Esophageal and Gastric Cancer

SCCA Comprehensive Oncology Review

September 2020

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Objectives

- Epidemiology and Risk Factors
- Pathology, Diagnosis, and Staging
- Stage I-III Esophageal Cancer
- Stage I-III Gastric Cancer
- Advanced Esophageal and Gastric Cancer

Epidemiology and Risk Factors

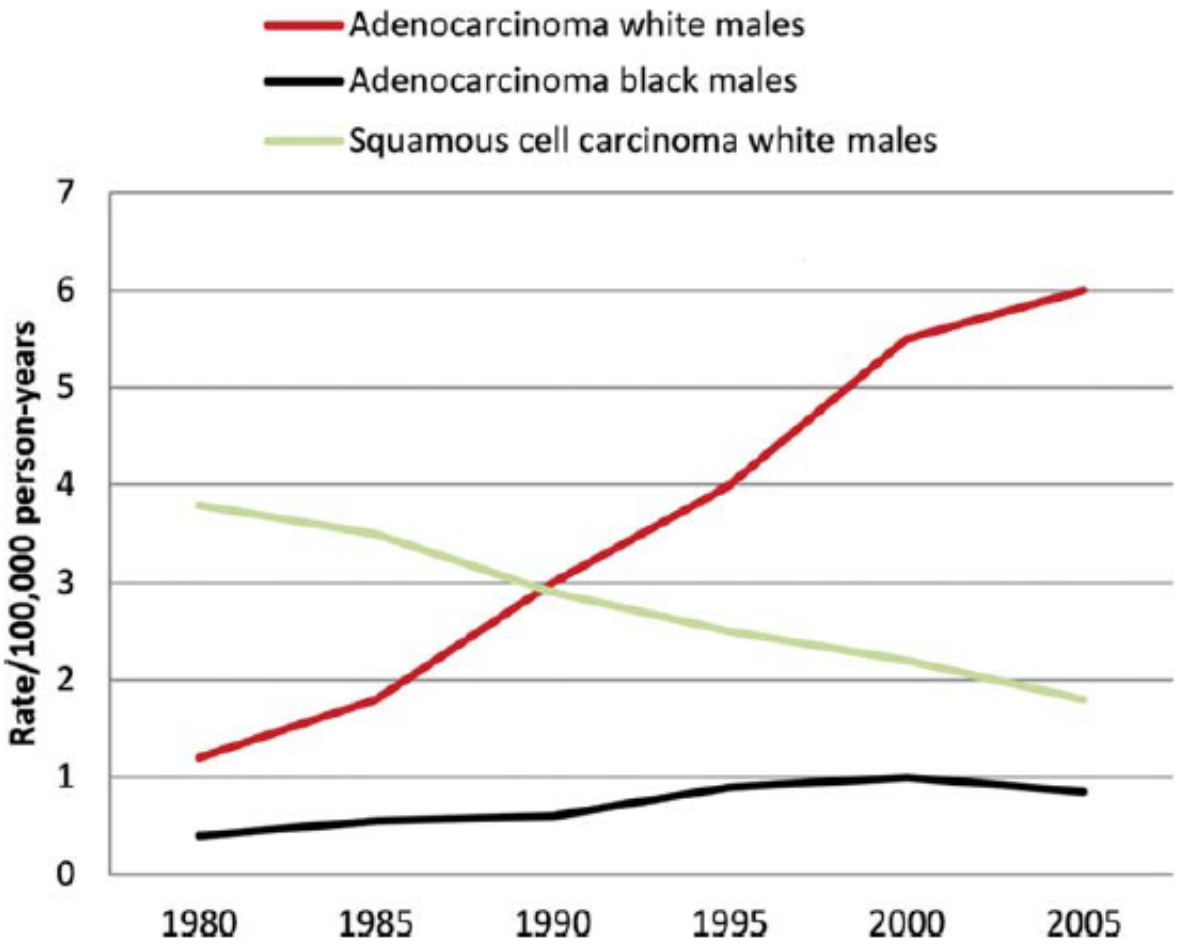
Incidence and Mortality - 2020

	Estimated new cases			Estimated deaths		
	Male	Female	**TOTAL**	Male	Female	**TOTAL**
Esophageal	14,350	4,090	**18,440**	13,100	3,070	**16,170**
Gastric	16,980	10,620	**27,600**	6,650	4,360	**11,010**

Esophageal Cancer: 6th most common cause of cancer death worldwide
Gastric Cancer: 3rd most common cause of cancer death worldwide

American Cancer Society, Facts & Figures, 2020

Esophageal Cancer Epidemiology



FRED HUTCH

Lagergren J and Lagergren P. *Cancer*. 2013; 64: 232-248.

Esophageal Cancer: Risk Factors

Squamous Cell Carcinoma	Adenocarcinoma
•***Tobacco (5-10 x risk)***	•Tobacco (2 x risk)
•***EtOH (3-7 x risk)***	•EtOH (1.2 x risk)
•Betel nut	•***GERD (7.7 x risk)***
•Hot liquids – burns	•***Obesity (3 x risk)***
•Nitroso compounds	

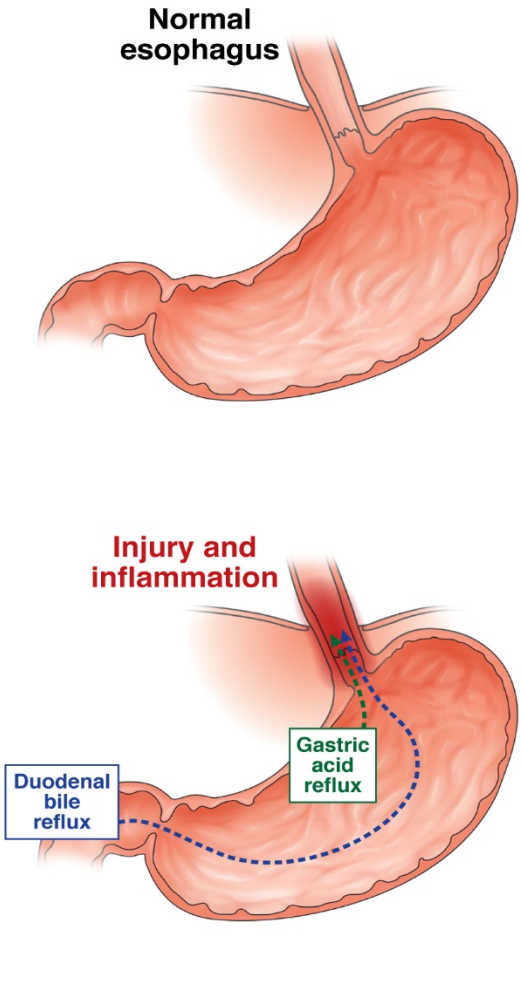
Crew, KD and Neuget AI. *World J Gastroenterology*. 2006 Jan; 12(3): 354-62
Lagergren, J et al. *NEJM*. 1999; 340(11): 825.
Lagergren, J et al. *Ann Intern Med*. 1999: 883-890

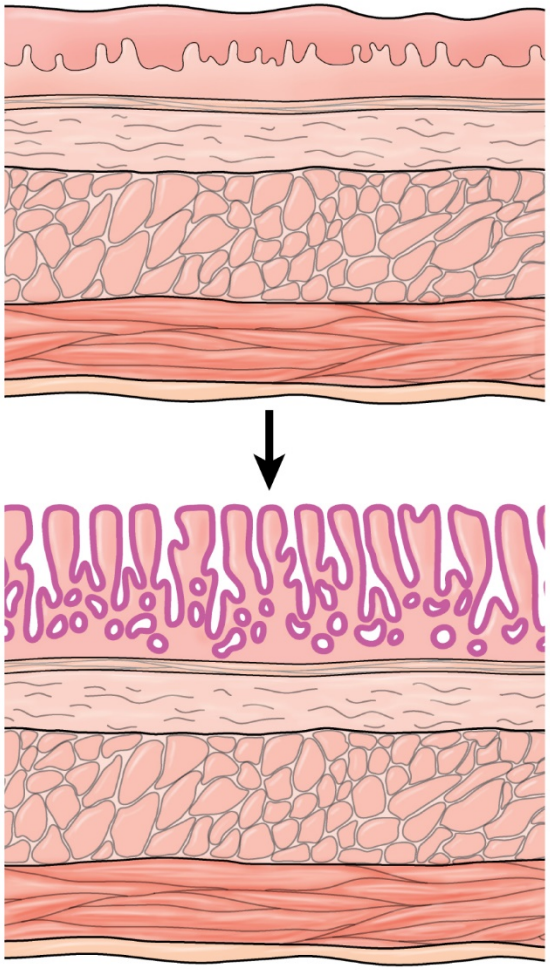
Symptomatic GERD

	Adjusted odds ratio (95% CI)		
	Esophageal adenocarcinoma	**Gastric cardia adenocarcinoma**	**Esophageal squamous cell ca**
No symptoms	1.0	1.0	1.0
Heartburn +/or regurgitation at least once a week	7.7 (5.3-11.4)	2.0 (1.4 – 2.9)	1.1 (0.7-1.9)
Heartburn +/or regurgitation at night at least once a week	10.8 (7.0-16.7)	2.4 (1.5 – 3.8)	0.9 (0.4-2.0)

Lagergren et al, N Eng J Med 340:825, 1999.

Barrett's Esophagus





A Normal squamous epithelium

B Metaplastic columnar tissue (BE)

6.6% Annual risk for adenocarcinoma with HIGH GRADE DYSPLASIA

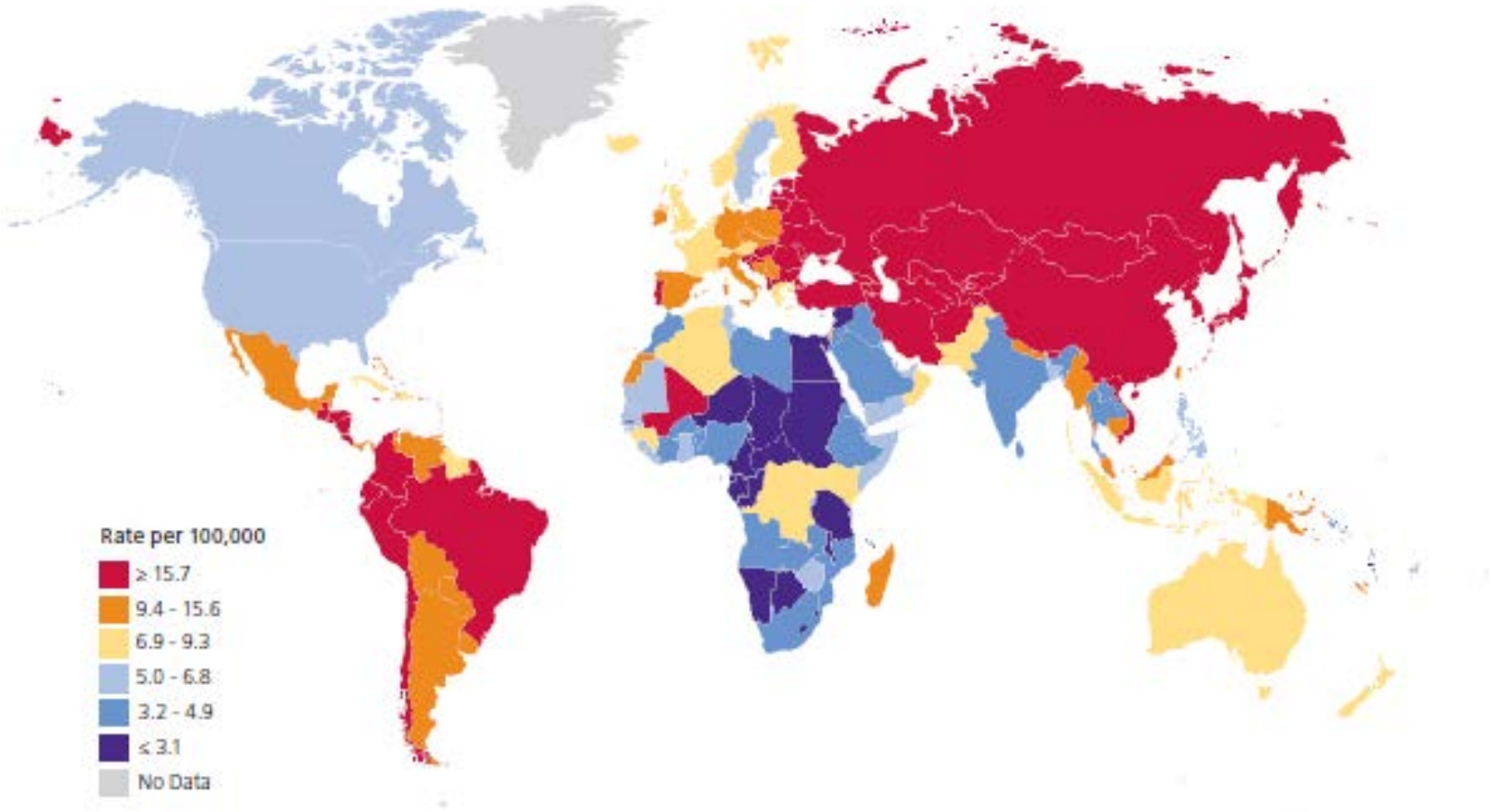
Morales CP et al. *Lancet*. 360: 9345, 2002
American Gastroenterological Association

Gastric Cancer: Risk Factors

Gastric Cancer
•Nitrite-containing, salt preserved foods •Smoking (distal gastric cancers) (OR 2.1 vs. nonsmoker) •GERD (cardia tumors) (OR 2.0) •Obesity (2-3x higher risk in obese vs. normal BMI) •**H. pylori** (intestinal subtype; body/distal) (1.2-16.7 fold increased risk, particularly CagA strain) •**Familial** (Hereditary diffuse gastric cancer (CDH1 mut; E. cadherin loss); HNPCC (Lynch); Peutz-Jehgers (STK11); Li-Fraumeni (p53); FAP (APC)

Gastric Cancer Trends

International variation in age-standardized gastric cancer incidence globally



FRED HUTCH

American Cancer Society, Global Facts & Figures 2nd ed, 2008

Gastric Cancer: Asian vs. Western

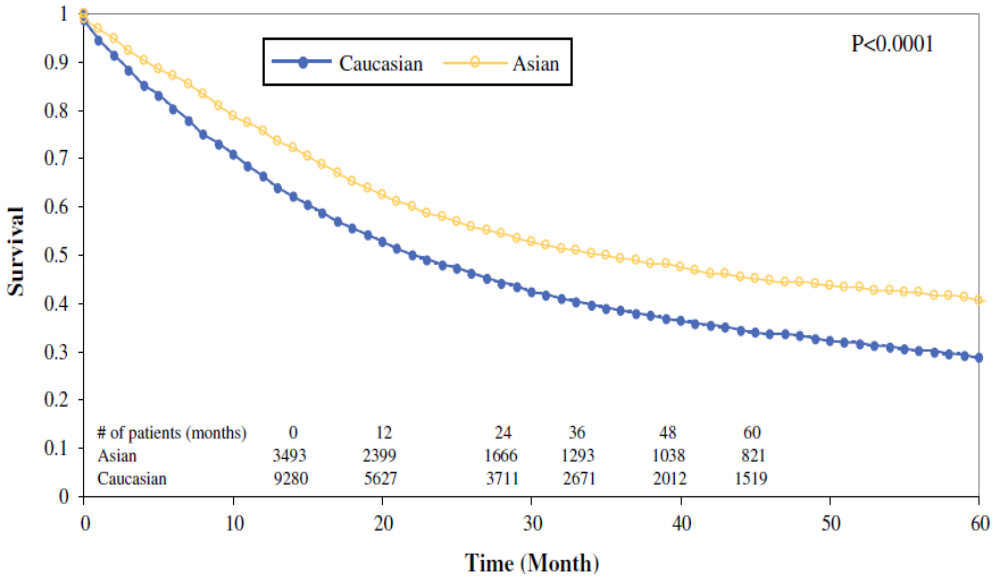
In Asia:

- Younger age at diagnosis
- More localized disease at presentation (53% in Japan vs. 27% in US) – screening programs
- More common in distal stomach
- More aggressive surgical resection
- More lines of systemic therapy

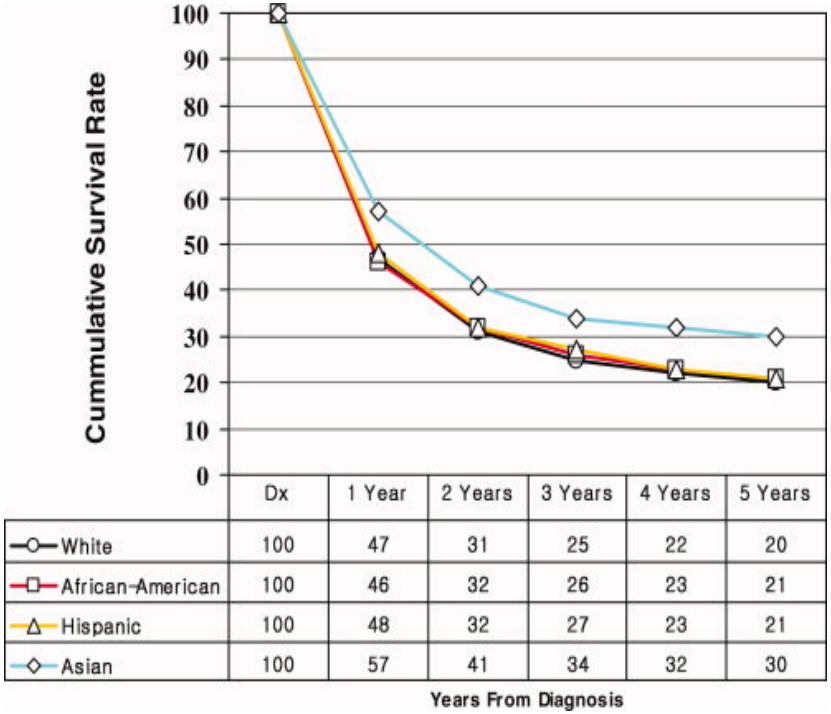
- ***Better Survival in Asia***

Gastric Cancer: Outcomes by Ethnicity

SEER-Medicare



National Cancer Database



	Dx	1 Year	2 Years	3 Years	4 Years	5 Years
White	100	47	31	25	22	20
African-American	100	46	32	26	23	21
Hispanic	100	48	32	27	23	21
Asian	100	57	41	34	32	30

Wang J. et al. Ann Surg Oncol, 2015; 22: 2965-2971
Al-Refaie W. et al. Cancer, 2008; 113(3): 461-469

Diagnosis, Staging, and Pathology

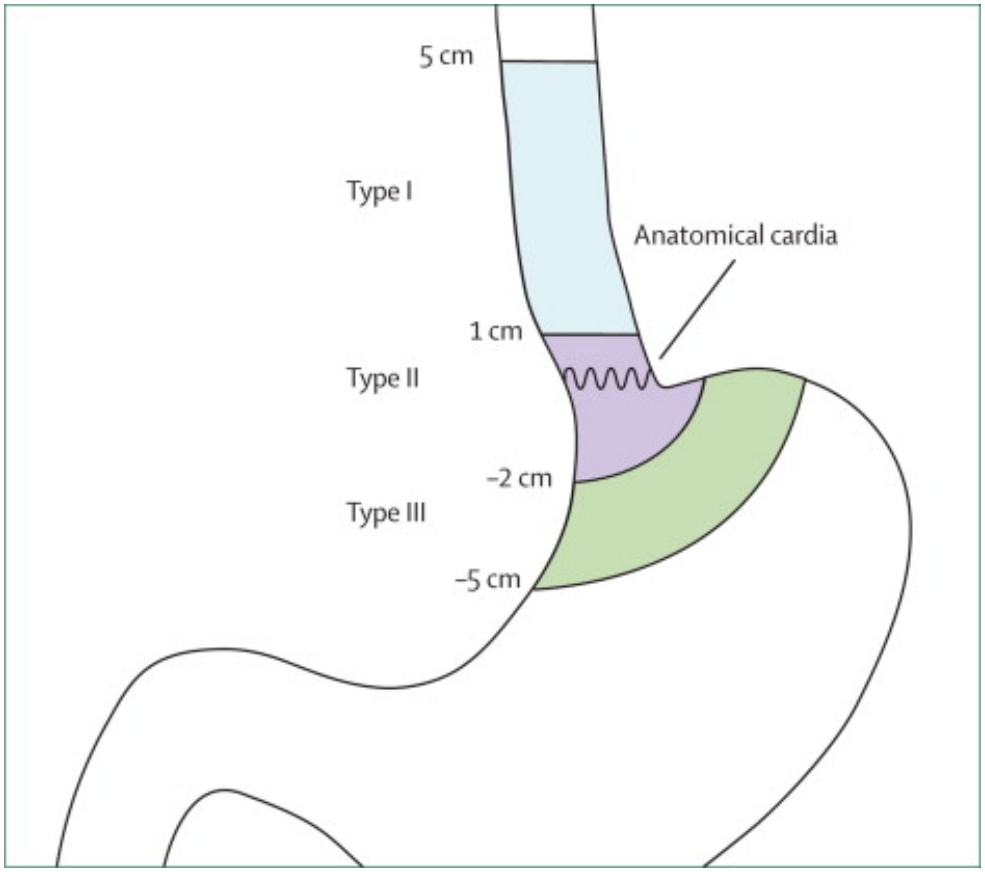
Esophageal Cancer Staging Workup

T-stage: EUS, Bronchoscopy (if above carina)

N-stage: EUS (FNA if possible), PET

M-stage: CT, PET, staging laparoscopy (GE jxn or cardia)

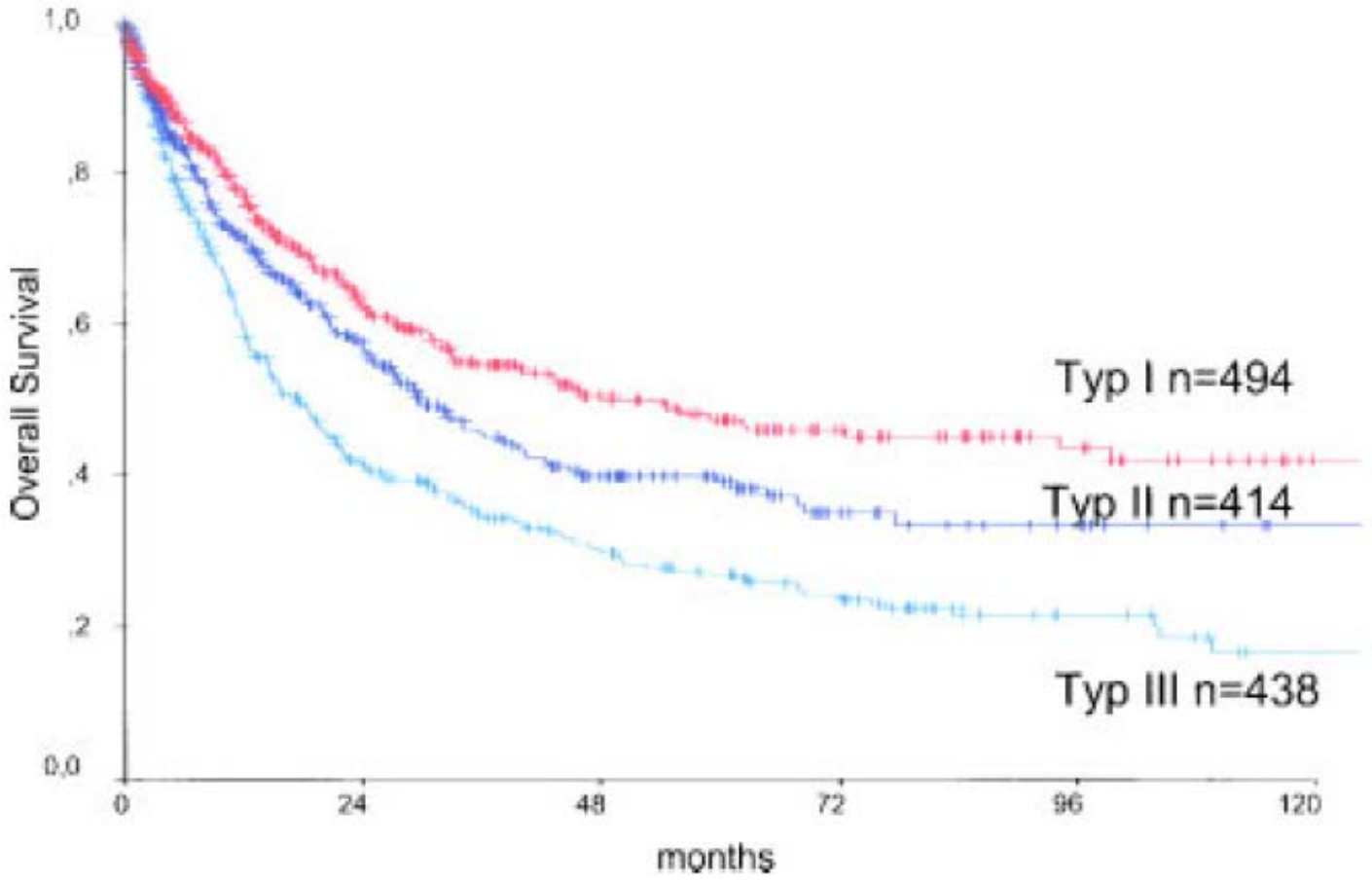
GE Junction– Siewert Classification



Type 1	Located between 1-5cm proximal to anatomic cardia
Type 2	Located between 1cm proximal and 2cm distal to anatomic cardia
Type 3	Located between 2 and 5cm distal to anatomic cardia

