

GASTRIC CANCER

David H. Ilson, M.D., Ph.D.
 Attending Physician
 Memorial Sloan-Kettering Cancer Center
 New York

Financial Disclosure

- **Research Support**
 - Roche / Genentech
 - Bristol Myers Squibb / Imclone
 - Sanofi-Aventis
 - Bayer

Question 1: Gastric Cancer and Heredity

- The following statements about gastric cancer and heredity are correct except:
- 1) Familial gastric cancer develops in patients with autosomal dominant E-cadherin mutation.
- 2) Gastric cancer occurs in patients with HNPCC, due to autosomal dominant DNA mismatch repair mutations.
- 3) Gastric cancer is associated with BRCA gene mutation carriers.
- 4) Susceptibility to the development of advanced gastric cancer may vary with genetic polymorphisms in inflammatory cytokines.

Esophageal and Gastric Carcinoma US Incidence in 2011

- **38,500 new cases**
 - Gastric: 21,520 (56%)
 - Esophagus: 16,980 (44%)
- **Male > Female**
- **Decline in Gastric Cancer Incidence**
- **Increase in Esophageal, GE JX, cardia adeno**
- **OS improvement, 1975-77, 1984-86, 1999-2006**
 - Gastric: 16% → 18% → 27%
 - Esophageal: 5% → 10% → 19%

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

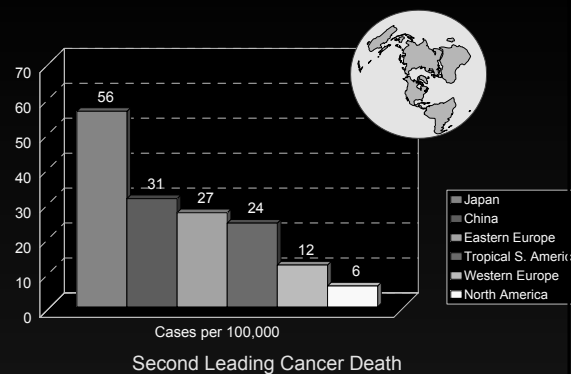
Gastric and Esophageal Cancer

- **11 million cancers diagnosed worldwide**
- **Gastric and Esophageal Cancer: 1.39 million cases**
 - 1.09 million deaths (78%)
- **Gastric Cancer: Second leading cause of cancer related death**
- **Estimate 50% are resectable (700,000)**
 - A 10% increment in survival = 70,000 lives saved



Kamangar et al, J Clin Oncol 24: 2137-50; 2006

Gastric Cancer: Worldwide Incidence



Factors Associated With Increased Risk of Developing Stomach Cancer

- **Nutritional/environmental**
 - Salted or smoked foods
 - High dietary nitrates
 - Low intake of fruits, vegetables, and vitamin A and C consumption
 - Low serum selenium
- **Medical**
 - Prior gastric surgery
 - *Helicobacter pylori* infection
 - Cag-1
 - Gastric atrophy and gastritis
 - Pernicious anemia
- **Social**
 - Low socioeconomic status

Helicobacter and Gastric Cancer

- **H. P. infection with CAG 1 antigen strain**
 - One third of all gastric cancers worldwide
 - Areas endemic for gastric cancer overlap with areas with H.P infection
 - Decline of HP infection in Western countries has led in part to a decline in gastric cancer incidence
- **Japanese series 1526 pts: EGD for gastric/duodenal ulcer or dyspepsia**
 - 1246 HP+ (82%), 280 HP – (28%)
 - F/U EGD at 1-3 yrs
 - 36 HP + (3%) had Gastric Cancer, None in HP –

Uemura, NEJM 2001

H.P. and the Host: Inflammatory Cytokines

- **Risk of gastric cancer with HP infection is low**
- **Autoimmune inflammatory processes contribute to gastric atrophy with HP infection**
- **Polymorphisms of genes for inflammatory cytokines may impact on risk:**
 - Host and environment interaction
- **Homozygous genotype IL-1RN*2/2 strongly associated with early gastric cancer, HP +**
- **Advanced-stage: other IL-1 alleles are more common (IL-1B-31C, IL-1B-511T, IL-1B-31C/IL-1B-511T haplotype)**

Glas J Clin Oncol 23: 4746; 2004

Gastric Cancer NSAID Use and COX-2

- **COX-2**
 - Over expressed in Gastric Cancers
- **Meta Analysis, 9 Case Control / Cohort Studies, 2831 pts gastric ca**
 - Regular use of aspirin or other NSAIDs:
 - Risk Reduction in Gastric ca of 28% (11-42% C.I.)
- **Trials of COX-2 Inhibition in High Risk Populations**

Wang et al JNCI 95:1784; 2003

Factors Associated with Risk of Developing Stomach Cancer

- **Familial:**
 - Mutation in CDH-1/E-cadherin gene
 - Calcium dependent cell adhesion protein
 - Autosomal dominant
 - Multifocal, diffuse cancers, young age
 - Lobular breast cancer
 - Prophylactic gastrectomy for carriers
 - Gastric ca develops in 3 of 4 carriers
- **FAP: polyposis colorectal ca, APC mutation, auto dominant**
- **HNPCC: nonpolyposis CRC, DNA mismatch repair mutation, auto dominant**

Hopkins Nature 392: 402; 1998 Huntsman NEJM 344: 1904; 2001

Gastric Cancer: Ethnic Differences and Natural History in the U.S.

- **MDACC: 1920 pts gastric ca, 1985-99**
- **70% Caucasian, 16% Latino, 8% African-American, 4% Asian**
- **Asians: more distal lesions, less M1 presentation**
 - Median Survival 26.7 mos, vs 10.5-12 mos
- **Whites, Latinos similar risk of death**
- **African Americans: 29% ↑ risk of death (p = 0.021) independent of stage, tumor location or gender**

Tseng J Clin Oncol 23: 3094; 2005

Question 1: Gastric Cancer and Heredity

- The following statements about gastric cancer and heredity are correct except:
- 1) Familial gastric cancer develops in patients with autosomal dominant E-cadherin mutation.
- 2) Gastric cancer occurs in patients with HNPCC, due to autosomal dominant DNA mismatch repair enzyme mutations.
- 3) Gastric cancer is associated with BRCA gene mutation carriers.
- 4) Susceptibility to the development of advanced gastric cancer may vary with genetic polymorphisms in inflammatory cytokines.

Gastric and Esophageal Cancer: New AJCC Staging

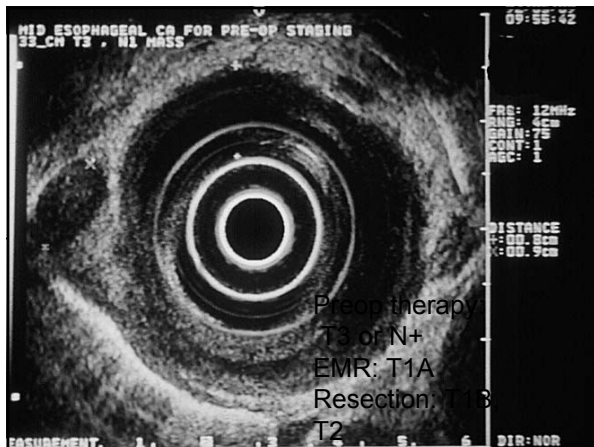
Gastric	Esophageal Adeno
• T1a: lamina propria/ musc mucosa	• T1a: intramucosal
• T1b: submucosal	• T1b: submucosal
• T2: muscle	• T2: muscle
• T3: transmural to adventitia	• T3: transmural / adventitia
• T4a: into serosa / peritoneum (old T3)	• T4a: pleura
• T4b: into adjacent organ	• T4b: aorta
• N1: 1-2 nodes	• N1: 1-2 nodes
• N2: 3-6 nodes	• N2: 3-6 nodes
• N3a: 7-15 nodes	• N3: 7+ nodes
• N3b: 16+ nodes	• M1: distant metastases
• M1: distant metastases	• Stage IAB: T1-2N0 (grade)
• Stage I: T1N0-1, T2N0	• Stage IIAB: T3N0, T1-2N1, T2N0 (gr)
• Stage II: T3N0, T2N1, T1N2,	• Stage IIIAB: T3N1-2, T4aN0, T1-2N2
• Stage III: T3N1-2, T4N0, T2N2,	• Stage IIIC: N3, T4aN1-2, T4b
• Stage IV: T4N1-4, M1	• Stage IV: M1

Gastric Cancer: Evaluation

- Endoscopy and biopsy
- CT scan of the abdomen and pelvis
 - Identify liver, peritoneal, nodal metastases
 - Pelvic imaging critical: carcinomatosis, ovarian metastases
- CT of the chest, or chest Xray
- Endoscopic ultrasound
- Laparoscopy
- PET Scan

