Carcinoma dell'esofago e della giunzione gastroesofagea

Terapia adiuvante e terapia della fase metastatica

Ospedale S. Cuore Don Calabria

Massimo Cirillo

Negrar 13 Dicembre 2016

Terapia adiuvante

chirurgia

Radioterapia

Chemioterapia

Radioterapia-Chemioterapia

Risultati discordanti
Pochi studi prospettici randomizzati
Casistiche eterogenee (istologia e sede)

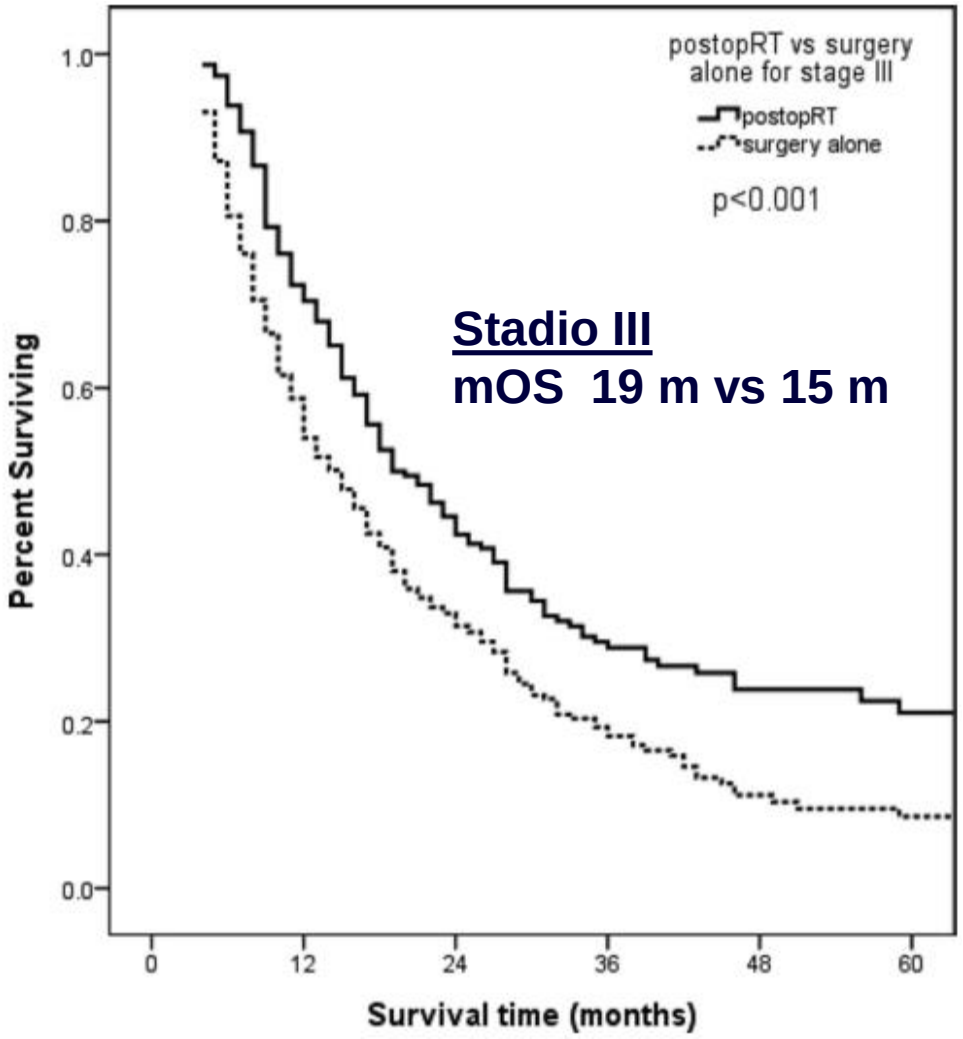
Carcinoma squamocellulare: esofago toracico/cervicale

AdenoCarcinoma: esofago inferiore e giunto gastroesofageo

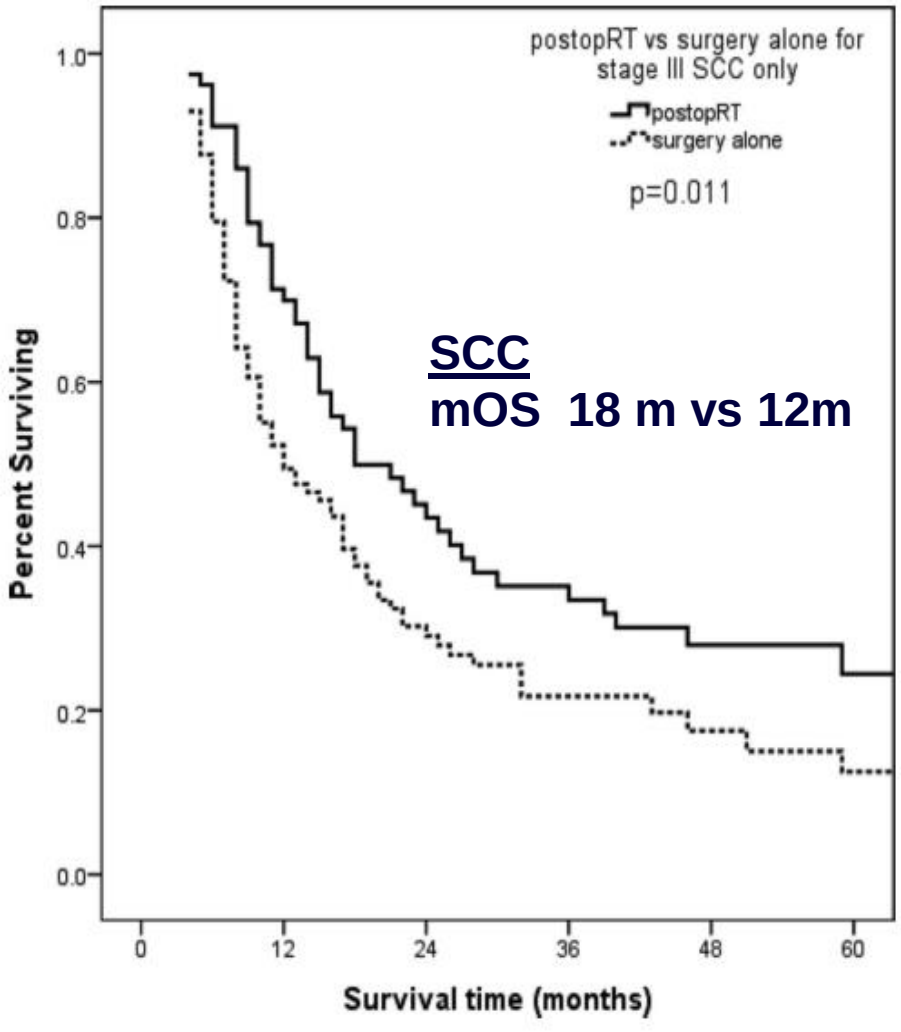
Impact of Postoperative Radiation after Esophagectomy for Esophageal Cancer

J Thorac Oncol 2010

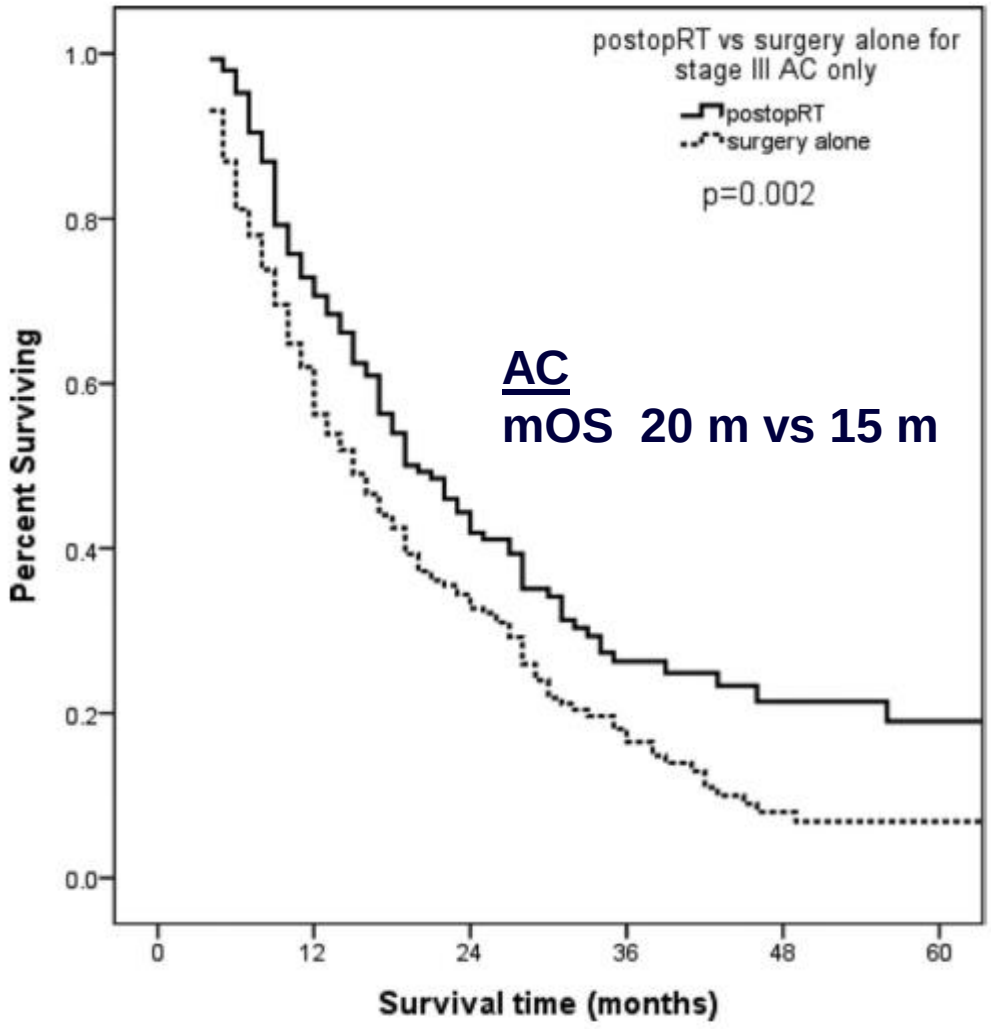
David Schreiber, MD, Justin Rineer, MD,† Dan Vongtama, MD,* Angela Wortham, MD,* Peter Han, MD,* David Schwartz, MD,* Kwang Choi, MD,* and Marvin Rotman, MD**



Stadio III
mOS 19 m vs 15 m



SCC
mOS 18 m vs 12m



AC

mOS 20 m vs 15 m

TABLE 4. Multivariate Analysis for Survival

Variable	CHR	95% CI	*p*
Age (continuous)	1.00	0.99–1.01	0.591
Gender			
Female	0.78	0.63–0.95	0.013
Male	1		
Postoperative radiation			
Yes	0.70	0.59–0.83	<0.001
No	1		
Histology			
Adenocarcinoma	1		
Squamous cell carcinoma	1.17	0.96–1.41	0.116
T-stage			
T1–2	1		
T3	1.73	1.40–2.15	<0.001
T4	2.11	1.60–2.77	<0.001
Positive lymph nodes			
Yes	1.94	1.59–2.35	<0.001
No	1		
Race			
Black	1.34	0.99–1.81	0.055
Other	0.87	0.61–0.95	0.43
White	1		

95% CI, 95% Confidence Interval; CHR, Cox hazard ratio.

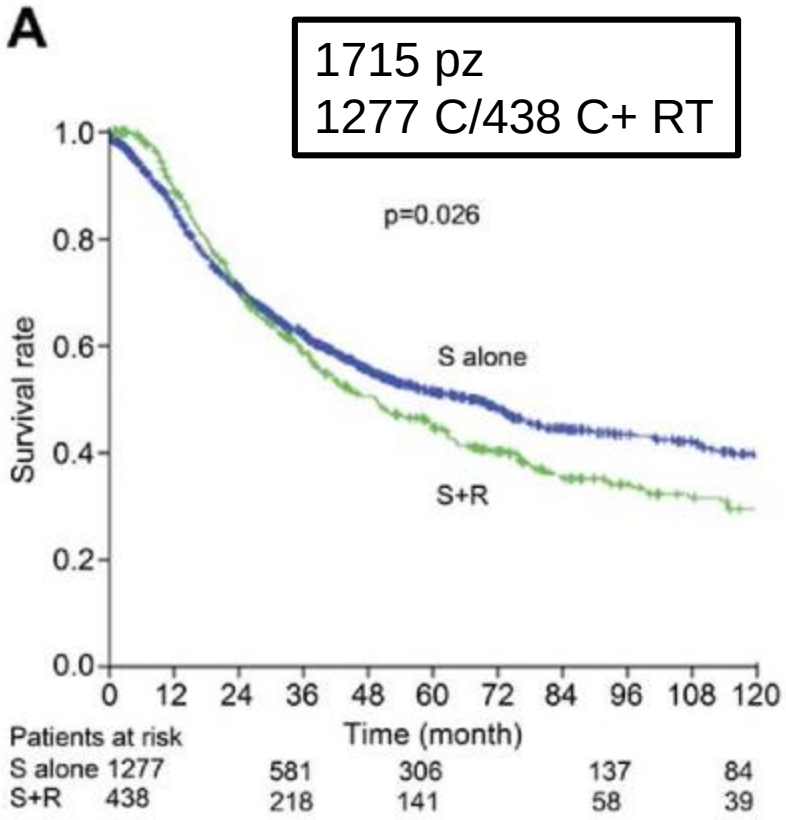
Conclusions: This large population-based review supports the use of postoperative radiation for stage III SCC and AC of the esophagus. Given the retrospective nature of this study, until appropriately powered randomized trials confirm these results, caution should be used before broadly applying these findings in clinical practice.

Postoperative Radiotherapy Improved Survival of Poor Prognostic Squamous Cell Carcinoma Esophagus

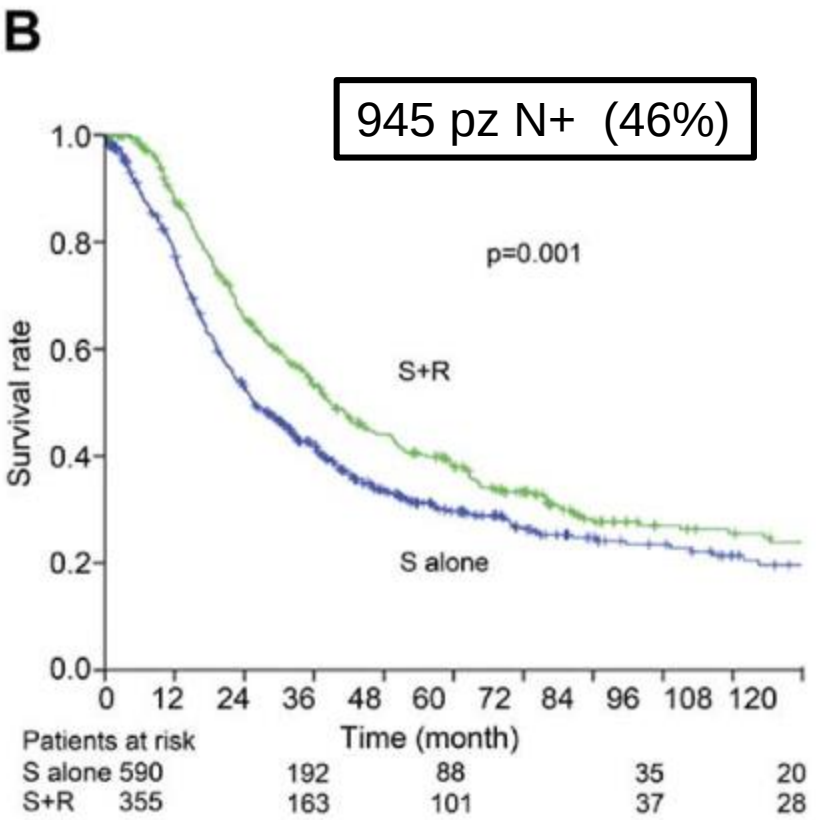
Junqiang Chen, MD, Ji Zhu, MD, Jianji Pan, MD, Kunshou Zhu, MD, Xiongwei Zheng, MD, Mingqiang Chen, MD, Jiezhong Wang, MD, and Zhongxing Liao, MD

