

## What is the role of postoperative adjuvant chemotherapy?

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## Possible Role of Chemotherapy in Rectal Cancer

In addition to perioperative radiotherapy:

enhance efficacy  
⇒ improves **local control** → resection and sphincter preservation

Adjuvant systemic therapy - after perioperative (chemo)radiation  
eradicates micrometastasis  
⇒ reduces rate of **distant relapse**

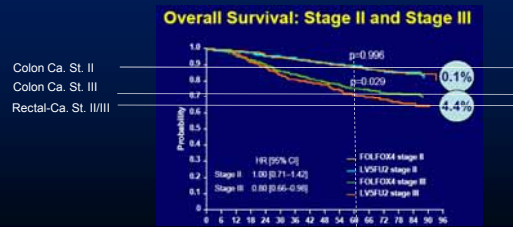
Before perioperative chemoradiation  
reduces local tumor size **and** eradicates micrometastases

## PreOP Trials: Patterns of Failure

		local failure		distant mets.		OS (5y)	
		vs.		vs.		vs.	
FFCD JCO 2006	RT vs. RChT	16%	8%	36%	38%	66%	67%
EORTC NEJM 2006	RT vs. RChT	17%	9%	32%	35%	65%	65%
AIO/CAO/ARO NEJM 2004	Pre vs. post	13%	6%	36%	38%	74%	76%*
Dutch trial Ann Surg 2007	5x5 vs. J.	11%	6%	28%	26%	64%	64%

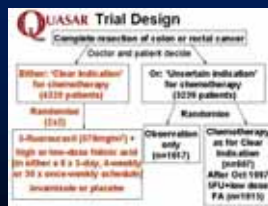
Despite significant reduction of local relapse,  
no influence on distant mets. and survival observed

## Overall Survival Data with 5-FU: Colon vs. Rectal Cancer

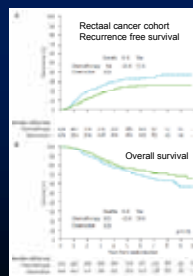


De Gramont et al., ASCO 2007

## QUASAR Trial

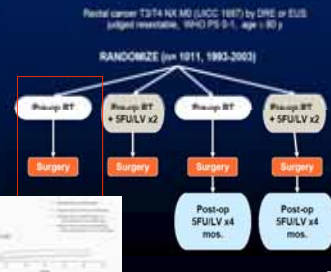


29% (n=948):  
stage II/III rectal cancer pts.

