

**Advances and Innovations in Endoscopic Oncology and
Multidisciplinary Gastrointestinal Cancer Care**

Optimal Multidisciplinary GI Cancer Staging: Evidence Based Approach (Esophageal)

Daniela Molena, MD

Associate Attending

Director of Esophageal Surgery

Thoracic Surgery Service

Memorial Sloan Kettering Cancer Center

New York, NY

Disclosures

- Consultant/Advisor for AstraZeneca, Boston Scientific, Bristol Myers Squibb, Johnson & Johnson, & Medtronic

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

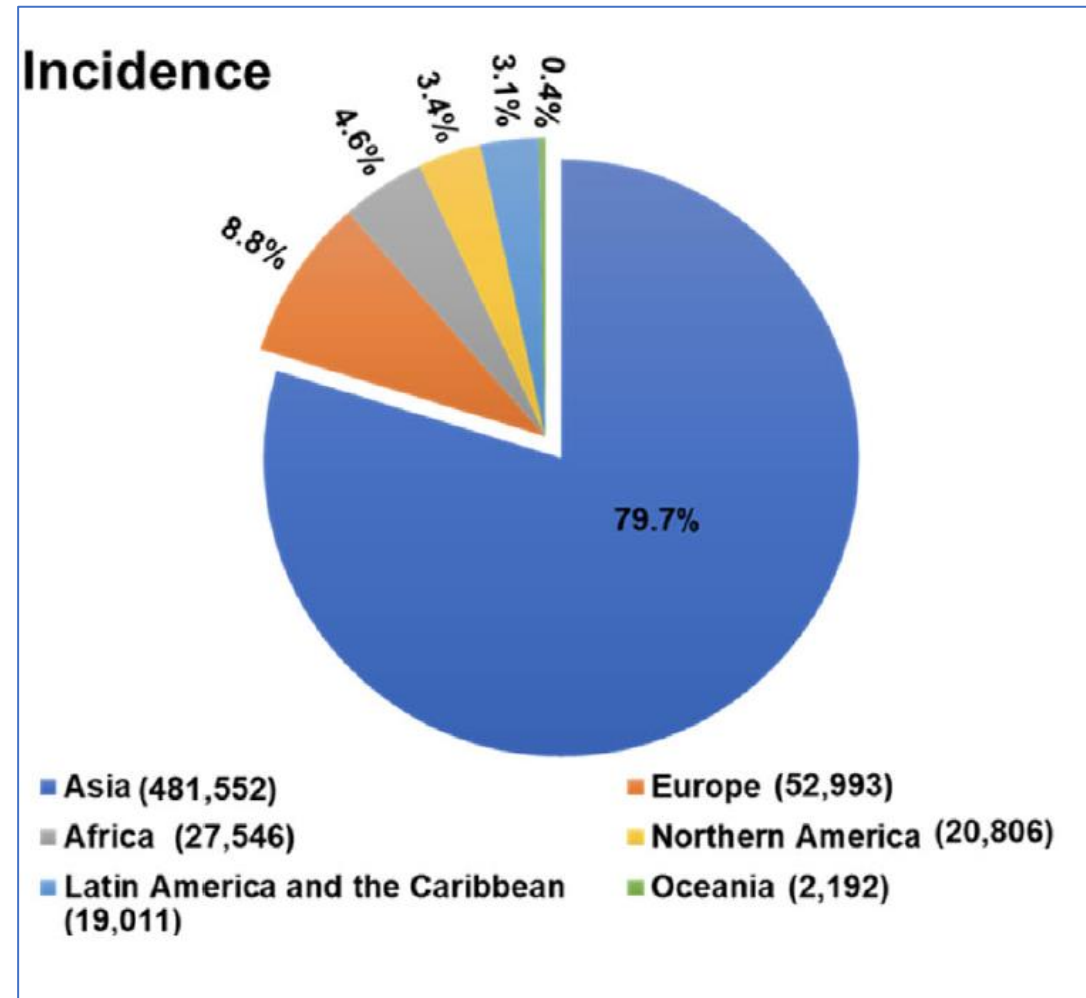
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Risk factors for adenocarcinoma and squamous cell carcinoma related to socioeconomic status and barriers to care*
- *The disease is more frequent in older males and women and young patients are diagnosed late because of it*

Some Facts

- Esophageal cancer is the eighth most commonly diagnosed cancer and is the sixth leading cause of cancer death worldwide
- Almost 80% of all cases occur in less developed countries/regions
- 20th most commonly diagnosed cancer and 11th leading cause of cancer-related death in US
- The lifetime risk of esophageal cancer in the United States is about 1 in 127 in men and about 1 in 434 in women

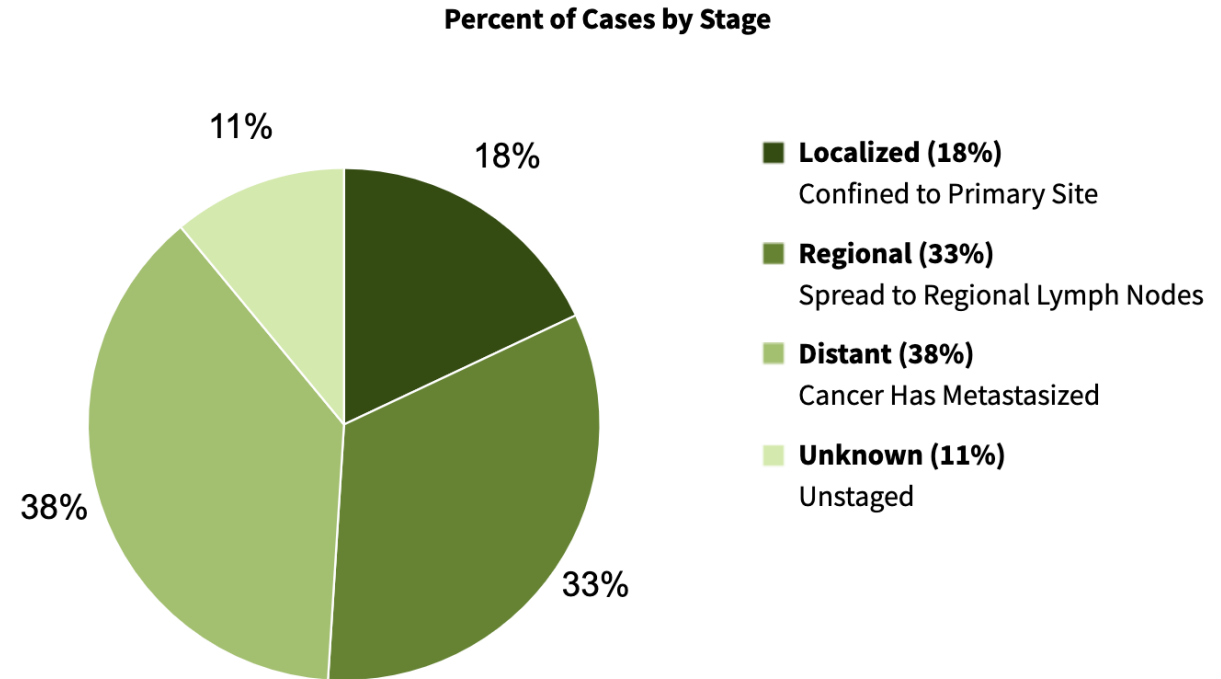
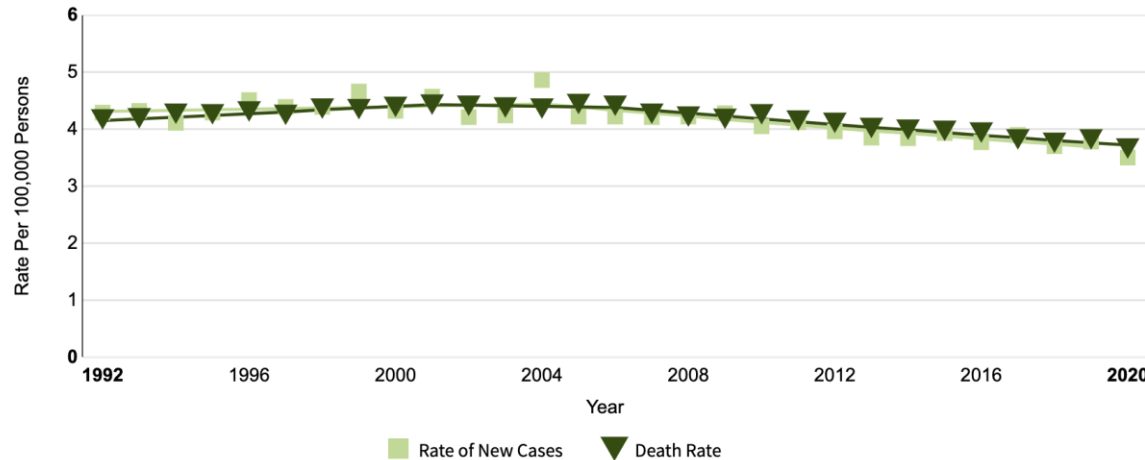


Liu CQ et al. Thorac Cancer. 2023

Rare but lethal

Estimated New Cases in 2023	21,560
% of All New Cancer Cases	1.1%
Estimated Deaths in 2023	16,120
% of All Cancer Deaths	2.6%

5-Year Relative Survival
21.7%
2013–2019

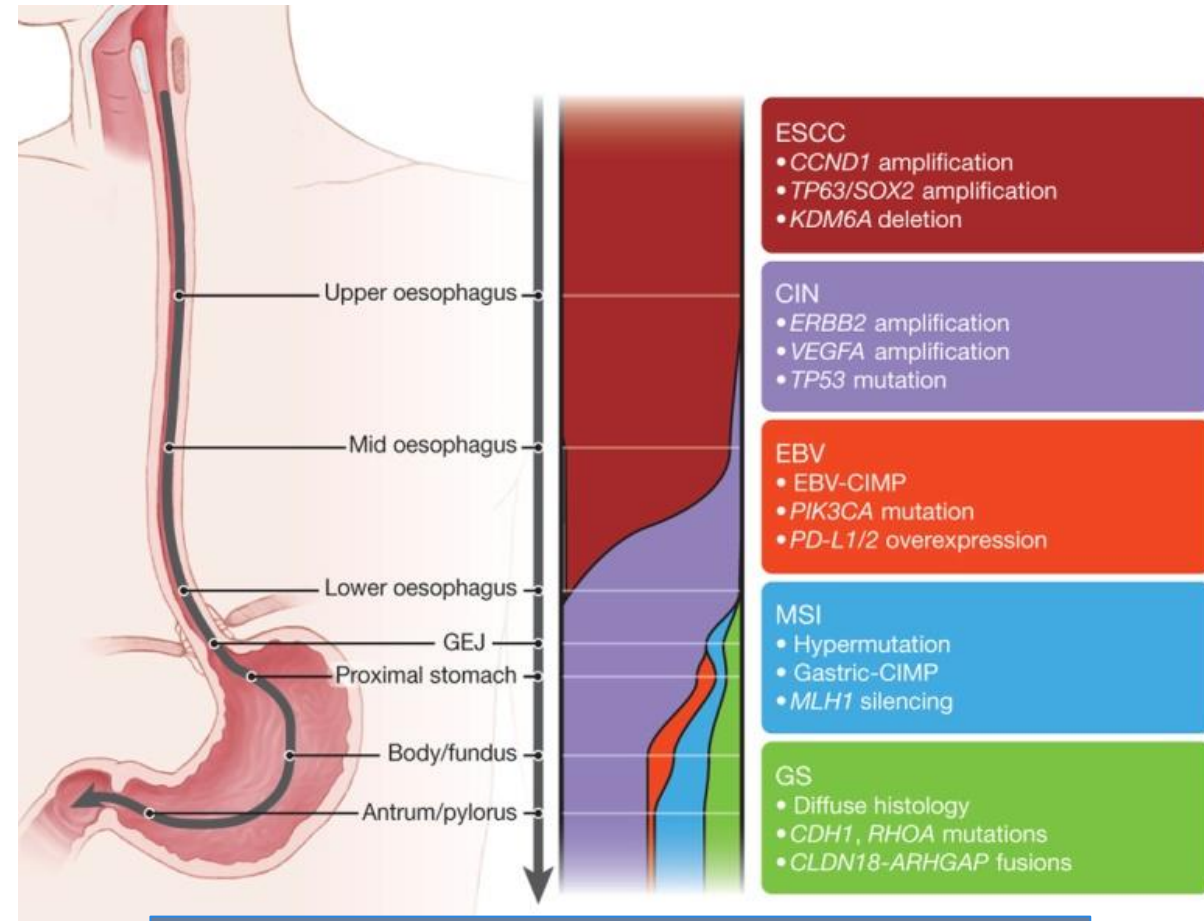


Main prognostic factor for recurrence is lymph node metastasis¹⁻²

<https://seer.cancer.gov/statfacts/html/esoph.html>

Histology

- Esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) are responsible for over 98% of esophageal cancer cases
- Rarer types include sarcoma, small cell, melanoma, etc.
- While clinical presentation may be similar, ESCC and EAC SHOULD BE considered two separate diseases



TCGA Research Network, Nature 2017

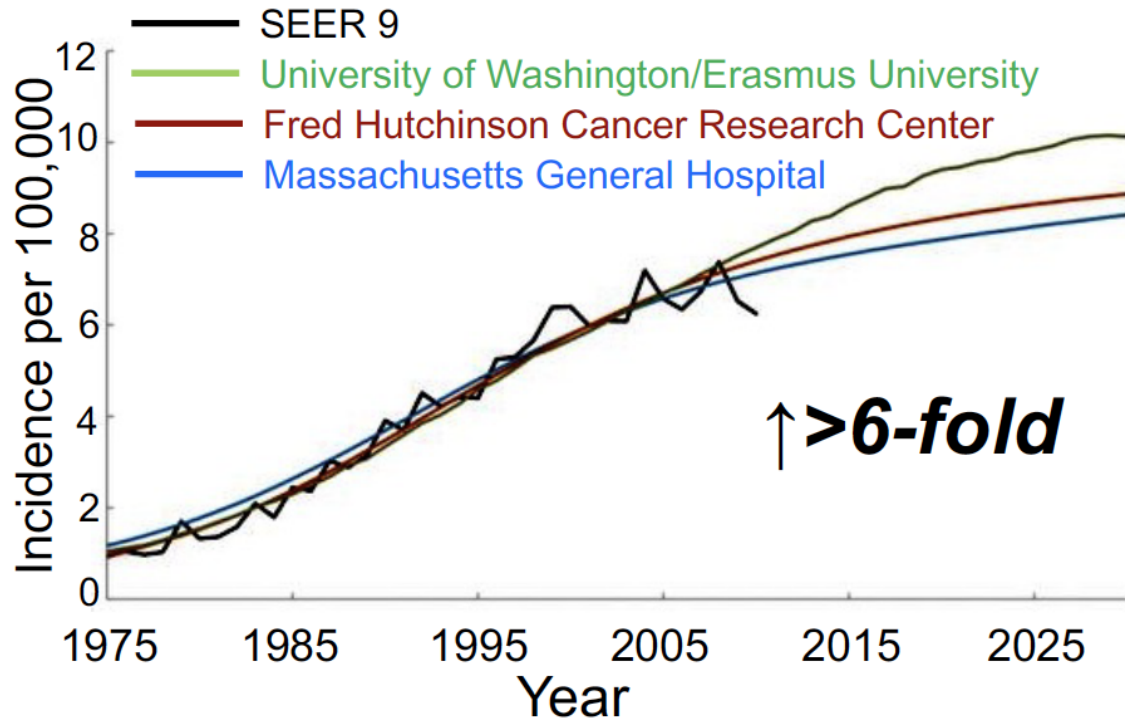
Comparison

	ESCC	EAC
Epidemiology	Predominant in East Asia and the Middle East	Most common in developed regions of western Europe and North America
Risk Factors	Tobacco smoking, alcohol use, thermal injury and regional micronutrient deficiency	Acid or bile reflux, Barrett's esophagus, and central or visceral obesity
Precursor Lesion	Squamous dysplasia → carcinoma in situ → invasive ESCC	Metaplasia → low-grade dysplasia → high-grade dysplasia → invasive EAC
Tumor Location	Upper and middle third of the esophagus	Distal esophagus
Frequent Comorbidity	Liver cirrhosis, COPD, synchronous/metachronous cancer of the aero-digestive tract, and atherosclerosis	Obesity and atherosclerosis
Diagnosis and Symptoms	Similar	Similar

