Terapia adyuvante en cáncer de colon

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TNM7 – Colorectal

Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- **T1** Tumor invades submucosa
- **T2** Tumor invades muscularis propria
- **T3** Tumor invades through the muscularis propria into pericolorectal tissues
- **T4a** Tumor penetrates to the surface of the visceral peritoneum[2]
- **T4b** Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)[4]

- **NX** Regional lymph nodes cannot be assessed
- **N0** No regional lymph node metastasis
- **N1** Metastasis in 1–3 regional lymph nodes
- **N1a** Metastasis in one regional lymph node
- **N1b** Metastasis in 2–3 regional lymph nodes
- **N1c** Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- **N2** Metastasis in 4 or more regional lymph nodes
- **N2a** Metastasis in 4–6 regional lymph nodes
- **N2b** Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- **M0** No distant metastasis
- **M1** Distant metastasis
- **M1a** Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- **M1b** Metastases in more than one organ/site or the peritoneum

TNM7 – Colorectal

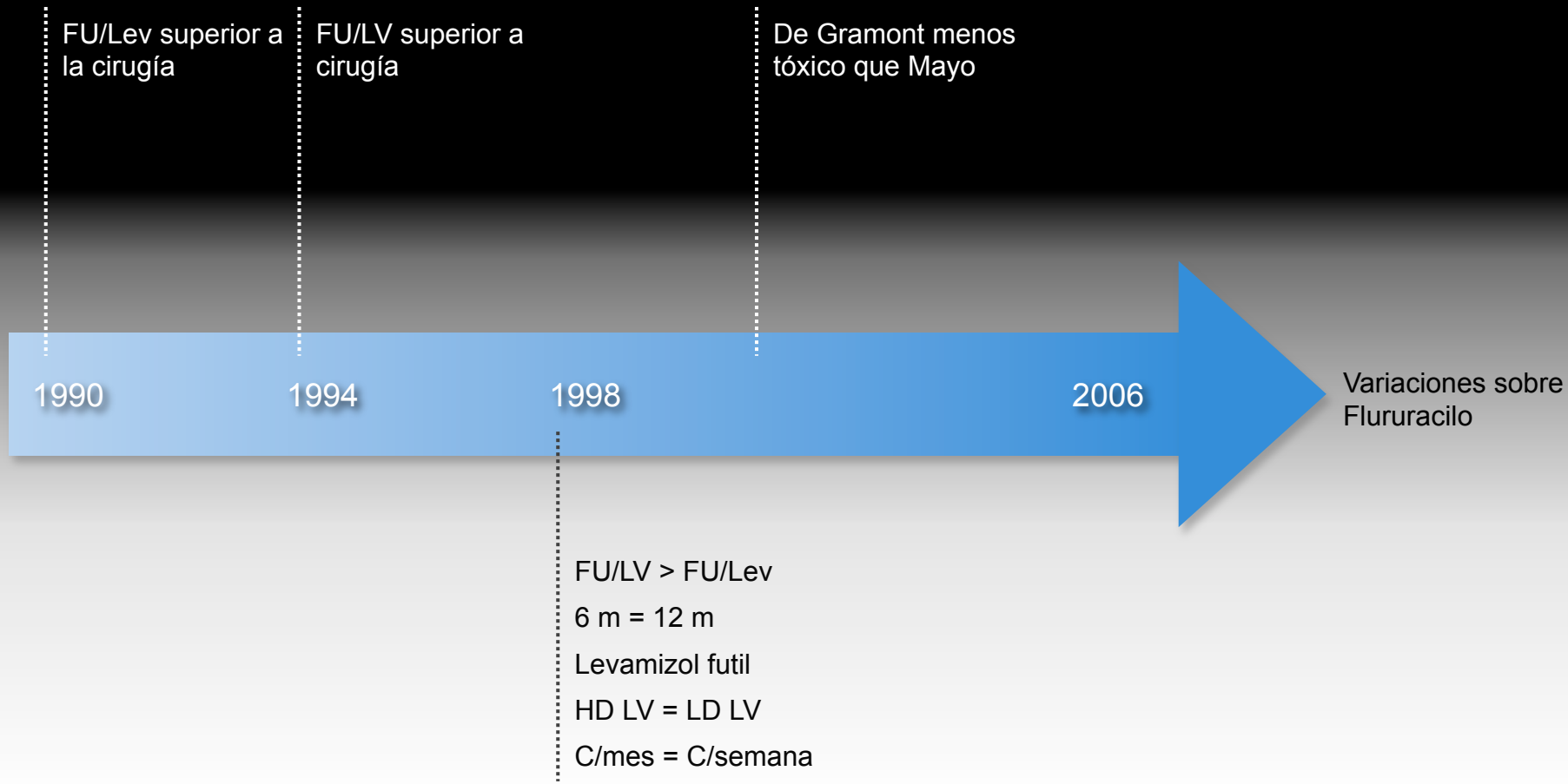
ANATOMIC STAGE/PROGNOSTIC GROUPS					
Stage	T	N	M	Dukes*	MAC*
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a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

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		

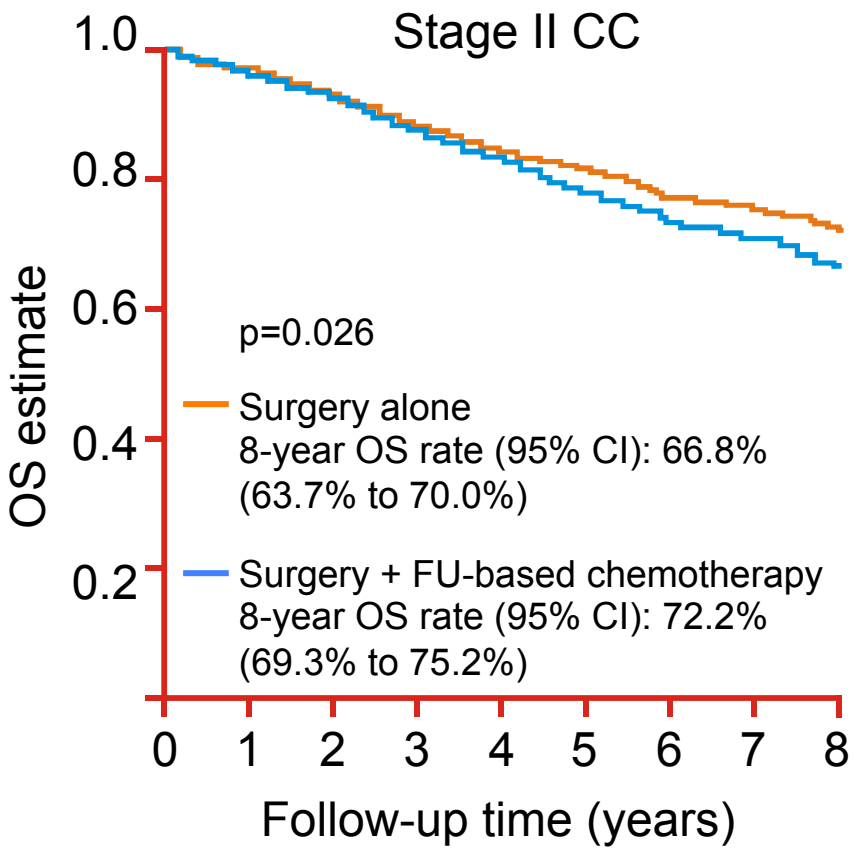
Coloprint: Rosenberg R. et al. ASCO GI 2011

