

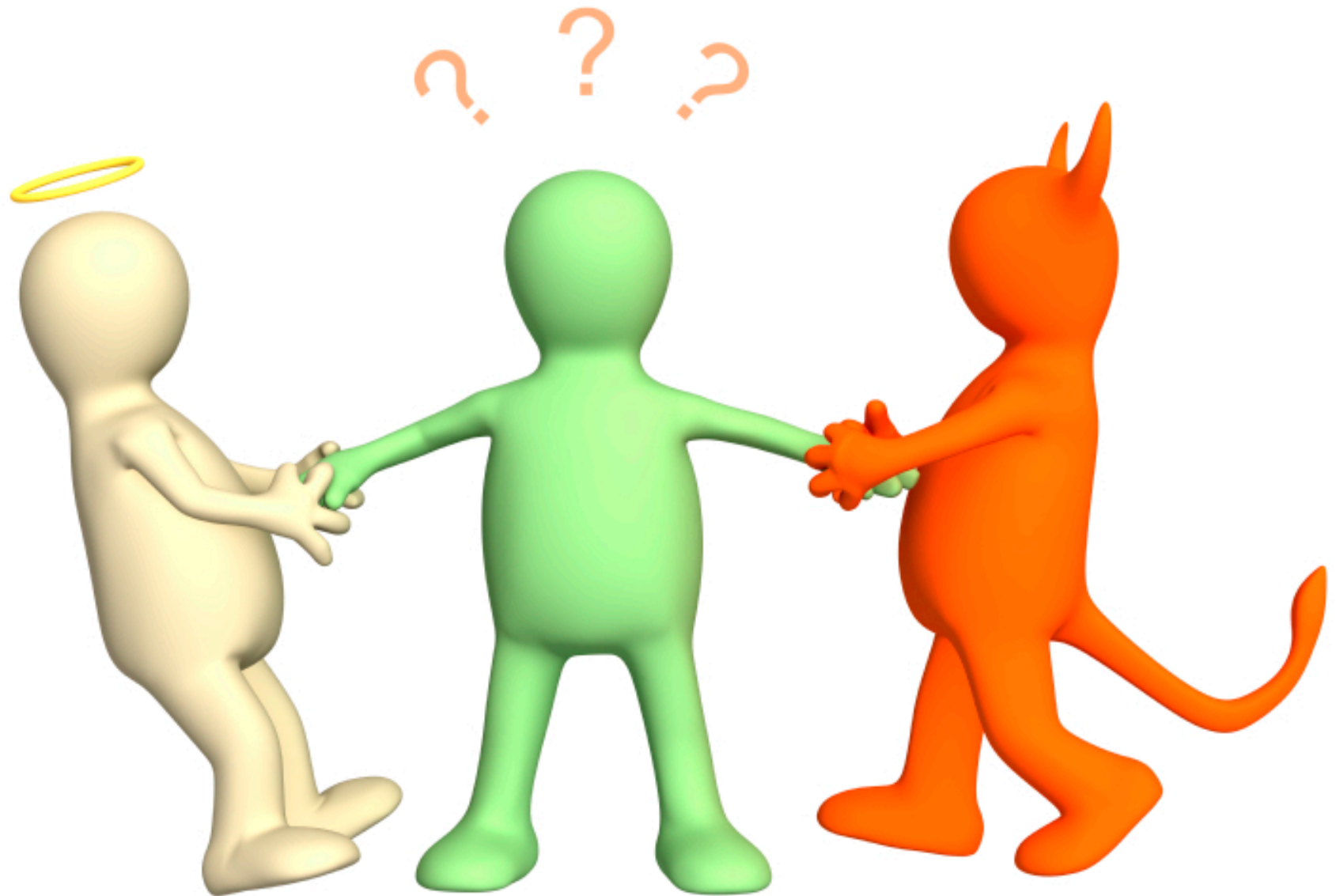
A photograph of a large iceberg floating in the ocean. The iceberg is mostly submerged, with only a small, flat-topped portion visible above the water. The water is a deep blue, and the sky is a lighter blue. The iceberg's reflection is clearly visible in the calm water.

Terapia neoadyuvante en cáncer de recto – Estado del arte

Mauricio Lema Medina MD

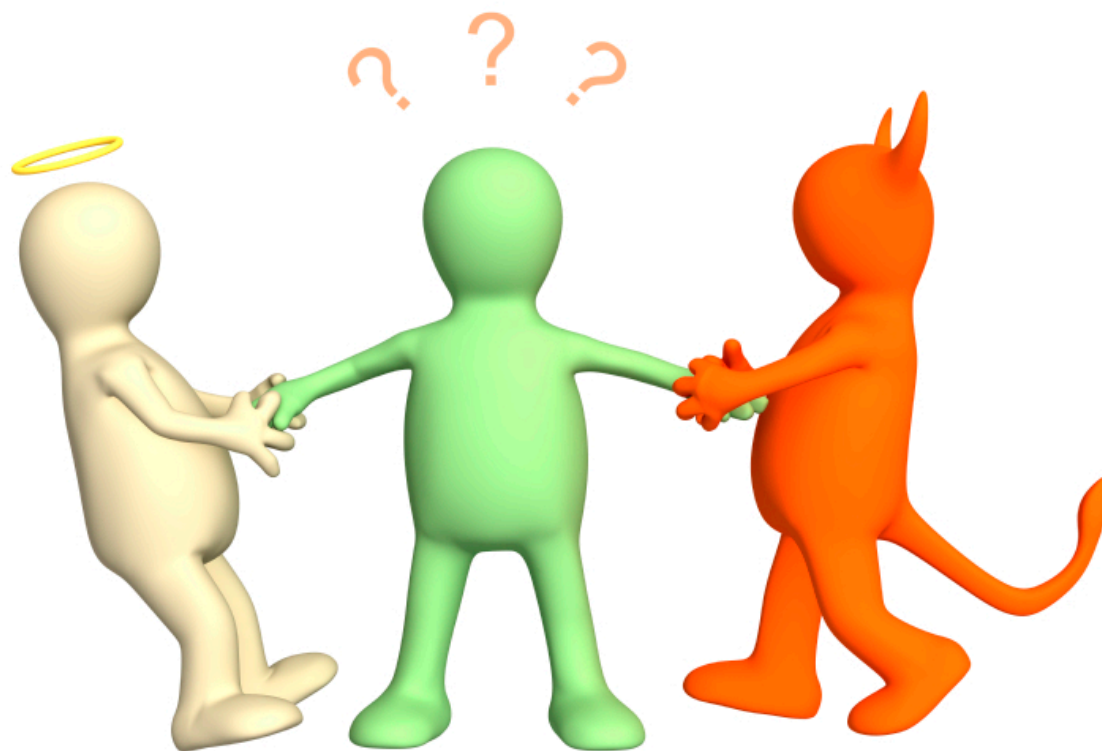
Clínica de Oncología Astorga / Clínica SOMA - Medellín, Colombia

Mauricio Lema: Conflicto de interés



Mauricio Lema: Conflicto de interés

Honorarios por conferencias de ROCHE,
manufacturador de Bevacizumab (AVASTIN) y
Capecitabina (XELODA)



Temario

El reto del cáncer del recto

Temario

El reto del cáncer del recto

Terapia multimodal – los inicios

Temario

El reto del cáncer del recto

Terapia multimodal – los inicios

*Quimiorradioterapia preoperatoria –
esquemas actuales*

TNM7 – Colorectal

ANATOMIC STAGE/PROGNOSTIC GROUPS

Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–



El recto es como el colon,

*El recto es como el colon, sólo
distinto*

Recto

Inmóvil

Rodeado de estructuras importantes

Termina en “el” esfínter...

*Una resección AMPLIA del recto es
casi por definición IMPOSIBLE...*

*De allí que la recurrencia local sea
un problema importante*

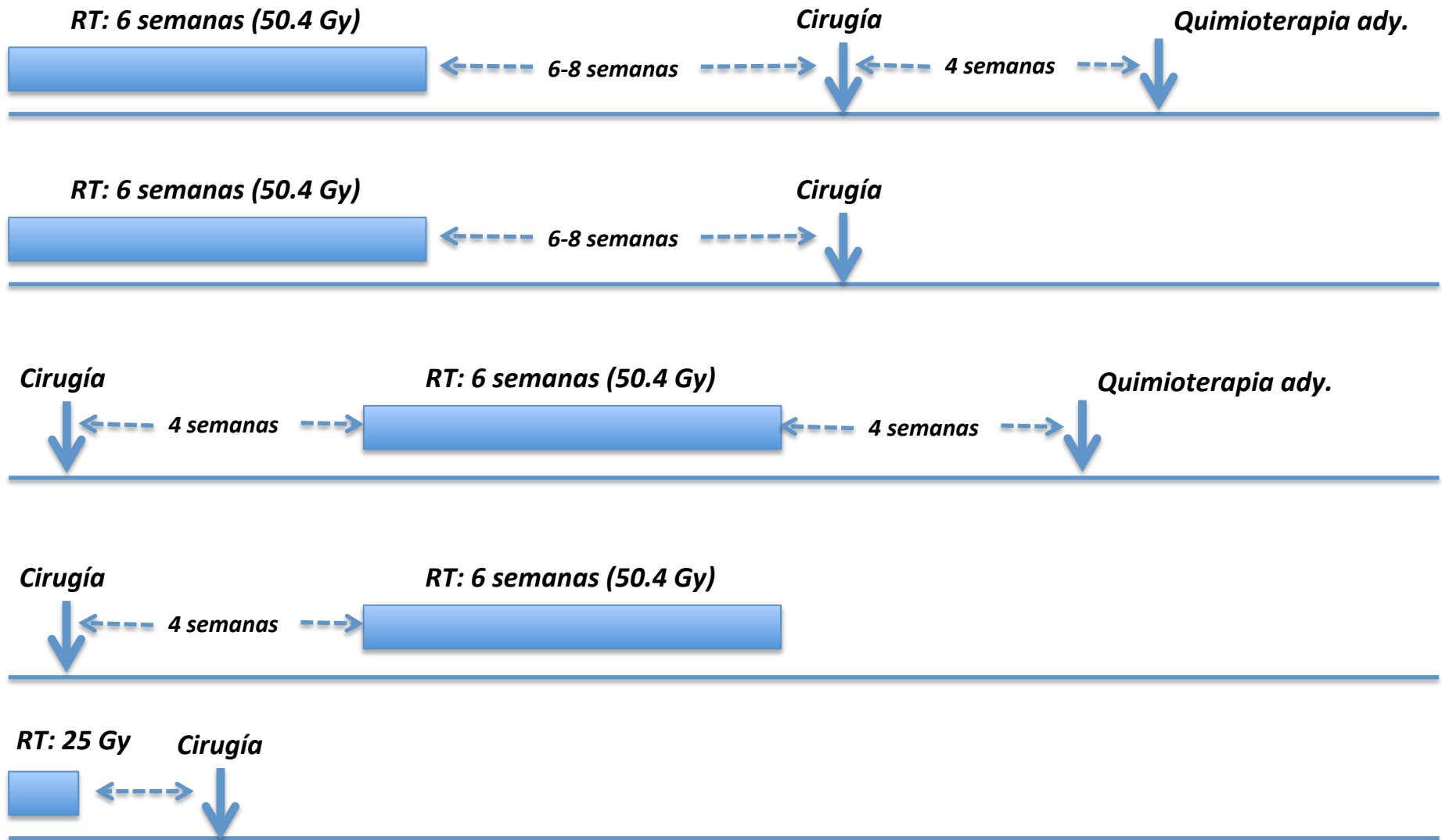
Incidence of local failure in Rectal Cancer

- **T1-2, No, Mo** < 10%
- **T3, No, Mo** 15-35%
- **T1, N1, Mo** 15-35%
- **T3-4, N1-2, Mo** 45-65%

