Gastic Cancer : Update

Dr Nidal KHEDER
Head of departement of oncology
Ibn alnafis Hospital – Damascus
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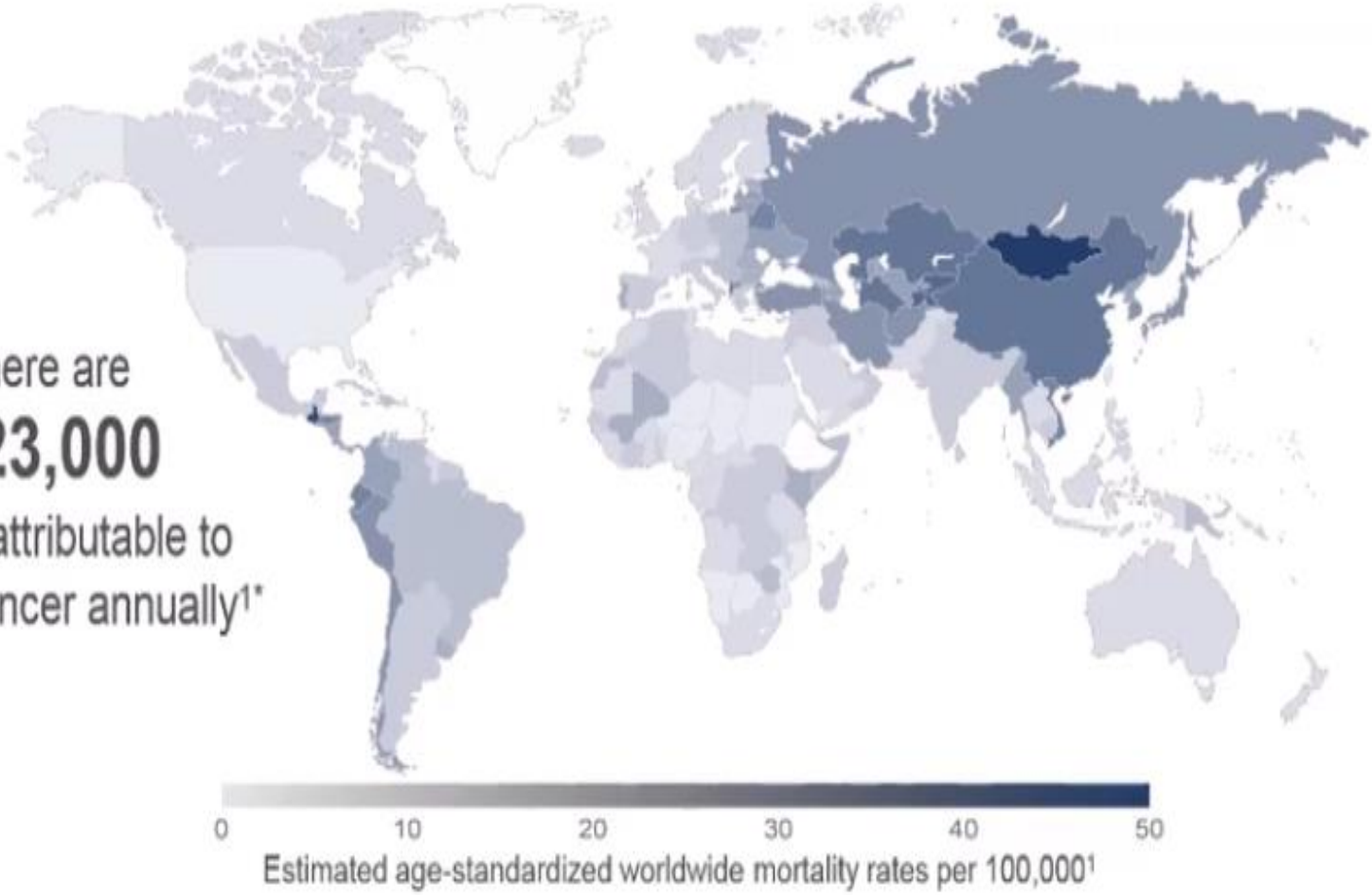
GASTRIC CANCER: MORTALITY

There are
723,000
deaths attributable to
gastric cancer annually[1*]



*Rates in men are ~2 times higher than in women; gastroesophageal junction adenocarcinoma included in gastric definition

1. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx Accessed June 2014

Risk factors

- Diet
  - nitroso compounds
  - low fruit/vegetable, high fried foods/processed meat
  - High salt intake
- Obesity
- Smoking (HR 2-3)
- ? Alcohol
- H. Pylori
- Low socioeconomic status
- Hereditary diffuse gastric cancer
  - 40-67% lifetime risk for men, 60-83% for women
- Immigrants from endemic areas
  - maintain native country risk, risk to offspring similar to new homeland

Clinical presentation

Symptom	Percent
Weight loss	62
Abdominal pain	52
Nausea	34
Dysphagia	26
Melena	20
Early satiety	18
Ulcer-type pain	17

Palpable abdominal mass: most common physical finding

If cancer spreads via lymphatics...

- Left supraclavicular node (Virchow's)
- Periumbilical node (Sister Mary Joseph)
- Left axillary node (Irish)
- Enlarged ovary (Krukenberg's tumor)
- Ascites

Adenocarcinoma Cancer types

- "Intestinal type" (more common)
  - Morphologically similar to intestinal adenocarcinomas.
- Diffuse-type
  - Lack of intercellular adhesions (germline mutation in protein E-cadherin)

Work up

- Proper staging required and multidisciplinary discussion
- Endoscopy – biopsy
- Blood tests (FBC, renal-liver function, CEA, CA19-9)
- CT with contrast chest-abdomen and ……
  - Laparoscopic staging
  - PET/CT
  - EUS
- Nutritional assessment (? PEG, NG or J-tube)

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 in US

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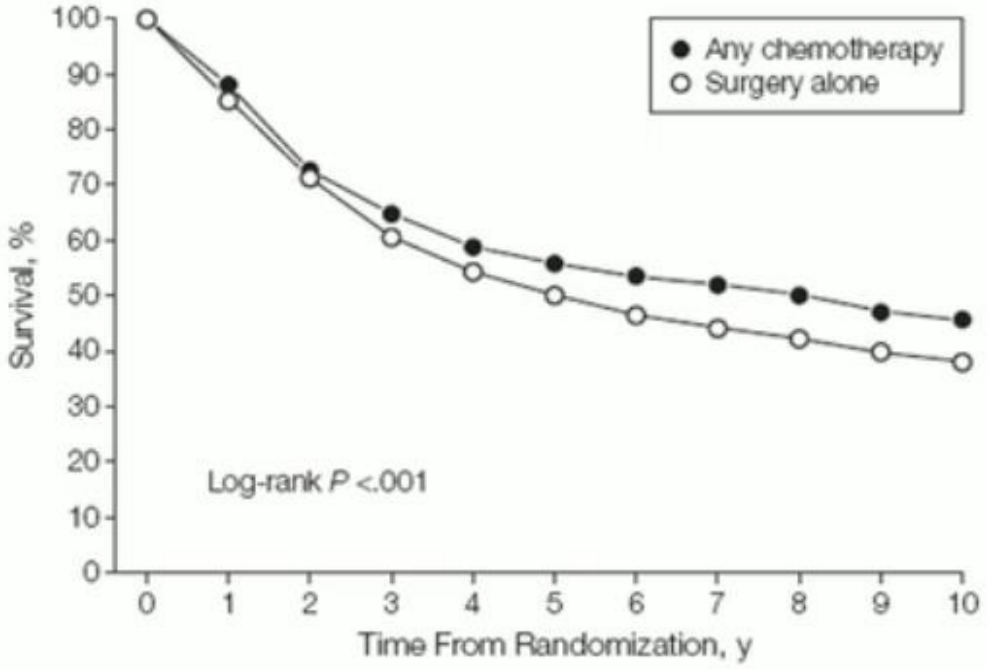
Meta-analysis of individual data of trials involving adjuvant chemotherapy versus surgery alone for gastric cancer

