Multidisciplinary interactive session

Management of localized gastric cancer

Fundación Investigación Clínico de Valencia

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VIENNA 2012 ESMO congress

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Disclosures

I have participated in Advisory Boards and I have been paid for giving educational lectures in satellite symposia by Roche, Genentech, Merck Serono, Bayer and Sanofi during the last two years.

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Management of localized gastric cancer

Case Presentation

72 year old female PS 1

No relevant previous diseases

Unspecific epigastric discomfort for 2 months

Significant asthenia and weight loss for 3 months

Occasional vomiting and fullness after eating small amounts of food

A diagnostic test was done: gastroscopy

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Management of localized gastric cancer

Case Presentation

Gastroscopy:
An ulcerated and infiltrating lesion of 5 cm was detected in the corpus/antrum of the stomach.

Multiple biopsies were done.

Poorly differentiated adenocarcinoma of the stomach of intestinal type

Staging procedures were ordered

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Management of localized gastric cancer

Case Presentation

Chest CT-scan: no lung or mediastinal mets

Abdominal and pelvic CT-scan:

No liver mets or peritoneal mets
Thickening of the whole gastric wall without invasion of any surrounding local structures
Multiple perigastric lymph nodes of 2 cm size, but no extraperigastric and paraortic lymph nodes.

A laparoscopy and an endoscopic ultrasonography were not considered

cT3 cN+ cM0

CLASSICAL APPROACH TO LOCALISED GASTRIC CANCER

Surgical resection

Pathology assessment and estimation of risk

Treatment based upon classical TNM stage

Postoperative Chemotherapy of limited value

Postoperative Chemoradiation if D0-D1

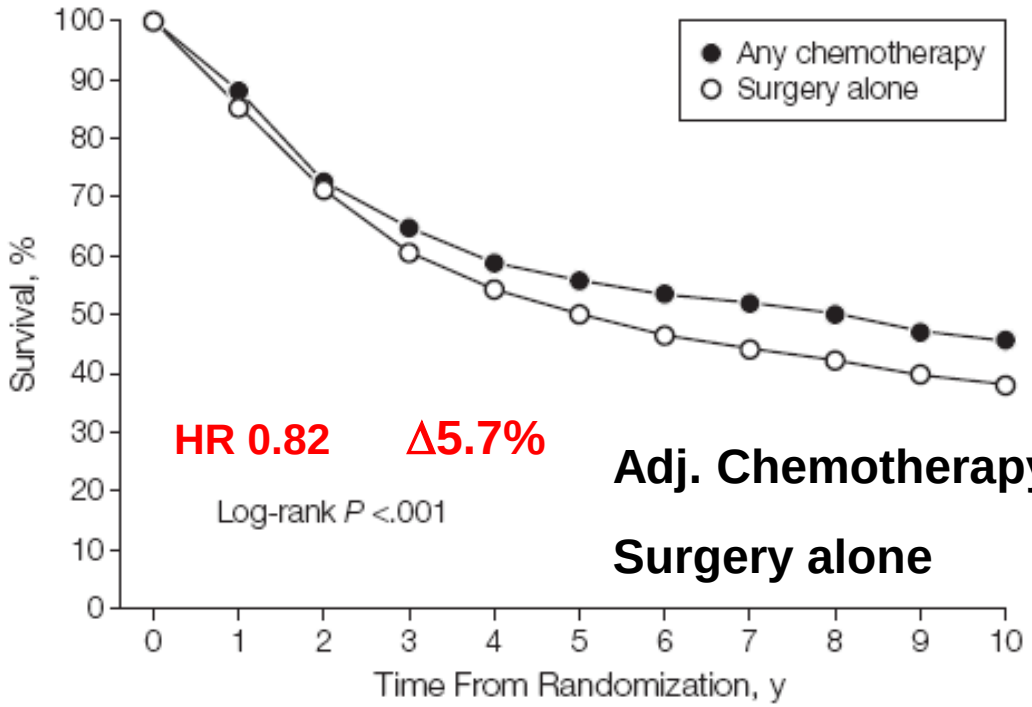
META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER-1

Meta-analysis	Year	No. Trials	No. Pts	Odds Ratio	95% CI	Conclusions
Hermanns J Clin Oncol	**1993**	**11**	**2096**	**0.88**	**0.78-1.08**	**No benefit**
Earle Eur J Cancer	**1999**	**13**	**1990**	**0.80**	**0.66-0.97**	**Small survival benefit In N+ patients**
Mari Ann Oncol	**2000**	**20**	**3658**	**0.82**	**0.75-0.89**	**Small survival benefit**
Januger Eur J Surg	**2002**	**21**	**3962**	**0.84**	**0.74-0.96**	**Very heterogeneous group of trials**
Western				0.96	0.83-1.12	
Asian				0.58	0.44-076	

META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER-2

Meta-analysis	Year	No. Trials	No. Pts	Odds Ratio	95% CI	Conclusions
Zhao et al Cancer Investigation	2008	15	3212	0.90	0.84-0.96	Marginal, though significant benefit P: 0.001
Liu et al Eur J Surg Oncol	2008	19	2286	0.85	0.80-0.90	Marginal, though significant benefit P< 0.0001
Gastric Group JAMA	2010	17	3871	0.82	0.76-090	P< 0.001

