

QUIMIOTERAPIA NEODYUVANTE EN LOS TUMORES DE CARDIAS

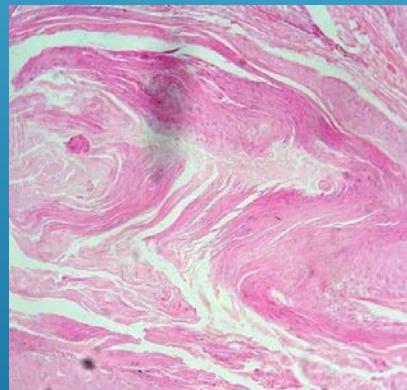
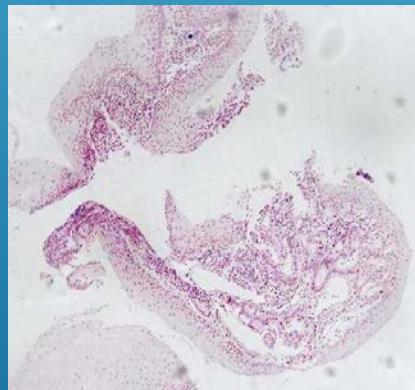
Dr. Carlos Garzón Hernández

Centro de Oncología **IM** Oncology Arturo Soria

20/11/2015

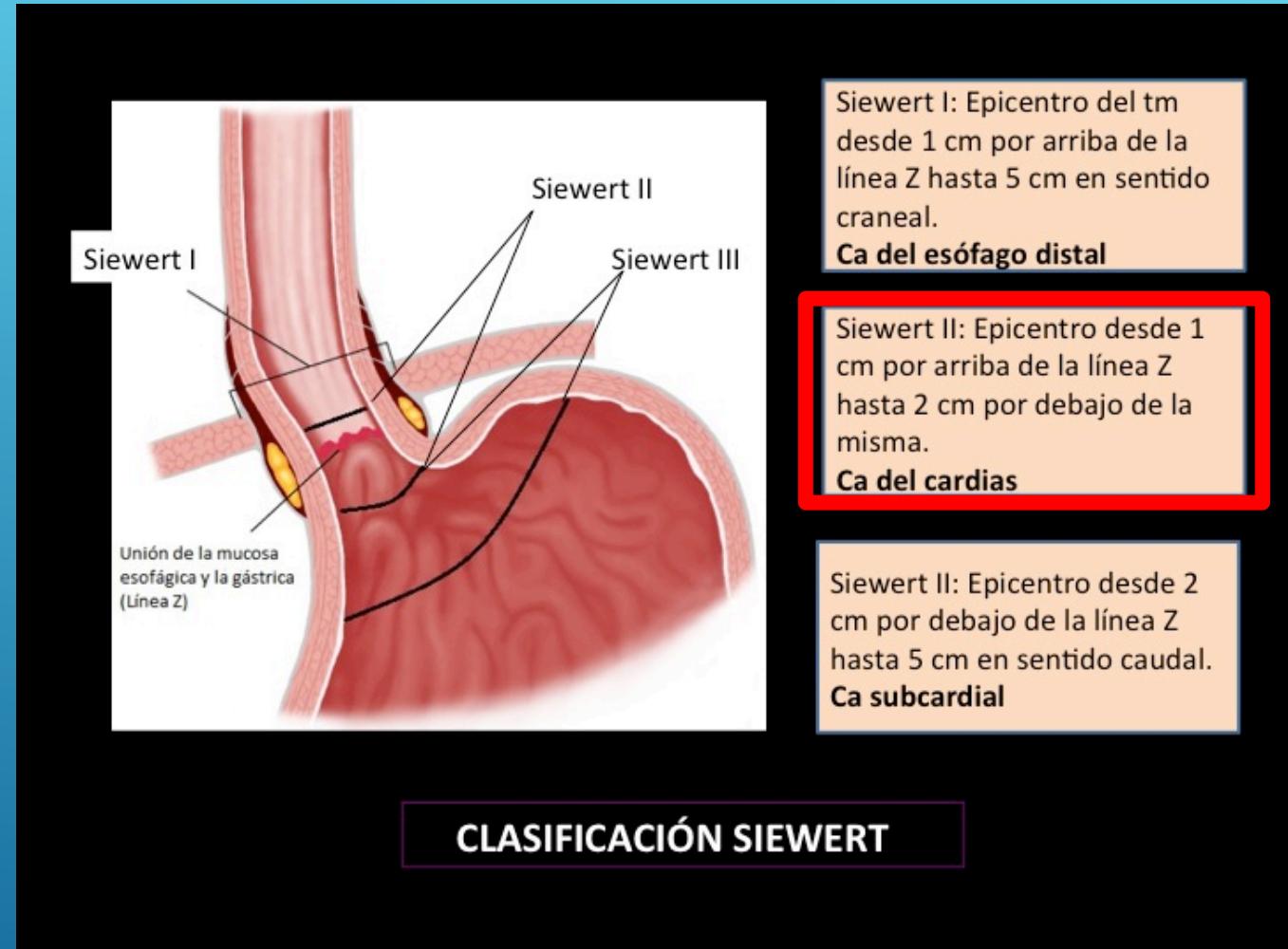


- Incidencia creciente de **adenocarcinomas** vs escamosos
- Diferente patogénesis
- Diferente perfil genético
- Diferente mortalidad operatoria.
- Diferente patrón de recaída.
- Distinto pronóstico.

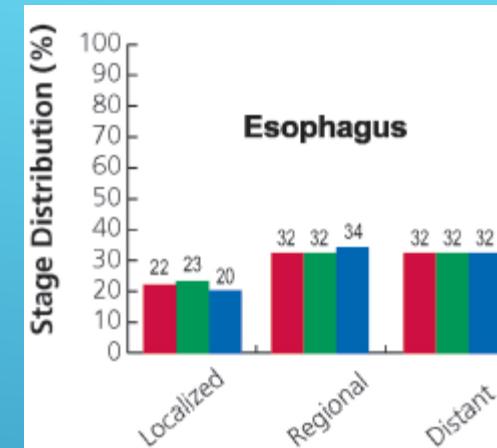
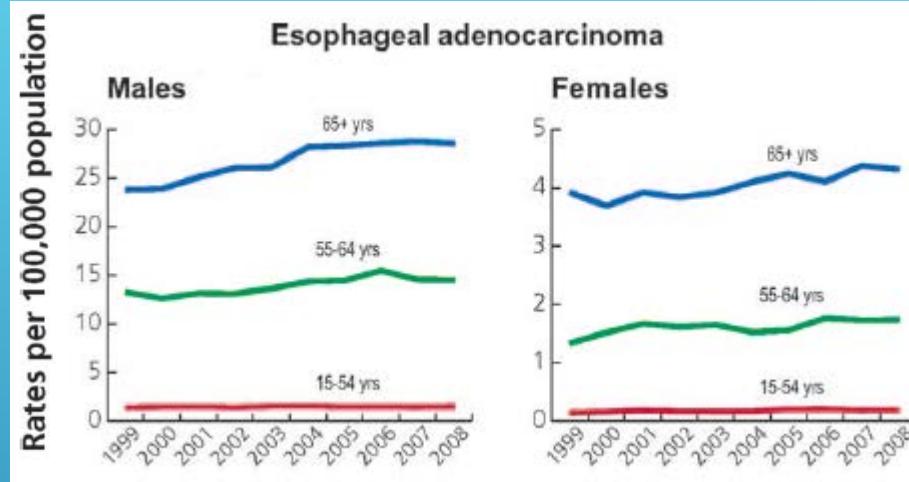


INTRODUCCIÓN

Tumores de la unión esófago-gástrica



¿Diferente tratamiento?