Figure 3. 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

The Gastric Group. JAMA 2010;303:1729–37

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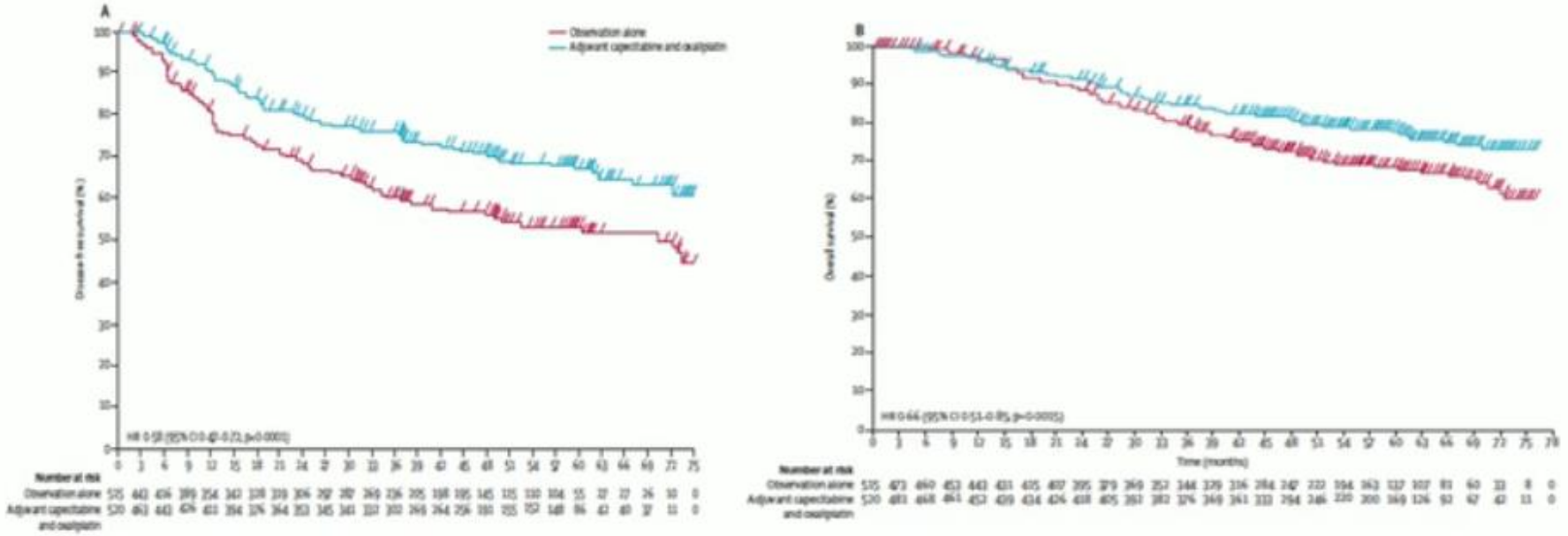
Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy versus surgery alone: 5-year follow-up of a randomised phase III trial



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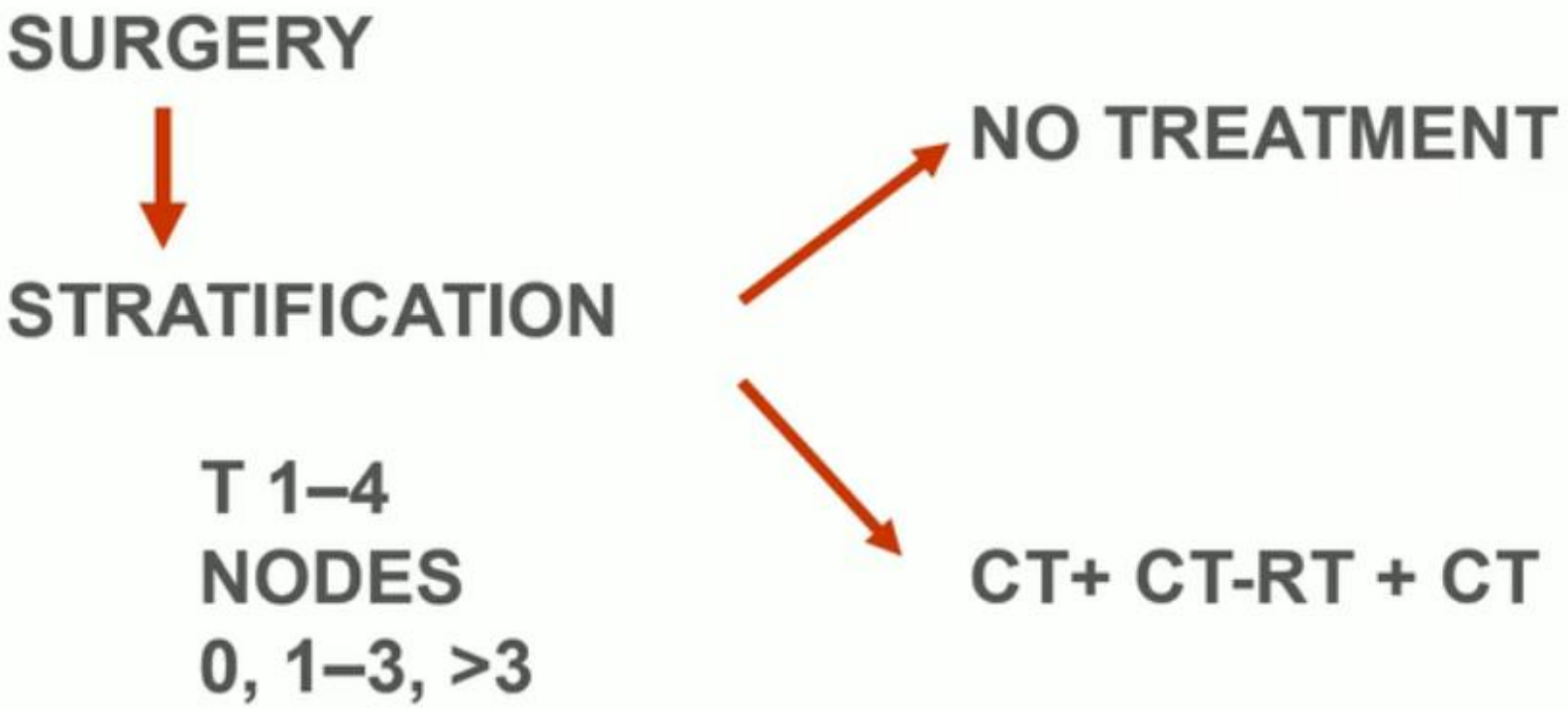
The role of radiation in the postoperative setting: Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: A randomised Phase III Trial

