

## Adjuvant Therapy for Rectal Cancer: Evidence from Randomized Trials and Applications to Practice

Bruce Minsky

## Colon vs. Rectal Cancer

- One organ with similar biology
- Higher local recurrence for rectal due to the surgical challenge (abdomen vs. pelvis)
- Chemotherapy developed first in colon cancer then moved to rectal cancer (CMT)

## INT 0114

7.4 Yr F/U

<u>Outcome (%)</u>	<u>5-Year</u>	<u>7-Year</u>
Local Failure	14	17
Survival	64	56

*Tepper et al JCO 2002*

## Recommendations for CMT

Ideal regimen (pre or postop):

- CI 5-FU
- Capecitabine (X-ACT)

? Avoid Postop RT:

- If TME with  $\geq 12$  LNs sampled then CT but no RT for T<sub>3</sub>N<sub>0</sub>

## Randomized Preop RT

- PMH
- MRC
- VA I
- VA II
- Stockholm I
- Stockholm II
- Norway
- MRC
- EORTC
- CVKO 95-04
- Swedish Rectal\*\*

- Meta-analysis
- JAMA 2000\*\*
  - Lancet 2001

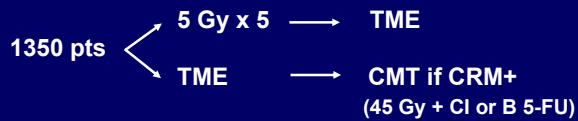
## CKVO 95-04 TME $\pm$ RT Trial

Ann Surg 2007

	<u>% 5-Yr Local Failure</u>
TME	11
TME+RT	6**

*21% LF with TME alone for Stage III*

## MRC CR07



- 4 Yr Median F/U
- ≤ 15 cm from the AV by rigid scope
- Clinically resectable – all stages
- 86% TME by path review
- 40-45% received adjuvant chemotherapy

Sebag-Montefiore et al Lancet 2009

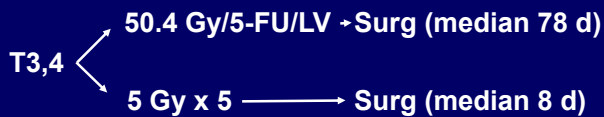
## MRC CR07

	Preop	Postop	P
# Randomized	674	676	
# CRM +	57 (10%)	77 (12%)	
Received CMT	-	53/77 (69%)	
% 3-Yr LF	4	11	0.0001
% 3-Yr DFS	78	72	0.013

- 10% pt have CRM+ and preop Rx is more effective
- Efficacy of 5 Gy x 5 vs. CMT not answered

Sebag-Montefiore et al Lancet 2009

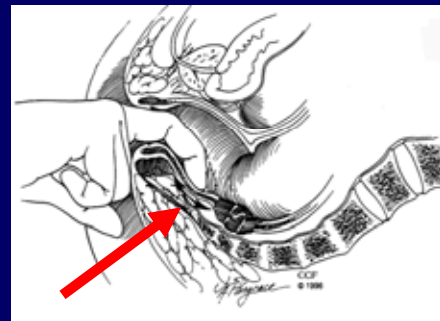
## Polish Preop Phase III Trial



- 316 pts
- no involvement of the sphincter
- TME only for distal tumors
- **no QA**

Bujko et al Br J Surg 2006

## Sphincter Preservation



## Polish Preop Phase III Trial

Results (%)	5 Gy x 5	50.4 Gy/CMT
pCR	1	16 *
% SP Preserv	61	58
% CRM+	13	4 *
% Compliance	98	69
% LF	9	14
% 4-Yr Surv	67	66