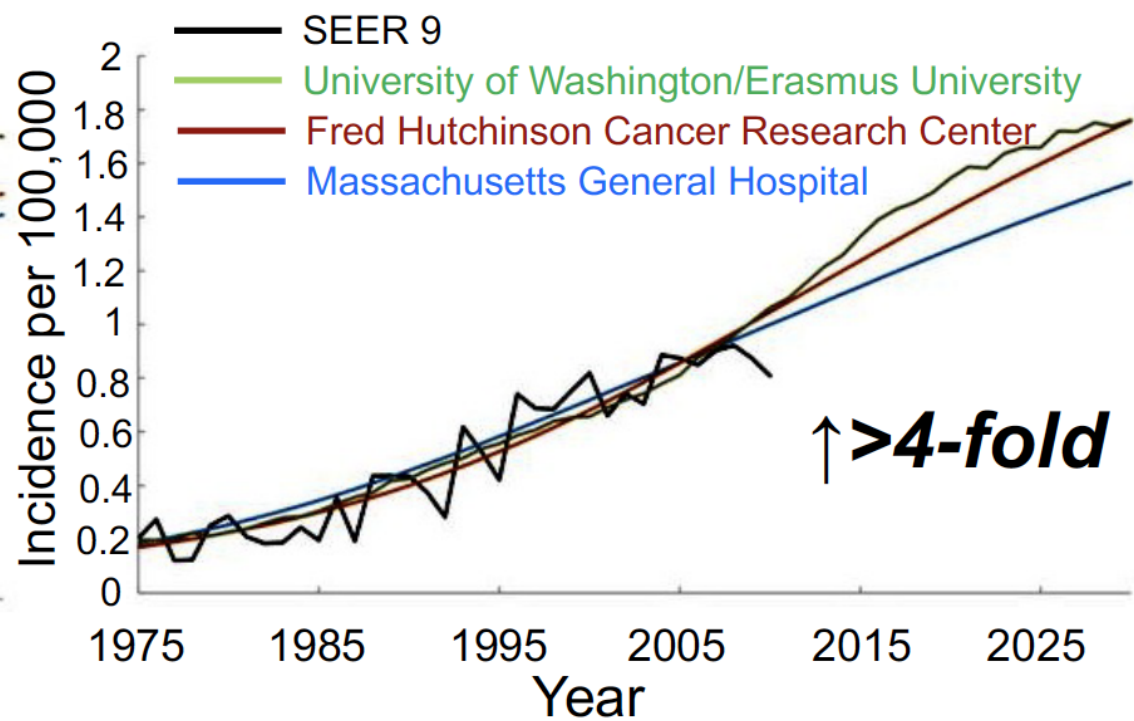
Projected Incidence of Esophageal Adenocarcinoma Based on 3 Independent Computer Models

(University of Washington/Erasmus University, Fred Hutchinson Cancer Research Center, Massachusetts General Hospital)

Men



Women

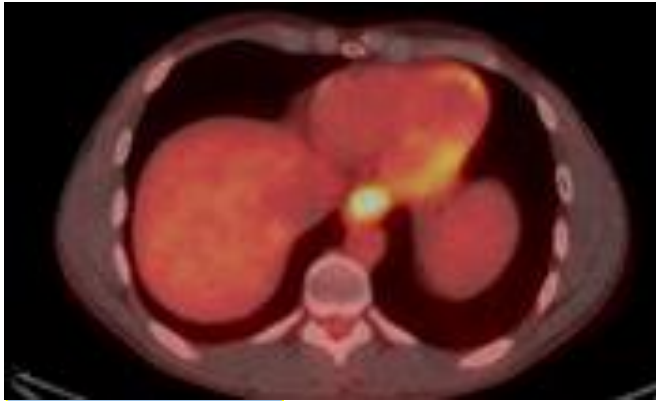


Kong CY. Cancer Epidemiol Biomarkers Prev 2014

Clinical Presentation

- Most commonly presents with dysphagia
- Difficulty swallowing to solids initially followed by both solids and liquids
- Asymptomatic patients with early-stage tumors infrequently diagnosed during screening EGD performed for Barrett's
- Associated findings:
 - Fatigue, weight loss
 - Retrosternal pain
 - Hoarseness/respiratory symptoms

A very diverse disease



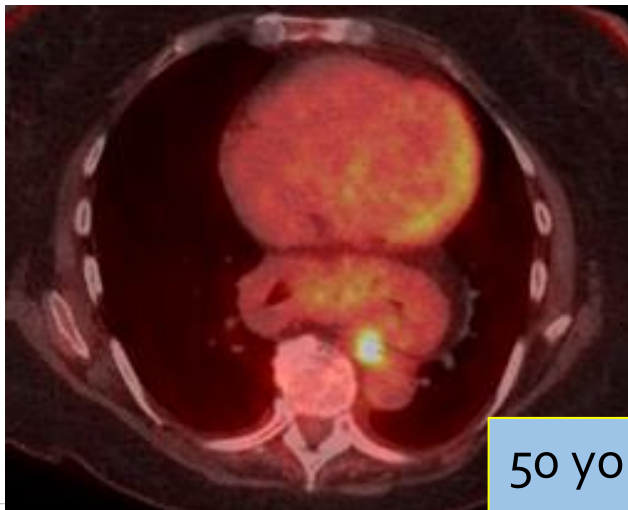
67 yo male



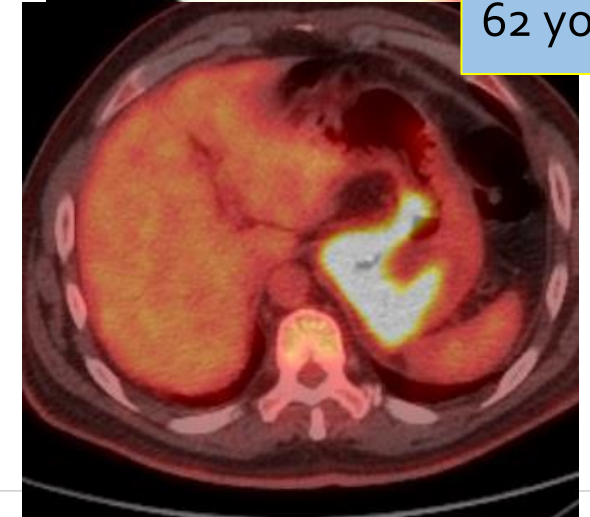
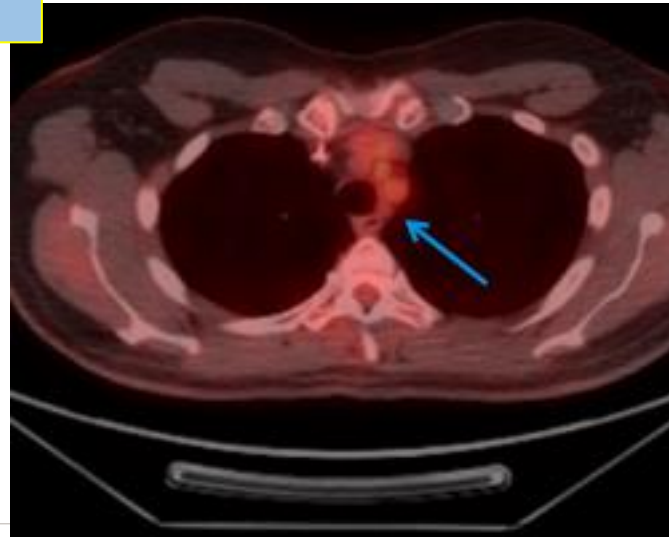
43 yo male



62 yo male



50 yo female



It all starts with an EGD

Quality of Endoscopy Reports for Esophageal Cancer Patients: Where Do We Stand?

J Gastrointest Surg. 2018

Arianna Barbetta¹, Shahdabul Faraz^{2,3}, Pari Shah², Hans Gerdes², Meier Hsu⁴, Kay See Tan⁴, Tamar Nobel¹, Manjit S. Bains¹, Matthew Bott¹, James M. Isbell¹, David B. Sewell¹, David R. Jones¹, and Daniela Molena¹

EGD QI (N = 11)

GEJ location

Barrett's esophagus

Barrett's Prague classification

Tumor proximal margin

Tumor distal margin

Luminal obstruction

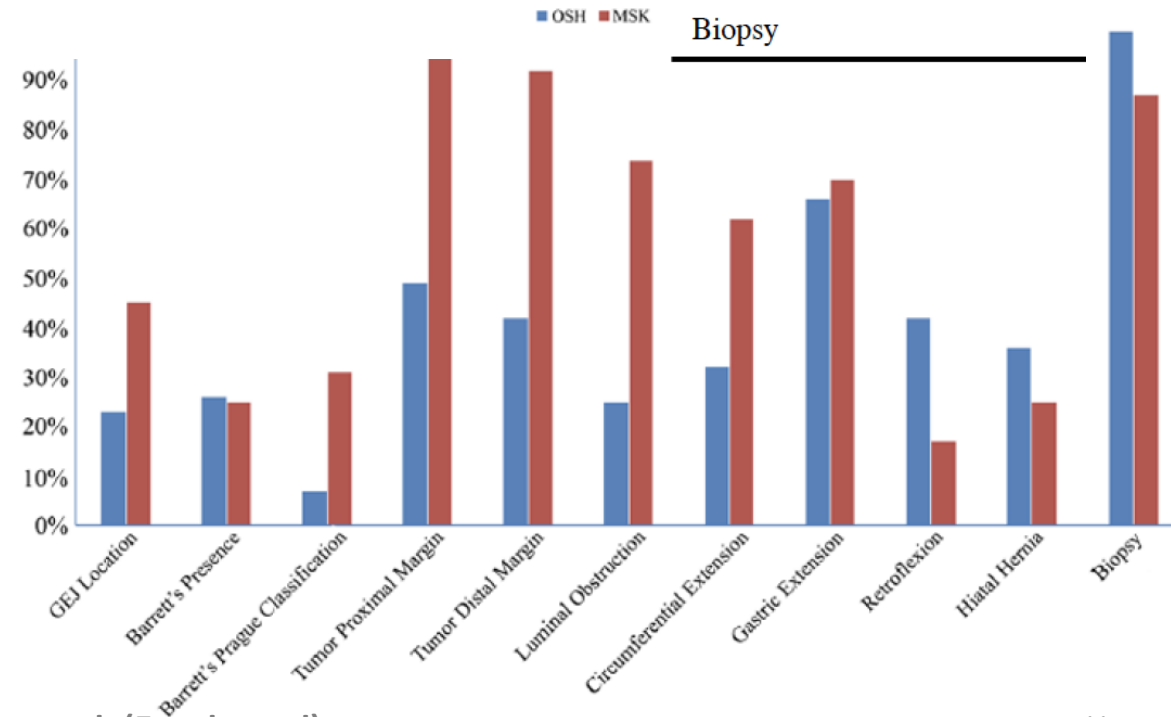
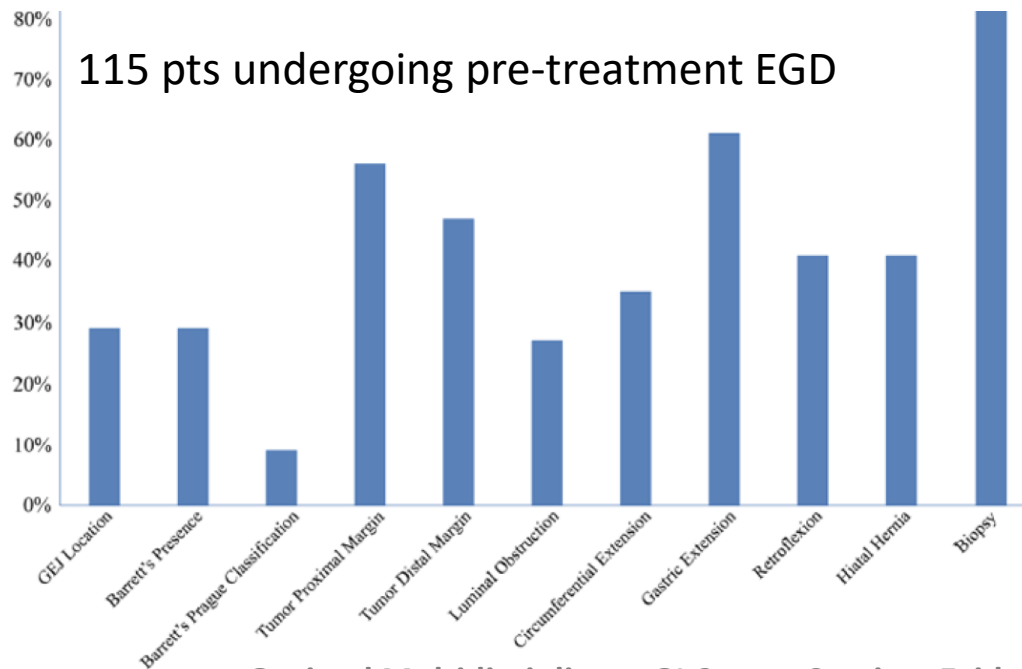
Circumferential extension

