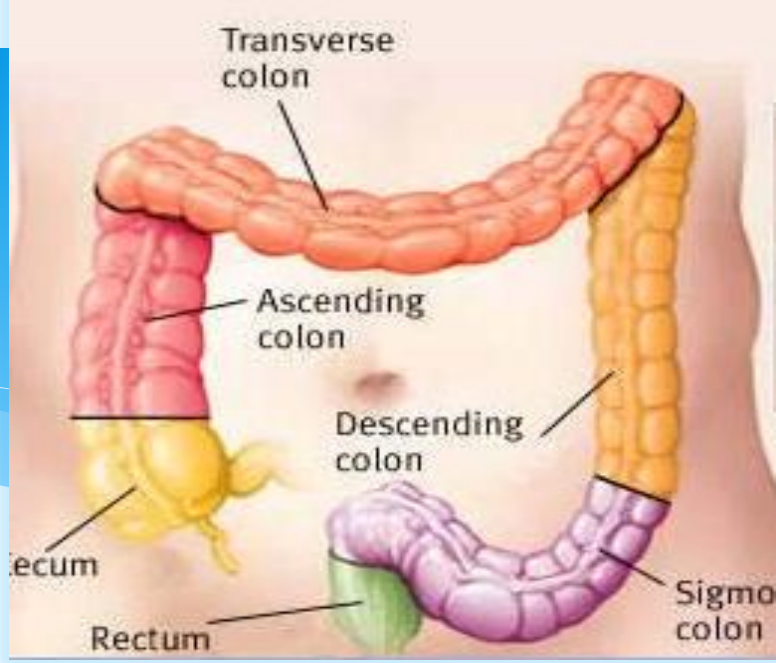
Neoadjuvant Treatment in Rectal Ca

Dr Yeh Chen Lee

Colorectal Ca



* 3rd most common Ca in Australia
  * 1 in 12 would develop CRC by age 85
  * Incidence projected to increase w aging population
* 2nd leading cause of Cancer death after Lung Ca
* 40% of Colorectal Ca occurs in the Rectum
* National Bowel Screening Program (2006)
  * Limited one-off test for age 50,55,and 65

Stage information for Rectal Cancer

Enlarge

Stage	T	N	M	Dukes[c]	MAC[c]
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	--	--

Timeline progression

* Surgical technique : TME
* Imaging technique
  * Stage migration
  * Better evaluation of localized disease
* Movement to pre-op Therapy

Standard of Care

* Stage 1 (T1-2 N0)
  * surgery alone
* Stage 2-3 (T3-4 or Node positive) :
  * pre-op chemorad tx– surgery – 4-6 mths postop chemo
* Preop Imaging w MRI essential

S2& S3 Rectal Cancer

* Neoadjuvant Chemoradtx
* Surgery : TME
* Adjuvant chemo

Issues:

- Benefit of Radtx in addition to TME?
- Chemoradtx before / after surgery?
- Radtx vs Chemoradtx?
- What Type of Chemotherapy?

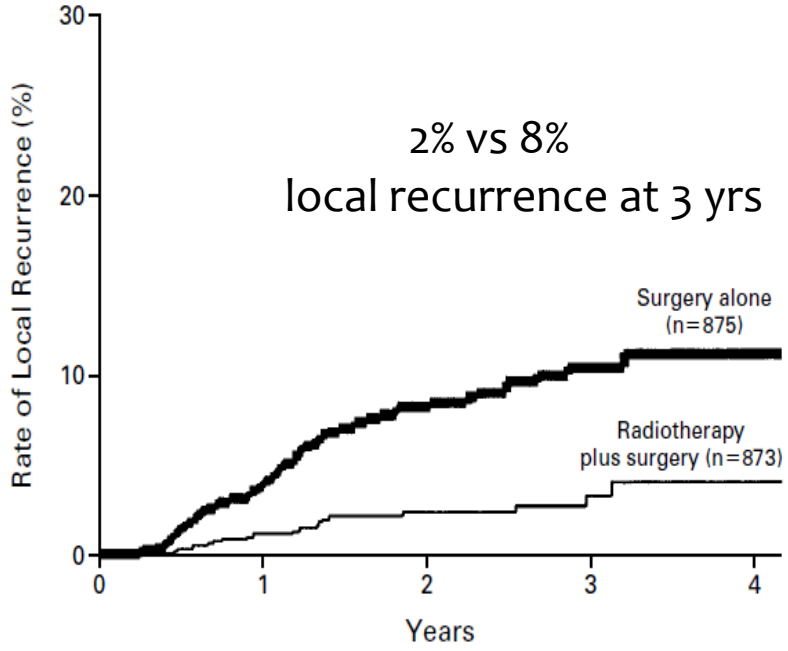
Benefit of Radtx

Dutch Colorectal Cancer Group

* 1861 Pt w rectal Ca, Ramdomized to :
  * 25 Gy in 5# + TME
  * TME alone

Kapitejin et al. N Engl J Med 2001

Dutch Colorectal Cancer Group



No. at Risk					
Radiotherapy plus surgery	873	691	407	170	30
Surgery alone	875	688	406	173	37

Figure 2. Rates of Local Recurrence in the Population of 1748 Eligible Patients Who Underwent Macroscopically Complete Local Resection, According to Treatment Group.

At two years, the rate of local recurrence was 2.4 percent in the group assigned to radiotherapy and surgery and 8.2 percent in the group assigned to surgery alone ($P<0.001$).

Kapitejin et al. N Engl J Med 2001

TABLE 4. RESULTS OF UNIVARIATE LOG-RANK ANALYSES OF TWO-YEAR RATES OF LOCAL RECURRENCE AMONG THE 1748 ELIGIBLE PATIENTS WITH A MACROSCOPICALLY COMPLETE LOCAL RESECTION, ACCORDING TO SELECTED PROGNOSTIC VARIABLES.*

VARIABLE	RADIOTHERAPY PLUS SURGERY		SURGERY ALONE		P VALUE
	NO. OF PATIENTS AT RISK	LOCAL RECURRENCE AT 2 YR	NO. OF PATIENTS AT RISK	LOCAL RECURRENCE AT 2 YR	
		%		%	
Overall	873	2.4	875	8.2	<0.001
Sex					
Male	555	2.5	557	7.2	<0.001
Female	318	2.2	318	9.8	<0.001
Distance of tumor from anal verge					
10.1–15 cm	262	1.3	271	3.8	0.17
5.1–10 cm	372	1.0	350	10.1	<0.001
≤5 cm	237	5.8	253	10.0	0.05
Type of resection					
Low anterior	577	1.2	603	7.3	<0.001
Abdominoperineal	248	4.9	232	10.1	0.02
Hartmann†	47	3.2	39	10.7	0.18
TNM stage					
I	265	0.5	244	0.7	0.15
II	251	1.0	241	5.7	0.01
III	298	4.3	324	15.0	<0.001
IV (distant metastases but complete local resection)	47	10.1	48	23.8	0.25

*Patients with missing data were excluded from the analysis of local recurrence. Twenty-eight patients without a tumor (TNM stage 0) were excluded from the multivariate analysis because they were not at risk for local recurrence. In a Cox proportional-hazards analysis of age (as a continuous variable), the hazard ratio for local recurrence at two years was 0.99 (95 percent confidence interval, 0.95 to 1.04; P=0.77) in the group of 873 patients assigned to radiotherapy and surgery and 1.01 (95 percent confidence interval, 0.99 to 1.04; P=0.21) in the group of 875 patients assigned to surgery alone. TNM denotes tumor–node–metastasis.

†A Hartmann resection is a low anterior resection without the construction of an anastomosis.