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



Adj. Chemotherapy 55.3 %

Surgery alone 49.6 %

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

The GASTRIC GROUP *JAMA*. 2010; 303:1729

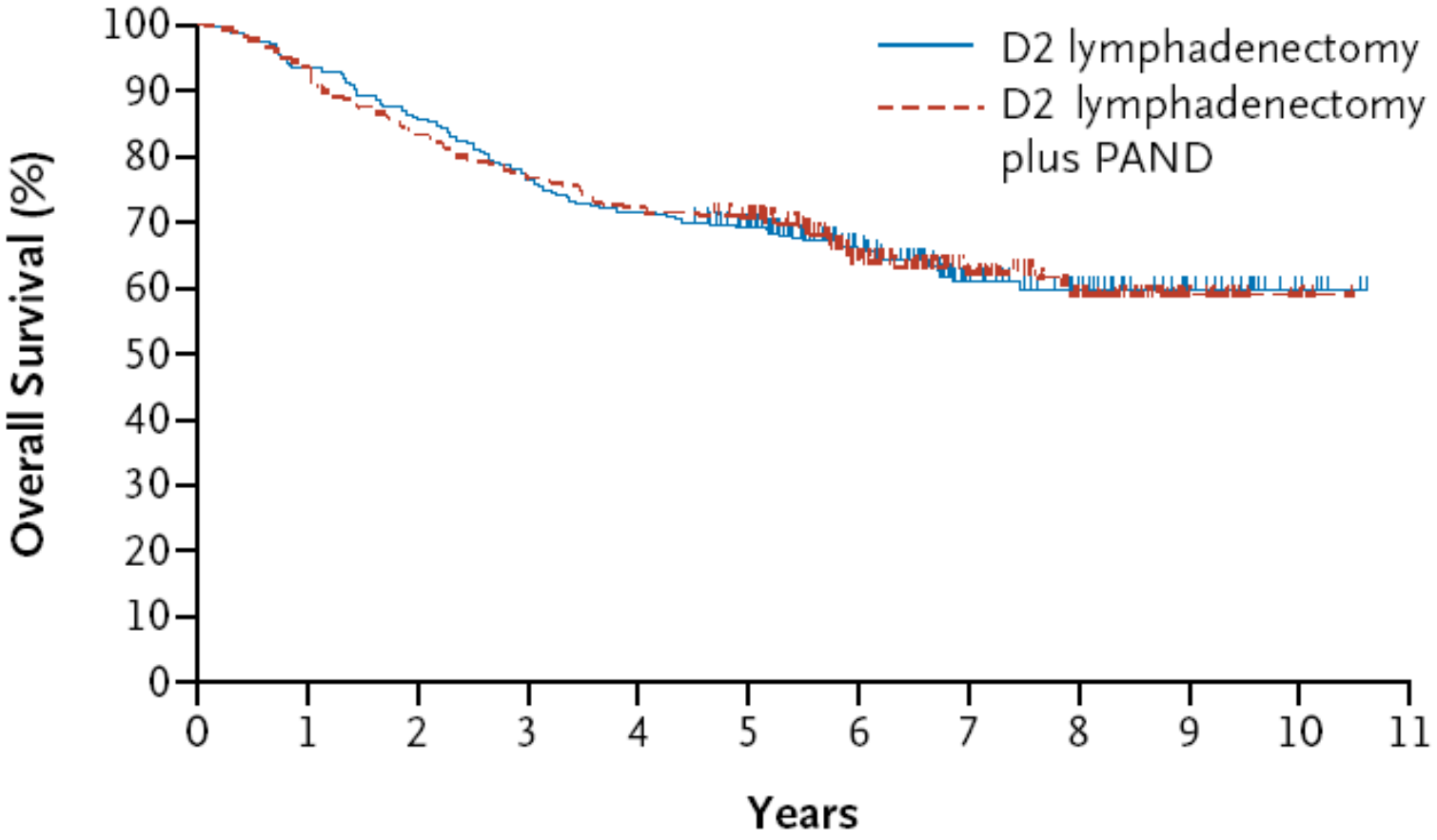
RECENT TRIALS OF ADJUVANT CT FOR LOCALIZED GASTRIC CA IN WESTERN COUNTRIES

Trial	CT	Nr. Pts Control	Nr. Pts CT	5-year Survival Control	Median Survival CT	HR (CI at 95%)
Di Constanzo JNCI 2008	PELF	128 No CT	130	48.7%	47.6 %	0.90 0.64-1.26
Cascinu JNCI 2007	PELFw	196 FU-LV	201	50%	52%	0.95 0.70-1.29
De Vita Ann Oncol 2007	ELFE	113 No CT	113	43.5%	48%	0.91 0.69-1.21
Bajetta Ann Oncol 2002	EAP 5FU-LV	137 No CT	137	48%	52%	0.93 0.65-1.34

POSTOPERATIVE CHEMOTHERAPY IN LOCALIZED GASTRIC CANCER

- LIMITED VALUE, IF ANY
- HRs BY 0.90
- NON SIGNIFICANT EFFECT IN MOST SINGLE TRIALS
- BUT…
  - NONSTANDARDIZED SURGERY
  - MANY SINGLE TRIALS UNDERPOWERED
  - HYPOTETIC BENEFIT OVERESTIMATED
  - STRATIFIED BY MANY AND DIFFERENT CLINICAL OR PATHOLOGICAL FACTORS
  - HETEROGENEOUS POPULATION ACCRUED
  - N NEGATIVE PATIENTS PREDOMINATE
  - SELECTED POPULATION OF PATIENTS WELL ADAPTED TO TOTAL OR PARTIAL GASTRECTOMY
  - BIOLOGICAL PREDICTIVE FACTORS UNKOWN AND THEREFORE NOT APPLIED TO STRATIFICATION