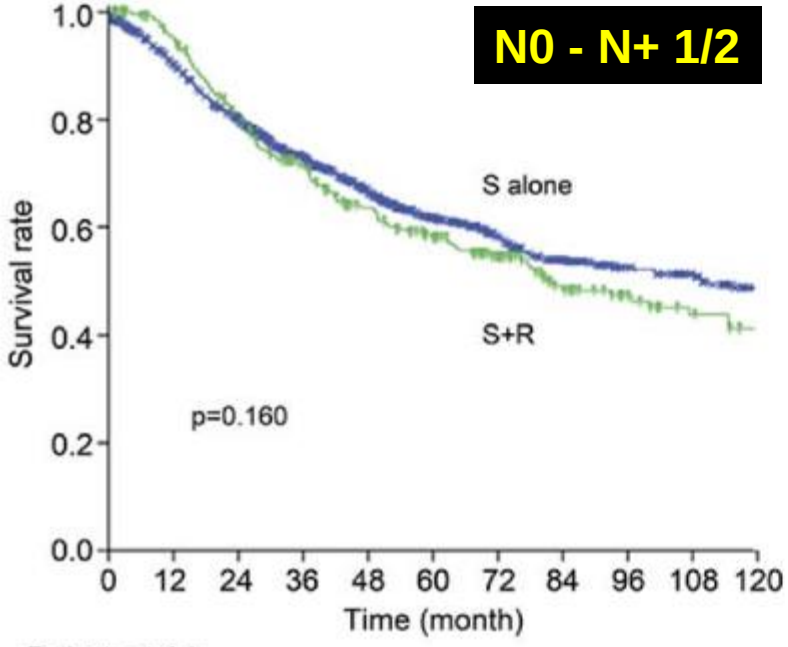
Ann Thorac Surg 2010

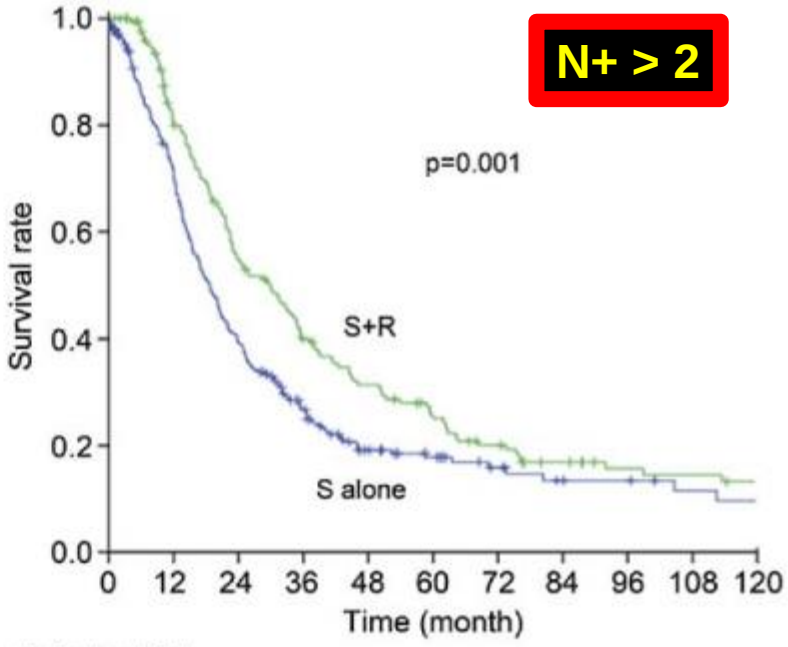
1715 pz
1277 C/438 C+ RT

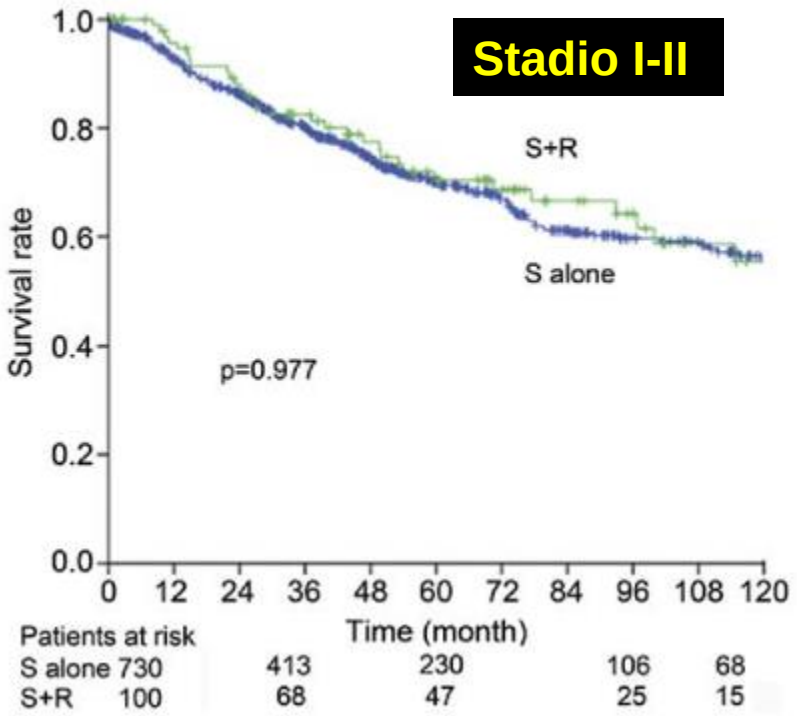


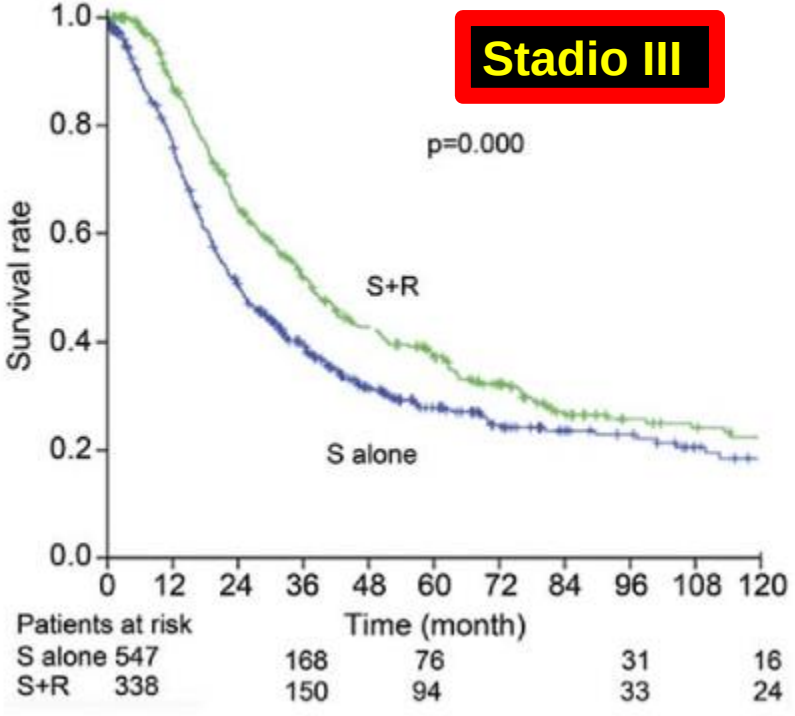
945 pz N+ (46%)




N0 - N+ 1/2
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
S alone
S+R
p=0.160
0 12 24 36 48 60 72 84 96 108 120
Time (month)


N+ > 2
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
p=0.001
S+R
S alone
0 12 24 36 48 60 72 84 96 108 120
Time (month)


Stadio I-II
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
S+R
S alone
p=0.977
0 12 24 36 48 60 72 84 96 108 120
Time (month)
Patients at risk
S alone 730 413 230 106 68
S+R 100 68 47 25 15


Stadio III
Survival rate
1.0
0.8
0.6
0.4
0.2
0.0
p=0.000
S+R
S alone
0 12 24 36 48 60 72 84 96 108 120
Time (month)
Patients at risk
S alone 547 168 76 31 16
S+R 338 150 94 33 24

Chemioterapia

- Gli studi randomizzati fanno riferimento al solo istotipo squamoso, no dati su Adenocarcinoma
- Non vantaggi in OS negli studi prospettici
- Vantaggi in OS solo in studi retrospettivi e comunque in sottogruppi a rischio (N3) ma non in studi randomizzati prospettici

Autore	Fase	N° Pz	trattamento	OS (Ch vs Adj)	altro
Pouliquen 1996	III	120	CDDP+5FU x 6-8	mOS 13 vs 14 mesi	R+ M+ Tossicità
Ando 1997	III	205	CDDP + VDS x 2	44.9 % vs 48%5 aa	
Ando 2003	III	242	CDDP+5FU x 2	5 aa 52% vs 61% p=.13	**aumento OS per N+**
Ando 2012	III	330	CDDP+5FU x 2 pre vs post CH	**5 aa 43% vs 55% p.04 Per CHT pre**	CHT post solo N+
Heroor 2003	Retr.	211	CDDP+ 5FU o VDS x 2	**Aumento OS solo se > 8 LN +**	
Jani 2000	Retr.	157	CHT +/- RT	**3 aa 16% vs 27% p.02**	
Xiao 2014	Retr.	349	CDDP+taxani o RT	**3 aa CH 53% vs RT 53 % vs CHT 65%**	**N + 2 o 3 39% vs 27% vs 52%**

Chemioterapia + Radioterapia

VOLUME 30 · NUMBER 19 · JULY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection

Stephen R. Smalley, Jacqueline K. Benedetti, Daniel G. Haller, Scott A. Hundahl, Norman C. Estes, Jaffer A. Ajani, Leonard L. Gunderson, Bryan Goldman, James A. Martenson, J. Milburn Jessup, Grant N. Stemmermann,† Charles D. Blanke, and John S. Macdonald

Neoplasie del giunto GE rappresentano solo il 20% della casistica

Resezione chirurgica subottimale (54%D0; 36% D1)

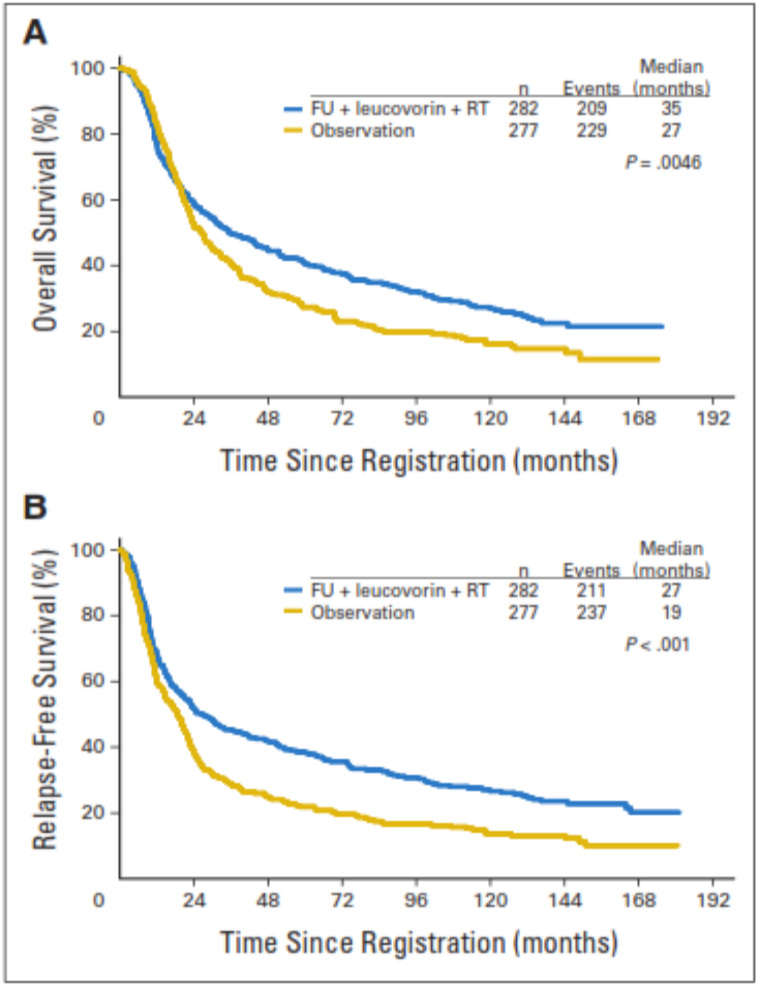
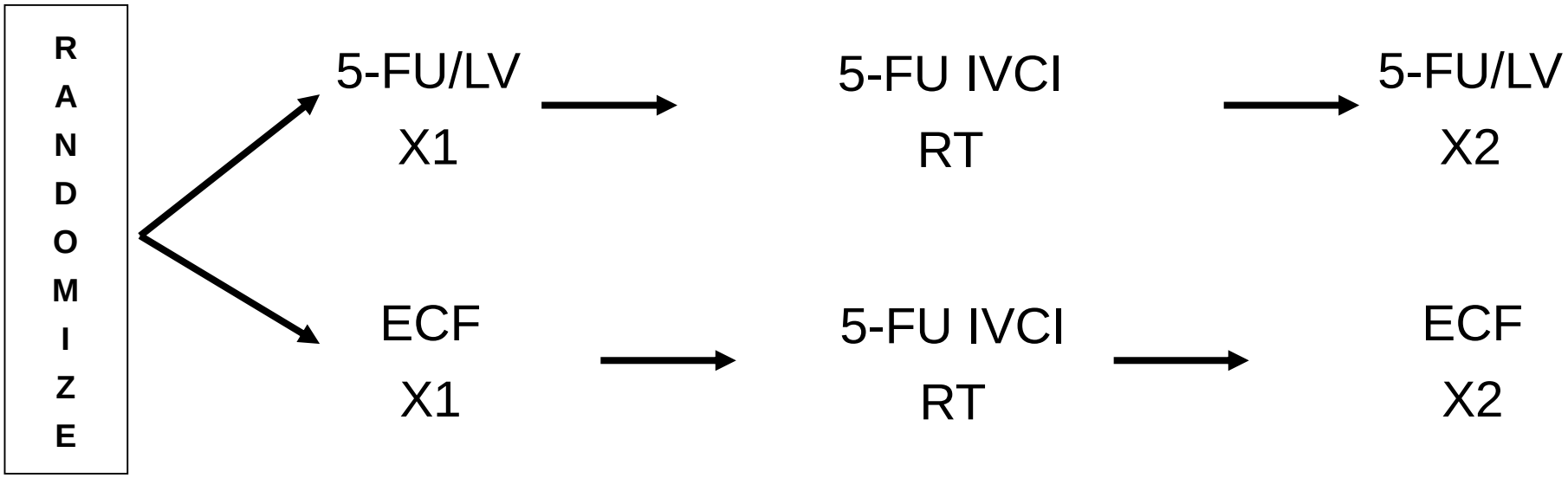


Fig 2. (A) Overall survival by arm; (B) relapse-free survival by arm. FU, fluorouracil; RT, radiotherapy.

Multicenter Pilot Study of Adjuvant Chemoradiation After Resection of Gastric or GE Junction Adenocarcinoma



280 pts in group A
266 pts in group B

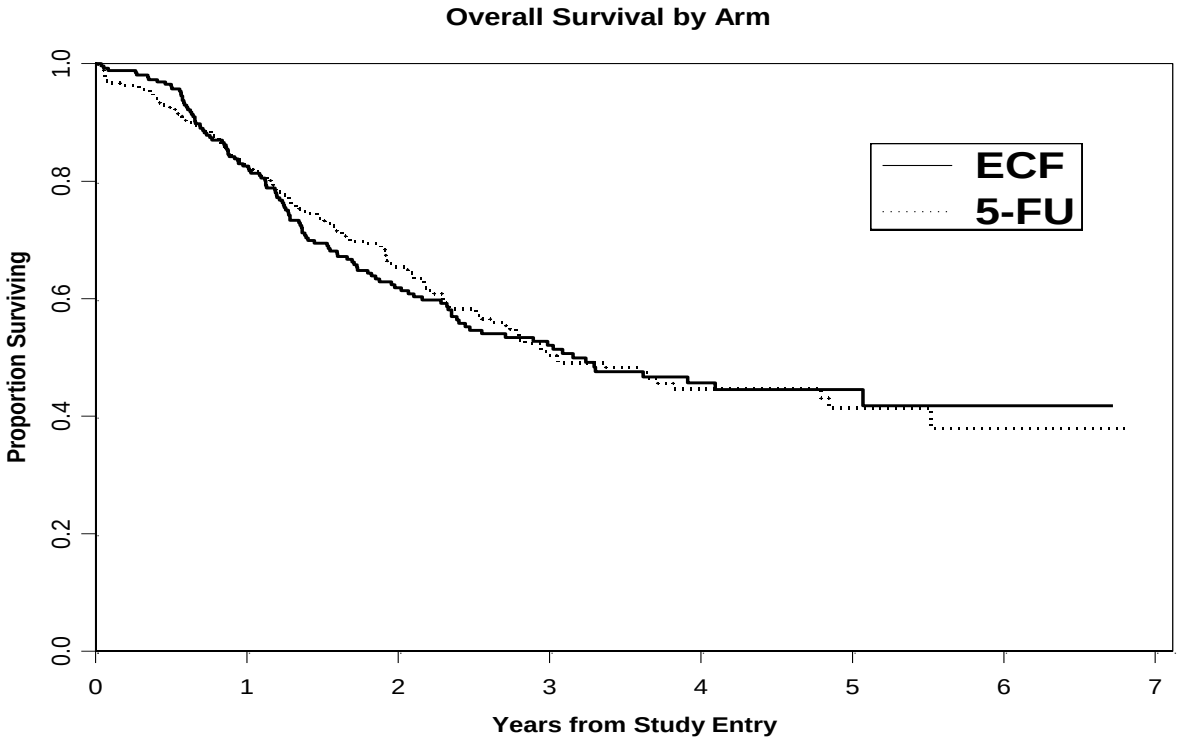
GEJ Adenocarcinoma 26%

- Fuchs CS et al ASCO 2011 -

CALGB 80101
Overall Survival by Treatment Arm

Arm	Median OS*	3-year OS	5-year OS	Hazard Ratio (95% CI)
5-FU/LV	36.6 mos	50%	41%	
ECF	37.8 mos	52%	44%	1.03 (0.80-1.34)

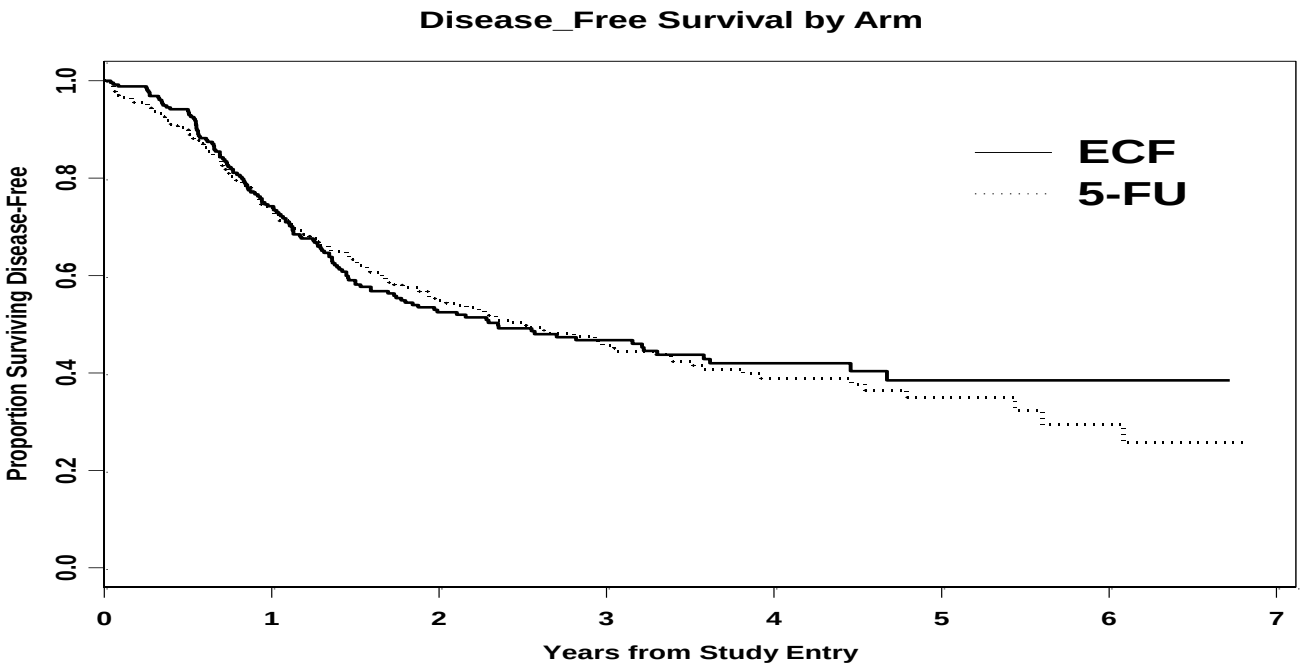
*P, log rank = 0.80



CALGB 80101
Disease-Free Survival by Treatment Arm

Arm	Median DFS	3-yr DFS	5-yr DFS	Hazard Ratio (95% CI)
5-FU/LV	30.1 mos	46%	35%	
ECF	28.2 mos*	47%	38%	1.00 (0.79-1.27)

*P, log rank = 0.99



Chemioterapia perioperatoria

MAGIC trial

The NEW ENGLAND JOURNAL of MEDICINE

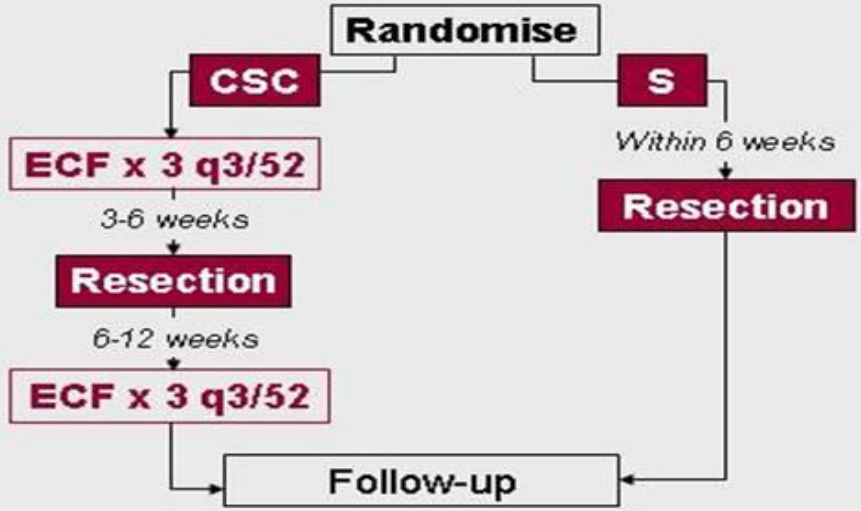
ESTABLISHED IN 1812 JULY 6, 2006 VOL. 355 NO. 1

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*

Design

MRC Clinical Trials Unit



ASCO May 2005

MRC ST02

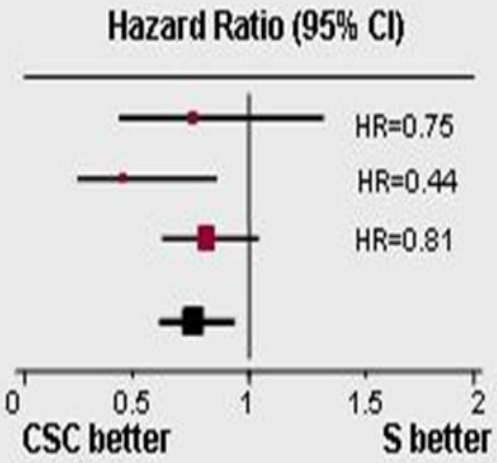
PRESENTED AT:

ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Treatment effect by primary site

MRC Clinical Trials Unit

	(no. events/no. entered) CSC	S
Oesophagus	23/37	25/36
Junction	13/28	23/30
Stomach	113/185	122/187
Total	149/250	170/253



Interaction $\chi^2_{(2)}$ =2.766, p=0.251; no evidence of heterogeneity by tumour site

Esofago inferiore 14.5%
Giunzione GE 11.5%
Stomaco 74%

VOLUME 29 · NUMBER 13 · MAY 1 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Table 1. Baseline Characteristics of Randomly Assigned Patients

Characteristic	CS Group (n = 113)		S Group (n = 111)		Total (N = 224)	
	No.	%	No.	%	No.	%
Age, years						
Median	63		63		63	
Range	36-75		38-75		36-75	
Sex						
Male	96	85	91	82	187	84
WHO performance status						
0	84	74	83	75	167	75
1	29	26	28	25	57	25
Site of tumor						
Lower esophagus	15	13	10	9	25	11
Oesophagogastric junction	70	62	74	67	144	64
Stomach	28	25	27	24	55	25
Weight loss ≥ 10%	21	19	16	14	37	17
Dysphagia						
Aphagia or semisolid or liquid diet	30	27	42	38	72	32
Normal diet with swallowing difficulty	43	38	29	26	72	32
No dysphagia	40	35	40	36	80	36

Abbreviations: CS, perioperative chemotherapy and surgery; S, surgery.

