Neo-adjuvant / Adjuvant in gastric cancer

The EU view

Pr Marc YCHOU

Montpellier - France

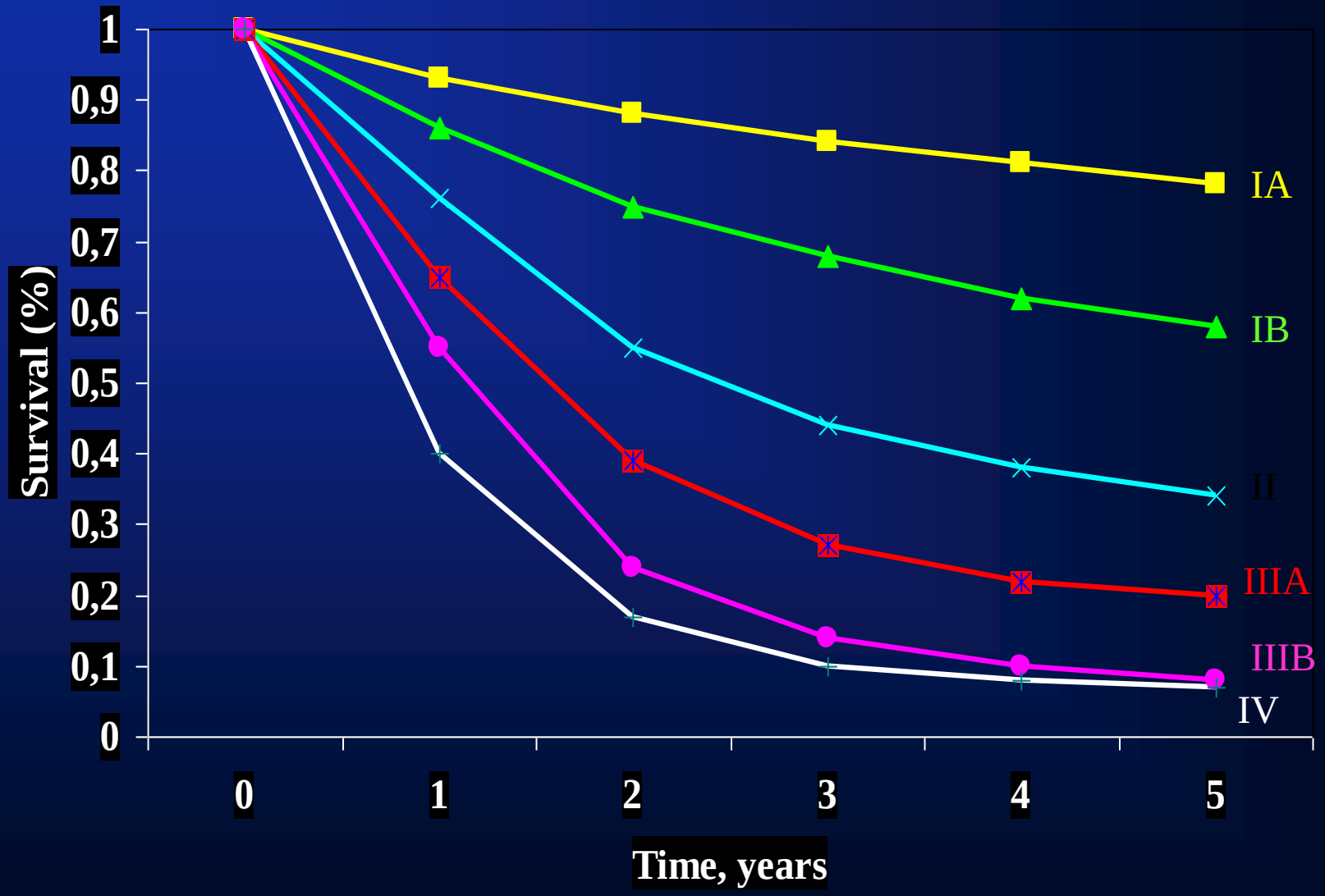
SIRIC MONTPELLIER CANCER
Site de Recherche Intégrée sur le Cancer

ICM
Institut régional du Cancer
Montpellier | Val d'Aurelle

Inserm
Institut national
de la santé et de la recherche médicale

Gastric Cancer Survival by Stage

National Cancer Data Base 1985-1996



Adjuvant Chemotherapyy

Adjuvant Chemotherapy for Gastric Cancer with S-1, an Oral Fluoropyrimidine

The NEW ENGLAND JOURNAL of MEDICINE 2007;357:1810-20

Shinichi Sakuramoto, M.D., Mitsuru Sasako, M.D., Toshiharu Yamaguchi, M.D.,

R

n=1059
Gastrectomie + D2
Stades II et III

S-1
40-60 mg x 2/j
4sem/6 **1 an**

Surveillance

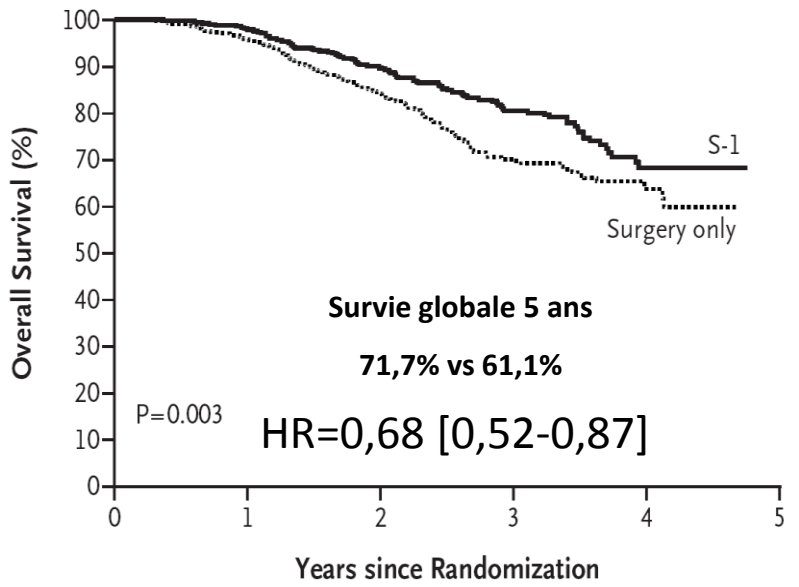
Tegafur
(prodrogue du 5-FU)