Newer Diagnostic Tools

Tool	Advantages	Disadvantages
Endoscopic ultrasound	1) Accurate T staging 2) Resectability	1) Less accurate N staging 2) Not available everywhere
Laparoscopy	1) Resectability 2) Identifies occult peritoneal / liver metastasis in 15-25%, assess peritoneal cytology	1) Invasive surgical staging procedure 2) Operator dependent
PET Scan	1) Identifies 15% with occult metastases	1) One third of tumors PET negative



Gastric Cancer and PET scan

- MSKCC
- 84 patients surgical candidates with gastric cancer
- 30 patients (36%) had no uptake on PET
 - Esophagus / GE junction ca (95% PET+)
- PET negative tumors more commonly diffuse, poorly differentiated, and distal cancers
 - No outcome difference for PET + / PET - tumors
- PET did not identify peritoneal disease
- PET Identified 17% of patients with M1 disease (bone, retroperitoneal nodes, liver)

Gastric Cancer

Laparoscopy and Staging

Author	Patients	Laparoscopy vs Surgical Stage	% M1
MDACC	71	97%	23%
Sao Paolo	49	100%	16%
Rome	100	100%	21%
MSKCC	111	99%	37%
Rotterdam	60	100%	13% (25% cardia)

ilson mskcc 2000

Positive peritoneal cytology = Stage IV disease

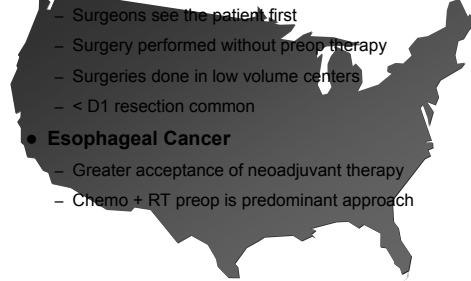
Esophageal and Gastric Carcinoma: U.S. Practice Patterns

• Gastric Cancer

- Surgeons see the patient first
- Surgery performed without preop therapy
- Surgeries done in low volume centers
- < D1 resection common

• Esophageal Cancer

- Greater acceptance of neoadjuvant therapy
- Chemo + RT preop is predominant approach



U.S. National Database: Gastric Cancer Surgical Outcome: 1985-1996

- 50,169 pts
- 63% 1 year survival
- 28% 5 year survival
- Poorer survival for males, proximal tumors
- Surgical Staging:
 - 27% had no or unknown LN's
 - 56% had <= 15 LN's
 - only 18% had > 15 LN's

Hundahl, Cancer 88:921; 2000

Randomized Study of D1 and D2 Dissection for Gastric Cancer

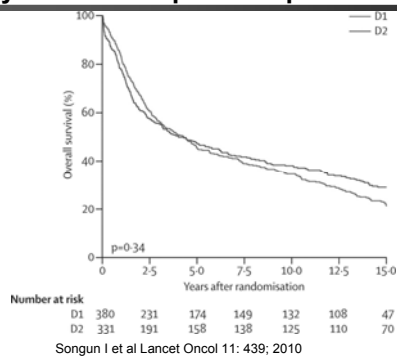
The Dutch Gastric Cancer Group

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: D2 Superior to D1



Question 2: Gastric Cancer

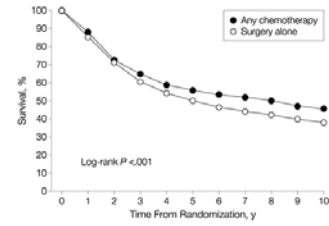
- Which of the following approaches improve disease free or overall survival in resectable gastric cancer?
- A) Pre and post operative chemotherapy with ECF.
- B) Post operative 5-FU and radiation therapy after surgery with less than a D1 resection.
- C) Post operative chemotherapy with S-1 or XELOX after a D2 resection.
- D) All of the above.
- E) A and B.
- F) None of the above.

Gastric Cancer: Adjuvant Therapy is Effective

- T3 or N + Adenocarcinoma: 3 competing approaches
 - Post op RT + chemo (U.S.)
 - INT 116: Post op 5FU-LV + RT, 10% 5 yr
 - Less than a D1 resection
 - Post op chemo (Asia)
 - ACTS-GC: S-1, 10% 3 yr
 - 1000 patients, all had D2 resection
 - Preop and post op chemo (U.K.)
 - MAGIC: ECF, 13% 5 yr
- Survival improvements with all approaches similar, modest

Cunningham NEJM 355: 11; 2006 Macdonald NEJM 345: 725; 2001 Sakuramoto NEJM 357: 1810; 2007

Surgery vs Adjuvant Chemo, Meta Analysis: Overall Survival increased by 6%



No. at risk
 Any chemotherapy 1924 1688 1385 1217 1080 929 709 526 390 297 243
 Surgery alone 1857 1568 1300 1092 952 782 583 407 267 172 138

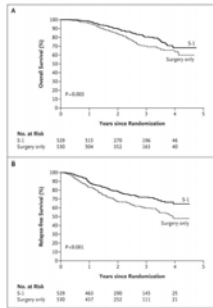
JAMA 2010;303:1729-1737

10 yr OS increased by 6%

JAMA

Copyright restrictions may apply.

Overall Survival and Relapse-free Survival: S1 for 1 yr vs Surgery Alone after D2 resection



Sakuramoto S et al. N Engl J Med 2007;357:1810-1820

Hazard Ratios for Death and P Values for the Interaction of Treatment Group and Baseline Characteristic among Eligible Patients.

