

# Advances in gastric cancer: How to approach localised disease?

Andrés Cervantes

Professor of Medicine



VNIVERSITAT  
ID VALÈNCIA



Fundación Investigación  
Clínica de Valencia

**incliva**  
Instituto de Investigación Sanitaria

# Classical approach to localised gastric cancer

- Surgical resection
- Pathology assessment and estimation of risk
- Treatment based upon classical TNM stage
- Postoperative chemotherapy of doubtful *versus* no value
- Postoperative chemoradiation

# Meta-analysis of trials involving adjuvant chemotherapy *versus* surgery alone for gastric cancer-1

Meta-analysis	Year	No. trials	No. pts	Odds Ratio	95% CI	Conclusions
Hermanns (1) J Clin Oncol	1993	11	2096	0.88	0.78-1.08	No benefit
Earle (2) Eur J Cancer	1999	13	1990	0.80	0.66–0.97	Small survival benefit In N+ patients
Mari (3) Ann Oncol	2000	20	3658	0.82	0.75–.89	Small survival benefit
Janunger (4) 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	

1. Hermanns J *et al.* J Clin Oncol, 1993, vol11, no 8, 1441-1447
2. Earle CC *et al.* Eur J Cancer 1999; 35 (7): 1059–1064.
3. Mari e *et al.* Ann Oncol 2000; 11(7):837-43
4. Janunger KG *et al.* Eur J Surg 2002; 168(11):597-608

# Meta-analysis of trials involving adjuvant chemotherapy *versus* surgery alone for gastric cancer-2

Meta-analysis	Year	No. trials	No. pts	Odds Ratio	95% CI	Conclusions
Zhao <i>et al.</i> (1) Cancer Investigation	2008	15	3212	0.90	0.84-0.96	Marginal, though significant benefit P: 0.001
Liu <i>et al.</i> (2) Eur J Surg Oncol	2008	19	2286	0.85	0.80-0.90	Marginal, though significant benefit P<0.0001
Gastric Group (3) JAMA	2010	17	3871	0.82	0.76-0.90	P<0.001

1. Zhao SL *et al.* Cancer Invest. 2008;26:317–325

2. Liu TS, *et al.* Eur J Surg Oncol 2008;34:1208-1216

3. The Gastric Group. Jama 2010: 303:1729-37

## Other trials of adjuvant chemotherapy for localised gastric cancer

<b>Trial</b>	<b>CT</b>	<b>No. pts control</b>	<b>No. pts CT</b>	<b>5-year survival control</b>	<b>Median survival CT</b>	<b>HR (CI at 95%)</b>
Di Constanzo (1) JNCI 2008	PELF	128 No CT	130	48.7%	47.6 %	0.90 0.64-1.26
Cascinu (2) JNCI 2007	PELFW	196 FU-LV	201	50%	52%	0.95 0.70-1.29
De Vita (3) Ann Oncol 2007	ELFE	113 No CT	113	43.5%	48%	0.91 0.69-1.21
Bajetta (4) Ann Oncol 2002	EAP 5FU-LV	137 No CT	137	48%	52%	0.93 0.65-1.34

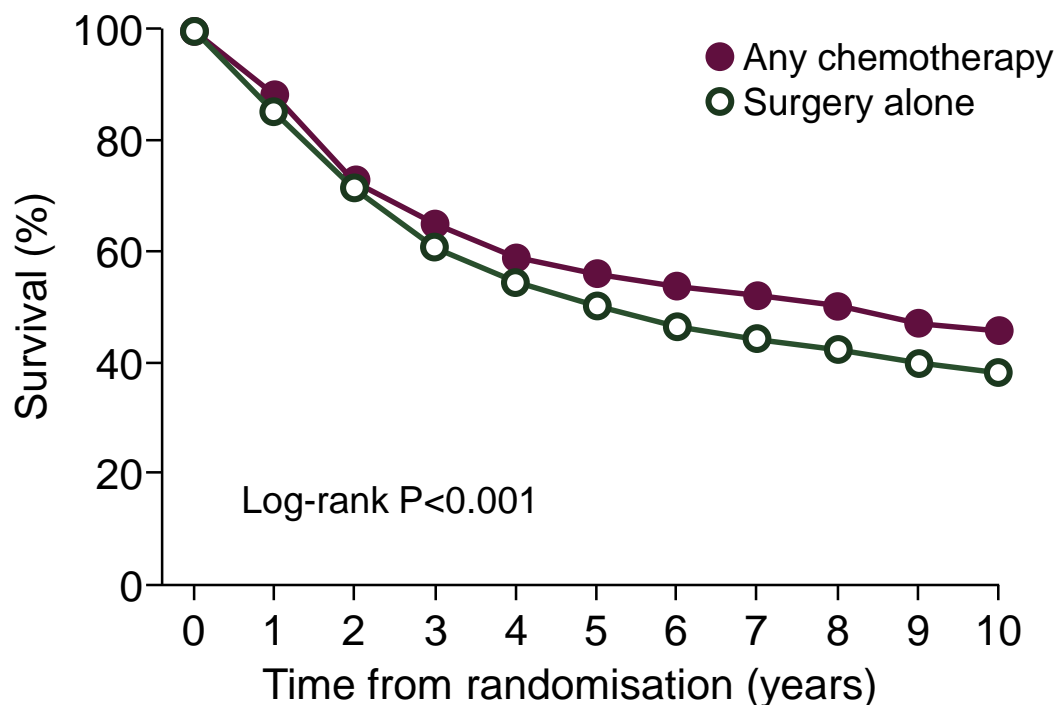
1. Di Costanzo F *et al.* JNCI J Natl Cancer Inst (2008) 100 (6): 388-398
2. Cascinu S *et al.* J Natl Cancer Inst 2007;99:601-7
3. De Vita F *et al.*, Ann Oncol (2007) 18 (suppl 6): 120-123
4. Bajetta E *et al.* Ann Oncol. 2002 Feb;13(2):299-307.

# Why has adjuvant chemotherapy failed to show any positive effect after surgery in gastric cancer?

- Non standard surgery
- High risk of local relapse
- Chemotherapy not very active in advanced disease: Complete response rate less than 10%
- Heterogeneous samples, low size samples, most patients n-
- Inadequate statistical design
- Prolonged and slow accrual

# Meta-analysis of individual data of trials involving adjuvant chemotherapy *versus* surgery alone for gastric cancer

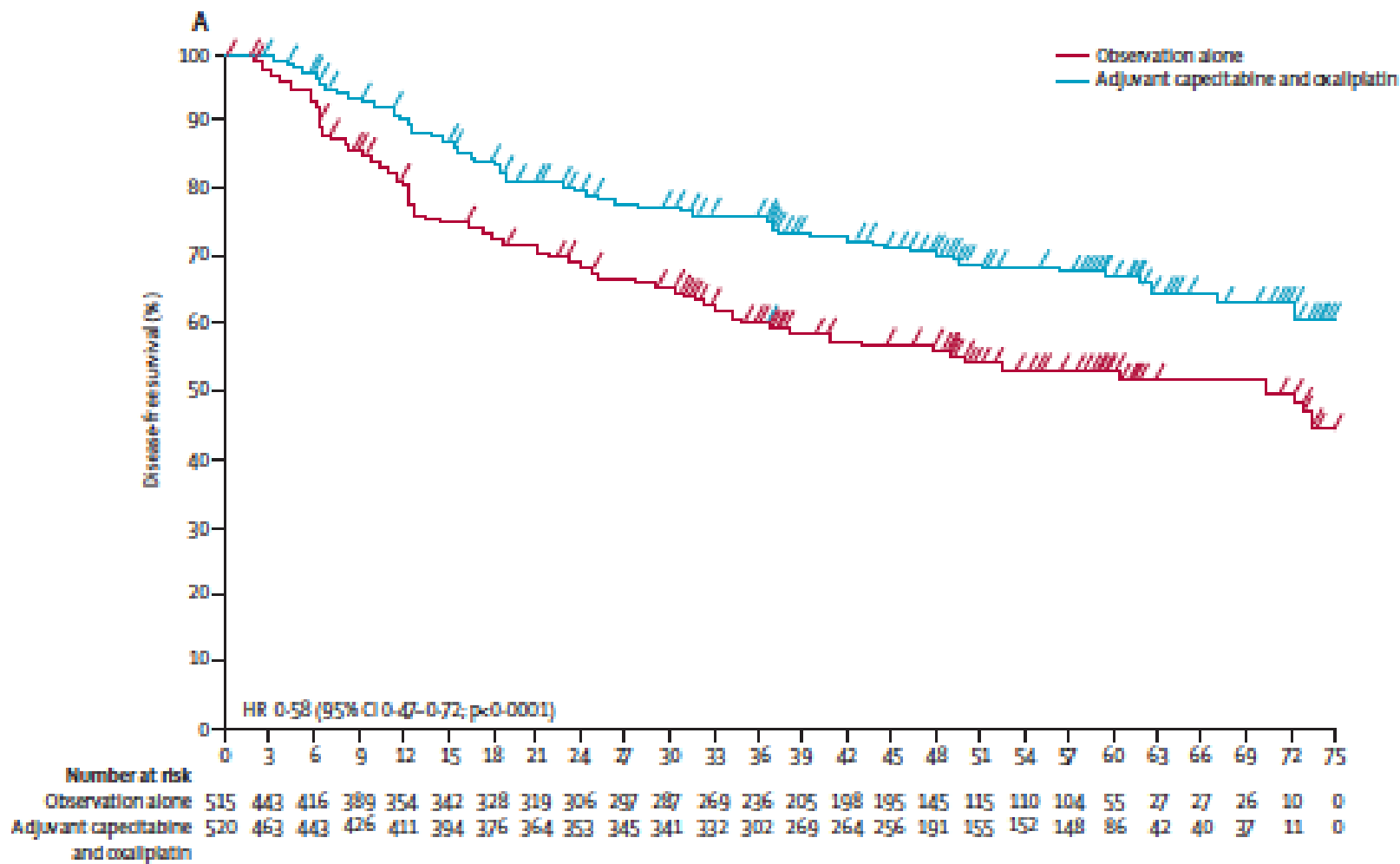
- Overall survival estimate after any chemotherapy or surgery alone truncated at 10 years