Gastric extension

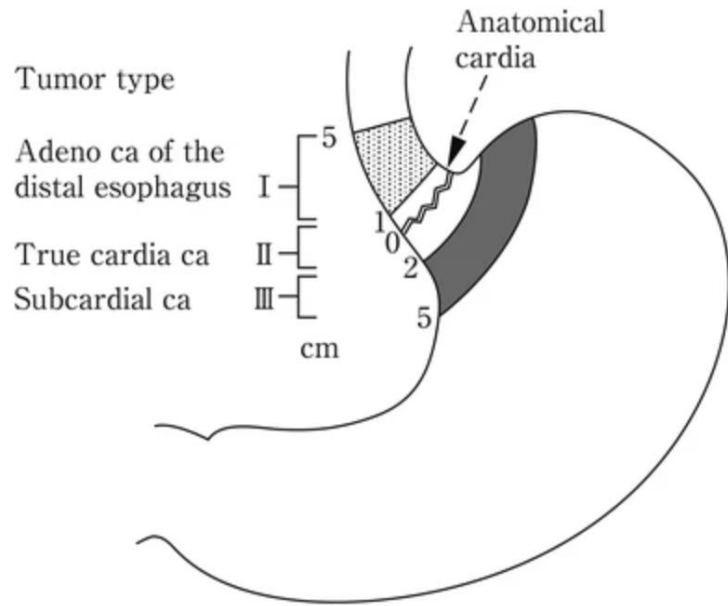
Retroflexion

Hiatal hernia

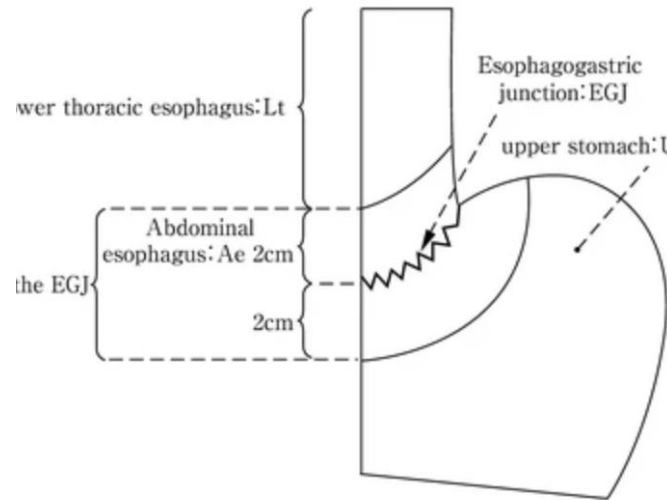
Biopsy



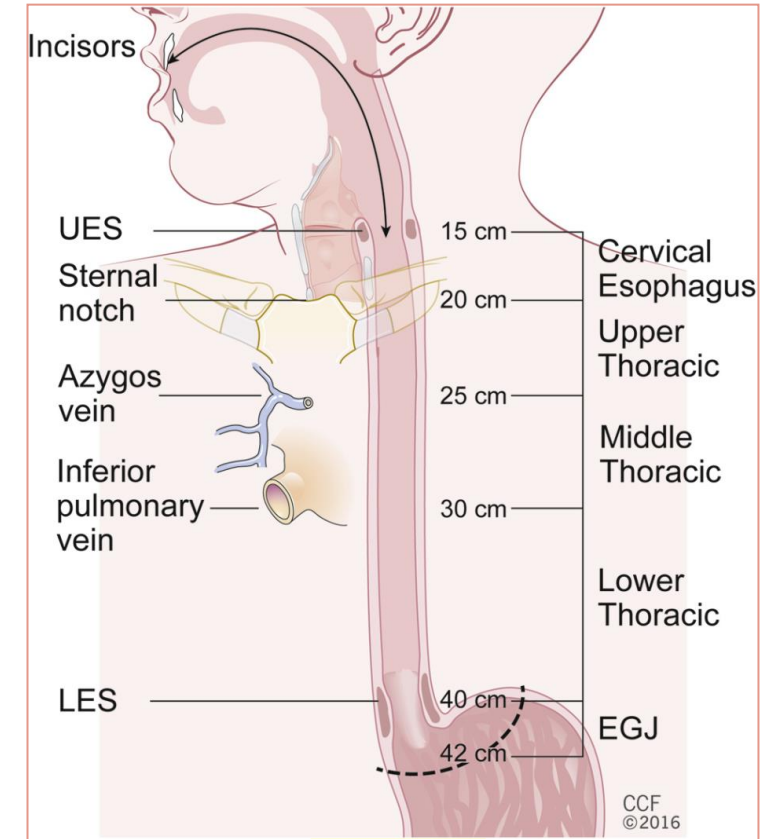
Endoscopic Classifications



Siewert



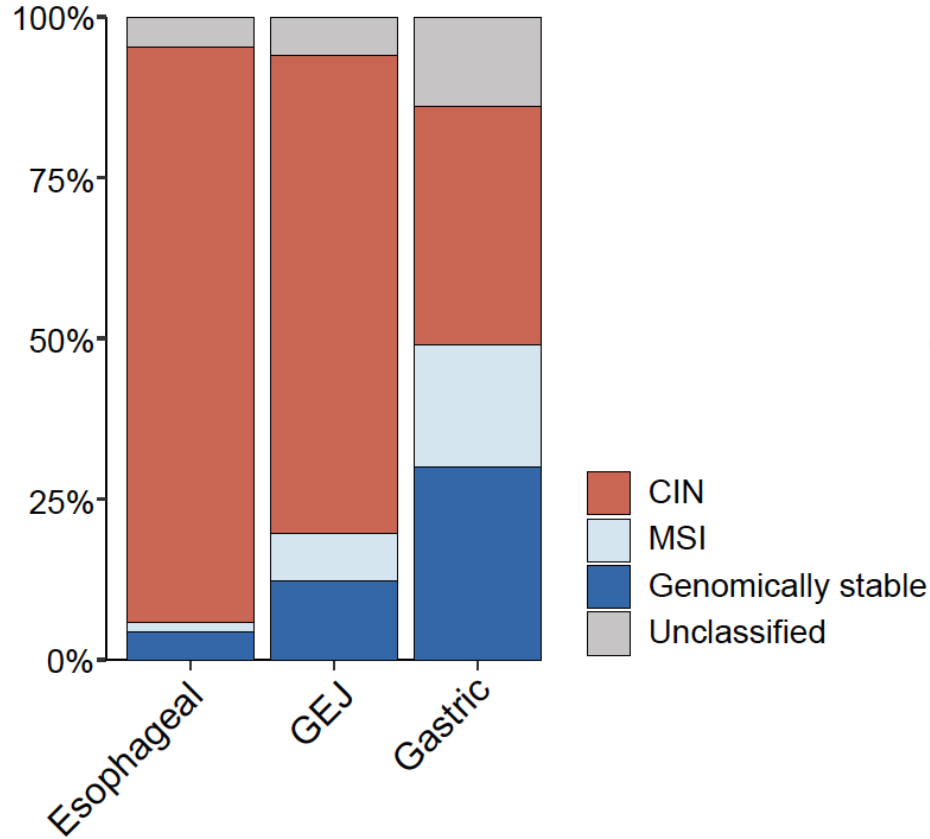
Nishi



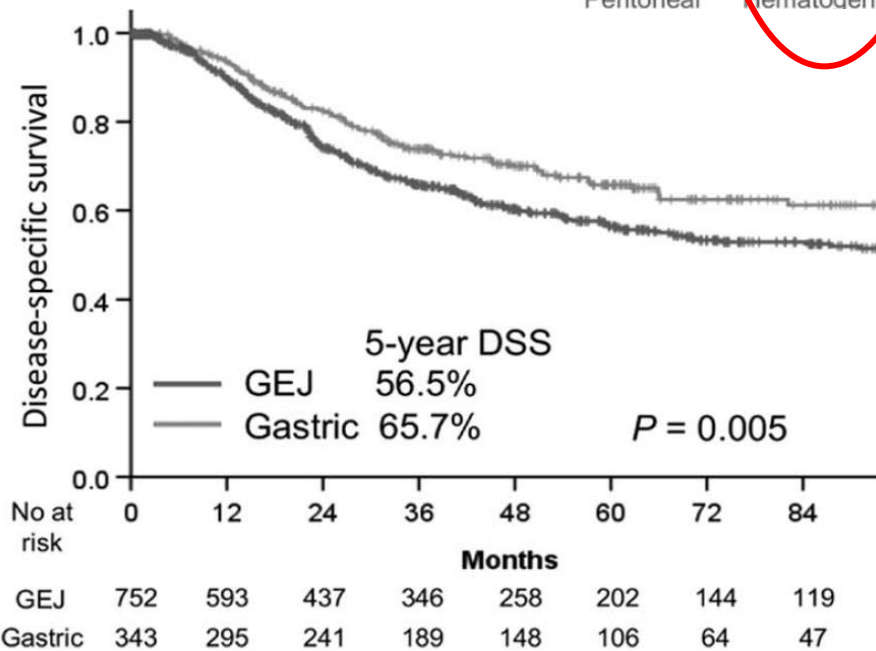
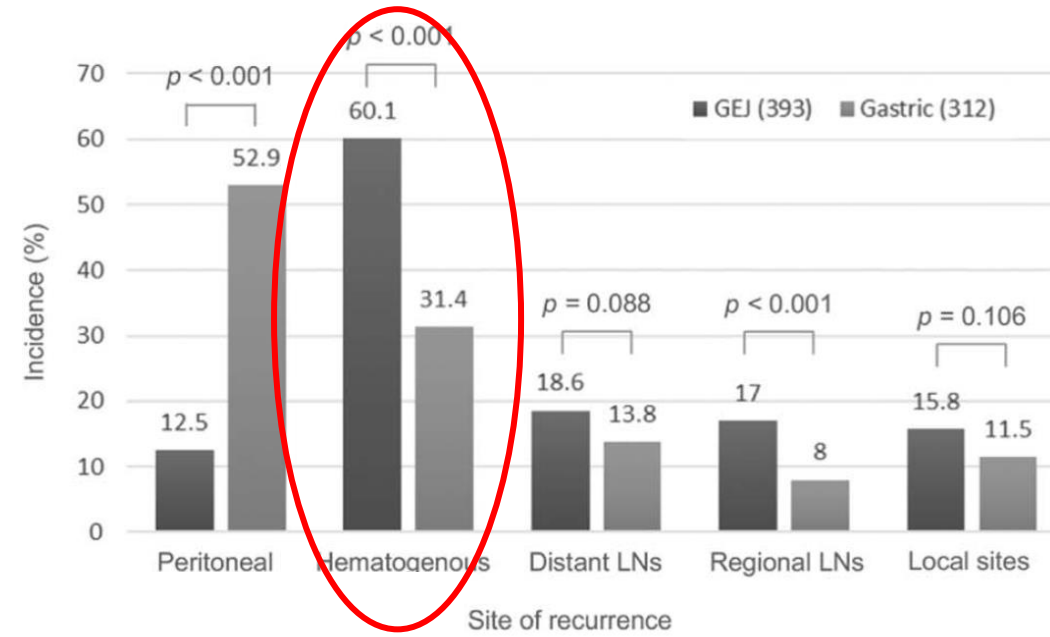
AJCC

Siewert JR et al. Chirurg 1987; Nishi MKT et al. Geka Shinryo (Surg Diagn Treat) 1973; Rice TW et al. Ann Cardiothorac Surg 2017

Does location really matter?

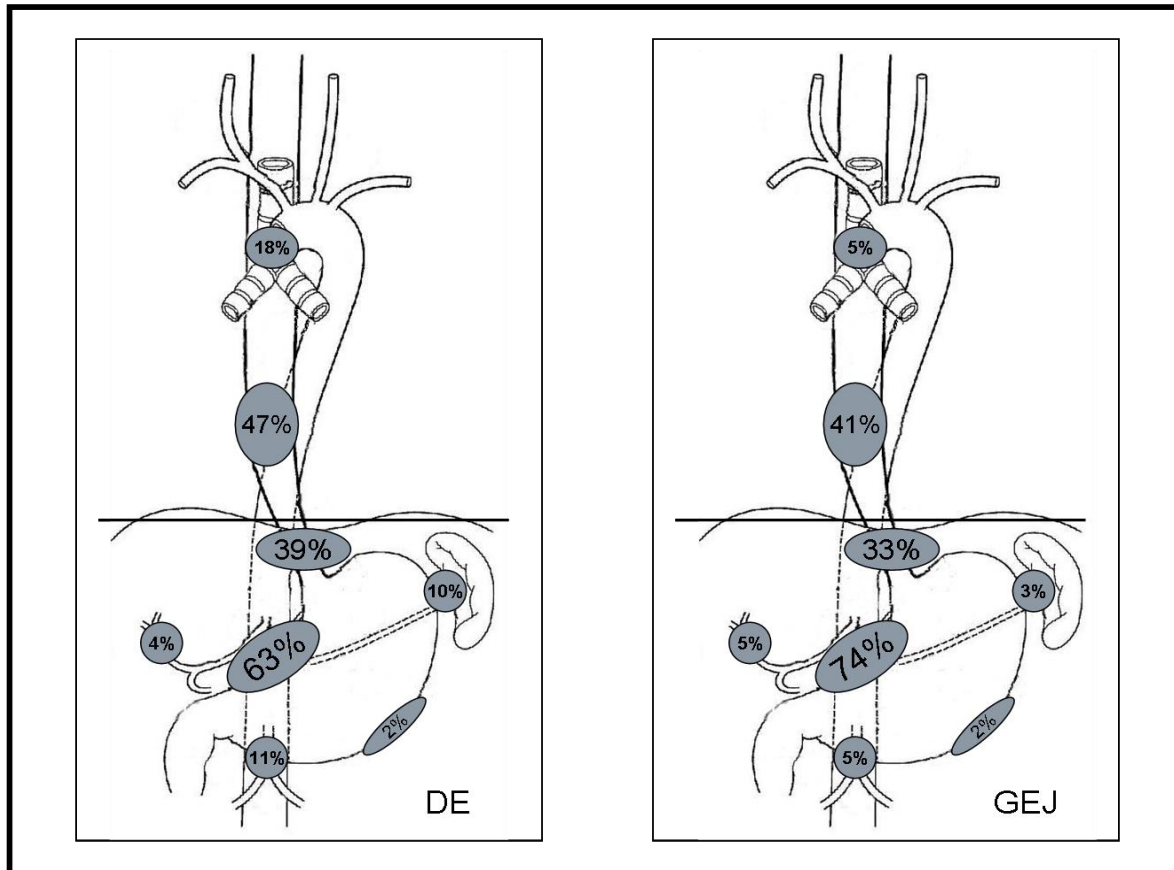


Sihag S, Molena D. AATS 2022



Nakauchi M, Molena D et al. Ann Surg 2023

Does location really matter?



150 patients

100 patients

- Mediastinal involvement in 26% DE and 25% GEJ
- At least one mediastinal node in 47% of DE and 41% GEJ with positive nodes
- In 9% of DE and 8% of GEJ tumors, a positive mediastinal node was the only site of lymph node involvement

Leers J, et al. *JTCVS*, 2009

Diagnosis is not enough!