+

(1) Gimeracil
(inhibiteur réversible de DPD)

(2) Oteracil Potassium

(1) Augmente la concentration de 5FU et donc l'effet anti-tumoral
(2) Réduit la toxicité digestive du 5FU



Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial

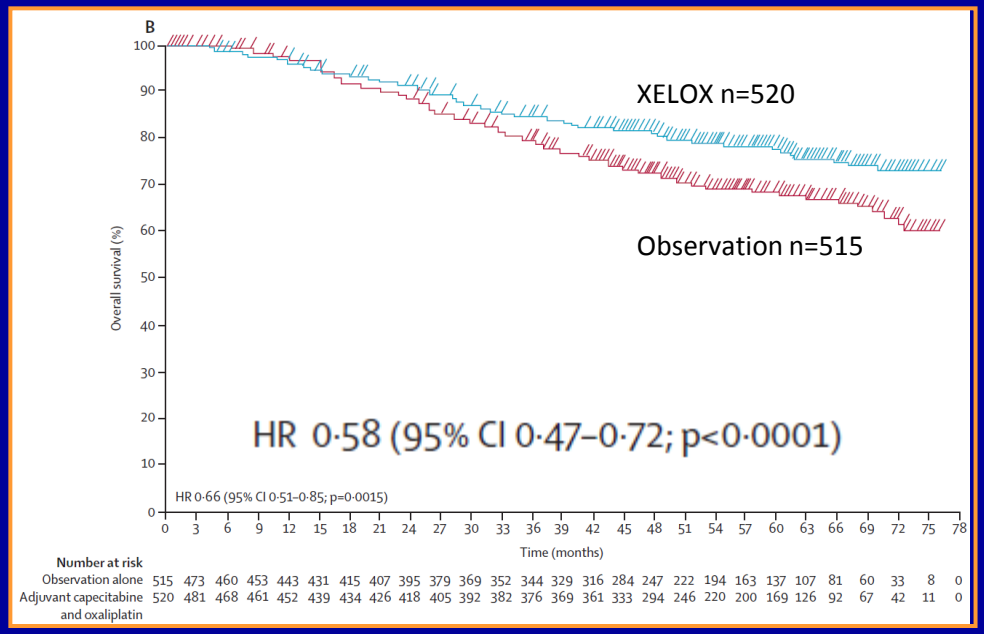
Sung Hoon Noh*, Sook Ryun Park, Han-Kwang Yang, Hyun Cheol Chung, Ik-Joo Chung, Sang-Woon Kim, Hyung-Ho Kim, Jin-Hyuk Choi, Hoon-Kyo Kim, Wansik Yu, Jong Inn Lee, Dong Bok Shin, Jiafu Ji, Jen-Shi Chen, Yunni Lim, Stella Ha, Yung-Jue Bang*, on behalf of the CLASSIC trial investigators†