**No. at risk**

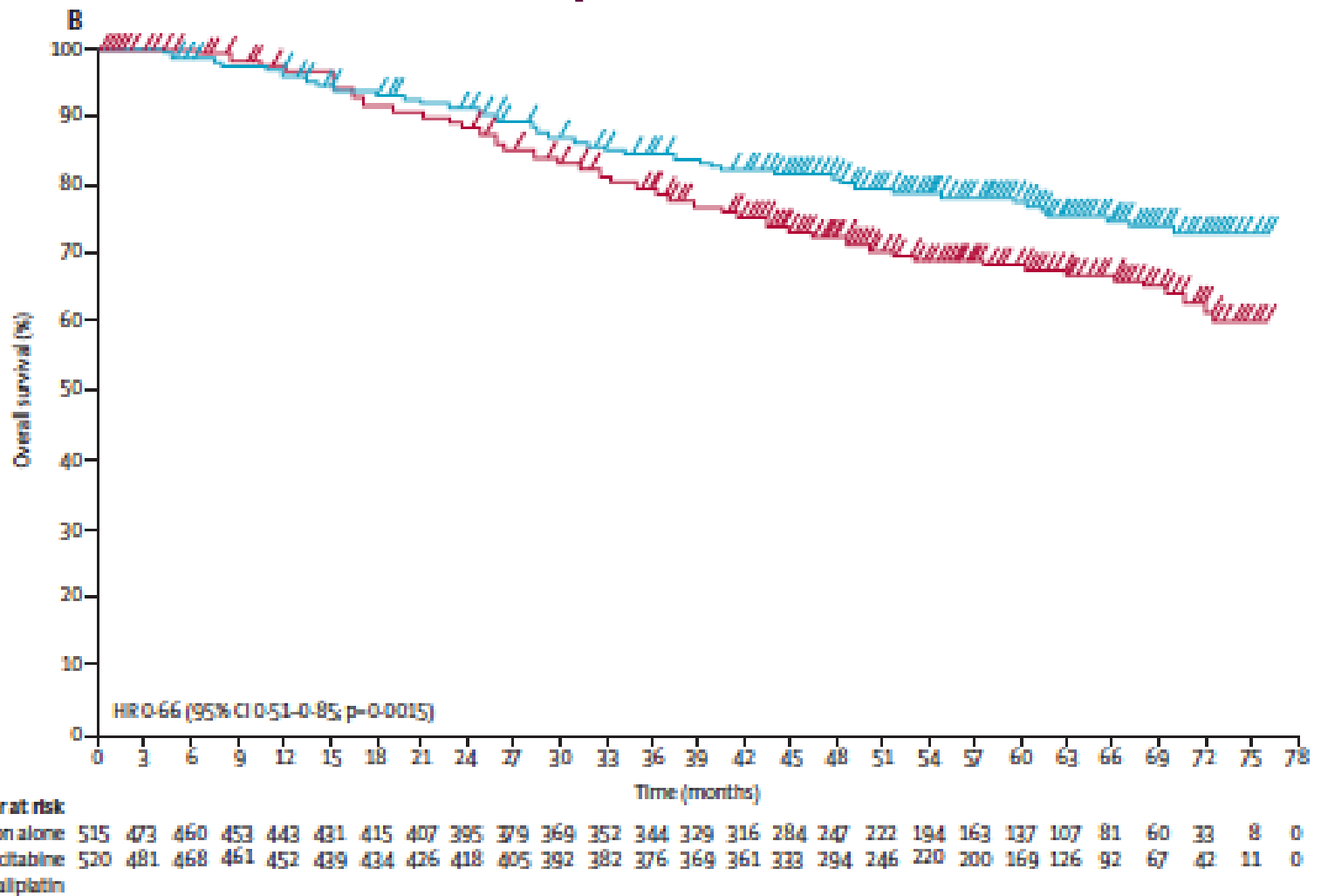
Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery	1857	1568	1300	1092	952	782	583	407	267	172	138

# Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy *versus* surgery alone: 5-year follow-up of a randomised phase III trial





# Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy *versus* surgery alone: 5-year follow-up of a randomised phase III trial



# The role of radiation in the postoperative setting: Adjuvant chemoradiotherapy for gastric cancer after surgery *versus* surgery alone: A randomised Phase III Trial