Evaluate extension of disease

- **Treatment** considerations
 - Staging/restaging
- **Operative** considerations
 - Resectability
 - Type of resection
 - Extension of lymphadenectomy
- **Reconstructive** considerations

EGD

EUS

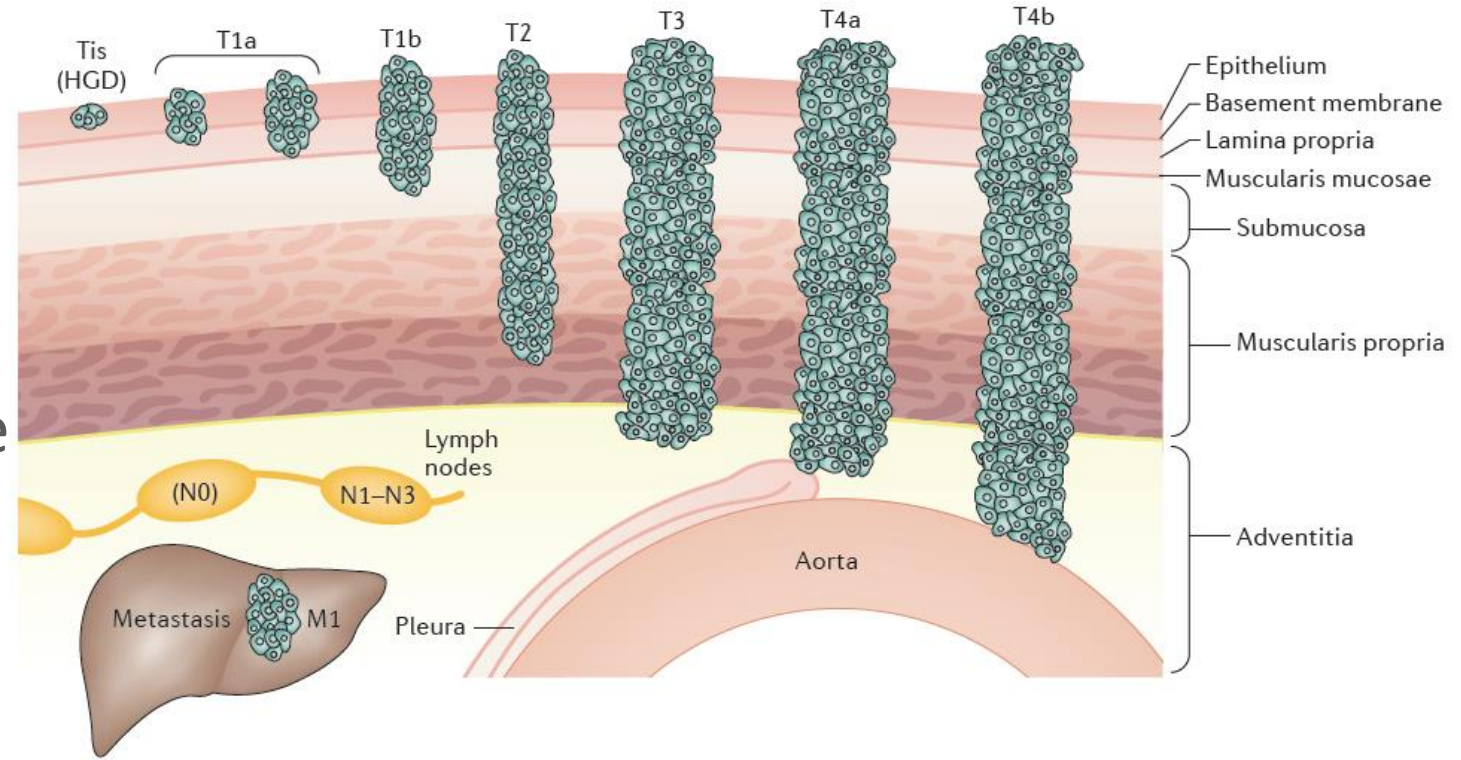
PET/CT



Staging
Laparoscopy

Staging

- Essential for appropriate management and to determine prognosis
- Clinical stage (cTNM) by EUS ~~FNA~~ and PET/CT
- Restaging after neoadjuvant therapy
- Pathologic classification (pTNM) determined after surgery

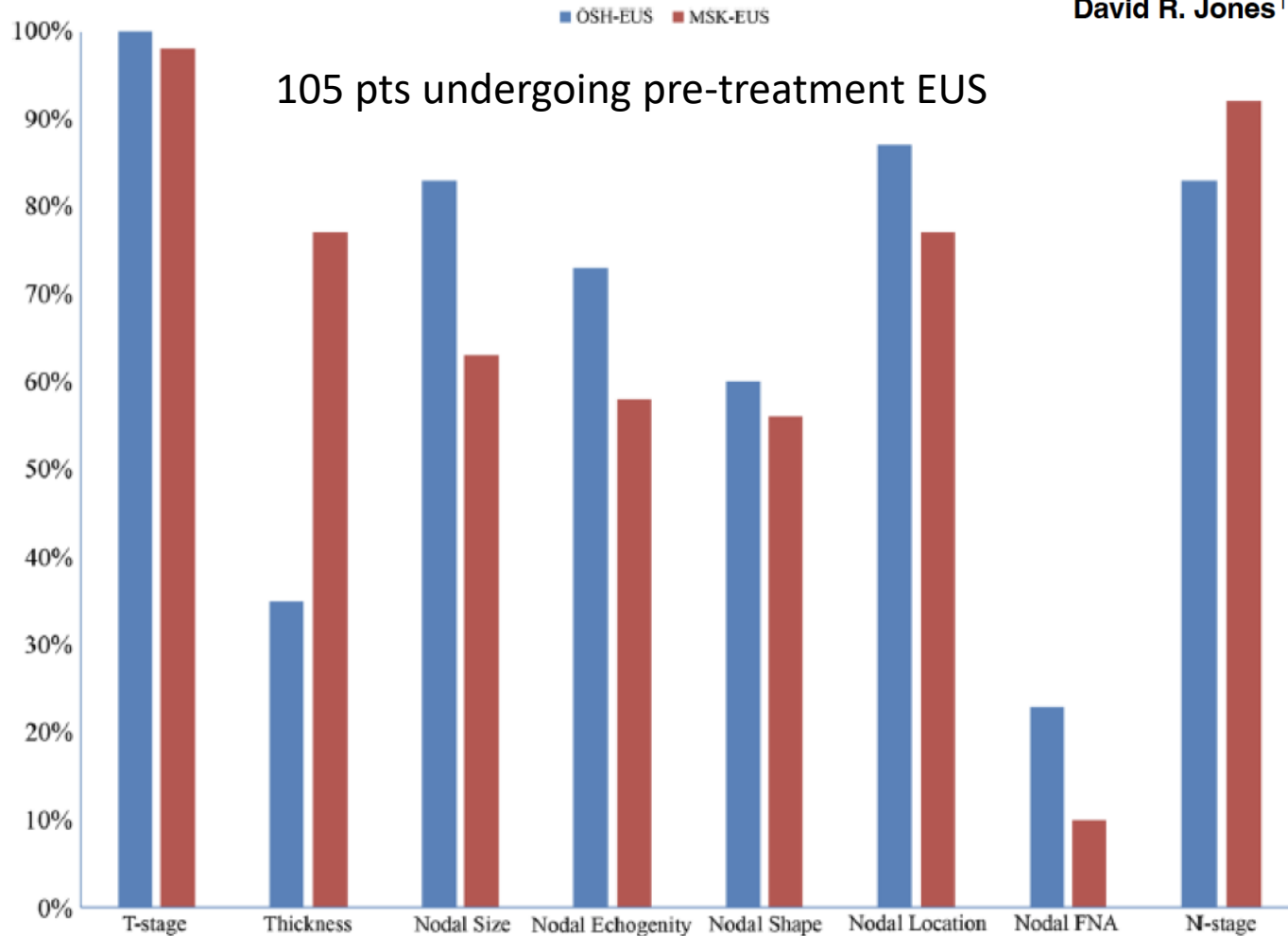


Quality of Endoscopy Reports for Esophageal Cancer Patients: Where Do We Stand?

Arianna Barbetta¹, Shahdabul Faraz^{2,3}, Pari Shah², Hans Gerdes², Meier Hsu⁴, Kay See Tan⁴, Tamar Nobel¹, Manjit S. Bains¹, Matthew Bott¹, James M. Isbell¹, David B. Sewell¹, David R. Jones¹, and Daniela Molena¹

J Gastrointest Surg. 2018

Staging with EUS



EUS QI (N = 8)

T-stage

Tumor thickness (mm)

Nodal size (mm)

Nodal echogenicity

Nodal shape

Nodal location

Nodal FNA

N-stage

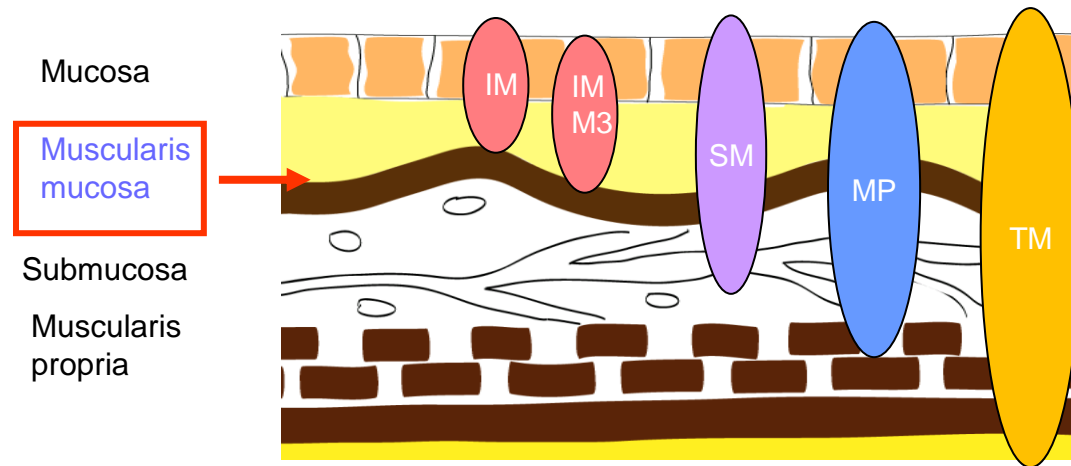
Best practical staging tools

- **Symptoms** → If dysphagia for solid at least T3
- **EMR/ESD** for diagnostic/therapeutic resection when → PET negative, small tumor, no symptoms, surveillance, feasible
- **EUS** for nodal FNA only for high-risk early-stage lesions → Size >2 cm, poor differentiation, LVI positive or T1b EAC (T1a muscularis mucosae ESCC)
- **PET/CT** → Always
- **Staging Laparoscopy** → for tumors extending ≥ 3 cm into the stomach and/or signet ring

Resectability

- Obvious with T4b
- Very hard to fully evaluate nodal disease in Stage IVA
- Difficult to evaluate esophago-gastric extension with signet ring cell
- **ALL TEST needed should be done BEFORE starting therapy!**

Only true local disease can be “cured” with endotherapy

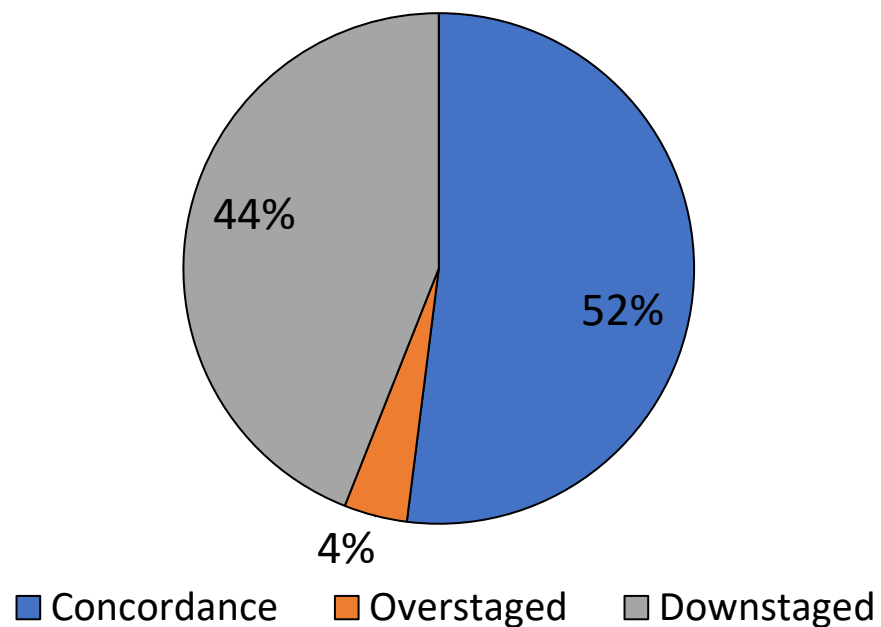


Frequency of Lymph Node Mets with Esophageal Cancer

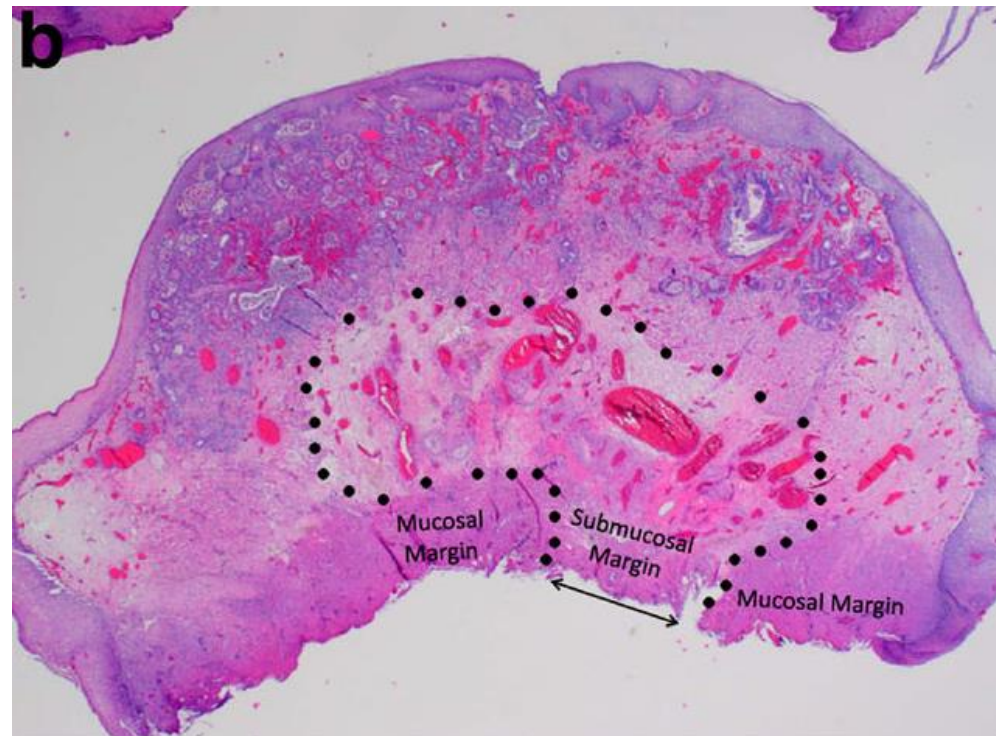
	T1a	T1M3	T1b	T2	T3
Adenocarcinoma	0-2%	1-2%	21%	75%	85%
Squamous cell	0-2%	12-15%	30%	70-80%	>80%

Be aware what you bet on

Depth of invasion



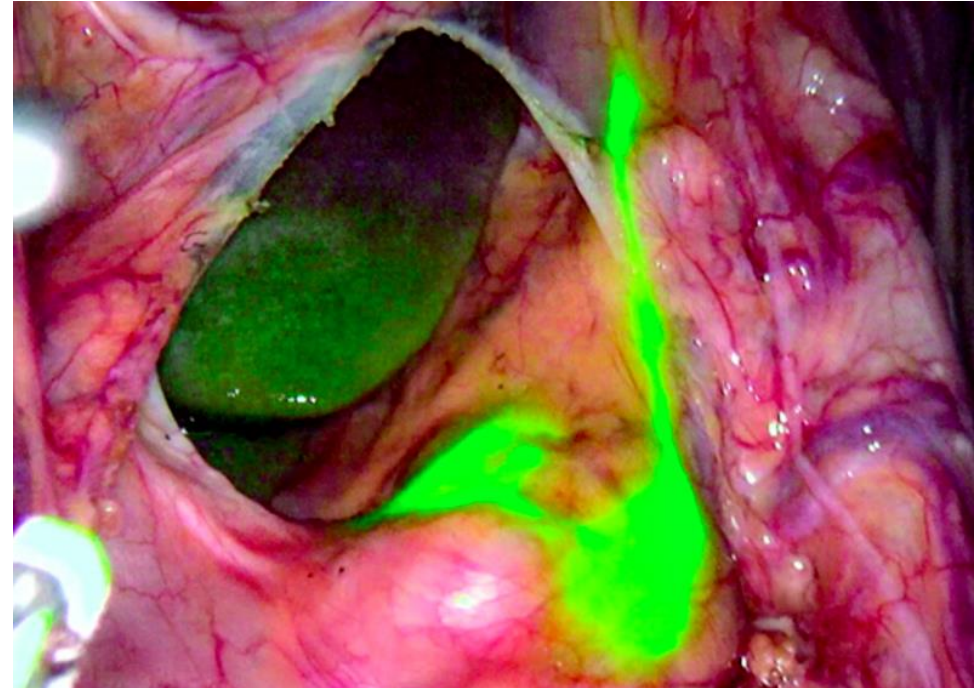
Worrell SG, et al. JOGS, 2016



Path Concordance	Original	Expert
Tumor Grade	56 %	80 %
LVI	75 %	88 %

Can we predict lymphatic drainage?