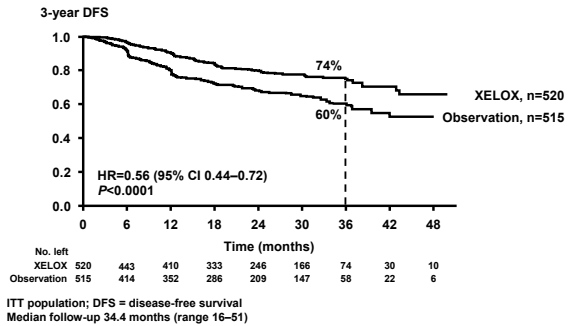
Baseline Characteristic	S:1	Surgery Only	Hazard Ratio for Death (95% CI)	P Value for Interaction
Total	1924	1857	0.95 (0.88, 1.02)	0.18
Sex				
Male	1018	987	0.95 (0.88, 1.02)	0.18
Female	906	870	0.95 (0.88, 1.02)	0.18
Age				
<65 yr	1018	987	0.95 (0.88, 1.02)	0.18
65-74 yr	406	393	0.95 (0.88, 1.02)	0.18
≥75 yr	500	477	0.95 (0.88, 1.02)	0.18
Cancer stage (operative classification)				0.86
Ia	437	420	0.95 (0.88, 1.02)	0.18
Ib	437	420	0.95 (0.88, 1.02)	0.18
IIa	437	420	0.95 (0.88, 1.02)	0.18
IIb	437	420	0.95 (0.88, 1.02)	0.18
Cancer stage (TNM classification)				0.89
Ic	363	348	0.95 (0.88, 1.02)	0.18
IIa	363	348	0.95 (0.88, 1.02)	0.18
IIb	363	348	0.95 (0.88, 1.02)	0.18
IIc	363	348	0.95 (0.88, 1.02)	0.18
IIIa	363	348	0.95 (0.88, 1.02)	0.18
IIIb	363	348	0.95 (0.88, 1.02)	0.18
IIIc	363	348	0.95 (0.88, 1.02)	0.18
IV	363	348	0.95 (0.88, 1.02)	0.18
IVa	363	348	0.95 (0.88, 1.02)	0.18
IVb	363	348	0.95 (0.88, 1.02)	0.18
IVc	363	348	0.95 (0.88, 1.02)	0.18
IVd	363	348	0.95 (0.88, 1.02)	0.18
IVe	363	348	0.95 (0.88, 1.02)	0.18
IVf	363	348	0.95 (0.88, 1.02)	0.18
IVg	363	348	0.95 (0.88, 1.02)	0.18
IVh	363	348	0.95 (0.88, 1.02)	0.18
IVi	363	348	0.95 (0.88, 1.02)	0.18
IVj	363	348	0.95 (0.88, 1.02)	0.18
IVk	363	348	0.95 (0.88, 1.02)	0.18
IVl	363	348	0.95 (0.88, 1.02)	0.18
IVm	363	348	0.95 (0.88, 1.02)	0.18
IVn	363	348	0.95 (0.88, 1.02)	0.18
IVo	363	348	0.95 (0.88, 1.02)	0.18
IVp	363	348	0.95 (0.88, 1.02)	0.18
IVq	363	348	0.95 (0.88, 1.02)	0.18
IVr	363	348	0.95 (0.88, 1.02)	0.18
IVs	363	348	0.95 (0.88, 1.02)	0.18
IVt	363	348	0.95 (0.88, 1.02)	0.18
IVu	363	348	0.95 (0.88, 1.02)	0.18
IVv	363	348	0.95 (0.88, 1.02)	0.18
IVw	363	348	0.95 (0.88, 1.02)	0.18
IVx	363	348	0.95 (0.88, 1.02)	0.18
IVy	363	348	0.95 (0.88, 1.02)	0.18
IVz	363	348	0.95 (0.88, 1.02)	0.18
IVaa	363	348	0.95 (0.88, 1.02)	0.18
IVab	363	348	0.95 (0.88, 1.02)	0.18
IVac	363	348	0.95 (0.88, 1.02)	0.18
IVad	363	348	0.95 (0.88, 1.02)	0.18
IVae	363	348	0.95 (0.88, 1.02)	0.18
IVaf	363	348	0.95 (0.88, 1.02)	0.18
IVag	363	348	0.95 (0.88, 1.02)	0.18
IVah	363	348	0.95 (0.88, 1.02)	0.18
IVai	363	348	0.95 (0.88, 1.02)	0.18
IVaj	363	348	0.95 (0.88, 1.02)	0.18
IVak	363	348	0.95 (0.88, 1.02)	0.18
IVal	363	348	0.95 (0.88, 1.02)	0.18
IVam	363	348	0.95 (0.88, 1.02)	0.18
IVan	363	348	0.95 (0.88, 1.02)	0.18
IVao	363	348	0.95 (0.88, 1.02)	0.18
IVap	363	348	0.95 (0.88, 1.02)	0.18
IVaq	363	348	0.95 (0.88, 1.02)	0.18
IVar	363	348	0.95 (0.88, 1.02)	0.18
IVas	363	348	0.95 (0.88, 1.02)	0.18
IVat	363	348	0.95 (0.88, 1.02)	0.18
IVau	363	348	0.95 (0.88, 1.02)	0.18
IVav	363	348	0.95 (0.88, 1.02)	0.18
IVaw	363	348	0.95 (0.88, 1.02)	0.18
IVax	363	348	0.95 (0.88, 1.02)	0.18
IVay	363	348	0.95 (0.88, 1.02)	0.18
IVaz	363	348	0.95 (0.88, 1.02)	0.18
IVba	363	348	0.95 (0.88, 1.02)	0.18
IVbb	363	348	0.95 (0.88, 1.02)	0.18
IVbc	363	348	0.95 (0.88, 1.02)	0.18
IVbd	363	348	0.95 (0.88, 1.02)	0.18
IVbe	363	348	0.95 (0.88, 1.02)	0.18
IVbf	363	348	0.95 (0.88, 1.02)	0.18
IVbg	363	348	0.95 (0.88, 1.02)	0.18
IVbh	363	348	0.95 (0.88, 1.02)	0.18
IVbi	363	348	0.95 (0.88, 1.02)	0.18
IVbj	363	348	0.95 (0.88, 1.02)	0.18
IVbk	363	348	0.95 (0.88, 1.02)	0.18
IVbl	363	348	0.95 (0.88, 1.02)	0.18
IVbm	363	348	0.95 (0.88, 1.02)	0.18
IVbn	363	348	0.95 (0.88, 1.02)	0.18
IVbo	363	348	0.95 (0.88, 1.02)	0.18
IVbp	363	348	0.95 (0.88, 1.02)	0.18
IVbq	363	348	0.95 (0.88, 1.02)	0.18
IVbr	363	348	0.95 (0.88, 1.02)	0.18
IVbs	363	348	0.95 (0.88, 1.02)	0.18
IVbt	363	348	0.95 (0.88, 1.02)	0.18
IVbu	363	348	0.95 (0.88, 1.02)	0.18
IVbv	363	348	0.95 (0.88, 1.02)	0.18
IVbw	363	348	0.95 (0.88, 1.02)	0.18
IVbx	363	348	0.95 (0.88, 1.02)	0.18
IVby	363	348	0.95 (0.88, 1.02)	0.18
IVbz	363	348	0.95 (0.88, 1.02)	0.18
IVca	363	348	0.95 (0.88, 1.02)	0.18
IVcb	363	348	0.95 (0.88, 1.02)	0.18
IVcc	363	348	0.95 (0.88, 1.02)	0.18
IVcd	363	348	0.95 (0.88, 1.02)	0.18
IVce	363	348	0.95 (0.88, 1.02)	0.18
IVcf	363	348	0.95 (0.88, 1.02)	0.18
IVcg	363	348	0.95 (0.88, 1.02)	0.18
IVch	363	348	0.95 (0.88, 1.02)	0.18
IVci	363	348	0.95 (0.88, 1.02)	0.18
IVcj	363	348	0.95 (0.88, 1.02)	0.18
IVck	363	348	0.95 (0.88, 1.02)	0.18
IVcl	363	348	0.95 (0.88, 1.02)	0.18
IVcm	363	348	0.95 (0.88, 1.02)	0.18
IVcn	363	348	0.95 (0.88, 1.02)	0.18
IVco	363	348	0.95 (0.88, 1.02)	0.18
IVcp	363	348	0.95 (0.88, 1.02)	0.18
IVcq	363	348	0.95 (0.88, 1.02)	0.18
IVcr	363	348	0.95 (0.88, 1.02)	0.18
IVcs	363	348	0.95 (0.88, 1.02)	0.18
IVct	363	348	0.95 (0.88, 1.02)	0.18
IVcu	363	348	0.95 (0.88, 1.02)	0.18
IVcv	363	348	0.95 (0.88, 1.02)	0.18
IVcw	363	348	0.95 (0.88, 1.02)	0.18
IVcx	363	348	0.95 (0.88, 1.02)	0.18
IVcy	363	348	0.95 (0.88, 1.02)	0.18
IVcz	363	348	0.95 (0.88, 1.02)	0.18
IVda	363	348	0.95 (0.88, 1.02)	0.18
IVdb	363	348	0.95 (0.88, 1.02)	0.18
IVdc	363	348	0.95 (0.88, 1.02)	0.18
IVdd	363	348	0.95 (0.88, 1.02)	0.18
IVde	363	348	0.95 (0.88, 1.02)	0.18
IVdf	363	348	0.95 (0.88, 1.02)	0.18
IVdg	363	348	0.95 (0.88, 1.02)	0.18
IVdh	363	348	0.95 (0.88, 1.02)	0.18
IVdi	363	348	0.95 (0.88, 1.02)	0.18
IVdj	363	348	0.95 (0.88, 1.02)	0.18
IVdk	363	348	0.95 (0.88, 1.02)	0.18
IVdl	363	348	0.95 (0.88, 1.02)	0.18
IVdm	363	348	0.95 (0.88, 1.02)	0.18
IVdn	363	348	0.95 (0.88, 1.02)	0.18
IVdo	363	348	0.95 (0.88, 1.02)	0.18
IVdp	363	348	0.95 (0.88, 1.02)	0.18
IVdq	363	348	0.95 (0.88, 1.02)	0.18
IVdr	363	348	0.95 (0.88, 1.02)	0.18
IVds	363	348	0.95 (0.88, 1.02)	0.18
IVdt	363	348	0.95 (0.88, 1.02)	0.18
IVdu	363	348	0.95 (0.88, 1.02)	0.18
IVdv	363	348	0.95 (0.88, 1.02)	0.18
IVdw	363	348	0.95 (0.88, 1.02)	0.18
IVdx	363	348	0.95 (0.88, 1.02)	0.18
IVdy	363	348	0.95 (0.88, 1.02)	0.18
IVdz	363	348	0.95 (0.88, 1.02)	0.18
IVea	363	348	0.95 (0.88, 1.02)	0.18
IVeb	363	348	0.95 (0.88, 1.02)	0.18
IVec	363	348	0.95 (0.88, 1.02)	0.18
IVed	363	348	0.95 (0.88, 1.02)	0.18
IVee	363	348	0.95 (0.88, 1.02)	0.18
IVef	363	348	0.95 (0.88, 1.02)	0.18
IVeg	363	348	0.95 (0.88, 1.02)	0.18
IVeh	363	348	0.95 (0.88, 1.02)	0.18
IVei	363	348	0.95 (0.88, 1.02)	0.18
IVej	363	348	0.95 (0.88, 1.02)	0.18
IVek	363	348	0.95 (0.88, 1.02)	0.18
IVel	363	348	0.95 (0.88, 1.02)	0.18
IVem	363	348	0.95 (0.88, 1.02)	0.18
IVen	363	348	0.95 (0.88, 1.02)	0.18
IVeo	363	348	0.95 (0.88, 1.02)	0.18
IVep	363	348	0.95 (0.88, 1.02)	0.18

