NEOADJUVANT AND ADJUVANT THERAPY FOR GASTROESOPHAGEAL ADENOCARCINOMA

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CONFLICT OF INTEREST DISCLOSURE

Employment: None; **Stock Ownership**: None

Consultant or Advisory Role: Merck Serono, Roche, Beigene, Bayer, Servier, Pierre Fabre, Novartis, Takeda, Astelas.

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Others: Executive Board member of ESMO, Director of Education ESMO, General and Scientific Director INCLIVA, Associate Editor: Annals of Oncology and ESMO Open, Editor in chief: Cancer Treatment Reviews.

“OLD” 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 OF ADJUVANT CHEMOTHERAPY VS SURGERY ALONE

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
Zhao et al (5) Cancer Invest	2008	15	3212	0.90	0.84-0.96	Significant benefit P: 0.001
Liu et al (6) Eur J Surg Oncol	2008	19	2286	0.85	0.80-0.90	Significant benefit P<0.0001
Gastric Group (7) JAMA	2010	17	3871	0.82	0.76-090	P<0.001

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. 5. Zhao SL, *et al.* Cancer Invest. 2008;26:317–325. 6. Liu TS, *et al.* Eur J Surg Oncol 2008;34:1208-1216.
7. The Gastric Group. Jama 2010:303:1729-37.

WHY HAS ADJUVANT CHEMOTHERAPY FAILED AFTER SURGERY IN WESTERN TRIALS?

Non standard surgery

High risk of local relapse

Chemotherapy nor very active in advanced disease: Complete response rate less than 10%

Heterogeneous samples, low size samples, most patients n-

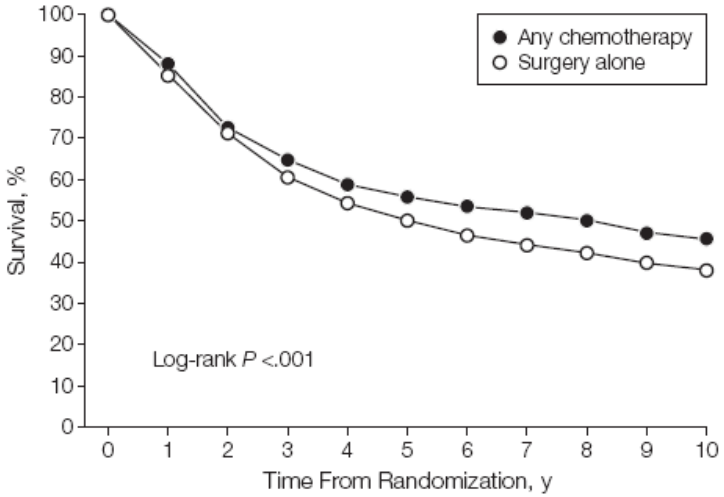
Inadequate statistical design

Prolonged and slow accrual

META-ANALYSIS

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 alone	1857	1568	1300	1092	952	782	583	407	267	172	138

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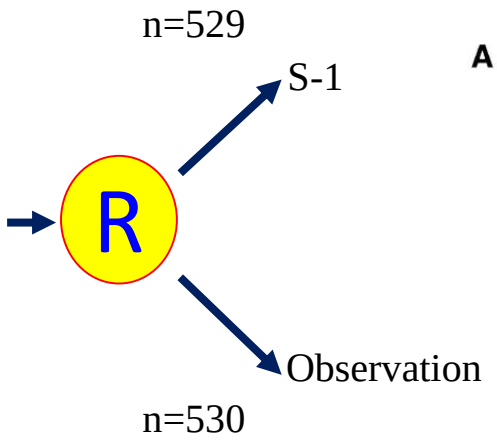
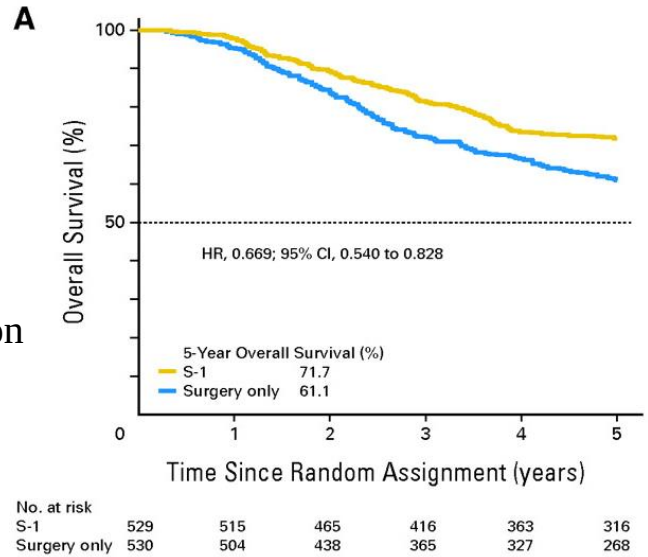
Adjuvant S-1 in gastric cancer (ACTS-GC)

Patients with stage II & III gastric cancer; D2 or more dissection



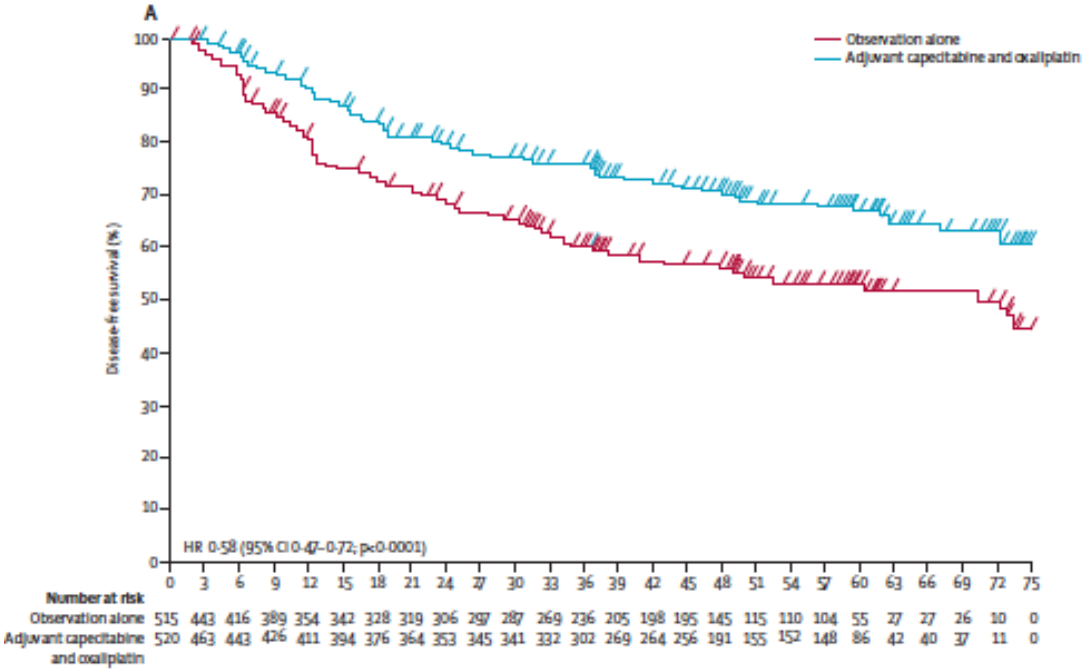
Overall survival (total population)



Sasako et al. J Clin Oncol 2011

ADJUVANT CAPECITABINE PLUS OXALIPLATIN

For gastric cancer after D2 gastrectomy *versus* surgery alone: 5-year follow-up of a randomised phase III trial



Reprinted from The Lancet Oncol, 15, Noh SH, *et al*. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial: 1389–1396, © (2014), with permission from Elsevier.