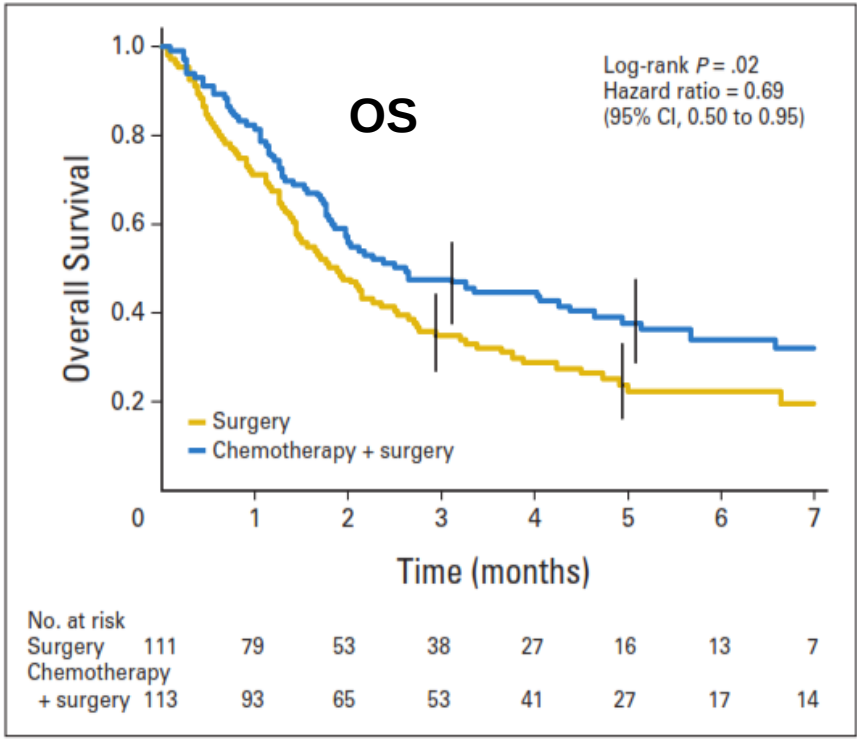


Fig 2. Kaplan-Meier curve showing overall survival from date of random assignment.

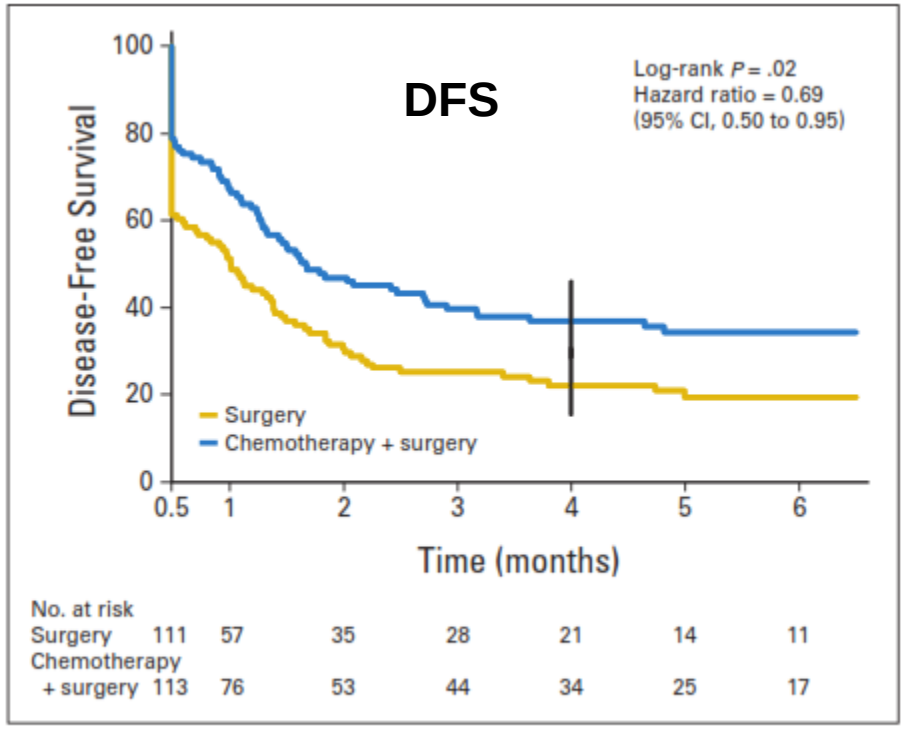


Fig 3. Kaplan-Meier curve showing disease-free survival from landmark time of 6 months after the date of random assignment.

5 ys Overal Survival: 38 vs 24%, HR 0.69; p .02
5 ys DFS : 34% vs 19%%, HR 0.65; p .003

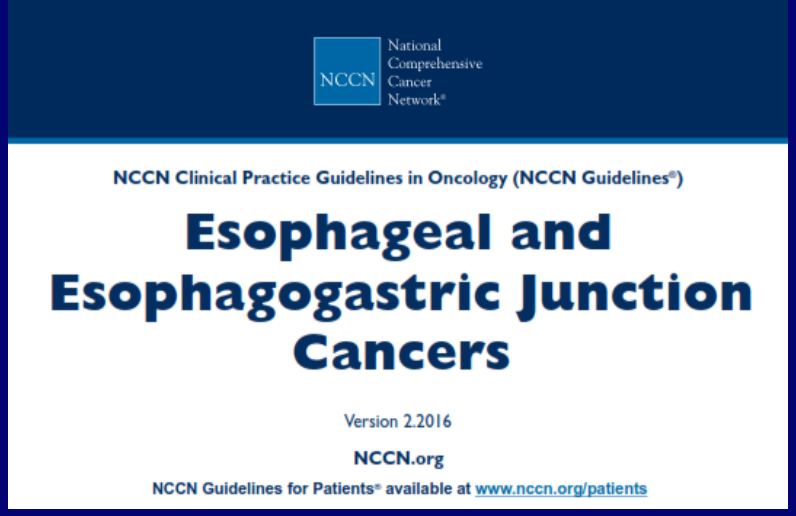
In the multivariable analysis, the favourable prognostic factor for survival were: peripoperative chemotherapy and stomach tumor localization

- Ychou et al JCO 2011 -

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
D*	I pazienti sottoposti a esofagectomia per carcinoma squamoso dell'esofago non dovrebbero essere sottoposti a trattamento chemioradioterapico adiuvante, anche nel sottogruppo di pazienti ad alto rischio di ricaduta locale e/o sistemica.	**Negativa debole**

Qualità dell'evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
A	I pazienti sottoposti a chirurgia per adenocarcinoma dell'esofago distale e della giunzione gastroesofagea potrebbero essere avviati ad un programma di chemioradioterapia adiuvante. (204)	**Positiva debole**
D*	Nel carcinoma dell'esofago e della giunzione gastroesofagea, il trattamento neoadiuvante (possibilmente chemioradioterapico) si fa preferire al trattamento adiuvante in termini di compliance, fattibilità, tossicità ed efficacia.	**Positiva forte**

*opinione espressa dal panel



- Efficacy of post operative treatment has not been established in randomized trials

- Available evidence for use of post operative chemoradiation (only for pts who have not received preoperative therapy) and perioperative chemotherapy for pts with adenocarcinoma of distal esophagus or EGJ come from prospective randomized trials involving pts with Gastric cancer

NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

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Discussion

SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR ADENOCARCINOMAS
(Patients Have Not Received Preoperative Chemoradiation or Chemotherapy)

TUMOR CLASSIFICATION[g]

POSTOPERATIVE MANAGEMENT

R0 resection[aa]

- Node negative
  - pTis and pT1 → Surveillance
  - pT2 → Surveillance or Consider chemoradiation (category 2B)[v,w,kk] for select patients[ii]
  - pT3, pT4a → Surveillance or Chemoradiation[v,w,kk] (Fluoropyrimidine-based)
- Node positive (pTis, pT1, pT2, pT3, pT4a) → Chemoradiation[v,w,kk] (Fluoropyrimidine-based)

R1 resection[aa] → Chemoradiation[v,w] (Fluoropyrimidine-based)

R2 resection[aa] → Chemoradiation[v,w] (Fluoropyrimidine-based) or Palliative Management (See ESOPH-19)

→ Follow-up (See ESOPH-18)

NCCN Guidelines Version 2.2016
Esophageal and Esophagogastric Junction Cancers

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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR ADENOCARCINOMAS (Patients Have Received Preoperative Chemoradiation or Chemotherapy)

POSTOPERATIVE MANAGEMENT

R0 resection[aa]

- **Node negative (yp Any T)[bb]** →
  - Observation until progression (if received preoperative chemotherapy or chemoradiation)
  - or
  - Chemotherapy[mm] if received perioperatively (category 1)[v]
- **Node positive (yp Any T)[bb]** →
  - Observation until progression (if received preoperative chemotherapy or chemoradiation)
  - or
  - Chemoradiation[v,w] (Fluoropyrimidine-based), only if not received preoperatively (category 2B)
  - or
  - Chemotherapy[mm] if received perioperatively (category 1)[v]

R1 resection[aa] →
- Observation until progression (if received preoperative chemotherapy or chemoradiation)
- or
- Chemoradiation[v,w] (Fluoropyrimidine-based), only if not received preoperatively

R2 resection[aa] →
- Chemoradiation[v,w] (Fluoropyrimidine-based), only if not received preoperatively
- or
- Palliative Management (See ESOPH-19)

→ Follow-up (See ESOPH-18)

[a] See Staging (ST-1) for tumor classification.
[v] See Principles of Systemic Therapy (ESOPH-F).

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Esophageal and Esophagogastric Junction Cancers

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SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA (Patients Have Not Received Preoperative Chemoradiation)

TUMOR CLASSIFICATION[g]

POSTOPERATIVE MANAGEMENT

- R0 resection[aa] → Node negative or Node positive → p Any T, Any N → Surveillance → Follow-up (See ESOPH-9)
- R1 resection[aa] → Chemoradiation[v,w] (Fluoropyrimidine-based) → Follow-up (See ESOPH-9)
- R2 resection[aa] → Chemoradiation[v,w] (Fluoropyrimidine-based) or Palliative management (See ESOPH-10) → Follow-up (See ESOPH-9)

SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR SQUAMOUS CELL CARCINOMA (Patients Have Received Preoperative Chemoradiation)

TUMOR CLASSIFICATION[g,bb]

POSTOPERATIVE MANAGEMENT

- R0 resection[aa] → Node negative or Node positive → yp any T, any N[bb] → Surveillance → Follow-up (See ESOPH-9)
- R1 resection[aa] → Observation until progression or Palliative Management (See ESOPH-10) → Follow-up (See ESOPH-9)
- R2 resection[aa] → Observation until progression or Palliative Management (See ESOPH-10) → Follow-up (See ESOPH-9)

malattia localmente avanzata in pz inoperabile

Grado di raccomandazione SIGN	Raccomandazione	Forza della raccomandazione clinica
A	Nei pazienti in buon performance status con carcinoma localmente avanzato non resecabile dell'esofago viene raccomandato un trattamento concomitante chemioradioterapico esclusivo, superiore sia alla sola radioterapia, sia ad un approccio sequenziale di chemioterapia seguita da radioterapia.	**Positiva forte**

- **Il trattamento combinato RT/CT rappresenta la scelta terapeutica di elezione e si dimostra superiore in OS vs sola RT**
(Cooper JS et al Jama 1999; Munro AJ et al Lancet 2004)
- **Incrementi di dosaggio della RT (> 50.4 Gy) non hanno determinato vantaggi in OS** (Minsky BD et al J Clin Oncol 2004)
- **La combinazione RT/CT concomitante si è dimostrata maggiormente efficace della CT seguita da RT**
(Roussel A et al J Clin Oncol 1994; Slabber CF et al Am J Clin Oncol 1994)
- **La CT di induzione seguita da combinazione RT/CT aumenta il rischio di polmoniti e danno da RT**
(Wang S et al J Thorac Oncol 2008)
- **Regimi con FU concomitante a RT forniscono risultati migliori vs regimi non contenenti FU**
(Ajani JA et al J Clin Oncol 2008)
-**Esperiemze recenti sostengono l'utilizzo di Carboplatino + Paclitaxel concomitante alla RT**
(Meerntens et al J Clin Oncol 2010)

Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial

Thierry Conroy, Marie-Pierre Galais, Jean-Luc Raoul, Olivier Bouché, Sophie Gourgou-Bourgade, Jean-Yves Douillard, Pierre-Luc Etienne, Valérie Boige, Isabelle Martel-Lafay, Pierre Michel, Carmen Llacer-Moscardo, Eric François, Gilles Créhange, Meher Ben Abdelghani, Beata Juzyna, Laurent Bedenne, Antoine Adenis, for the Fédération Francophone de Cancérologie Digestive and UNICANCER-GI Group

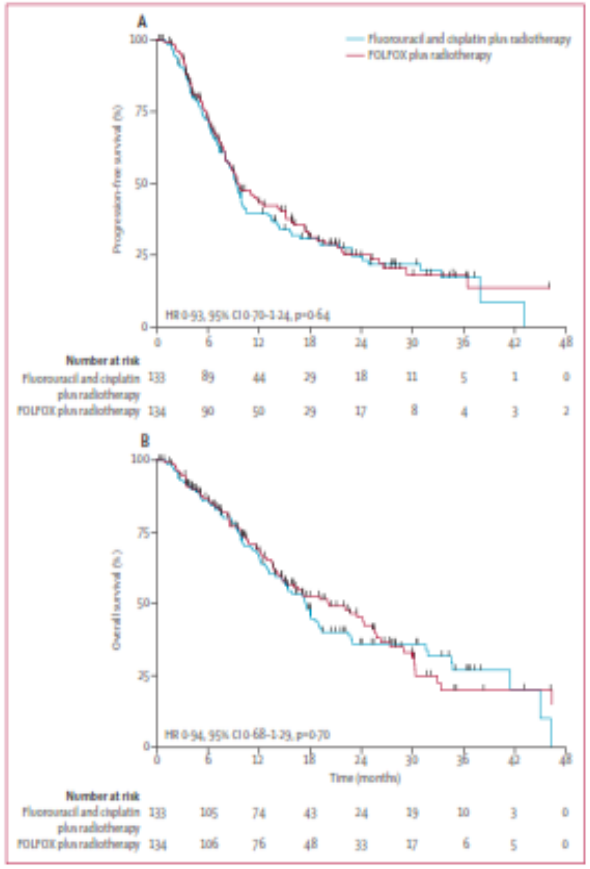


Figure 2: Kaplan-Meier curves for (A) progression-free survival and (B) overall survival
FOLFOX=fluorouracil, leucovorin, and oxaliplatin. HR=hazard ratio.

	FOLFOX group (n=134)	Fluorouracil and cisplatin group (n=133)
Overall response (RECIST)	86 (67%; 58–75)	83 (65%; 56–74)
Complete response	57 (44%; 35–53)	55 (43%; 34–52)
Partial response	29 (22%; 16–31)	28 (22%; 15–30)
Stable disease	14 (11%; 6–18)	10 (8%; 4–14)
Progressive disease	11 (9%; 4–15)	12 (9%; 5–16)
Not evaluable	6 (5%; 2–10)	7 (6%; 2–11)
Not assessed	12 (9%; 5–16)	15 (12%; 7–19)
Missing	5	6
Endoscopic response assessed by investigator[22]*		
Complete response	61 (53%; 44–62)	57 (48%; 38–57)
No complete response	45 (39%; 30–49)	46 (38%; 30–48)
Not evaluable	2 (2%; 0–6)	4 (3%; 1–8)
Not assessed	7 (6%; 2–12)	13 (11%; 6–18)
Missing	19	13

Data are n (%; 95% CI). FOLFOX=fluorouracil, leucovorin, and oxaliplatin. RECIST=Response Evaluation Criteria In Solid Tumours.[21] *115 patients assessable in the FOLFOX group and 120 assessable in the fluorouracil and cisplatin group.

***Table 2*: Tumour response to treatment**

- Lancet Oncol 2014 -

Malattia metastatica

Chemioterapia nella malattia metastatica

- Regimi di combinazione platino/fluoropirimidine hanno rappresentato i trattamenti di riferimento negli anni 70/80 con RR 35-40%
- La sopravvivenza resta ancora insoddisfacente con OS a 5 anni di circa il 20%

- **Fluorouracile**
- **Cisplatino**

- Carboplatino
- Irinotecan
- Oxaliplatino
- Capecitabine

CDDP + FU ic vs CDDP ha determinato aumento di OS , aumento di RR ma maggiore tossicità
(Bleibergh et al. Eur J Cancer 1997)

FU può essere sostituito con Capecitabine
CDDP può essere sostituito da L-OHP
(Cunningham et al. N Engl J Med 2008)

Irinotecan in associazione a FU sembra essere efficace sia in I^{a} che II^{a} linea
(Dank et al. Ann Oncol 2008)

Oxaliplatino + FU/Capecitabine può esser utilizzato sia in I^{a} che II^{a} linea
(Al Batran et al. JCO 2088)

Taxani nella malattia metastatica

Dati provenienti da studi che includono pazienti affetti da Adenocarcinoma gastrico e della giunzione gastro-esofagea.

