



**Brigham and Women's Hospital**  
Founding Member, Mass General Brigham

# **Gastrointestinal Cancers**

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  - Clinical focus: Gastrointestinal Cancers
  - Research focus: Esophagogastric Cancers

# DISCLOSURES

- I have no financial disclosures

# OBJECTIVES

- Review the epidemiology of:
  - Gastric cancer
  - Esophageal cancer
  - Colorectal cancer
  - Pancreatic cancer
- Use case vignettes to discuss the workup and management of patients with these gastrointestinal cancers

# ANNUAL INCIDENCE AND MORTALITY

|                    | <u>United States (2025)</u><br><small>Siegel et al. <i>CA Cancer J Clin.</i> 2025</small> |                | <u>Worldwide (2022)</u><br><small>Bray et al. <i>CA Cancer J Clin.</i> 2024</small> |                  |
|--------------------|-------------------------------------------------------------------------------------------|----------------|-------------------------------------------------------------------------------------|------------------|
|                    | New Cases                                                                                 | Deaths         | New Cases                                                                           | Deaths           |
| <b>GI Cancers:</b> | <b>362,200</b>                                                                            | <b>174,520</b> | <b>4,903,481</b>                                                                    | <b>3,322,825</b> |
| Esophageal         | 22,070                                                                                    | 16,250         | 510,716                                                                             | 445,129          |
| Gastric            | 30,300                                                                                    | 10,780         | 968,350                                                                             | 659,853          |
| Liver              | 42,240                                                                                    | 30,090         | 865,269                                                                             | 757,948          |
| Pancreas           | 67,440                                                                                    | 51,980         | 510,566                                                                             | 467,005          |
| Colorectal         | 154,270                                                                                   | 52,900         | 1,926,118                                                                           | 903,859          |
| Lung               | 226,650                                                                                   | 124,730        | 2,480,301                                                                           | 1,817,172        |
| Breast             | 319,750                                                                                   | 42,680         | 2,308,897                                                                           | 665,684          |
| Prostate           | 313,780                                                                                   | 35,770         | 1,466,680                                                                           | 396,792          |

# Gastric Cancer

# RISK FACTORS FOR GASTRIC ADENOCARCINOMA

- Nutritional
  - Low fat or protein consumption
  - Salted meat or fish
  - High nitrate consumption
- Environmental
  - Poor food preparation (smoked)
  - Lack of refrigeration
  - Poor drinking water (well water)
  - Occupation (rubber, coal workers)
  - Smoking
  - Heavy alcohol use
  - Low socioeconomic class
- Medical
  - Prior gastric surgery
  - *Helicobacter pylori* infection (2-8x)
  - Gastric atrophy and gastritis
- Hereditary
  - E-cadherin mutation families

## Case: Gastric Cancer

A 59-year-old woman presents to the Emergency Department after an episode of hematemesis. She is found to be markedly anemic and requires stabilization with IV fluids and transfusion of packed red blood cells. She is admitted and evaluated by Gastroenterology; she undergoes upper endoscopy and colonoscopy the following day.

During endoscopy, a 2.5 cm mass is found in the gastric antrum. This mass is biopsied and pathology reveals a moderately-differentiated adenocarcinoma.

# TREATMENT OF GASTRIC CANCER

|                                 |                                                                                                                                      |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <b>Early stage disease</b>      | Surgery                                                                                                                              |
| <b>Locally advanced disease</b> | <b>Perioperative chemotherapy:</b><br>Chemotherapy → Surgery →<br>Chemotherapy                                                       |
| <b>Metastatic disease</b>       | Systemic therapy <ul style="list-style-type: none"><li>• Chemotherapy</li><li>• Targeted therapies</li><li>• Immunotherapy</li></ul> |

## Case: Gastric Cancer

CT of the chest/abdomen/pelvis shows a region of wall thickening in the distal stomach. No evidence of distant metastatic disease is visible.

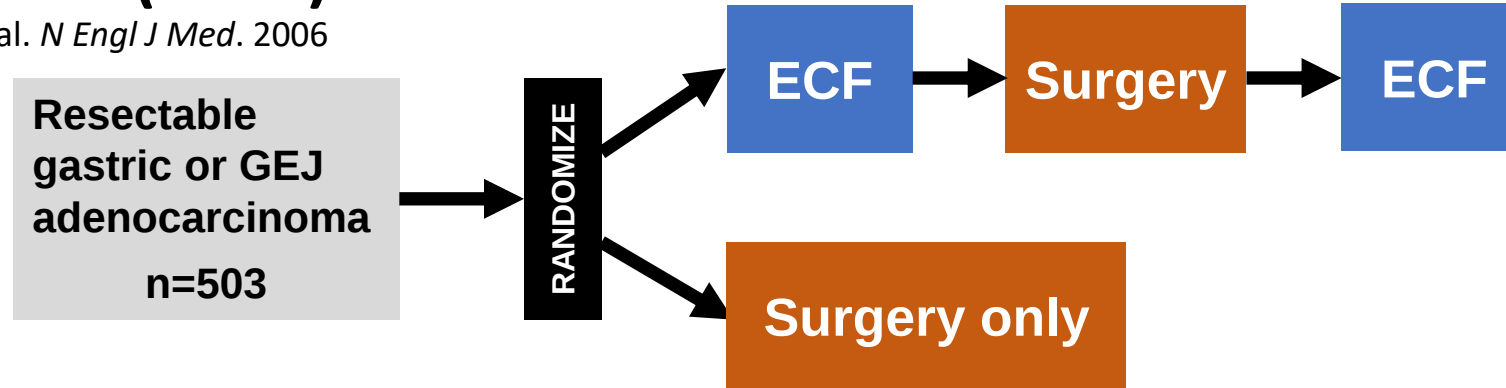
PET/CT showed moderately increased FDG uptake corresponding to this region of distal gastric wall thickening. Two regional lymph nodes also demonstrate FDG uptake. No abnormal FDG-avid lesions are visible elsewhere.

The patient is seen by a surgical oncologist and undergoes a diagnostic laparoscopy. No findings of metastatic disease are found.

# PERIOPERATIVE CHEMOTHERAPY

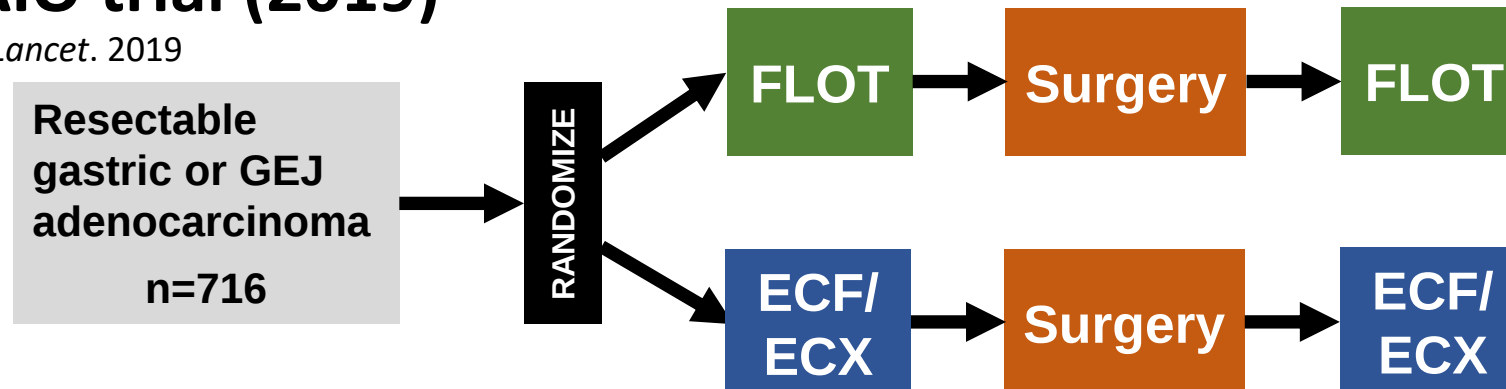
- **MAGIC trial (2006)**

Cunningham et al. *N Engl J Med.* 2006



- **FLOT4-AIO trial (2019)**

Al-Batran et al. *Lancet.* 2019



## Case: Gastric Cancer

The patient completes x4 cycles of preoperative FLOT. She undergoes a distal gastrectomy and surgical pathology shows a ypT2N1 tumor. She then completes x4 further cycles of postoperative FLOT, with dose reductions made to avoid progression of neuropathy.