ADJUVANT CAPECITABINE PLUS OXALIPLATIN

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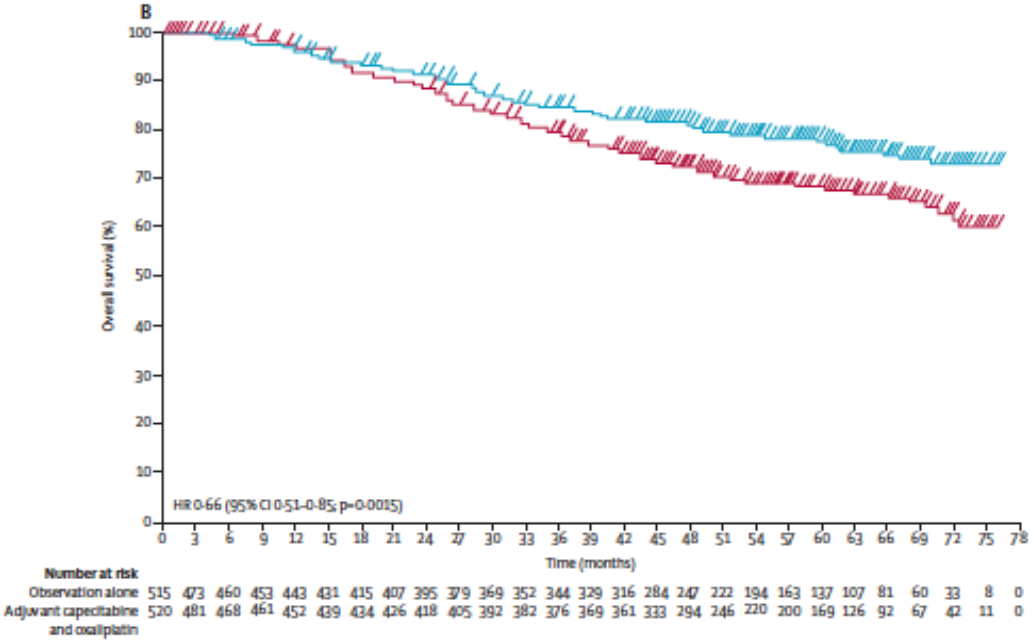
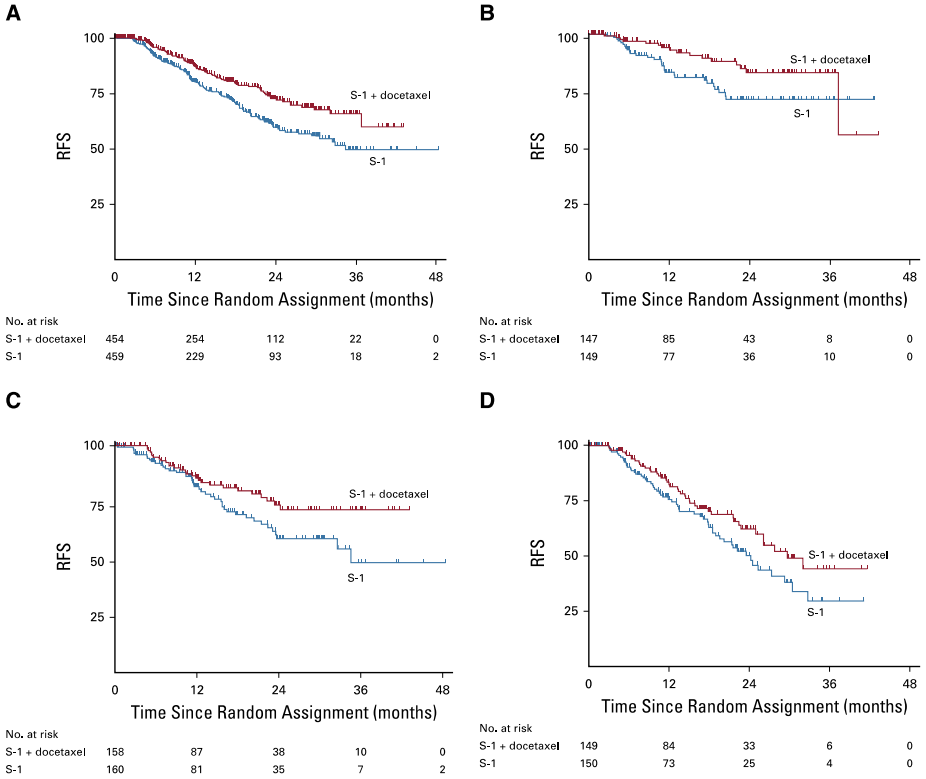


Reprinted from The Lancet Oncol, 15, Noh SH, *et al.* Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial: 1389–1396, © (2014), with permission from Elsevier..

Addition of Docetaxel to Oral Fluoropyrimidine Improves Efficacy in Patients With Stage III Gastric Cancer: Interim Analysis of JACCRO GC-07

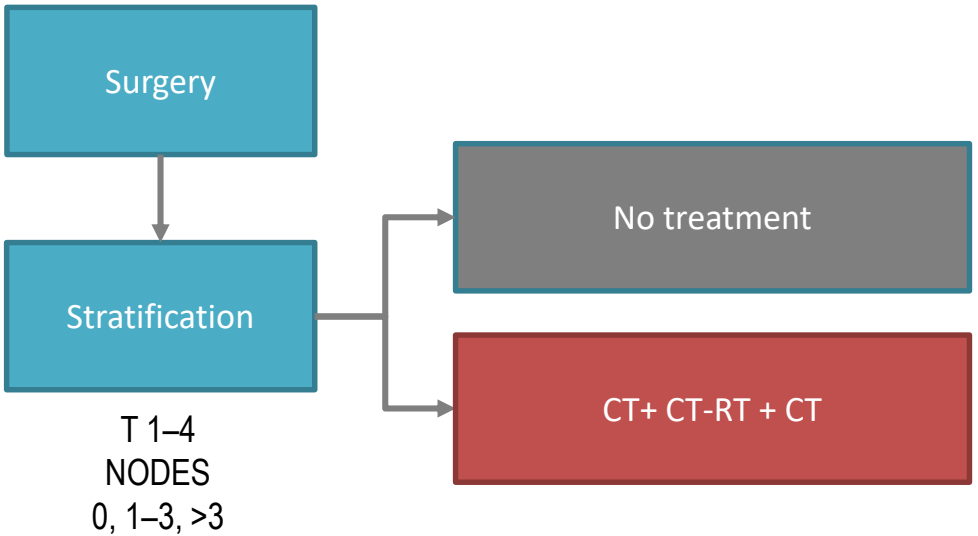


Yoshida K, et al. J Clin Oncol 2019; 37:1296-1304

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

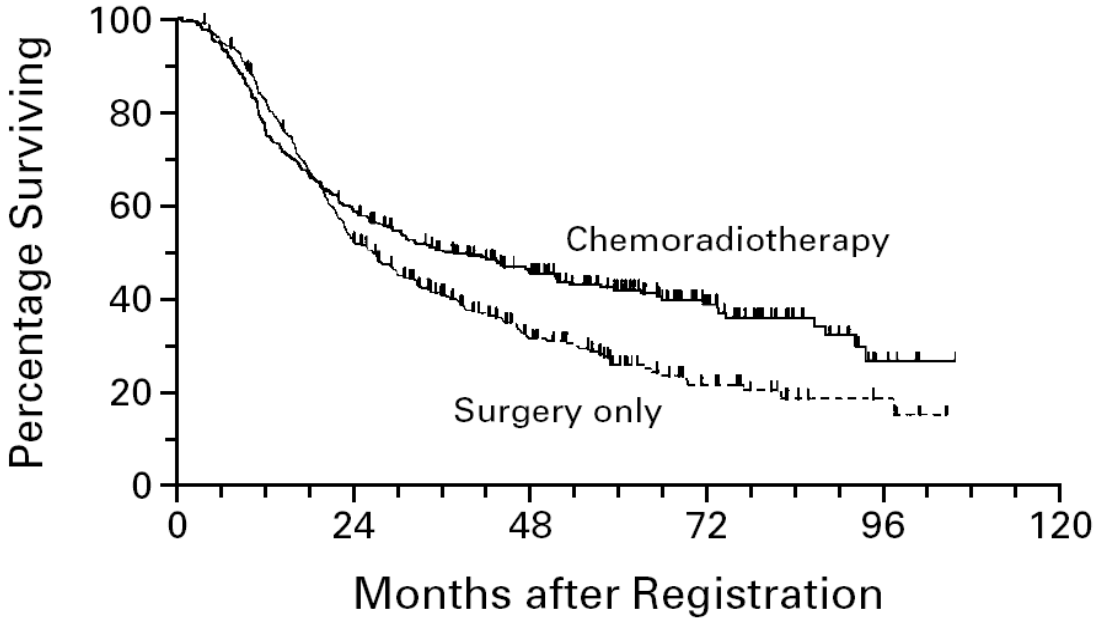


MacDonald JS, *et al.* N Engl J Med 2001;345:725–730.

ADJUVANT CHEMORADIOTHERAPY FOR GASTRIC CANCER AFTER SURGERY *VERSUS* SURGERY ALONE

A randomised Phase III Trial

Overall survival among all eligible patients, according to treatment-group assignment

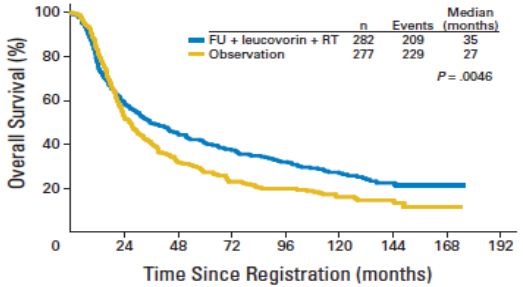


From N Engl J Med, MacDonald JS, *et al.* Chemoradiotherapy after Surgery Compared with Surgery Alone for Adenocarcinoma of the Stomach or Gastroesophageal Junction, 345:725–730. Copyright © 2001 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

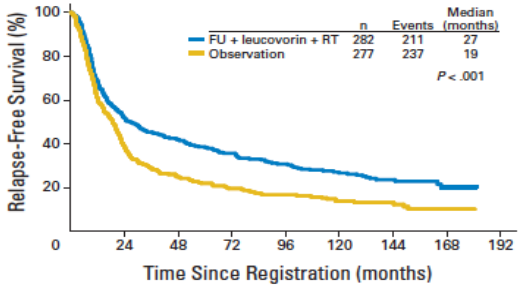
ADJUVANT CHEMORADIOTHERAPY FOR GASTRIC CANCER AFTER SURGERY *VERSUS* SURGERY ALONE

Long term results of a randomised Phase III Trial

Overall survival by arm



Relapse-free survival by arm



Patterns of failure by arm

	Radiochemo-therapy		Control (surgery alone)		Total	
Relapse Status	**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 (χ^2); P= .012 for sites of relapse (among those with sites reported, χ^2 test for trend).