R

n=1035
Gastrectomie + D2
Stades II et III

Capecitabine 1000 mg/m²x2/j J1-J14
Oxaliplatine 130 mg/m² IV
J1=J21 6 mois

Surveillance



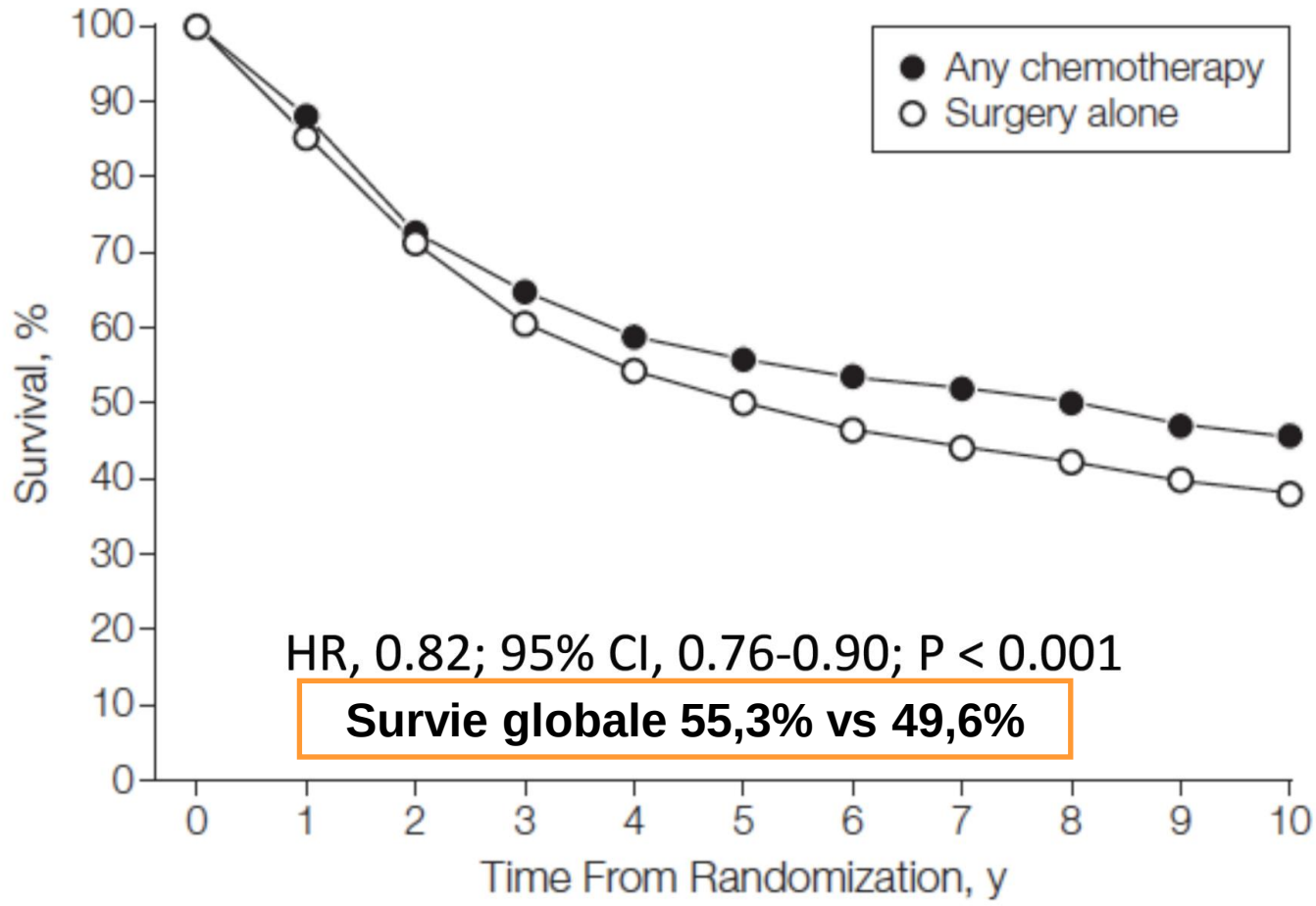
Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

A Meta-analysis

JAMA, May 5, 2010—Vol 303, No. 17

R0 CT

GASTRIC Group
(Global Advanced/Adjuvant Stomach Tumor Research International Collaboration)



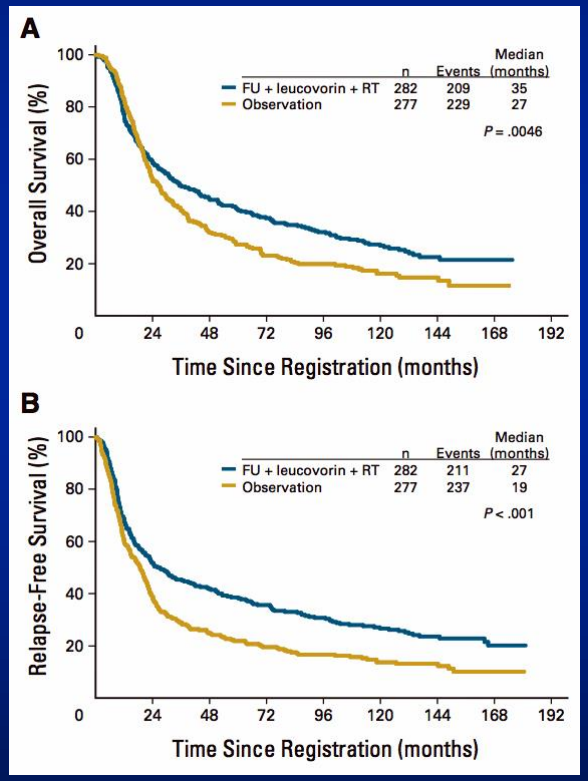
HR, 0.82; 95% CI, 0.76-0.90; P < 0.001

Survie globale 55,3% vs 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

- 17 trials
- n=3838

Adjuvant radio-chemotherapy in gastric cancer: INT 0116



- Long standing effect
- Robust treatment effect in subset analysis with an exception for diffuse histology

