# Current Epidemiology and Incidence of Esophageal Cancer: East vs West; Implications on Clinical Trials

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# Case 1

- 63 year old female with HTN, CAD, epilepsy, Plummer Vinson syndrome who presented after several months of painful swallowing and 25-lb weight loss.
- CT chest: 9-cm esophageal mass
- EGD: invasive squamous cell carcinoma arising in background of high-grade dysplasia/carcinoma in situ.
- PET-CT: avidity in the primary lesion but no adenopathy and R adrenal asymmetric FDG uptake concerning for metastasis.
- An esophageal stent was placed but subsequently removed due to pain.
- MRI abd/pelvis was more compatible with adrenal hyperplasia than metastasis.
- PEG was placed

# Outline

- Epidemiology of esophageal cancer
- Definitive treatment of locally advanced disease
- Systemic treatment for metastatic disease
- Novel therapeutic directions
- Translational investigation at CUIMC

# How Common is Esophageal Cancer in the US?

| | Common Types of Cancer | Estimated New Cases 2024 | Estimated Deaths 2024 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 310,720 | 42,250 |
| 2. | Prostate Cancer | 299,010 | 35,250 |
| 3. | Lung and Bronchus Cancer | 234,580 | 125,070 |
| 4. | Colorectal Cancer | 152,810 | 53,010 |
| 5. | Melanoma of the Skin | 100,640 | 8,290 |
| 6. | Bladder Cancer | 83,190 | 16,840 |
| 7. | Kidney and Renal Pelvis Cancer | 81,610 | 14,390 |
| 8. | Non-Hodgkin Lymphoma | 80,620 | 20,140 |
| 9. | Uterine Cancer | 67,880 | 13,250 |
| 10. | Pancreatic Cancer | 66,440 | 51,750 |
| | - | - | - |
| 17. | Esophageal Cancer | 22,370 | 16,130 |

Esophageal cancer represents 1.1% of all new cancer cases in the U.S.

# Who is Affected by Esophageal Cancer?

**Rate of New Cases per 100,000 Persons by Race/Ethnicity & Sex: Esophageal Cancer**

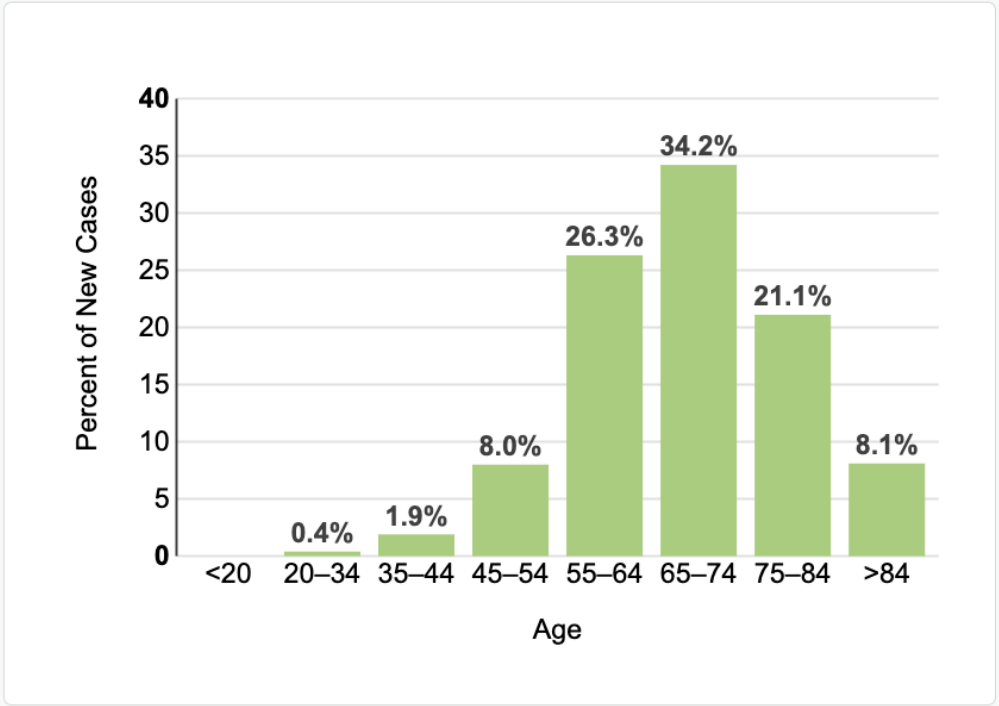
| MALES | |
|---|---|
| All Races | 7.1 |
| Hispanic | 4.7 |
| Non-Hispanic American Indian/Alaska Native | 9.0 |
| Non-Hispanic Asian/Pacific Islander | 3.6 |
| Non-Hispanic Black | 5.2 |
| Non-Hispanic White | 8.3 |

| FEMALES | |
|---|---|
| All Races | 1.7 |
| Hispanic | 1.0 |
| Non-Hispanic American Indian/Alaska Native | 2.2 |
| Non-Hispanic Asian/Pacific Islander | 1.0 |
| Non-Hispanic Black | 1.9 |
| Non-Hispanic White | 1.9 |

SEER 22 2017–2021, Age-Adjusted

# When is Esophageal Cancer Most Likely to be Diagnosed?

**Percent of New Cases by Age Group: Esophageal Cancer**




Esophageal cancer is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis

**68**

SEER 22 2017–2021, All Races, Both Sexes

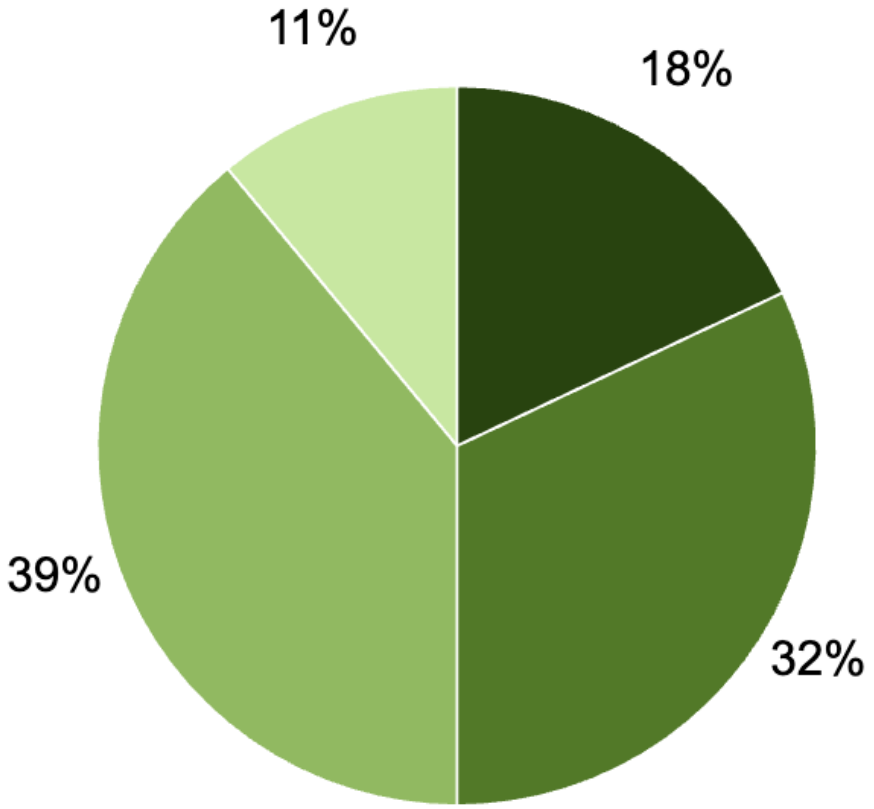
# In the US…

| | |
|---|---|
| Estimated New Cases in 2024 | 22,370 |
| % of All New Cancer Cases | 1.1% |

| | |
|---|---|
| Estimated Deaths in 2024 | 16,130 |
| % of All Cancer Deaths | 2.6% |

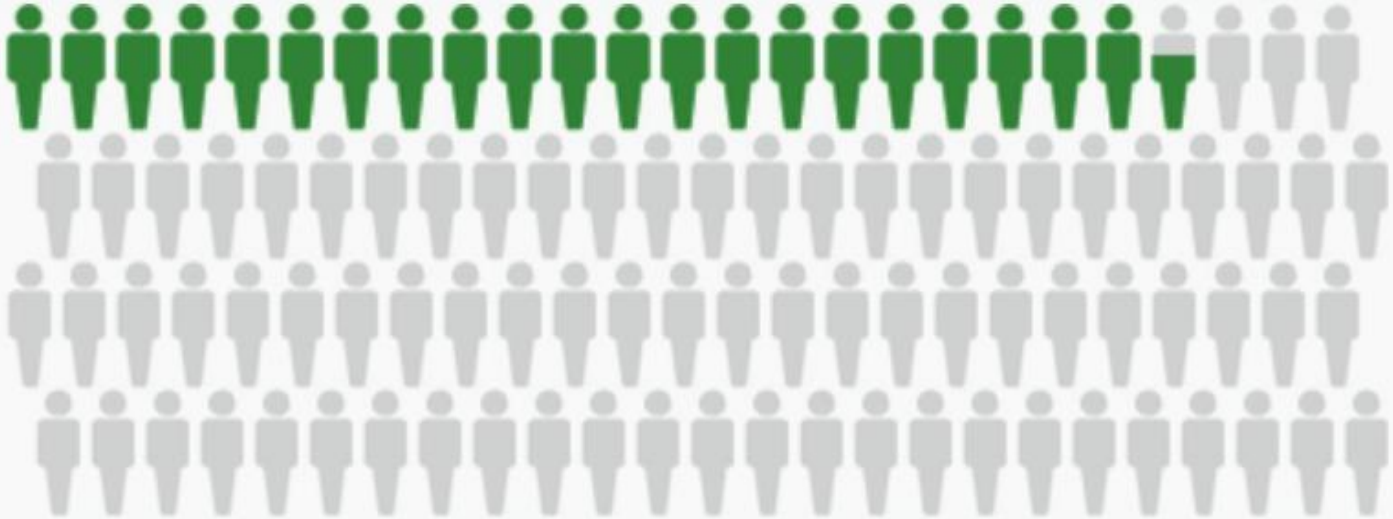
- Incidence: 22,070 (17,430 in men and 4,640 in women)
- Deaths: 16,250 (12,940 in men and 3,310 in women)
- Lifetime risk: 1 in 127 (men) and 1 in 434 (women)
- Rates in the US have been stable for years but decreasing slightly over the past decade
- Demographics:
  - Adenocarcinoma most common in White people
  - Squamous cell carcinoma most common in African Americans

# Incidence by Stage




- **Localized (18%)**
  Confined to Primary Site
- **Regional (32%)**
  Spread to Regional Lymph Nodes
- **Distant (39%)**
  Cancer Has Metastasized
- **Unknown (11%)**
  Unstaged

# 5-year Survival



5-Year
Relative Survival

**21.6%**

Based on data from SEER 22 (Excluding IL/MA) 2014–2020. Gray figures represent those who have died from esophageal cancer. Green figures represent those who have survived 5 years or more.

# Who is at Greatest Risk of Dying from Esophageal Cancer?

**Death Rate per 100,000 Persons by Race/Ethnicity & Sex: Esophageal Cancer**

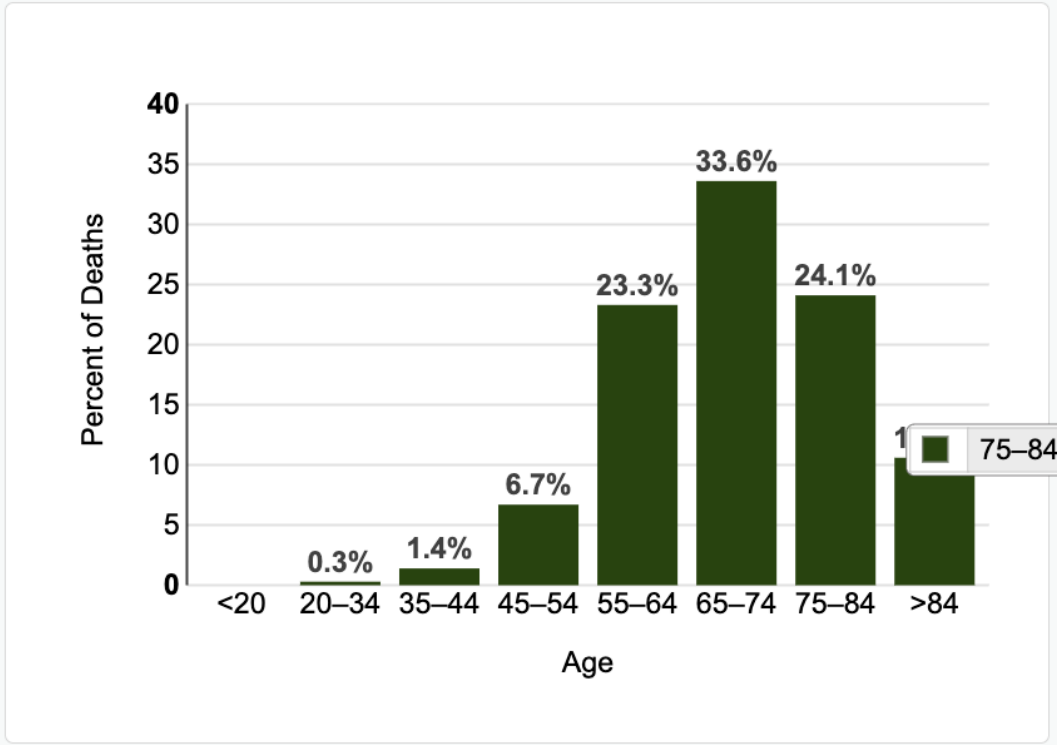
| MALES | |
|---|---|
| All Races | 6.5 |
| Hispanic | 3.4 |
| Non-Hispanic American Indian/Alaska Native | 6.5 |
| Non-Hispanic Asian/Pacific Islander | 2.6 |
| Non-Hispanic Black | 4.5 |
| Non-Hispanic White | 7.5 |

| FEMALES | |
|---|---|
| All Races | 1.4 |
| Hispanic | 0.7 |
| Non-Hispanic American Indian/Alaska Native | 1.6 |
| Non-Hispanic Asian/Pacific Islander | 0.7 |
| Non-Hispanic Black | 1.5 |
| Non-Hispanic White | 1.5 |

U.S. 2018–2022, Age-Adjusted

# What Age Group is at Greatest Risk of Dying from Esophageal Cancer?

**Percent of Deaths by Age Group: Esophageal Cancer**

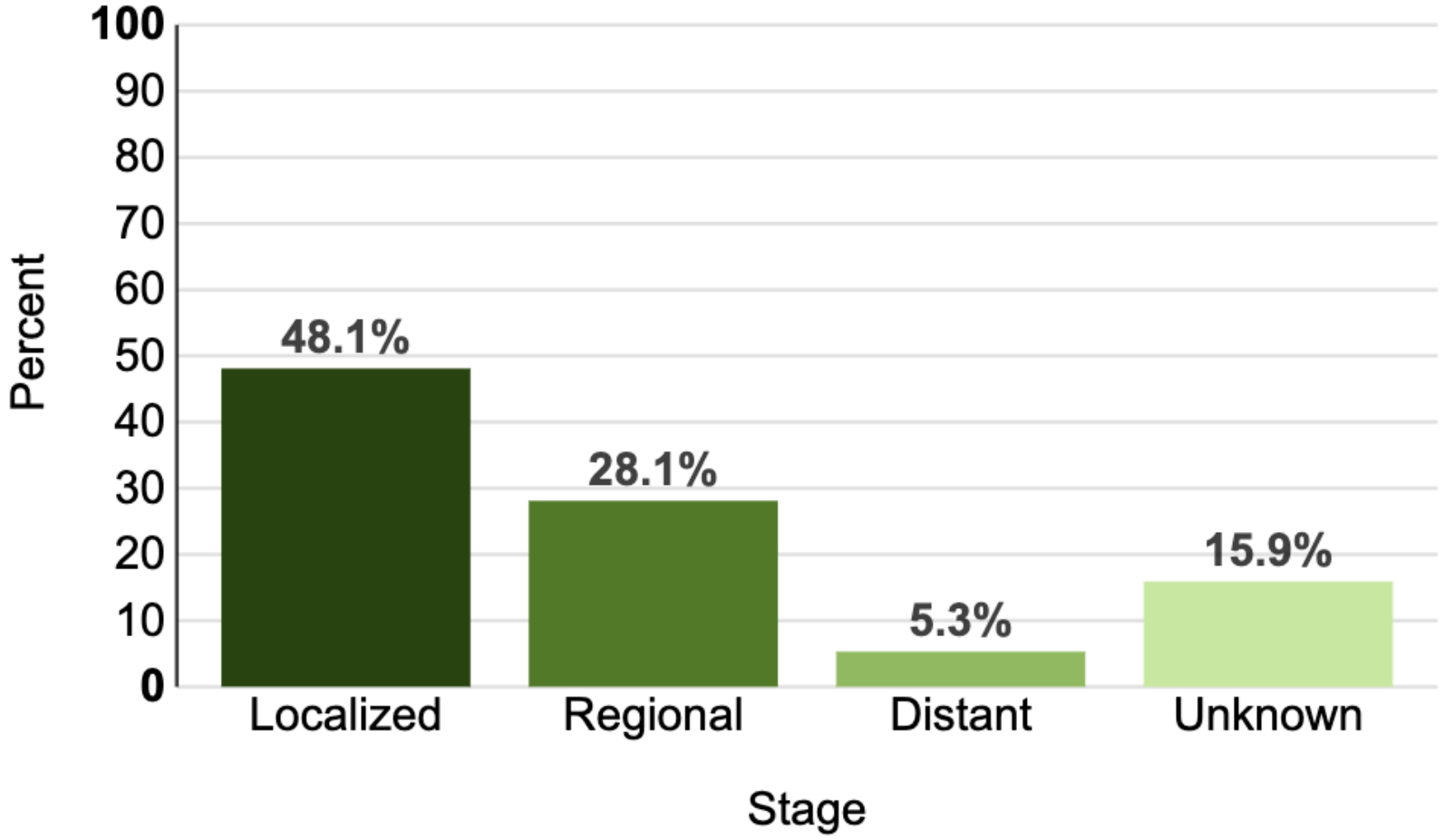



The percent of esophageal cancer deaths is highest among people aged 65–74.