## Study design

**SURGERY**



**STRATIFICATION**

**T 1–4**  
**NODES**  
**0, 1–3, >3**

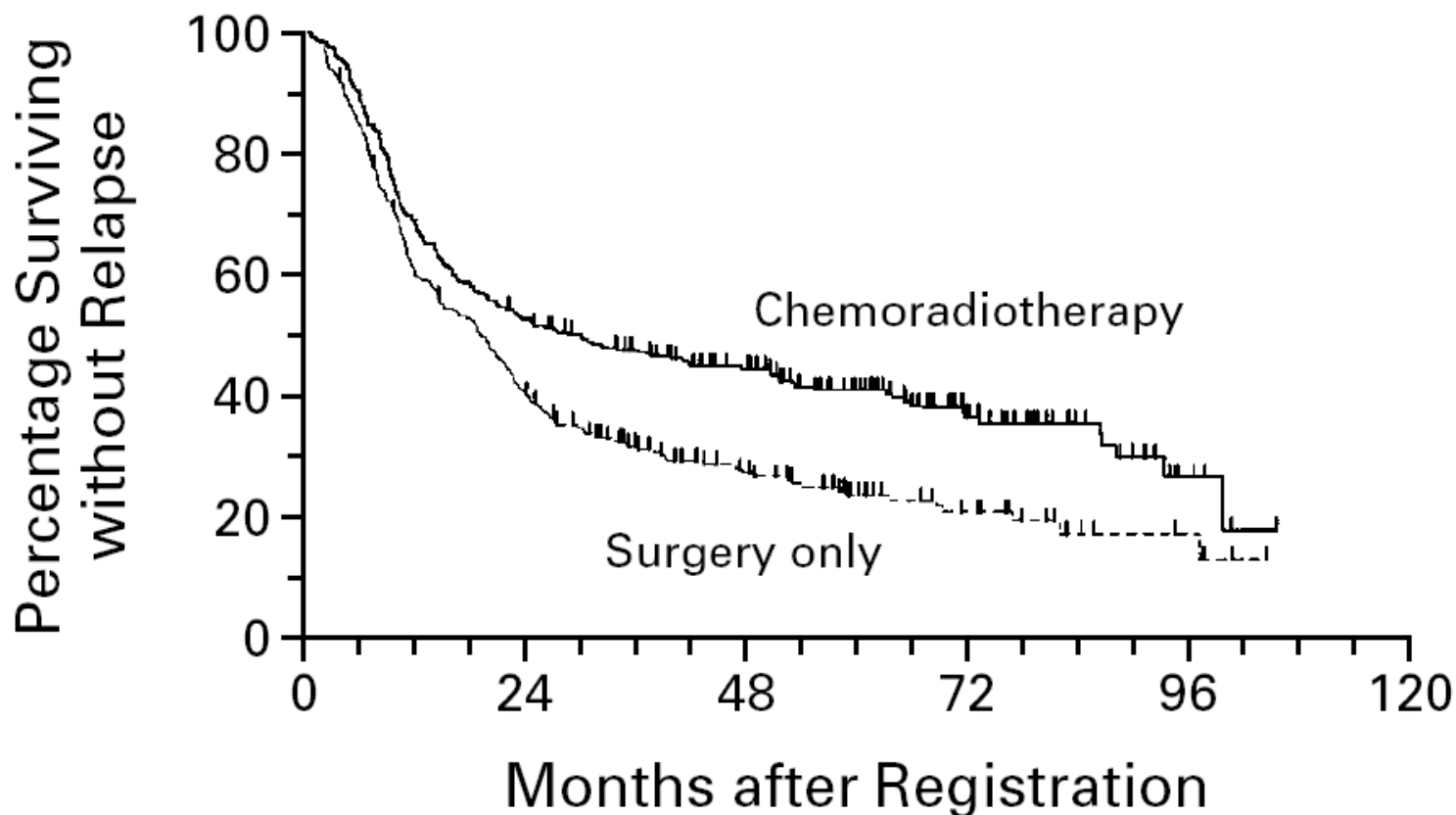


**NO TREATMENT**



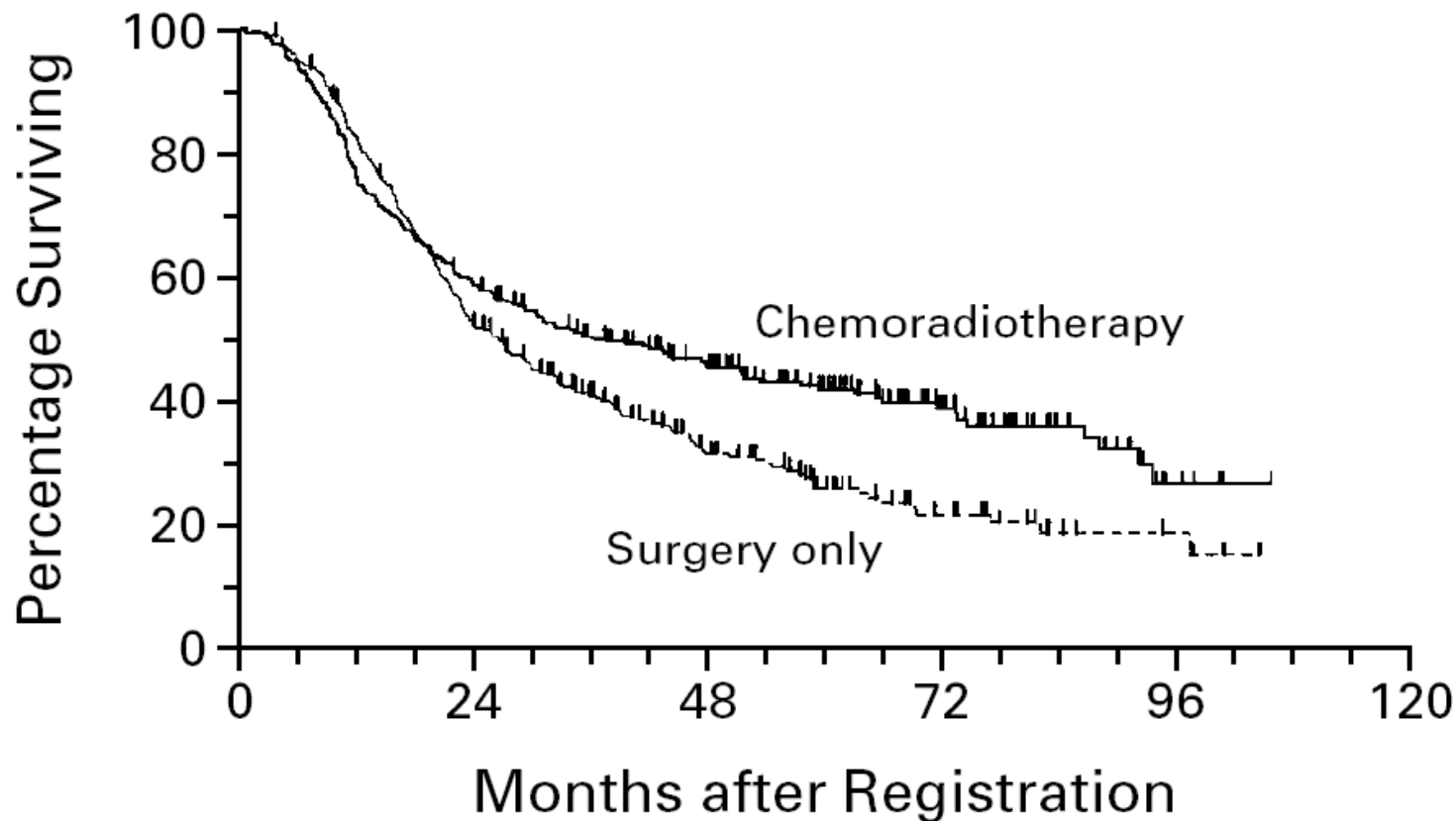
**CT+ CT-RT + CT**

# Adjuvant chemoradiotherapy for gastric cancer after surgery *versus* surgery alone: A randomised Phase III Trial



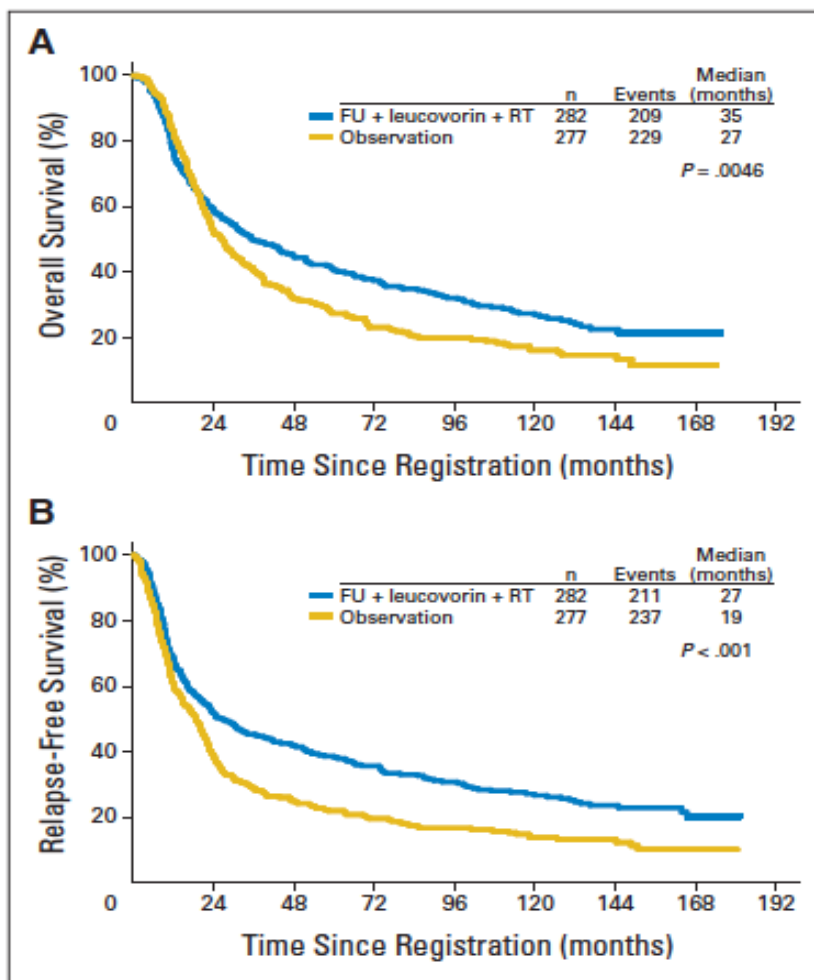
**Figure 2.** Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.