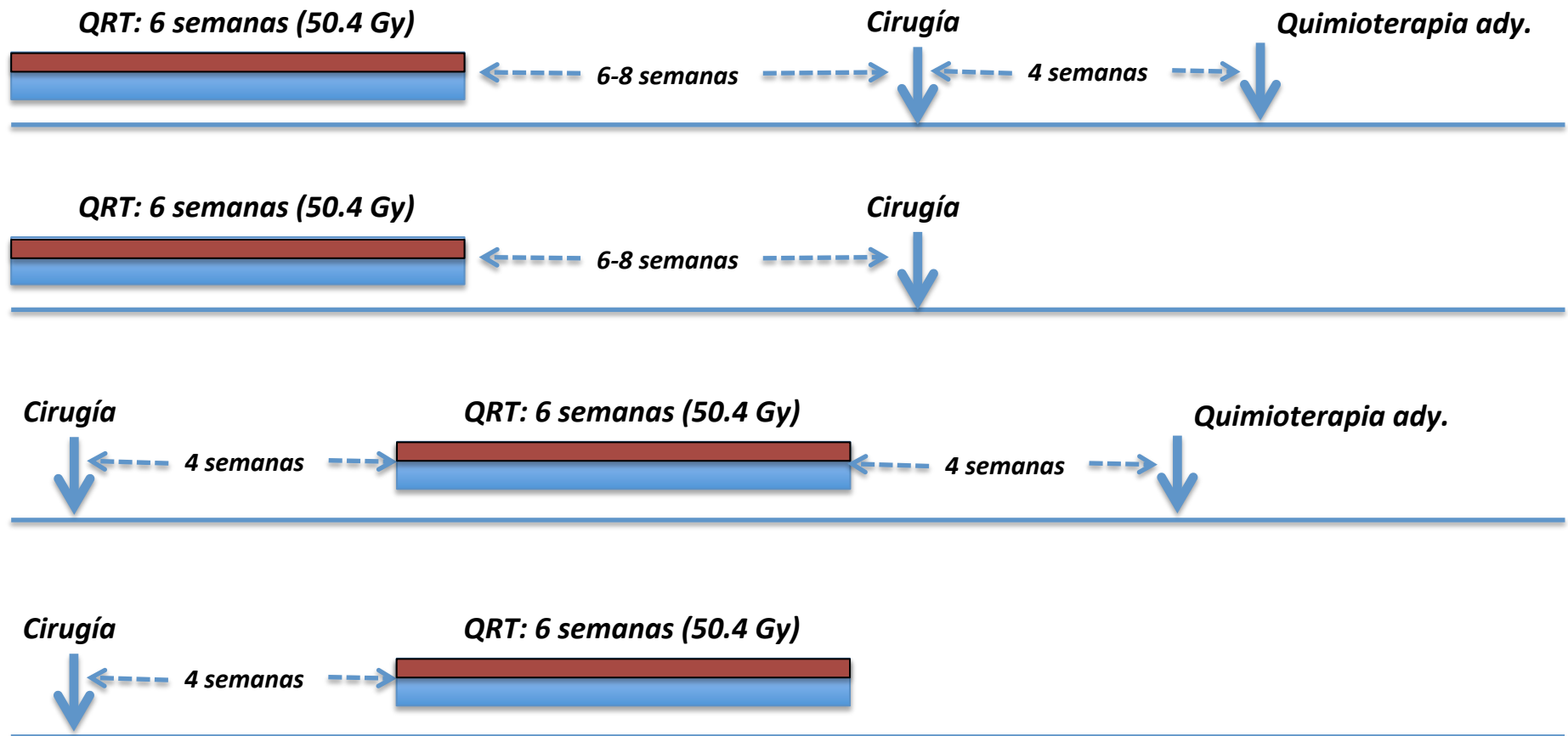


**Múltiples estándares de manejo de
cáncer de recto...**

Cáncer de recto estadio II o III



Cáncer de recto estadio II o III



Capecitabina 825 mg/m² vía oral cada 12 horas durante la RT

FU 1000 mg/m² por día, días 1-5, primera y última semana de RT

FU 350 mg/m² en infusión de 24 horas cada día durante la RT

Folinato 20 mg/m² + **FU** 325 mg/m² por día, días 1-5, primera y última semana de RT

*¿Si todos son estándares, cuál
es el sentido de esta
conferencia?*

*Vamos a buscar cuál (o cuáles) es
el estándar idóneo de manejo de
quimiorradioterapia en cáncer de
recto*

A satellite photograph of North America at night, showing the continent illuminated by city lights. The lights are concentrated in the eastern and central parts of the continent, with a few scattered lights in the western part. The image is in shades of blue and white, with a dark blue background representing the night sky. The curvature of the Earth is visible at the top of the frame.

Ahhhh! merica

Effective Surgical Adjuvant Therapy for High-Risk Rectal Carcinoma

n=209

Cirugía



QRT: 5 semanas (45 Gy)



FU 500 mg/m² bolo día 1-3, semana 1 y 5 de RT

Cirugía



RT: 5 semanas (45 Gy)

Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991;324:709-715

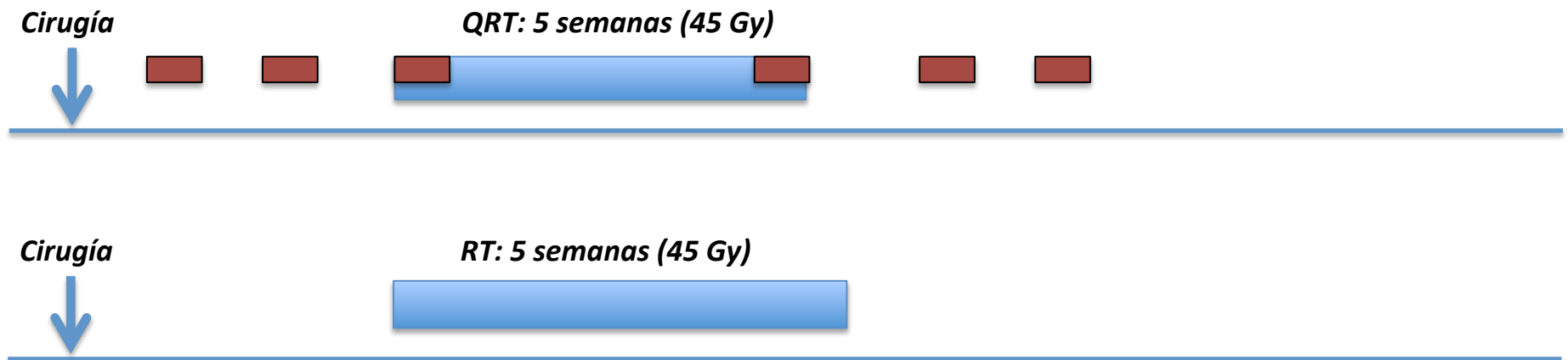


Postoperative radiochemotherapy

		GITSG	NCCTG	NSABP-R01
Number of pts.		202	204	555
<hr/>				
Surgery alone	LF (%)	24		25
	S (%)	43		43
Radiotherapy	LF (%)	20	25	16
	S (%)	52	47	41
Chemotherapy	LF (%)	27		21
	S (%)	21		53
Chemoradioth.	LF (%)	11	14	8
	S (%)	59		58

Slide stolen from somewhere in the www

Effective Surgical Adjuvant Therapy for High-Risk Rectal Carcinoma



Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. **N Engl J Med** 1991;324:709-715

Gastrointestinal Tumor Study Group. Adjuvant therapy of colon cancer -- results of a prospectively randomized trial. **N Engl J Med** 1984;310:737-743

National Institutes of Health Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. **JAMA** 1990;264:1444-1450

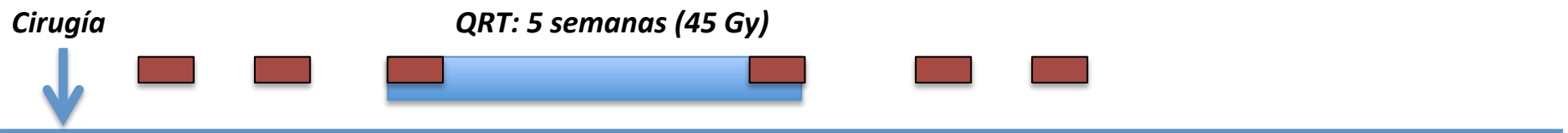
*El CONSENSO de la NIH de los
Estados Unidos de 1990
“decretó” como estándar para
T3/T4 o N+ la
quimiorradioterapia y
quimioterapia postoperatoria*

Entre tanto, los Europeos...

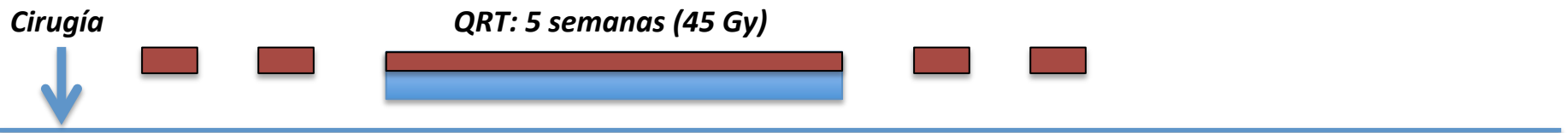
*No estaban tan seguros de que
la QUIMIOTERAPIA después de
la radioterapia fuera tan
importante...*

Improving Adjuvant Therapy for Rectal Cancer by Combining Protracted-Infusion Fluorouracil with Radiation Therapy after Curative Surgery

n=680



O'Connell MJ, et al. Improving Adjuvant Therapy for Rectal Cancer by Combining Protracted-Infusion Fluorouracil with Radiation Therapy after Curative Surgery. *N Engl J Med* 1994; 331:502-507



FU 225 mg/m² en infusión de 24 horas cada día durante la RT

FU 500 mg/m² bolo por día, días 1-3, primera y última semana de RT



Protacted Infusion of 5-FU

660 patients with stage II,III rectal cancer

	PI-FU	Bo-FU	
Local recurrence	ns	ns	p=0.11
4-year DFS	63%	53%	p=0.01
4-year OS	70%	60%	p=0.005

O`Connell. NEJM 1994;331:331

Optimal combination of chemo- radiotherapy?

- If radiochemotherapy is used postoperatively, protracted infusion of 5-FU is superior to bolus 5-FU during radiotherapy

O`Connell. NEJM 1994;331:331





*Y llegaron
los
Suecos...*

Preoperative RT in resectable RC

RT: 25 Gy Cirugía



Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997;336:980-987

Swedish Rectal Cancer Trial

1168 patients randomised to 25 Gy (5x5) PRT or no RT

	Surgery alone	Preop. RT	
Rate of local recurrence	27%	11%	p<0.001
5-year overall survival	48%	58%	p=0.004

Swedish Rectal Cancer Trial. *NEJM* 1997;336:980

El esquema de RT corta de los Suecos (5x5) es una opción válida cuando NO hay probabilidades de salvar el esfínter, y el tumor puede ser resecado completamente sin esperar que disminuya su tamaño (bajo volumen)

La quimiorradioterapia con fluoropirimidinas DESPUÉS de la cirugía mejora desenlaces relevantes, QUÉ PASA si la damos ANTES de la cirugía?

Vienen los
Alemanes...

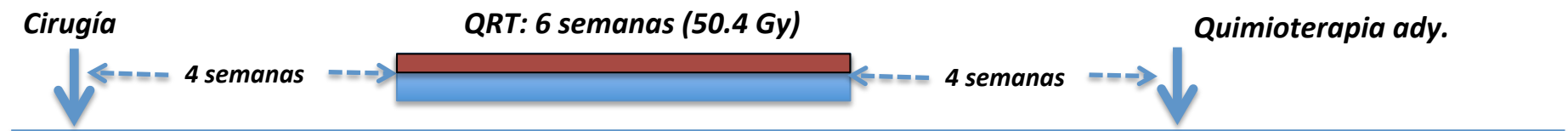
8 E48 E52
München 30 km



Cáncer de recto estadio II o III



Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731-1740



FU 1000 mg/m² por día, días 1-5, primera y última semana de RT

Preoperative vs Postoperative Chemoradiotherapy for Rectal Cancer

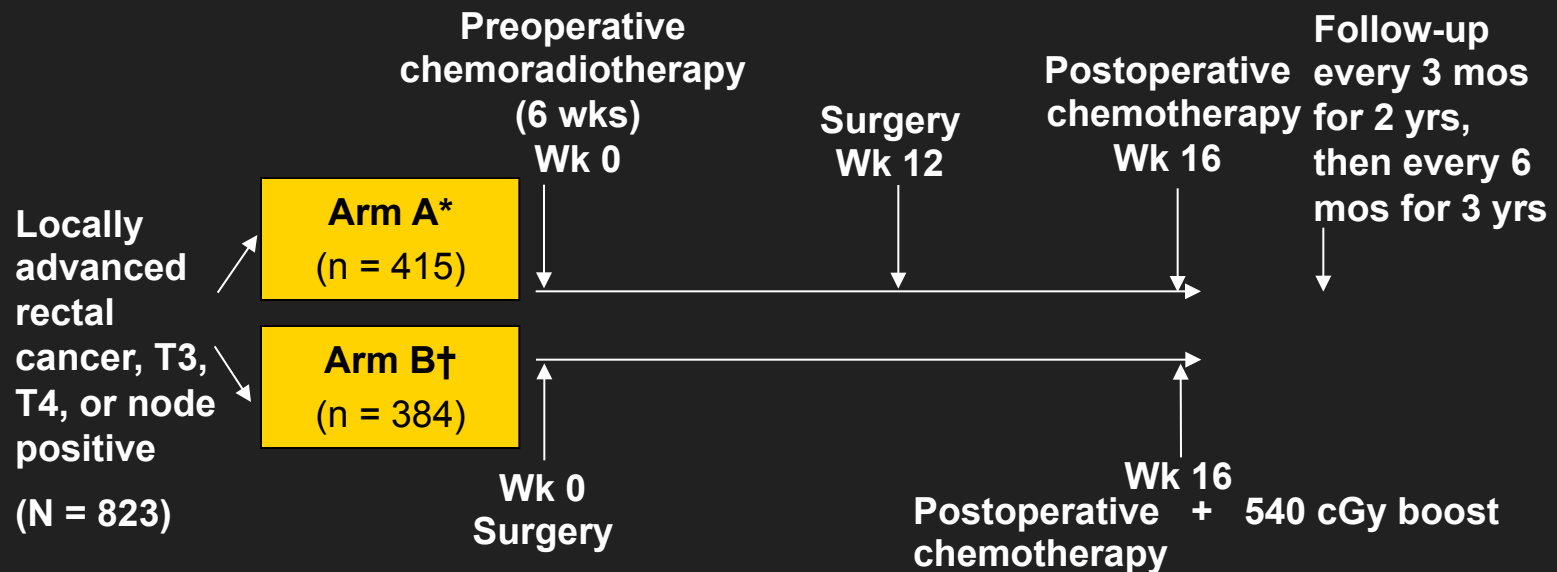
Sauer R, Becker H, Hohenberger W, et al.