DCCG Study - Conclusions

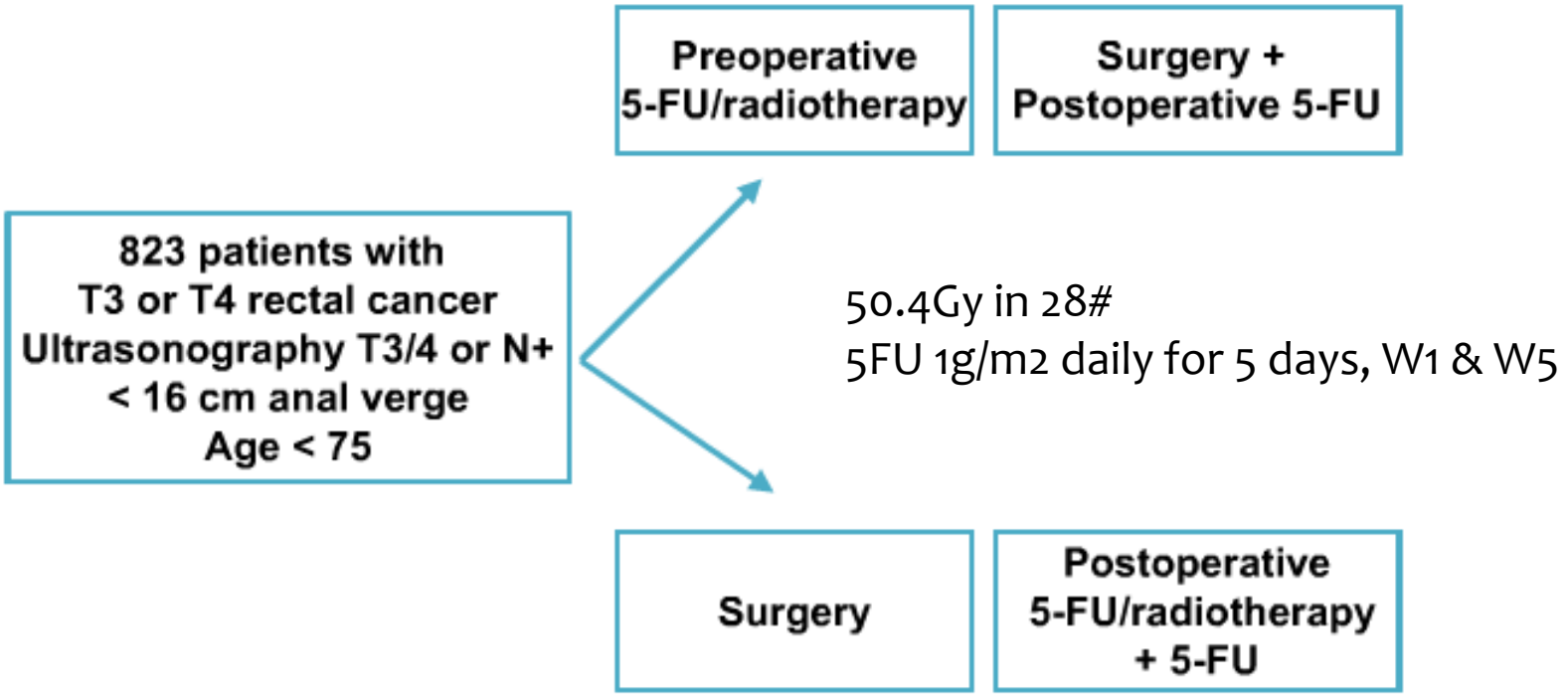
* Pt w Stage 2 and 3 Rectal Ca would receive significant benefit from

  pre-op Radiotherapy

* However
  * In patients with S2 disease with high rectal Ca ?

Chemoradtx: Pre-op vs Post-op

* German Rectal Trial



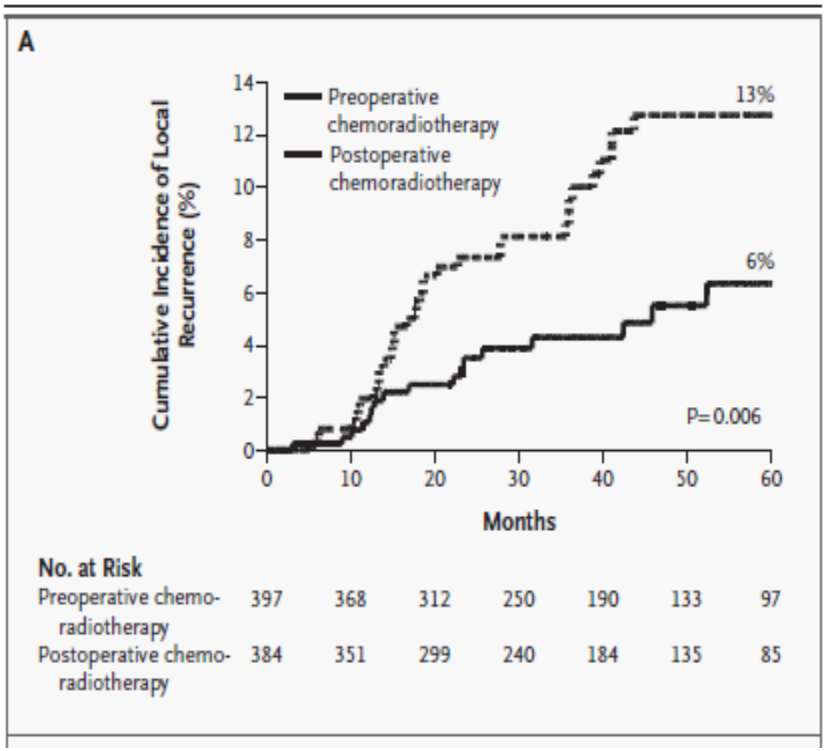
Sauer et al. N Engl J Med 2004

Table 3. Postoperative Pathological Tumor Stage, Type of Surgery, and Completeness of Resection, According to Actual Treatment Given.*

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Histopathological finding (%)			<0.001
Complete response	8	0	
TNM stage			
I	25	18	
II	29	29	
III	25	40	
IV	6	7	
Unknown	6	6	

