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ULUSAL
ONKOLOJİK
ARAŞTIRMALAR
ÇALIŞTAYI



SEQUENCING OF THERAPY IN RECTUM CANCER

DR. LEYLA ÖZER

MEDICAL ONCOLOGY DEPARTMENT
MEHMET ALİ AYDINLAR UNIVERSITY
ACIBADEM ATAKENT HOSPITAL

OUTLINE

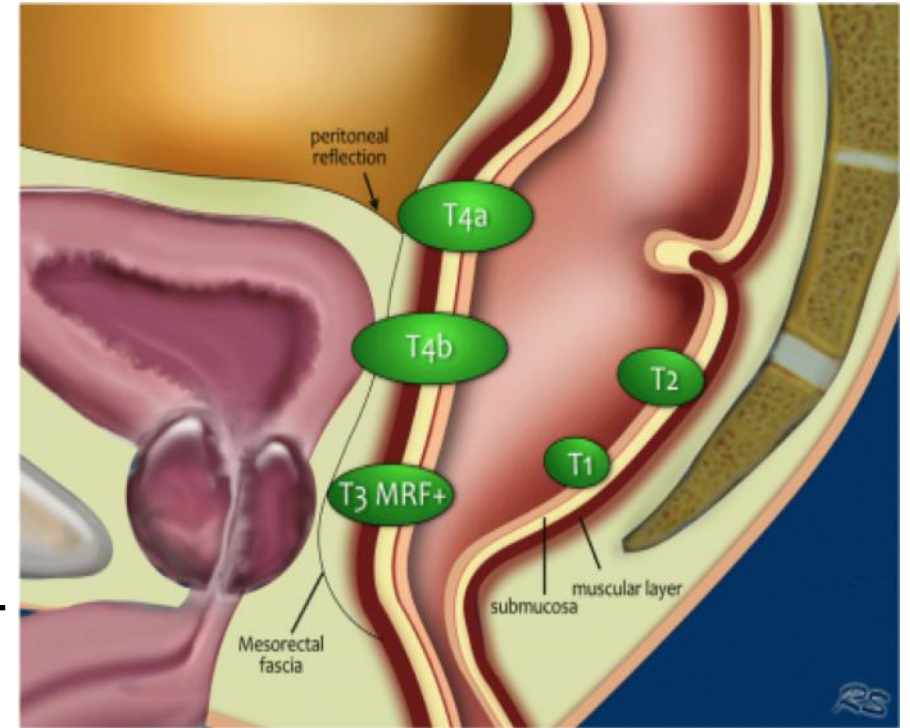
A. Neoadjuvant systemic therapy

- ✓ To whom ?
- ✓ Which chemotherapy protocol?

B. Adjuvant Systemic Therapy

1. For those who have not received neoadj. therapy;

- ✓ To whom ?
 - ✓ Which regimen?
- #### 2. For those who have received neoadj therapy;
- ✓ To whom?
 - ✓ Relation with response to NACRT?
 - ✓ Which regimen?



C. Total neoadjuvant therapy

- ✓ To whom?
- ✓ Sequencing (CRT/CT or CT/CRT-RT)
- ✓ Duration of therapy
- ✓ Evaluation of response (method and timing)
- ✓ *RT modality (long course/short term?)*

➤ **Selective elimination of RT?**

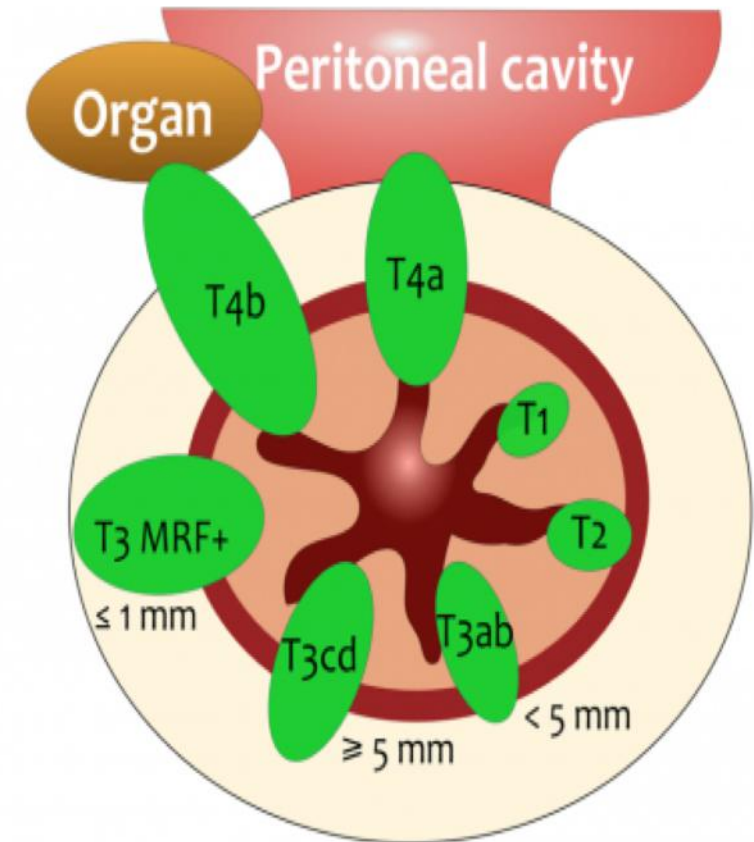
➤ **Avoidance of radical surgery for complete responders?**

Neoadjuvant CRT for whom? Ideal chemotherapy combination ?

- cT3-T4 (those who will require adj CRT)
- Clinical node (+)
- Distal rectum tm (who may need APR)
- Extramural penetration depth (>5 mm invasion)
- MRF invasion(+) or threatened (in preop imaging modalities)(probability of tm free CRM does not seem to be possible)

➤ cT3NO (upper rectum tm) ??

- Node (-) in preop. Imaging, surgery after CRT – 22% lymph node involvement (+)



<https://radiologyassistant.nl/abdomen/rectal-cancer-mr-staging-2-0>

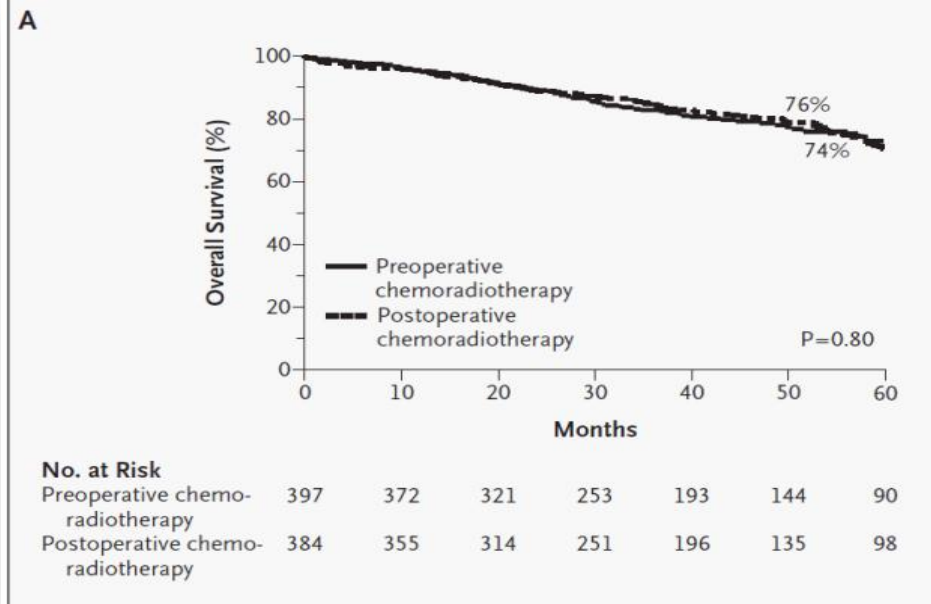
Quirke P et al . Lancet 1986
Merkel S et al. Int J Colorectal Dis 2001
Kapitejin E et al. N Eng J Med 2001
Peeters KC et al. Ann Surg 2007
Ruppert R et al. Br J Surg 2018
Guillem JG et al. J Clin Oncol 2008

Neoadjuvant RT + CT or adj ?

ORIGINAL ARTICLE

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D.,
Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D.,
Peter Martus, Ph.D., Jörg Tschmelitsch, M.D., Eva Hager, M.D.,
Clemens F. Hess, M.D., Johann-H. Karstens, M.D., Torsten Liersch, M.D.,
Heinz Schmidberger, M.D., and Rudolf Raab, M.D.,
for the German Rectal Cancer Study Group*



N=823, no difference in OS (76% vs 74%,
 $p=0.8$)

Local recurrence rates higher in the postop.
CRT arm 7% vs 10% ($p=0.006$)

Grade 3-4 acute side effects; 27% vs 40%
($p=0.001$)

Late side effects; 14% vs 24% ($p=0.01$)

More sphincter preserving surgery for distal
tumors; %39 vs %19

Optimal concomitant chemotherapy with RT ?

- Infusional 5-FU (higher pCR rates compared with bolus 5-FU) ; similar efficacy?
- NCCTG trial: Better OS with inf. 5-FU vs bolus.
- Capecitabine (similar efficacy compared to 5-FU inf. , different toxicity profile)
- Addition of oxaliplatin?