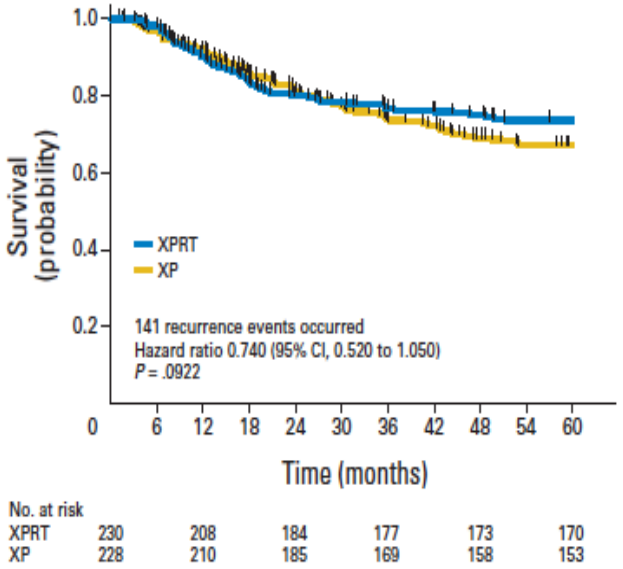
FU, fluorouracil; RT, radiotherapy.

Smalley S, *et al.* J Clin Oncol 2012;30:2327–2333Reprinted with permission. © (Year of publication being used) American Society of Clinical Oncology. All rights reserved.

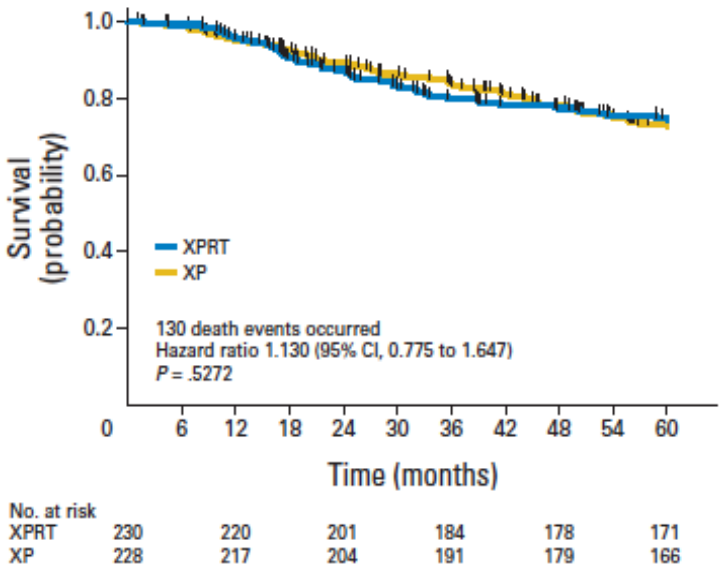
ARTIST: THE ROLE OF RADIATION IN THE POSTOPERATIVE SETTING

Adjuvant cisplatin and capecitabine *versus* chemoradiation for gastric cancer after surgery: A randomised phase III Trial

Disease-free survival



Overall survival

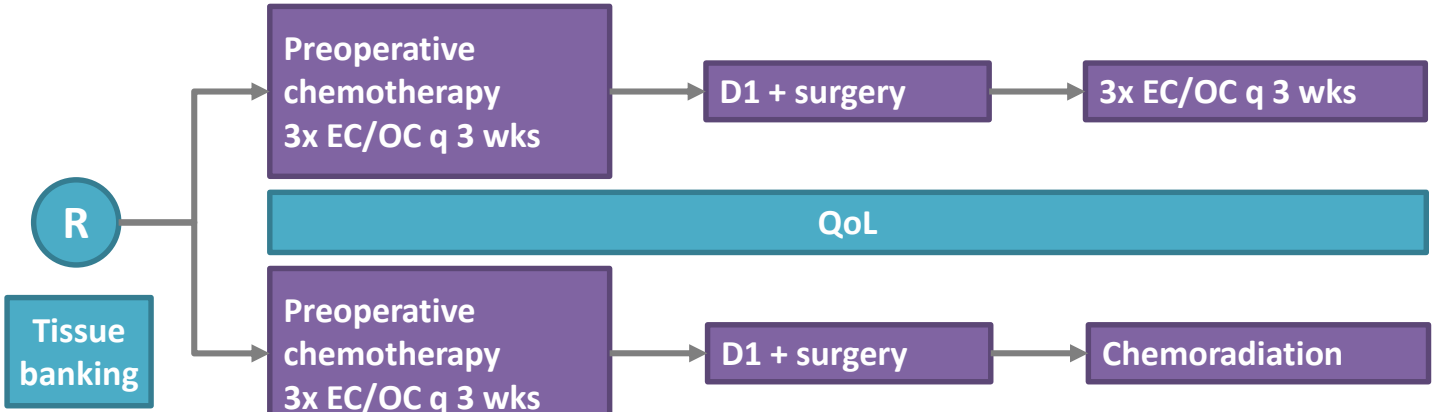


XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Park SH, *et al.* J Clin Oncol 2015; 33: 3130-3136. Reprinted with permission. © 2015 American Society of Clinical Oncology. All rights reserved.

CRITICS TRIAL

Design: 788 pts: 393 CT and 395 CRT

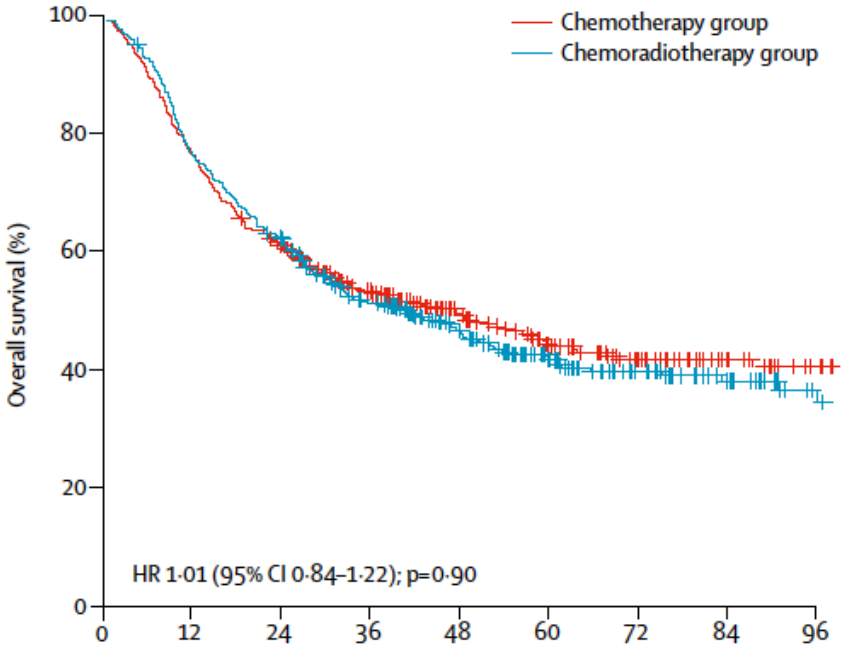


Stratified for:
- Center
- Histological type
- Localisation of tumour

45 Gy/25 fx + capecitabine cisplatin

Cats A, *et al.* Lancet Oncol 2018; 19:616-628.

FINAL RESULTS FROM CRITICS

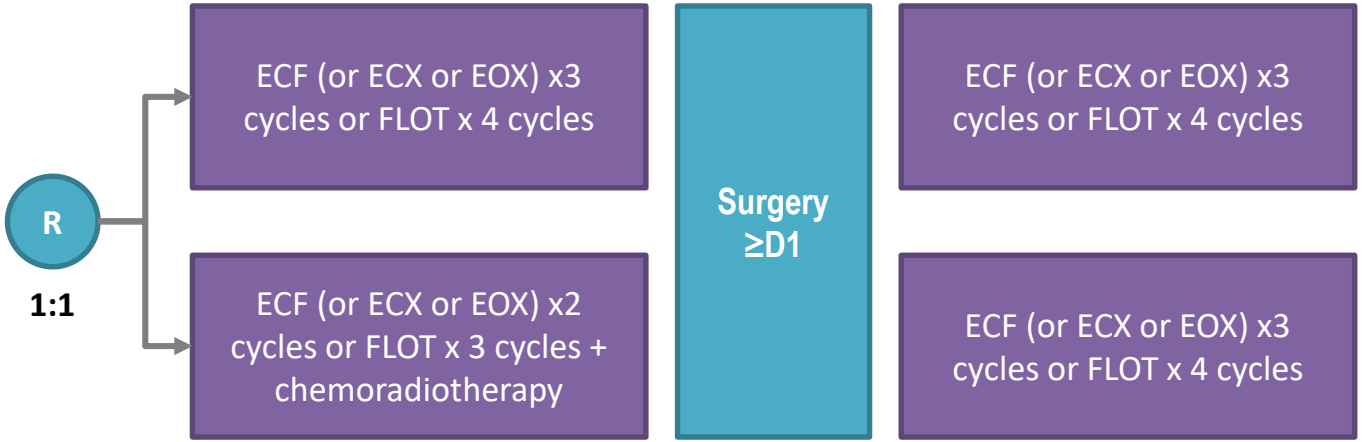


Reprinted from The Lancet Oncol, 19, Cats A, *et al.* Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial :616-628.Copyright 2018, with permission from Elsevier.