Sauer et al. N Engl J Med 2004

GRT -results



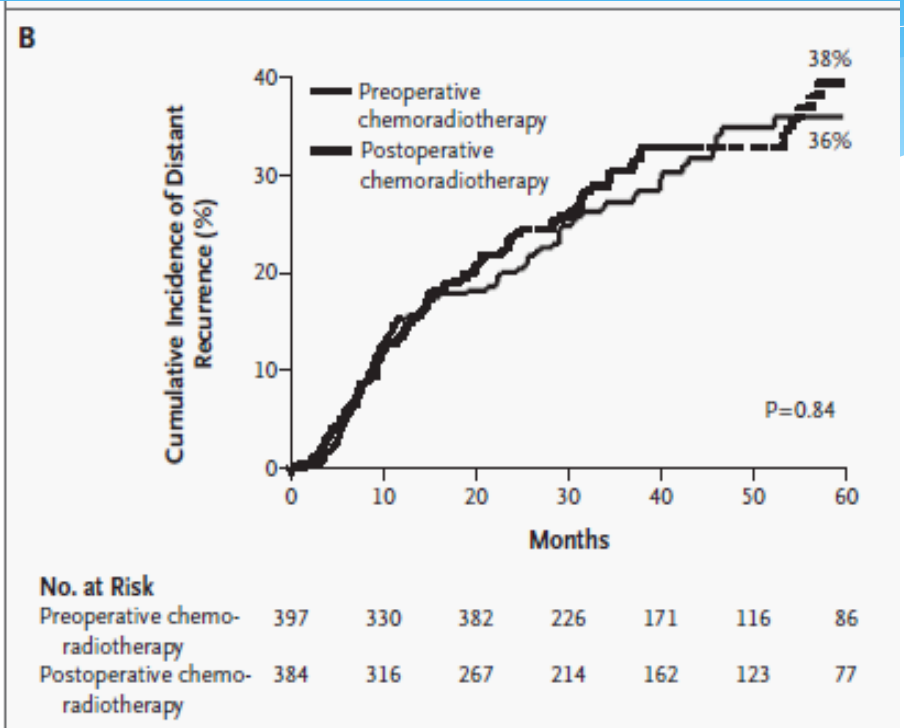
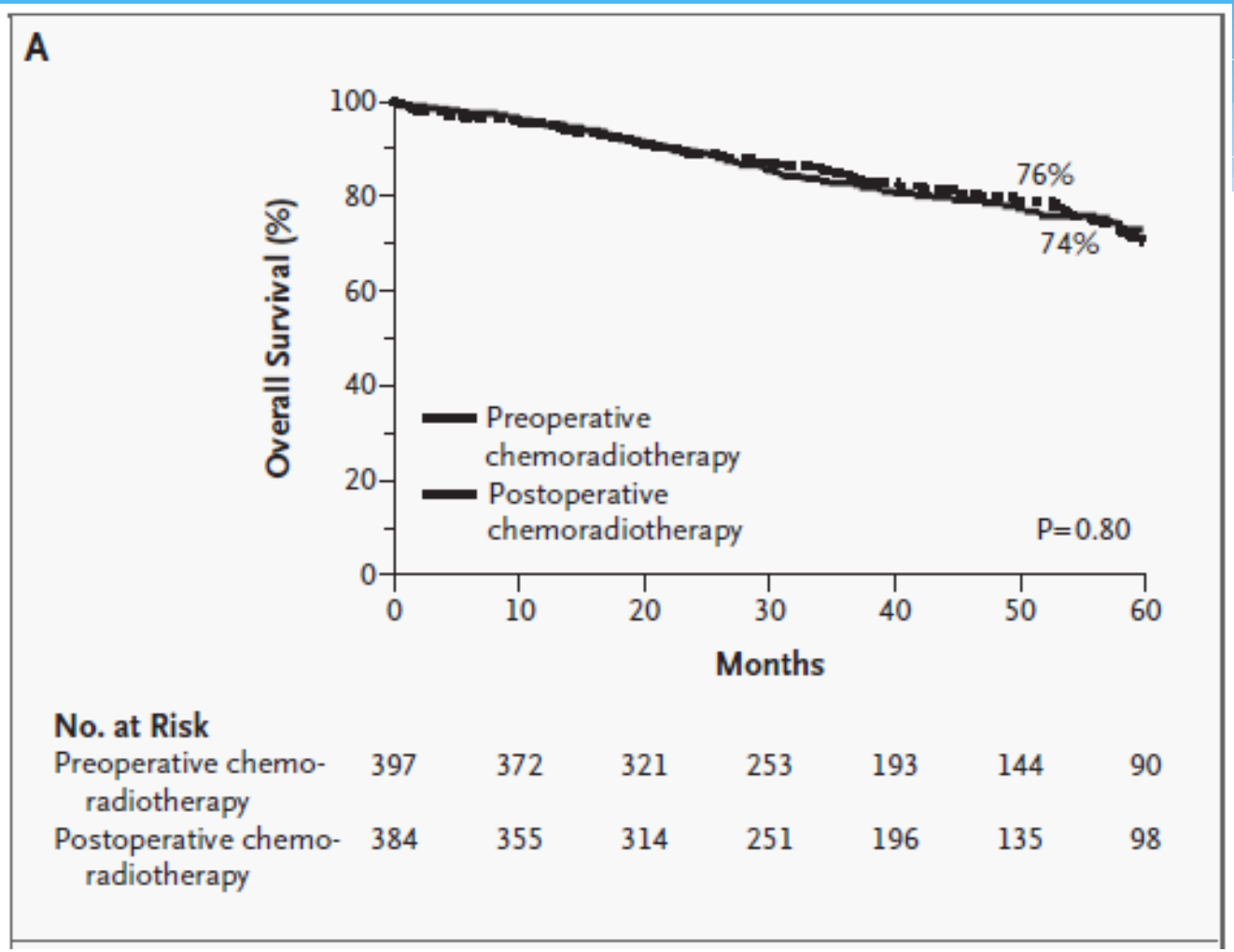


Figure 2. Cumulative Incidence of Local Recurrences (Panel A) and Distant Recurrences (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.

Follow-up data were available for 781 patients.

Sauer et al. N Engl J Med 2004

GRT -results



Sauer et al. N Engl J Med 2004

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

Table 5. Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.*

Type of Toxic Effect	Preoperative Chemoradiotherapy (N=399)	Postoperative Chemoradiotherapy (N=237)	P Value
	% of patients		
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long-term			
Gastrointestinal effects†	9	15	0.07
Strictures at anastomotic site	4	12	0.003
Bladder problems	2	4	0.21
Any grade 3 or 4 toxic effect	14	24	0.01

* All patients who received any preoperative or postoperative radiotherapy according to protocol were included in this analysis. Some patients had more than one toxic effect.
† The gastrointestinal effects were chronic diarrhea and small-bowel obstruction. The incidence of small-bowel obstruction requiring reoperation was 2 percent in the preoperative-treatment group and 1 percent in the postoperative-treatment group (P=0.70).

Sauer et al. N Engl J Med 2004

German Rectal Trial - conclusions

	PRE-op Chemoradtx	POST-op Chemoradtx	P value
5-yr Local recurrence	6%	13%	0.006
5-yr Overall survival	76%	74%	0.8
Sphincter-preservation surgery	39%	19%	0.004
Toxicity profile- acute	27%	40%	0.001
Toxicity profile – long-term	14%	24%	0.01

Sauer et al. N Engl J Med 2004

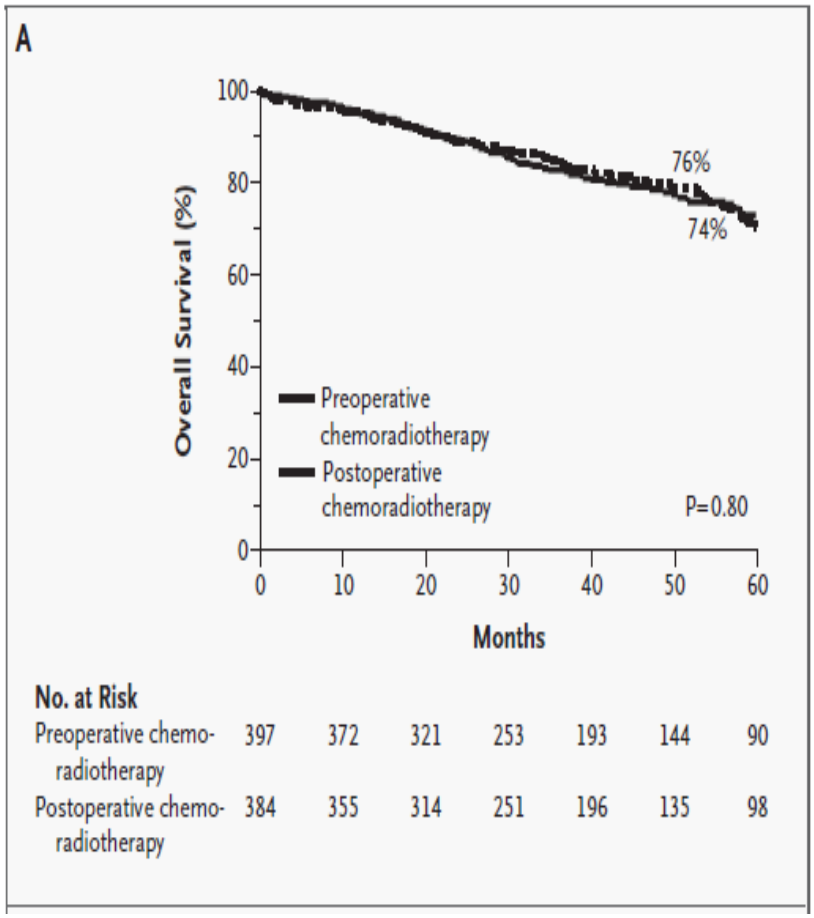
German Rectal Trial at 11 yrs now

Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

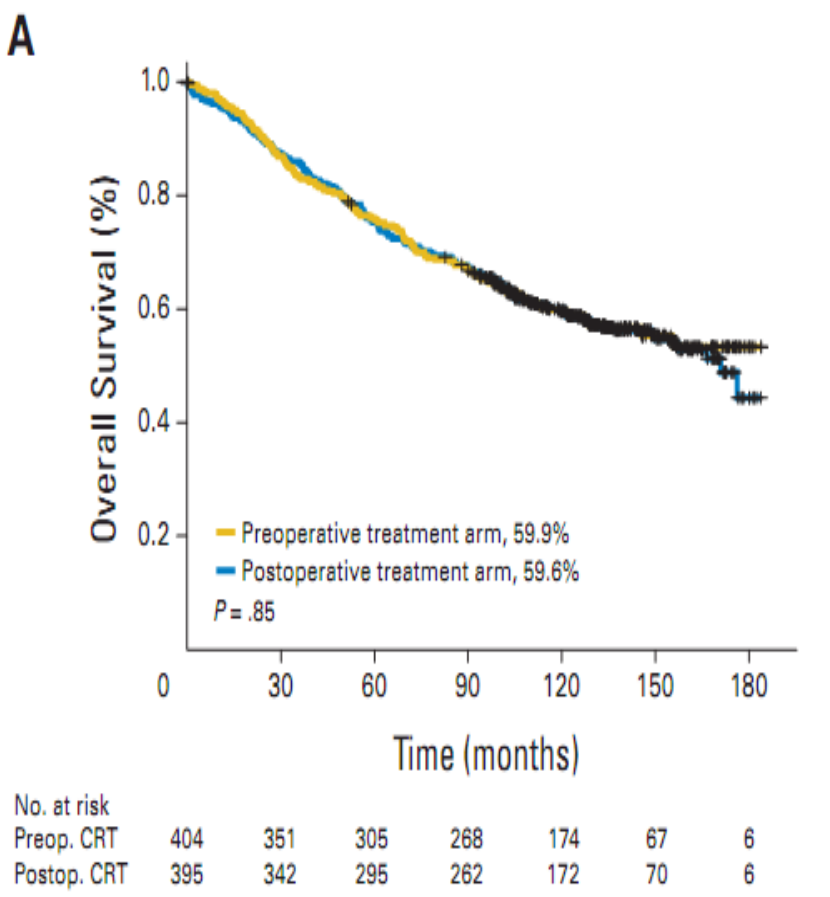
Rolf Sauer, Torsten Liersch, Susanne Merkel, Rainer Fietkau, Werner Hohenberger, Clemens Hess, Heinz Becker, Hans-Rudolf Raab, Marie-Therese Villanueva, Helmut Witzigmann, Christian Wittekind, Tim Beissbarth, and Claus Rödel