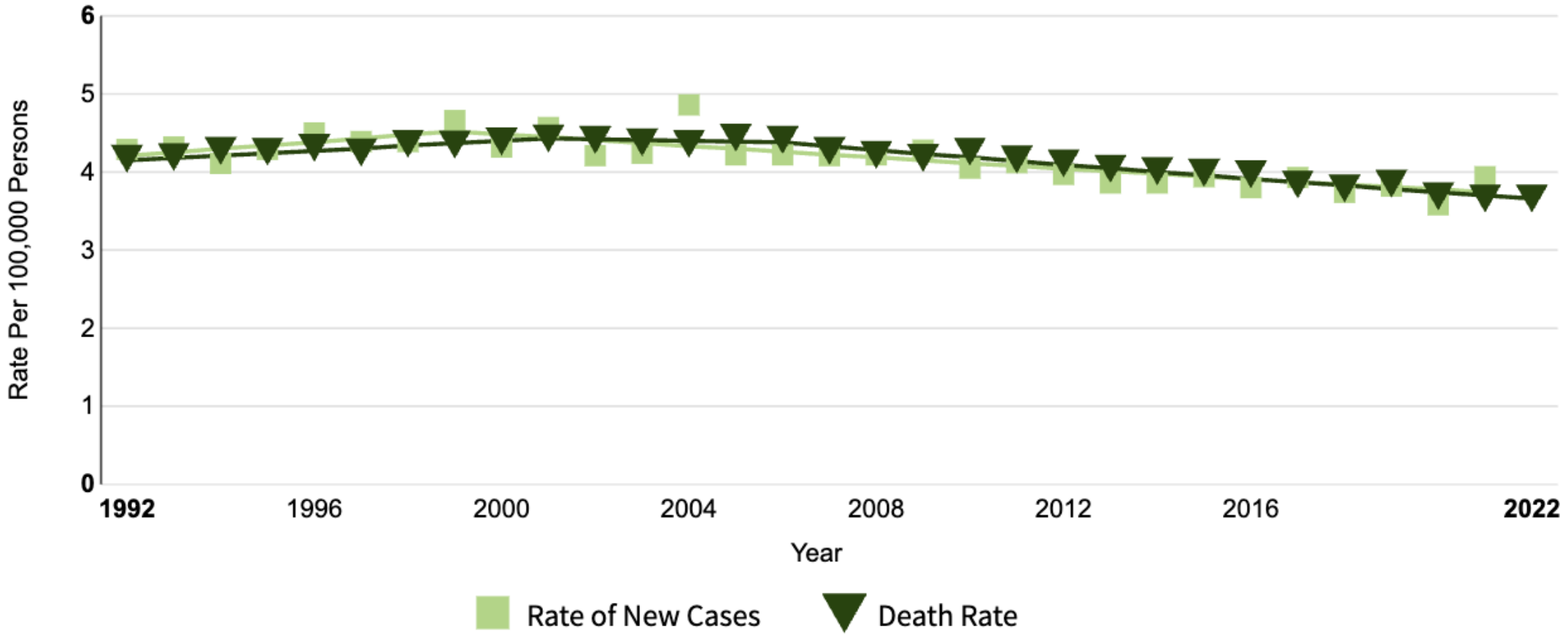
| Median Age At Death |
| --- |
| 70 |

U.S. 2018–2022, All Races, Both Sexes

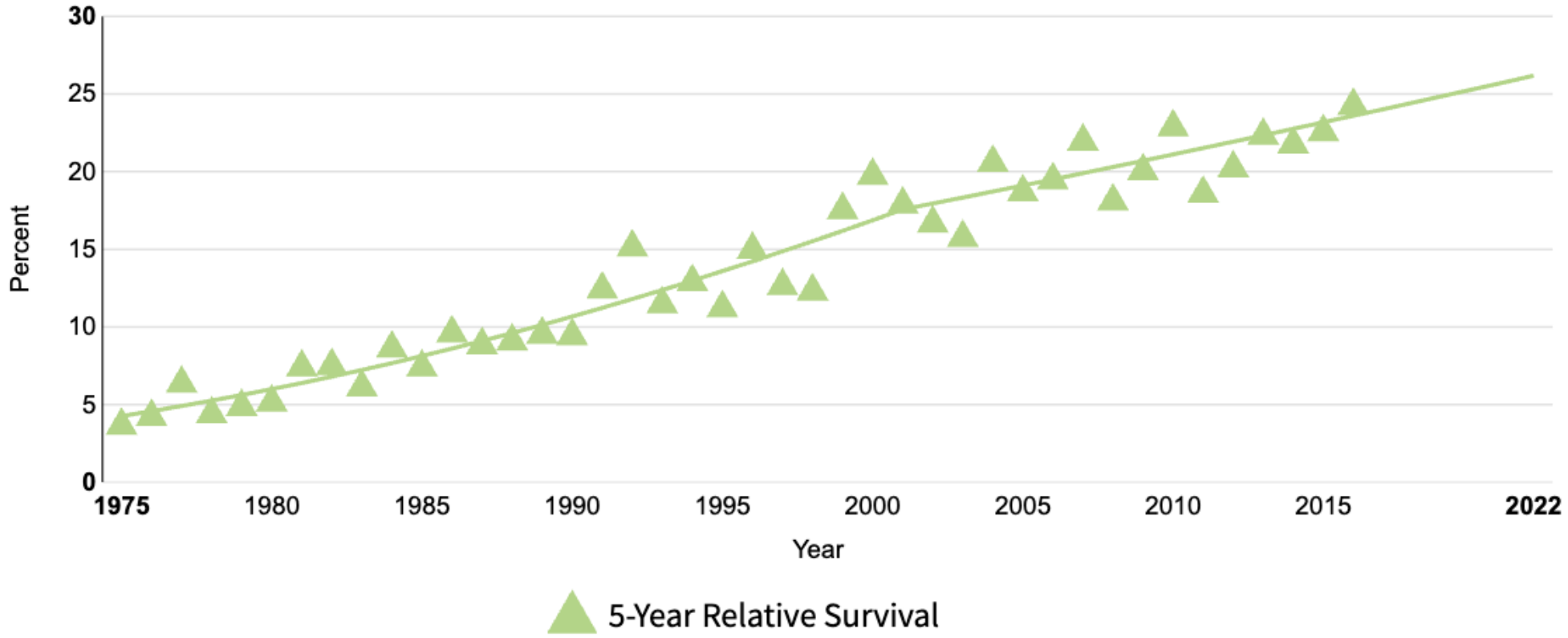
# 5-Year Survival by Stage



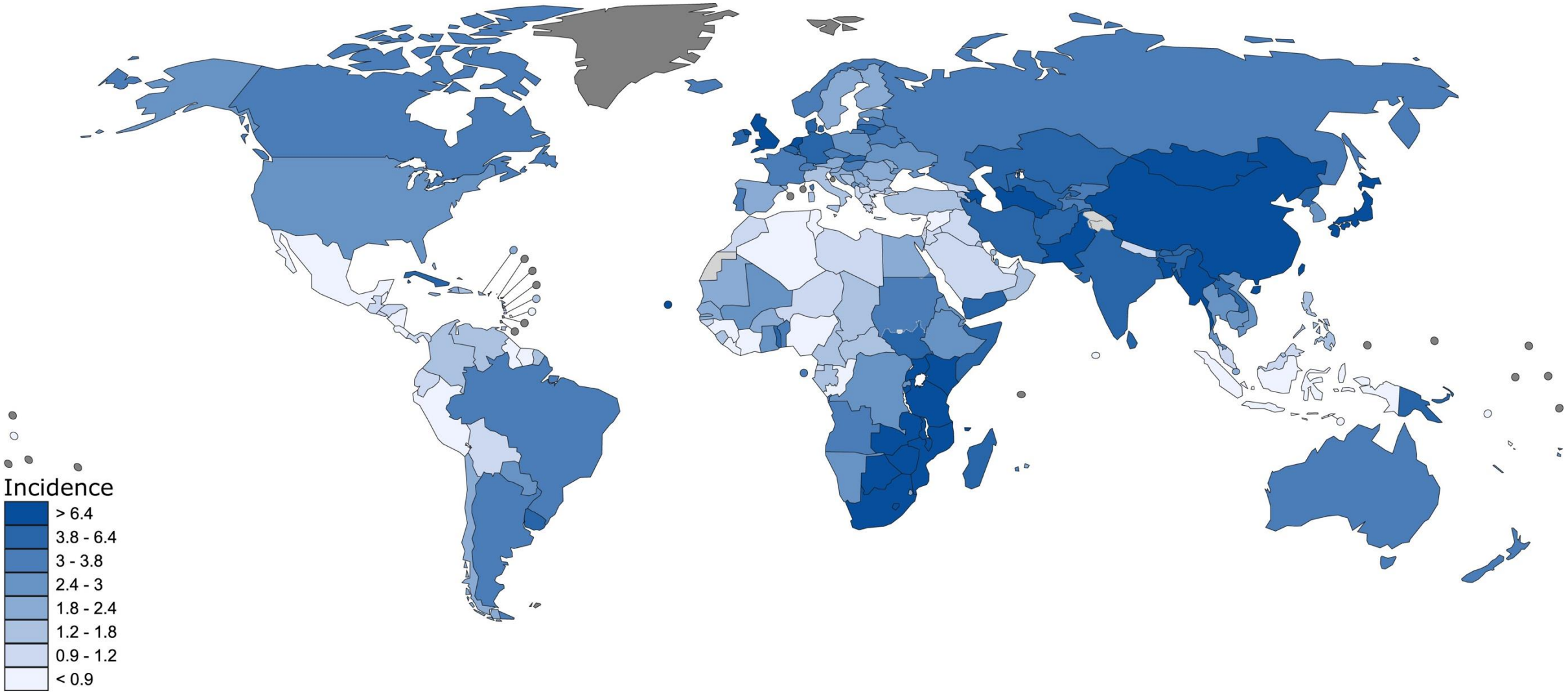
# Incidence and Mortality Over Time



# Relative Survival is Improving Over Time



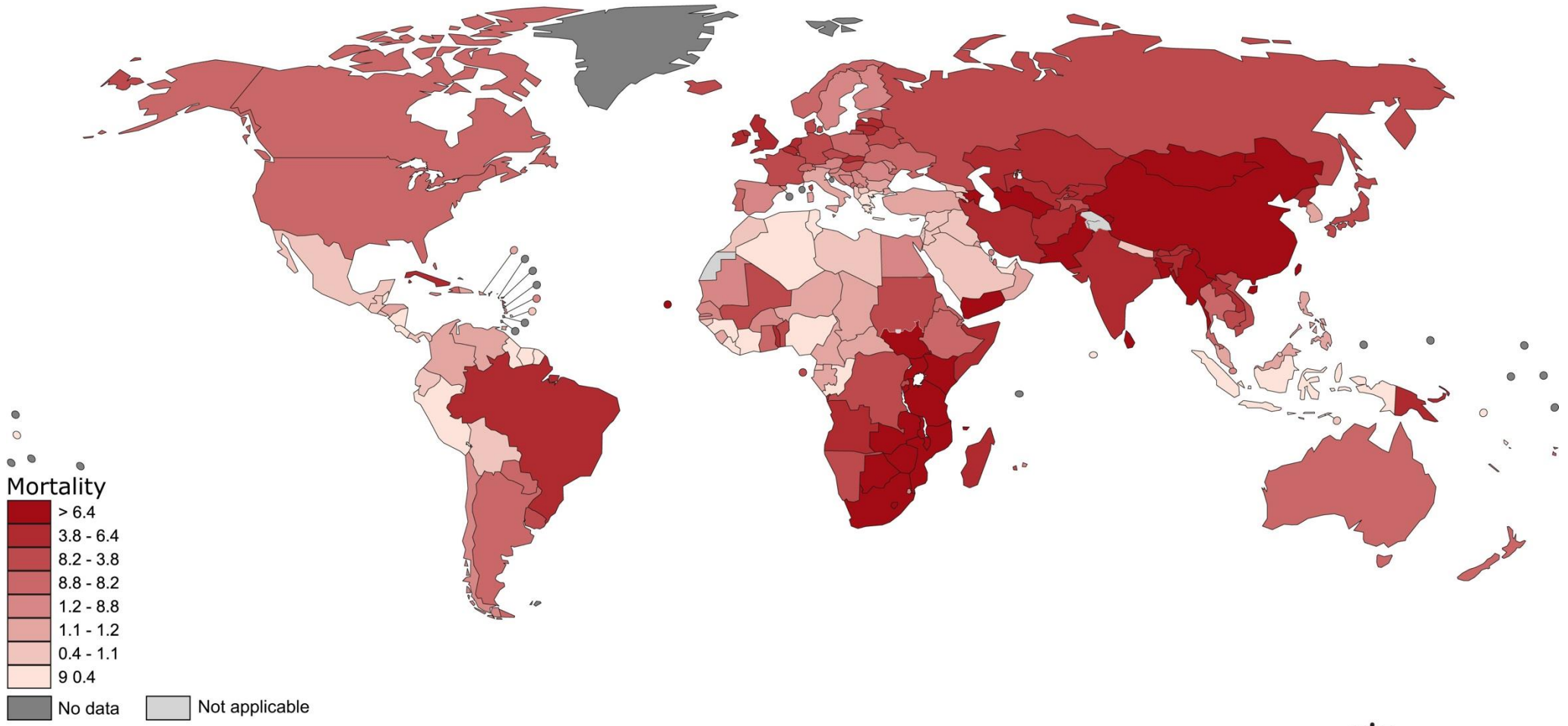
# Global Incidence of Esophageal Cancer






Morgan, *Gastroenterology* 2022

# Global Mortality of Esophageal Cancer



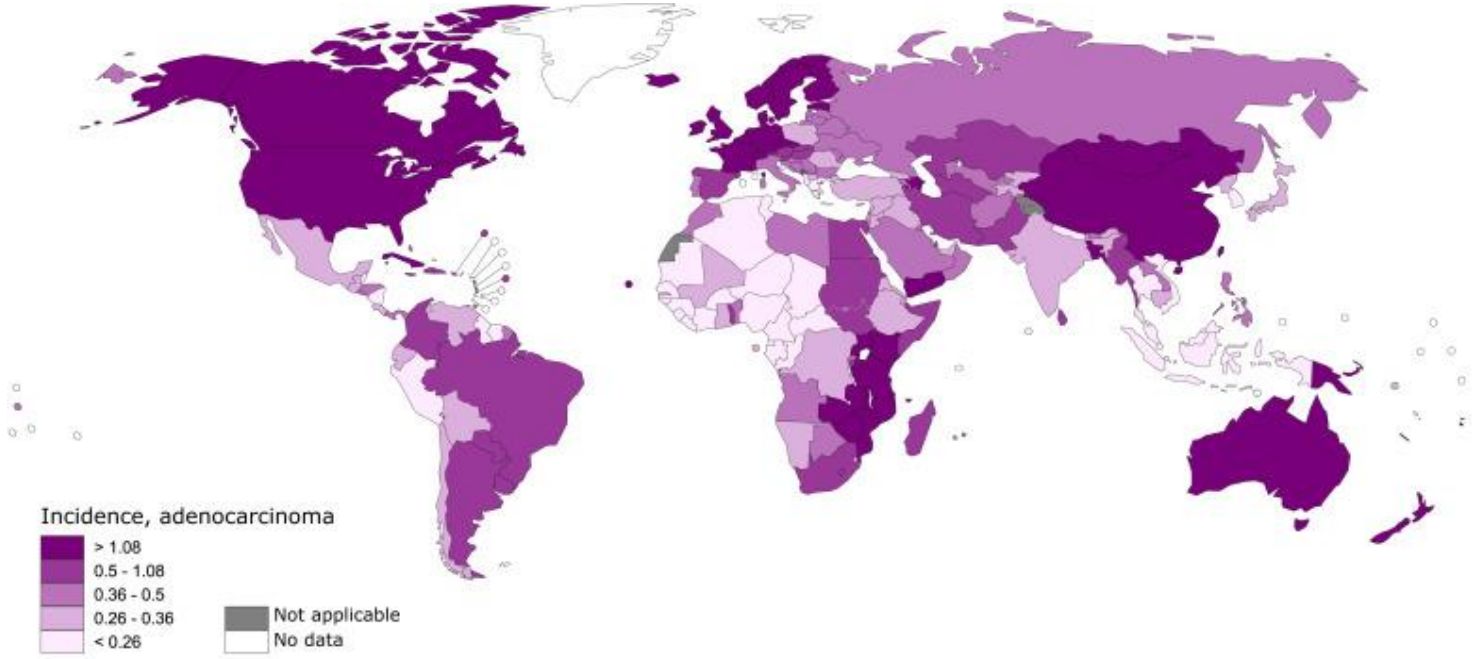

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data source: Globocan 2020
Map production: CSU
World Health Organization

World Health Organization

# Epidemiology of Esophageal Cancer

| Adenocarcinoma |
| --- |
| • GEJ/lower third of esophagus |
| • Better prognosis |
| • N America<br>• Western Europe |
| • Obesity<br>• GERD<br>• Barrett's esophagus<br>• M>F |
| • Familial Barrett's |

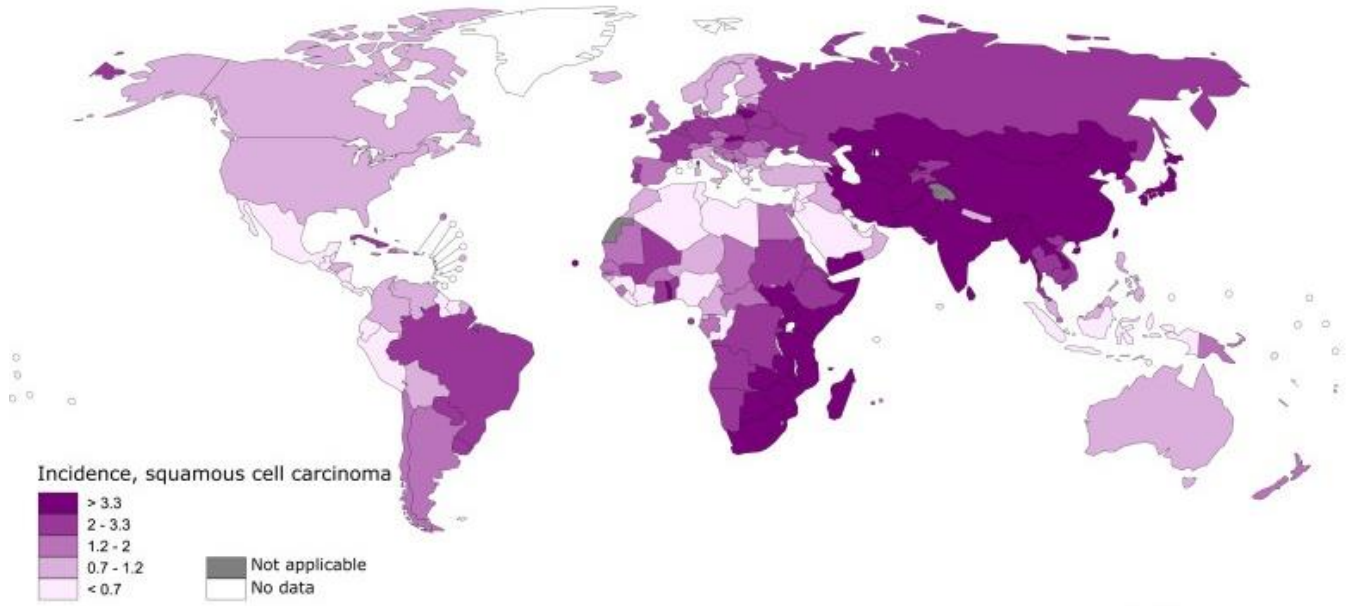



**Incidence:** 20,6040 in the United States
>500,000 globally → 1M by 2040

**Mortality:** 16,410 in the United States
>500,000 globally