Recurrence

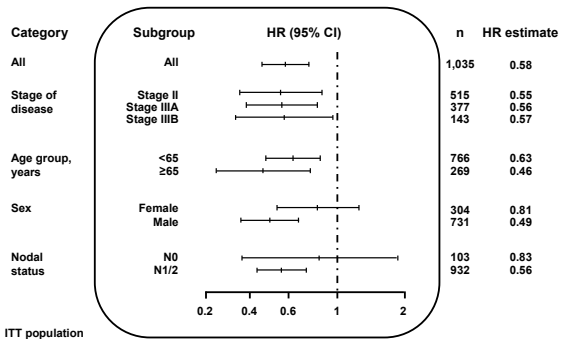
	Observation n=515	XELOX n=520
Patients with recurrence, n (%)	155 (30.1)	94 (18.1)
Location of recurrence, n		
Loco-regional	44	23
Peritoneal	59	48
Distant	78	44

ITT population, percentages based on the number of patients with recurrence, patients may have had 21 recurrence location

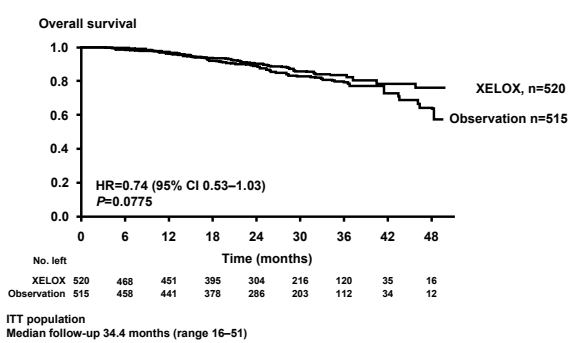
Primary endpoint (3-year DFS) met at interim analysis



3-year DFS by stratification factors

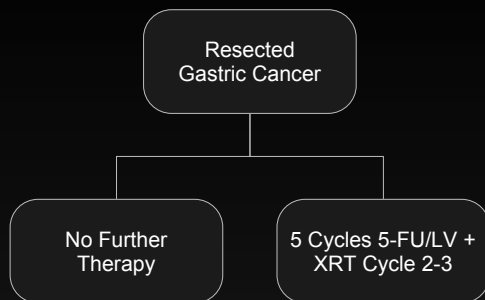


Overall survival at interim analysis



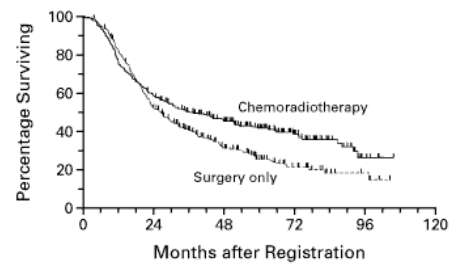
U.S. Intergroup 116 (SWOG 9008)

Gastric Cancer: Adjuvant 5-FU + RT



Macdonald NEJM 345: 725-730; 2001

Overall Survival: INT 116

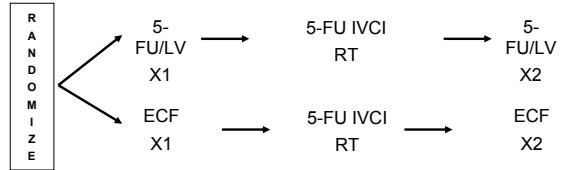


Macdonald NEJM 345: 725-730; 2001

INT 116: Gastric Cancer Conclusions

- Biggest impact in decreasing local recurrence
- Surgical resection: > 50% had less than a D1 resection
- Standard of care for gastric cancer in <D1 resection
- Will better surgery obviate chemoXRT?
 - INT 4 yr 46% chemoXRT = Dutch D1 5 yr 43%
 - INT series had more T3, N + patients

CALGB 80101: Study Schema



5-FU/LV: 5-FU 425 mg/m² d1-5, LV 20 mg/m² d1-5

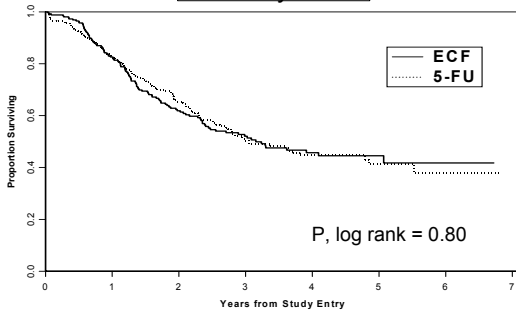
RT: 45 Gy (1.8 Gy X 25 fractions) with 5-FU 200 mg/m²/d CI

ECF (pre-RT): Epirubicin 50 mg/m² d1, Cisplatin 60 mg/m² d1, & 5-FU 200 mg/m²/d CI d1-21

ECF (post-RT): Epirubicin 40 mg/m² d1, Cisplatin 50 mg/m² d1, & 5-FU 200 mg/m²/d CI d1-21

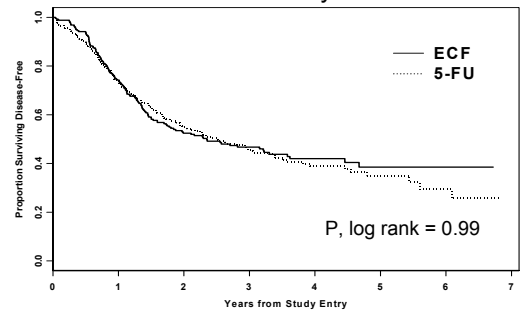
CALGB 80101

CALGB 80101
Overall Survival by Treatment Arm



CALGB 80101

CALGB 80101
Disease-Free Survival by Treatment Arm



CALGB 80101

CALGB 80101 and INT 0116
Overall Survival by Treatment

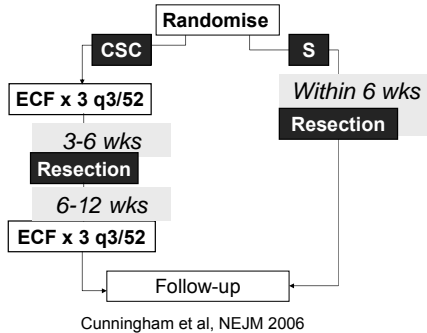
	CALGB 80101		INT 0116	
	5-FU/LV	ECF	5-FU/RT	Control
Median OS (mos)	37	38	36	27

CALGB 80101

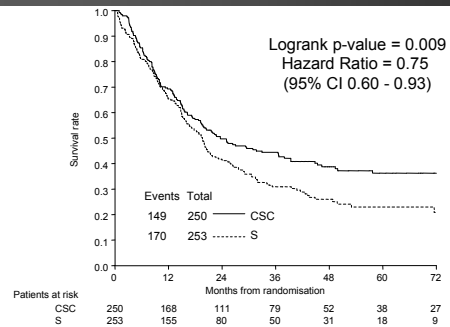
European / Asian Gastric Adjuvant Trials: Is RT required post op?

- Korea ARTIST trial: randomization + / - RT
 - Post op Capecitabine/Cisplatin
 - + / - Post op RT
 - D2 resection required
- CRITICS Trial (NL): randomization + / - RT
 - Preop ECX
 - D1 resection
 - Post op ECX versus Capecitabine/Cisplatin + RT
 - RTOG will not participate
- TROG (Australia): Preop ECF + / - RT
 - Esophageal and gastric, 750 pts

MAGIC Trial: Pre and Post Op ECF



Survival



MAGIC TRIAL: Preop Chemo in Gastric Cancer

- **Significant down staging**
 - No improvement in rate of R0 resection, no path CR
- **Survival Improved**
- **Supports preop chemo as a standard of care**
- **Survival benefit + 13%, without RT**
 - Comparable to U.S. 5-FU + RT: + 10%

MAGIC 2 Trial

- **In the U.K.: Preop chemo is the standard of care for gastric and esophageal cancer**
- **MAGIC 2:**
- **3 cycles of pre, 3 cycles of post op chemo**
- **ECX: epirubicin, cisplatin, capecitabine**
- **Randomization: + / - Anti VEGF Antibody Bevacizumab (Avastin)**

Adjuvant Therapy: Chemo, RT or Both?