See accompanying editorial on page 1901; listen to the podcast by Dr Hong at www.jco.org/podcasts

Sauer et al. JCO 2012



Sauer et al. N Engl J Med 2004



Sauer et al. JCO 2012

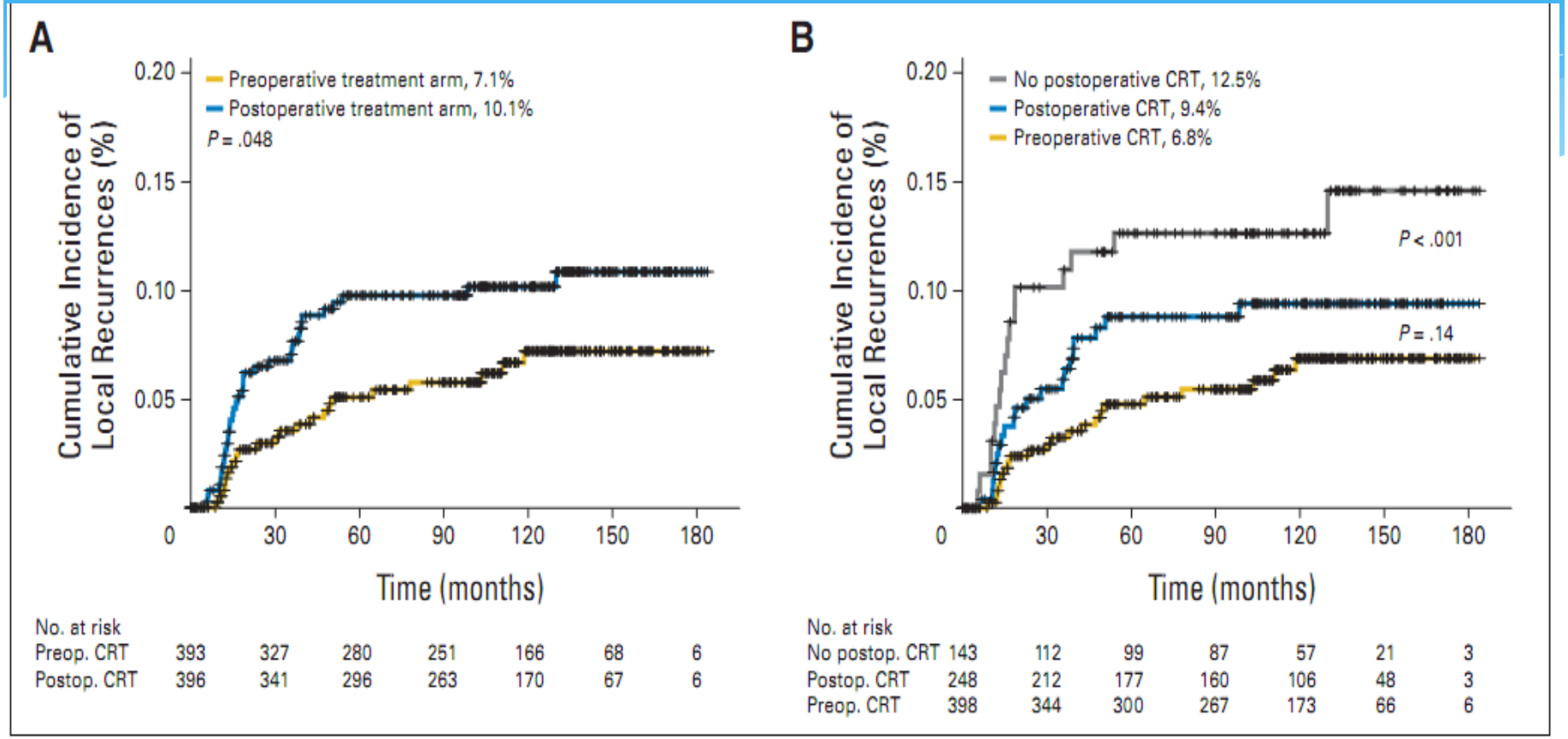


Fig 3. Cumulative incidence of local recurrences after macroscopically complete local tumor resection in the intention-to-treat population (A) and according to treatment received (B). CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.

Sauer et al. N Engl J Med 2004

Sauer et al. JCO 2012

Timing of Chemoradtx

Neoadjuvant Chemoradiation

is the

preferred option

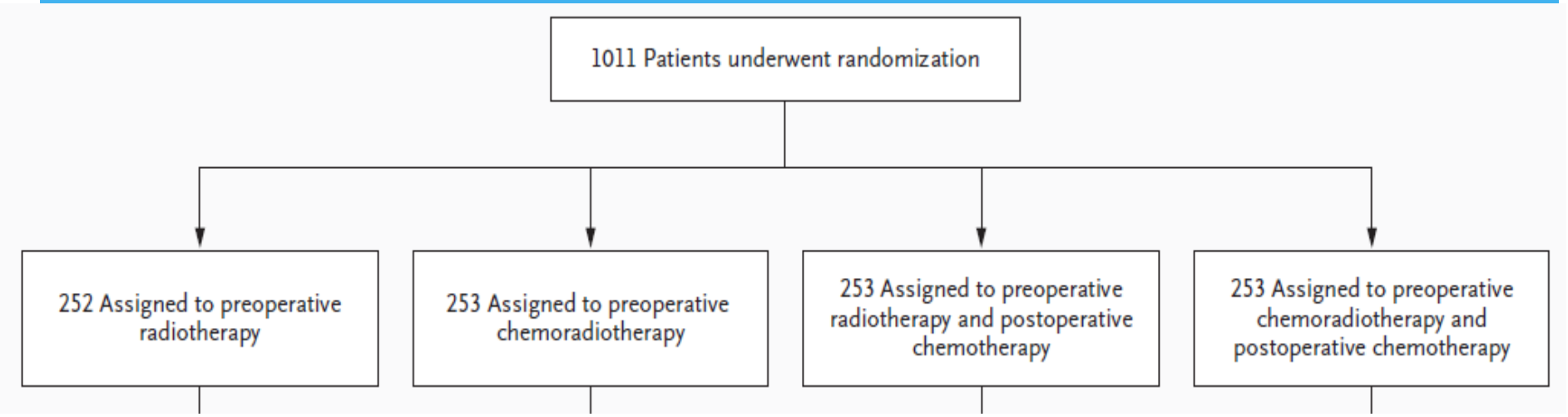
MORE Questions

In Neoadjuvant setting

What about

* Radtx alone vs Chemoradtx?

