

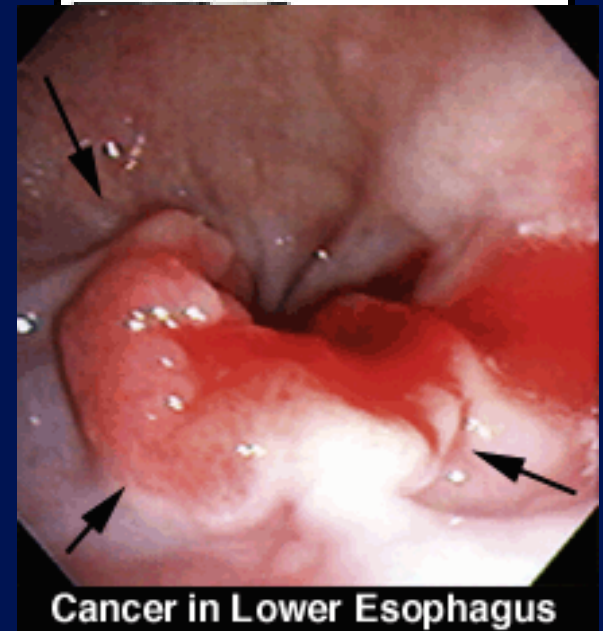
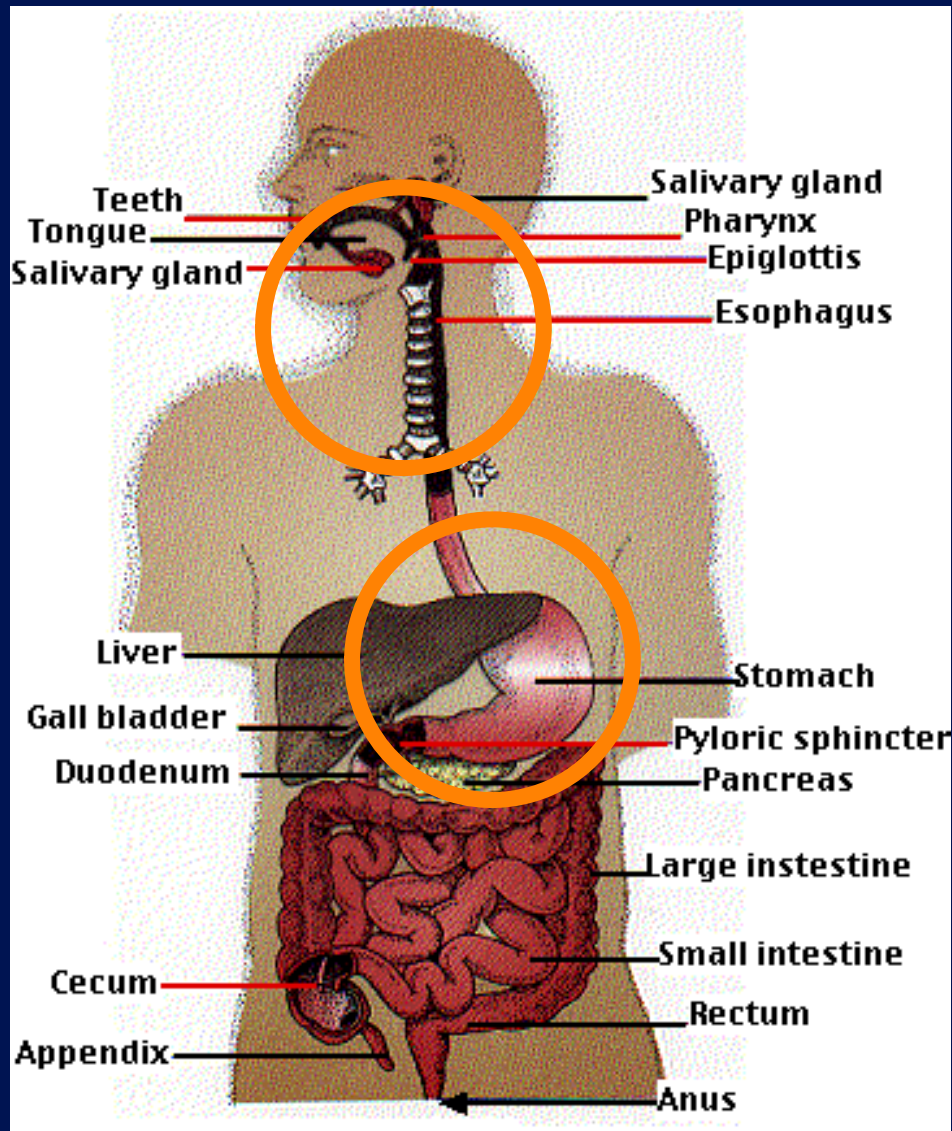
Esophageal and Gastric Cancer: Updates in Treatment Options