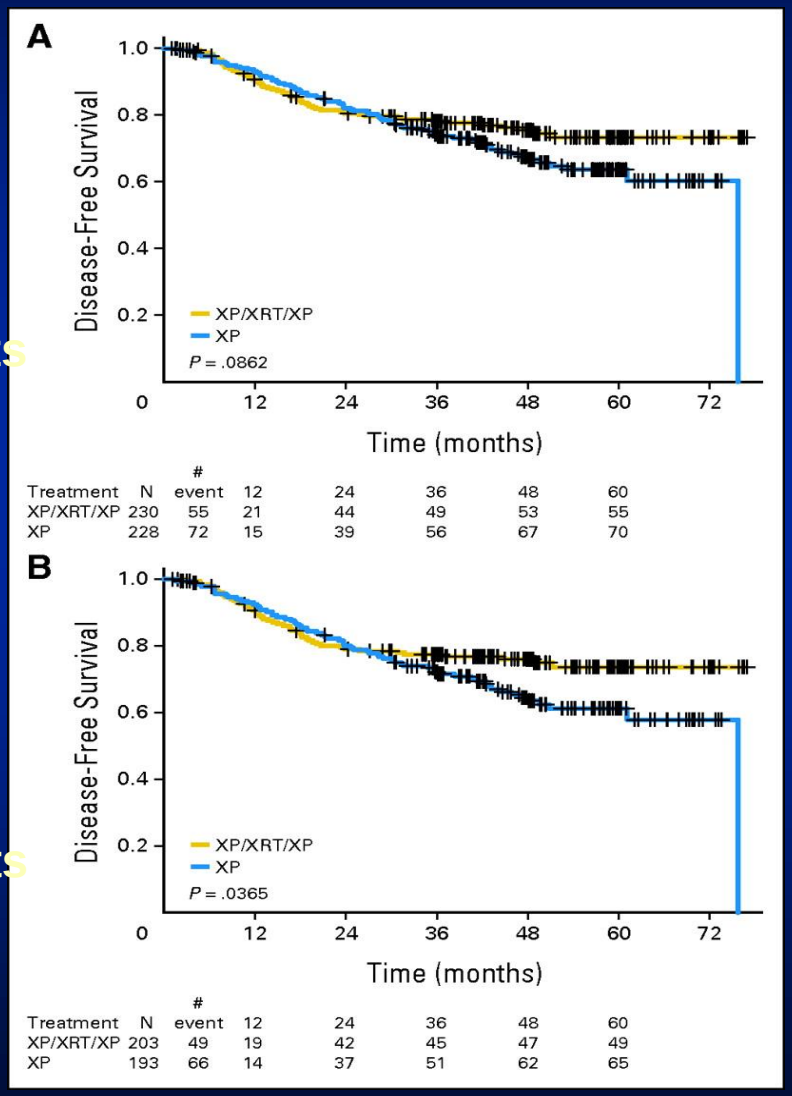
BUT

- **54%** of patients with insufficient surgery (<D1)
- Grade 3/4 toxicity **41%/32%!**
- **33%** of inadequate RxTTT planning (corrected by central review)

Smalley JS, JCO May 14th 2012, ahead of print

The ARTIST trial: adjuvant XP ± RxTTT

All patients



N+ patients

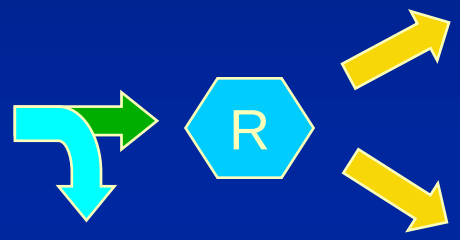
458 patients
60% stage IB –II

DFS significant in N+ patients

Lee J et al. JCO 2012;30:268-273

Adjuvant treatment in gastric cancer: The reality!

SURGERY



CONTROL

ADJUVANT TREATMENT

- Delayed surgical recovery
- Poor food intake
- Dumping syndrome etc.
- Poor performance status
- Treatment refusal

(~50%?)

<u>BUT</u>:
frequent poor patient tolerance with
- Retreatment delays
- Dose reductions
- Early termination

=> Adjuvant TTT for fit patients only!

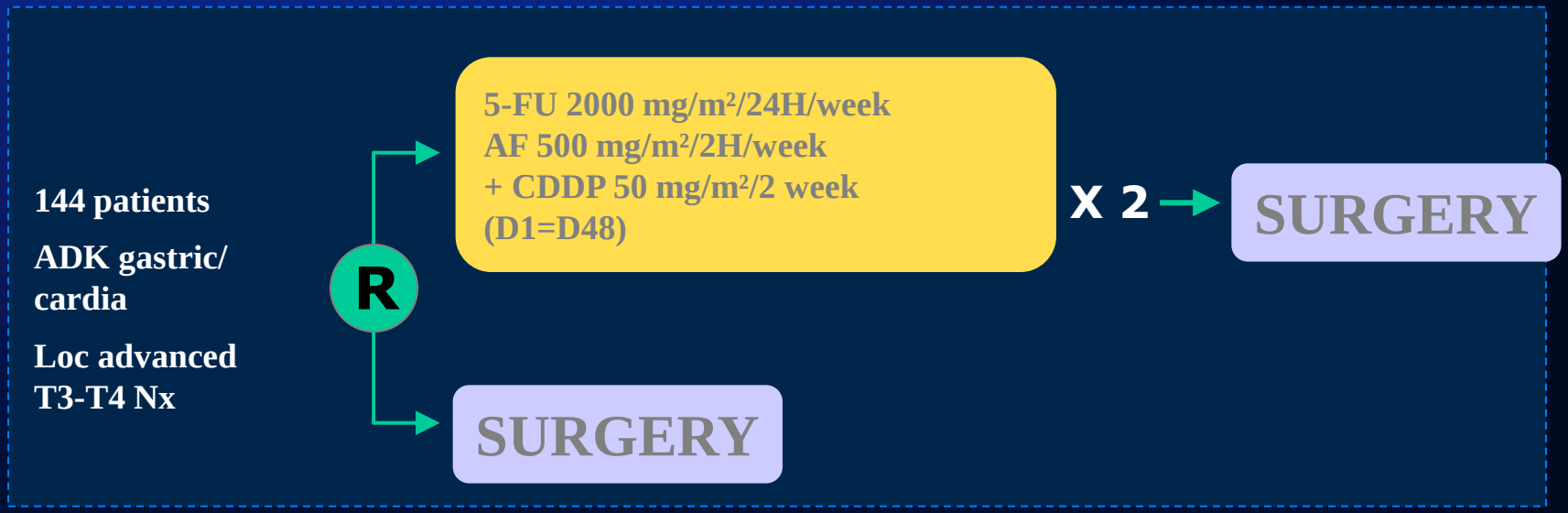
NEOADJUVANT CHEMOTHERAPY : ADVANTAGES

- Better safety of chemotherapy before post-op morbidity
- Downstaging / Downsizing and improving of R0 resection
- To treat micrometastatic disease before surgery
- To evaluate chemosensitivity