Surveillance imaging approximately 18 months after the completion of chemotherapy shows 2 new liver lesions. One of these is biopsied and pathology confirms metastatic gastric adenocarcinoma. Subsequent immunohistochemistry shows the tumor to be HER-2 positive (IHC 3+) and to have a PD-L1 combined positive score of 5.

# SYSTEMIC THERAPY FOR METASTATIC DISEASE

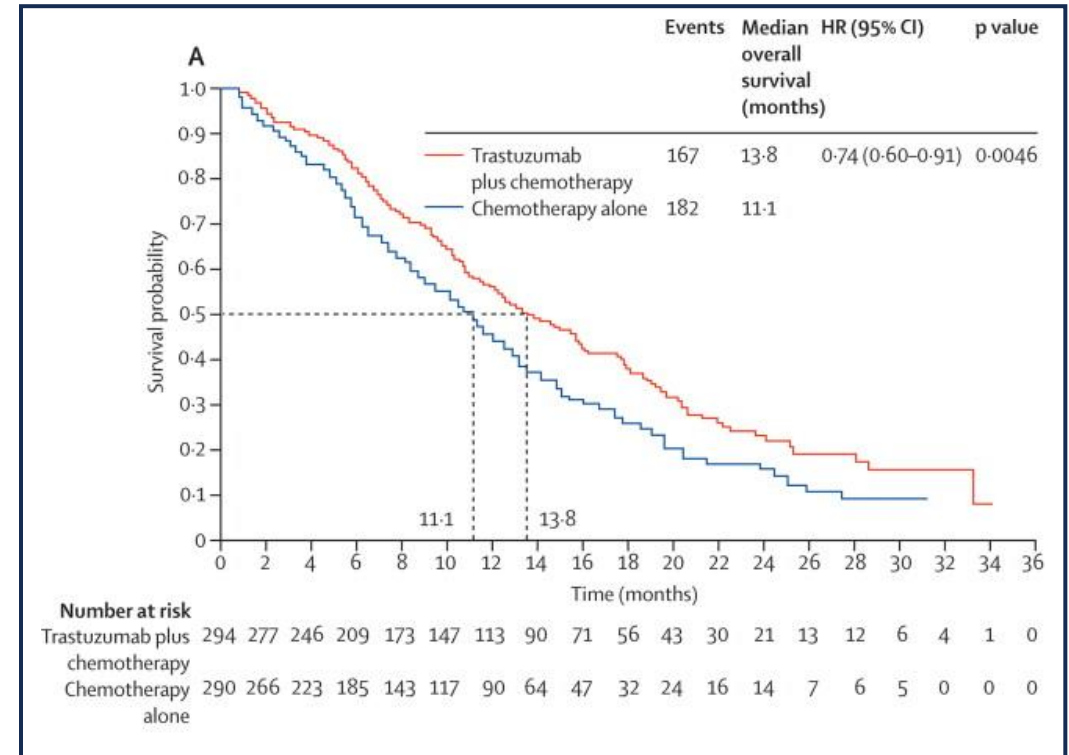
- No single standard regimen for patients with metastatic disease
  - First-line chemotherapy typically platinum-based combination regimens
- Expectations of current treatment options
  - Response rates 30-60%
  - Median overall survival 7-14 months
- Biomarkers help guide treatment decisions for patients with advanced/metastatic disease
  - HER2-directed therapies for patients with HER2-positive tumors
  - Addition of immunotherapy to first-line chemotherapy may improve outcomes in certain patients

# TRASTUZUMAB IN HER2-POSITIVE

- HER2 is overexpressed or amplified in 15-25% of gastric adenocarcinoma
- For patients with HER2-positive gastric cancer, survival benefit demonstrated with the addition of the anti-HER2 antibody trastuzumab to first-line chemotherapy

## TOGA Trial

Bang et al. *Lancet*. 2010



# IMMUNOTHERAPY IN ESOPHAGOGASTRIC CANCER

- Programmed death ligand-1 (PD-L1) expression in gastric and esophageal cancer measured with the Combined Positive Score (CPS)

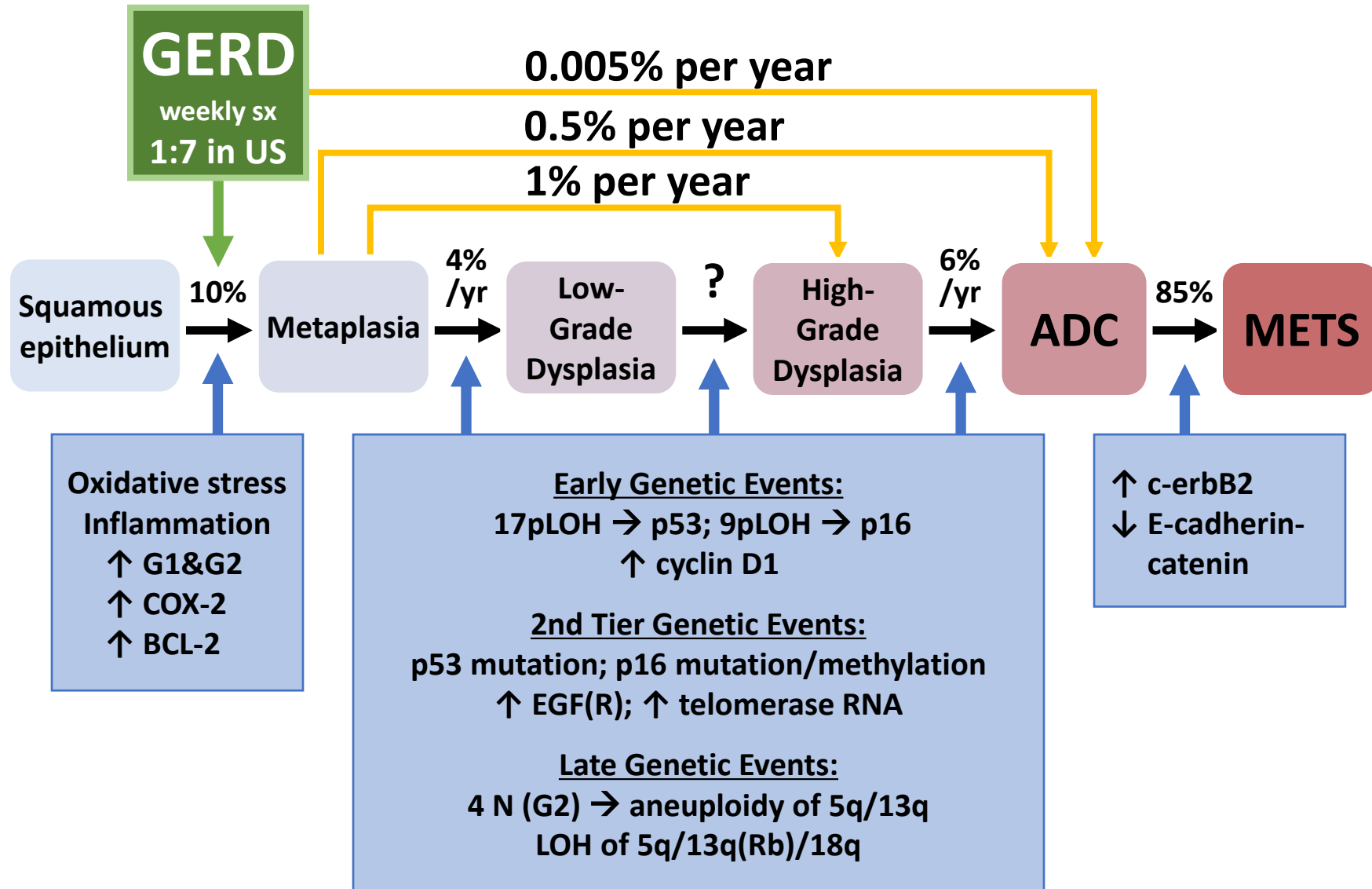
$$\text{CPS} = \frac{\text{no. of PD-L1-positive cells} \text{ (tumor cells, lymphs, macrophages)}}{\text{total no. of tumor cells} \text{ (PD-L1-positive and negative)}} \times 100$$