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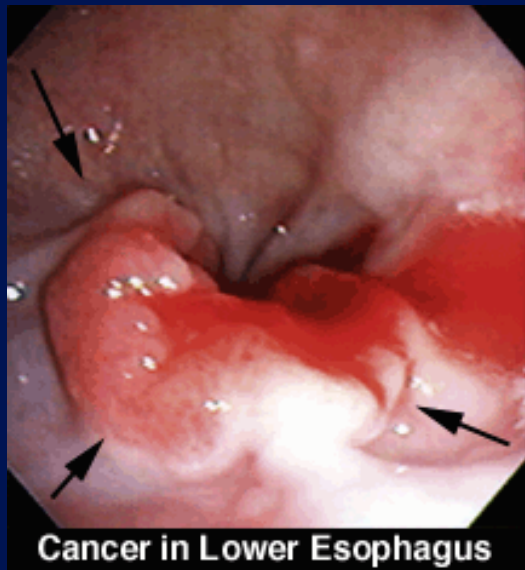
Abramson Cancer Center



One “Organ System”, Three Cancers

- 35,000 cases/yr
- Three distinct pathologic entities
 - Squamous cell carcinoma of the esophagus
 - Adenocarcinoma of the distal esophagus and junction with stomach (“GE junction”)
 - Adenocarcinoma of the distal stomach

Esophageal Cancer



- Epidemiology: M:F = 7:1, Asia
- Etiology: tobacco, EtOH, diet, Barrett's Esophagus
- Signs and Symptoms: dysphagia (difficulty swallowing), weight loss, cough, odynophagia (pain)
- Diagnosis: endoscopy, endoscopic ultrasound, CT scan, PET scan

Staging of Esophageal Cancer

- **TNM Classification**

- **Clinical Staging**

- Localized and resectable (T1-2, N0)
- Potentially resectable (T3 or N1: Stage II or III)
- Locally advanced unresectable
- Metastatic

Timing of Oncology Treatment

Neoadjuvant: treatment PRIOR to surgery

Adjuvant: treatment AFTER surgery

Metastatic: systemic treatment
not associated with surgery

Esophageal Cancer: Treatment Approaches

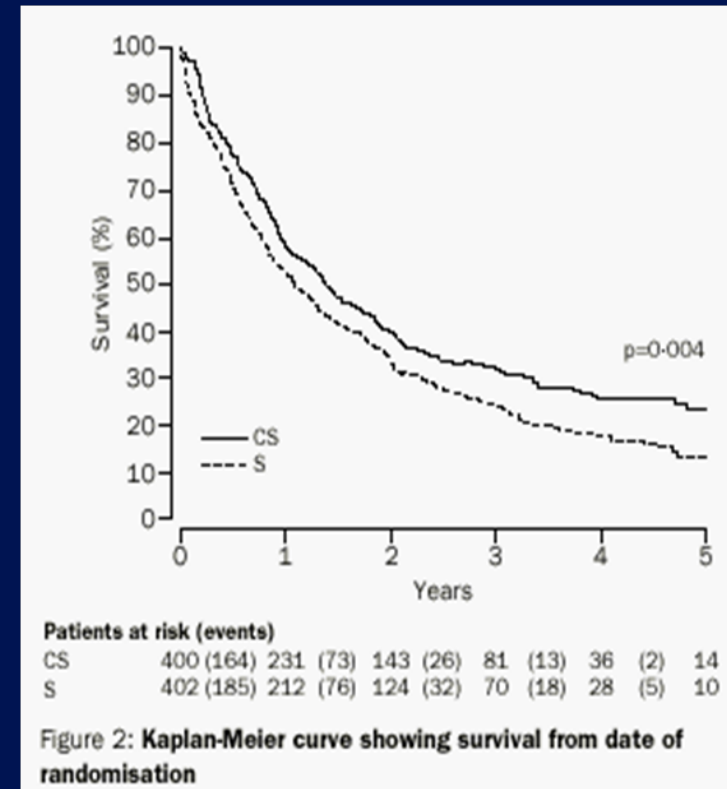
- Localized disease (Stage 0-II):
 - Surgery
 - Chemoradiation (platinum, 5-FU)
 - Combination neoadjuvant (preoperative) chemoradiation and surgery

Neoadjuvant Therapy for Esophageal Cancer

- Neoadjuvant = PREoperative therapy
- Chemotherapy alone
- Radiation alone
- Chemotherapy plus radiation (chemoradiotherapy)

Neoadjuvant Chemotherapy of Esophageal Cancer: Phase III Trial

- n = 802 patients
- 5-FU / cisplatin
- Median survival:
 - 16.8 mo. versus 13.3 mo.
- 2 year survival:
 - 43% versus 34%



MRC Esophageal Working Party.

Preoperative Chemoradiation of Esophageal Cancer: Phase III Trials

Inconclusive results in late phase trials

Study	N	3-year Survival, %	
		Surgery	Combined
Walsh	113	6	32
Urba	100	16	30
EORTC	282	35	37