# Adjuvant chemoradiotherapy for gastric cancer after surgery *versus* surgery alone: A randomised Phase III Trial



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

# Adjuvant chemoradiotherapy for gastric cancer after surgery *versus* surgery alone: Long term data of a randomised Phase III Trial



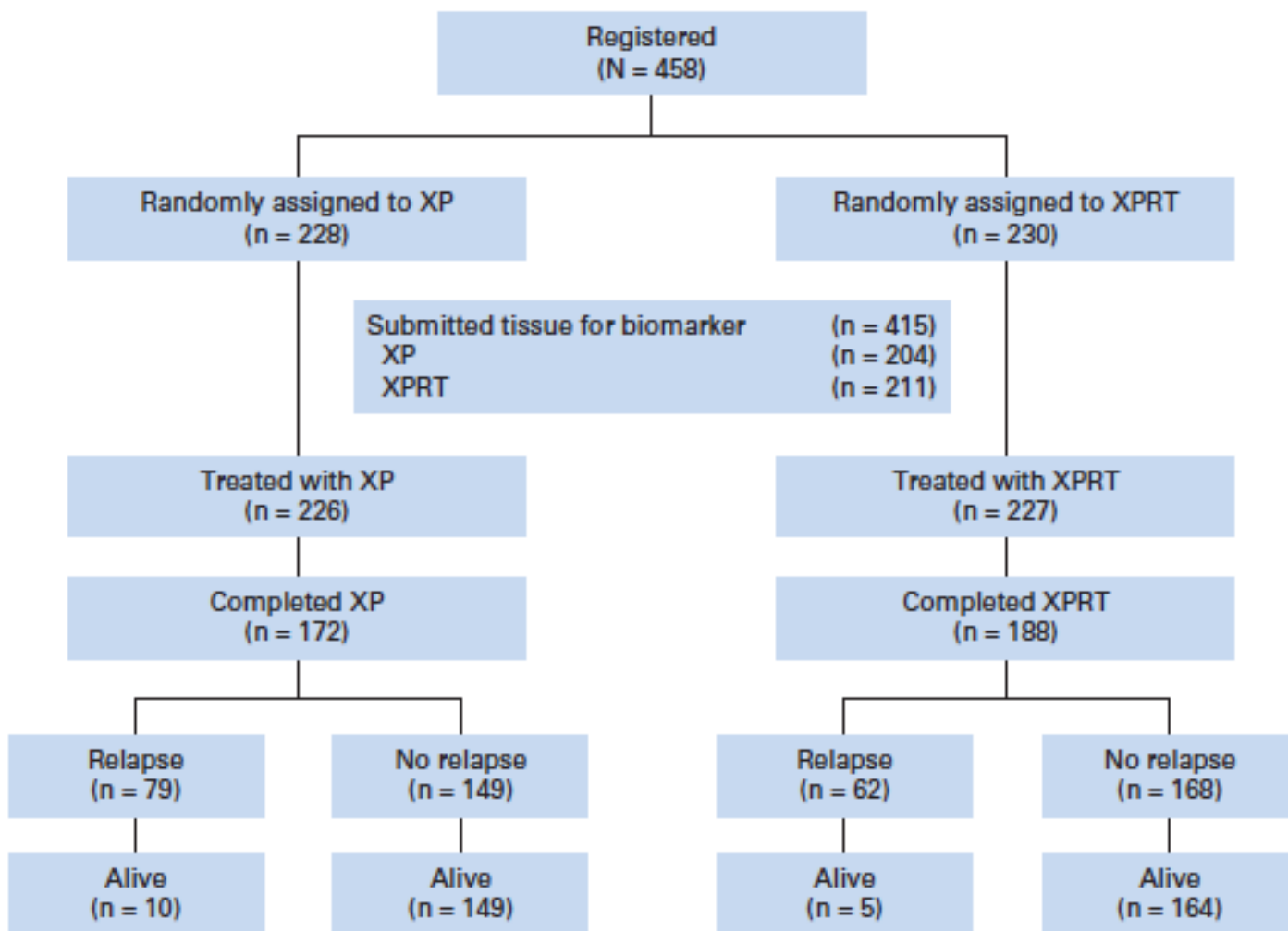
**Fig 2.** (A) Overall survival by arm; (B) relapse-free survival by arm. FU, fluorouracil; RT, radiotherapy.

**Table 2. Patterns of Failure by Arm**

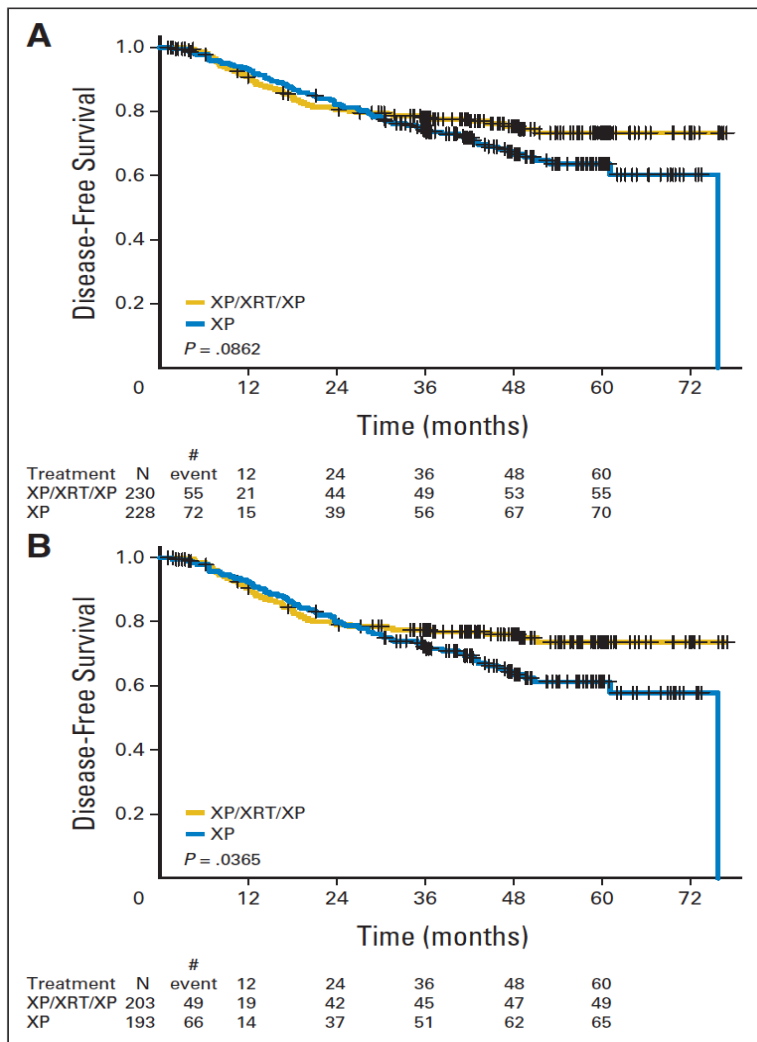
Relapse Status	Radiochemo-therapy		Control (surgery alone)		Total	
	No.	%	No.	%	No.	%
No relapse*	135	48	67	24	202	36
Relapse*	147	52	210	76	357	64
Sites of relapse (% of those randomly assigned)*						
Local	7	2	21	8	28	5
Regional	62	22	109	39	171	31
Distant	46	16	49	18	95	17
Unknown site	32	11	31	11	63	11
Total	282		277		559	

\*Indicates statistically significant comparisons.  $P < .001$  for relapse v no relapse ( $\chi^2$ );  $P = .012$  for sites of relapse (among those with sites reported,  $\chi^2$  test for trend).

# The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine *versus* chemoradiation for gastric cancer after surgery: A randomised Phase III Trial



# The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine *versus* chemoradiation for gastric cancer after surgery: A randomised Phase III Trial



**Fig 2.** Disease-free survival in (A) all patients and (B) lymph node-positive patients. XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.

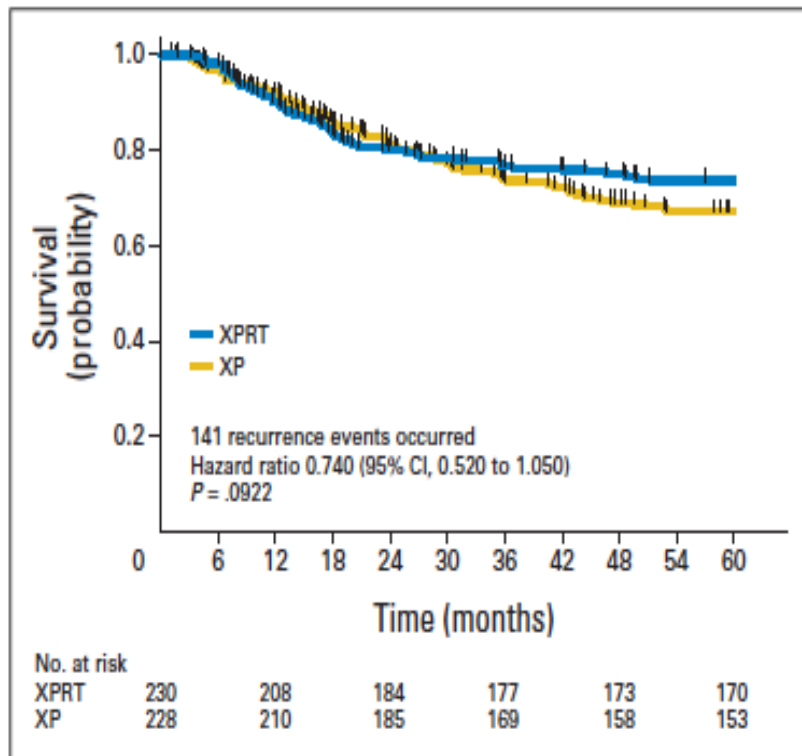
**Table 3.** Pattern of Recurrence

Pattern of Recurrence*	XP Arm		XP/XRT/XP Arm		P
Locoregional recurrence†	19	8.3	11	4.8	.3533
Distant metastasis‡	56	24.6	47	20.4	.5568