# Epidemiology of Esophageal Cancer

| Adenocarcinoma | Squamous Cell Carcinoma |
|---|---|
| • GEJ/lower third of esophagus | • Proximal-mid esophagus |
| • Better prognosis | • Poorer prognosis |
| • N America<br>• Western Europe | • Asia<br>• Africa<br>• Eastern Europe |
| • Obesity<br>• GERD<br>• Barrett's esophagus<br>• M>F | • Tobacco<br>• EtOH<br>• Nutrient/vitamin deficiency<br>• M>F |
| • Familial Barrett's | • Tylosis<br>• Bloom Syndrome<br>• Fanconi anemia |




**Incidence:** 20,6040 in the United States
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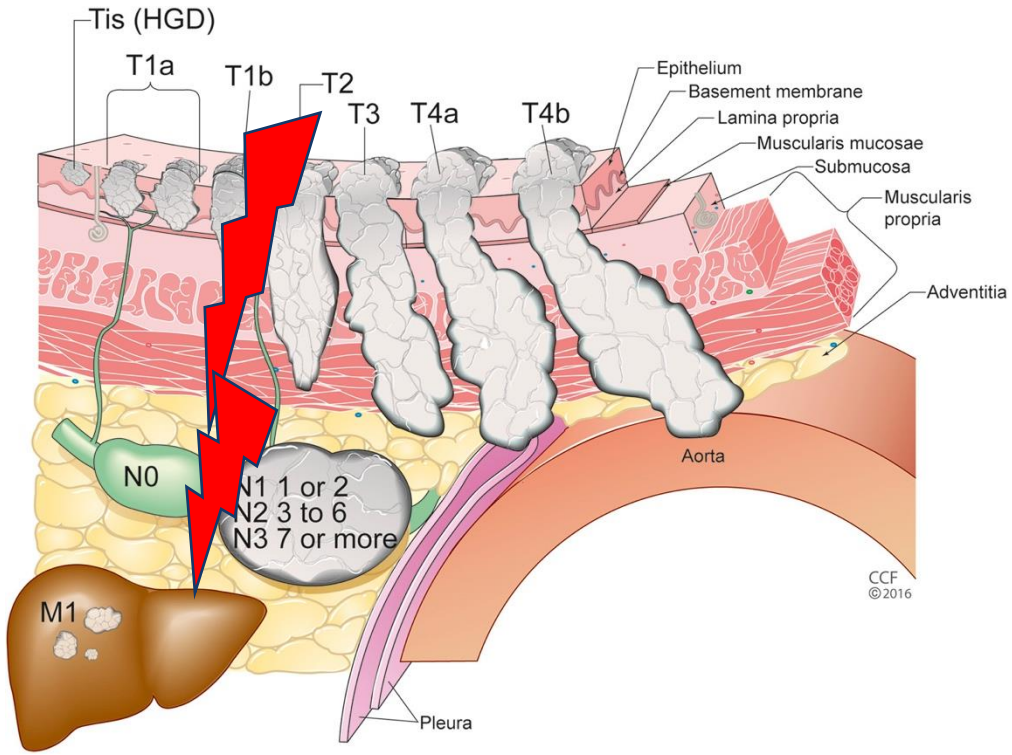
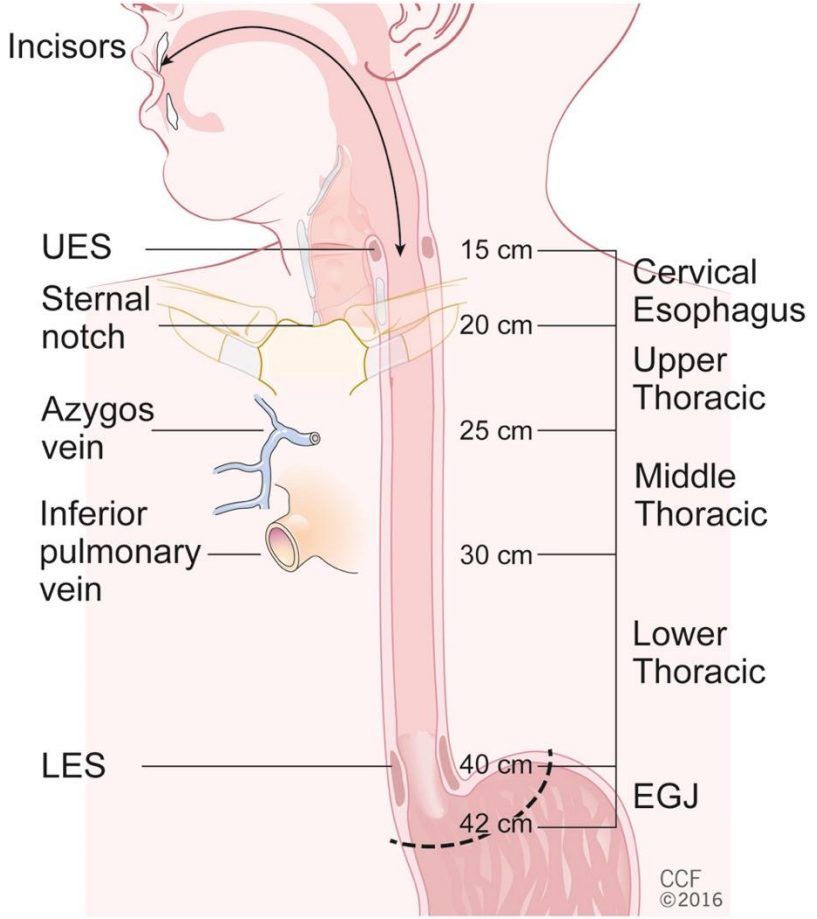
**Mortality:** 16,410 in the United States
>500,000 globally

# Treatment Approach: Localized Disease




**A** **pTNM Adenocarcinoma**

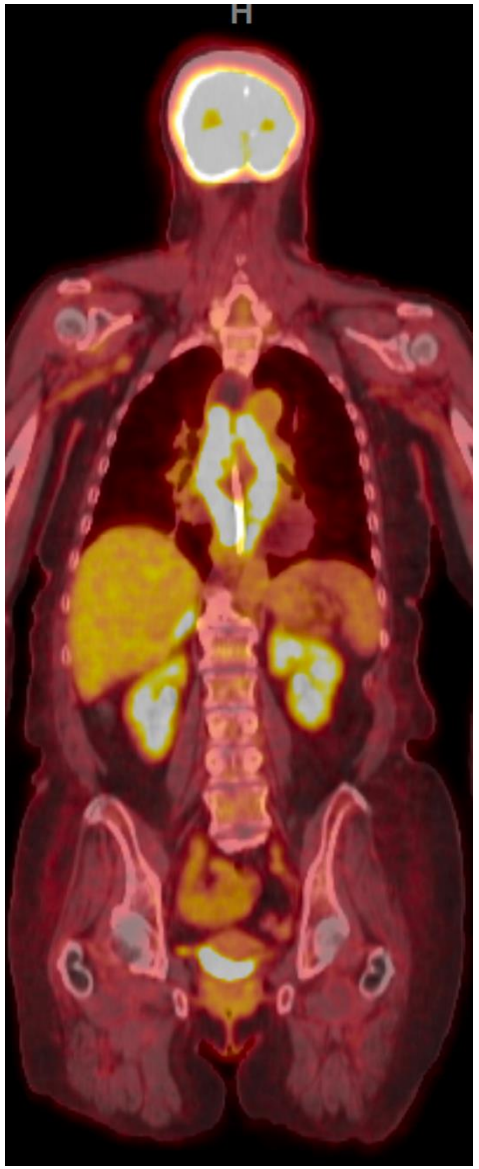
| | N0 | N1 | N2 | N3 | M1 |
|---|---|---|---|---|---|
| Tis | 0 | | | | |
| T1a G1 G2 G3 | IA IB IC | IIB | IIIA | IVA | IVB |
| T1b G1 G2 G3 | IB IC | IIB | IIIA | IVA | IVB |
| T2 G1 G2 G3 | IC IIA | IIIA | IIIB | IVA | IVB |
| T3 | IIB | IIIB | IIIB | IVA | IVB |
| T4a | IIIB | IIIB | IVA | IVA | IVB |
| T4b | IVA | IVA | IVA | IVA | IVB |