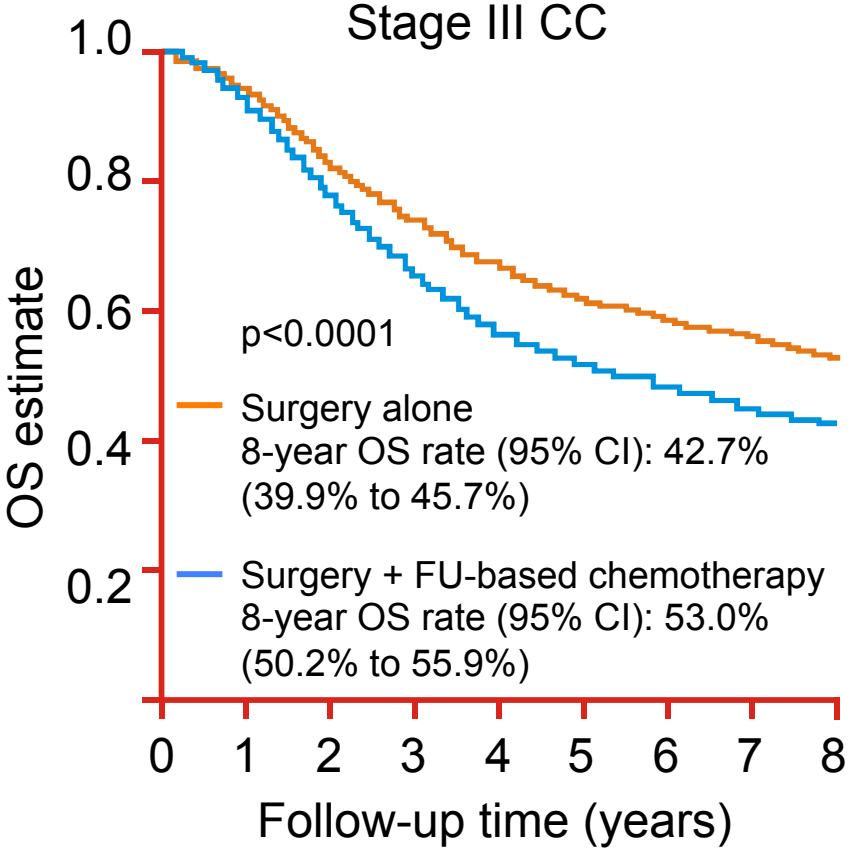
Timeline – Terapia adyuvante en cáncer de colon

Fluoropirimidinas



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





CC=colon cancer
OS=overall survival

Sargent, et al. JCO 2009

Capecitabina

Se convierte en FU por metabolismo

Administración	▪ Tomarla con agua, 30 minutos después de la comida
Dosis	▪ 1250 mg/m^2 2 veces por día, vía oral, por 2 semanas, seguidpo por una semana de descanso (ciclos cada 3 semanas)
Contraindicada	▪ DPD ▪ Falla renal severa (<30 mL/min) ▪ Hipersensibilidad
Precauciones	▪ Disminución de dosis 25% en pacientes con insuficiencia renal moderada (30-50 mL/min) ▪ Precaución con fenitoína y warfarina

X-ACT: Xeloda Adjuvant Chemotherapy Trial of stage III colon cancer

Chemotherapy-naive
stage III
Resection ≤8 weeks
n=1987

RANDOMISATION

Xeloda
1250mg/m^2 bid d1–14
q3w

Bolus 5-FU/LV
5-FU 425mg/m^2 +
LV 20mg/m^2 d1–5
q4w

Twelves, et al. ASCO GI 2008

X-ACT: Capecitabine non inferior to bolus FU/FA (follow-up 6.9 years)

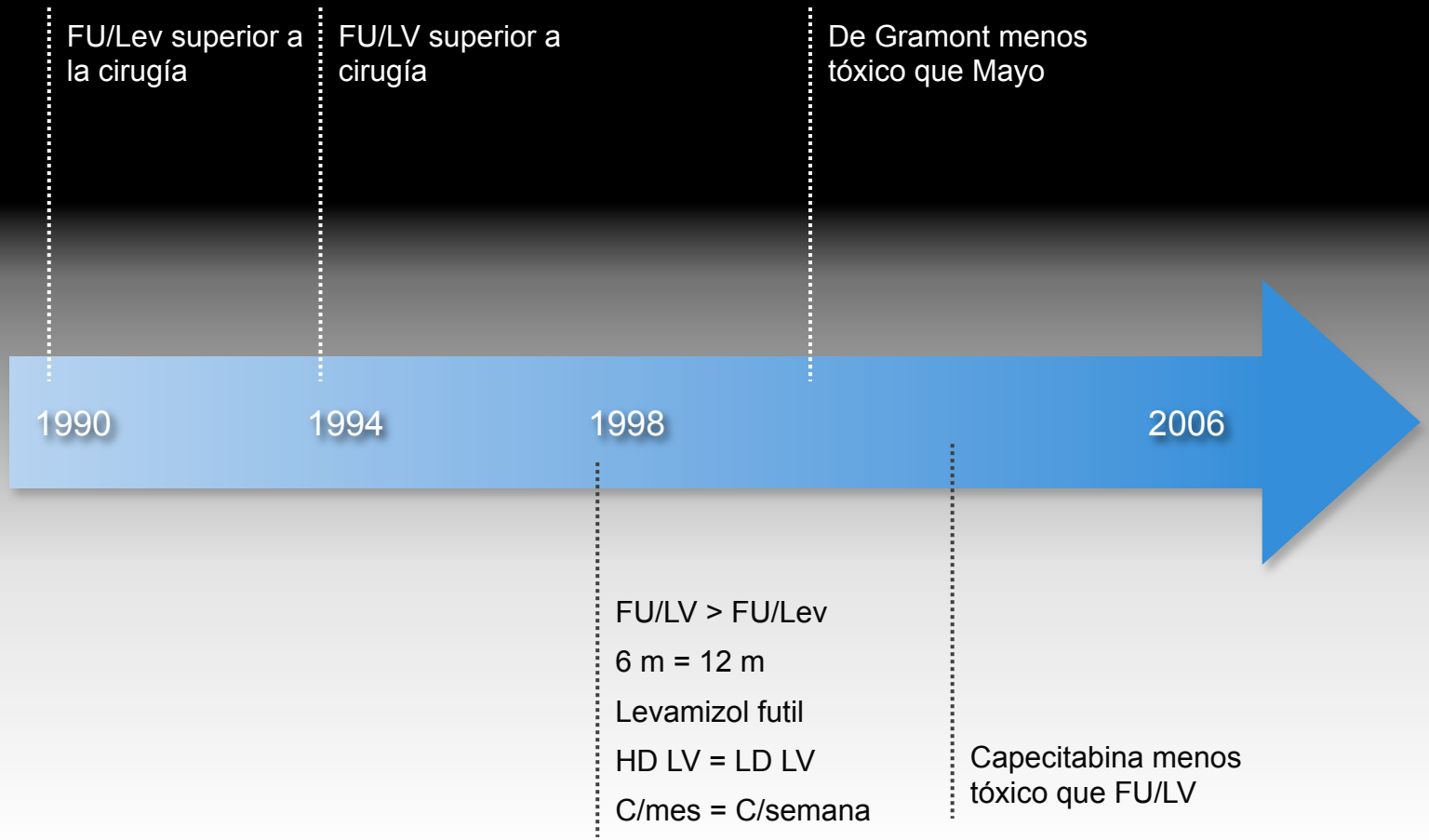
	5-years			P value	
	Cape	5FU/LV	HR (95% CI)	Equivalence	Superiority
DFS	60.8%	56.7%	0.88	<0.0001	0.068
OS	71.4	68.4	0.86	0.00016	0.060

*Predefined non-inferiority margin of <1.20
†Predefined non-inferiority margin of <1.14