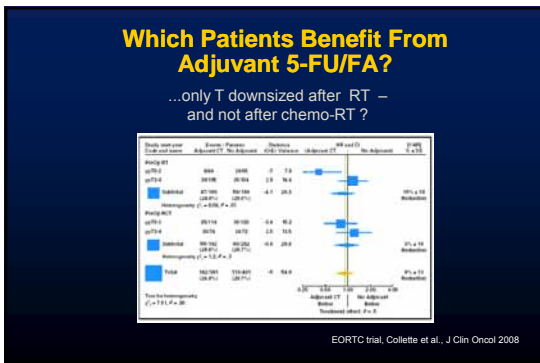
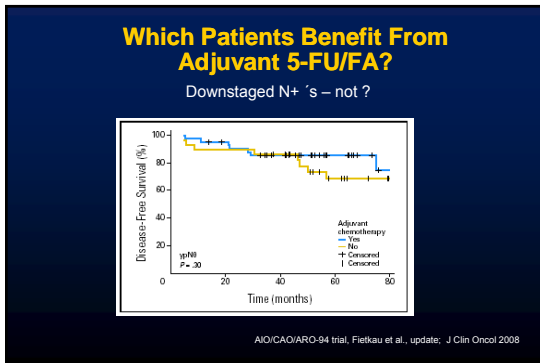
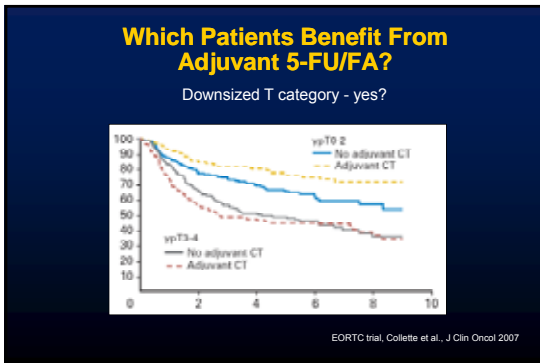
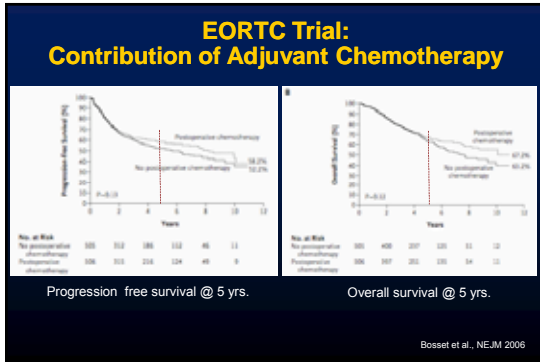
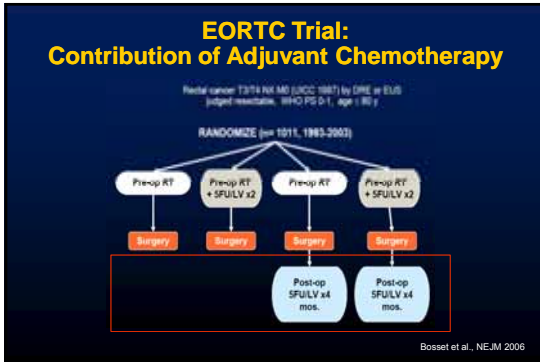


Quasar Collaborative Group; Lancet 2007

## EORTC Trial: Contribution of Chemotherapy



Bosset et al., NEJM 2006



- ### What could be other selection criteria?
- Molecular profile?**
    - But yet differences for stage II and III colon cancer (Roth et al., ASCO 2009; WCGIC 2009)
    - Conflicting data about predictive value of MSI and LOH18q (Sargent et al., ASCO 2008; Tejpar et al., ASCO 2009)
    - 18 gene set from QUASAR, for stage II rectal cancer? (Kerr et al., ASCO 2009)
  - Patient characteristics?**
    - No oxaliplatin for pts. > 70y? (McCleary et al., ASCO 2009)

## 2 Conclusions, so far:

Although we do not have level 1A evidence, it is obvious that systemic treatment contributes to cure

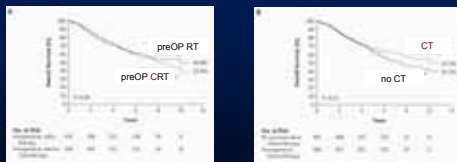
...but 5-FU/FA is not the solution

## How to improve treatment?

More impact from intensive preop chemorad or from adjuvant treatment?

How to optimize adjuvant treatment?

## EORTC Study: What has more impact on patients' prognosis?



PreOP Chemo-RT vs. RT only

PostOP Chemo vs. observation only

Bosset et al., NEJM 2006

## Preoperative Chemoradiation: Add Oxaliplatin to 5FU or Cape?

	PRODIGE 2 N=563		STAR N=732	
	Cape 45 Gy	Cape-Ox 50 Gy	FU 50 Gy	FU-Ox 50 Gy
ypCR	14%	19%	16%	16%
CRM +ve	12%	7%	6%	4%

Gérard et al., ASCO 2009; Aschele et al., ASCO 2009; WCGIC 2009;

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M1 at resection	4%	3%		

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M1 at resection	4%	3%	3%	0.5%
Cumulative Oxaliplatin		250		360