# Esophageal Cancer

# RISK FACTORS FOR ESOPHAGEAL CANCER

| Risk Factor                                         | Squamous Cell Carcinoma | Adenocarcinoma |
|-----------------------------------------------------|-------------------------|----------------|
| Tobacco use                                         | +++                     | ++             |
| Alcohol use                                         | +++                     | -              |
| Barrett's esophagus                                 | -                       | ++++           |
| Weekly reflux symptoms                              | -                       | +++            |
| Obesity                                             | -                       | ++             |
| Poverty                                             | ++                      | -              |
| Achalasia                                           | +++                     | -              |
| Caustic injury to the esophagus                     | ++++                    | -              |
| Nonepidermolytic palmoplantar keratoderma (tylosis) | ++++                    | -              |
| Plummer–Vinson syndrome                             | ++++                    | -              |
| History of head and neck cancer                     | ++++                    | -              |
| History of breast cancer treated with XRT           | +++                     | +++            |

# PROGRESSION OF BARRETT'S ESOPHAGUS



## Case: Esophageal Cancer

A 71-year-old gentleman presents for evaluation of progressive dysphagia over several months. He describes initially noting difficulty with certain foods. This has progressed over the last several months and he now has difficulties with most solids and some liquids.

The patient is referred to a gastroenterologist and undergoes an upper endoscopy, which reveals a mid-esophageal tumor. The mass is biopsied and pathology reveals a moderately-differentiated squamous cell carcinoma. PD-L1 testing shows a CPS of 55.

# TREATMENT OF ESOPHAGEAL CANCER

|                                 |                                                                                                                                                                                      |
|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Early stage disease</b>      | Surgery                                                                                                                                                                              |
| <b>Locally advanced disease</b> | <b>Neoadjuvant chemoradiation:</b><br>Chemoradiation → Surgery<br>→ Immunotherapy<br><br><b>OR</b><br><b>Perioperative chemotherapy:</b><br>Chemotherapy → Surgery →<br>Chemotherapy |
| <b>Metastatic disease</b>       | Systemic therapy <ul style="list-style-type: none"><li>• Chemotherapy</li><li>• Targeted therapies</li><li>• Immunotherapy</li></ul>                                                 |

## Case: Esophageal Cancer

PET/CT shows a bulky mass extending from the mid to distal esophagus. This mass is FDG-avid. Several periesophageal lymph nodes are enlarged and also FDG-avid. No evidence of distant metastatic disease is visible.

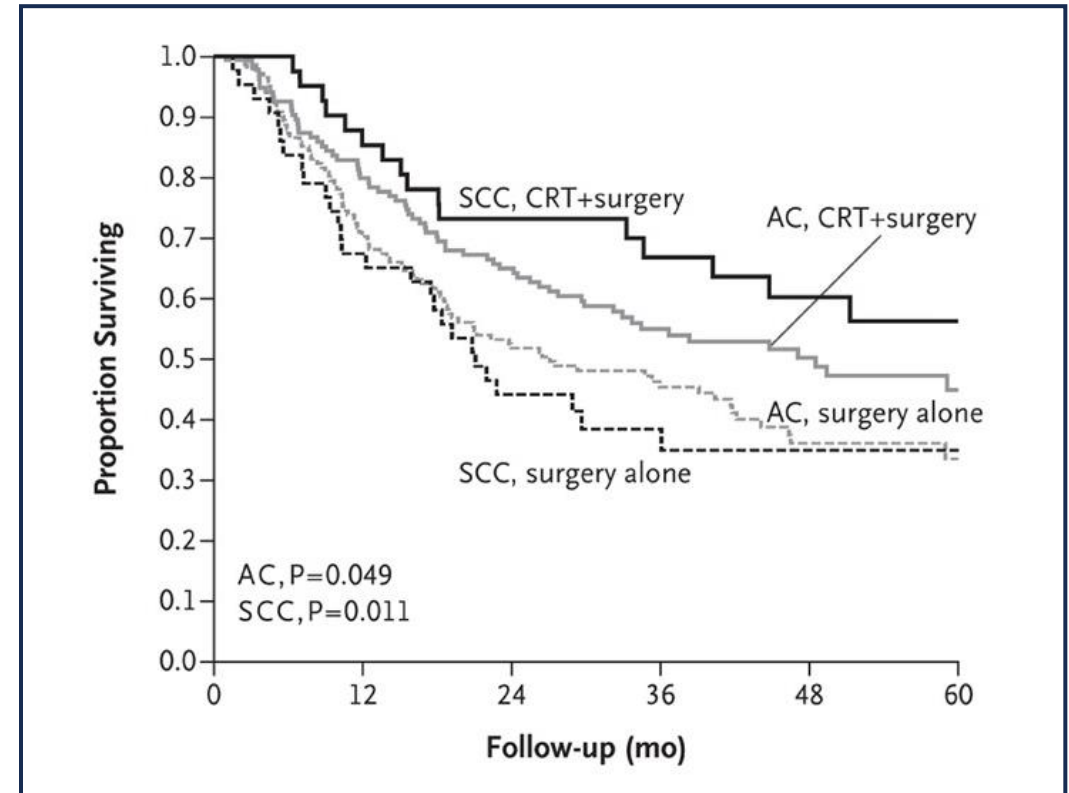
The patient is evaluated by a thoracic surgeon. He has a feeding tube placed and is started on supplemental enteral nutrition.

# NEOADJUVANT CHEMORADIATION

- Surgery alone
  - Resectability rates: 54-69%
  - Periop mortality: 4-10%
  - Periop complications: 26-41%
  - 2-year survival: 35-42%
  - 5-year survival: 15-24%
- Multiple trials have shown improved outcomes with chemoradiation prior to surgery

## CROSS Trial

van Hagen et al. *N Engl J Med.* 2012

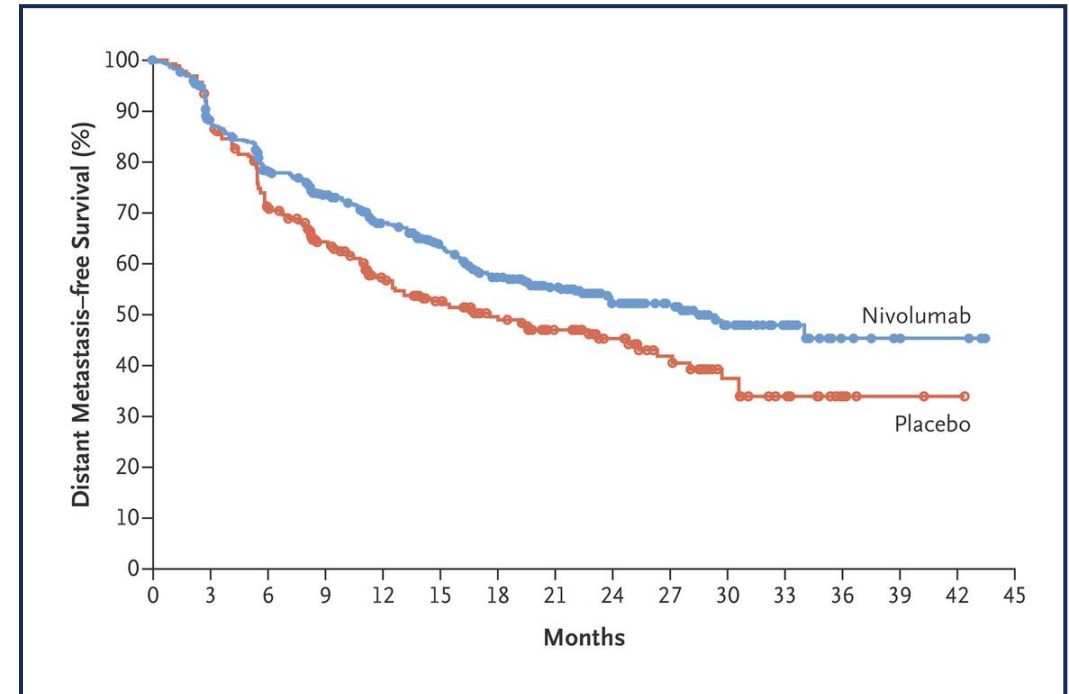


# ADJUVANT IMMUNOTHERAPY

- Phase 3 trial of adjuvant nivolumab vs placebo in patients with resected (R0) stage II or III esophageal or GEJ cancer who received neoadjuvant chemoradiotherapy and had residual pathological disease
- Significant improvement in disease-free survival for patients receiving adjuvant nivolumab