Mohiuddin M et al. Int J Radiat Oncol Biol Phys 2000

Smalley SR et al. J Clin Oncol 2006

O'Connell MJ et al. N Eng J Med 1994

Hofheinz RD et al. Lancet Oncol 2012

O'Connell MJ et al. J Clin Oncol 2014

Higher toxicity with oxaliplatin , no difference in survival.

Table 1. Oxaliplatin as a Component of Neoadjuvant Therapy

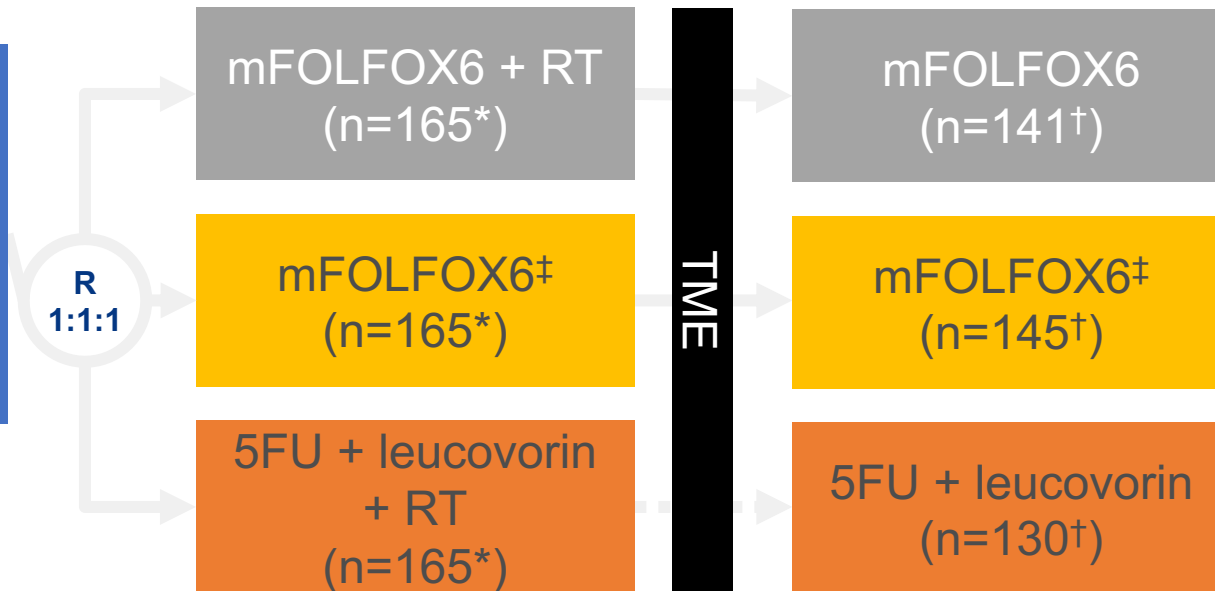
Study	No. Patients	Chemoradiotherapy			pCR	AEs (Grade 3/4)	Outcomes
		Chemo	RT				
STAR-01[42]	379	5-FU 225 mg/m ² /d	50.4 Gy in 28 daily fractions		16%	8%	APR: 19%
	368	5-FU 225 mg/m ² /d + oxaliplatin 60 mg/m ² /d	50.4 Gy in 28 daily fractions		16%	24%	21%
ACCORD[43]	295	Capecitabine 800 mg/m ² twice daily for 5 days	45 Gy in 25 fractions		14%	11%	OS: 88%
	292	Capecitabine 800 mg/m ² twice daily + oxaliplatin 50 mg/m ² /wk	50 Gy in 25 fractions		19%	25%	88%
PETACC-6[44,45]	544	Capecitabine 825 mg/m ² twice daily	45 Gy in 25 fractions		11.3%	15.1%	3-yr DFS: 74.5%
	537	Capecitabine 825 mg/m ² twice daily + oxaliplatin 50 mg/m ² /wk	45 Gy in 25 fractions		13.3%	36.7%	73.9%
German CAO/ARO/AIO-04[47]	623	5-FU 1,000 mg/m ² /d	50.4 Gy in 28 fractions		13%	20%	3-yr DFS: 71.2%
		FOLFOX	50.4 Gy in 28 fractions		17%	24%	75.9%
NSABP R-04[46]	719	5-FU (CI) ± oxaliplatin 50 mg/m ² /wk	50.4 Gy in 28 fractions		18.8%		
	707	Capecitabine 825 mg/m ² ± oxaliplatin 50 mg/m ²	50.4 Gy in 28 fractions		22.2%		

5-FU = fluorouracil; AEs = adverse events; APR = abdominoperineal resection; chemo = chemotherapy; CI = continuous infusion; DFS = disease-free survival; FOLFOX = leucovorin + fluorouracil + oxaliplatin; NSABP = National Surgical Adjuvant Breast and Bowel Project; OS = overall survival; pCR = pathologic complete response; RT = radiation therapy.

FOWARC trial

n, %	FOLFOX-RT (n=141)	FOLFOX (n=145)	5FU-RT (n=130)
pCR	%29	%6.9	%13.1

- **Resectable rectum ca**
 - <12 cm from anal verge
 - Stage II/III
 - ECOG PS 0–1
- (n=495)



Primary end point

- 3-yr DFS

Secondary end points:

- response rate, recurrence, DFS, OS

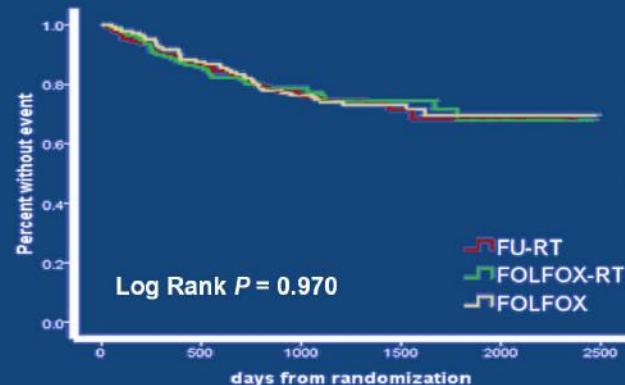
mFOLFOX6 (-/+) RT in neoadjuvant treatment of locally advanced rectal cancer: Final results of the Chinese FOWARC multicenter randomized trial – Deng Y, et al

n, %	FOLFOX-RT (n=141)	FOLFOX (n=145)	5FU-RT (n=130)
pCR	41 (29.1)	10 (6.9)	17 (13.1)
ypT0–2N0	80 (56.8)	53 (36.6)	47 (36.2)
TRG 0–1	97 (68.8)	48 (33.1)	63 (48.4)

Results;

- For locally-advanced rectal cancer, no difference in DFS for mFOLFOX6 ± RT vs. Neoadj 5FU -CRT .
- mFOLFOX + RT vs. both arms :
 - Higher pCR rates, more patients underwent ‘watch & wait’ strategy.
 - Less liver metastases.
- mFOLFOX alone (with no RT) 3-yr DFS or local control is not worse.
- Longer follow-up required for OS difference.

Disease Free Survival



Treatment	3y-DFS (%)	HR (95% CI)
FU-RT	75.7±3.8	Ref
FOLFOX-RT	77.1±3.6	0.944 (0.594-1.499)
FOLFOX	74.9±3.6	0.968 (0.615-1.524)

• Events: FU-RT 35 (26.9%), FOLFOX-RT 37 (26.2%), FOLFOX 40 (27.6%)

□ Addition of platinum agents during RT?

A meta-analysis (n=5599), (9 oxaliplatin and 1 cisplatin study)

- ✓ Increased likelihood of a pCR at the time of surgery (OR 1.31, 95% CI 1.10-1.55)
- ✓ Reduced likelihood of distant recurrence (OR 0.78, 95% CI 0.66-0.92).
- ✓ No improvement in OS or local recurrence
- ✓ The addition of a platinum agent increased rates of grade 3 or 4 toxicities, including diarrhea, nausea, neurosensory toxicity, and fatigue.

Adjuvant Therapy

2 Main Questions to be Answered;

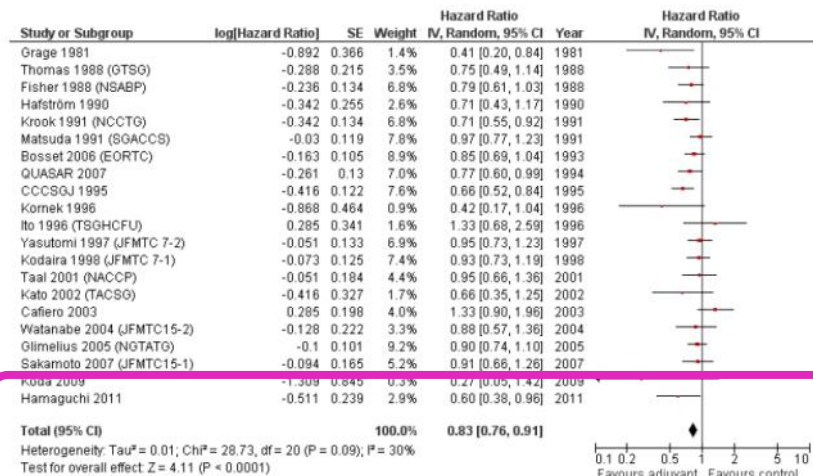
- What is the optimal adjuvant therapy if no preop treatment was given ?