Study design



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

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

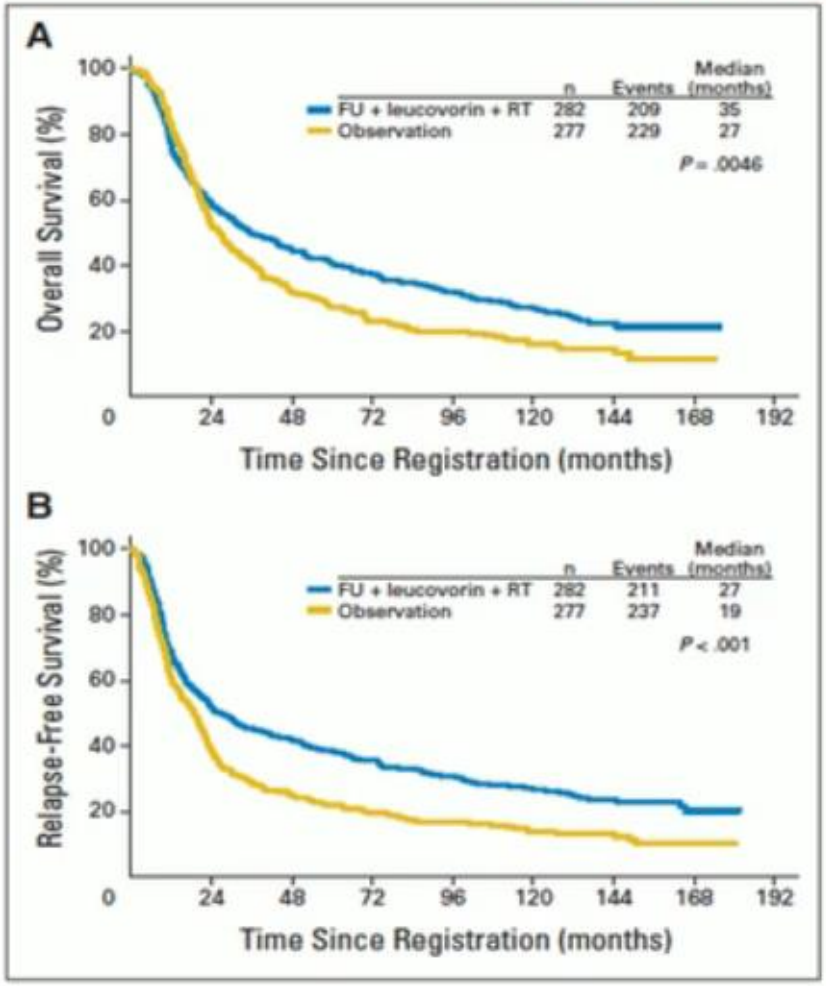

Fig 2. (A) Overall survival by arm; (B) relapse-free survival by arm. FU, fluorouracil; RT, radiotherapy.

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 (χ^2); $P = .012$ for sites of relapse (among those with sites reported, χ^2 test for trend).

Smalley S, et al. J Clin Oncol 2012;30:2327–2333

ARTIST: The role of Radiation in the Postoperative Setting Adjuvant Cisplatin and Capecitabine versus Chemoradiation for Gastric Cancer after Surgery: A Randomized phase III Trial

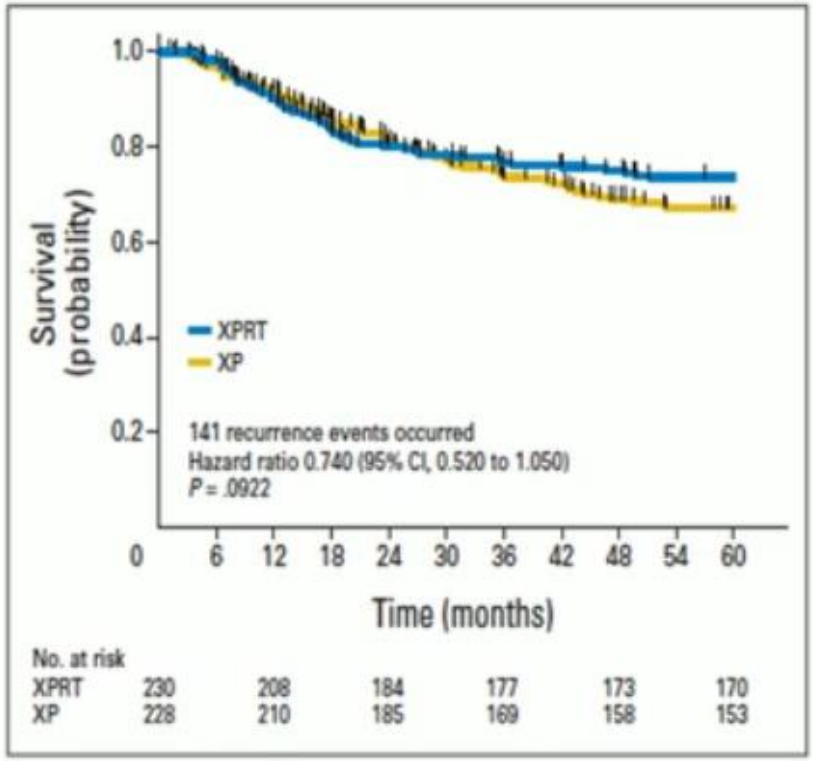

Fig 2. Disease-free survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

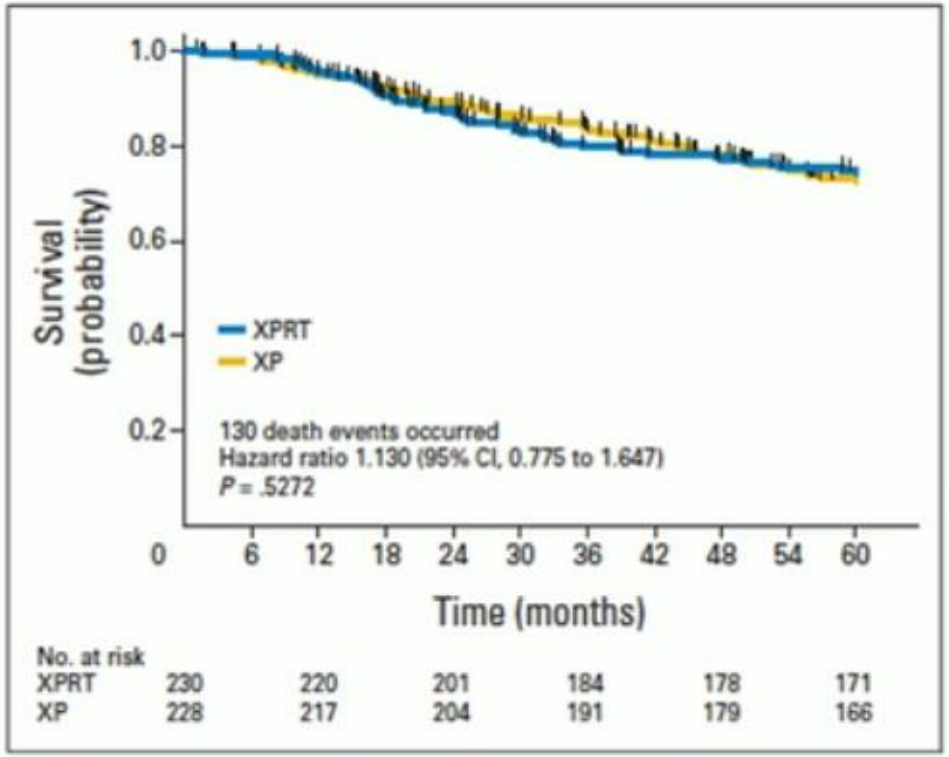

Fig 3. Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Park SH, et al. J Clin Oncol 2015; 33: 3130-3136