## CheckMate 577

Kelly et al. *N Engl J Med.* 2020

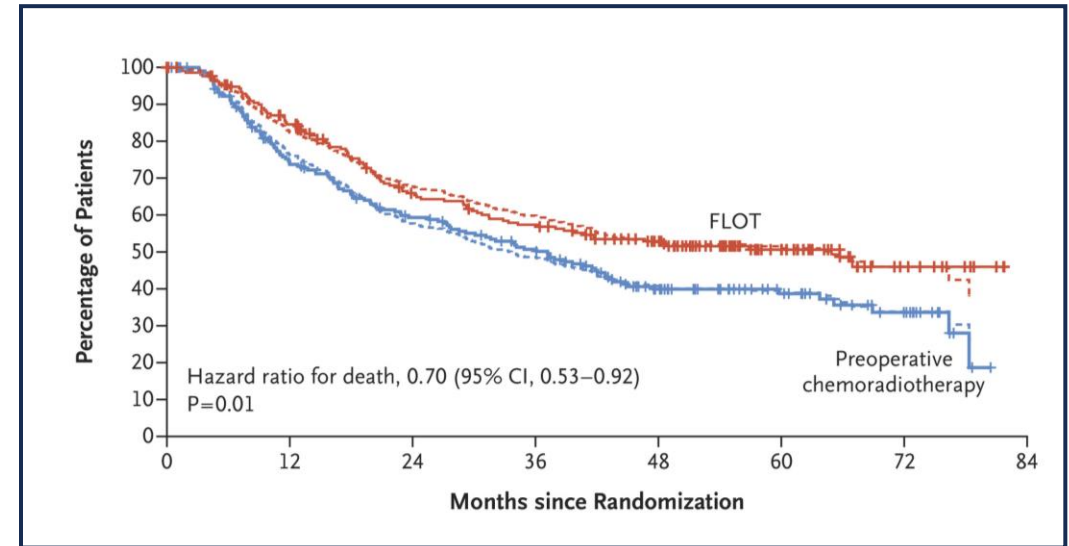


# PERIOPERATIVE CHEMOTHERAPY

- Phase 3 trial of neoadjuvant chemoradiation (CROSS) vs perioperative chemotherapy (FLOT) in patients with resectable **esophageal adenocarcinoma**
- Significant improvements in progression-free and overall survival with FLOT
- Should be considered for fit patients with esophageal, GEJ, or gastric **adenocarcinoma**

## ESOPEC

Hoeppner et al. *N Engl J Med.* 2025



## Case: Esophageal Cancer

The patient completes 6 weeks of concurrent carboplatin and paclitaxel. Restaging PET/CT shows a decrease in the SUV of both the primary esophageal tumor and adjacent lymph nodes.

The patient then undergoes a minimally-invasive esophagectomy. Surgical pathology shows a near complete response, with only scattered clusters of residual tumor cells. No residual disease is found in any of the resected regional lymph nodes. The patient's tumor is staged ypT1N0.

The patient is seen by his medical oncologist in follow-up and is recommended 1 year of adjuvant immunotherapy with nivolumab.

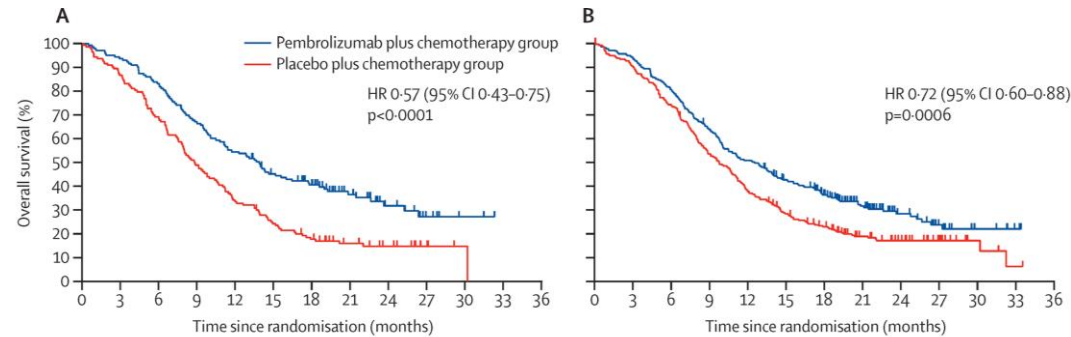
# SYSTEMIC THERAPY FOR METASTATIC DISEASE

- No single standard regimen for patients with metastatic disease
  - First-line chemotherapy typically platinum-based combination regimens
- Expectations of current treatment options
  - Response rates 30-60%; Median overall survival 7-14 months
  - Relief of dysphagia (without radiation) up to 80%
- Esophageal/GEJ adenocarcinoma is often treated under the same framework as that used for gastric adenocarcinoma

# FIRST-LINE COMBINATION CHEMOIMMUNOTHERAPY

## KEYNOTE-590

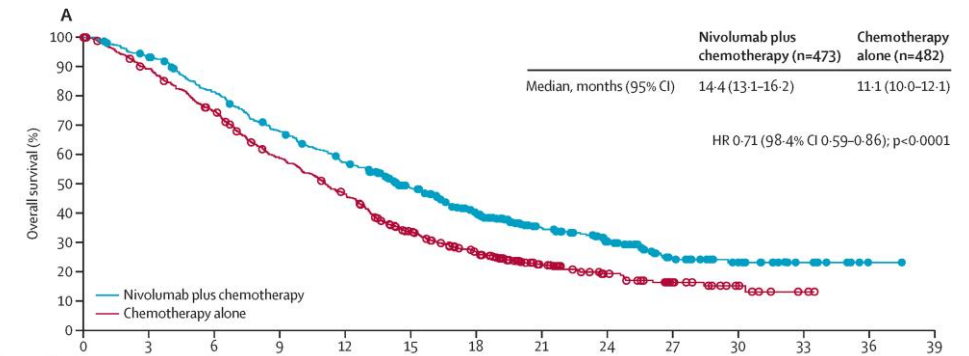
Sun et al. *Lancet*. 2021



- Unresectable esophageal or Siewert type 1 GEJ cancer
- Chemotherapy + pembrolizumab vs chemotherapy alone
- OS in pts with tumors with PD-L1 CPS  $\geq 10$ , OS and PFS in ESCC

## CheckMate 649

Janjigian et al. *Lancet*. 2021



- Unresectable, HER2-negative gastric, GEJ, or esophageal adenocarcinoma
- Chemotherapy + nivolumab vs chemotherapy alone
- OS or PFS in pts with tumors with PD-L1 CPS  $\geq 5$

# CHEMOIMMUNOTHERAPY

- Multiple trials have now demonstrated improvements in survival with the addition of immunotherapy (pembrolizumab, nivolumab) to first-line chemotherapy for metastatic esophageal and gastric cancers
- Phase III trial has also shown improved survival with the addition of pembrolizumab to chemotherapy and trastuzumab for HER2-positive gastric and GEJ adenocarcinomas
- These benefits are seen primarily in patients with PD-L1-positive tumors (PD-L1 CPS  $\geq 1$ )
- Immunotherapy alone may be appropriate for patients with squamous cell carcinoma

# Colorectal Cancer

## Case: Colorectal Cancer

A 45-year-old gentleman undergoes his first routine screening colonoscopy; he does not have any concerning symptoms prior to the procedure.

A malignant-appearing mass is found in the ascending colon. The mass is biopsied and the site is tattooed. Pathology confirms an invasive adenocarcinoma, well-differentiated.

CT shows a region of bowel wall thickening in the right colon. No evidence of distant metastatic disease is visible.