-Observation (stage I and..)

-5-FU alone (Meta-analysis, RCTs)

-5-FU+oxaliplatin

Figure 1. Forest plot of comparison: 1 Adjuvant vs No Adjuvant' ALL, outcome: 1.1 Overall Survival (OS).



Cochrane Database of Systematic Reviews

Postoperative adjuvant chemotherapy in rectal cancer operated for cure. (Review)

Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S

Included 21 RCTs , N=9785

1975-2011

Adj CT vs No CT

TME was not standart

Old drugs; semustine, levamisole ,vincristine+ FU

For OS HR:0.83 ,for DFS HR:0.75

Adjuvant Therapy

- What is the optimal adjuvant therapy if preop CRT/RT was given ?
 - Observation
 - 5-FU alone
 - 5-FU+Oxaliplatin

PATHOLOGIC FINDINGS AFTER TRANSABDOMINAL RESECTION FOR T1-2, N0

ADJUVANT TREATMENT^{c,p,q}
(6 MO PERIOPERATIVE TREATMENT PREFERRED)^s

pT1-2, N0, M0

Observe

No oxaliplatin –different 5-FU regimens

pT3, N0, M0

Infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT^o followed by 5-FU/leucovorin (infusional preferred) or capecitabine or Observation^f

Oxaliplatin preferred -RT in between chemo or initially

pT4, N0, M0
pT1-4, N1-2

FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin/RT (preferred) or capecitabine/RT (preferred) or infusional 5-FU/leucovorin/RT^o followed by FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine/RT (preferred) or bolus 5-FU/leucovorin/RT^o followed by FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine

ADJUVANT CHEMO FOR EVERY c/p T3T4 or N+ disease

CLINICAL STAGE

NEOADJUVANT THERAPY

PRIMARY THERAPY

T3, N any with clear circumferential margin (CRM) (by MRI);¹ T1-2, N1-2

Chemo/RT
• Capecitabine/long-course RT^q or infusional 5-FU/long-course RT^q (category 1 and preferred for both) or
• Bolus 5-FU/leucovorin/long-course RT^{o,q}
or
RT^q
• Short-course RT^t or

Consider restaging^c

T1-2, N1-2 before chemo/RT

FOLFOX or CAPEOX

[Surveillance](#)
(See REC-11)

Resection contraindicated

Systemic therapy^w
(See REC-F)

ESMO RECTAL CANCER GUIDELINES 2017

TREATMENT AFTER DIRECT SURGERY

Table 7. Potential indications for postoperative chemoradiotherapy if preoperative chemoradiotherapy not given

Sufficient and necessary

CRM \leq 1 mm
pT4b
pN2 extracapsular spread close to MRF
Extranodal deposits (N1c)

pN2 if poor mesorectal quality/defects

Sufficient

pN2 low tumours within 4 cm of anal verge (risk of involved LPLN)
Extensive extramural vascular invasion/perineural invasion close to MRF

Borderline sufficient

pN2 in mid/upper rectum if good mesorectal quality
CRM 1–2 mm
Circumferential obstructing tumours

CRM, circumferential resection margin; LPLN, lateral pelvic lymph node; MRF, mesorectal fascia.

Insufficient and unnecessary

pT1/pT2
pT3
CRM > 2 mm
pT4a above peritoneal reflection
pN1
If good quality smooth intact mesorectum

TREATMENT AFTER NEOADJUVANT (CHEMO)RADIOTHERAPY

Summarising, it is reasonable to consider adjuvant ChT in rectal cancer patients after preoperative CRT/RT with yp stage III (and 'high-risk' yp stage II). The level of scientific evidence for sufficient benefit is much lower than in colon cancer and is probably limited to DFS rather than to OS [II, C]. Hence, the decision on postoperative ChT (fluoropyrimidine alone or combined with oxaliplatin) should be risk-balanced, taking into account both the predicted toxicity for a particular patient and the risk of relapse, and should be made jointly by the individual and the clinician.

WHICH FACTORS MAKE STAGE II 'HIGH RISK' ?

	I-CNR-RT ²⁷	PROCTOR-SCRIPT ²⁵	EORTC 22921 ⁷	CHRONICLE ²⁶
Preoperative treatment				
Chemoradiotherapy	25 doses of 1.8 Gy and fluorouracil-based chemotherapy	25 doses of 1.8–2.0 Gy and fluorouracil-based chemotherapy	25 doses of 1.8 Gy and fluorouracil-based chemotherapy	45 Gy and fluorouracil-based chemotherapy
Radiotherapy	..	Five doses of 5 Gy or 25 doses of 1.8–2.0 Gy	25 doses of 1.8 Gy	..
Adjuvant treatment	Six courses of fluorouracil (350 mg/m ²) and folinic acid (20 mg/m ²)	Mayo regimen: six courses of fluorouracil (425 mg/m ²) and folinic acid (20 mg/m ²) Nordic regimen: 12 courses of fluorouracil (500 mg/m ²) and folinic acid (60 mg/m ²); eight courses every 3 weeks of oral capecitabine (1250 mg/m ²) twice daily for 14 days	Four courses every 3 weeks of fluorouracil (350 mg/m ²) and folinic acid (20 mg/m ²)	Six courses every 3 weeks of oxaliplatin (130 mg/m ²) and oral capecitabine (1000 mg/m ²) twice daily for 14 days
Start of accrual	September, 1992	March, 2000	April, 1993	November, 2004
End of accrual	January, 2001	January, 2013	March, 2003	April, 2008
Disease stage	Clinical stage T3, T4*	(y)pTNM II, III	Clinical stage T3, T4*	(y)pTNM II, III
Resection margin	R0	R0, R1	R0	R0
Total mesorectal excision done?	No	Yes	Halfway inclusion	Yes
Timing of randomisation	Before surgery	After surgery	Before surgery	After surgery
Number of patients eligible for analysis in original report	634	437	1011	113
Number of patients eligible for analysis for this meta-analysis	245	403	473	75

EORTC 22921 (n=1011)

Preop treatment heterogeneous
(RT/CRT)

Bolus regimen 😞

TME recommended 😞

Adherence to postop chemo 43% 😞

Result: Chemo (before/after Surgery)
improves LOCAL CONTROL only

No OS or DFS benefit

Subgroup analysis: OS benefit for
ypT0-2?

I-CNR-RT (n=634)

Homogeneous (all pts received
preop CRT)

Bolus regimen 😞

TME not specifically recommended
Adherence to postop chemo 70%

Result: No OS or RFS benefit

PROCTOR/SCRIPT

Preop treatment heterogenous (short course RT/CRT)

Could not reach full accrual (840 pts planned; 470 enrolled)

Bolus chemo regimen (Mayo/Nordic) or capecitabine

Adherence to adj chemo 73%

RESULTS: No OS or DFS difference

CHRONICLE

Homogeneous preop treatment (CRT)

Could not reach full accrual (800 pts planned, 113 enrolled)