- **Preop and post chemo with ECF improves survival in gastric cancer (MAGIC)**
- **Post op chemo 5-FU + RT improves survival in gastric cancer (U.S. INT)**
 - In pts with less than a D1 resection
- **Post op chemo S1 or XELOX improves survival**
 - After D2 resection (Japan, Korea)

Question 2: Gastric Cancer

- **Which of the following approaches improves disease free or overall survival in resectable gastric cancer?**
- **A) Pre and post operative chemotherapy with ECF.**
- **B) Post operative 5-FU and radiation therapy after surgery with less than a D1 resection.**
- **C) Post operative chemotherapy with S-1 or XELOX after a D2 resection.**
- **D) All of the above.**
- **E) A and B.**
- **F) None of the above.**

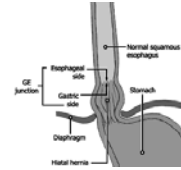
Ongoing Neoadjuvant RCTs for GC

Study	Country	Patient Number	Treatment	Surgery
MRC-ST03	U.K.	1100	ECX + / Bev	Preop
CRITICS	Holland	788	ECC + / - RT	Preop
JCOG0501	Japan	316	Surgery + S-1 vs S-1/Cis → Surgery → S-1	Pre and post op vs postop

Gastroesophageal Junction Tumors: Classification and Treatment

• Siewert Classification¹

- Type I: lesions with center 1-5 cm proximal to the GE junction
- Type II: lesions with center 1 cm proximal to and 2 cm distal to the GE junction
- Type III: lesions with center 2-5 cm distal to the GE junction



• Surgery is most common treatment

- 30% of GE junction tumors are unresectable²
- > 50% relapse following complete resection²

1. Siewert et al. *Ann Surg.* 2000;232:353.
2. Stahl. *Onkologie.* 2004;27:33.

Esophageal Adenocarcinoma: Consensus on Adjuvant Therapy

- T3 or N+: Something more than surgery alone should be done
- Preoperative chemotherapy ECF, CF improves overall survival in some but not all trials
 - MAGIC (ECF): 13% ↑ OS at 5 yr (esophageal, 120 pts)
 - FFOCD / FNLC (CF): 14% ↑ OS at 5 yr (esophageal cancer, 180 pts) → same as MAGIC, no epirubicin

Cunningham *NEJM* 355: 11; 2006, Boige *J Clin Oncol*, MRC

Esophageal Adenocarcinoma: Consensus on Adjuvant Therapy

- Trials focusing purely on esophageal and GE junction cancers
- Preoperative chemotherapy CF failed:
 - MRC 0E0-2 (CF): 800 pts
 - 5 year update: 6%
 - U.S. INT 113 (CF): 450 pts
 - No impact on OS
 - EORTC 40954 (CF): 70 pts
 - No impact on OS

Allum *J Clin Oncol* 2009, Kelsen *NEJM* 1988, Schuhmacher *J Clin Oncol* 27 (15s): abs 4510; 2009

Erasmus MC



Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study.

A. van der Gaast, P. van Hagen, M. Hulshof, M.I. van Berge Henegouwen, G.A. Nieuwenhuijzen, J.T. Plukker, J.J. Bonenkamp, E.W. Steyerberg, H.W. Tilanus. CROSS study group

Courtesy van der Gaast

Abstr 4004

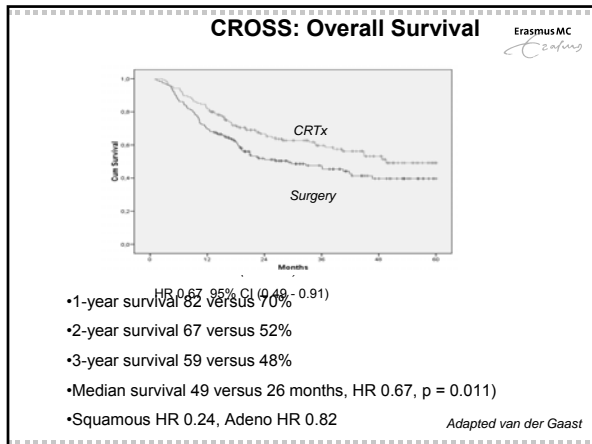
CROSS Active Treatment Arm

Erasmus MC

	Week 1							Week 2							Week 3							Week 4							Week 5						
	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S
XRT	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼	▼
CTX	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

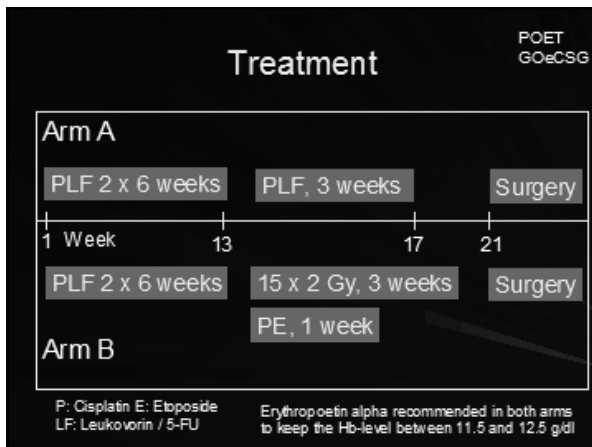
- Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29
- Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy
- Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)
- Major eligibility: Adeno- or squamous histology; N1 or ≥T2, PS ≤ 2

• Primary objective: Median overall survival 22 months (versus 16)



PreOperative Chemotherapy or Radiochemotherapy in Esophago-gastric Adenocarcinoma Trial POET

Michael Stahl
on behalf of the
German Oesophageal Cancer Study Group



Preop Chemo vs Chemo RT: Stahl

- EUS, laparoscopy staged pts
- Siewert I-III, T3-4 adenocarcinoma

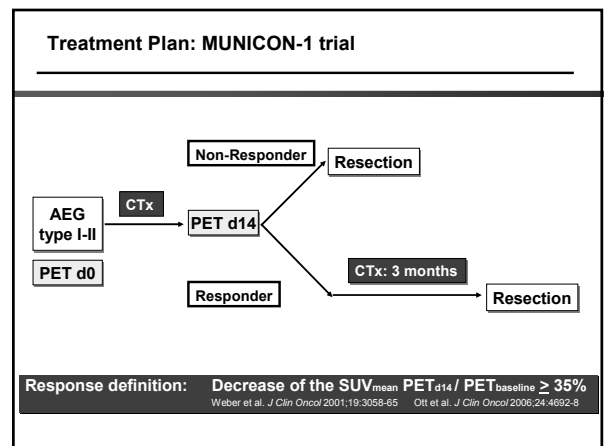
Arm	Pts	R0	pCR	N0	Median Survival	3 yr OS	Local Control
Chemo	59	70%	2%	37%	21 mos	28%	59%
Chemo RT	60	72%	16%	64%	33 mos	47% P = 0.07	77% P = 0.06

Stahl J Clin Oncol: 27: 836; 2009

Benefit from Preop Chemo assessed by PET scan

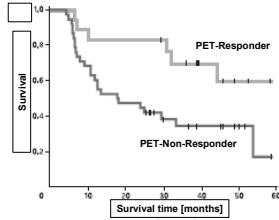
- Ott: 65 pts, preop chemo 12 wks 5-FU Cisplatin
- PET responders: SUV decline > 35% day 14
- Major pathologic response in 18% of all pts
- Benefit, response were limited to PET responders
 - Pathologic response: 44% vs 5%
 - 3 yr OS: 70% vs 35%
- Lordick: MUNICON Trial: PET non responders referred for immediate surgery, PET responders completed 12 wks of preop therapy
- CALGB 80803: PET scan during induction chemo selects chemotherapy during subsequent chemo + RT

Ott J Clin Oncol 24:4692;2006 Lordick Lancet Oncol 8: 797;2007



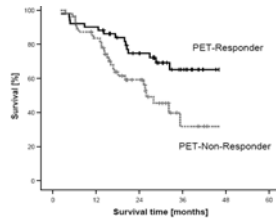
Comparison with historic cohort

Ott et al. *J Clin Oncol* 2006;24:4692-8
CTX for 12 weeks in all patients



Survival (median)
Responders: not reached
Non-Responders: 18 months

MUNICON-1 study, 2007
CTX stopped after 2wks in Non-Responders



Survival (median)
Responders: not reached
Non-Responders: 26 months

PET Scan Directed Therapy Trial Design: CALGB 80803

T3/4 or N1
Esophageal
Adenoca

PET/CT: Induction
Chemo: modified
FOLFOX6 days
1,15, 22 or
Carbo/Taxol days
1,8,22,29

PET Scan
day 29-35

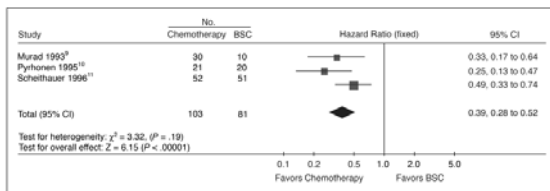
PET-responders: $\geq 35\%$
SUV decrease: continue
same chemo + concurrent
RT (5040cGy in 180cGy fx)

Surgical resection
6 weeks post-RT

PET- nonresponders: $< 35\%$
SUV decrease:
Cross over to alternate
chemo + RT (5040cGy in
180cGy fx)

Hypothesis: changing chemo in PET non
responding patients will improve pCR
during chemo + RT

Best Supportive Care vs Chemotherapy



Wagner *J Clin Oncol* 24: 2903; 2006

Question 3: GE Junction Cancer

- A 55 yo pt presents with a GE junction mass and multiple hepatic masses.
- The tumor should be tested for:
 - A) HER2
 - B) KRAS
 - C) BRAF
 - D) EGFR
 - E) All of the above

