University of Colorado Cancer Center

Diagnosis and Treatment of Gastroesophageal Cancers

W. Thomas Purcell, MD, MBA
Gastrointestinal Oncology Team
Executive Medical Director
University of Colorado Cancer Center
tom.purcell@ucdenver.edu

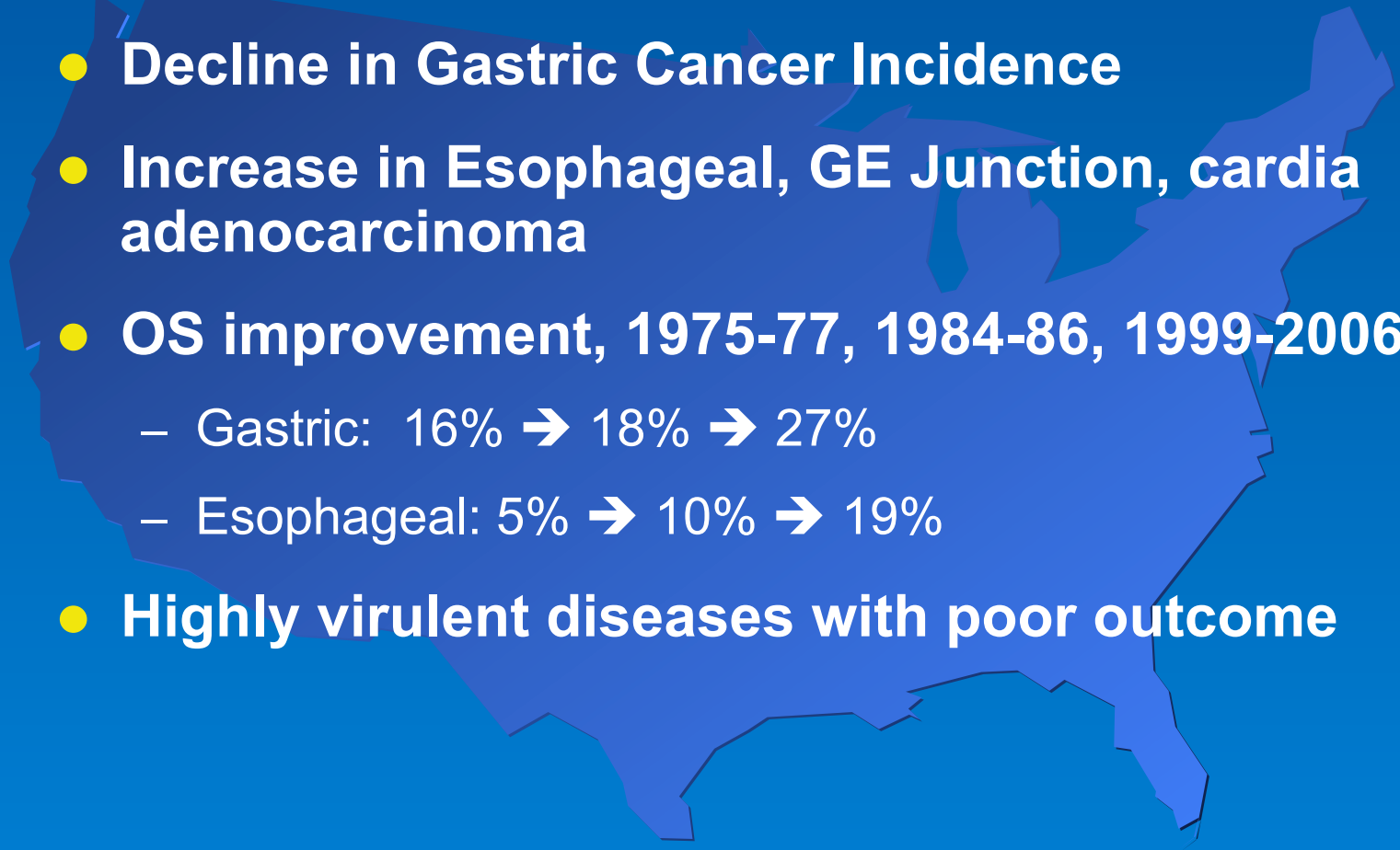
Oncology Service Line
University of Colorado Health

University of Colorado
Cancer Center

Outline

- Overview – key facts
- Squamous and Adenocarcinoma of the mid-esophagus
- Distal esophageal and GE Junction adenocarcinoma
- Gastric adenocarcinoma
- GIST
- Questions

Esophageal and Gastric Carcinoma US Incidence

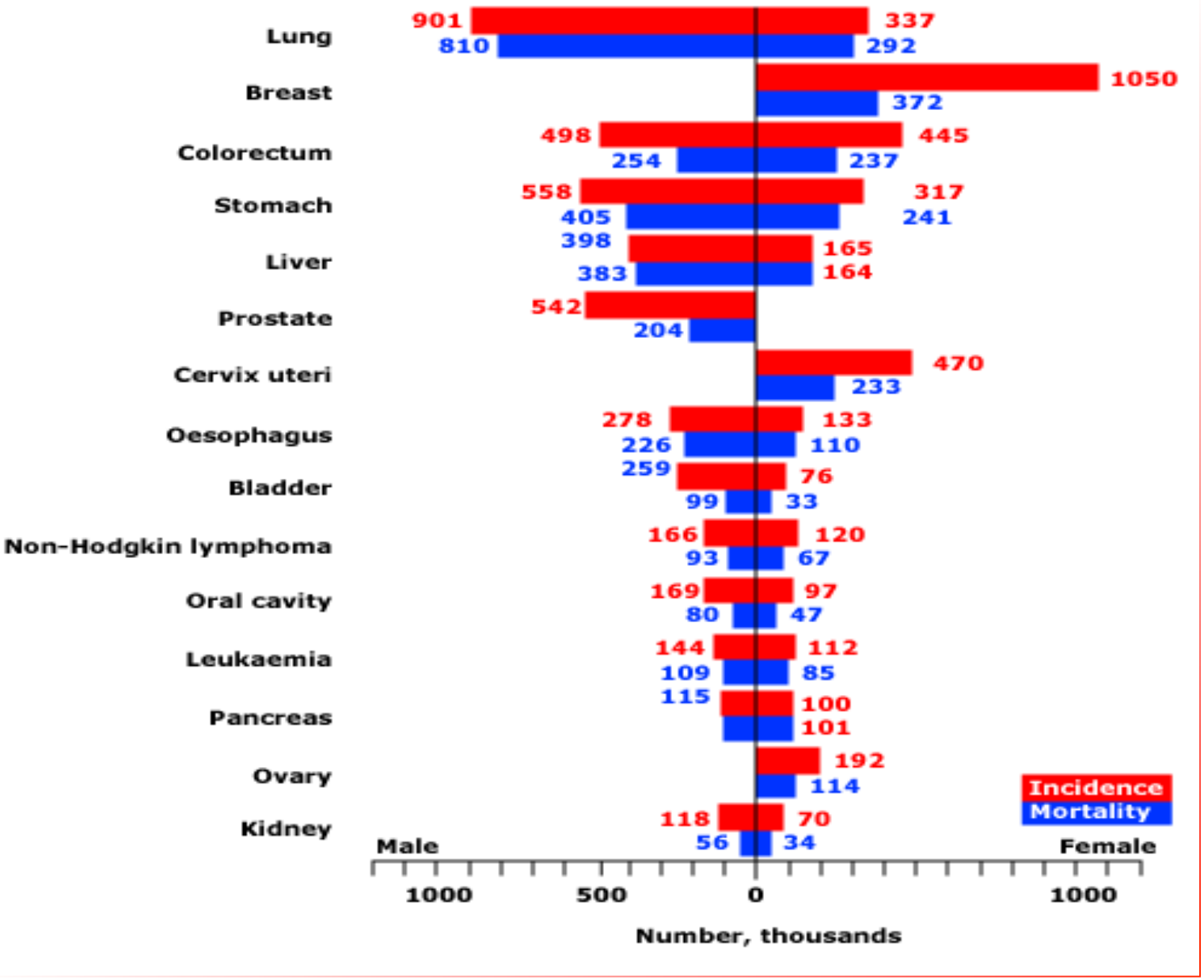


- 38,500 new cases per year
- Decline in Gastric Cancer Incidence
- Increase in Esophageal, GE Junction, cardia adenocarcinoma
- OS improvement, 1975-77, 1984-86, 1999-2006
  - Gastric: 16% → 18% → 27%
  - Esophageal: 5% → 10% → 19%
- Highly virulent diseases with poor outcome

Jemal et al, CA 61: 212-236; 2011

University of Colorado Cancer Center

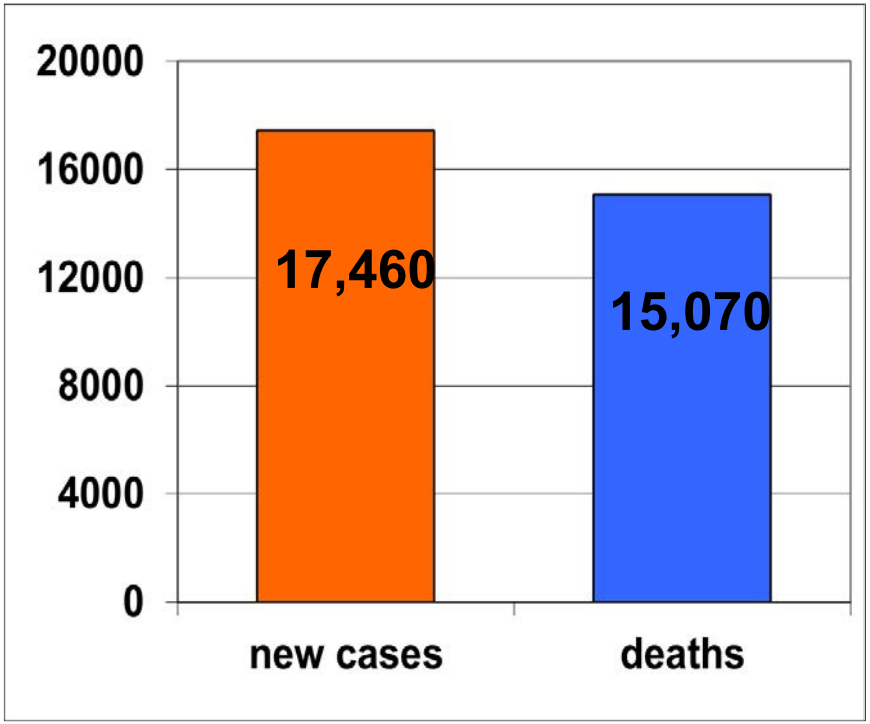
Worldwide



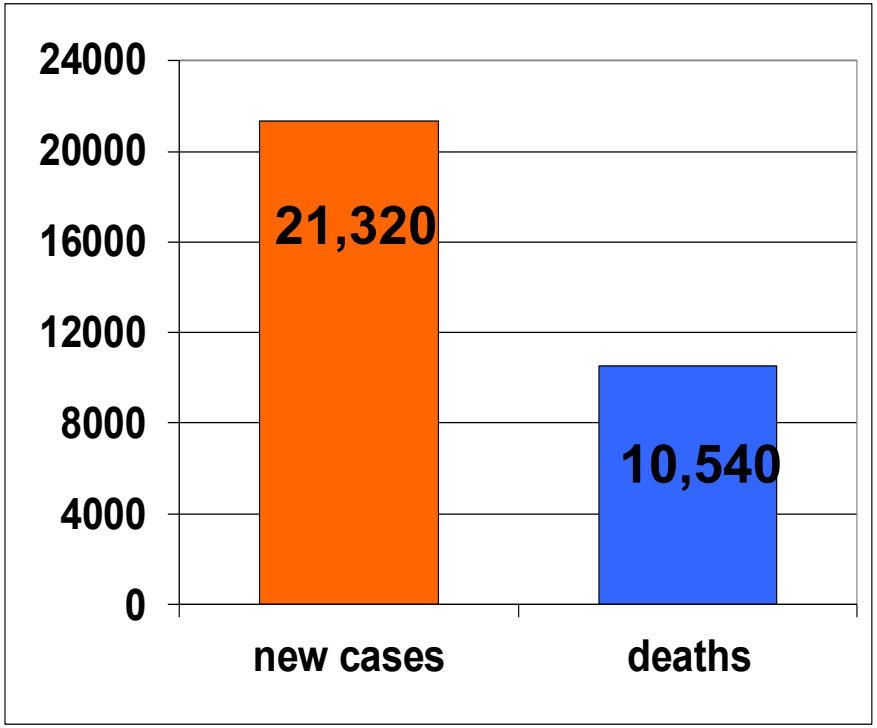
University of Colorado Cancer Center

Esophageal/Gastric Cancer Incidence / Mortality 2012

Esophageal Cancer



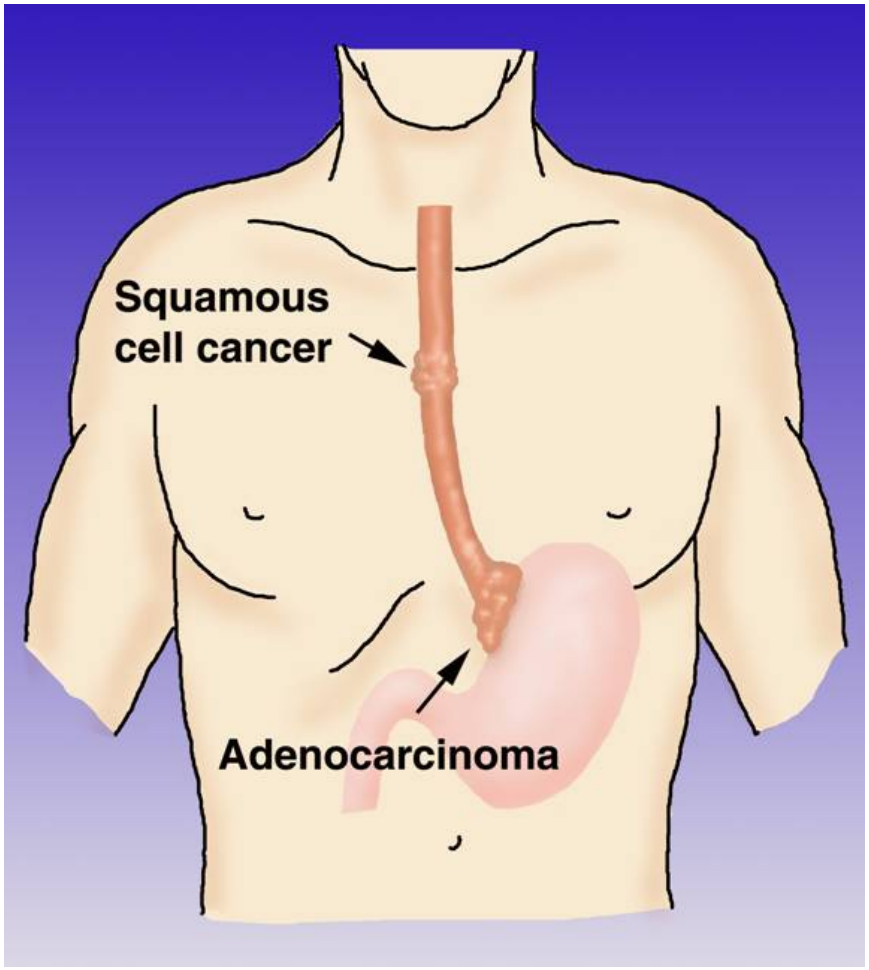
Stomach Cancer

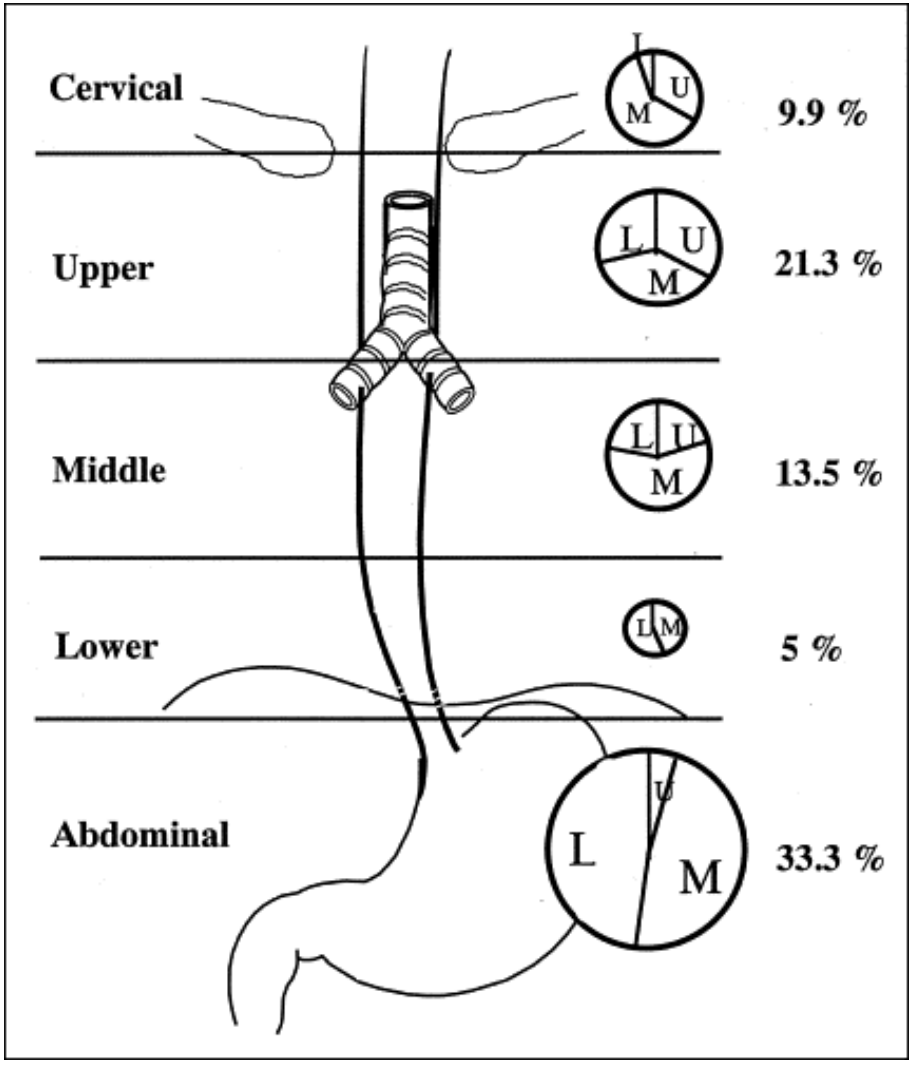


Ca Cancer J Clin 2012; 62: epub

University of Colorado
Cancer Center

Esophageal Cancer





University of Colorado Cancer Center

Confusing?

Squamous v. Adenocarcinoma
Esophageal v. GEJ v. Gastric

- Evolving incidence and pathology
- Variable incidence across globe
- Surgical technique
- Radiation technique
- Better staging…. EUS

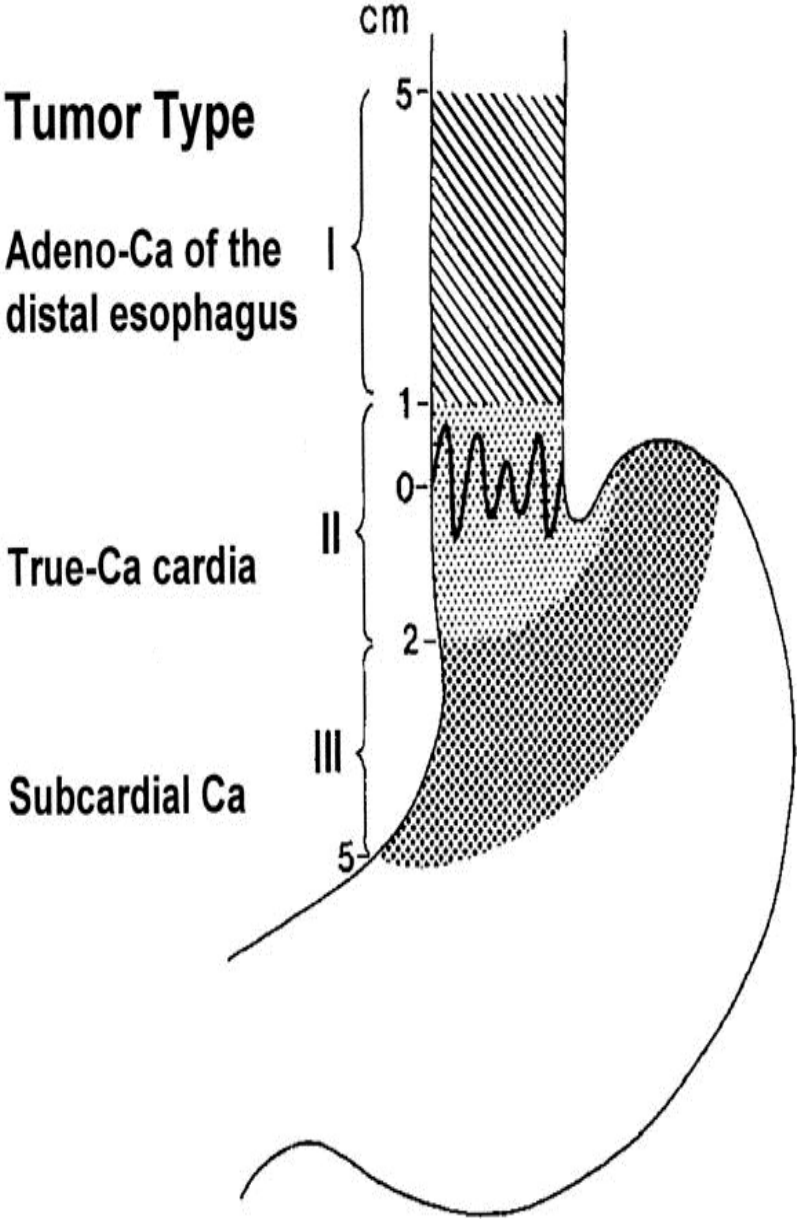
University of Colorado Cancer Center

Siewert Classification for GE Junction Adenocarcinoma

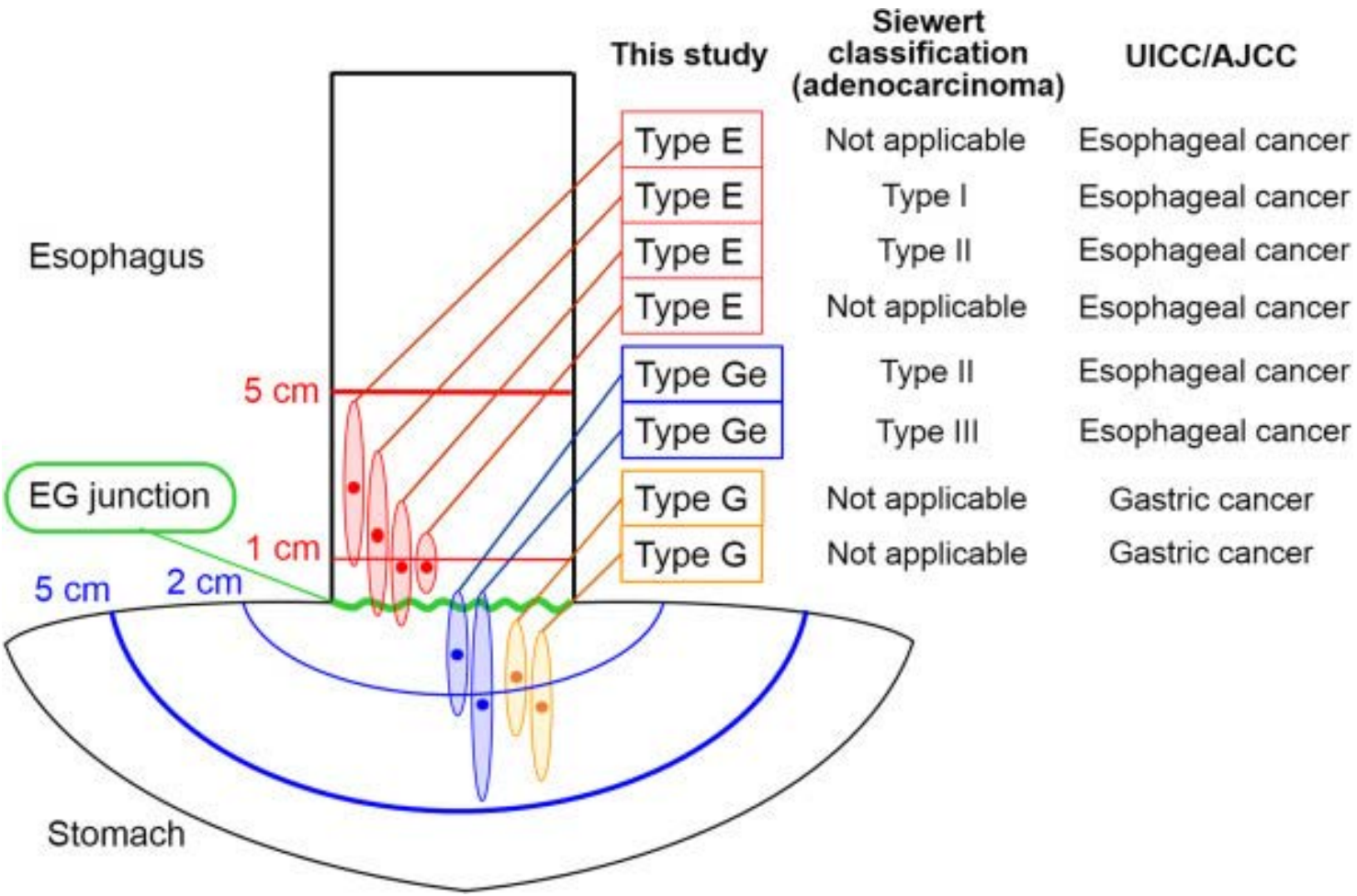
- Siewert I, in esophagus, growing down to GE junction
- Siewert II, "at GE junction"
- Siewert III, in Cardia of stomach, growing up into esophagus

- Siewert III may act more like gastric cancer – and signet cells sometimes seen

- Siewert I most often associated with Barrett's esophagus



University of Colorado
Cancer Center



Cardia Cancers: two different etiologies??