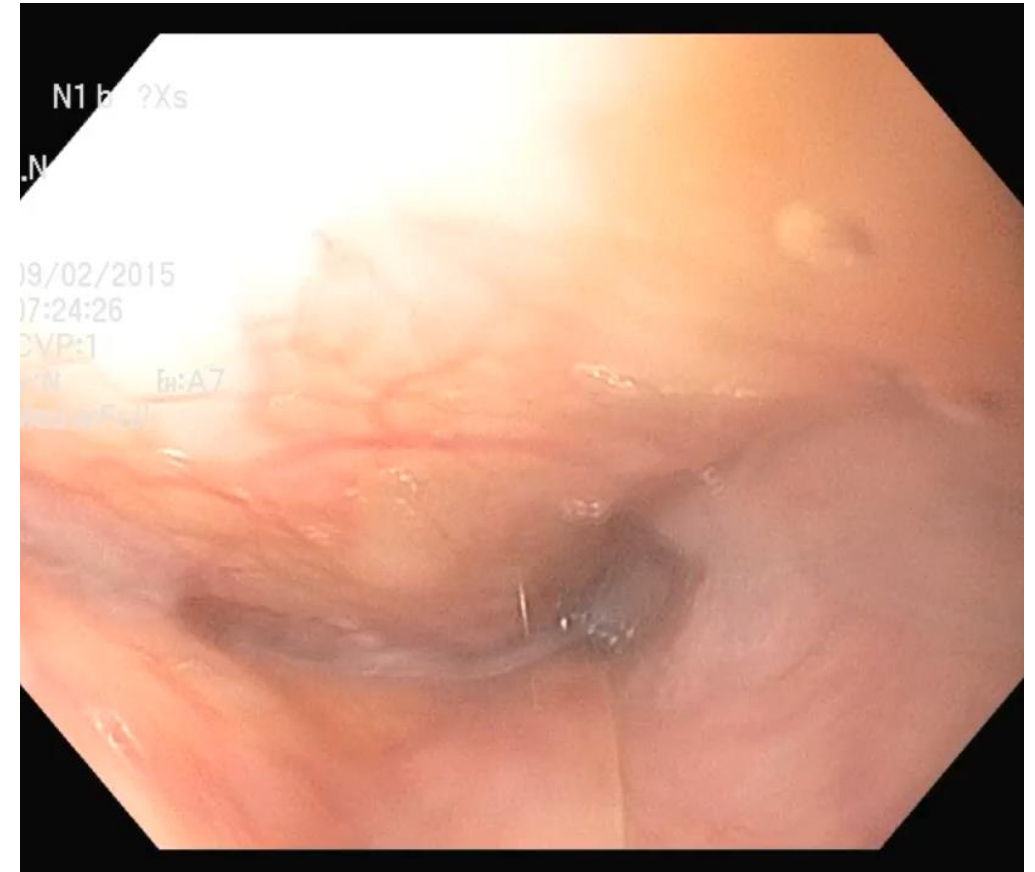
- 9 patients
- ICG injected at 4 quadrants around tumor
- 88.9% left gastric a.
- 11.1% diaphragmatic nodes
- 33.3% positive nodes all identified within first basin



Schlottman F, Molena D. et al. *JLAST*, 2017

Sentinel Node Trial

- 65 patients enrolled
- 48 patients evaluable
- 5 patients had a positive sentinel node
- Only in 1 patient the positive sentinel node was the only positive node
- 8 patients had a positive node with negative sentinel node
- Sensitivity = 38%
- PPV = 12%



Locally advanced disease

- Patients with locally advanced disease receive neoadjuvant chemo +/- radiation
- Esophagectomy without induction therapy reserved for:
 - Patients who are not a candidate for esophagus-preserving endoscopic interventions
 - Selected patients with T2N0M0 disease (low risk of nodal disease)
 - Patients medically unfit to receive tri-modality therapy
 - Emergency surgery for obstruction, bleeding or perforation

Is Radiation Still needed?

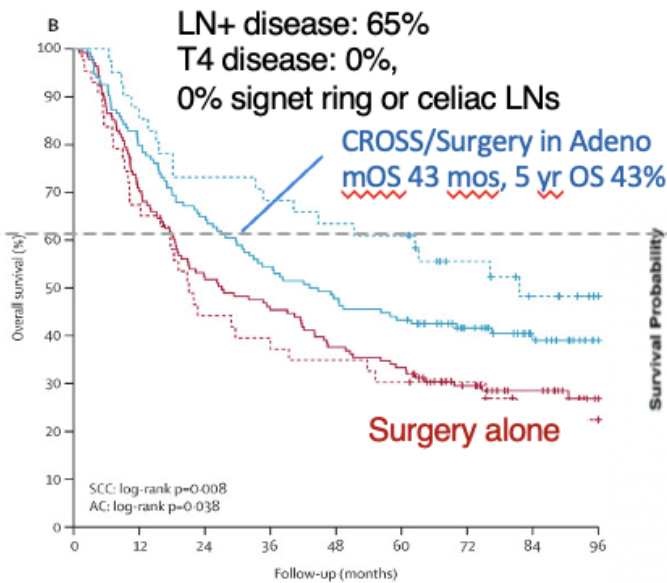
CROSS (PC/RT) vs Surgery

Neo-AEGIS-ECX vs. CROSS

FLOT vs ECX

CROSS best in SCC >> Adeno

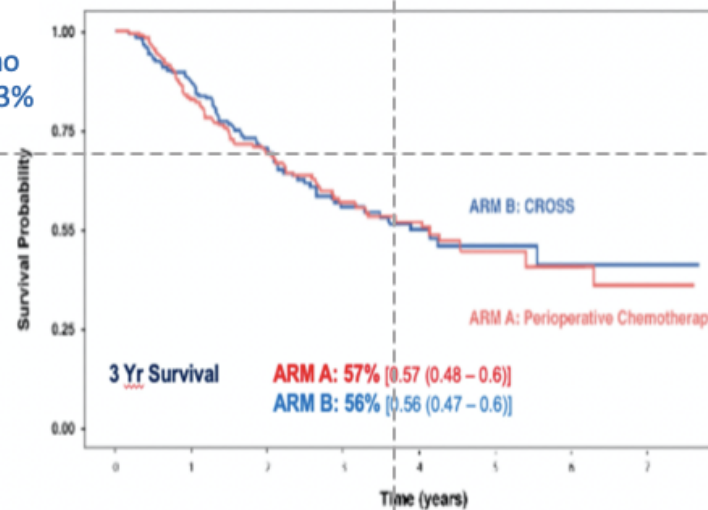
Adeno HR 0.75 CROSS /surgery vs. surgery alone



ECX alone non inferior to CROSS

3-year OS 57% ; Ro 82% vs 95%

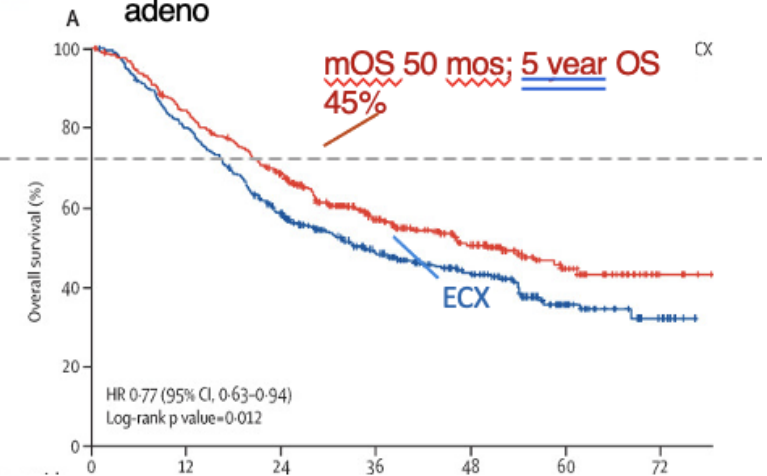
14% (n=27) FLOT; T4 disease: 0%; LN+ 60%



FLOT is better than ECX

LN+ disease: 78%; T4 disease: 8%
27% signet ring/PD

Adeno HR 0.76 FLOT vs ECX for GEJ adeno

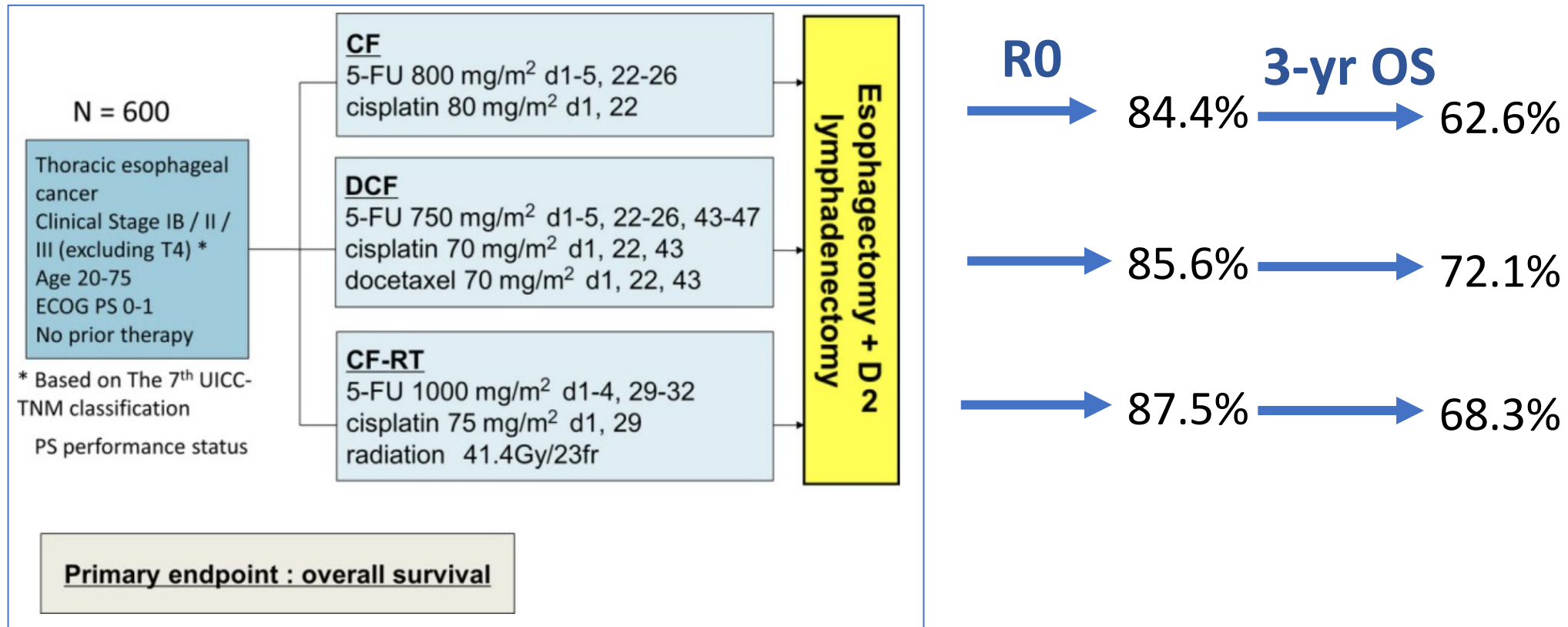


Best treatment of systemic disease and micro-metastasis is all is needed...for good quality surgeries!!