2 of 3 studies show benefit for chemoradiation

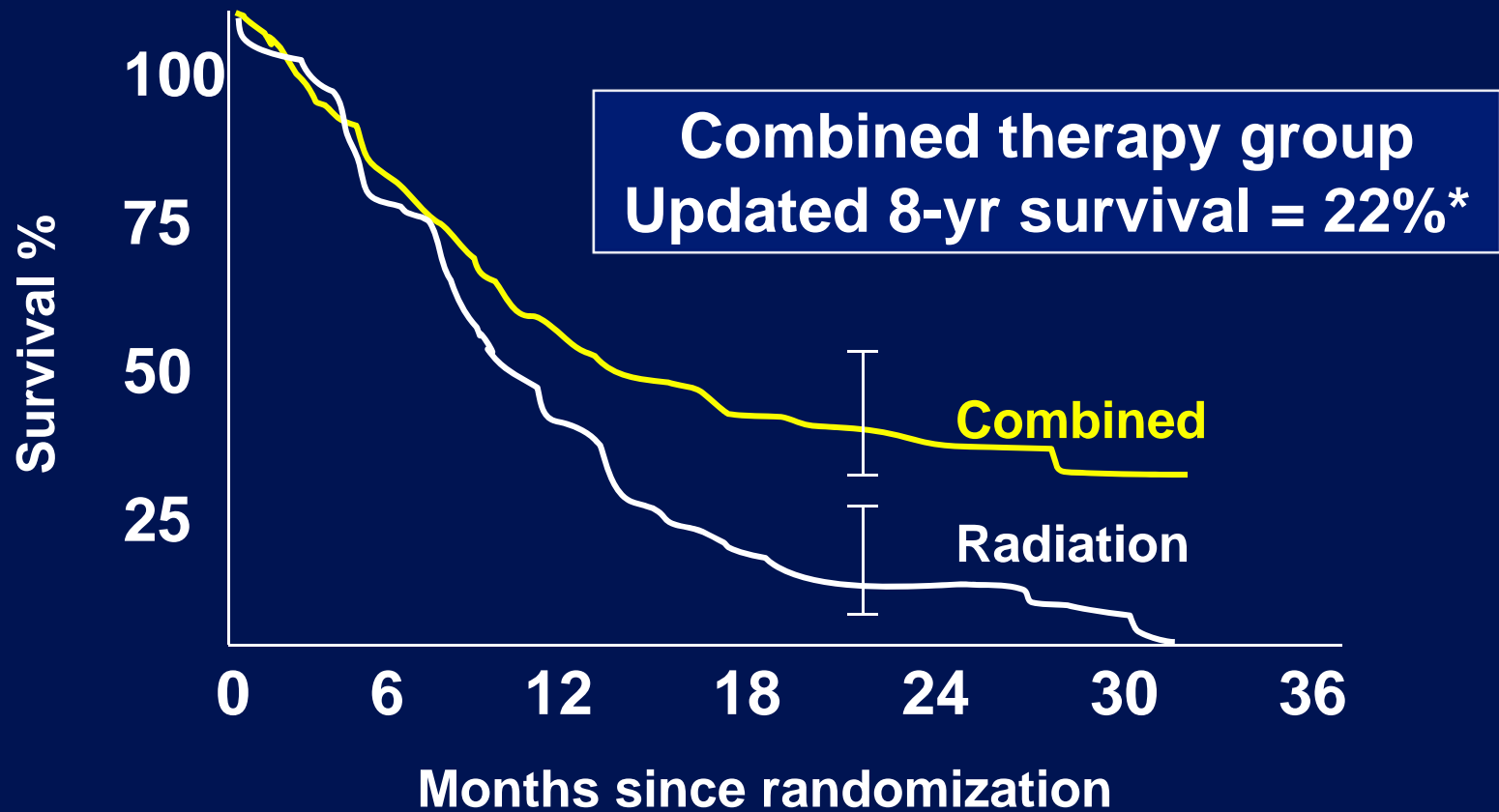
Preoperative Chemoradiation of Esophageal Cancer

- Pathologic Complete Response in 20-40% of patients at surgery
- 5 year Disease Free Survival 25-35%
- Significant toxicity
- 5-FU + Cisplatin + Radiation Therapy
- Severe GI toxicity
 - Requirement for tube feeding

Localized Esophageal Cancer: Primary Chemoradiation

- RTOG 8501
 - Chemoradiation (5-FU plus XRT) versus Radiation alone (64 Gy)
 - 5 year Survival: 27% versus 0 % benefit for chemoradiation

RTOG 8501: Survival

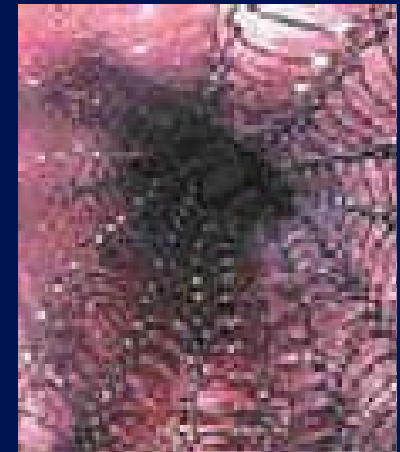


New Agents For Combined Modality Treatment with Radiation Therapy

- Irinotecan
 - Combined with cisplatin
- Taxanes
 - Combined with cisplatin or 5-FU
- Oxaliplatin
 - Combined with 5-FU
- Biological agents (in clinical trials)
 - Cetuximab (Erbix)
 - Bevacizumab (Avastin)

Treatment: Metastatic Disease

- Preventing or treating luminal obstruction
 - Stent placement
 - Tube feeding
- Treatment of metastatic disease
 - Chemotherapy



Chemotherapy for Advanced Esophageal Cancer

- Single Agents:
5FU, platinum, taxanes, irinotecan
- Combination Therapy:

Regimen	RR
5FU + cisplatin	34%
Cisplatin + etoposide	48%
Cisplatin + paclitaxel + 5FU	60%
Cisplatin + irinotecan	51-57%
Irinotecan + paclitaxel	27

Adenocarcinoma of the Esophagus: Ongoing Debates

- Preoperative multimodal therapy is a reasonable treatment option
 - Is “a” standard of choice NOT “the” standard
- New combinations of existing chemotherapies to balance efficacy and toxicity
- Questions remain:
 - Who goes to surgery?
 - Who gets all 3 modalities (surgery, chemotherapy, radiation therapy)
 - How best to manage debilitated or elderly patient?