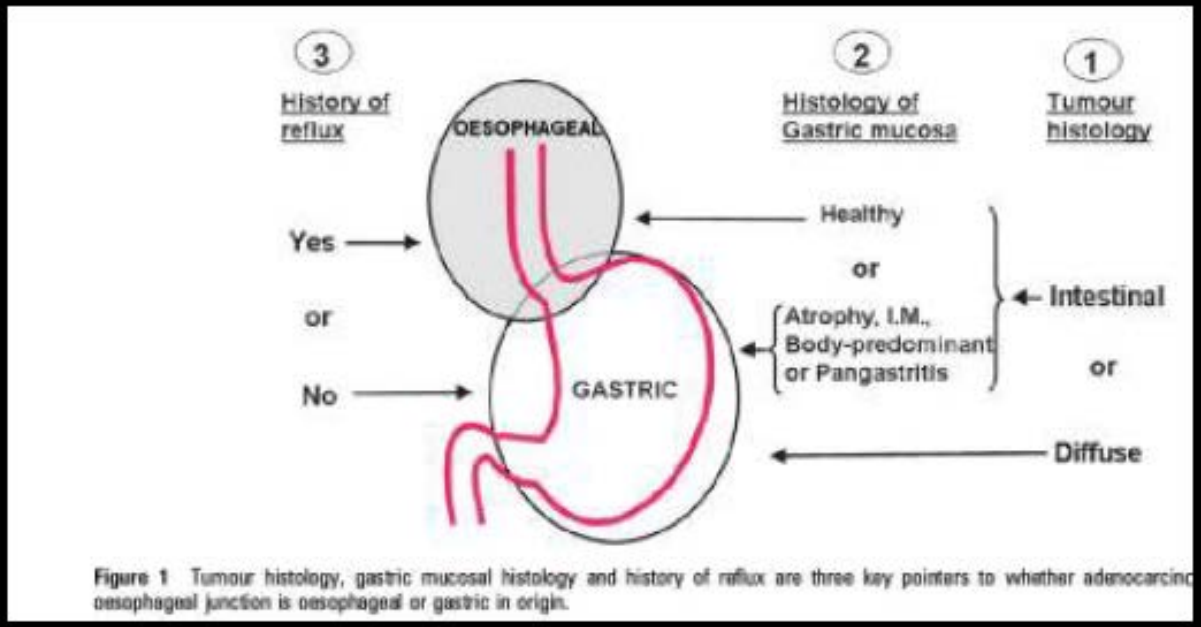


Figure 1 Tumour histology, gastric mucosal histology and history of reflux are three key pointers to whether adenocarcinc oesophageal junction is oesophageal or gastric in origin.

Key to differentiating type II is histology of the stomach well clear of the cancer

atrophy/H-pylori – gastric

healthy stomach, no H-pylori, reflux Sx - esophagus

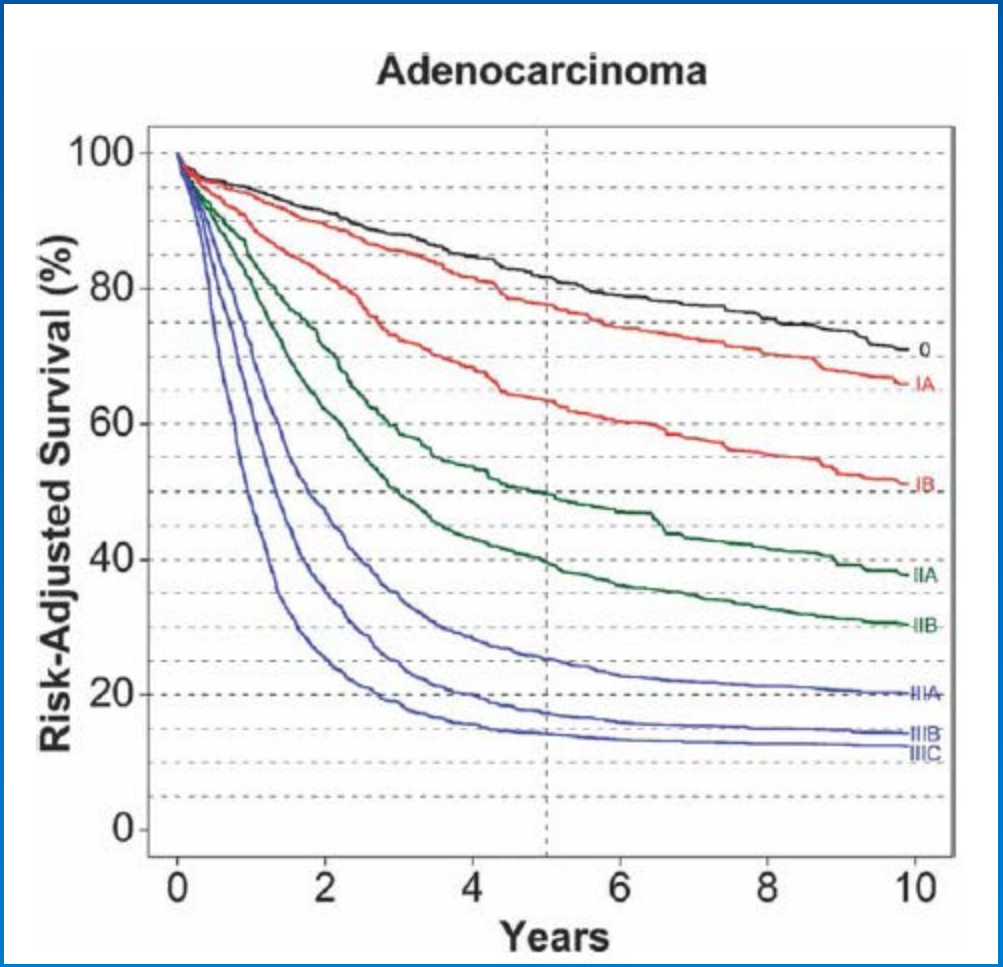
Gut March 2010 Vol 59 No 3

University of Colorado
Cancer Center

Esophagus Staging Form

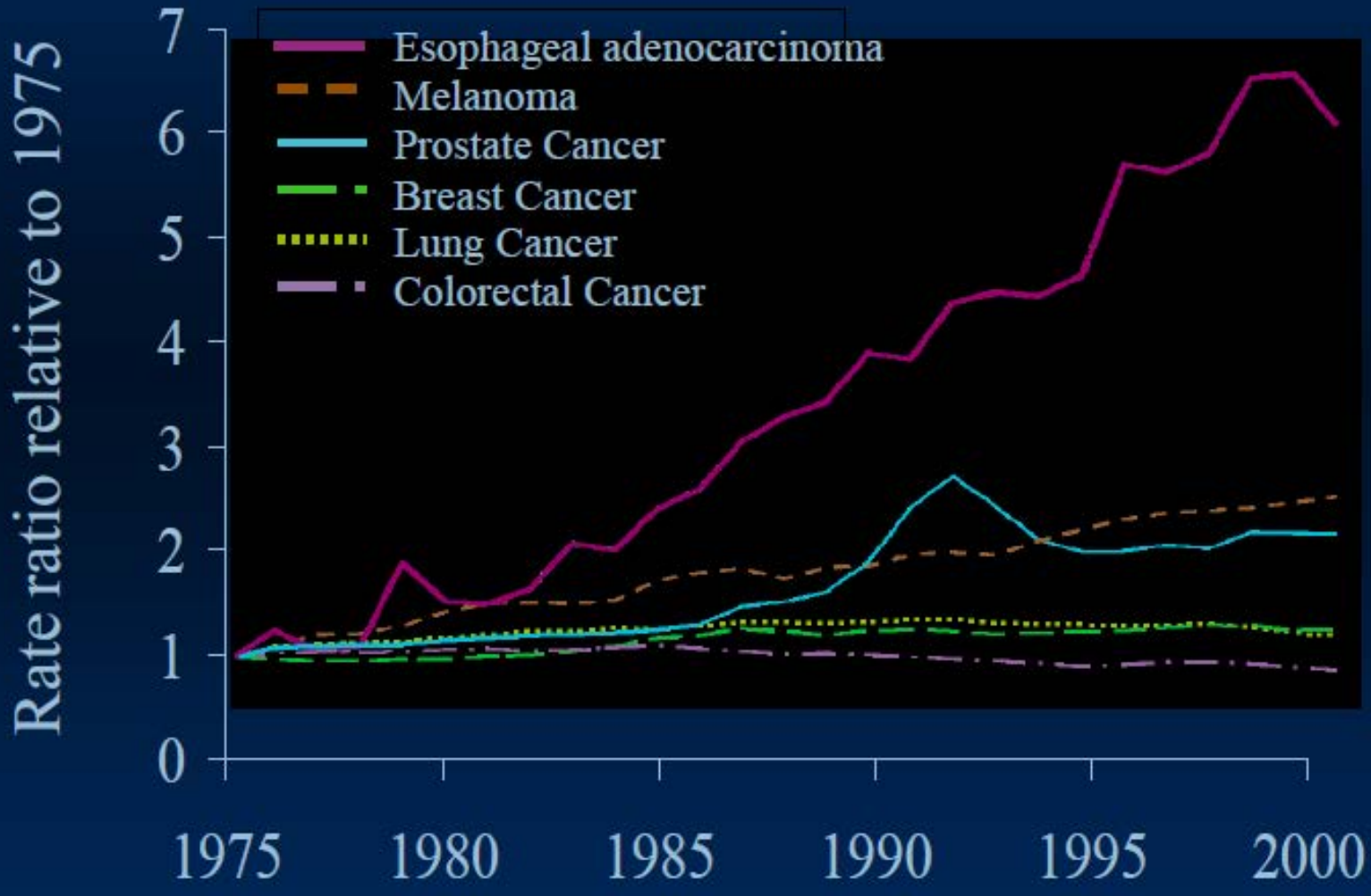
Clinical *Extent of disease before any treatment*	Stage Category Definitions	Pathologic *Extent of disease through completion of definitive surgery*
❒ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	**Tumor Size:** _____ **Laterality:** ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	Primary Tumor (T)	
❒ TX	Primary tumor cannot be assessed	❒ TX
❒ T0	No evidence of primary tumor	❒ T0
❒ Tis	High-grade dysplasia *	❒ Tis
❒ T1	Tumor invades lamina propria, muscularis mucosae, or submucosa	❒ T1
❒ T1a	Tumor invades lamina propria or muscularis mucosae	❒ T1a
❒ T1b	Tumor invades submucosa	❒ T1b
❒ T2	Tumor invades muscularis propria	❒ T2
❒ T3	Tumor invades adventitia	❒ T3
❒ T4	Tumor invades adjacent structures	❒ T4
❒ T4a	Resectable tumor invading pleura, pericardium, or diaphragm	❒ T4a
❒ T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.	❒ T4b
	*High-grade dysplasia includes all non-invasive neoplastic epithelium that was formerly called carcinoma *in situ*, a diagnosis that is no longer used for columnar mucosae anywhere in the gastrointestinal tract.	
	Regional Lymph Nodes (N)	
❒ NX	Regional lymph nodes cannot be assessed	❒ NX
❒ N0	No regional lymph node metastasis	❒ N0
❒ N1	Regional lymph node metastases involving 1 to 2 nodes	❒ N1
❒ N2	Regional lymph node metastases involving 3 to 6 nodes	❒ N2
❒ N3	Regional lymph node metastases involving 7 or more nodes	❒ N3
	Distant Metastasis (M)	
❒ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)	
❒ M1	Distant metastasis	❒ M1

New AJCC Staging: Survival in over 4600 pts with esophageal and GEJ cancer



Rice Cancer 2010

Relative Change in Incidence of Esophageal Adenocarcinoma and Other Malignancies



Pohl H and Welch HG. J Natl Cancer Inst 2005;95:142-146

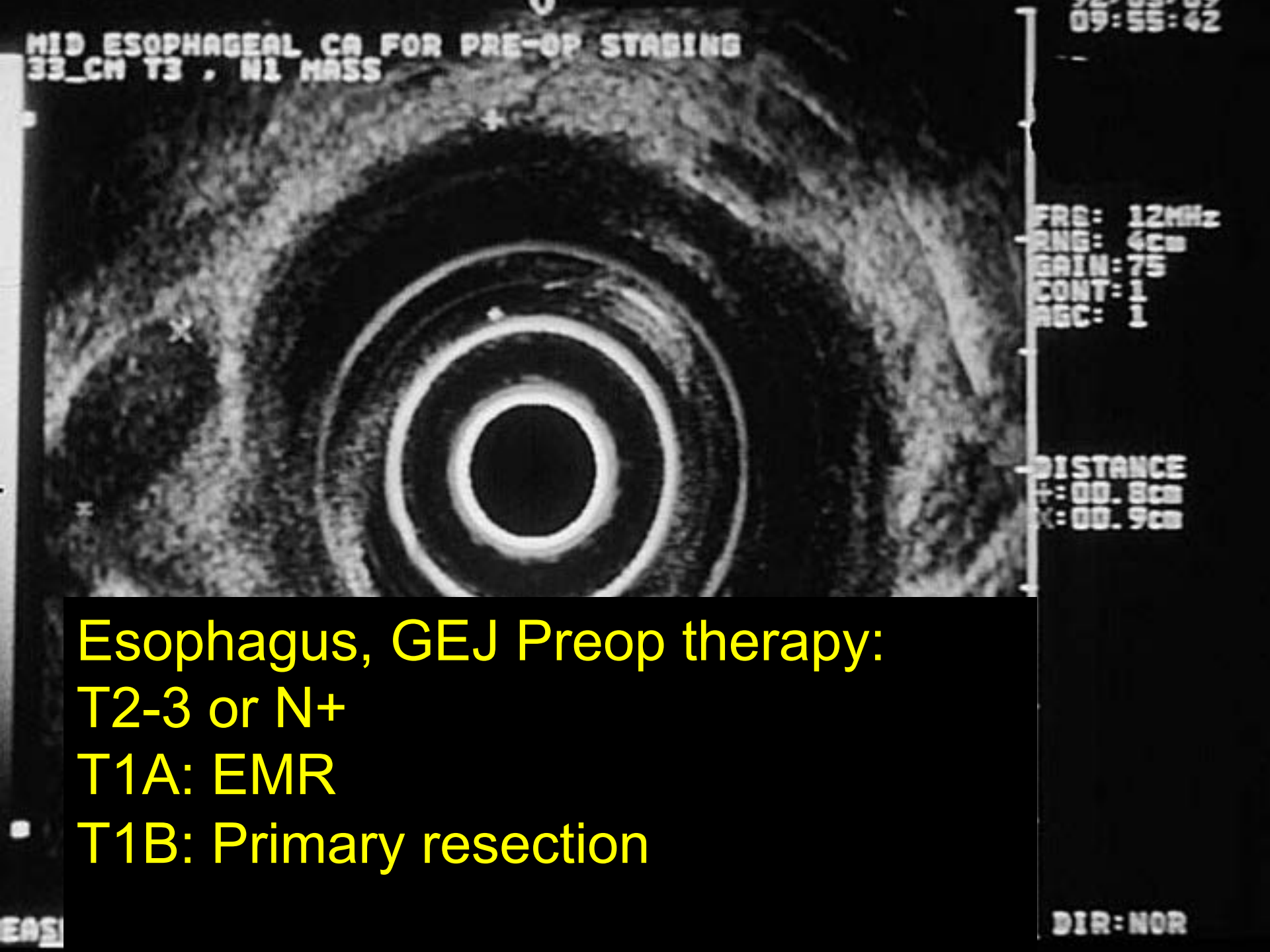
	Squamous Cell Carcinoma	Adenocarcinoma
Epidemiology	Declining	Rising and fast!
	“Esophageal Cancer Belt”	5W:1B 8M:1F
Risk Factors	Smoking & Alcohol	GERD
	N-nitroso compounds	Smoking
	Betel nut	Obesity
	Achalasia / caustic stricture	H Pylori protective
	Prior Gastrectomy	↑acid exposure / ↓ LES
	Atrophic gastritis	Cholecystectomy
	HPV	NSAID is protective
	Tylosis	
	Bisphosphates	
	SCC of the URTI	

Risk Factors of Esophageal Adenocarcinoma

- GERD →Barrett's metaplasia → Esophageal AdenoCa
- Smoking (2.08 X)
- Obesity (OR 2.78 if BMI > 30kg/m2)
- High serum EGF
- H. Pylori infection maybe beneficial! (OR 0.52)
- Increased esophageal acid exposure (Zollinger Ellison syndrome)
- Use of drugs that lower ES pressure: Nitroglycerin, anticholinergics, beta adrenergic agonists, aminophylline, benzodiazepines
- Cholecystectomy… increase in reflux
- Nitroso compounds
- Possible protective effective of cereal fibers & NSAID

Esophageal Cancer – Clinical Features

- Dysphagia (Solid → Liquid)
- Weight loss
- Anemia
- Hoarseness
- Aspiration pneumonia
- Odynophagia
- Tracheobronchial fistulas (mainly SCC)



Esophagus, GEJ Preop therapy:

T2-3 or N+

T1A: EMR

T1B: Primary resection

Gastric Ca Intestinal type

- **Precursor lesions:**
  - Progression from chronic gastritis to chronic atrophic gastritis, to intestinal metaplasia, dysplasia, and eventually to adenocarcinoma
- **Usually presents as ulcerated masses**
- **Cardia cancers are biologically more aggressive with a worse prognosis, stage for stage, than distal cancers.**
- **Gene expression studies: Respond better to 5FU and oxaliplatin?**

Gastric Ca Diffuse type

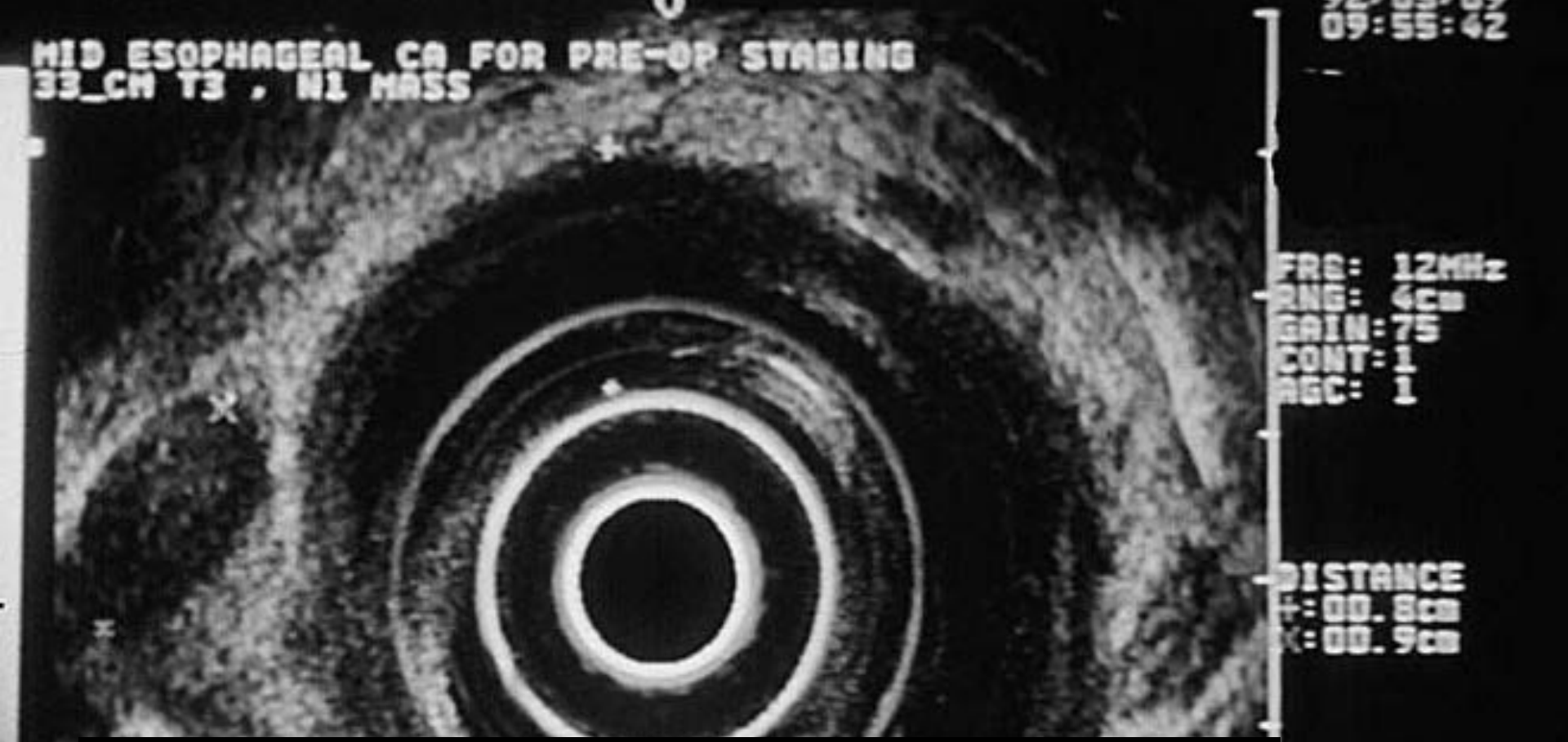
- There is no clearly defined precancerous lesion.
- Defective intercellular adhesion molecules therefore, there is an inability for cells to form glands or tubules
  - Loss of E-Cadherin
- Highly metastatic and characterized by rapid disease progression and poor prognosis.
- Linitis plastica = rigid thickened stomach
- Mutations in E-cadherin gene (CDH1)
- Gene expression studies: Respond better to Cisplatin?