ASSESSING PREOPERATIVE CHEMORADIATION *VS.* CHEMOTHERAPY ALONE

In gastro-esophageal adenocarcinomas: The TOPGEAR Trial

Phase II/III (Part I= 120: Part II= 500)



Stratified by:

Age: <50 yrs *vs.* 50 yrs – 70 yrs *vs.* >70 yrs
Primary tumour site
Clinical tumour stage: T1-2 *vs.* T3-4
Clinical nodal stage: N+ve *vs.* N-ve
Chemotherapy regimen: ECF/ECX *vs.* EOX *vs.* FLOT
Gender, site, PET, EUS, laparoscopy

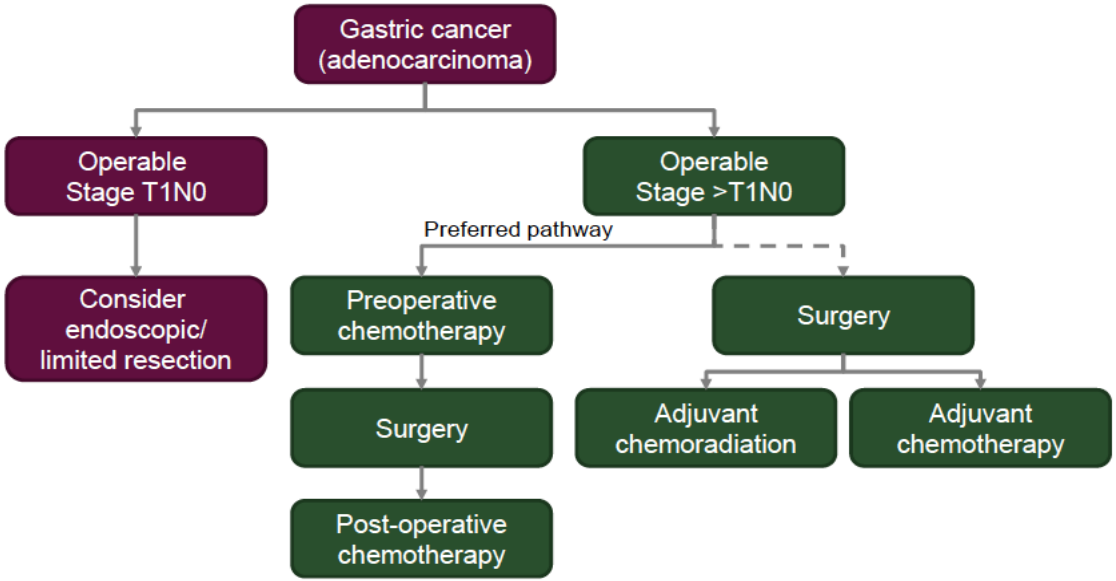
EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

ESMO

TREATMENT FOR LOCALISED GASTRIC CANCER

What is standard of care?

- Algorithm for the management of gastric cancer



Smyth EC, *et al.* Ann Oncol 2016;27 (Suppl5):38–49.

MAGIC TRIAL: STUDY DESIGN

Eligible patients:

- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease

Primary

Overall survival

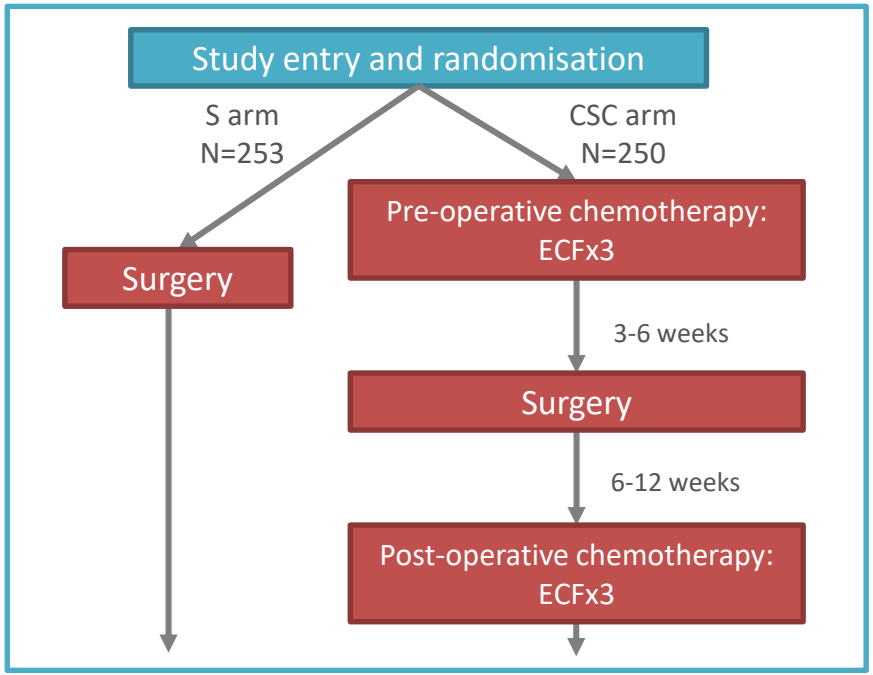
Secondary

Progression-free survival
Surgical resectability
Quality of Life

Chemotherapy (ECF):

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

Recruitment: July 1994-April 2002



Cunningham D, *et al.* N Engl J Med 2006;355:11–20.

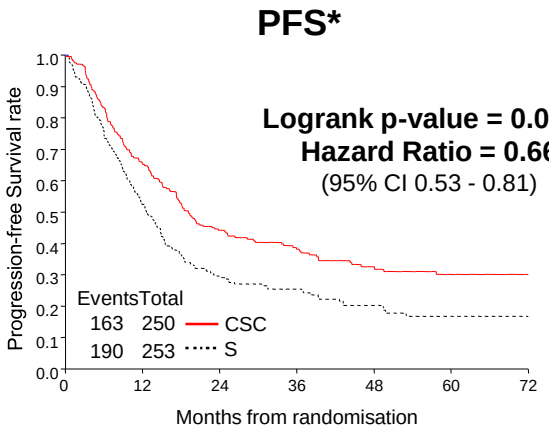
MAGIC TRIAL

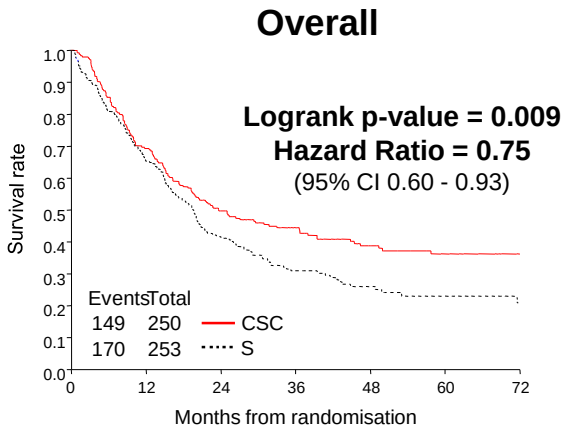
Postoperative morbidity/mortality

	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 D, *et al.* N Engl J Med 2006;355:11–20.

MAGIC TRIAL RESULTS





	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

From N Engl J Med, Cunningham D, *et al.* Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer;355:11–20. Copyright © 2006 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

MAGIC TRIAL

Conclusions

In operable gastric and lower oesophageal cancer, perioperative chemotherapy with ECF:

- Leads to downsizing of primary tumour
- pCR rate 8%
- Significantly improves progression-free survival
- Significantly improves overall survival

Cunningham D, *et al.* N Engl J Med 2006;355:11–20.