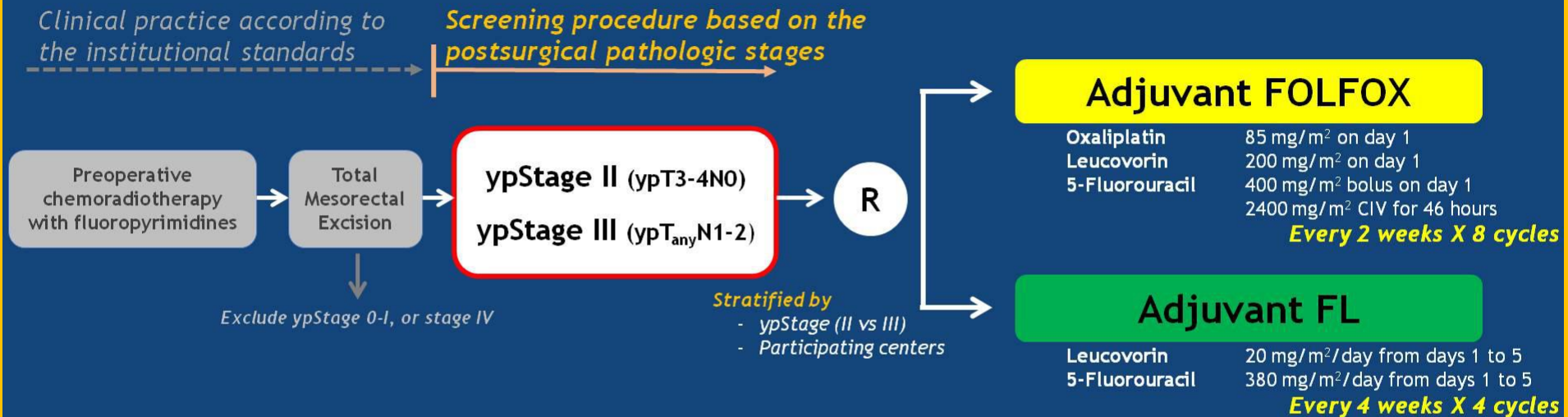
Adjuvant XELOX vs observation

48% completed 6 cycles

RESULTS : No OS difference

ADORE - PHASE 2 DESIGN

Study design and Rationale



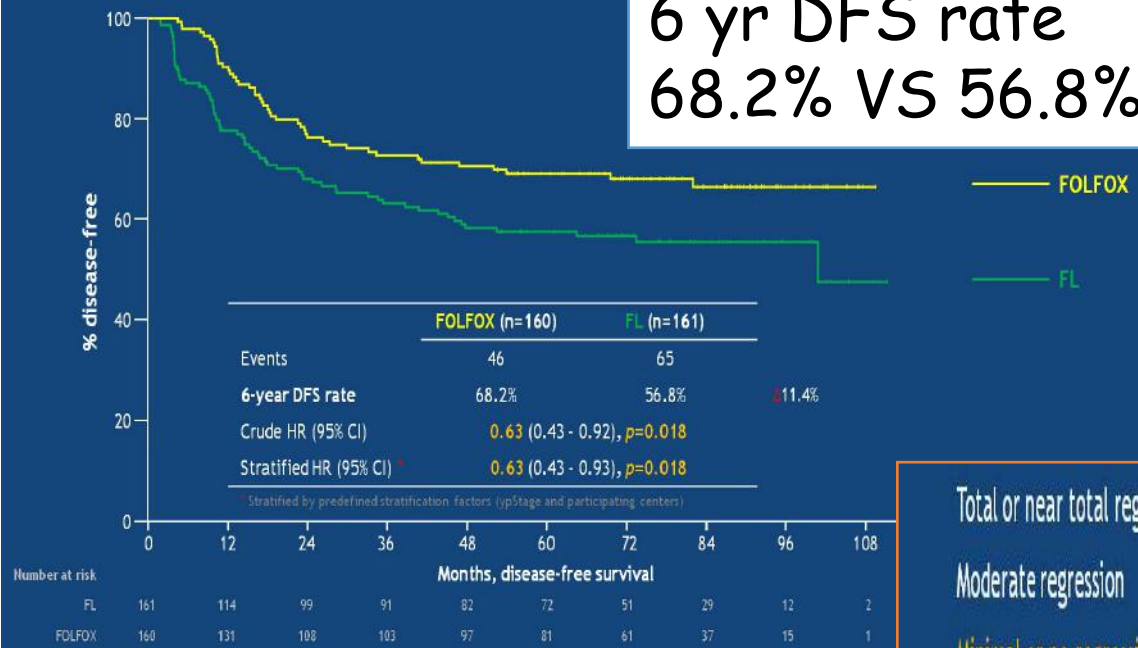
Key inclusion criteria

- Preoperative chemoradiotherapy with fluoropyrimidines alone; *oxaliplatin or other combined regimens were not allowed.*
- Total mesorectal excision (TME) was mandatory.
- Curative surgery (no microscopic residual tumor), ≤ 8 weeks prior to randomization.

ADORE UPDATED RESULTS

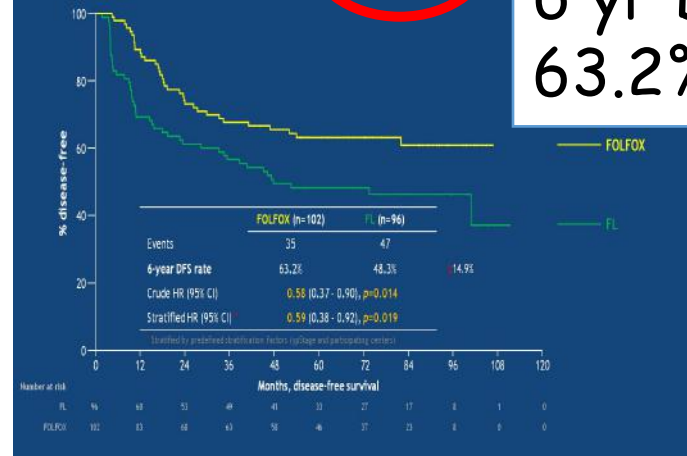
Disease-free survival, ITT population

6 yr DFS rate
68.2% VS 56.8%



Disease-free survival, ypStage III

6 yr DFS rate
63.2% vs 48.3%



Total or near total regression

Moderate regression

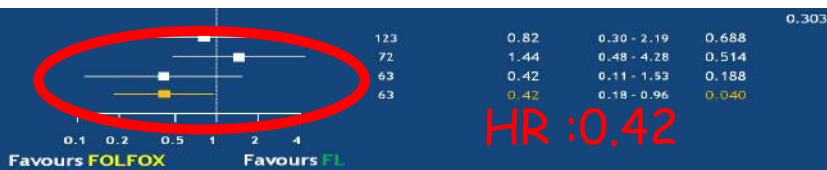
Minimal or no regression



Pathologic N stage

ypN0
ypN1a
ypN1b
ypN2

N2



Is response to neoadjuvant therapy predictive of adjuvant benefit?

1. For nonresponders (ypT3-T4,N+)-- Is it necessary? **Probably YES**
Does it work?
2. For responders (ypT0N0)-- Is it necessary? **Probably NO**
Does it work?

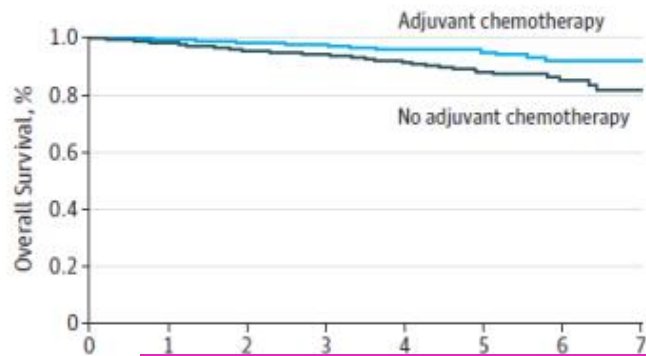
ADJUVANT CHEMOTHERAPY FOR pCR?

JAMA Oncology | Original Investigation

Association Between Adjuvant Chemotherapy and Overall Survival in Patients With Rectal Cancer and Pathologic Complete Response After Neoadjuvant Chemotherapy and Resection

Figure 2. Kaplan-Meier Survival Curves

A All patients with pCR treated with and without adjuvant chemotherapy



No. at risk
No chemotherapy 667
Chemotherapy 667

FOR THE WHOLE GROUP;
5-YEAR OS 95% VS 88.2% (HR:0.44)

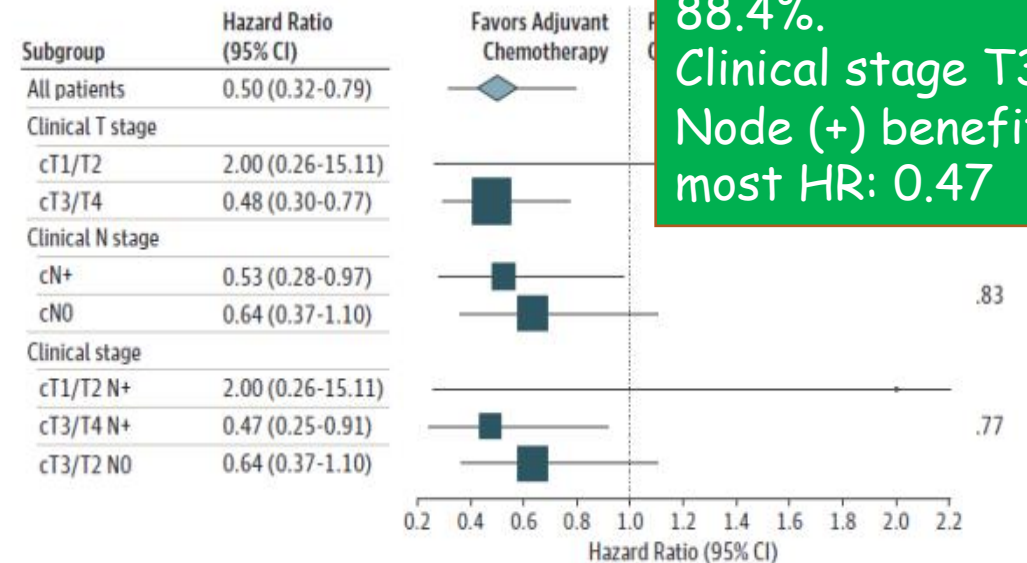
FOR PRETREATMENT NODE (+)
GROUP;

5-YEAR OS 94.7% VS 91.2 (HR:0.21)

JAMA Oncology | Original Investigation

Association of Adjuvant Chemotherapy With Overall Survival in Patients With Rectal Cancer and Pathologic Complete Response Following Neoadjuvant Chemotherapy and Resection