- **Fluorouracile**
- **Cisplatino**

- Irinotecan
- Oxaliplatino
- Capecitabine

- Docetaxel
- Paclitaxel

PTX in monochemioterapia può essere indicato in pz "unfit" per CDDP/FU
(Ilson et al Ann Oncol 2007)

Docetaxel nello schema DCF si è dimostrato più efficace in OS e TTP rispetto a CDDP + FU
(Van Cutsem et al J Clin Oncol 2006)

DCF si è dimostrato più efficace in OS e OR rispetto a ECF e DC
(Roth et al J Clin Oncol 2007)

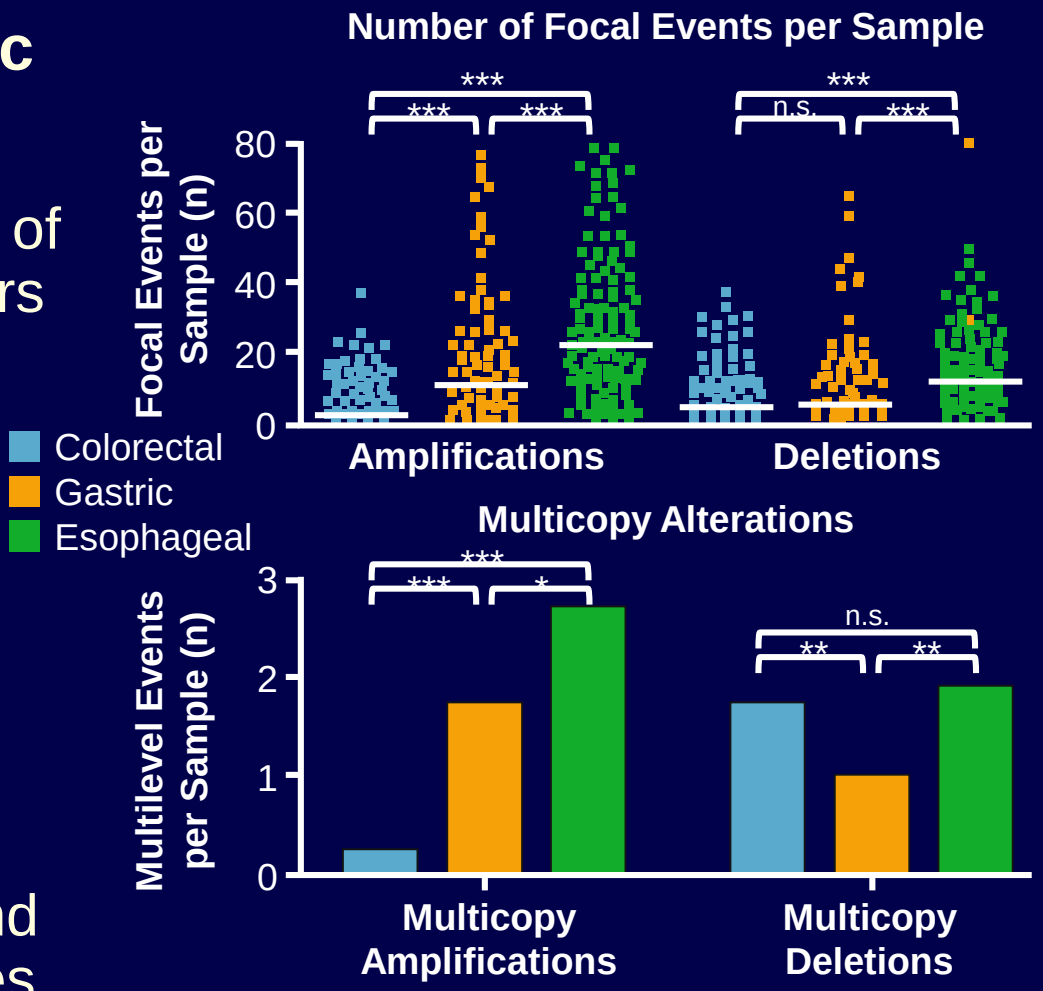
Variazioni nello schema DCF si sono dimostrati equivalenti ma meno tossici
(Shah et al J Clin Oncol 2015; Overman et al Cancer 2010)

Target Therapy

Genome Atlas Project: Gene Amplification in Esophagogastric Cancer

296 Esophageal/Gastric Cancers; 190 CRCs

- Amplified genes in 37% of gastroesophageal tumors
  - *EGFR*
  - *HER2*
  - *MET*
  - *FGFR1-2*
  - *KRAS*
- Targetable receptors and receptor tyrosine kinases



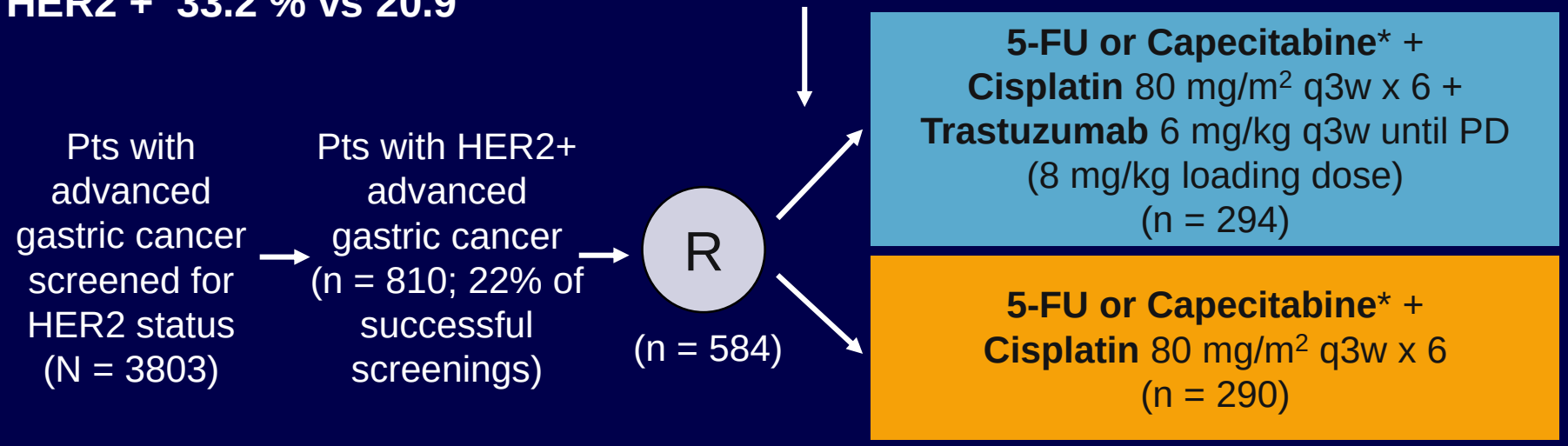
Dulak AM, et al. Can Res. 2012;72:4383-4393.

Phase III ToGA: Trastuzumab + Chemo in Advanced HER2+ Gastric Cancer

- **GEJ 18% CG 82%**

Stratified by ECOG PS, advanced vs metastatic, gastric vs GEJ, measurable disease, capecitabine vs 5-FU

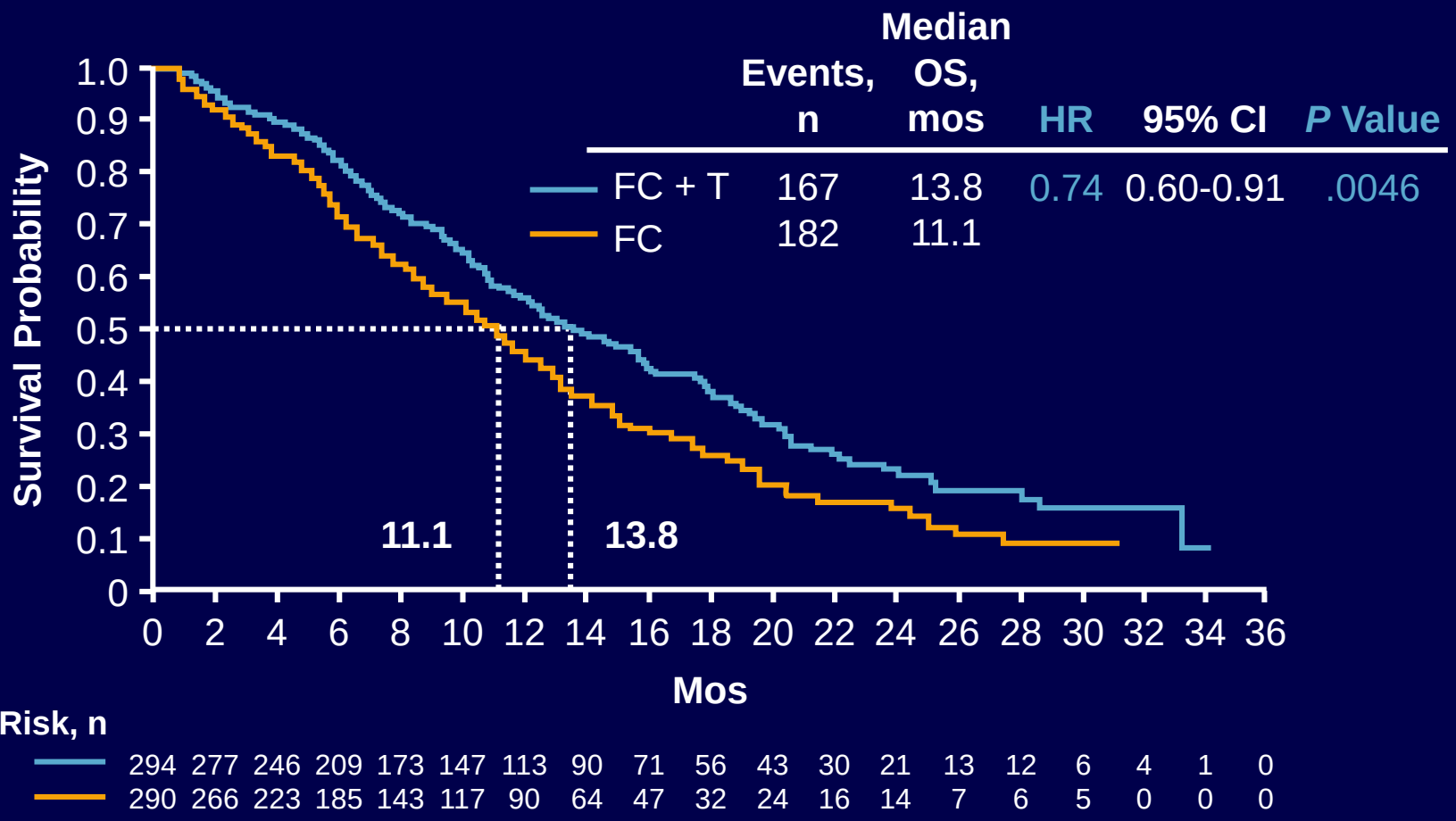
HER2 + 33.2 % vs 20.9



- Primary endpoint: OS

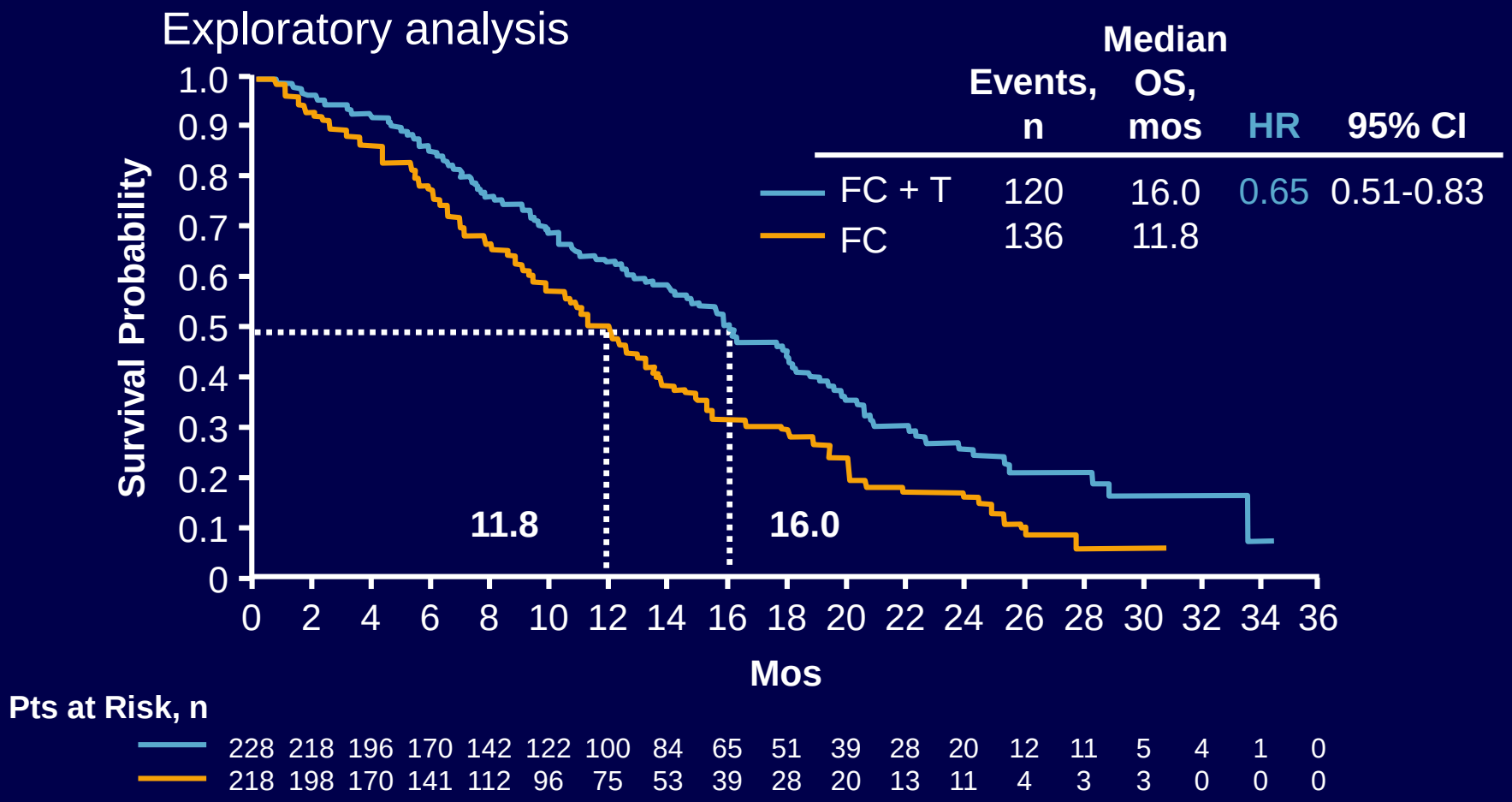
Bang YJ, et al. Lancet. 2010;376:687-697.

Phase III ToGA: OS



Bang YJ, et al. Lancet. 2010;376:687-697.

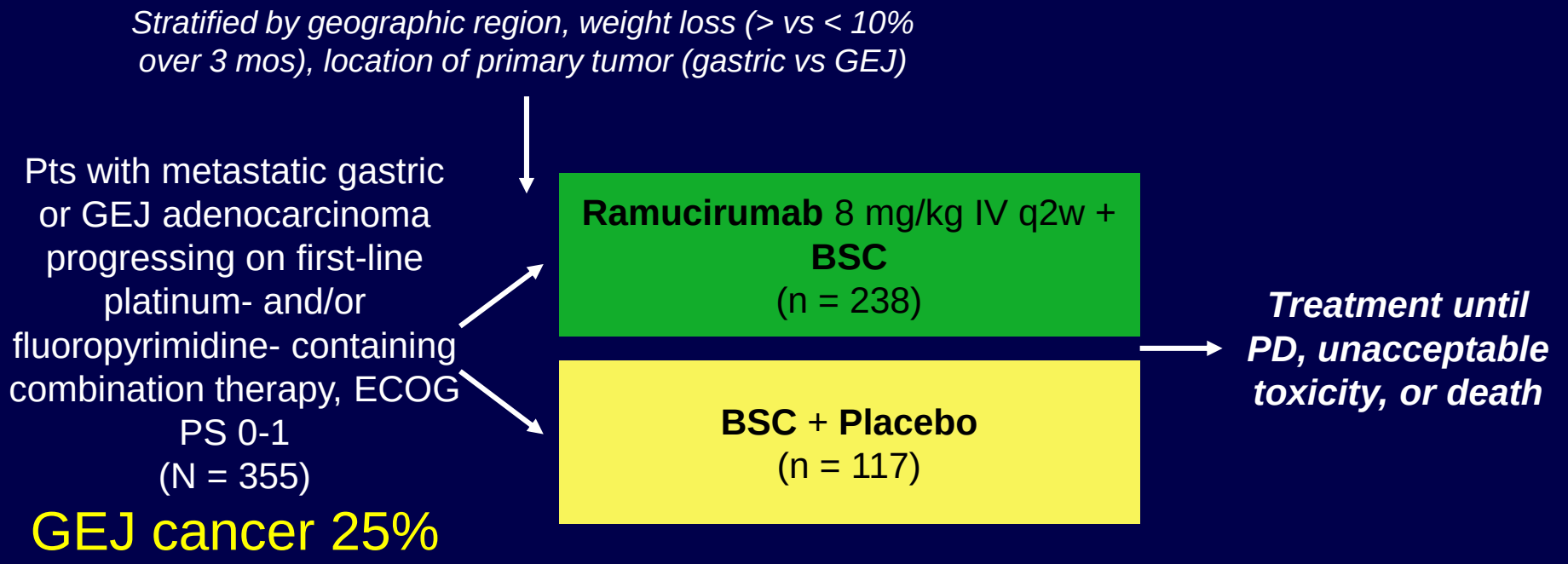
Phase III ToGA: OS in Pts With IHC 3+ or FISH+ and IHC 2+



	Events, n	Median OS, mos	HR	95% CI
FC + T	120	16.0	0.65	0.51-0.83
FC	136	11.8		

Bang YJ, et al. Lancet. 2010;376:687-697.