Al-Batran et al. Phase III FLOT4. *Lancet* 2019; Van Hagen et al. Phase III CROSS, *NEJM* 2012; Shapiro et al. *Lancet Oncol* 2015; Reynolds, et al. *ASCO* 2021

DOES RT increase R0

JCOG 1109



Kato K et al. Journal of Clinical Oncology 2022

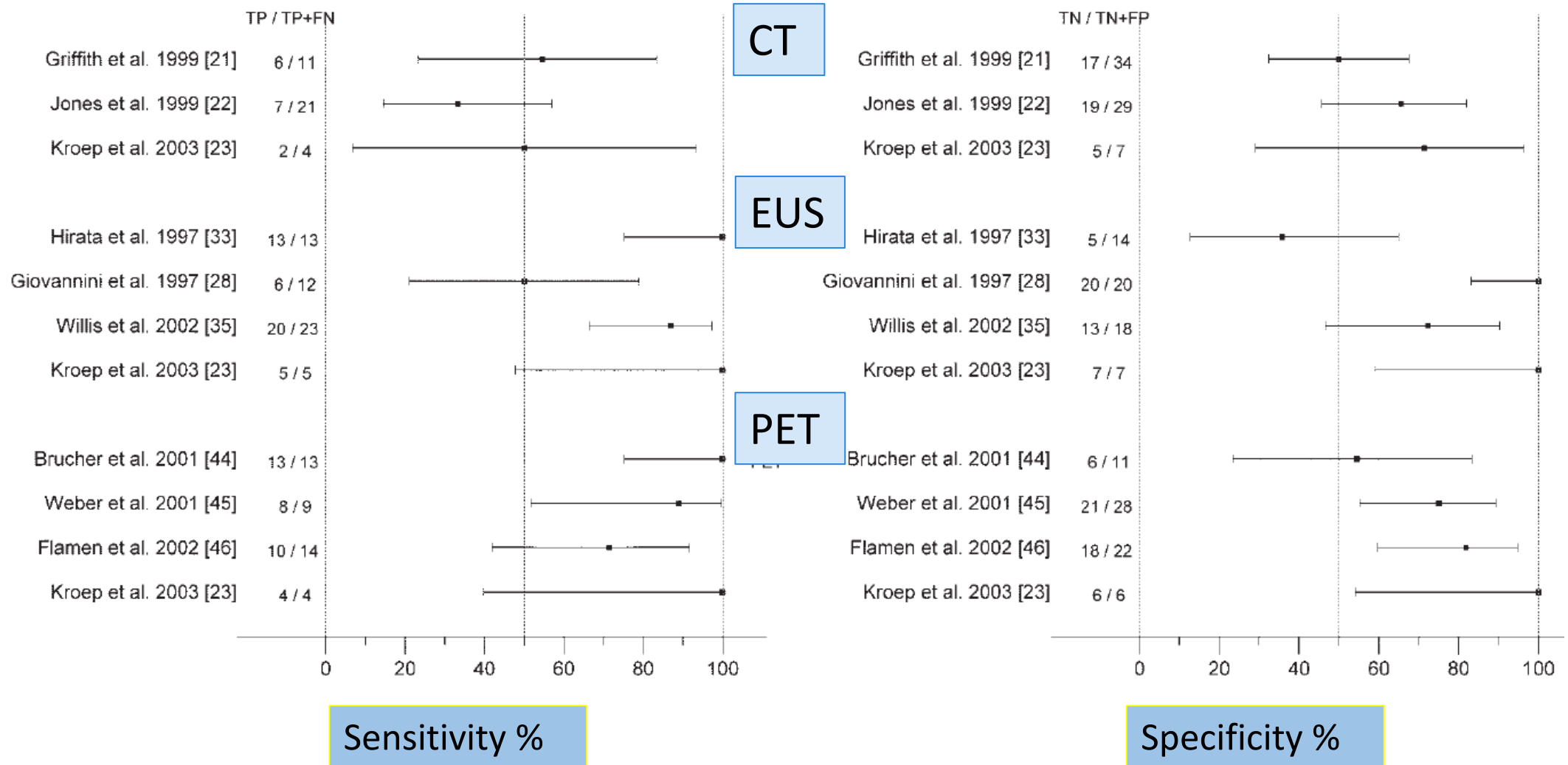
When do I prefer Radiation?

- ESCC
- Patients unfit for surgery
- Extended disease with unclear ability to achieve radial R0 (T4b, bulky nodes)
- Elevated CPS score

BIOMARKERS: MMR, HER2, Claudin 18.2, CPS

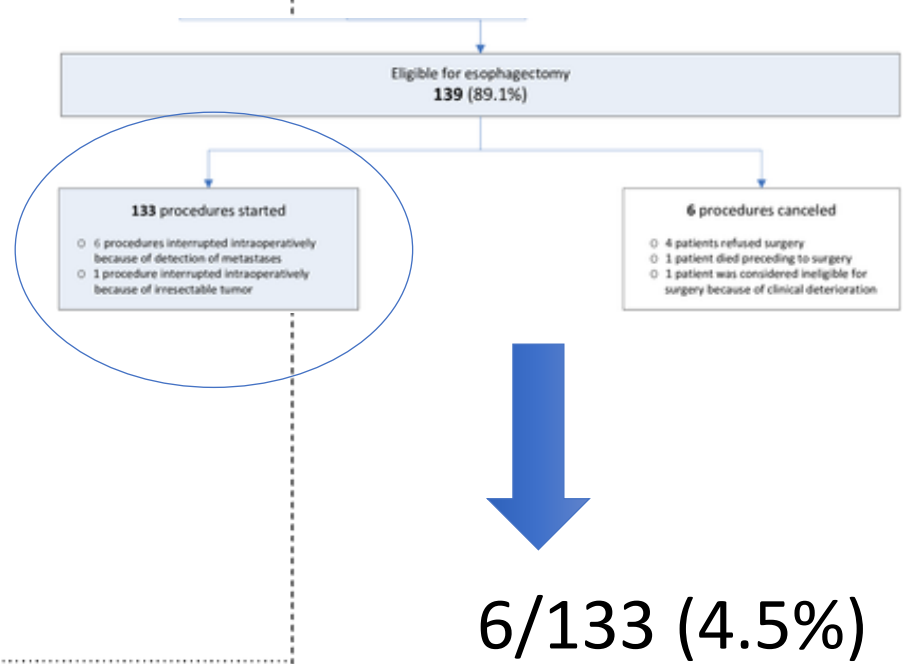
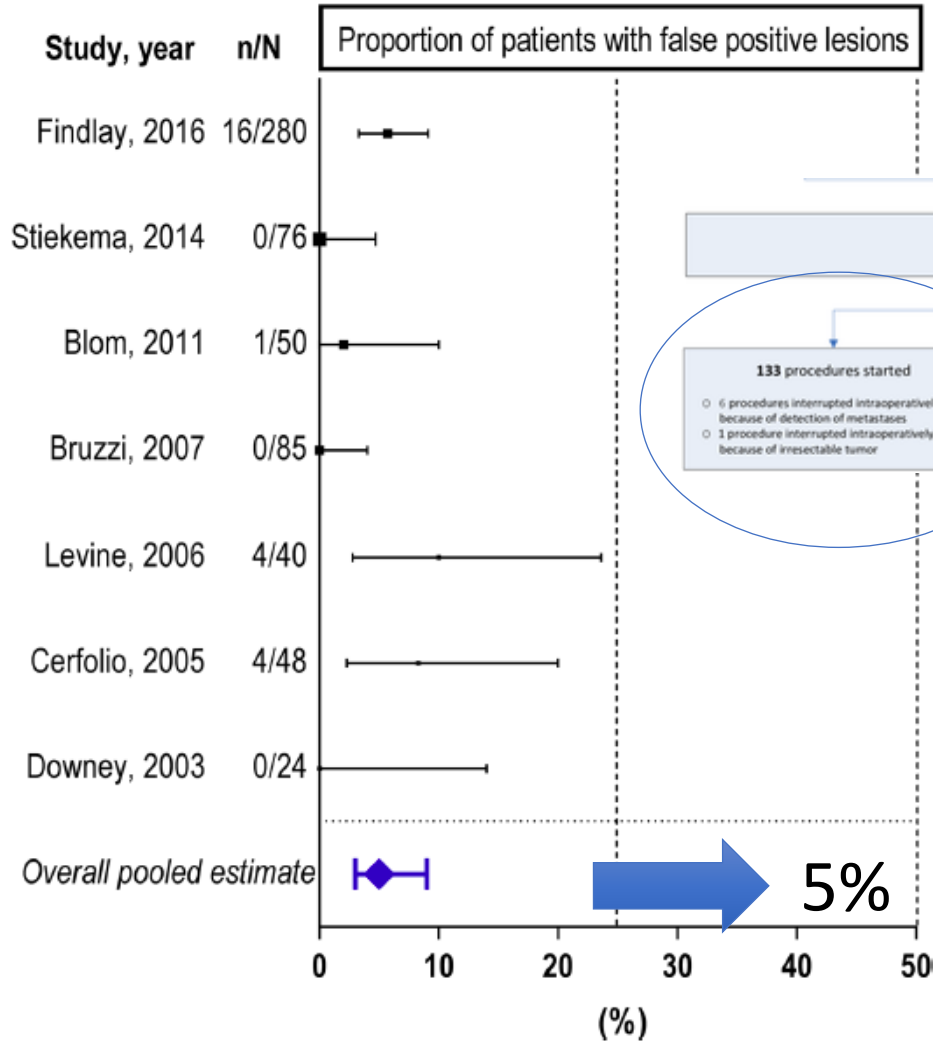
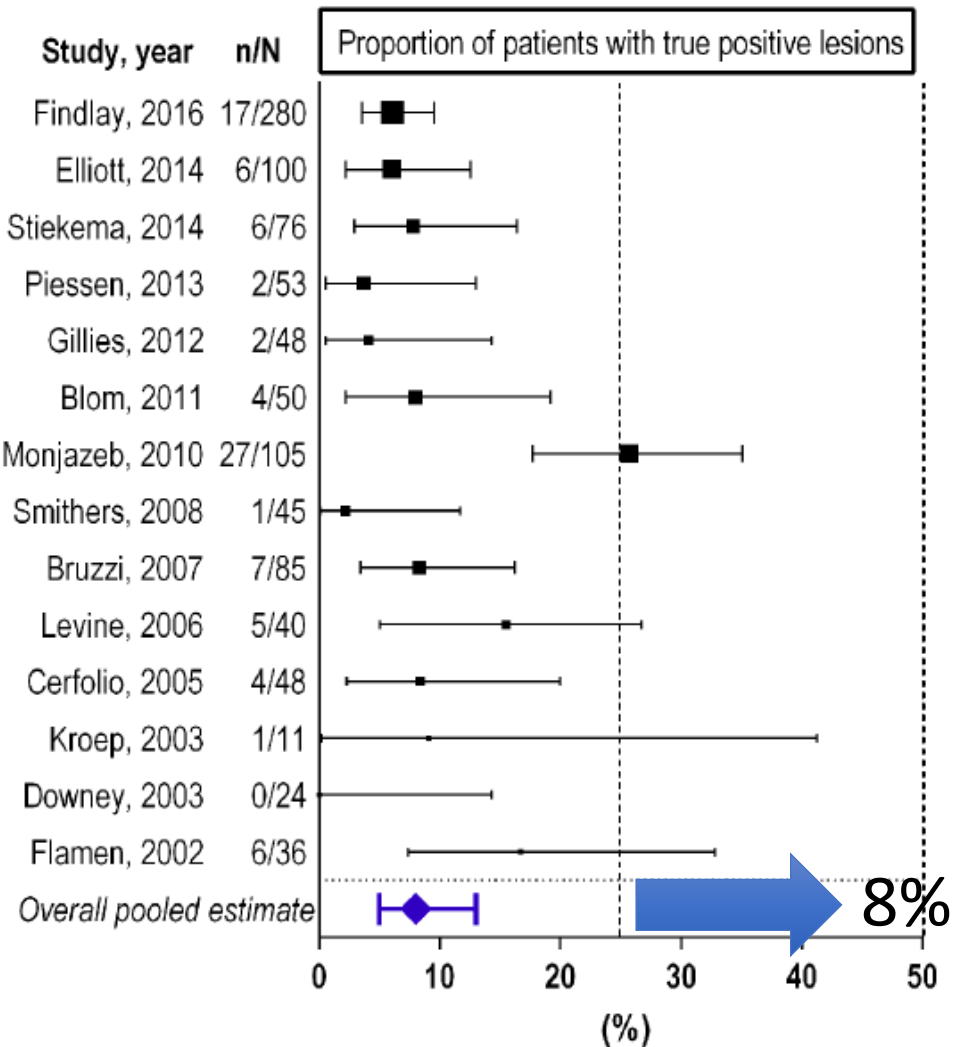
True personalized medicine is coming!

Re-staging

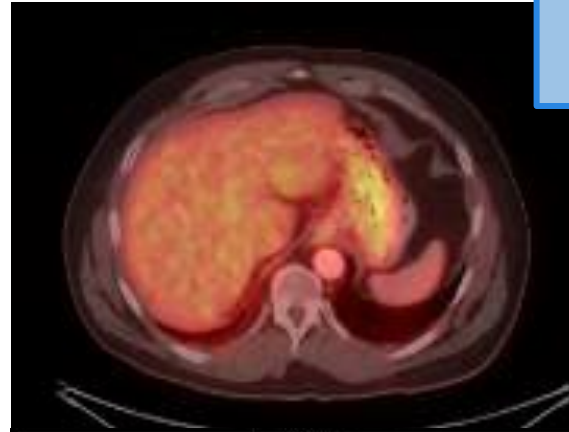


Westerterp M et al. Radiology 2005;236:841-851

Re-staging



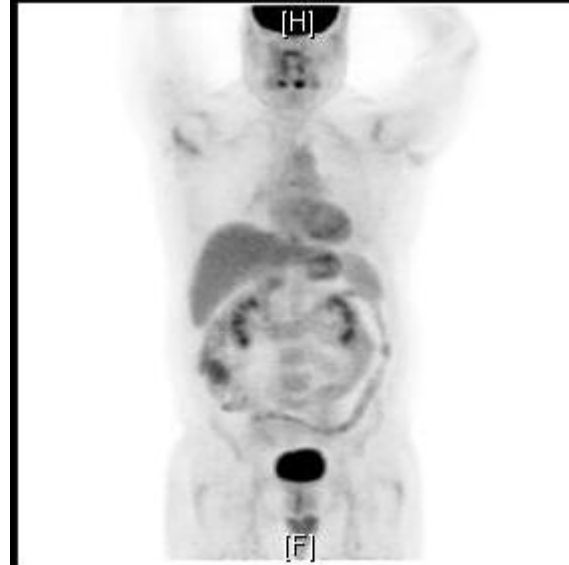
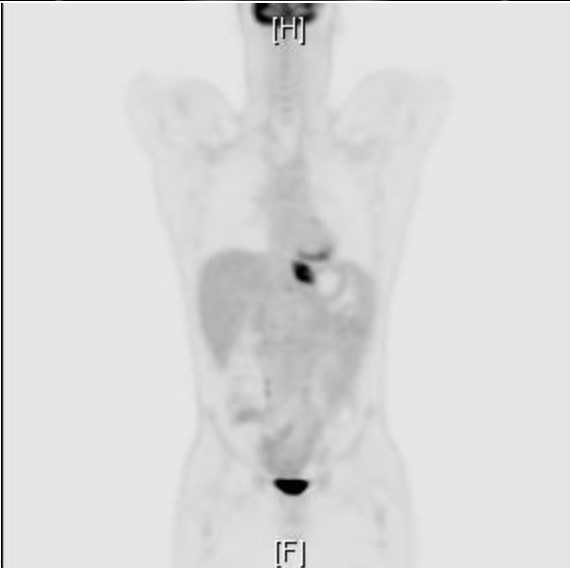
The illusion of cCR



Pathological CR in CROSS
23% EAC
49% ESCC



PT3N2



Even pCR is not = cure

Patterns and risk of recurrence in patients with esophageal cancer with a pathologic complete response after chemoradiotherapy followed by surgery Check for

Arianna Barbetta, MD,^a Smita Sihag, MD,^a Tamar Nobel, MD,^a Meier Hsu, MS,^b Kay See Tan, PhD,^b Manjit Bains, MD,^a David R. Jones, MD,^a and Daniela Molena, MD^a

JCTVS 2018

TABLE 2. Distribution of recurrence sites by histology

Site of recurrence	EAC (N = 43)	ESCC (N = 18)
Loco-regional		
Mediastinal LN	3 (7%)	6 (33%)
Anastomosis/conduit	1 (2.3%)	1 (5.5%)
Supraclavicular LN	1 (2.3%)	2 (11%)
Multiple sites	3 (7%)	0
Distant		
Brain	12 (28%)	1 (5.5%)
Liver	4 (9.3%)	2 (11%)
Bone	2 (4.7%)	0
Retroperitoneal LN	1 (2.3%)	0
Lung	2 (4.7%)	5 (27.8%)
Peritoneum	1 (2.3%)	0
Multiple organs	13 (30.2%)	1 (5.5%)

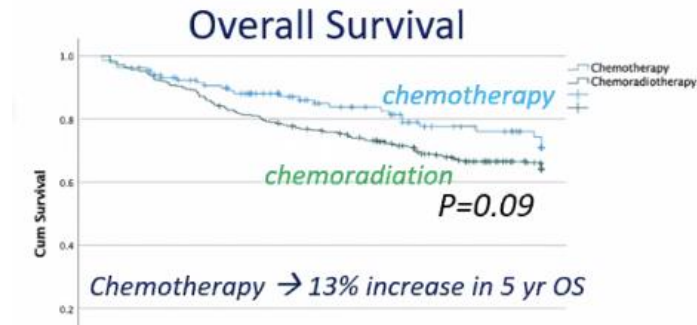
EAC, Esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; LN, lymph node.