Figure 3. Mortality Hazard Ratios According to Clinical Stage Subgroup



5-year OS 94.7% vs 88.4%.
Clinical stage T3/T4
Node (+) benefited
most HR: 0.47

Dossa F et al. JAMA Oncol 2018

Polanco PM et al. JAMA Oncol 2018

META-ANALYSIS BASED ON PUBLISHED DATA



Available online at www.sciencedirect.com

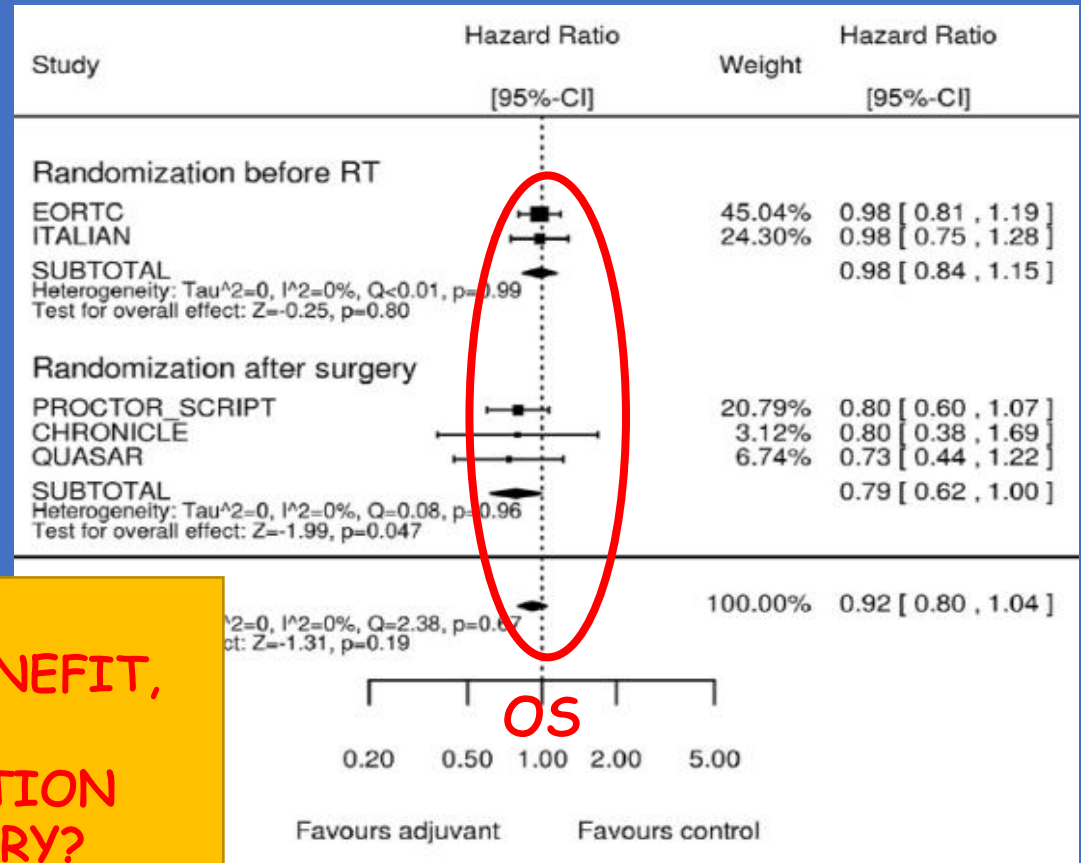
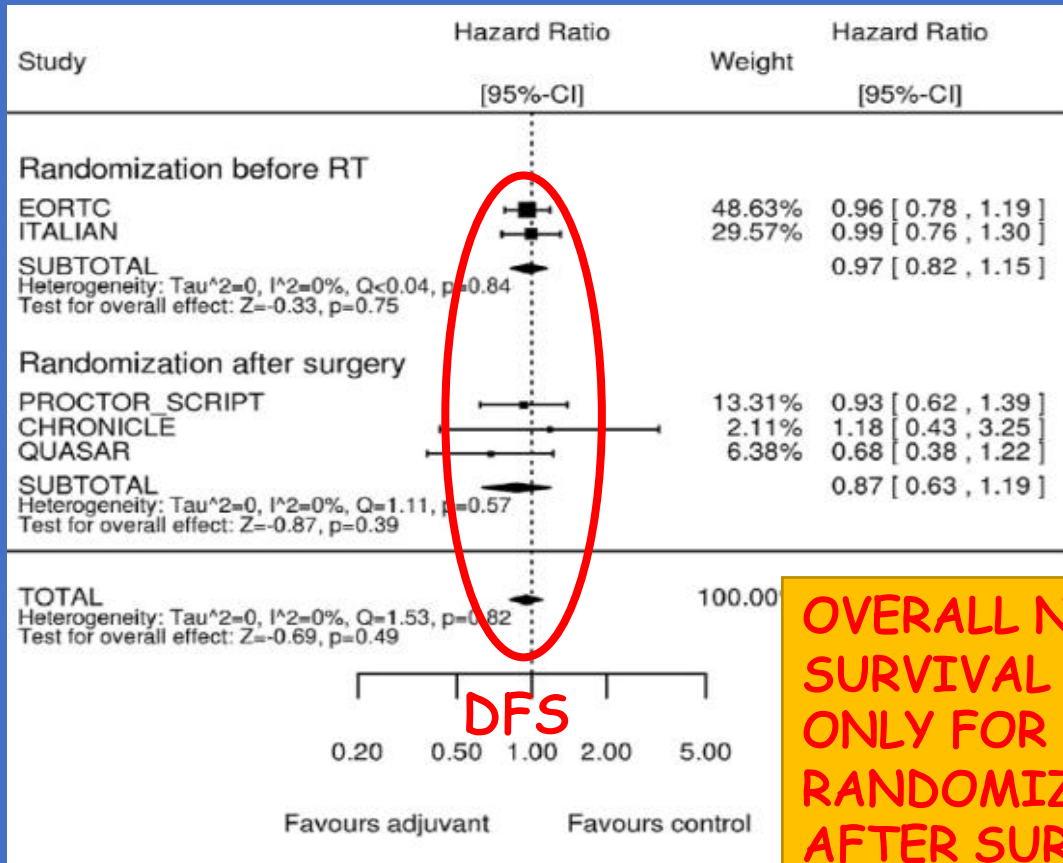
ScienceDirect

EJSO 41 (2015) 713–723

Review

Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: A meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin

K. Bujko ^{a,*}, B. Glimelius ^{b,c}, V. Valentini ^e, W. Michalski ^d, M. Spalek ^a

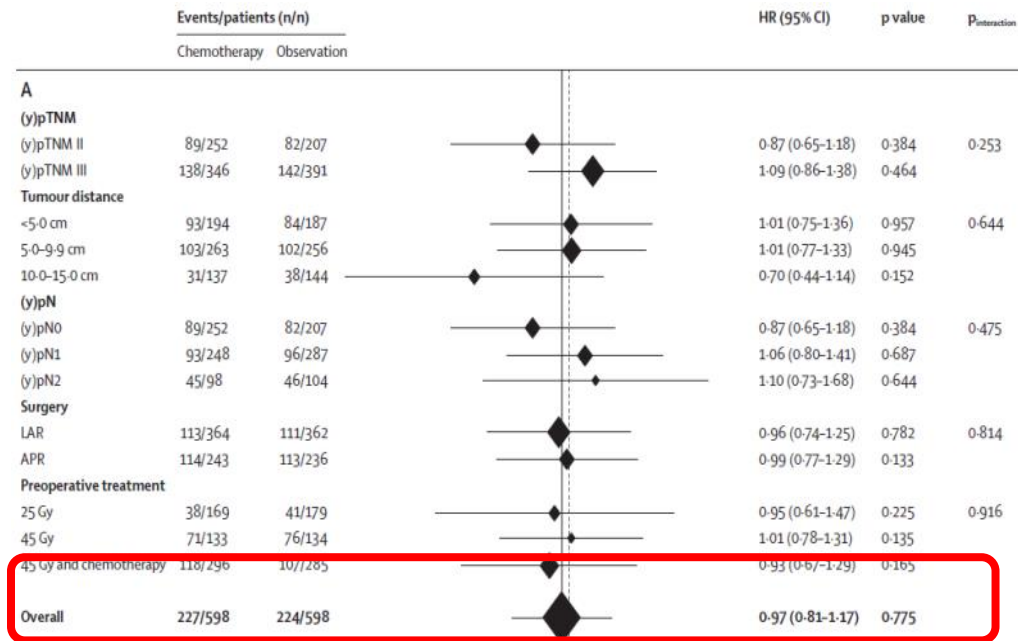


**OVERALL NO
SURVIVAL BENEFIT,
ONLY FOR
RANDOMIZATION
AFTER SURGERY?**



Adjuvant chemotherapy after preoperative (chemo)radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data

Anne J Breugom*, Marloes Swets*, Jean-François Bosset, Laurence Collette, Aldo Sainato, Luca Cionini, Rob Glynn-Jones, Nicholas Counsell, Esther Bastiaannet, Colette B M van den Broek, Gerrit-Jan Liefers, Hein Putter, Cornelis J H van de Velde



FOUR TRIALS , 2 PREMATURELY INTERRUPTED

1198 INDIVIDUAL PATIENT DATA

ALL PATIENTS RECEIVED RT/CRT

NO OS OR DFS BENEFIT (HR:0.97 AND 0.91)