The patient undergoes a laparoscopic right hemicolectomy. Surgical pathology reveals a 5.5 cm well-differentiated adenocarcinoma arising from the ascending colon. The tumor extends through the muscularis propria into pericolonic tissue. Two of 22 regional lymph nodes resected are positive for malignancy.

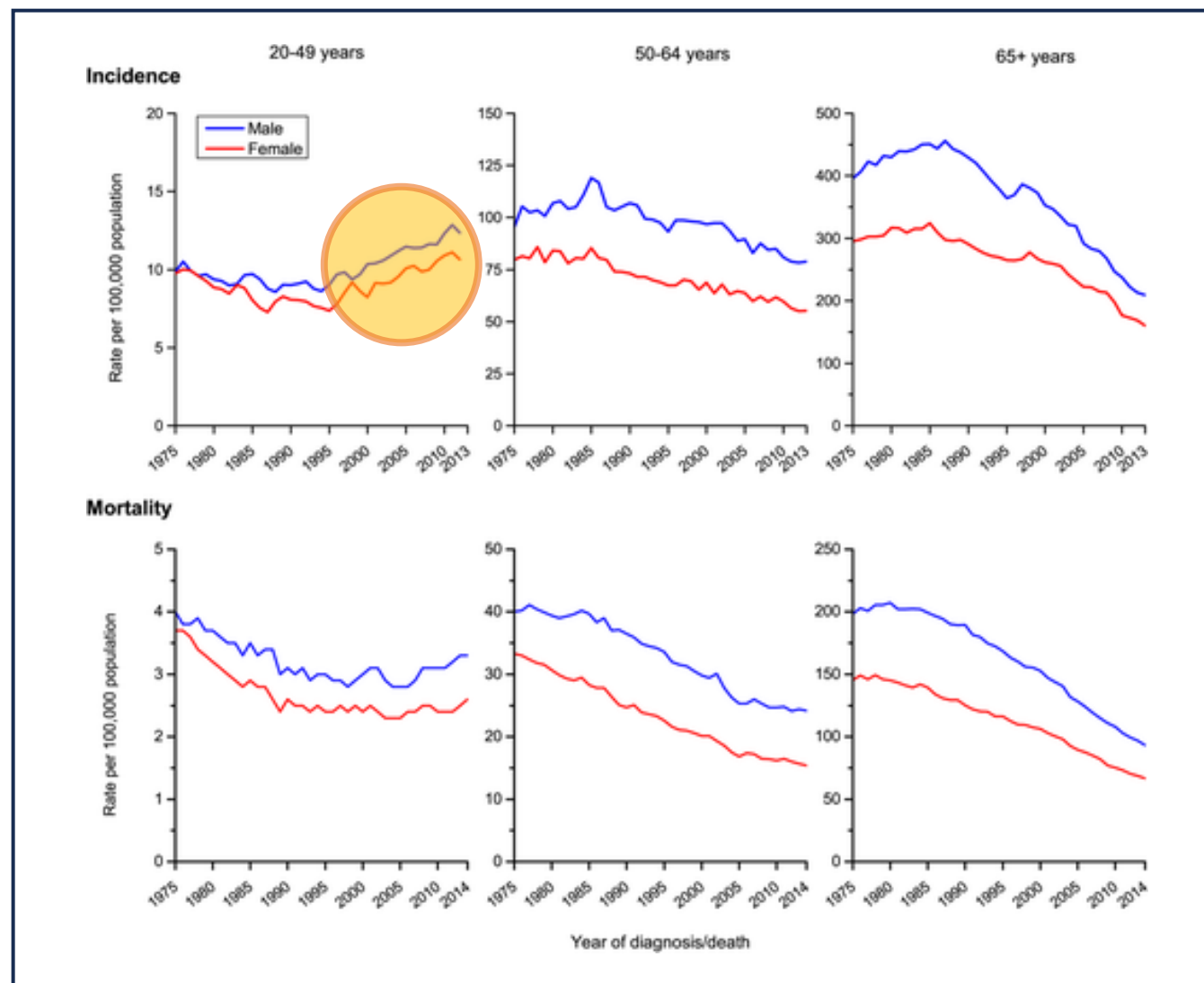
# RISK FACTORS FOR COLORECTAL CANCER

| Decrease Risk            | Increase Risk  | Uncertain Impact  |
|--------------------------|----------------|-------------------|
| Screening                | Family history | Statins           |
| Exercise                 | IBD            | Fiber             |
| Vitamin D                | Diabetes       | Glycemic index    |
| Aspirin / NSAIDs         | Obesity        | Fruits/Vegetables |
| Post-menopausal estrogen | Red meat       | Folic Acid        |
| Calcium                  | Western diet   |                   |
|                          | Alcohol        |                   |
|                          | Smoking        |                   |

# HEREDITARY RISK FACTORS

- Hereditary
  - Familial syndromes (approx. 5% of CRC)
    - Familial adenomatous polyposis (FAP)
    - Hereditary nonpolyposis colorectal cancer (HNPCC)
  - Family history (or personal history) (10-15%)
    - 2x risk of developing CRC
    - Depending on age at diagnosis of relative and # of relatives

# YOUNG-ONSET COLORECTAL CANCER



# COLORECTAL CANCER SCREENING

## American Cancer Society (ACS) Guideline 2018:

- Recommends that adults 45 and older with an average risk of CRC undergo regular screening
  - Recommendation to begin screening at 45 is a qualified recommendation.
  - Recommendation for regular screening in adults 50 and older is a strong recommendation
  - Average-risk adults with life expectancy >10 years continue screening through age 75
  - Clinicians individualize screening decisions for individuals 76-85
  - Discourage individuals over 85 from continuing screening

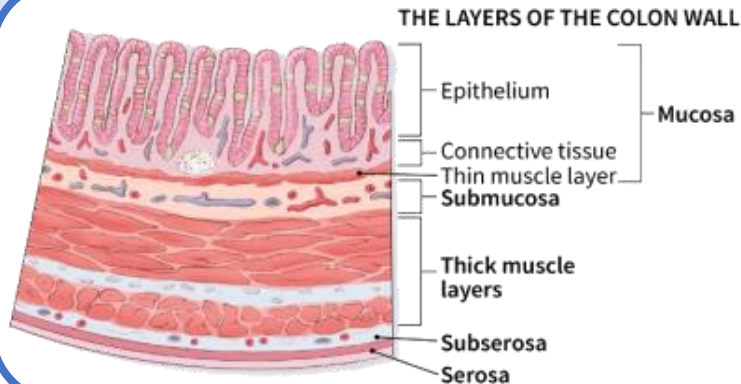
## Options for Screening:

- Structural examinations
  - Colonoscopy every 10 years
  - Flexible sigmoidoscopy every 5 years
  - CT colonography every 5 years
- Stool-based tests
  - High-sensitivity, guaiac-based fecal occult blood test (FOBT) every year
  - Fecal immunochemical test (FIT) every year
  - Multitarget stool DNA test every 3 years
- All positive non-colonoscopy screening tests should be followed up colonoscopy

# TNM STAGING: AJCC 8

## Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ: intraepithelial or intramucosal carcinoma
- T1: Tumor invades submucosa
- T2: Tumor invades muscularis propria
- T3: Tumor invades through the muscularis propria into the pericolorectal tissues
- T4: Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure



## Distant Metastasis (M)

- MX: Metastases cannot be assessed
- M0: No distant metastases
- M1: Metastases to 1 or more distant sites or organs

## Regional lymph nodes (N)

- NX: Regional LNs cannot be assessed
- N0: No regional LN metastasis
- N1: Metastasis in 1-3 LNs
- N2: Metastasis in 4+ LNs

# TREATMENT OF COLORECTAL CANCER

| Stage                             | Colon                         | Rectal                                     | 5-year Overall Survival |
|-----------------------------------|-------------------------------|--------------------------------------------|-------------------------|
| I ( $T_1$ - $T_2$ $N_0$ $M_0$ )   | Surgery only                  | Surgery only                               | >90%                    |
| II ( $T_3$ - $T_4$ $N_0$ $M_0$ )  | Surgery +/-<br>Chemotherapy   | Surgery +<br>Chemotherapy +/-<br>Radiation | 70-85%                  |
| III ( $T_{any}$ $N_{1-2}$ $M_0$ ) | Surgery →<br>Chemotherapy     |                                            | 30-70%                  |
| IV ( $T/N_{any}$ $M_1$ )          | Chemotherapy<br>(+/- Surgery) | Chemotherapy<br>(+/- Surgery)              | 8-10%                   |