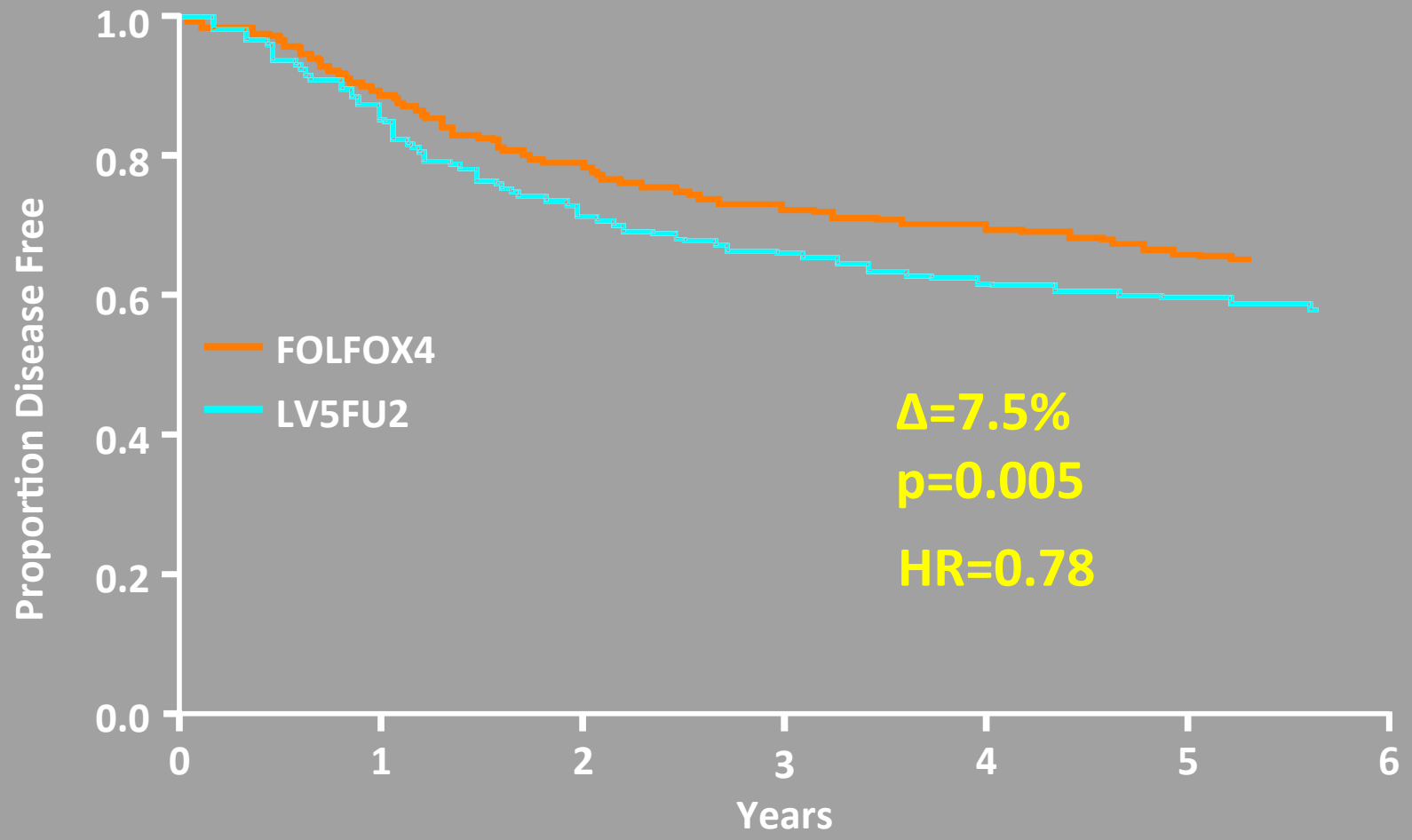
Twelves et al. ASCO GI 2008:Abst 274

Timeline – Terapia adyuvante en cáncer de colon

Fluoropirimidinas & Oxaliplatino

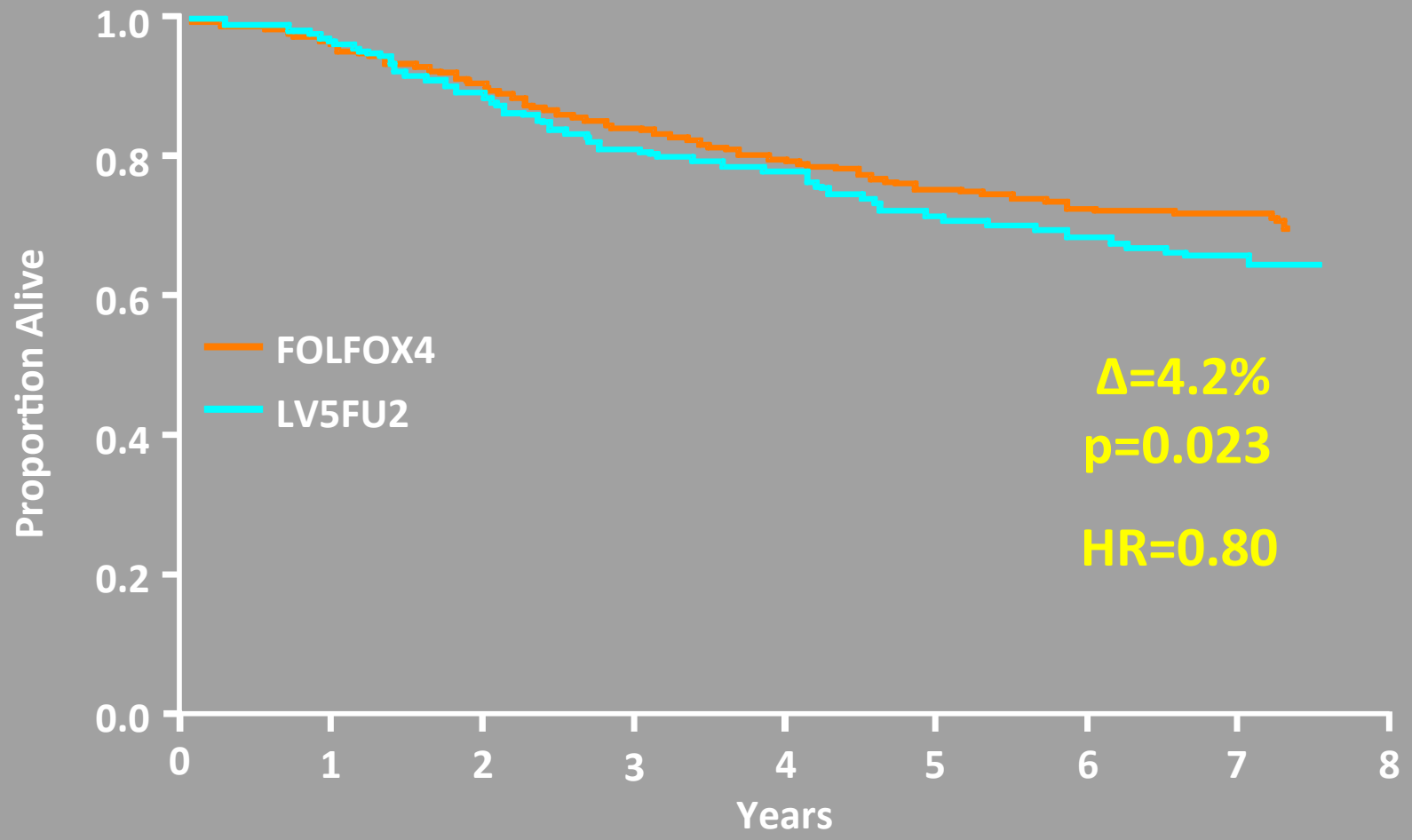


MOSAIC
DFS@5yrs: FOLFOX vs. 5-FU Stage III



Andre et al., J Clin Oncol 2009

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



Andre et al., J Clin Oncol 2009

DFS in stage III disease: MOSAIC and NO16968 (XELOXA)