Tumour distance	Chemotherapy	Observation	HR (95% CI)	p value	Pinteraction
<5.0 cm	93/194	84/187	1.01 (0.75-1.36)	0.957	0.644
5.0-9.9 cm	103/263	102/256	1.01 (0.77-1.33)	0.945	
10.0-15.0 cm	31/137	38/144	0.70 (0.44-1.14)	0.152	

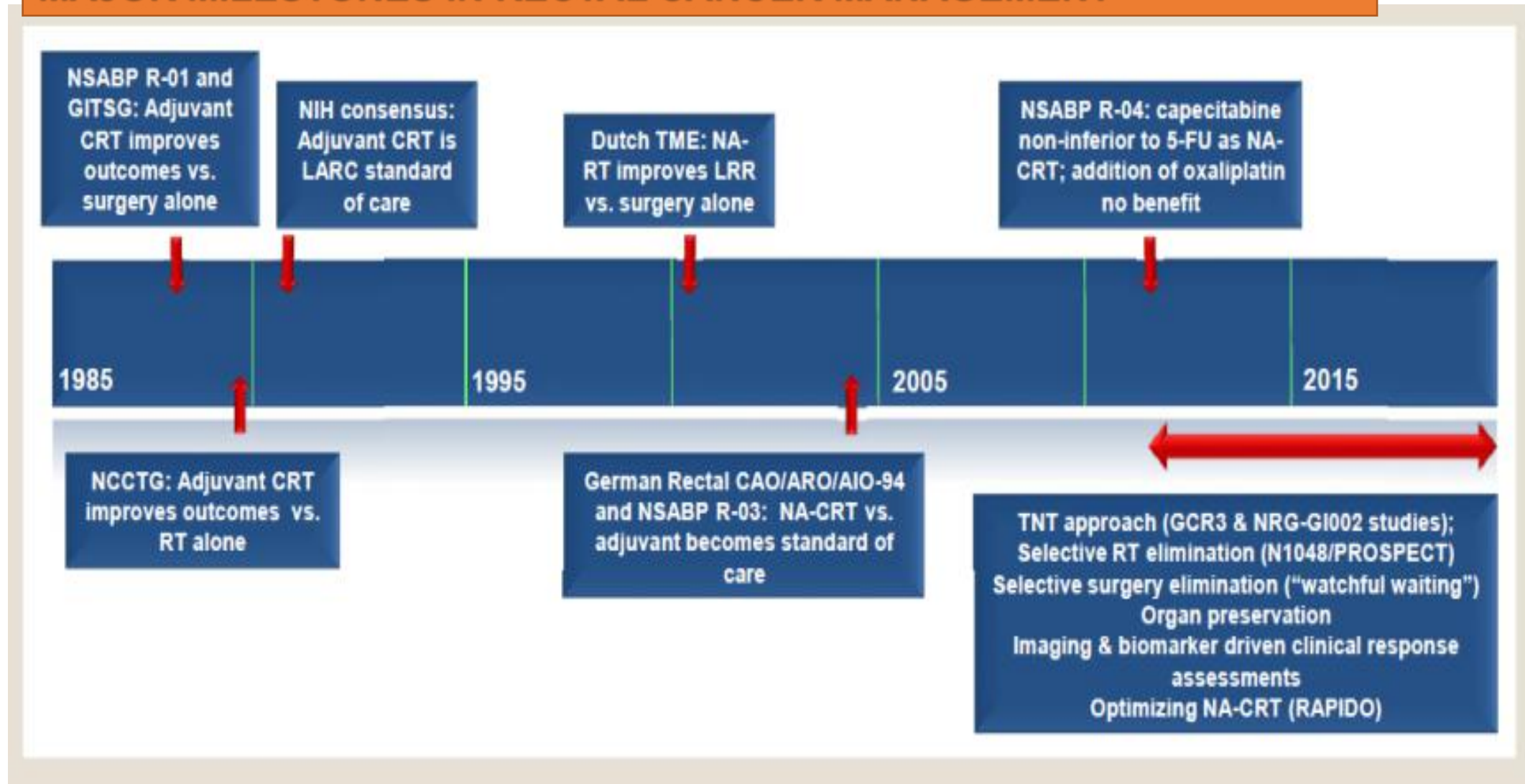
TUMOR BETWEEN 10-15 CM ABOVE ANAL VERGE , BETTER DFS (HR:0.59) AND FEWER DISTANT RECURRENCE(HR: 0.61)

CONCLUSION (regarding adjuvant therapy)

- Adjuvant chemotherapy after direct surgery can be considered for high risk patients (positive or close CRM, nodal positivity +/- ECE, low quality TME, pT3?T4).
- There is no strong evidence supporting the survival benefit for adjuvant chemotherapy following NACRT/RT.
- Guidelines are inconsistent regarding the selection of patients for adjuvant chemotherapy following NACRT/RT.
- Addition of oxaliplatin to inf FU/Cape in the adjuvant setting may provide DFS benefit for c/pT3-T4,N+ rectal cancer .
- Response to neoadjuvant chemo/radiotherapy seems to have prognostic rather than predictive value (conflicting results).
- Insisting on adjuvant chemotherapy is somehow a result of extrapolation from colon cancer studies.

- The decision about adjuvant chemotherapy for each case should be made jointly by the clinician and patient .

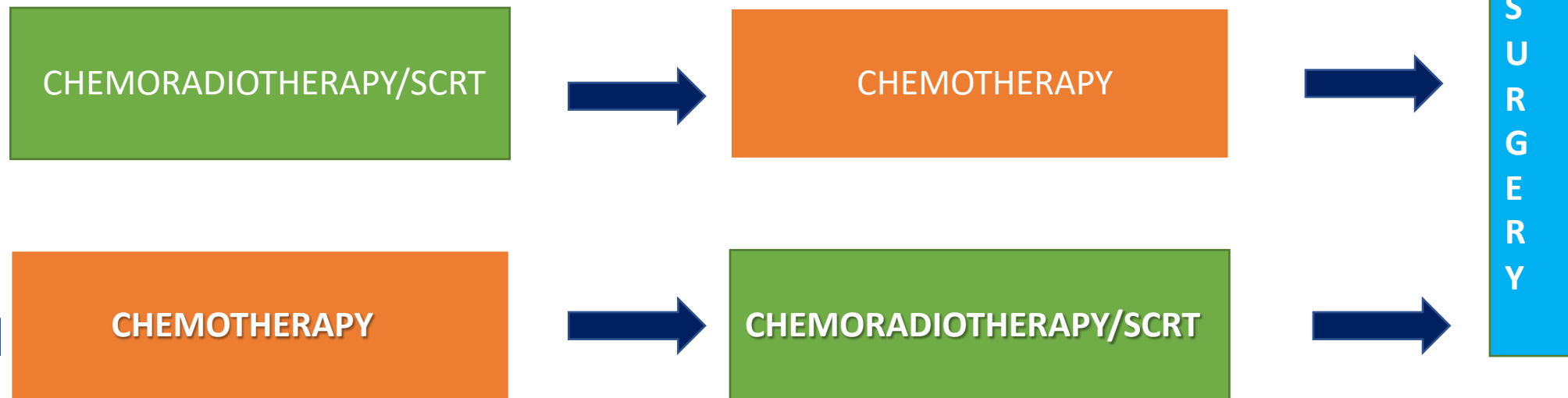
MAJOR MILESTONES IN RECTAL CANCER MANAGEMENT



Advantage and disadvantages of TNAT?

- Higher compliance rates with chemotherapy in the preoperative setting
- Increased local control rates ? (more tm down-staging)
- Earlier stoma closure
- Higher organ preservation rates ??

-Local disease progression ?
-Increased surgical complications?
-PS may be deteriorated due to prolonged chemo exposure



Advantage of induction CT: More chemo penetration through intact vascular structures??
More myelosuppression after CRT may delay administration of further chemotherapy

Who may be candidate for TNAT?