SUMMARY OF PHASE III CONTROLLED TRIALS

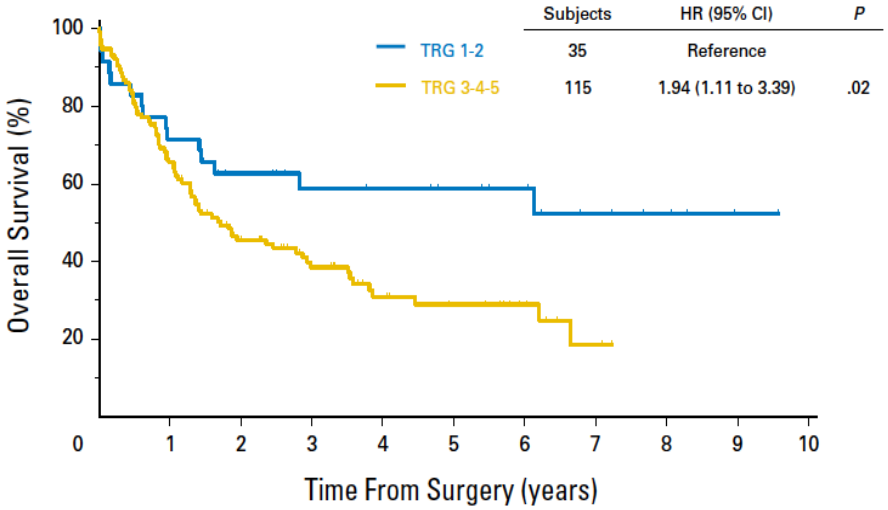
Perioperative chemotherapy for localised oesophago-gastric cancer

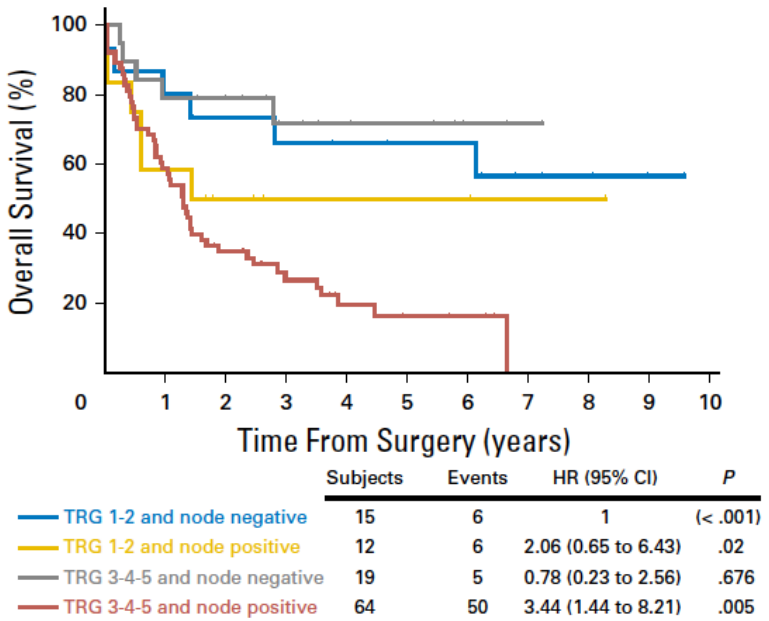
Trial	CT	No. pts control	No. pts CT	5-year survival control	5-year survival CT	HR (CI at 95%)
Cunningham D, N Eng J Med 2006	ECF	253 No CT	250	23%	36 %	0.75 0.60-0.93 p=0.009
Ychou M, J Clin Oncol 2011	CDDP 5-FU	111 No CT	113	24%	38%	0.69 0.50-0.95 p=0.021
Allum W, J Clin Oncol 2009	CDDPFU	402 No CT	400	17,6%	25.5%	0.84 0.72-0.98 P=0.03

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.
3. Allum W, *et al.* J Clin Oncol 2009; 27:5062-5067. Only esophageal cancer

REGRESSION GRADE AFTER NEOADJUVANT ECF AND OVERALL SURVIVAL

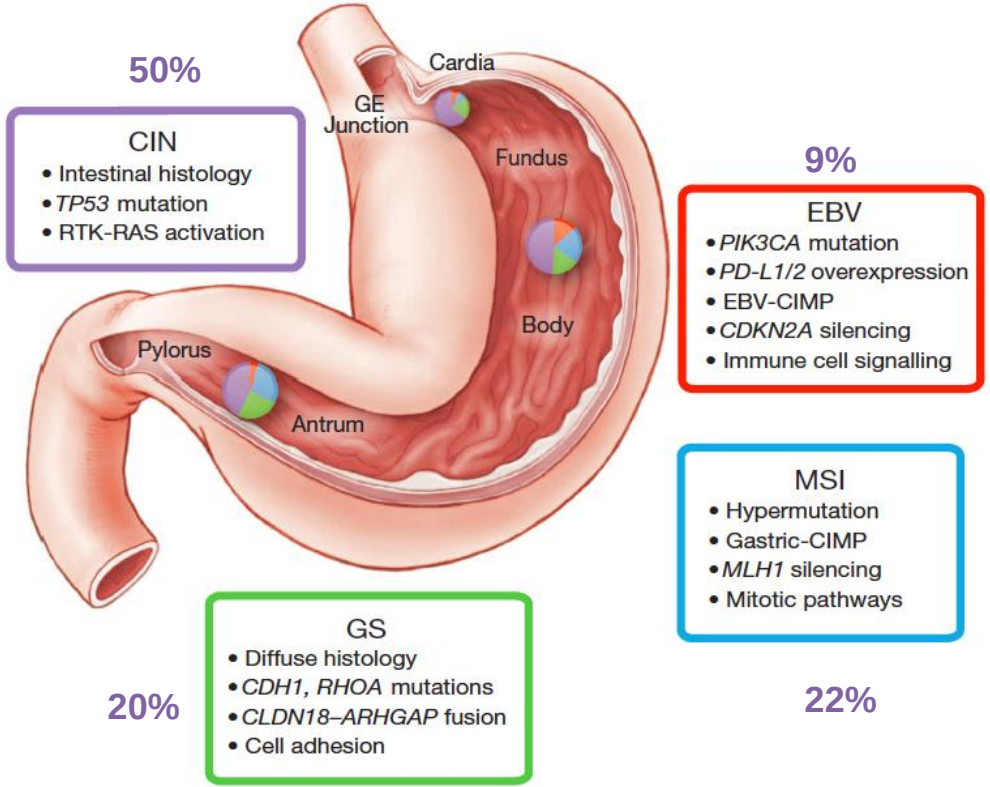
In oesophagogastric cancer in MAGIC





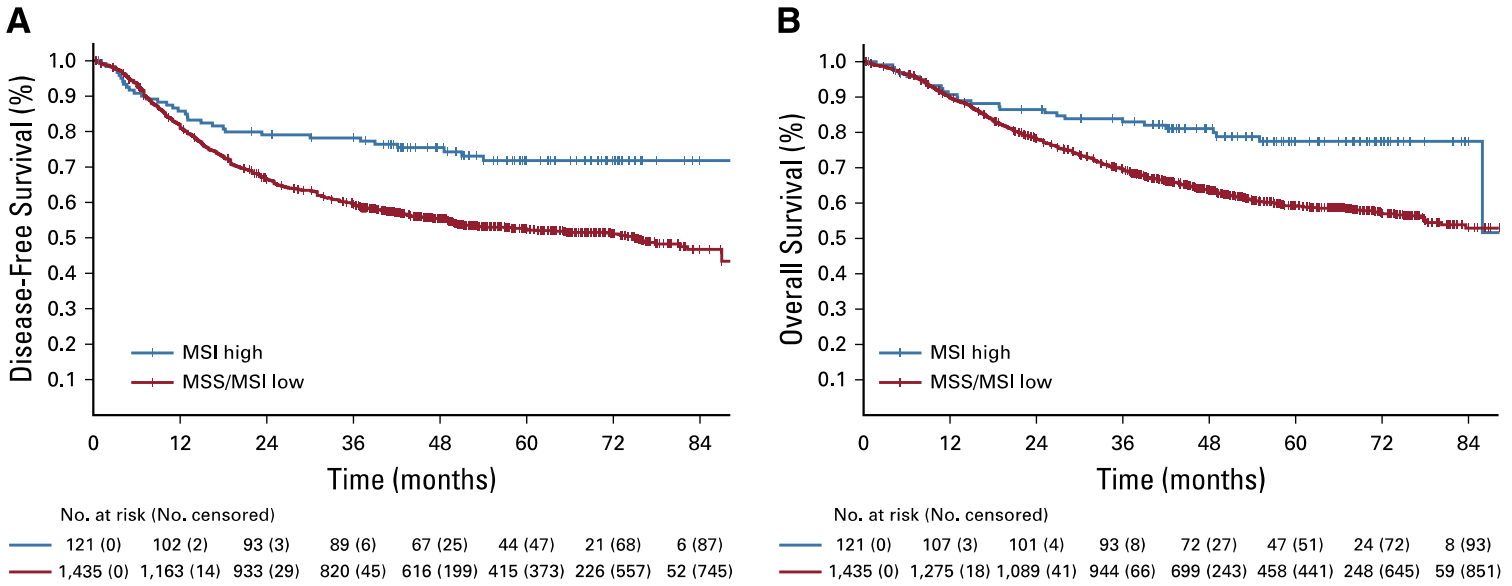
Smyth EC, *et al.* J Clin Oncol; 34(23) 2016:2721.2727. Reprinted with permission. © 2016. American Society of Clinical Oncology. All rights reserved.