Gastric Cancer



- Epidemiology: M:F = 2.3:1, median age 70
- 40% of cases are in China
- Blood Group A – higher incidence
- Signs and Symptoms: advanced presentation: pain, weight loss, vomiting, early satiety
- Dx: Endoscopy, CT, EUS, PET
- Pathology: adenoca – 95%

Gastric Cancer: Worldwide incidence

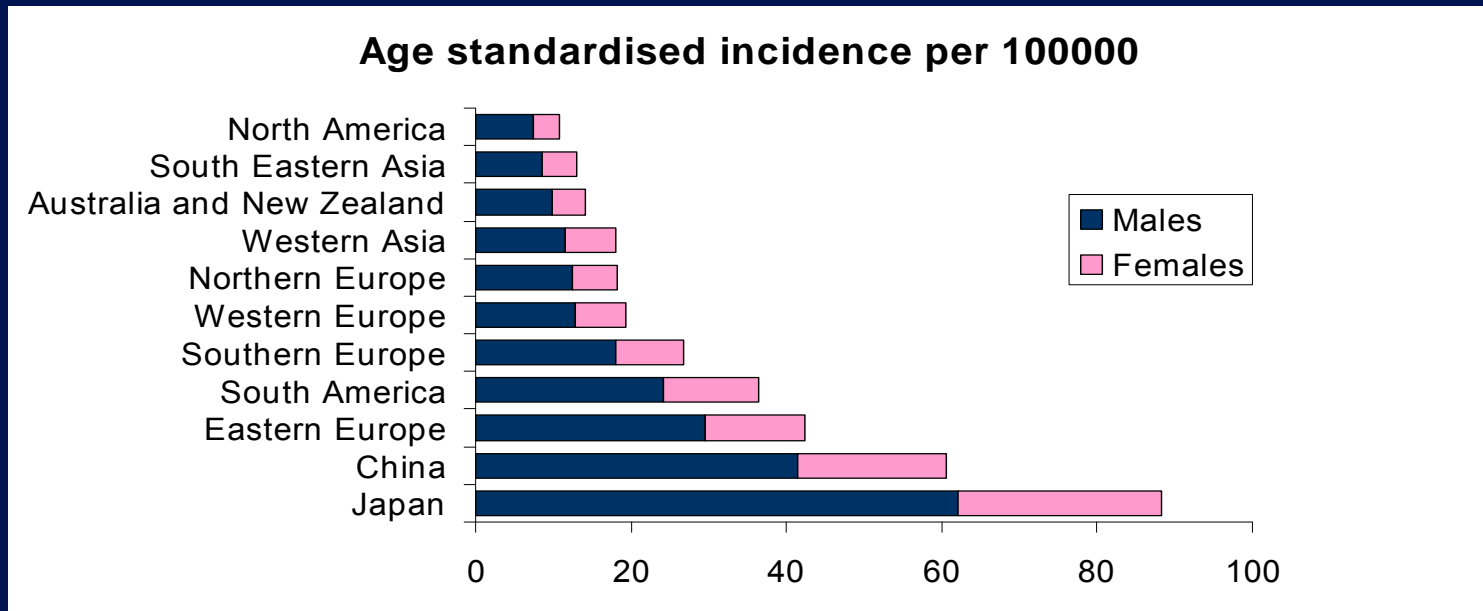


Western Europe	Male	16.4
	Female	8.2
Eastern Europe	Male	36.3
	Female	16.9
Japan	Male	77.9
	Female	33.3
Australia/ New Zealand	Male	10.8
	Female	4.9
China	Male	43.6
	Female	19.0
Northern Africa	Male	5.9
	Female	2.6
Southern Africa	Male	11.5
	Female	4.3
Central America	Male	18.6
	Female	13.3
North America	Male	8.4
	Female	4.0

798,000 New Cases in 1990

:A global problem

- Incidence of gastric cancer is declining^{1,2}
- Highest incidence remains in East Asia^{1,2}
- Incidence of GE junction tumors rising
- Possibly associated with obesity, GERD & Barrett's^{2,3}



Gastric Cancer Treatment in the 21st Century

- Chemotherapy is palliative but better than best supportive care
- Combination chemotherapy is better than monotherapy
- Quality of Life measures more common for clinical trials and show QOL IS associated with efficacy