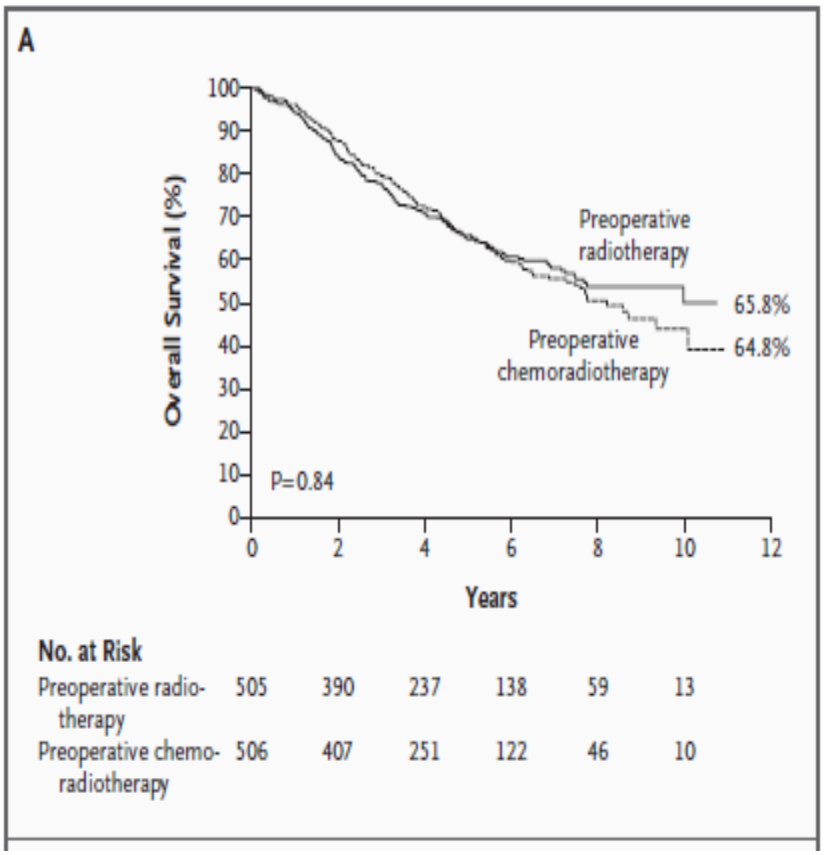
EORTC 22921



* Resectable T3-T4 Tumour
* Pre-op radtx 45 Gy
* Pre-op 5-FU bolus on wk1 &wk5
* Primary End Point = OS

Bosset et al. N Engl J Med 2006

EORTC - results



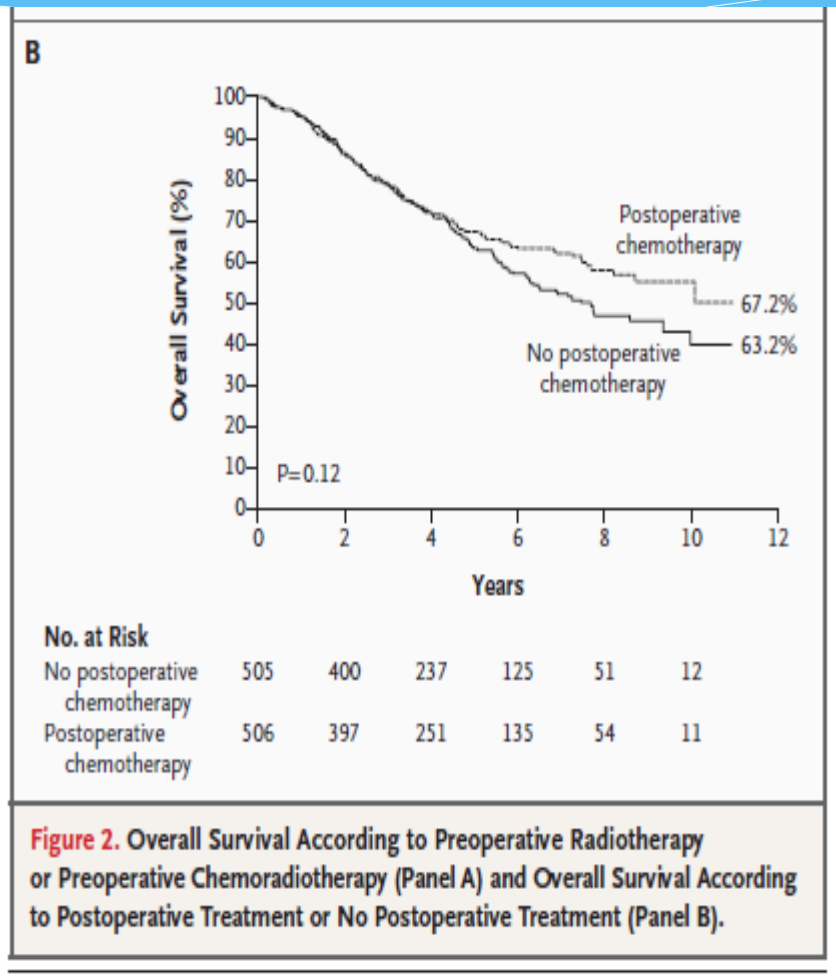
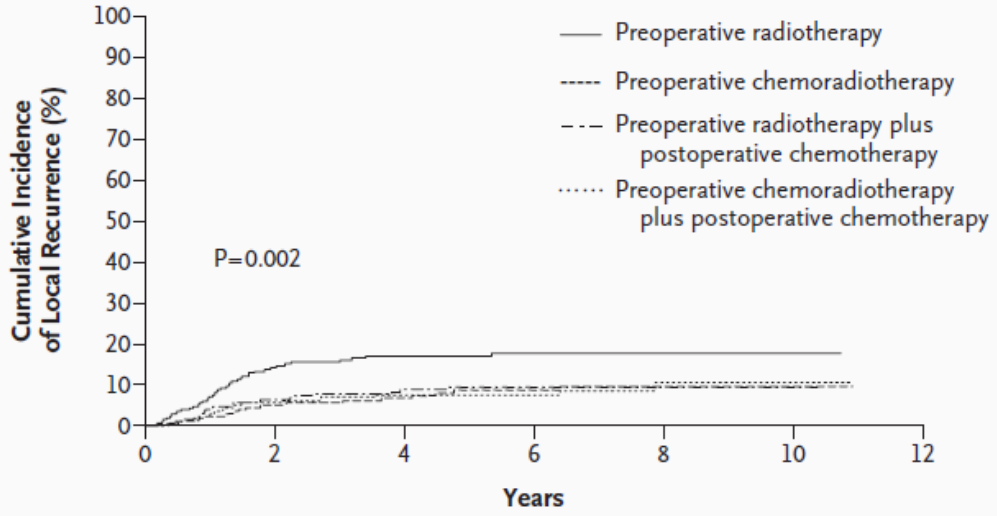


Figure 2. Overall Survival According to Preoperative Radiotherapy or Preoperative Chemoradiotherapy (Panel A) and Overall Survival According to Postoperative Treatment or No Postoperative Treatment (Panel B).

