birth – *thus the risk of cancer is present at early age*
- We routinely find early cancers in asymptomatic patients from their teens to old age
- Unlike the aggressive nature of advanced gastric cancer, these early cancers seem able to remain dormant for a lifetime

Why this is important?

- How these cancer cells remain dormant (or decide to grow) may provide a key to developing cancer prevention strategies
- How/Why these cancer cells ultimately metastasize to other parts of the body may help us understand the process of peritoneal cancer dissemination
  * This includes lobular breast cancer, which can metastasize to peritoneum also

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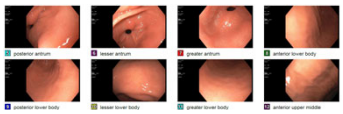
Gastric Cancer

Clinical Scenario #2

37 yr-old woman undergoes endoscopic surveillance

- Endoscopy shows normal gastric mucosa
- Random biopsy reveals a microscopic focus of invasive carcinoma

- She is unsure if she should undergo total gastrectomy
  - What is the influence of her family history on gastric cancer risk?
  - Can she safely undergo cancer surveillance?



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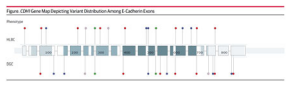
Gastric Cancer

CDH1 variants increase gastric cancer risk irrespective of family history

- Study of 283 patients with *CDH1* gene variants from our natural history cohort
- Analysis of patients with no family history of gastric cancer
- Some patients chose prophylactic gastrectomy due to ↑gastric cancer risk
- **94%** had early-stage gastric cancer on final pathology – despite no family history
- No explanation why some *CDH1* families do not develop advanced stomach cancer



Gamble et al. *JAMA Surg* 2021.

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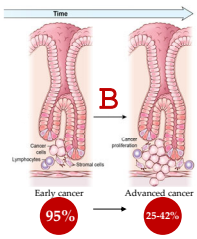
Our Research Question



Gamble, Heller, Davis. *JAMA Surg* 2021
Xicola et al. *J Med Genet* 2019; Roberts et al. *JAMA Oncol* 2019

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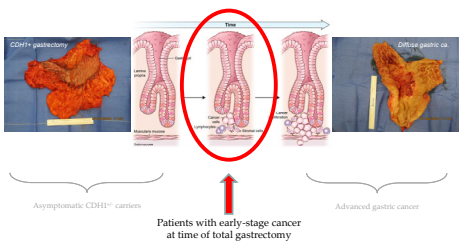
Gastric Cancer

Research on the Spectrum of Disease



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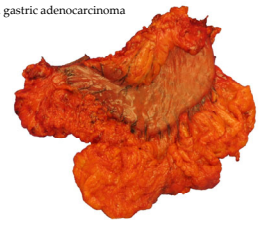
Gastric Cancer

Clinical Scenario #2 – Outcome

37 yr-old woman undergoes prophylactic total gastrectomy

- Multiple, microscopic foci of intramucosal signet ring cell carcinomas (pT1a)
- No lymph node metastases
- Diagnosis: Stage Ia gastric adenocarcinoma



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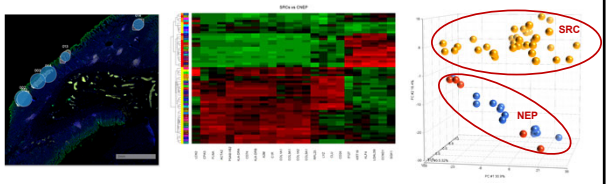
Tumor Microenvironment

Early stomach cancers and their microenvironment may hold clues

- Gastric tissue with SRCs from *CDH1* patients underwent spatial gene expression analysis
- SRCs distinguished from fibroblasts and infiltrating immune cells
- Pathway analysis: upregulated immune signaling in SRCs compared to normal mucosa



Gamble/Neckers, *unpublished*

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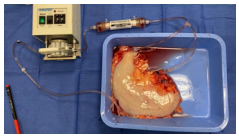
Gastric Cancer

Human Tissue Model of Diffuse Gastric Cancer

Patients undergo total gastrectomy for *CDH1*

- In the OR, we remove the stomach & immediately cannulate the gastroepiploic and gastric arteries
- Oxygenated perfusion of the stomach using patient's own plasma at 4˚C
- Multiple stomachs with biopsies at 24-72hr show no autolysis or tissue architecture loss



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Gastric Cancer

Summary Part II

Germline *CDH1* mutations significantly increase lifetime risk of gastric cancer

Nearly all patients with CDH1 mutations have early cancer in their stomachs

These early-stage cancers have a unique immunosuppressive microenvironment

The human stomach from CDH1 patients may help us understand the origins of diffuse-type stomach cancer

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Gastric Cancer

Conclusions

Diffuse-type gastric cancer is aggressive and its causes are not well understood

CDH1 mutation carriers harbor early-stage gastric cancers *(almost universally)*

We don't know why patients with *CDH1* will/won't develop advanced cancer

The earliest gastric cancers appear to elicit a unique immune response

We are studying diffuse-type gastric cancers using novel human tissue models

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Gastric Cancer

Thank You

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