- ✓ Tm ≤ 1 mm to MRF ,
- ✓ Tm at or below levators
- ✓ Tm extending ≥ 5 mm into the perirectal fat
- ✓ cT4 and cT1-2N2 tumors

❑ Distal or mid-rectum cT3-T4 , and/or node (+)

➤ NCCN : T3 N any with involved CRM or T4 ,Nany or locally unresectable or medically inoperable patients

Chau I et al. J Clin Oncol
2006

Cercek A et al. JAMA Oncol
2018
Fernandez-Martos C et al.
Ann Oncol 2015

INDUCTION CHEMOTHERAPY FOLLOWED BY CRT

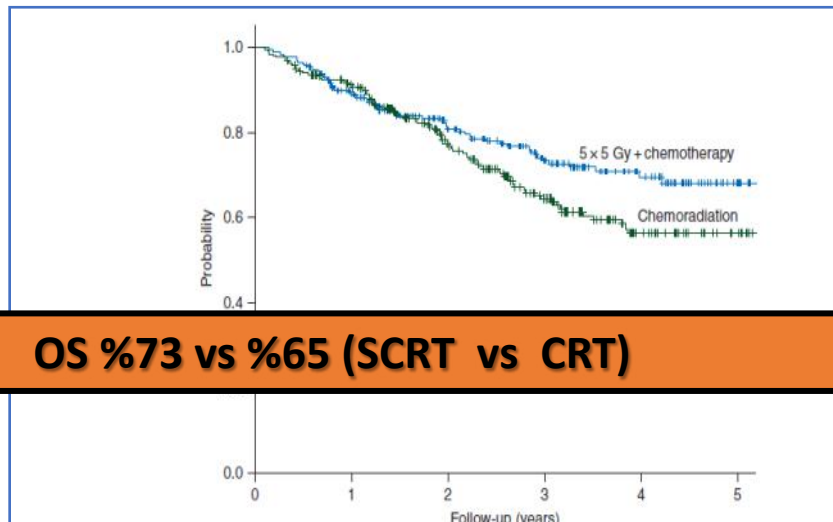
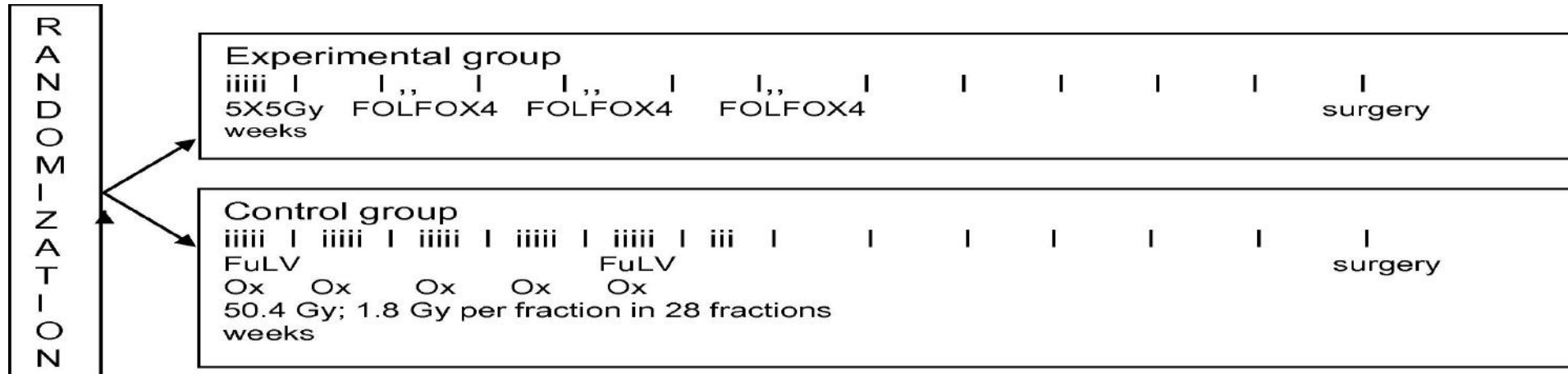
Study	No. Patients	Induction Chemotherapy	CRT Regimen	Adjuvant Chemotherapy	pCR	Outcomes
EXPERT[53] (phase II)	105	CAPOX × 12 wks	CRT with capecitabine	Capecitabine × 12 wks	20%	3-yr DFS = 68% 3-yr OS = 83%
GCR-3[56] (phase II, randomized)	108	–	CRT with CAPOX	CAPOX (4 cycles)	13%	Distant metastases = 21% 5-yr DFS = 62% 5-yr OS = 77%
		CAPOX (4 cycles)	CRT with CAPOX	–	14%	Distant metastases = 23% 5-yr DFS = 64% 5-yr OS = 74%
CONTRE[52]	39	FOLFOX (8 cycles)	CRT with capecitabine	–	33%	R0 resection rate = 100%
Maréchal et al (2012) [57] (phase II, randomized)	57	–	CRT with infusional 5-FU	–	34%	Closed prematurely for futility
		FOLFOX (2 cycles)	CRT with 5-FU	–	32%	
Schou et al (2012) [54]	85	CAPOX (2 cycles)	CRT with capecitabine	–	23%	5-yr DFS = 63% 5-yr OS = 67%
Koeberle et al (2008) [55]	60	XELOX (1 cycle)	CRT with CAPOX	–	23%	R0 resection rate = 98% Sphincter preservation = 84%

5-FU = fluorouracil; CAPOX = capecitabine + oxaliplatin; CRT = chemoradiotherapy; DFS = disease-free survival; FOLFOX = leucovorin + fluorouracil + oxaliplatin; OS = overall survival; pCR = pathologic complete response; XELOX = capecitabine + oxaliplatin.

NEOADJUVANT CRT FOLLOWED BY CHEMOTHERAPY

Study (Citation)	Year of Publication	Design	No.	CRT Regimen	NAC Regimen	Adjuvant Therapy	pCR rate, % ^a	R0 Resection Rate, % ^a	DFS (3-year), %	OS (3-year), %
Garcia-Aguilar ²⁰	2015	Phase 2 non-randomized four-arm	259	CRT (w/5-FU)	None	mFOLFOX6 (8 cycles) recommended, but not mandatory.	18	98	NR	NR
				CRT (w/5-FU)	mFOLFOX6 (2 cycles)	mFOLFOX6 (6 cycles) recommended, but not mandatory.	25	100	NR	NR
				CRT (w/5-FU)	mFOLFOX6 (4 cycles)	mFOLFOX6 (4 cycles) recommended, but not mandatory.	30	96	NR	NR
				CRT (w/5-FU)	mFOLFOX6 (8 cycles)	mFOLFOX6 (2 cycles) recommended, but not mandatory.	38	100	NR	NR
Bujko (Polish II trial) ²⁰	2016	Phase 3 randomized two-arm	515	RT (5x 5Gy)	FOLFOX4 (3 cycles)	Not reported; left to treating physician discretion.	16	77	53	73
				CRT (w/5-FU/ leucovorin/ oxaliplatin)	None	Not reported; left to treating physician discretion.	12	71	52	65
Gao ²⁰	2014	Prospective single-arm	36	CRT (w/CAPOX)	CAPOX (1 cycle)	Unspecified adjuvant ChT given.	36	100	NR	NR
Gao ²¹ (sandwich regimen)	2014	Phase 2 single-arm	51	CRT (w/CAPOX)	CAPOX (1 cycle prior to CRT, and 1 cycle after CRT)	CAPOX (4 cycles)	42	100	NR	NR
Zhu ²²	2013	Phase 2 single-arm	42	CRT (w/ CAPOX)	Cape (1 cycle)	CAPOX (5-8 cycles)	16	92	57	66
Zampino ²³	2009	Prospective single-arm	51	CRT (w/Cape)	Cape (2 cycles)	Adjuvant ChT tailored to degree of pathologic response.	18	100	85 (5-year)	NR

SHORT COURSE RT WITH TNAT (Phase 3, POLISH II TRIAL)



Similar DFS, local control rates and distant metastases.

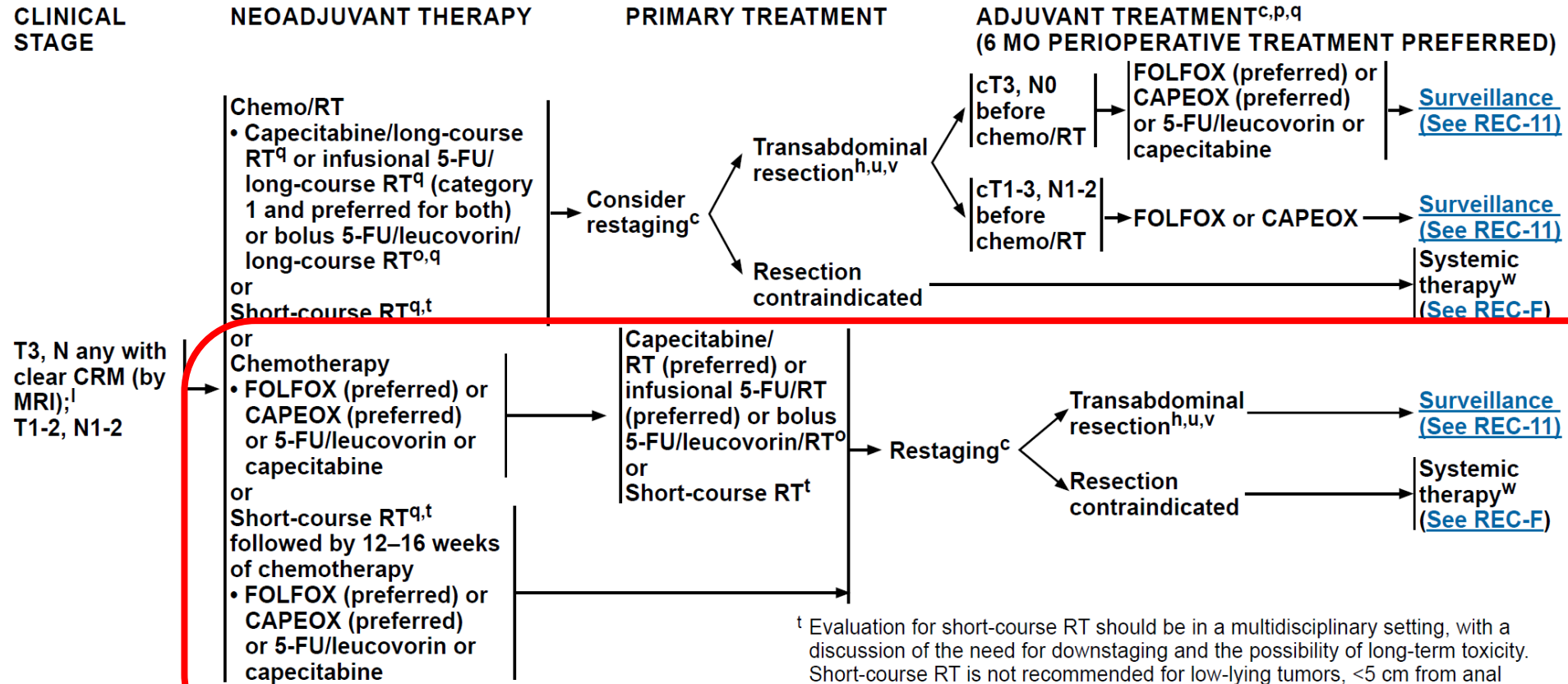
Early OS rates were better in SCRT arm (%73 vs %65, p=0.04) but;