D2 LYMPHADENECTOMY ALONE OR WITH PARA-AORTIC NODAL DISSECTION FOR GASTRIC CANCER



Sasako et al. N Eng J Med 2008; ; 359; 453

ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE

TRIAL DESIGN

SURGERY

RANDOMIZED

N= 1059

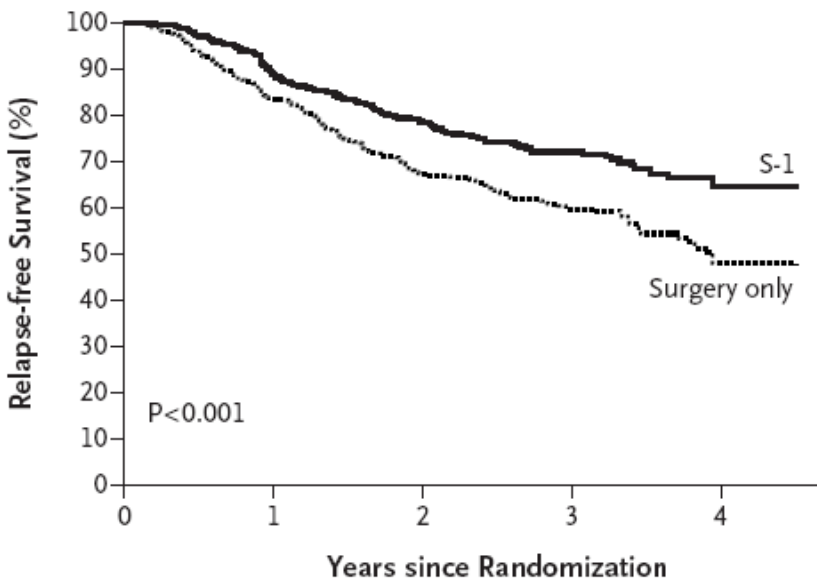
STRATIFIED

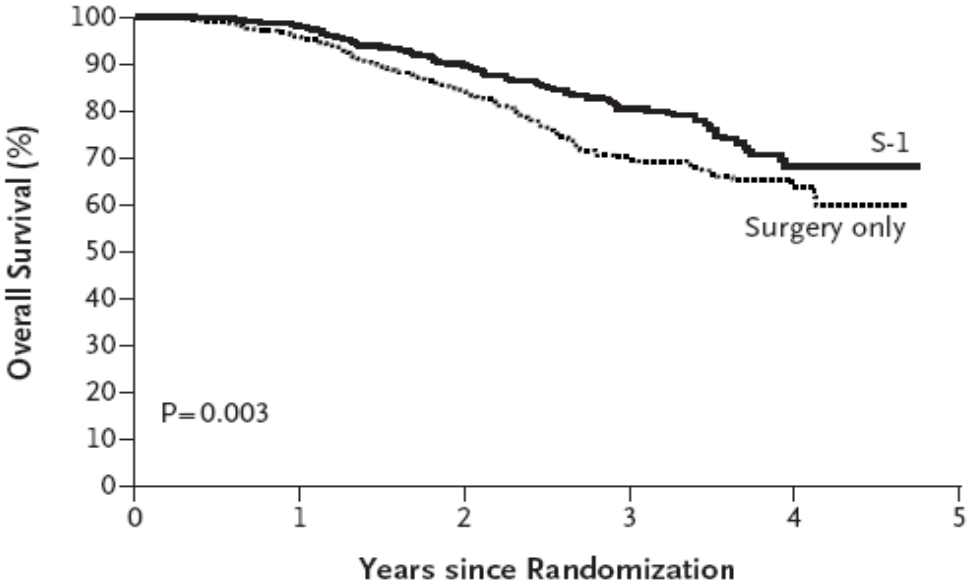
STAGE II, IIIA, IIIB

NO TREATMENT

S1 40 MG/M^2 BID

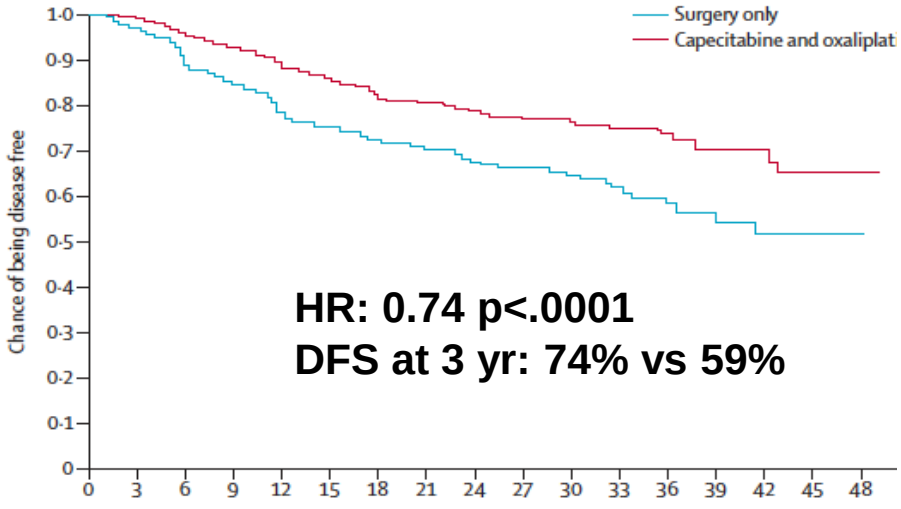
ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER WITH S1: AN ORAL FLUOROPYRIMIDINE





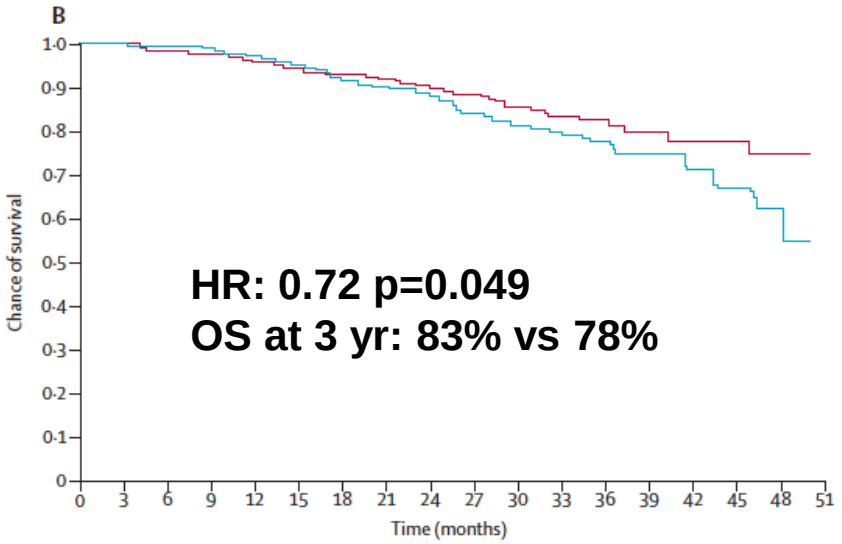
Sakuramoto et al N Eng J Med 2007; 357:1810