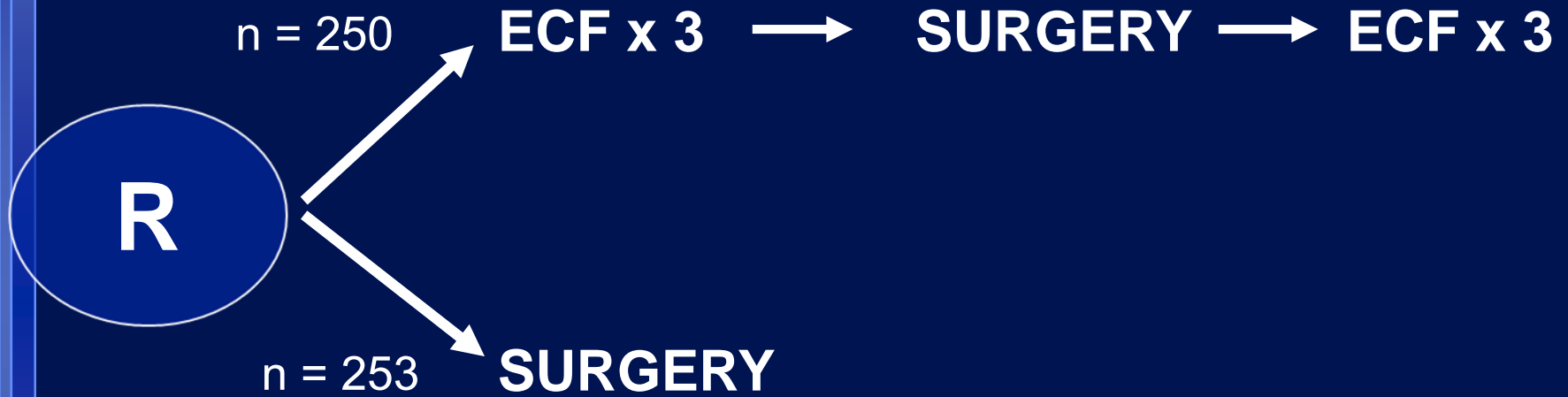
Chemotherapy in Gastric Cancer

Doublet (fluoropyrimidine/platinum) and triplet (adding epirubicin or docetaxel) regimens are routinely used in clinical practice

Neoadjuvant Question in Gastric Cancer

- Only a few studies that investigate either chemotherapy or chemoradiotherapy prior to surgery and they need to be confirmed
- Open area of study

The “MAGIC” Trial: Neo/Adjuvant Study in Gastric Cancer



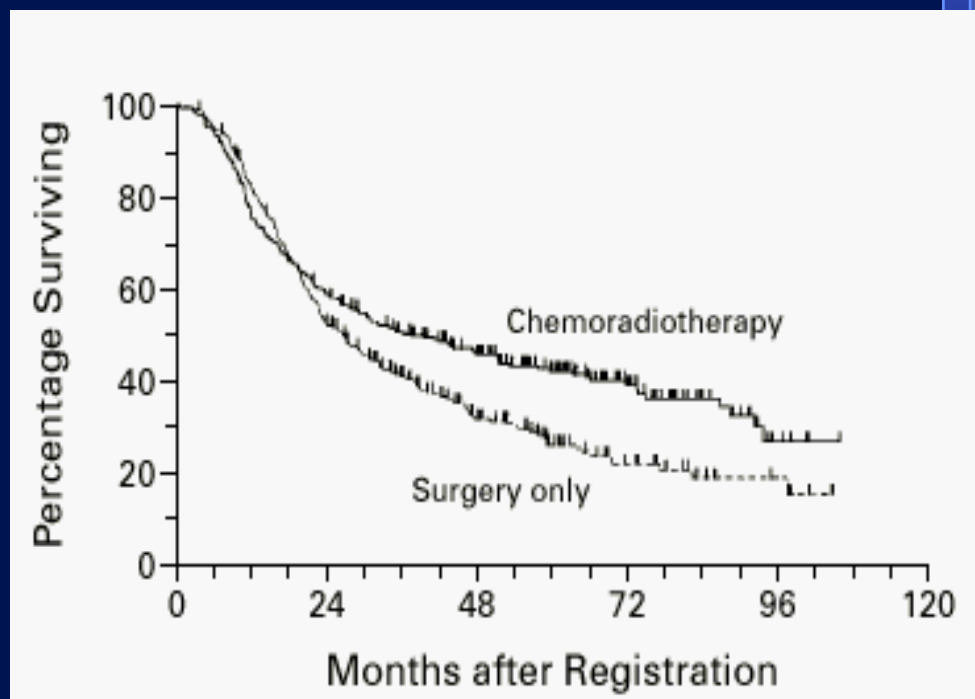
- 5-year survival: 36% vs 23%
- Time to recurrence improved: ($P = 0.0001$)
- Increase in R0 resections: 79% versus 69%
- Distant mets in 24% with chemo and 37% without

Treatment of Localized Disease

- Surgery: only chance for cure
- Subtotal vs total gastrectomy
- Adjuvant therapy – survival advantage with postoperative chemo/RT (5-FU)

Adjuvant Chemoradiation Therapy for Gastric Cancer

- INT 0116 (NEJM 2001)
 - n = 556 pts
 - 5FU/LV + XRT
 - Median survival:
36 mo vs 27 mo



Unresectable Gastric Cancer

- Survival without therapy: < 6 months
- Radiation therapy for palliation of bleeding/obstruction
- Single agent chemotherapy (many)
- Combination (ECF: Epirubicin, inf 5-FU, Cisplatin)
- Clinical trials

The Role of Chemotherapy in Advanced Gastric Cancer

- Chemotherapy better than best supportive care (BSC)
 - For trials measuring QoL, significant improvement favoring chemotherapy-treated groups
- 5-FU and cisplatin-based regimens considered reference regimen for many years
- Several new drugs have emerged which provide more effective and better tolerated regimens