	DFS	Combination (%)	Monotherapy (%)	HR [95% CI]
MOSAIC	3-yr[1]	FOLFOX4 72.2	LV5FU2 65.3	0.76 [0.62–0.92]
NO16968	3-yr[2]	XELOX 70.9	5-FU/LV 66.5 p=0.0045	0.80 [0.69–0.93]
MOSAIC	5-yr[3]	FOLFOX4 66.4	LV5FU2 58.9	0.78 [0.65–0.93] p=0.005
NO16968	5-yr[2]	XELOX 66.1	5-FU/LV 59.8	

ITT population

1. André et al. NEJM 2004; 2. Haller et al. ESMO 2009; 3. André et al. JCO 2009

Overall survival in stage III disease: MOSAIC and NO16968 (XELOXA)

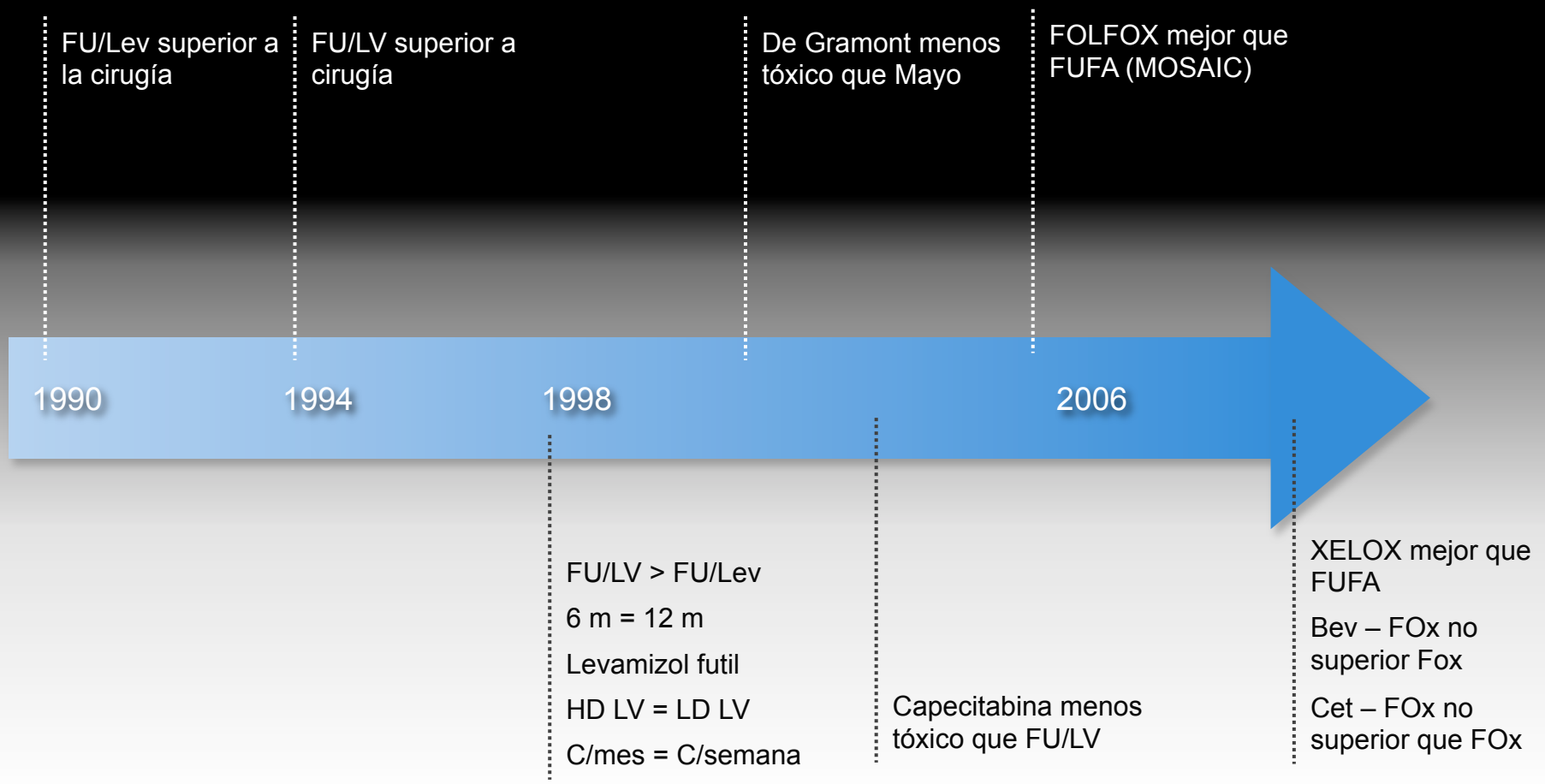
	DFS	Combination (%)	Monotherapy (%)	HR [95% CI]
MOSAIC	4-year[1]	FOLFOX4 80.2	LV5FU2 77.0	0.86 [0.69–1.08]
NO16968	5-year[2]	XELOX 77.6	5-FU/LV 74.2	0.87 [0.72–1.05] p=0.1486
MOSAIC	6-year[3]	FOLFOX4 72.9	LV5FU2 68.7	0.80 [0.65–0.97] p=0.023

ITT population

1. de Gramont et al. ASCO 2005
2. Haller et al. ESMO 2009; 3. André et al. JCO 2009