ADJUVANT CHEMOTHERAPY FOR GASTRIC CANCER CONTROL VS XELOX (CLASSIC)



ıber at risk

urgery only	515	442	415	388	353	332	289	255	211	188	148	120	58	25	22	20	6
apecitabine	520	462	442	425	409	379	332	295	246	218	166	147	73	31	30	25	10
oxaliplatin																	



Number at risk

Surgery only	515	473	460	453	443	424	380	338	288	238	204	156	112	43	34	31	12	0
Capecitabine and oxaliplatin	520	481	468	461	451	425	396	352	306	255	217	169	120	39	36	33	16	0

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BANG YJ et al LANCET 2012; 379:315

POSTOPERATIVE CHEMORADIOTHERAPY FOR LOCALISED GASTRIC CANCER

TRIAL DESIGN

SURGERY

RANDOMIZED

N= 556

STRATIFIED

T 1-4

NODES 0, 1-3, >3

NO TREATMENT

ChT+ ChRT +

McDonald JS et al (N Engl J Med 2001;345:725-30.)

POSTOPERATIVE CHEMORADIOTHERAPY FOR LOCALISED GASTRIC CANCER

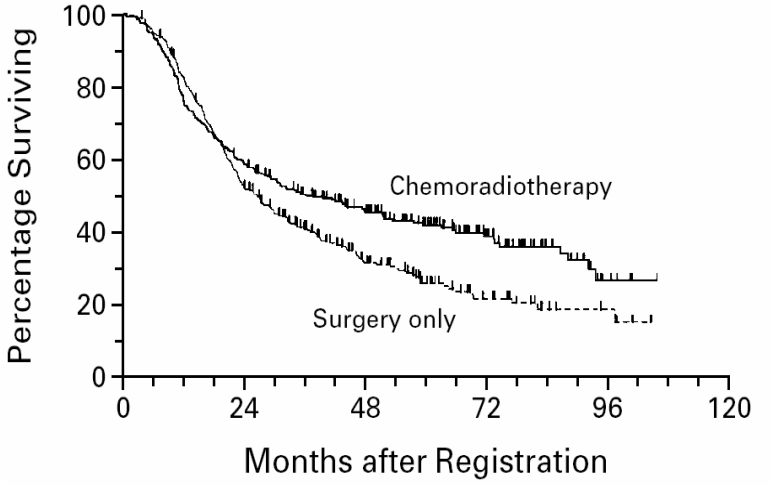


Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

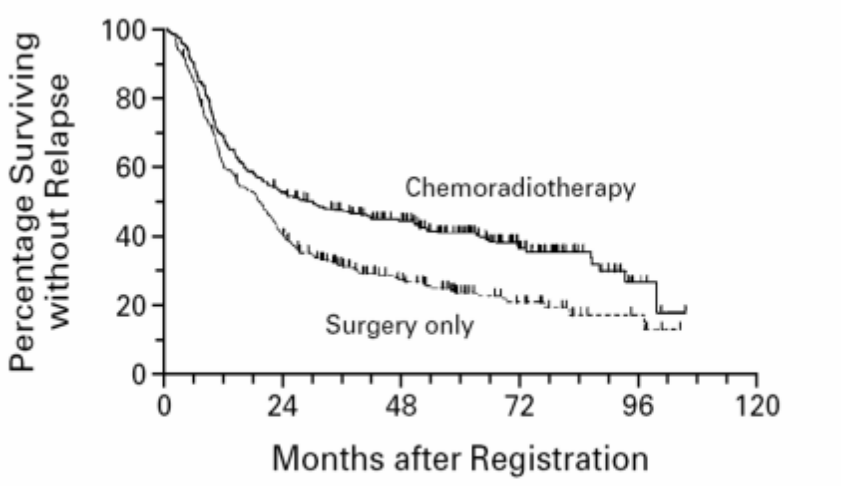


Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

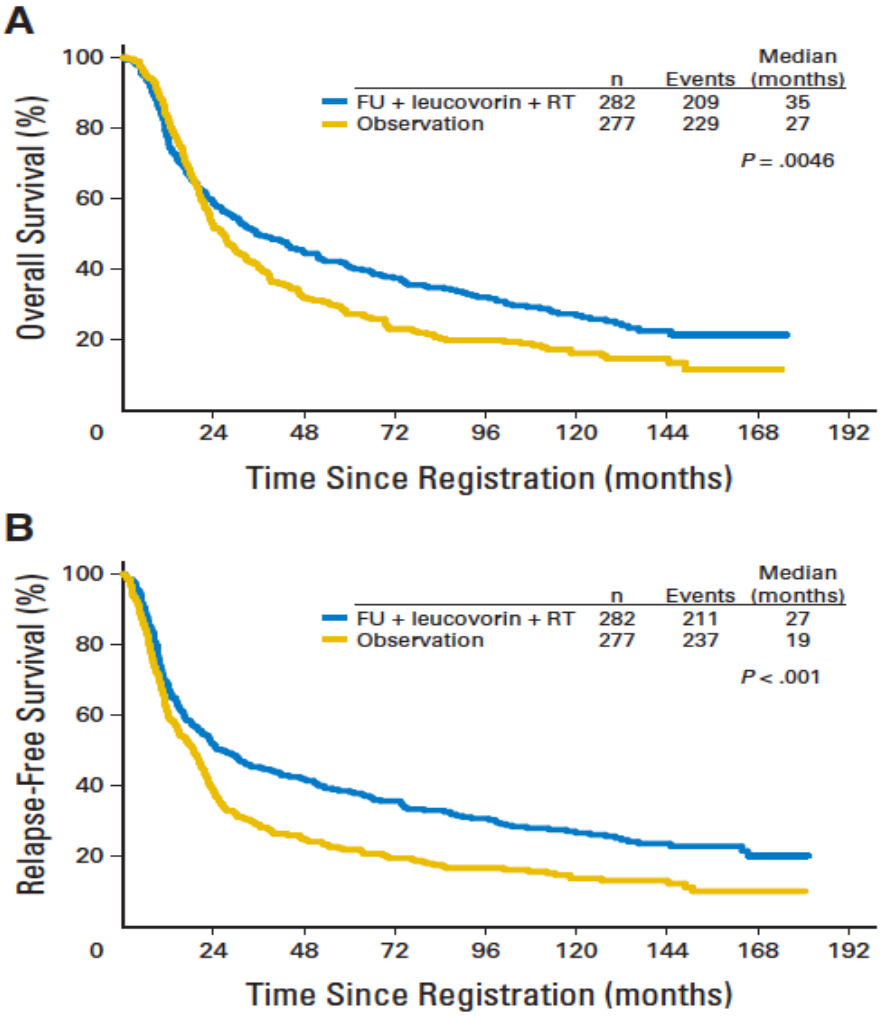
Clear benefit in disease free and overall survival with median follow-up of 6 years. Risk reduction of death by 24%.