Question 4: Gastric Cancer

- A 45 y.o. male presents with a complaint of epigastric pain and early satiety for 3 months. Endoscopy reveals a mass in the GE junction extending into the gastric cardia and a biopsy reveals adenocarcinoma. CT scan reveals bilobar hepatic metastases, lung nodules, and extensive celiac and retroperitoneal lymph nodes.
- IHC for HER2 is 3+ positive. EGFR stains 3+ positive.
- The most appropriate treatment is:
 - A) 5-FU + cisplatin
 - B) Capecitabine + cis or oxaliplatin
 - C) Cetuximab + 5-FU + cisplatin
 - D) Epirubicin + cisplatin + 5-FU
 - E) Trastuzumab + 5-FU + cisplatin
 - F) Docetaxel + cisplatin + 5-FU

Meta Analysis of Chemotherapy Trials

- 27 trials analyzed, gastric and esophageal adenocarcinoma
- Combination chemo superior to single agent 5-FU
 - 1 month survival increase
- Irinotecan combination therapy trended superior to 5-FU + cisplatin
 - 1 month survival increase
- 5-FU + Cisplatin + / - Anthracycline
 - 2 month survival increase for anthracycline
 - Largely based on MRC trial of ECF vs Mito-CF (more toxic)

Wagner *J Clin Oncol* 24: 2903; 2006

Esophago-Gastric Cancer: Metastatic Disease

- CIV 5-FU + cisplatin
 - 4-5 day to 6 week 5-FU infusion
 - RR 20-30%, OS 8-9 months
 - This schedule should be abandoned
- Superior toxicity for CRC scheduling (every 2 week schedule), FOLFOX and FOLFIRI are acceptable therapy
- Capecitabine = CIV 5-FU, Oxaliplatin = Cisplatin
- Adding a third drug:
 - Epirubicin (ECF): RR 40-45%, Med S 9 mos
 - Docetaxel (DCF): RR 36%, Med S 9 mos
 - 10% increment in response rate
 - 1 month increment in survival

Is ECF a Superior Regimen?

- 2 phase III trials, 854 pts
 - ECF (CIV 5-FU) superior to FAMTX (bolus 5-FU)
 - ECF = Mitomycin + CF
 - Absence of difference Epi vs Mito: 3rd drug does not add to CF
- Meta Analysis (Wagner JCO 2006):
 - Anthracycline + CF: + 2 month survival
 - Based on subset analysis from one trial
- Supports infusional over bolus 5-FU
- Supports lower dose cisplatin (60/m)

Gastric Cancer: European Phase III Trials in Advanced Disease, 1990's

Regimen	Patients	Response Rate	Median Survival
ELF vs	245	9%	31 weeks
FAMTX vs		12%	28 weeks
Cisplatin-5-FU		21%	31 weeks
FAMTX vs	274	21%	23 weeks
ECF		45%	35 weeks

Van Hoef J Clin Oncol 18: 2648; 2000 Webb J Clin Oncol 15: 261; 1997

REAL-2 Trial: Phase III Comparing Capecitabine With 5-FU and Oxaliplatin With Cisplatin

ECF (N=249)

Epirubicin 50 mg/m² iv 3 wkly
Cisplatin 60 mg/m² iv 3 wkly
5 FU 200 mg/m²/d iv given continuously

ECX (N=241)

Epirubicin 50 mg/m² iv 3 wkly
Cisplatin 60 mg/m² iv 3 wkly
Capecitabine 625 mg/m² bid po continuously

EOF (N=235)

Epirubicin 50 mg/m² iv 3 wkly
Oxaliplatin 130 mg/m² iv 3 wkly
5 FU 200 mg/m²/d iv given continuously

EOX (N=239)

Epirubicin 50 mg/m² iv 3 wkly
Oxaliplatin 130 mg/m² iv 3 wkly
Capecitabine 625 mg/m² bid po continuously

- 2 X 2 Randomization, 8 cycles

- Non-inferiority of X over F and O over C with 1-yr survival of 35% with a 1 side α of 5%

Cunningham NEJM 2008

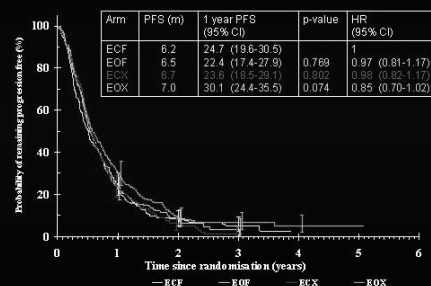
REAL 2: Response

Best overall Response

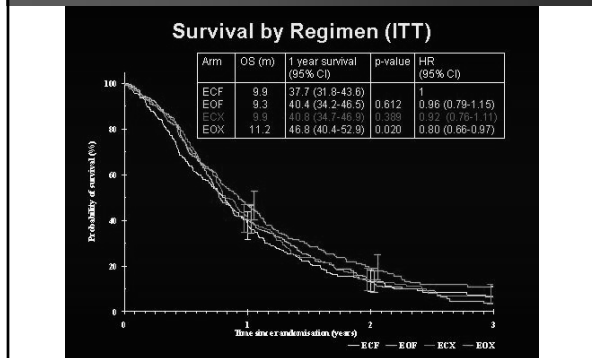
Response (%)	ECF n=249	ECX n=241	EOF n=235	EOX n=239
Evaluable	246	237	231	234
CR	4.1%	4.2%	2.6%	3.9%
PR	36.6%	42.2%	39.8%	44.0%
CR + PR	40.7%	46.4%	42.4%	47.9%
95% CI	(34.5-46.8)	(40.0-52.8)	(36.1-48.8)	(41.5-54.3)
p-value vs ECF		0.202	0.694	0.112
SD	31.3%	32.1	15.2%	27.8%
PD or died	28.0%	21.5%	24.7%	24.4%

REAL 2: PFS

Progression-free survival (ITT)



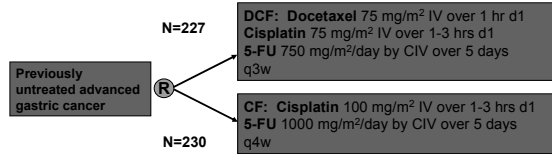
REAL 2: Overall Survival



TAX325: Phase III Cisplatin / 5-FU vs Docetaxel / Cisplatin / 5-FU (DCF)

Primary endpoint: Time to progression (TTP) from 4 → 6 months

Secondary endpoints: Overall survival (OS), response rate (RR), safety, QoL, clinical benefit



Van Cutsem et al. V325. JCO 2006

Docetaxel + 5-FU/Cis (DCF) vs 5-FU/Cis (CF)

	DCF	CF
Age	55	55
Number	221	224
Met disease	96%	97%
RR	37%	25% (p=0.011)
TTP	5.6 months	3.7 months (p=0.0004)
OS	9.2 months	8.6 months (p=0.0201)

Van Cutsem et al J Clin Oncol 2006

DCF vs CF: Toxicity

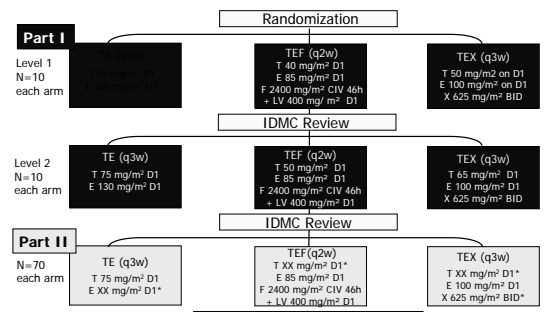
Grade 3/4 Toxicity	DCF	CF
Stomatitis	21%	27%
Diarrhea	19%	8%
Nausea/vomiting	14%	17%
Neutropenia	82%	57%
Neutropenic fever	29%	12%
Toxic deaths	3.6%	5.4%
Off therapy for AE or consent withdrawal	49%	37%

Van Cutsem J Clin Oncol 2006

DCF: Alternative Regimens

- **Doce + Cis vs CF phase III: No Difference**
 - RR 24%, TTP 5.8-6.6 mos, OS 8.2-9.5 mos
- **Doce + 5-FU evaluated in 1 randomized phase II trial**
 - Docetaxel 75 mg/m² + CIV 5-FU 200 mg/m²/daily
 - RR 38%, TTP 5.5 mos, OS 9.5 mos
 - Neutropenia 42%, neutropenic fever 4%
- **DF a more tolerable combination**

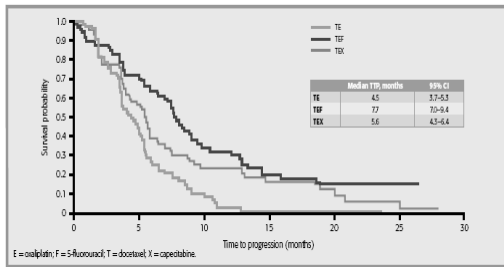
GATE Study Design



*XX: optimal dose was to be recommended by the IDMC after review of safety data

T, docetaxel; E, oxaliplatin; F, fluorouracil; X, capecitabine; LV, leucovorin; CIV, continuous infusion; IDMC, independent data monitoring committee; D1, day 1