Timeline – Terapia adyuvante en cáncer de colon

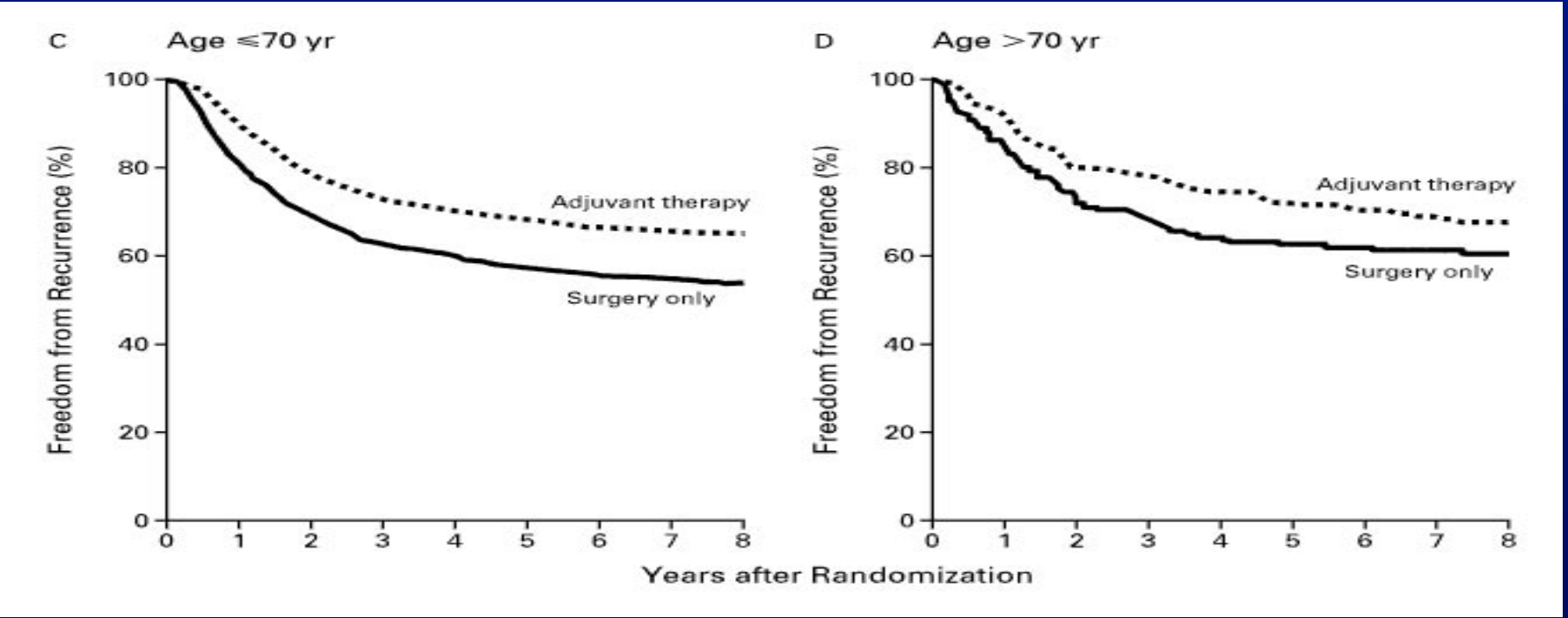
Fluoropirimidinas & Oxaliplatino



Quimioterapia adyuvante en el anciano

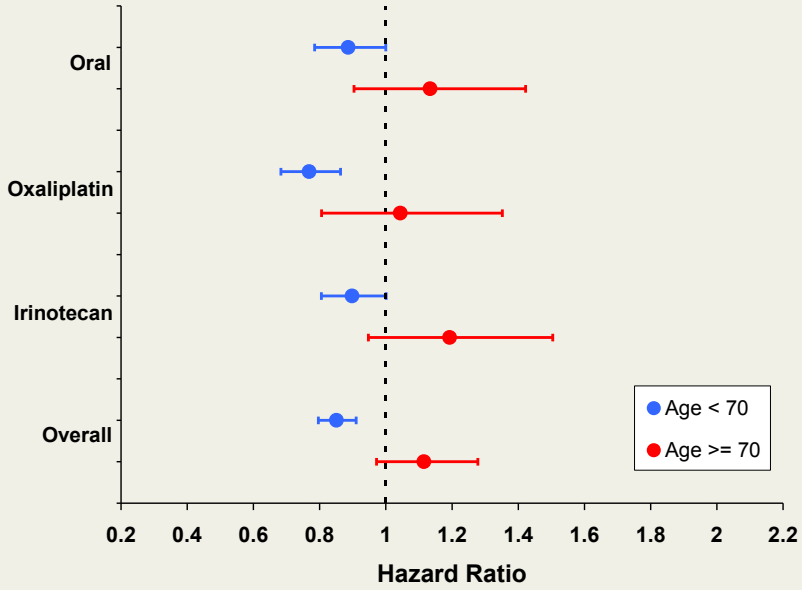
Treatment of Colorectal Cancer in Elderly Patients

- Adjuvant setting
  - Sargent NEJM 2001 – N=3351 (15% ≥ 70 yrs)
    - 7 trials of 5-FU + levamisole/leucovorin v surgery
    - No significant interaction observed between age and efficacy of treatment