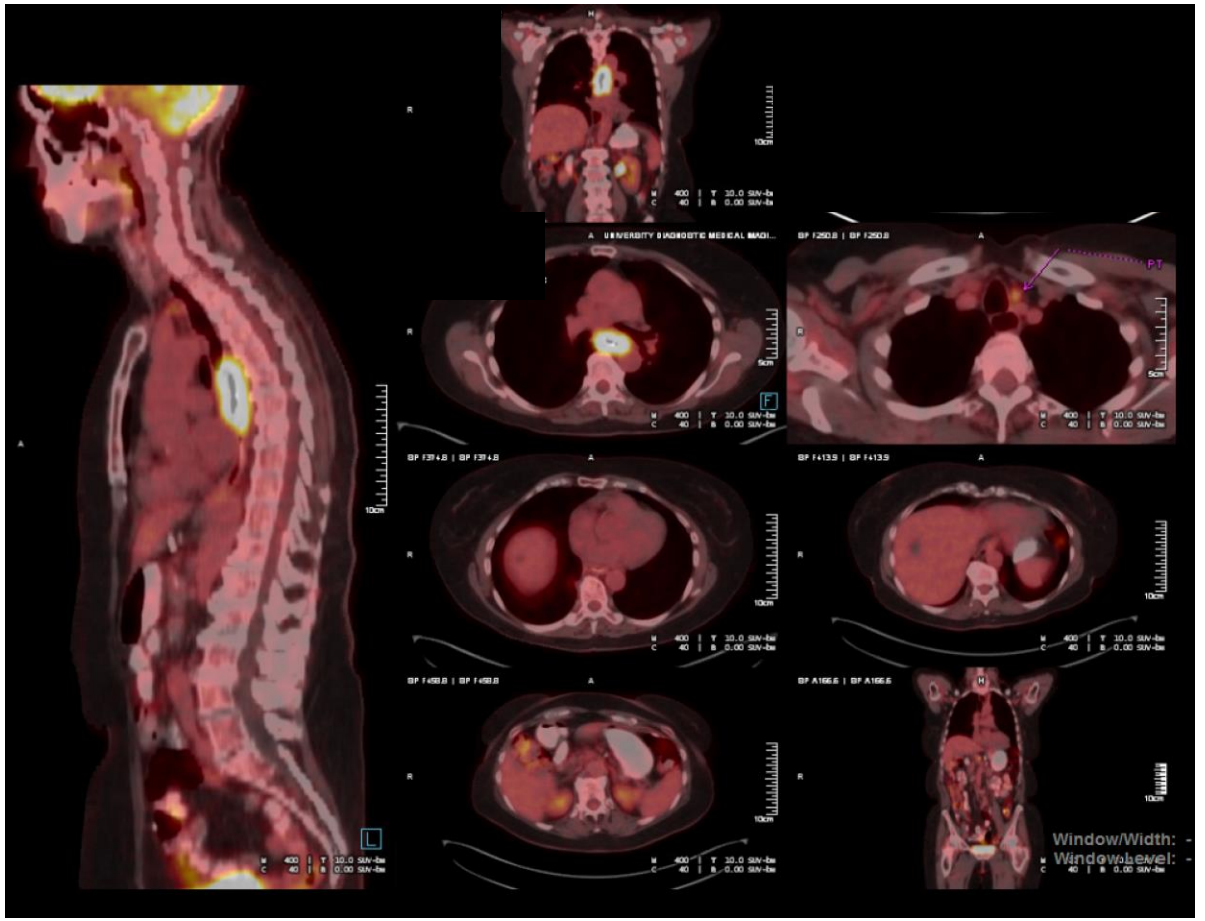
**B** **pTNM Squamous Cell Carcinoma**

| | N0 | | N1 | N2 | N3 | M1 |
|---|---|---|---|---|---|---|
| | L | U/M | | | | |
| Tis | 0 | | | | | |
| T1a G1 G2-3 | IA | IA | IIB | IIIA | IVA | IVB |
| | IB | IB | | | | |
| T1b | IB | | IIB | IIIA | IVA | IVB |
| T2 G1 G2-3 | IB | IB | IIIA | IIIB | IVA | IVB |
| | IIA | IIA | | | | |
| T3 G1 G2-3 | IIA | IIA | IIIB | IIIB | IVA | IVB |
| | IIA | IIB | | | | |
| T4a | IIIB | | IIIB | IVA | IVA | IVB |
| T4b | IVA | | IVA | IVA | IVA | IVB |

**Definitive approach if <IVB:**

- **T1bN0 or less → endoscopic/surgical only**
- **Otherwise multimodality approach**

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# Outline

- Epidemiology of esophageal cancer
- Definitive treatment of locally advanced disease
- Systemic treatment for metastatic disease
- Novel therapeutic directions
- Translational investigation at CUIMC

# Treatment Modalities

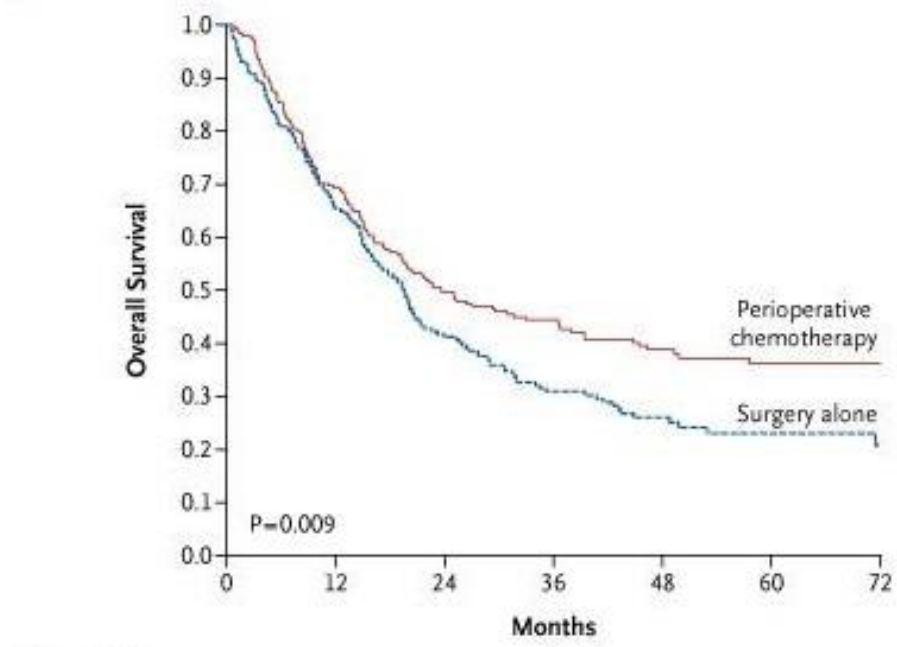
- Surgery
- Chemotherapy
- Radiation
- Immunotherapy
- Targeted therapy

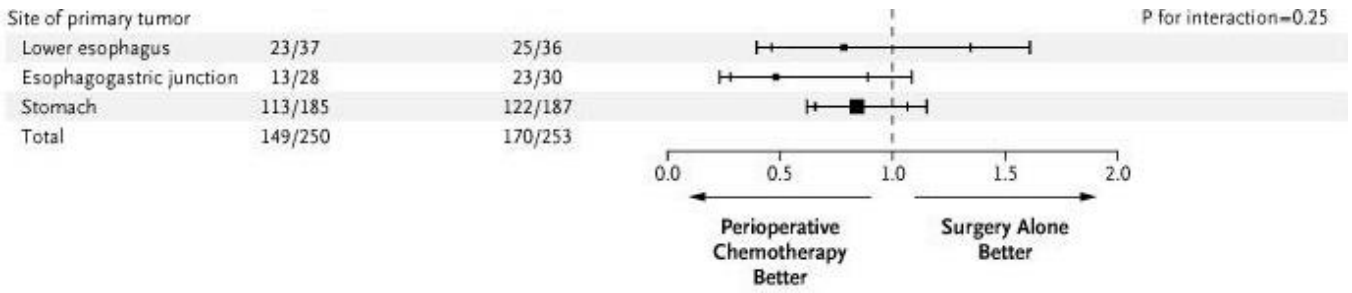
# Management of Locally Advanced Disease

- Surgery – is it better to give chemo before/after?
  - MAGIC
  - FFCD

# Perioperative Chemotherapy: MAGIC

- Surgery alone vs perioperative ECF (epirubicin/cisplatin/5-FU) x 3 Q21d cycles before and after surgery
- Esophagus/GEJ: 65-66/arm (27% of patients)



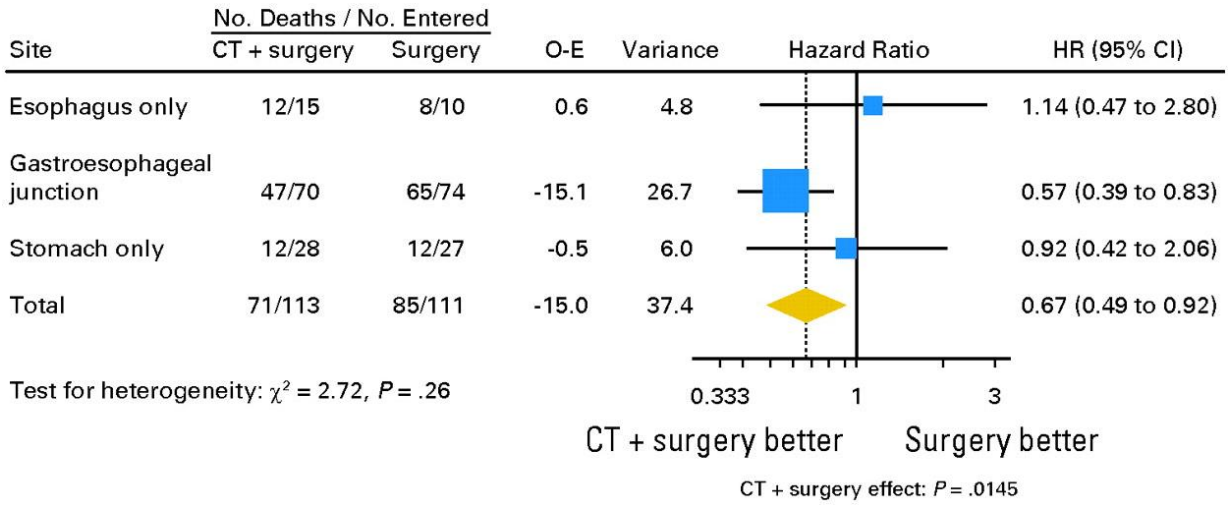





Cunningham, *N Engl J Med* 2006; Ychou *JCO* 2011

# Perioperative Chemotherapy: FFCD

- Surgery vs perioperative CF (cisplatin/5-FU) x 2-3 Q28d cycles before and after surgery
- Esophagus/GEJ: 160/arm (75% of patients)

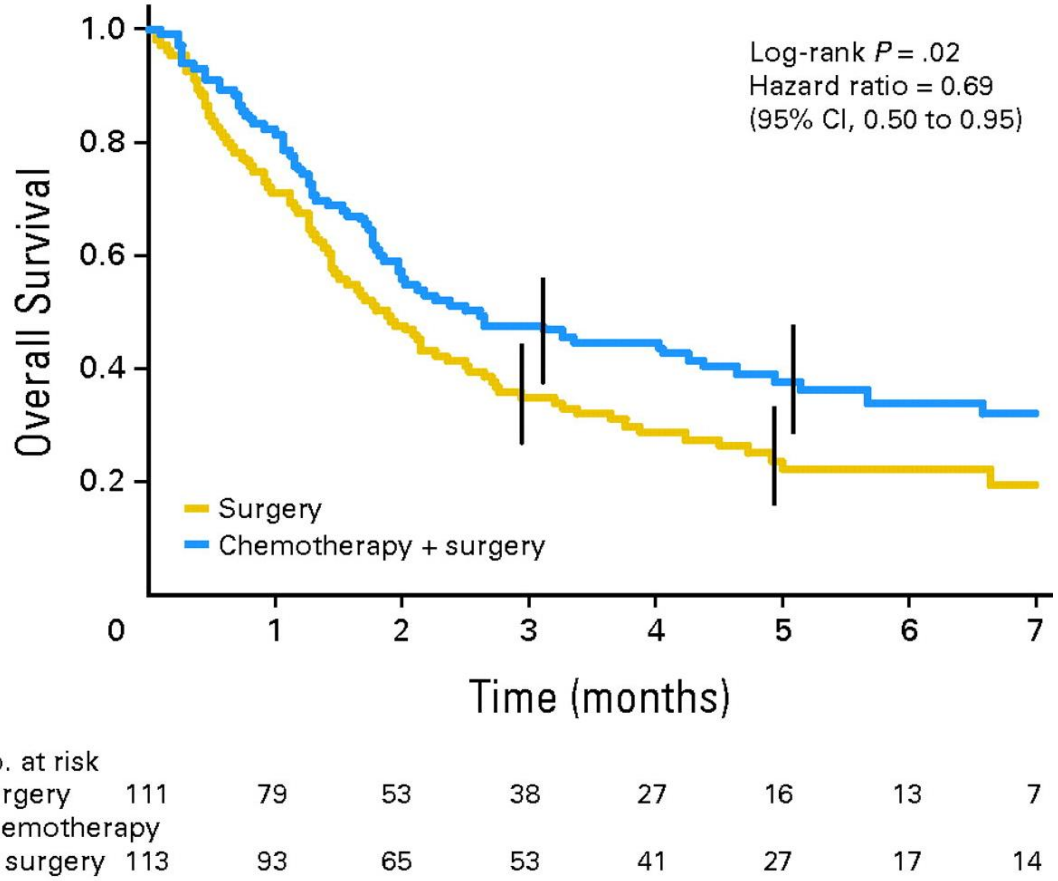


| Site | No. Deaths / No. Entered: CT + surgery | Surgery | O-E | Variance | HR (95% CI) |
|---|---|---|---|---|---|
| Esophagus only | 12/15 | 8/10 | 0.6 | 4.8 | 1.14 (0.47 to 2.80) |
| Gastroesophageal junction | 47/70 | 65/74 | -15.1 | 26.7 | 0.57 (0.39 to 0.83) |
| Stomach only | 12/28 | 12/27 | -0.5 | 6.0 | 0.92 (0.42 to 2.06) |
| Total | 71/113 | 85/111 | -15.0 | 37.4 | 0.67 (0.49 to 0.92) |



Test for heterogeneity: $\chi^2 = 2.72$, $P = .26$

CT + surgery effect: $P = .0145$




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Surgery | 111 | 79 | 53 | 38 | 27 | 16 | 13 | 7 |
| Chemotherapy + surgery | 113 | 93 | 65 | 53 | 41 | 27 | 17 | 14 |