# SURGERY IN COLON AND RECTAL CANCER

- Surgical resection cures a large percentage of patients with early-stage disease
  - 80% of patients present without detectable metastases
- Colon cancer
  - At least 12-14 nodes should be included in sample
  - Evidence for equivalent outcomes with laparoscopic colectomy
- Rectal cancer
  - Low anterior resection (LAR) – preserves sphincter
  - Abdominoperineal resection (APR) – low tumors → permanent colostomy

# RADIATION IN RECTAL CANCER

- Why is radiation beneficial in rectal but not in colon cancer?
  - Related to risk of local recurrence (radiation is a local treatment)
    - Colon cancer: <2% risk of local recurrence
    - Rectal cancer: up to 30% local recurrence rate with surgery alone
- Toxicities with Chemoradiation:
  - Acute: Skin, bladder, bowel, hematologic
  - Long-Term: Fecal/urinary incontinence, sexual dysfunction, fertility issues, pelvic floor fractures
  - Both are more common in women

| Stage | Colon                       | Rectal                                   |
|-------|-----------------------------|------------------------------------------|
| II    | Surgery +/-<br>Chemotherapy | Surgery +<br>Chemotherapy +<br>Radiation |
| III   | Surgery →<br>Chemotherapy   |                                          |

# LOCALLY ADVANCED RECTAL CANCER

- Neoadjuvant chemoradiation → Surgery → Adjuvant chemotherapy
  - Standard of care for 20+ years
- **Total neoadjuvant therapy (TNT):**  
Neoadjuvant radiation/chemoradiation + chemotherapy → Surgery
  - Significantly higher clinical and pathologic response rates
  - In certain patients with more advanced disease (high T-stage, node-positive), has been shown to improve disease-free and overall-survival
- **Preoperative chemotherapy:**  
Neoadjuvant chemotherapy → NO chemoradiation if good response  
→ Surgery → Adjuvant chemotherapy
  - Phase III **PROSPECT** trial: In patients with locally advanced rectal cancer eligible for sphincter-sparing surgery, disease-free survival with preoperative chemotherapy was noninferior to preoperative chemoradiation

# ADJUVANT CHEMOTHERAPY

- Stage III

- Adjuvant fluoropyrimidine reduces the risk of disease recurrence by 40% and overall mortality by 33%
- Three trials have demonstrated further improvements with the addition of oxaliplatin to fluoropyrimidine
  - Downside: Neurotoxicity
  - Patients with 'low-risk' stage III colon cancer may have equivalent outcomes with 3 vs 6 months of combination chemotherapy

- Stage II

- No randomized trials with enough stage II patients to draw definitive recommendations
- ASCO Consensus Panel concluded that based on available evidence, benefit between 0-5%
- High risk patients may be appropriate – T4 lesions, obstruction or perforation, few lymph nodes in sample
- Various gene panels are prognostic but not predictive

## Case: Colorectal Cancer

The patient completes adjuvant chemotherapy with capecitabine and oxaliplatin without complications. He remains without evidence of disease for 2 years, when surveillance CT scans shows a new liver lesion. This site is biopsied and pathology confirms adenocarcinoma consistent with metastasis from a colorectal primary.

The biopsy tissue is sent for additional testing. Immunohistochemistry for mismatch repair proteins MLH1, MSH2, MSH6, and PMS2 reveals intact nuclear staining in all tumor cells. Mutational profiling shows no relevant mutations in *KRAS*, *NRAS*, or *BRAF*.

# METASTATIC COLORECTAL CANCER

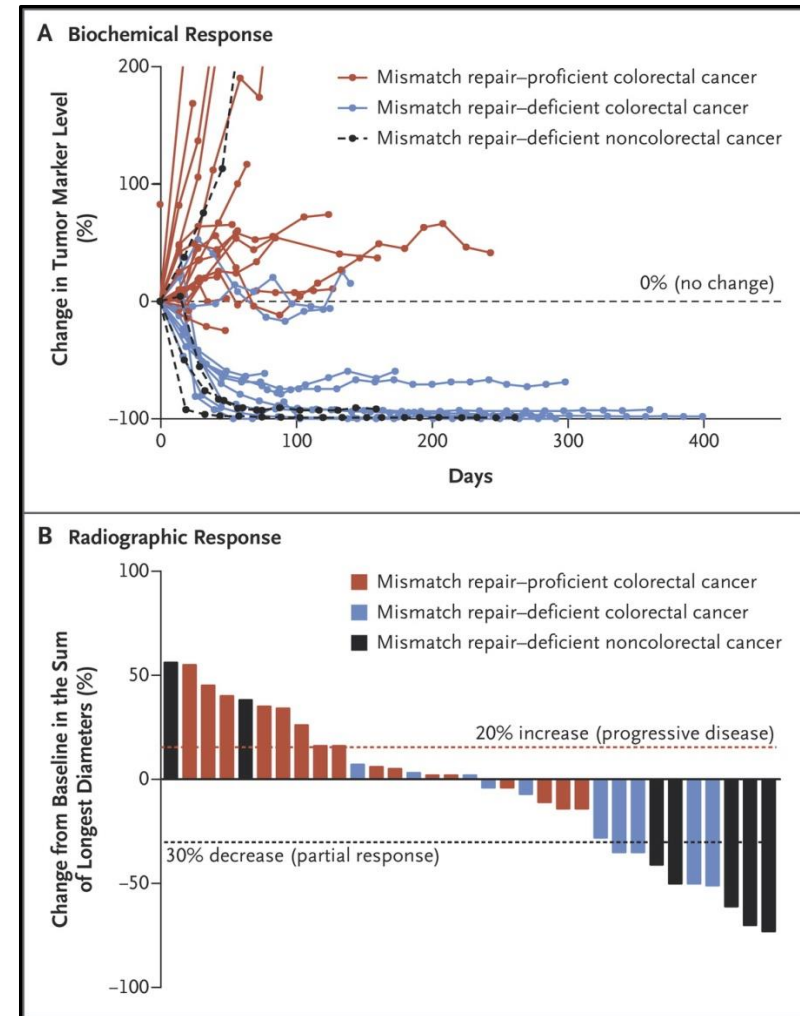
- In general, not curable
- Patients with isolated metastases (e.g. liver, lung) that can be resected should be considered for surgery
  - Up to 30% may have long-term survival
  - Still need chemotherapy
- Chemotherapy known to improve cancer-related symptoms and to prolong life
  - Median survival without chemotherapy is approximately 6 months

# SYSTEMIC THERAPY FOR METASTATIC DISEASE

| 1998 | 5-FU                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2025 | <p>First/Second-line Chemotherapy</p> <ul style="list-style-type: none"><li>• 5-FU or capecitabine</li><li>• FOLFOX</li><li>• FOLFIRI</li><li>• +/- bevacizumab OR +/- cetuximab/panitumumab (if <b>RAS/BRAF</b> wildtype)</li></ul> <p>Refractory <b>RAS/BRAF</b> wildtype:</p> <ul style="list-style-type: none"><li>• Cetuximab/panitumumab +/- irinotecan</li></ul> <p>After above therapies:</p> <ul style="list-style-type: none"><li>• Trifluridine/tipiracil +/- bevacizumab</li><li>• Regorafenib</li><li>• Fruquitinib</li></ul> | <p><b>MSI-high</b> tumors:</p> <ul style="list-style-type: none"><li>• Pembrolizumab</li><li>• Nivolumab +/- ipilimumab</li></ul> <p><b>BRAF</b>-mutated:</p> <ul style="list-style-type: none"><li>• Encorafenib + cetuximab/panitumumab +/- binimetinib</li><li>• Vemurafenib + irinotecan + cetuximab</li></ul> <p><b>HER2</b>-amplified (and <b>RAS/BRAF</b> wt):</p> <ul style="list-style-type: none"><li>• fam-trastuzumab deruxtecan-nxki</li><li>• Trastuzumab + lapatinib</li><li>• Trastuzumab + pertuzumab</li></ul> <p><b>NTRK fusion</b>-positive:</p> <ul style="list-style-type: none"><li>• Larotrectinib</li><li>• Entrectinib</li></ul> |