Type of surgery: D2 resection less than 10%

Planning of Radiation to be modified after central review in 35% of cases due to minor/minor deviations

McDonald JS et al (N Engl J Med 2001;345:725-30.)

POSTOPERATIVE CHEMORADIOTHERAPY FOR LOCALISED GASTRIC CANCER: UPDATED RESULTS



HR:0.68

HR:0.49

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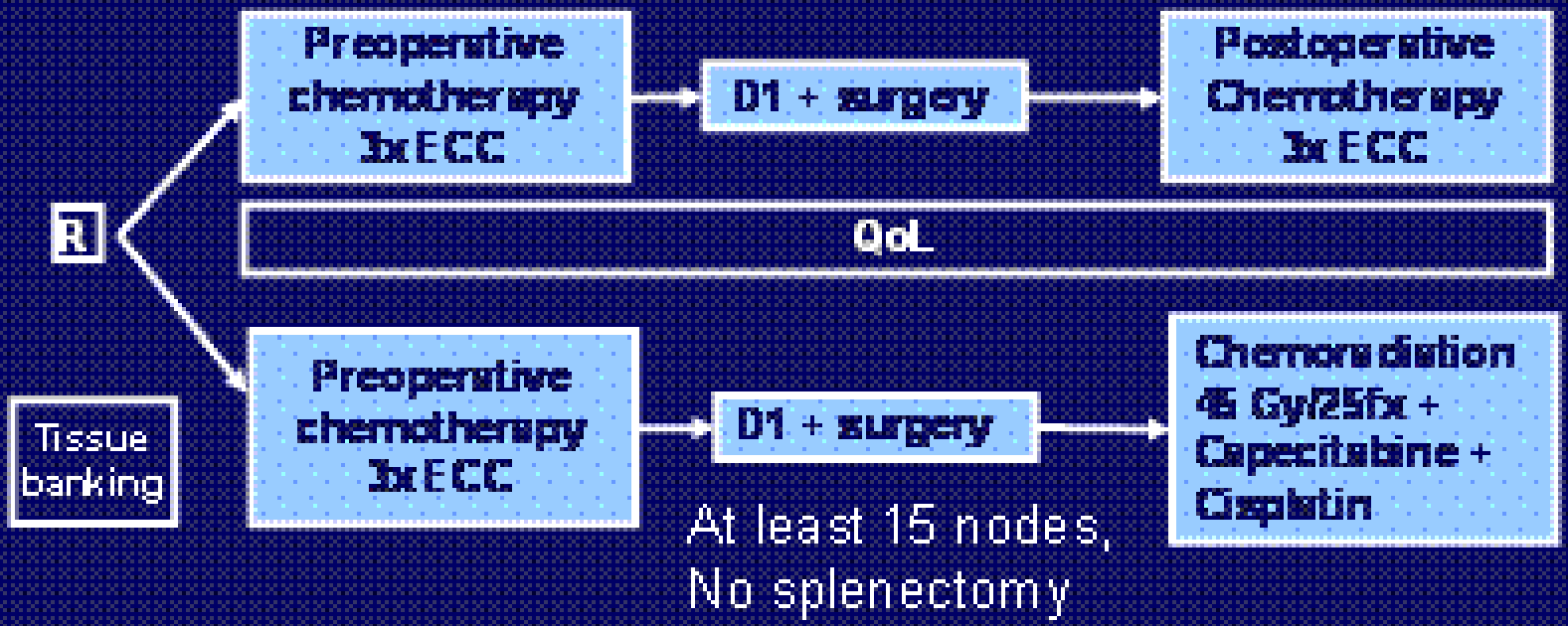
Smalley SR et al. J Clin Oncol 2012; 30;:2327

CRITICS (ChemoRadiotherapy after Induction ChemoTherapy in Cancer of the Stomach) Trial



Quality assurance

- Surgery: surgical audit to individual surgeons
- Pathology: pathology audit to individual pathologists
- Radiotherapy:
  - check of RT plan before start of treatment
  - RT atlas

DISADVANTAGES OF POST-OPERATIVE TREATMENT

Efficacy of treatment used is unknown

Treatment appears to be less well tolerated after major surgery

Commencement of post-operative treatment may be delayed by slow recovery from surgery or peri-operative morbidity

Important morbidity related with total gastrectomy, specially altered nutritional status