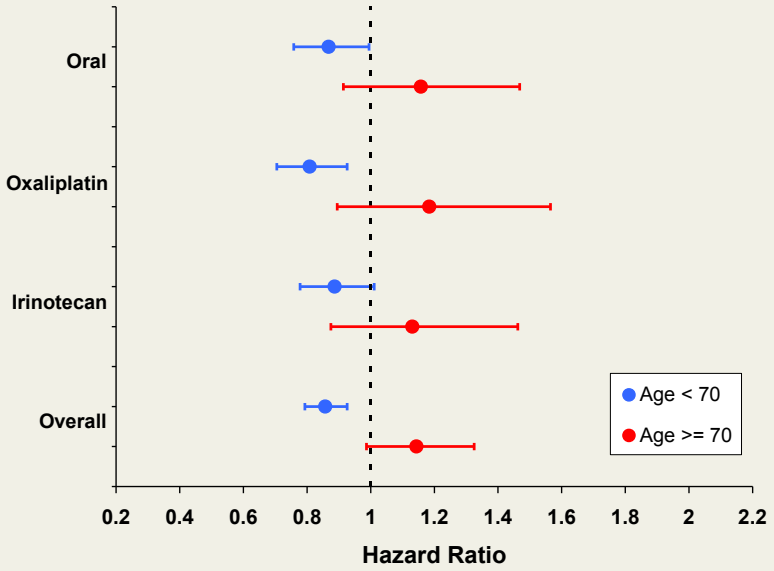


Results from ACCENT database

Disease free survival

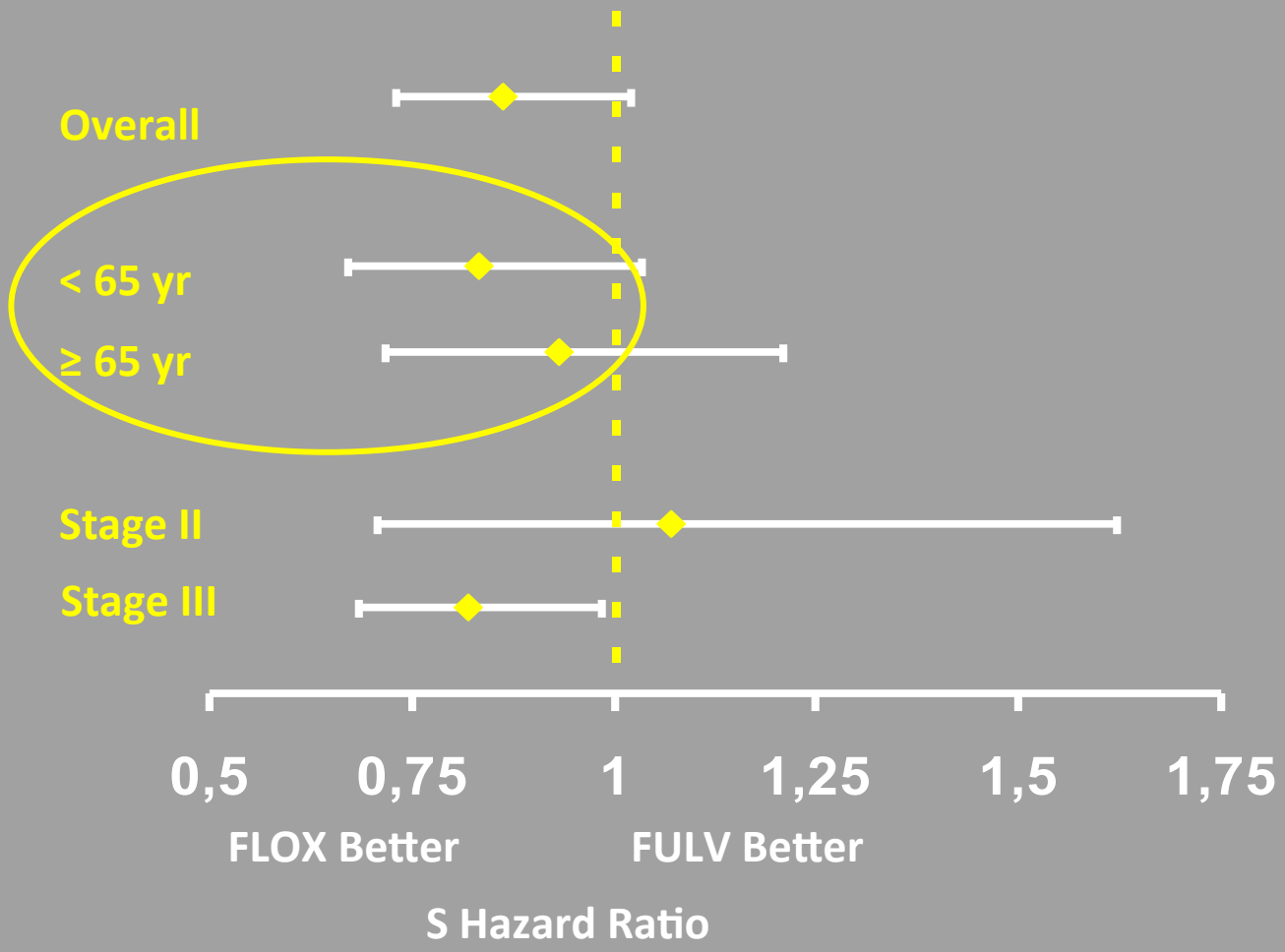


Overall survival



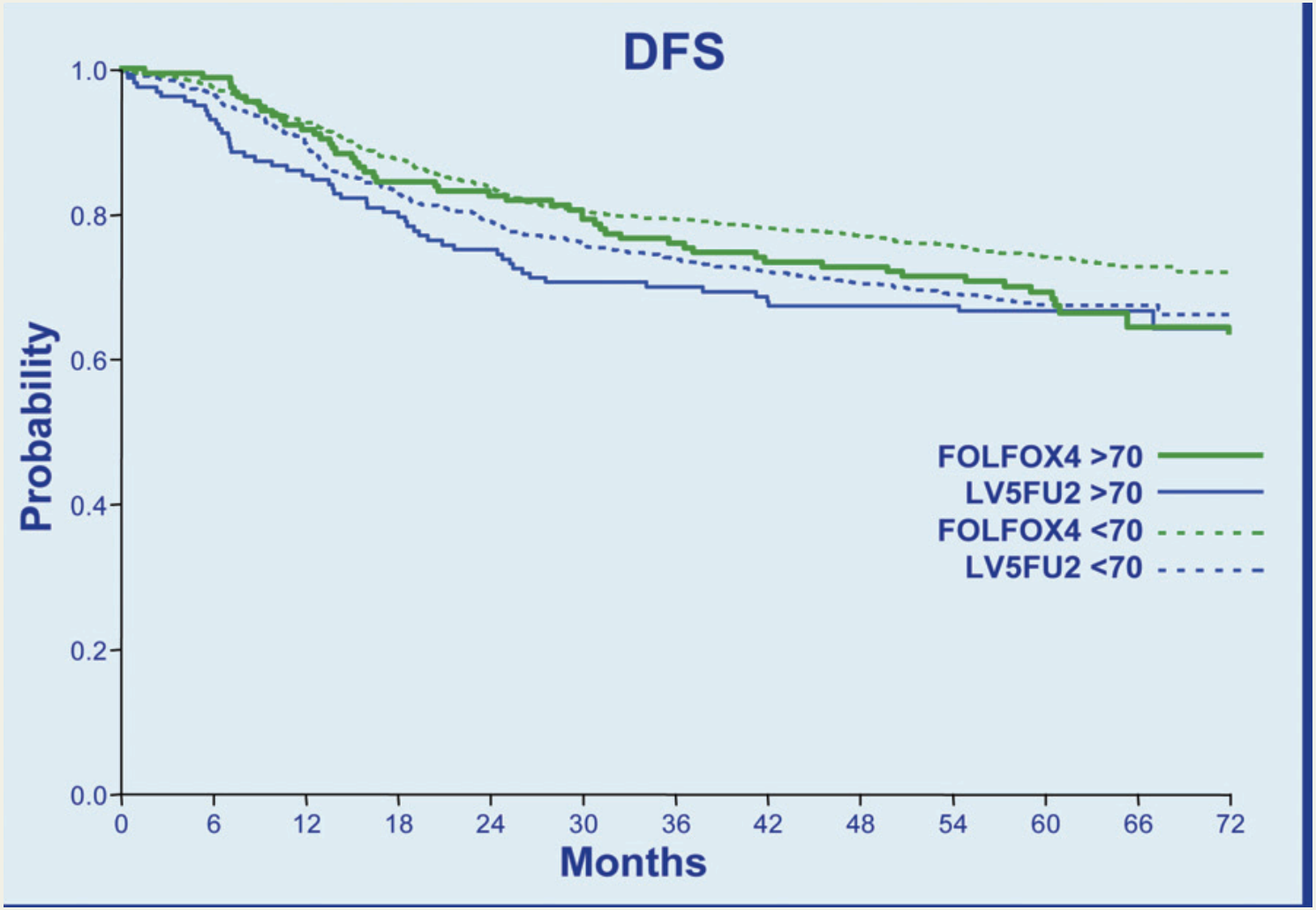
McCleary et al., abst. 4010, ASCO 2009

DFS Subgroup analysis NSABP C-07



Wolmark et al., ASCO 2008

MOSAIC: FOLFOX vs. 5-FU
DFS: stage II/III



HR 0.91

Tournigand et al., ASCO 2010

NO16968 (XELOXA): DFS by age

Age group	3-year DFS XELOX	3-year DFS 5-FU/LV	Hazard ratio (95% CI)
<65 vs. ≥65 years			
<65 years (n=1142)	72%	69%	0.80 (0.65–0.98)
≥65 years (n=744)	68%	62%	0.81 (0.64–1.03)
<70 vs. ≥70 years			
<70 years (n=1477)	72%	69%	0.79 (0.66–0.94)
≥70 years (n=409)	66%	60%	0.87 (0.63–1.18)
No interaction of age by treatment*			p=0.6222

*Multiple Cox regression for <70 vs. ≥70 years subgroup

ITT population

This non-significant p-value indicates that XELOX efficacy is positive, irrespective of age

Comparison with ACCENT analysis

N	Hazard ratio (95% CIs)* DFS	OS
ACCENT analysis†		
<70 years, n=3877	0.77 (0.68,0.86)	0.81 (0.71,0.93)
≥70 years, n=703	1.04 (0.80,1.35)	1.18 (0.90,1.57)
Interaction of age by treatment	p=0.016	p=0.037
NO16968		
<70 years, n=1477	0.79 (0.66,0.94)	0.86 (0.69,1.08)
≥70 years, n=409	0.87 (0.63,1.18)	0.94 (0.66,1.34)
No Interaction of age by treatment	p=0.6222	p=0.7065

*Values <1 favor oxaliplatin-based therapy vs. 5-FU/LV; †Data for oxaliplatin-based regimens

McCleary et al. J Clin Oncol 2009;27(Suppl. 15s):Abst 4010

X-ACT: subgroup analysis by age

Age group	5-year (%)		Hazard ratio (95% CI)
	Capecitabine	5-FU/LV	
Disease-free survival			
<70 years (n=1,589)	59.0	54.0	0.87 (0.75–1.00)
≥70 years (n=396)	58.8	55.8	0.97 (0.72–1.31)
Interaction of age by treatment			p=0.50
Overall survival			
<70 years (n=1,589)	71.0	68.0	0.86 (0.72–1.02)
≥70 years (n=396)	68.8	65.0	0.91 (0.65–1.26)
Interaction of age by treatment			p=0.78