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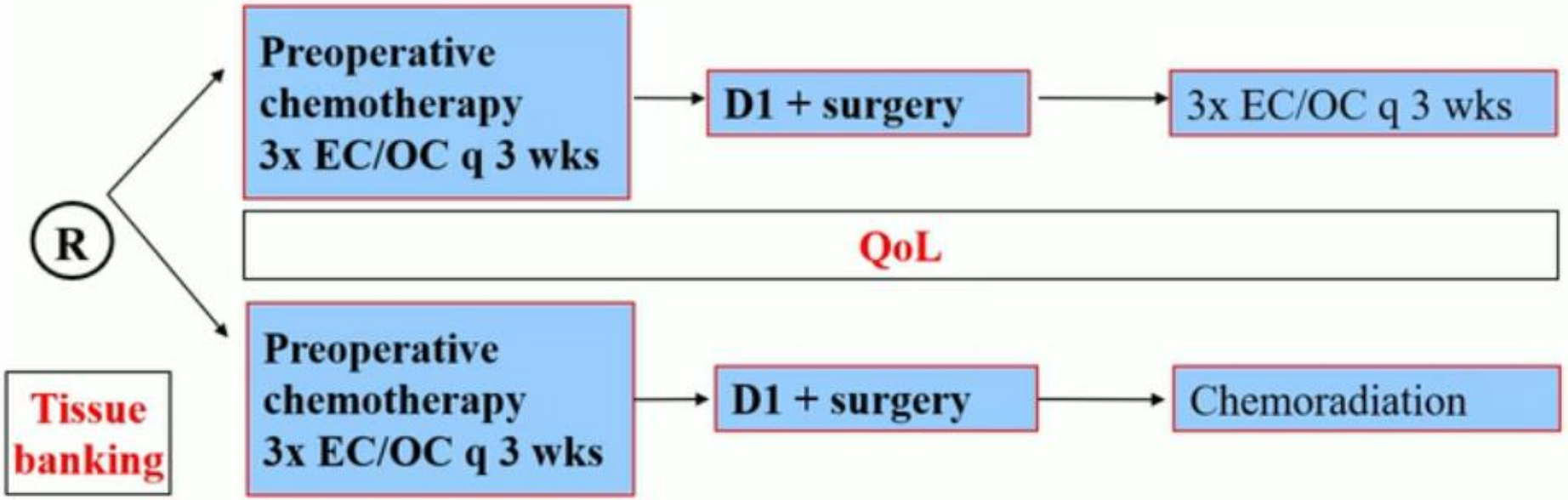
CRITICS TRIAL

Design: 788 pts: 393 CT and 395 CRT



45 Gy/25 fx +
capecitabine
cisplatin

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

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

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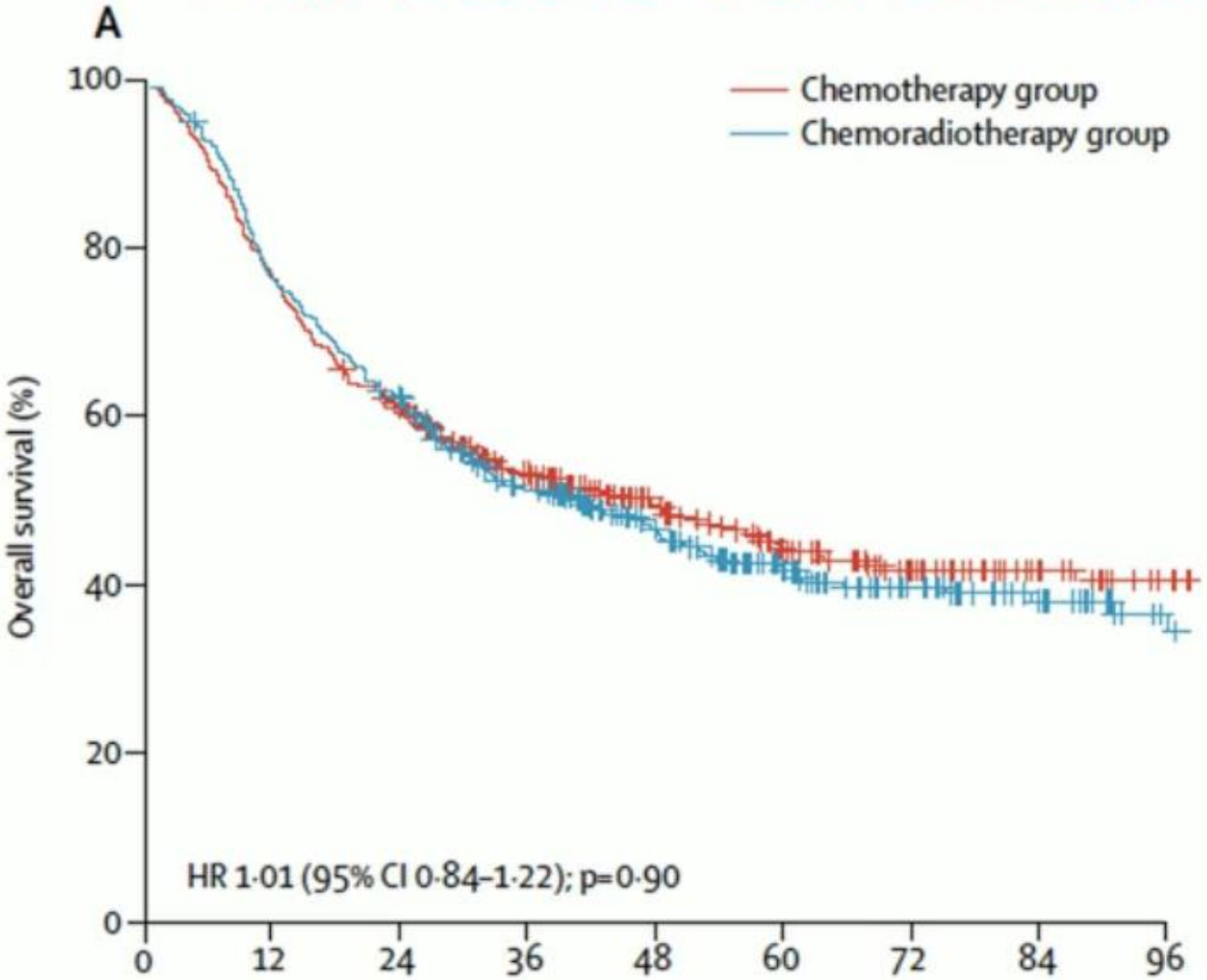
Final Results from CRITICS