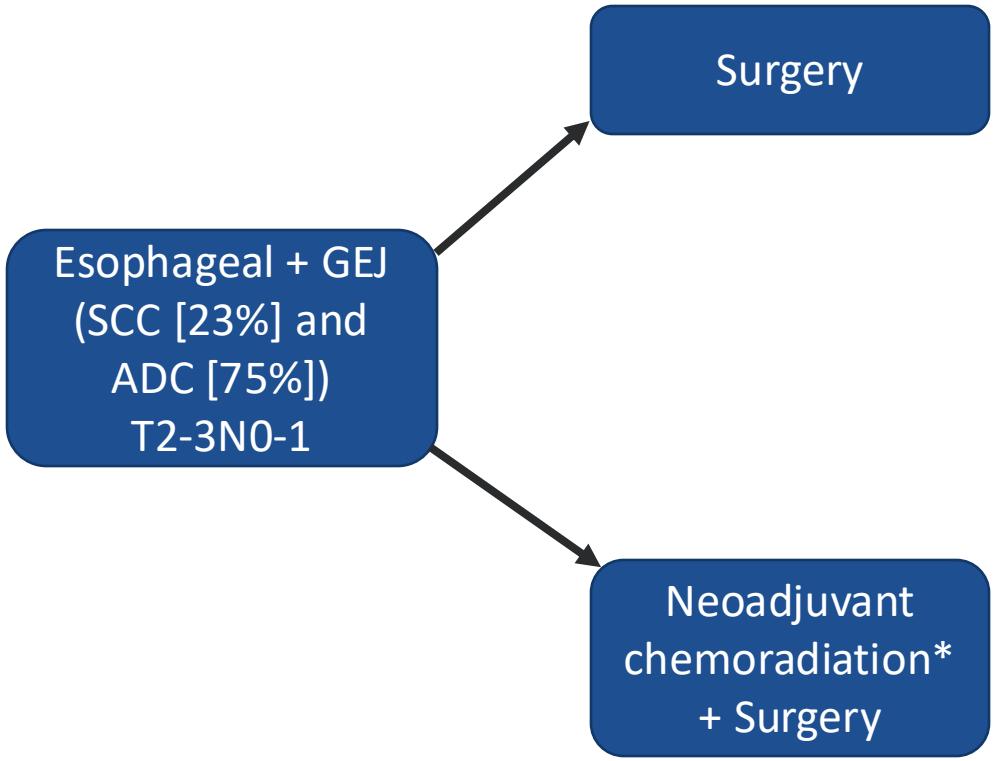


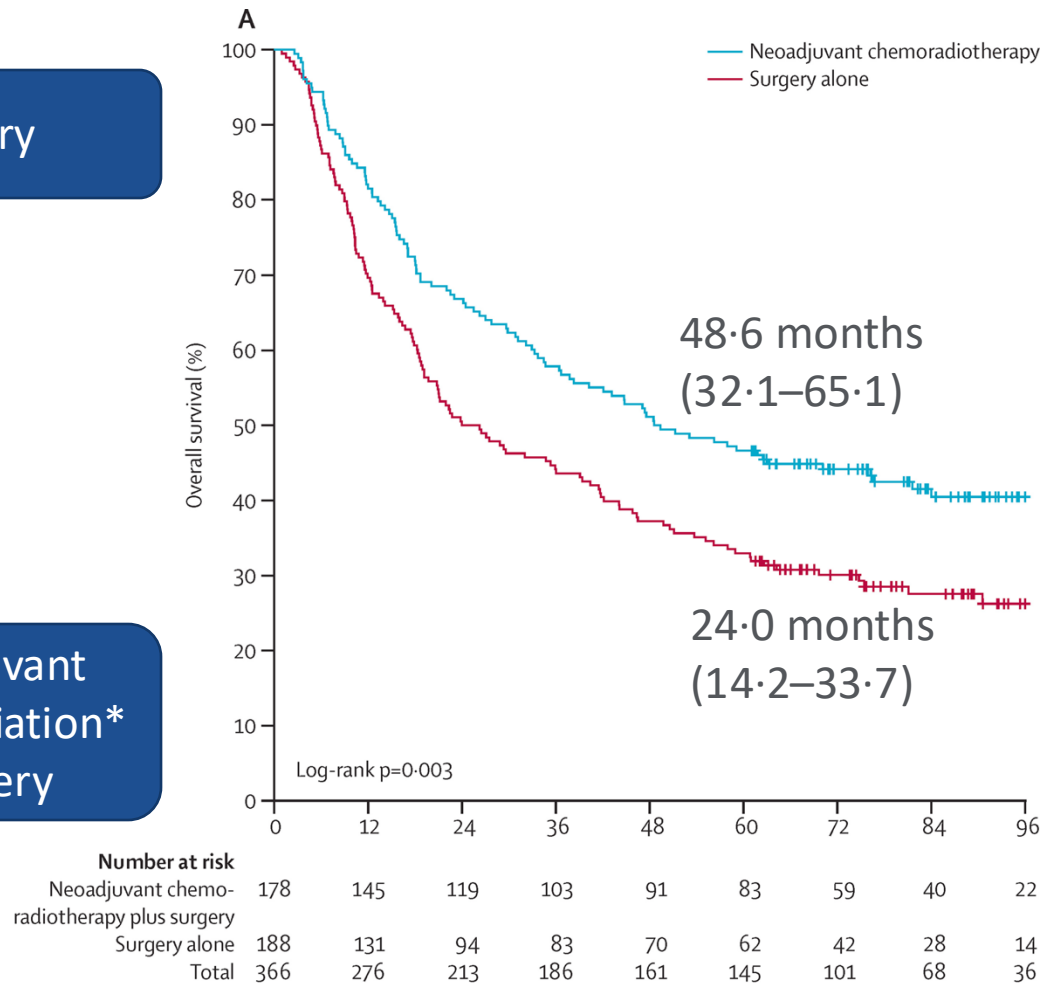
Cunningham, *N Engl J Med* 2006; Ychou *JCO* 2011

# Management of Locally Advanced Disease

- Surgery – is it better to give chemo before/after? YES!
  - MAGIC
  - FFCD
- What about RT?
  - CROSS

# Trimodality therapy vs surgery alone: CROSS



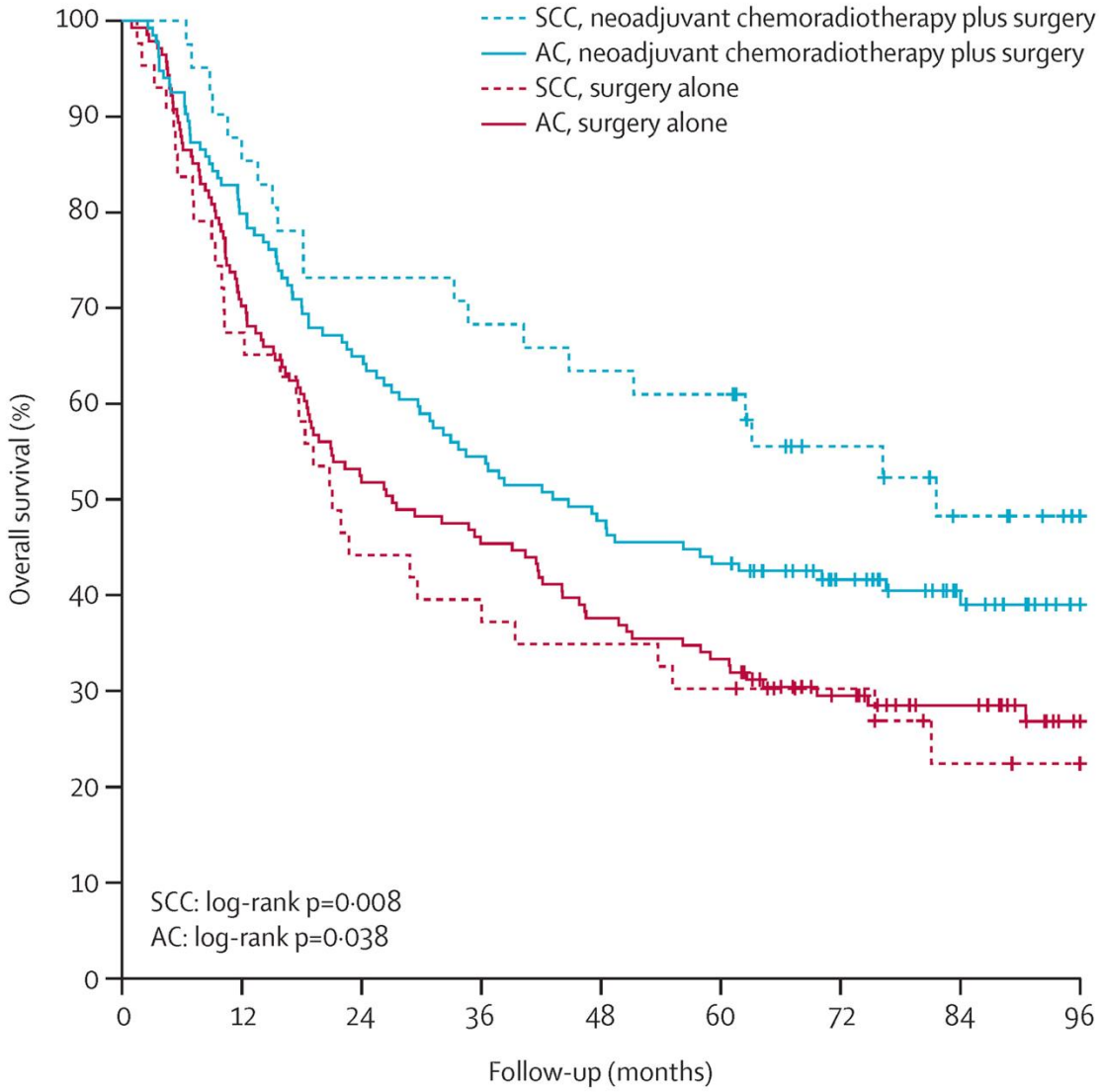




*Chemotherapy: paclitaxel 50 mg/m2 + carboplatin AUC2 weekly x5
Radiation: 41 Gy



van Hagen, *N Engl J Med* 2012; Shapiro, *Lancet Oncol* 2015

# Trimodality therapy vs surgery alone: CROSS




| | Neoadjuvant chemoradiotherapy plus surgery (n=178) | Surgery alone (n=188) | Interaction p value | Univariable analysis | |
|---|---|---|---|---|---|
| | | | | HR (95% CI) | p value |
| All patients | 105 (59%) | 135 (72%) | 0·078 | 0·68 (0·53–0·88) | 0·003 |
| Sex | | | 0·451 | | |
| Women | 25 (14%) | 24 (13%) | | 0·83 (0·47–1·45) | 0·502 |
| Men | 80 (45%) | 111 (59%) | | 0·65 (0·49–0·86) | 0·003 |
| Tumour histology | | | 0·207 | | |
| Squamous cell carcinoma | 21 (12%) | 32 (17%) | | 0·48 (0·28–0·83) | 0·009 |
| Adenocarcinoma | 81 (46%) | 101 (54%) | | 0·73 (0·55–0·98) | 0·037 |
| Clinical nodal (cN) stage | | | 0·170 | | |
| cN0 | 27 (15%) | 42 (22%) | | 0·50 (0·31–0·80) | 0·004 |
| cN1 | 77 (43%) | 85 (45%) | | 0·81 (0·59–1·10) | 0·176 |
| WHO performance score | | | 0·729 | | |
| 0 | 84 (47%) | 117 (62%) | | 0·66 (0·50–0·88) | 0·004 |
| 1 | 21 (12%) | 18 (10%) | | 0·75 (0·40–1·41) | 0·367 |

# Case 1

- 63 year old female with HTN, CAD, epilepsy, Plummer Vinson syndrome who presented to CUIMC in after several months of painful swallowing and 25-lb weight loss.
- CT chest: 9-cm esophageal mass
- EGD: invasive squamous cell carcinoma arising in background of high-grade dysplasia/carcinoma in situ.
- PET-CT: avidity in the primary lesion but no adenopathy and R adrenal asymmetric FDG uptake concerning for metastasis.
- An esophageal stent was placed but subsequently removed due to pain.
- MRI abd/pelvis was more compatible with adrenal hyperplasia than metastasis.
- PEG was placed
- IMRT (4500 Gy to esophagus over 25 fractions) + carbo/paclitaxel
- Underwent 3-hole esophagectomy on 10/20/2020, final path ypT2N0 SCC.

# Management of Locally Advanced Disease

- Surgery – is it better to give chemo before/after?
  - MAGIC
  - FFCD
  - FLOT-4
- What about RT?
  - CROSS

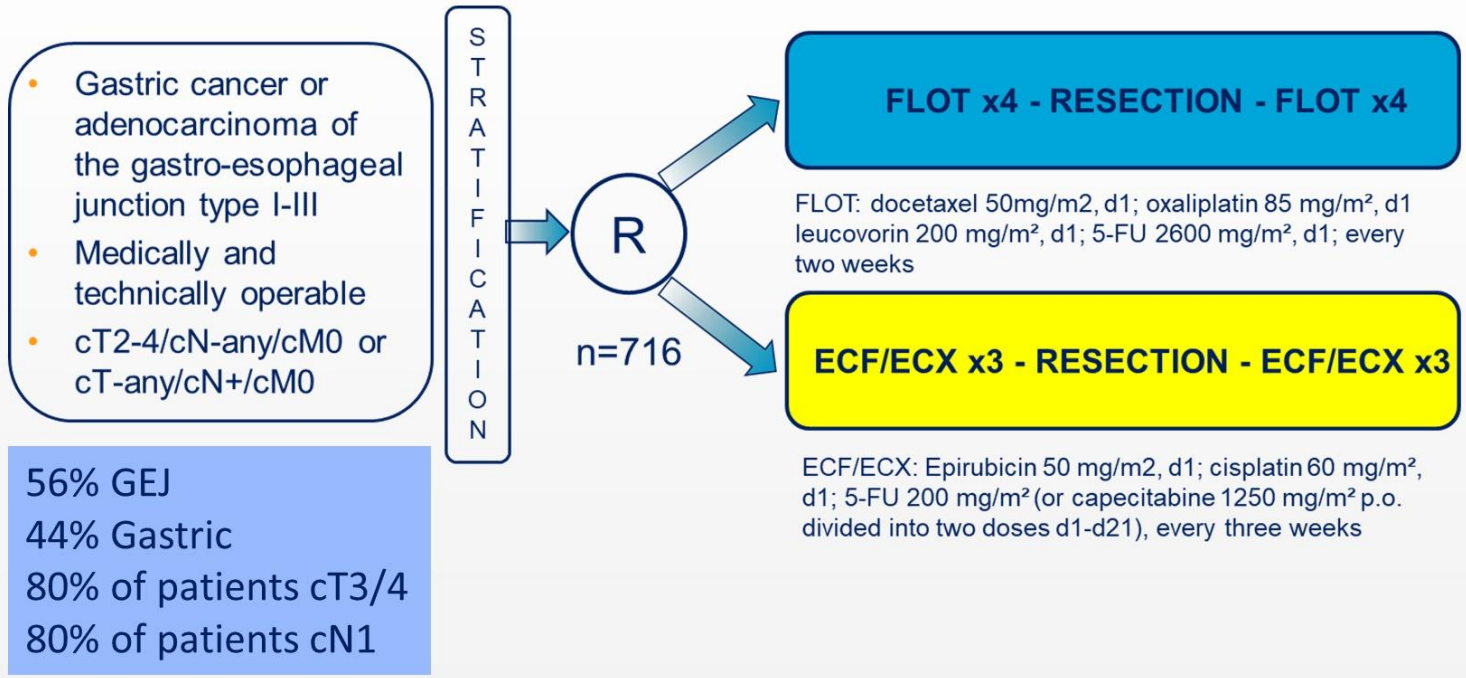
YES!

Even better!

But wait….

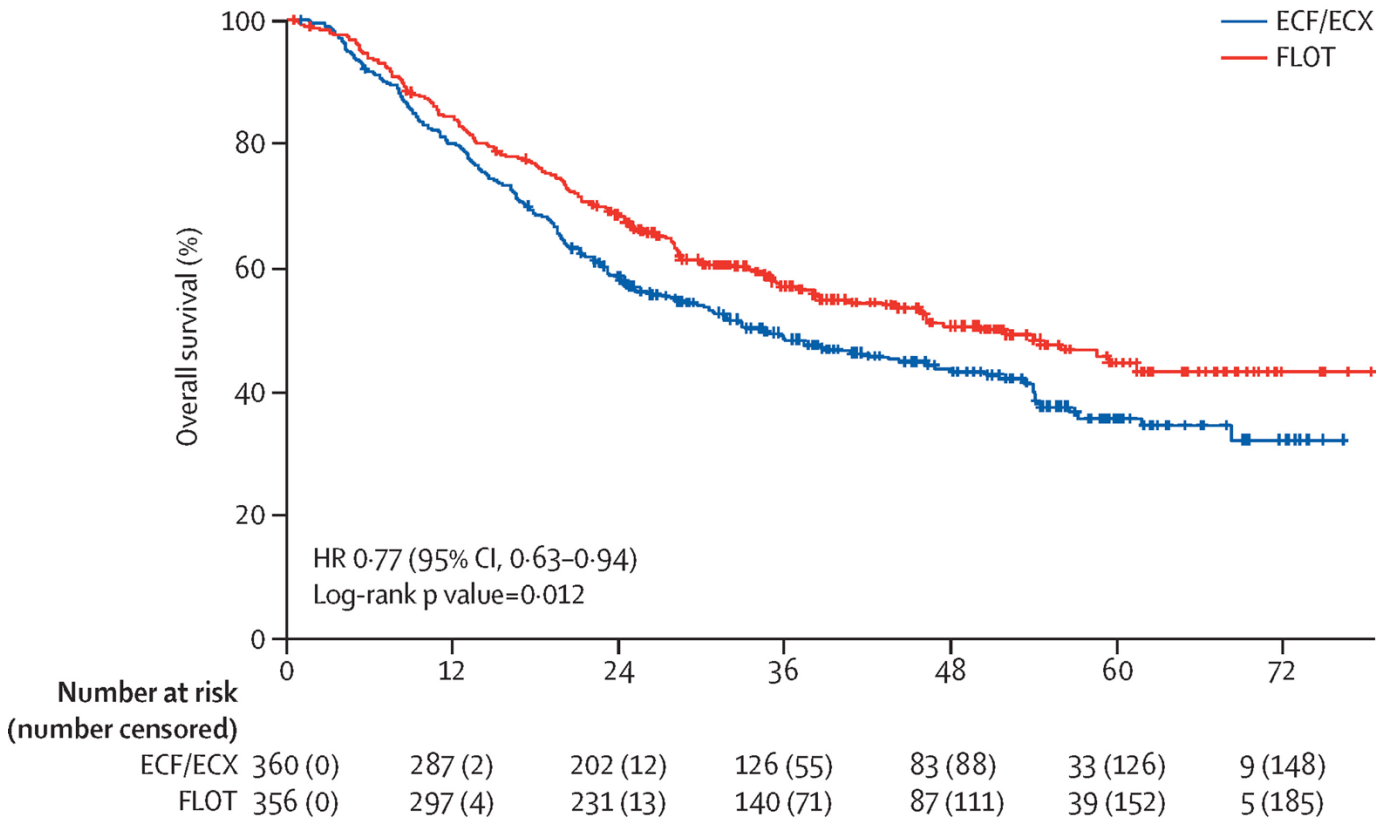
# Return to perioperative chemo?