Predefined analysis

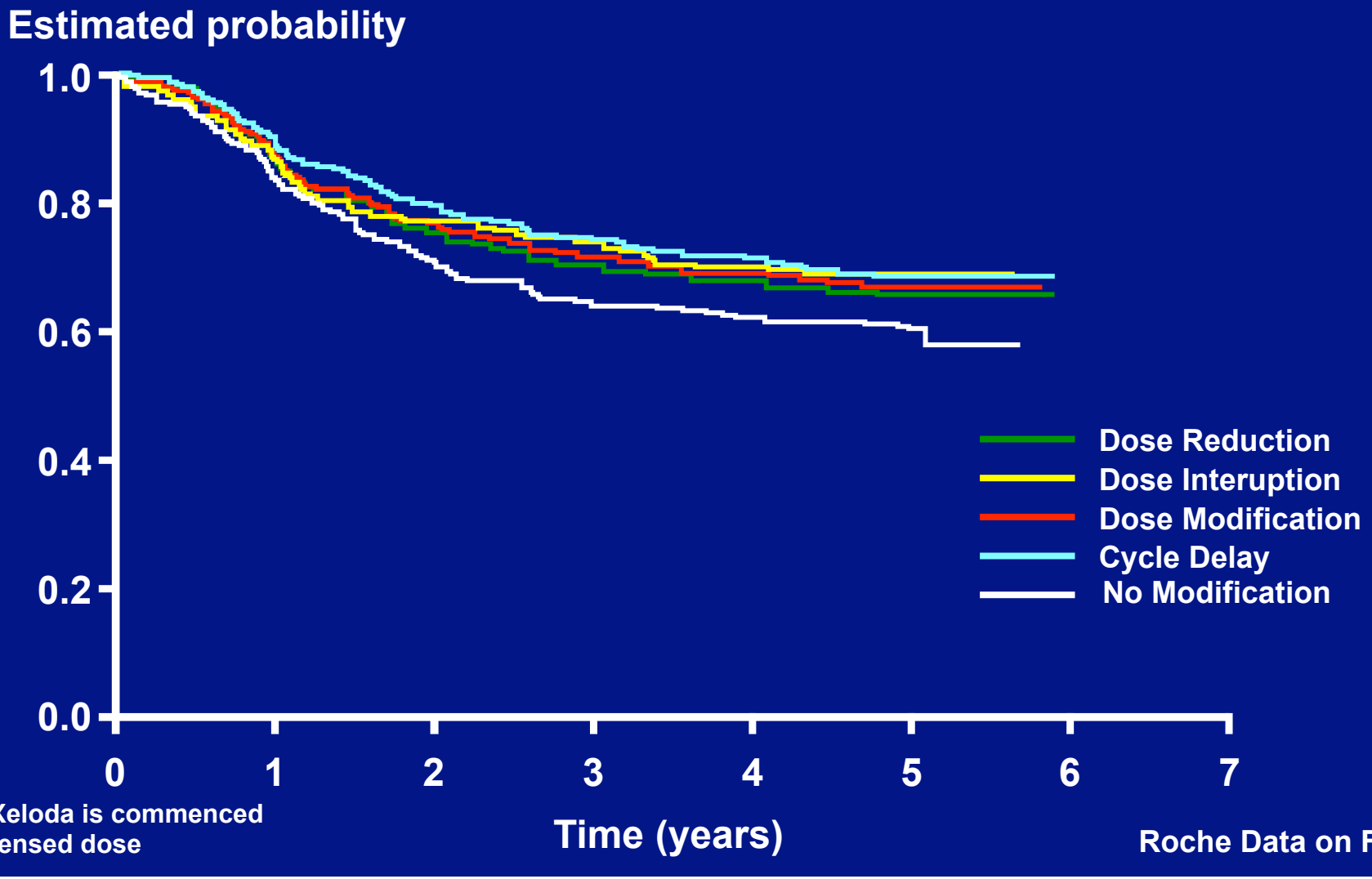
X-ACT trial: NO Impact of dose reduction

Group	Capecitabine N	Capecitabine Total events	Capecitabine 5-year KM (%)	5-FU+LV N	5-FU+LV Total events	5-FU+LV 5-year KM (%)	Relative risk (95% CI)
Total	1004	319	70.90	983	351	67.77	0.86 (0.74, 1.01)
No HFS	391	139	66.31	888	317	67.72	1.03 (0.84, 1.26)
Grade 1–3	613	180	73.78	95	34	68.12	0.79 (0.54, 1.13)

Twelves et al., ASCO-GI 2008

OS after median follow up of 7 yrs

NO16968 XELOXA Trial*
Dose modification does not affect DFS



*Where Xeloda is commenced at the licensed dose

Roche Data on File

Intervalo entre cirugía y terapia adyuvante en cáncer colo-rectal

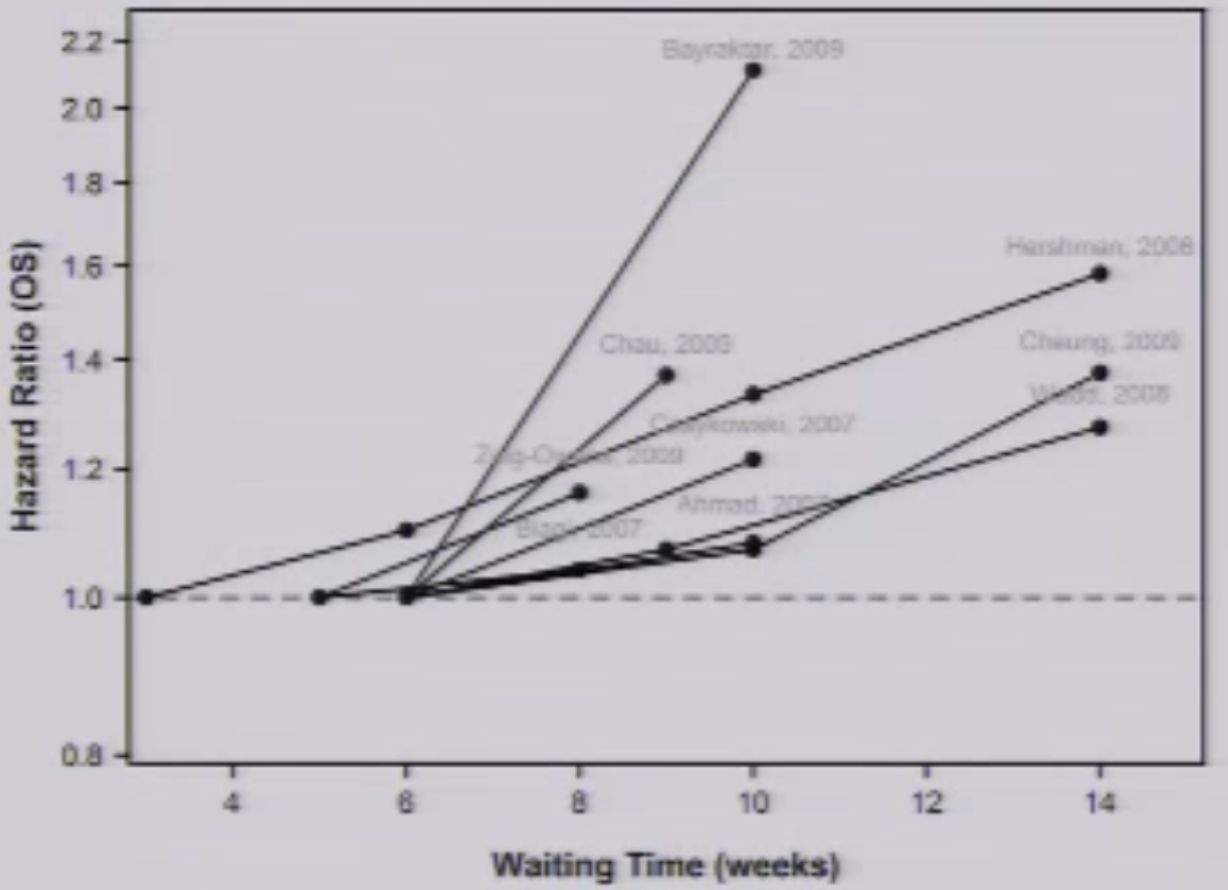
Time to Adjuvant Chemotherapy in CRC

Systematic Review & Meta-Analysis

1	▪ Beneficio de quimioterapia adyuvante disminuye con inicio tardío de quimioterapia
2	▪ Meta-Análisis de estudios con fluoropirimidinas (sin Oxaliplatino) en los que se especifica el TTAC y los desenlaces
3	▪ Incluye estudiios publicados / abstract
4	▪ ...