Risk Factors – Gastric Ca

- **Diet**
  - High salt intake and salt-preserved food
  - Nitroso Compounds (Nitrates → Nitrites)
  - Fruits & vegetables are protective
- **Obesity (OR 1.22-1.55 for BMI >25)**
- **Smoking (OR 2 -2.2)**
- **H. Pylori (mainly intestinal type)**
  - Worse with high salt intake
  - Protective effect of NSAID
- **EBV (2-16% of all gastric cancers)**
- **Alcohol**
- **Socioeconomic status (Low = Low, High = High)**
- **Gastric surgery (RR 1.5-3)**
- **Reproductive hormones – Protective effective for women?**

Host Risk Factors

- **Blood Group ("A" have 20% higher incidence)**
- **Familial Predisposition**
  - H. Pylori infection
  - Chronic atrophic gastritis
  - Syndromes: HNPCC, FAP, Peutz Jegher
  - Hereditary diffuse gastric cancer (CDH1 mutations)
- **Genetic polymorphisms: IL-1B, Interferon gamma receptor**
- **Gastric Polyps**
- **Hypertrophic gastropathy and immunodeficiency sydromes**
- **Gastric ulcer – common risk factor as Ca?**
- **Pernicious Anemia**



Gastric Cancer Preop therapy:

T2-3 or N+

T1A: EMR

T1B, T2: Primary resection

Laparoscopy in Gastric Cancer

- **CT and PET scan may miss small volume liver or peritoneal disease**
- **For gastric cancer, laparoscopy detects peritoneal or liver disease in 20-30% of patients**
  - Not mandated for GEJ cancers: < 5% positive lap findings
- **A positive cytology = Stage IV disease**
  - Patients do not benefit from immediate gastrectomy
  - They should be treated with palliative chemotherapy
  - ? Reassess response and consider selective surgery
    - No long term survivors with + cytology

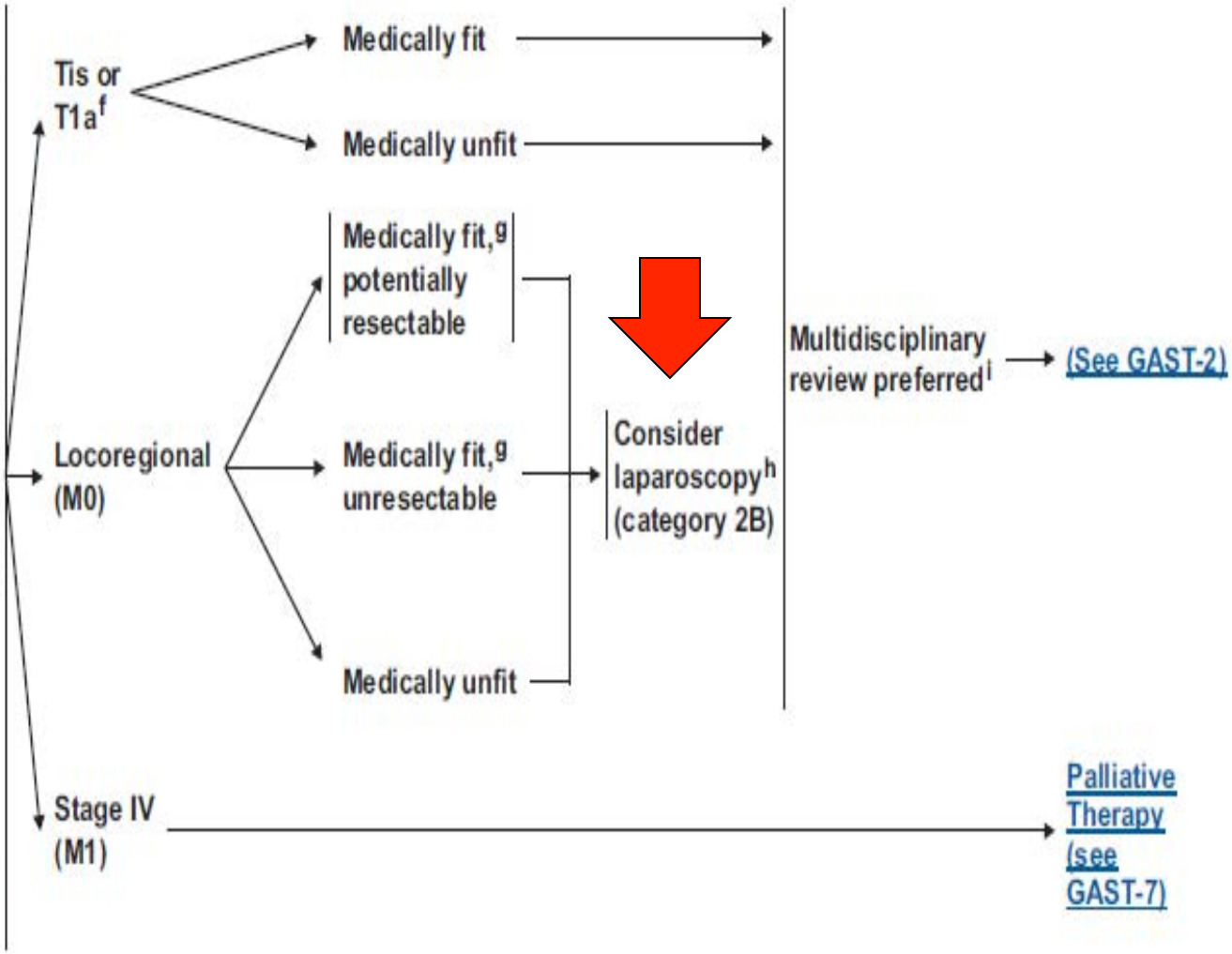
NCCN Guidelines Version 1.2013
Gastric Cancer

WORKUP

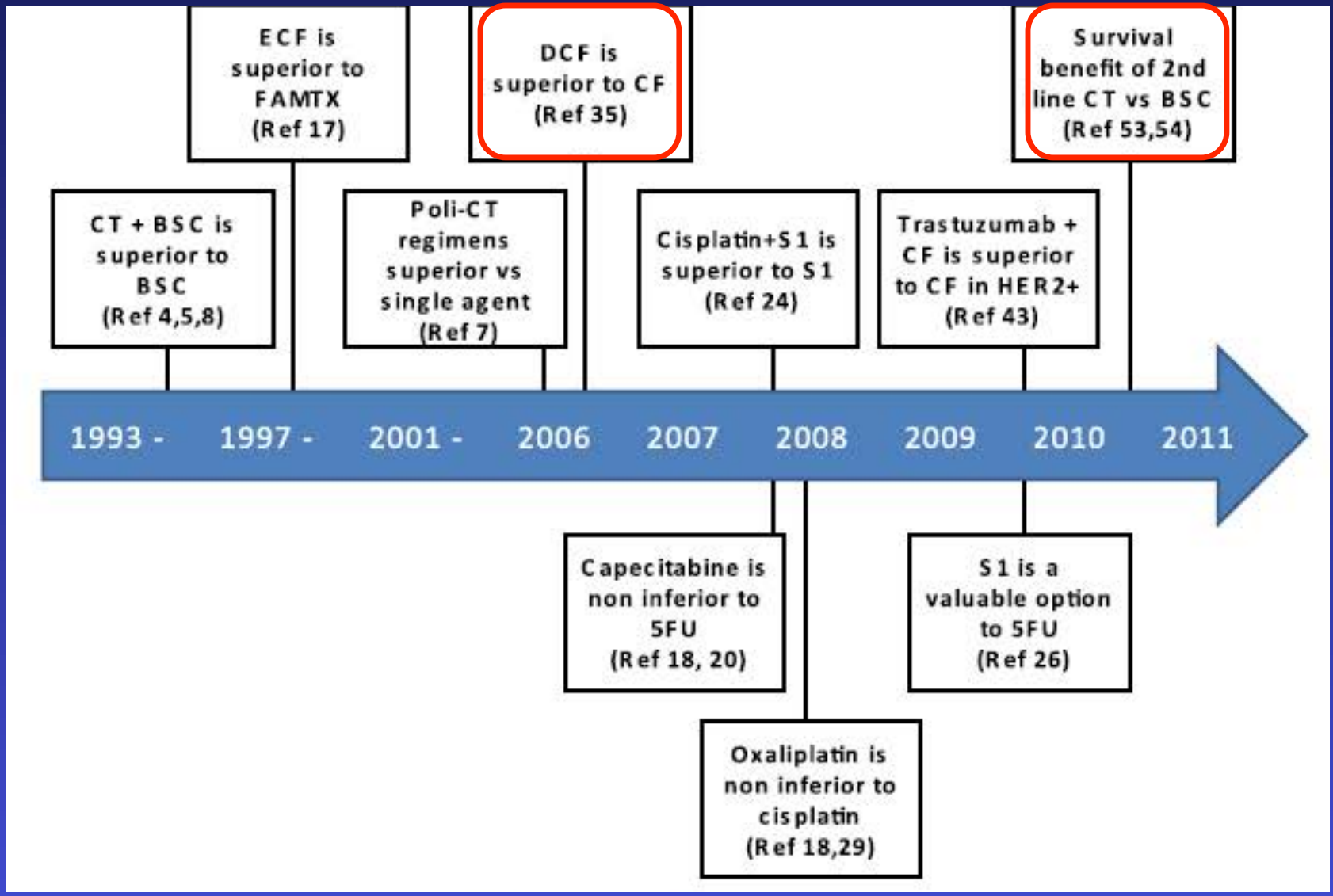
- H&P
- Upper GI endoscopy and biopsy[a]
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT as clinically indicated
- PET-CT evaluation if no evidence of M1 disease[b]
- CBC and chemistry profile
- Endoscopic ultrasound (EUS) if no evidence of M1 disease (preferred).
- Endoscopic mucosal resection (EMR) may contribute to accurate staging of early stage cancers[c]
- Nutritional assessment and counseling
- Biopsy of metastatic disease as clinically indicated
- HER2-neu testing if metastatic adenocarcinoma is documented/ suspected[d]
- Smoking cessation advice, counseling and pharmacotherapy[e]

CLINICAL STAGE

ADDITIONAL EVALUATION



Key Discoveries in Gastric Cancer



Cervantes, Cancer Treatment Reviews 2013

H. pylori
Esophageal vs. Gastric Cancer

Serologic test results†	Case subjects, N (%)	Control subjects, N (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)‡
		Noncardia gastric cancer		
H. pylori negative	12 (7)	43 (25)	1.00 (referent)	1.00 (referent)
H. pylori positive				
CagA-negative strains	51 (29)	44 (25)	5.05 (2.11 to 12.07)	6.55 (2.31 to 18.53)
CagA-positive strains	110 (64)	86 (50)	5.64 (2.47 to 12.88)	8.93 (3.27 to 24.40)
		Gastric cardia cancer		
H. pylori negative	25 (41)	15 (25)	1.00 (referent)	1.00 (referent)
H. pylori positive				
CagA-negative strains	11 (18)	24 (39)	0.34 (0.14 to 0.85)	0.21 (0.06 to 0.81)
CaA-positive strains	25 (41)	22 (36)	0.81 (0.35 to 1.85)	0.43 (0.12 to 1.52

Kamangar F et al. J Natl Cancer Inst. 2006;

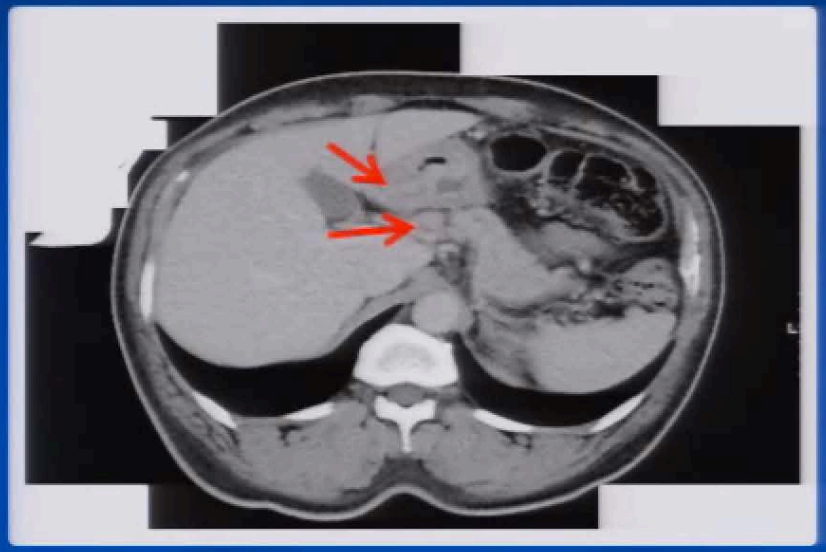
Case Presentation

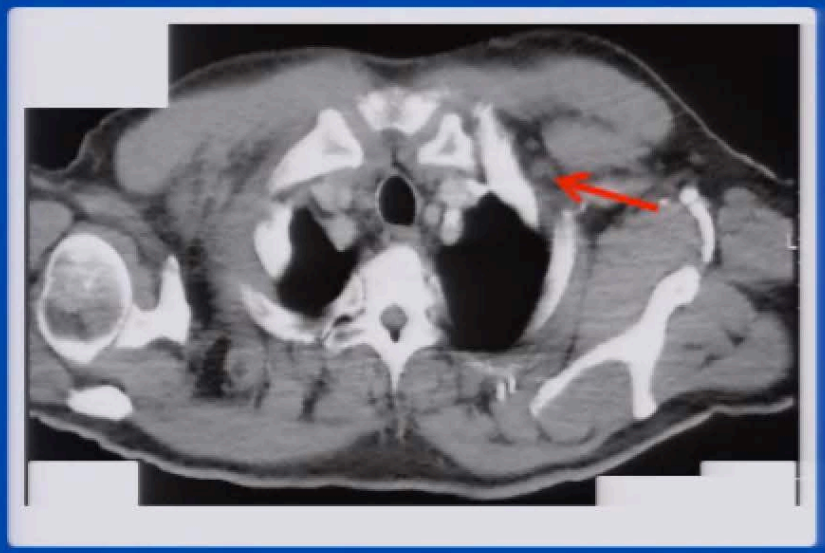
- 50 year old man presents with epigastric discomfort, early satiety and 5kg weight loss
- Endoscopy demonstrates ulcerated lesion at pylorus
- Biopsy consistent with moderately differentiated adenocarcinoma. Her-2 negative
- EUS confirms T3N1 lesion
- Past medical history hypertension, hypercholesterolemia
- ECOG PS=1

Case presentation – gastric cancer

Thickening of gastric antrum

Peri-gastric lymph node 17mm





Enlarged lymph node in left supraclavicular fossa

What would you do next?

1. Assume the supraclavicular lymph node represents advanced disease and proceed with palliative treatment
2. Assume the supraclavicular lymph node does not represent advanced disease and proceed with radical treatment
3. Biopsy the left supraclavicular lymph node
4. PET-CT

PET/CT for Gastric Cancer Staging

J Korean Surg Soc. 2011 Aug;81(2):104-10. doi: 10.4174/jkss.2011.81.2.104. Epub 2011 Aug 3.

F18-fluorodeoxyglucose-positron emission tomography and computed tomography is not accurate in preoperative staging of gastric cancer.

Ha TK, Choi YY, Song SY, Kwon SJ.

Department of Surgery, Hanyang University College of Medicine, Seoul, Korea.

Abstract

PURPOSE: To investigate the clinical benefits of F18-fluorodeoxyglucose-positron emission tomography and computed tomography ((18)F-FDG-PET/CT) over multi-detector row CT (MDCT) in preoperative staging of gastric cancer.

METHODS: FDG-PET/CT and MDCT were performed on 78 patients with gastric cancer pathologically diagnosed by endoscopy. The accuracy of radiologic staging retrospectively was compared to pathologic result after curative resection.

RESULTS: Primary tumors were detected in 51 (65.4%) patients with (18)F-FDG-PET/CT, and 47 (60.3%) patients with MDCT. Regarding detection of lymph node metastasis, the sensitivity of FDG-PET/CT was 51.5% with an accuracy of 71.8%, whereas those of MDCT were 69.7% and 69.2%, respectively. The sensitivity of (18)F-FDG-PET/CT for a primary tumor with signet ring cell carcinoma was lower than that of (18)F-FDG-PET/CT for a primary tumor with non-signet ring cell carcinoma (35.3% vs. 73.8%, $P < 0.01$).

CONCLUSION: Due to its low sensitivity, (18)F-FDG-PET/CT alone shows no definite clinical benefit for prediction of lymph node metastasis in preoperative staging of gastric cancer.

PMID: 22066108 [PubMed] PMCID: PMC3204564 **Free PMC Article**

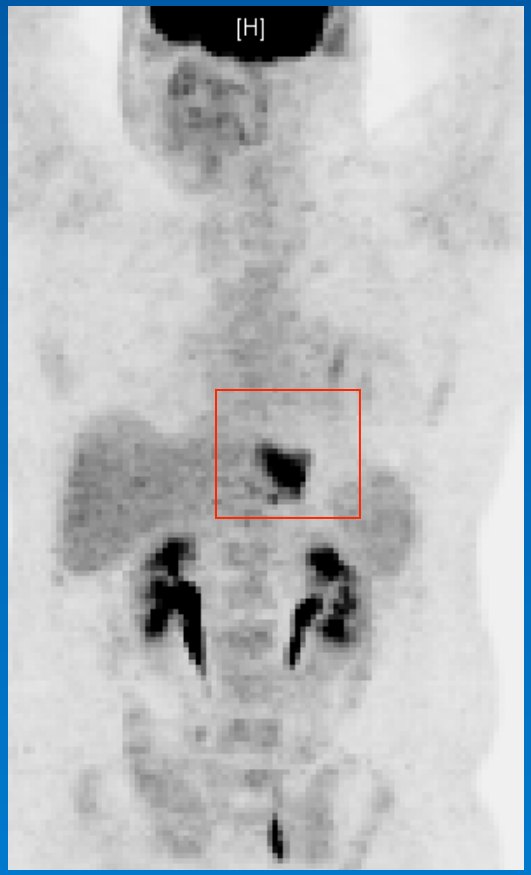
Value of PET Esophageal vs. Gastric Cancer

	Primary (sensitivity)	Metastases (undetected)
Esophageal	**> 95%**	**20%**
Gastric	**~ 65%**	**10%**

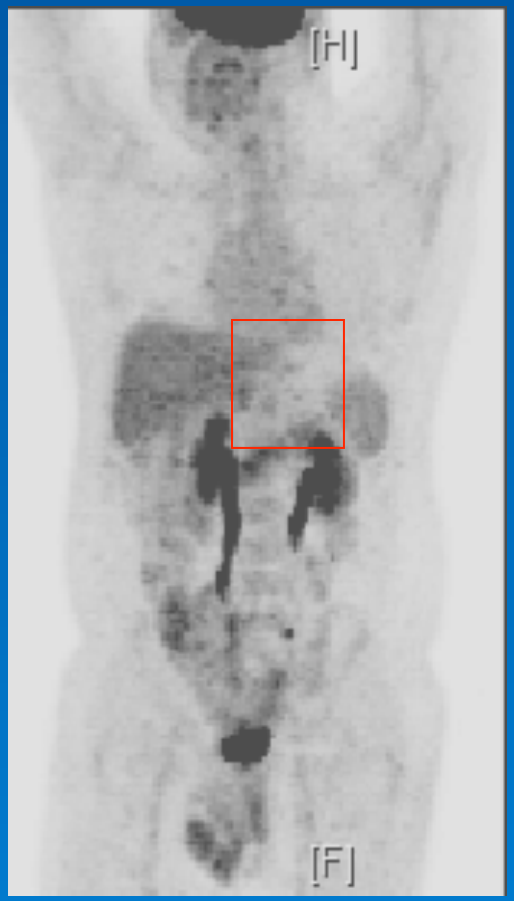
Heeren PA et al. J Nucl Med. 2004

Smyth E et al. Cancer 2012

PET SCAN:
Staging (15% occult mets), and Determine Response to Preop Chemo



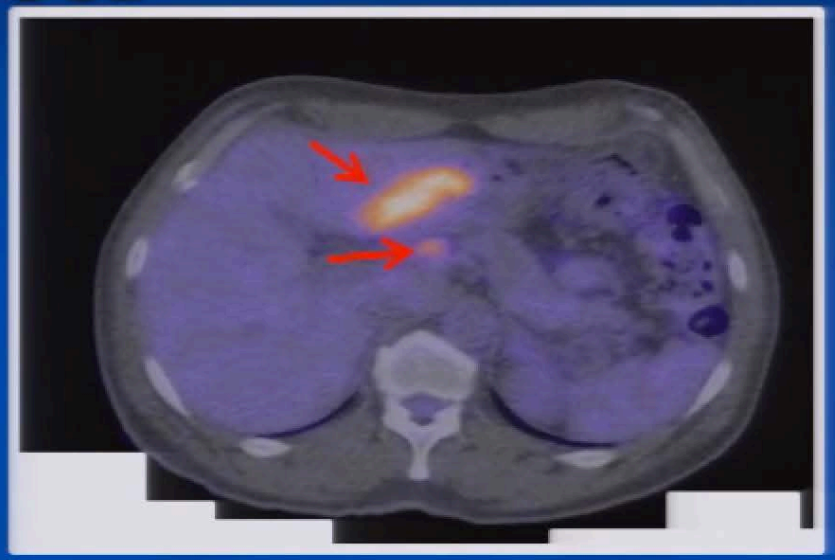
SUV = 10.6

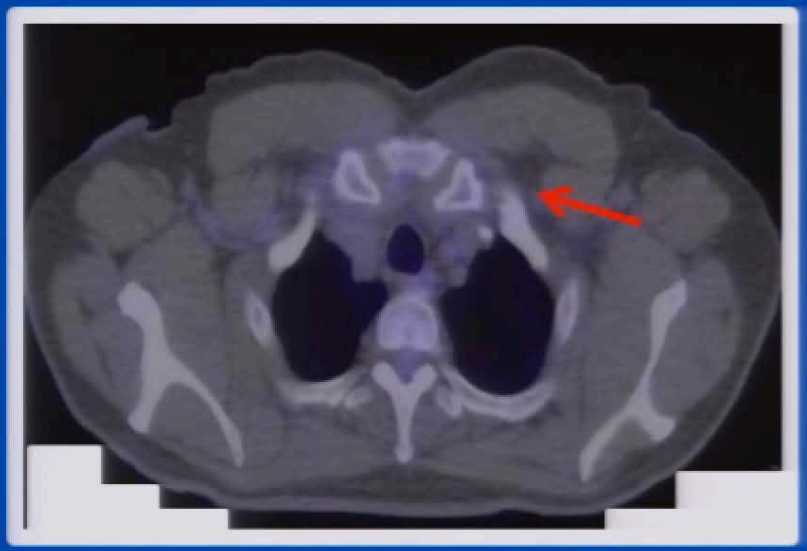


SUV = 2.2

Case presentation – gastric cancer

FGD avid lesions at gastric antrum and local lymph nodes





No increased uptake in left supraclavicular fossa lymph node

Case Study

- Biopsy of the lymph node was negative
- Laproscopic evaluation did not reveal and peritoneal metastases.

What would you do next?

1. Peri-operative chemotherapy
2. Pre-operative chemoradiotherapy
3. Proceed to surgery

Case Study

- Following a MDT discussion, a decision is made to offer the patient peri-operative chemotherapy.

Which peri-operative chemotherapy would you choose?