***N Engl J Med.* 2004;351:1731-1740.**

Background and Rationale

- **Adjuvant radiotherapy with or without chemotherapy improves outcomes in patients with rectal cancer**
 - Unclear whether preoperative or postoperative chemoradiotherapy affords greater benefit
- **In locally advanced disease**
 - Chemoradiotherapy improves local control and overall survival
 - Unclear whether preoperative or postoperative chemoradiotherapy is superior
- **Current trial conducted by German Rectal Cancer Study Group**

Summary of Study Design



**Arm A: Preoperative chemoradiotherapy: 28 fractions (180 cGy/day, 5 x/wk) radiotherapy plus 5-fluorouracil (5-FU) as 120-hr continuous infusion (1000 mg/m²/day) in Wks 1 and 5 of RT*

Postoperative chemotherapy: bolus 5-FU (500 mg/m² 5 x/wk) every 4 wks for 4 cycles

†Arm B: Chemotherapy: bolus 5-FU (500 mg/m²/day) for 5 days, every 4 wks for 4 cycles

Preoperative vs Postoperative Chemoradiotherapy for Locally-Advanced Rectal Cancer

	Preoperative (n=197)	Postoperative (n=195)	p
<i>OS @ 5yr</i>	76%	74%	NS
<i>DFS @ 5yr</i>	68%	65%	NS
<i>Completion CRT</i>	99%	72%	<0.01
<i>Acute toxicity (G3/4)</i>	27	40	<0.01
<i>Long-Term toxicity (G3/4)</i>	24	12	0.01
<i>Local relapse @ 5yr</i>	6%	13%	0.006

OS: Overall survival, DFS: Disease-free survival

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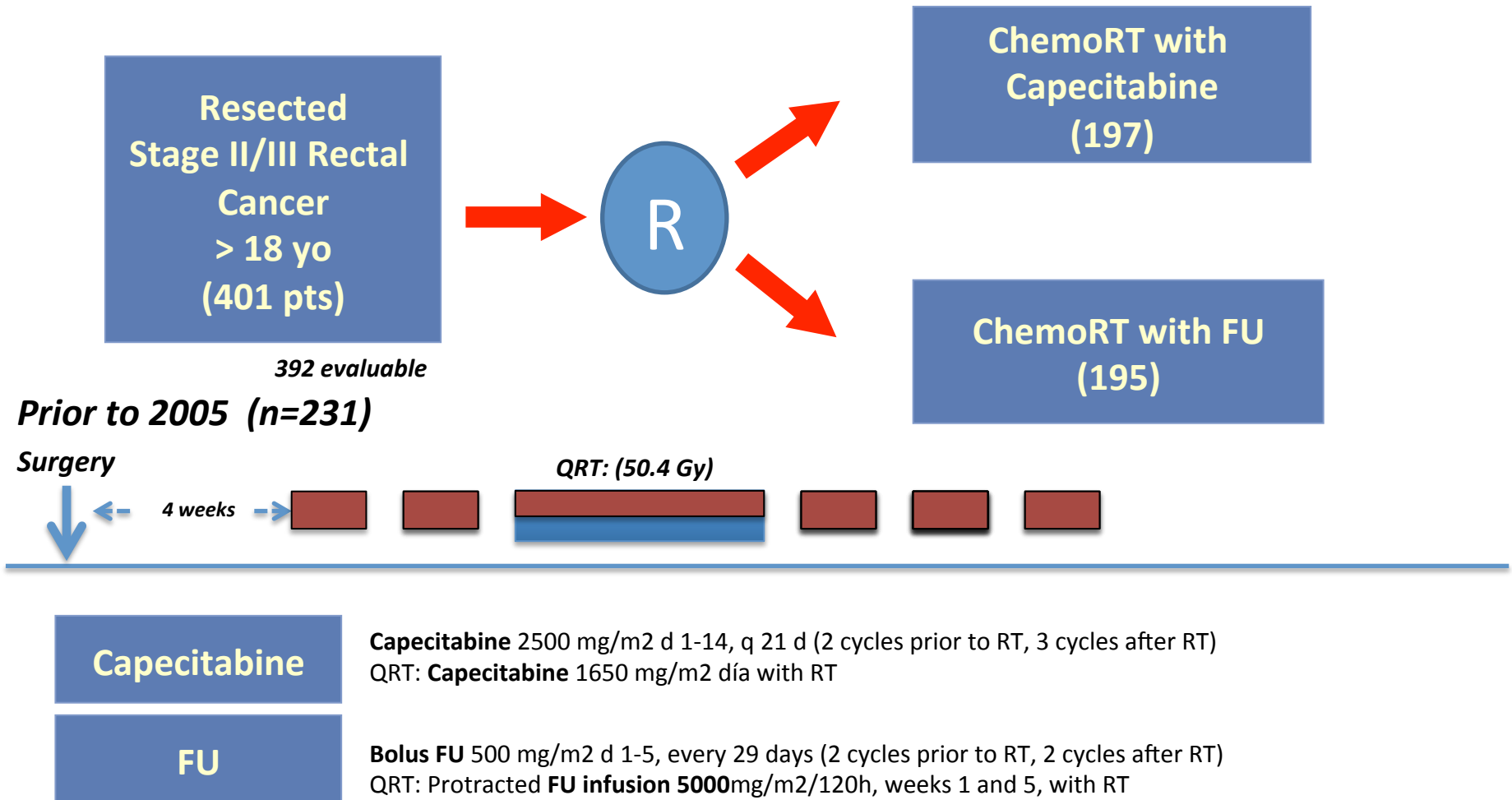
Key Conclusions

- **Compared with postoperative chemotherapy, preoperative chemoradiotherapy in patients with locally advanced rectal cancer:**
 - Improves
 - » Local control
 - » Treatment compliance
 - » Rates of sphincter preservation
 - Reduces long-term toxicity
 - Does *not* improve overall survival or disease-free survival
- **Preoperative chemoradiotherapy should be considered first-line therapy for patients with locally advanced rectal cancer**

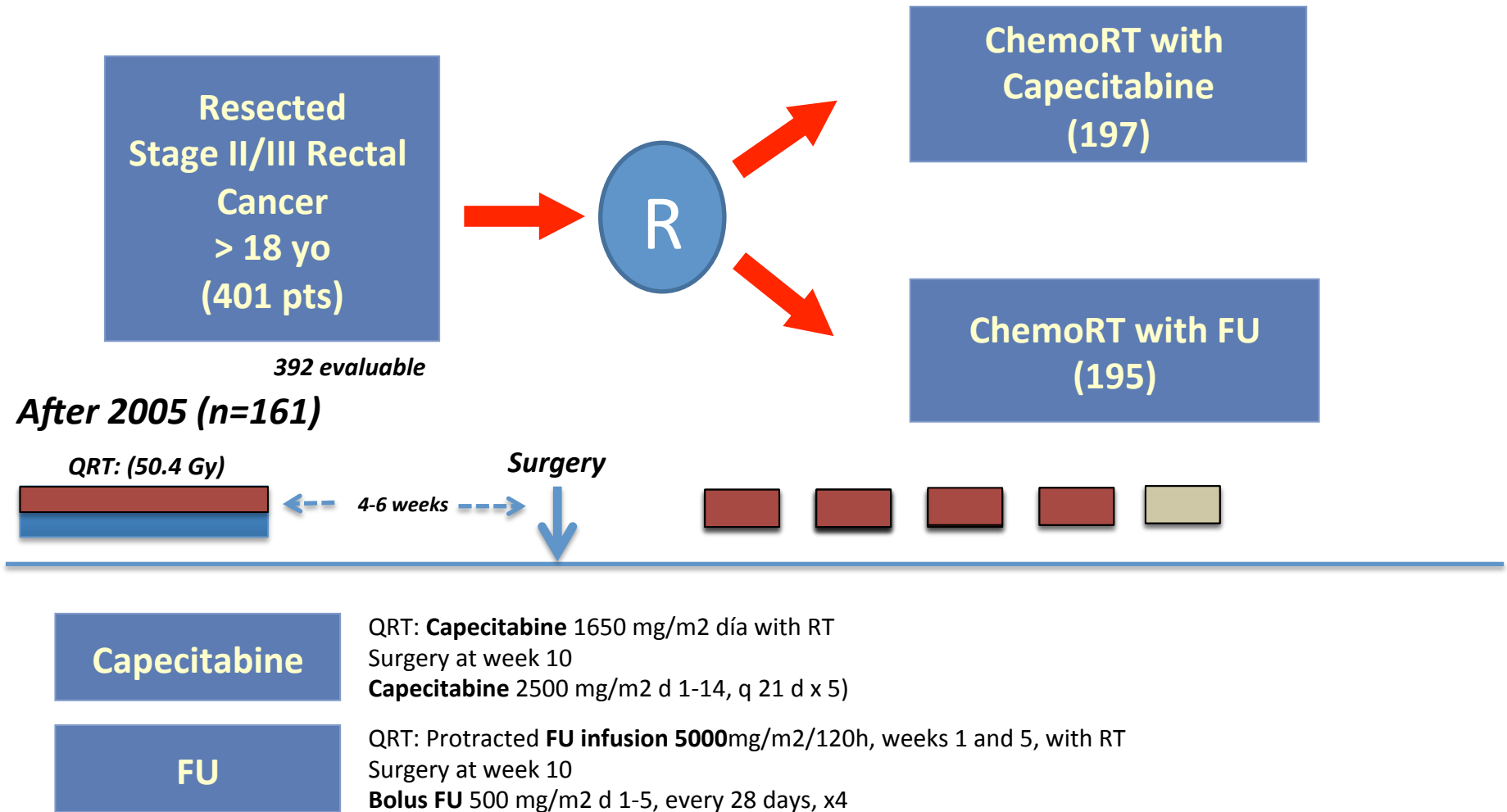


Refinando la terapia con Fluoropirimidinas

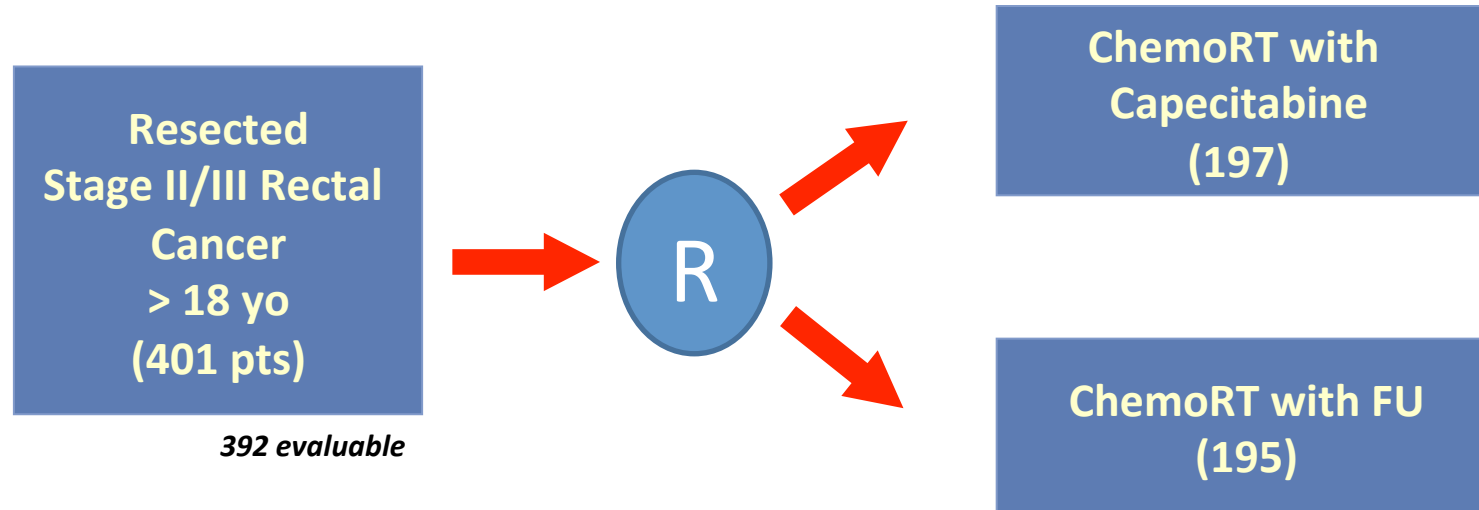
Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial



Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial



Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial



Primary endpoint: Non-inferiority of capecitabine in terms of 5-year **overall survival** on all patients with post-randomisation data

Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial

	Capecitabine (n=197)	Fluoruracilo (n=195)	p
<i>OS @ 5 yr</i>	76%	67%	0.004 / 0.05
<i>pCR</i>	10/73 (14%)	4/74 (5%)	0.09
Site of recurrence			
Local	12 (6%)	14 (7%)	NS
Distant	37 (19%)	54 (28%)	0.04
Deaths			
Total	38 (19%)	55 (28%)	0.04
Disease-related	26 (13%)	37 (19%)	NS

OS: Overall survival, pCR: Pathologic complete response

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Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial

	Capecitabine (n=197)	Fluoruracilo (n=195)	p
<i>Leucopenia (G3/4)</i>	3	16	0.04
<i>Diarrhea (G1/2)</i>		4/74 (5%)	0.09
Site of recurrence			
Local	12 (6%)	14 (7%)	NS
Distant	37 (19%)	54 (28%)	0.04
Deaths			
Total	38 (19%)	55 (28%)	0.04
Disease-related	26 (13%)	37 (19%)	NS