An international cohort study of prognosis associated with pathologically complete response following neoadjuvant chemotherapy vs. chemoradiotherapy of surgical treated esophageal adenocarcinoma

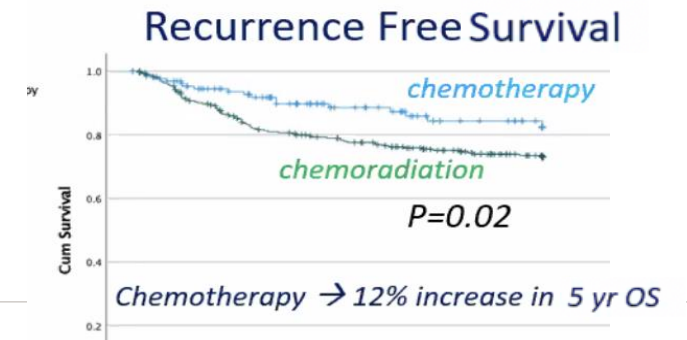
- Sheraz R. Markar,* Jonathan Cools-Lartigue, Carmen Mueller, Wayne Hofstetter, Magnus Nilsson, Ilkka Ilonen, Henna Soderstrom, Jari Rasanen, Suzanne Gisbertz, George B Hanna, Jessie Elliott, John Reynolds, Aaron Kisiel, Ewen Griffiths, Mark Van Berge Henegouwen, **Lorenzo Ferri.***

Annals of Surgery 2022

nCT = 132



nCRT=333



The Price of Salvage Surgery

- 1,137 patients with esophagectomy between 2001 and 2019
- 173 (15%) of these were treated with SE

Patients who underwent SE were statistically significantly:

- *more likely* to have **vascular invasion** (40% vs 22%, $p < 0.0001$)
- *more likely* to have **neural invasion** (42% vs 22%, $p < 0.0001$)
- *more likely* to have a **poor or non-response to chemoradiation** (48% vs 16%, $p < 0.0001$)
- *less likely* to have an **R0 resection** (90% vs 95%, $p = 0.009$)

Patients who underwent SE were statistically significantly:

- *more likely* to experience a **serious post-operative complication** (33% vs 17%, $p < 0.0001$)
- *more likely* to experience a **serious post-op pulmonary complication** (27% vs 14%, $p < 0.0001$)
- **No differences** in anastomotic leaks, chyle leaks, other serious GI complications, serious cardiac complications

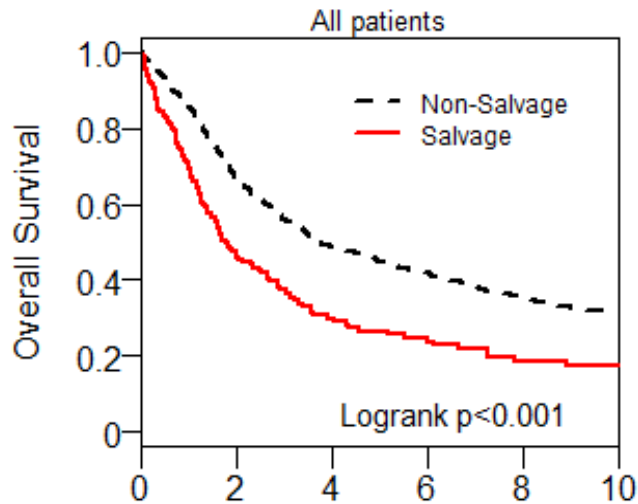
30- day mortality: 1.7% NSE vs 3.5% for SE ($p = 0.13$)

Boerner T, Molena D et al. Ann Surg. 2023

The Price of Salvage Surgery

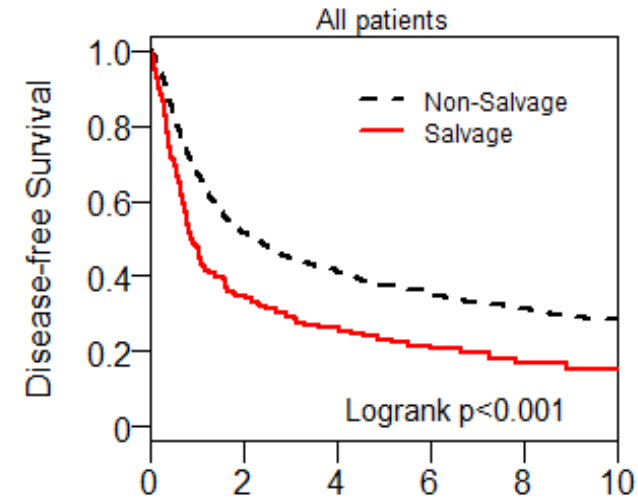
- 1,137 patients with esophagectomy between 2001 and 2019
- 173 (15%) of these were treated with SE

Overall Survival
45% vs 26.5% for SE (p<0.001)



No. At Risk	Years since surgery					
	0	2	4	6	8	10
Non-Salvage	964	541	322	214	122	72
Salvage	173	70	37	24	16	10

Disease Free Survival
37.7% vs 23.1%, p<0.001



No. At Risk	Years since surgery					
	0	2	4	6	8	10
Non-Salvage	964	416	277	183	111	66
Salvage	173	52	34	22	15	9

Boerner T, Molena D et al. Ann Surg. 2023

Surgical Principles

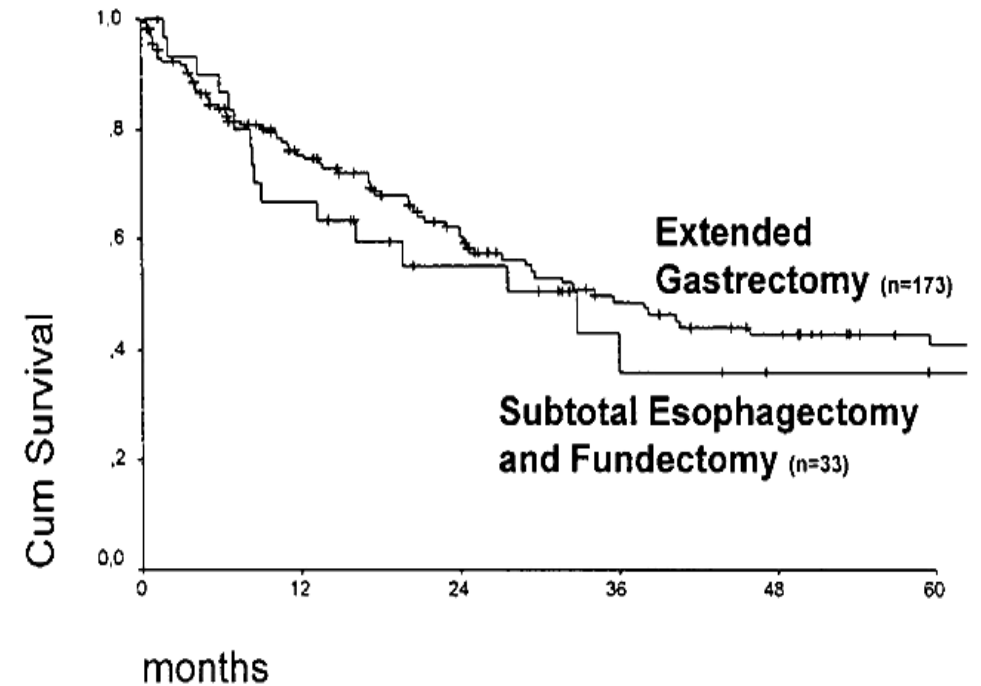
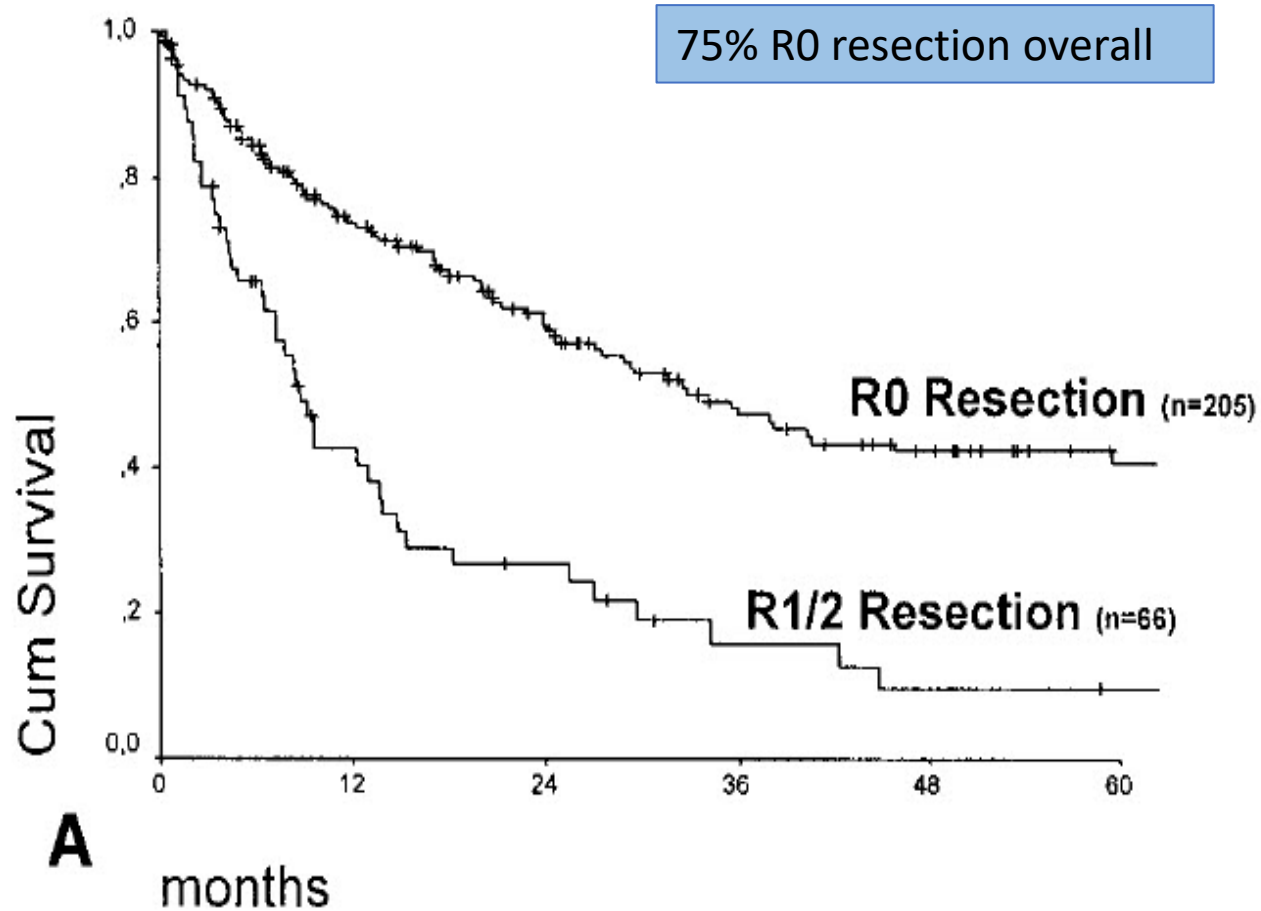


Figure 4. Survival rates of patients with R0-resected (no residual macroscopic or microscopic tumor) true carcinoma of the cardia (type II tumors) according to type of resection. No significant difference was found between extended gastrectomy and esophagectomy.