# IMMUNOTHERAPY IN MSI-HIGH

- Microsatellite instability (MSI) is a hypermutable phenotype
- MSI is detected in about 15% of all colorectal cancers
  - 3% associated with Lynch syndrome
  - 12% sporadic
- MSI-high colorectal tumors have shown higher response rates to immunotherapy

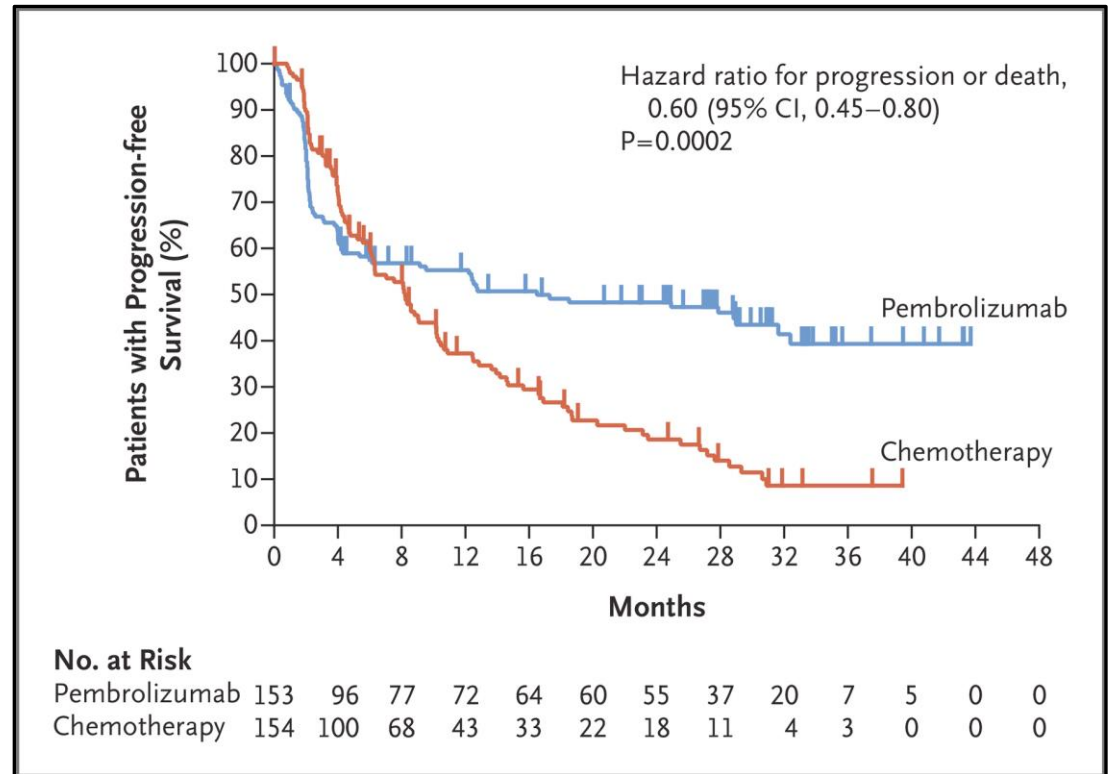


# FIRST-LINE IMMUNOTHERAPY IN MSI-H

- Phase 3 study of pembrolizumab vs chemotherapy as first-line treatment in pts with MSI-H advanced CRC
- Significant improvement in progression-free survival
- No significant difference in overall survival
- Immunotherapy for first-line treatment of pts with unresectable/met MSI-H CRC

## KEYNOTE-177

André et al. *N Engl J Med.* 2020



# Pancreatic Cancer

# RISK FACTORS FOR PANCREATIC CANCER

- Hereditary
  - Hereditary breast and ovarian cancer syndrome
    - BRCA1, BRCA2, PALB2
  - Hereditary pancreatitis
  - Peutz-Jeghers syndrome
  - Ataxia-telangiectasia
  - Lynch syndrome
- Diabetes (x2)
- Smoking
- Obesity
- Chronic pancreatitis (mixed data)
- History of partial gastrectomy

Germline testing is recommended for any patient with confirmed pancreatic cancer

# TREATMENT OF PANCREATIC CANCER

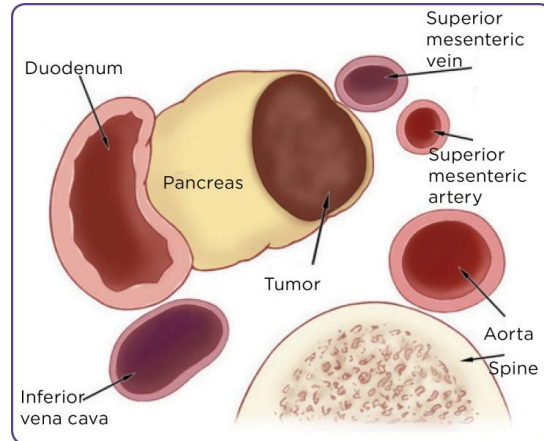
|                              |                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------|
| <b>Localized/Resectable</b>  | Surgery → Chemotherapy                                                                |
| <b>Borderline-Resectable</b> | <b>Neoadjuvant Therapy:</b><br>Chemotherapy +/- Radiation<br>→ Surgery, if resectable |
| <b>Locally Advanced</b>      | Chemotherapy +/-<br>Radiation or Chemoradiation                                       |
| <b>Metastatic</b>            | Chemotherapy                                                                          |

## Case: Pancreatic Cancer

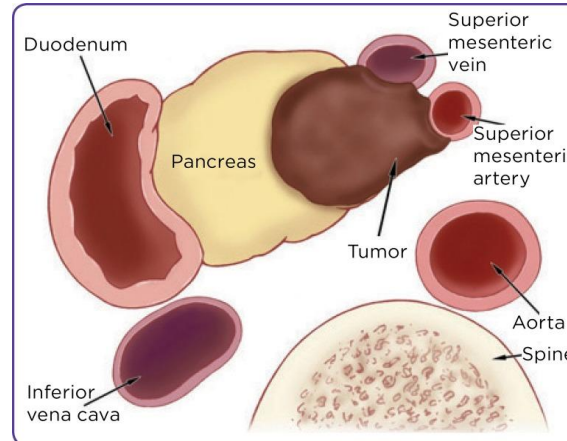
A 59-year-old woman presents to the Emergency Department with painless jaundice. Liver function tests reveal severe hyperbilirubinemia. CT imaging then shows a 1.2 cm mass in the head of the pancreas, with associated pancreatic and biliary ductal dilatation. No evidence of distant metastatic disease is seen.

The patient undergoes upper endoscopy with ERCP and EUS. During ERCP, a malignant-appearing stricture is seen in the distal common bile duct and a plastic biliary stent is placed. EUS shows a 1.4 cm hypoechoic mass in the pancreatic head with irregular borders. No involvement of the surrounding vessels is seen. Fine needle biopsy of the mass is performed and pathology returns positive for adenocarcinoma.