OS: Overall survival, pCR: Pathologic complete response

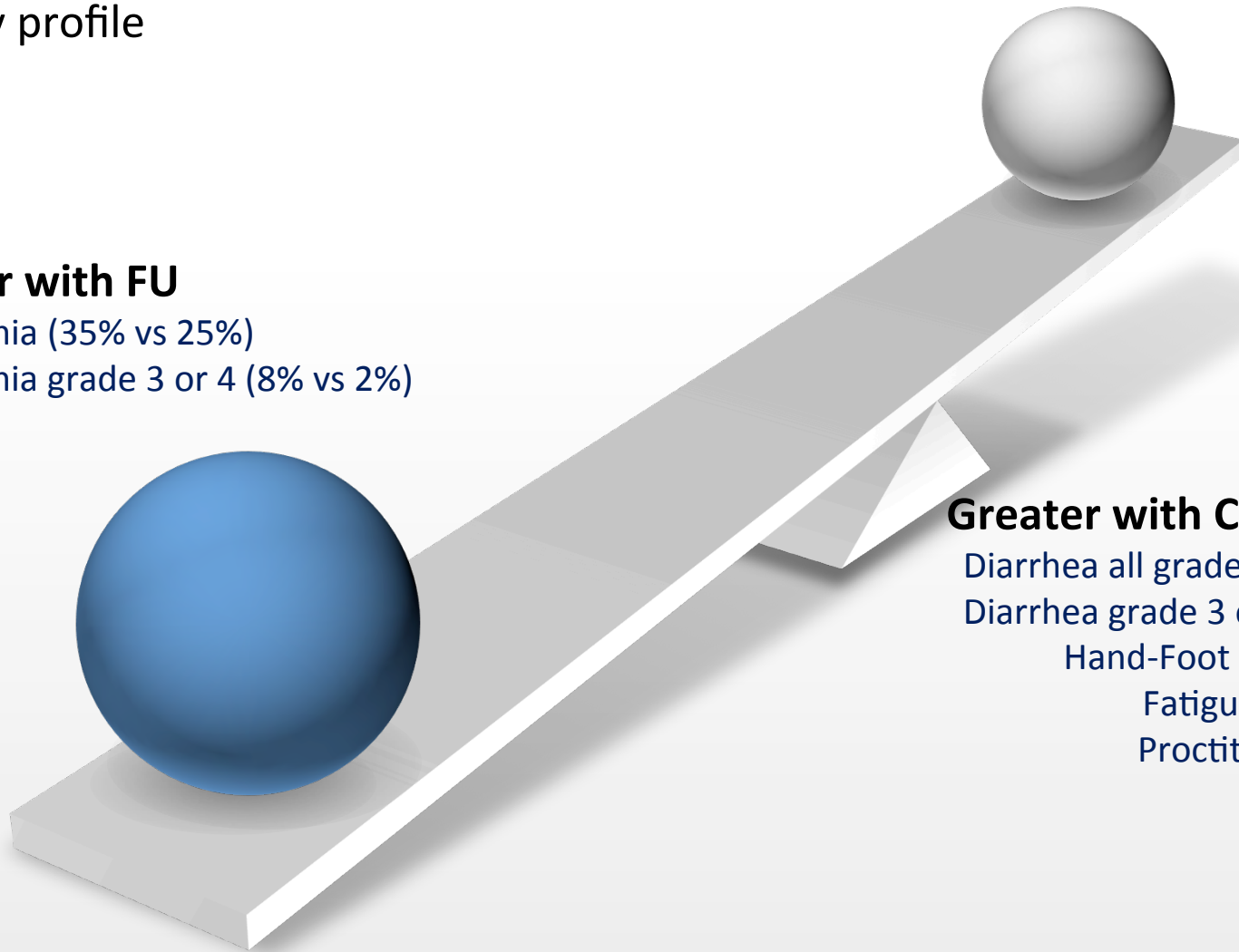
Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial

Toxicity profile

Greater with FU

Leucopenia (35% vs 25%)

Leucopenia grade 3 or 4 (8% vs 2%)



Greater with Capecitabine

Diarrhea all grades (53% vs 44%)

Diarrhea grade 3 or 4 (9% vs 2%)

Hand-Foot SR (31% vs 2%)

Fatigue (28% vs 15%)

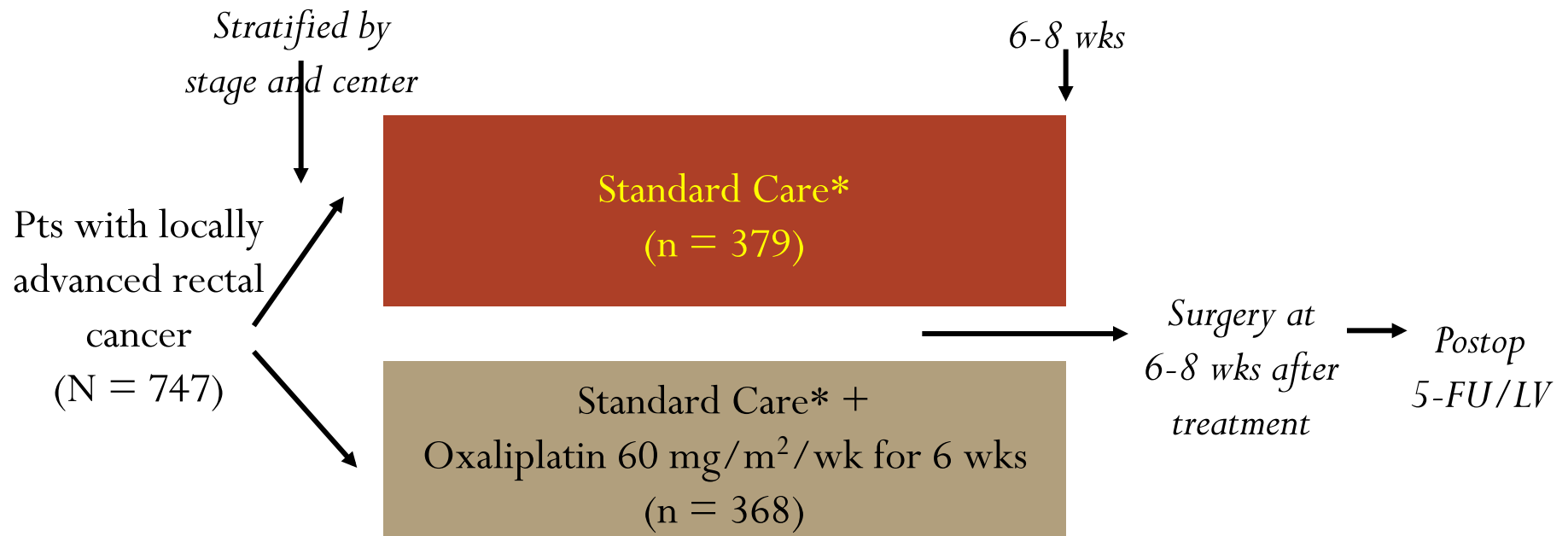
Proctitis (16% vs 1%)



Oxaliplatino radiosensibilizante

Oxaliplatino + RT en Cáncer de Recto

Ph III STAR-01: Preoperative 5-FU/RT ± Oxaliplatin in Locally Adv. Rectal Cancer



*RT 50.4 Gy/day, 28 daily fractions, + 5-FU 225 mg/m²/day administered by protracted venous infusion.

- Primary endpoint: OS
- Secondary endpoints: pCR, DFS, safety

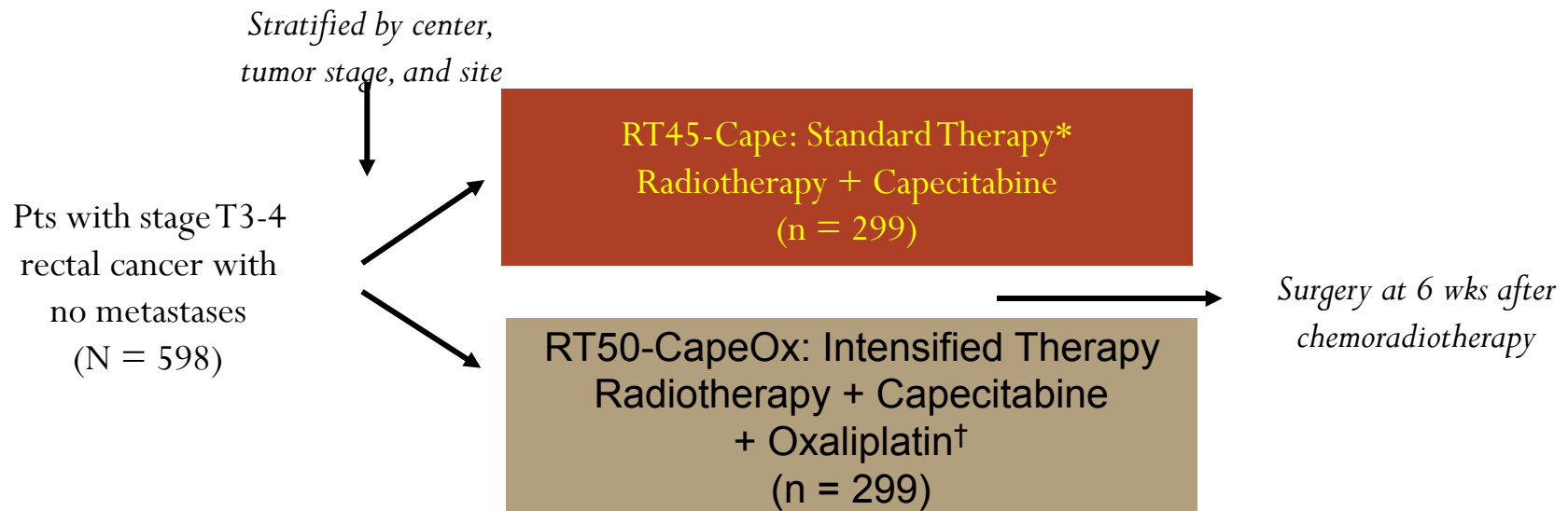
STAR-01: Efficacy Results

- Current analysis focused on pCR
- **16% (95% CI: 13% to 20%) of pts in both groups achieved pCR**
- No difference in tumor response (downgrade of tumor size, stage, or nodal involvement) at surgery between treatment arms
- Addition of oxaliplatin did not affect ability of pts to go on to surgery
- Significantly fewer occult metastases detected at surgery in oxaliplatin arm

Subclinical Metastases, n	Oxaliplatin + 5-FU/RT (n = 368)	5-FU/RT (n = 368)
Liver	1	6*
Peritoneal	1	4
Nodes	0	1

* $P = .014$

Phase III ACCORD 12: RT45-Cape vs RT50-CAPEOX in Locally Adv. Rectal Cancer



*Dosing: radiotherapy 45 Gy/5 wks, capecitabine 800 mg/m² BID, excluding weekends.

†Dosing: radiotherapy 50 Gy/5 wks, capecitabine 800 mg/m² BID, excluding weekends, oxaliplatin 50 mg/m²/wk.

- Primary endpoint: pCR (ie, complete sterilization of operative specimen using Dworak-Quirke criteria)
- Secondary endpoints: circumferential rectal margin, toxicity, local control, DFS, OS, bowel and sexual functionality assessment

Phase III Prodigie ACCORD 12: Results

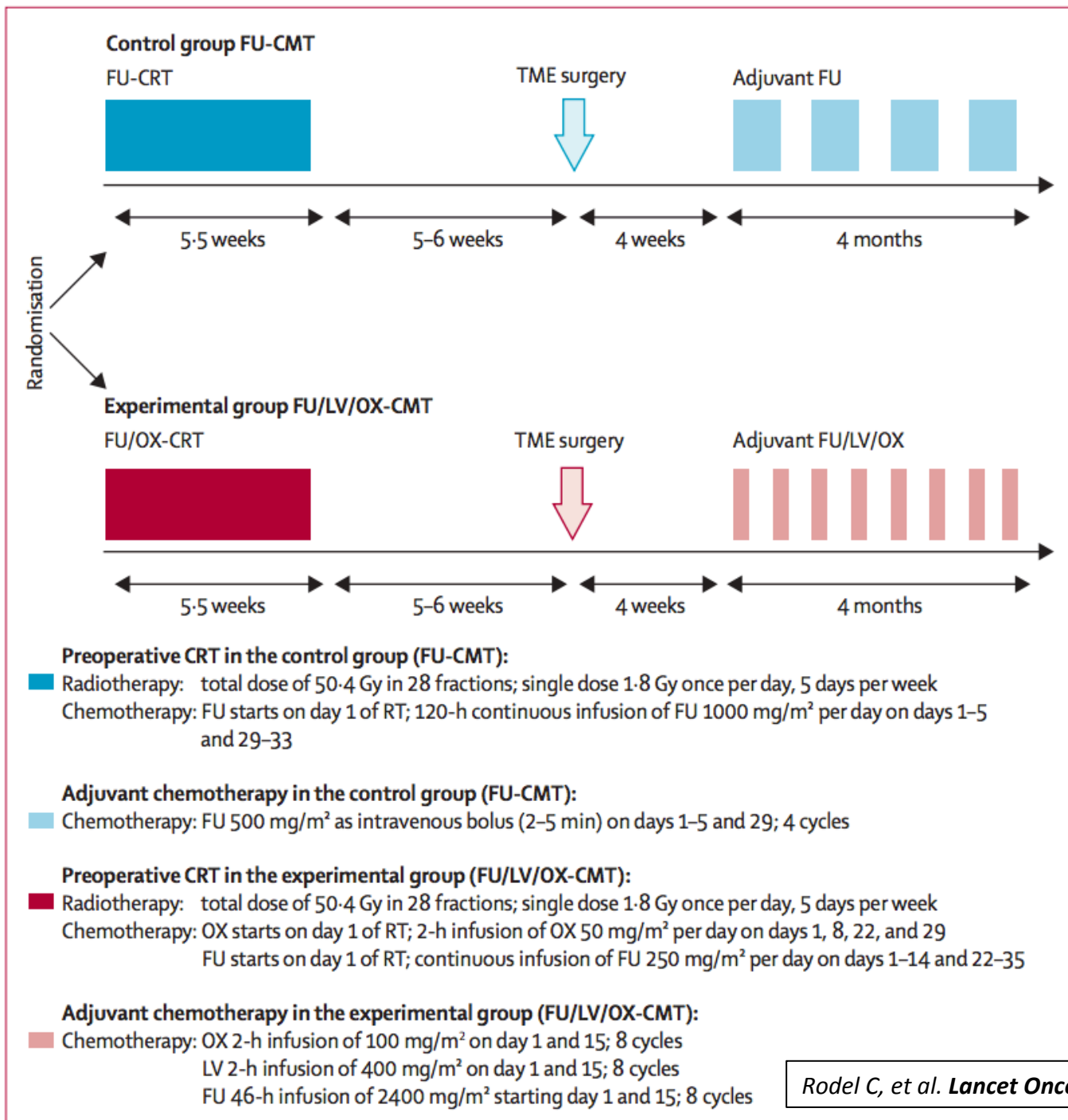
- Similar rate of tumor response between treatment arms; no significant benefit to addition of oxaliplatin to standard RT preoperative regimen
 - Trend toward higher pCR rates in RT50-CapeOx arm 41% vs 30% for standard RT arm ($P = .008$)
 - Subgroup analysis using pt characteristics also showed no significant effect on tumor response; surgical outcomes similar between treatment groups
- Circumferential rectal margin decreased in pts receiving RT50-CapeOx intensified therapy; effect on pelvic local control unknown