Siewert JR, et al. *Ann Surg*, 2000

Surgical Principles

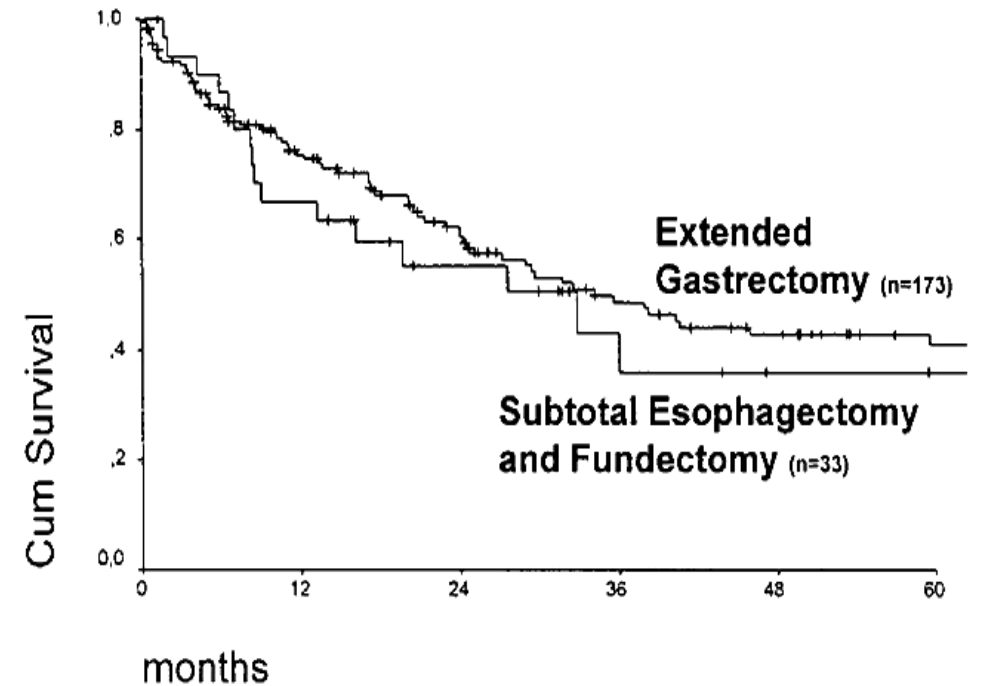
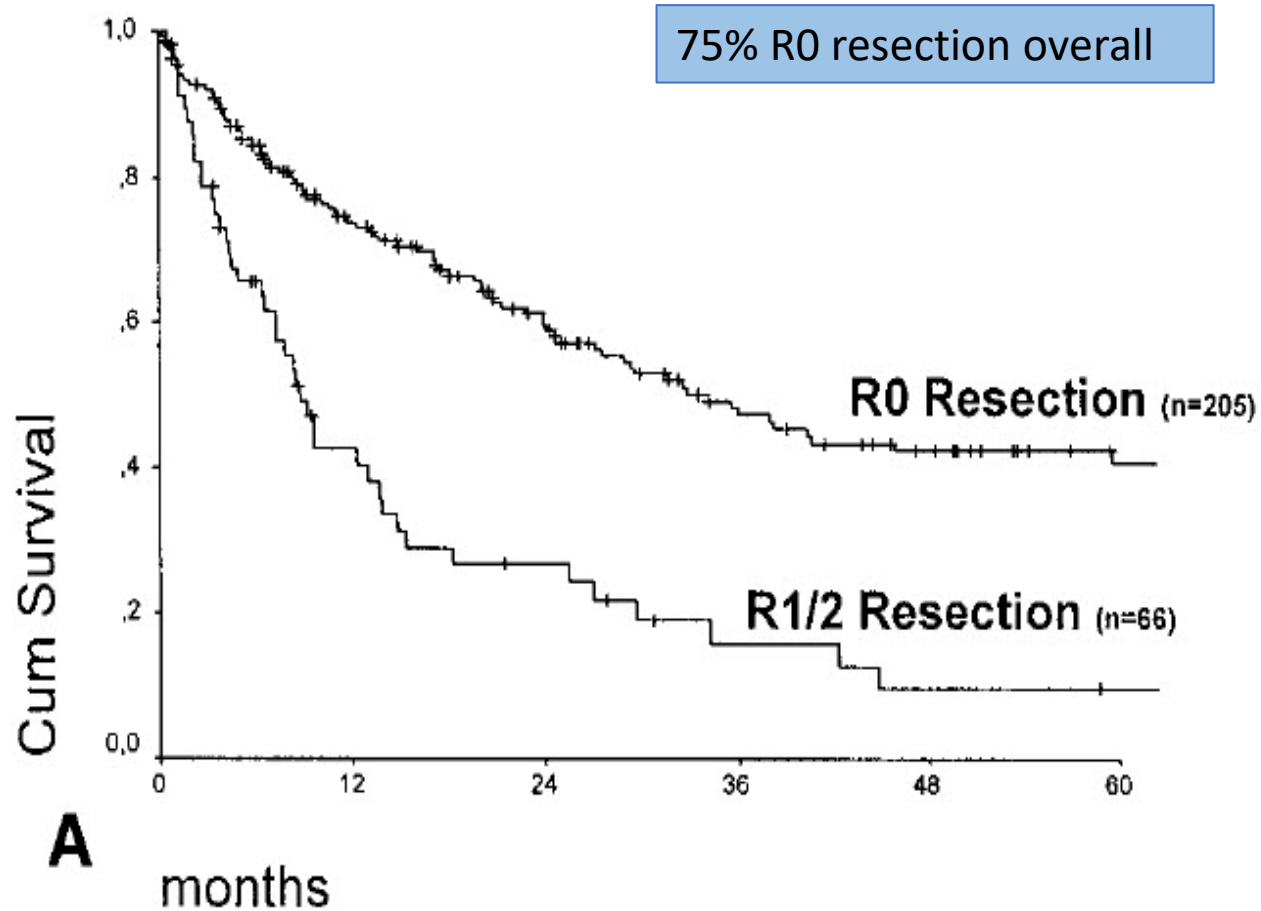
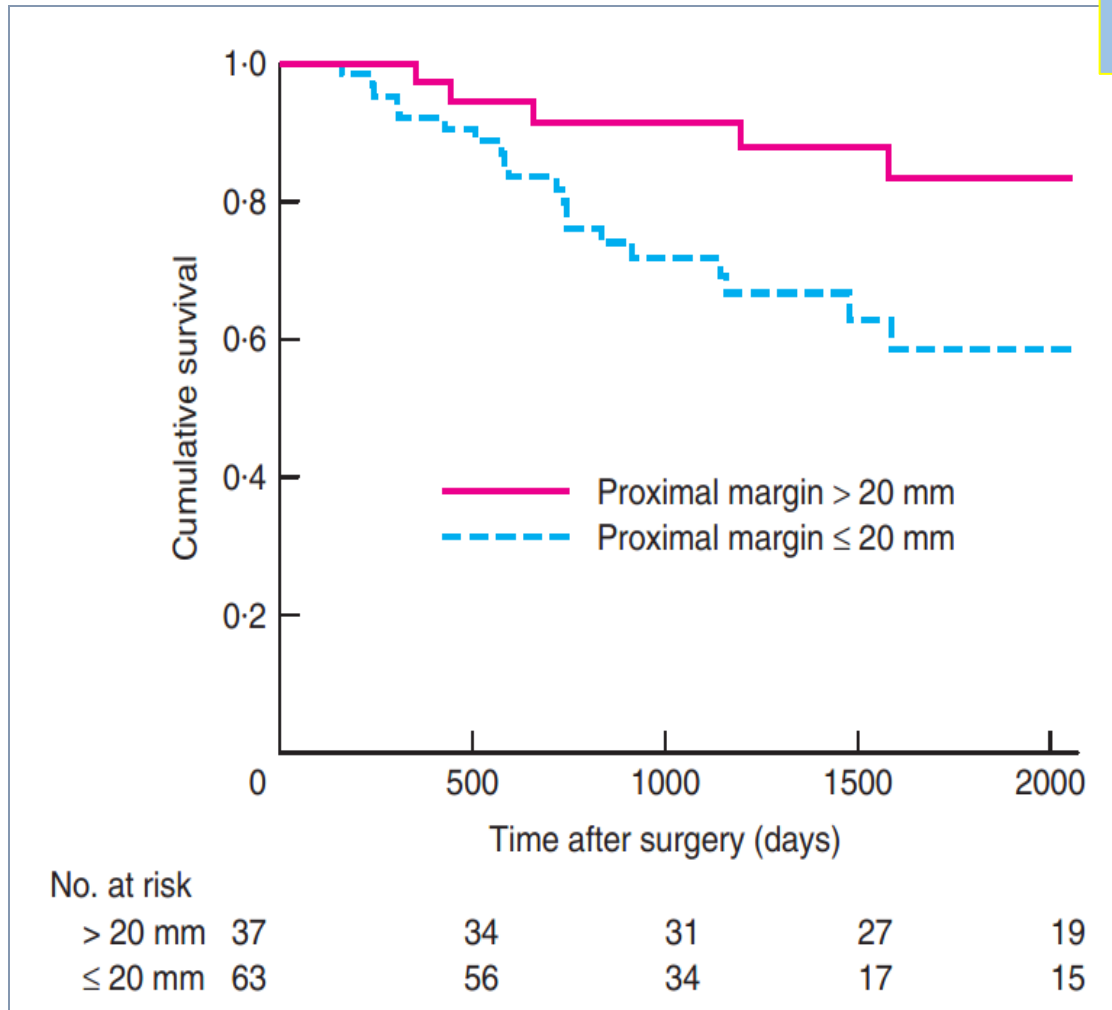


Figure 4. Survival rates of patients with R0-resected (no residual macroscopic or microscopic tumor) true carcinoma of the cardia (type II tumors) according to type of resection. No significant difference was found between extended gastrectomy and esophagectomy.

Siewert JR, et al. *Ann Surg*, 2000

Surgical Principles

Do the operation you want but get GOOD margins



	Hazard ratio	P
Pathological tumour category (pT3-4 versus pT2)	7.47 (0.98, 56.71)	0.052
Pathological node category (pN3 versus pN2 versus pN0-1)	1.76 (1.08, 2.86)	0.024
Proximal margin (≤ 20 versus > 20 mm)	3.56 (1.39, 9.14)	0.008

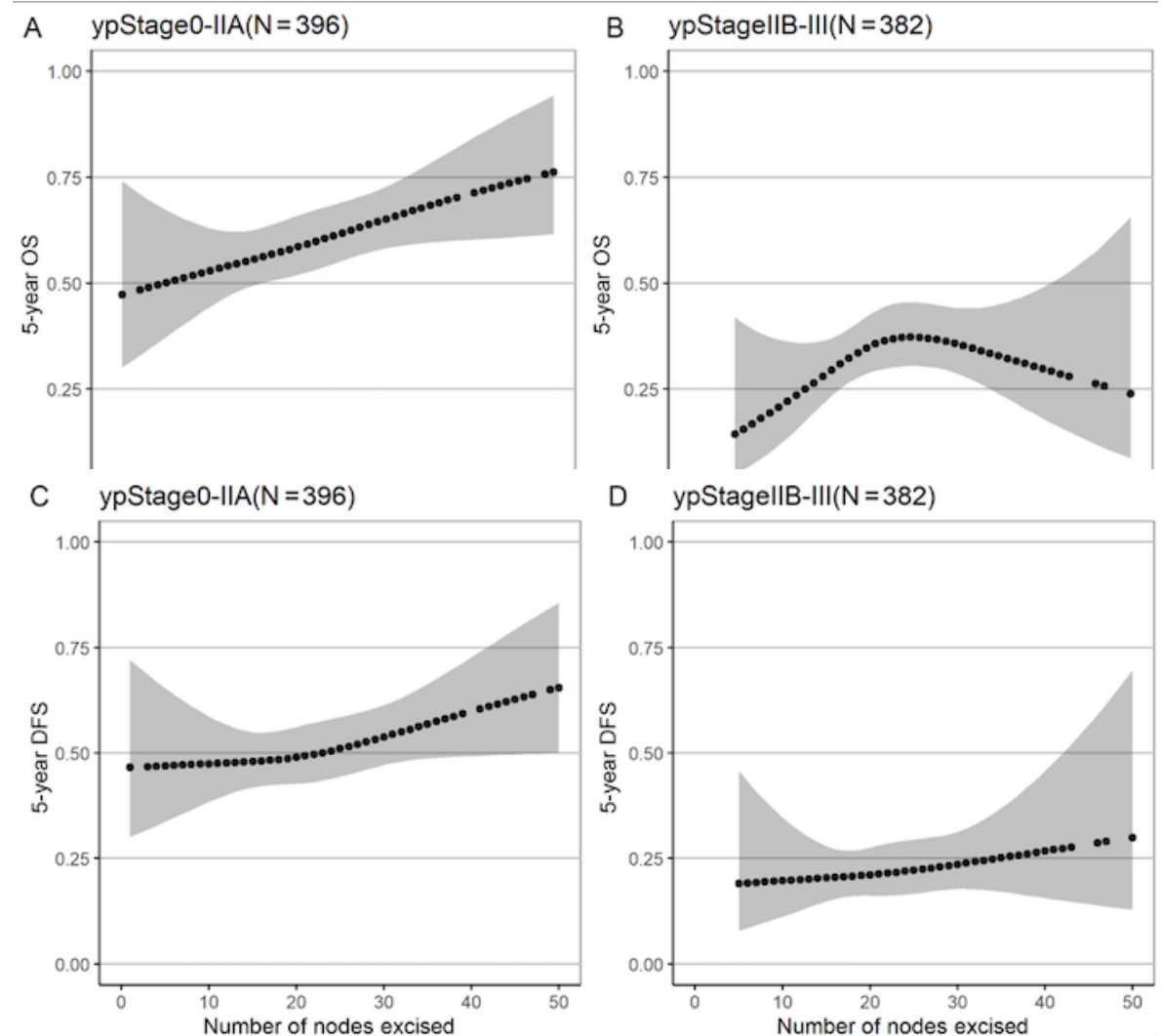
Values in parentheses are 95 per cent confidence intervals.

Mine S, et al. *Br J Surg*, 2013

Surgical Principles

- Better **OS** and **DFS** with higher number of nodes removed, especially in down-staged patients
- For patients with minimal response the improvement peaked with **20-25 nodes** removed

TAKE the NODES!

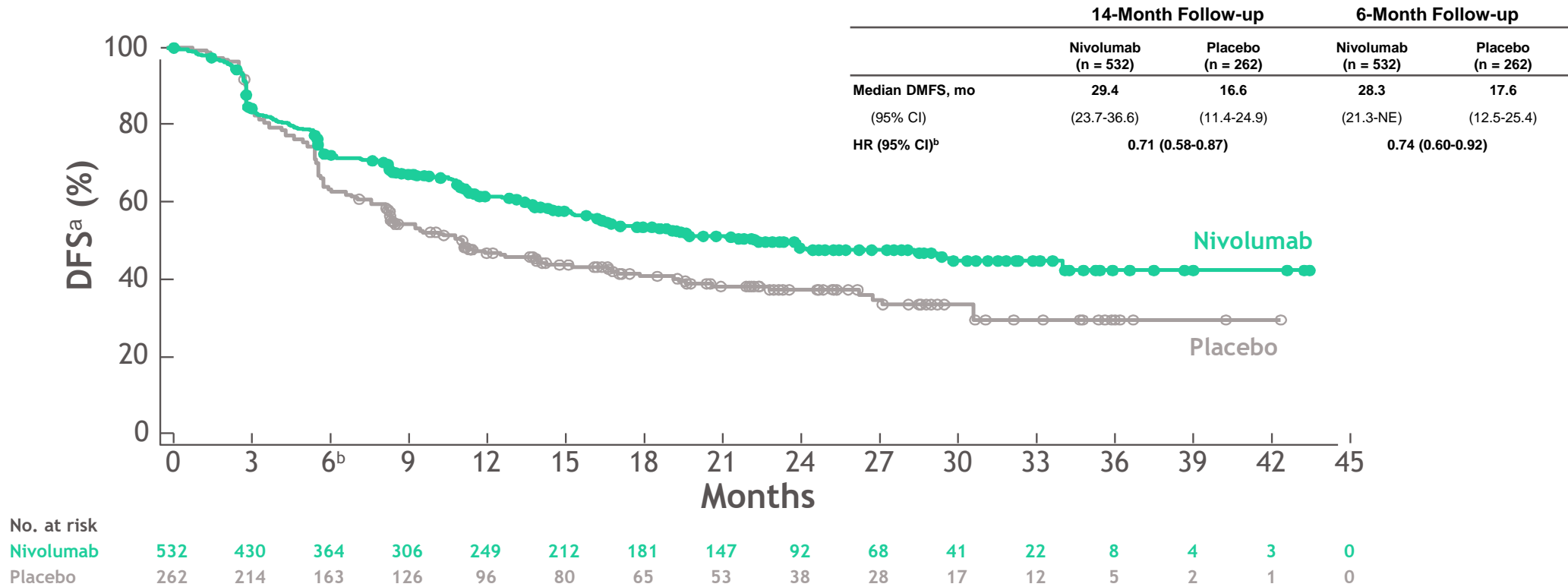


Sihag S, Molena D. et al, Ann Surg 2022

Other Surgical Considerations

- Resect according to initial extension of disease
- Technical consideration to limit morbidity
 - Conduit type and size
 - Type and location of anastomosis
 - Pyloric drainage
- Post-operative care (ERAS pathways)

Adjuvant Therapy



- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo
- HR numerically decreased with an additional 8 months of follow-up (HR=0.67 [95% CI: 0.55-0.81])

Kelly RJ et al. *N Engl J Med.* 2021;384:1191-1203.

Moehler M et al. Poster presentation at ESMO 2021. Abstract 1381P.

Conclusions

- Esophageal cancer is not one size fits all – **end the CROSS for all approach!**
- Neoadjuvant therapy tailored to patient and disease (personalization)
- Respect surgical principles (R0, lymphadenectomy)
- Chose the appropriate operation based on extension of disease – **If you can offer all you will offer what's right**

Thank you!

Email: molenad@mskcc.org

Twitter: [@Daniela_Molena](https://twitter.com/Daniela_Molena)
[@MSK_Thoracic](https://twitter.com/MSK_Thoracic)