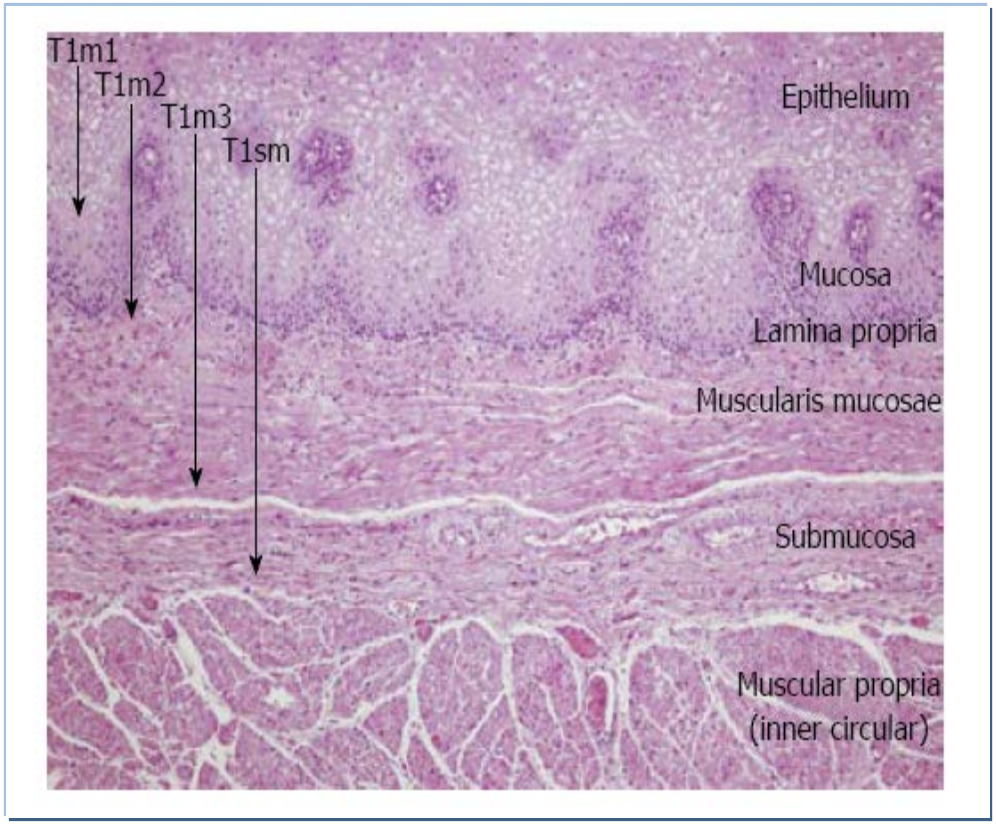
1. ECX
2. EOX
3. Cisplatin / 5-FU
4. FOLFOX
5. Something else

University of Colorado Cancer Center

Case 2 - Early Esophageal

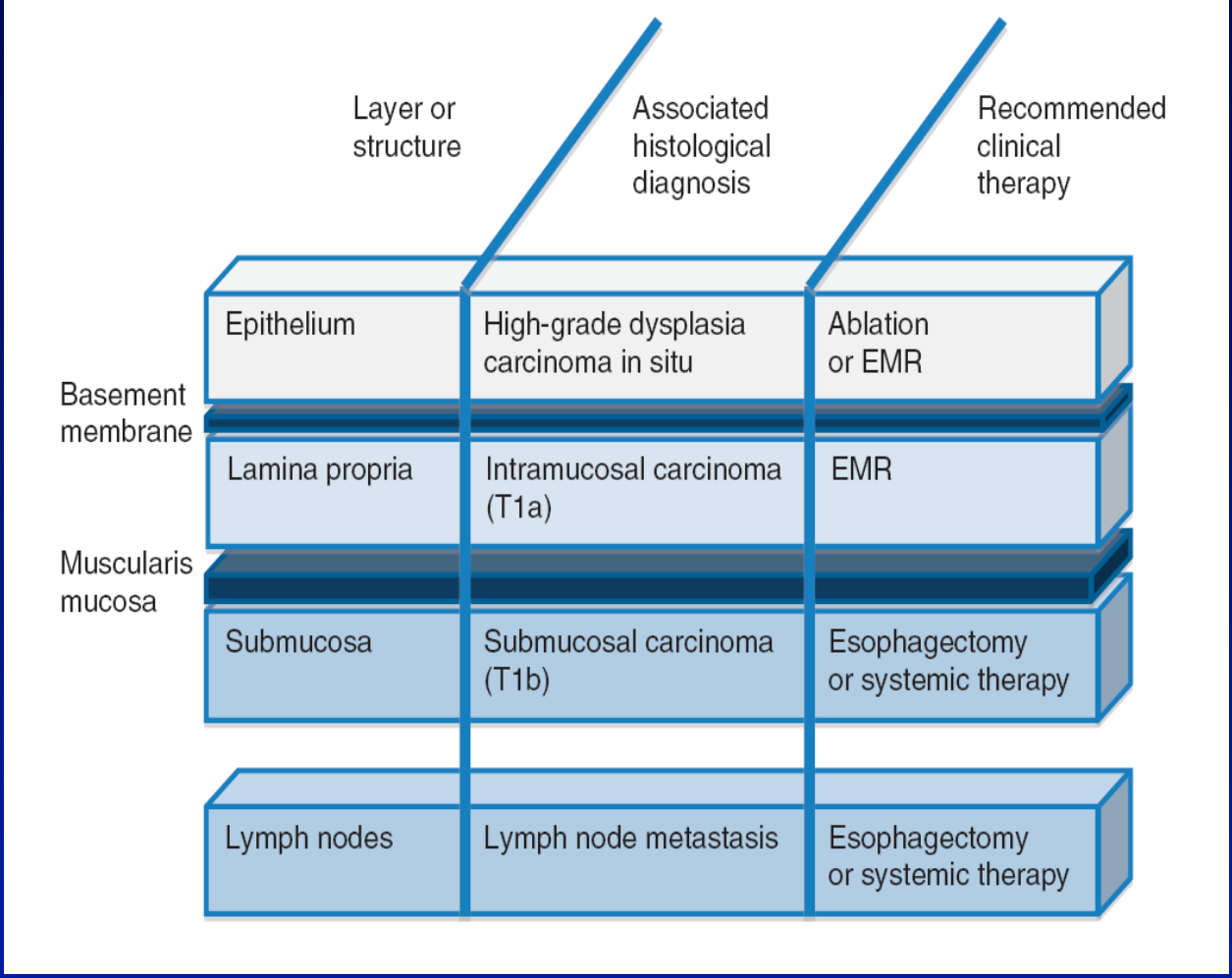
- 52 yo M colleague with long-standing GERD your tells you he was recently dx'ed with Barrett's esophagus with High Grade Dysplasia. EUS confirmed no invasion and no suspicious lymph nodes.
- He met with a surgeon who told him he will require distal esophagectomy.
- What would you recommend?

Esophageal Malignancy
Depth of Invasion



Ortiz-Fernando-Sorto J et al. World J Gastrointest Endosc. 2011

Esophageal Malignancy Histology Dictating Therapy



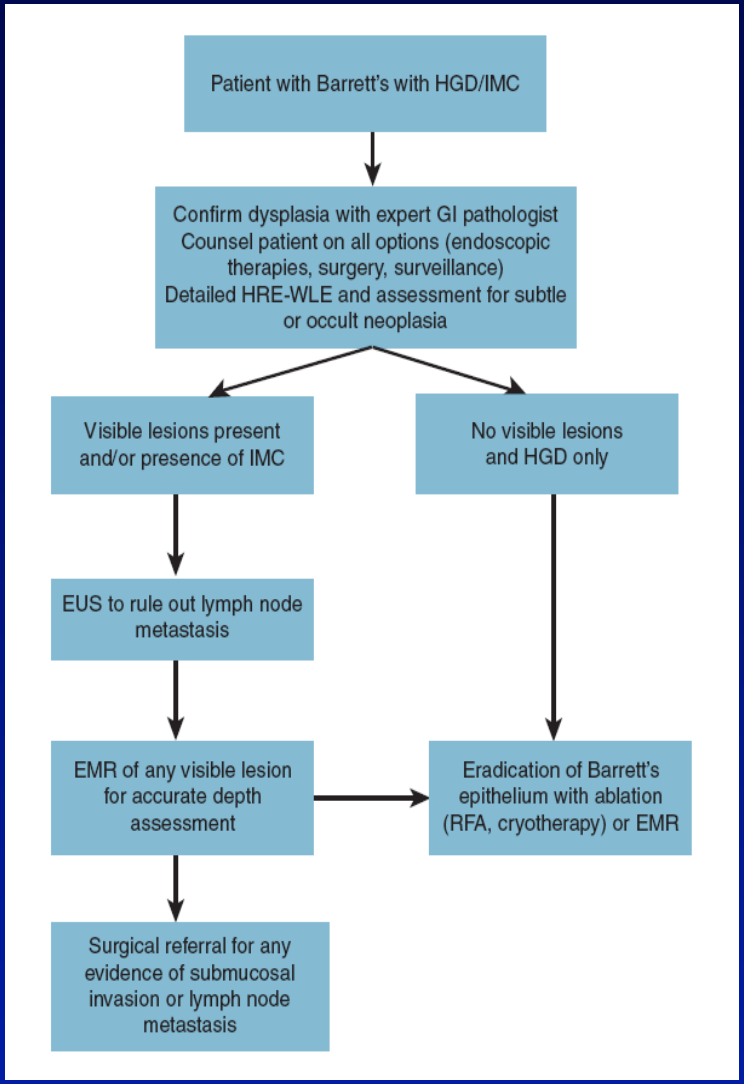
Konda VJ et al.Am J Gastroenterol. 2012

Endoscopic Mucosal Resection Barrett's Esophagus

Author	*n*	Complete regression of intestinal metaplasia (%)	Complete regression of dysplasia/esophageal cancer (%)	Sessions (%)	Recurrence (%)	Progression (%)	Follow-up (mo)
Seewald *et al*[65], 2003	12	100	100	2.5	0	0	9
Giovannini *et al*[66], 2004	21	75	86	2	14	0	18
Peters *et al*[67], 2006	39	89	95	3	0	0	11
Larghi *et al*[68], 2007	24	87	100	1.8	4	0	28
Lopes *et al*[69], 2007	41	76	90	1.5	12	0	31.6
Chennat *et al*[60], 2009	49	97	100	2.1	0	0	17
Moss *et al*[54], 2010	35	97	97	2	0	0	31
Pouw *et al*[63], 2010	169	97.6	85.2	2	1.8	0.6	27

Ortiz-Fernando-Sorto J et al. World J Gastrointest Endosc. 2011

“Early” Esophageal Cancer Treatment Algorithm



Konda VJ et al.Am J Gastroenterol.

University of Colorado
Cancer Center

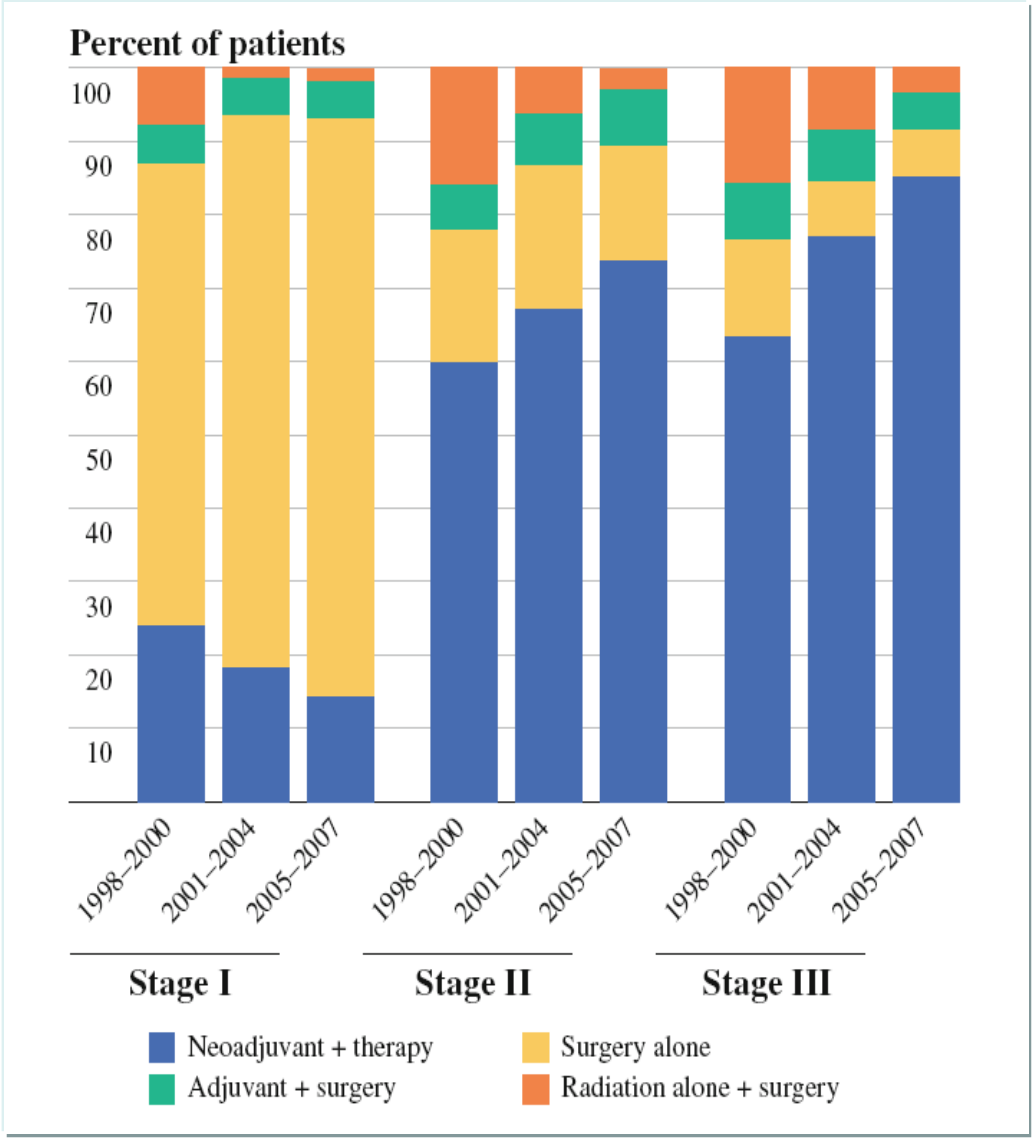
Key Trials

- CROSS
- McDonald
- MAGIC
- REAL
- ToGA

University of Colorado Cancer Center

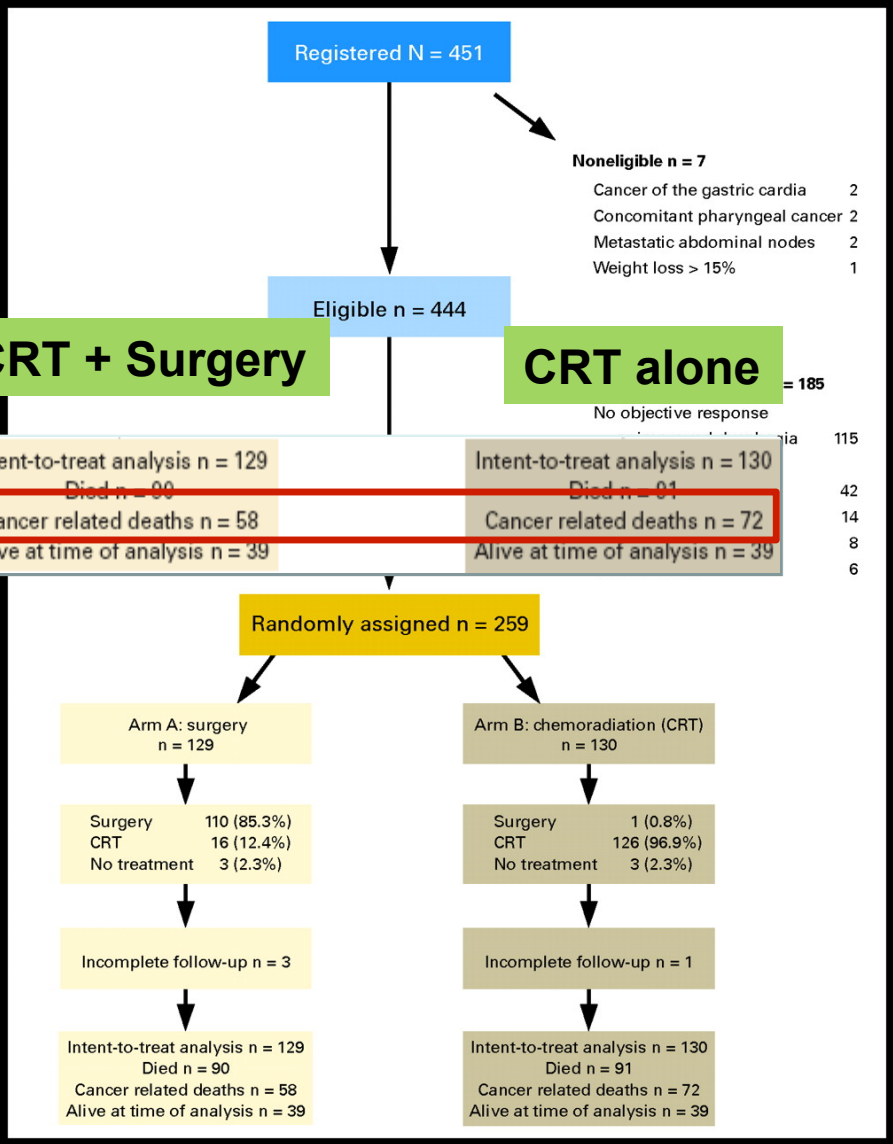
Esophageal Cancer - Neoadjuvant Therapy Trends in Utilization

Neoadjuvant + surgery



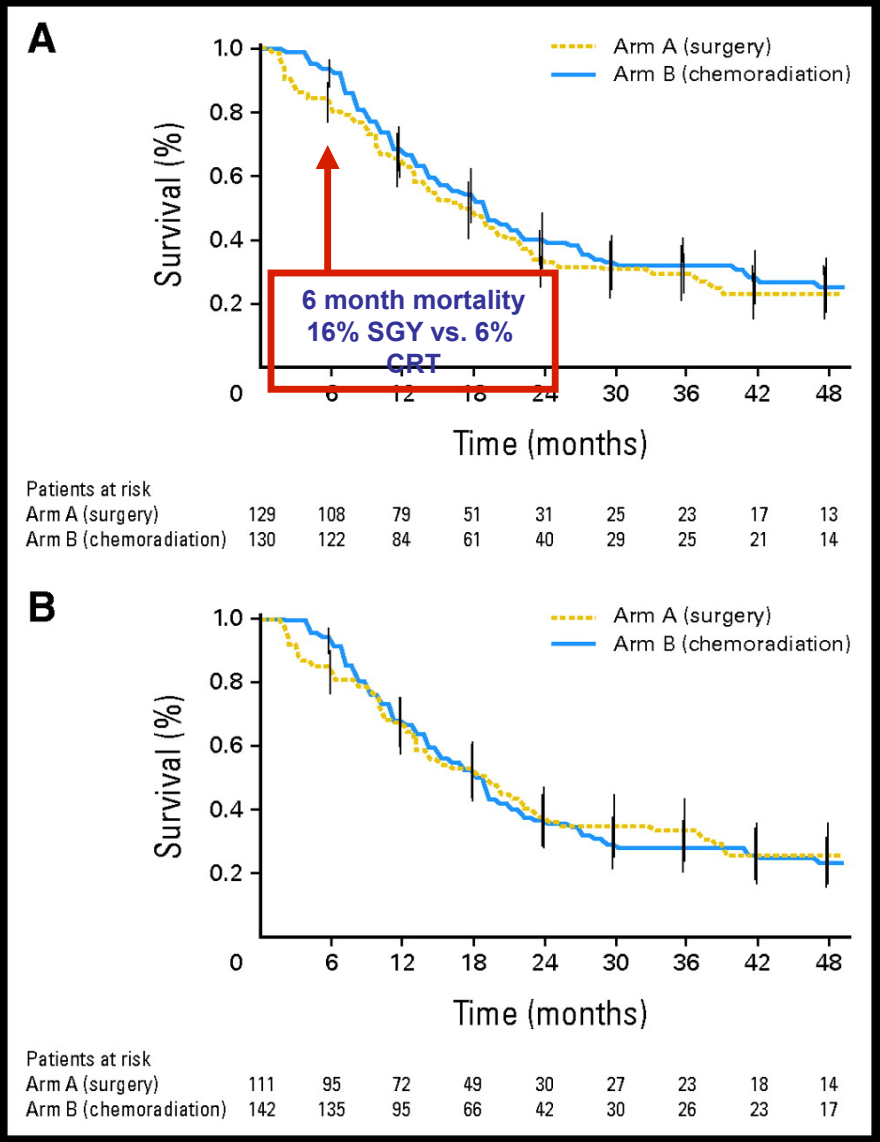
Merkow RP et al. Ann Surg Oncol. 2012

Esophageal Cancer – Squamous Cell CA
Role of Surgery



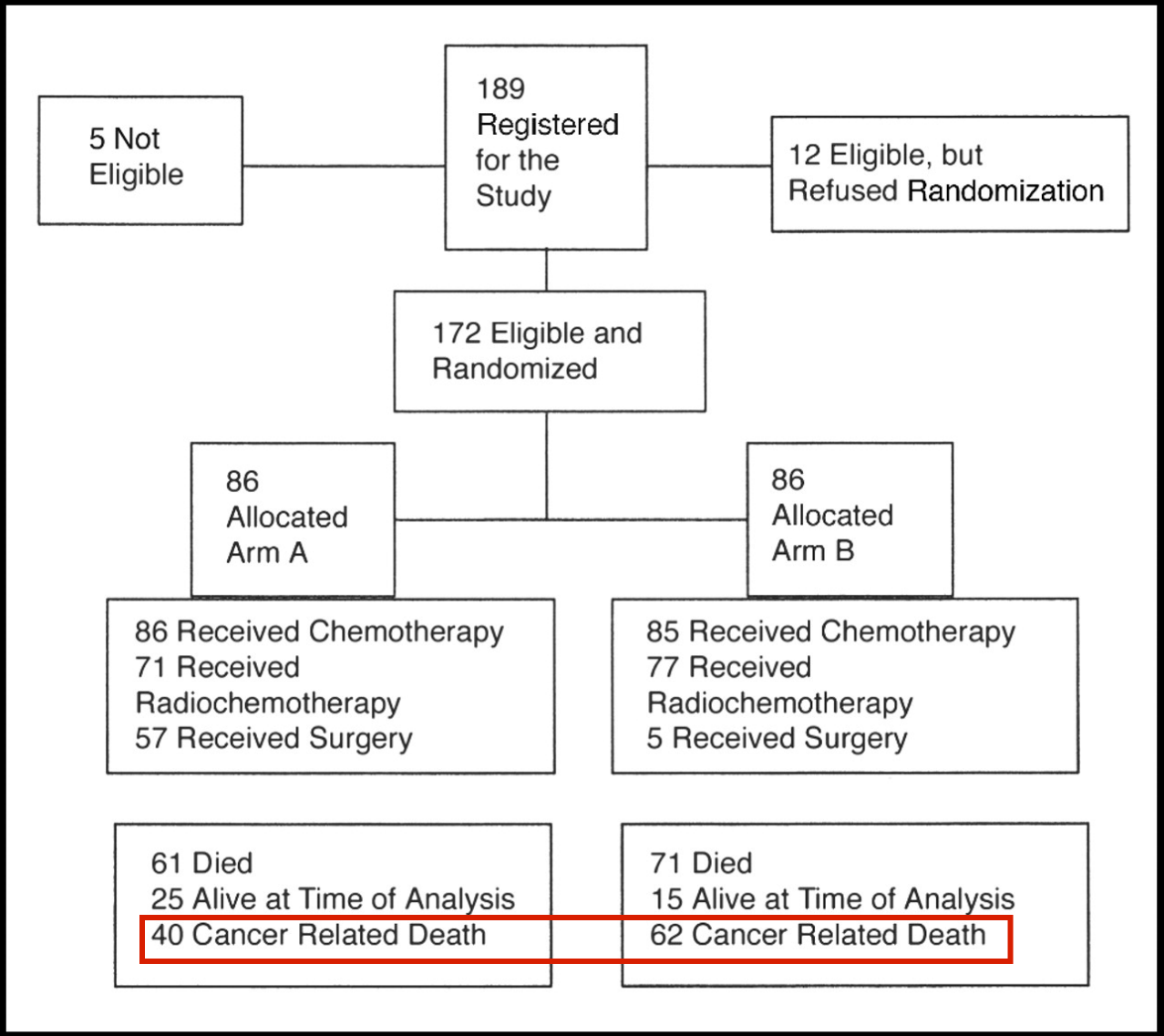
Bedenne, L. et al. J Clin Oncol; 25:1160-1168 2007

Esophageal Cancer – Squamous Cell CA
Role of Surgery



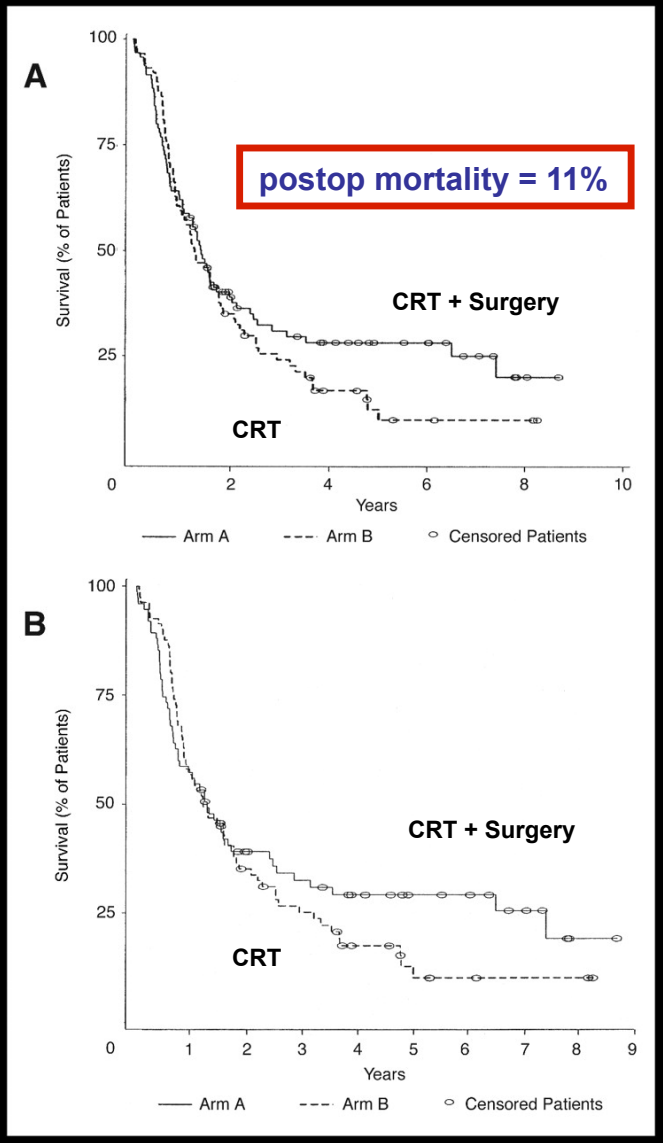
Bedenne, L. et al. J Clin Oncol; 25:1160-1168 2007