Trends in 5-Year Relative Survival Rates* (%) by Year of Diagnosis, United States, 1975 to 2007

	ALL RACES		
	1975 TO 1977	1987 TO 1989	2001 TO 2007
All cancers combined	49	56	67†
Esophagus	5	10	19†
Stomach	15	20	27†

Five-Year Relative Survival Rates for Cancers With Increasing Incidence in the United States by Anatomic Site, Stage, and Calendar Period at Diagnosis

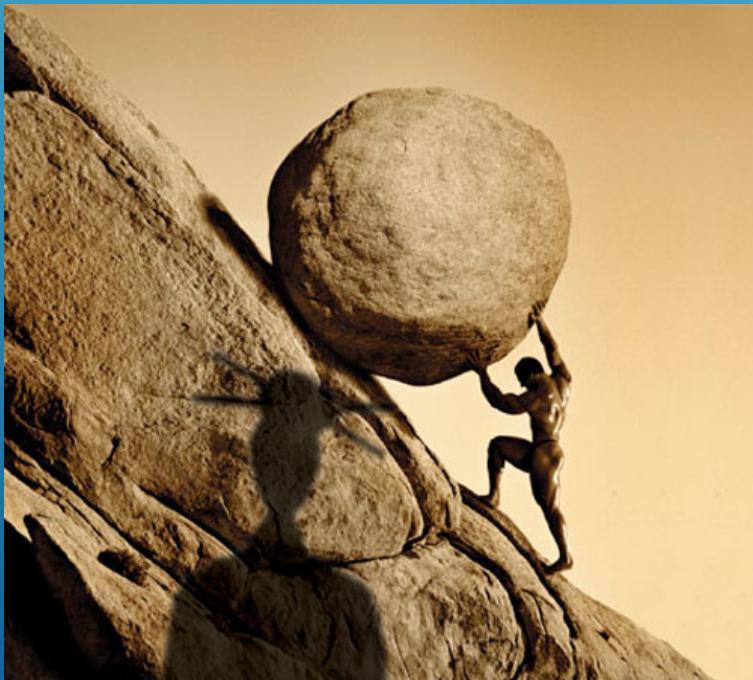
ANATOMIC SITE AND CALENDAR PERIOD	LOCALIZED, %			REGIONAL, %			DISTANT, %		
	1992-1995	1996-1999	2000-2007	1992-1995	1996-1999	2000-2007	1992-1995	1996-1999	2000-2007
Esophageal adenocarcinoma	33.5	37.7	47.8	9.4	15.3	20.7	1.9	1.7	2.9

TUMORES ESOFAGO-GASTRICOS

Cirugía

Sólo 30-40% resecables al diagnóstico

Spv 5 años: 15-20%



TRATAMIENTO NEOADYUVANTE

RT + Quimioterapia

Quimioterapia periop/neoady

Quimioterapia ➤ RT/QT



TRATAMIENTO NEOADYUVANTE

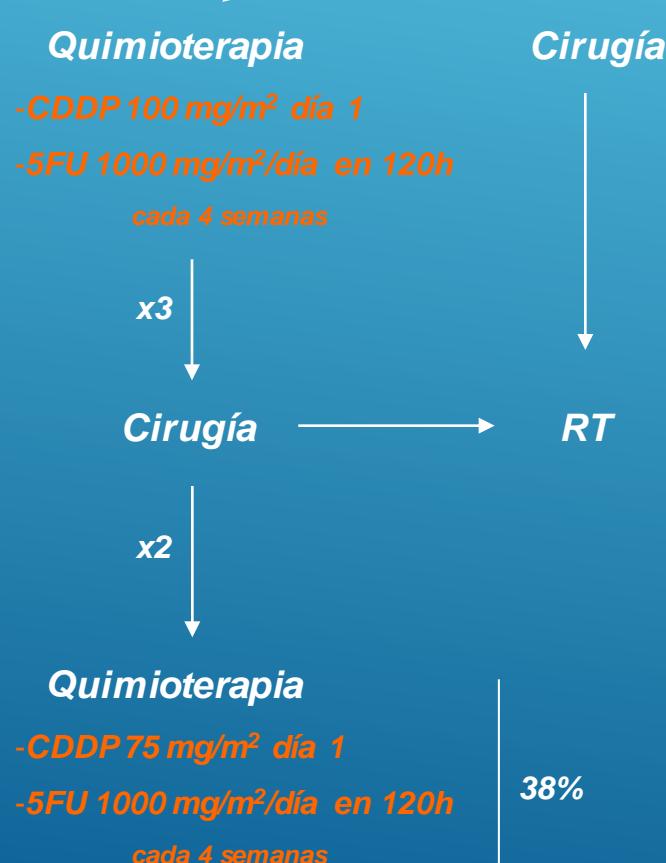


QUIMIOTERAPIA PERIOPERATORIA

TRATAMIENTO NEOADYUVANTE

Quimioterapia perioperatoria

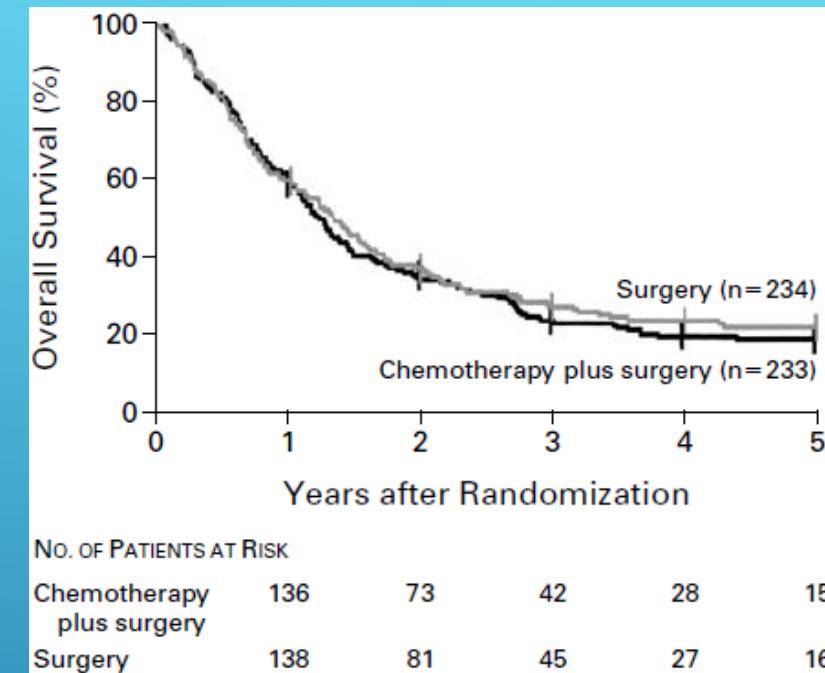
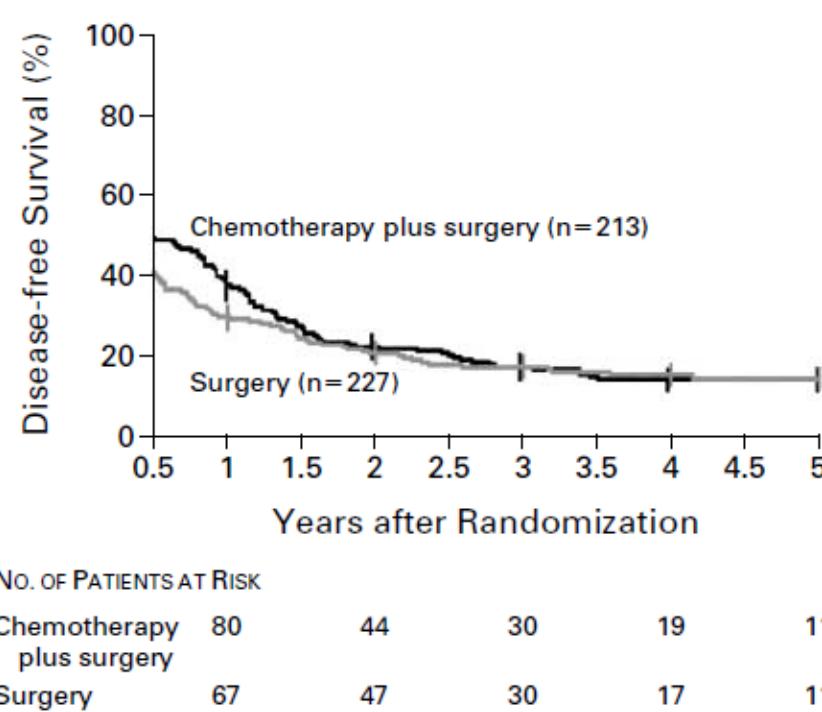
Intergroup 0113



- 440 pacientes (54% ADC); Esófago
- nº desconocido de tumores UGE

CHARACTERISTIC	TREATMENT GROUP	
	CHEMOTHERAPY PLUS SURGERY	SURGERY
Eligible, with adequate follow-up data (no.)		
All	227	213
Epidermoid cancer	106	98
Adenocarcinoma	121	115