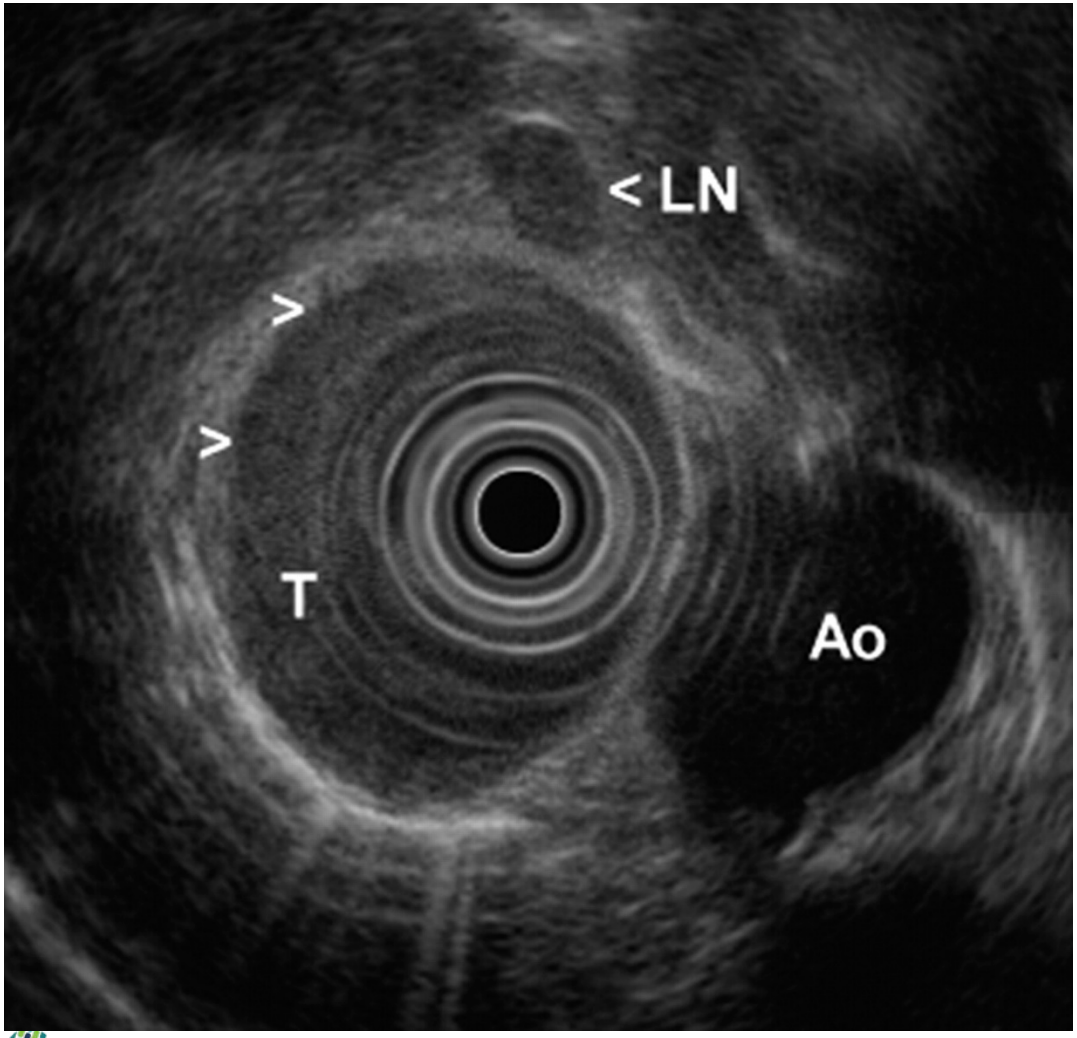
Gronnier C, et al. *Journal of Visceral Surgery*. 149:1, Feb 2012

Siewert Classification



Siewert R et al. *J Surg Onc*. 90; 139-46, 2005

Endoscopic Ultrasound



Malignant lymph nodes

- Round
- Hypoechoic
- Smooth borders
- 1cm or greater

Lennon A M , Penman I D Br Med Bull 2007;84:81-98

Esophageal Cancer Staging Principles

- Squamous cell and Adenocarcinoma = Different stage groupings
- TNM, Grade, Location (Squamous only)
- Clinical staging (u or c prefix)
- Pathologic staging after chemoRT (yp prefix)
- Example: uT3N1 (stage IIIB) distal esophageal adeno → chemoRT → surgery → ypT1N0

Esophageal Cancer Staging: AJCC 8th ed

AJCC 8th Edition - Esophageal Cancer Staging	
T stage	Tis = high grade dysplasia T1a = Tumor invades lamina propria or muscularis mucosae T1b = Tumor invades submucosa) T2 = Tumor invades muscularis propria T3 = Tumor invades adventitia T4a = Resectable tumor invading pleura, pericardium, or diaphragm T4b = Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.)
N stage	N0 = No lymph node metastases N1 = Metastases in 1-2 regional lymph nodes N2 = Metastases in 3-6 regional lymph nodes N3 = Metastases in 7 or more regional lymph nodes
M stage	M0 = no distant metastases M1 = distant metastases

Squamous Cell Ca: AJCC 8th ed

Stage Groupings: Squamous Cell Carcinoma

Stage	T	N	M	G	Location
Stage 0	Tis	N0	M0#	N/A	Any
Stage IA	T1a	N0	M0	1 or X	Any
Stage IB	T1a	N0	M0	2 or 3	Any
	T1b	N0	M0	Any	Any
	T2	N0	M0	1	Any
Stage IIA	T2	N0	M0	2, 3, or X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	1	Upper, middle
Stage IIB	T3	N0	M0	2 or 3	Upper, middle
	T3	N0	M0	X	Any
	T3	N0	M0	Any	location X
	T1	N1	M0	Any	Any
Stage IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Adenocarcinoma: AJCC 8th ed

Stage Grouping: Adenocarcinoma

Stage	T	N	M	G
Stage 0	Tis (HGD#)	N0	M0	N/A
Stage IA	T1	N0	M0	1 or X
Stage IB	T1a	N0	M0	2
	T1b	N0	M0	1, 2, or X
Stage IC	T1	N0	M0	3
	T2	N0	M0	1 or2
Stage IIA	T2	N0	M0	3 or X
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1-2	M0	Any
	T4a	N0-1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0-2	M0	Any
	Any	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Gastric Cancer Staging

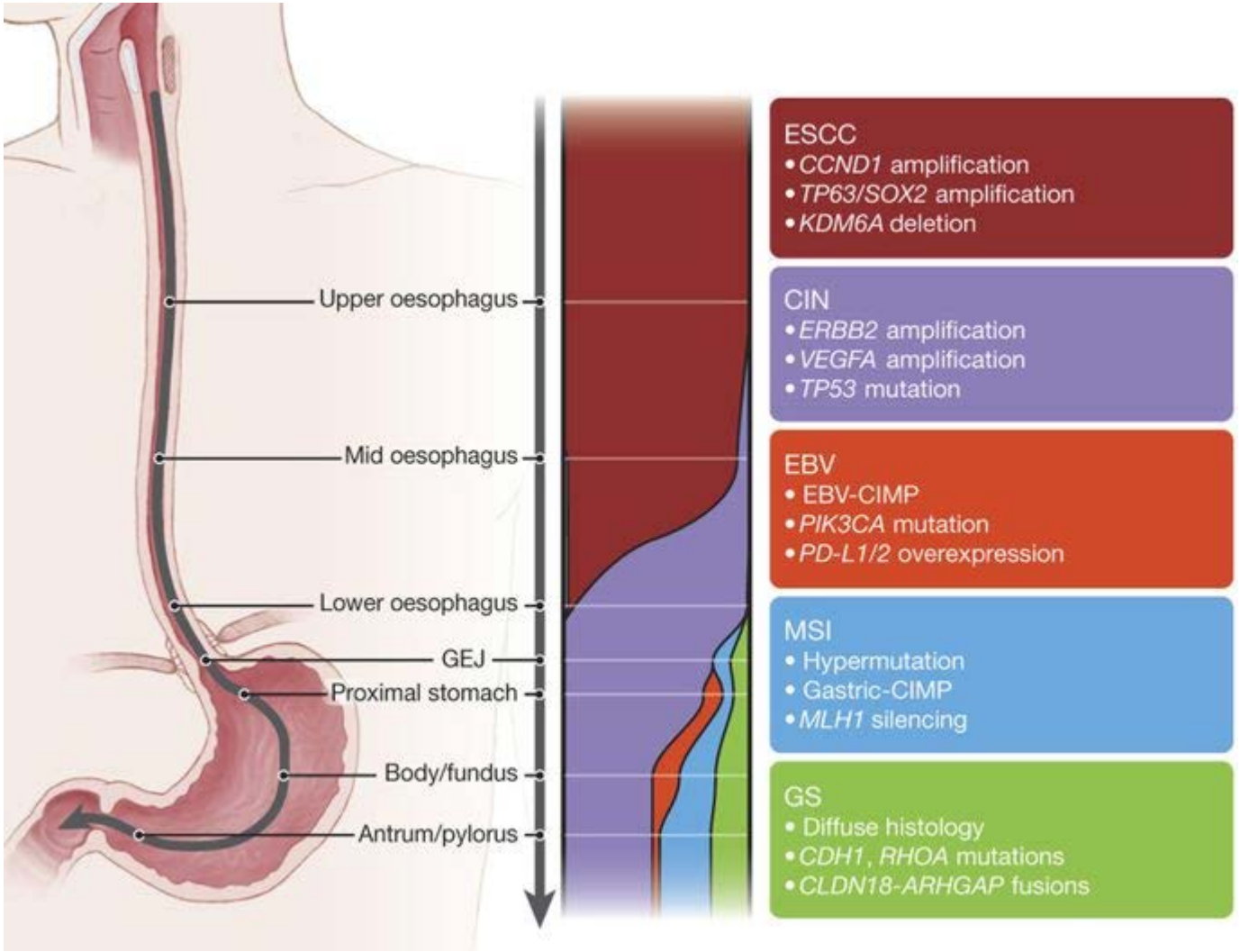
Incorporates diagnostic laparoscopy

- Evaluation of the peritoneum
- + cytology = pM1

Stage Groupings for pTNM			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage 1B	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1-2	M0
	T4b	N0	M0
Stage IIIB	T1-2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1-2	M0
Stage IIIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a or N3b	M0
Stage IV	Any T	Any N	M1

College of American Pathologists June 2017

Upper GI Cancer Molecular Subtypes



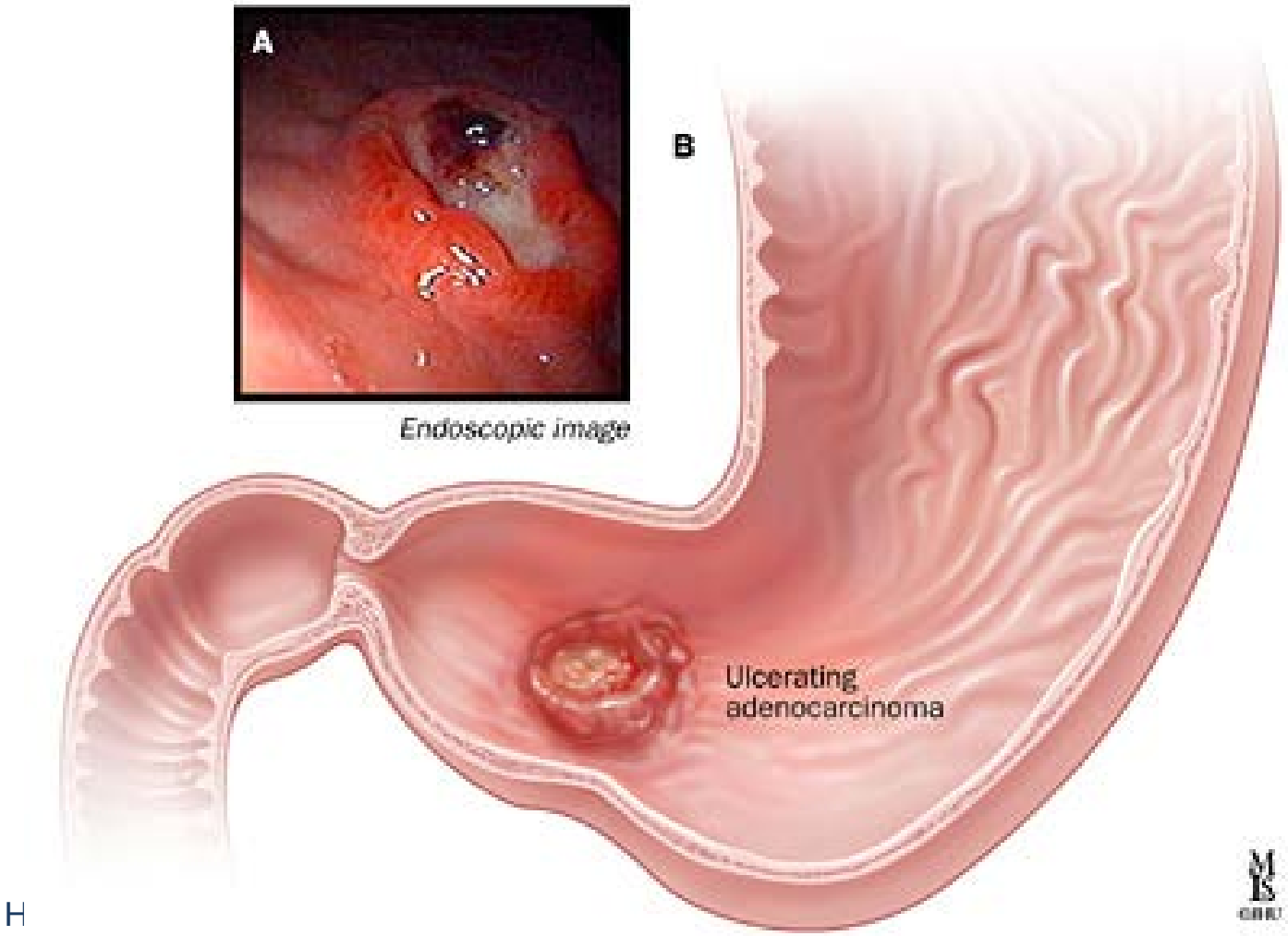
The Cancer Genome Atlas Research Network. *Nature*, 2017. 541: 69–175

Lauren Classification - Adenocarcinoma

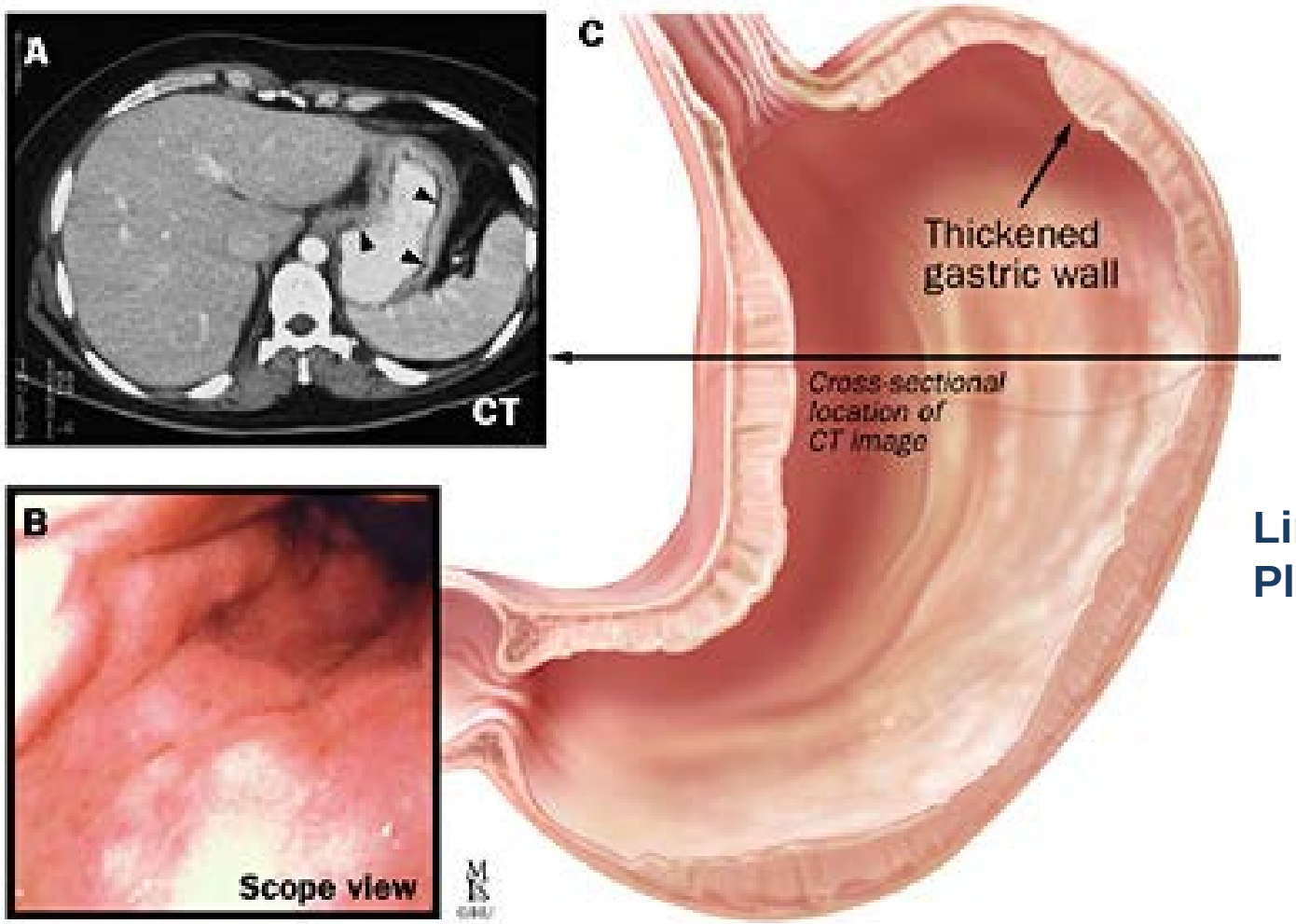
Intestinal	Diffuse
• **Inflammation** present *(H. pylori, atrophic gastritis, glandular dysplasia)* • '**Cascade**' of events: inflammation → intestinal metaplasia → dysplasia → invasive carcinoma • **Mucosal mass** • Develop over years, **better prognosis**	• **No inflammation** • Loss of E-cadherin **-- no clear precancerous lesion** • No clear mucosal mass - **Invades gastric wall** (e.g. linitis plastica) • Highly metastatic, invasive, **poor prognosis**

Lauren, P. *Acta Pathol Microbiol Scand*. 1965; 64(31).
Shah, M. et al. *Clin Cancer Research*. 2011; 17: 2693-2701

Intestinal Type Adenocarcinoma



Diffuse Type Adenocarcinoma



Linitis Plastica

Hereditary Diffuse Gastric Cancer

Germline mutations in CDH1 gene (leading to loss of E-cadherin)

- Autosomal dominant with > 70% penetrance
- Diffuse, signet ring type adenocarcinoma
- Increased incidence lobular breast cancer
- Prophylactic gastrectomy should be considered

Huntsman, et al. New England Journal of Medicine. 344;1904, 2001

Her2 + Esophageal and Gastric Cancers

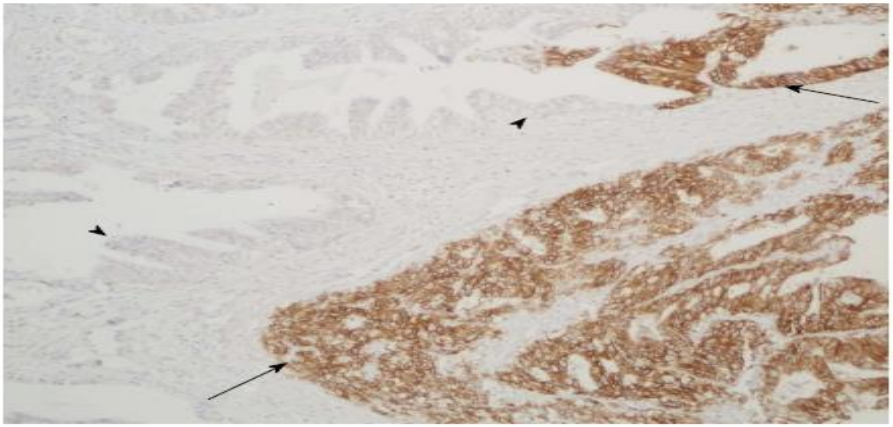
- **15-20%** of all gastric/esophageal adenocarcinoma (distal esophageal, GE junction, intestinal-type)

- Her2 3+ OR FISH + (*HER2*/CEP17 ratio ≥2.0) considered eligible

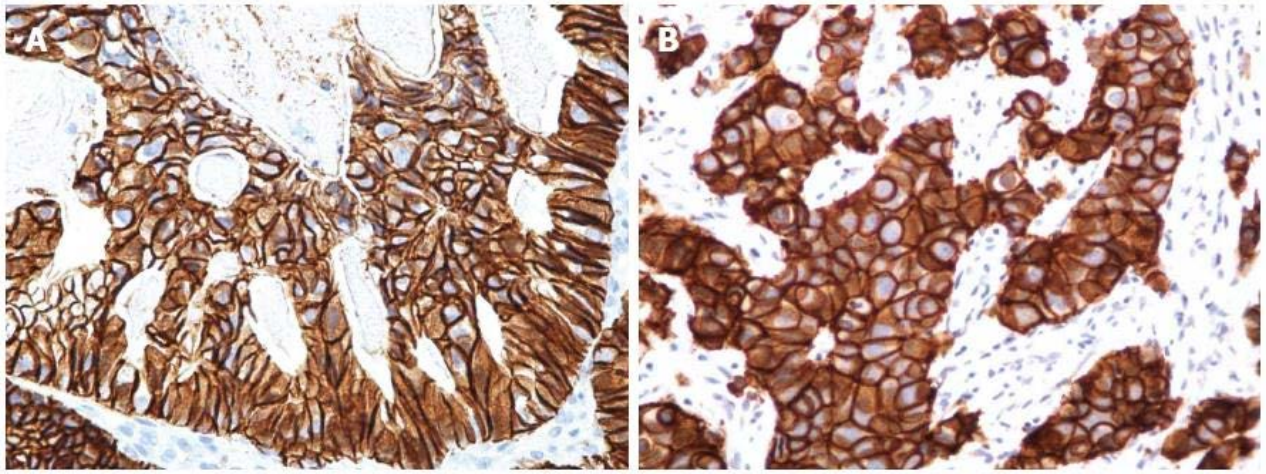
Gastric / Eso	**Breast**
• Heterogeneous expression • Interpretation criteria differs between biopsy and resection • Apical membrane often does not stain - + result requires only lateral / basolateral staining	• Uniform expression • Same interpretation criteria regardless of specimen • Complete circumferential staining required for positive result.