Esophageal Cancer – Squamous Cell CA
Role of Surgery



Stahl, M. et al. J Clin Oncol; 23:2310-2317 2005

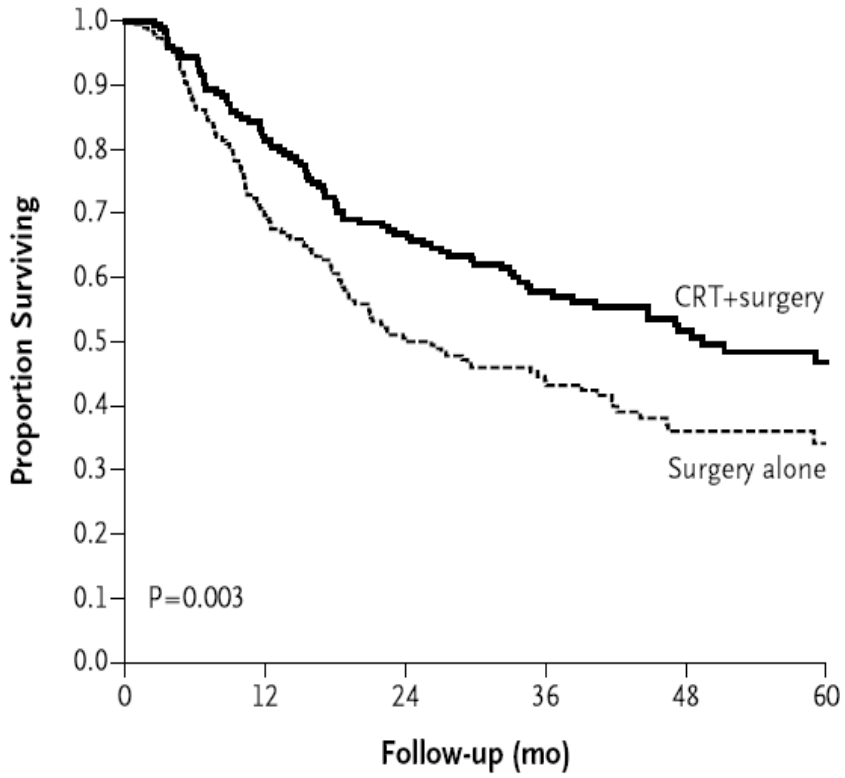
Esophageal Cancer – Squamous Cell CA
Role of Surgery



Stahl, M. et al. J Clin Oncol; 23:2310-2317 2005

Preoperative Chemoradiotherapy CROSS Trial

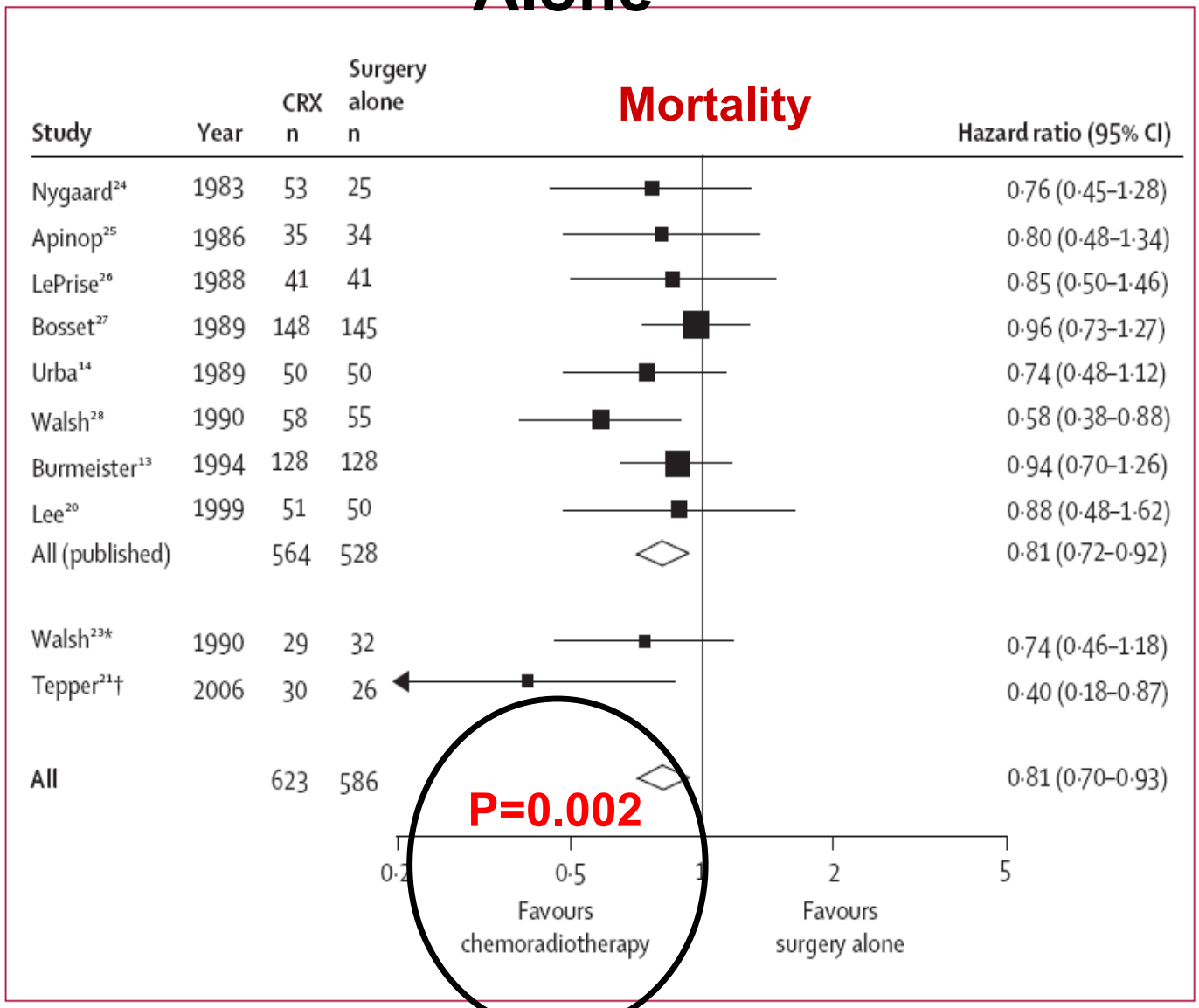
A Survival According to Treatment Group



No. at Risk						
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

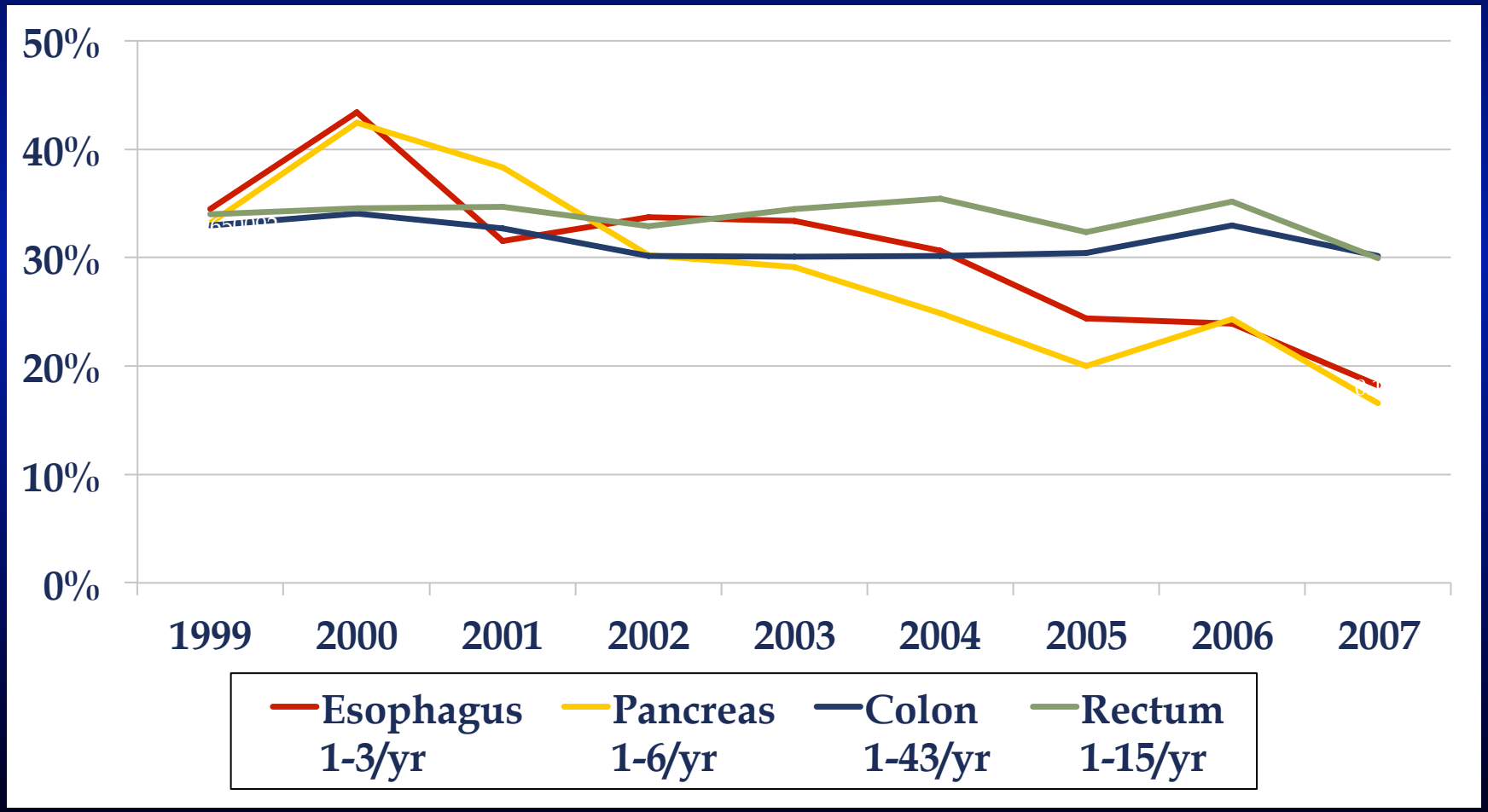
Van Hagen P et al. N Engl J Med. 2012

Esophageal Cancer
Neoadjuvant Chemoradiotherapy vs. Surgery Alone



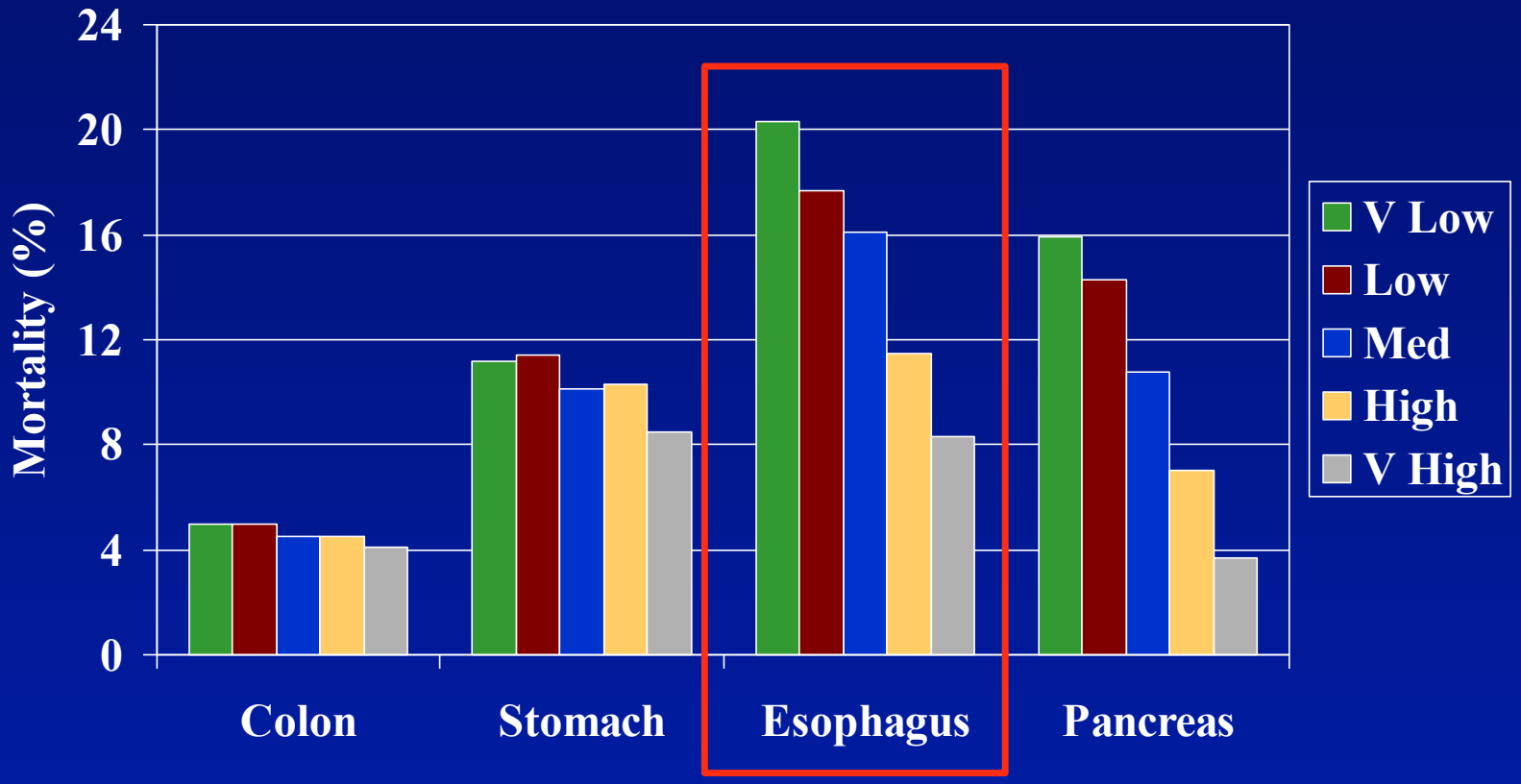
Gebski V et al. Lancet Oncol 8: 226-34, 200

Proportion of population-wide extirpative procedures performed at low volume centers



Birkmeyer J SSO 2011

GI Cancer Resections



Birkmeyer J SSO 2011

University of Colorado
Cancer Center

University of Colorado
Cancer Center

Gastric Adenocarcinoma

Adjuvant vs Neoadjuvant?
Radiation vs Chemoradiation?

University of Colorado Cancer Center

Radiation?

- Who uses it?
  - Yes: US
  - No: UK and Japan
- Why do we use?
  - GITSG studies in locally advanced pancreatic cancer and gastric adenocarcinoma

University of Colorado
Cancer Center

US Standard of Care…

Historical
Adjuvant Chemoradiation

University of Colorado
Cancer Center

CHEMORADIOTHERAPY AFTER SURGERY COMPARED WITH SURGERY ALONE FOR ADENOCARCINOMA OF THE STOMACH OR GASTROESOPHAGEAL JUNCTION

JOHN S. MACDONALD, M.D., STEPHEN R. SMALLEY, M.D., JACQUELINE BENEDETTI, PH.D., SCOTT A. HUNDAHL, M.D., NORMAN C. ESTES, M.D., GRANT N. STEMMERMANN, M.D., DANIEL G. HALLER, M.D., JAFFER A. AJANI, M.D., LEONARD L. GUNDERSON, M.D., J. MILBURN JESSUP, M.D., AND JAMES A. MARTENSON, M.D.

ABSTRACT

Background Surgical resection of adenocarcinoma of the stomach is curative in less than 40 percent of cases. We investigated the effect of surgery plus postoperative (adjuvant) chemoradiotherapy on the survival of patients with resectable adenocarcinoma of the stomach or gastroesophageal junction.

Methods A total of 556 patients with resected adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to surgery plus postoperative chemoradiotherapy or surgery alone. The adjuvant treatment consisted of 425 mg of fluorouracil per square meter of body-surface area per day, plus 20 mg of leucovorin per square meter per day, for five days, followed by 4500 cGy of radiation at 180 cGy per day, given five days per week for five weeks, with modified doses of fluorouracil and leucovorin on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five-day cycles of fluorouracil (425 mg per square meter per day) plus leucovorin (20 mg per square meter per day) were given one month apart.

Results The median overall survival in the surgery-only group was 27 months, as compared with 36 months in the chemoradiotherapy group; the hazard ratio for death was 1.35 (95 percent confidence interval, 1.09 to 1.66; $P=0.005$). The hazard ratio for relapse was 1.52 (95 percent confidence interval, 1.23 to 1.86; $P<0.001$). Three patients (1 percent) died from toxic effects of the chemoradiotherapy; grade 3 toxic effects occurred in 41 percent of the patients in the chemoradiotherapy group, and grade 4 toxic effects occurred in 32 percent.

Conclusions Postoperative chemoradiotherapy should be considered for all patients at high risk for recurrence of adenocarcinoma of the stomach or gastroesophageal junction who have undergone curative resection. (N Engl J Med 2001;345:725-30.)

MacDonald Study

N Engl J Med, Vol. 345, No. 10 · September 6, 2001

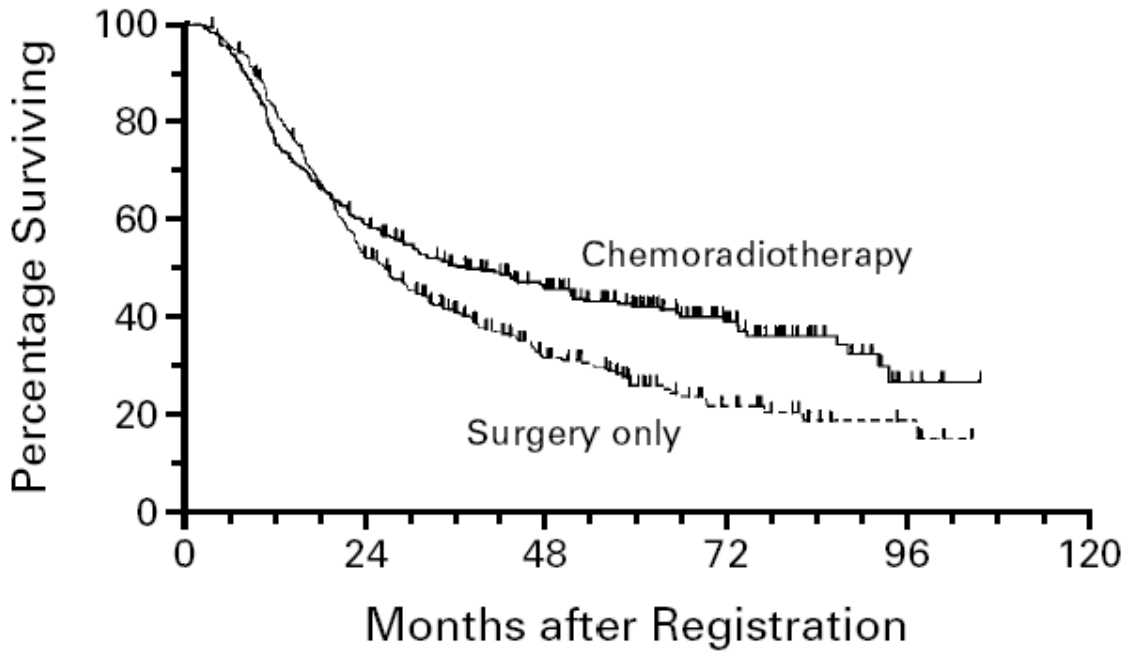


Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

The median duration of survival was 27 months in the surgery-only group and 36 months in the chemoradiotherapy group. The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 169 of the 281 patients in the chemoradiotherapy group and 197 of the 275 patients in the surgery-only group died during the follow-up period.

University of Colorado Cancer Center

Authors Conclusions

- Chemoradiotherapy after curative resection of adenocarcinoma of the gastric /GE junction significantly improves relapse free and overall survival

- Limitations of the study:
  - Adequacy of the surgical resection?

University of Colorado
Cancer Center

UK Standard of Care

Neoadjuvant /Adjuvant Chemotherapy

University of Colorado Cancer Center

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer

David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

ABSTRACT

BACKGROUND

A regimen of epirubicin, cisplatin, and infused fluorouracil (ECF) improves survival among patients with incurable locally advanced or metastatic gastric adenocarcinoma. We assessed whether the addition of a perioperative regimen of ECF to surgery improves outcomes among patients with potentially curable gastric cancer.

METHODS

We randomly assigned patients with resectable adenocarcinoma of the stomach, esophagogastric junction, or lower esophagus to either perioperative chemotherapy and surgery (250 patients) or surgery alone (253 patients). Chemotherapy consisted of three preoperative and three postoperative cycles of intravenous epirubicin (50 mg per square meter of body-surface area) and cisplatin (60 mg per square meter) on day 1, and a continuous intravenous infusion of fluorouracil (200 mg per square meter per day) for 21 days. The primary end point was overall survival.

RESULTS

ECF-related adverse effects were similar to those previously reported among patients with advanced gastric cancer. Rates of postoperative complications were similar in the perioperative-chemotherapy group and the surgery group (46 percent and 45 percent, respectively), as were the numbers of deaths within 30 days after surgery. The resected tumors were significantly smaller and less advanced in the perioperative-chemotherapy group. With a median follow-up of four years, 149 patients in the perioperative-chemotherapy group and 170 in the surgery group had died. As compared with the surgery group, the perioperative-chemotherapy group had a higher likelihood of overall survival (hazard ratio for death, 0.75; 95 percent confidence interval, 0.60 to 0.93; P=0.009; five-year survival rate, 36 percent vs. 23 percent) and of progression-free survival (hazard ratio for progression, 0.66; 95 percent confidence interval, 0.53 to 0.81; P<0.001).

CONCLUSIONS

In patients with operable gastric or lower esophageal adenocarcinomas, a perioperative regimen of ECF decreased tumor size and stage and significantly improved progression-free and overall survival. (Current Controlled Trials number, ISRCTN93793971.)

From the Departments of Medicine (D.C., Y.J.C.) and Surgery (W.H.A., J.N.T.), Royal Marsden Hospital, Surrey and London; the Medical Research Council Clinical Trials Unit, Cancer Group, London (S.P.S., R.E.L., M.V., S.W.); the Department of Oncology, Aberdeen Royal Infirmary, Aberdeen (M.N.); the Department of Medical Oncology, Christie Hospital, Manchester (J.H.S.); the Department of Medical Oncology, St. George's Hospital, London (F.J.L.); the Department of Oncology, Bristol Haematology and Oncology Centre, Bristol (S.J.F.); the Medical Oncology Unit, Southampton General Hospital, Southampton (T.J.I.); and the Clatterbridge Centre for Oncology, Liverpool (D.B.S.) — all in the United Kingdom; and the Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands (C.J.H.V.V.). Address reprint requests to Prof. Cunningham at the Department of Medicine, Royal Marsden Hospital, Downs Rd., Sutton, Surrey SM2 5PT, United Kingdom, or at david.cunningham@rmh.nhs.uk.

*Participants in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial are listed in the Appendix.

N Engl J Med 2006;355:11-20.

MAGIC

Background

MRC Clinical Trials Unit

Epirubicin 50mg/m^2, IV bolus, day 1
Cisplatin 60mg/m^2, 4-hour infusion, day 1
5-FU 200mg/m^2/day, continuous infusion, days 1-21

Cycles repeated every 3 weeks

- ECF: high response rate in two randomised clinical trials of locally advanced and metastatic oesophagogastric cancer
- MAGIC:
  Does this effect translate into a survival advantage in operable disease?