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

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MAGIC: Study design

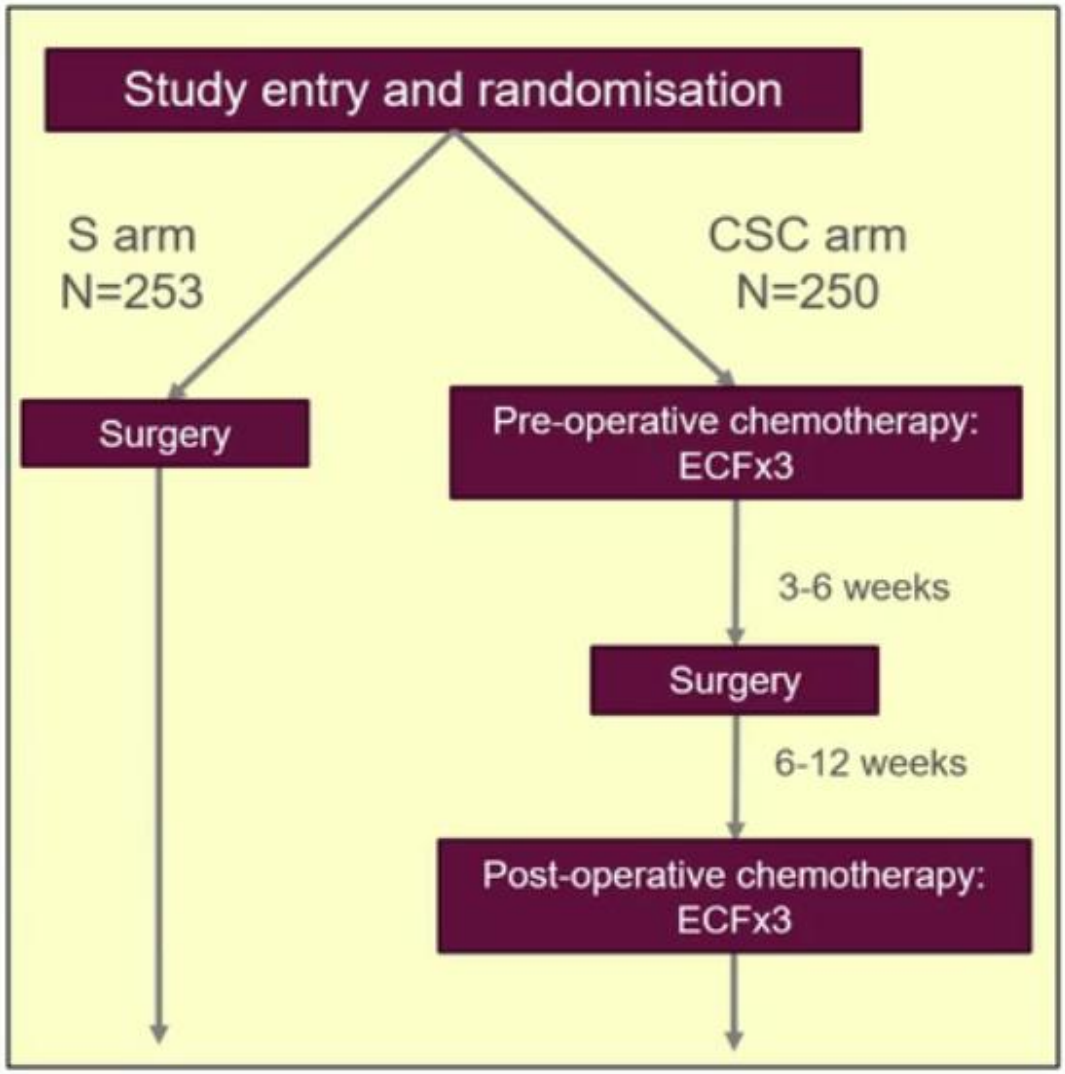
Eligible patients:
- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease
- Stage II or greater

Primary
Overall survival

Secondary
Progression-free survival
Surgical resectability
Quality of Life

Chemotherapy (ECF):
Epirubicin 50 mg/m^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

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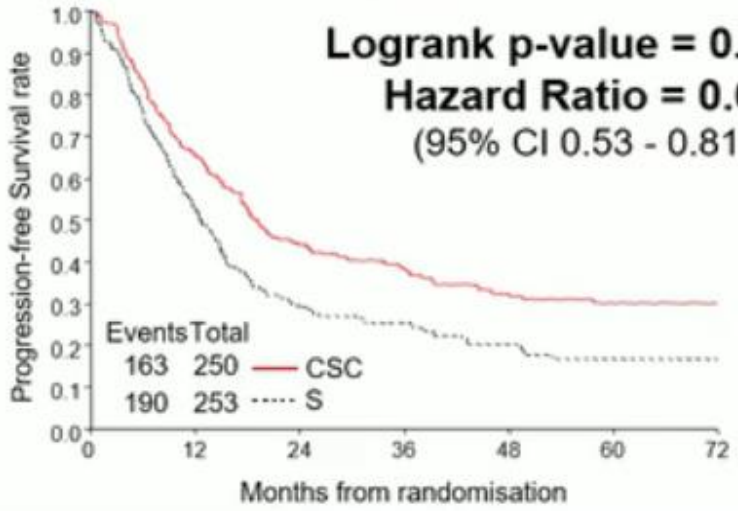
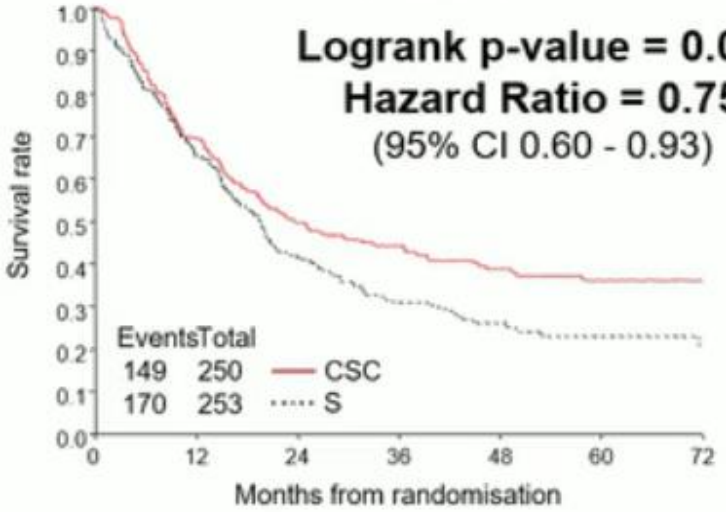
MAGIC Trial results

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

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Summary of trials of perioperative chemotherapy for localized Oesophago-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
Allum J Clin Oncol 2009	CDDP FU	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

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FLOT-4 Study

Randomized, multicenter, 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**

STRATIFIKATION

R

n=716

FLOT x4 - RESECTION - FLOT x4

FLOT: Docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; Leucovorin 200 mg/m², d1; Oxaliplatin 85 mg/m², d1, q2w

ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; Cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or Capecitabin 1250 mg/m² p.o. geteilt in 2 doses d1-d21), q2w

Stratification: **ECOG** (0 or 1 vs. 2), **localization** (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