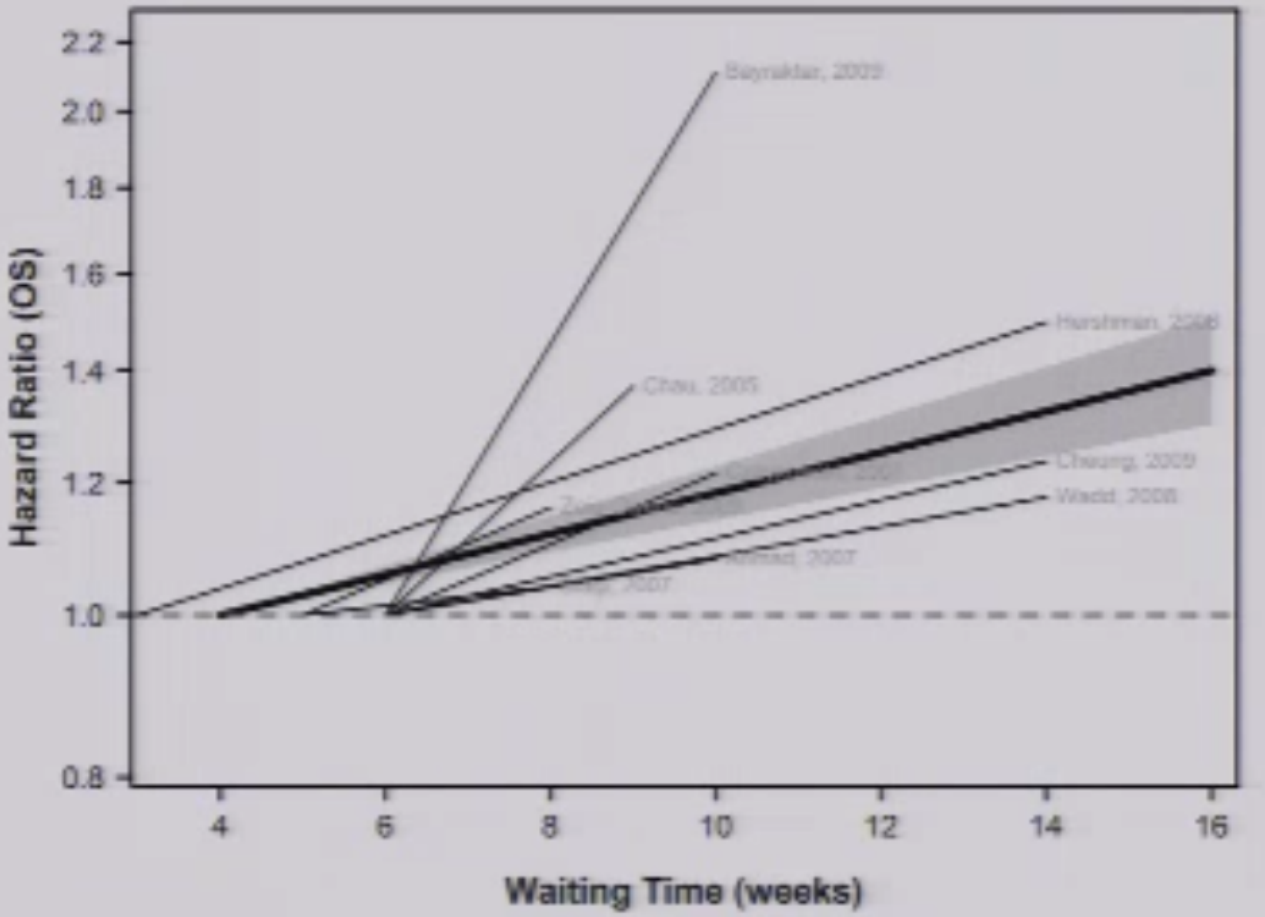
TTAC: Biagi JJ et al. ASCO GI 2011

Relationship between WT categories and OS in each study



TTAC: Biagi JJ et al. ASCO GI 2011

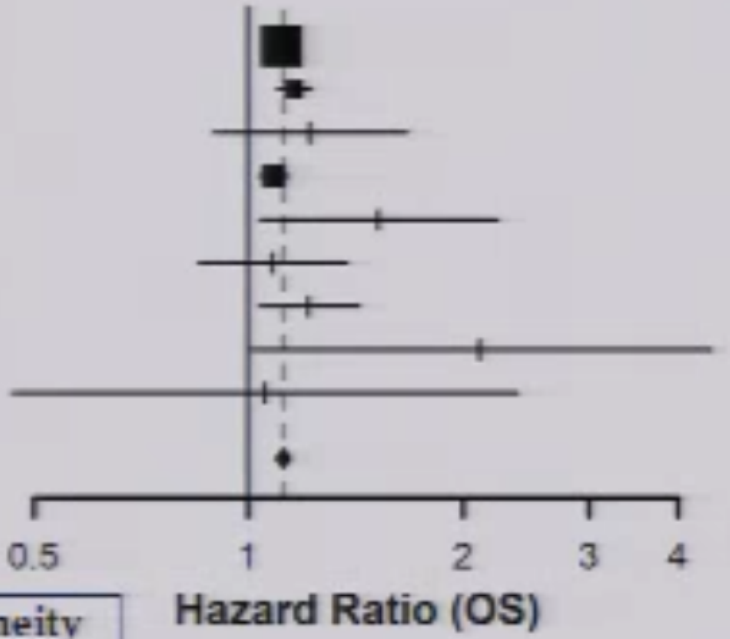
Relationship between WT and OS in each study per 4 weeks



TTAC: Biagi JJ et al. ASCO GI 2011

Meta-Analysis – Overall Survival

Study	*HR (95% CI)*	*Weight (%)*
Cheung, 2009	1.11 (1.07-1.15)	47.37
Hershman, 2006	1.16 (1.10-1.22)	21.34
Zeig-Owens, 2009	1.22 (0.89-1.67)	0.62
Wadd, 2008	1.08 (1.03-1.14)	26.63
Chau, 2005	1.52 (1.04-2.23)	0.41
Ahmad, 2007	1.08 (0.85-1.37)	1.07
Czaykowski, 2007	1.22 (1.04-1.43)	2.36
Bayraktar, 2009	2.11 (1.00-4.45)	0.11
Biagi, 2007	1.05 (0.47-2.38)	0.09
Overall	**1.12 (1.09-1.15)**	



Cochrane $\chi 2$ test showed no evidence of heterogeneity (p-value= 0.2629), justifying fixed-effect model

TTAC: Biagi JJ et al. ASCO GI 2011

Time to Adjuvant Chemotherapy in CRC

Implicaciones...

TTAC	T2 N3 M0
▪ 4 semanas PO ≈ óptimo ▪ 8 semanas ↓ 12% ▪ 12 semanas ↓ 25%	

TTAC: Biagi JJ et al. ASCO GI 2011

Adjuvant Online - Colon

TNM			Mortalidad por cáncer a 5 años (%)		
T	N	M	Sin QT	FU	Oxaliplatino
1	0	0	3		
2	0	0	6		
3	0	0	10	8,2	7,6
4	0	0	19	15,7	14,7
1	1	0	12,9	8,2	5,9
2	1	0	18,9	12,1	8,6
3	1	0	31,9	20,9	17,8
4	1	0	42,8	28,8	24,6
1	2	0	25	16,1	13,7
2	2	0	36	23,7	20,2
3	2	0	52	35,6	30,7
4	2	0	70	50,7	44,4
1	3	0	44	29,5	25,3
2	***3***	***0***	***60***	***42,8***	***37,2***
3	3	0	80	60,5	53,6
4	3	0	93,6	78,5	71,5

https://www.adjuvantonline.com/

Time to Adjuvant Chemotherapy in CRC

Implicaciones...

TTAC	T2 N3 M0	
▪ 4 semanas PO ≈ óptimo ▪ 8 semanas ↓ 12% ▪ 12 semanas ↓ 25%	▪ 4 semanas: 60% ▪ 8 Semanas: 55% ▪ 12 semaas: 50% ▪ No QT: 45%	▪ Importante reportar el TTAC en estudios clínicos ▪ Importante tratar los pacientes lo más pronto posible ▪ Beneficio de QT adyuvante se extiende más allá de 12 semanas

TTAC: Biagi JJ et al. ASCO GI 2011