Margin, %	RT50-CapeOx Intensified Therapy (n = 147)	RT45-Cape Standard Therapy (n = 162)
▪ ≤ 1 mm	7	12
▪ ≤ 2 mm	9	19*

* $P = .017$

**Preoperative chemoradiotherapy and
postoperative chemotherapy with
fluorouracil and oxaliplatin vs fluorouracil
alone in locally advanced rectal cancer:
initial results of the German CAO/ARO/
AIO-04 randomised phase 3 trial**

Rodel C, et al, of the German Rectal Cancer
Study Group. Lancet Oncol 2012; 13:
679-87



Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin vs fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial

	Oxaliplatin + FU (n=613)	FU (n=623)	p
G3/4 toxicity	23%	27%	NS
G3/4 Diarrhea	12%	8%	
G3/4 Nausea/Vomit	4%	1%	
pCR	17%	13%	0.038

pCR: pathologic complete response

Higher pCR may be of clinical significance, awaiting mature results

Faith Versus Facts

WE HAVE TWO OPTIONS.
EITHER AN EVIDENCE -
BASED TREATMENT OR
AN EXCITING, RISKY
ALTERNATIVE.

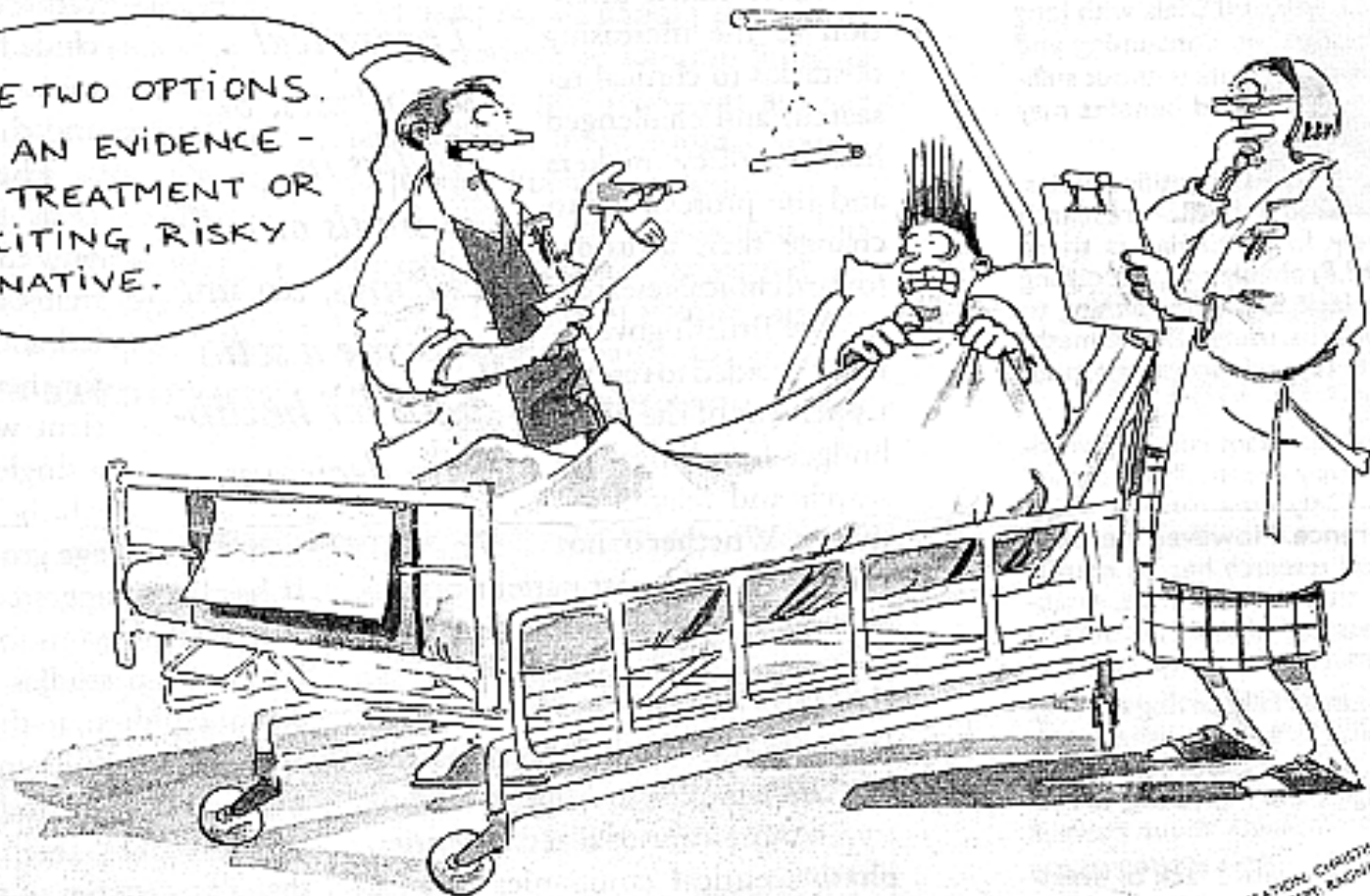
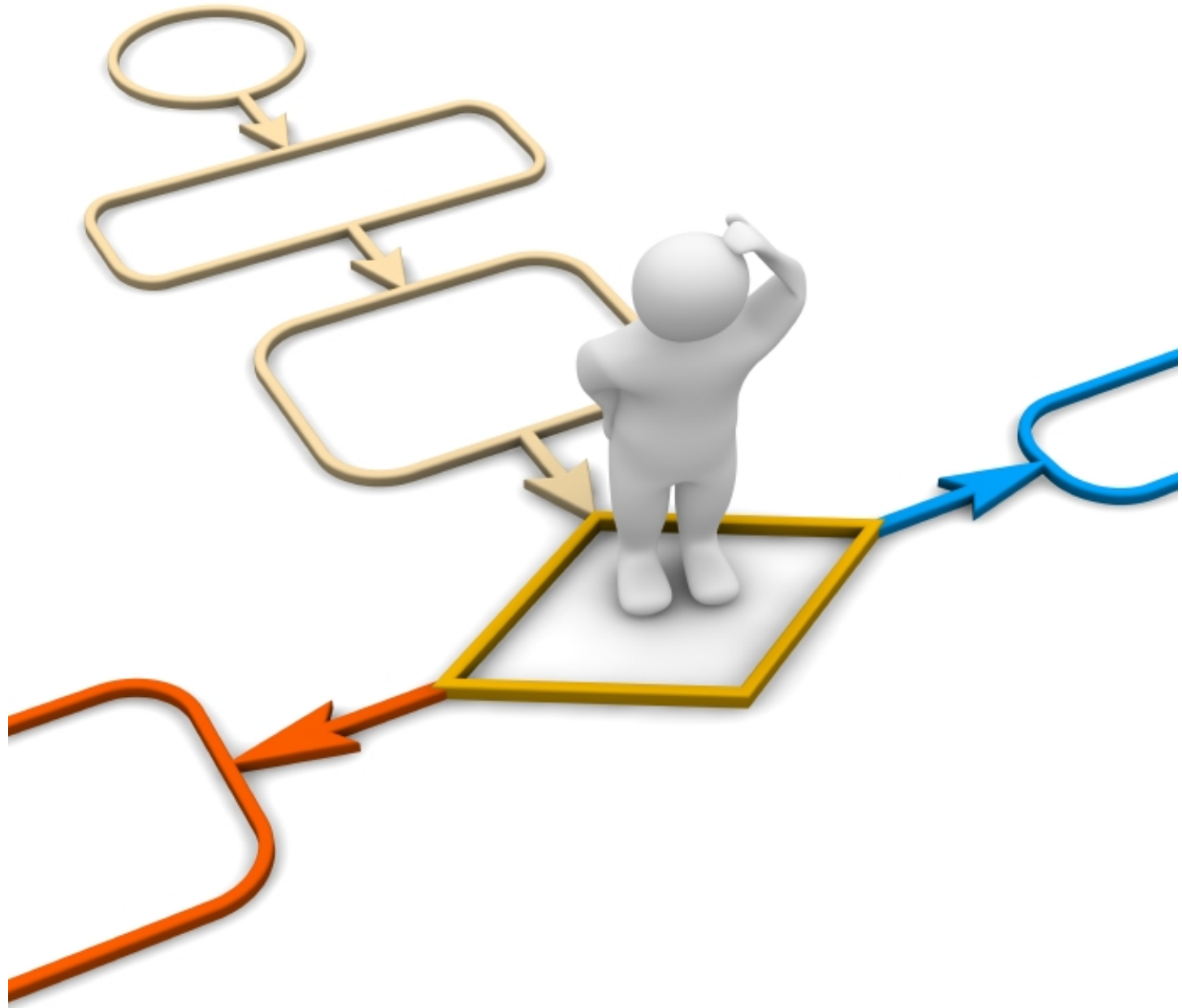


ILLUSTRATION: CHRISTINA ALONSO
CONCEPT: RAGNAR LEVI



Recapitulando...

RT PostOp
>
Cirugía (LR)

Recapitulando...

RT PostOp
>
Cirugía (LR)

Quimio y QuimioRT PostOp
>
RT PostOp (LR, OS)

NIH, NEJM - 1990

Recapitulando...

RT PostOp
>
Cirugía (LR)

Quimio y QuimioRT PostOp
>
RT PostOp (LR, OS)

NIH, NEJM - 1990

QuimioRT(FU infusional (PVI)) PostOp + Quimio
>
QuimioRT(FU bolo) PostOp + Quimi (OS)

O'Connell, NEJM - 1994

Recapitulando...

RT PostOp
>
Cirugía (LR)

Quimio y QuimioRT PostOp
>
RT PostOp (LR, OS)

NIH, NEJM - 1990

QuimioRT(FU infusional (PVI)) PostOp + Quimio
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QuimioRT(FU bolo) PostOp + Quimi (OS)

O'Connell, NEJM - 1994

QuimioRT (FU PVI) PreOp + Quimio PostOp
>
QuimioRT(FU PVI) PostOp + Quimio PostOP (LR)

Sauer, NEJM - 2004

Recapitulando...

RT PostOp
>
Cirugía (LR)

Quimio y QuimioRT PostOp
>
RT PostOp (LR, OS)

NIH, NEJM - 1990

QuimioRT(FU infusional (PVI)) PostOp + Quimio
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QuimioRT(FU bolo) PostOp + Quimi (OS)

O'Connell, NEJM - 1994

QuimioRT (FU PVI) PreOp + Quimio PostOp
>
QuimioRT(FU PVI) PostOp + Quimio PostOP (LR)

Sauer, NEJM - 2004

QuimioRT (Cape) Pre/PostOp + Quimio PostOp
:: No inferior ::
QuimioRT (FU PVI) Pre/PostOp + Quimio PostOP (OS)

Hofheinz, Lancet Oncol - 2012

Recapitulando...