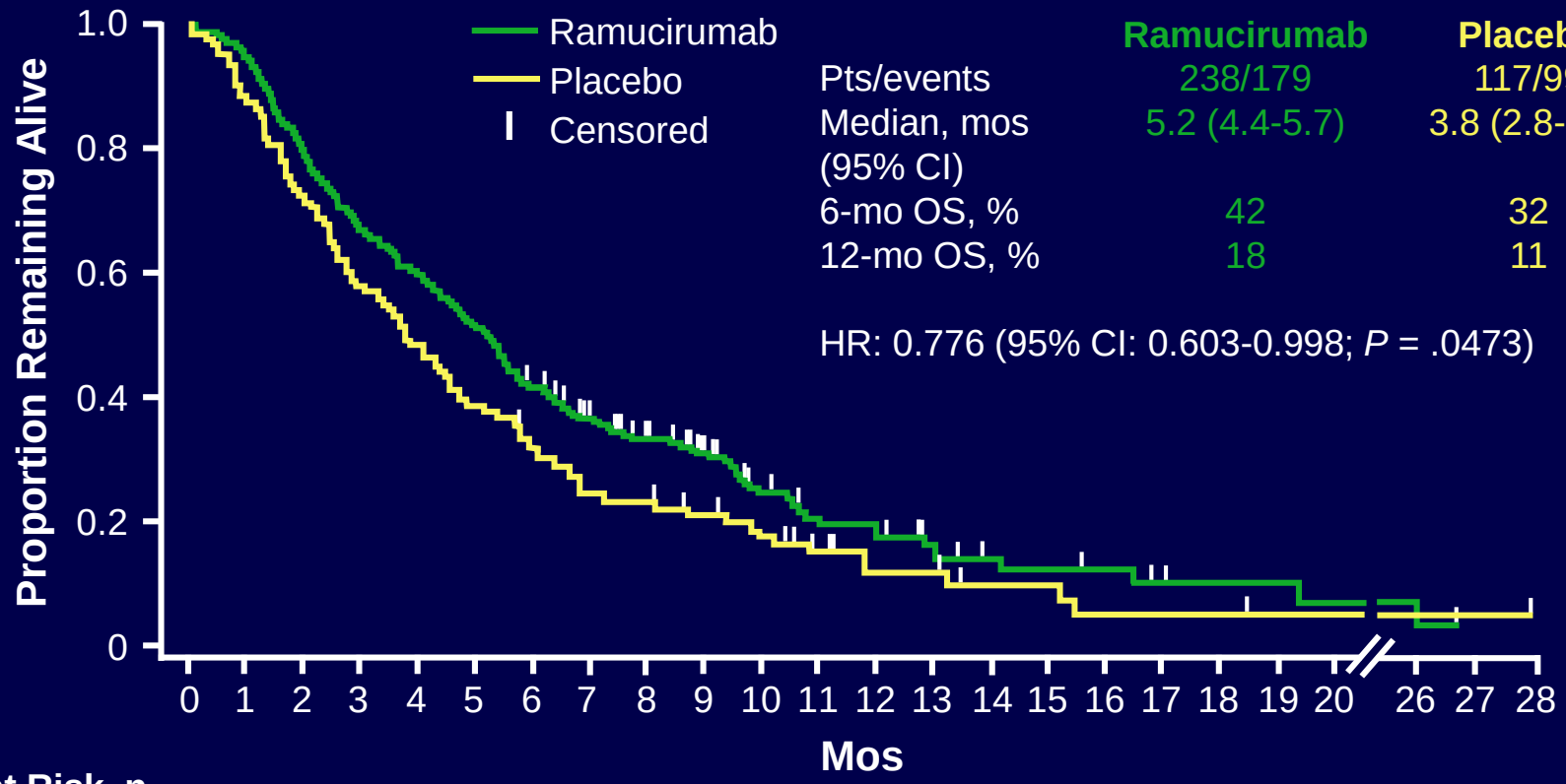
Phase III REGARD Trial: BSC ± Ramucirumab in Met Gastric or GEJ Cancer



- Primary objective: OS
- Secondary endpoints: PFS, 12-wk PFS, ORR, DoR, QoL, safety

Fuchs CS, et al. Lancet. 2014;383:31-39.

BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer (REGARD): OS



	Ramucirumab	Placebo
Pts/events	238/179	117/99
Median, mos (95% CI)	5.2 (4.4-5.7)	3.8 (2.8-4.7)
6-mo OS, %	42	32
12-mo OS, %	18	11

HR: 0.776 (95% CI: 0.603-0.998; *P* = .0473)

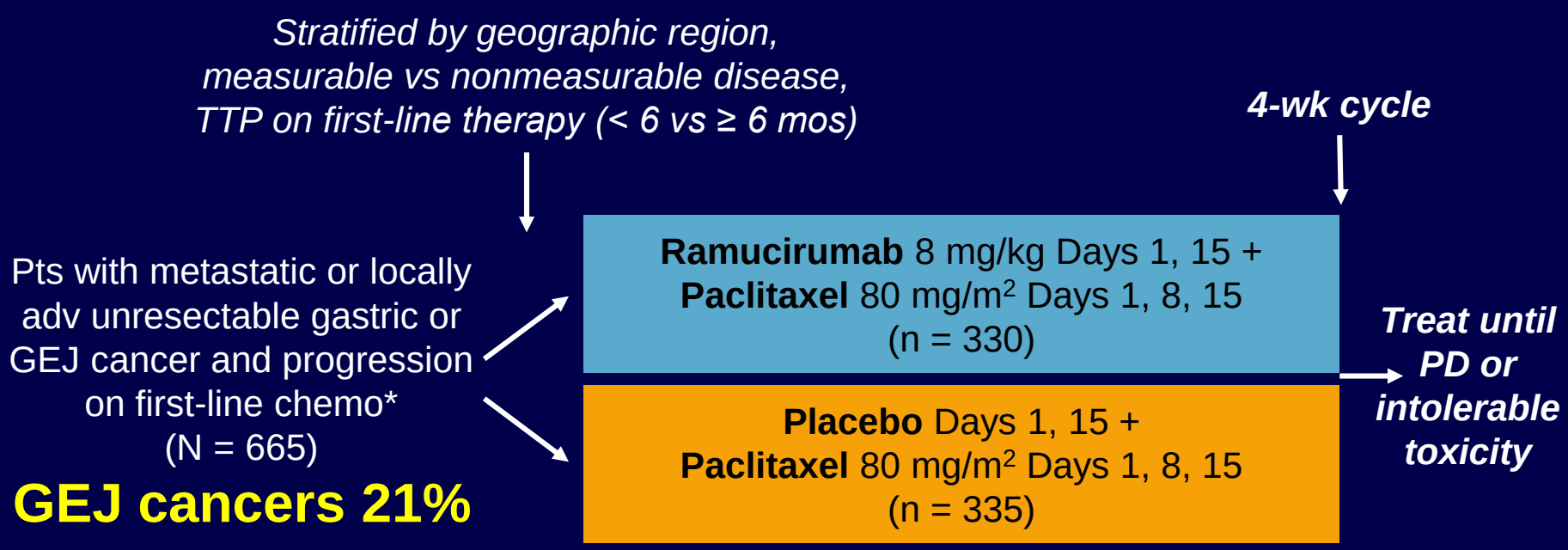
Pts at Risk, n

Ramucirumab	238	154	92	49	17	7	3	0	0
Placebo	117	66	34	20	7	4	2	1	0

Fuchs CS, et al. Lancet. 2014;383:31-39.

RAINBOW: Second-line Paclitaxel ± Ramucirumab in Advanced Gastric Cancer

- Randomized, double-blind phase III trial

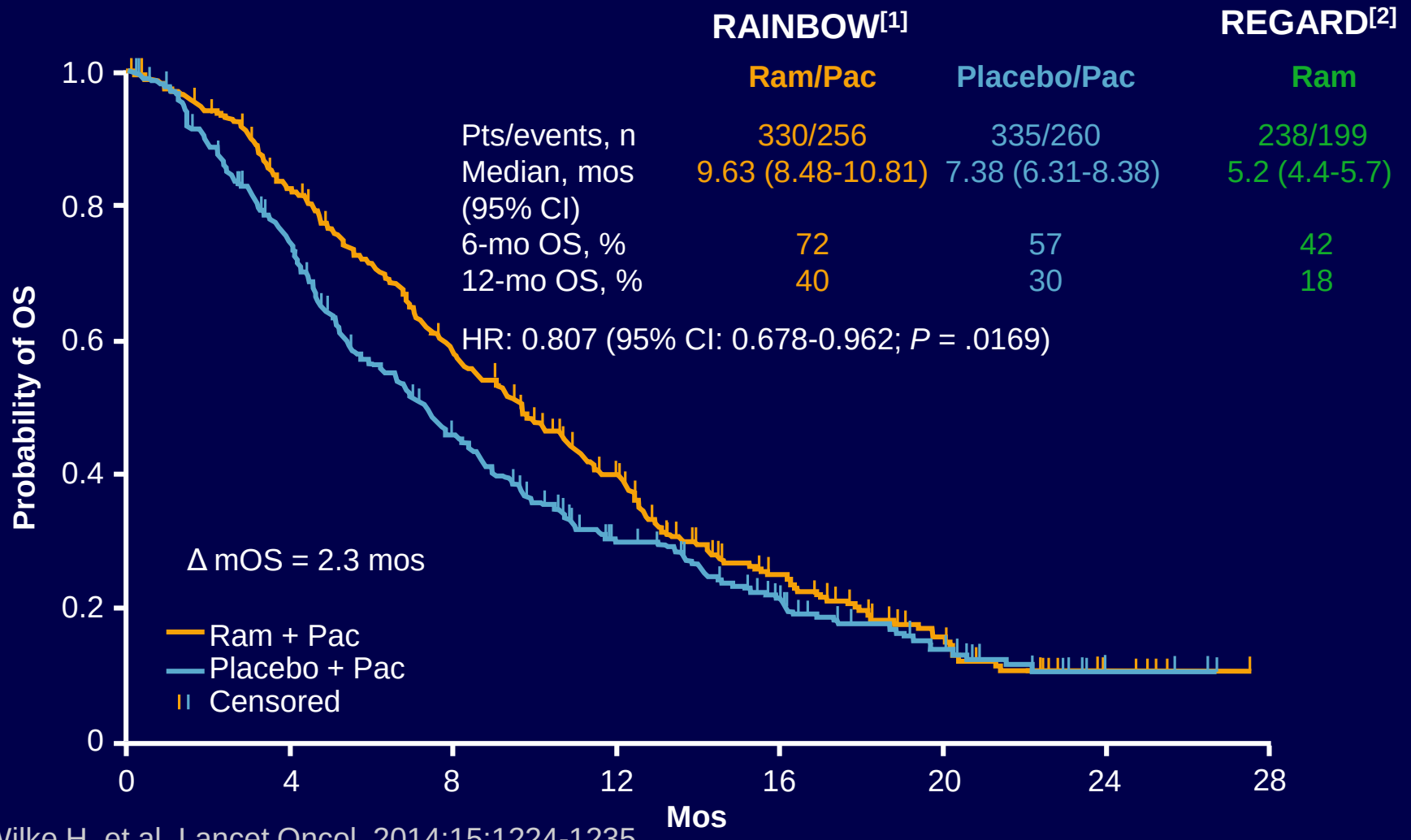


*Platinum agent plus fluoropyrimidine ± anthracycline.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, TTP

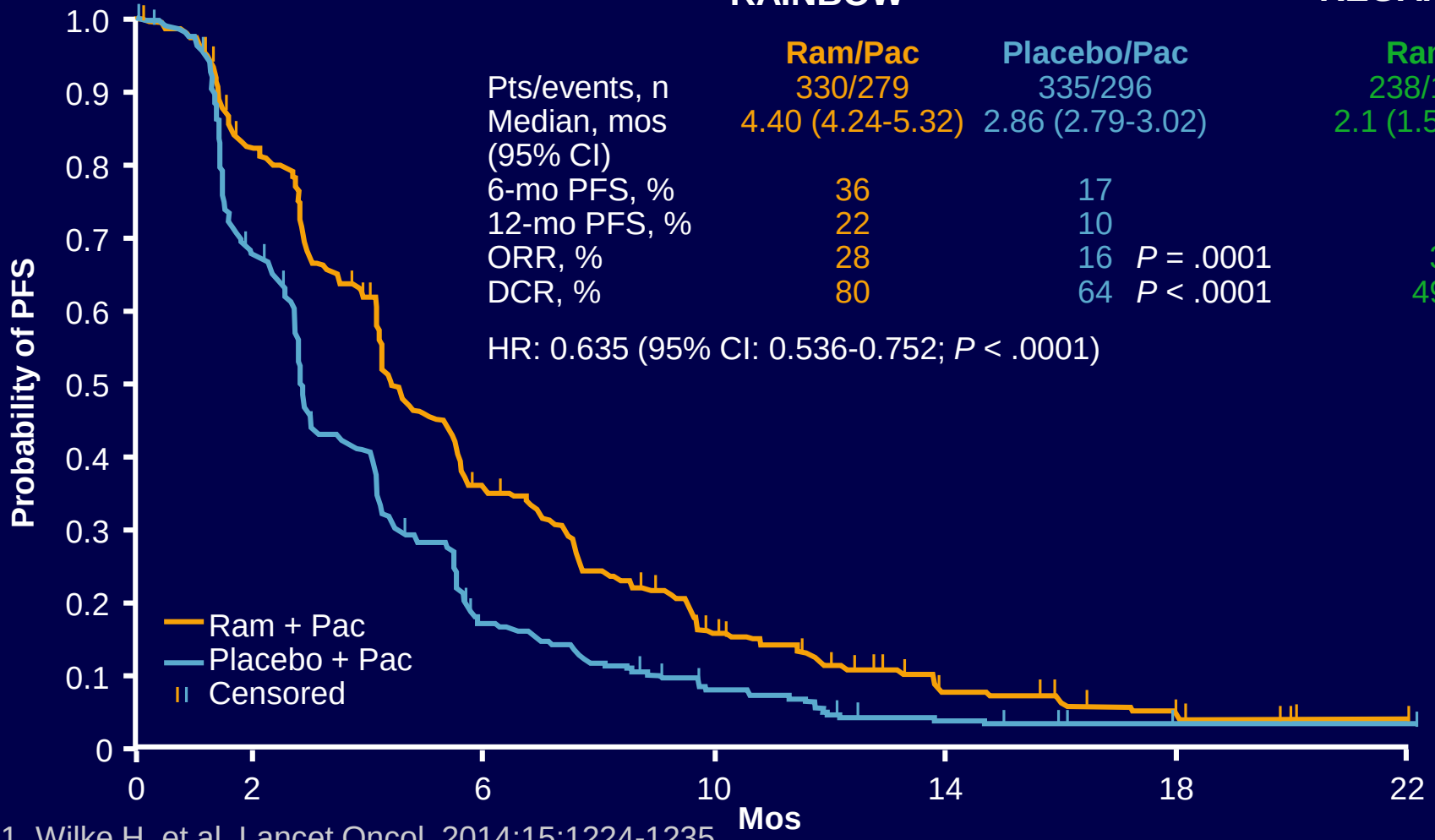
Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.

2nd-Line Ramucirumab in Advanced Gastric Cancer (RAINBOW): OS



1. Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.
2. Fuchs CS, et al. Lancet. 2014;383:31-39.

Second-line Ramucirumab in Adv Gastric Cancer (RAINBOW): PFS, Responses



1. Wilke H, et al. Lancet Oncol. 2014;15:1224-1235.
2. Fuchs CS, et al. Lancet. 2014;383:31-39.

Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial

Lancet Oncol 2013

Tom Waddell, Ian Chau, David Cunningham, David Gonzalez, Alicia Frances Clare Okines, Andrew Wotherspoon, Claire Saffery, Gary Middleton, Jonathan Wadsley, David Ferry, Wasat Mansoor, Tom Crosby, Fareeda Coxon, David Smith, Justin Waters, Timothy Iveson, Stephen Falk, Sarah Slater, Clare Peckitt, Yolanda Barbachano

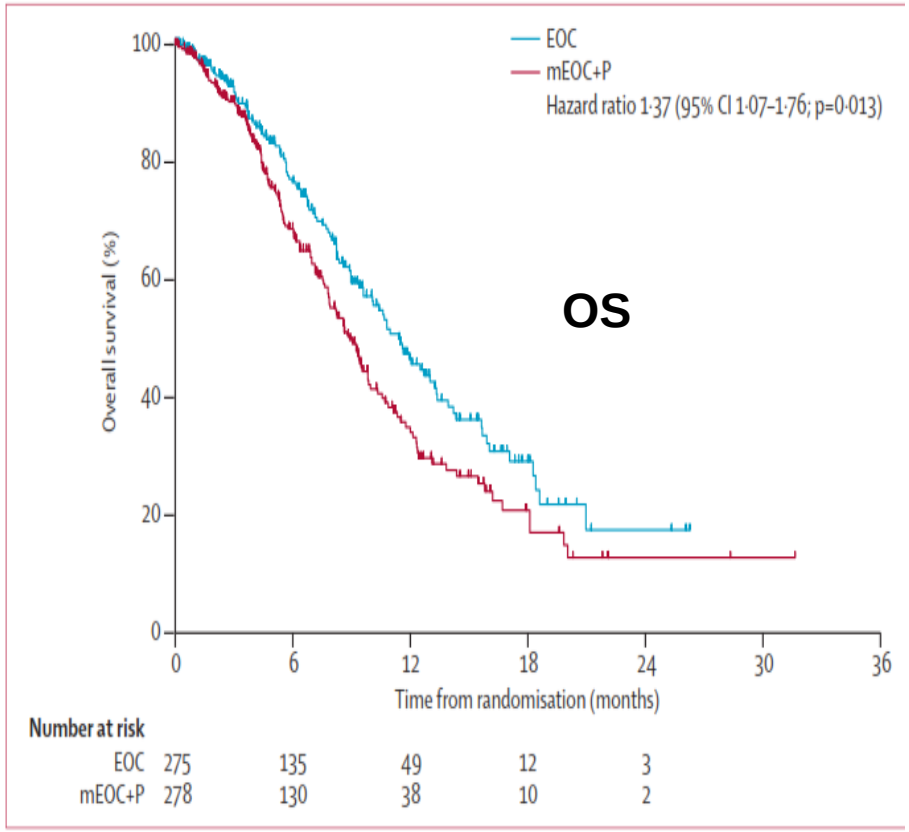


Figure 2: Overall survival in 553 patients in the intention-to-treat population, by treatment group

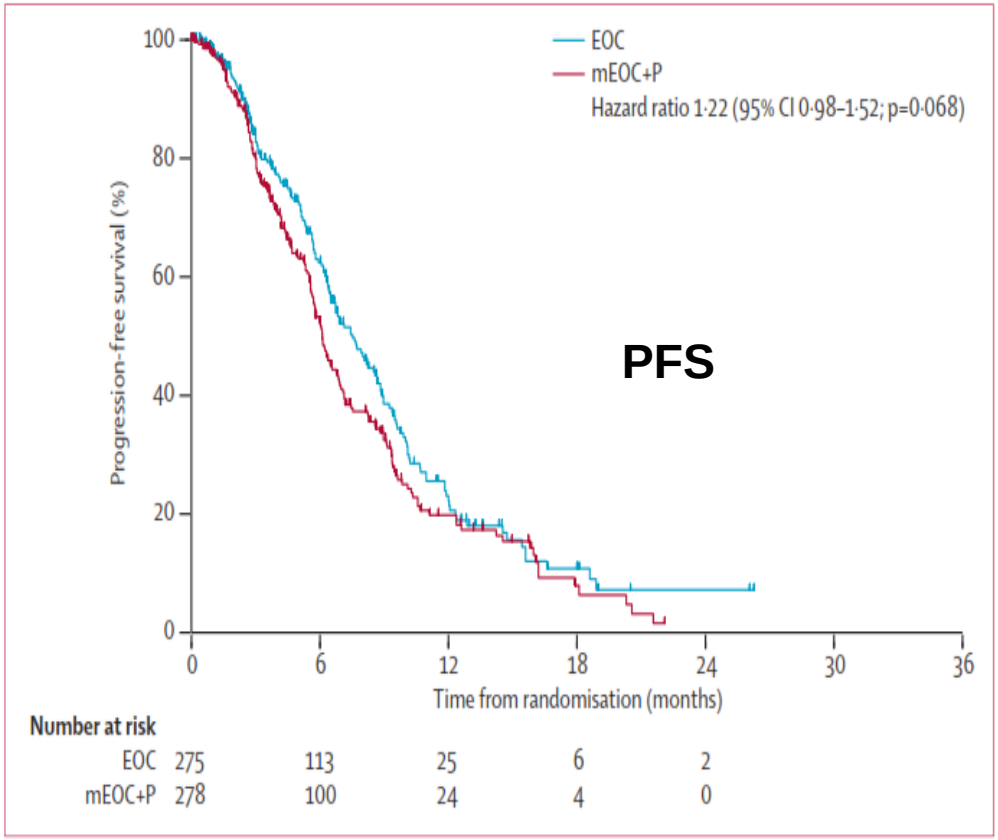
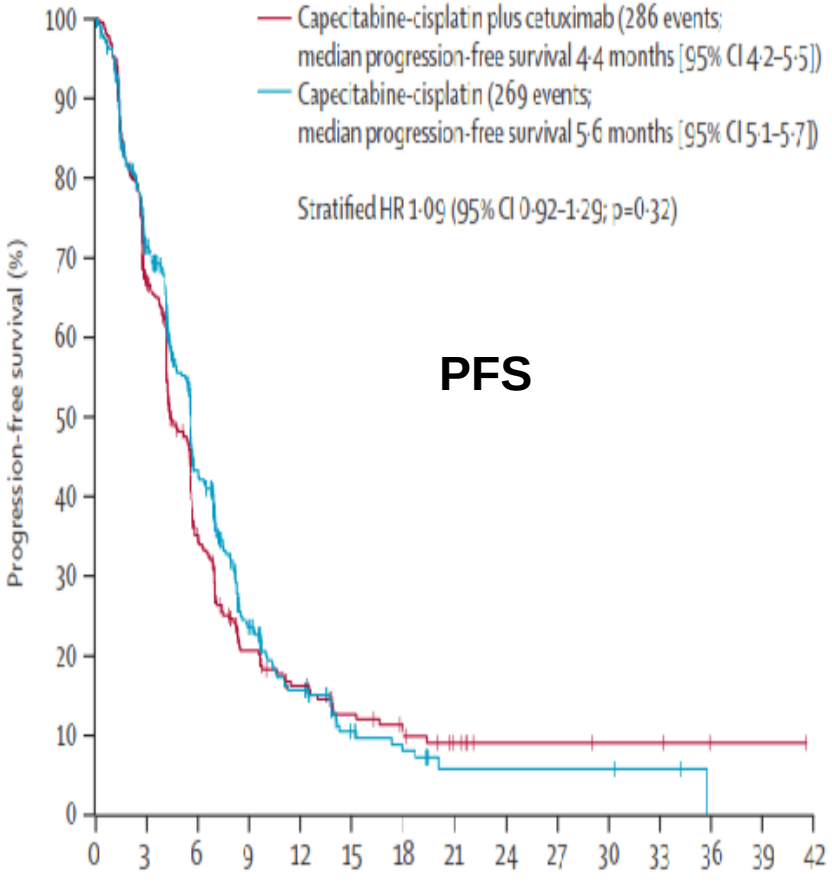