College of American Pathologists 2013; Questions Relating to Immunohistochemistry for Her2 on Gastric and Gastroesophageal Junction Adenocarcinoma

Her2 + Esophageal and Gastric Cancers



Heterogeneity

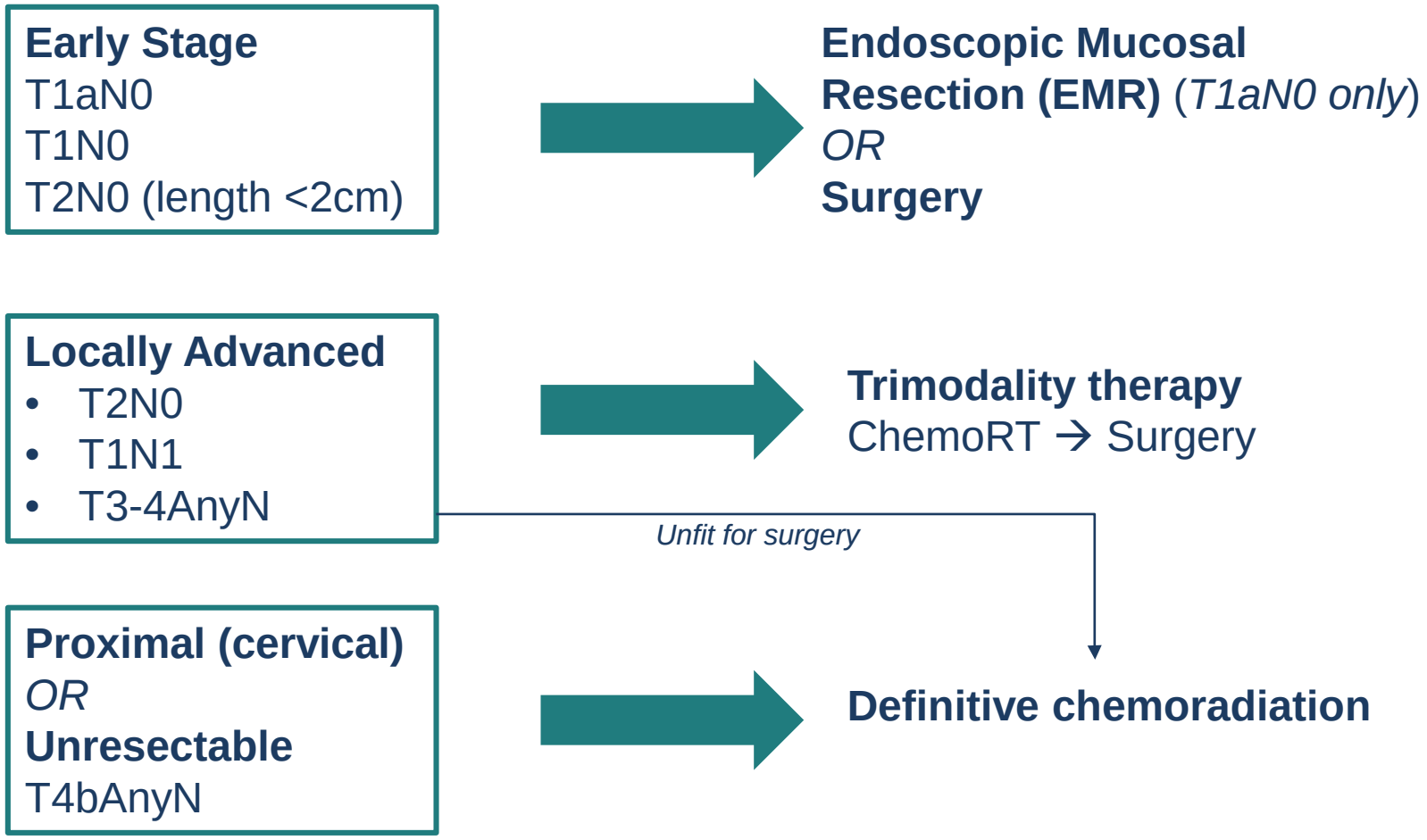


Basolateral vs. Circumferential and Apical staining

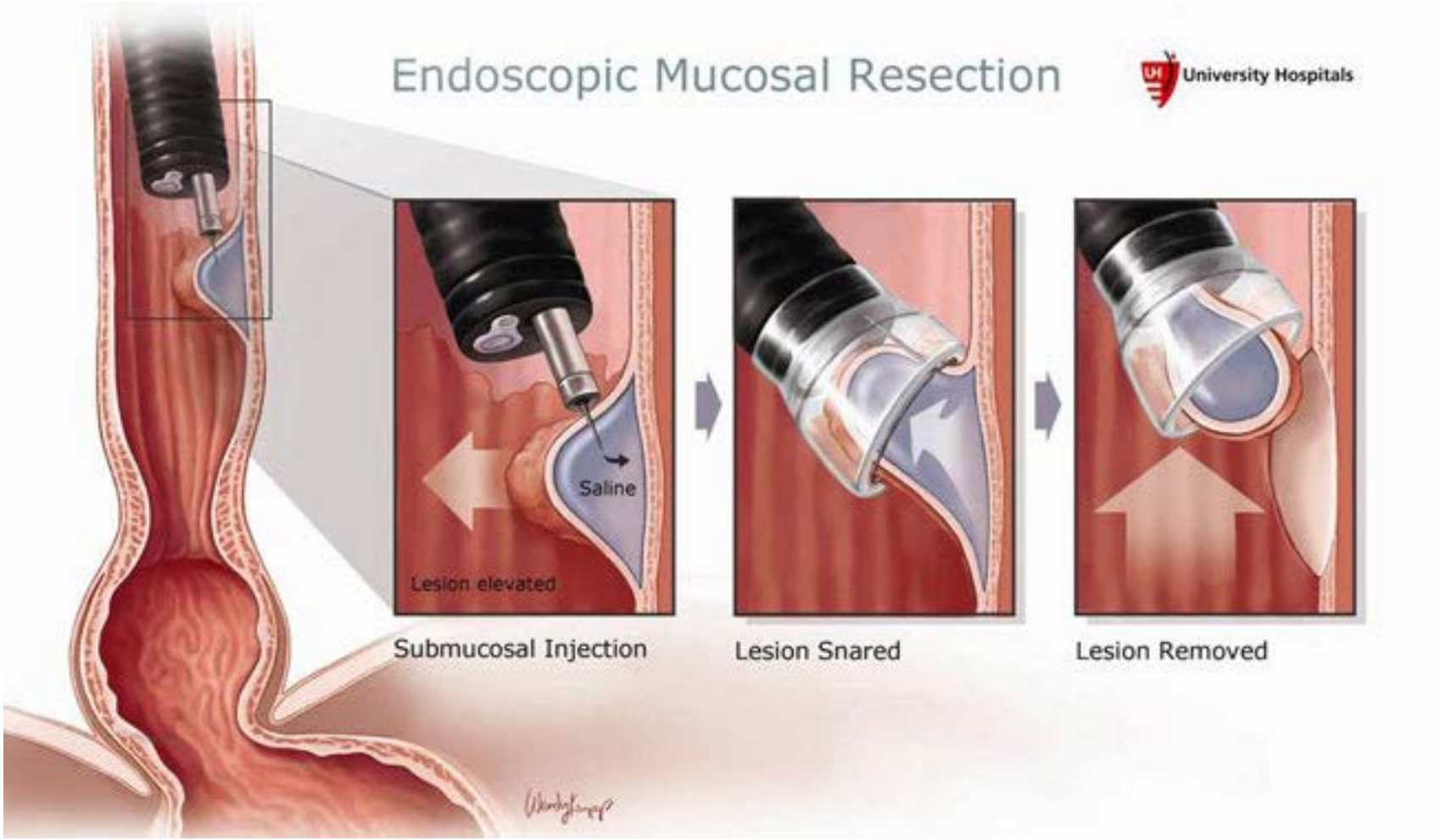
Abrahao-Machado, et al. World J Gastroenterol. 2016; 22(19): 4619-4625.

Stage I-III Esophageal Cancer

Esophageal Cancer Treatment Algorithm



Endoscopic Mucosal Resection – T1a lesions



Surgery (Esophagectomy)

Transhiatal approach	Transthoracic (Ivor Lewis)
• Blind dissection of tumor	• Direct visualization of tumor
• **Thoracotomy not required**	• **Thoracotomy required**
• Anastomotic leak more common, but easier to manage	• Anastomotic leak less common, but mediastinal leaks difficult to manage – higher morbidity
• Abdominal and cervical incisions	• Abdominal and thoracic incisions
• Shorter ICU / hospital stay	

Surgery should be done at a high volume center

FRED HUTCH

Barreto and Posner. *World J Gastroenterol*. Aug 2010
Chang AC, et al. Ann Thoracic Surgery. 85(2), 2008.

Neoadjuvant ChemoRT: Randomized Trials

Citation	# Pts	Preoperative Treatment	Path CR	Survival
Walsh, TN *NEJM* 1996	113 (adeno only)	Cis/5-FU/RT (40 Gy)	25%	16 vs. 11 months (p=0.01)
Bosset, JF *NEJM* 1997	282 (SCC only)	Cis/RT (37 Gy)	26%	18.6 months both groups
Urba, SG *JCO* 2001	100 (75% adeno)	Cis/5FU/ Vinblastine/RT (45 Gy)	28%	17.6 vs. 16.9 months (p=0.15)
Burmeister, BH *Lancet Oncol* 2005	256 (60% adeno)	Cis/5FU/RT (35 Gy)	16%	21.7 vs. 18.5 months (p=NS)
Tepper, J *JCO* 2008	56 (75% adeno)	Cis/5FU/RT (50.4 Gy)	40%	4.48 years vs 1.79 years (p=0.02)
Van Hagen, P *NEJM* 2012	363 (75% adeno)	Paclitaxel/Carbo/RT (41.4 Gy)	32.6%	49 vs. 24 months (p=0.011)

Neoadjuvant Chemoradiation: Meta-Analyses

Citation	# Studies	# Pts	Result
Urschel, JD Am J Surg, 2003	9 RCTs	1,116 pts	3-year survival HR 0.66 (p=0.016)
Gebski, V Lancet Oncol 2007	10 RCTs	1,209 pts	HR 0.81, p=0.002 (benefit seen in both histologies)
Jin, HL World J Gastroenterol 2009	11 RCTs	1,208 pts	5-year survival OR 1.46 (p=0.02) (benefit seen only in adenocarcinoma)
Sjoquist, KM Lancet Oncol 2011	12 RCTs	1,854 pts	HR 0.78 (p<0.001) Adeno HR 0.75, p=0.02 SCC HR 0.80, p=0.004

Dutch CROSS Trial

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

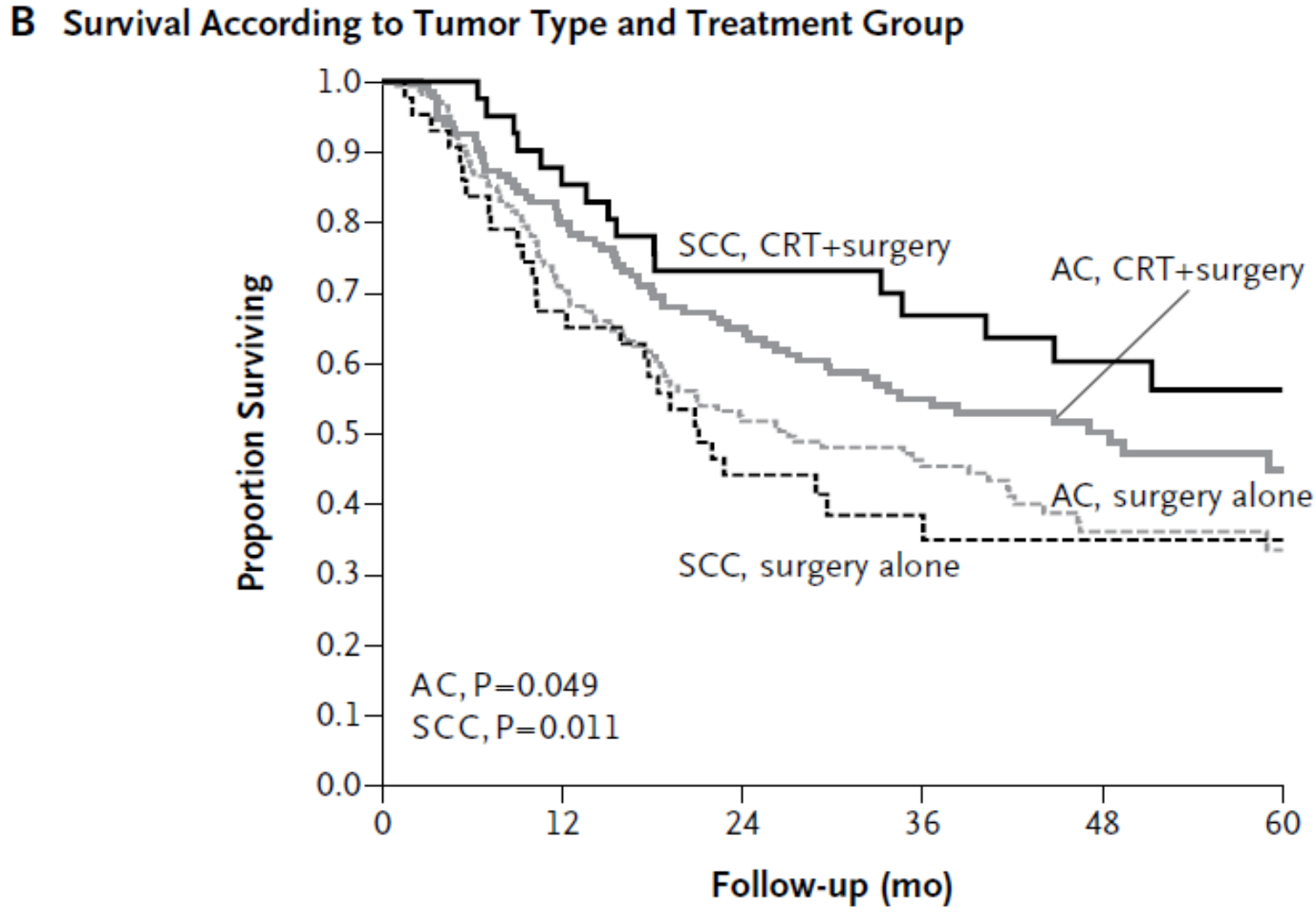
P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

Dutch CROSS Trial

Rationale	• Does **preoperative chemoradiation** add to benefit of surgery?
N = 368	• 188 surgery vs 180 chemoRT + surgery
Inclusion	• **Adenocarcinoma or SCC** • Esophagus and GE Junction (Siewert 3 excluded); T1N1, T2-3N0-1
Treatment Arms	• **Surgery alone** (Transthoracic for mid-thoracic tumors, Transhiatal for distal tumors) • **Preoperative chemoRT→ surgery** o Total Radiation Dose = 41.4 Gy o Weekly Carboplatin AUC 2 + Paclitaxel 50mg/m2

Van Hagen P et al. *NEJM*. 366;22, 2012

Histologic Subtype and Survival



Dutch CROSS Trial – Key Results

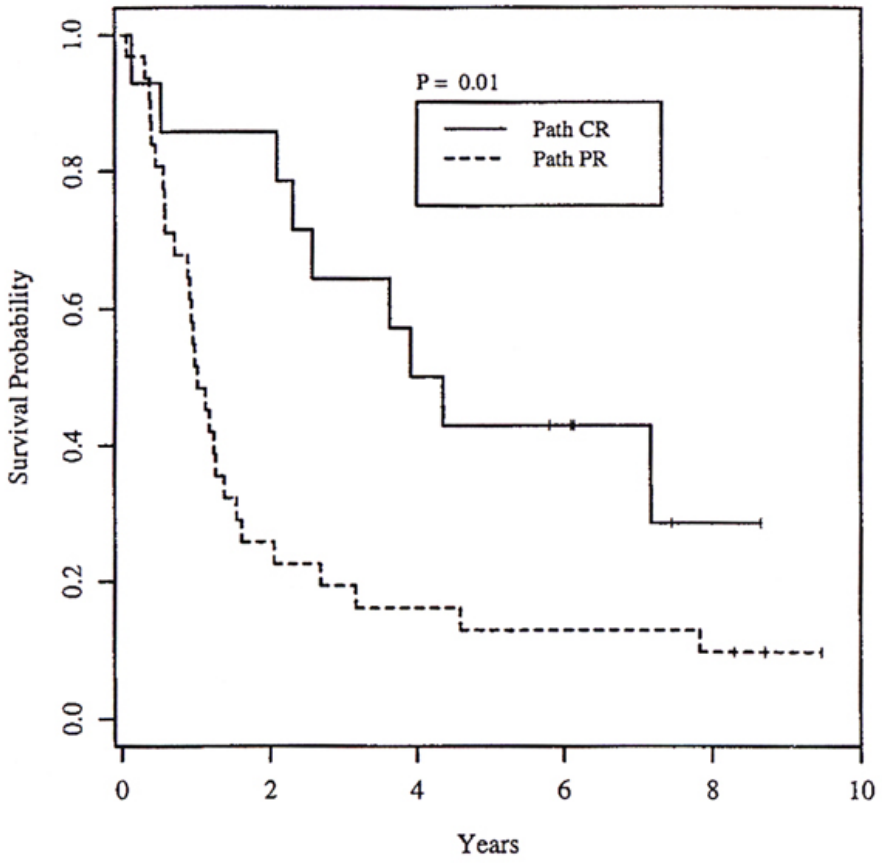
	Surgery alone	CRT + surgery
N	188	175
R0 resection rate	67%	92.3%
Path complete response	N/A	32%
Med survival	**26 months**	**49 months**
1-year survival	70%	82%
3-year survival	48%	59%
Anastomotic leakage	25%	22%
In-hospital mortality	3.8%	3.4%

Tumor Regression Grading

Modified Ryan Scheme	
Description	**Tumor Regression Score**
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more then single or rare groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Ryan, R. et al. *Histopathology*. 2005; 47(2): 141-146

Pathologic Response after Trimodality Therapy



Path CR vs. Residual Disease

Median Survival (49.7 vs. 12 months)

3-yr survival (64% vs. 19%)

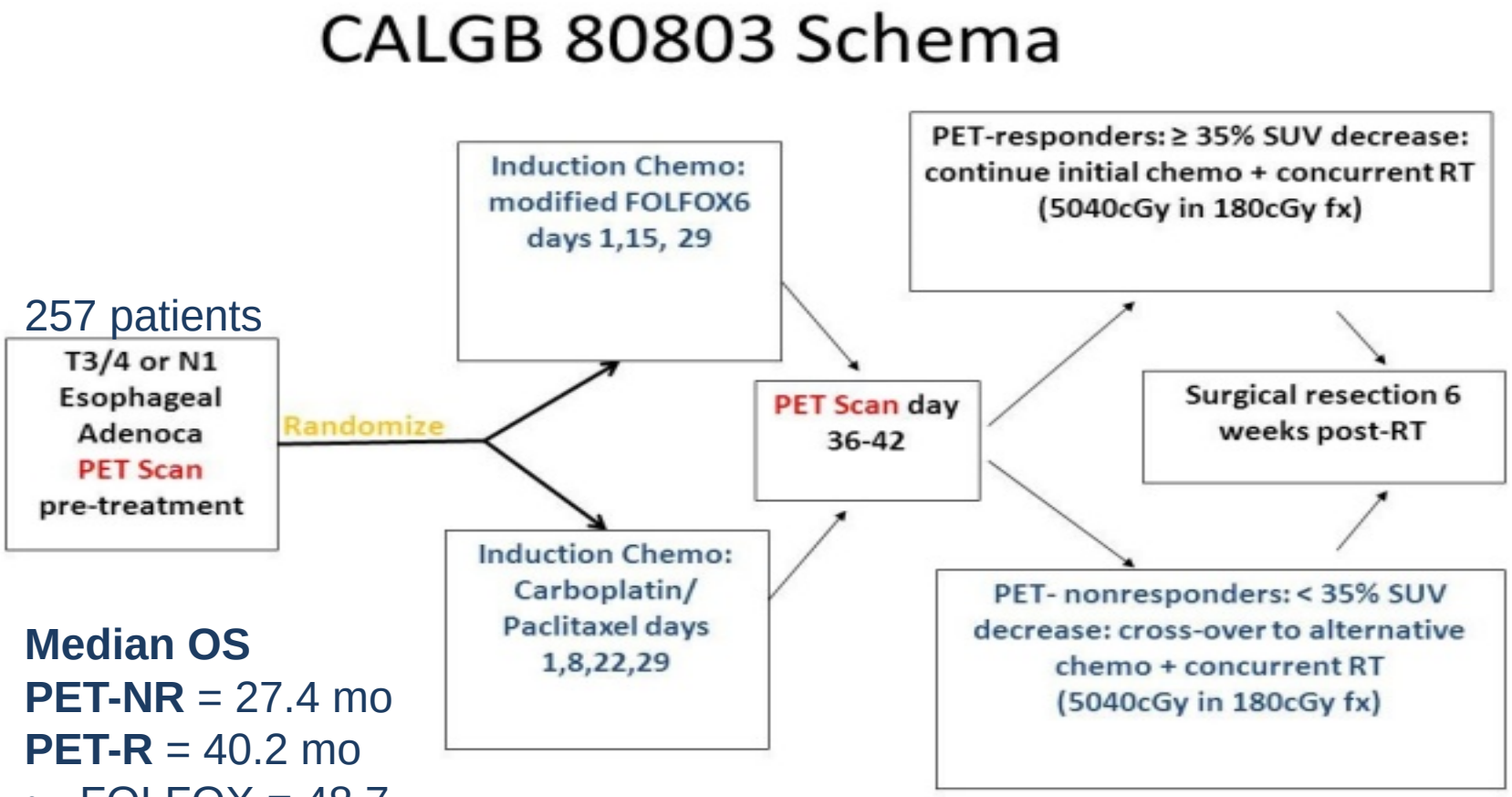
Urba S. *J Clin Oncol*. 19(2), 2001

Trimodality Therapy: Completed Trials

CALGB 80803: Randomized Phase II Trial of PET Scan-Directed Combined Modality Therapy in Esophageal Cancer

RTOG 1010: A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of Her2-Overexpressing Esophageal Adenocarcinoma

CALGB 80803



Median OS
PET-NR = 27.4 mo
PET-R = 40.2 mo
- FOLFOX = 48.7

FRED HUTCH

Goodman, KA et al. J Clin Oncol. 2018: 36 (suppl; abstr 4012)

RTOG 1010

Step 1: Registration

Mandatory Central Her2 Testing

Step 2: Randomization (stratification by celiac lymphadenopathy > or ≤ 2cm (n=571)

Arm 1

1. Radiation (50.4 Gy), paclitaxel, carboplatin, and **trastuzumab**
2. Surgery
3. Maintenance trastuzumab, q3 wks x 13

Arm 2

1. Radiation (50.4 Gy), paclitaxel, carboplatin
2. Surgery

ASCO 2020: Addition of trastuzumab does not improve DFS – HR 0.97, 95% CI 0.69, 1.36)

Safran H. et al. *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 4500-4500.

What to do after Trimodality therapy?

Routine Surveillance

NCCN Guidelines

- Years 1-2: q3-4 month clinical assessment and labs
- Years 3-5: q6 month clinical assessment and labs
- Years 1-5: Annual CT imaging

Poor Responders (Extensive residual disease – tumor regression scores 2-3)

- Adjuvant chemotherapy?
- Immune checkpoint inhibition being studied

Nutrition / Dietary Counseling – Learning how and what to eat!

Do we need all 3 components of trimodality therapy?