FEATURES OF CHEMOTHERAPY DELIVERY	No. OF PATIENTS	CISPLATIN		FLUOROURACIL
		percent of planned dose		
Preoperative cisplatin–fluorouracil				
Eligible	213			
Adequate chemotherapy data	204			
Received all three cycles	144			
Received two cycles	26			
Received one cycle	32			
Received none	2			
Portion of planned preoperative dose administered				
First cycle	202	100		100
Second cycle	198	86		82
Third cycle	190	72		68
Postoperative cisplatin–fluorouracil				
Eligible	126			
Received both cycles	48			
Received one cycle	18			
Received none	60			



mOS: 14,9 vs 16,1 meses p= 0,53



RP: 2,5% de los pacientes del brazo de QT

VARIABLE	CHEMOTHERAPY	
	SURGERY	PLUS SURGERY
	no. of patients (%)	
Eligible patients	227	213
Surgery performed	217	171
Resections achieved*		
R0	135 (59)	133 (62)
R1	35 (15)	8 (4)
R2	33 (15)	21 (10)
None	24 (11)	51 (24)

NS

	SG 1a	SG 2a	SG 3a
QT + Cirugía	59%	35%	23%
Cirugía	60%	37%	26%

TRATAMIENTO NEOADYUVANTE

Quimioterapia neoadyuvante

- 802 pacientes (67% ADC, 31% SCC); Esófago
- 73,6% tercio inferior y cardias (10,4%)

MRC OEO2



Quimioterapia

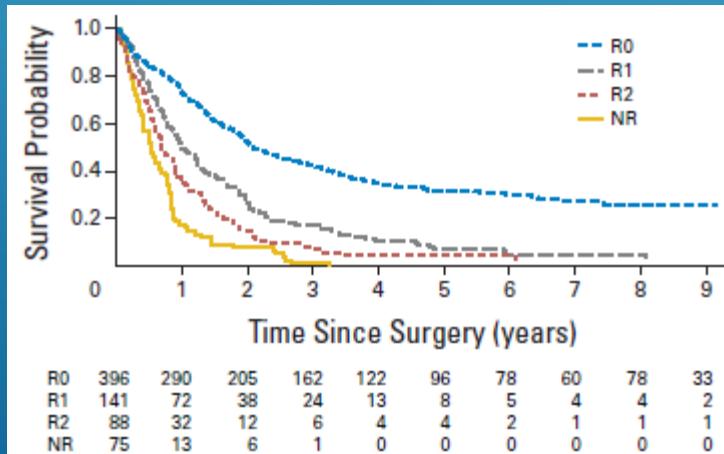
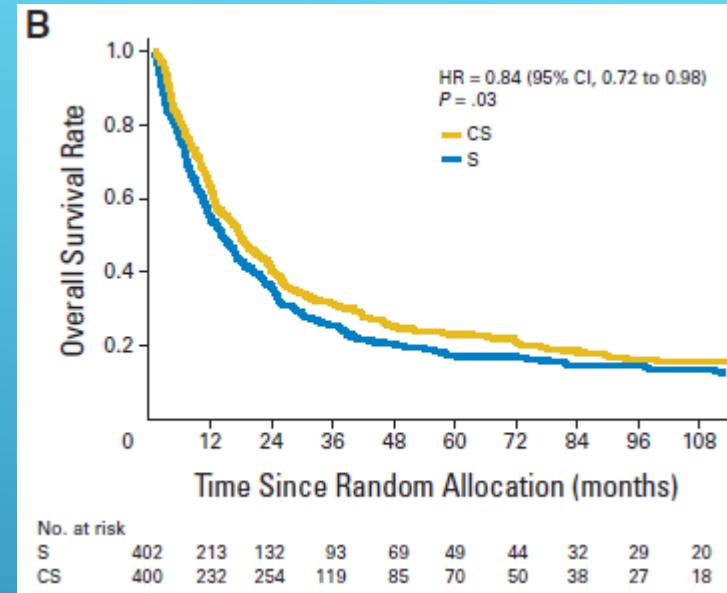
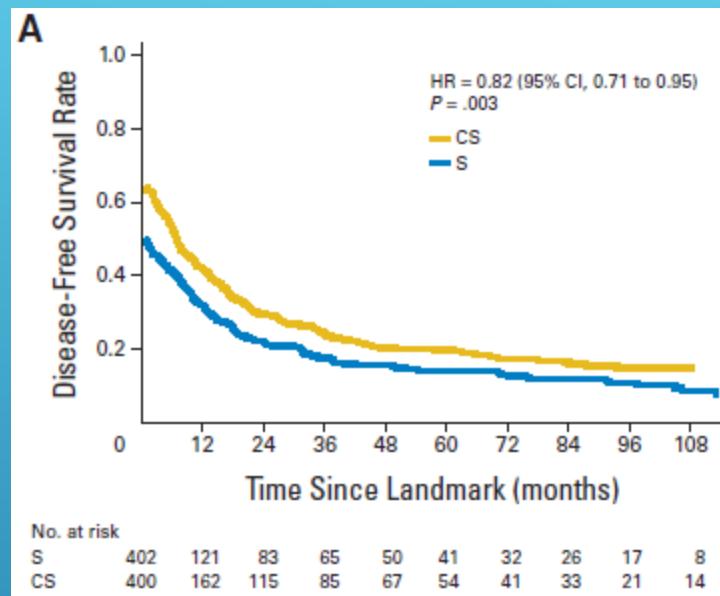
- CDDP 80 mg/m² día 1
- 5FU 1000 mg/m²/día en 96h

cada 3 semanas.

x2

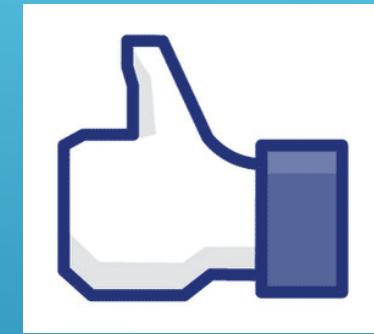
Cirugía

Pretreatment Patient Characteristic	S Group (n = 402)		CS Group (n = 400)		Total (N = 802)	
	No.	%	No.	%	No.	%
Age, years						
< 60	156	38.8	160	40.0	316	39.4
60-69	167	41.5	154	38.5	321	40.0
≥ 70	79	19.7	86	21.5	165	20.6
Median	63		63		63	
Range	30-80		36-84		30-84	
Sex						
Male	299	74.4	306	76.5	605	75.4
Female	103	25.6	94	23.5	197	24.6
Site of tumor						
Upper third	4	1.0	3	0.8	7	0.9
Middle third	102	25.4	97	24.3	199	24.8
Lower third	254	63.2	260	65.0	514	64.1
Cardia	42	10.4	40	10.0	82	10.2
Histology						
Squamous	124	30.8	123	30.8	247	30.8
Adenocarcinoma	268	66.7	265	66.3	533	66.5
Undifferentiated	10	2.5	11	2.8	21	2.6
Not known	0	0.0	1	0.3	1	0.1
Degree of dysphagia						
0	48	12.9	60	15.7	108	14.3
1	148	39.9	170	44.4	318	42.2
2	123	33.2	111	29.0	234	31.0
3	48	12.9	38	9.9	86	11.4
4	4	1.1	4	1.0	8	1.1
Not recorded	31		17		48	
WHO performance status						
0	267	66.4	265	66.3	532	66.3
1	122	30.3	125	31.3	247	30.8
2	12	3.0	9	2.3	21	2.6
3	0	0.0	1	0.3	1	0.1