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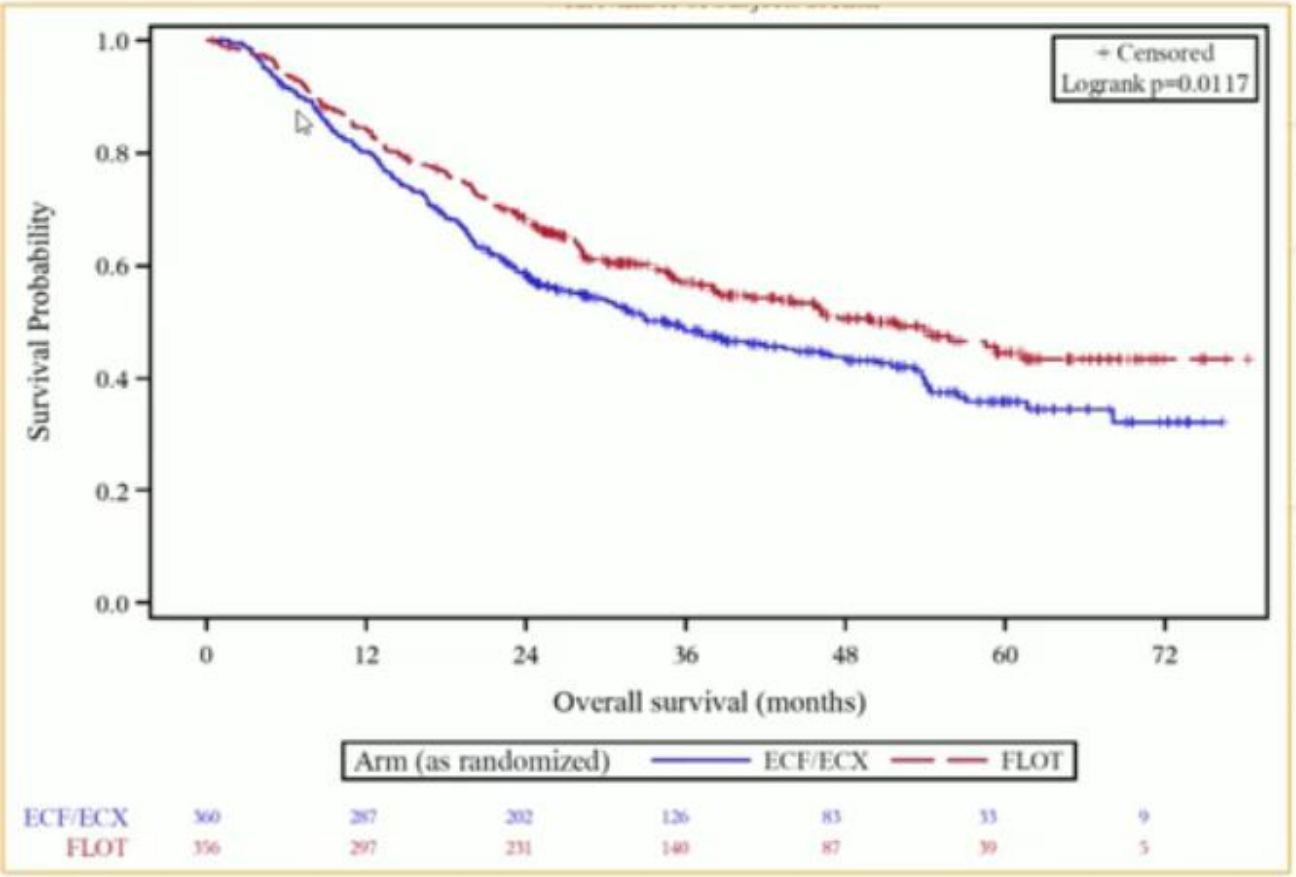
Survival ECF/ECX versus FLOT



	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

Median follow-up time: 43 months

Al-Batran et al. *J Clin Oncol 2017;* 35(suppl): #4004

PERIOPERATIVE TREATMENT FOR LOCALIZED GASTRIC CANCER
AIO-FLOT

Chemotherapy-Related Toxicity

Grade 3-4 >5%	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
Diarrhea	13 (4%)	34 (10%)	0.002
Vomiting	27 (8%)	7 (2%)	<0.001
Nausea	55 (16%)	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	
Infections	30 (9%)	63 (18%)	<0.001
Leukopenia	75 (21%)	94 (27%)	
Neutropenia	139 (39%)	181 (51%)	0.002
Sensory	7 (2%)	24 (7%)	0.002
Thromboembolic	22 (6%)	9 (3%)	0.03
Anemia	20 (6%)	9 (3%)	0.04

Al-Batran et al. *ASCO* 2017; abstract 4006

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Allum J Clin Oncol 2009	CDDP FU	402 No CT	400	17,6%	25.5%	0.84 0.72-0.98 P=0.03
Al-Batran ASCO 2017	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 SA, et al 2017; 35(suppl): #4004

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Perioperative chemotherapy for localized 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 N Eng J Med 2006	ECF	503	0% vs 8%	23% vs 36 %	0.75 0.60-0.93 p=0.009
Al-Batran ASCO 2017	FLOT	716	5,8% vs 15,6%	36% vs 45%	0.77 0.63-0.94 P=0.012
Alderson + Lancet Oncol 2017	ECX	897	3% vs 11%	39% vs 42%*	0.90 0.77-1.05 0.19
Cunningham 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 SA, et al 2017; 35(suppl): #4004
3. Alderson D. et al Lancet Oncol 2017 on line +Only Esophageal, *3 year OS
4. Cunningham D, et. Lancet Oncology 2017; 18:357-370

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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
- Localised gastric cancer requires a multidisciplinary team approach
- Further research on biological predictive factors is needed

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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
- Radiotherapy still experimental
- No biological agents (Bevacizumab) to be used in this setting