RT: Radioterapia

Quimio: Quimioterapia

PreOp / PostOp: Preoperatoria / Postoperatoria

PVI: Infusión venosa continua larga

LR: Recurrencia local

OS: Supervivencia global

pCR: Respuesta patológica completa

RT PostOp
>
Cirugía (LR)

Quimio y QuimioRT PostOp
>
RT PostOp (LR, OS)

NIH, NEJM - 1990

QuimioRT(FU infusional (PVI)) PostOp + Quimio
>
QuimioRT(FU bolo) PostOp + Quimi (OS)

O'Connell, NEJM - 1994

QuimioRT (FU PVI) PreOp + Quimio PostOp
>
QuimioRT(FU PVI) PostOp + Quimio PostOP (LR)

Sauer, NEJM - 2004

QuimioRT (Cape) Pre/PostOp + Quimio PostOp
:: No inferior ::
QuimioRT (FU PVI) Pre/PostOp + Quimio PostOP (OS)

Hofheinz, Lancet Oncol - 2012

QuimioRT (OxFU PVI) PreOp + Quimio PostOp
>
QuimioRT (FU PVI) PreOp + Quimio PostOP (pCR)

Rodel, Lancet Oncol - 2012

Estado del arte de neoadyuvancia de cáncer de recto

Conclusiones



RT-Fluoropirimidina

Estadíos II-III

OS 5a: 75% /
Recurrencia local: 6%

Sin cambios sustanciales desde 2004



RT-Capecitabina

Estadíos II-III

No inferior

Conveniente



RT-FU-Oxaliplatino

No indicado

Incrementa la toxicidad y la respuesta patológica completa

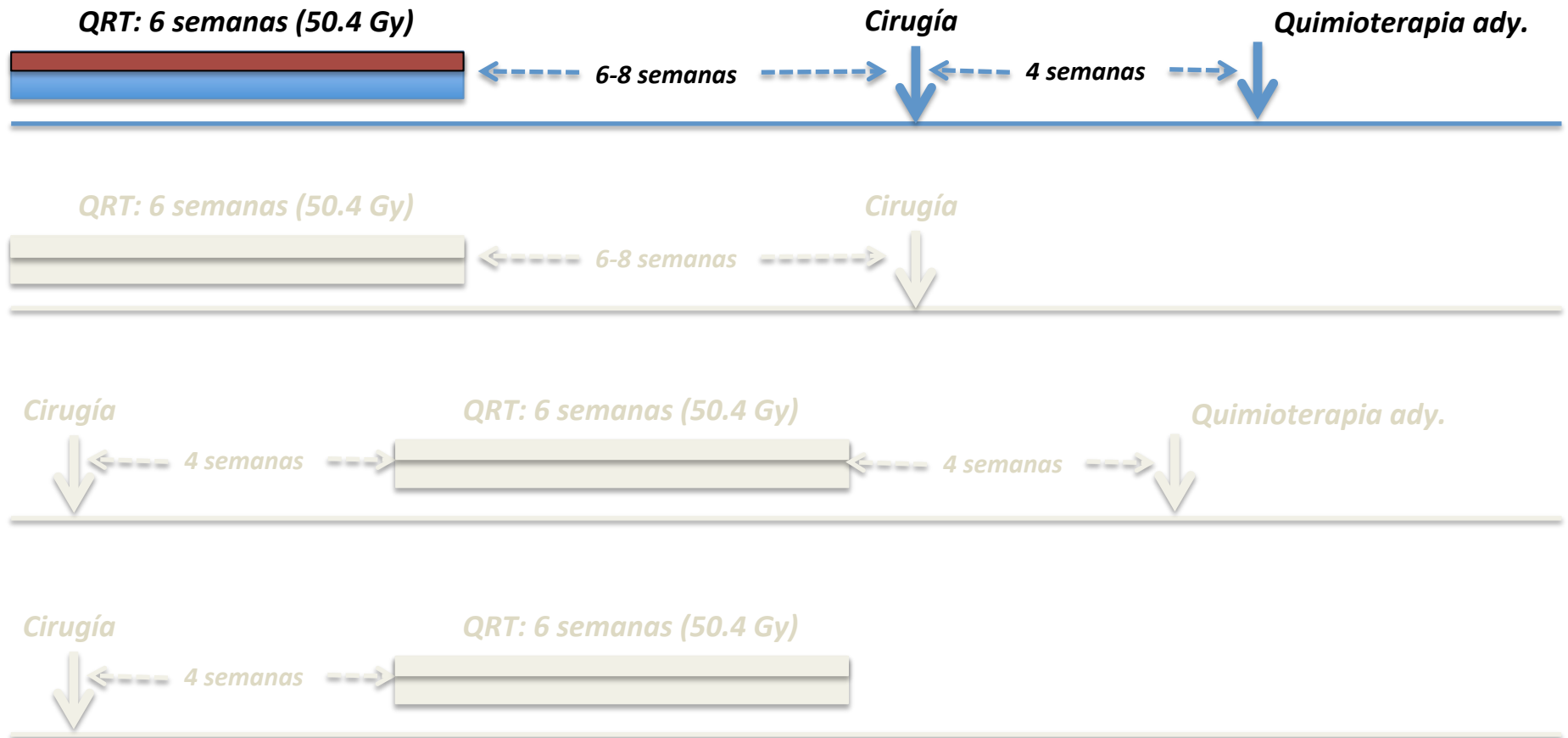


RT-FU-Biológicos

No indicado

En investigación – resultados poco alentadores

Cáncer de recto estadio II o III



Capecitabina 825 mg/m² vía oral cada 12 horas durante la RT
FOLFOX o FU o Capecitabina adyuvante por 4 meses

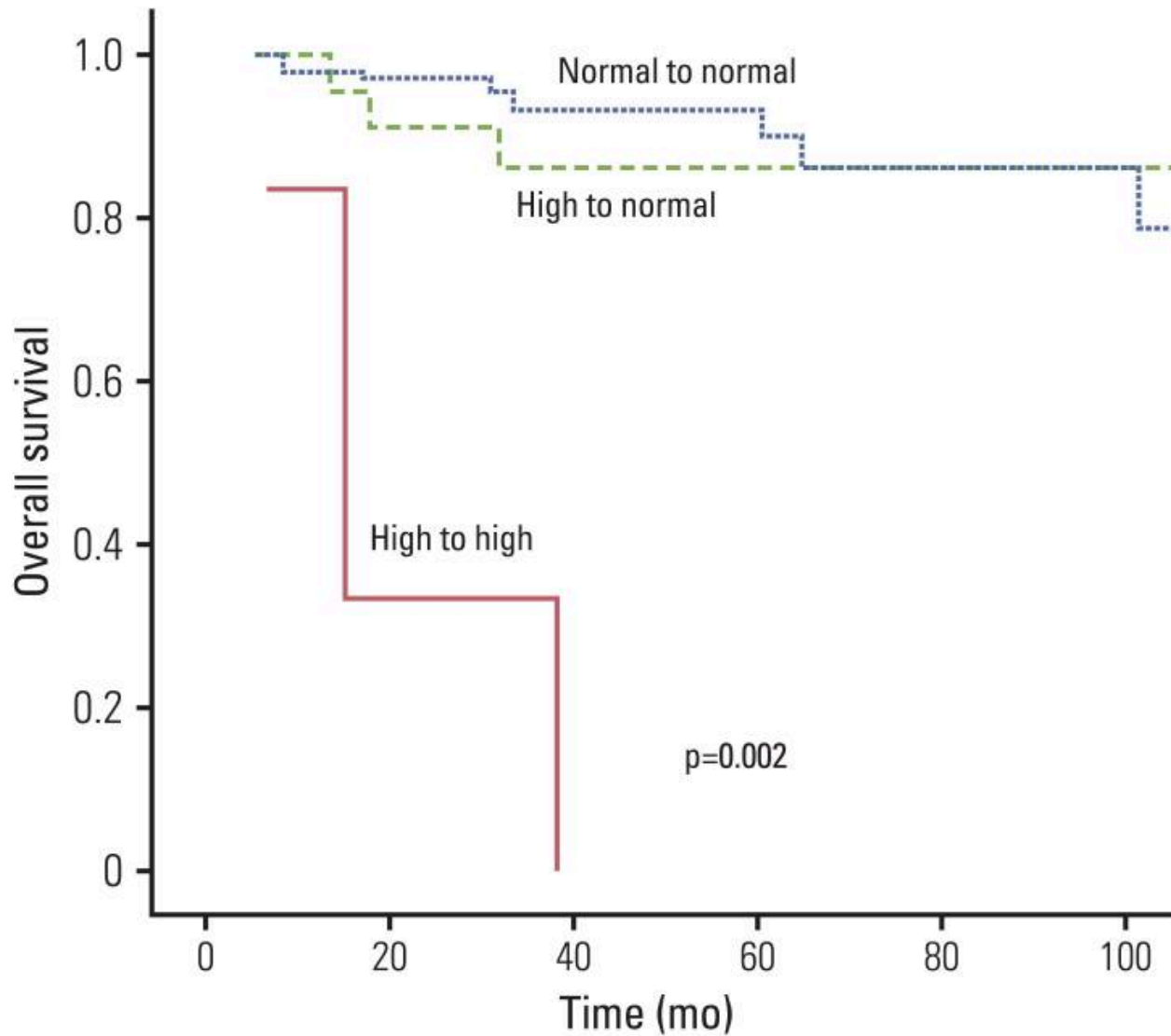
mauriciolema@yahoo.com



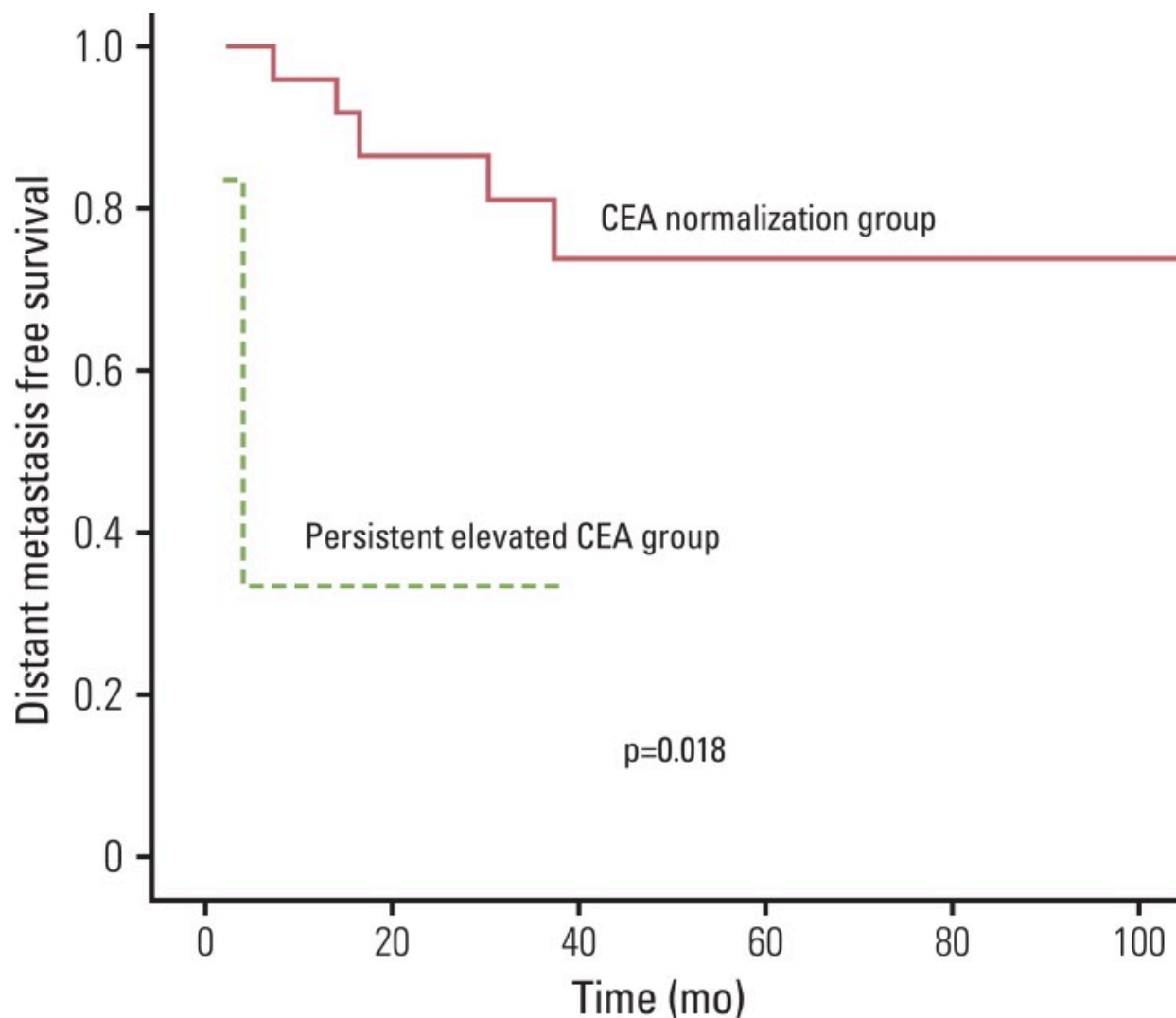


Quimioterapia adyuvante en cáncer de recto: Back-up Slides

Prognostic Significance of Serum CEA Normalization on Survival in Rectal Cancer Treated with Preoperative Chemoradiation



Prognostic Significance of Serum CEA Normalization on Survival in Rectal Cancer Treated with Preoperative Chemoradiation