POTENTIAL ADVANTAGES FOR PRE-OPERATIVE TREATMENT

Tumour downstaging/downsizing prior to surgery

- Reduction of microscopic marginal involvement with tumour
- Increase likelihood of curative resection

Eliminating disseminated micrometastatic disease and achieving systemic control

Demonstrates in vivo sensitivity to systemic treatment

Improvement of tumour related symptoms

Better tolerated than post-operative therapy

More patients may benefit from therapy

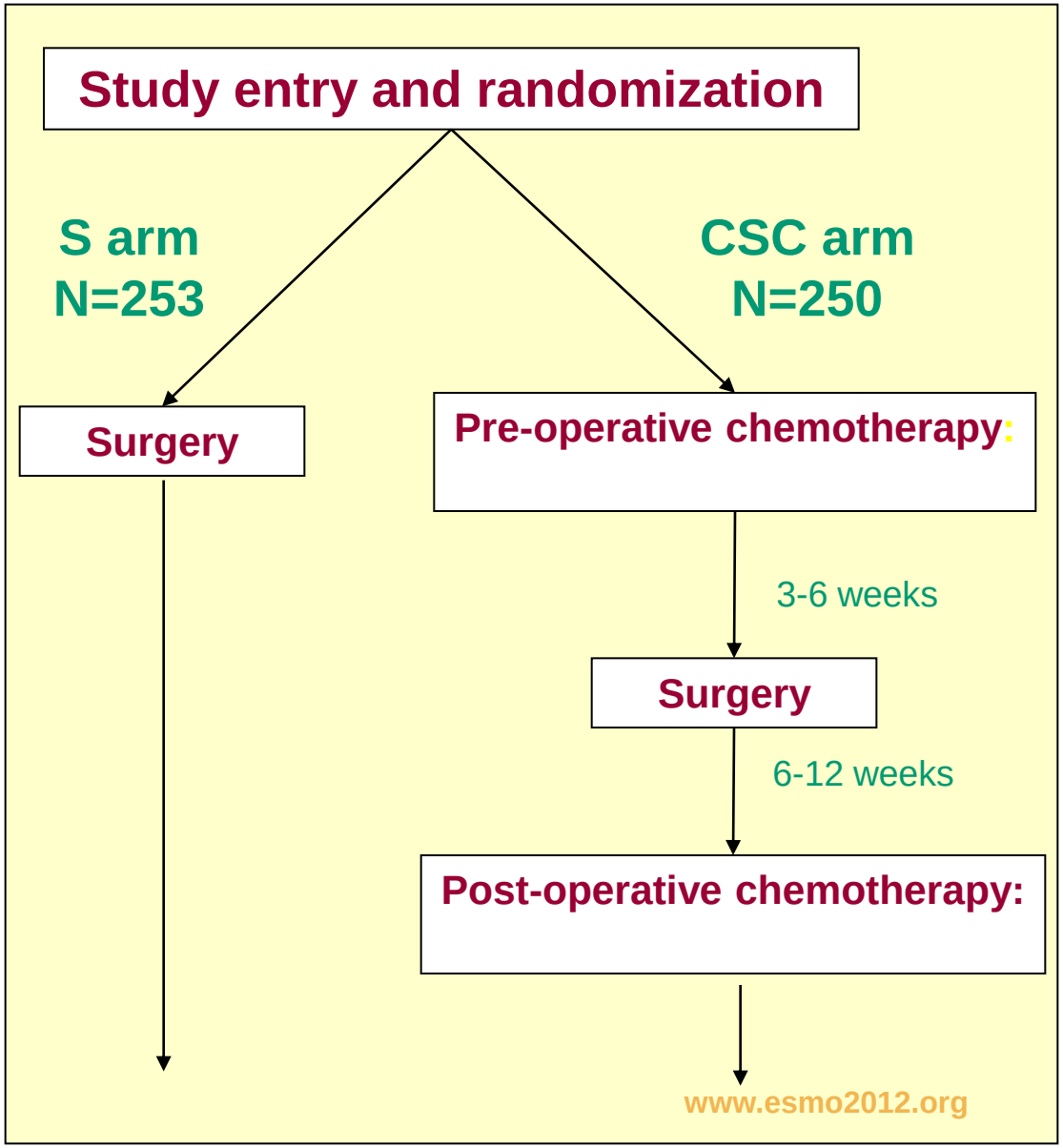
STUDY DESIGN

Eligible patients:
- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease
- Stage II or greater

Primary
Overall survival

Secondary
Progression-free survival
Surgical resectability
Quality of Life

Chemotherapy (ECF):
Epirubicin 50mg/m2, IV day 1
Cisplatin 60mg/m2, IV day 1
5-FU 200mg/m2/day, continuous infusion, days 1-21
(cycles repeated every 3 weeks)



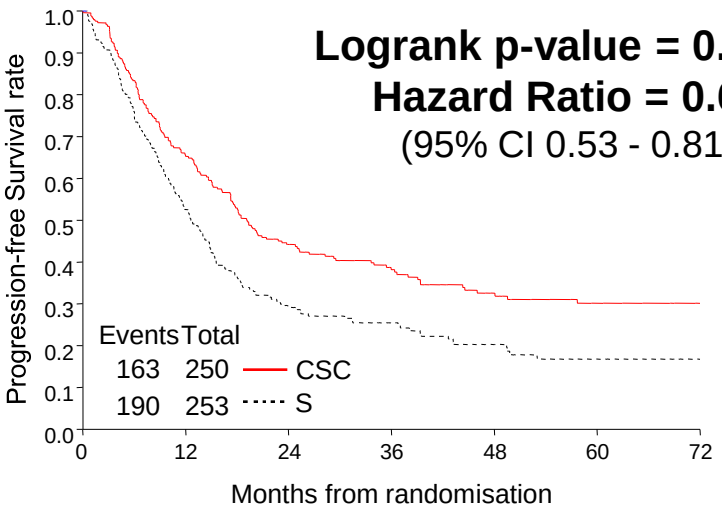
POSTOPERATIVE MORBIDITY/MORTALITY

	CSC	S
Postoperative deaths	6% (14/219)	6% (15/240)
Postoperative complications	46%	46%
Median duration of post-operative hospital stay	13 days	13 days