Neoadjuvant chemotherapy in gastric cancer

EORTC Phase III trial (Schumacher et al, JCO 2010)

Primary endpoint :
Overall Survival (360 pts needed : 17 -> 24 months)
Early stop of accrual



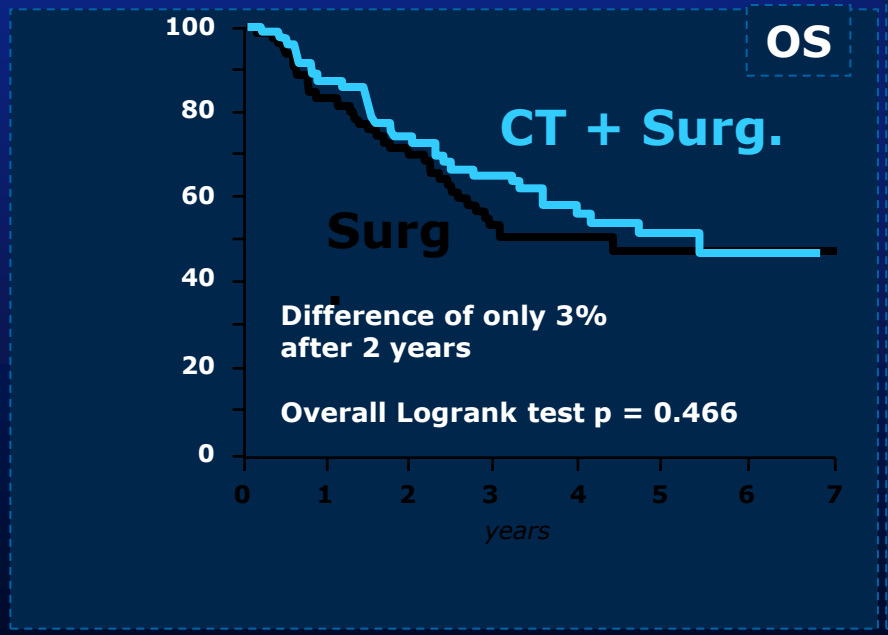
C Schuhmacher et al., ASCO 2009, A 4510

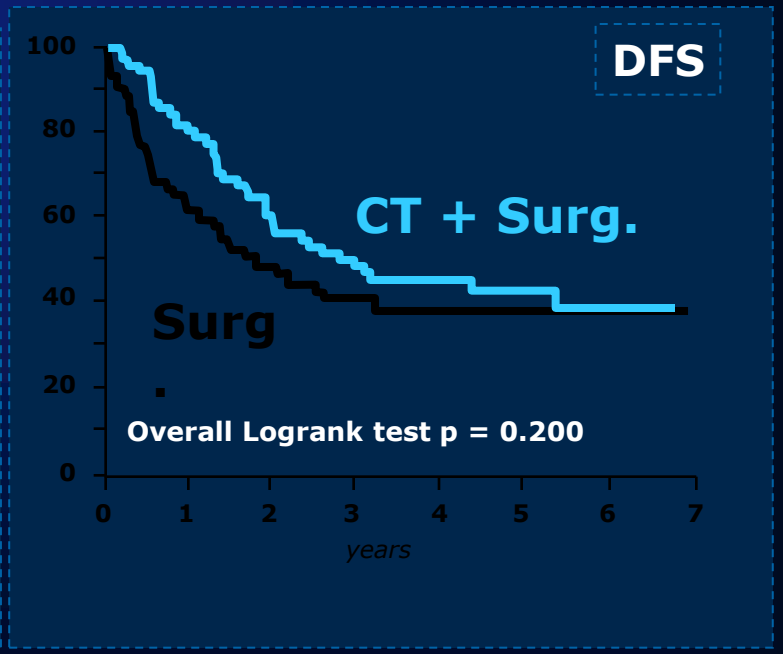
Neoadjuvant chemotherapy in gastric cancer
EORTC Phase III trial (Schumacher et al, JCO 2010)

Results

Median follow up : 4,4 years

	CT + Surg	Surg	p
R0 resection (%)	81,9	66,7	0,036





MAGIC : Design

N = 250

R

N = 253

ECF X 3 → 219 (88%) Surgery → ECF X 3

240 (95%) Surgery

MAGIC
(Medical Research Council Adjuvant Gastric Infusional Chemotherapy)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1
Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer
David Cunningham, M.D., William H. Allum, M.D., Sally P. Stenning, M.Sc., Jeremy N. Thompson, M.Chir., Cornelis J.H. Van de Velde, M.D., Ph.D., Marianne Nicolson, M.D., J. Howard Scarffe, M.D., Fiona J. Lofts, Ph.D., Stephen J. Falk, M.D., Timothy J. Iveson, M.D., David B. Smith, M.D., Ruth E. Langley, M.D., Ph.D., Monica Verma, M.Sc., Simon Weeden, M.Sc., and Yu Jo Chua, M.B., B.S., for the MAGIC Trial Participants*

Cunningham et al. NEJM 2006

FNCLCC -FFCD 9703: Design

N = 113

R

N = 111

FP* x 2 → 109 (96%) Surgery → FP* x 4

110 (99%) Surgery

VOLUME 29 · NUMBER 13 · MAY 1 2011
JOURNAL OF CLINICAL ONCOLOGY
Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial
Marc Ychou, Valérie Boige, Jean-Pierre Pignon, Thierry Conroy, Olivier Bouché, Gilles Lebreton, Muriel Ducourtieux, Laurent Bedenne, Jean-Michel Fabre, Bernard Saint-Aubert, Jean Genève, Philippe Lasser, and Philippe Rougier