Maybe not in certain scenarios …

Definitive Chemoradiation: RTOG 8501

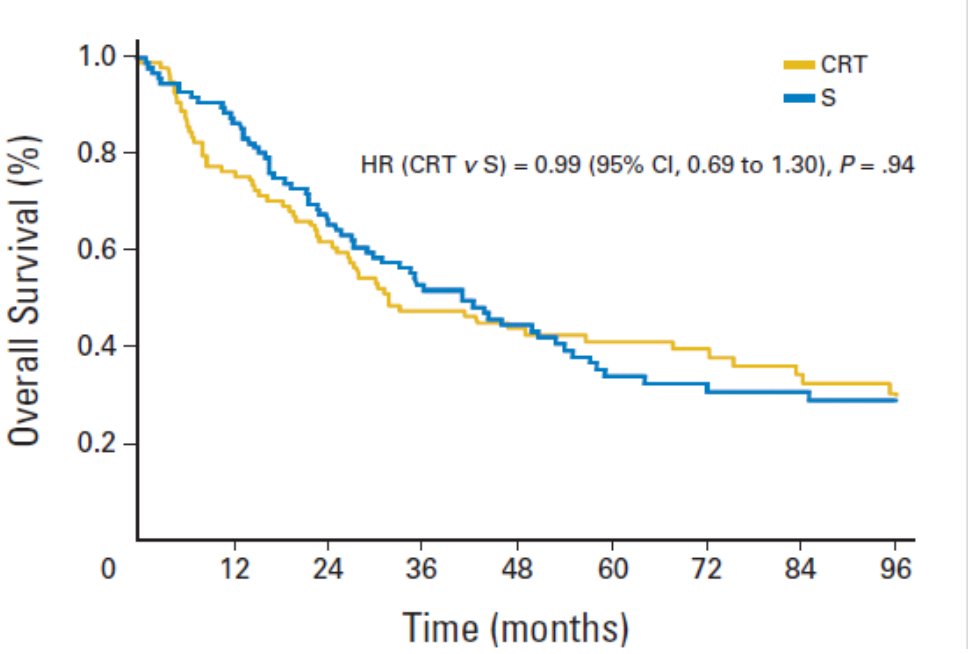
Survival Estimates by Histologic Type after Combined Modality Therapy		
Year	Adenoca (% alive)	Squamous Cell (% alive)
0	100%	100%
1	52%	59%
2	22%	38%
3	17%	30%
4	13%	26%
5	13%	21%

Is ChemoRT Mandatory ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Surgery Alone Versus Chemoradiotherapy Followed by Surgery for Stage I and II Esophageal Cancer: Final Analysis of Randomized Controlled Phase III Trial FFCD 9901

Christophe Mariette, Laetitia Dahan, Françoise Mornex, Emilie Maillard, Pascal-Alexandre Thomas, Bernard Meunier, Valérie Boige, Denis Pezet, William B. Robb, Valérie Le Brun-Ly, Jean-François Bosset, Jean-Yves Mabrut, Jean-Pierre Triboulet, Laurent Bedenne, and Jean-François Seitz



Mariette C, et al. J Clin Oncol. 2014; 32(23): 2416-22

Radiation Esophagitis

- **Topical anesthetics** (e.g. viscous lidocaine)
- **Analgesics and antiinflammatories** (narcotics, dex elixir, carafate)
- **Dietary modification** (bland, soft, pureed, less acidic, room temp, converting to liquid medication when possible
- **Supplementary nutrition**
  - Avoid PEG/G tubes in surgical candidates; NG / Dobhoff tube feedings preferred in the short term preoperatively

Take-home points: Esophageal Cancer

- Endoscopic resection for T1a lesions
- For T2+ or N1+ tumors, **trimodality therapy** is still the standard of care
- How can we improve path response to chemoRT?
- PET response may be prognostically useful and may guide treatment
- No additional therapy after trimodality, regardless of pathologic response

Stage I-III Gastric Cancer

Gastric Cancer Treatment Algorithm

Early Stage
- T1-T2N0

→ **Surgery**

Locally Advanced
- T1-2N1
- T3-4AnyN

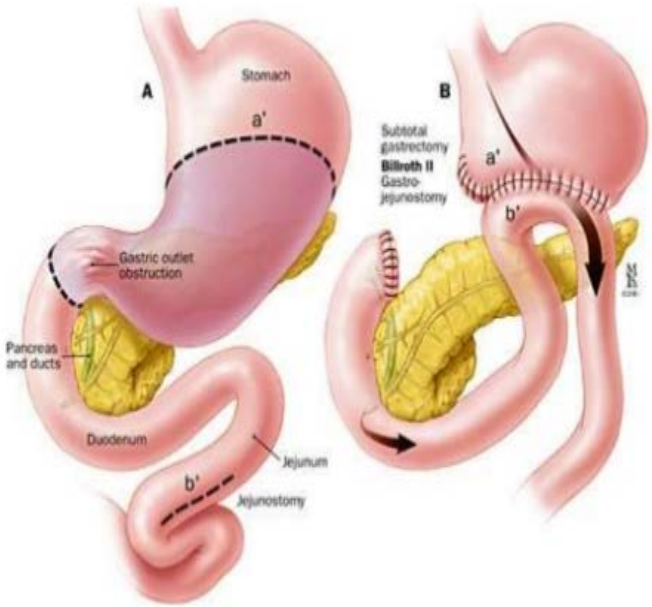
→ **Perioperative chemo**
OR
Postoperative chemo *(Asia)*
OR
Postoperative chemoRT
(margin positive)

Peritoneal washings positive
AnyTAnyNpM+ (cytology)

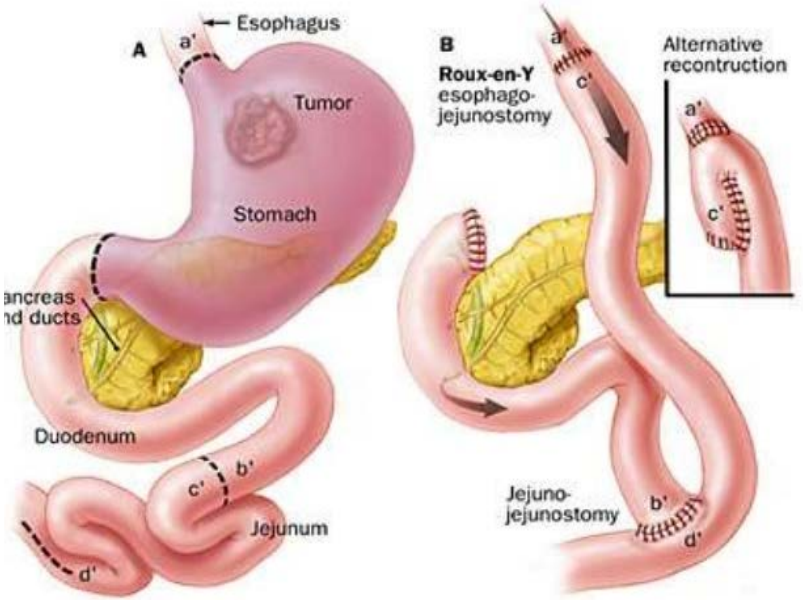
→ **Chemotherapy alone**
(consider surgery in very fit patients who clear peritoneal cytology after upfront chemo)

Gastric Resection

Distal Gastrectomy



Total Gastrectomy



Post-Gastrectomy Considerations

- Inability to store and break down food – frequent SMALL meals
- Vitamin B12 deficiency – lack of instrinsic factor production (cardia)
- Iron deficiency – decreased gastric acid
- Dumping syndrome – rapid emptying into small bowel – lightheadedness, nausea, diarrhea

Gastric Cancer Lymph Node Dissection

Lymph Node Dissection	Description
D1	lesser and greater curvature, paracardial
D2	Left gastric, hepatic, celiac, splenic (could require pancreatectomy or splenectomy to access these nodes)
D3	D2 + portahepatic, hepatoduodenal
D4	retropancreatic, root of mesentery, transverse mesocolon, paraaortic

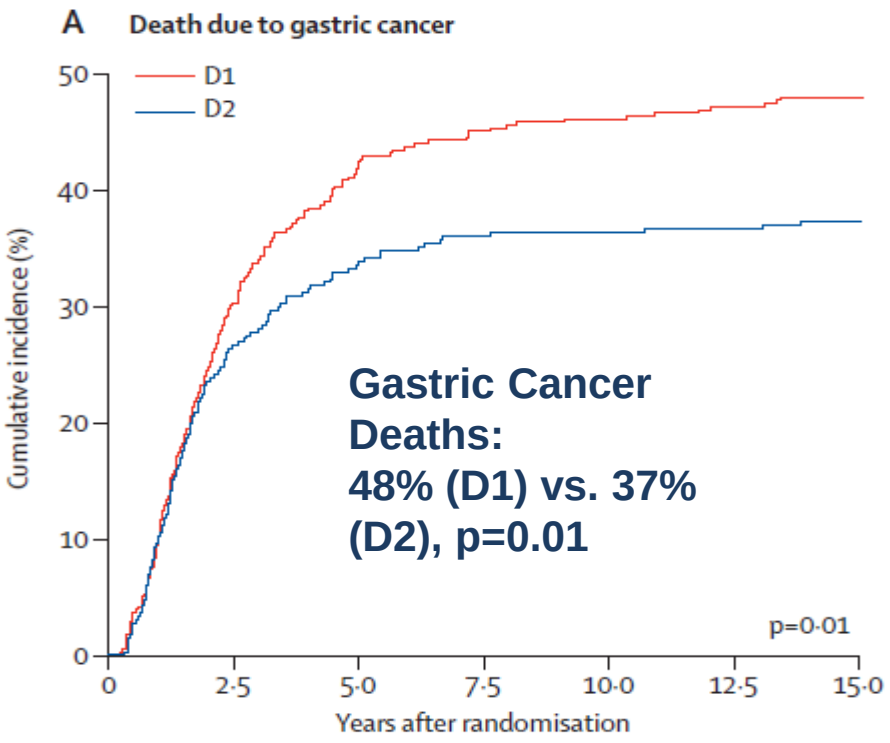
The Dutch Gastric Cancer Group: D1 vs. D2

711 patients undergoing curative resection of gastric cancer

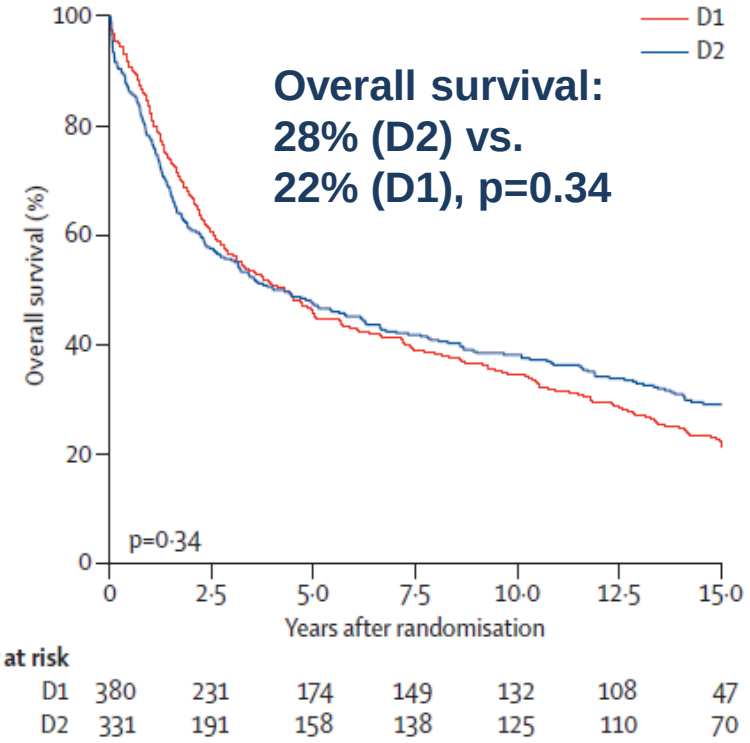
	Peri operative morbidity	Peri operative mortality	5-yr survival
D1	25%	4%	45%
D2	43%	10%	47%

Bonenkamp JJ et al, NEJM 1999; 340:908-914

15 Year Follow Up



Gastric Cancer Deaths: 48% (D1) vs. 37% (D2), p=0.01



Overall survival: 28% (D2) vs. 22% (D1), p=0.34

Number at risk

D1	380	231	174	149	132	108	47
D2	331	191	158	138	125	110	70

Songun, I et al. Lancet Oncology. 2010; 11:439-49.

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The Dutch Gastric Cancer Group: D1 vs. D2

	D2	D1
N stage		
N0	**144 (44%)**	**171 (45%)**
N1	113 (34%)	138 (36%)
N2	47 (14%)	50 (13%)
N3	27 (8%)	21 (6%)

- High rates of over and under dissection
- Higher than anticipated number of node negative cases

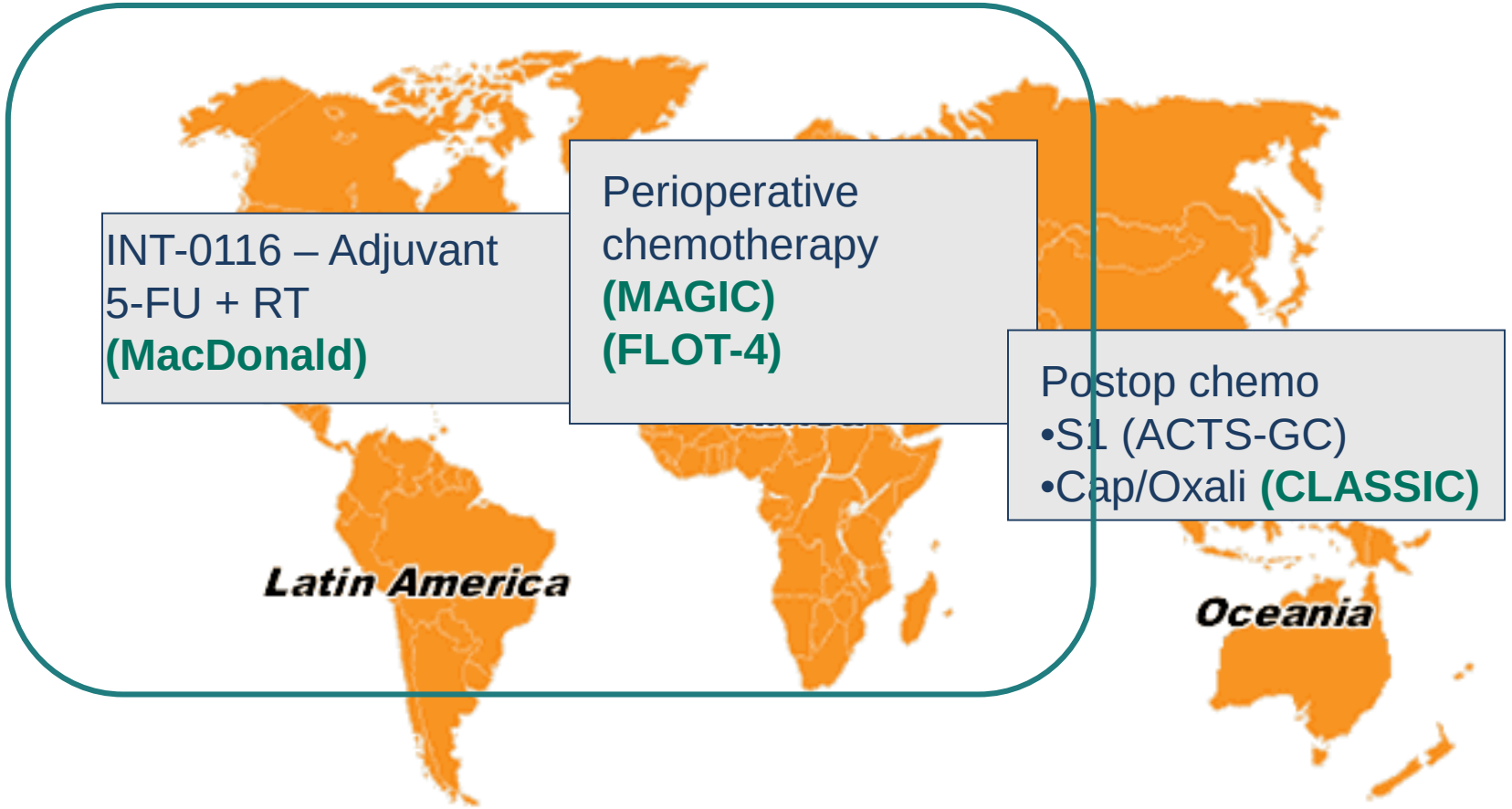
Songun, I et al. Lancet Oncology. 2010; 11:439-49.

D1 vs. D2 Lymph Node Dissection

D2 lymph node dissection is preferred over D1 dissection, only when the surgery can be performed without increasing morbidity

Pancreas and spleen – preserving D2 dissection is generally preferred

Adjuvant and Neoadjuvant Treatment

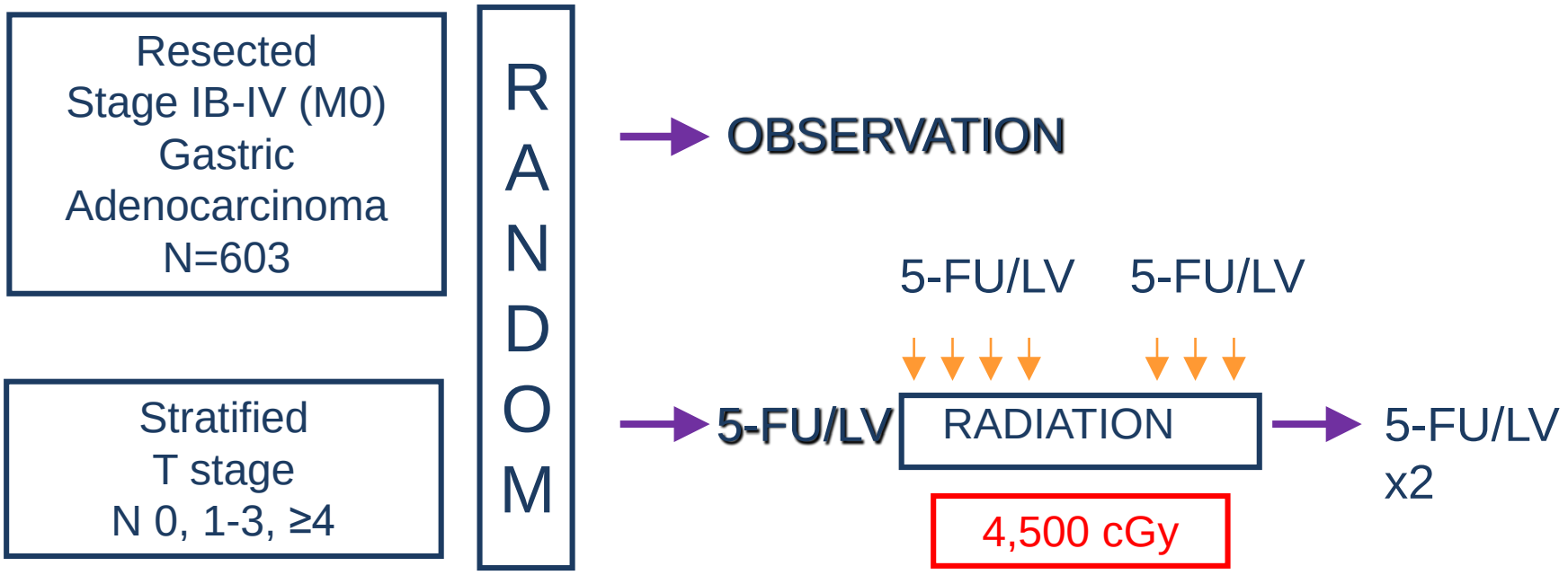


Sasako, M. et al. *J Clin Oncol*. 2011; 29(33): 4387
Cunningham, D et al. *NEJM*. 2006; 355(1): 11
MacDonald, JS et al. *NEJM*. 2001; 345(10): 725