Time to Progression*



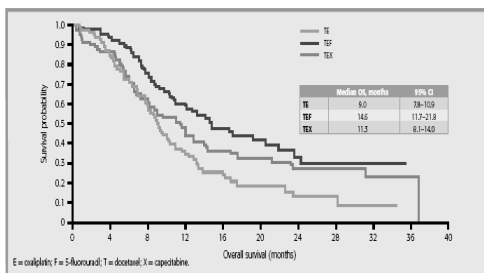
*Assessed in the full analysis population

Overall Response Rate*

	% of patients		
	TE (n=78)	TEF (n=88)	TEX (n=82)
ORR (95% CI)	23.1 (14.3-34.0)	46.6 (35.9-57.5)	25.6 (16.6-36.4)
Complete response	2.6	9.1	4.9
Partial response	20.5	37.5	20.7
No change/stable disease	47.4	35.2	46.3
Progressive disease	21.8	10.2	15.9
Not evaluable	7.7	8.0	12.2

*Response rate was assessed by WHO criteria in the full analysis population
T, docetaxel; E, oxaliplatin; F, fluorouracil; X, capecitabine

Overall Survival*



*Assessed in the full analysis population

Oxaliplatin vs Cisplatin? Colorectal Cancer 5-FU Dosing, Gastric Cancer

- FLO vs FLP
 - Oxaliplatin 85/m2 vs Cisplatin 50/m2 q 2 weeks
- 24 hr CIV 5-FU 2000-2600/m2 + LV 200/m2 weekly or bi-weekly
- 210 pts randomized
- TTP primary endpoint
- Non inferiority for Oxaliplatin
- Superiority for patients > 65

	FLO	FLP	P
TTP	5.8 mo	3.9 mo	.077
OS	10.7 mo	8.8 mo	NS
% RR	35 %	25%	NS

AI-Batran JCO 26: 1435; 2008

Toxicity: FLO vs FLP, CRC Schedule

Non-hematological Adverse Events (SP)

	Gr. 1/2 %		Gr. 3/4 %		Gr. 1-4 %		p-value ¹
	FLO	FLP	FLO	FLP	FLO	FLP	
Nausea	59	75	10	9	69	84	.025
Vomiting ¹	22	43	3	5	25	48	.0042
Diarrhea	31	32	6	7	37	39	NS
Stomatitis	8	12	3	4	12	16	NS
Alopecia	21	39	-	-	21	39	.0054
Renal	13	37	1	0	14	37	.0004
Fatigue	20	31	4	9	24	40	.024
Sensory	48	22	13 ³	3	60	25	<.0001

¹Thompson for trend
²Using the test for trend cycle (8 weeks)
³Oxaliplatin specific scale

Toxicity: FLO vs FLP, CRC Schedule

Grade 3/4 Hematological Abnormalities / Severe Adverse Events (SP)

	FLO	FLP	p-value ¹
Leukopenia	8%	12%	<.05
Neutropenia	10%	15%	NS
Anemia	6%	10%	<.05
Thrombos	4%	4%	NS
Feb. neutropenia	4%	3%	NS
Severe adverse events			
At least one	32%	38%	NS
Related	9%	19%	<.05 ²
Discontinuation toxicity + consent withdrawal	15%	23%	

¹Chi square for trend
²Fisher's exact

Pooled analyses favor capecitabine, oxaliplatin

- **Meta Analysis of Gastric cancer trials of capecitabine**
 - 1318 patients, REAL-2 and Kang Trials
 - OS favored capecitabine over 5-FU, HR 0.87, p = 0.02
 - Response favored capecitabine, odds ratio 1.38, p = 0.006
- **Thromboembolic events in U.K. trials**
 - REAL -2 Trial
 - 964 pts, venous TE 12% arterial TE 2%
 - Fewer TE's with oxaliplatin than cisplatin (7.6% vs 15.1%, p 0.0003)

Okinos Ann Oncol 20: 1529; 2009 Starling J Clin Oncol 27:3786; 2009

Gastric + GE Junction Cancer Chemotherapy: What regimen to use?

- Oxaliplatin = Cisplatin, Capecitabine = 5-FU
- DCF > CF: more toxicity
- Doublets: Preferred for most pts, CRC like scheduling (FOLFOX and FOLFIRI)
- IF = CF: less toxicity

	Oxaliplatin EOX or EOF	Cape ECX or EOX	XP	FLO	FUFIRI	DCF	ECF
Pts	489	513	160	109	170	221	126
%RR	44%	45%	41%	34%	32%	36%	45%
TTP, mos	6.7	6.5	5.6	5.5	5.0	5.6	7.4
OS, mos	10.9	10.4	10.5	--	9.0	9.2	8.9

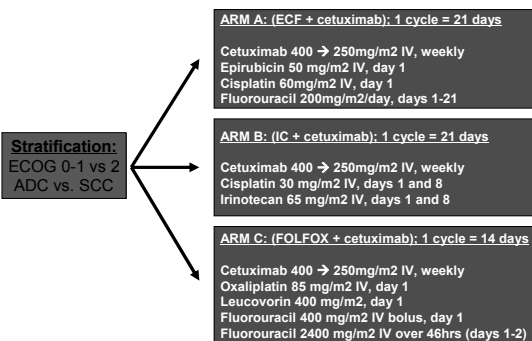
S-1

- S-1: a novel oral fluorouracil formulation
- FT: Tegafur, 5-FU prodrug +
- CDHP: DPD inhibitor +
- Oxo: bowel protectant
- Molar ratio of 1.0 : 0.4 : 1.0
- Developed as orally absorbed 5-FU preparation with potentially less bowel toxicity
- Phase III (Japan): S-1 + Cisplatin superior to S-1 alone, S-1 superior to CIV 5-FU
- Phase III FLAGS (U.S.): S-1 + cisplatin no better than 5-FU + Cisplatin

CALGB 80403 / ECOG 1206: Randomized Phase II Study of Standard Chemotherapy + Cetuximab for Metastatic Esophageal Cancer

PC Enzinger, BA Burtness, DR Hollis,
D Niedzwiecki, DH Ilson, AB Benson 3rd,
RJ Mayer, RM Goldberg

CALGB 80403 / ECOG E1206: Schema

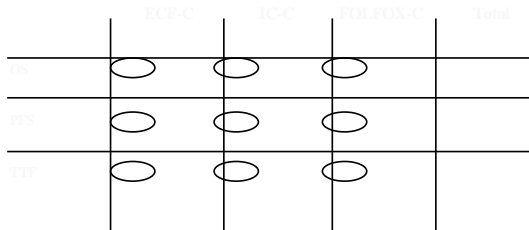


CALGB 80403/ECOG 1206: Response

	ECF-C N=84	IC-C N=82	FOLFOX-C N=83
Response			
Objective Response rate*	57.8	45.6	53.6
Response duration (mos)	6.1	5.3	5.7

*RECIST - confirmed; restaging every 6 weeks

CALGB 80403/ECOG 1206: Survival



Targeted Therapies

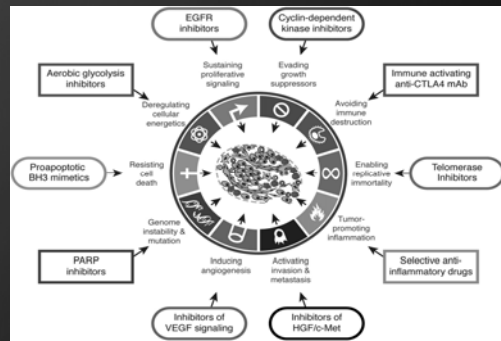
- Conventional, cytotoxic chemotherapy has limited benefit
- Targeted agents: attempt to block specific tumor growth pathways
- Monoclonal antibodies
- Tyrosine kinase inhibitors
- Soluble receptors to growth factors
- Inhibition of pathways involved in protein synthesis and degradation

Molecular Targets: Gastric Cancer

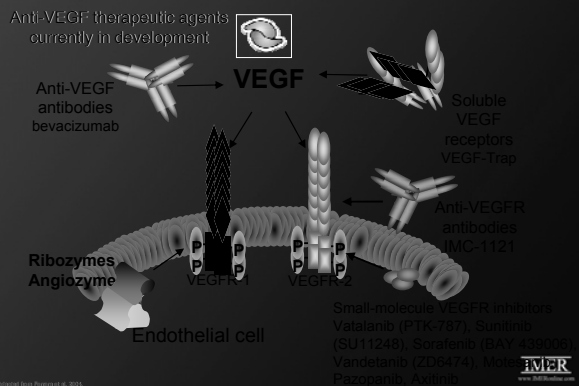
- KRAS mutation: < 5-10%
- BRAF mutation: < 5%
- EGFr over expression: 50-80%
 - TKI's inactive in phase II (0-9% RR, rapid POD)
 - Cetuximab monotherapy inactive phase II (3% RR, rapid POD, PFS 1.8 mos)
- EGFr mutation: < 5%
- CMET: < 10%
- HER2 over expression: 10-25%
- Except for HER2, no predictive markers have been identified