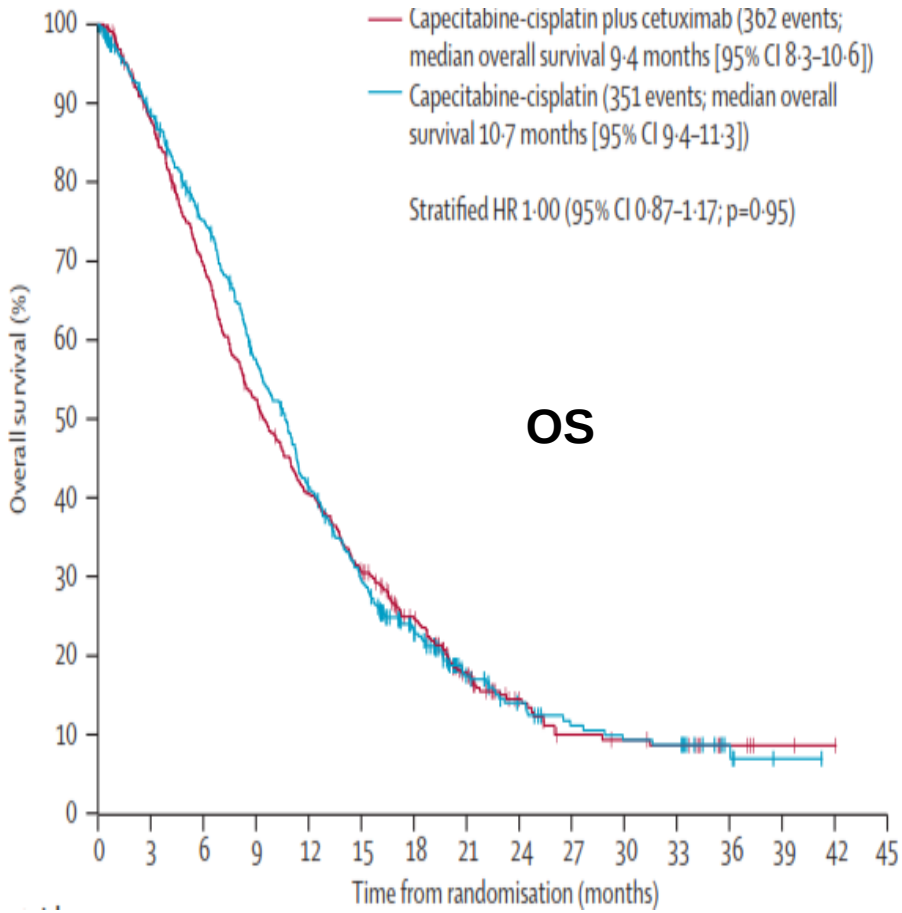
Figure 4: Progression-free survival in 553 patients in the intention-to-treat population, by treatment group

Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial

*Florian Lordick, Yoon-Koo Kang, Hyun-Cheol Chung, Pamela Salman, Sang Cheul Oh, György Bodoky, Galina Kurteva, Constantin Volovat, Vladimir M Moiseyenko, Vera Gorbunova, Joon Oh Park, Akira Sawaki, Ilhan Celik, Heiko Götte, Helena Melezínková, Markus Moehler, on behalf of the Arbeitsgemeinschaft Internistische Onkologie (AIO) and EXPAND Investigators**

Lancet Oncol 2013





Targeting cMET

MetGastric (FOLFOX ± ONARTUZUMAB) *Shah et al J Clin Oncol 2015*

Nessun impatto in OS, PFS, RR
Forse vantaggi in pz non asiatici

RILOMET (ECX ± RILOTUMUMAB) *Iveson et al Lancet Oncol 2014*
GEJ 20%

Vantaggio significativo in PFS, no vantaggi in OS ed aumento tossicità

In futuro ?

- **anti PDL-1: Pemprolizumab**
- **PARP inibitori: Olaparib + Taxani**

THANK YOU !

Ospedale Sacro Cuore-Don Calabria, Negrar (VR)
Presidio Ospedaliero Accreditato- Regione Veneto

Targeting EGFR pathway

Targeting HER 2: TRASTUZUMAB

TOGA trial: incremento significativo in OS, PFS, OR

GEJ 18%

Targeting EGFR:

CETUXIMAB (**EXPAND trial**): incremento n.s. in PFS, OS/OR sovrapponibili **GEJ 17%**

PANITUMUMAB (**REAL 3 trial**): decremento significativo in OS e PFS **GEJ 70**%

Doppia inibizione: LAPATINIB

TRIO 013-LOGiC trial: incremento n.s. in OS, vantaggio in PFS, OR

Vantaggio significativo in OS nei pz asiatici ed età < 60 anni

GEJ 12%

Targeting VEGF

AVAGAST: CDDP + Capecitabine ± BEVACIZUMAB

GEJ 14 %

incremento n.s. in OS, incremento significativo in PFS, OR
incremento significativo in OS nei pz non asiatici con alto VEGF-A e bassa NLP1

REGARD (RAMUCIRUMAB vs BSC) **GEJ 25%**
RAINBOW (Paclitaxel ± RAMUCIRUMAB) **GEJ 21%**

Vantaggio significativo in OS, PFS, (OR in RAINBOW)

FOLFOX ± RAMUCIRUMAB **GEJ 75%**

168 pz trattati in 1 linea (esofago 47% - GEJ 29%)
No vantaggi in PFS e OS
circa 45% carcinoma esofageo

APATINIB (Doppia inibizione: TKI + VEGF2)

267 pz trattati > II^{a} linea **GEJ 22%**
incremento significativo in OS e PFS
267 pz asiatici con 35% > 2 linee di CT

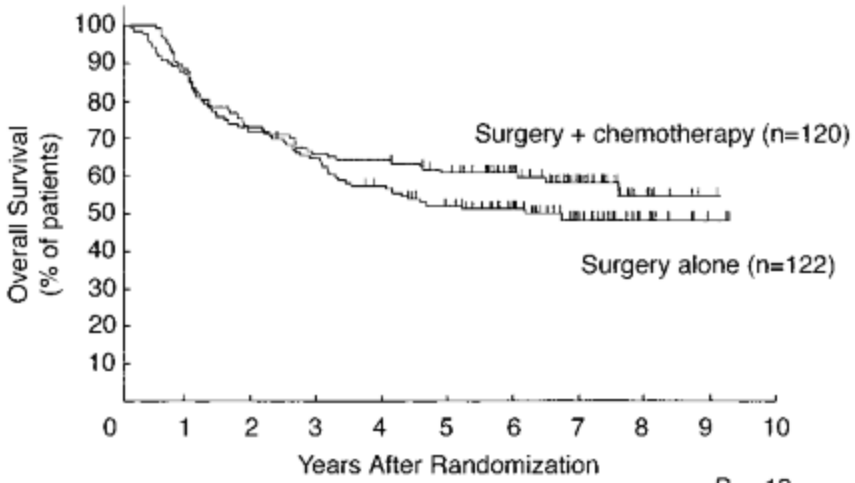
Radioterapia

Poche esperienze riferite agli anni ‘90

Dati riferiti al solo istotipo squamoso, no dati su Adenocarcinoma

Riduzione delle recidive locali e linfonodali ma senza aumento della sopravvivenza

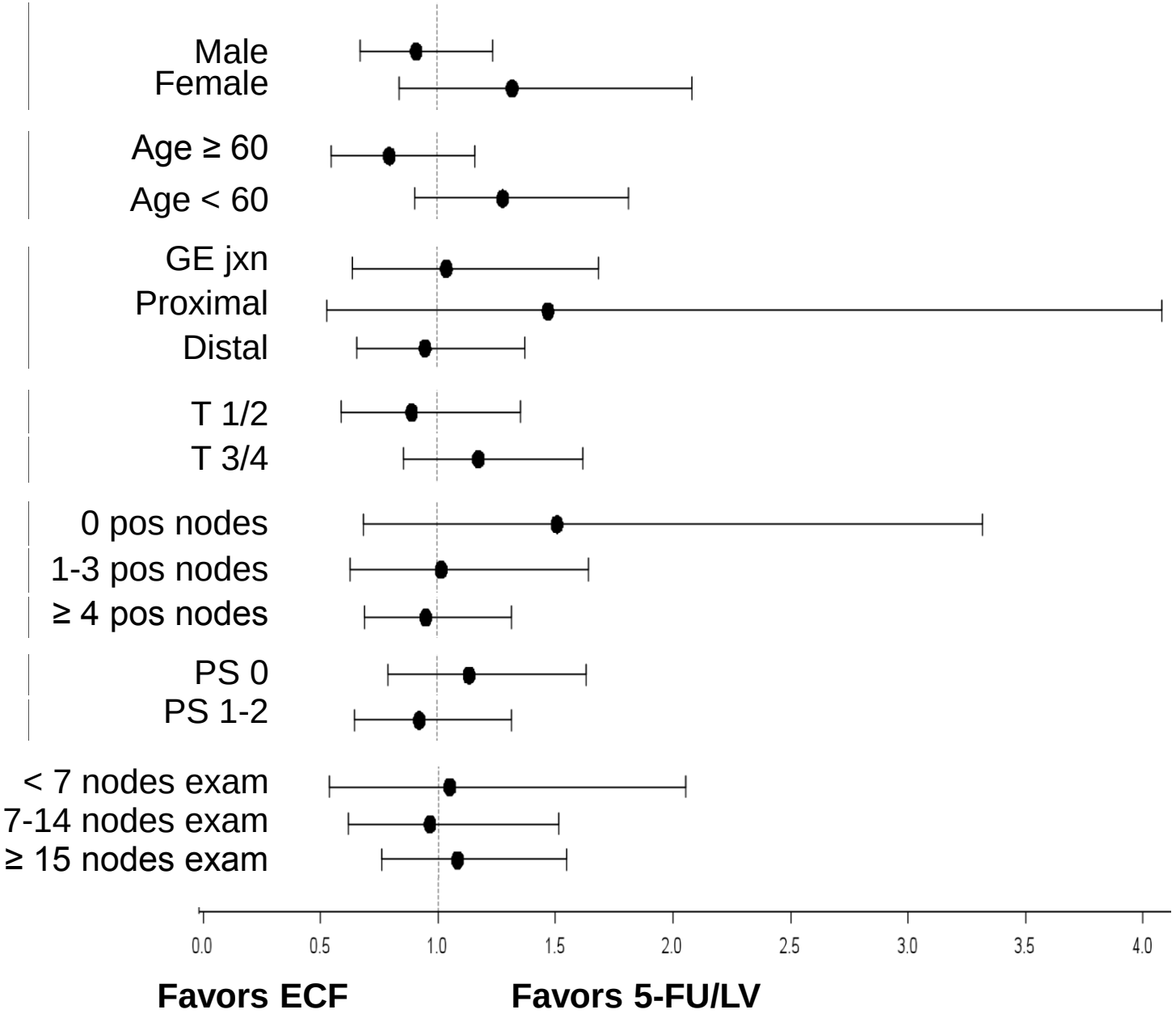
Autori	fase	Ad/Sq (n°)	trattamento	OS (CH vs RT)	altro
Xiao 2003	III	0/100 (495)	60 Gy ln sovracl. bilaterali mediastino	**5 aa 13% vs35%**	Riduzione recidive No analisi ITT
Teniere 1991	III	0/100 (221)	45-55 Gy ln sovracl. Bilat. + mediastino + ln celiaci	5 aa 19% vs 19%	Riduzione recidive per N+
Fok 1993	III	(130) R0/R1/R2	49 Gy(R0) e 52Gy (R2)/3.5 Gy 5 cm dal margine	**15.2 % vs 8.7% Detrimentale**	Ridotte recidive **per R1 R2**
Scheriber 2010	SEER	66/34 (1046)	Non noto	**3 aa 18% vs 29% Per stadi III**	No beneficio per stadi II
Chen 2009	Retrosp	0/366 (366)	Non noto	**Non nota**	**Riduzione recidive per RT**



No. at Risk									
Surgery + chemotherapy	120	105	86	79	77	70	52	30	10
Surgery alone	122	108	89	78	67	57	43	24	9

Fig 3. Overall survival curves of all registered patients. The 5-year overall survival was 52% in patients with surgery alone and 61% in patients with surgery plus chemotherapy ($P = .13$).

HRs (95% CI) for Mortality According to Baseline Characteristics

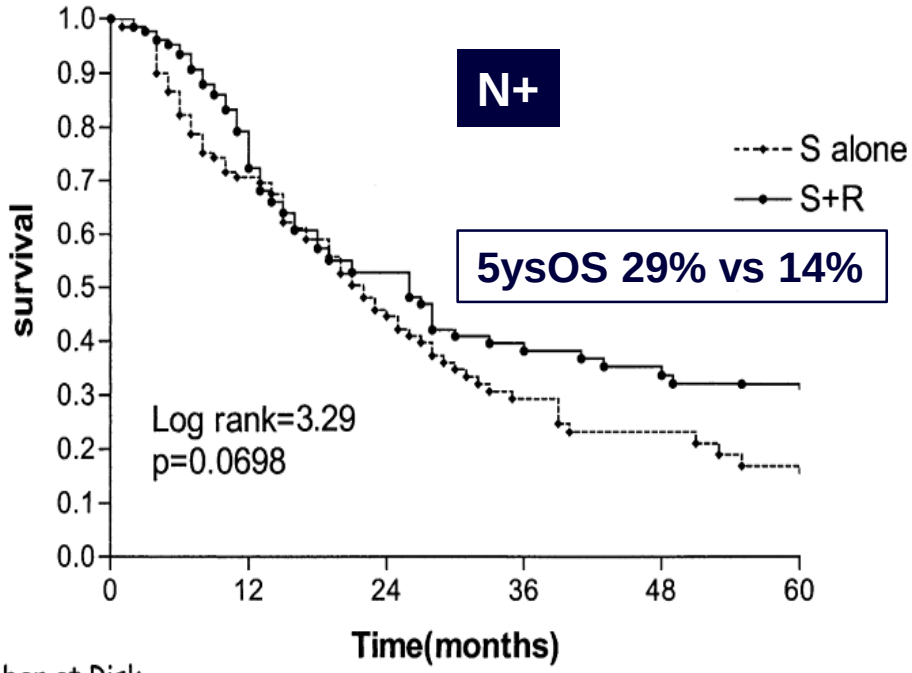


Value of Radiotherapy After Radical Surgery for Esophageal Carcinoma: A Report of 495 Patients

Ze Fen Xiao, MD, Zong Yi Yang, MD,* Jun Liang, MD, Yan Jun Miao, MD, Mei Wang, MD, Wei Bo Yin, MD, Xian Zhi Gu, MD, De Chao Zhang, MD, Ru Gang Zhang, MD, and Liang Jun Wang, MD

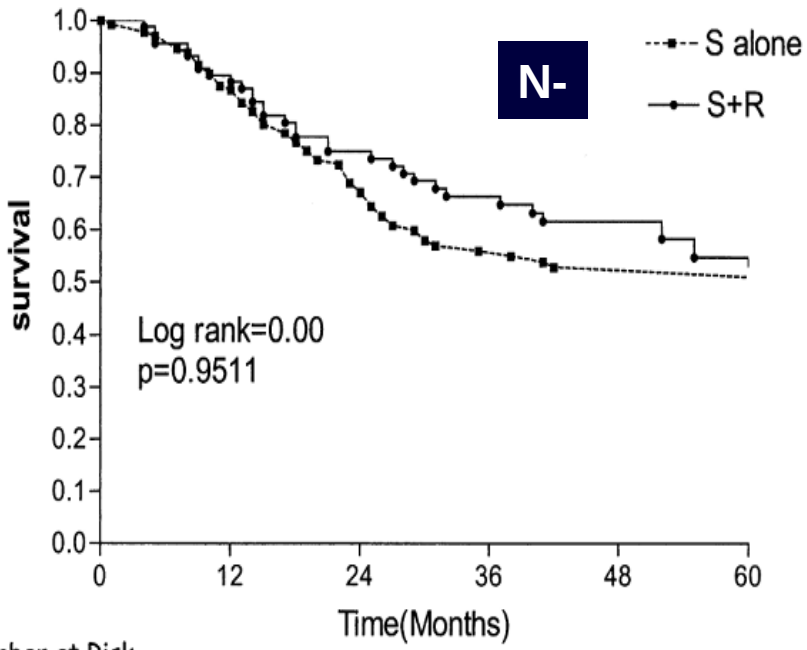
Departments of Radiation Oncology and Thoracic Surgical Oncology, Cancer Institute (Hospital), Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China