New Drugs in the Treatment of Advanced Gastric Cancer

- Irinotecan (Camptosar)
- Taxanes
- Oxaliplatin
- Capecitabine (Xeloda = oral 5-FU)
- **HERCEPTIN**

Taxotere in Advanced Gastric Cancer: Conclusions (V325)

- Taxotere with cisplatin/5-FU produces a high response rate and promising survival outcomes – better than Cisplatin/5-FU alone
- More hematologic toxicities but manageable
- Quality of Life indices much higher with TCF
- Taxotere/Cisplatin/5-FU (TCF) is an acceptable alternative to the standard Epirubin/Cisplatin/5-FU (ECF)

More tolerable treatment options

The NEW ENGLAND JOURNAL of MEDICINE

Jan 2008

ORIGINAL ARTICLE

Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer

David Cunningham, M.D., F.R.C.P., Naureen Starling, M.R.C.P.,

Recent evaluation of capecitabine (xeloda), an oral 5-FU pro-drug, and oxaliplatin, a newer generation platinum agent

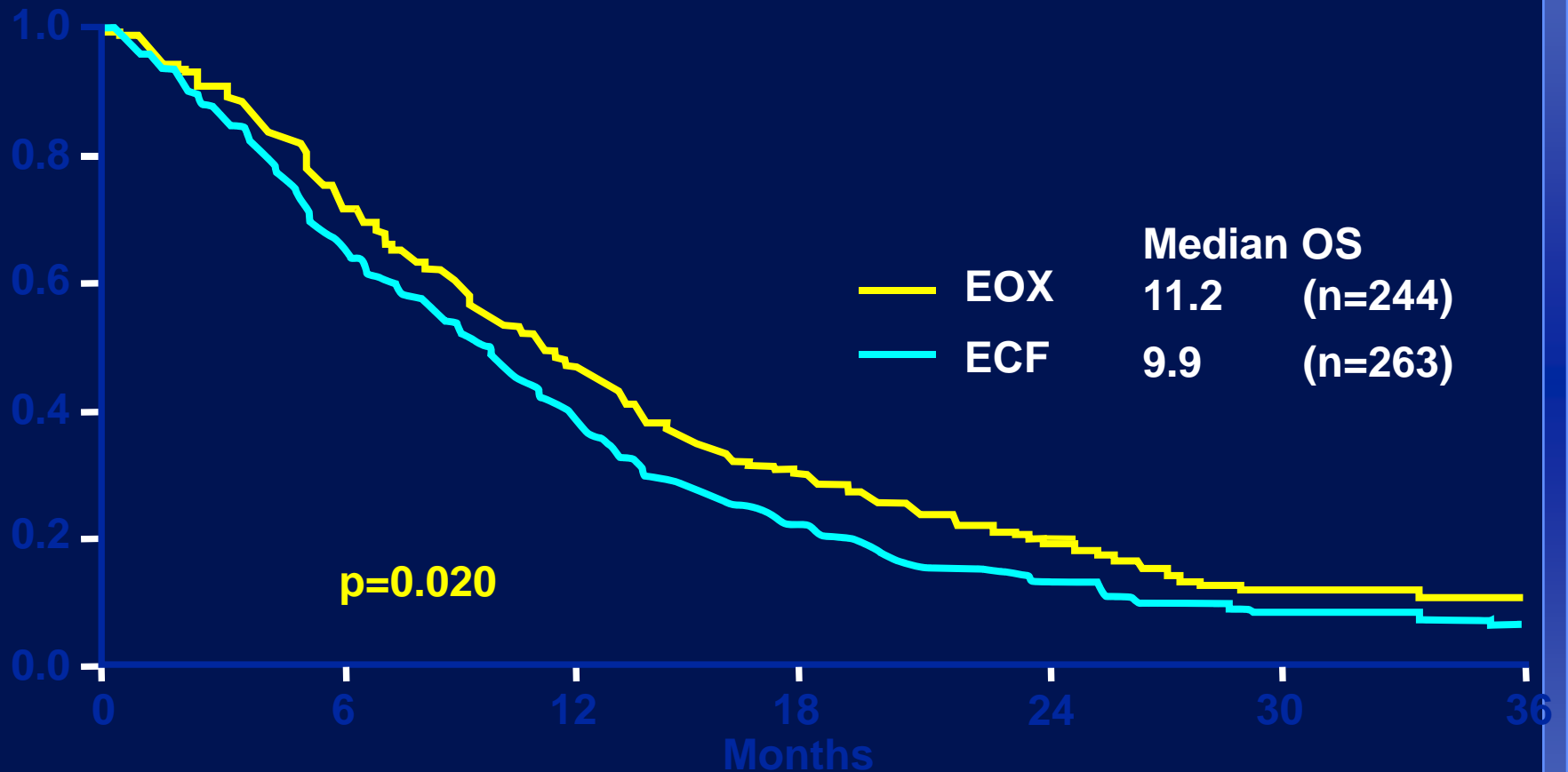
Phase III Trial in Metastatic Gastroesophageal
Adenocarcinoma with Fluorouracil, Leucovorin Plus Either
Oxaliplatin or Cisplatin: A Study of the Arbeitsgemeinschaft
Internistische Onkologie