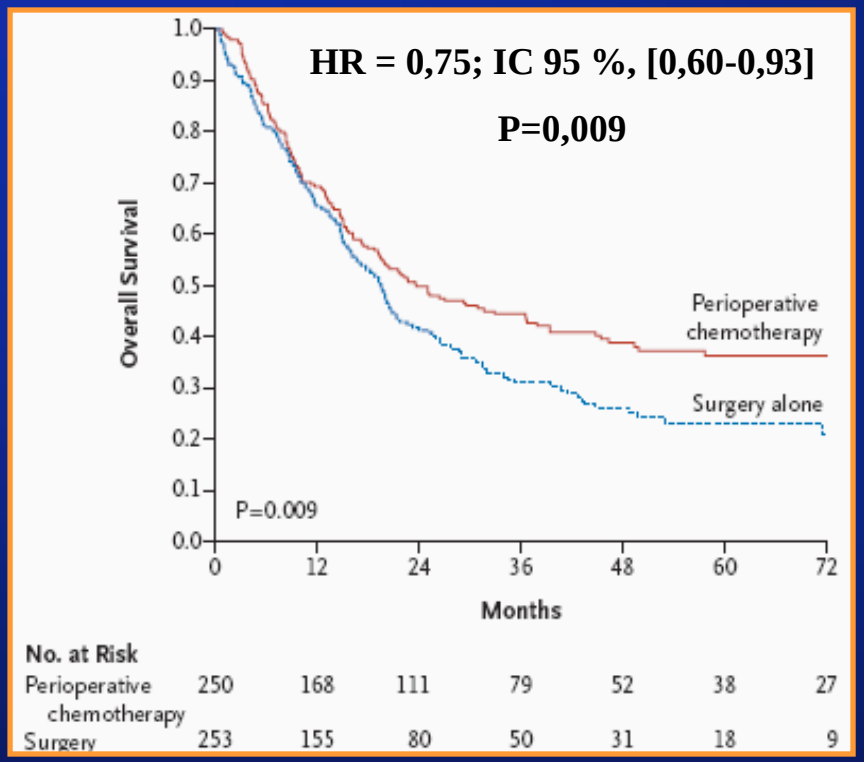
Ychou et al. J Clin Oncol 2011

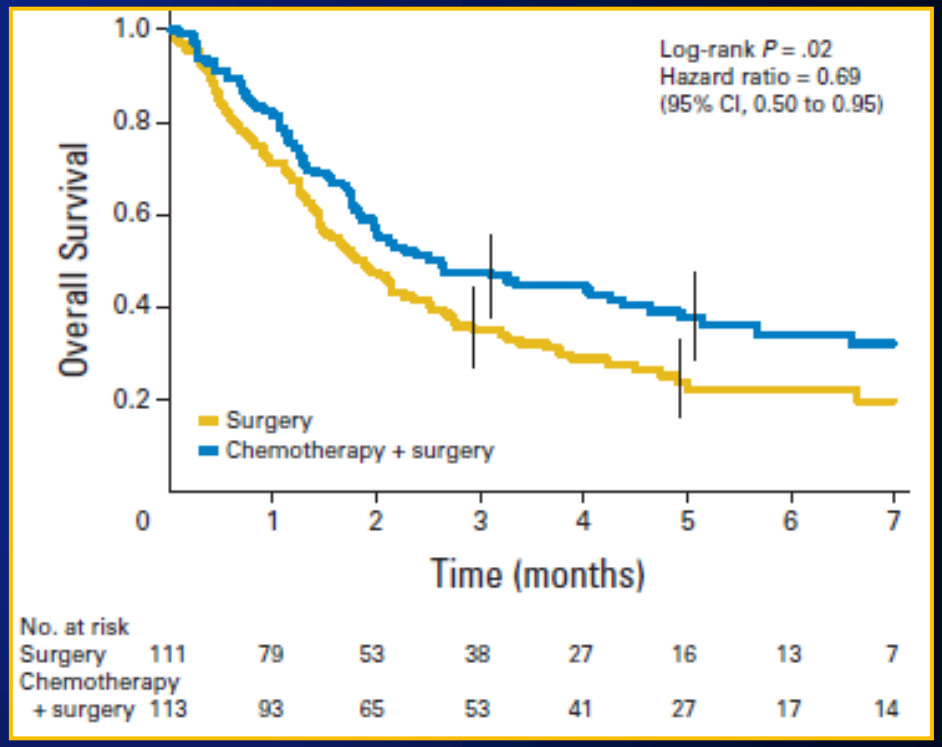
* FP = 5FU : 800 mg/m² CI x 5 Days -CDDP : 100 mg/m² D1 or D2 1 h

Characteristics of patients

	MAGIC		FNCLCC-FFCD	
	ECF n=250	S n=253	FP n=113	S n=111
Median Age (y) (range)	62 (29-85)	62 (23-81)	63 (36-75)	63 (38-75)
Sex: M (%)	82 %	76 %	85 %	82 %
WHO status 0/1	68/32	68/32	74/26	75/25
Stomach	74 %	74 %	25 %	24 %
LOG / Junction	26 %	26 %	75 %	76 %
Tumor size (cm)	5	5	4	4