THE MOLECULAR CLASSIFICATION OF GASTRIC CANCER ACCORDING TO THE CANCER GENOME ATLAS



Cancer Genome Atlas Research Network. Nature 2014;513:202–9. Reproduced under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported (CC-BY-NC-SA 3.0) licence. Available at: https://creativecommons.org/licenses/by-nc-sa/3.0/; accessed May 2019.

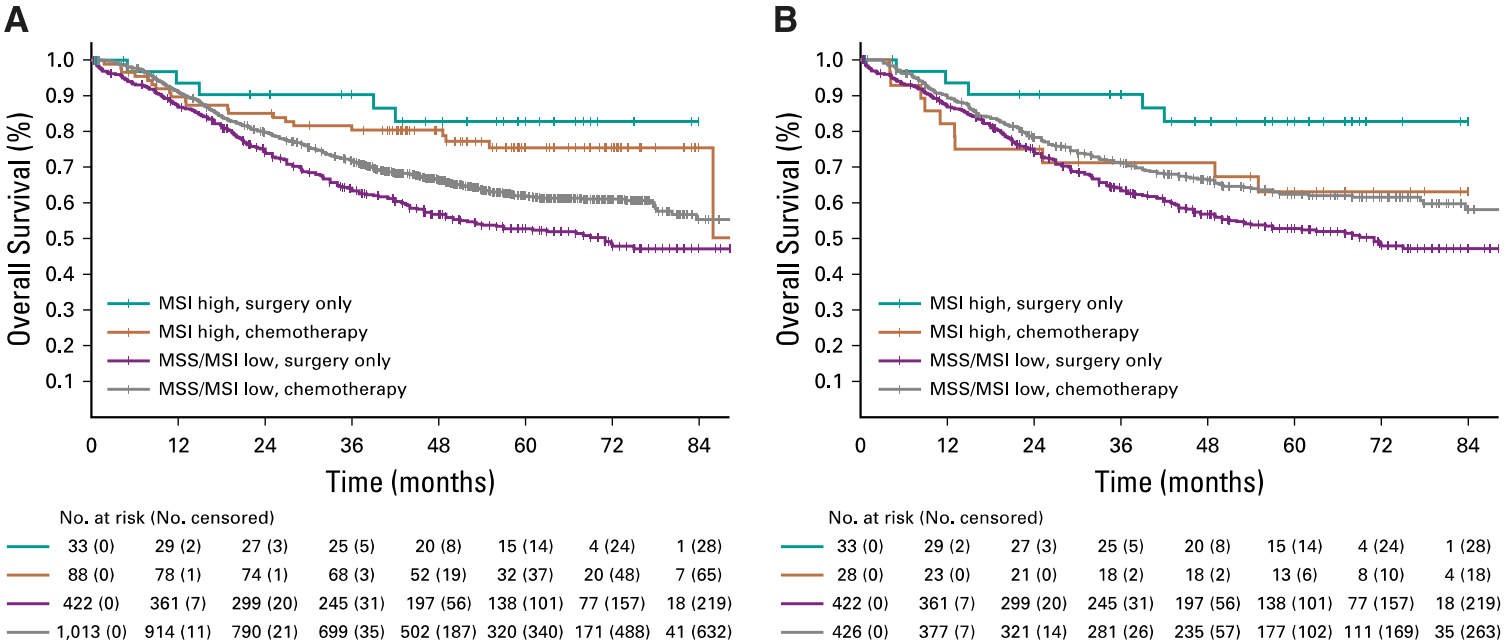
INDIVIDUAL DATA PATIENT META-ANALYSIS OF MSI STATUS IN LOCALIZED GASTRIC CANCER



Petrantonio F, et al J Clin Oncol 2019; 37 DOI https://doi.org/10. 1200/JCO.19.01124

INDIVIDUAL DATA PATIENT META-ANALYSIS OF MSI STATUS IN LOCALIZED GASTRIC CANCER

Overall survival by microsatellite instability (MSI) status and treatment arm in the study patients



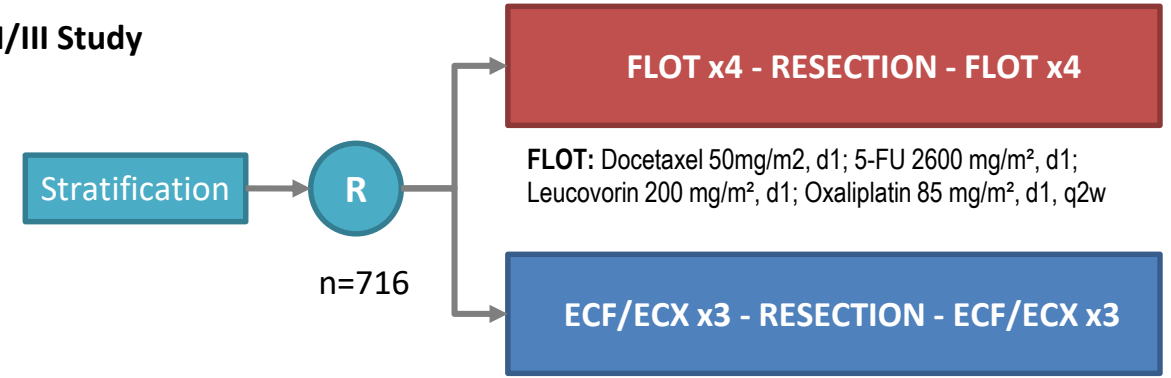
Petrantonio F, et al J Clin Oncol 2019; 37 DOI https://doi.org/10. 1200/JCO.19.01124

5-FU, LEUCOVORIN, OXALIPLATIN AND DOCETAXEL *VS* ECF/ECX AS PREOPERATIVE CHEMOTHERAPY

For gastro-oesophageal adenocarcinoma: The FLOT-4 Study

Randomised, multicentre, Phase II/III Study

- Gastric or EGJ cancer typ I-III
- Medically and anatomically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0



Stratification: **ECOG** (0 or 1 *vs.* 2), **localisation** (GEJ Type I *vs.* Type II/III *vs.* Gastric), **age** (< 60 *vs.* 60-69 *vs.* ≥70 years) and **nodal status** (cN+ *vs.* cN-)

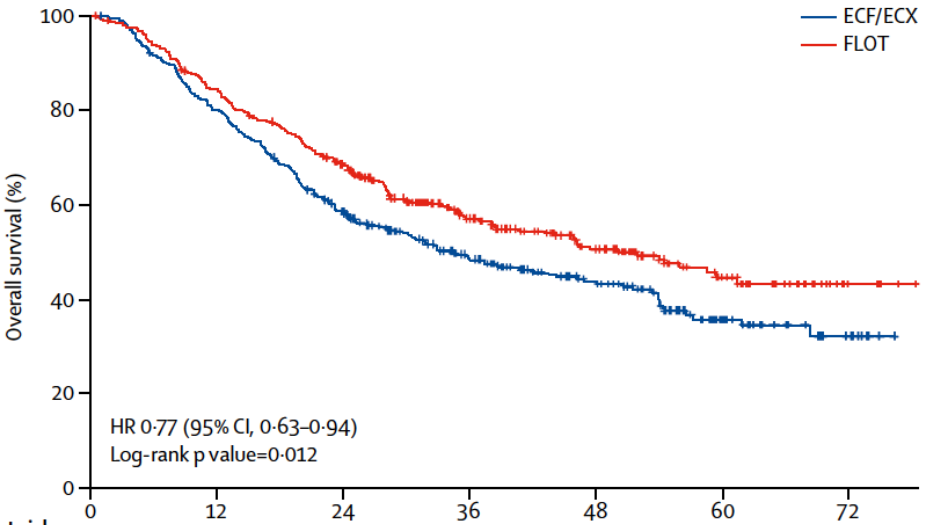
23% had Siewert type I
33% had Siewert type II/III

Al-Batran SE, *et al.* Lancet 2019;393(10184):1948–57.

5-FU, LEUCOVORIN, OXALIPLATIN AND DOCETAXEL *vs* ECF/ECX AS PREOPERATIVE CHEMOTHERAPY

For gastro-oesophageal adenocarcinoma: The FLOT-4 Study

Results on overall survival



	ECF/ECX	FLOT
mOS	35 months [27-46]	50 months [38-na]
HR	**0.77 [0,63 – 0,94] p=0.012 (log rank)**	

OS rate*	ECF/ECX	FLOT
2y.	59%	68%
3y.	48%	57%
5y.	36%	45%

*projected OS-rates

Reprinted from The Lancet, 393(10184), Al-Batran SE, *et al*. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial, 1948–57. Copyright 2019, with permission from Elsevier.