Ann Thorac Surg 2003



Number at Risk

S alone	132	68	38	16	10	7
S+R	129	73	45	28	21	10



Number at Risk

S alone	143	107	76	54	28	28
S+R	91	70	53	41	34	28

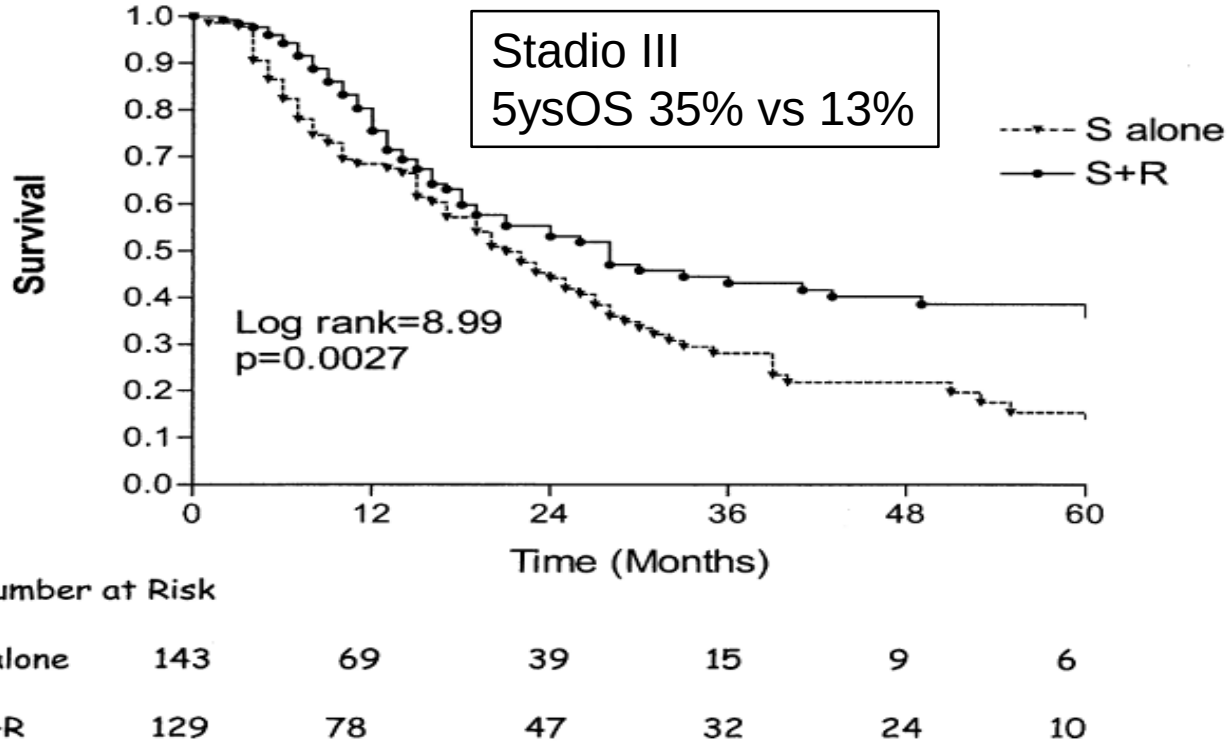


Table 2. Cause of Failure as Related to Treatment

	S (n = 243)		S+R (n = 191)			
	n	%	n	%	χ^2	*p*
Intrathoracic lymph node metastasis	63	25.0	31	16.2	5.925	0.015
Anastomotic recurrence	14	5.8	1	0.5	8.793	0.003
Supraclavicular lymph node metastasis	38	13.2	6	3.1	13.439	0.000
Intraabdominal metastasis	24	9.9	14	7.3	0.868	0.351
Hematogenous metastasis	44	18.1	45	23.6	1.951	0.162

S = surgery alone; S+R = surgery plus radiotherapy.

Cisplatin or Carboplatin?

- No direct comparison of carboplatin- vs. cisplatin-based CRT
- Retrospective analyses suggest cisplatin-based regimens may be more active against distant micrometastatic disease than carboplatin/paclitaxel
- A single institution review of 71 patients demonstrated no difference in operative complications between cisplatin/5-FU/RT and carboplatin/paclitaxel/RT
  - median time to recurrence 31 months for cisplatin-based therapy vs. 18 months for carboplatin-based regimen[1]

Thomay et al. J Clin Oncol. 2014;32 (suppl 3; abstr 126).

PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Presented By Barbara Burtness at 2014 ASCO Annual Meeting

CALGB 80101 and INT 0116
Overall Survival by Treatment

	CALGB 80101		**INT 0116**	
	5-FU/LV	ECF	5-FU/RT	Control
Median OS (mos)	37	38	36	27

Phase III LOGiC: CapeOx ± Lapatinib in HER2+ Advanced Gastric Cancer

Stratified by prior neo/adjuvant therapy, region (Asia vs North America vs rest of the world)

Pts with HER2-amplified locally advanced, unresectable, or metastatic gastric, esophageal, or GEJ cancer
(N = 545)
GEJ 12%

CapeOx* + **Lapatinib** 1250 mg QD
21-day cycles

CapeOx* + Placebo

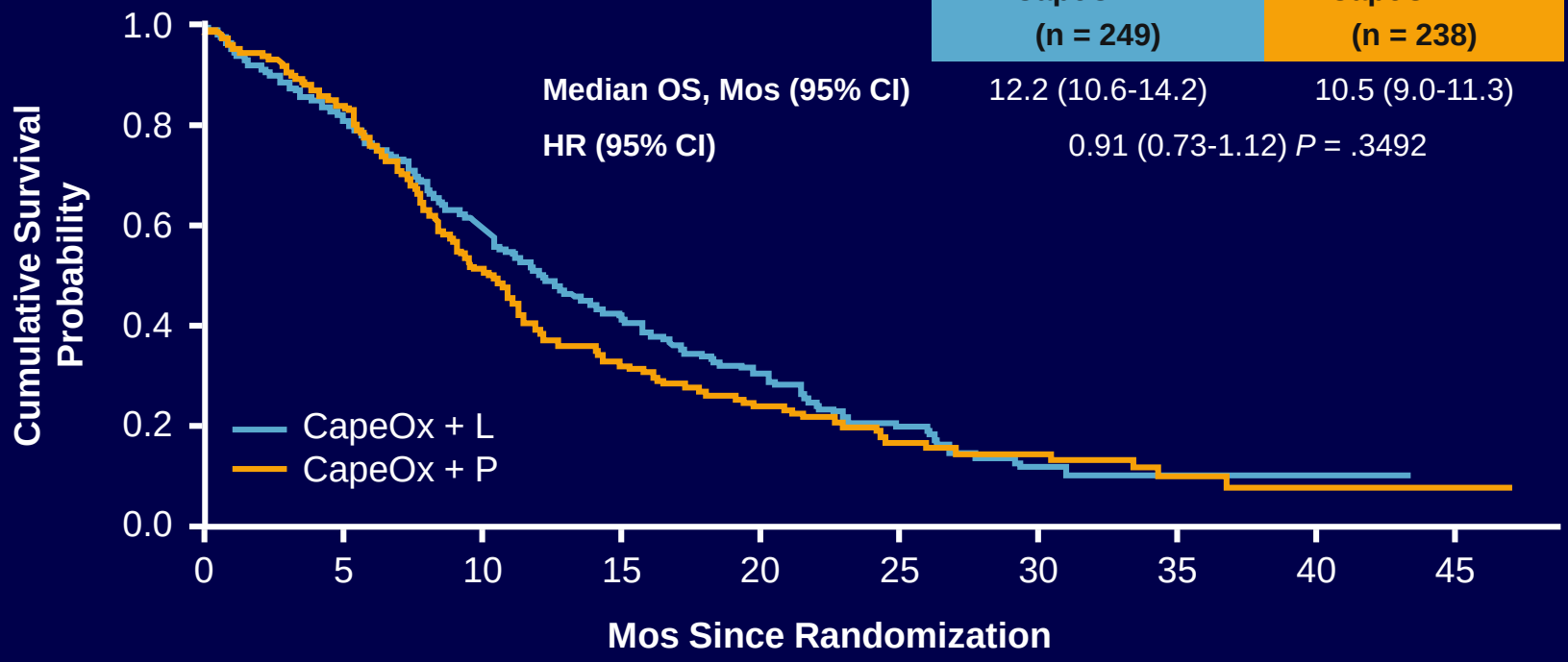
*Day 1: oxaliplatin 130 mg/m^2, Days 2-14: capecitabine 850 mg/m^2 BID.

- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, DoR, CBR, safety/toxicity, QoL, molecular and pharmacogenetics analyses

Hecht J, et al. J Clin Oncol. 2015

CapeOx ± Lapatinib in HER2+ Advanced Gastric Cancer (LOGiC): OS

	CapeOx + L (n = 249)	CapeOx + P (n = 238)
Median OS, Mos (95% CI)	12.2 (10.6-14.2)	10.5 (9.0-11.3)
HR (95% CI)	0.91 (0.73-1.12) *P* = .3492	



Pts at Risk, n

CapeOx + L	249	199	133	83	47	24	9	3	3
CapeOx + P	238	189	106	53	34	17	11	7	2	2

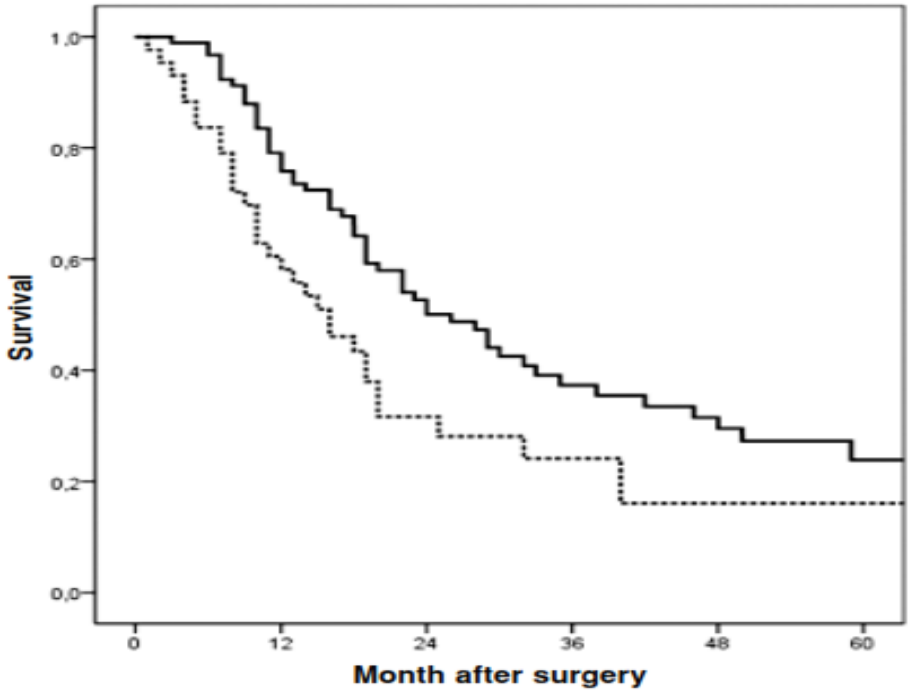
ITT analysis HR: 0.91

Hecht J, et al. J Clin Oncol. 2015

Scandinavian Journal of Surgery 101: 26–31, 2012

SURVIVAL AFTER ADJUVANT CHEMORADIOTHERAPY OR SURGERY ALONE IN RESECTABLE ADENOCARCINOMA AT THE GASTRO-ESOPHAGEAL JUNCTION

S. C. Kofoed[1], A. Muhic[2], L. Baeksgaard[2], M. Jendresen[1], J. Gustafsen[1], J. Holm[1], L. Bardram[1], B. Brandt[3], J. Brenø[3], L. B. Svendsen[3]



Number at risk

Month after surgery	*0*	*12*	*24*	*36*	*48*	*60*
Surgery + adjuvant therapy	91	67	38	20	15	4
Surgery alone	43	25	9	6	4	3

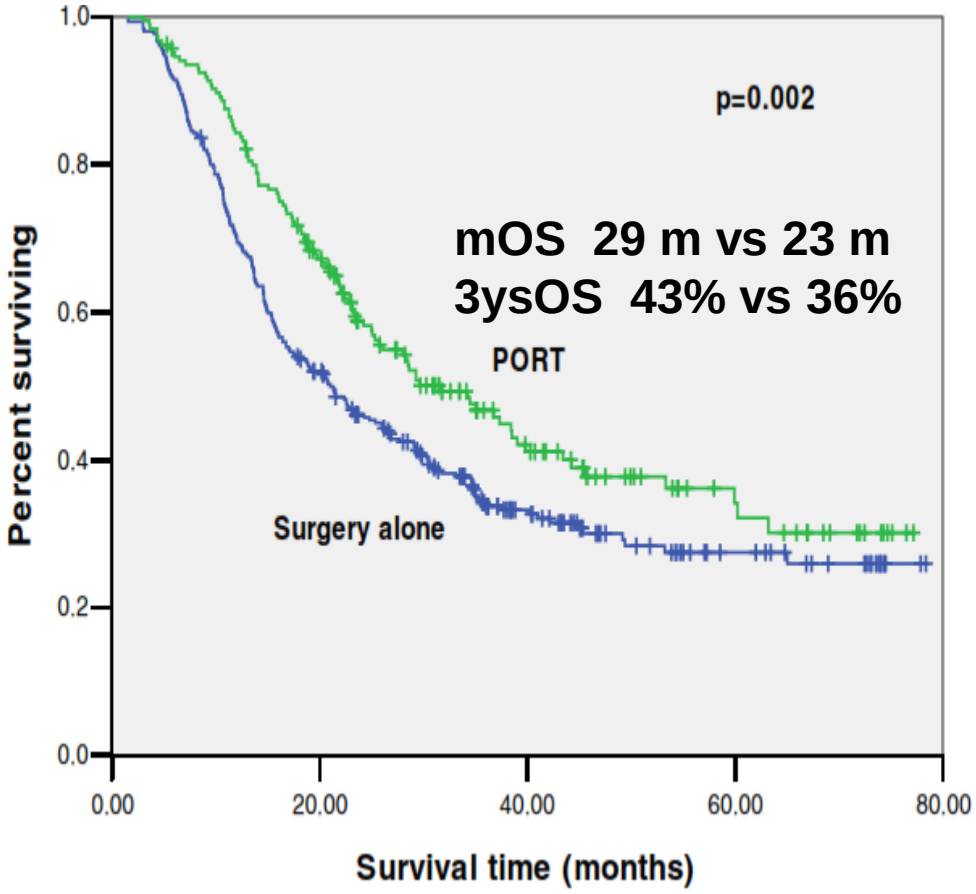
mOS 16 mos vs 26 mos

p 0.014

Prognostic impact of postoperative radiation in patients undergoing radical esophagectomy for pathologic lymph node positive esophageal cancer

Rad Oncol 2013

Yaping Xu[1†], Jinshi Liu[2†], Xianghui Du[1†], Xiaojiang Sun[1], Yuanda Zheng[1], Jianxiang Chen[1], Bo Li[2], Wei Liu[2], Hao Jiang[1] and Weimin Mao[2*]



Studio retrospettivo su 725 pz (2001/09)
- 476 pz solo Chirurgia
- 258 Chirurgia + Radioterapia
- 167/258 Chirurgia + RT + CHT

Alla analisi multivariata vantaggio significativo nei pz:
-T3/T4
-N2/N3
Non significativo
- aggiunta di CT alla RT
- età
- grading

NHMRC Clinical Trials Centre

INTEGRATE
GI CANCER CLINICAL TRIAL

AGITG
AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

INTEGRATE: A randomized, phase II, double-blind, placebo-controlled study of regorafenib in refractory advanced oesophagogastric cancer (AOGC): A study by the Australasian Gastrointestinal Trials Group (AGITG) Final overall and subgroup results

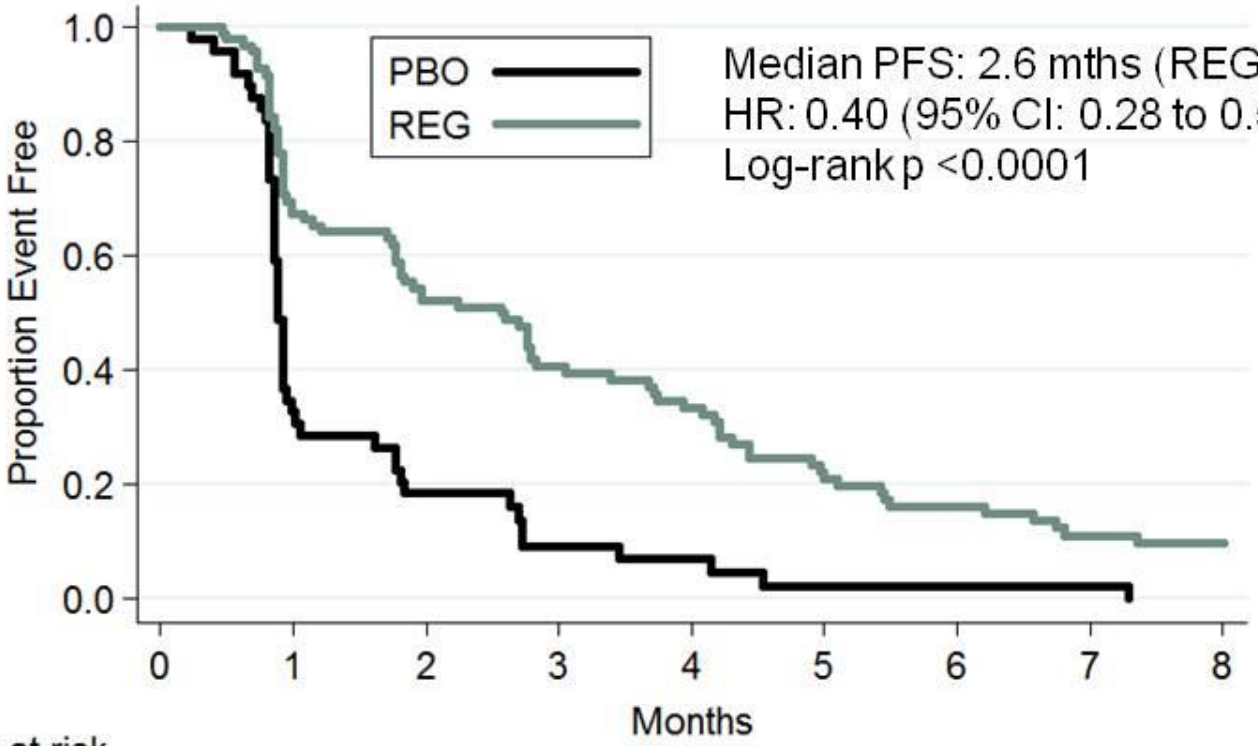
Pavlakis N*, Sjoquist KM*, Tsobanis E, Martin A, Kang YK, Bang YJ, O'Callaghan CJ, Tebbutt NC, Rha SY, Lee J, Cho JY, Lipton L, Burnell M, Alcindor T, Strickland AH, Kim JW, Yip S, Simes J, Zalcberg J, Goldstein D*.