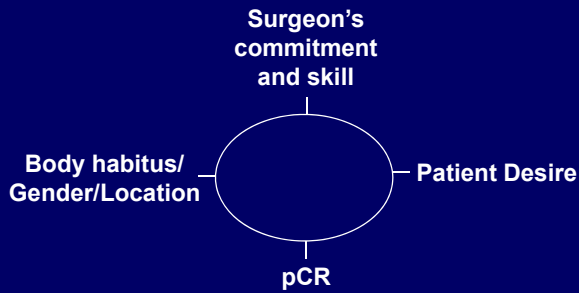
\* = statistically significant

## Is Surgery Necessary After a cCR?

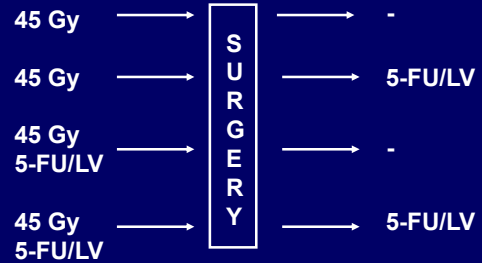
- 265 pts – preop 50.4/5-FU/LV
- 27% cCR with negative biopsy
- Mean F/U: 57 months
- 3% luminal recurrence
- 4% distant metastasis
- 100% 5-year survival

Habr-Gama et al Ann Surg 2004

## Sphincter Preservation



## EORTC 22921



**FFCD 9203 – arms 2 versus 4**

## EORTC 22921

- 1011 pts, median f/u = 5.4 yr, 37% TME
  - 73% received any postop chemotherapy
  - only 43% received  $\geq 95\%$  of the planned dose
- |              |         |       |            |
|--------------|---------|-------|------------|
| • Local Fail | Any CT: | 8-10% | (p<0.0001) |
|              | No CT:  | 17%   |            |
- 5-Yr Survival: 65%

*Bosset et al NEJM 2006*

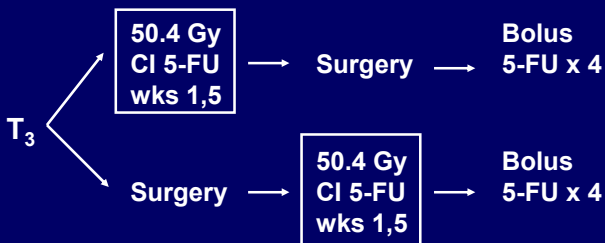
## FFCD 9203

- N = 742 T3/4
- 73% received postop 5-FU/LV

	Preop CMT (%)	Preop RT (%)	p
• Gr 3-4 Toxicity	15	3	< 0.05
• pCR	11	4	< 0.05
• Sp preservation	53	52	ns
• Local failure	8	17	< 0.05
• 5-Yr Surv	68	67	ns

*Gerard et al JCO 2006*

## CAO/ARO/AIO 94



## CAO/ARO/AIO 94

Median F/U 46 m

	Pre-op	Post-op	P
Evaluable #	405	394	-
5-Yr LF %	6	15	0.006
5-Yr Survival %	74	76	ns
Acute toxicity	27	40	0.001
Chronic toxicity	14	24	0.012
5-Yr DF %	36	38	ns
Sphincter Preservation	45/116 (39%)	15/78 (20%)	0.004

*Sauer et al NEJM 2004*

## cT3N0 @ 10 cm: CMT vs. LAR

### PREOP CMT

- improved local control
- less toxicity
- **but** over treat 20% (pT1-2N0)

### SURGERY

- avoid RT
- **but** if N+ (22% s/p preop CMT\*) then need postop CMT
- decreased local control
- higher toxicity
- poor function

Guillem et al JCO 2008

## Selected New Agents in Colorectal Cancer

### Cytotoxics

- CPT-11
- Oxaliplatin
- Capecitabine
- UFT
- Tomudex

### Targeted

- EGFR
  - MAb: Cetuximab, Panitumumab
  - TK: Gefitinib, Erlotinib
- VEGF
  - MAb: Bevacizumab
  - TK: Vatalanib

## Preop RT/CAPOX + Bevacizumab

	Czito et al <u>IJROBP 2007</u>	Crane et al <u>Proc ASCO 2008</u>
# Pts	11	25
Bev	15 mg/kg LD then 10 mg/kg W 1,3	5 mg/kg q 2 wks
% pCR	18	24

## R-0012 Phase II Preop

- T3,4
- 45.6 Gy (1.2 Gy **BID**)  
Boost: 9.6 Gy (T3) - 14.4 Gy (T4)
  - 5-FU CI (225 mg/m<sup>2</sup>)
  - 45 Gy (1.8 Gy/**q day**)  
Boost: 5.4 (T3) - 9 Gy (T4)
  - 5-FU CI (225 mg/m<sup>2</sup>)
  - CPT-11 (50 mg/m<sup>2</sup> q week x 4)