Eligibility criteria

MRC Clinical Trials Unit

- Histologically-proven adenocarcinoma of the stomach or (later) lower third of the oesophagus, suitable for curative resection
- Non-metastatic disease
- Stage II or greater
- WHO performance status 0 or 1
- Fit to receive chemotherapy
- Informed consent

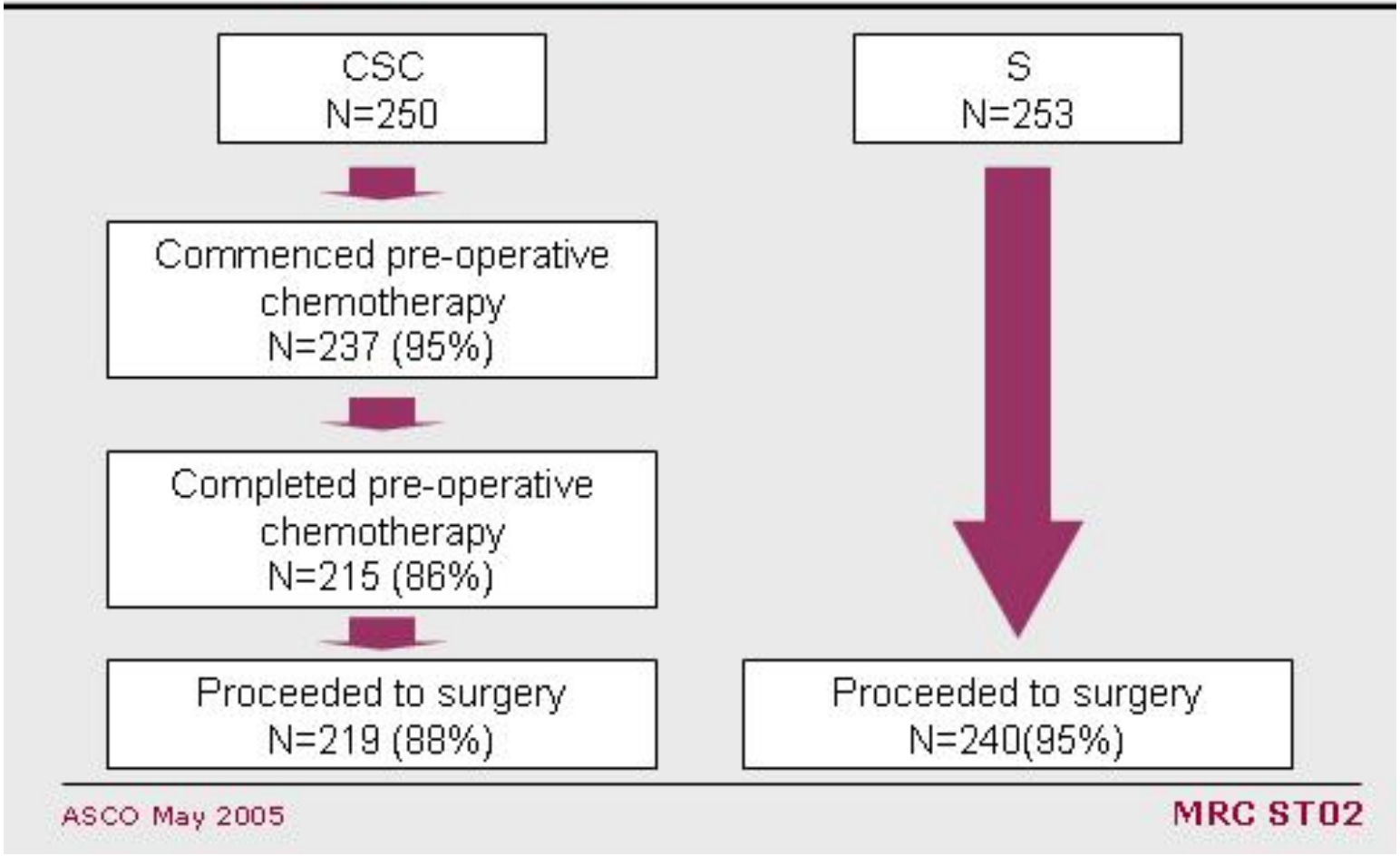
Surgery - Protocol Guidelines

MRC Clinical Trials Unit

- Type of resection: discretion of the participating surgeon
- No recommendation given regarding D1 or D2 surgery as previous MRC trial comparing these techniques had yet to be fully reported
- Nodes recommended for dissection:
  - -Gastric primary: perigastric nodes (gastric patients)
  - -Oesophageal primary: sub-carinal mediastinal and coeliac nodes
- Further lymphadenectomy at discretion of participating surgeon
- Guidelines for assessment of curability included in protocol

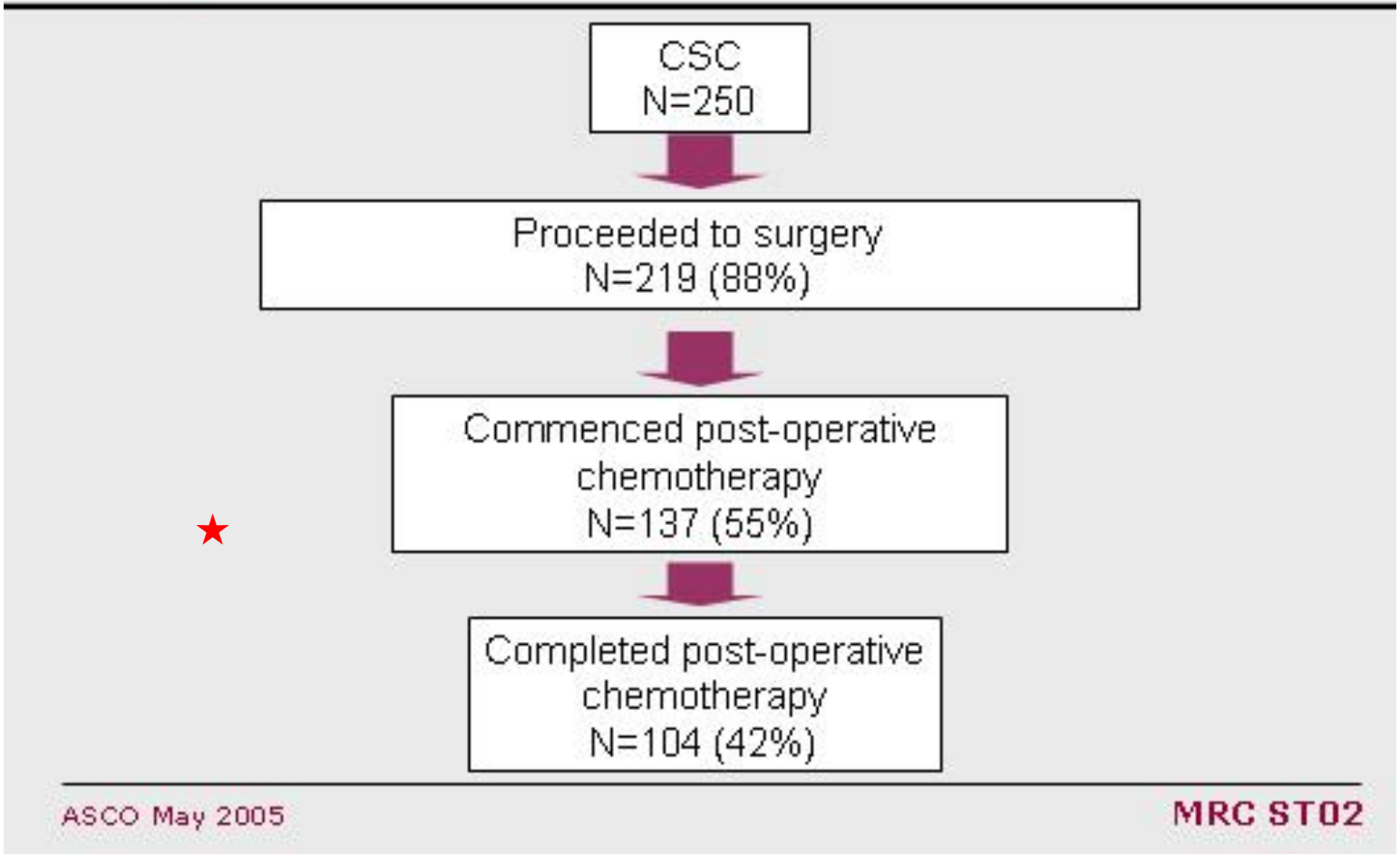
Pre-operative chemotherapy and surgery trial profile

MRC Clinical Trials Unit



Post-operative chemotherapy trial profile

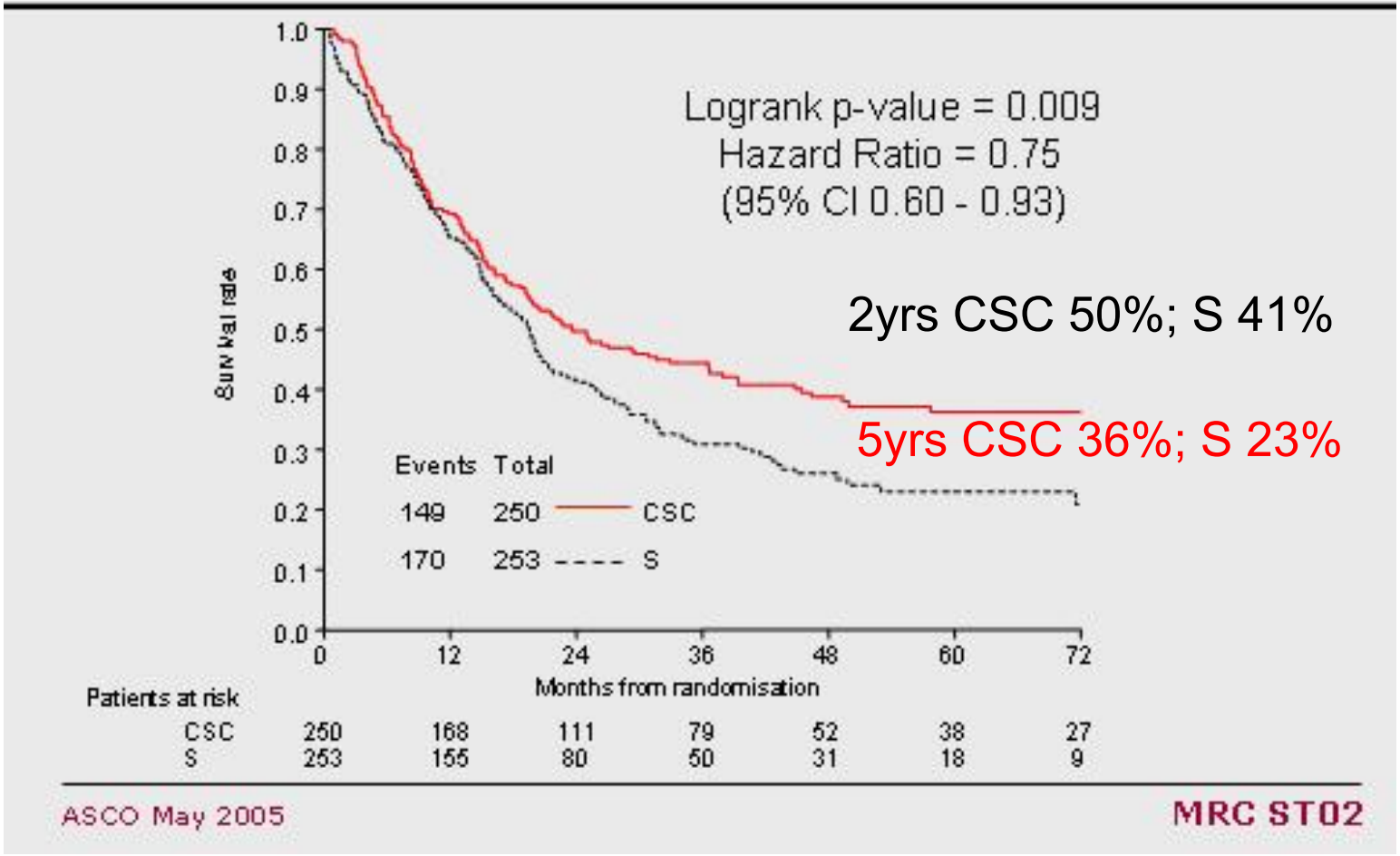
MRC Clinical Trials Unit



University of Colorado Cancer Center

Survival

MRC Clinical Trials Unit



ASCO May 2005

MRC ST02

In conclusion

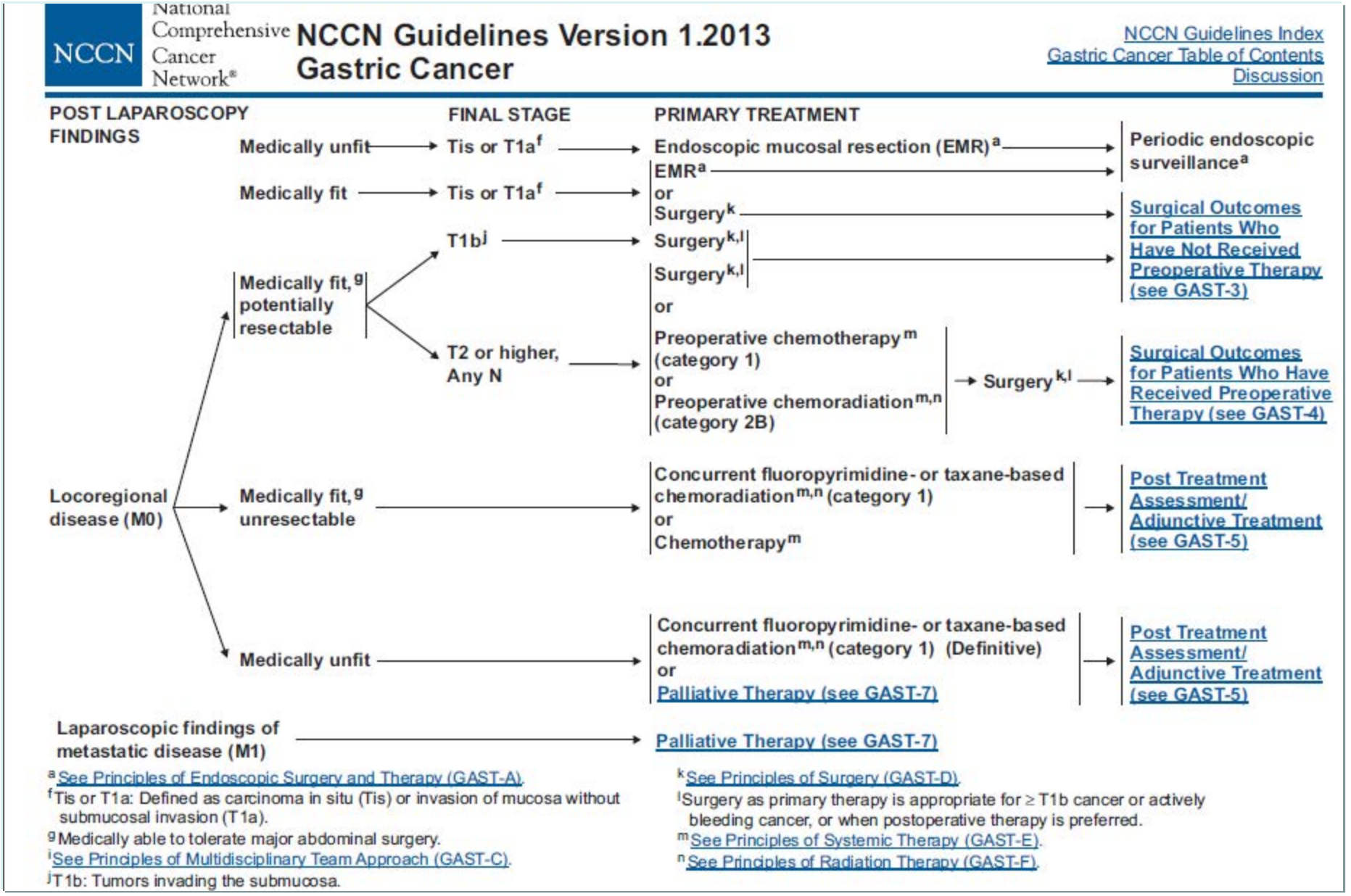
MRC Clinical Trials Unit

In operable gastric and lower oesophageal cancer, perioperative chemotherapy:

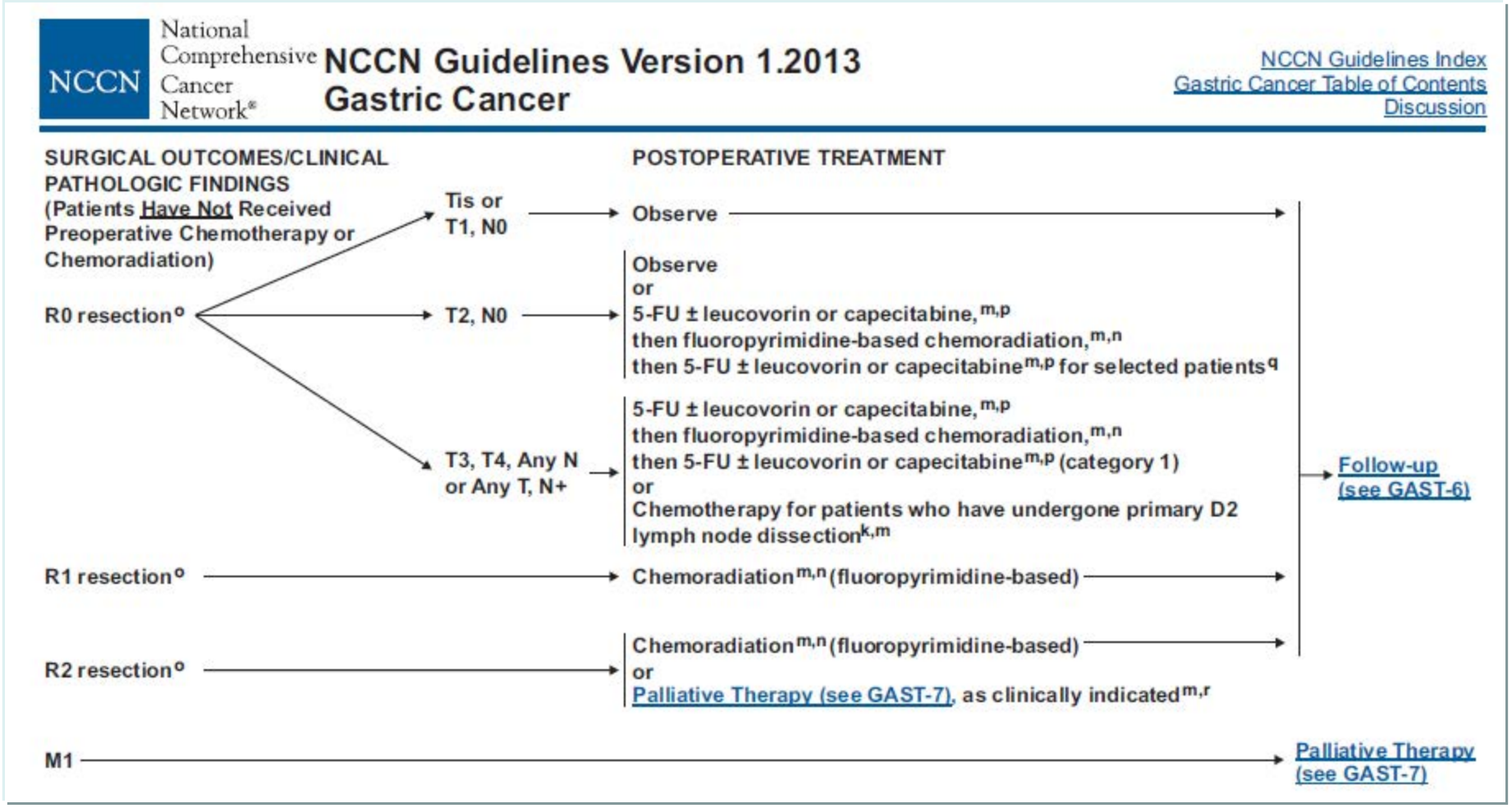
- leads to downsizing of primary tumour
- significantly improves progression-free survival
- significantly improves overall survival

University of Colorado Cancer Center

Bottom Line….



University of Colorado
Cancer Center



Universi
Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

David Cunningham, M.D., F.R.C.P., Naureen Starling, M.R.C.P., Sheela Rao, M.R.C.P., Timothy Iveson, M.D., F.R.C.P., Marianne Nicolson, M.D., F.R.C.P., Fareeda Coxon, F.R.C.P., Gary Middleton, M.D., F.R.C.P., Francis Daniel, M.B., Ch.B., R.C.S.I., F.F.R., Jacqueline Oates, and Andrew Richard Norman, Ph.D., for the Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom

ABSTRACT

BACKGROUND

We evaluated capecitabine (an oral fluoropyrimidine) and oxaliplatin (a platinum compound) as alternatives to infused fluorouracil and cisplatin, respectively, for untreated advanced esophagogastric cancer.

METHODS

In a two-by-two design, we randomly assigned 1002 patients to receive triplet therapy with epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX) or triplet therapy with epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX). The primary end point was noninferiority in overall survival for the triplet therapies containing capecitabine as compared with fluorouracil and for those containing oxaliplatin as compared with cisplatin.

RESULTS

For the capecitabine–fluorouracil comparison, the hazard ratio for death in the capecitabine group was 0.86 (95% confidence interval [CI], 0.80 to 0.99); for the oxaliplatin–cisplatin comparison, the hazard ratio for the oxaliplatin group was 0.92 (95% CI, 0.80 to 1.10). The upper limit of the confidence intervals for both hazard ratios excluded the predefined noninferiority margin of 1.23. Median survival times in the ECF, ECX, EOF, and EOX groups were 9.9 months, 9.9 months, 9.3 months, and 11.2 months, respectively; survival rates at 1 year were 37.7%, 40.8%, 40.4%, and 46.8%, respectively. In the secondary analysis, overall survival was longer with EOX than with ECF, with a hazard ratio for death of 0.80 in the EOX group (95% CI, 0.66 to 0.97; P=0.02). Progression-free survival and response rates did not differ significantly among the regimens. Toxic effects of capecitabine and fluorouracil were similar. As compared with cisplatin, oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity, and thromboembolism but with slightly higher incidences of grade 3 or 4 diarrhea and neuropathy.

CONCLUSIONS

Capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer. (Current Controlled Trials number, ISRCTN51678883.)

From Royal Marsden Hospital National Health Service Foundation Trust, Surrey and London (D.C., N.S., S.R., J.O., A.R.N.); Southampton University Hospital National Health Service Trust, Southampton, and Salisbury Hospital National Health Service Foundation Trust, Salisbury (T.I.); Aberdeen Royal Infirmary, Aberdeen (M.N.); Northern Centre for Cancer Treatment, Newcastle upon Tyne (F.C.); St. Luke's Cancer Centre, Guildford (G.M.); and Plymouth Oncology Centre, Plymouth (F.D.) — all in the United Kingdom.

N Engl J Med 2008;358:36-46.

REAL Study

NEJM 2008

University Cancer Ce

SCC

Table 1. Baseline Demographic and Clinical Characteristics (Per-Protocol Population).*

Variable	ECF (N=249)	ECX (N=241)	EOF (N=235)	EOX (N=239)
Age (yr)				
Median	65	64	61	62
Range	22–83	25–82	33–78	25–80
Sex (%)				
Male	81.1	80.5	81.3	82.8
Female	18.9	19.5	18.7	17.2
Subsite of tumor (%)				
Esophagus	34.9	29.5	39.6	34.3
Gastroesophageal junction	28.9	28.2	23.4	22.2
Stomach	36.1	42.3	37.0	43.5
Performance-status score (%)†				
0 or 1	88.4	87.6	91.5	90
2	11.6	12.4	8.5	10.0
Extent of disease (%)				
Metastatic	79.5	76.8	77.0	75.7
Locally advanced	20.5	23.2	23.0	24.3
Type of tumor (%)				
Adenocarcinoma	90.0	89.6	86.0	87.4
Squamous-cell carcinoma	7.6	9.5	12.8	12.1
Undifferentiated carcinoma	2.4	0.8	1.3	0.4
No. of metastatic sites (%)				
0 or 1	63.5	59.3	60.9	64.4
≥2	36.5	40.7	39.1	35.6
Previous surgery (%)	7.6	7.5	7.7	8.8

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).

† Performance was evaluated according to guidelines of the Eastern Cooperative Oncology Group, with a score of 0 indicating normal performance status, 1 mildly symptomatic, 2 symptomatic but in bed less than half the day, 3 symptomatic and in bed more than half the day, and 4 in bed the whole day.

Table 2. Analysis of Efficacy (Intention-to-Treat Population).*

Variable	ECF (N=263)	ECX (N=250)	EOF (N=245)	EOX (N=244)
Death				
No. of patients	225	213	213	199
Hazard ratio (95% CI)		0.92 (0.76–1.11)	0.96 (0.79–1.15)	0.80 (0.66–0.97)
P value		0.39	0.61	0.02
Overall survival				
Median — mo	9.9	9.9	9.3	11.2
At 1 yr — % (95% CI)	37.7 (31.8–43.6)	40.8 (34.7–46.9)	40.4 (34.2–46.5)	46.8 (40.4–52.9
Progression-free survival				
Median — mo	6.2	6.7	6.5	7.0
Patients who had progression or died	237	231	221	213
Hazard ratio (95% CI)		0.98 (0.82–1.17)	0.97 (0.81–1.17)	0.85 (0.70–1.02)
P value		0.80	0.77	0.07
Response				
Overall — % (95% CI)†	40.7 (34.5–46.8)	46.4 (40.0–52.8)	42.4 (36.1–48.8)	47.9 (41.5–54.3)
Complete — %	4.1	4.2	2.6	3.9
Partial — %	36.6	42.2	39.8	44.0
P value		0.20	0.69	0.11

* Patients were randomly assigned to receive one of four triplet therapies: epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX), or epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX).
† Overall response could be evaluated in 246 patients in the ECF group, 237 patients in the ECX group, 231 patients in the EOF group, and 234 patients in the EOX group.