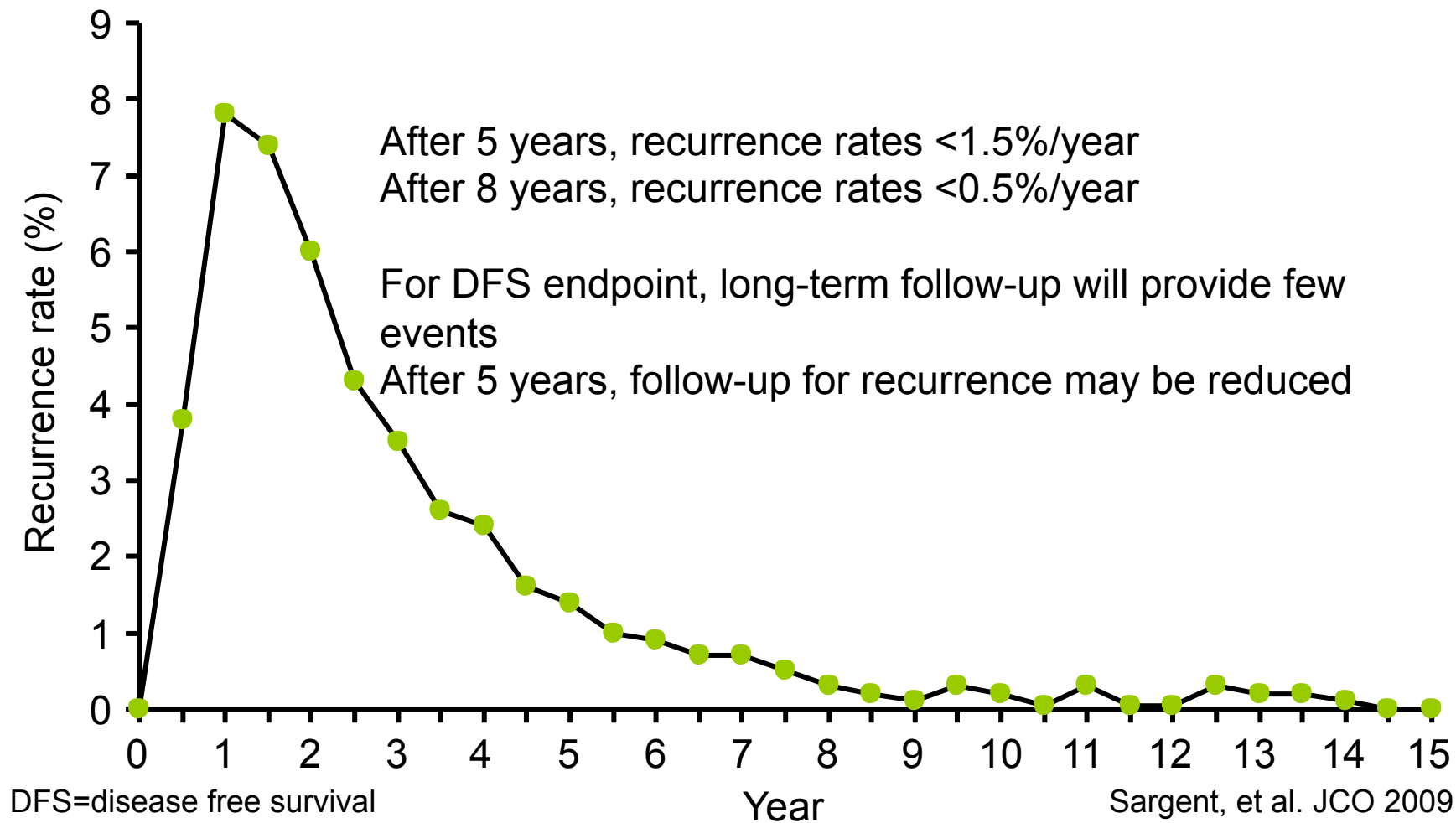




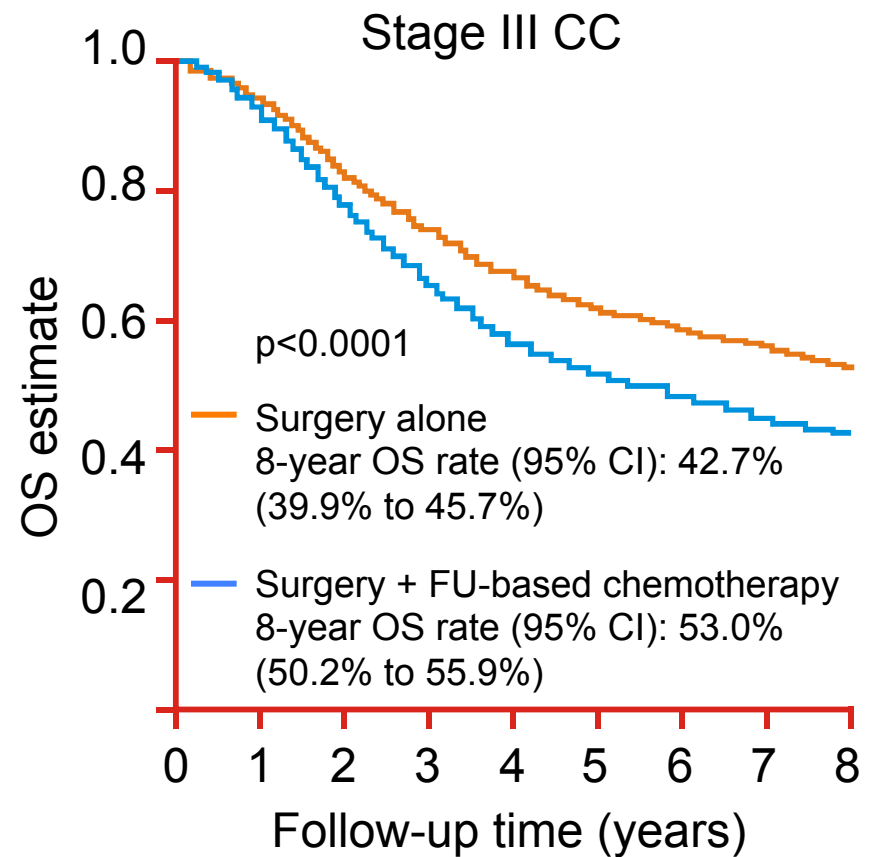
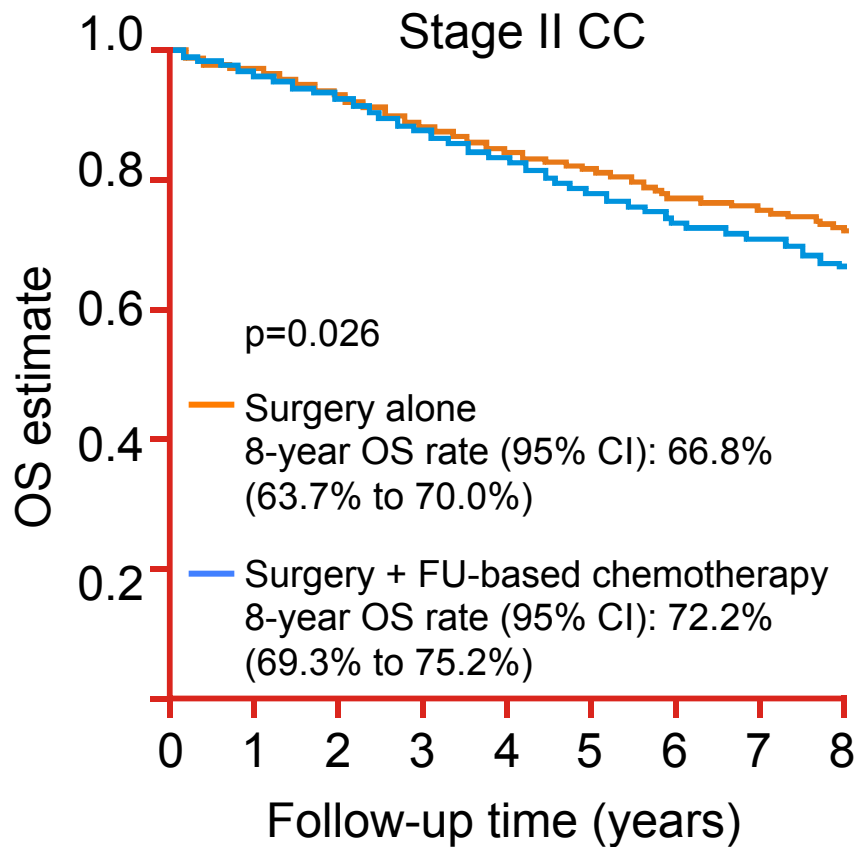
Supervivencia a 5 años de cáncer colo-rectal de acuerdo con el TNM7

Estadío	% de pacientes	Supervivencia a 5 años
I	23.9	96%
IIA	23.8	90%
IIB	2.4	84%
IIC	2.1	87%
IIIA	3.8	89%
IIIB	16.1	72%
IIIC	5.9	36%
IVA	14.5	15%
IVB	2.9	10%

N=2229; 1990-2006



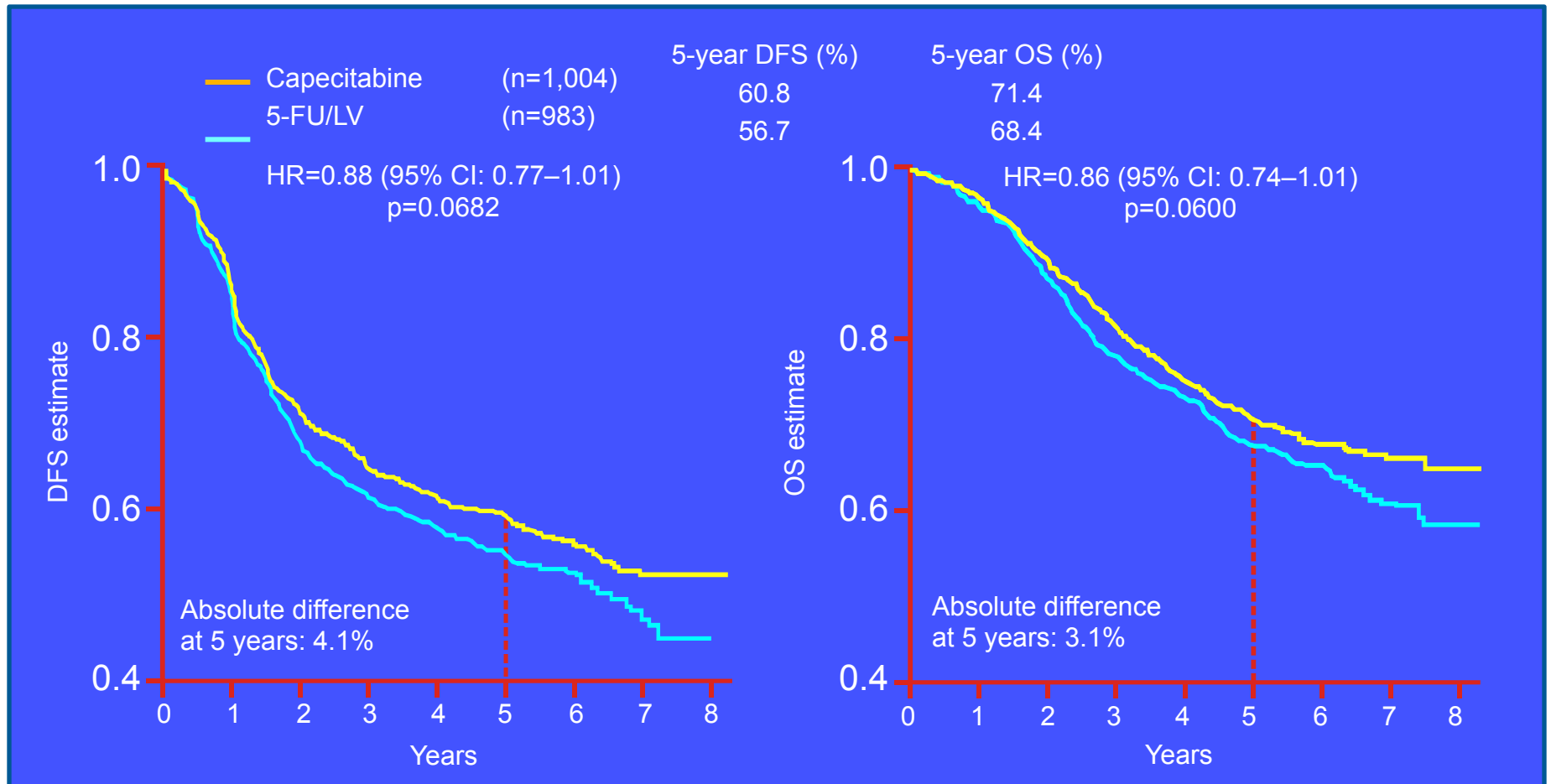
Adjuvant therapy increases the chance of survival: evidence in 20,898 CC patients



CC=colon cancer
OS=overall survival

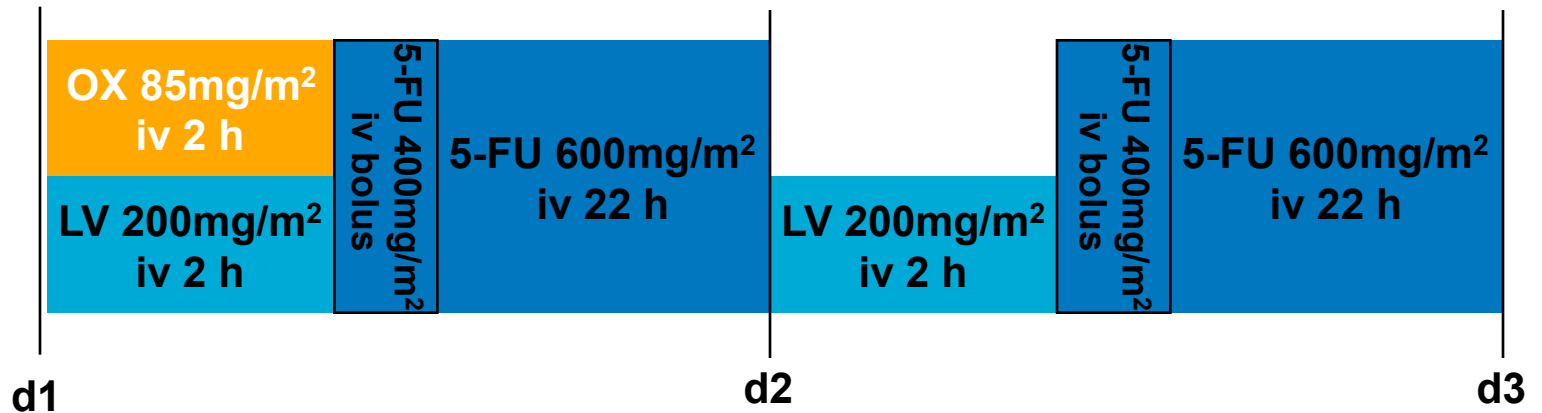
Sargent, et al. JCO 2009

X-ACT: 5-year DFS and OS updated data



FOLFOX-4

FOLFOX4: ciclo de 14-días



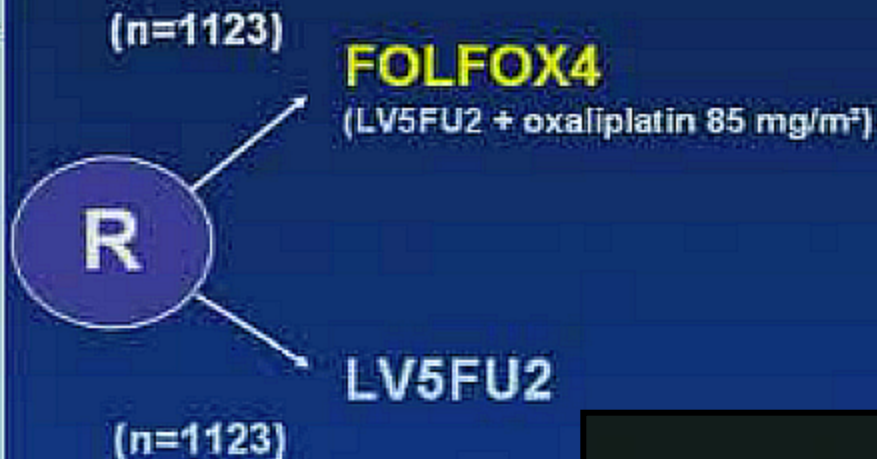
5-FU = 5-fluorouracilo; LV = leucovorin (Folinato de calcio); OX = oxaliplatino