## R-0012 Phase II Preop

	<u>5-FU/BID RT</u>	<u>FOLFIRI/RT</u>
# entered	52	54
% Gr 3+ tox	42	55
% pCR	26	26

Mohiuddin et al JCO 2006

## ACCORD 12/0405 Preop

- 598 Pts, all TME
- cT3 and/or N+

	(%)			
	Gr3+ tox	SSS	pCR	CRM+
45 Gy CAPE (800 mg/m <sup>2</sup> BID)	11	75	14	11
	(<0.001)			
50 Gy CAPOX (50 mg/m <sup>2</sup> /w)	25	78	19	6

Gerard et al Proc ASCO 2009

## STAR-01 Preop

- 747 Pts
- cT3 and/or N+

	<u>Gr3+ tox</u>	<u>pCR</u>
50.4 Gy CI 5-FU	8	16
50.4 Gy CI 5-FU/Oxali (60 mg/m <sup>2</sup> /w)	24	15

(%)

(<0.001)

Aschele et al Proc ASCO 2009

## Phase III Trials of CMT with Oxaliplatin

CAO/ARO/AIO 06	50.4 Gy CI 5-FU	± Oxali
PETACC-6	45 Gy Cape	± Oxali
NSABP R-04	50.4 Gy/Cape vs. 50.4 Gy/CI 5-FU	± Oxali

## Induction Cap-Ox → CMT

77 Induction CAPOX  
↓  
70 Cap + 50.4-54 Gy  
↓  
67 Surgery

- 24% pCR
- 48% micro residual

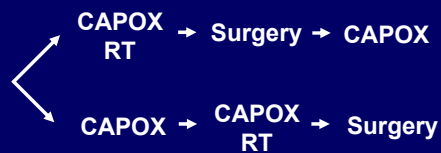
Chau et al JCO 2006

## Objective responses by MRI

	Post Chemotherapy	Post Chemo/RT
CR	3 (4%)	14 (21%)
PR	57 (84%)	52 (77%)
SD	8 (12%)	2 (3%)
PD	0	0
ORR	88%	97%

## GCR-3 Randomized Phase II

- 108 pts



Fernandez-Martos et al. ProcASCO 2009

## GCR-3 Randomized Phase II

	<u>Induction</u>	<u>Standard</u>	<u>p</u>
% pCR	14	13	-
% Gr 3-4 toxicity	17	51	0.00004
% received all 4 cycles	93	51	0.0001

Fernandez-Martos et al. ProcASCO 2009

## Preop CMT: Cetuximab

Site	#	Regimen	Toxicity	% Gr 3+	%pCR
MSKCC	20	CI 5-FU	5-15		12
Erlangen	48	CapOx	7-19		9
Belgium	30	Cap	3-15		5
Heidelberg	20	Capiri	10-20		25
Modena	38	Cetux	15		8

## Biomarkers to Predict Response to Cetuximab CMT

- 41 Pts with T3-4 and/or N+
- Cetuximab LD (400) then 250 qW

	Cetuximab LD	→	Cetuximab Cape/45 Gy	→	Surgery
Day	-7		0		36
Bx/Blood	▲		▲		▲

Debuquoy et al JCO 2009

## Biomarkers to Predict Response to Cetuximab CMT

- k-RAS, cDNA microarrays, ICH (EGFR & Ki-67)
- Proteomics & ELISAs
- Pre-CMT cetuximab LD: ↓ tumor cell proliferation  
Ki67 (p=0.01) and TGF- $\alpha$  (p=0.001)
- Cape/RT needs proliferating cells to work.....
- No correlation with k-RAS

Debuquoy et al JCO 2009

## Conclusions

- If need CMT (LN+) - use preop
- New questions:
- 5 Gy x 5 vs. CMT ? (Polish trial)
  - Is postop chemo needed ? (EORTC, FFCD)
  - Treatment of uT3N0 @ 10cm ?
  - Identify LN+ preoperatively ?
  - Novel CMT regimens Phase II: ↑ pCR  
but Oxali not confirmed in Phase III