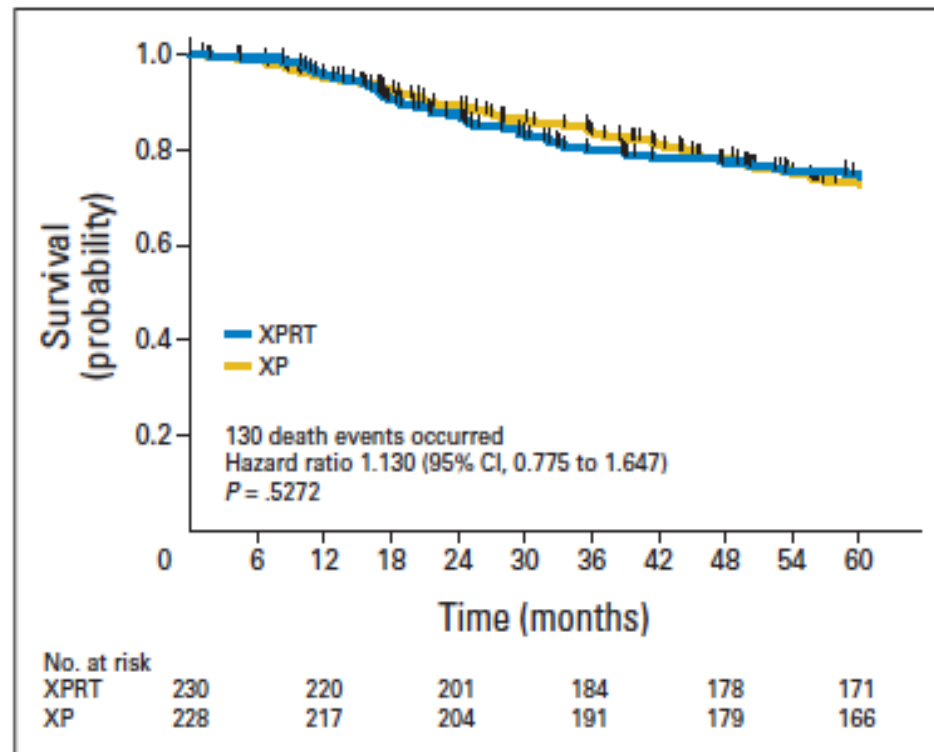
Abbreviations: XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.

Lee J, *et al.* J Clin Oncol 2012;30:268–73. Reprinted with permission. © (2012) American Society of Clinical Oncology. All rights reserved.

# The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine *versus* chemoradiation for gastric cancer after surgery: A randomised Phase III Trial



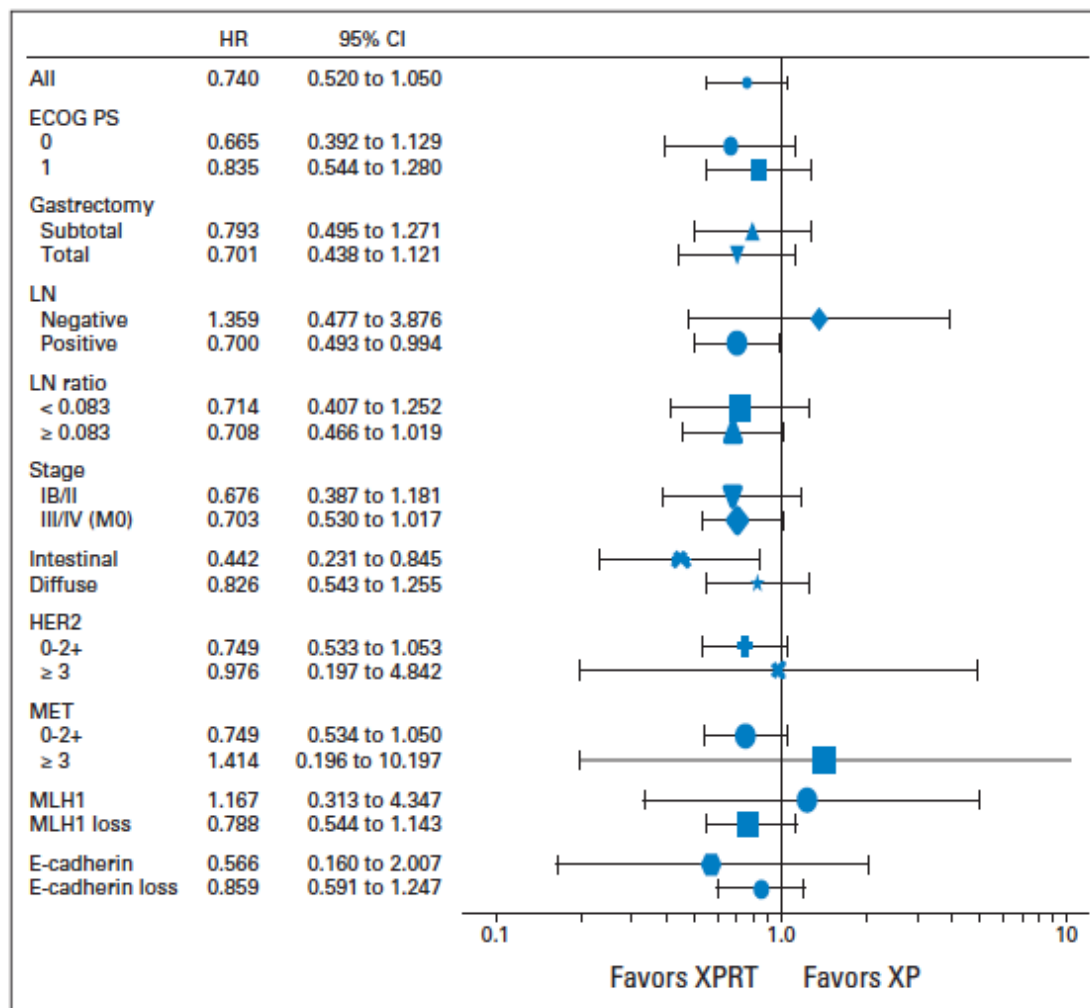
**Fig 2.** Disease-free survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.