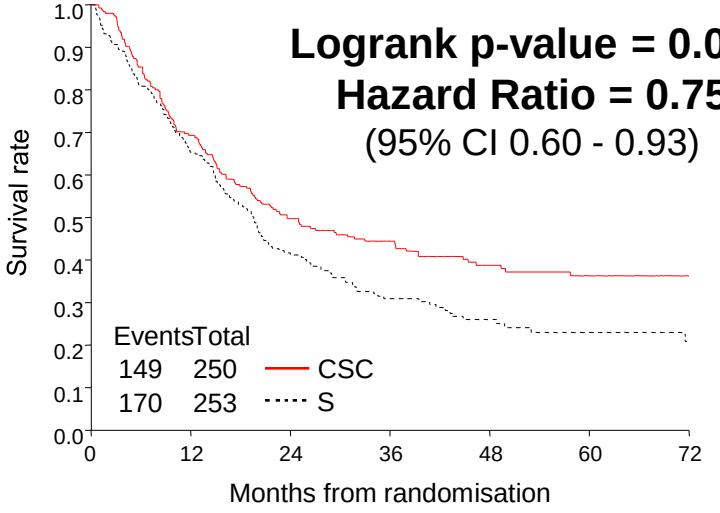
Cunningham et al NEJM 2006

MAGIC TRIAL: SURVIVAL

PFS*



Overall



	2 year survival	5 year survival	Median survival
CSC	50%	36%	24 mo
S	41%	23%	20 mo
Benefit to CSC arm	9%	13%	4 mo

- On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender
- Hazard ratio for death
  - Adjusted: 0.74 (95%CI: 0.59-0.93)
  - Unadjusted: 0.75

*Included relapse, PD and death from any cause.

Cunningham et al NEJM 2006

CAN MAGIC BE COMPARED TO INT0116?

	MAGIC[1] (N=503)		INT116[2] (N=556)	
	Peri-op chemo + surgery N=250	Surgery only N=253	Post-op chemoRT + surgery N=282	Surgery only N=277
2 year survival	50%	41%	58%*	50%*
5 year survival	36%	23%	40%*	26%*
Median survival	24 months	20 months	35 months	27 months
Hazard ratio (95% CI)	0.75 (0.60-0.93) P=0.009		0.76 (0.62-0.93) P=0.006	

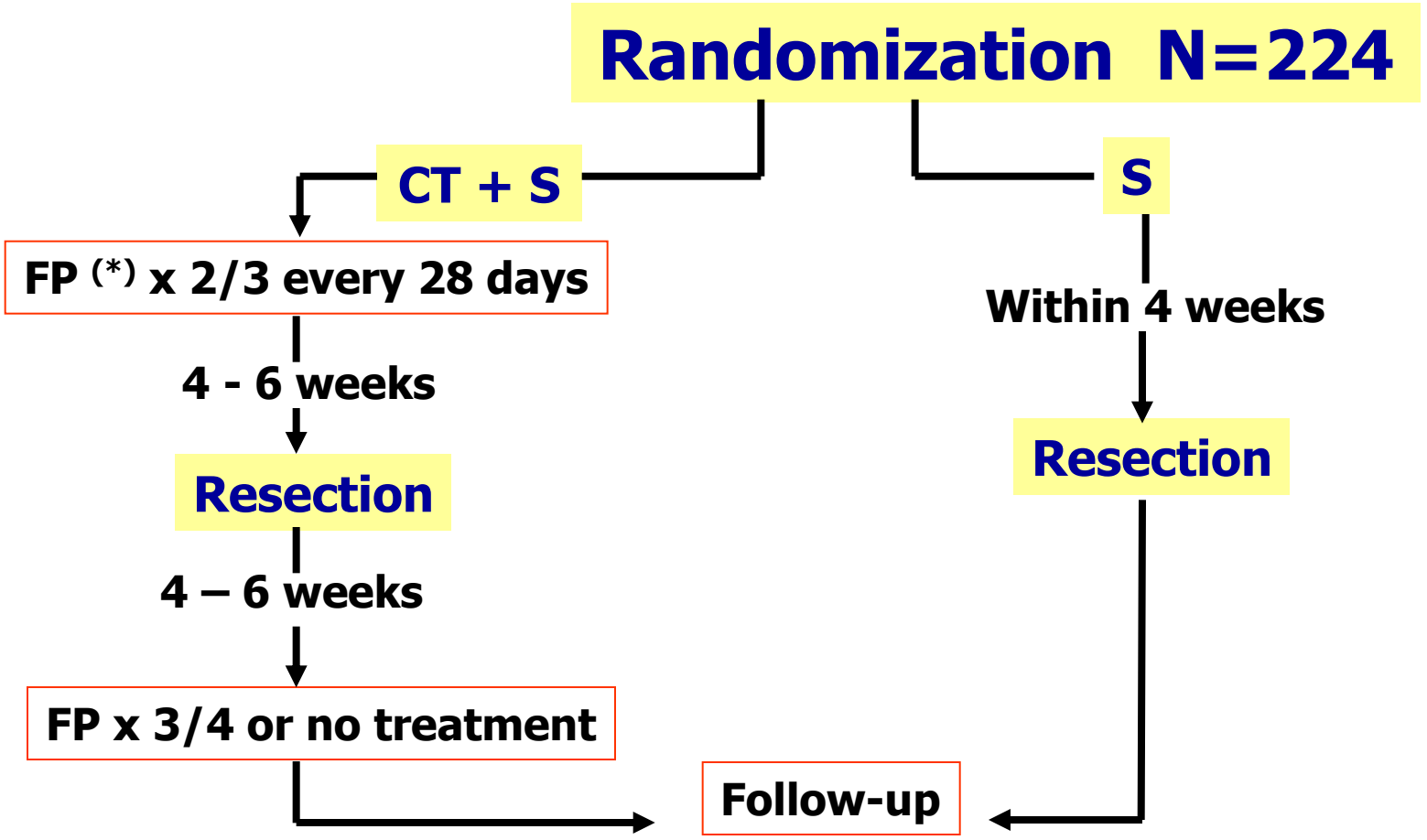
Direct comparison of results is difficult due to different inclusion criteria and different time of randomization.