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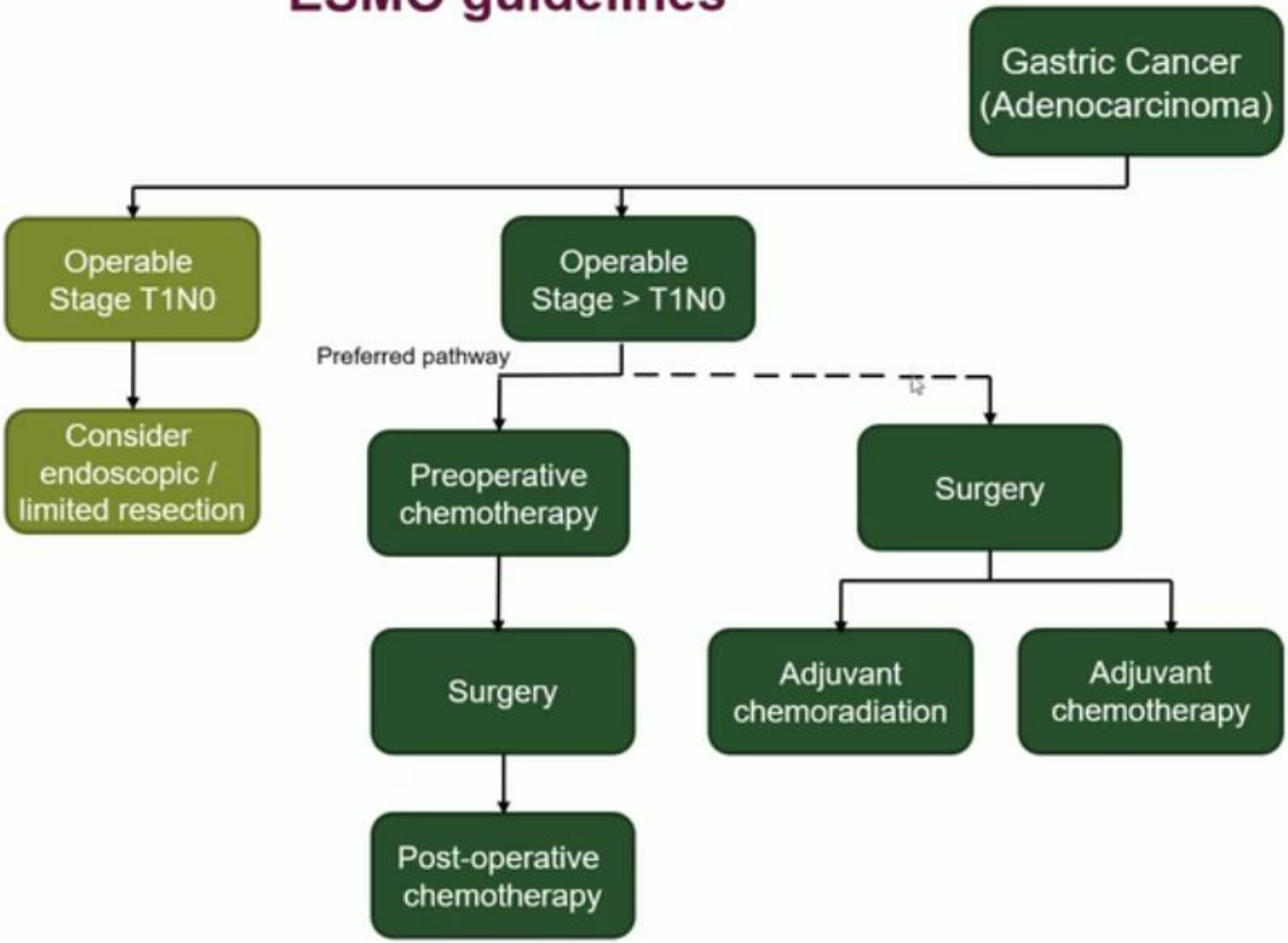
Treatment for localised gastric cancer: What is standard of care? ESMO guidelines



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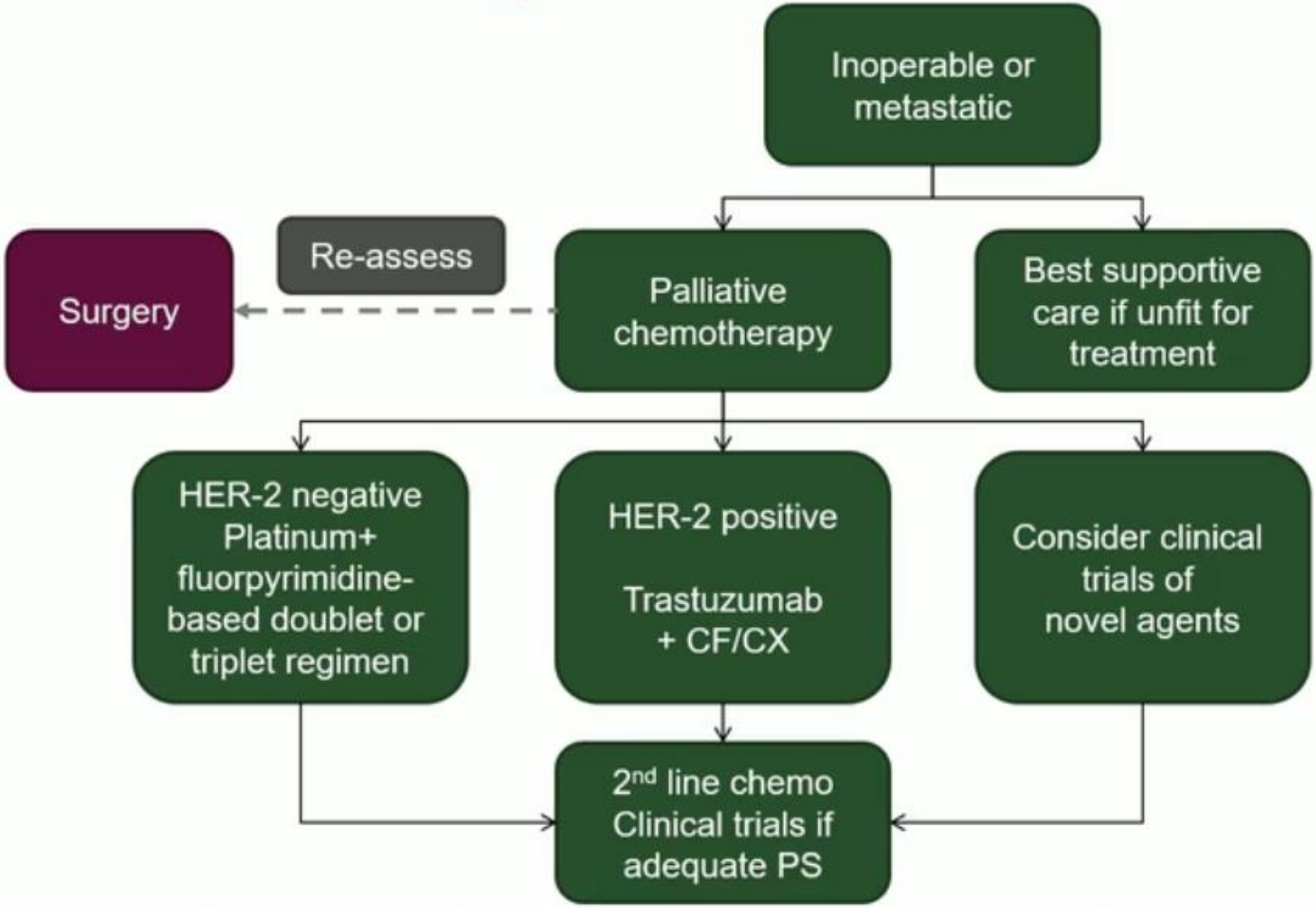
Treatment for advanced gastric cancer: What is standard of care? ESMO guidelines



Smyth EC, et al. Ann Oncol 2016;27(Suppl 5):38–49. By permission of the European Society of Medical Oncology