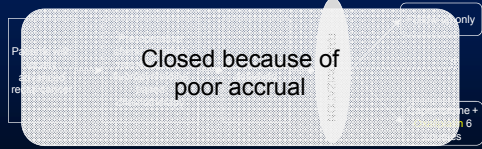
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Adjuvant continuation?	According to site		According to site	

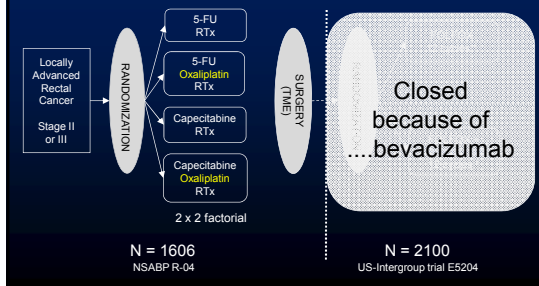
Gerard et al., ASCO 2009; Aschele et al., ASCO 2009; WCGIC 2009;

### CHemoTherapy Or No chemotherapy In CLEarmargins after neoadjuvantchemoradiationin locally advanced rectal cancer (CHRONICLE).

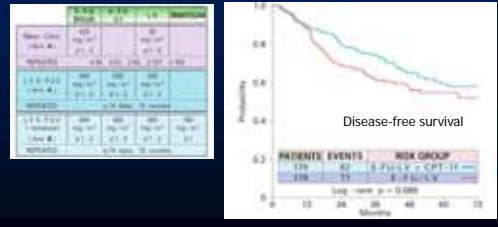


- With 800 patients and p<0.05:
- Primary endpoint: 3-yr DFS-85% power to detect a 10% increase ie. 40% - 50%
- Secondary endpoints: overall survival, toxicity

### NSABP US-Intergroup Trial - Rectal Cancer

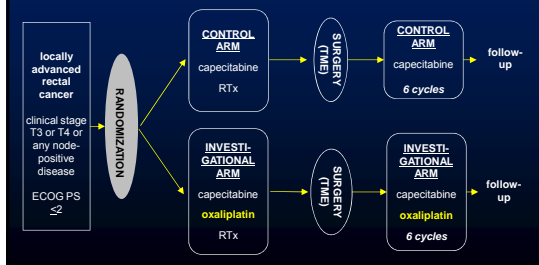


### Postoperative Chemotherapy: 5FU/FA vs. FOLFIRI



Piedbois et al., ASCO 2009

### Treatment Arms in PETACC-6 Trial Intending DFS improvement of 7% @ 3y



### Adjuvant Treatment Characteristics

	Pre OP CRT	Patients starting adjuvant CT
FFCD 9293	5FU-RT or RT	75%
EORTC 22921	5FU-RT or RT	77%
ARO/AIO/CAO	5FU-RT pre / post	80%

Bosset et al., JCO 2006; Gerard et al., NEJM 2006; Sauer et al., NEJM 2004; Gerard et al., ASCO 2009; Sebag-Montferrer et al., ASCO 2009; Rödel, Arnold et al., JCO 2007

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FFCD 9293	5FU-RT or RT	75%
EORTC 22921	5FU-RT or RT	77%
ARO/AIO/CAO	5FU-RT pre / post	80%
PRODIGE-2*	5FU-RT	42%*
	Cape-Ox-RT	30%*

\*recommendation for CT

Bosset et al., JCO 2006; Gerard et al., NEJM 2006; Sauer et al., NEJM 2004  
Gerard et al., ASCO 2009; Sebag-Montflore et al., ASCO 2009; Rödel, Arnold et al., JCO 2007

## Adjuvant Treatment Characteristics

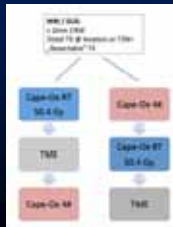
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PRODIGE-2*	5FU-RT	
	Cape-Ox-RT	
UK CORE	Cape-Ox-RT	
German Phase II	Cape-Ox-RT	

\*recommendation for CT

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## Inverse Course of Treatment, Starting with Chemotherapy?