[1] Cunningham NEJM 2006

[2] MacDonald NEJM 2001; 2004 GI Cancers Symposium

*Estimated from curve

PERIOPERATIVE CHEMO: FNLCC 94012-FFCD 9703 TRIAL



Trial accrual 1995-2003

Median FU 5.7 yrs

5-Fluorouracil 800 mg/m2 d1-5
+ Cisplatin 100 mg/m2 day 1

Ychou et al J Clin Oncol 2011; 29:1715

PERIOPERATIVE CHEMO: FNLCC 94012-FFCD 9703 TRIAL

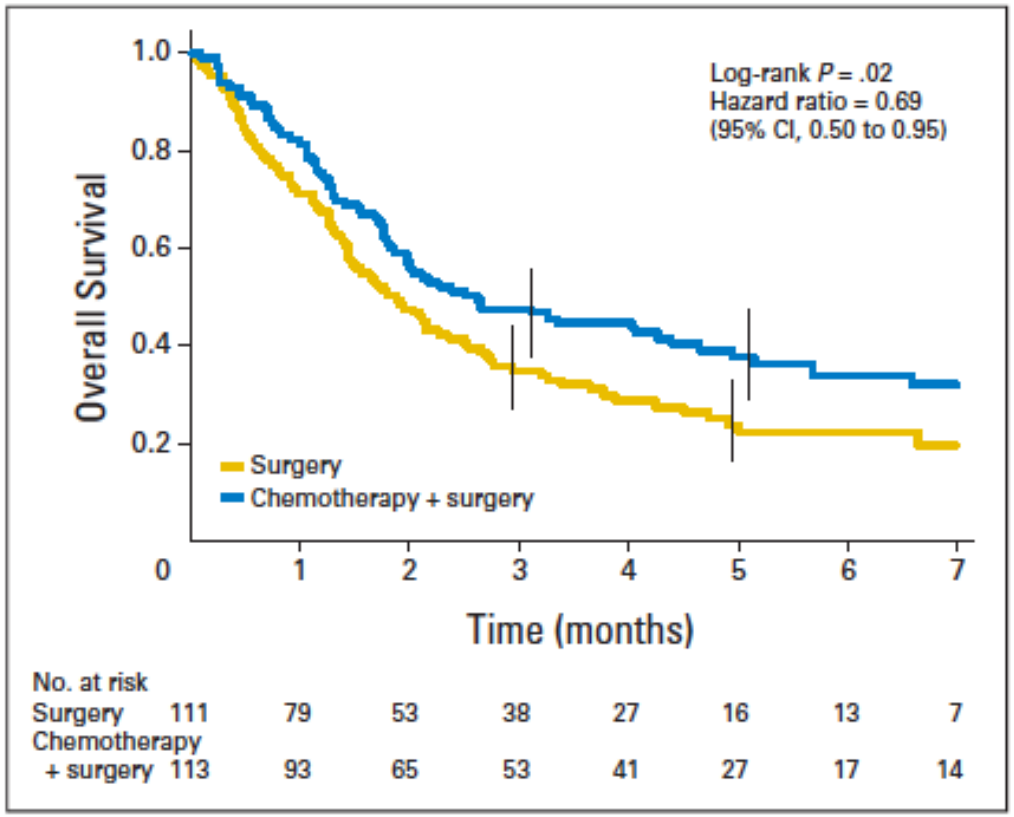


Fig 2. Kaplan-Meier curve showing overall survival from date of random assignment.

	2 year survival	5 year survival	Median survival
Periop CT	58%	38%	29 mo
Surgery	47%	24%	20 mo
Benefit to CSC arm	10%	14%	9 mo

Ychou et al J Clin Oncol 2011; 29:1715

SUMMARY OF TRIALS OF PERIOPERATIVE CHEMOTHERAPY FOR LOCALIZED GASTRO-ESOPHAGEAL CANCER

Trial	CT	Nr. Pts Control	Nr. Pts CT	5-year Survival Control	5-year Survival CT	HR (CI at 95%)
Cunningham NEJM 2006	**ECF**	**253 No CT**	**250**	**23%**	**36 %**	**0.75 0.60-0.93 p=.009**
Ychou JCO 2011	**CDDP 5-FU**	**111 No CT**	**113**	**24%**	**38%**	**0.69 0.50-0.95 p=.021**
Allum JCO 2009 Esophageal only	**CDDP 5-FU**	**402 N0 CT**	**400**	**17.1%**	**23%**	**0.84 0.72-0.78 p=.03**

CURRENT APPROACH TO LOCALISED GASTRIC CANCER

- Clinical staging with CT-Scan/endoscopic ultrasonography
- Preoperative Chemotherapy if cT3-4 or cN+
- Surgical resection
- Pathology assessment and estimation of risk
- Postoperative Chemotherapy if feasible

FUTURE DIRECTIONS IN THE TREATMENT OF LOCALISED GASTRIC CANCER

- **More active systemic treatment combinations, including targeted therapies**
- **Defining role of radiotherapy in relation to systemic therapy**
- **Diagnostic/assessment**
- **Assessing response to treatment earlier (i.e. role of PET)**
- **Translational: prognostic and predictive markers**