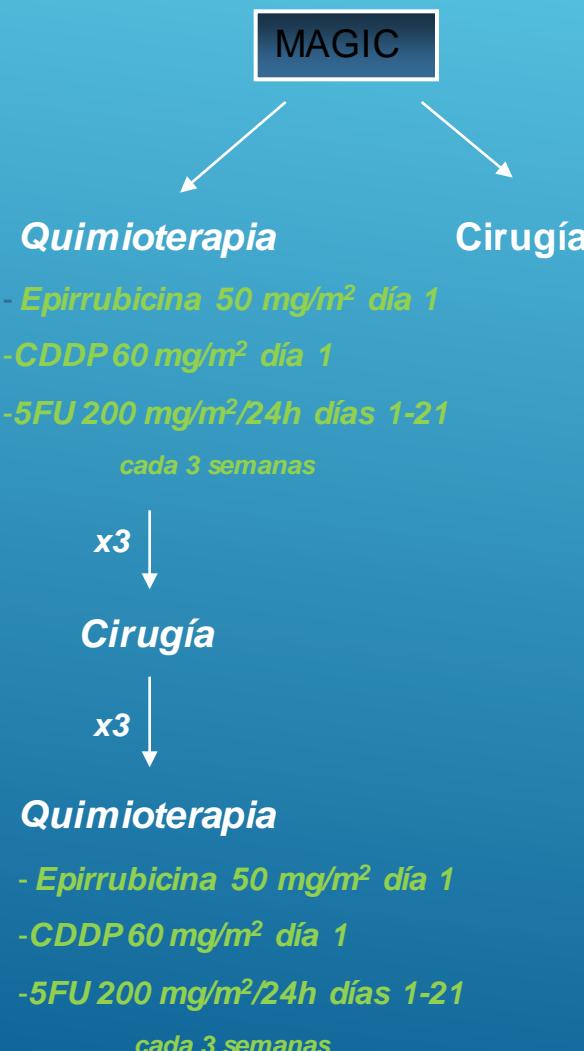
	<i>N+</i>	No resecables	<i>SG 5a</i>	<i>SLP</i>	<i>SG</i>
<i>QT+ Cirugía</i>	58%	14,3%	23%		
<i>Cirugía</i>	68%	26,4%	17,1%		
<i>p-valor</i>	0,009	<0,001		0,003	0,03

* No DS en supervivencia por histología



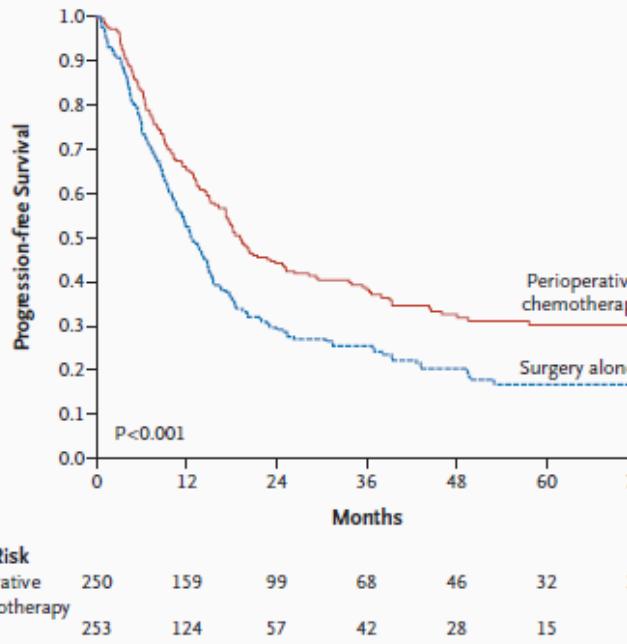
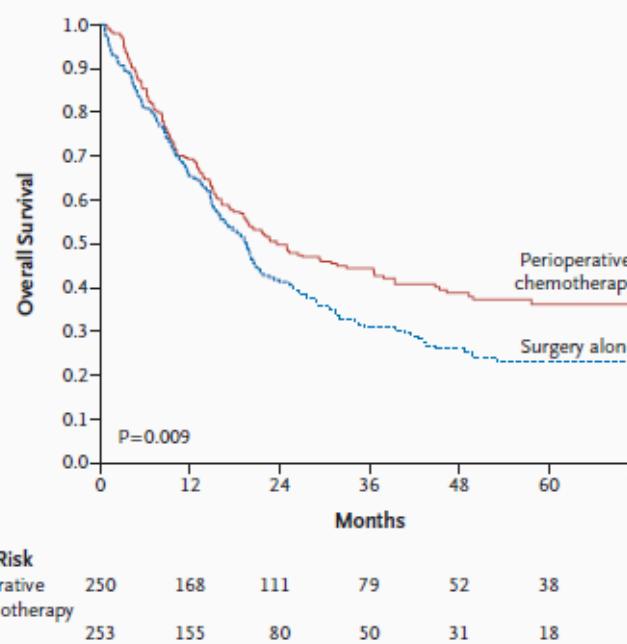
TRATAMIENTO NEOADYUVANTE

Quimioterapia perioperatoria



- 503 pacientes (100% ADC; 27% UGE Siewert I y II; 73 % Estómago).
- Disminución de tamaño tumores resecados:
 - 3 vs 5cm; p<0,001
 - T1 y T2 (52% vs 37%); p=0,002

Variable	Perioperative-Chemotherapy Group (N=250)	Surgery Group (N=253)
	number of patients/total number (percent)	
Pathology reports		
Tumor stage (all patients)		
T1	27/172 (15.7)	16/193 (8.3)
T2	62/172 (36.0)	55/193 (28.5)
T3	75/172 (43.6)	106/193 (54.9)
T4	8/172 (4.7)	16/193 (8.3)
Nodal status (patients with gastric cancer)		
N0	42/135 (31.1)	42/156 (26.9)
N1 (<7 nodes involved)	72/135 (53.3)	68/156 (43.6)
N2 (7-14 nodes involved)	19/135 (14.1)	34/156 (21.8)
N3 (>14 nodes involved)	2/135 (1.5)	12/156 (7.7)

A**B**

Toxicidad: Neutropenia 23% (G3-4 <12%)

	HR	p
SLP	0,66	<0,001

Sólo el 42% de los pacientes completan el protocolo

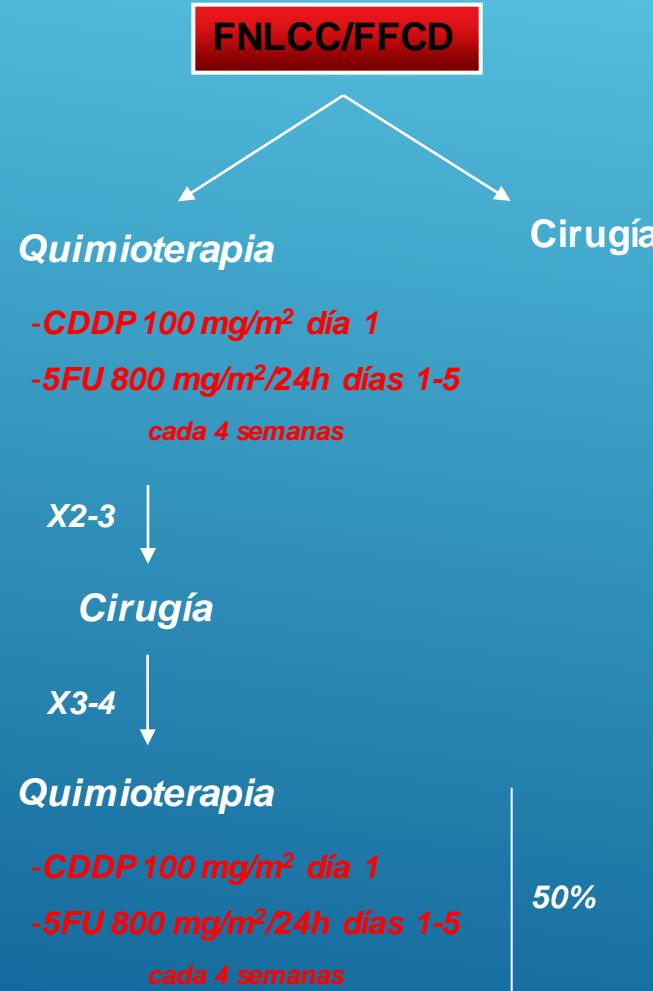


	QT – Cirugía - QT	Cirugía
Sv (5 años)	36%	23%
Recidiva Local	14%	21%
Recidiva Distancia	24%	37%

Cunningham Det al. N Engl J Med 2006; 355: 11-20

TRATAMIENTO NEOADYUVANTE

Quimioterapia perioperatoria



- 224 pacientes (100% Adenocarcinoma)

- Esófago distal (11%), UGE (64%), Estómago (25%),-
- Todos tumores potencialmente resecables.

Table 2. Grade 3 to 4 Toxicity Occurring During Preoperative Chemotherapy (CS group, n = 109)

WHO Grade 3 to 4 Toxicity	No.	%
Neutropenia	22	20.2
Leukopenia	6	5.5
Thrombocytopenia	6	5.5
Nausea/vomiting	10	9.2
Cardiotoxicity	4	3.7
Mucositis	4	3.7
Diarrhea	2	1.8
Neurotoxicity	1	0.9
Nephrotoxicity	1	0.9
Fever	1	0.9
Ototoxicity	1	0.9
Other	5	4.6

Abbreviation: CS, perioperative chemotherapy and surgery.