Oxaliplatin has reduced toxicity compared to
Cisplatin

OXALIPLATIN

- Less anemia
- Less nausea/vomiting
- Less hair loss
- Less fatigue
- Less kidney toxicity
- More peripheral neuropathy

Phase III Study Comparing Capecitabine (X) With 5-FU and Oxaliplatin With Cisplatin (REAL-2 Trial)



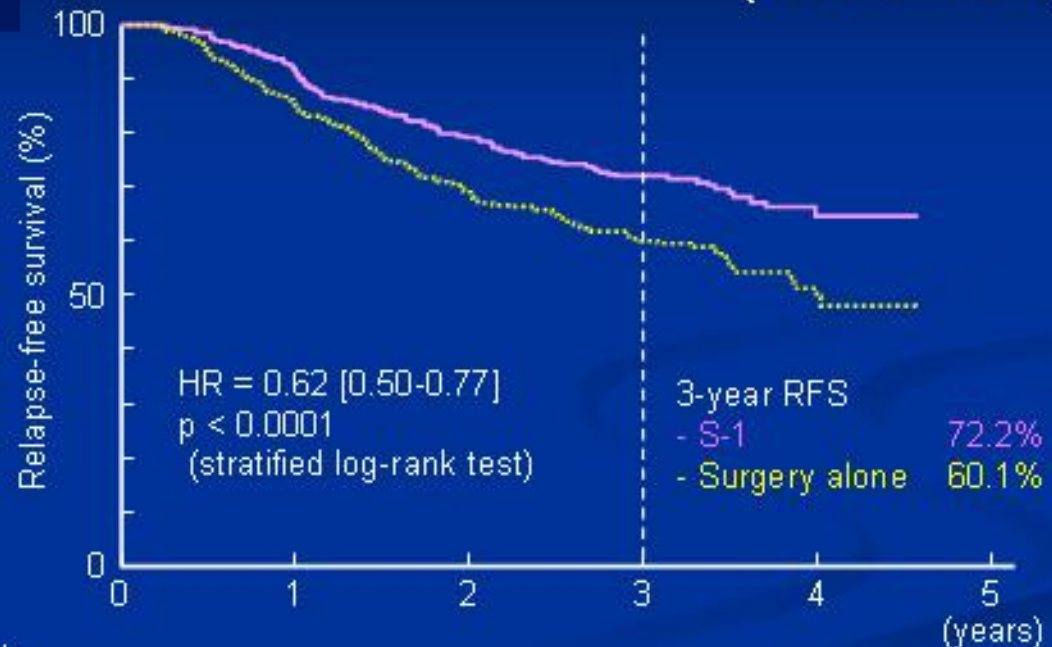
superior overall survival with EOX vs ECF

S1: Promising Drug under Investigation

Possibilities for
adjuvant and
metastatic therapy

Relapse-free survival

(All randomized)



No. at risk	0	1	2	3	4	5
S-1	529	476	322	169	38	
Surgery alone	530	446	285	136	33	

Biologic Agents: Possible Treatments for the Future

- Avastin – bevacizumab
Antiangiogenic (block tumor from growing blood vessels to feed itself)
- Erbitux (cetuximab) – “Martha Stewart drug” - epidermal growth factor receptor inhibitor



ECOG/CALGB 80403

Group A

Epirubicin, Cisplatin,
Fluorouracil & Cetuximab

**Treatment Plan
(1 cycle=21 days):**

Before any treatment:

- Medicine to help reduce side-effects

Days 1, 8 & 15:

- Cetuximab (Day 1 = 2 hours, Day 8 & 15 = 1 hour)

Day 1:

- Epirubicin (60 min.) followed by cisplatin (60 min.)

Day 1-21:

- Fluorouracil (continuous infusion)

Group B

Cisplatin, Irinotecan &
Cetuximab

**Treatment Plan
(1 cycle=21 days):**

Before any treatment:

- Medicine to help reduce side-effects

Days 1, 8 & 15:

- Cetuximab (Day 1 = 2 hours, Day 8 & 15 = 1 hour)

Day 1 & 8:

- Cisplatin (30 min.) followed by irinotecan (90 min.)

Group C

Oxaliplatin, Fluorouracil,
Leucovorin & Cetuximab

**Treatment Plan
(1 cycle=14 days):**

Before any treatment:

- Medicine to help reduce side-effects

Days 1 & 8:

- Cetuximab (Day 1 = 2 hours, Day 8 = 1 hour)

Day 1:

- Oxaliplatin (2 hours) followed by leucovorin (2 hours) followed by fluorouracil injection & (continuous infusion)

AVASTIN (bevacizumab)

- Two thirds of patients with metastatic gastroesophageal cancer responded to a regimen of docetaxel-based (Taxotere) chemotherapy plus bevacizumab (Avastin) – ASCO 2009
- AVAGAST press release Feb 23 – did not meet OS goal – await ASCO 2010

ASCO GI 2009: Advanced Esophageal Cancer Benefits from Multimodality Neoadjuvant Therapy

**Patients with locally advanced
esophageal and gastric cancer had a
high rate of pathologic complete
response and resectability with
neoadjuvant cetuximab (Erbix) and
chemoradiation**