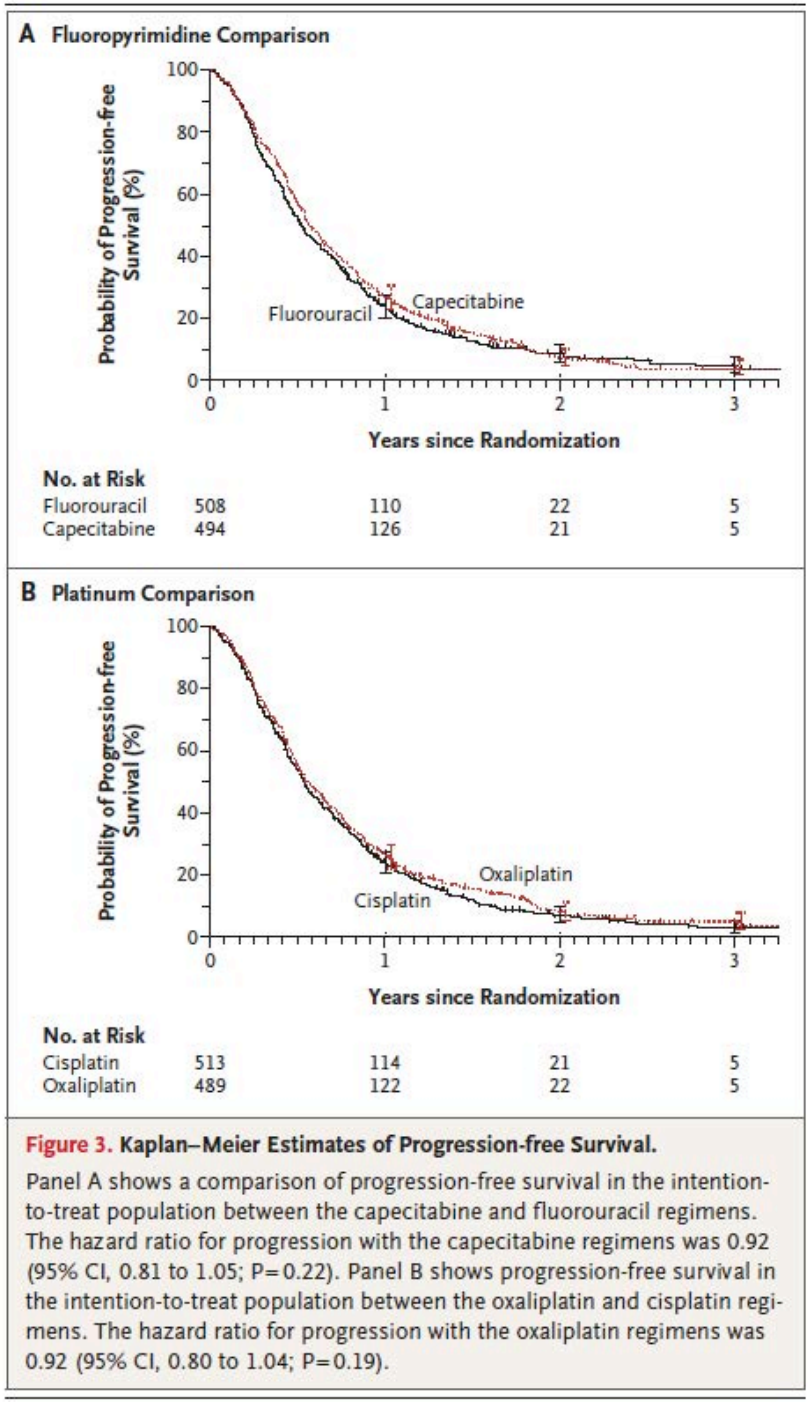


Figure 3. Kaplan–Meier Estimates of Progression-free Survival.

Panel A shows a comparison of progression-free survival in the intention-to-treat population between the capecitabine and fluorouracil regimens. The hazard ratio for progression with the capecitabine regimens was 0.92 (95% CI, 0.81 to 1.05; P=0.22). Panel B shows progression-free survival in the intention-to-treat population between the oxaliplatin and cisplatin regimens. The hazard ratio for progression with the oxaliplatin regimens was 0.92 (95% CI, 0.80 to 1.04; P=0.19).

Trend towards better OS

Capecitabine > 5FU
Oxaliplatin > Cisplatin

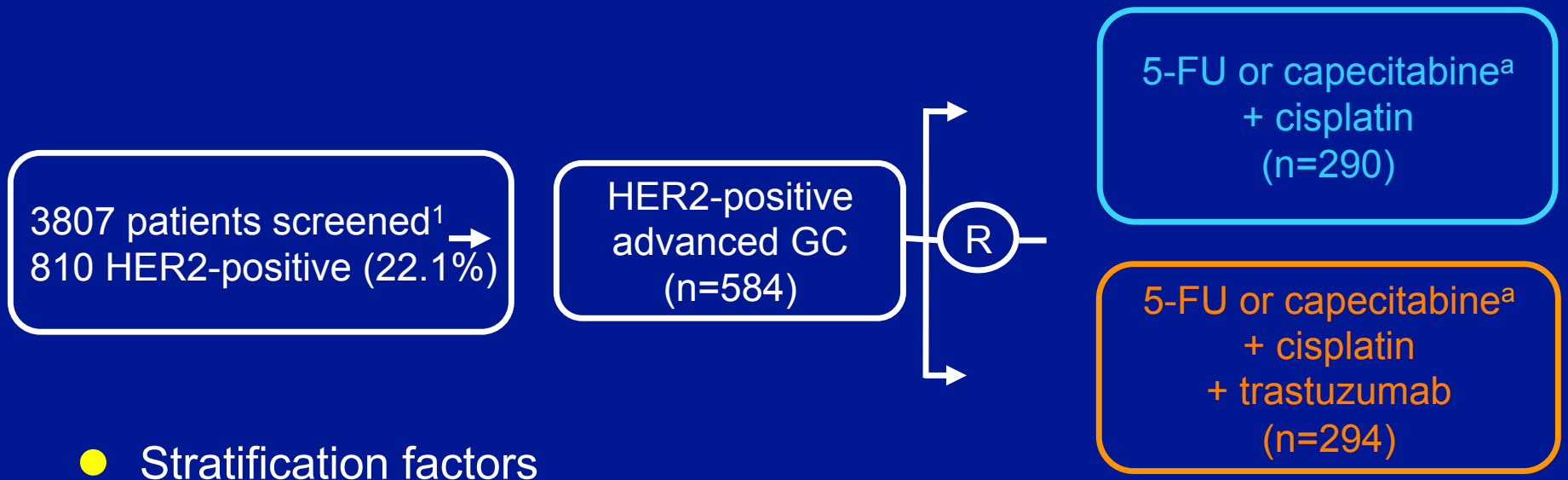
Molecular Targets: Esophagogastric Cancer

- KRAS mutation: < 5-10%
- BRAF mutation: < 5%
- EGFr over expression: 50-80%
- EGFr mutation: < 5%
- CMET: < 10%
- HER2 over expression: 10-25%

Galizia W J Surg 31: 1458; 2007 Mammano Anticancer Res 26: 3547; 2006
Lee Oncogene 22: 6942; 2003 Yano Oncol Rep 15: 65; 2006

ToGA trial design

Phase III, randomized, open-label, international, multicenter study

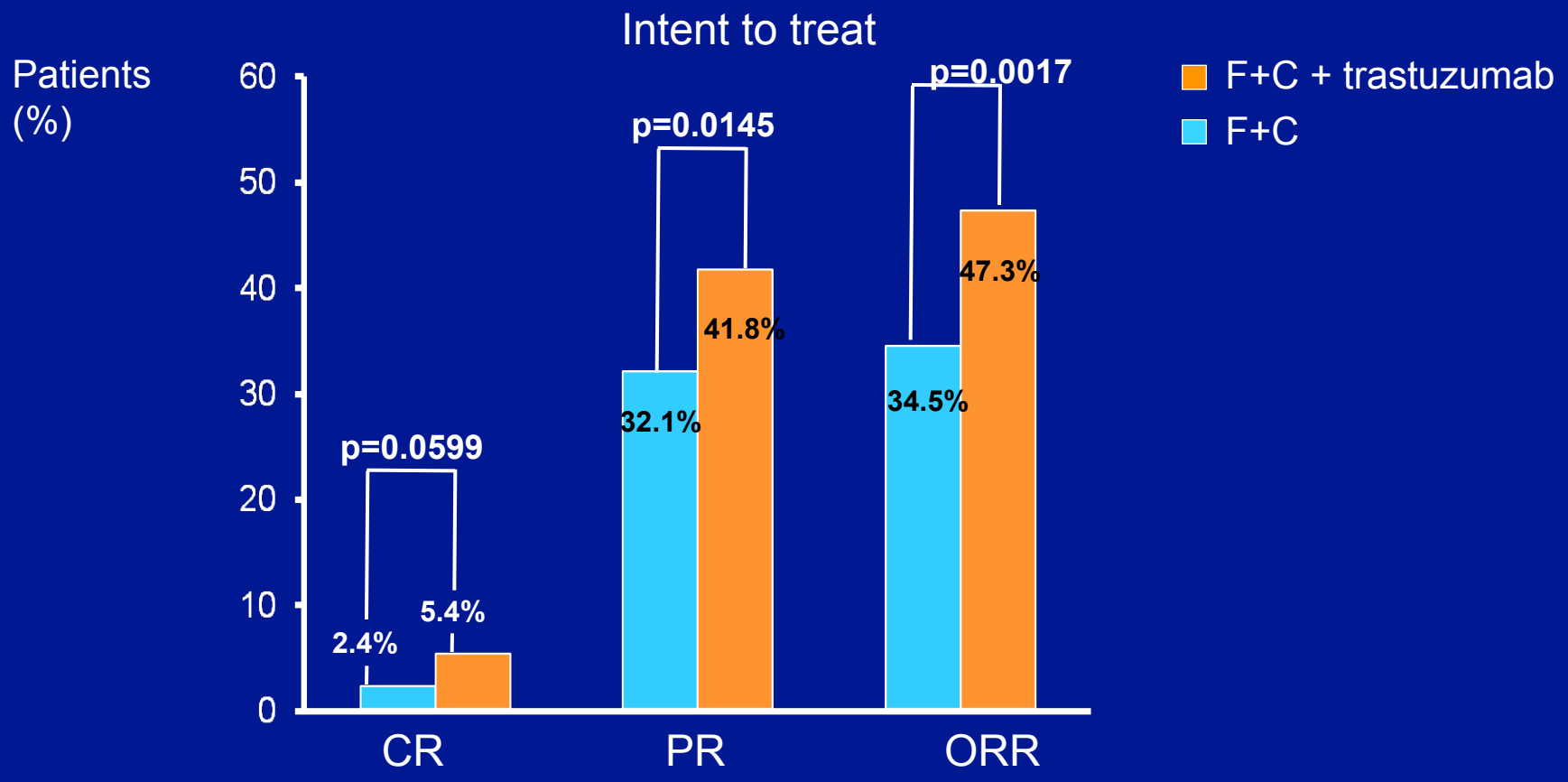


- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

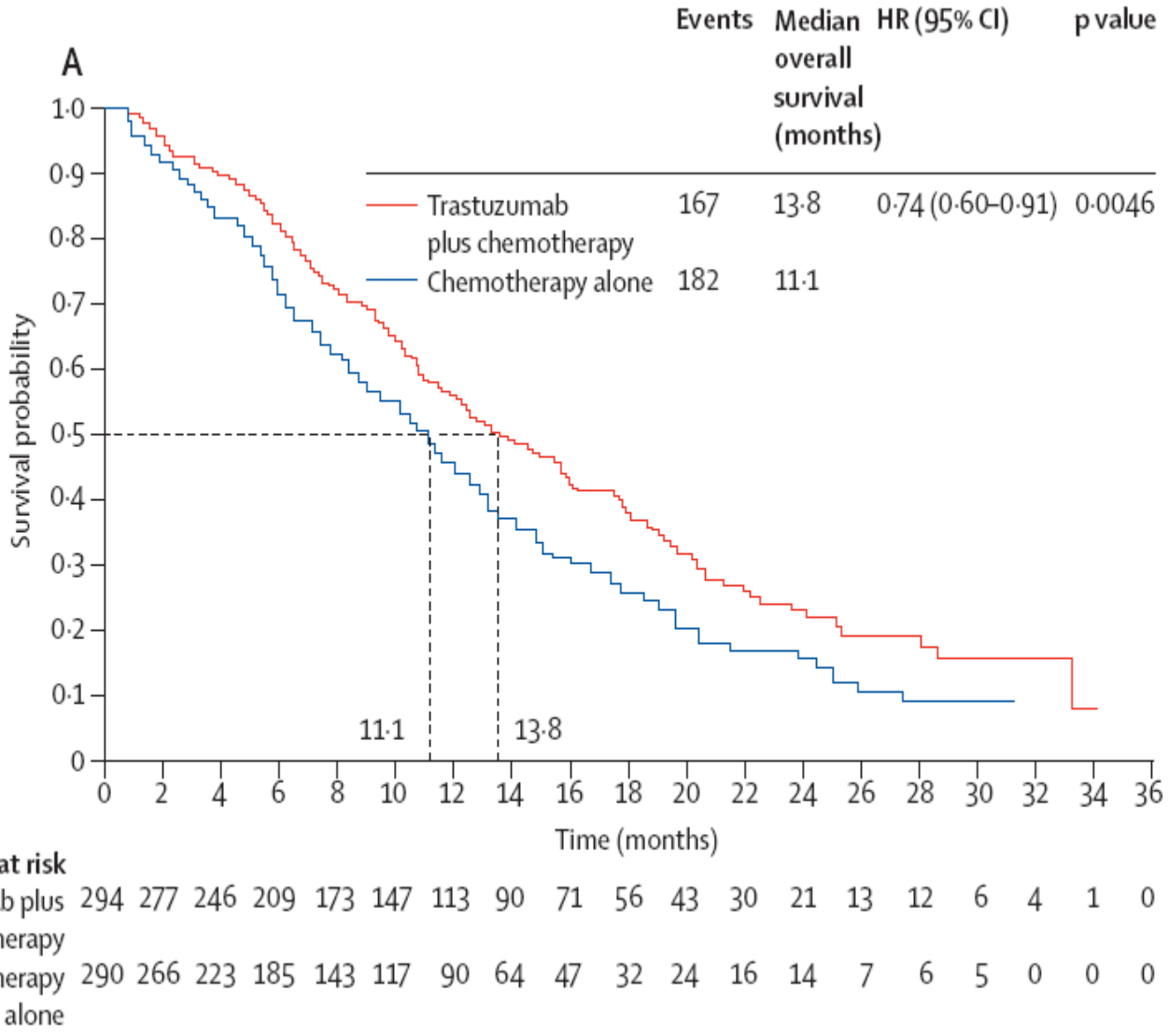
[1]Bang et al; Abstract 4556, ASCO 2009

Secondary end point: tumor response rate



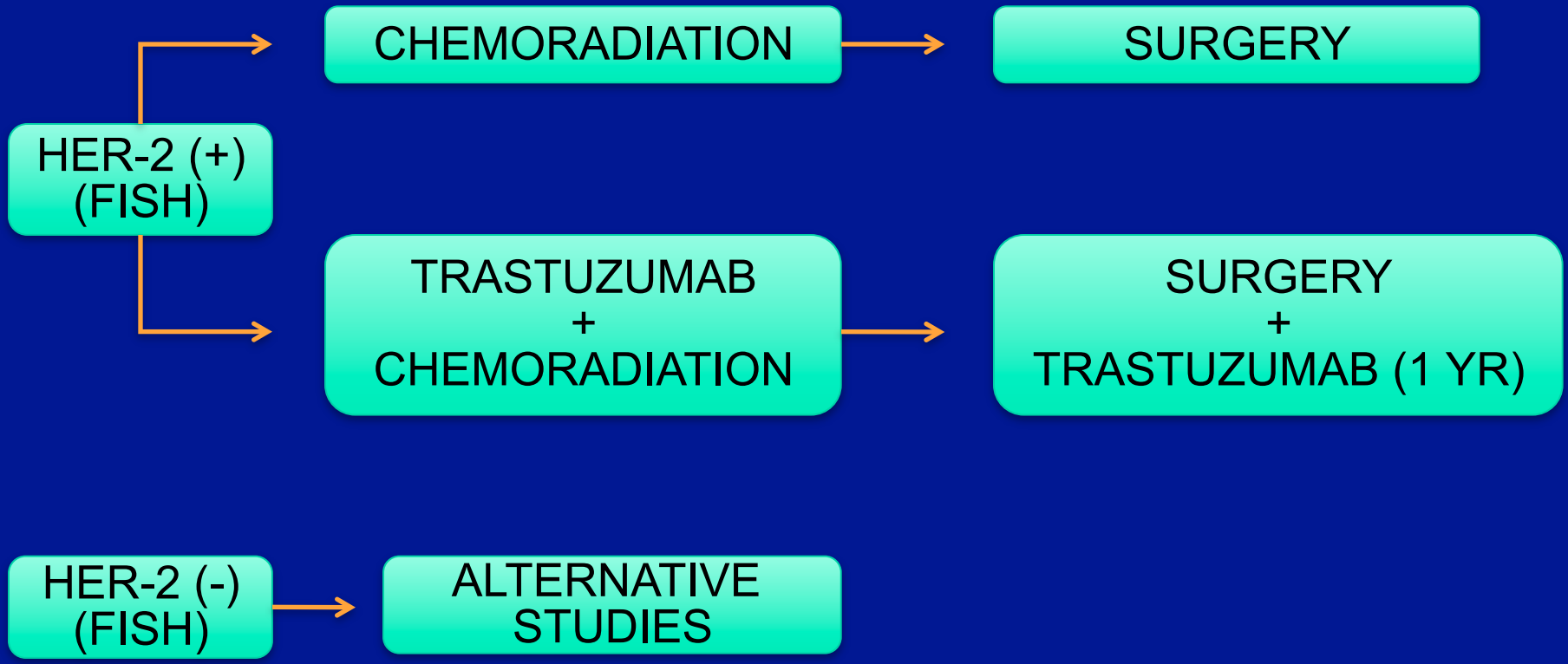
ORR= CR + PR
CR, complete response; PR, partial response

Gastric Cancer
Targeted Agents – ToGA Trial



Bang YJ et al. Lancet. 2010

RTOG 1010: Phase II Study of Neoadjuvant Trastuzumab and Chemoradiation for Esophageal Adenocarcinoma (Siewert I, II)



- Chemoradiation: Carbo + Paclitaxel, RT 5040 cGy ➔ Surgery Maintenance trastuzumab post op
- Sample Size = 130 Her-2 (+) Pts, Increase 3-Yr Survival from 30% to 50%. 520+ pts to be screened

1

Phase I/II's

(selected studies in Her2+ gastric/GEJ)

Combination Studies: trastuzumab plus

HM781-36B (pan-Her)/**paclitaxel** (NCT01746771; Seoul)
Pertuzumab/chemo (NCT01774786)
Pertuzumab 840mg v 420mg/chemo (NCT01461057)
MM-111/Paclitaxel (NCT01774851)
IL-12/Paclitaxel (NCT00028535)
Afatinib (Phase I gastric/breast; NCT01649271)

Trastuzumab derivatives:

Trastuzumab emtansine/capecitabine (NCT01702558)
Pb212-Trastuzumab radioimmunotherapy (NCT01384253)

Phase I/II's

(selected studies in Her2+ gastric/GEJ)

Chemo Backbone Studies: Trastuzumab plus

CAPOX (NCT01503983, 01364493, 01396707, 01130337)
CAPOX/Bev (CT01191697)
CAPOX and chemorads ("TOXAG"; NCT01748773)
CAPOX/Bev/Docetaxel (NCT01359397)
TS-1/cisplatin (NCT01736410; NCT01228045)
Docetaxel/oxali/cape ("TEX"; NCT01295086)

Perioperative Trastuzumab plus

5-FU/LV/Oxali/Docetacel (FLOT) (NCT01472029)

Phase I/II's

(selected studies in Her2+ gastric/GEJ)

Monotherapy Studies (no trastuzumab)

Afatinib (BIBW 2992; NCT01522768)
MGAH22 (optimized Fc domain; NCT01148849)
ARRY-543/ASLAN001 (pan-HER; NCT01614522)
LMJ-716 (mAb to HER3; NCT01598077)
PF-00299804 (Pan-HER; NCT01152853)

Lapatinib:

Phase III: CAPOX +/- lapatinib (NCT00680901) "LOGiC"
Phase III: Paclitaxel +/- lapatinib (NCT00486954) "TYTAN"

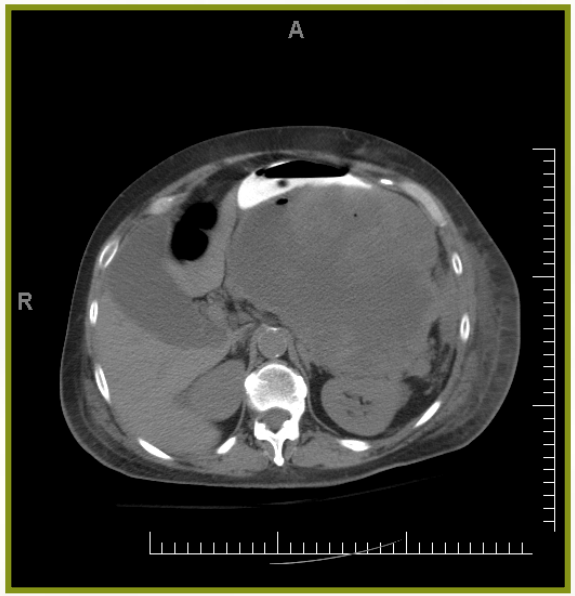
Terminated:

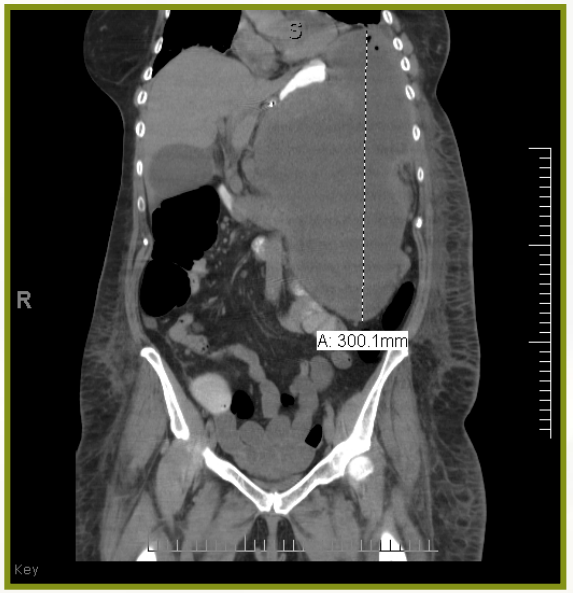
AUY922 (HSP90) + Trastuzumab (NCT01402401)

University of Colorado
Cancer Center

GIST

- >90% tumors → KIT or PDGFRα mutation
- >80% metastatic GIST patients benefit from imatinib mesylate
- Resected primary GIST: 5-yr survival = 54%