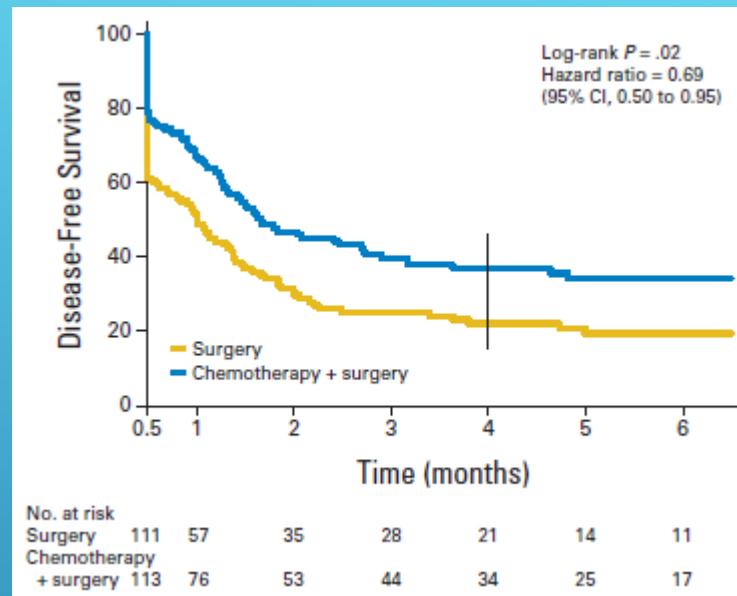
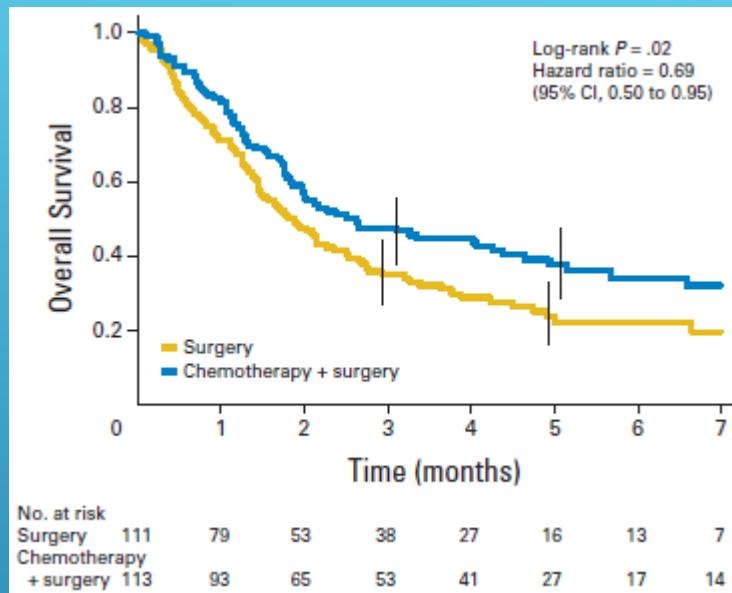


Table 4. Patterns of Recurrence, Survival Status, and Cause of Death

Parameter	CS Group (n = 113)		S Group (n = 111)	
	No.	%	No.	%
Recurrence	63	55	71	64
Locoregional only	14	12	9	8
Distant only	35	30	42	38
Both	14	12	20	18
Death	71	63.8	85	77
Cancer related	59		70	
Surgery related	5		5	
Drug related	1		1*	
Other	6		9	

Abbreviations: CS, perioperative chemotherapy and surgery; S, surgery.
*One of the patients who received postoperative chemotherapy.

	Cirugía	QT perioperatoria
R0	74 %	87 %*
pT3-4	68%	58%**
N+	80%	67%**
SLP a 5 años	21 %	34 %*
SG (5a)	24 %	38 %*

*S; **NS



TRATAMIENTO NEOADYUVANTE

Quimioterapia neoadyuvante

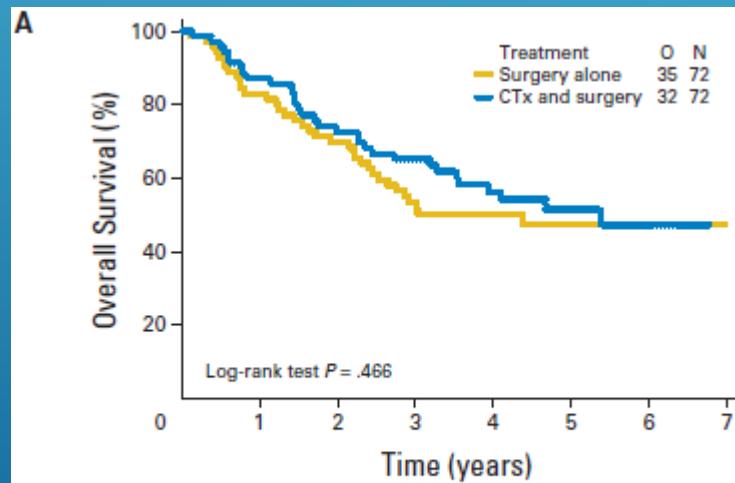
EORTC 40954

Quimioterapia → **Cirugía**

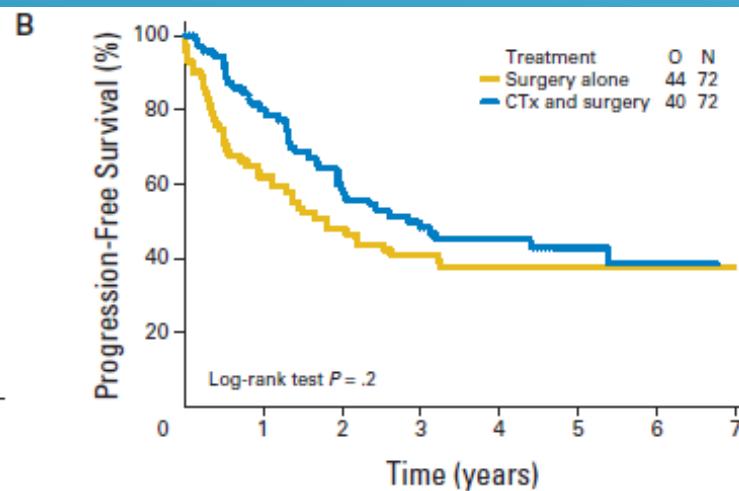
-CDDP 50 mg/m² en 48h días 1, 15 y 29.
-5FU 2000 mg/m²+ Folínico 500 mg/m²/24h
días 1, 8, 15, 22, 29 y 36.

Cirugía

Cerrado por bajo reclutamiento

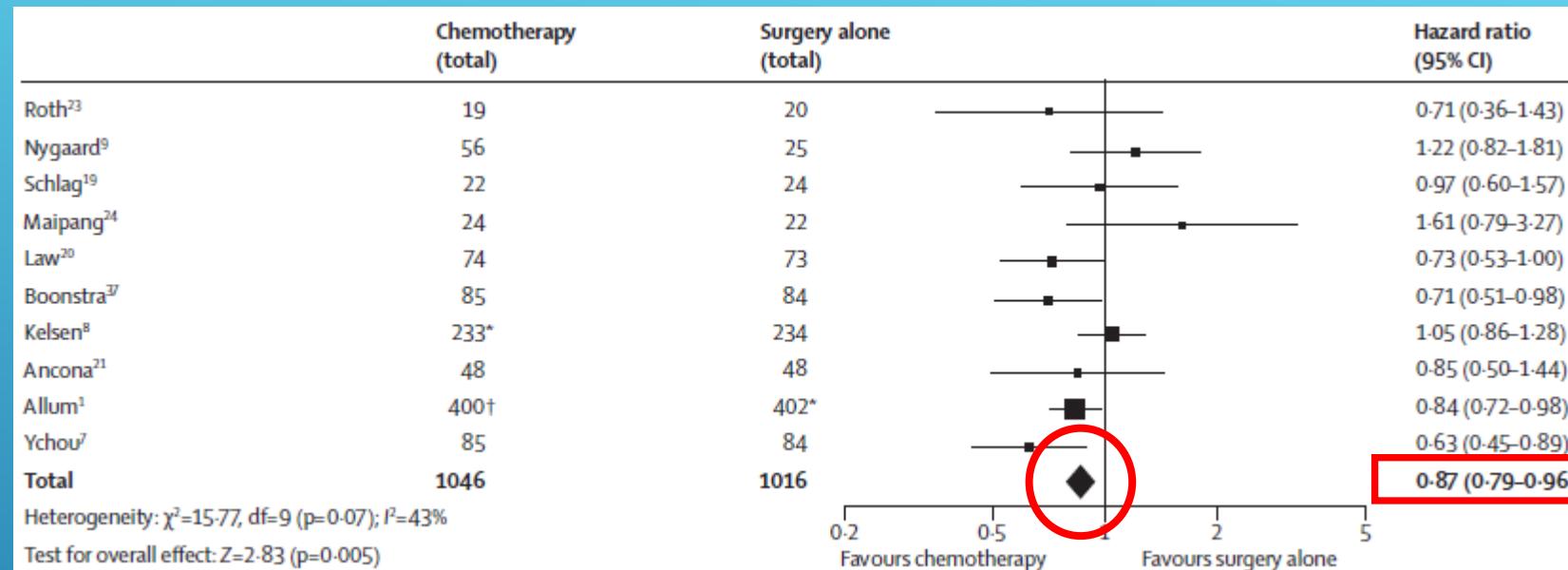


	58	48	34	20	11	4
No. at risk						
Surgery alone	58	48	34	20	11	4
CTx and surgery	61	49	41	29	15	6