Adjuvant ChemoRT: INT 0116/SWOG 9008

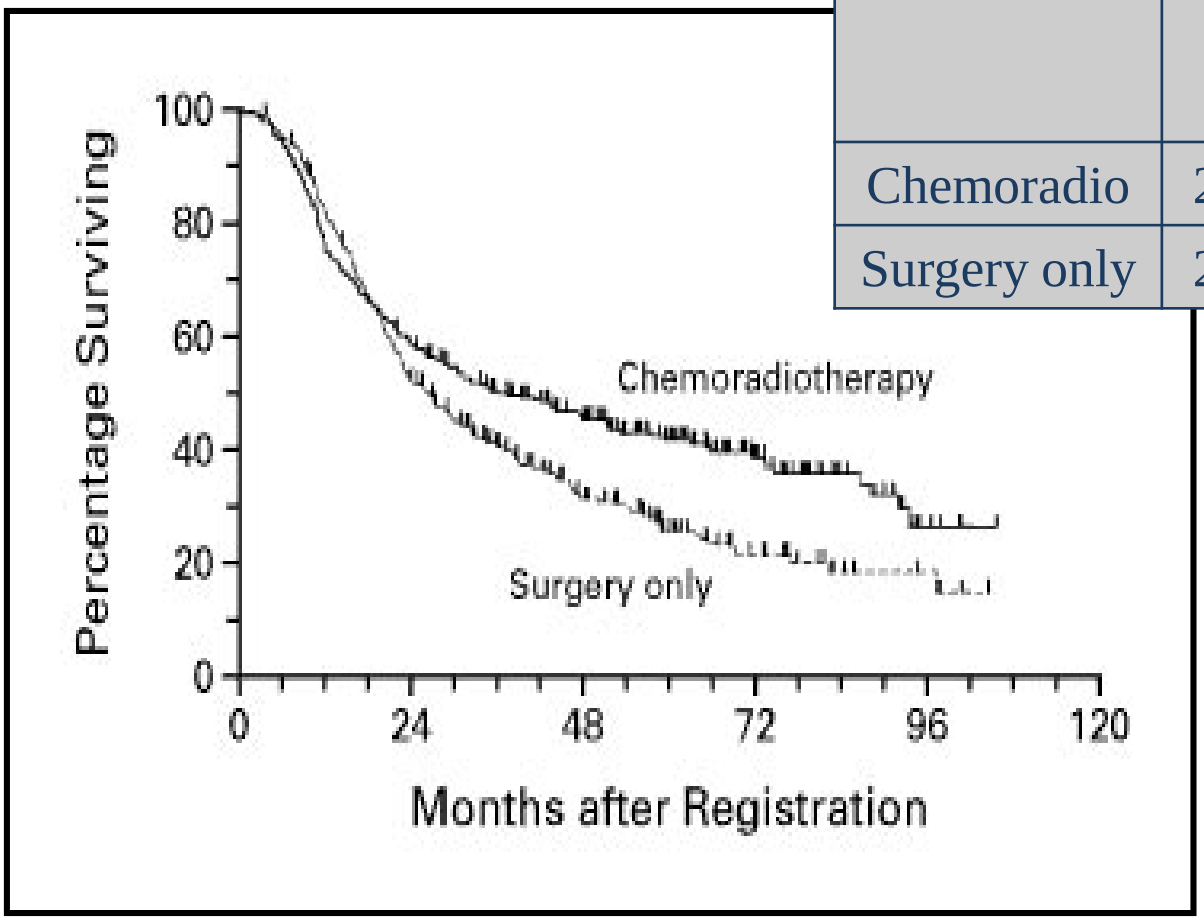
SCHEMA

20% GE Junction



Macdonald *NEJM* 2003; 345: 725-730

Adjuvant ChemoRT: INT 0116/SWOG 9008



	N	Events	Median (mos)
Chemoradio	282	192	35
Surgery only	277	214	27

P = .006

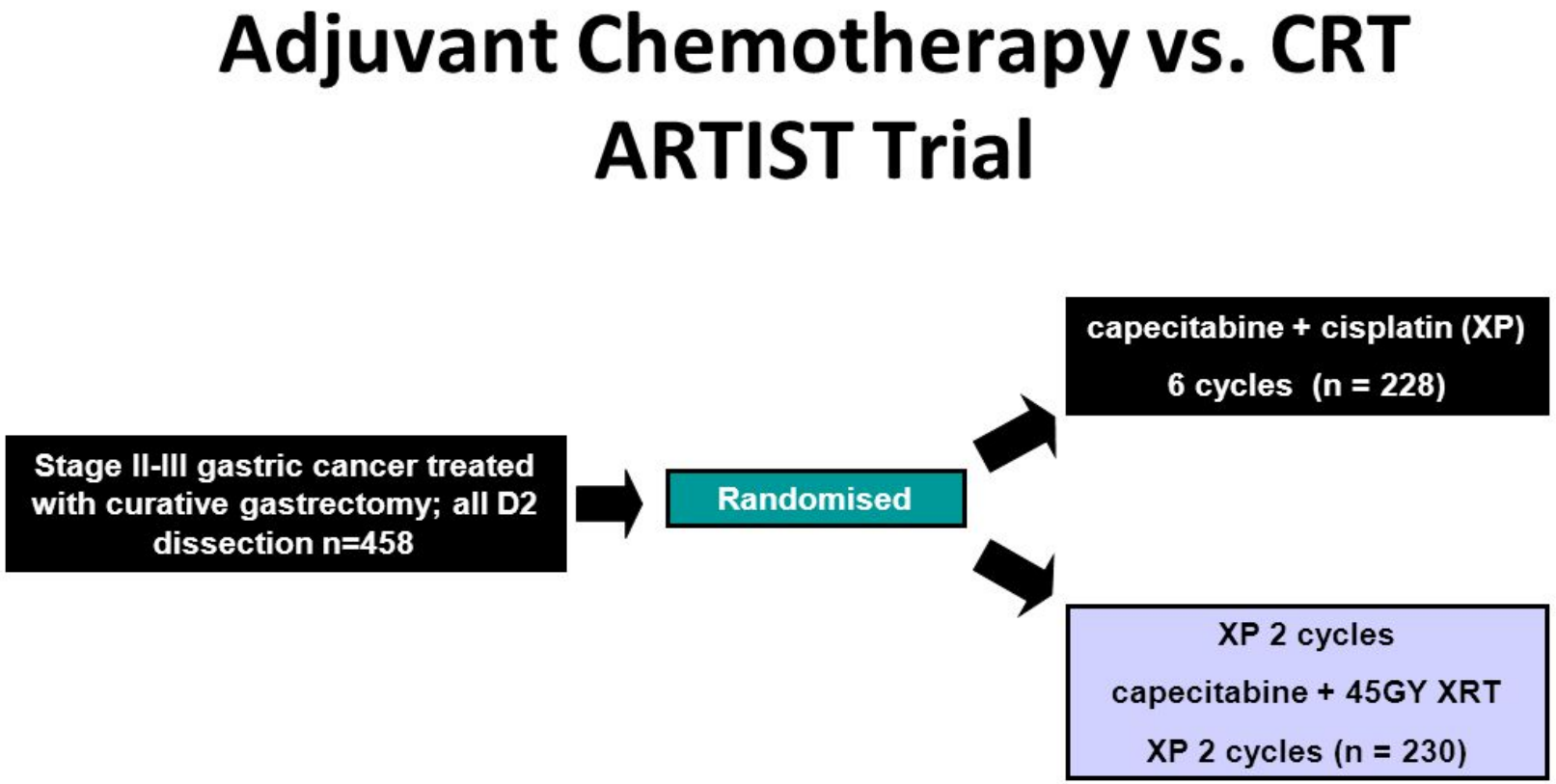
Macdonald *NEJM* 2003; 345: 725-730

Adjuvant ChemoRT: INT 0116/SWOG 9008

Level of lymph node dissection	%
< D1	**54%**
D1	36%
D2	10%

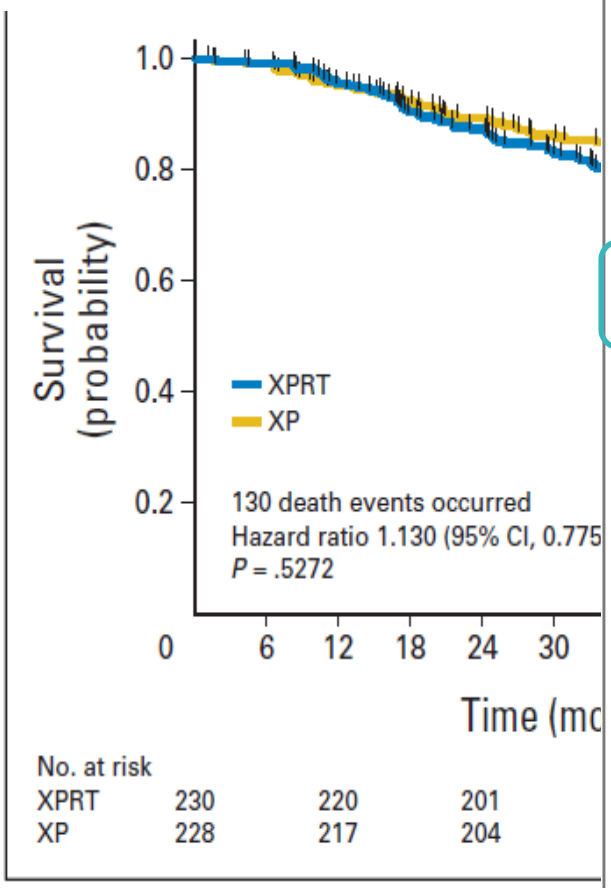
Macdonald *NEJM* 2003; 345: 725-730

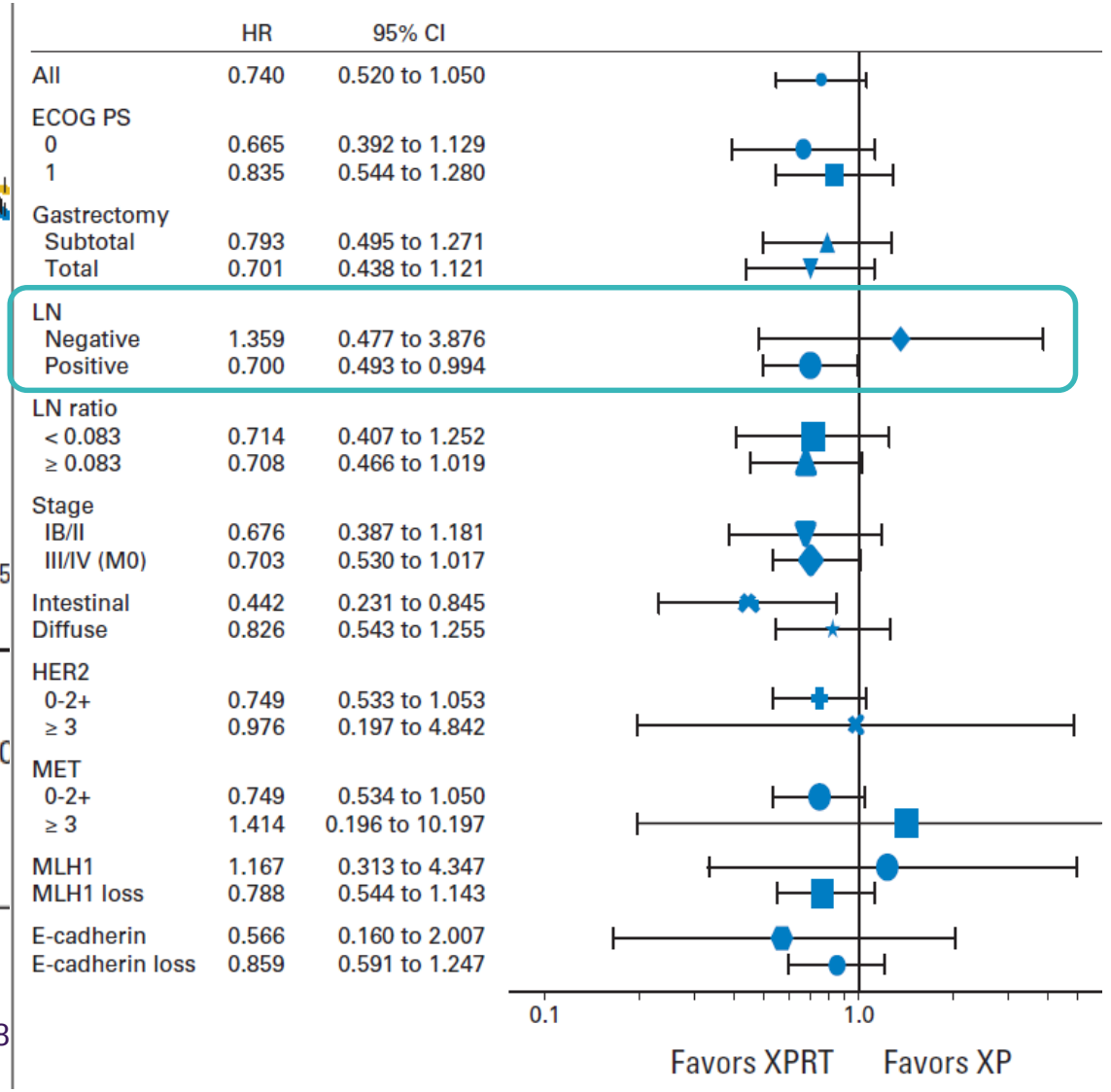
ARTIST Trial: Adjuvant Chemo vs. RT



Park, S. et al. J Clin Oncol. 2015; 33(28)

ARTIST: Adjuvant Chemo vs. chemoRT





Park, S. et al. J Clin Oncol. 2015; 33(28

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ARTIST-II: Adjuvant chemo vs. chemoRT (Node+)

Randomize 900 patients
with D2 resected NODE
POSITIVE Gastric Cancrer

Key Results

- SOX and SOXRT >> S1 alone
- **No difference in DFS between SOX and SOXRT** (HR 0.91, p=0.67)

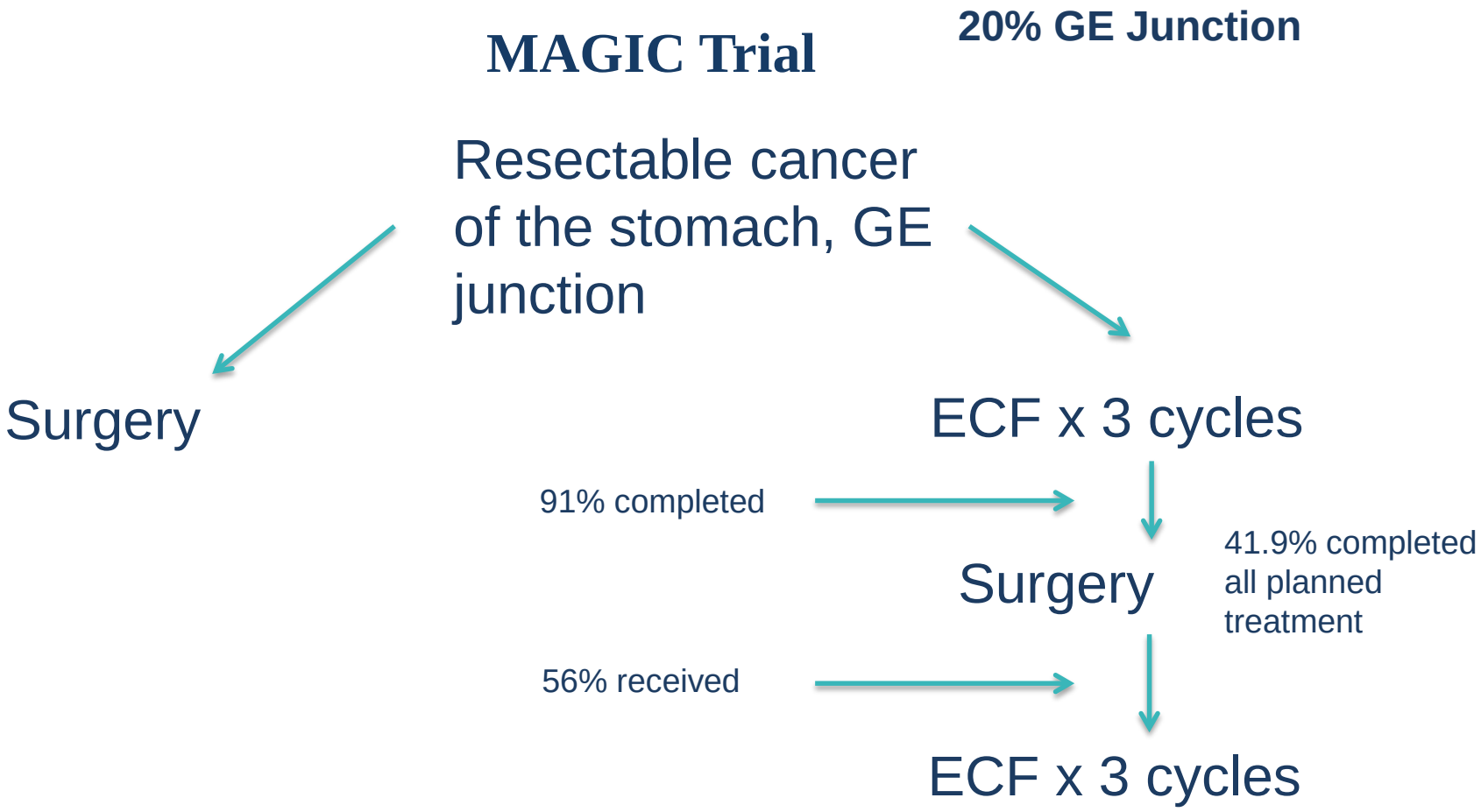
Park, SH et al. 2019 May ASCO / J Clin Oncol

Is there a role for Postoperative Radiation?

NO, except …

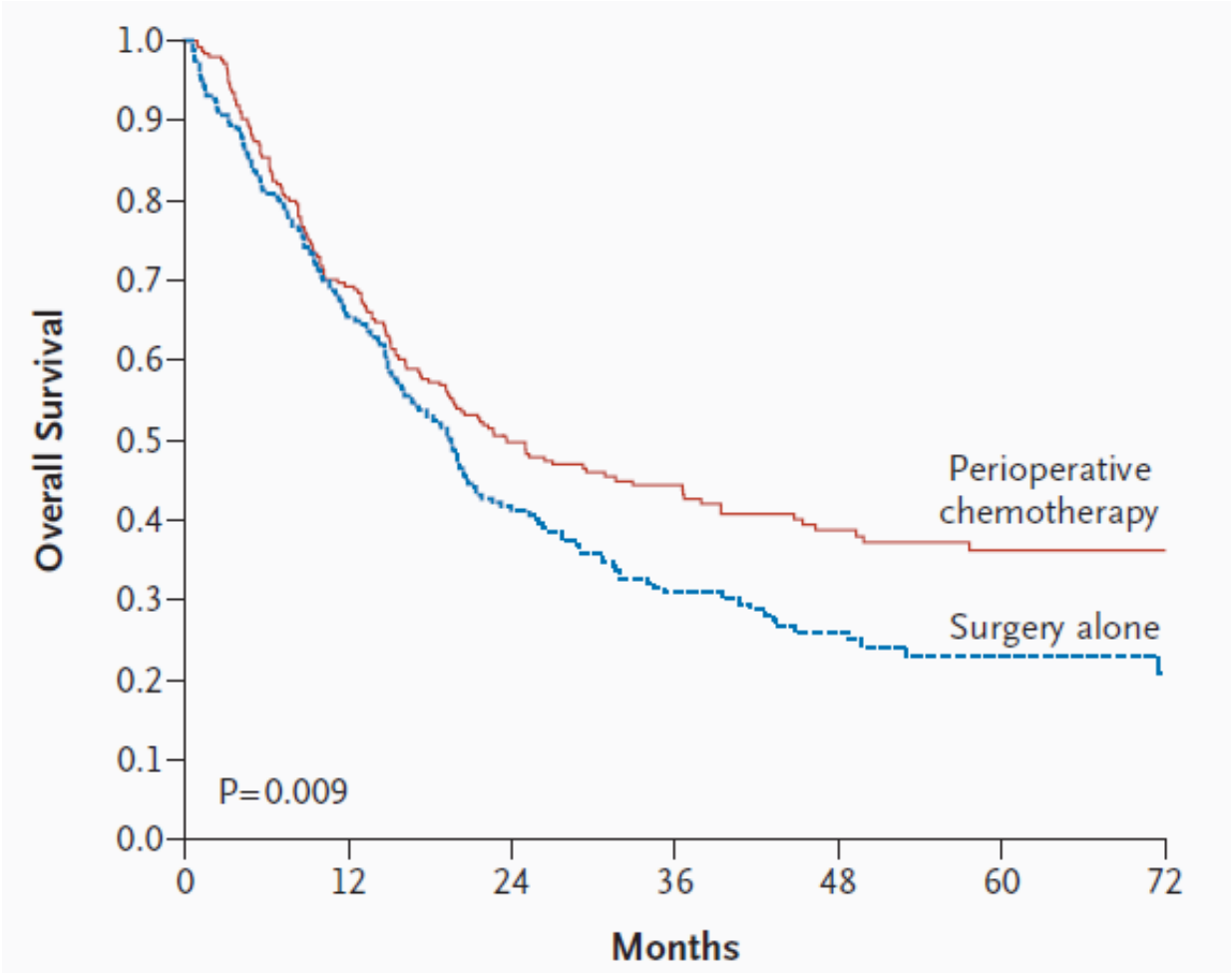
- Inadequate resections / lymph node dissection
- Positive margin (R1 resection)

Perioperative Chemotherapy: MAGIC Trial



Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: MAGIC Trial

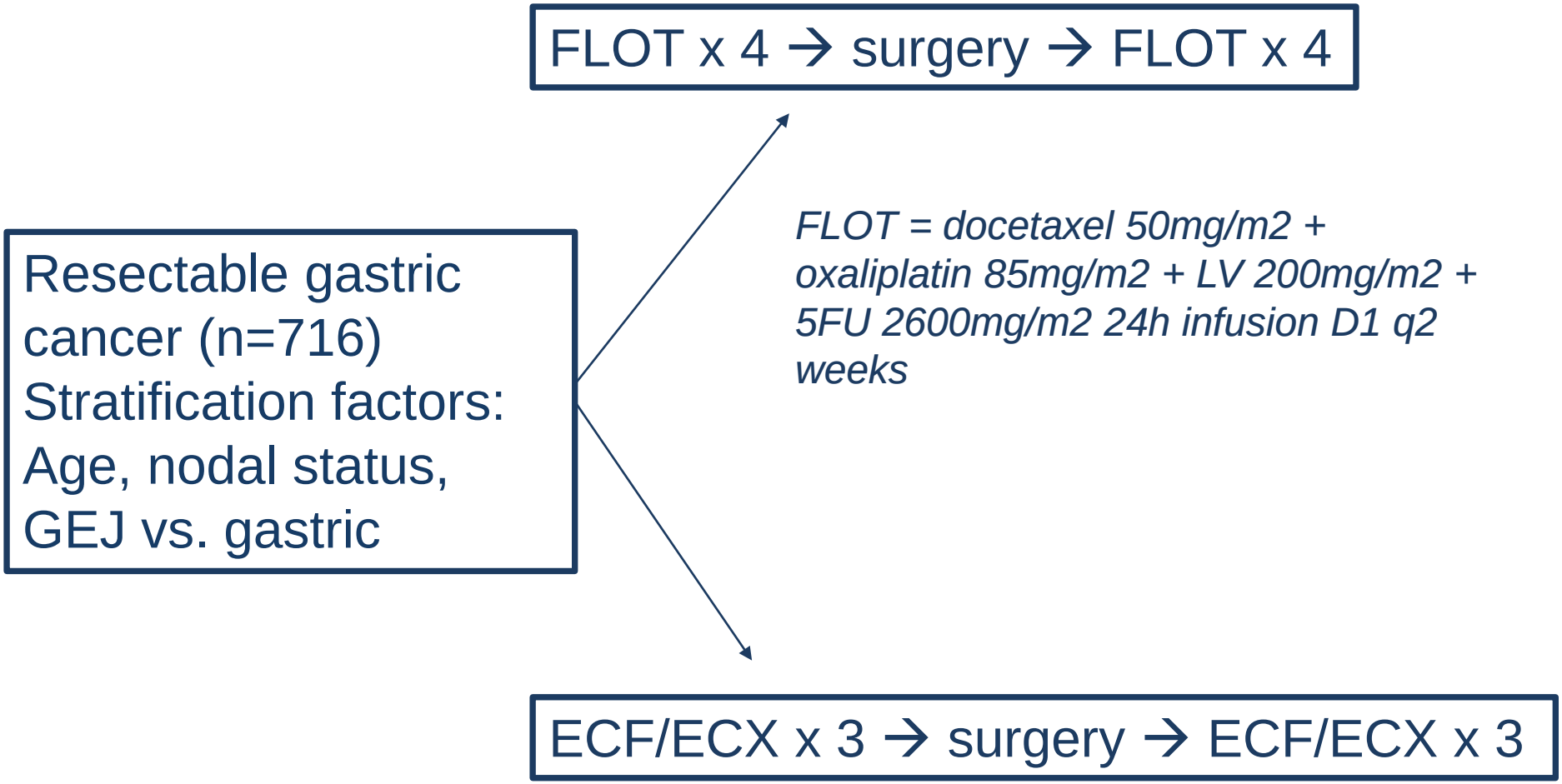


5-year survival
- 36.3% (Chemo)
- 23.0% (Surgery)

Median Survival
- 24 months (Chemo)
- 20 months (Surgery)

Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: FLOT-4



Al-Batran S, et al. ASCO 2017 Annual Meeting.

Perioperative Chemotherapy: FLOT-4

Key Results:

- 50% FLOT vs. 37% ECF/X completed post-operative chemotherapy
- Median OS 50 months vs. 35 months (HR 0.77, p=0.012)
- 3yr OS 57% FLOT vs. 48% ECF/X
- Postop complications and 30/90 day mortality were similar

Al-Batran S, et al. ASCO 2017 Annual Meeting.

FLOT-4 – ASCO 2020 Updates

PETRARCA study (phase II/III)

- 81 patients randomized
- No benefit with addition of trastuzumab to FLOT – path CR, R0 resection rate, DFS, OS
- Study ended early and did not proceed to phase III

FLOT-4 +/- Ramucirumab (phase II/III)

- 180 patients randomized
- Endpoints: Path response, R0 resection rate, safety
- Findings: Increased AEs, Improved R0 resection rate (97% vs. 83%, p=0.0049), similar path response

Hofheinz, RD et al. ASCO 2020
Al Batran, SE et al. ASCO 2020

Take Home Points: Localized and Locally Advanced Gastric Cancer

Post-gastrectomy B12 and iron supplementation

D2 gastrectomy should be performed when possible

Perioperative chemotherapy – general approach for Western patient

Vanishing role of radiation therapy in gastric cancer treated with D2 lymph node dissection

Metastatic Esophageal and Gastric Cancer

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Initial Diagnostic Evaluation

Clinical Assessment

- ECOG PS
- Comorbidities
- Nutritional status
  - Stent
  - G or J tube

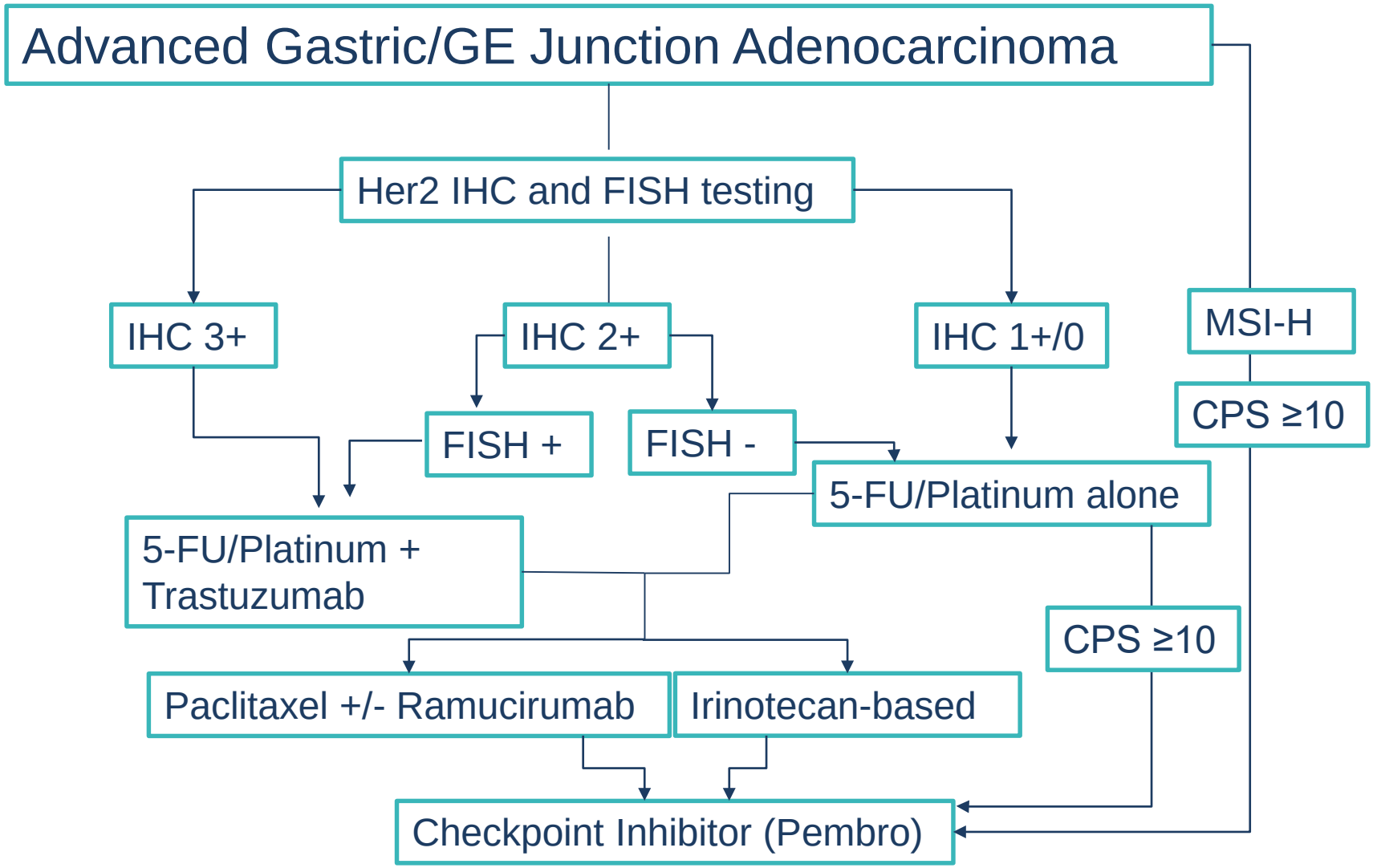
Labs and Imaging

- CT C/A/P w/ IV contrast (peritoneal dz)
- CEA
- CA 19-9

Molecular testing

- Her2 IHC and FISH (3+ or FISH+)
- PDL1 (CPS score)
- MSI
- EBV (Gastric)
- *NGS for most – tumor mutational burden (Pembro for TMB-high)*

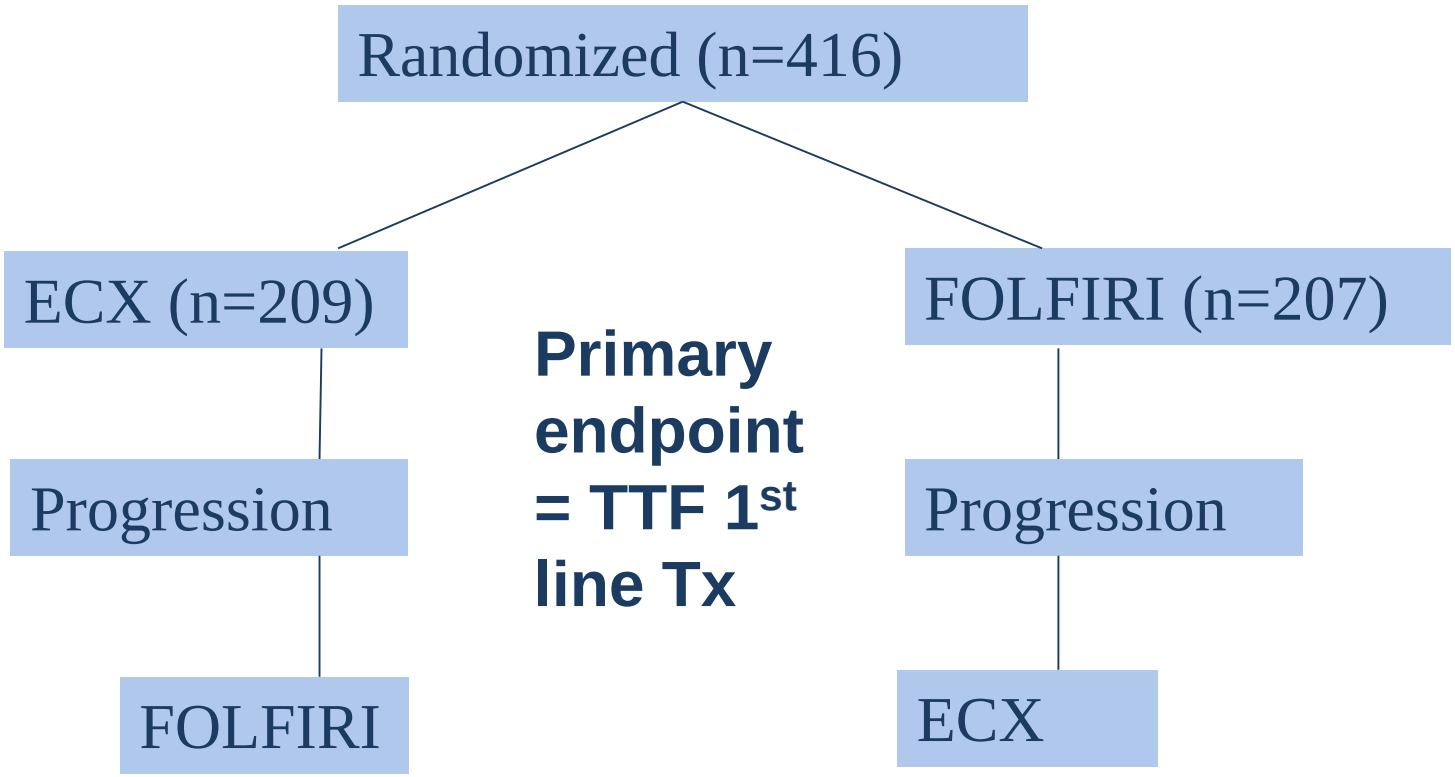
Initial Treatment Algorithm



First-Line Chemotherapy Backbones

Author	Regimen	RR	Median OS (months)
Van Cutsem, 2006	DCF	37%	9.2
Cunningham, 2008	ECF ECX EOF EOX	40.7% 46.4% 42.4% 47.9%	9.9 9.9 9.3 11.2
Al Batran, 2008	FLO	41.3%	10.7
Shah, 2010	Modified DCF	50%	14.9
Boku, 2009	Cisplatin/Irinotecan	38%	12.3
Narahara, 2011	Irinotecan/S-1	41.5%	12.8

2 Drugs vs. 3 Drugs



TTF = Time between randomization and treatment d/c, progression, death

Guimbaud, R et al. J Clin Oncol. 2014, Nov 1; 32(21): 3250-6.