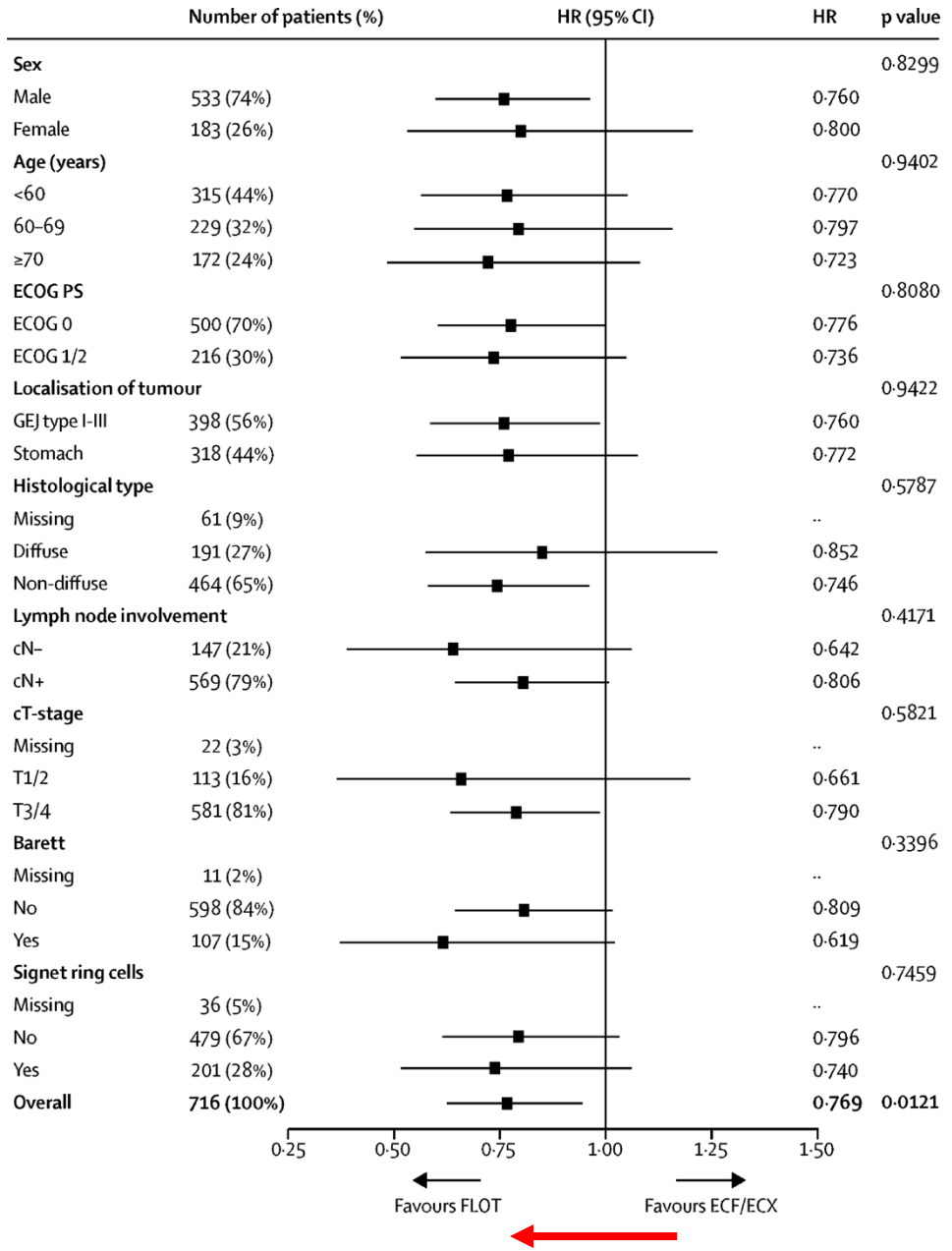
## FLOT4-AIO Study Design




Primary endpoint OS; HR 0.76; 2-sided log rank test a 5% significance level; median OS ECF/ECX 25 months

# Return to perioperative chemo?

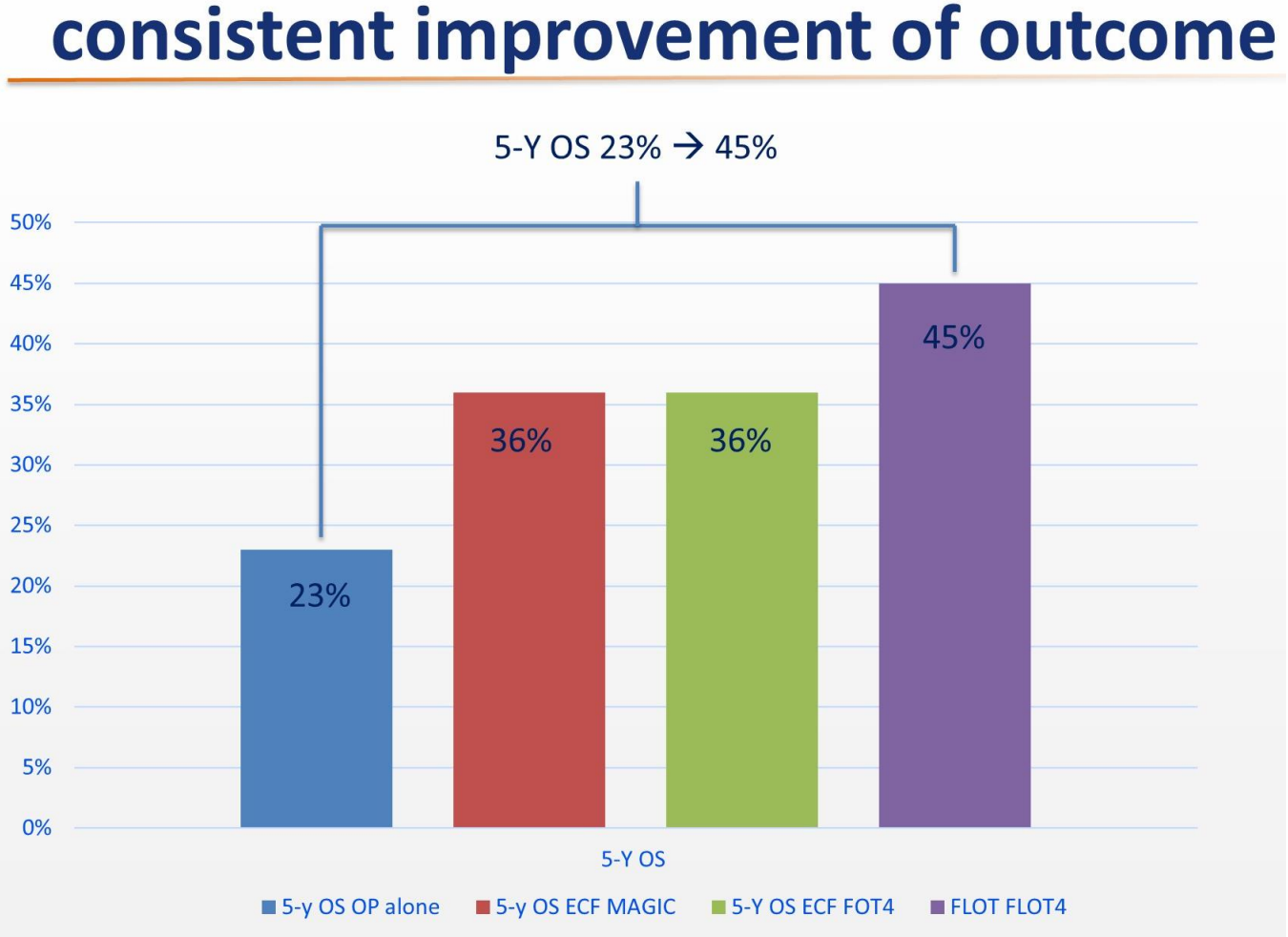



- Higher R0 resection rate with higher pT1 rate
- Improved 3-yr and median OS with FLOT
- Consistent benefit across subtypes

# Return to perioperative chemo?

## Peri-operative chemotherapy: consistent improvement of outcome



# …or not?

## Clinical Toxicity (Acute)

### FLOT

- **Grade ≥3 toxicity**

Neutropenia (50%) **(no px G-CSF)**

Leukopenia (27%) **(no px G-CSF)**

Infections **(18%)**

All else each <10%

**Any Grade (non-Hematologic)**

**Neuropathy (71%)**

**Nausea (67%)**

**Alopecia (63%)**

**Diarrhea (62%)**

**Stomatitis/mucositis (29%)**

**(Includes 4 post-op doses: 4 months of treatment total)**

### 41.4 Gy CROSS

- **Grade ≥3 toxicity (<25%)**

Each <10%

**Any grade**

**Fatigue (67%)**

**Leukopenia (60%)**

**Thrombocytopenia (54%)**

**Nausea (53%)**

**Anorexia (30%)**

**Esophagitis (19%)**

Diarrhea (15%)

Neurotoxic (15%)

Alopecia (15%)

(Includes 5.5 weeks of preop treatment)

### Grade 3-5

**46 Gy FFCD 9102**

28%

**50 Gy SCOPE**

63%

**50.4 Gy RTOG-0496**

68%

# …or not?

## Clinical Toxicity (Acute)

**FLOT**

- **Grade ≥3 toxicity**

Neutropenia (50%) **(no**
Leukopenia (27%) **(no**
Infections **(18%)**
All else each <10%

**Any Grade (non-Hematologic)**

**Neuropathy (71%)**
**Nausea (67%)**
**Alopecia (63%)**
**Diarrhea (62%)**
**Stomatitis/mucositis (29%)**

**(Includes 4 post-op doses: 4 months of treatment total)**

**41.4 Gy**
**CROSS**

- **Grade >3 toxicity (<25%)**

**Leukopenia (60%)**
**Thrombocytopenia (54%)**
**Nausea (53%)**
**Anorexia (30%)**
**Esophagitis (19%)**
Diarrhea (15%)
Neurotoxic (15%)
Alopecia (15%)

(Includes 5.5 weeks of preop treatment)

**Grade 3-5**

**46 Gy**
**FFCD 9102**
28%

**50 Gy**
**SCOPE**
63%

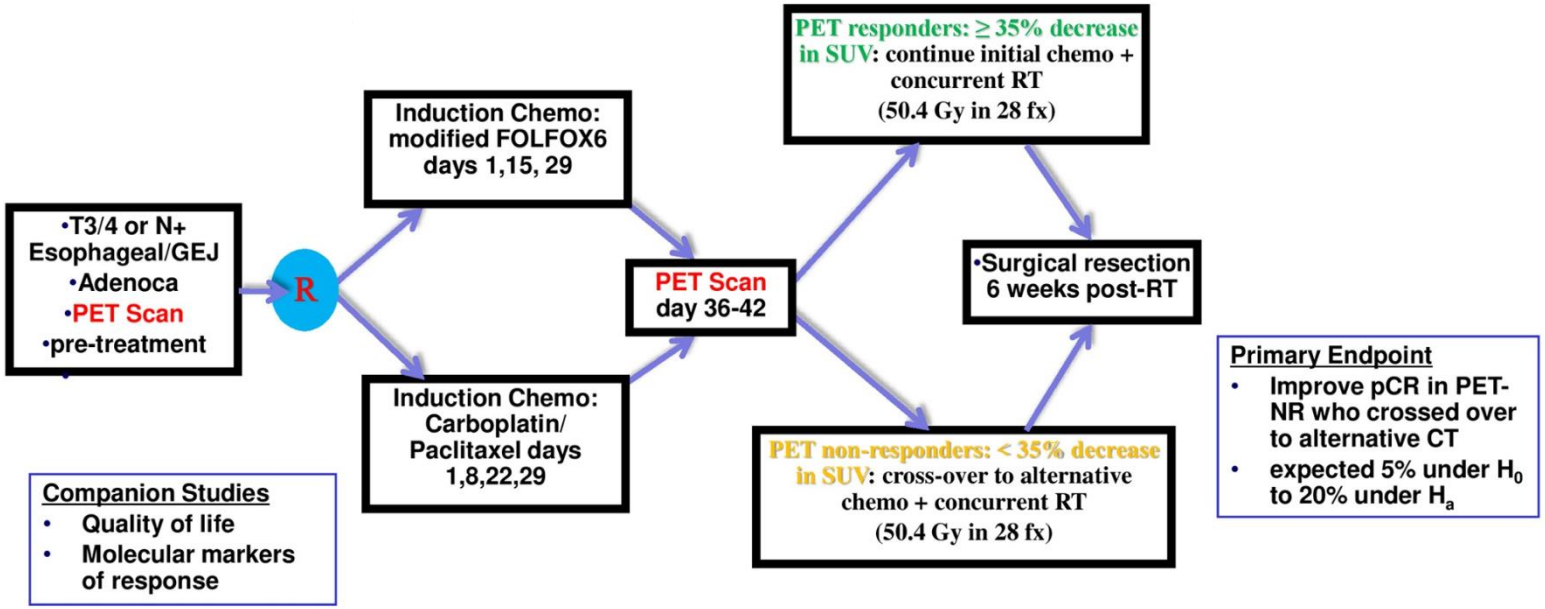
**50.4 Gy**
**RTOG-0496**
68%

ESOPEC Trial – Dr. Shah will teach us more shortly…

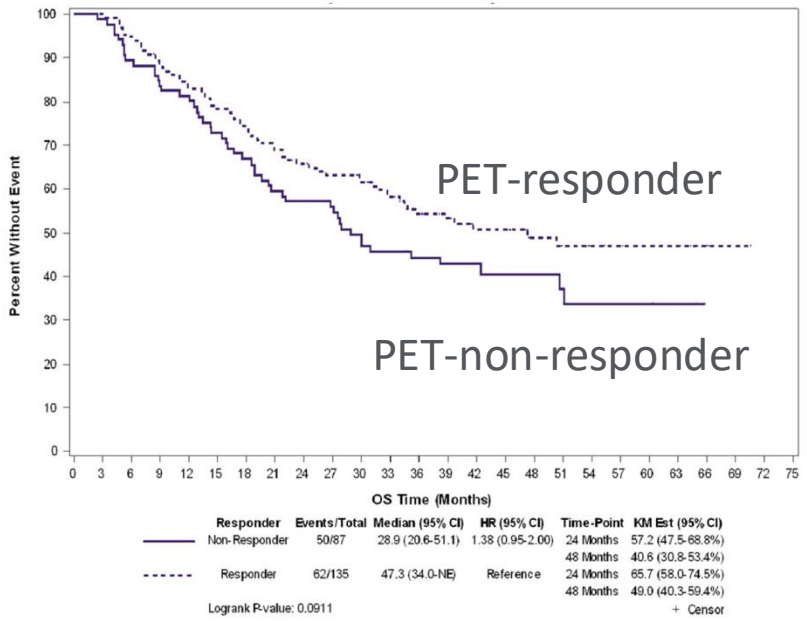
# Management of Locally Advanced Disease

- Surgery – is it better to give chemo before/after?
  - MAGIC
  - FFCD
  - FLOT-4
- What about RT?
  - CROSS
- Chemoselection → RT → Surgery?
  - CALGB 80803