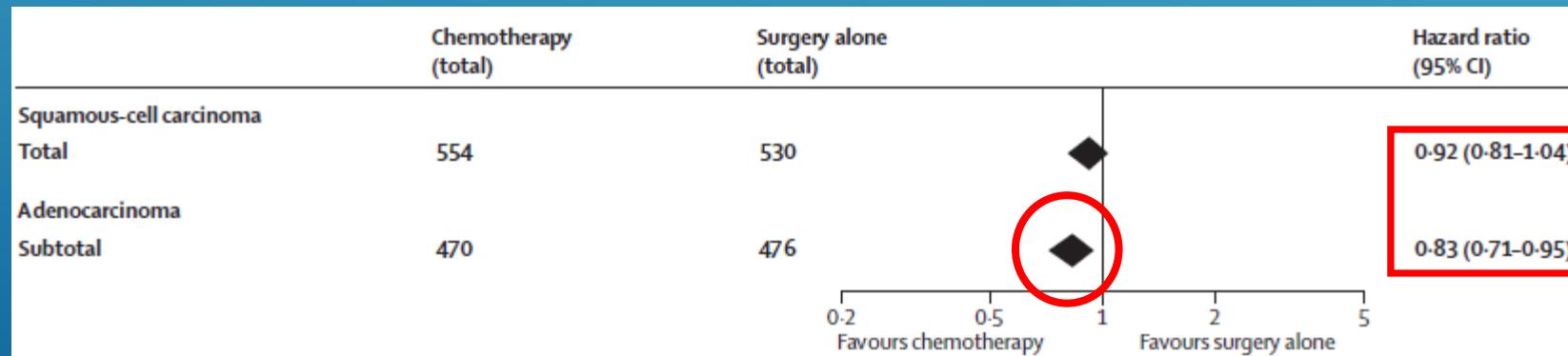


	44	34	28	16	11	4
No. at risk						
Surgery alone	44	34	28	16	11	4
CTx and surgery	56	41	31	24	13	5

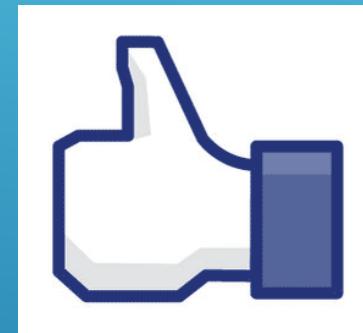
Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal carcinoma: an updated meta-analysis

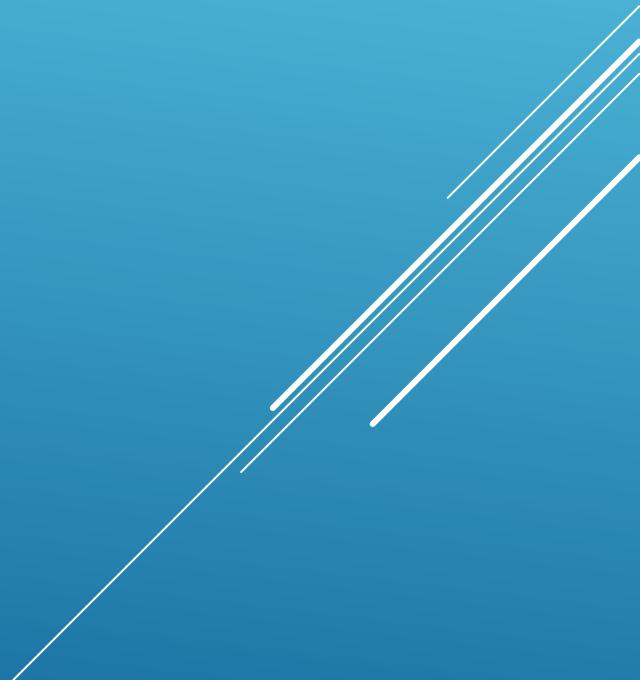


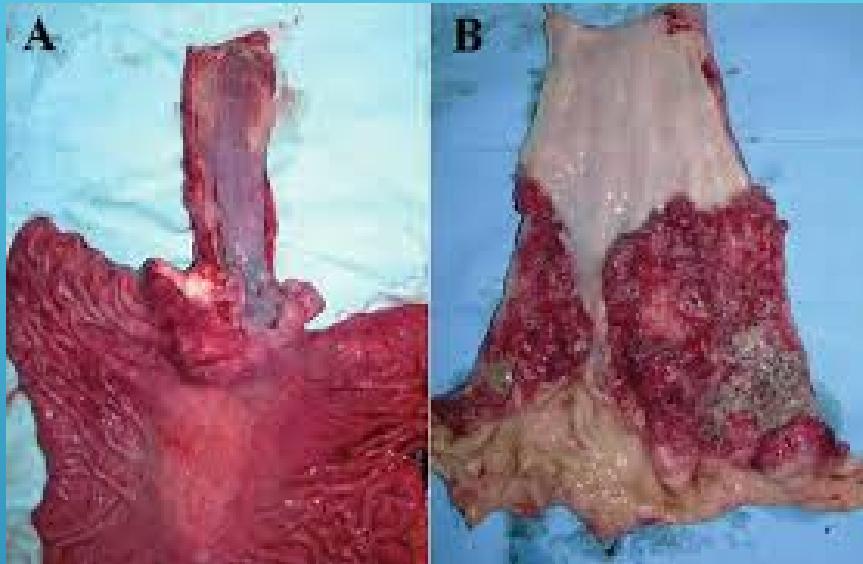
META-ANÁLISIS



- Beneficio en Spv: 5,1% a 2 años.
- NNT: 19







Quimioterapia neoadyuvante

- Tratamiento de la enfermedad micrometastásica
- Mejoría clínica y mejor tolerancia quirúrgica
- Mejor tolerancia a la quimioterapia
- Mejora Tasa de R0
- Incrementa la conversión de tumores irresecables en resecables

Mejora la supervivencia global

CONCLUSIONES (I)

Quimioterapia perioperatoria



- Adenocarcinoma esofágico inferior/UGE T2-4; N+
- Pacientes “UNFIT”
- Sospecha de enfermedad micrometastásica

CONCLUSIONES (II)