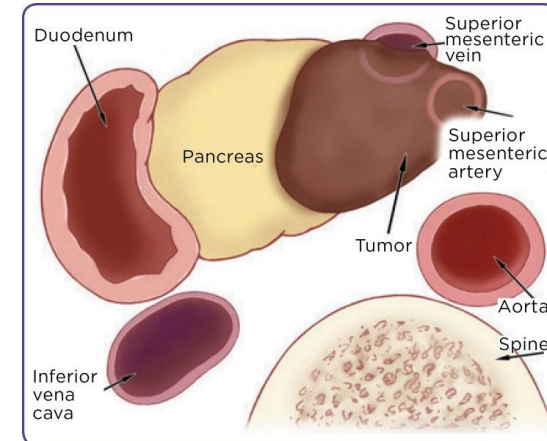
# RESECTABILITY OF PANCREATIC CANCER



**Resectable**



**Borderline-Resectable**



**Locally Advanced**

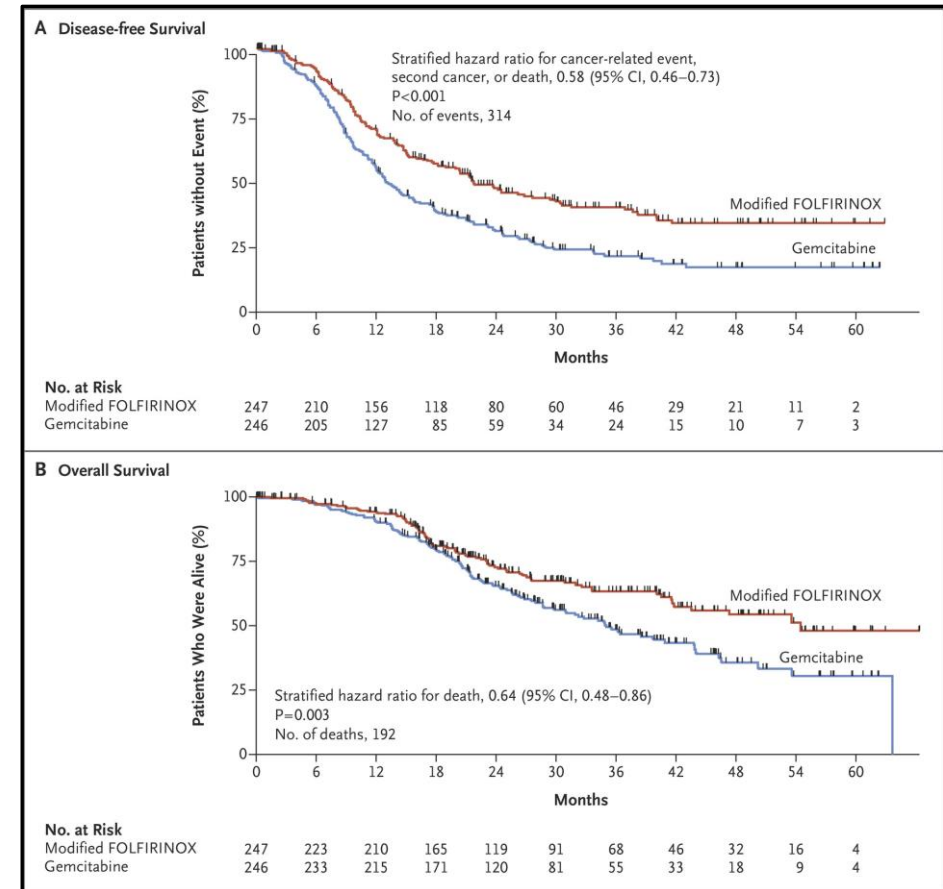
- Criteria vary between institutions/societies
- Increasing evidence for the role of neoadjuvant therapy in patients with borderline-resectable disease

# RESECTABLE PANCREATIC CANCER

- Upfront curative-intent resection is possible in only 15% of all patients
- Adjuvant therapy
  - Postoperative chemotherapy shown to be beneficial in multiple clinical trials over past 15 years
  - Postoperative chemoradiation conflicting results

## PRODIGE 24/CCTG PA.6

Conroy T, et al. *N Engl J Med.* 2018



# METASTATIC PANCREATIC ADENOCARCINOMA

- Treated with chemotherapy
  - First-line treatment consists of combination chemotherapy regimens for those patients who are able to tolerate more aggressive treatment
  - Median overall survival: 6-11 months
- Targeted therapy: PARP inhibitor olaparib
  - FDA approved as maintenance therapy for:
    - germline BRCA-mutated pancreatic cancer
    - have not progressed on at least 16 weeks of first-line platinum-based chemotherapy

# Board Questions

# Board Question 1

Your patient is a 48-year-old woman who underwent colonoscopy after presenting with rectal bleeding. A malignant polypoid mass was identified in the ascending colon, for which the patient then undergoes a laparoscopic hemicolectomy. Surgical pathology showed a 1.5 cm well-differentiated adenocarcinoma. The tumor was seen to invade into the muscularis propria. None of the 24 regional lymph nodes resected showed any cancer involvement. The tumor was staged pT2N0.

CT imaging prior to surgery had not shown any evidence of distant metastatic disease in the chest, abdomen, or pelvis.

The most appropriate next step is:

- A. Establishing a schedule for surveillance
- B. Postoperative chemotherapy with capecitabine
- C. Postoperative chemotherapy with capecitabine plus oxaliplatin
- D. Postoperative immunotherapy with pembrolizumab

# Board Question 1

A. Establishing a schedule for surveillance

B. Postoperative chemotherapy with capecitabine

C. Postoperative chemotherapy with capecitabine plus oxaliplatin

D. Postoperative immunotherapy with pembrolizumab

- There is no evidence supporting any form of adjuvant therapy in patients with resected stage I colon cancer
- The benefits of adjuvant chemotherapy have only been clearly established in stage III disease
- No current role for immunotherapy in the adjuvant setting
- Surveillance following surgery for stage I colorectal cancer consists primarily of interval colonoscopy

## Board Question 2

Your patient is a 54-year-old gentleman with newly diagnosed metastatic gastric adenocarcinoma. Immunohistochemistry showed that his tumor was positive for HER2 (IHC 3+) and for PD-L1 (combined positive score 75). CT imaging showed a bulky gastric cardia tumor and innumerable metastases in both lobes of the liver.

The patient is able to perform his daily activities without assistance and remains active, exercising daily. He has hypertension, well-managed, and no other medical comorbidities. He is dealing with mild intermittent right-sided and epigastric abdominal pain, currently managed with acetaminophen.

Which of the following options is the best option for first-line treatment:

- A. Capecitabine and oxaliplatin
- B. FOLFOX (5-fluorouracil and oxaliplatin) plus pembrolizumab
- C. FOLFOX plus trastuzumab and pembrolizumab
- D. Nivolumab and ipilimumab

## Board Question 2

- A. Capecitabine and oxaliplatin
  - B. FOLFOX (5-fluorouracil and oxaliplatin) plus pembrolizumab
  - C. FOLFOX plus trastuzumab and pembrolizumab
  - D. Nivolumab and ipilimumab
- 
- First-line treatment for metastatic esophageal and gastric cancer involves combination chemotherapy
  - In HER2-positive disease, the addition of trastuzumab to first-line chemotherapy has been shown to improve survival
  - With a PD-L1 CPS  $\geq 1$ , the addition of pembrolizumab to first-line chemoimmunotherapy has been shown to further improve survival
  - There is no role for combination immunotherapy alone in metastatic esophageal or gastric adenocarcinoma (may be used in squamous cell carcinoma)

# MOC REFLECTIVE STATEMENT

## GASTRIC AND ESOPHAGEAL CANCER

- H. pylori is the most important risk factor for gastric cancer and should be treated
- Locally advanced gastric cancer should be treated with perioperative chemotherapy, before and after surgery
- Patients with locally advanced esophageal squamous cell carcinoma should undergo neoadjuvant chemoradiation prior to surgery, followed by adjuvant immunotherapy if there is residual disease
- Fit patients with esophageal and GE junction adenocarcinoma should be treated with perioperative chemotherapy
- Treatment for metastatic esophageal and gastric cancer should receive chemotherapy
- Patients with HER2-positive esophageal or gastric adenocarcinoma should have trastuzumab added to first-line chemotherapy
- Patients with PD-L1 positive esophageal or gastric cancer should have immunotherapy added to first-line treatment

# MOC REFLECTIVE STATEMENT

## COLORECTAL CANCER

- The incidence of colorectal cancer in persons under age 50 is rising
- Guidelines now recommend beginning colorectal cancer screening at age 45
- Patients with resected stage III colon cancer should receive adjuvant chemotherapy
- Patients with locally advanced rectal cancer should receive preoperative treatment with chemotherapy and sometimes with radiation
- Metastatic colorectal cancer is primarily treated with chemotherapy; first-line treatment for metastatic MSI-H colorectal cancer involves immunotherapy

## PANCREATIC CANCER

- Patients diagnosed with pancreatic cancer should receive genetic counseling regarding germline testing
- Patients with resected pancreatic cancer should receive adjuvant chemotherapy
- Treatment for metastatic pancreatic cancer generally involves combination chemotherapy

# Thank You!

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