2 Drugs vs. 3 Drugs

Table 3. Maximum Severity Grade for Toxicities

Toxicity and Grade	ECX Arm No.	ECX Arm %	FOLFIRI Arm No.	FOLFIRI Arm %	*P**
First-line	200		203		
Nonhematologic					.81
Grade 0 to 2	85	42.5	90	44.3	
Grade 3 to 4	107	53.5	108	53.2	
Missing	8	4.0	5	2.5	
Hematologic					< .001
Grade 0 to 2	60	30.0	120	59.1	
Grade 3 to 4	129	64.5	78	38.4	
Missing	11	5.5	5	2.5	
Overall					< .001
Grade 0 to 2	25	12.5	58	28.6	
Grade 3 to 4	167	83.5	140	69.0	
Missing	11	5.5	5	2.5	

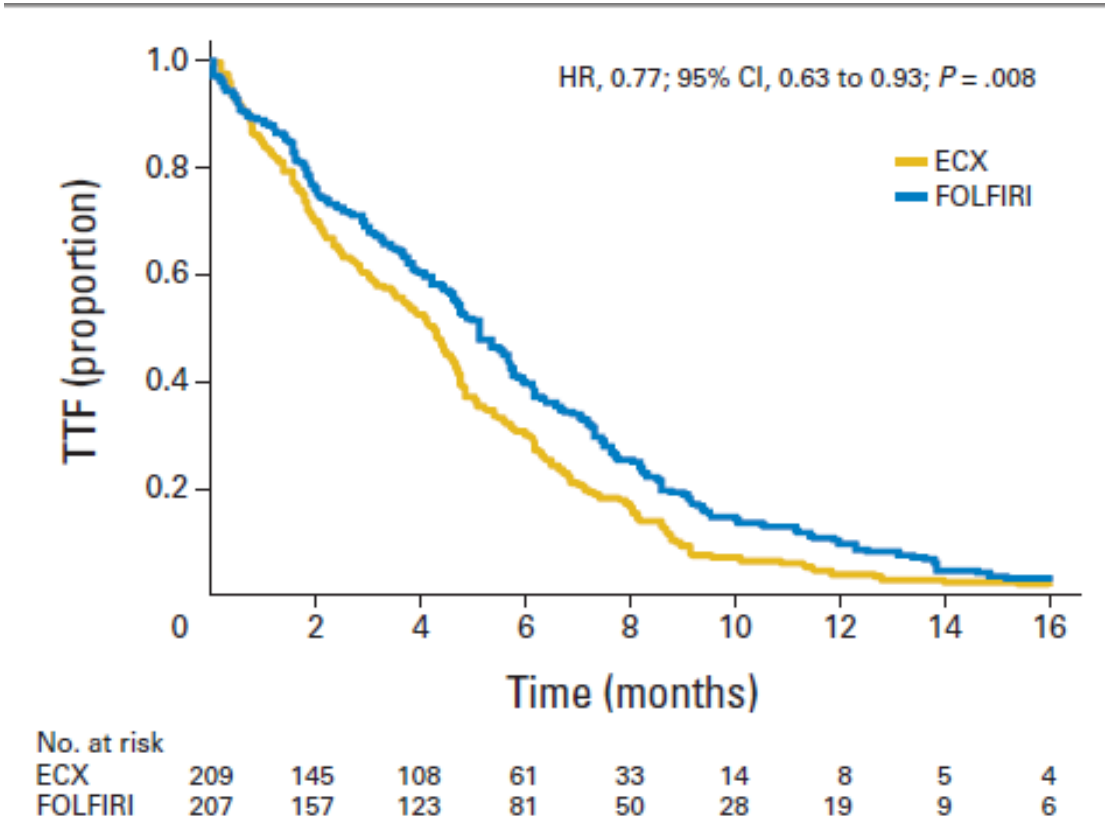
Guimbaud, R et al. J Clin Oncol. 2014, Nov 1; 32(21): 3250-6.

2 Drugs vs. 3 Drugs

TTF:
4.24 mo (ECX)
5.08 mo (FOLFIRI)
P=0.008

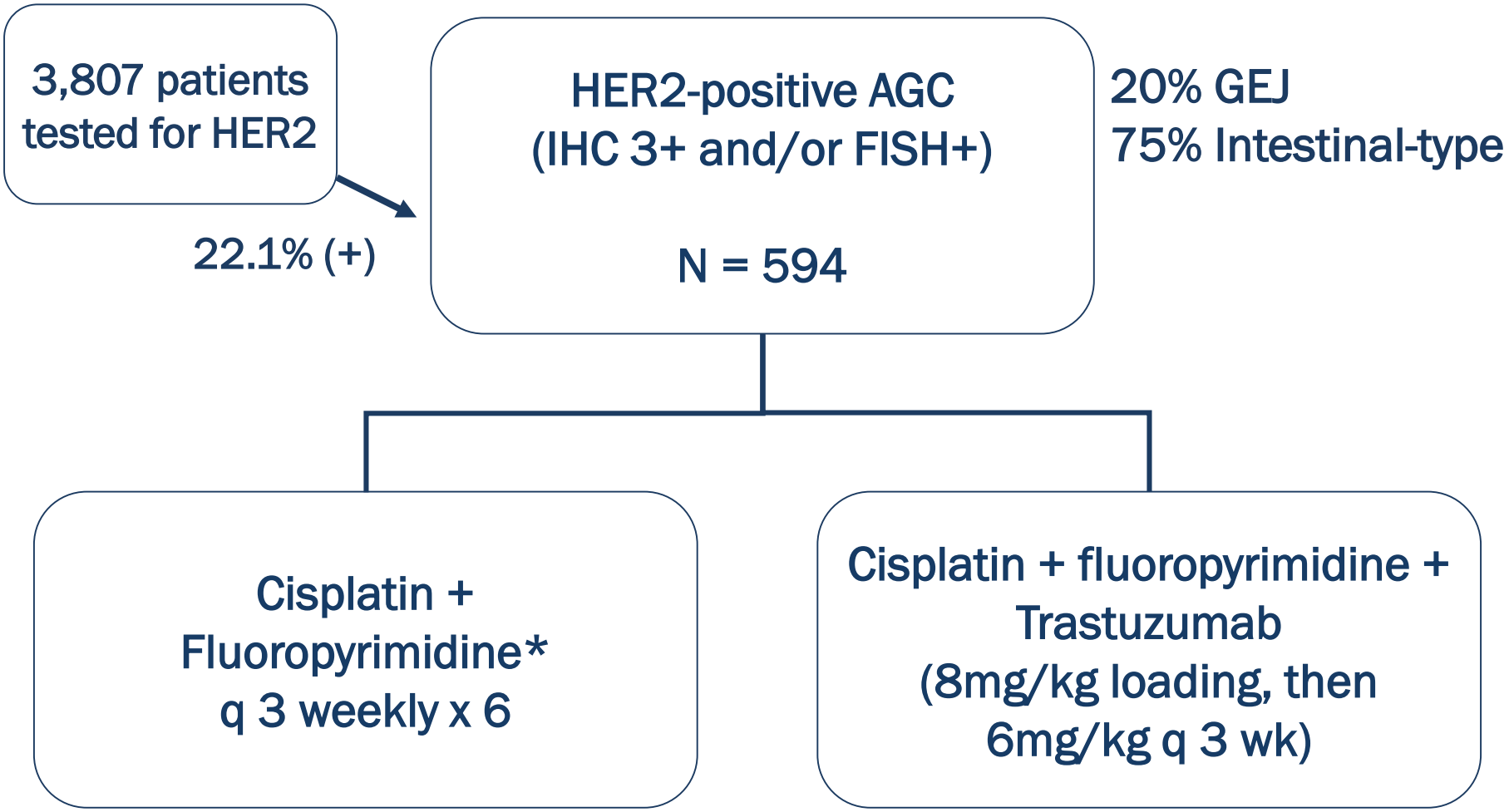
PFS:
5.29 mo (ECX)
5.75 mo (FOLFIRI)
P=0.96

OS:
9.49 mo (ECX)
9.72 mo (FOLFIRI)
P=0.95



In U.S., most typical 2-drug first-line regimen is FOLFOX

Targeting Her2 – TOGA Trial



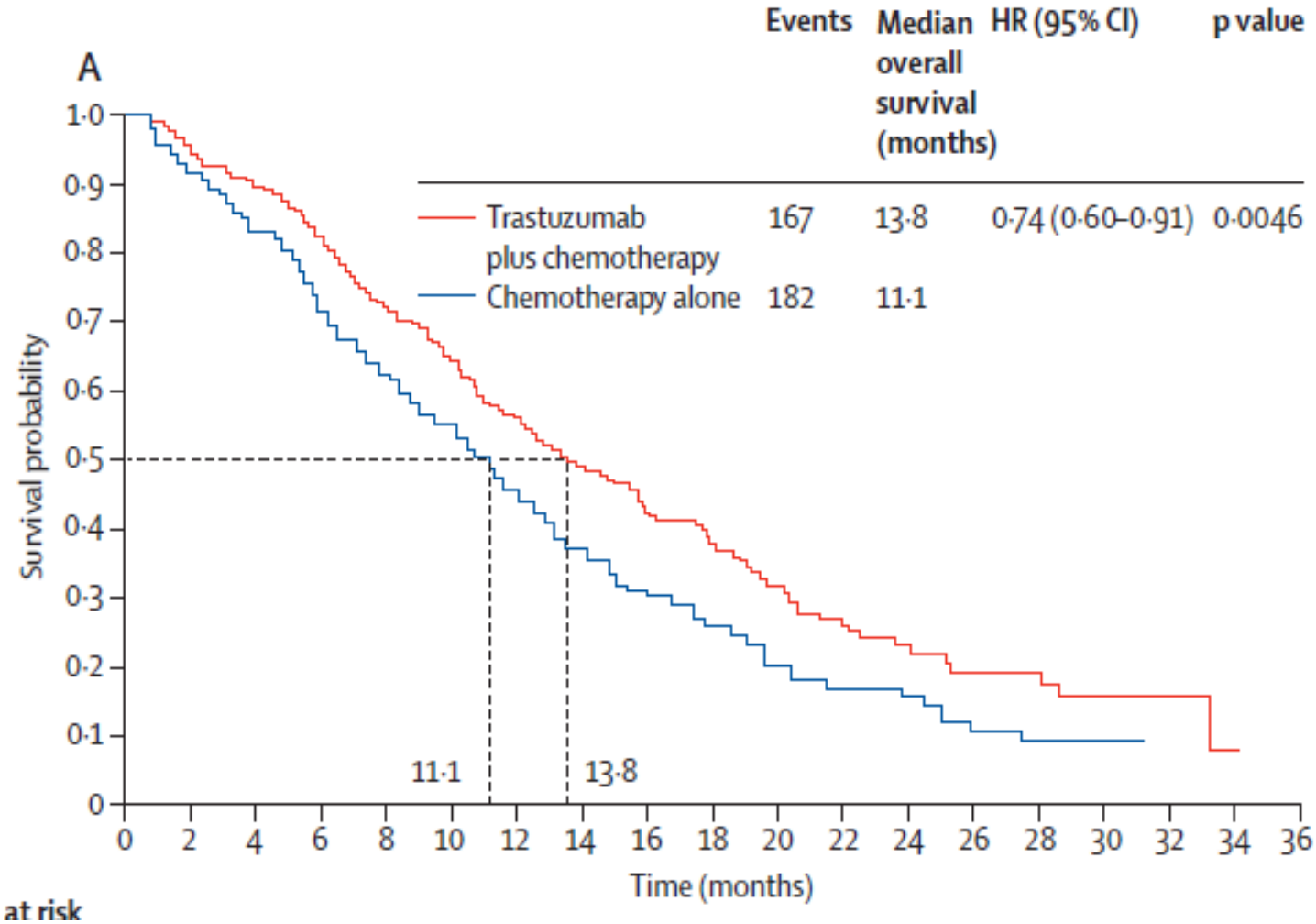
Bang, YJ et al. *Lancet* 2010; 376: 698-97

TOGA Trial - Results

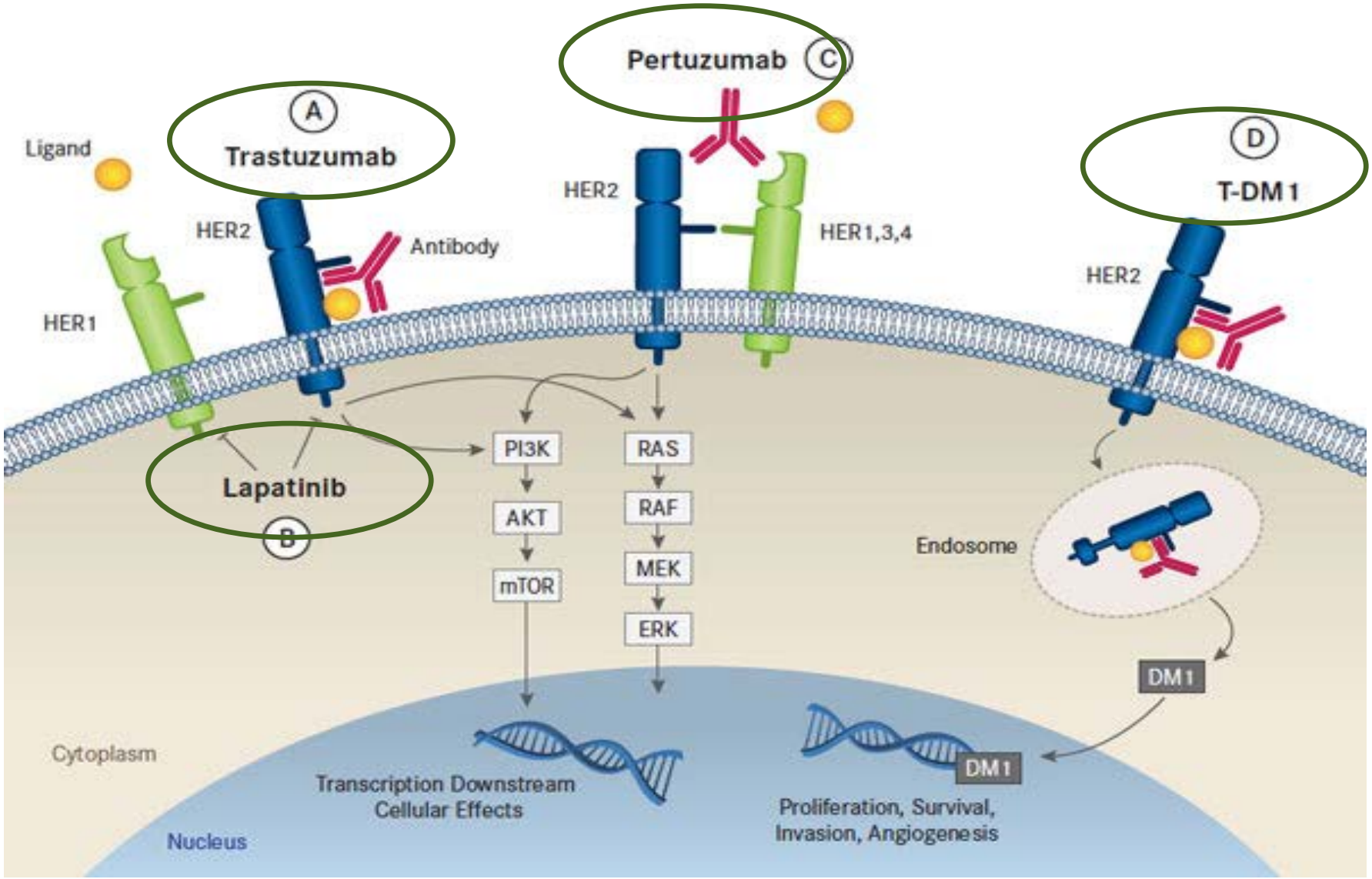
	Chemo alone	Chemo + trastuzumab	P value
ORR	34.5%	47.3%	P=0.0017
Median PFS	5.5 months	6.7 months	P=0.0002, HR 0.71
Median survival	11.1 months	**13.8 months**	P=0.0048, HR 0.74

Bang, YJ et al. *Lancet* 2010; 376: 698-97

TOGA Trial - Results



Anti-Her2 agents – Mechanism of Action



Her2 Agents in Gastric Cancer

TRIO-013/LOGiC 1st line: CapOx +/- **Lapatinib**

JACOB Trial 1st line: FU+Cis+Trastuzumab +/- **Pertuzumab**

TyTAN study 2nd line: Paclitaxel +/- **Lapatinib**

GATSBY trial 2nd line: Taxane vs. **TDM-1**

Hecht, R et al. J Clin Oncol. 2016, 34(5): 443-451.
Satoh, T et al. J Clin Oncol. 2014, 32(19): 2039-49
Thuss-Patience, PC et al. Lancet Oncol. 2017, 18(5): 640-53
Tabernero, J et al. ESMO 2017.

Trastuzumab Deruxtecan

- Randomized phase II study in Japan and Korea
- Patient population: Her2 positive gastric and GE jxn cancer patients who received at least 2 prior lines of therapy (including prior trastuzumab)
- 188 patients randomized (2:1) to trastuzumab deruxtecan versus physician's choice (irinotecan or paclitaxel)
- Primary endpoint = objective response

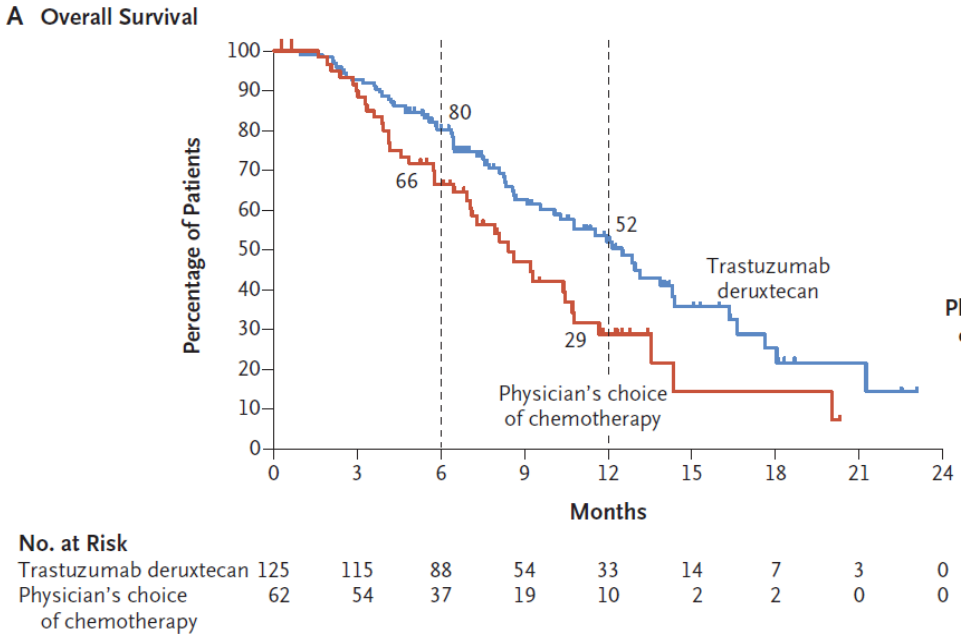
Shitara, K. et al. NEJM 2020; 382:2419-30.

Trastuzumab Deruxtecan

OR: 51% vs. 14%

PFS: 5.6 vs. 3.5 months (HR 0.47, 95% CI 0.31, 0.71)

Safety: neutropenia (51% vs. 24%) and ILD or pneumonitis (10%)



Median OS: 12.5 vs. 8.4 months

HR 0.59, 95% CI 0.39-0.88)

Shitara, K. et al. NEJM 2020; 382:2419-30.

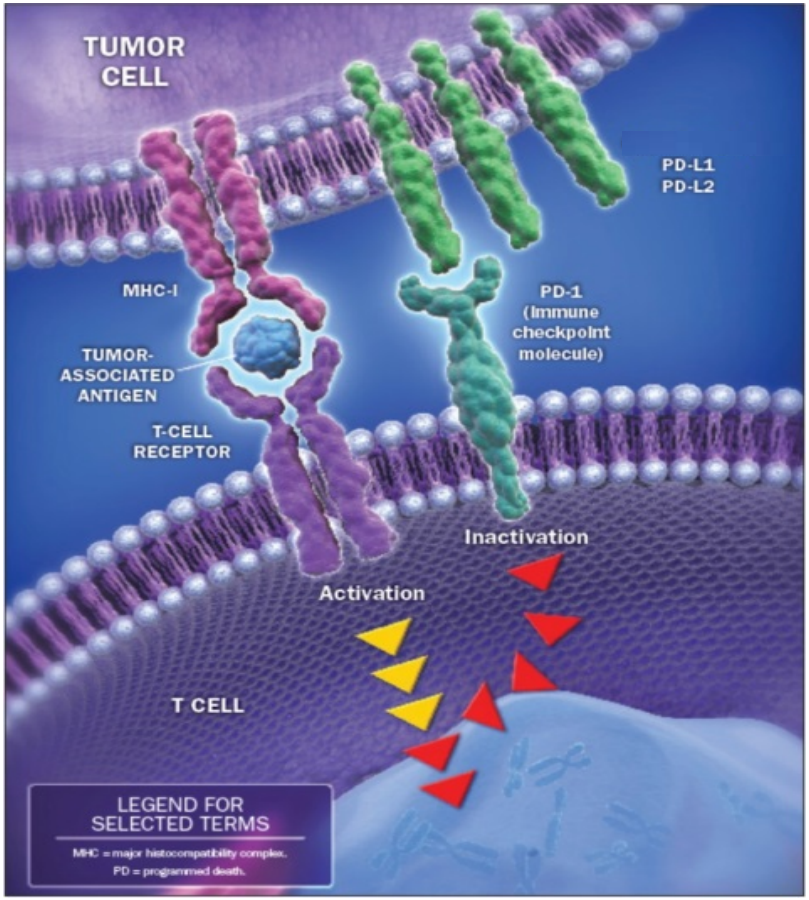
Trastuzumab “Beyond Progression”

WJOG Study: 2nd line paclitaxel +/- trastuzumab *(in Her2+ pts who progressed on 5-FU/platinum + trastuzumab)*

- No PFS benefit with trastuzumab
- In cases where pre-treatment biopsies could be performed, only 1/3 retained Her2 positivity (IHC 2/3+)

Sukawa, Y. et al. ASCO 2018

First-Line Checkpoint Inhibitor ?