# CALGB 80803: PET-Adapted Approach



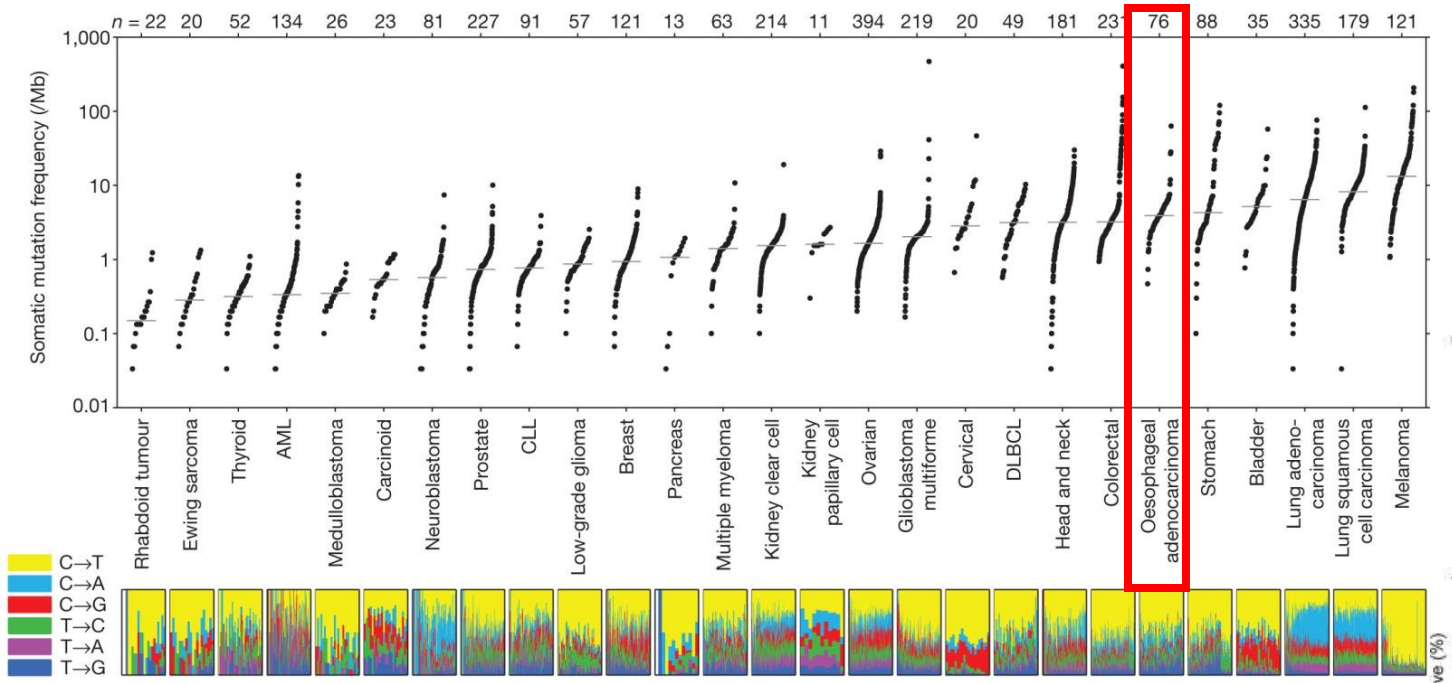

| Regimen | pCR Rate | |
|---|---|---|
| CP → FOLFOX (non-responder) | 17% | 18% 95% CI: (10%,28%) |
| FOLFOX → CP (non-responder) | 19% | |
| FOLFOX → FOLFOX (responder) | 37.5% | 26% 95% CI: (18%,35%) |
| CP → CP (responder) | 12.5% | |

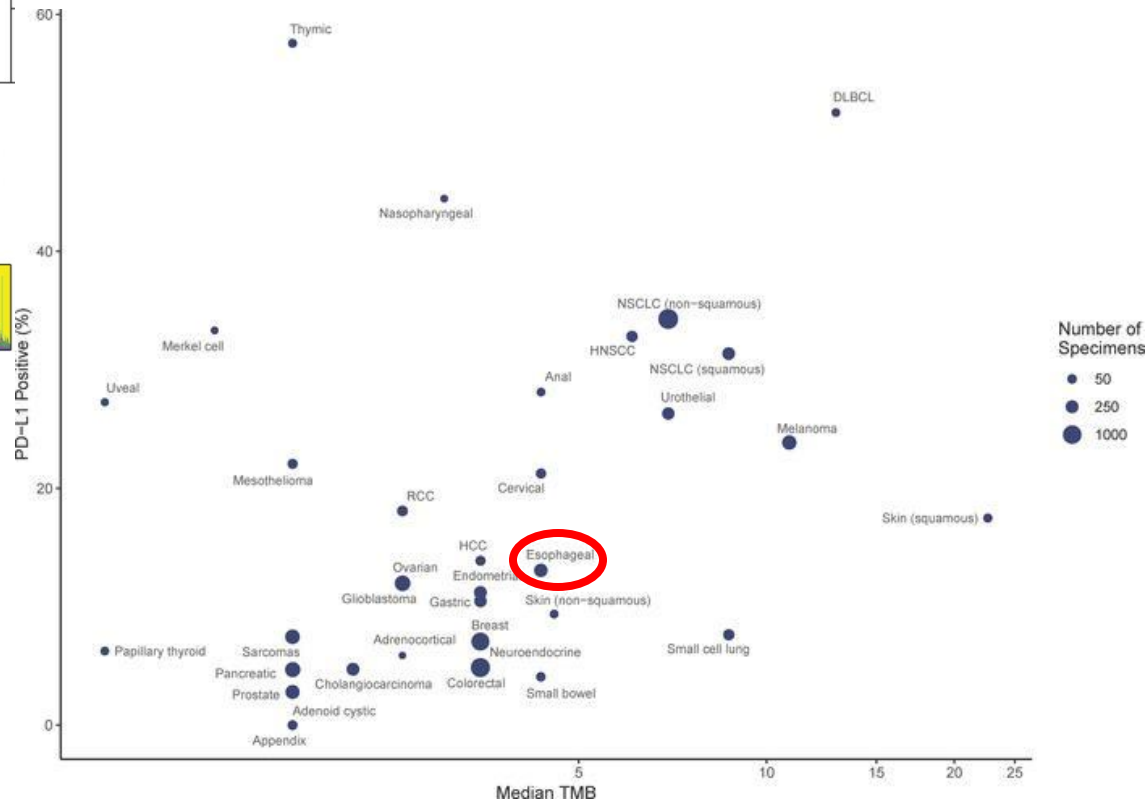


# Treatment Modalities

- Surgery
- Chemotherapy
- Radiation
- Immunotherapy
- Targeted therapy

# Esophageal Cancer as a Candidate for Immunotherapy

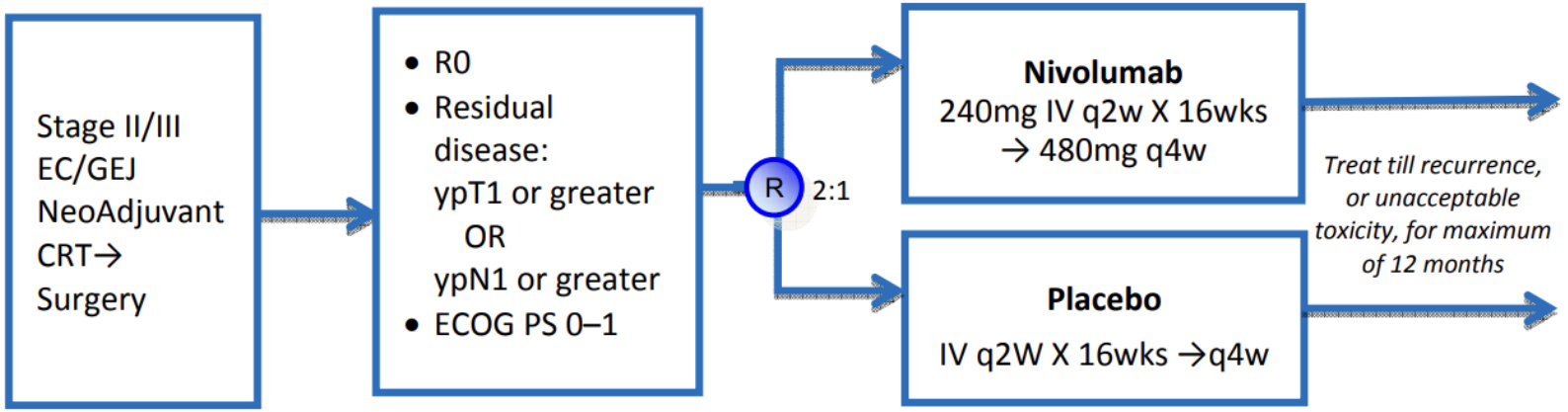


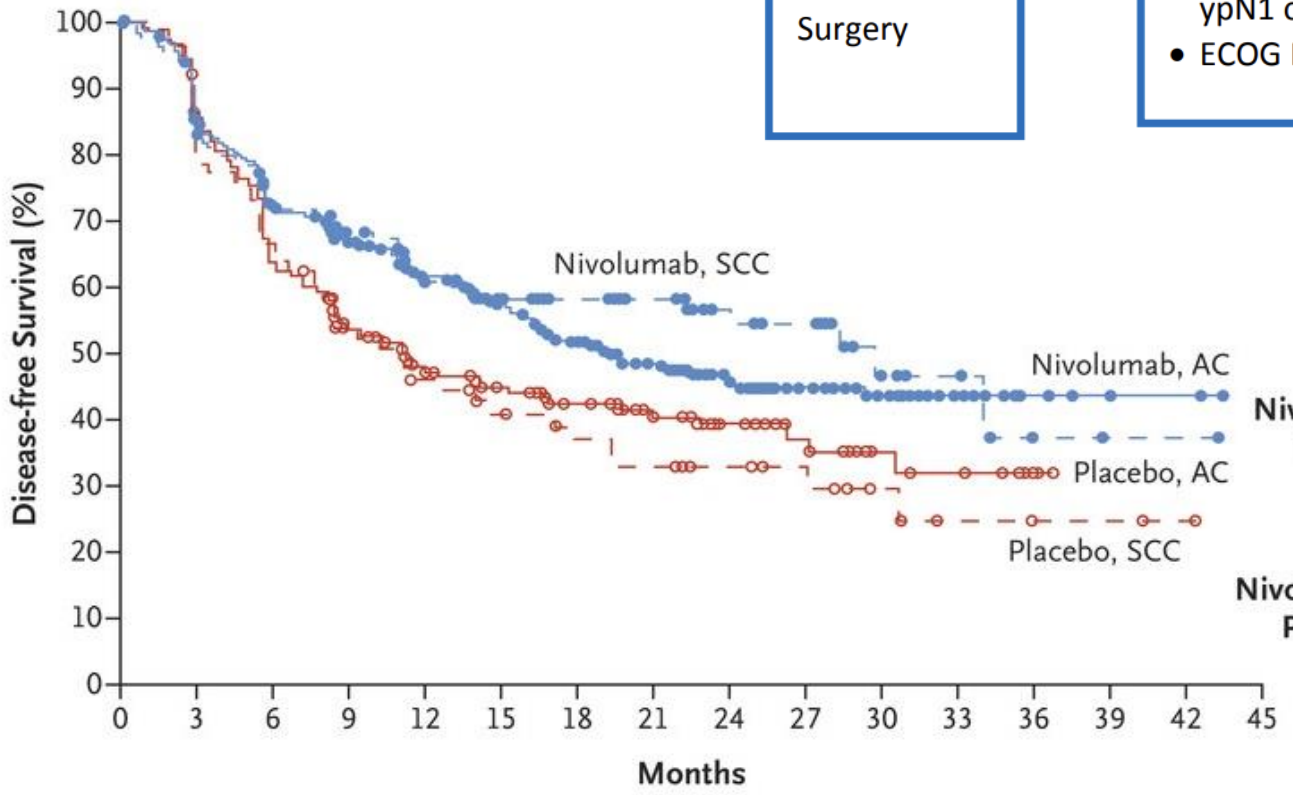



Lawrence, *Nature* 2013; Yarchoan, *JCI Insight* 2019

# CheckMate 577




**Disease-free Survival According to Histologic Type**




| | No. of Patients | Median Disease-free Survival |
|---|---|---|
| | | *mo (95% CI)* |
| **Nivolumab, AC** | 376 | 19.4 (15.9–29.4) |
| **Placebo, AC** | 187 | 11.1 (8.3–16.8) |
| Hazard ratio for disease recurrence or death, 0.75 (95% CI, 0.59–0.96) | | |
| **Nivolumab, SCC** | 155 | 29.7 (14.4–NE) |
| **Placebo, SCC** | 75 | 11.0 (7.6–17.8) |
| Hazard ratio for disease recurrence or death, 0.61 (95% CI, 0.42–0.88) | | |

**No. at Risk**

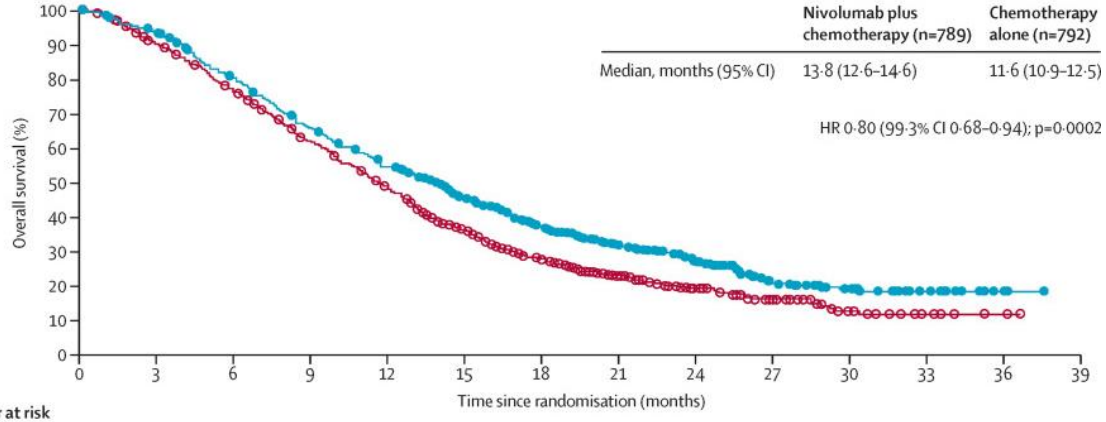
| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab, AC | 376 | 305 | 257 | 219 | 178 | 151 | 125 | 99 | 65 | 45 | 32 | 16 | 6 | 3 | 2 | 0 |
| Nivolumab, SCC | 155 | 124 | 106 | 87 | 71 | 61 | 56 | 48 | 27 | 23 | 9 | 6 | 2 | 1 | 1 | 0 |
| Placebo, AC | 187 | 156 | 114 | 92 | 68 | 57 | 47 | 37 | 26 | 18 | 11 | 9 | 3 | 0 | 0 | 0 |
| Placebo, SCC | 75 | 58 | 49 | 34 | 28 | 23 | 18 | 16 | 12 | 10 | 6 | 3 | 2 | 2 | 1 | 0 |

# Outline

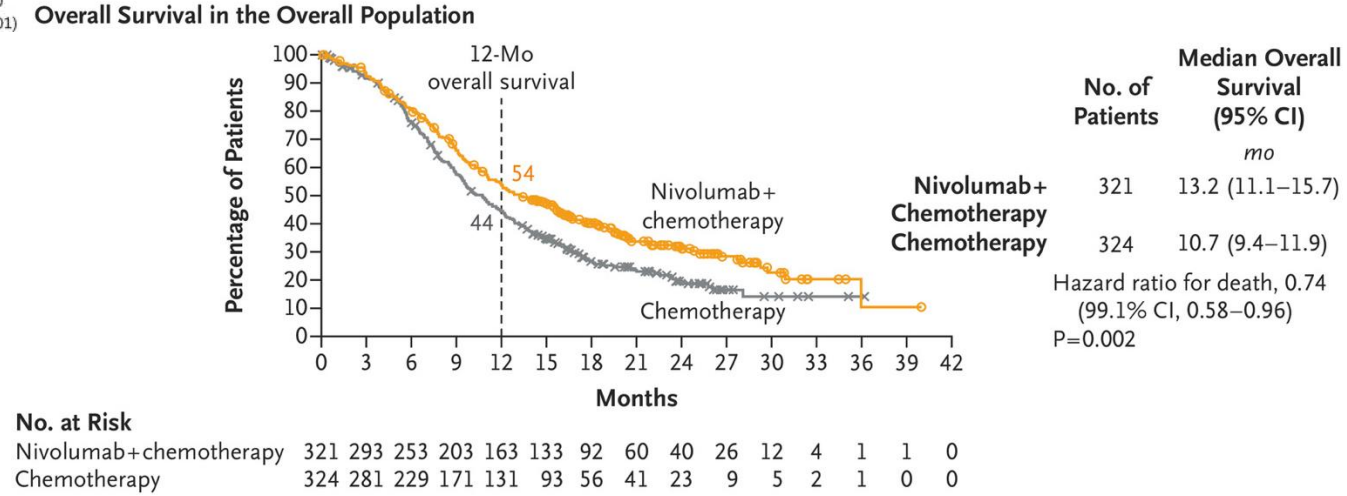
- Epidemiology of esophageal cancer
- Definitive treatment of locally advanced disease
- Systemic treatment for metastatic disease
- Novel therapeutic directions
- Translational investigation at CUIMC