**Fig 3.** Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

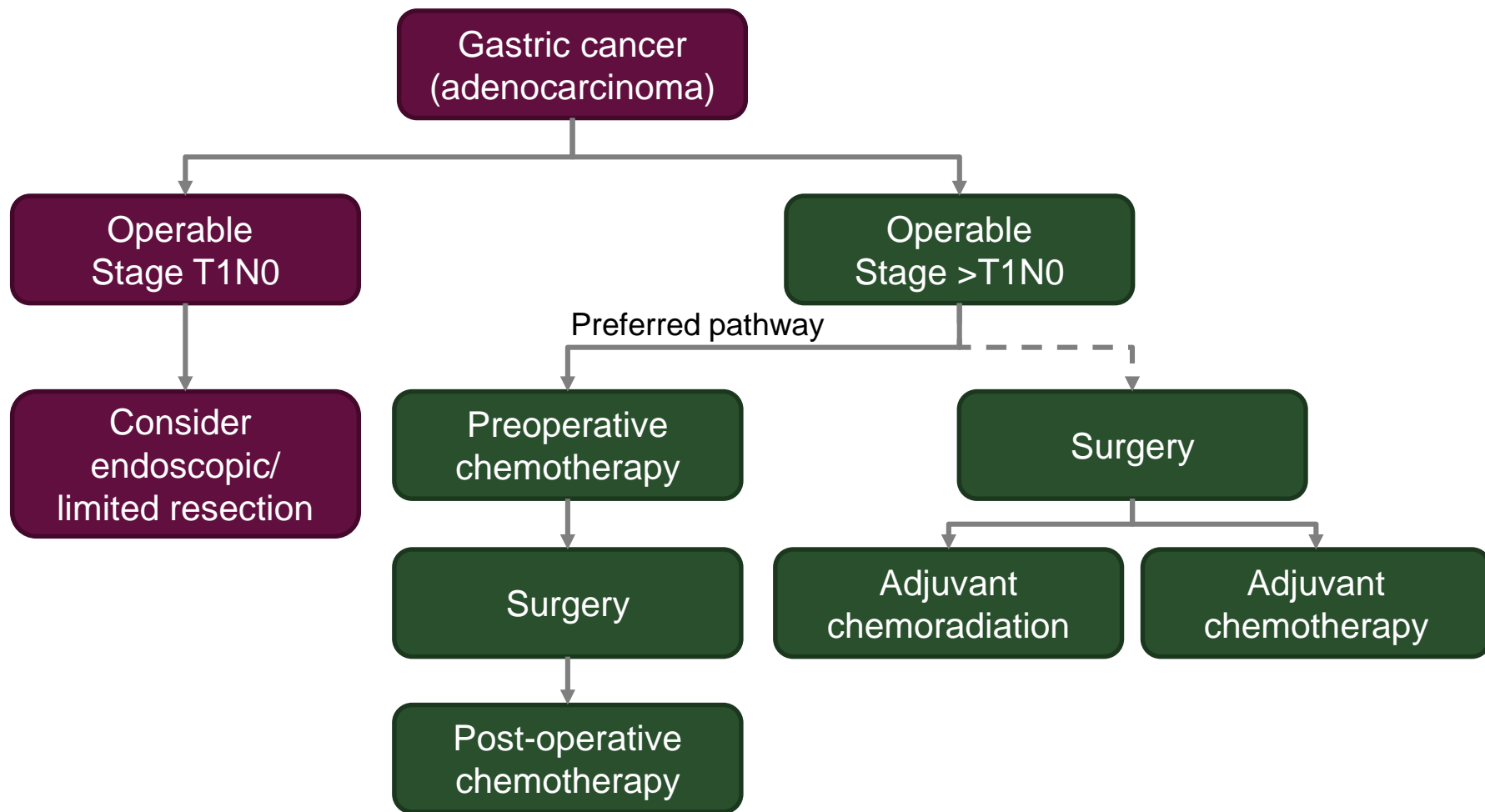


# The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine *versus* chemoradiation for gastric cancer after surgery: A randomised Phase III Trial



# Treatment for localised gastric cancer: What is standard of care?

## ■ Algorithm for the management of gastric cancer



# Localised gastric cancer: Aims of neoadjuvant therapy

- To increase R0 resection rate
- Early treatment of micrometastases
- To reduce locoregional relapses
- Biological studies

# 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

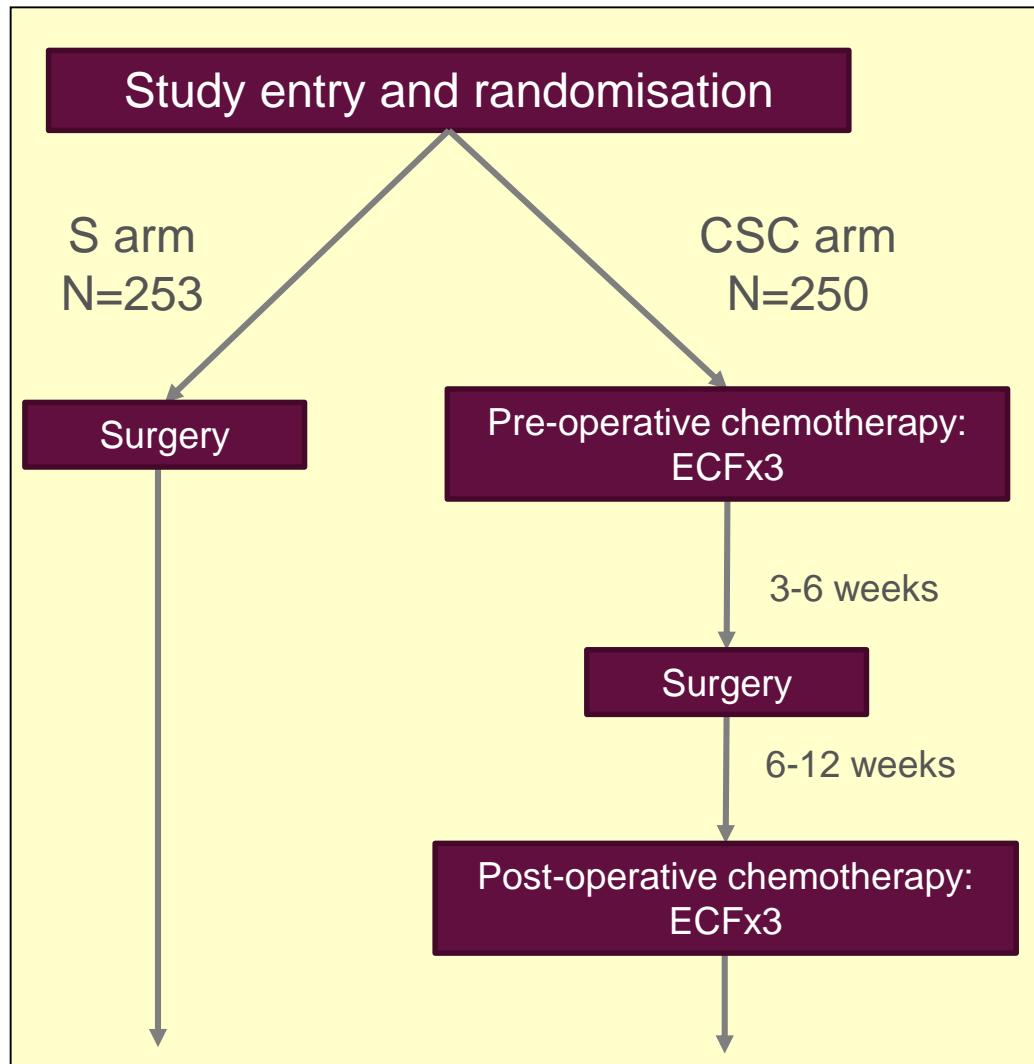
## Secondary

Progression-free survival  
Surgical resectability  
Quality of Life

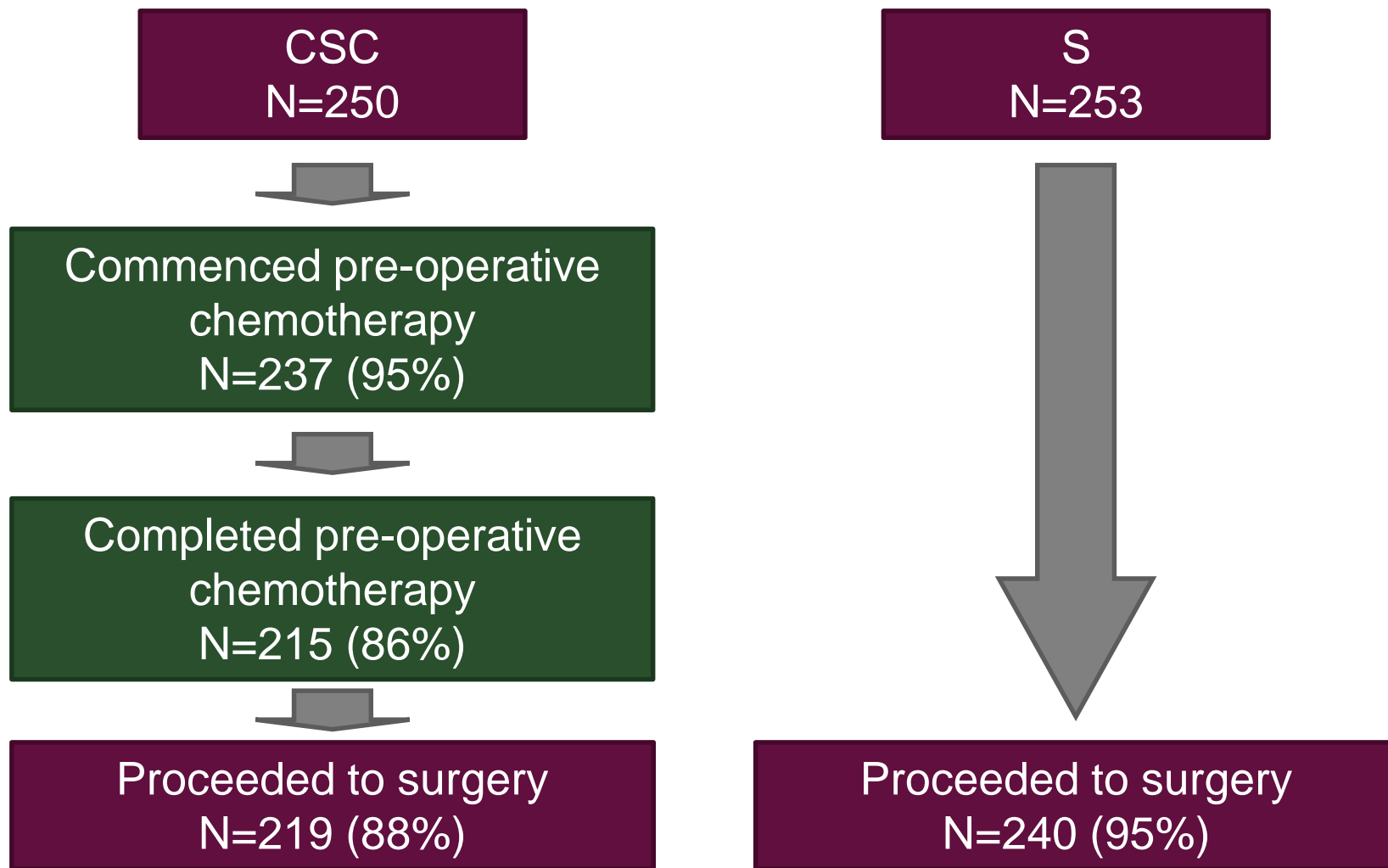
## Chemotherapy (ECF):