- **Pembrolizumab** was approved by the FDA in Sept 2017 for PDL1 overexpressing (CPS ≥ 1) gastric and esophagogastric cancers progressed on 2 or more prior lines of therapy
- In Japan, **Nivolumab** approved for refractory gastric cancer (3rd line and beyond) in October 2017

Keir ME, et al. *Annu Rev Immunol*. 2008;26:677-704.
Pardoll DM, et al. *Nat Rev Cancer*. 2012;12:252-64.

Immune Checkpoint Inhibitors

Study	Drug	Population	N	RR	OS
Keynote 012	Pembro 10mg/kg q2 wks	Refractory PDL1+	39	22%	11.4 mo
Attraction-2	Nivolumab 3mg/kg q2 wks vs. Placebo	Refractory any PDL1	493	11.2%	5.32 vs. 4.14 mo (HR 0.63, p<0.0001)
Keynote 059 (cohort 1)	Pembro 200mg q3 wk	Refractory any PDL1	259	11.2% *PDL1+ 15.5%* *PDL1- 5.5%*	NR
Checkmate 032	• Nivo 3mg/kg q2 • Nivo 1mg/kg + Ipi 3mg/kg • Nivo 3mg/kg + Ipi 1mg/kg	Refractory any PDL1	160	16% Overall 14% N3 26% N1+I3 10% N3+I1	 5.0 mo 6.9 mo 4.8 mo

Muro, K et al. *Lancet Oncology*. 17(7), 2016.
Al-Batran, S. et al. ACSO 2017 Annual Meeting
Janjigian, E. et al. ASCO 2016
Fuchs, CS et al. ASCO 2017.

Pembrolizumab – Keynote 059

Advanced gastric cancer, progressed after 2 or more prior therapies

Table 1. Objective Tumor Response

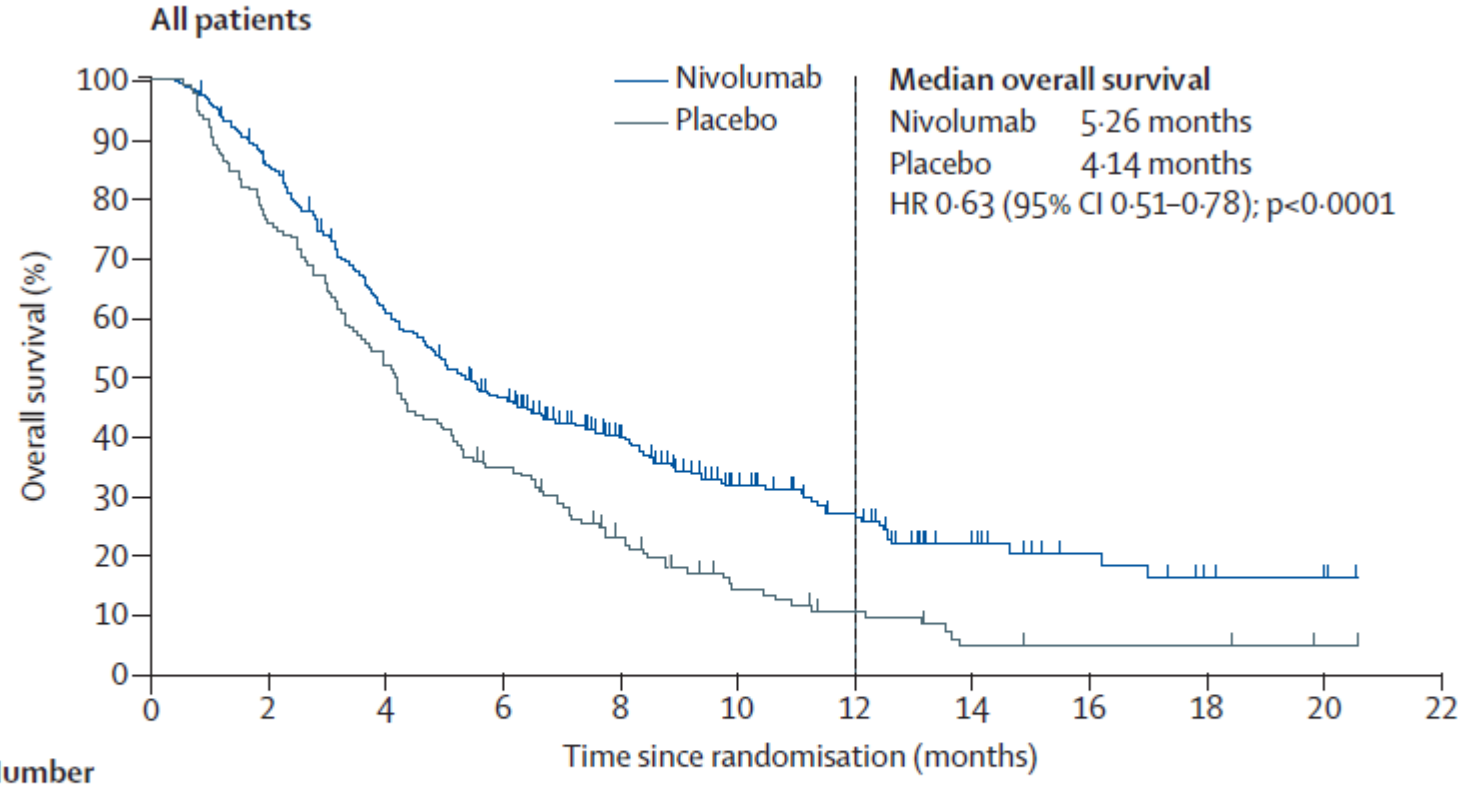
Best Overall Response[a]	Participants (n = 259) No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo	8.4 (1.6+ to 17.3+)[c]	

15.5% PDL1 +

6.4% PDL1 -

Fuchs, C et al. JAMA Oncology. 2018, 4(5): e180013

Nivolumab vs. BSC: ATTRACTION 2 Trial



Number at risk (censored)												
Nivolumab	330 (0)	275 (6)	192 (10)	141 (16)	94 (45)	56 (65)	38 (75)	19 (88)	10 (96)	5 (99)	3 (101)	0 (104)
Placebo	163 (0)	121 (3)	82 (4)	53 (6)	32 (10)	16 (15)	10 (17)	4 (18)	3 (19)	3 (19)	1 (21)	0 (22)

Kang, Y et al. Lancet. 2017, 390: 2461-2471.

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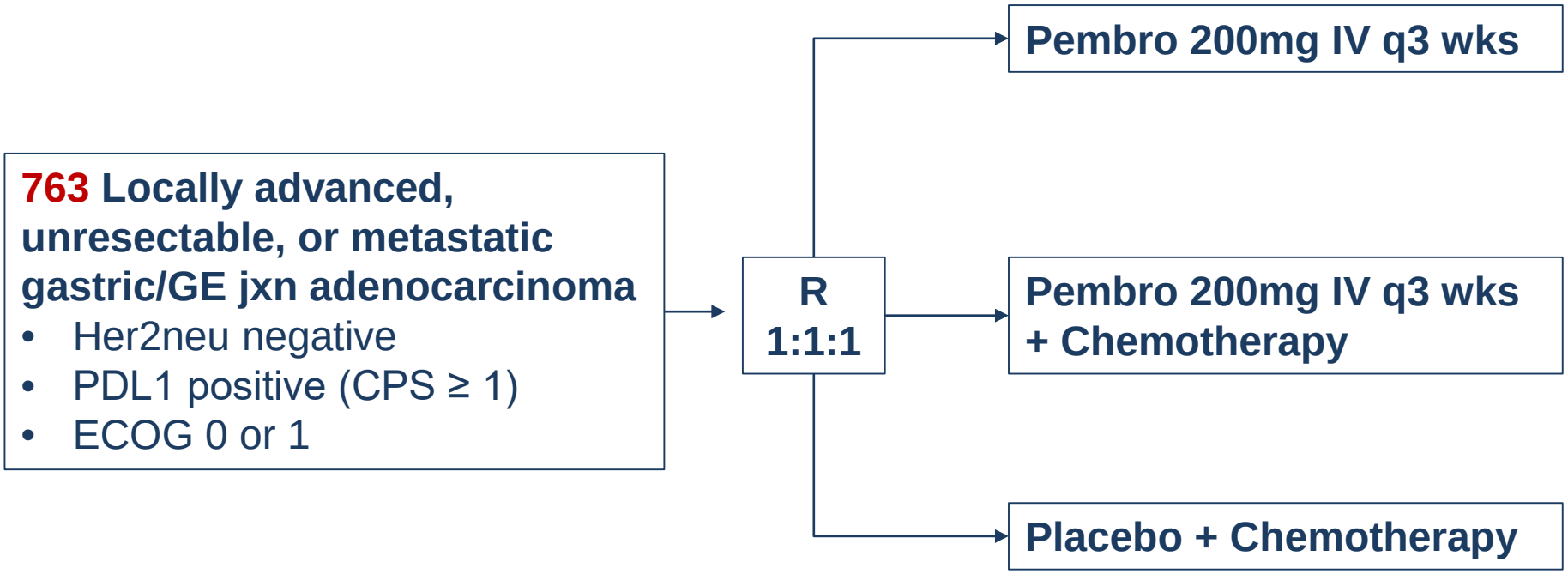
First-line pembrolizumab – Keynote 062



Primary endpoints = noninferiority OS (pembro vs. chemo) ; superiority OS (pembro+chemo vs. chemo)
Chemotherapy = 5-FU or capecitabine + cisplatin

Tabernero, J. et al. 2019. ASCO Annual Meeting

First-line pembrolizumab – Keynote 062

Pembro versus Chemotherapy

- Noninferior OS Pembro vs. Chemo (10.6 months vs. 11.1 months) HR 0.91, p=NS
- Superior OS in CPS ≥ 10 subgroup (17.4 vs. 10.8 months) HR = 0.69
- Lower Grade 3 or higher AEs (17% P, 71% pembro +chemo, 68% chemo)

Pembro + Chemo versus Chemo

- OS ***not*** superior Pembro + chemo vs. chemo (12.5 mo vs. 11.1 mo) HR 0.85
- ORR slightly better in pembro + chemo vs. chemo alone (48.6% vs. 36.8%
- OS not superior in CPS ≥ 10 subgroup (12.3 mo vs. 10.8 mo) HR 0.85

Tabernero, J. et al. 2019. ASCO Annual Meeting

When to use first-line pembrolizumab?

Monotherapy in CPS ≥ 10 (if you can get this information quickly and if covered by insurance

Lower burden of disease, lower symptom burden

Elderly or frail patients with CPS ≥ 10 who cannot tolerate chemo

Second Line Therapy

For patients who retain good PS

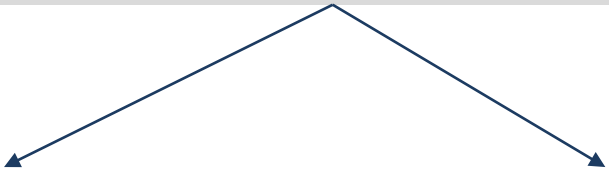
- Paclitaxel (+ Ramucirumab)
- Docetaxel
- Irinotecan
- Ramucirumab
- Pembrolizumab (CPS ≥ 10)

???????

- Neuropathy
- Bleeding from primary tumor
- Pace and extent of disease progression

WJOG 4007: 2nd Line Irinotecan vs. Paclitaxel

Advanced Gastric Cancer without Severe Peritoneal Metastases – After Progression through 5-FU + Platinum (n=223)

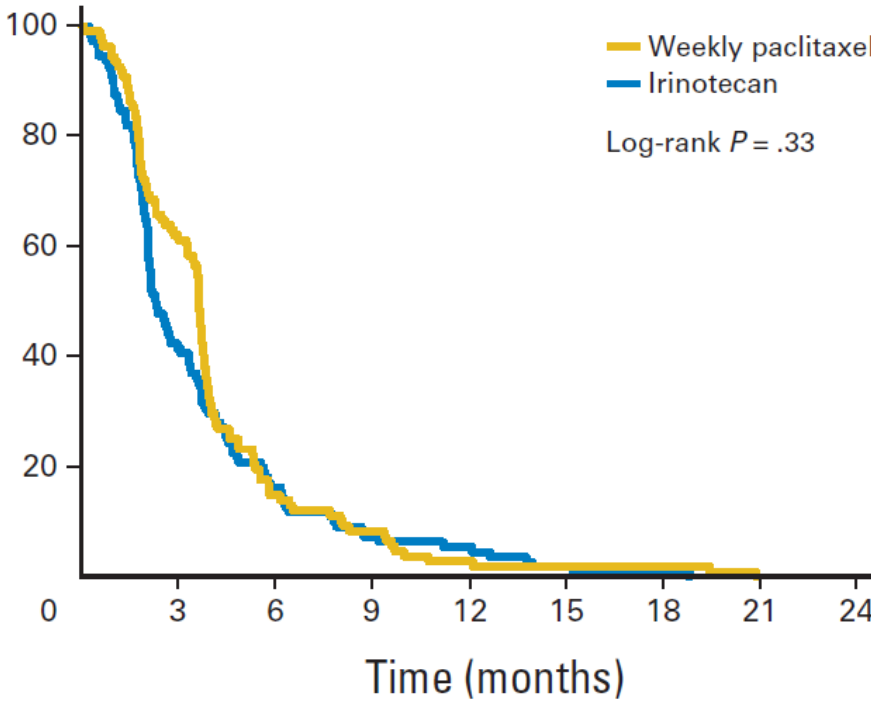


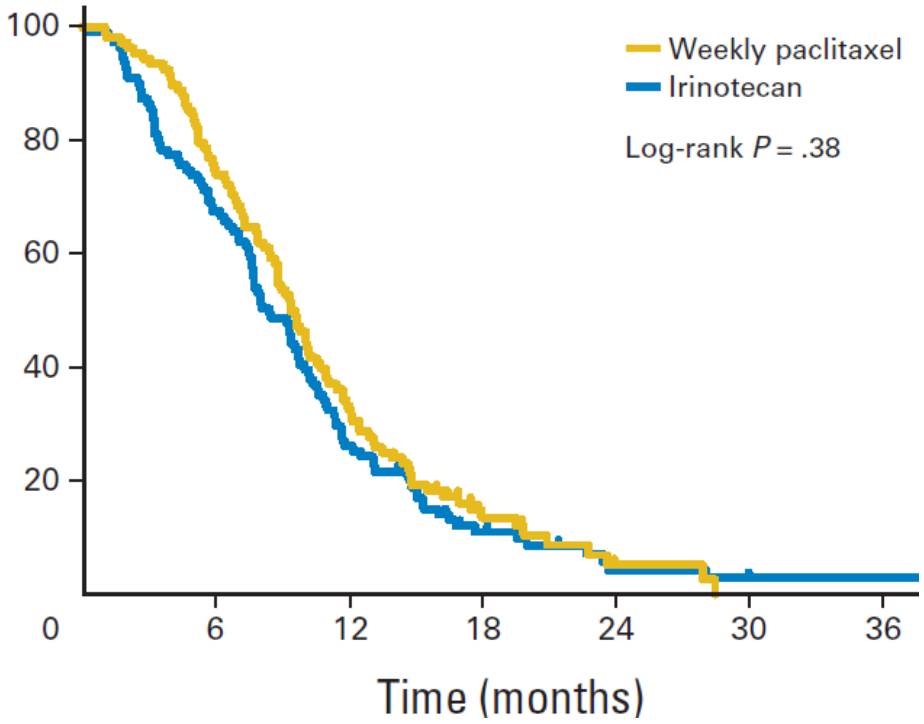
Weekly Paclitaxel 80mg/m2 Days 1, 8, 15 q28 days (n=111)

Irinotecan 150 mg/m2 Days 1,15 q28 days (n=112)

Hironaka S et al. J Clin Oncol, 2013; 31: 4438-4444.

WJOG 4007: 2nd Line Irinotecan vs. Paclitaxel





PFS: 3.6 mo (paclitaxel) vs. 2.3 mo (irinotecan)

OS: 9.5 mo (paclitaxel) vs. 8.4 mo (irinotecan)

Versus 5.2 mo in docetaxel arm of Cougar-2 study

Hironaka S et al. J Clin Oncol, 2013; 31: 4438-4444.

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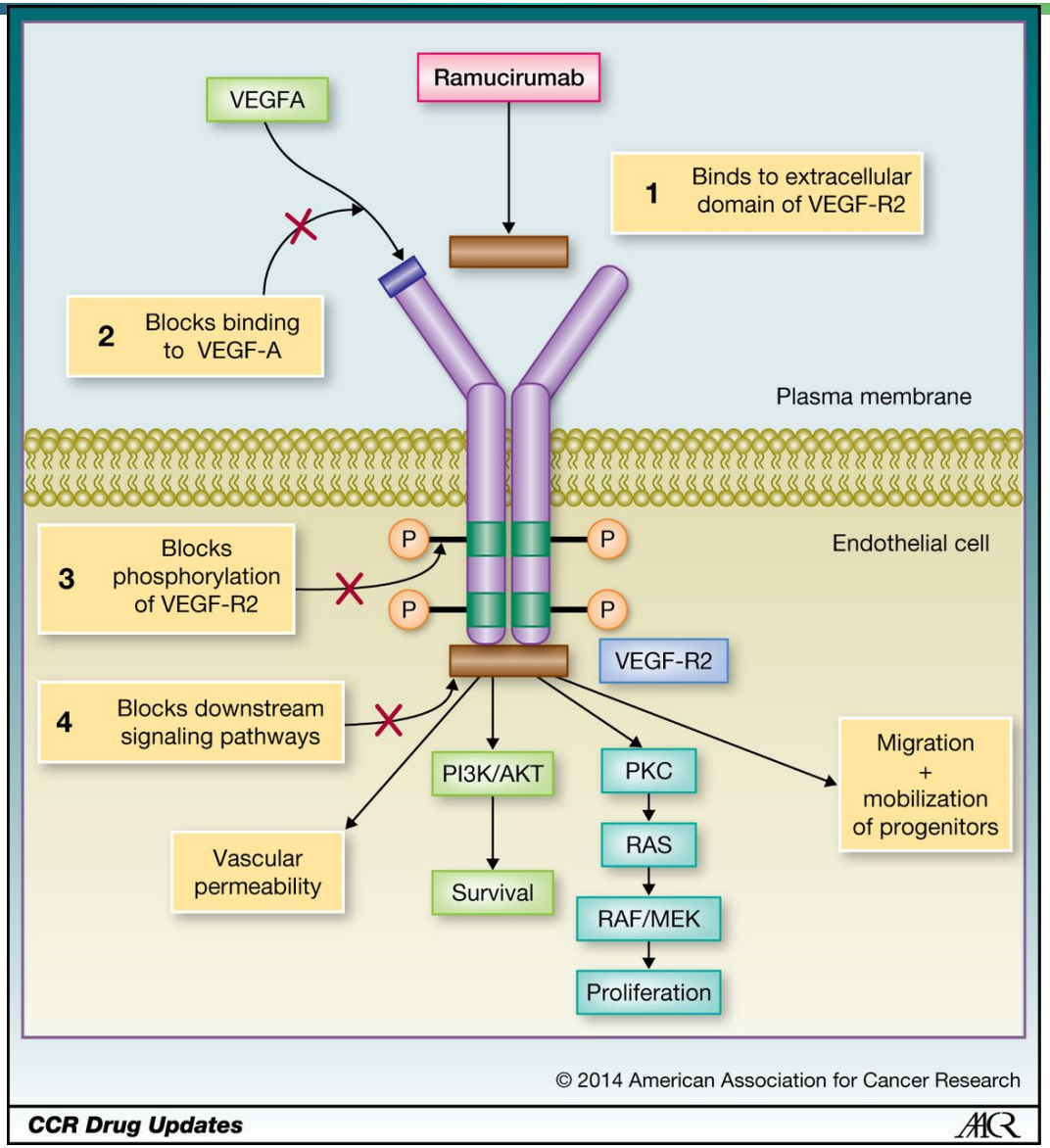
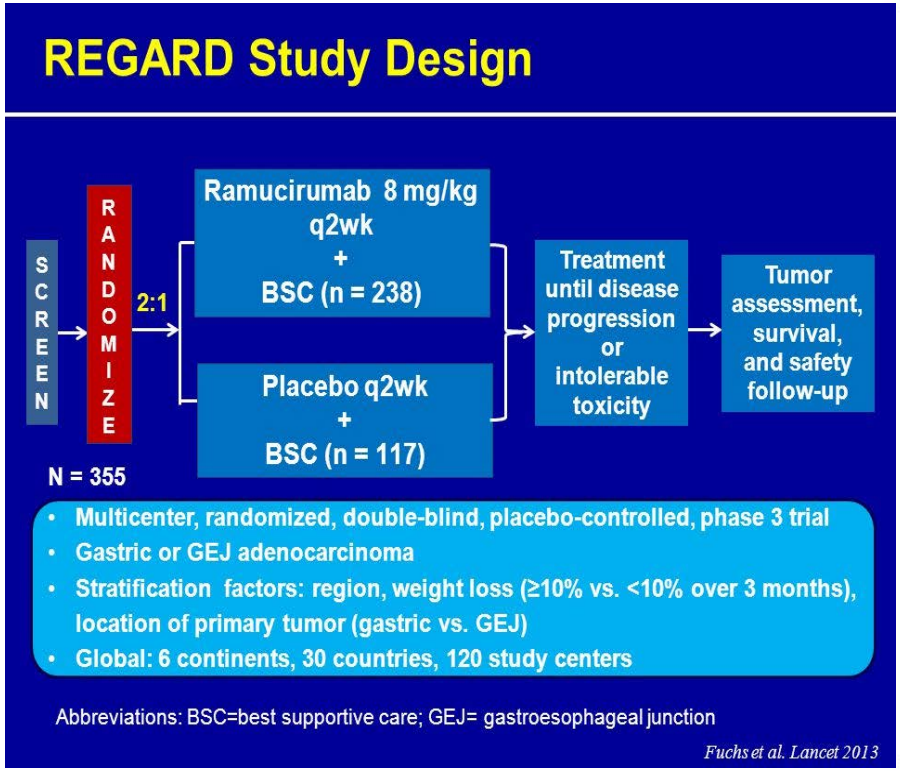
Ramucirumab and VEGF Pathway

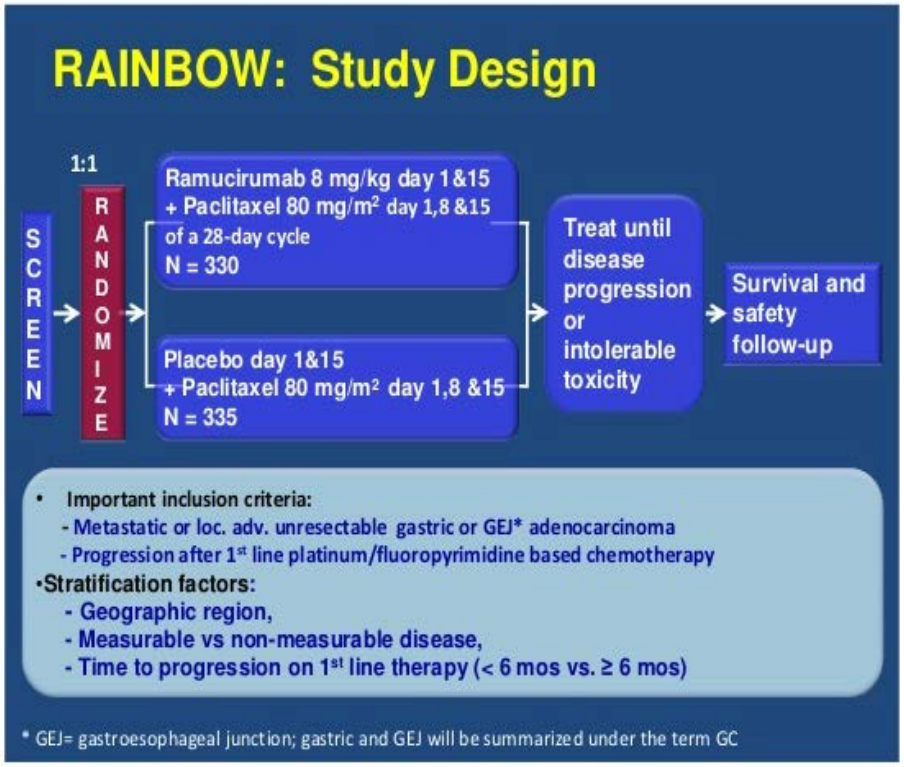


Javle, M et al. Clinical Cancer Research. 2014. 20(23)