Diseño del estudio MOSAIC

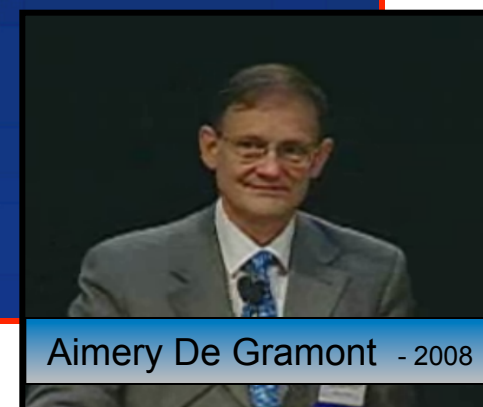
n=2246

Enrolment:
Oct 1998–Jan 2001 (146 centres;
20 countries)

- Completely resected colon cancer
- Stage II, 40%; Stage III, 60%
- Age 18–75 years
- KPS \geq 60
- No prior chemotherapy



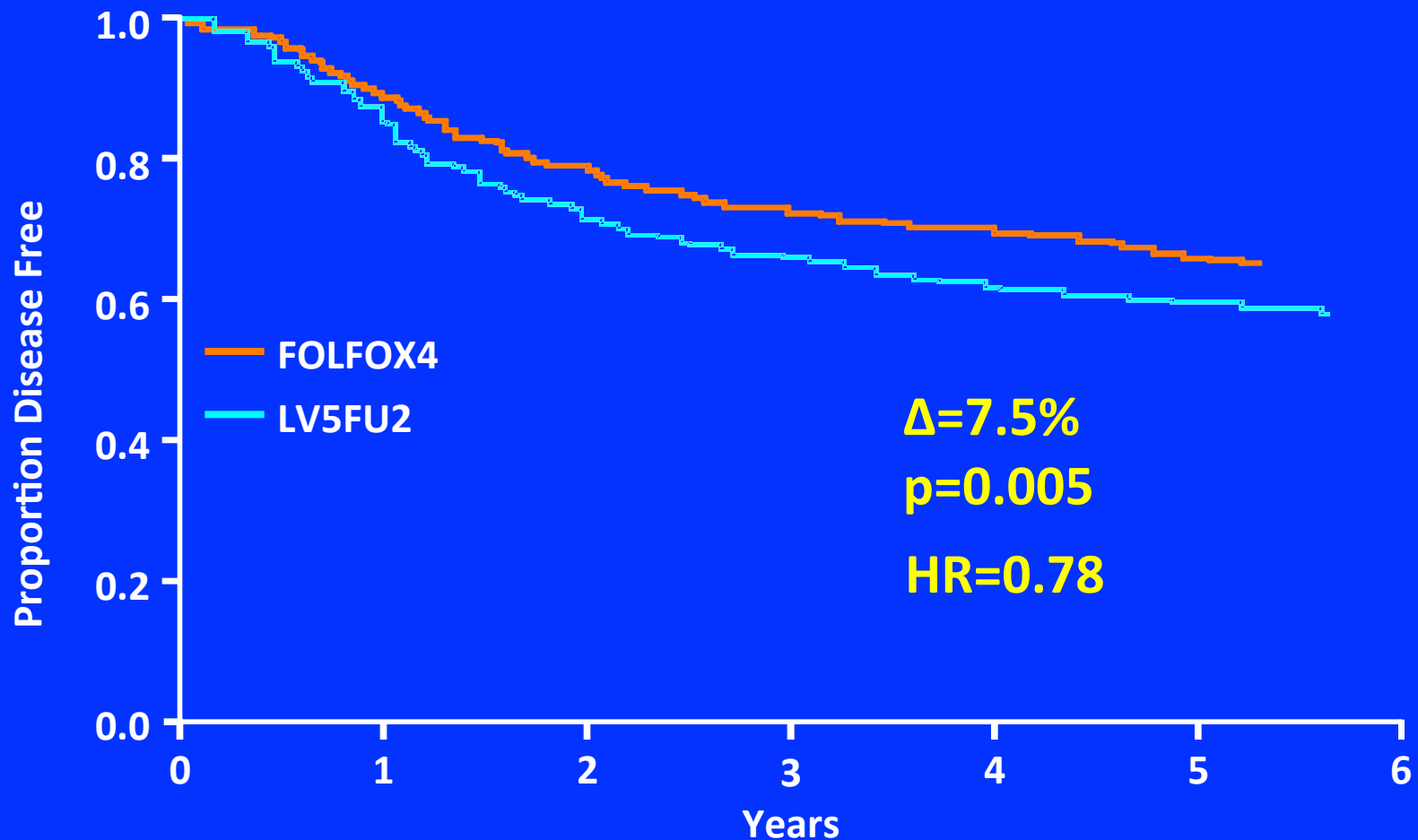
Primary end-point: disease-free survival
Secondary end-points: safety, overall survival



Aimery De Gramont - 2008

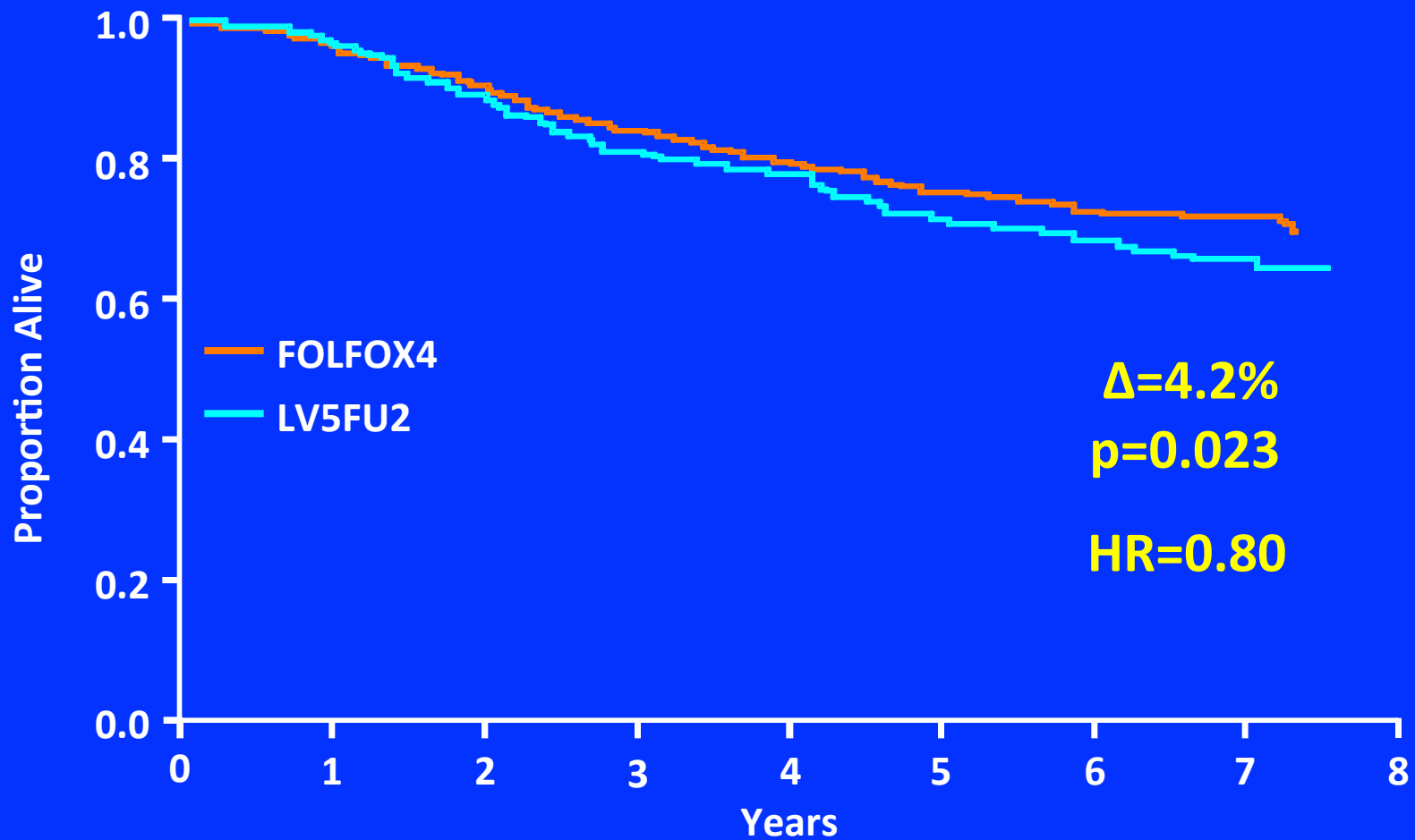
MOSAIC

DFS@5yrs: FOLFOX vs. 5-FU Stage III



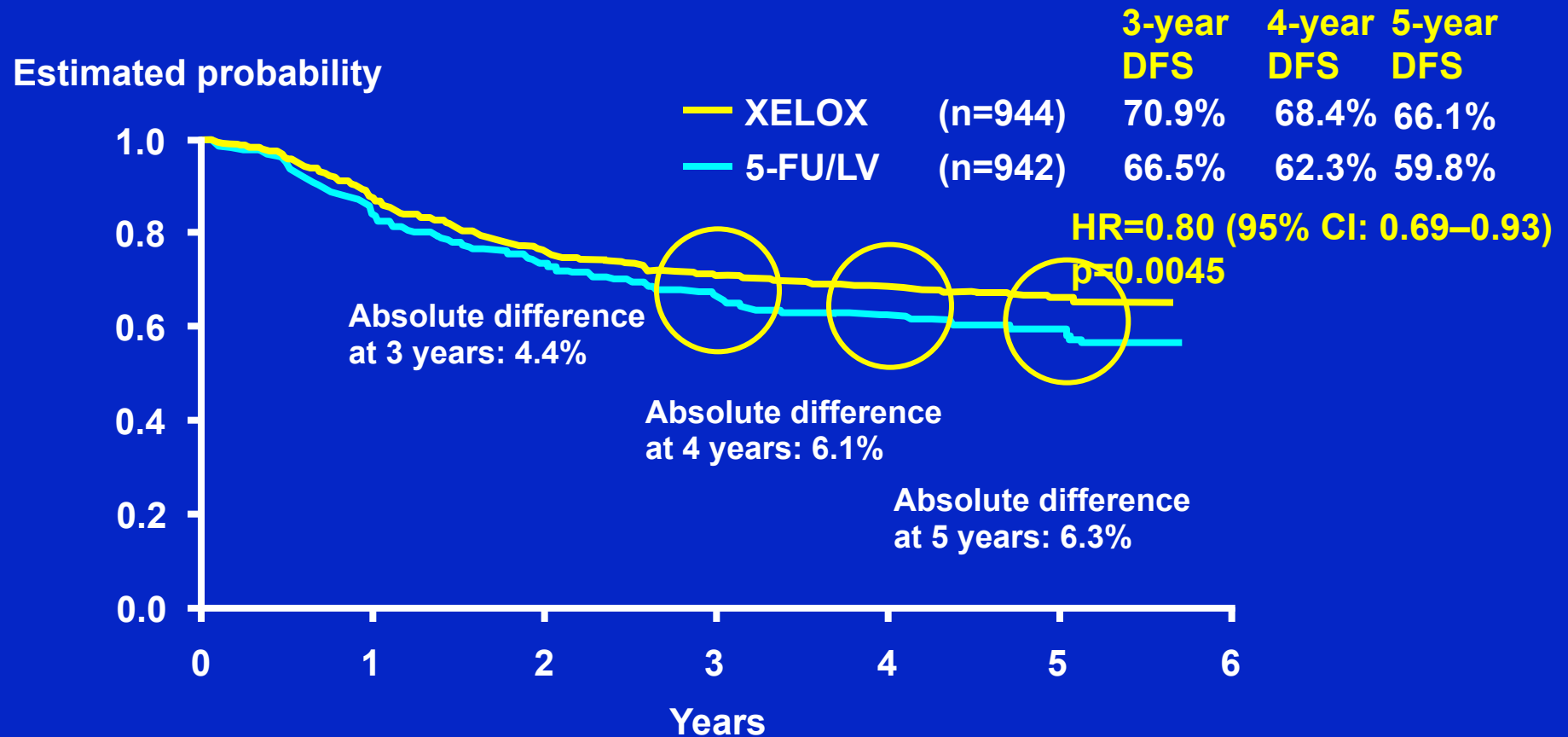
Andre et al., J Clin Oncol 2009

OS@6yrs: FOLFOX vs. 5-FU (MOSAIC)



Andre et al., J Clin Oncol 2009

Superior DFS with XELOX



ITT population

Haller et al. ECCO/ESMO 2009



MOSAIC – Neuropatía sensorial por oxaliplatino