Epirubicin 50 mg/m<sup>2</sup>, IV day 1  
Cisplatin 60 mg/m<sup>2</sup>, IV day 1  
5-FU 200 mg/m<sup>2</sup>/day, continuous infusion, days 1-21  
(cycles repeated every 3 weeks)

Recruitment: July 1994-April 2002



# Pre-operative chemotherapy and surgery trial profile



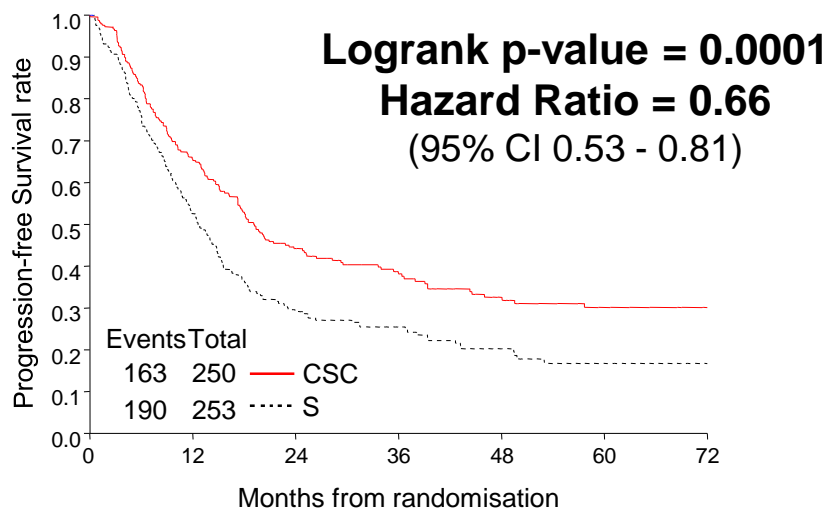
# MAGIC Trial: Postoperative morbidity/mortality

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

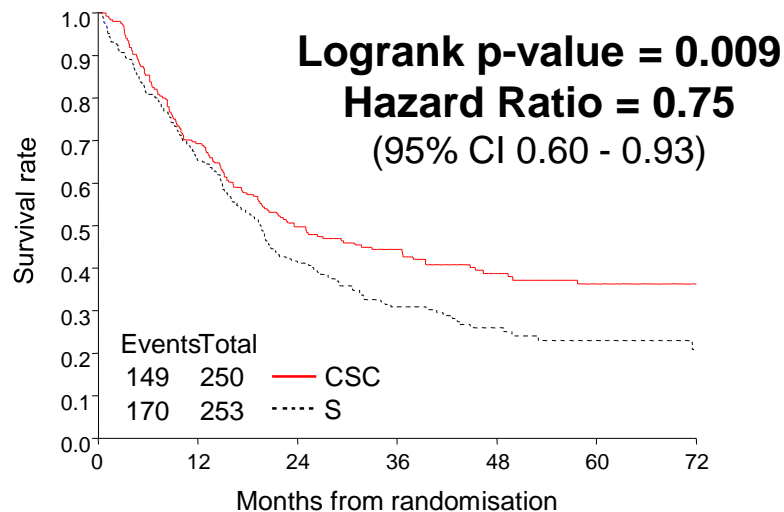
# MAGIC Trial results

European Society for Medical Oncology

## PFS\*



## Overall



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

- 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

## MAGIC: Conclusions

- In operable gastric and lower oesophageal cancer, perioperative chemotherapy:
  - Leads to downsizing of primary tumour
  - Significantly improves progression-free survival
  - Significantly improves overall survival

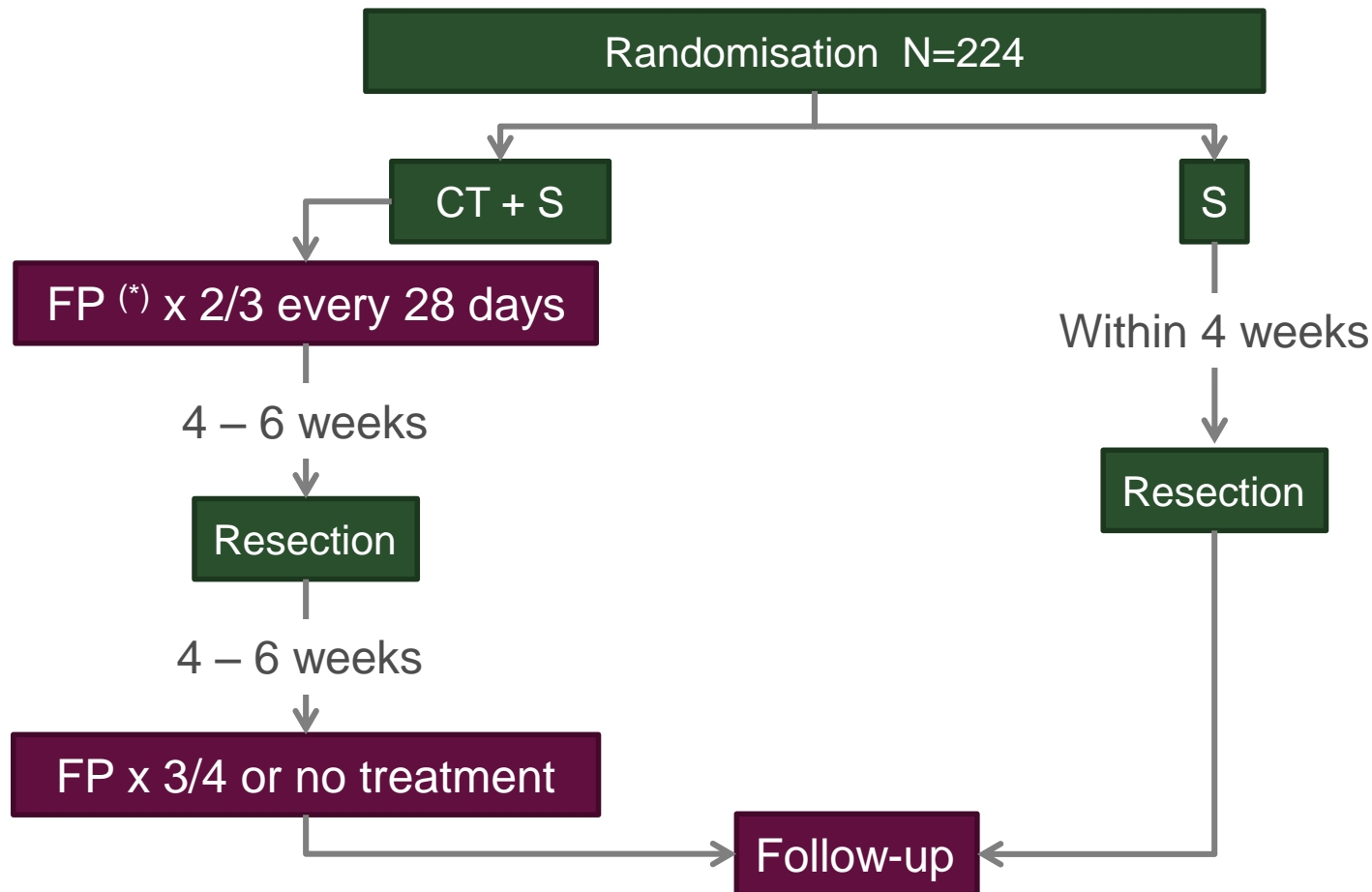


## Can MAGIC be compared to INT0116?

	MAGIC <sup>1</sup> (N=503)		INT116 <sup>2</sup> (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 randomisation