Spanish randomized phase II trial



	Arm A; N=49	Arm B; N=54	p
Any 3,4 tox @ CRT	29%	23%	n.s.
Any 3,4* tox @ CT	51%	17%	0.0004
ypCR	13%	14%	n.s.
R0	92%	88%	n.s.
Dose density for CT	0.74	0.96	0.0001

Fernandez-Martos et al., ASCO 2009

## While waiting for phase III's: What should be regarded as a standard ?

5-FU / (FA)

Standard in post-OP-CRT era

Positive trials: EORTC (trend), QUASAR (subgroup)

Capecitabine? (→ colon transfer, AIO rand. phase 2 Hofheinz, ASCO 2009)

5-FU/ Oxaliplatin?

Standard in colon cancer stage III/II high risk → colon transfer?

Capecitabine / Oxaliplatin?

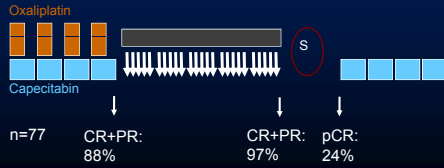
Large phase II dataset in rectal cancer (CORE, German Trial)

„Targeted drug“ combinations?

not – (yet?)

### Neoadjuvant XELOX followed by Chemoradiation in MRI defined Poor-Risk Rectal Cancer

Poor Risk:  $\geq 5\text{mm}$  into perirectal fat or  $\leq 1\text{mm}$  to mesorectal fascia T3 at or below levators T1-4N2



n=77 CR+PR: 88% CR+PR: 97% pCR: 24%

Chau et al., J Clin Oncol 2006

### Rectal Cancer different from Colon Cancer?

**specific anatomical location:**

yes, but only a risk for local relapse, not for survival

**metastatic behavior different:**

no data demonstrating real difference

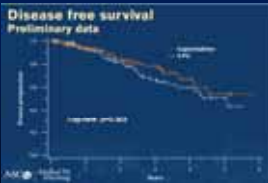
**different sensitivity to chemotherapy:**

rectal vs colon primary tumor: no sign. difference

**different biology/gene signature:**

probably, but not related to clinical behavior, chemosensitivity etc.

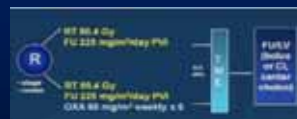
### Chemorad: Substitute FU by Capecitabine?



Capecitabine	N=197
3%	
55%	
62% (3.4: 4%)	
7% (n.s.)	
T downstaging	Trend (p=0.17)
N Downstaging	Improved (P=0.03)

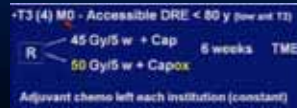
Hofheinz et al., ASCO 2009

### Chemorad: Add Oxaliplatin to FU or Cape?



STAR; N=732

ypCR: 12→25%  
3yDFS: 75→82%

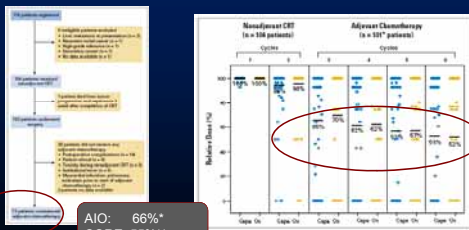


PRODIGE-2; N=563

ypCR: 11→20%

Aschele et al., Gérard et al., both ASCO 2009

### Phase II Trials with Pre- and postoperative CapeOx (AIO: N=110; CORE N=85)



AIO: 66%\*  
CORE: 55%\*\*

\*Rödel, Arnold et al. J Clin Oncol 2007; \*\*Sebag-Montefiore et al. ASCO GI 2009