Bosset et al. N Engl J Med 2006

EORTC - results



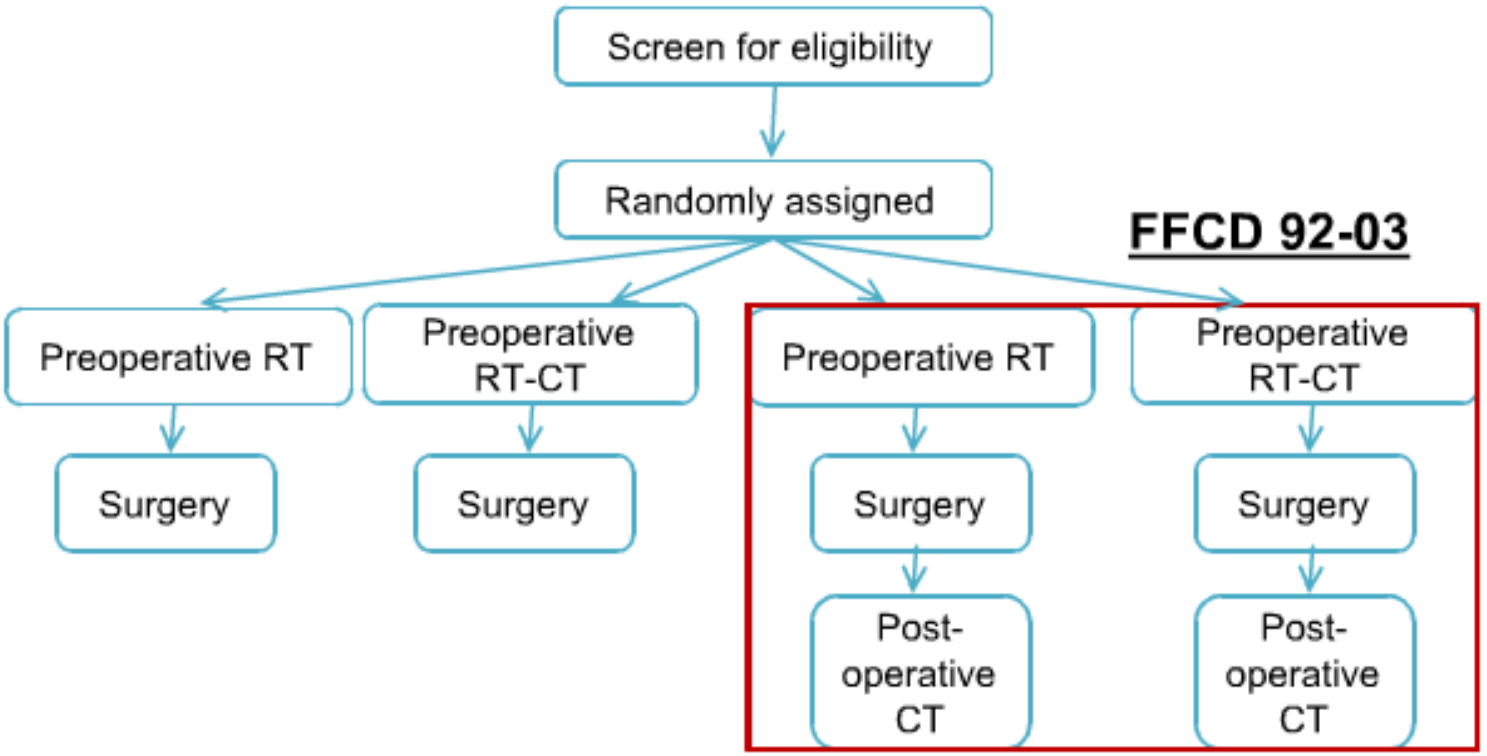
No. at Risk						
Preoperative radiotherapy	252	147	87	60	24	6
Preoperative chemoradiotherapy	253	165	99	52	22	5
Preoperative radiotherapy plus postoperative chemotherapy	253	156	103	65	29	6
Preoperative chemoradiotherapy plus postoperative chemotherapy	253	159	113	59	20	3

Figure 4. Cumulative Incidence of Local Recurrence as a First Event.

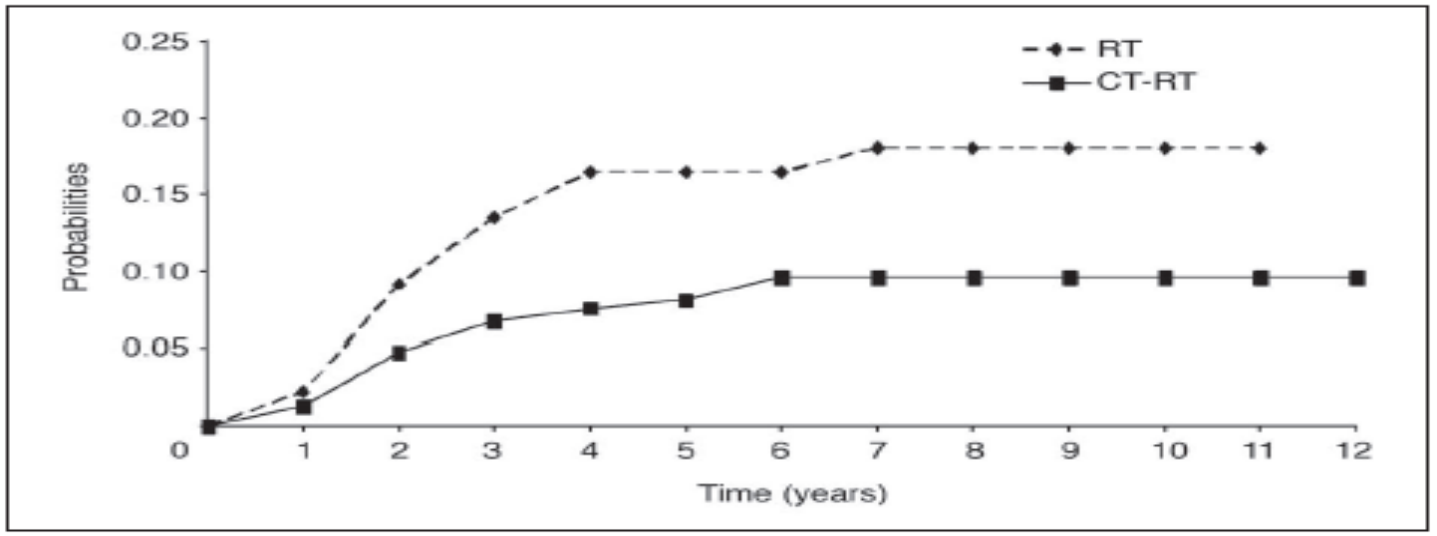
The cumulative incidence of local recurrence as a first event at 5 years was 17.1% in the preoperative-radiotherapy group, 8.7% in the preoperative-chemoradiotherapy group, 9.6% in the group receiving preoperative radiotherapy and postoperative chemotherapy, and 7.6% in the group receiving preoperative chemoradiotherapy and postoperative chemotherapy.

Bosset et al. N Engl J Med 2006

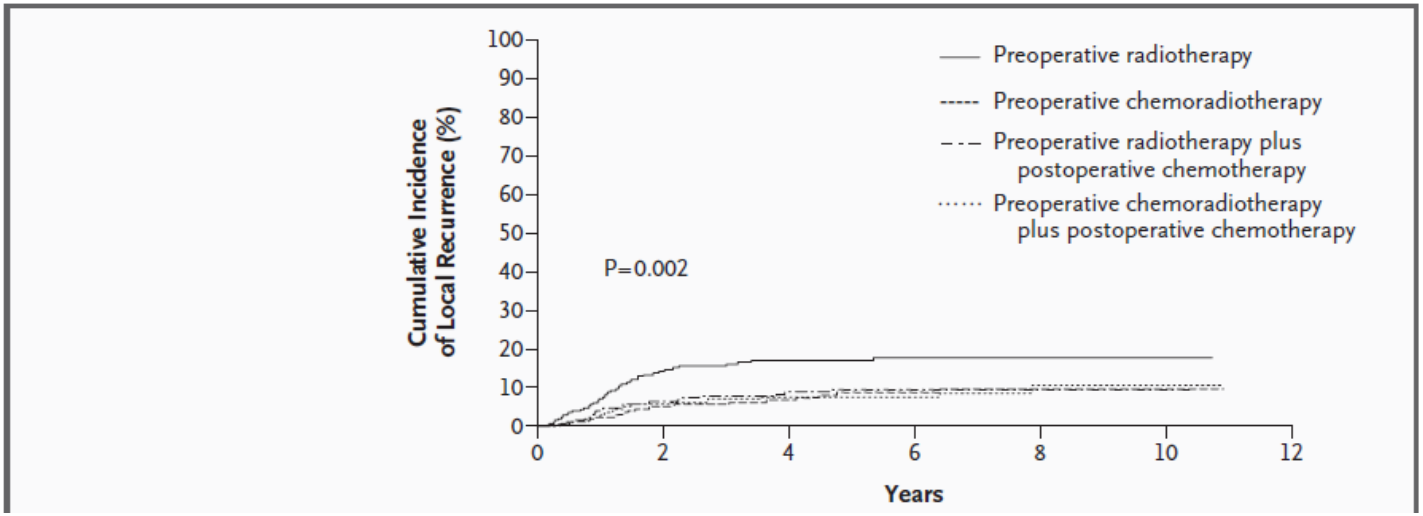
FFCD 92-03



Gerard et al. JCO 2006



Gerard et al. JCO 2006



Bosset et al. N Engl J Med 2006

conclusion from EORTC & FFCD

* Preop-radiotherapy alone had higher local recurrence rate, however not affecting the overall survival.
* Addition of Chemotherapy confers significant benefit in local control
* critisism
  * only 36% receive TME,
  * Bolus 5FU

More, MORE Questions!

Now that we established that

neoadjuvant chemoradtx is necessary and beneficial,

What About

- The use of Capecitabine?
- The addition of Oxaliplatin?