ASCO 2009 ToGA Trial

- **Efficacy results from the ToGA trial:**
A phase III study of trastuzumab added to standard chemotherapy (CT) in first-line human epidermal growth factor receptor 2 (HER2)-positive advanced gastric cancer (GC).
- **22% positive – 11.1 vs 13.5 mo OS**

ToGA trial design

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

3807 patients screened¹
810 HER2-positive (22.1%)

HER2-positive
advanced GC
(n=584)

R

5-FU or capecitabine^a
+ cisplatin
(n=290)

5-FU or capecitabine^a
+ cisplatin
+ trastuzumab
(n=294)

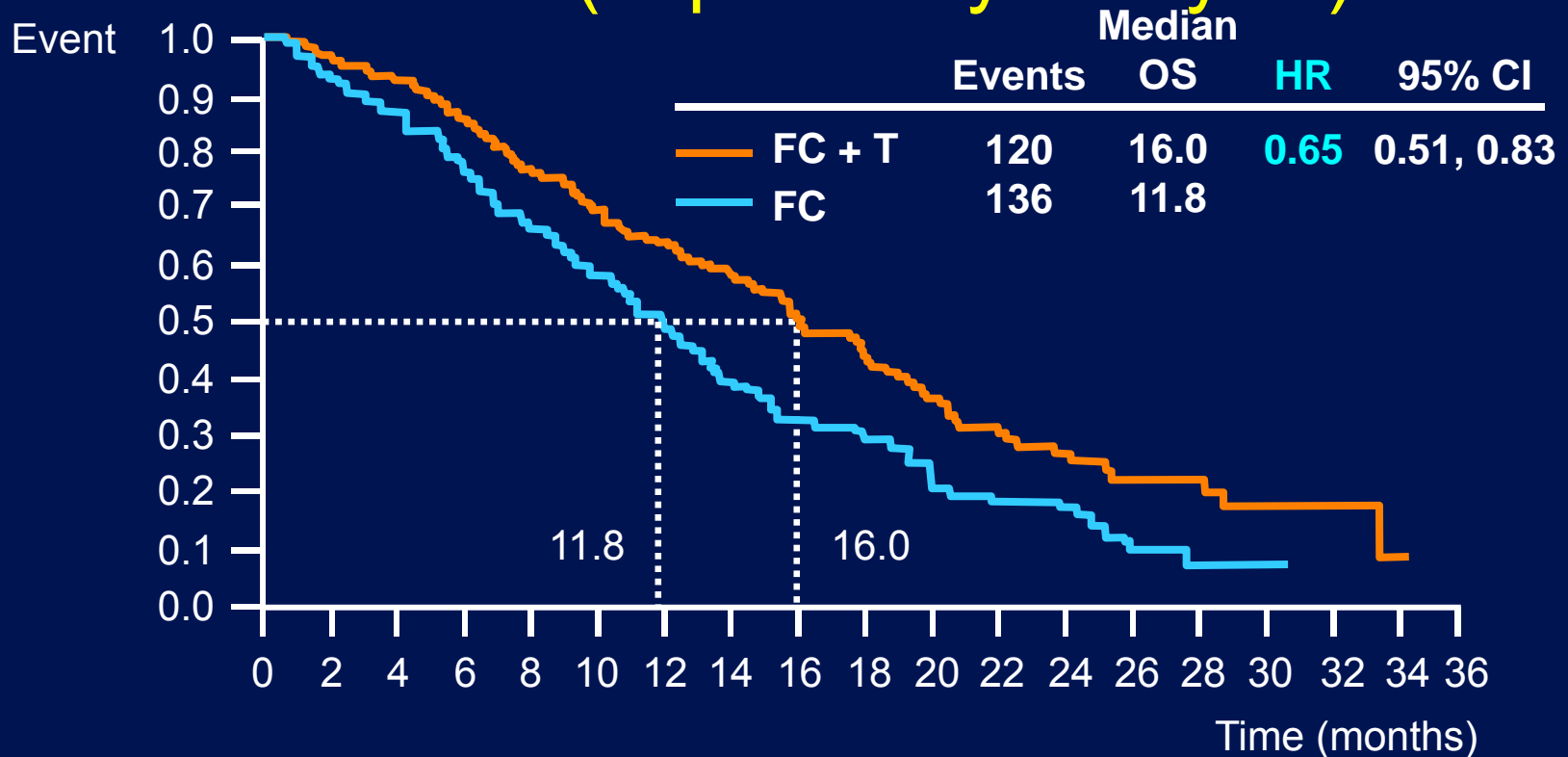
- Stratification factors

- 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

OS in IHC2+/FISH+ or IHC3+ (exploratory analysis)



No. at risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36
FC + T	228	218	196	170	142	122	100	84	65	51	39	28	20	12	11	5	4	1	0
FC	218	198	170	141	112	96	75	53	39	28	20	13	11	4	3	3	0	0	0

ToGA: Conclusions

- Trastuzumab combined with doublet chemotherapy (fluoropyrimidine/cisplatin) improved median survival over doublet chemotherapy alone
- No significant increase in toxicity

Nutritional Support May Improve Survival in Esophageal Cancer

- Retrospective study of 138 patients
- Longer median survival in patients that received nutritional supplements (21.2 compared to 14.4 months)
- Changes in hemoglobin, albumin and weight may correlate with survival