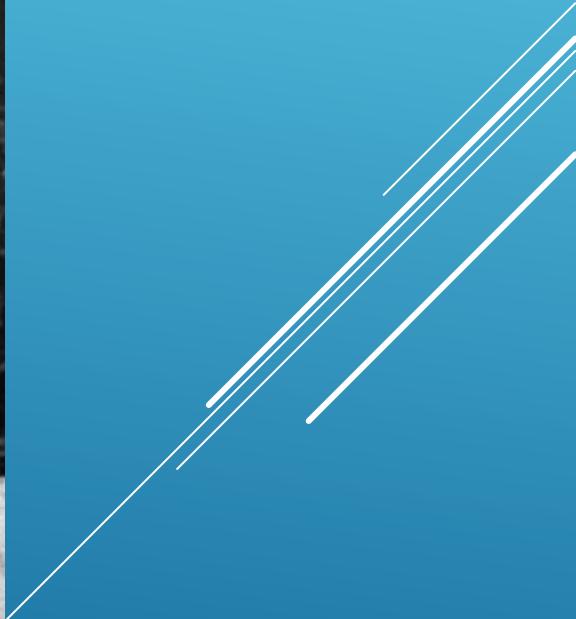
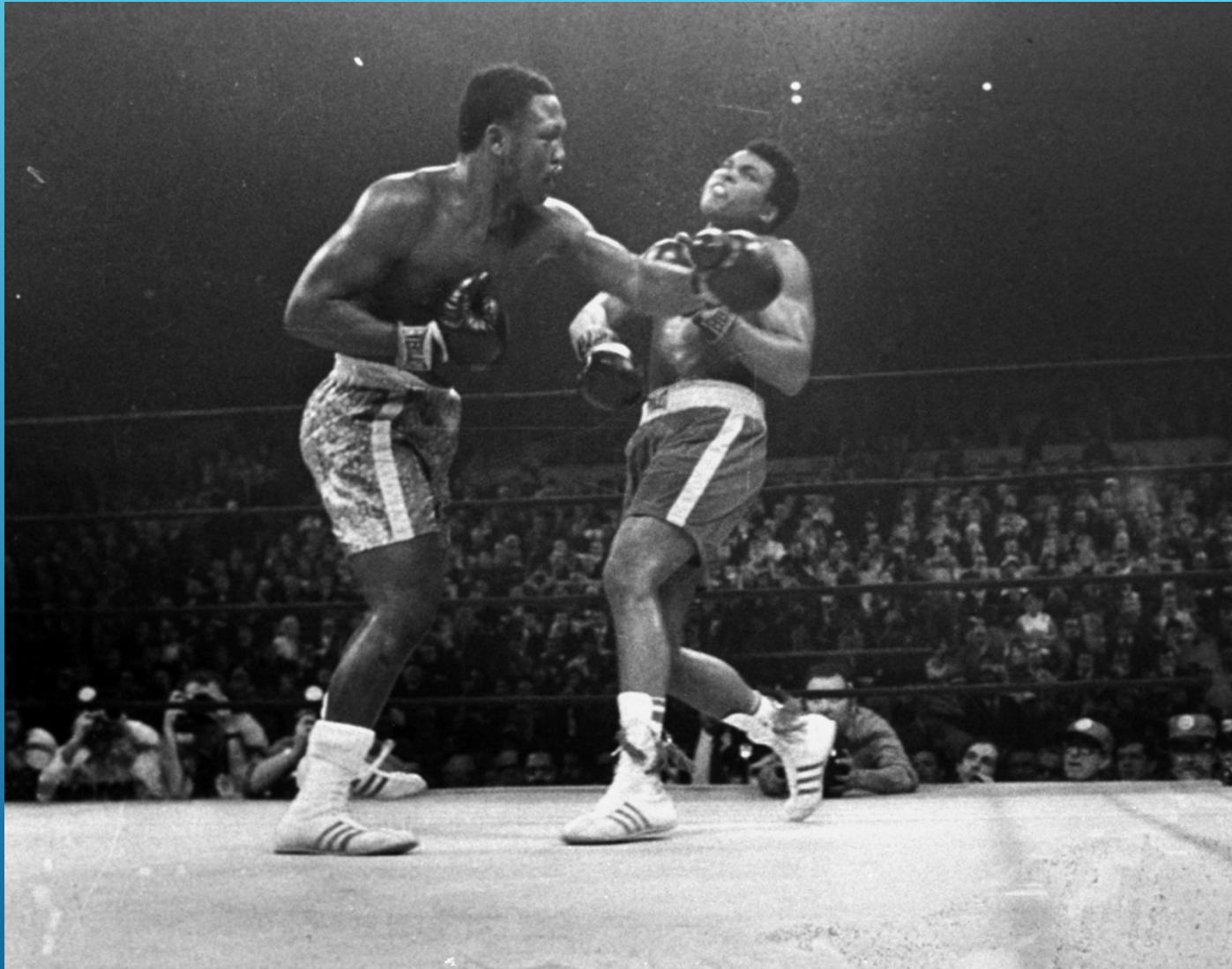


Cuanto mayor es la ignorancia, mayor es el
dogmatismo.

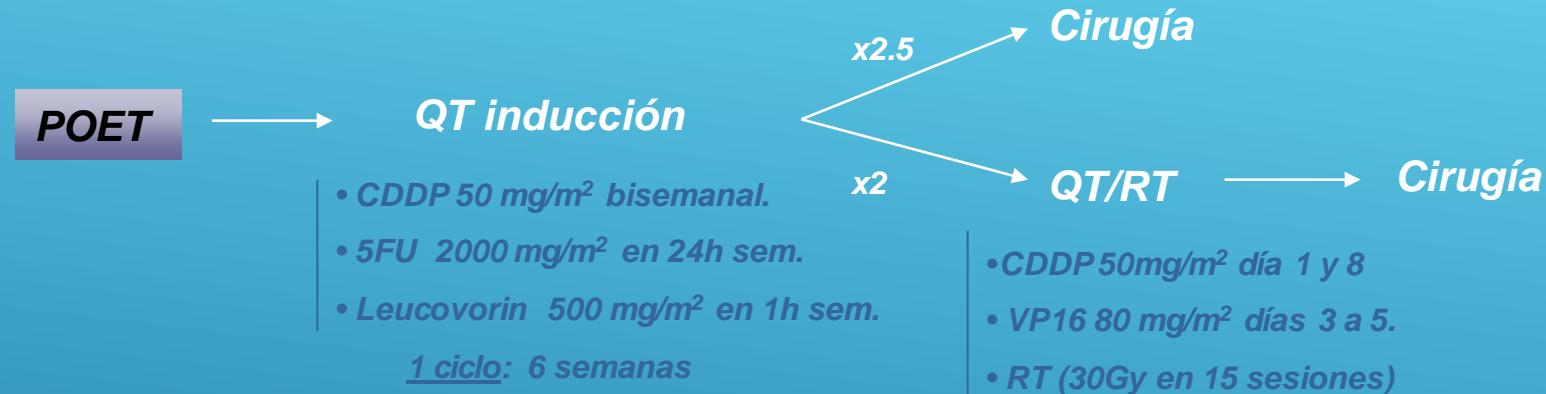
(William Osler)

GRACIAS

QT/RT vs QT NEOADYUVANTE



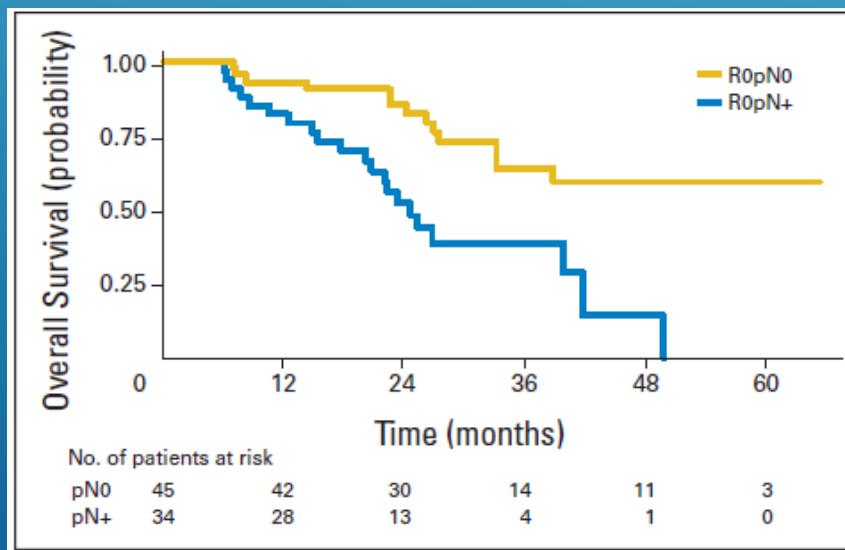
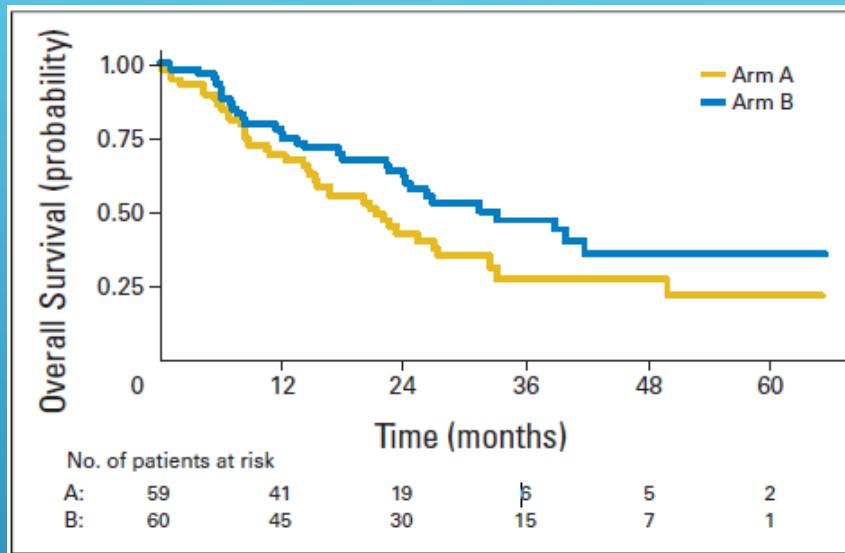
QT/RT vs QT NEOADYUVANTES



- 126 pacientes con adenocarcinoma de la UGE T3-4 Nx M0.