5-FU, LEUCOVORIN, OXALIPLATIN AND DOCETAXEL *vs* ECF/ECX AS PREOPERATIVE CHEMOTHERAPY

For gastro-oesophageal adenocarcinoma: The FLOT-4 Study
Treatment related toxicities according to treatment arm

	ECF/ECX (n=354)		FLOT (n=354)		Difference in grade 3 or 4 events (p value)	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4		
Diarrhoea	103 (29%)	13 (4%)	182 (52%)	34 (10%)	0·0016	FLOT
Vomiting	102 (29%)	27 (8%)	113 (32%)	7 (2%)	<0·001	ECX/ECF
Nausea	215 (61%)	55 (16%)	211 (60%)	26 (7%)	<0·001	ECX/ECF
Constipation	86 (24%)	1 (<1%)	75 (21%)	2 (1%)	0·56	
Stomatitis or mucositis	107 (30%)	10 (3%)	99 (28%)	5 (1%)	0·19	
Leukopenia	175 (49%)	75 (21%)	180 (51%)	94 (27%)	0·098	
Neutropenia	93 (26%)	139 (39%)	84 (24%)	181 (51%)	0·0017	FLOT
Anaemia	282 (80%)	20 (6%)	283 (80%)	9 (3%)	0·036	ECX/ECF
Thrombocytopenia	123 (35%)	11 (3%)	137 (39%)	7 (2%)	0·34	
Serum AST	41 (12%)	1 (<1%)	116 (33%)	3 (1%)	0·31	
Serum ALT	55 (16%)	1 (<1%)	127 (36%)	8 (2%)	0·019	FLOT
Fever	29 (8%)	2 (1%)	77 (22%)	4 (1%)	0·41	
Peripheral neuropathy	120 (34%)	7 (2%)	228 (64%)	24 (7%)	0·0018	FLOT
Pain	171 (48%)	14 (4%)	166 (47%)	21 (6%)	0·23	
Alopecia*	147 (42%)	74 (21%)	122 (35%)	98 (28%)	NA	
Renal	99 (28%)	1 (<1%)	38 (11%)	0 (0)	0·32	
Infections	62 (18%)	30 (9%)	61 (17%)	63 (18%)	<0·001	FLOT
Thromboembolic	31 (9%)	21 (6%)	13 (4%)	9 (3%)	0·025	ECX/ECF
Toxic death†	..	2 (<1%)	..	2 (<1%)	1·0	

Reprinted from The Lancet, 393(10184), Al-Batran SE, *et al*. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial, 1948–57. Copyright 2019, with permission from Elsevier.

FLOT AS PERIOPERATIVE CHEMOTHERAPY FOR LOCALISED OESOPHAGO-GASTRIC CANCER

A new standard

Trial	CT	No. pts control	No. pts CT	5-year survival control	5-year survival CT	HR (CI at 95%)
Cunningham D, N Eng J Med 2006	ECF	253 No CT	250	23%	36 %	0.75 0.60-0.93 p=0.009
Ychou M, J Clin Oncol 2011	CDDP 5-FU	111 No CT	113	24%	38%	0.69 0.50-0.95 p=0.021
Allum W, J Clin Oncol 2009	CDDPFU	402 No CT	400	17,6%	25.5%	0.84 0.72-0.98 P=0.03
Al-Batran SE, Lancet 201	FLOT	360 ECF	356 FLOT	36%	45%	0.77 0.63-0.94 P=0.012

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;
3. Allum W, *et al.* J Clin Oncol 2009; 27:5062-5067. Only esophageal cancer; 4. Al-Batran SE, *et al.* Lancet 2019;393(10184):1948–57.

FLOT AS PERIOPERATIVE CHEMOTHERAPY FOR LOCALISED OESOPHAGO-GASTRIC CANCER

A new standard

Trial	CT Experimental	No. pts	pCR Control vs Experimental	5-year survival Control vs Exp	HR (CI at 95%)
Cunningham D, N Eng J Med 2006	ECF	503	0% vs 8%	23% vs 36 %	0.75 0.60-0.93 p=0.009
Al-Batran SE, Lancet 2019	FLOT	716	5,8% vs 15,6%	36% vs 45%	0.77 0.63-0.94 P=0.012
Alderson D, Lancet Oncol 2017	ECX	897	3% vs 11%	39% vs 42%*	0.90 0.77-1.05 0.19
Cunningham D, Lancet Oncol 2017	BEV-ECX	1063	8% vs 11%	50% vs 48%*	1.09 0.91-1.29 0.36

1. Cunningham D, *et al.* N Engl J Med 2006;355:11–20; 2. Al-Batran SE, *et al.* Lancet 2017; doi.org/10.1016/ S0140-6736(18)33189-1;
3. Alderson D, *et al.* Lancet Oncol 2017 on line +Only Esophageal, *3 year OS; 4. Cunningham D, *et al.* Lancet Oncology 2017; 18:357-370.

FLOT as perioperative chemotherapy for localized Esophago-gastric cancer: a new standard

ESMO Magnitude of Clinical Benefit Scale v1.1

Form 1: for new approaches to adjuvant therapy or new potentially curative therapies

Name of study:			
Study drug:	**Indication:**		
First author:	**Year:**	**Journal:**	
Name of evaluator:			

Grade A	Mark with X if relevant
>5% improvement of survival at ≥3 years follow-up	
Improvements in DFS alone (primary endpoint) (HR <0.65) in studies without mature survival data	

9% (> 5%) increase in OS at 3 years
from 48% for ECF/ECX to 57% for FLOT: Grading A
No concerns from toxicity

Al-Batran SE, et al. Lancet 2019;393(10184):1948–57
Cherny NI, et al. Ann Oncol 2017; 28:2340-2366.

PRODIGY: Randomised phase III study in gastric and GEJ adenocarcinoma of peri-op vs. post-op chemotherapy

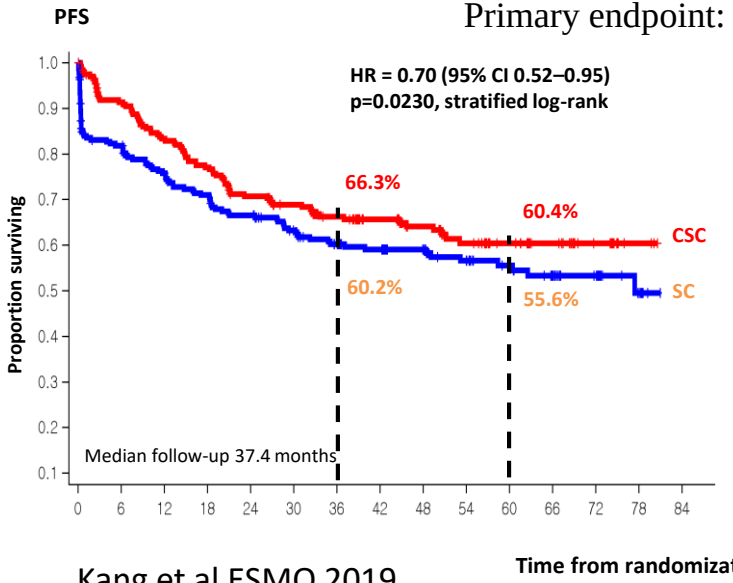
Histologically confirmed cT2, 3 / N(+) or $cT4N_{any}$ gastric or GEJ adenocarcinoma

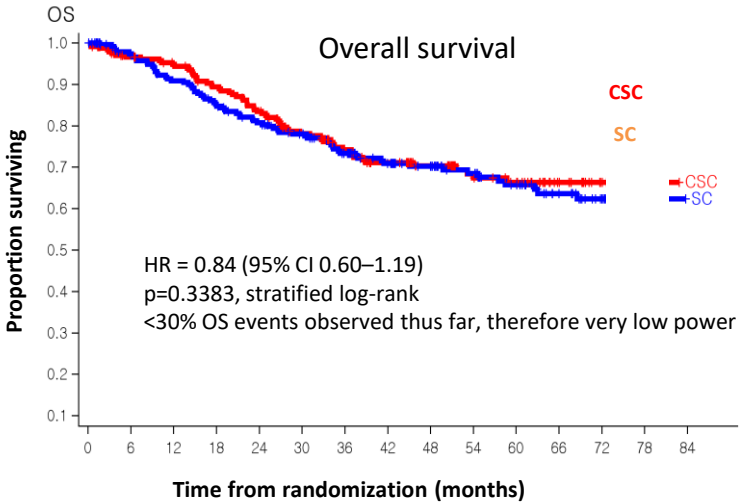
R

n=266
CSC
DOS × 3 → D2 resection → S-1 ×8

n=264
SC
D2 resection → S-1 ×8

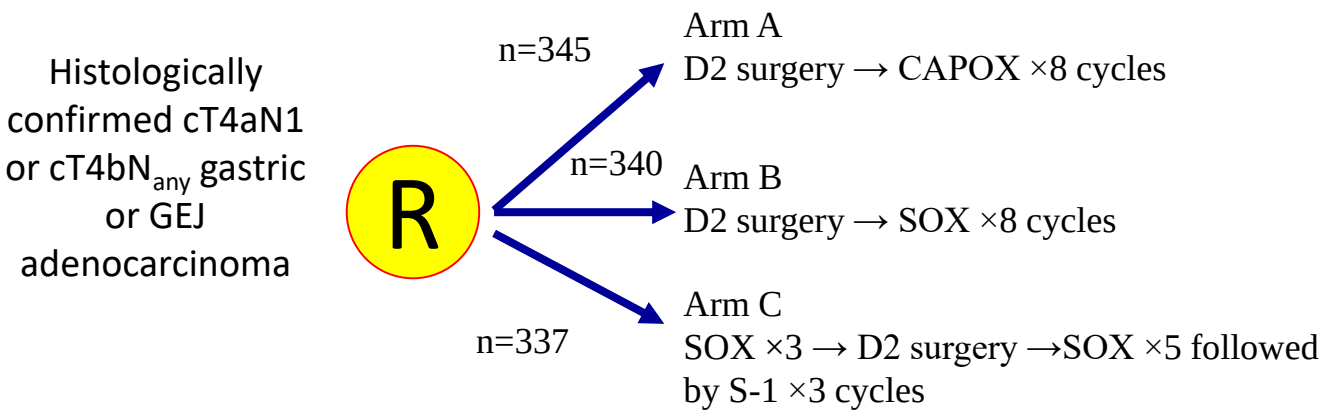
Primary endpoint: 3-year PFS





Kang et al ESMO 2019

Randomised phase III study in gastric and GEJ adenocarcinoma of peri-operative SOX vs. post-op SOX vs. post-op CAPOX (RESOLVE)