REGARD and RAINBOW

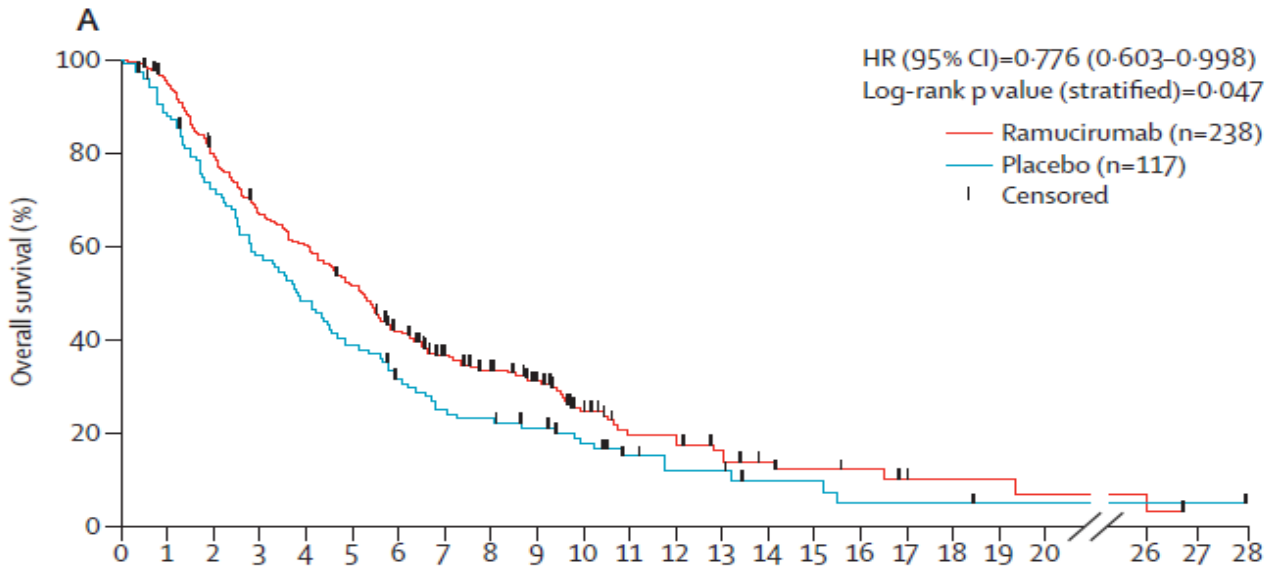


Fuchs, C et al. *Lancet*. Oct 3, 2013



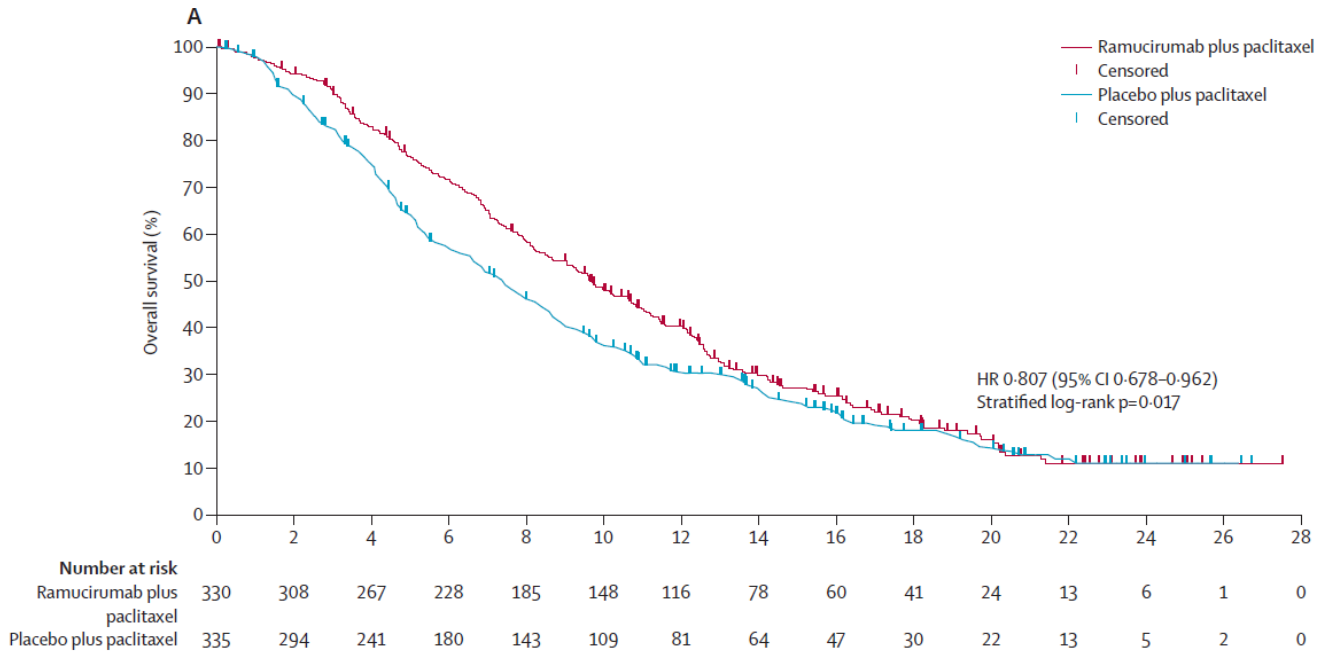
Wilke, H et al. Lancet Oncology. 2014, 15(11): 1224-35.

Ramucirumab: REGARD Study



	Ram	Placebo	P
PFS	2.1 mo	1.3 mo	<0.001
OS	**5.2 mo**	**3.8 mo**	**0.047**

Ramucirumab: RAINBOW



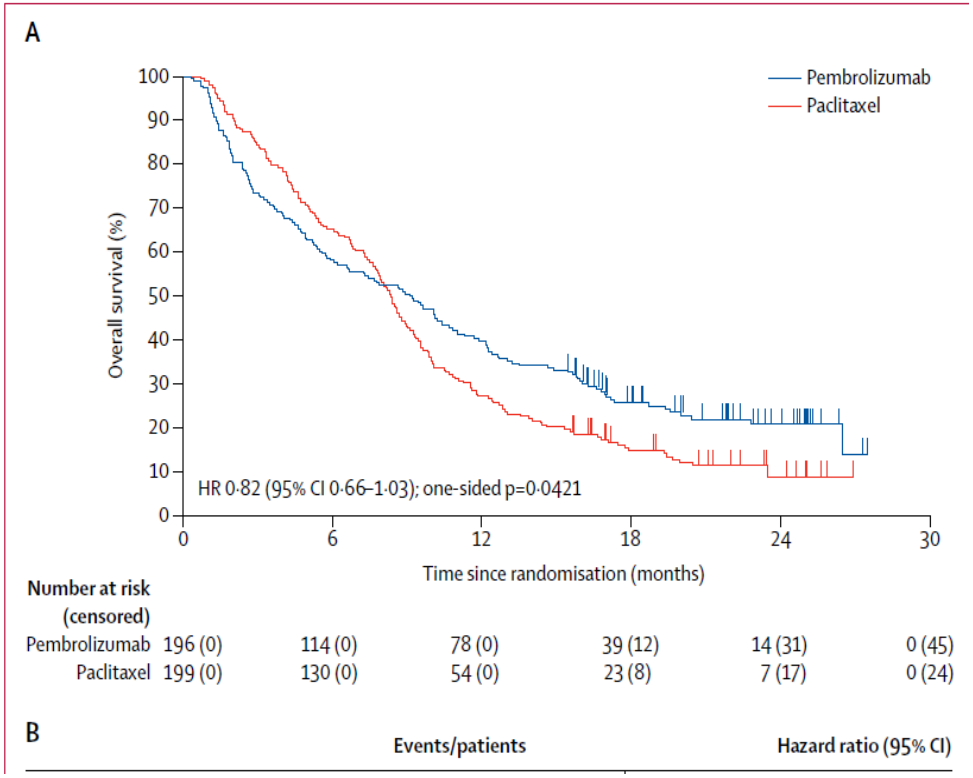
Endpoint	Ram + Paclitaxel	Placebo + Paclitaxel	Δ	p value
RR	28%	16%	12%	0.0001
DCR	80%	64%	16%	<0.0001
PFS	4.4 mo	2.86 mo	1.5	<0.0001
OS	9.63 mo	7.36 mo	2.3	0.0169

Ramucirumab Adverse Events

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	39 (12%)	12 (4%)	3 (<1%)	0	28 (9%)	11 (3%)	2 (<1%)	0
Hypertension	34 (10%)	48 (15%)	0	0	10 (3%)	9 (3%)	0	0
Gastrointestinal haemorrhage†	21 (6%)	10 (3%)	1 (<1%)	1 (<1%)	15 (5%)	3 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	17 (5%)	2 (<1%)	0	0	12 (4%)	0	0	0
Renal failure	16 (5%)	4 (1%)	2 (<1%)	0	11 (3%)	0	1 (<1%)	2 (<1%)
Congestive heart failure	6 (2%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Venous thromboembolic events	5 (2%)	7 (2%)	0	1 (<1%)	7 (2%)	8 (2%)	1 (<1%)	2 (<1%)
Arterial thromboembolic events	3 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	1 (<1%)
Gastrointestinal perforation	0	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0

Second-line Pembrolizumab: Keynote 061

592 pts with advanced gastric cancer randomized to paclitaxel weekly versus pembro 200mg IV q3 wks. Trial amended to include only PDL1 CPS ≥1 pts.



- **Pembro did not significantly prolong OS** (9.1 vs 8.3 mo, HR 0.82, 95% CI 0.66-1.03). ORR was similar (16 versus 14 %)
- P threshold 0.0135 for superiority
- **Pembro toxicity profile favorable** (14% vs. 35% grade ≥ 3 AE)
- Potentially greater effect in CPS ≥10 and MSI-h

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Shitara, K. et al. Lancet. 2018; 392: 123-133.

Second-line Pembrolizumab: Keynote 061

Efficacy Outcomes.

	Pembrolizumab CPS ≥1 n = 196	Paclitaxel CPS ≥1 n = 199	Pembrolizumab CPS ≥5 n = 95	Paclitaxel CPS ≥5 n = 91	Pembrolizumab CPS ≥10 n = 53	Paclitaxel CPS ≥10 n = 55
OS, deaths, n (%)	176 (89.8)	190 (95.5)	84 (88.4)	86 (94.5)	44 (83.0)	51 (92.7)
OS, months, median (95% CI)	9.1 (6.2-10.7)	8.3 (7.6-9.0)	10.4 (6.7-15.5)	8.3 (6.8-9.4)	10.4 (5.9-18.3)	8.0 (5.1-9.9)
HR (95% CI)	0.81 (0.66-1.00)	—	0.72 (0.53-0.99)	—	0.69 (0.46-1.05)	—
P	0.03	—	0.02	—	0.04	—
PFS, months, median (95% CI)	1.5 (1.4-2.0)	4.1 (3.2-4.3)	1.6 (1.4-2.8)	4.0 (2.8-4.4)	2.7 (1.4-4.3)	4.0 (2.7-4.4)
HR (95% CI)	1.25 (1.02-1.54)	—	0.98 (0.71-1.34)	—	0.79 (0.51-1.21)	—
ORR, % (n)	16.3 (32)	13.6 (27)	20.0 (19)	14.3 (13)	24.5 (13)	9.1 (5)
DOR, months, (range)	19.1 (1.4+ to 47.1+)	5.2 (1.3+ to 16.8)	32.7 (4.1 to 47.1+)	4.8 (1.3+ to 15.3)	NR (4.1 to 47.1+)	6.9 (2.6 to 6.9)

Fewer drug-related AEs with Pembrolizumab

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Fuchs, C et al. ASCO 2020

Second-line Pembrolizumab: Keynote 181

401 pts with SCC and 222 pts with CPS ≥10

628 patients with advanced or metastatic **squamous cell cancer** of the esophagus or **adenocarcinoma** of the esophagus / GE jxn

- Progressed on 1L therapy
- ECOG 0 or 1

R
1:1

Pembrolizumab 200mg q3wk

Investigator choice chemo

- Paclitaxel 80mg/m2 D 1,8,15 q28d
- Docetaxel 75mg/m2 q3wk
- Irinotecan 180mg/m2 q2wk

Primary endpoints: OS in SCC, CPS ≥10, and total population

Kojima, T. et al. 2019 GI Cancers Symposium

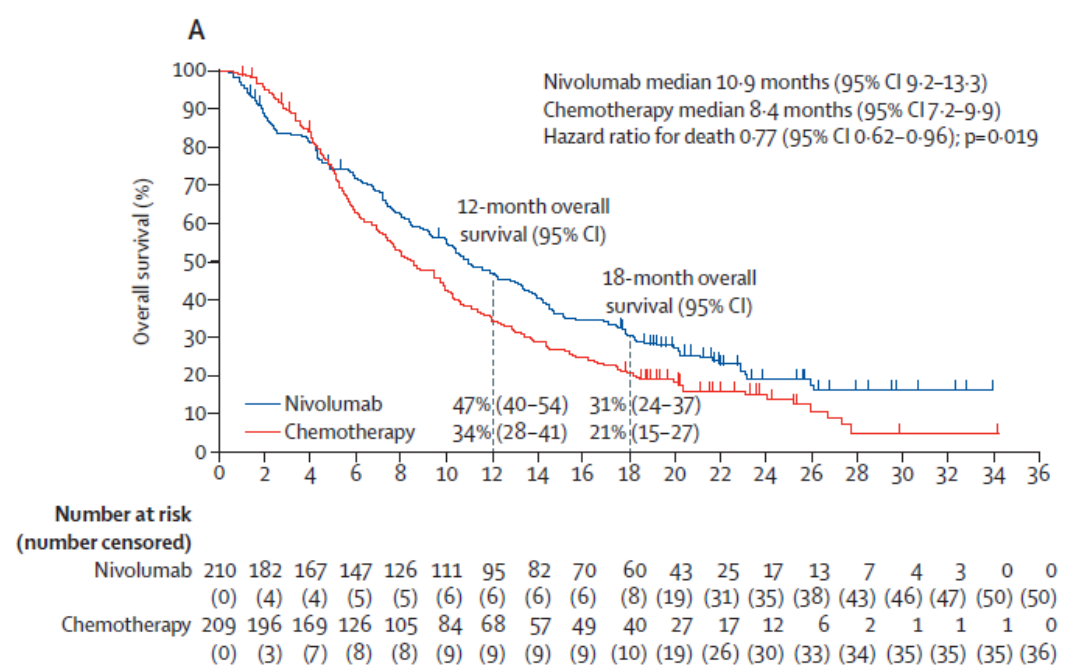
Pembro approved in July 2019 for 2nd line treatment of SCC esophagus with CPS ≥ 10 based on results from Keynote 181

Key Results

- Pembrolizumab was superior to chemo for OS in CPS ≥10 (9.3 vs. 6.7 mo; HR 0.69; 95% CI 0.52-0.93; *P*=0.0074).
- SCC subgroup: Improvement in OS with pembrolizumab vs chemo, (8.2 mo vs 7.1 mo; HR 0.78; 95% CI 0.63, 0.96; *P*=0.0095).
- Fewer any-grade (64% vs 86%) or grade 3-5 (18% vs 41%) drug-related AEs with pembrolizumab vs chemo.

Nivolumab 2nd line – ATTRACTION 3

- Open-label phase 3 randomized trial Nivolumab vs. Chemotherapy
- Patient population: Advanced squamous cell carcinoma ; 1 prior line of therapy
- Primary endpoint: Overall survival



Kato K, et al. Lancet Oncology. 2019; 20: 1506-17

What didn’t work?

CMET Inhibitors -- (RILOMET 1 – worse survival in Txarm)

EGFR Inhibitors – Cetuximab, Panitumumab (REAL3, E1206/CALGB 80403)

mTOR inhibitors – Everolimus vs. BSC

Napabucasin (BRIGHTER trial)

Take-home points: Metastatic Gastric/Eso

- 2 drug combinations rather than 3 drug combinations (5-FU+platinum) represents a standard of care worldwide in 1st line therapy
- Trastuzumab in 1st line for Her2 positive tumors
- In 2nd line, irinotecan, paclitaxel, docetaxel all viable standard chemotherapeutic options
- Ramucirumab in 2nd line therapy (alone or with Paclitaxel)
- Pembrolizumab in PDL1 + or MSI-high tumors (3rd line)
  - First line monotherapy, particularly in CPS ≥10
  - Second line, in CPS ≥10 (SCC) and MSI-H

THANK YOU

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Extra Slides

Siewert Classification

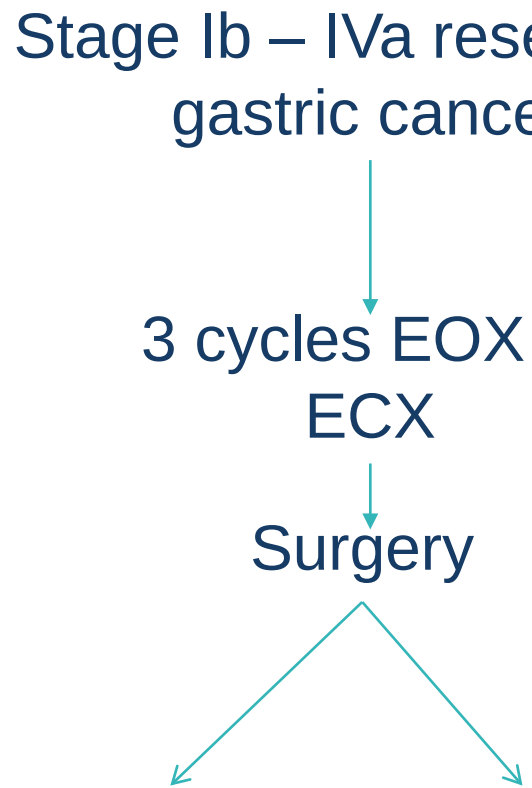
	Type 1 (n= 494)	Type II (n= 414)	Type III (n= 438)
Mean age at presentation	60.1 ± 10.3	60.7 ± 11.4	62.7 ± 12.0
Male: Female Ratio	9.9 : 1	4.8 : 1	2.1 : 1
Associated Barrett's	76.9%	9.8%	2.0%
Prevalence of Grade 3/4 tumors	52.6%	58.7%	72.6%
Intestinal type histology	81.1%	41.3%	39.1%

Siewert R et al. *J Surg Onc*. 90; 139-46, 2005

Chemo (PeriOp vs. PostOp) vs. ChemoRT

Citation	# Pts	Treatment	3 or 5 year OS in Treatment Arm
MacDonald, JS 2001 (INT-0116)	**556**	**Arm A: Surgery alone** **Arm B: Surgery → 5-FU/LV + RT**	**50%**
Fuchs, CS 2011 (CALGB 80101)	546	Arm A: Surgery → 5-FU/LV/RT Arm B: Surgery → ECF/RT	52%
Cunningham, D 2006 (MAGIC)	**503**	**Arm A: Surgery alone** **Arm B: ECF(3) → surgery → ECF(3)**	**36%**
Sasako, M 2011 (ACTS-GC)	1,059	Arm A: Surgery (D2) Arm B: Surgery → S1 x 1 year	71.7%
Bang, Y. 2011 (CLASSIC)	**1,035**	**Arm A: Surgery (D2)** **Arm B: Surgery (D2) →XELOX x 8 cycles**	**83%**

CRITICS Trial: (MAGIC vs. MacDonald?)



KEY RESULTS

5-year survival: 41.3 % (chemo) vs. 40.9% (RT), p=0.99

87% underwent D2 dissection

Poor postoperative treatment compliance in both arms

Cats, A. et al. Lancet Oncology. 2018, 19(5): 616-628

2nd Line Therapy --- Cougar-2 Study

Advanced Esophagogastric Cancer (n=168)

Progression within 6 mo of 5FU/platinum

ECOG 0-2

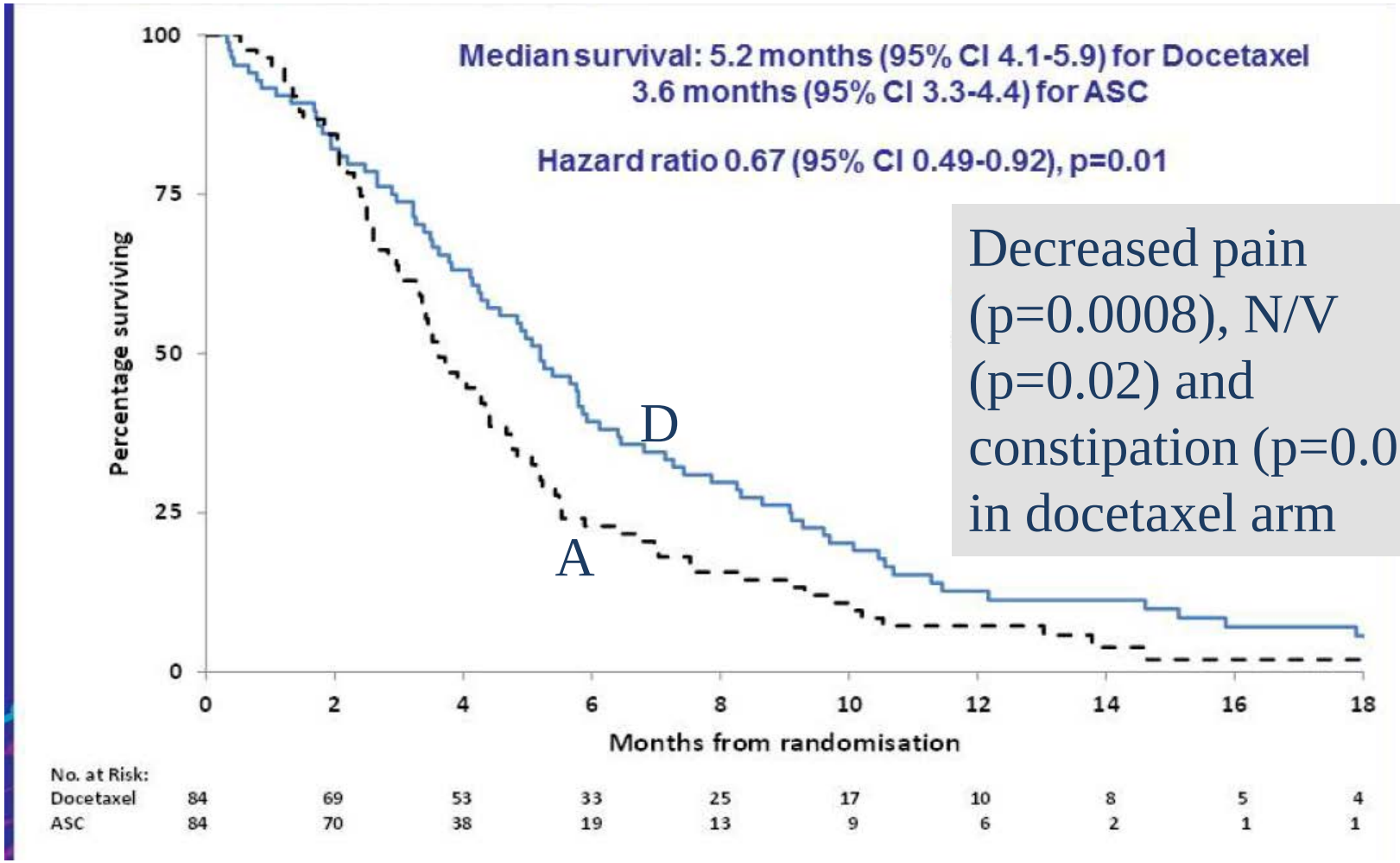
→ Docetaxel 75mg/m2 q3w X 6 cycles

→ Active symptom control

OS (primary endpoint),
HRQOL (secondary endpoint)

Ford H et al. Lancet Oncology 2014; 15: 78-86

2nd Line Therapy --- Cougar-2 Study



Decreased pain (p=0.0008), N/V (p=0.02) and constipation (p=0.02) in docetaxel arm

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Ford H et al. Lancet Oncology 2014; 15: 78-86