Capecitabine / infusional 5 FU

NSABP-R-04:

P3 Randomized Study in US

1608 pt w Clinical S2/3 Rectal Ca ,

undergoing pre-op Radtx (45Gy + boost) +

1)Continuous infusion 5-FU

2)Continuous infusion 5-FU+ oxaliplatin

3)Capecitabine (825mg/m2 BD 5 days/wk)

4)Capecitabine + Oxaliplatin (50mg/m2/wk x 5)

Primary End point: pCR, SSS, surgical downstaging

Roh et al. ASCO, 2011

Interim Results

Endpoint	5-FU (± OX)	CAPE (± OX)	P value
pCR	135/719 = 18.8%	157/707 = 22.2%	0.12
SSS	445/727 = 61.2%	445/710 = 62.7%	0.59
SD	39/188 = 20.7%	43/187 = 23.0%	0.62
Grade 3/4 diarrhea	70/625 = 11.2%	68/628 = 10.8%	0.86
Endpoint	**(FU or CAPE) No OX**	**(FU or CAPE) + OX**	**P value**
pCR	111/580 = 19.1%	121/578 = 20.9%	0.46
SSS	370/582 = 63.6%	353/584 = 60.4%	0.28
SD	35/152 = 23.0%	29/151 = 19.2%	0.48
Grade 3/4 diarrhea	41/622 = 6.6%	97/631 = 15.4%	< 0.0001

Abstract presentation from the 2011 ASCO Annual Meeting

* NO Sig Difference btw 5FU vs CAPE regimen
* No Sig Difference btw regimens with or without OX
* Increase G3/4 toxicity w Ox

Roh et al. ASCO, 2011

Capecitabine / infusional 5 FU-2

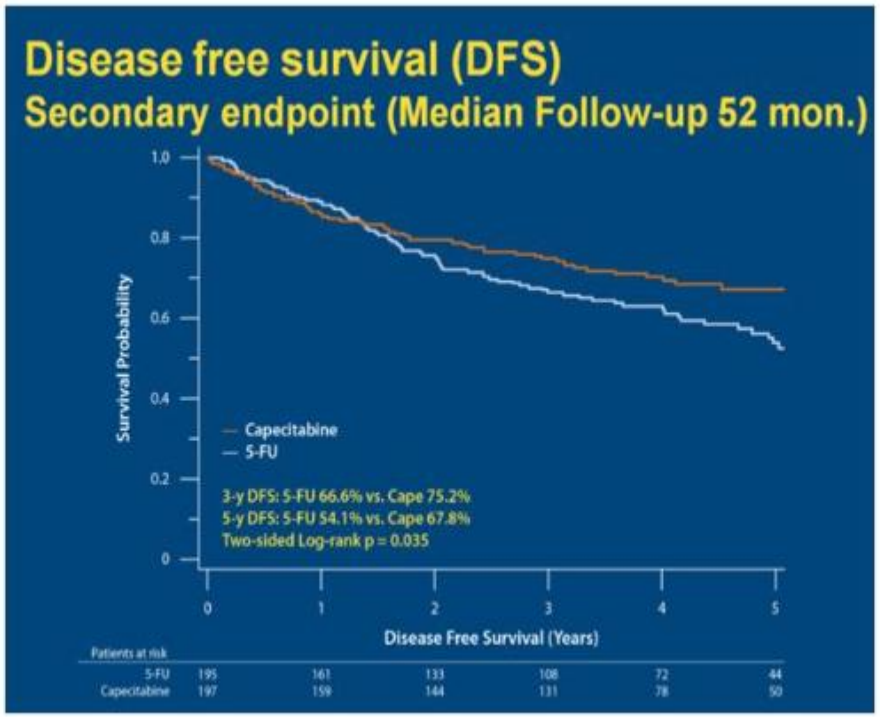
Hofheinz et al

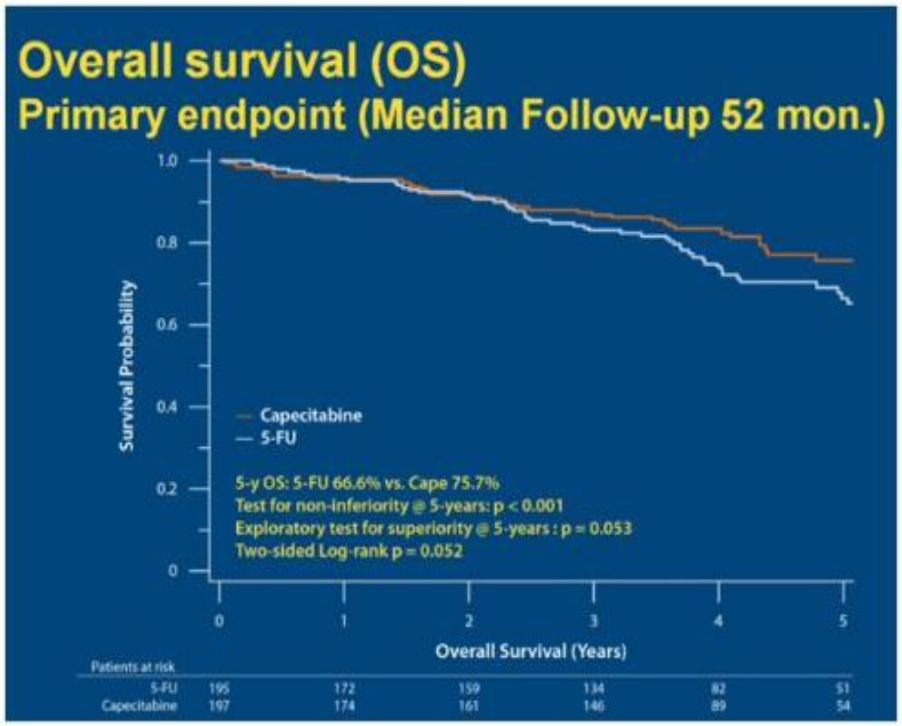
* Non-inferiority P3 study of 401 pt w S2,S3 Rectal Ca, all pt receive pre-op radtx +
  * 2 arm (CAPE vs 5 FU)
  * 2 Strata (Neoadjuvant vs adjuvant)

* Primary End point : OS
* 2nd End points : DFS and safety

Hofheinz et al. ASCO, 2011

Hofheinz et al - result





* CAPE not inferior to 5FU regimen in 5 yrOS
* Significant difference in 3 yr DFS, favouring CAPE
* Neoadjuvant better tolerated + improve nodal downstaging

Hofheinz et al. ASCO, 2011

NSABP-R-04 + Hofheinz et al

* capecitabine = CVI 5FU in preop CRT
* The addition of oxaliplatin DID NOT improve preliminary outcomes but added significant toxicities
* Mature data to follow

Roh et al. ASCO, 2011

Hofheinz et al. ASCO, 2011

Finally
In S2, S3 Rectal Cancer

* Surgery : TME is SOC

* In Neoadjuvant setting :
  * Pre- op > Post-op Chemoradiation therapy
  * CAPE = 5FU regimen
  * Addition of Oxaliplatin increase toxicity

Thank you


This Kid is in the
FIGHT
against
Rectal
Cancer
because it messed
with someone I love!

Additional Slides

Adjuvant Chemotherapy

Derived From :

MOSAIC study

* P3 study in Europe
* 2246 pt w S2, S3 Colon Ca
* FL +/- Oxaliplatin for 6 mth
* De Gramont Regimen
* 1' end point was DFS

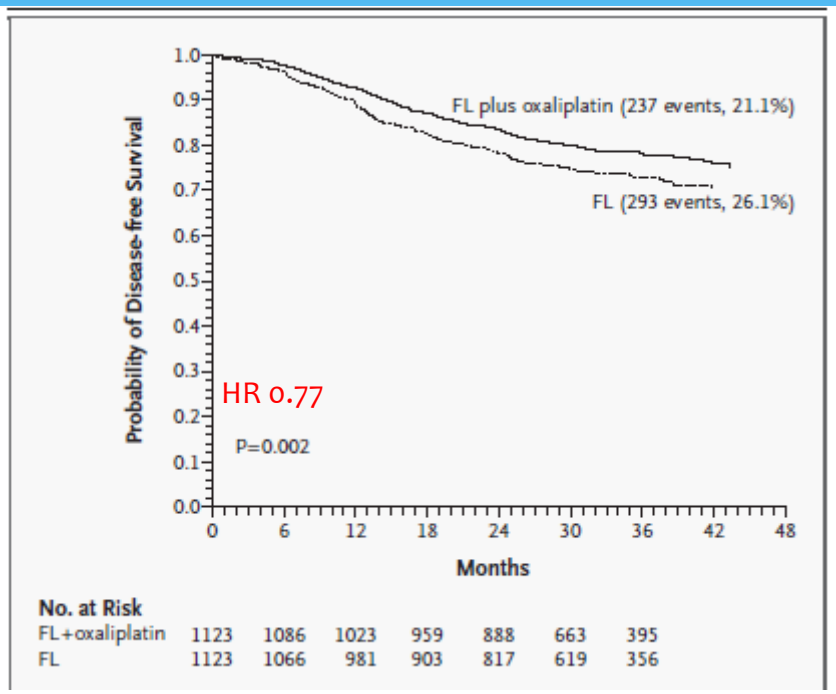
Andre et al. N Engl J Med 2004

NSABP C-07

* P3 study in US
* 2407 Pt w S2, S3 Colon Ca
* FL +/- Oxaliplatin for 6 mth
* Roswell-Park Regimen
* 1' end point was DFS