# Perioperative chemo: FNLCC 94012-FFCD 9703 Trial

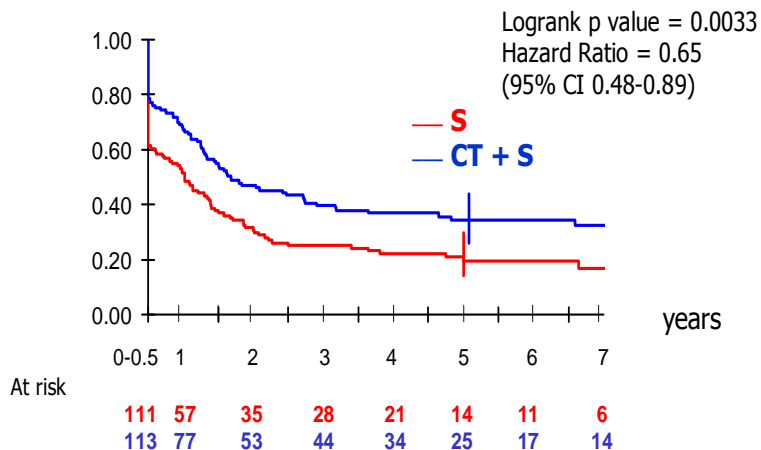


\*5-Fluorouracil 800 mg/m<sup>2</sup> d1-5\*  
+ Cisplatin 100 mg/m<sup>2</sup> day 1

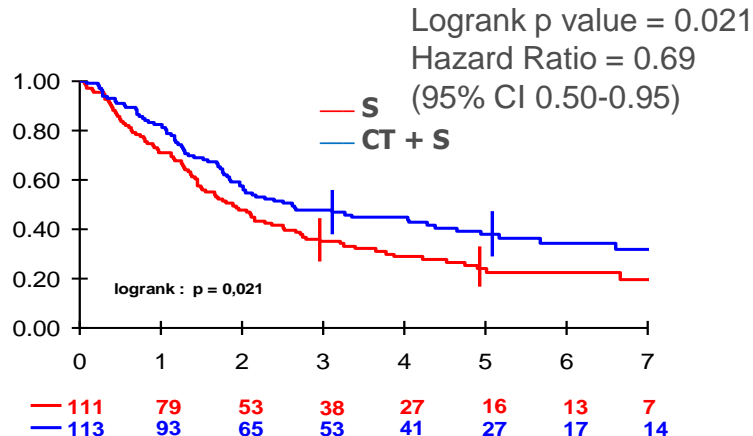
Trial accrual 1995-2003  
Median FU 5.7 yrs

# Perioperative chemo: FNLCC 94012-FFCD 9703 Trial

## PFS\*



## Overall



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

Median follow up: 5.7 years

- On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender
- Prognostic variables in Cox multivariate analysis:
  - Preoperative CT
  - Gastric location

# Summary of trials of perioperative chemotherapy for localised gastric cancer

Trial	CT	No. pts control	No. pts CT	5-year survival control	5-year survival CT	HR (CI at 95%)
Cunningham N Eng J Med 2006	ECF	253 No CT	250	23%	36 %	0.75 0.60-0.93 p=0.009
Ychou J Clin Oncol 2011	CDDP 5-FU	111 No CT	113	24%	38%	0.69 0.50-0.95 p=0.021

1. Cunningham D, *et al.* N Engl J Med 2006;355:11–20;
2. Ychou M, *et al.* J Clin Oncol 2011;29:1715–1726.

# Neoadjuvant chemotherapy in gastric cancer: Conclusions

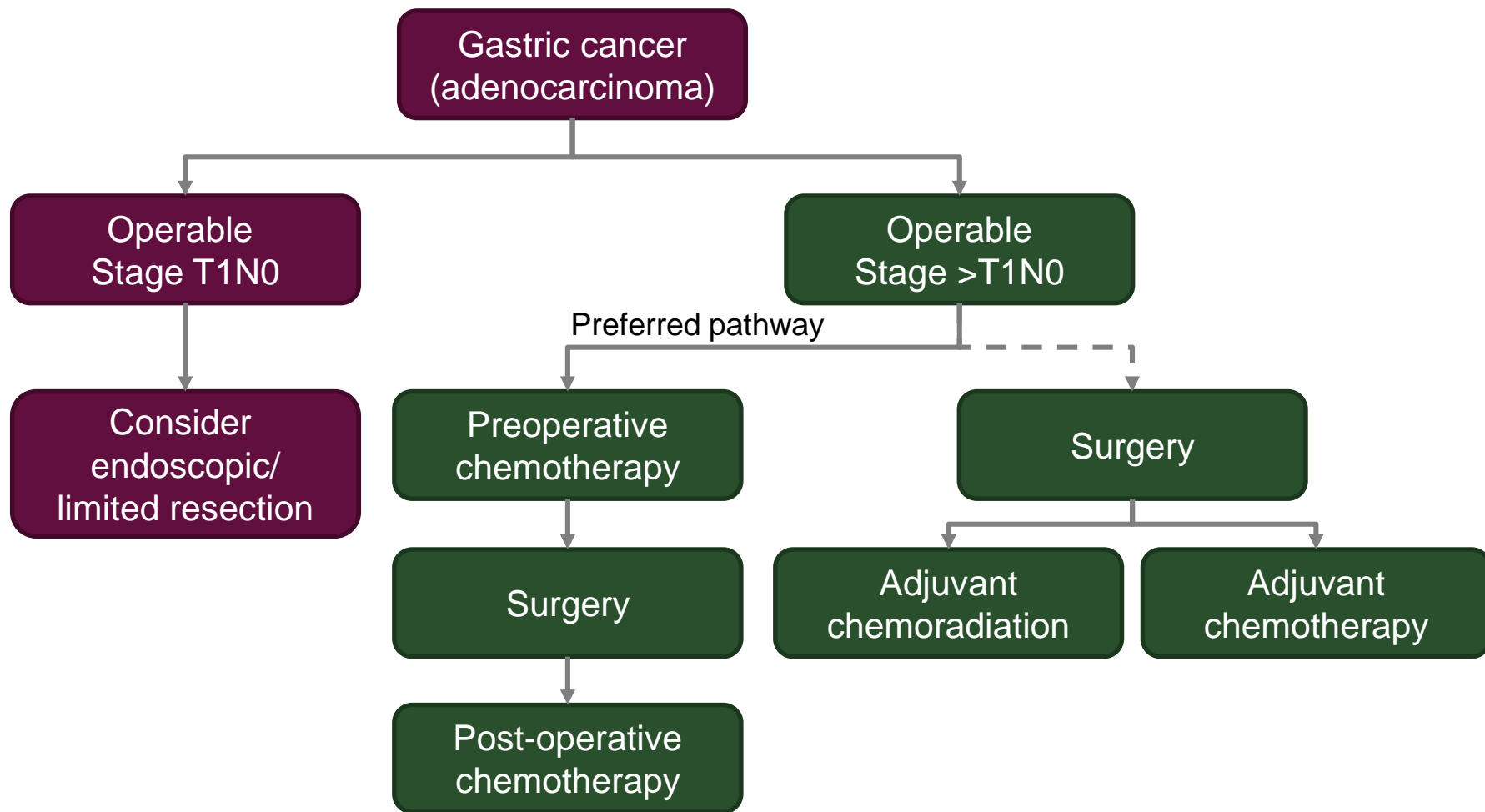
- Perioperative chemotherapy:
  - Induces downstaging
  - May increase the R0 resection rate
  - Prolongs disease free survival
  - Improves overall survival
  
- Evidence level I based upon 2 well designed and properly conducted randomised trials
- Preoperative therapy is better tolerated than postoperative
- Localised gastric cancer requires a multidisciplinary team approach
- Further research on biological predictive factors is needed

## Currently recommended approach to localised gastric cancer

- Clinical assessment and staging
- Multidisciplinary team discussion
- Preoperative treatment in all patients with clinical stage II and III
- Surgical resection after chemotherapy
- Pathology assessment and estimation of risk
- Postoperative chemotherapy if tolerated
- Participation in trials

# Treatment for localised gastric cancer: What is standard of care?

## ■ Algorithm for the management of gastric cancer



# Advances in gastric cancer: How to approach localised disease? Conclusions

- Multidisciplinary approach needed for localised disease: Preoperative treatment preferred
- Quality of surgery essential
- Radiotherapy for localised disease still experimental



**THANK YOU!**