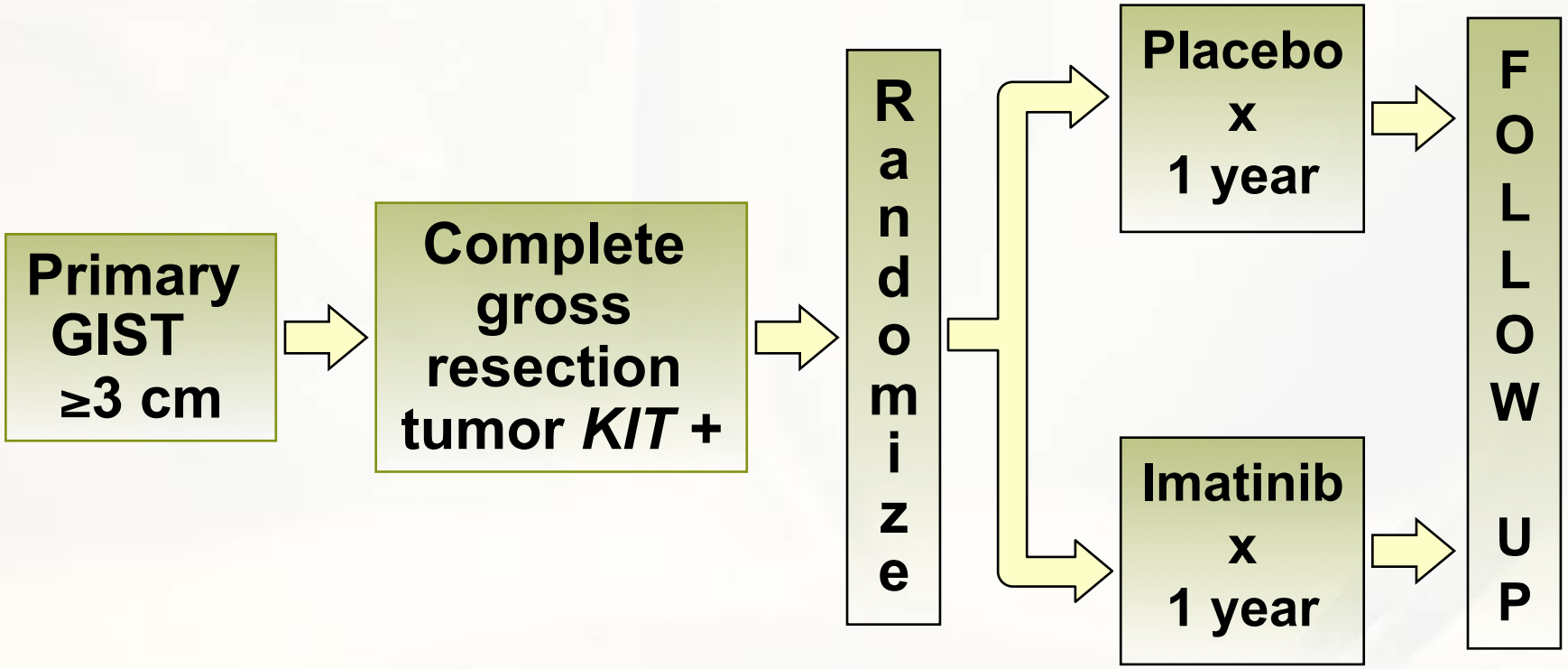




GIST – Adjuvant

Z9001

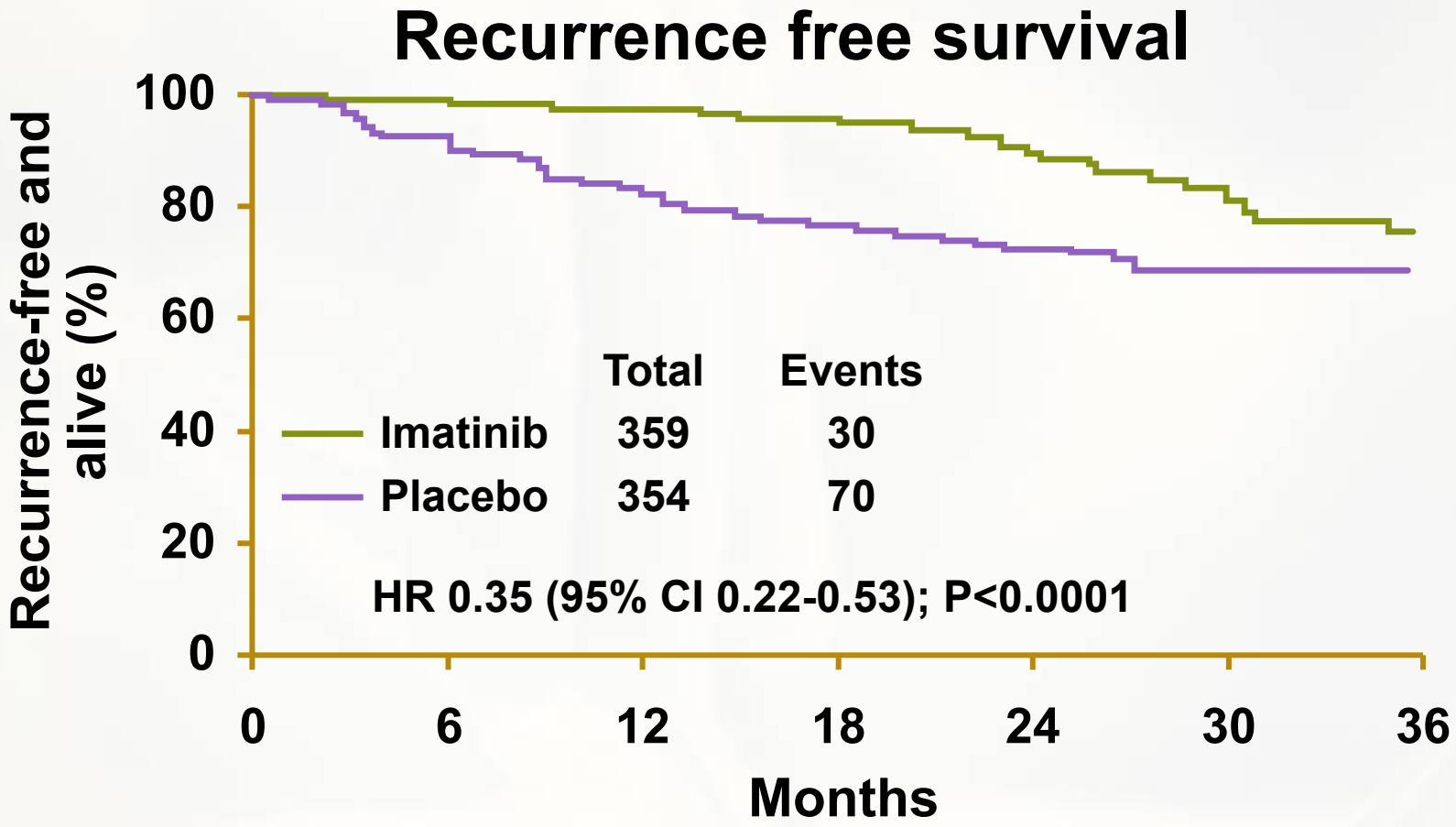
A phase III randomized double-blind study of adjuvant imatinib vs placebo in patients following resection of primary GIST



PI: Ron DeMatteo

GIST – Adjuvant

Z9001



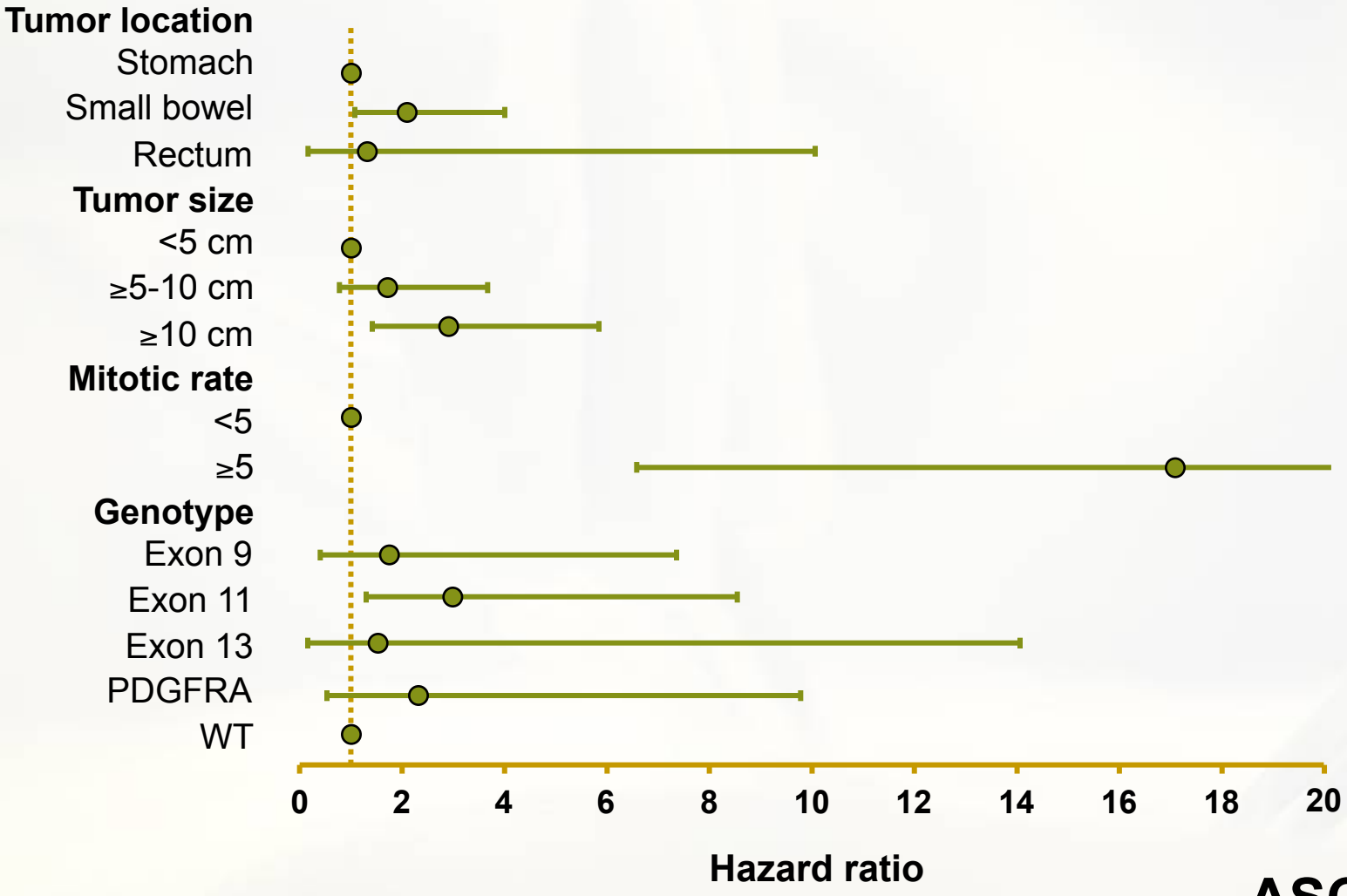
Placebo	359	207	105	33
Imatinib	354	188	89	34

Lancet. 2009 Mar 28;373(9669):1097-104

GIST – Adjuvant

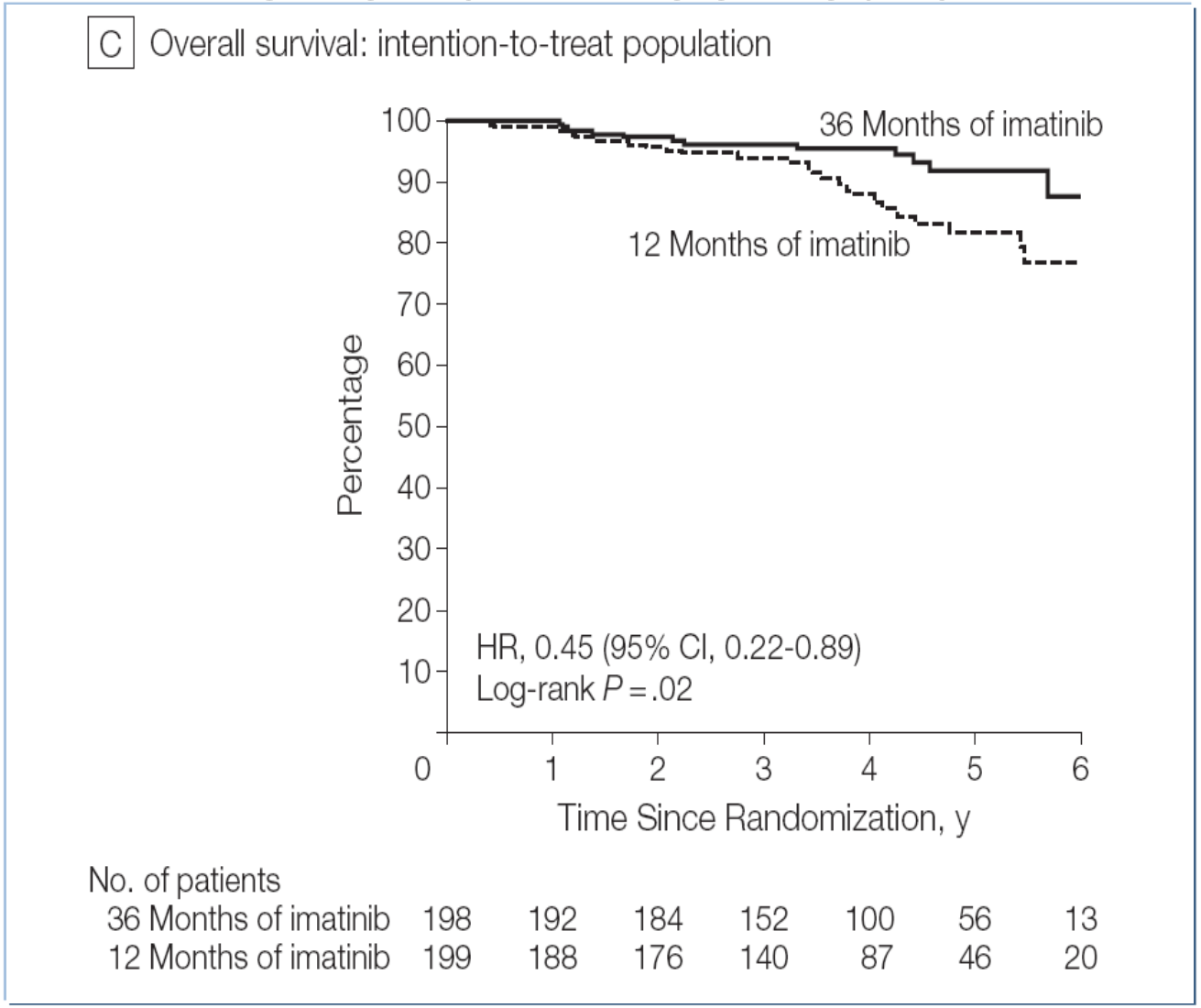
Z9001

Multivariate Analyses For Recurrence: Placebo Group



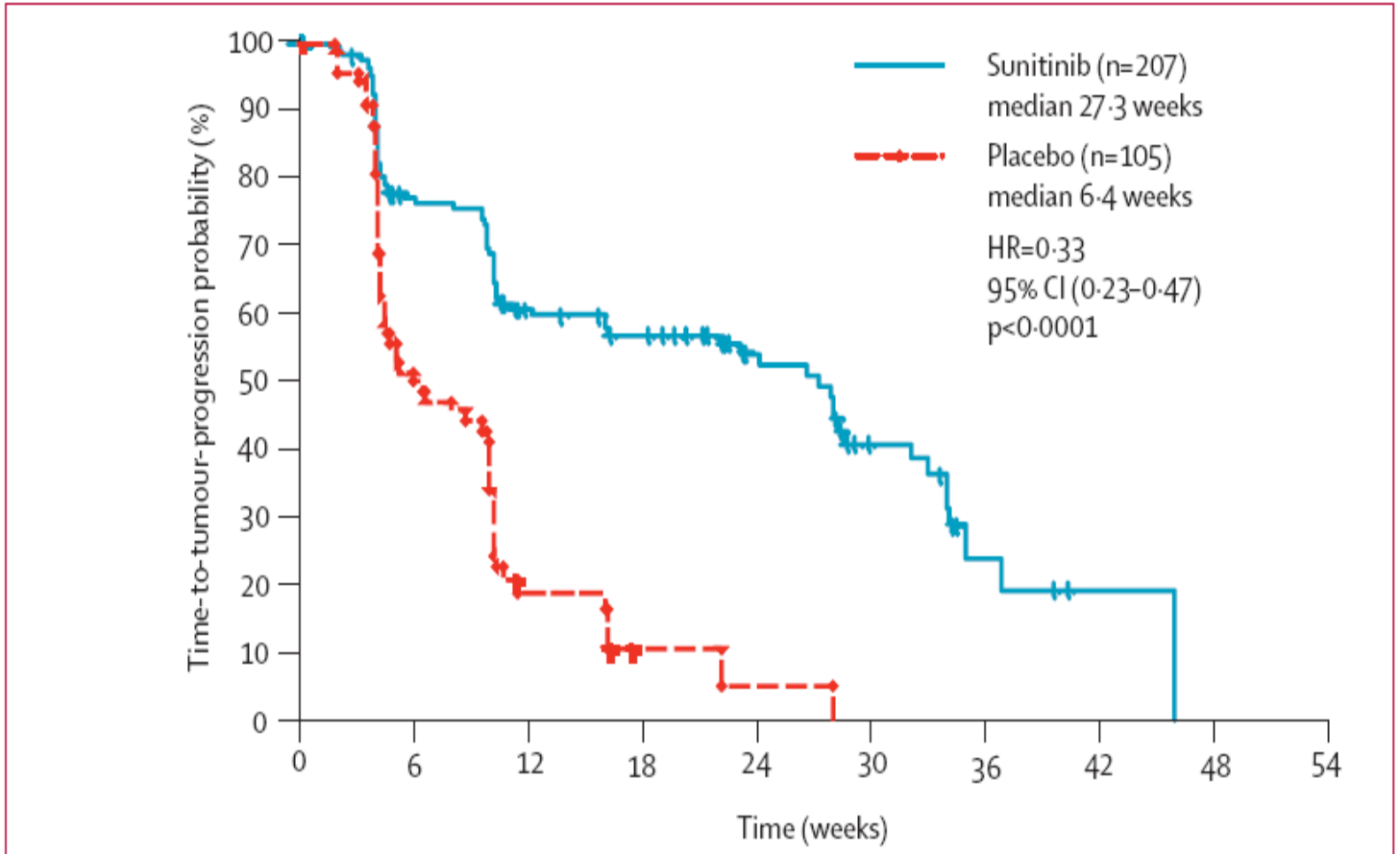
ASCO 2010

GIST – Adjuvant Imatinib One vs. Three Years



Joensuu H et al. JAMA 2012

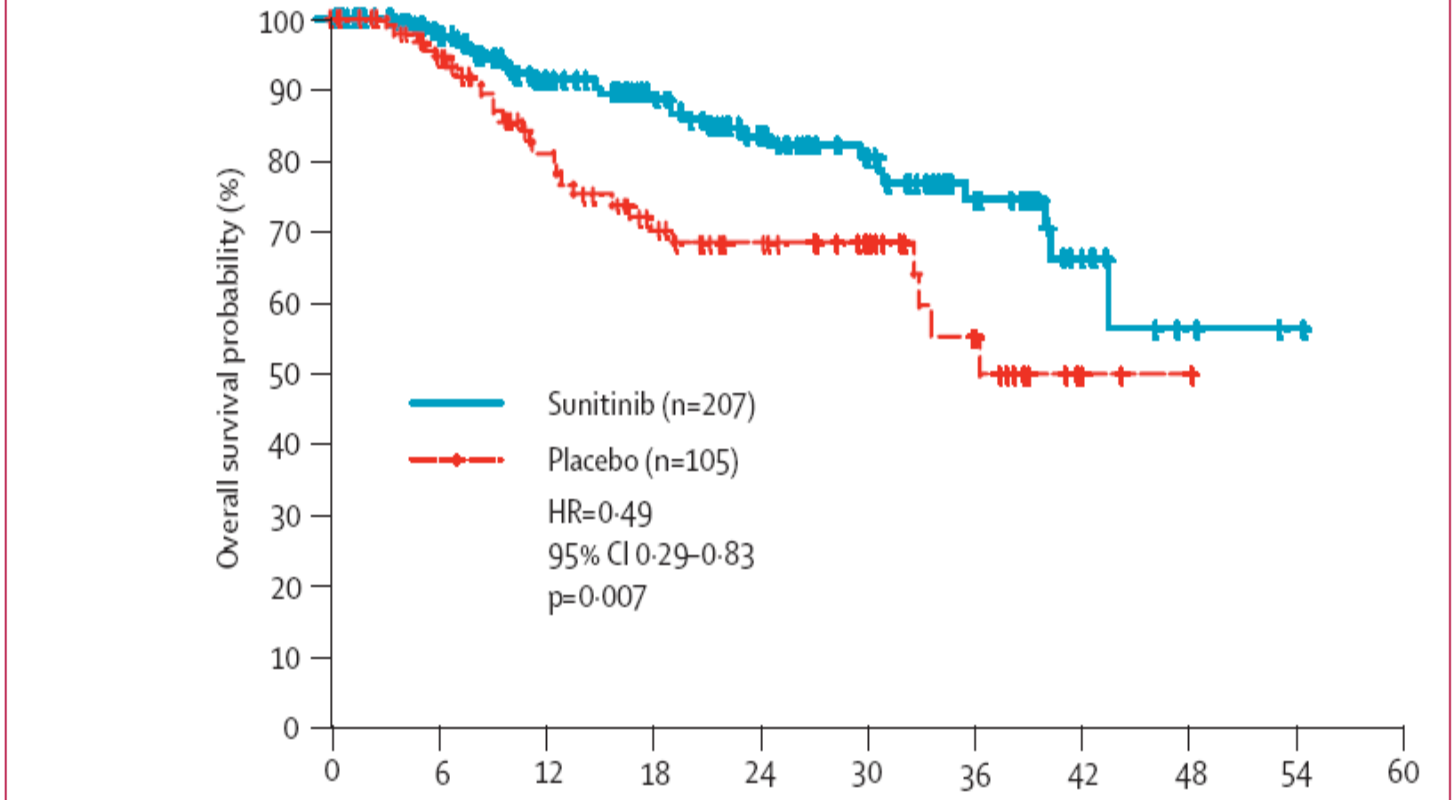
Advanced GIST
Sunitinib in Imatinib Resistant GIST



Number at risk

Sunitinib	207	106	67	53	34	18	5	1	0
Placebo	105	36	9	2	1	0	0	0	0

Advanced GIST
Sunitinib in Imatinib Resistant GIST



Number at risk											
Sunitinib	207	167	117	97	71	50	31	11	3	1	0
Placebo	105	85	57	43	31	22	13	3	1	0	0

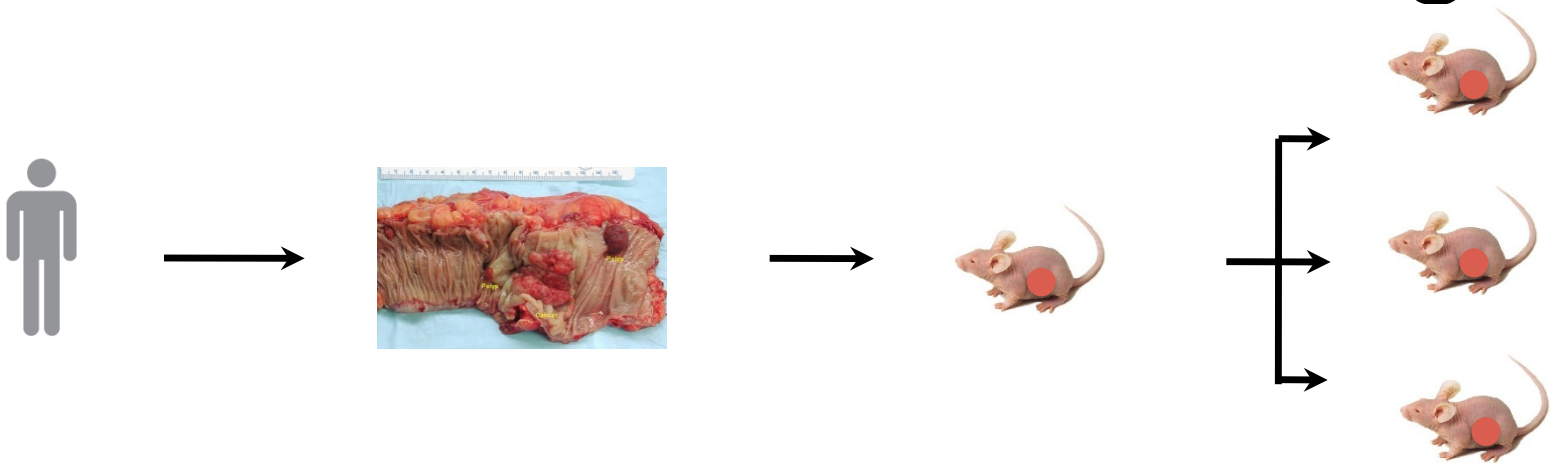
University of Colorado Cancer Center

University of Colorado GI Tumor Bank

- "Bank" of patient's blood and tumor
- Provides a collection of GI tumors that will used for research
- The bank can used to "identify" potential targets for drug development
- The molecular profile of tumors in the bank can be linked to information in our clinical database to provide insight on the relationship between molecular events and clinical outcome.

University of Colorado Cancer Center

Patient Derived Xenograft Program



Consented patient undergoing surgery for the neuroendocrine cancer

Tumor removed

Tumor transplanted into mice

Tumor is then transplanted into more mice for research

- Drug testing
- Biomarker / Mutations Discovery

University of Colorado
Cancer Center

GI Oncology Team

University of Colorado
Cancer Center

THANK YOU