Kuebler et al. JCO 2007

chemotherapy



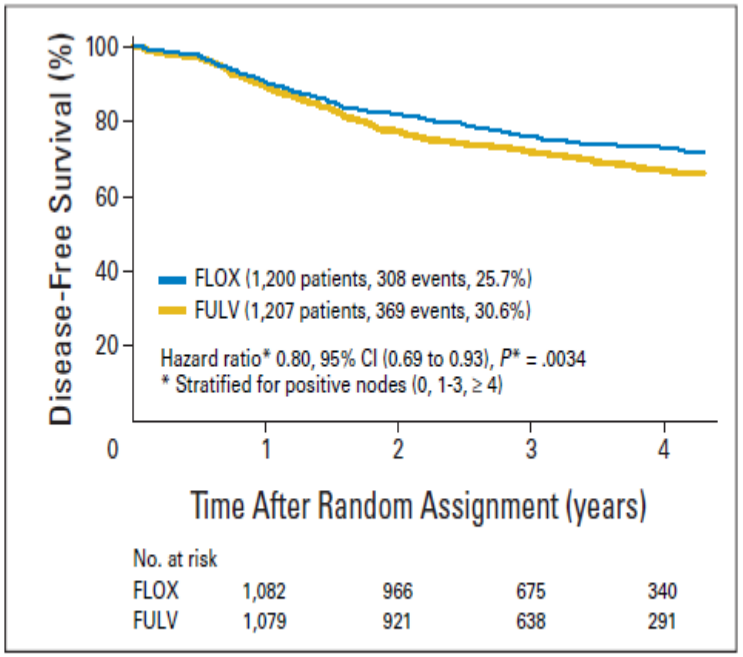


Fig 2. Kaplan-Meier estimates of disease-free survival by treatment. FLOX, fluorouracil, leucovorin, and oxaliplatin; FULV, fluorouracil and leucovorin.

* Significant DFS at 3 yrs (77.8% vs. 72.9%; *P* = .01) in favour of FOLFOX4
* No significant difference in OS

Andre et al. N Engl J Med 2004

* Significant DFS at 4 yrs (73.2% vs. 67%; *P* = <.004) in favour of FLOX
* No significant difference in OS

Kuebler et al. JCO 2007

Adjuvant Chemotherapy

* Current Gold-standard adjuvant chemotherapy schedule is extrapolated from Colon Ca Trial

  Oxaliplatin-based Chemotherapy

MOSAIC vs NSABP-C07

MOSAIC – De Gramont Regimen

* FOLFOX 4: 2 hr 200 mg/m2 leucovorin, bolus 5FU 400mg/m2 then 22hr 600mg/m2 5 FU on 2 consecutive days every 14 days for 12 cycle
* +/- 2 hr oxaliplatin 85mg/m2

NSABP-C-07 – Roswell Park Regimen

* FLOX : 2 hr leucovorin 500mg/m2, bolus 5FU 500mg/m2 D1,8,15,22,29, 36 then 2 wk rest period
* +/- 2 hr oxaliplatin 85mg/m2 on D1, 15,29 of 8 wk cycle

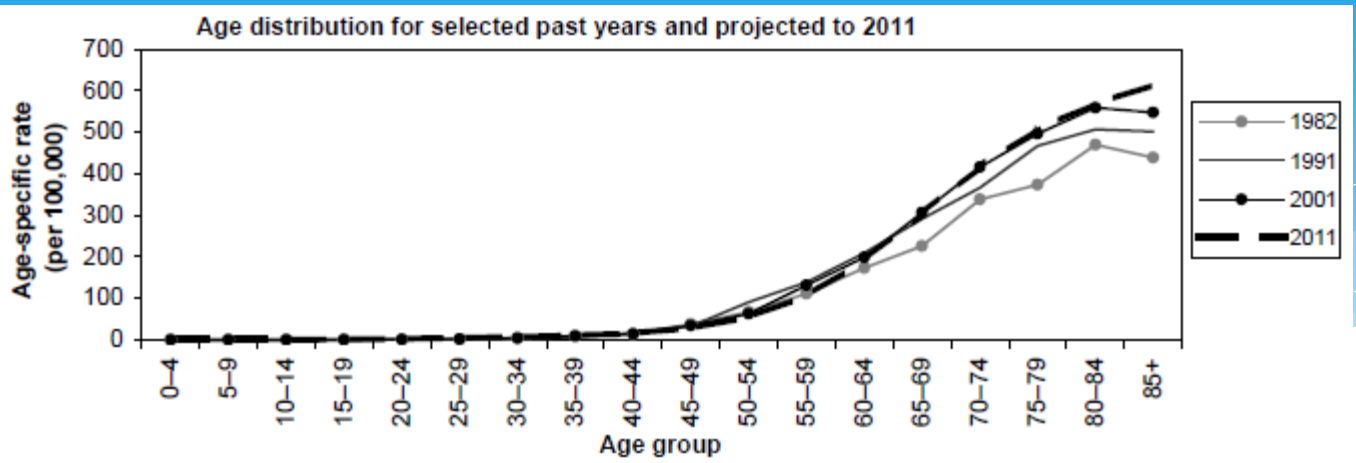


Figure 22: Cancers of the colon, rectum and anus (ICD-10 C18–C21), Australia, males

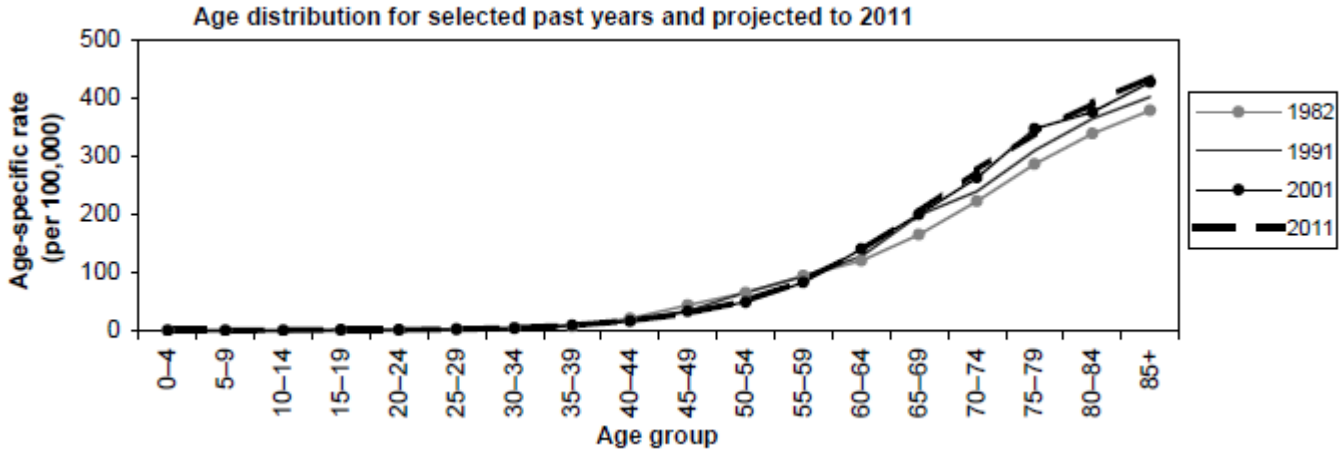


Figure 21: Cancers of the colon, rectum and anus (ICD-10 C18–C21), Australia, females