Galizia W J Surg 31: 1458; 2007 Mammano Anticancer Res 26: 3547; 2006
 Lee Oncogene 22: 6942; 2003 Yano Oncol Rep 15: 65; 2006 Gold GI CA
 Symp 2008 Abs 96

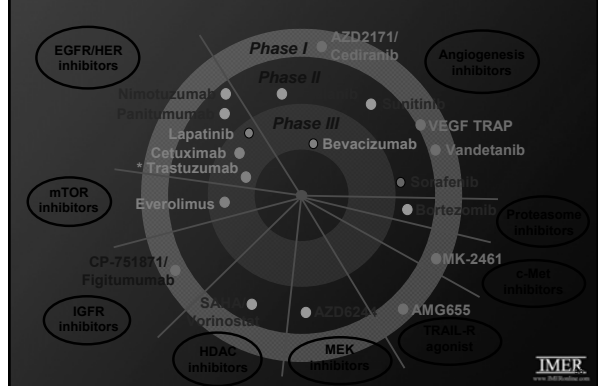
Therapeutic Targeting of Hallmarks



Agents Targeting the VEGF Pathway



Targeted Agents Under Investigation in GC



Targeted Agents Phase III: Met Disease

- **AVAGAST (Roche): Cape-Cisplatin + / - Bevacizumab**
 - Negative trial of overall survival endpoint
- **REAL 3: ECX + / - Panitumumab (U.K.)**
- **EXPAND: Cape-Cis + / Cetuximab (E.U.)**
- **LOGIC: Cape-Ox + / - Lapatinib (HER2+)**
- **TOGA: Her-2 + positive gastric cancer**
 - Cape-Cisplatin + / - Trastuzumab
 - Improved RR, PFS, OS

HER2 Expression in Gastric/GEJ Cancer

- According to the ToGA trial, approximately 22% of patients with gastric/GEJ cancer are HER2+¹
 - HER2 status should be included in the diagnostic protocol for metastatic GC

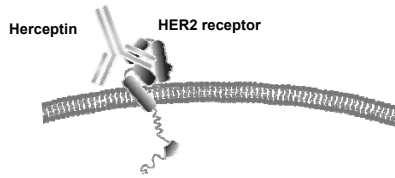
Incidence of HER2 Expression by IHC or FISH ¹⁻⁶		
All GC tumors	—	13%-23%
Histology	Intestinal	16%-34%
	Diffuse	6%-7%
	Mixed	20%
	Unknown	14%
Primary tumor location	GEJ	25%-34%
	Gastric	9%-20%

DFS=disease-free survival; FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; OS=overall survival.

1. Bang YJ et al. *Lancet*. 2010;6736(10):61121-61132; 3. Gravalos C, Jimeno A. *Ann Oncol*. 2008;19:1523-1529; 4. Yano T et al. *J Clin Oncol*. 2004;22:145 [Abstract 4053]; 5. Gravalos C et al. 2007:130 [Abstract 89]; 6. Lordick F et al. *Eur J Cancer*. 2007;5:271 [Abstract 354].



Proposed Herceptin Mechanism of Action



Based on preclinical studies, Herceptin is designed to¹⁻⁸:

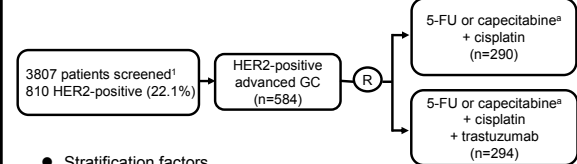
- Block downstream HER2 signalling to inhibit proliferation of cells
- Bind to HER2+ tumor cells and flag them for destruction by the immune system
- Enhance the effects of chemotherapy

1. Yakes FM et al. *Cancer Res*. 2002;62:4132-4141; 2. Arnold L et al. *Br J Cancer*. 2006;94:259-267; 3. Bianco AR. *J Chemother*. 2004;16:52-54; 4. Lewis GD et al. *Cancer Immunol Immunother*. 1993;37:255-263; 5. Yarden Y. *Oncology*. 2001;61:1-13; 6. Program MD et al. *J Natl Cancer Inst*. 2004;96:739-749; 7. Basaglia J. *Cancer Res*. 1998;58:2925-2931; 8. Molina MA et al. *Cancer Res*. 2001;61:4744-4749.



ToGA trial design

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

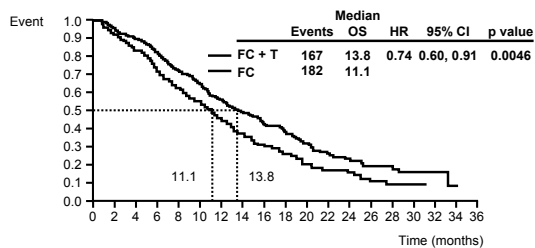


- Stratification factors
 - advanced vs metastatic
 - GC vs GEJ
 - measurable vs non-measurable
 - ECOG PS 0-1 vs 2
 - capecitabine vs 5-FU

^aChosen at investigator's discretion
GEJ, gastroesophageal junction

¹Bang et al; Abstract 4556, ASCO 2009

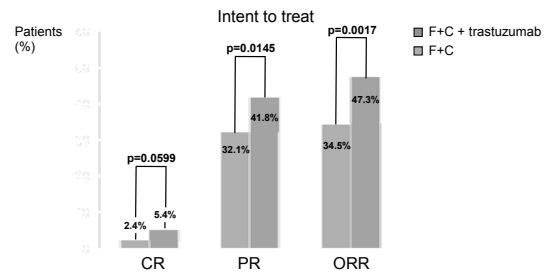
Primary end point: OS



No. at risk
 FC+T: 294, 277, 246, 209, 173, 147, 113, 90, 71, 56, 43, 30, 21, 13, 12, 6, 4, 1, 0
 FC: 290, 266, 223, 185, 143, 117, 90, 64, 47, 32, 24, 16, 14, 7, 6, 5, 0, 0, 0

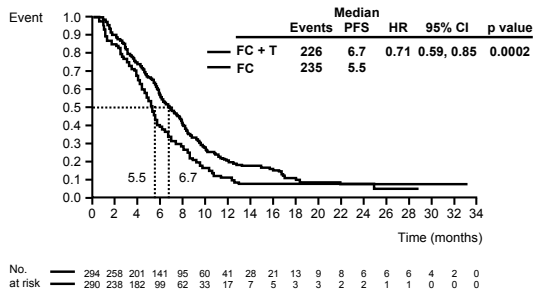
T, trastuzumab

Secondary end point: tumor response rate



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

Secondary end point: PFS



Question 3: GE Junction Cancer

- A 55 yo pt presents with a GE junction mass and multiple hepatic masses.
- The tumor should be tested for:
 - A) HER2
 - B) KRAS
 - C) BRAF
 - D) EGFR
 - E) All of the above

Question 4: Gastric Cancer

- A 45 y.o. male presents with a complaint of epigastric pain and early satiety for 3 months. Endoscopy reveals a mass in the GE junction extending into the gastric cardia and a biopsy reveals adenocarcinoma. CT scan reveals bilobar hepatic metastases, lung nodules, and extensive celiac and retroperitoneal lymph nodes.
- IHC for HER2 is 3+ positive. EGFR stains 3+ positive.
- The most appropriate treatment is:
 - A) 5-FU + cisplatin
 - B) Capecitabine + oxaliplatin
 - C) Cetuximab + 5-FU + cisplatin
 - D) Epirubicin + cisplatin + 5-FU
 - E) Trastuzumab + 5-FU + cisplatin

Gastric Cancer: Summary

- Rare cancers, adeno Eso/GE jxn increasing
- Poor survival with Surgery Alone (20-30%)
- Adjuvant Therapy for Gastric Cancer
 - Post op 5-FU + RT (less than D1)
 - Preop and post op chemo without RT: MAGIC trial in gastric cancer
 - Post op chemo after D2 resection (Asia)
- Adjuvant Therapy in GE Junction Cancer
 - Preop Chemo, ChemoRT improve survival
 - Trends support chemoRT over chemo alone
 - Carboplatin, paclitaxel, RT a new standard

Esophageal and Gastric Cancer: Summary

- Metastatic Disease
 - CF +third drug, Epirubicin or Docetaxel increases RR by 10%, survival by one month
 - Two drug alternatives (FOLFOX, XELOX, FOLFIRI) less toxic
- Targeted therapies
 - Trastuzumab improves outcome in HER2+ esophagogastric ca