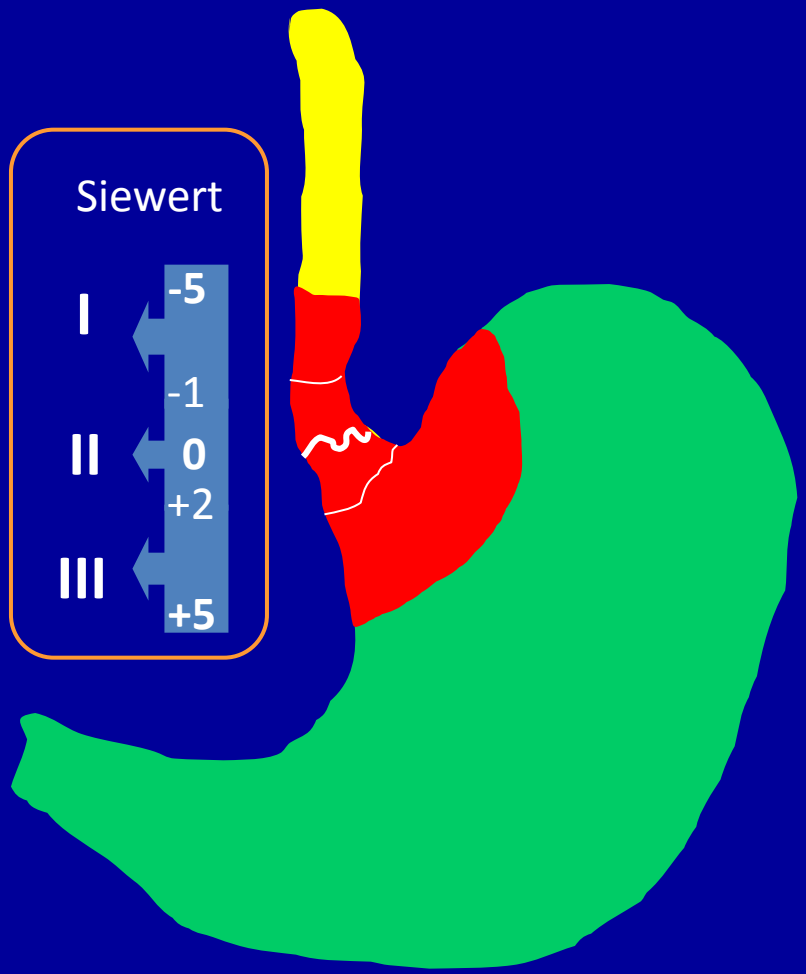
Overall survival





	MAGIC		FNCLCC-FFCD	
OS	ECF	Surgery	FP	Surgery
5-years	36%	23%	38 %	24 %
HR (p)	0,75 (p=0,009)		0,69 (p=0,002)	

OesoGastric Junction Adenocarcinomas



international union against cancer

uicc global cancer control

Stomach 7th edition

T1	Lamina propria, submucosa
T1a	Lamina propria
T1b	Submucosa
T2	Muscularis propria
T3	Subserosa *(was T2b)*
T4a	Perforates serosa *(was T3)*
T4b	Adjacent structures
N1	1 to 2 nodes
N2	3 to 6 nodes *(was N1)*
N3a	7 - 15 nodes *(was N2)*
N3b	16 or more *(was N3)*

Changes from 6th edition

Stage IA	T1	N0
Stage IB	T2	N0
	T1	N1
Stage IIA	T3	N0
	T2	N1
	T1	N2
Stage IIB	T4a	N0
	T3	N1
	T2	N2
	T1	N3
Stage IIIA	T4a	N1
	T3	N2
	T2	N3
Stages IIIB, IIIC, IV...		

Stages: most changed

INTERNATIONAL UNION AGAINST CANCER www.uicc.org

Siewert JR, Dis Esophagus 1996;9:173-82

TNM classification of malignant tumours. UICC 7e édition 2009. Sobin LH and Wittekind C ed New York: Wiley-Liss 2002

Preoperative chemo(radio)therapy versus primary surgery for gastroesophageal adenocarcinoma: Systematic review with meta-analysis combining individual patient and aggregate data

U. Ronellenfitsch et al., EJC 2013

- 14 trials, 2422 pts
- 8 trials (1049 pts, 43.3%) with individual data
- Preop chemo associated with longer OS:
  - HR = 0.81, 95% CI 0.73-0.89, P<0.0001
  - 5y OS: 23% versus 32%
- Larger benefit for GE jonction and for ChemoRadiotherapy but NS
- Longer DFS, Higher R0 resection, downstaging
- No more post operative complications

Cross Trial: Surgery vs ChemoRadio + Surgery

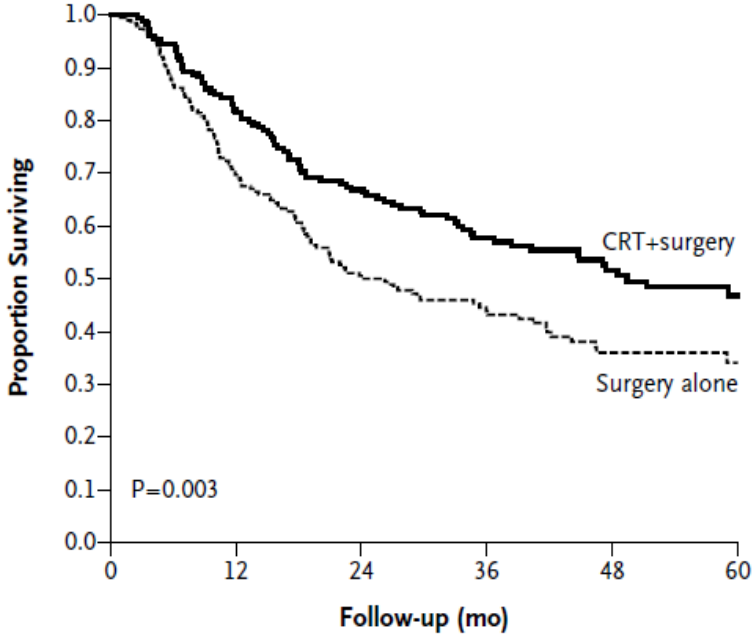
- N=368, œsophagus and OGJ
- ADK (75%), SCC (23%)