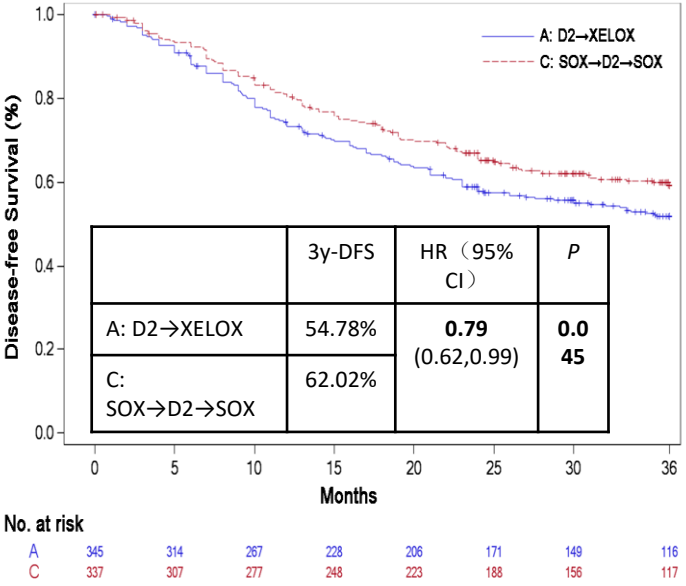
Primary endpoint: 3-year DFS

Arms A vs. C: superiority; A vs. B: non-inferiority

Ji et al ESMO 2019

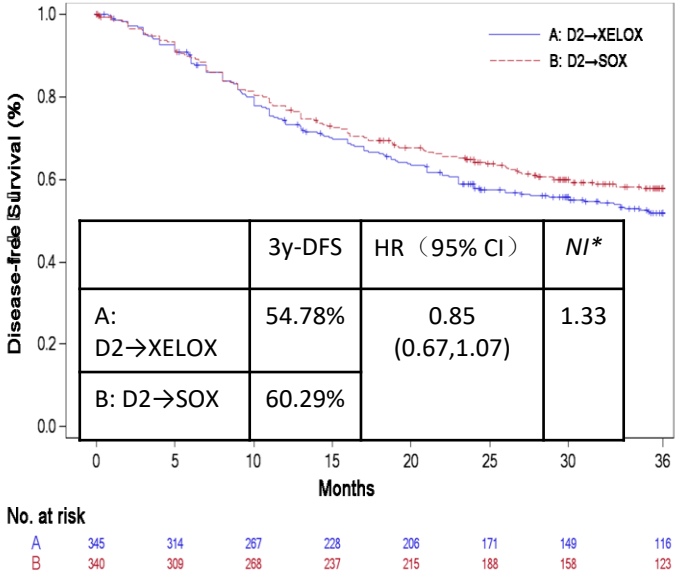
RESOLVE Primary comparisons

ARMs A vs. C



	3y-DFS	HR（95% CI）	*P*
A: D2→XELOX	54.78%	**0.79** (0.62,0.99)	**0.045**
C: SOX→D2→SOX	62.02%		

ARMs A vs. B



	3y-DFS	HR（95% CI）	*NI**
A: D2→XELOX	54.78%	0.85 (0.67,1.07)	1.33
B: D2→SOX	60.29%		

Ji et al ESMO 2019

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.

FLOT is current standard of care

Preoperative therapy is better tolerated than postoperative

Quality of surgery essential

Localised gastric cancer requires a multidisciplinary team approach

Adjuvant or neoadjuvant chemotherapy does not seem to benefit patients with MSI

EXPERIMENTAL APPROACHES IN LOCALISED GASTRO-OESOPHAGEAL ADENOCARCINOMAS

Postoperative chemoradiation of limited value if D2 surgery performed or preoperative chemotherapy given

Preoperative chemoradiation under scrutiny in TOPGEAR trial

Radiotherapy still experimental

No biological agents (bevacizumab) to be used in this setting

Further research on biological predictive factors is needed

The addition of trastuzumab *vs*. trastuzumab/pertuzumab under investigation in the INNOVATION trial

Immunotherapy experimental

CURRENTLY RECOMMENDED APPROACH TO LOCALISED GASTRIC CANCER

Clinical assessment and staging

Multidisciplinary team discussion

FLOT preoperative treatment in clinical stage II and III patients

Surgical resection after FLOT chemotherapy

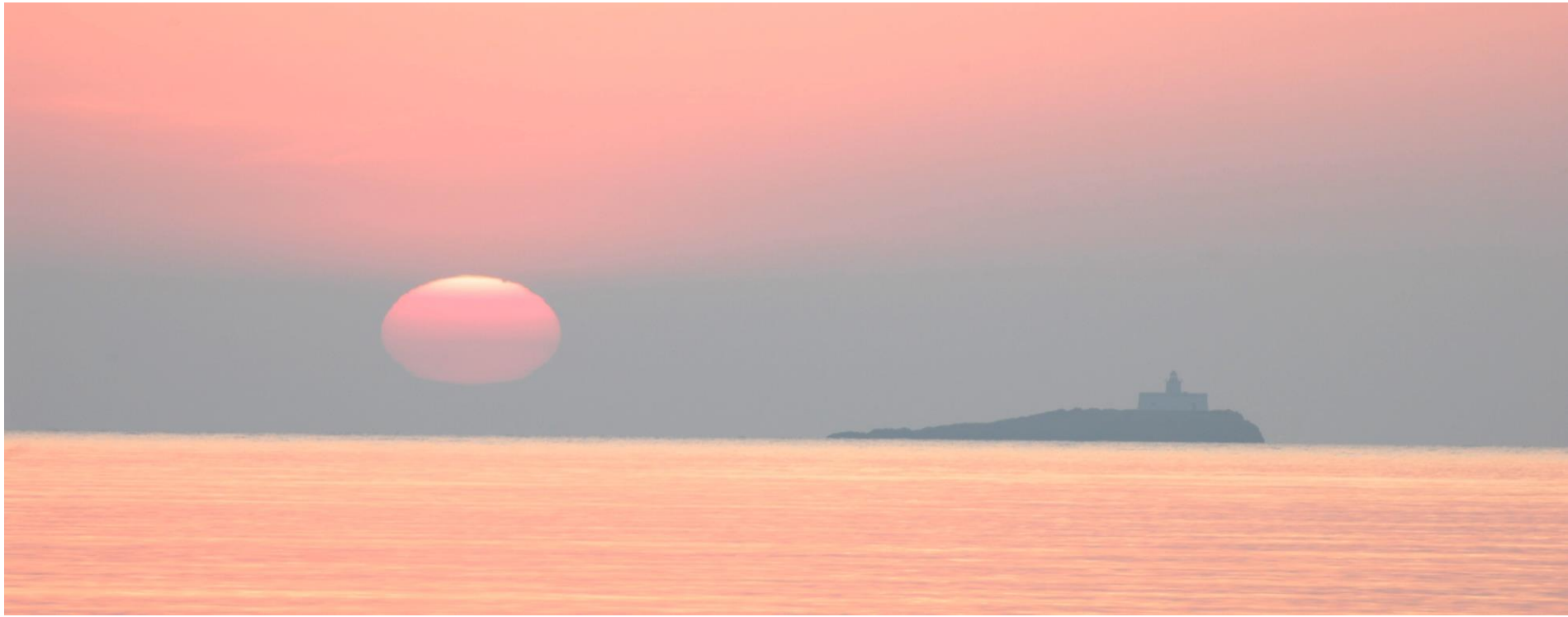
Pathology assessment and estimation of risk

Postoperative chemotherapy if tolerated

THANK YOU!

VNIVERSITAT
DE VALÈNCIA

Fundación Investigación
Clínico de Valencia
incliva
Instituto de Investigación Sanitaria

ESMO

Thanks