# First-Line Recurrent/Metastatic IO + Chemo

## CheckMate 649: advanced gastric, GEJ, EAC



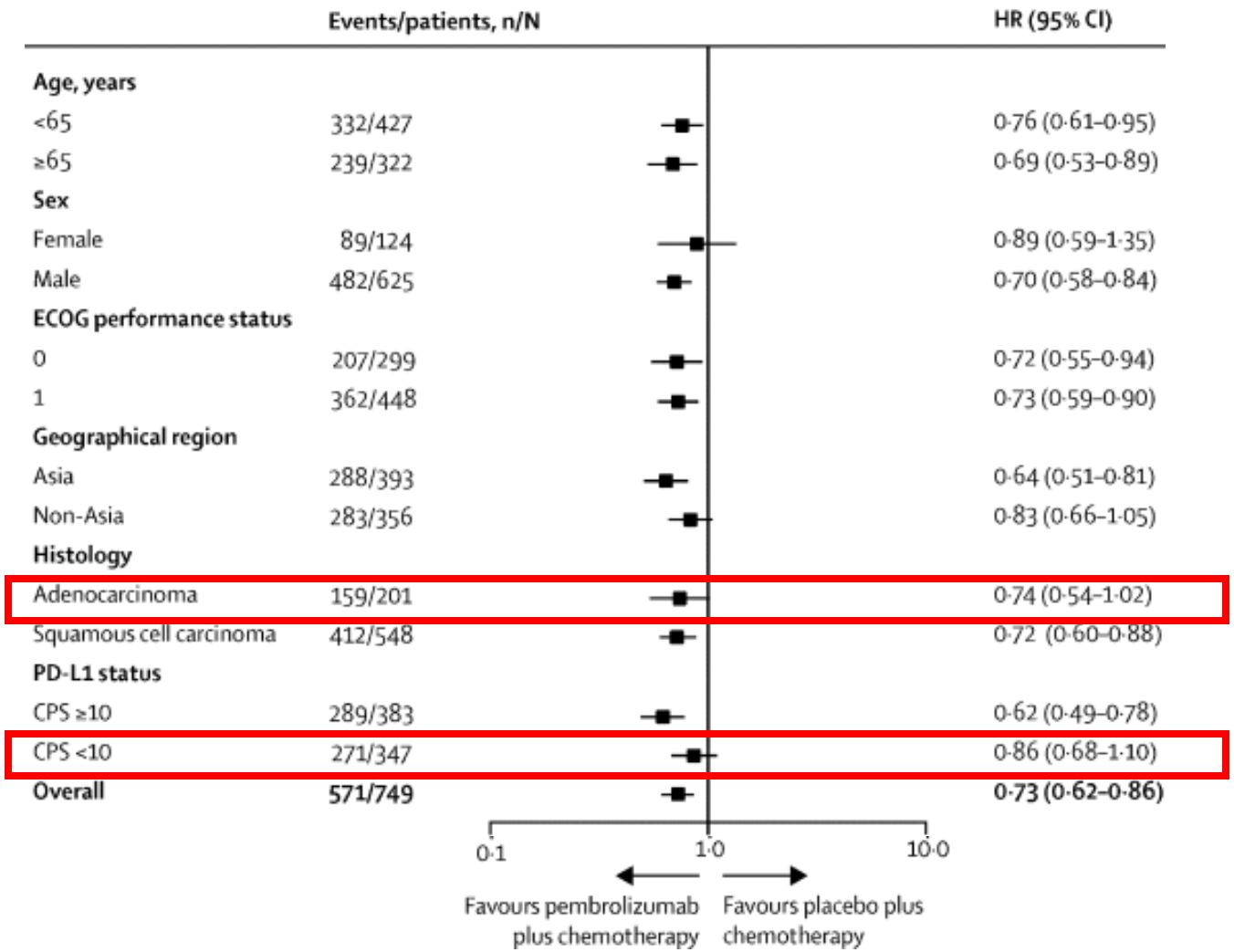

## CheckMate 648: ESCC






Janjigian, *Lancet* 2021; Doki, *NEJM* 2022

# First-Line Recurrent/Metastatic IO: Pembrolizumab



# NCCN Guidelines for IO in 1L

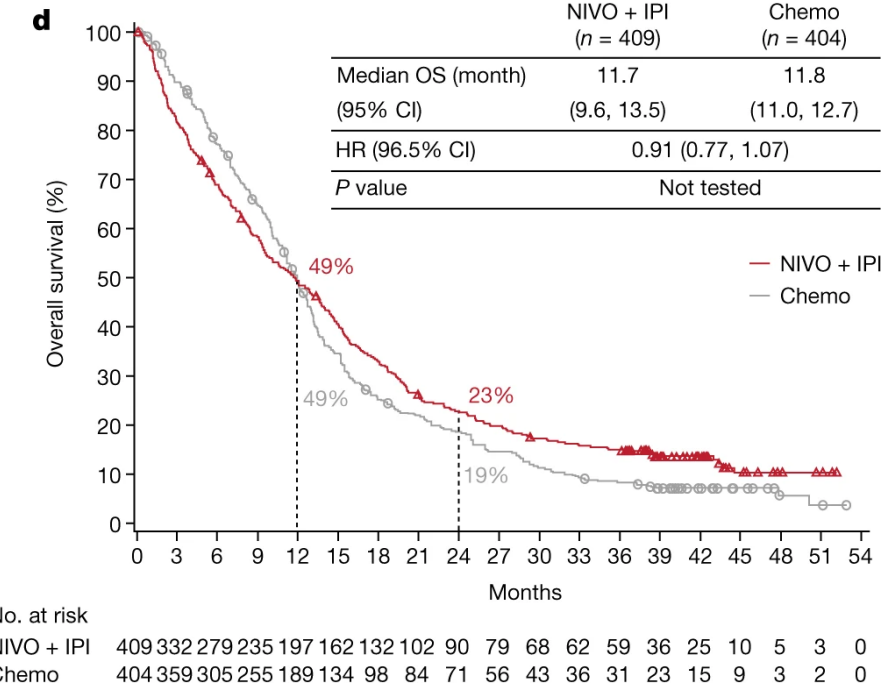
| ADENOCARCINOMA |
| --- |
| **First-Line Therapy**<br>• Oxaliplatin is preferred over cisplatin due to lower toxicity. |
| **Preferred Regimens**<br>• HER2 overexpression negative[r]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab (category 1 for PD-L1 CPS ≥ 5; category 2B for PD-L1 CPS <5)[d,g,19]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[21-23]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[21,24-26] |

# NCCN Guidelines for IO in 1L

| SQUAMOUS CELL CARCINOMA |
| --- |
| **First-Line Therapy**<br>• Oxaliplatin is preferred over cisplatin due to lower toxicity. |
| **Preferred Regimens**<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and nivolumab[d,g,41]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), oxaliplatin, and pembrolizumab (category 2A for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and oxaliplatin[21-23]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and nivolumab[d,g,41]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine), cisplatin, and pembrolizumab (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS <10)[d,g,20]<br>▸ Fluoropyrimidine (fluorouracil[b] or capecitabine) and cisplatin[21,24-26]<br>▸ Nivolumab and ipilimumab[d,g,41] |

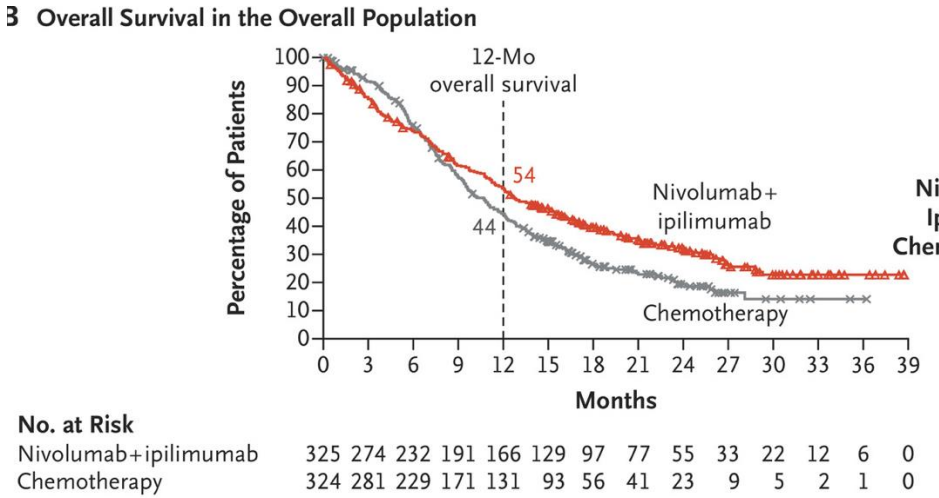
# Nivo + Ipi – Watch Out for Histology

## CheckMate 649: advanced gastric, GEJ, EAC




| | NIVO + IPI (*n* = 409) | Chemo (*n* = 404) |
|---|---|---|
| Median OS (month) | 11.7 | 11.8 |
| (95% CI) | (9.6, 13.5) | (11.0, 12.7) |
| HR (96.5% CI) | 0.91 (0.77, 1.07) | |
| *P* value | Not tested | |

## CheckMate 648: ESCC




| | No. of Patients | Median Overall Survival (95% CI) |
|---|---|---|
| | | *mo* |
| Nivolumab+ Ipilimumab | 325 | 12.7 (11.3–15.5) |
| Chemotherapy | 324 | 10.7 (9.4–11.9) |

Hazard ratio for death, 0.78 (98.2% CI, 0.62–0.98)
P=0.01

# Outline

- Epidemiology of esophageal cancer
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- Novel therapeutic directions
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# Treatment Modalities

- Surgery
- Chemotherapy
- Radiation
- Immunotherapy
- Targeted therapy

Dr. Grady will teach us more shortly…

# A word on trial demographics…

- CROSS trial: demographics unavailable
- MAGIC trial: demographics unavailable

**Table 1 Completed and ongoing phase III trials of perioperative chemotherapy and chemoradiation in gastric cancer**

| | Timing, intervention | Treatment arms (*n*) | Results |
|---|---|---|---|
| INT0116[4]<br>United States | Adjuvant, chemoradiation | Surgery alone (n = 275) | Median OS: 27 mo<br>HR = 1.35, 95%CI: 1.09-1.66<br>(*P* = 0.005) |
| | | Surgery + 5-FU/LV/RT (*n* = 281) | Median OS: 36 mo |
| ARTIST[5]<br>South Korea | Adjuvant, chemoradiation | Surgery (D2 resection) + capecitabine/cisplatin (*n* = 228)<br>Surgery (D2 resection) + capecitabine/cisplatin/RT (n = 230) | 3-yr DFS: 74.2%<br>3-yr DFS: 78.2%<br>(*P* = 0.08) |
| ARTIST II[24]<br>South Korea | Adjuvant, chemoradiation | Surgery (D2 resection, node-positive only) + capecitabine/cisplatin<br>Surgery (D2 resection, node-positive only) + capecitabine/cisplatin/RT | In progress |
| ACTS-GC[6]<br>Japan | Adjuvant, chemotherapy | Surgery alone (D2 resection) (n = 30)<br>Surgery (D2 resection) + oral S-1 postop (n = 529) | 5-yr OS: 61.1%<br>5-yr OS: 71.7<br>HR = 0.67, 95%CI: 0.54-0.83 |
| CLASSIC[9]<br>South Korea | Adjuvant, chemotherapy | Surgery alone (D2 resection) (*n* = 515)<br>Surgery (D2 resection) + 8 cycles oral capecitabine + IV oxaliplatin (*n* = 520) | 3-yr DFS: 59% (53%-64%)<br>3-yr DFS: 74% (69%-79%)<br>HR = 0.56, 95%CI: 0.44-0.72<br>(*P* < 0.0001) |
| MAGIC[10]<br>United Kingdom | Perioperative, chemotherapy | Surgery alone (n = 253)<br>3 cycles ECF preop + surgery + 3 cycles ECF postop (n = 250) | 5-yr OS: 23%<br>5-yr OS: 36%<br>HR = 0.75, 95%CI: 0.60-0.93<br>(*P* = 0.009) |
| FNCLCC/FFCD[11]<br>France | Perioperative, chemotherapy | Surgery alone (n = 111)<br>5-FU/cisplatin preop + surgery + 5-FU/cisplatin postop (*n* = 113) | 5-yr OS: 24%<br>5-yr OS: 38%<br>HR = 0.69, 95%CI: 0.50-0.95<br>(*P* = 0.02) |
| POET[13]<br>Germany | Neoadjuvant, chemoradiation | 2.5 cycles PLF preop + surgery (*n* = 59)<br>2 cycles PLF then PLF/RT preop + surgery (*n* = 60) | 3-yr OS: 27.7%<br>3-yr OS: 47.4%<br>HR = 0.67, 95%CI: 0.41-1.07<br>(*P* = 0.07) |
| CRITICS[7]<br>The Netherlands | Perioperative, combination | 3 cycles ECX/EOX preop + surgery + capecitabine/cisplatin/RT postop<br>3 cycles ECX/EOX preop + surgery + 3 cycles ECX/EOX postop | In progress |
| TOPGEAR[12]<br>Australia/New Zealand/ Europe/Canada | Perioperative, combination | 3 cycles ECF preop + surgery + 3 cycles ECF postop<br>2 cycles ECF with 5-FU/RT preop + surgery + 3 cycles ECF postop | In progress |
| Neo-AEGIS[31]<br>Ireland | Perioperative, combination | 3 cycles ECF preop + surgery + 3 cycles ECF postop<br>Carboplatin/paclitaxel/RT preop + surgery | In progress |
| MAGIC-B[32]<br>United Kingdom | Perioperative, chemotherapy | 3 cycles ECX preop + surgery + 3 cycles ECX postop<br>3 cycles ECX with lapatinib or bevacizumab preop + surgery + 3 cycles ECX with lapatinib or bevacizumab postop | In progress |

# A word on trial demographics…

- CROSS trial: demographics unavailable
- MAGIC trial: demographics unavailable
- Checkmate 577

| Subgroup | No. of Patients | Median Disease-free Survival | | Unstratified Hazard Ratio (95% CI) |
|---|---|---|---|---|
| | | Nivolumab | Placebo | |
| | | *mo* | | |
| Overall | 794 | 22.4 | 11.0 | 0.70 (0.58–0.86) |
| Age | | | | |
| <65 yr | 507 | 24.4 | 10.8 | 0.65 (0.51–0.84) |
| ≥65 yr | 287 | 17.0 | 13.9 | 0.80 (0.57–1.12) |
| Sex | | | | |
| Male | 671 | 21.4 | 11.1 | 0.73 (0.59–0.91) |
| Female | 123 | Not reached | 11.0 | 0.59 (0.35–1.00) |
| Race | | | | |
| White | 648 | 21.3 | 10.9 | 0.71 (0.57–0.88) |
| Asian | 117 | 24.0 | 10.2 | 0.70 (0.41–1.22) |
| Black | 9 | 14.4 | 8.3 | 0.43 (0.06–3.06) |
| Other | 20 | Not reached | 14.1 | 0.48 (0.11–2.02) |
| Region | | | | |
| Asia | 106 | 24.0 | 14.3 | 0.78 (0.43–1.41) |
| Other | 688 | 21.4 | 11.0 | 0.69 (0.56–0.86) |

# Conclusions

- Esophageal cancer is not common in the US but is deadly, especially when diagnosed late
- Global incidence is much higher, and squamous histology is more common in the East than in the West
- Risk factors vary substantially with respect to histology
- Practice-defining trials have largely been established in Western populations and later confirmed in independent studies in the East
- Emerging trials now including demographic information to help contextualize study results