ANZCTR 12612000239864

PRESENTED AT: ASCO Annual '15 Meeting

Baseline Characteristic	Regorafenib (N=97)	Placebo (N=50)
Female	19 (20%)	10 (20%)
Primary site		
Oesophago-gastric junction	37 (38%)	19 (38%)
Stomach - diffuse	5 (5%)	3 (6%)
Stomach - distal	22 (23%)	14 (28%)
Stomach - NOS	11 (11%)	8 (16%)
Stomach - proximal	16 (17%)	6 (12%)
Other	6 (6%)	0 (0%)
Prior Lines of therapy for advanced disease		
1	41 (42%)	21 (42%)
2	56 (58%)	29 (58%)
ECOG Performance		
0	42 (43%)	20 (40%)
1	55 (57%)	30 (60%)
Region		
ANZ/Canada	62 (64%)	31 (62%)
Korea	35 (36%)	19 (38%)

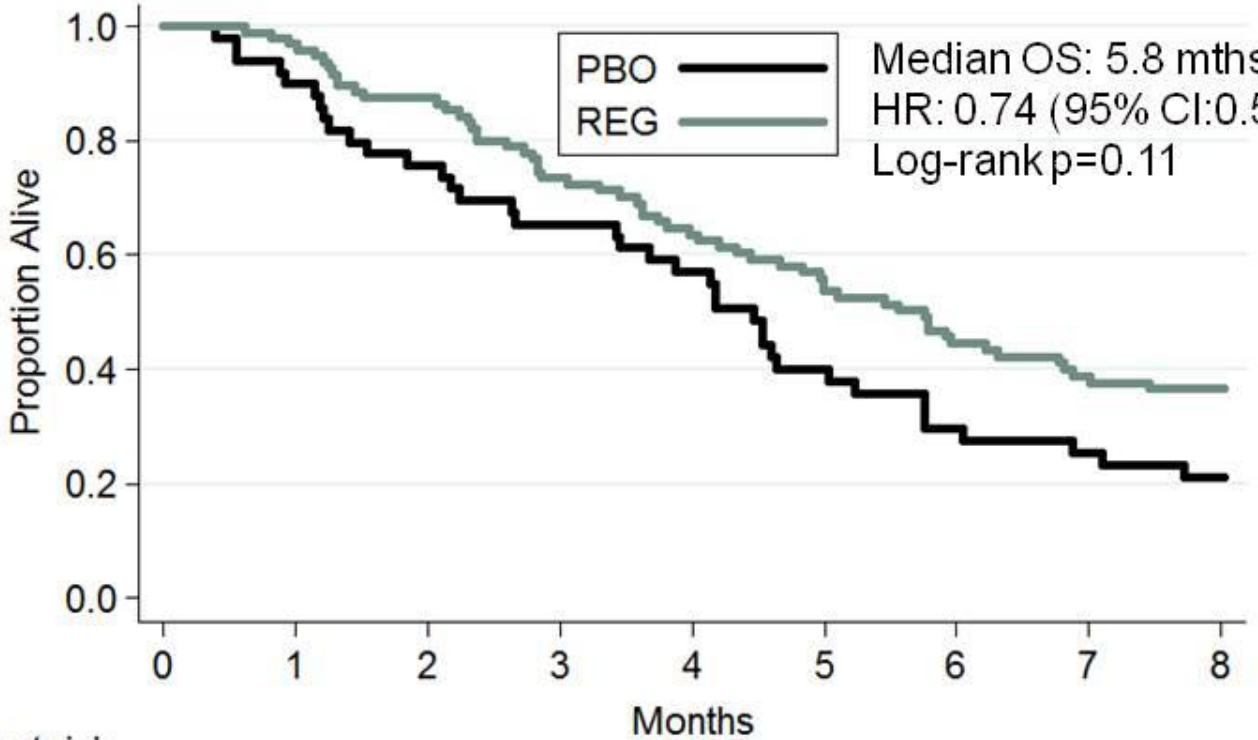
Primary endpoint: Progression-Free Survival (PFS)



Number at risk

PBO	50	16	9	4	3	1	1	1	0
REG	97	63	48	34	27	17	13	9	8

Secondary endpoint: Overall Survival (OS)



Number at risk

PBO	50	44	37	31	27	19	14	12	10
REG	97	93	83	67	58	48	39	34	32

PRESENTED AT: ASCO Annual '15 Meeting

Carcinoma squamocellulare

Chemioterapia + Radioterapia consigliata se interventi R1/R2 e non eseguito trattamento pre-operatorio

Se già eseguito trattamento pre-operatorio nei pz in R1 può essere proposto follow up

AdenoCarcinoma

Chemioterapia + Radioterapia consigliata nei pz T3/T4 e T1/T2 se N+
Consigliata anche in T2N0 se G3, LVI, PNI, età < 50 anni)

Consigliata se interventi R1/R2

Nei pz T3/T4 N0 può esser proposto follow up

se il pz ha eseguito una CT preoperatoria questa va proposta anche se N0 e chirurgia R0

Surgery Plus Chemotherapy Compared With Surgery Alone for Localized Squamous Cell Carcinoma of the Thoracic Esophagus: A Japan Clinical Oncology Group Study—JCOG9204

By Nobutoshi Ando, Toshifumi Iizuka, Hiroko Ide, Kaoru Ishida, Masayuki Shinoda, Tadashi Nishimaki, Wataru Takiyama, Hiroshi Watanabe, Kaichi Isono, Norio Aoyama, Hiroyasu Makuuchi, Otsuo Tanaka, Hideaki Yamana, Shunji Ikeuchi, Toshiyuki Kabuto, Kagami Nagai, Yutaka Shimada, Yoshihide Kinjo, and Haruhiko Fukuda

J Clin Oncol 2003

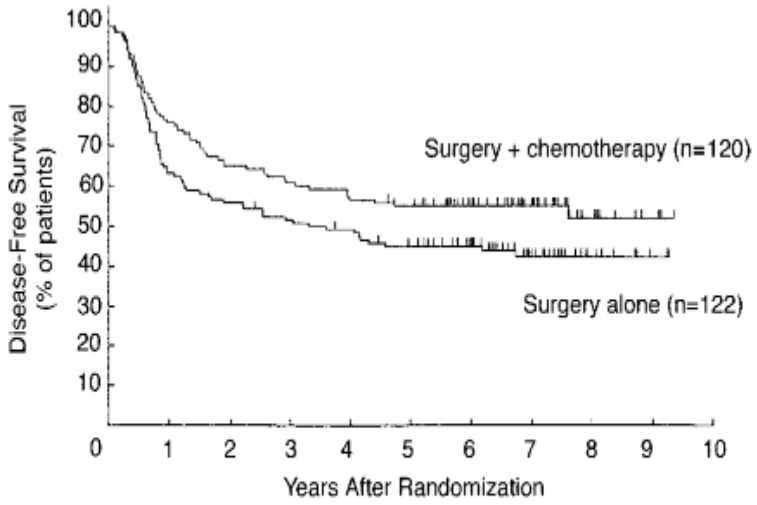


Fig 1. Disease-free survival curves of all registered patients. The 5-year disease-free survival was 45% in patients with surgery alone and 55% in patients with surgery plus chemotherapy ($P = .037$).

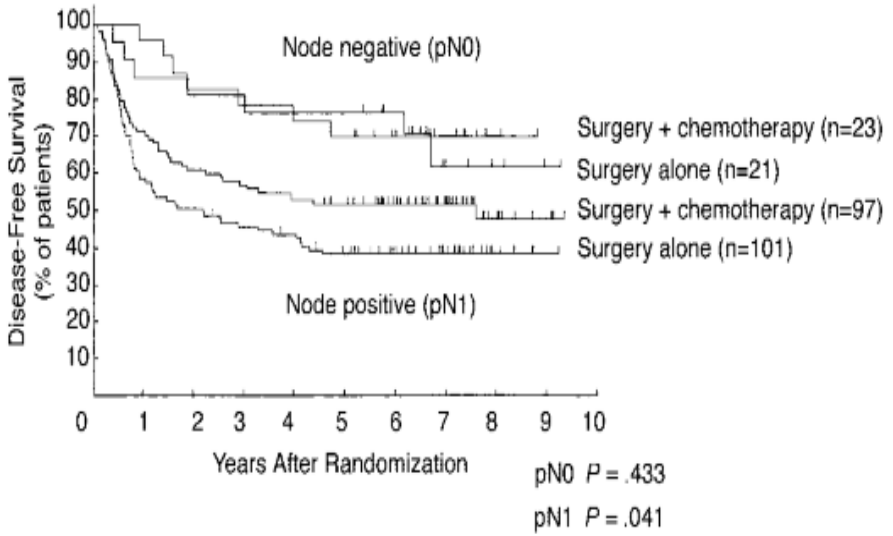


Fig 2. In the pN0 subgroup, the 5-year disease-free survival was 76% in surgery-alone group and 70% in surgery plus chemotherapy group ($P = .433$). In the pN1 subgroup, it was 38% in surgery-alone and 52% in surgery plus chemotherapy ($P = .041$).

Journal of Surgical Oncology 2014;110:864–868

Adjuvant Chemotherapy After Esophagectomy: Is There a Role in the Treatment of the Lymph Node Positive Thoracic Esophageal Squamous Cell Carcinoma?

XIAO LYU, MD,[1] JING HUANG, MD,[1]* YOUSHENG MAO, MD,[2] YUTAO LIU, MD,[1] QINFU FENG, MD,[3] KANG SHAO, MD,[2] SHUGENG GAO, MD,[2] YONG JIANG, MPH,[4] JINWAN WANG, MD,[1] AND JIE HE, MD[2]

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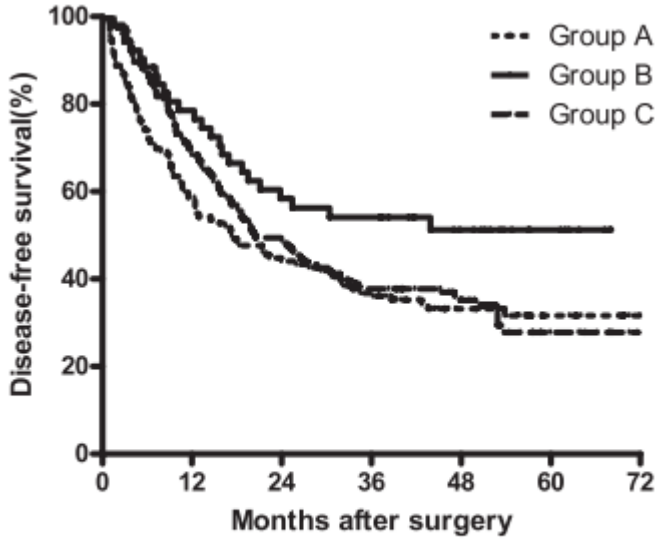
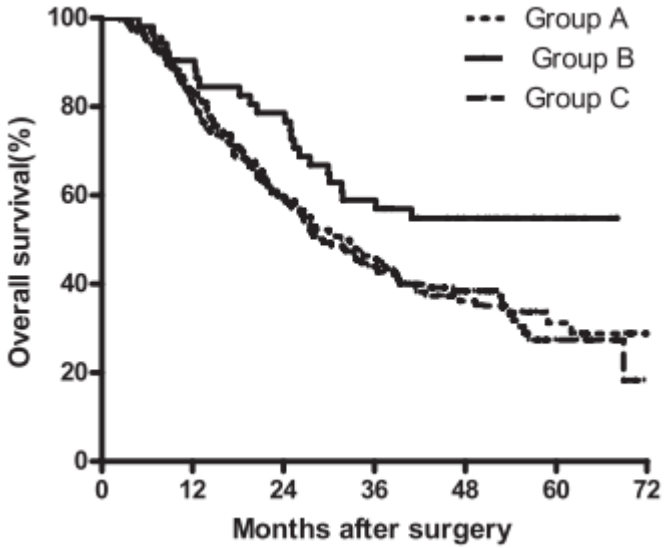




Analisi retrospettiva su 349 pz N+ sottoposti a chirurgia con CSC
A) Chirurgia 143 pts B) chemioterapia 52 pts C) RT 154 pts

- 3ys OS: A) 47.7% B) 59% C: 44

Analisi multivariata significativa per chemioterapia adiuvante e pz N2/N3

Ann Surg Oncol 2012

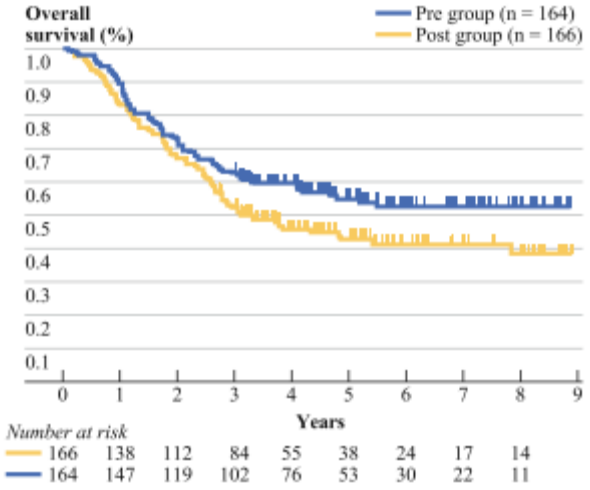
A Randomized Trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-Fluorouracil Versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of the Thoracic Esophagus (JCOG9907)

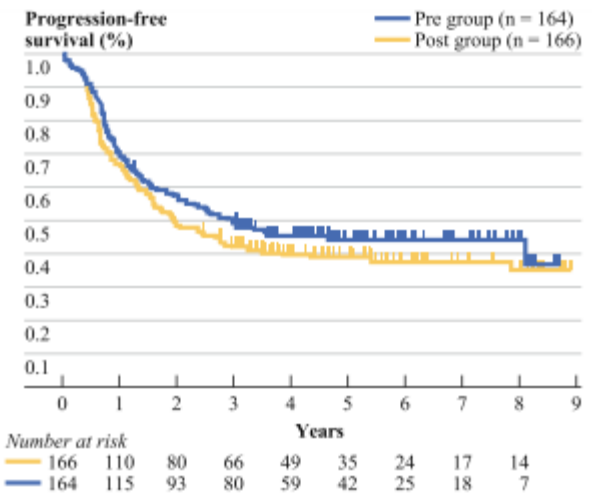
Nobutoshi Ando, MD, FACS[1], Hoichi Kato, MD[2], Hiroyasu Igaki, MD[2], Masayuki Shinoda, MD[3], Soji Ozawa, MD, FACS[4], Hideaki Shimizu, MD[5], Tsutomu Nakamura, MD[6], Hiroshi Yabusaki, MD[7], Norio Aoyama, MD[8], Akira Kurita, MD[9], Kenichiro Ikeda, MD[10], Tatsuo Kanda, MD[11], Toshimasa Tsujinaka, MD[12], Kenichi Nakamura, MD[13], and Haruhiko Fukuda, MD[13]

330 pts
carcinoma squamocellulare
Stadio II/III (escluso T4)

Chirurgia seguita da CDDP+FU x 2

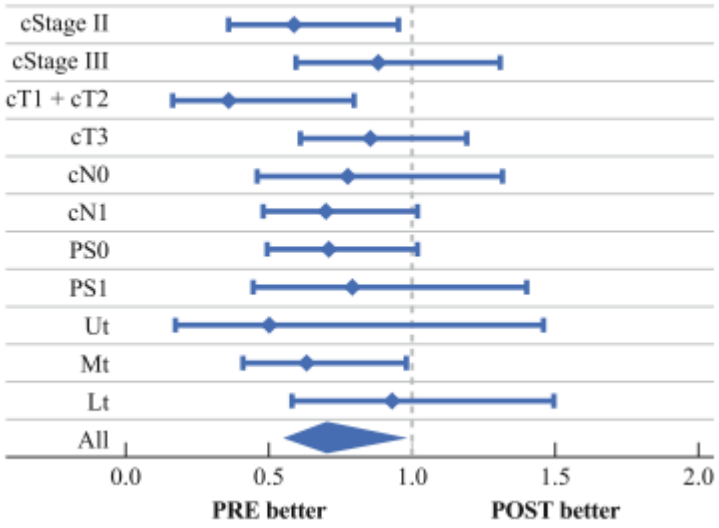
CDDP+FU x 2 seguita da Chirurgia





5 ys PFS: 39% vs 44% p 0.22

5 ys OS: 43% vs 55% p 0.04



Radioterapia

Poche esperienze con studi prospettici riferite agli anni ’90

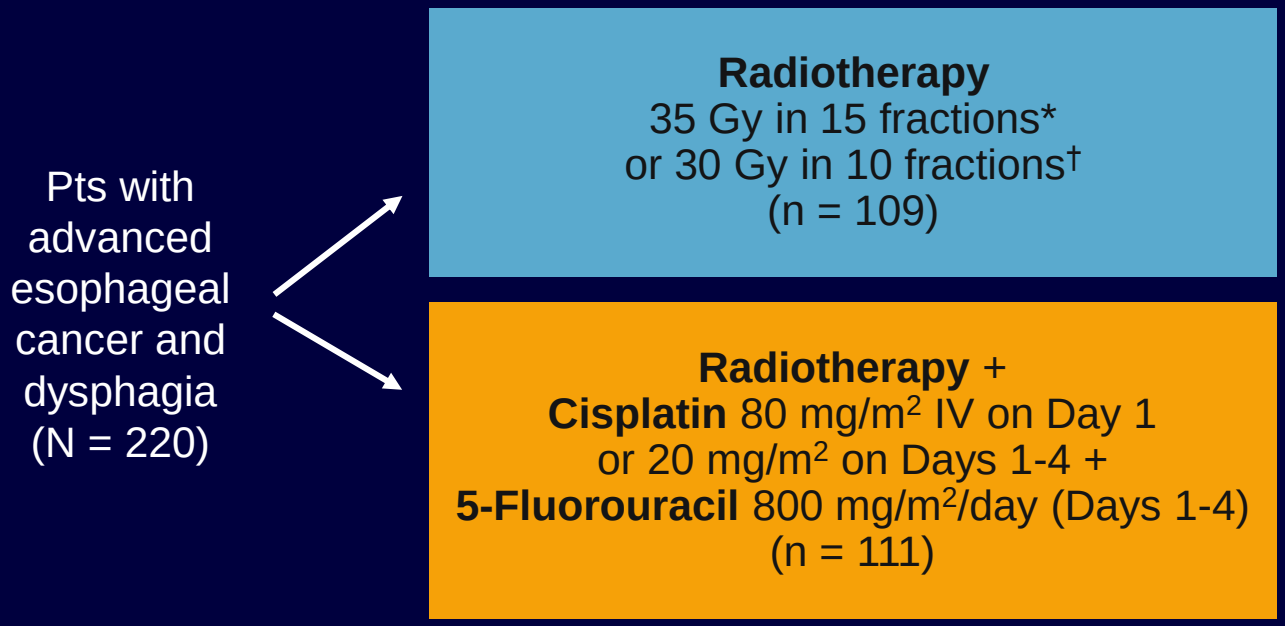
Dati a favore retrospettivi e ricavati da casistiche eterogenee con prevalenza di istotipo squamoso

No dati su Adenocarcinoma

Riduzione delle recidive locali ma senza significativo aumento della sopravvivenza tranne in alcune analisi retrospettive per specifici sottogruppi

Qualità dell’evidenza SIGN	Raccomandazione	Forza della raccomandazione clinica
D	I pazienti sottoposti a intervento di esofagectomia per carcinoma squamoso dell’esofago non dovrebbero essere sottoposti a trattamento radioterapico adiuvante. La radioterapia adiuvante potrebbe essere presa in considerazione solo in casi selezionati e nelle forme ad alto rischio di ricaduta locale. (194)	**Negativa debole**

Phase III Study: RT ± Cisplatin/5-FU for Dysphagia in Adv Esophageal Cancer



*Australia and New Zealand.
†Canada and United Kingdom.

- Primary endpoint: relief of dysphagia at Wks 9-13

Penniment MG, et al. ASCO GI 2015. Abstract 06.

RT ± Cisplatin/5-FU in Adv Esophageal Cancer (Phase III): Results & Conclusions

Response, %	RT (n = 109)	RT + Cisplatin/ 5-FU (n = 111)	*P* Value
Pts achieving response	68	74	.34
Maintained response at Wk 13	42	47	.43

- RT alone remains the standard of care for palliation of dysphagia in pts with esophageal cancer

- No difference in dysphagia, PFS, OS, quality of life between treatment arms
- Median survival
  - RT: 203 days
  - RT + cisplatin/5-FU: 210 days
- Significantly increased toxicity with RT + cisplatin/ 5-FU including nausea ($P < .01$) and vomiting ($P < .01$)

Penniment MG, et al. ASCO GI 2015. Abstract 06.