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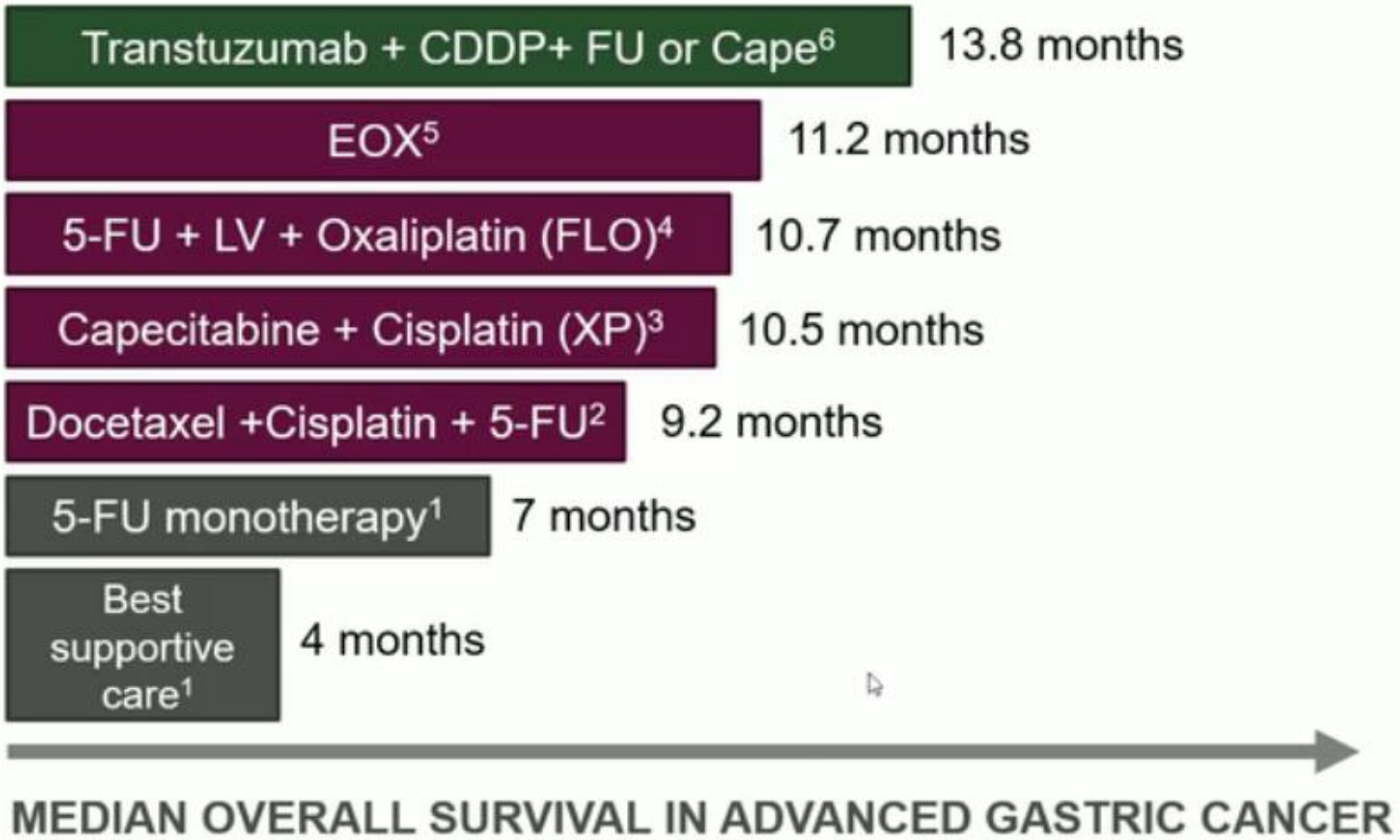
Have we made any progress in the treatment of advanced gastric cancer?



1. Wagner A, et al. JCO 2006. 2. van Cutsem E, et al. J Clin Oncol 2006;24:4991–4997. 3.Kang YK et al, Ann Oncol 2009; 20:666–73. 4. Al Batran SE, et al. J Clin Oncol 2008;26:1435–1442. 5. Cunningham D, et al. N Engl J Med 2008;358:36-46. 6. Bang YJ, et al. Lancet 2010;376:687–697
EOX: Epirubicin/Oxaliplatin/Capecitabine.

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Targeted therapies in first-line treatment for advanced gastric cancer: Summary of Phase III Trials

Trial	Chemotherapy	Biological	HR OS	P value	Increase in median survival
ToGA[1]	Cisplatin+5-FU/ capecitabine	Trastuzumab	0.74	0.04	+2.8 months
AVAGAST[2]	Cisplatin+ capecitabine	Bevacizumab	0.87	0.10	+2.0 months
EXPAND[3]	Cisplatin+ capecitabine	Cetuximab	1.00	0.95	-1.3 months
REAL-3[4]	Oxaliplatin+ epirubicin + capecitabine	Panitumumab	1.37	0.013	-2.5 months
RILOMET-1[5]	Cisplatin+ epirubiicin+ capecitabine	Rilotumumab	--	--	Stopped in futility analysis
METGASTRIC[6]	FOLFOX6	Onartuzumab	1.06	0.83	-0.6 months

1. Bang YJ, et al. Lancet 2010;376:687–697. 2. Van Cutsem E, J Clin Oncol 2012;30 (17):2119–2127. 3. Lordick F, Lancet Oncol 2013;14:490–499. 4. Waddell T, Lancet Oncol 2013;14:481–489. 5. Cunigham ASCO 2015.. 6. Shah M. J Clin Oncol 2015;33(15)

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Targeted therapies against HER2 in advanced gastric cancer: Summary of Phase III Trials on tratuzumab, lapatinib, TDM-1 and pertuzumab

TRIAL	Chemotherapy backbone	Line of therapy number	HR OS	P value	Response rate	Increase in median survival
ToGA[1]	Cisplatin+5-FU/ capecitabine	First 584	0.74	0.04	51% vs 37% p=0.0017	**+2.8 months**
LOGiC[2]	Oxaliplatin/ capecitabine +/- Lapatinib	First 545	0.91	0.35	53% vs 39% p=0.031	**+1.7 months**
TyTAN[3]	Paclitaxel+/- Lapatinib	Second 261	0.84	0.20	27% vs 9% p=0.001	**+2.1 months**
GATSBY[4]	TDM-1 vs Taxane	Second 345	1.15	0.85	NP	**- 0,7 months**
JACOB[5]	Cisplatin+5-FU/ cap/Trastu +/- Pertuzumab	First 780	0.84	0.056	56% vs 48%	**3.3 months**

1. Bang YJ, et al. Lancet 2010;376:687–697.2. Hecht JR, et al. ASCO abstract 2013 LBA4001.
3. Satoh N, et al. J Clin Oncol 2014; 32:2039–2049. 4. Kang YK et al. ASCO GI 2016 5. Tabernero j, et al. ESMO 2017

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Gastric cancer: Second or further line Immunotherapy randomized trials comparing with BSC or active treatment

Trial author	Year	Patients random (n)	Treatment	HR OS	P value	mOS and Gain in median survival
Shitara, et al.[1] **KEYNOTE-061 Second line**	2018	592 1:1	**Pembrolizumab** vs wk Paclitaxel	0.82	ns	9.1 vs 8.3 0.8 months
Bang, et al.[2] **JAVELIN 300 Third or further lines**	2018	371 1:1	**Avelumab** vs Investigator choice of Chemotherapy	1.10	ns	4,6 vs 5.0 -0.4 months
Kang, et al[3] **ATTRACTION-2 Third or further lines**	2017	493 2:1	**Nivolumab** vs BSC	0.63	0.0001	5.26 vs 4.14 1.12 months

1. Shitara, K. et al. Lancet 2018; 392:123–133. 2. Bang YJ, et al. Ann Oncol 2018; doi: 10.1093/annonc/myd264
3. Kang JK, et al. Lancet 2017;390:2461-2471.

Thanks