- RT 41,4 Gy,
- Weekly CT CarboP-Taxol

- **postOp mortality: 6% idem**
- **R0: 92% vs 69%**

- **Decrease risk of death 34%, in favor of preOp ChemoRadio**

A Survival According to Treatment Group



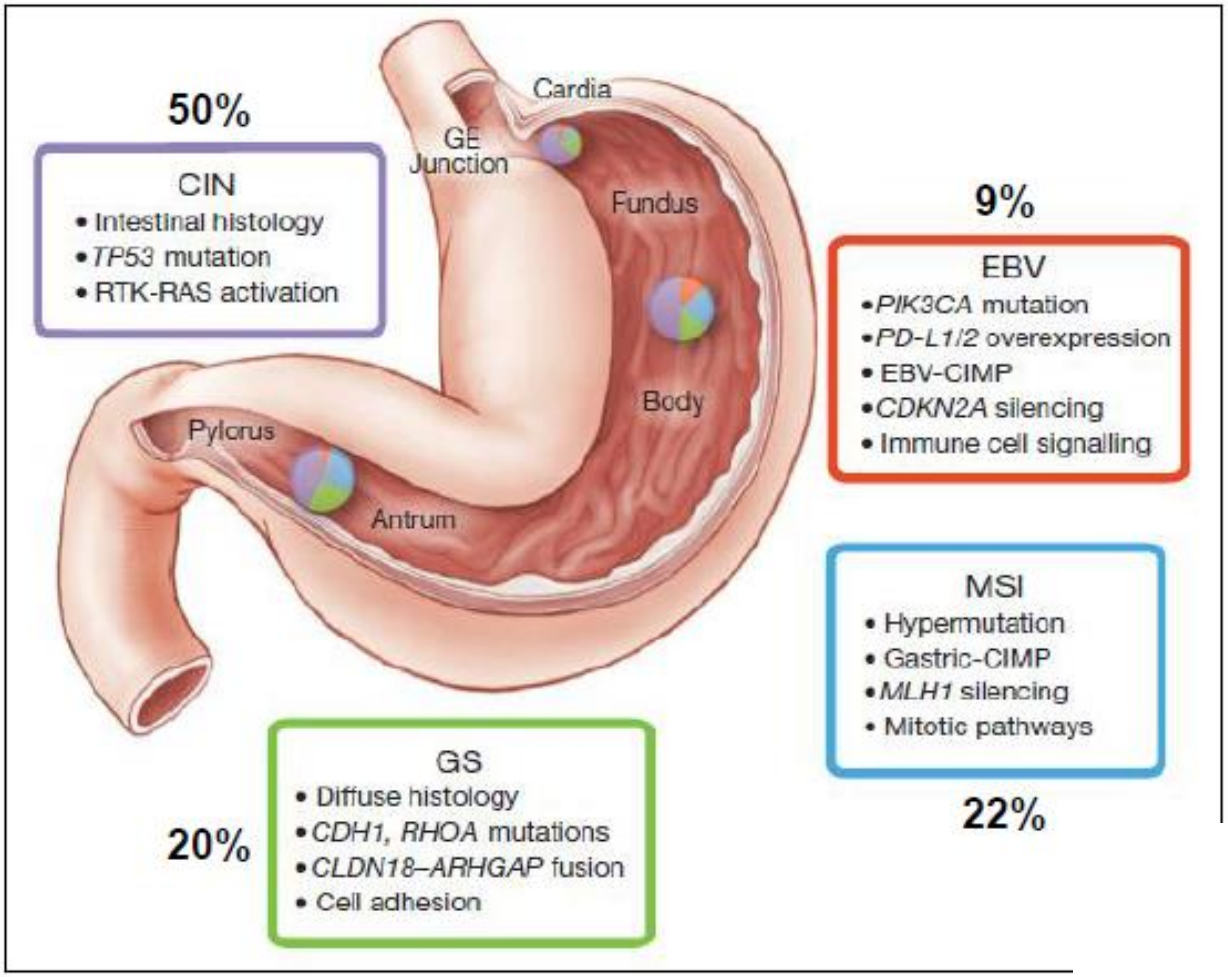
No. at Risk

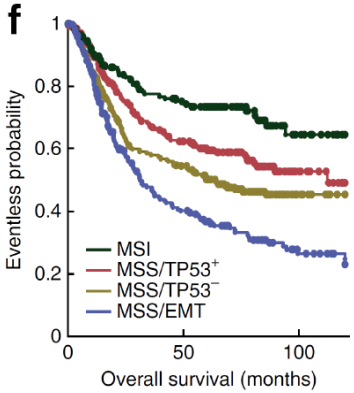
CRT+surgery	178	145	119	75	49	28
Surgery alone	188	131	94	62	33	17
Total	366	276	213	137	82	45

Van Hagen, NEJM 2012

EU VIEW: CONCLUSIONS

- Aduvant chemotherapy or adjuvant chemoradiotherapy are options
  - Limited to selected patients
  - Nutritional status is an issue
- Neoadjuvant chemotherapy alone: no positive Phase III trial
- Perioperative chemotherapy is a standard with 2 positive phase III trials
- For OGJ tumors: pre-operative chemoradiotherapy can be preferred to peri-operative chemotherapy





nature medicine