- Cerrado prematuramente por bajo reclutamiento

	R0	RCp		Mortalidad postcirugía	SG 3a	Pacientes sin recidiva local 3a
		ypT0 N0	ypN0			
QT-Cirugía	69,5%	2%	36,7%	3,8%	27,7%	59%
QT-QT/RT-Cirugía	72%	15,6%	64,5%	10,2%	47,4%	76,5%
p-valor		0,03	0,01	0,26	0,07	0,06



Treatment	Arm A		Arm B		<i>P</i>
	No.	%	No.	%	
Patients with resection	49	100.0	45	100.0	
pT0 N0 M0	1	2.0	7	15.6	.03*
pT1-4 N0 M0	17	34.7	22	48.9	
pT0-4 N0 M0†	18	36.7	29	64.4	.01*
pT0-4 N0 M0	18	36.7	29	64.4	.01*
pTall N+ M0	27	55.1	14	31.1	
pTall N+ M1	4	8.2	2	4.5	

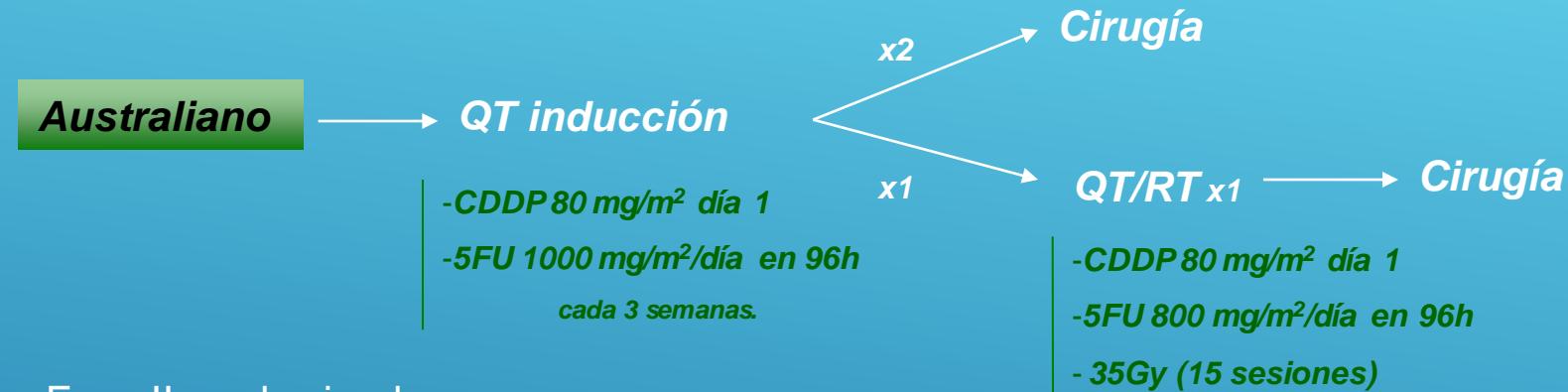
*Fisher's exact test.
†Bold text indicates data summarized from patients with pT0 N0 M0 and pT1-4 N0 M0.

- OS a 3 años:

R0 ypN0 vs N1: 64,2% vs 38,8%; *p* = 0,001

ypN0 (A vs B): 56,9% vs 68,1%; *p* = 0,94

QT/RT vs QT NEOADYUVANTES



- Fase II randomizado
- 75 pacientes con adenocarcinoma del esófago o de la UGE estadios IIA-B y III.
- **Cerrado prematuramente por bajo reclutamiento**

	QT	QT/RT	p
R0	80,5%	84,6%	0,61
R1	11%	0%	0,04
pCR	0%	13%	0,02
pCR mayor (<10%)	8%	31%	0,01
No resecados	8%	15%	

	QT	QT/RT
R0	80,5%	84,6%
R1	11%	0%
R2	0%	0%
No resecados	8%	31%
R0 (operados)	86%	100%

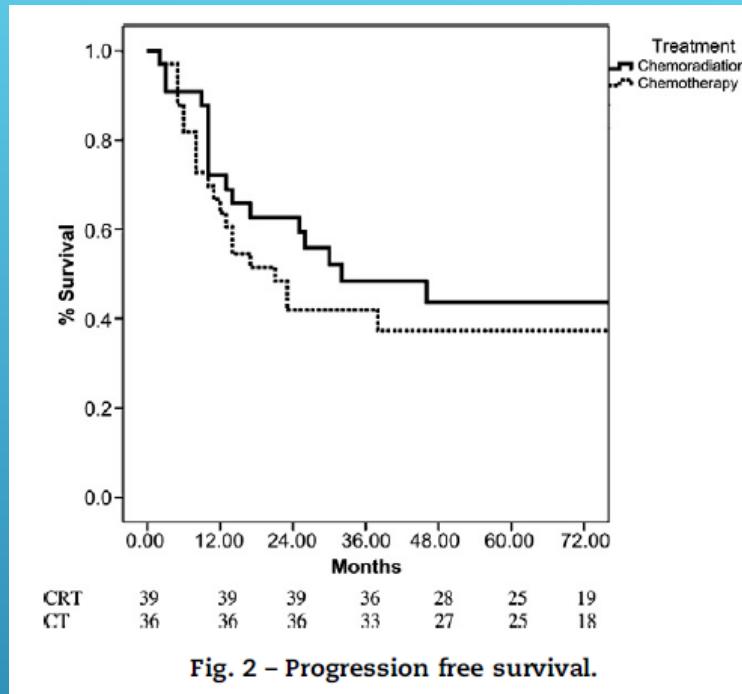


Fig. 2 – Progression free survival.

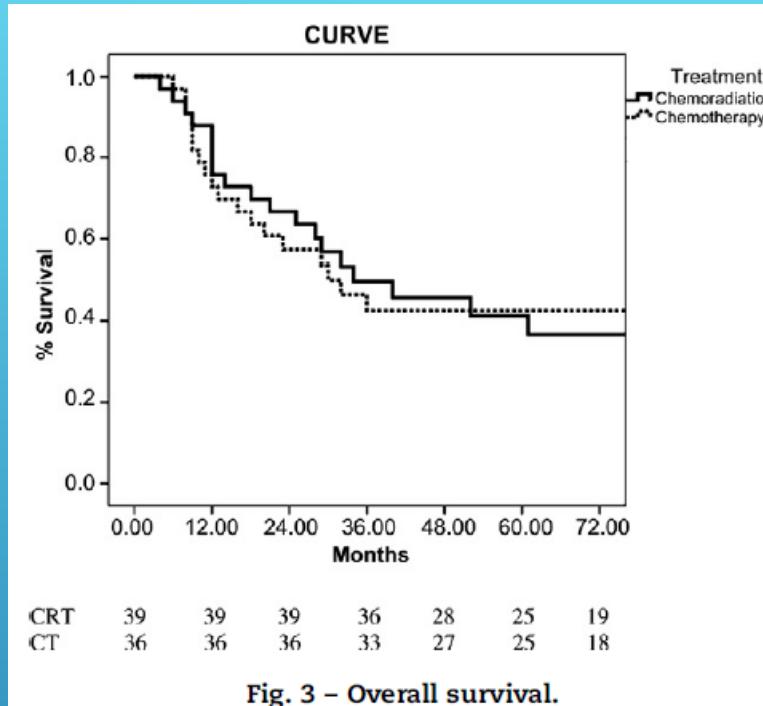


Fig. 3 – Overall survival.

	QT	QT/RT	p
Median TTP (meses)	14	26	0,37
Median OS (meses)	29	32	0,83
Spv 3a	49%	52%	0,97
Spv 5a	36%	45%	0,60
Recurrencia LR/D	-	-	ns