Long term follow-up 8-yr OS rates identical : 49%



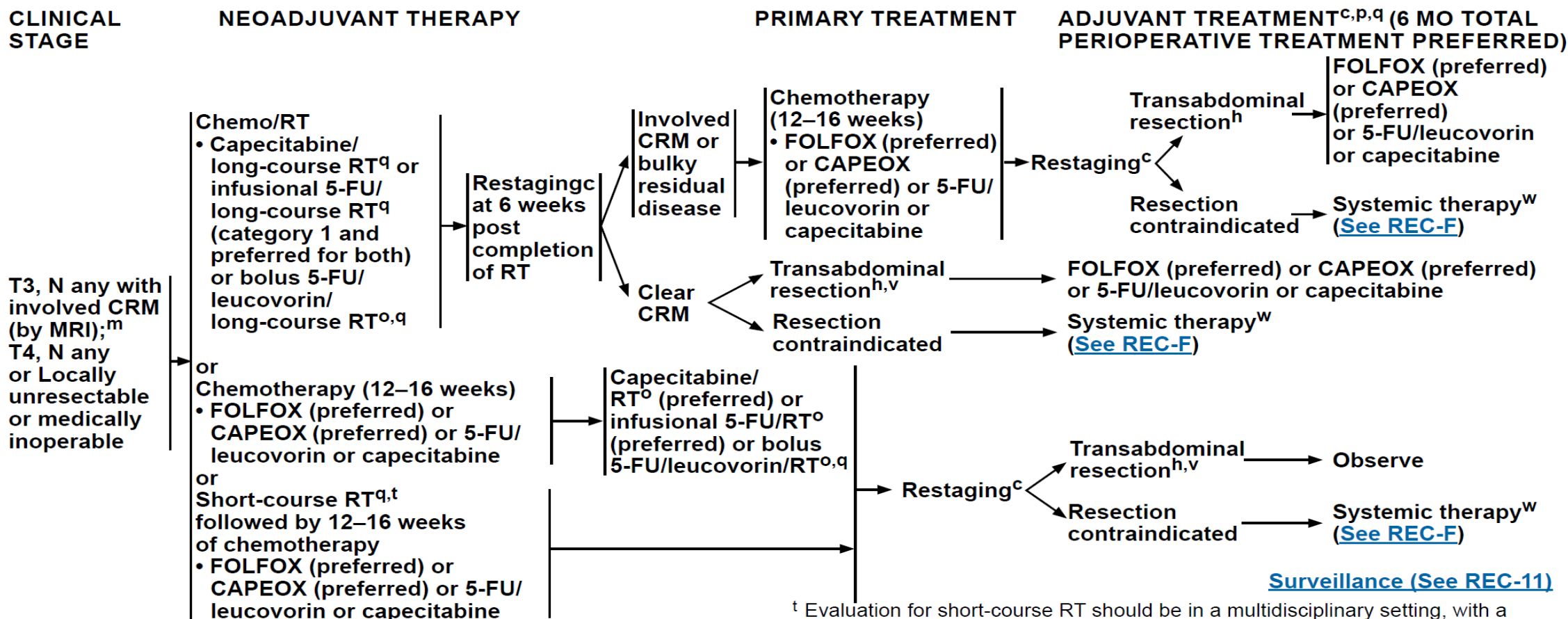
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Rectal Cancer



^t Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge.

^u If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.



Surveillance (See REC-11)

^t Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.

□ **METHODS FOR RESPONSE EVALUATION ?**

-THERE IS NO SINGLE TEST CAPABLE OF IDENTIFYING PATIENTS WITH COMPLETE TUMOR REGRESSION.

- Response evaluation has not been outlined in detail in older studies.
- At the end of induction chemotherapy or CRT ? Two months of intervals? (DRE, proctoscopy, CT, MRI)
- cCR may not be correlated with pCR (MSKCC; evaluated with preop DRE or proctoscopy; 75% of cCR have persistent tumor foci +)
- Not easy to evaluate LN met (Risk of LN metastases or mesorectal deposits in ypT0 up to 12%)
- MRI: small residual tm – fibrosis? (overestimation of tm?)
- PET-CT ; low predictive value (39% of cCR found to be pCR in a systematic review)

Hiotis SP et al. J Am Coll Surg 2002

Stipa F et al. Ann Surg Oncol 2004

Habr-Gama A et al. J Gastrointest Surg 2005

Kristiansen C et al. Dis Colon Rectum 2008

ROLE FOR DIFFERENT RADIOTHERAPY SENSITIZERS??



Advancing Research. Improving Lives.™



NRG-GI002: A Phase II Clinical Trial Platform using Total Neoadjuvant Therapy (TNT) in Locally-advanced Rectal Cancer: First Experimental Arm Initial Results

Thomas J. George,^{1,2} Greg Yothers,^{1,3} Theodore S. Hong,^{1,4} Marcia M. Russell,^{1,5} Y. Nancy You,⁶ William Parker,^{1,7} Samuel A. Jacobs,^{1,8} Peter C. Lucas,^{1,3} Marc Jeffrey Gollub,⁹ William A. Hall,^{1,10} Lisa A. Kachnic,^{1,11} Namrata Vijayvergia,^{1,12} Norman Wolmark^{1,13}

on behalf of TNT Investigators and Patient Partners

¹NRG Oncology; ²University of Florida Health Cancer Center, Gainesville, FL; ³University of Pittsburgh, Pittsburgh, PA; ⁴Massachusetts General Hospital, Boston, MA; ⁵VA Greater Los Angeles Healthcare System, and David Geffen School of Medicine at UCLA, Los Angeles, CA; ⁶University of Texas MD Anderson Cancer Center, Houston, TX; ⁷McGill University Health Centre, Montréal, QC; ⁸University of Pittsburgh Cancer Institute, Pittsburgh, PA; ⁹Memorial Sloan Kettering Cancer Center, New York, NY; ¹⁰Medical College of Wisconsin, Milwaukee, WI; ¹¹Vanderbilt University Medical Center and Vanderbilt-Ingram Cancer Center, Nashville, TN/SWOG; ¹²Fox Chase Cancer Center, Philadelphia, PA/EGOG-ACRIN; ¹³Allegheny Health Network Cancer Institute, Pittsburgh, PA

NCT02921256

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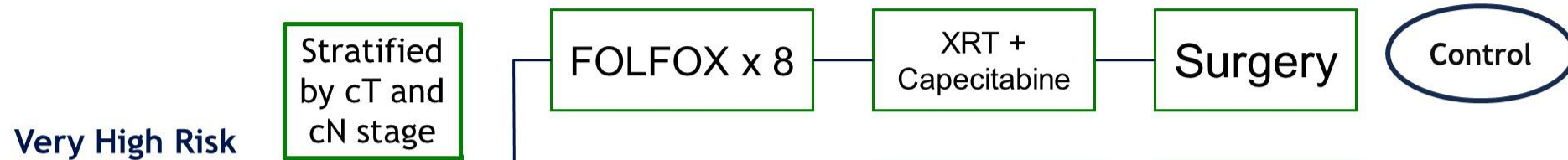
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PRESENTED BY: George, TJ

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NRG-GI002 (TNT) Schema

Nested randomized phase II experimental arms



Very High Risk
Stage II & III

- Low lying
- Bulky
- N2
- APR required

Locally
advanced
Rectal
Cancer

Primary Endpoint

	Control	Veliparib	p-value
Mean NAR Score	12.6 (95%CI: 9.8-15.3)	13.7 (95%CI: 10.2-17.2)	p=0.69
Controlling for stratification variables and SSS candidacy (p=0.78)			

Addition
of
adjuvant
protocol

Available Secondary Endpoints			
pCR	21.6%	33.8%	p=0.14
R0 Resection	85.1%	83.1%	P=0.82
cCR	28.2%	33.3%	p=0.60
SSS	52.5%	59.3%	p=0.43

Median follow-up among the 161 pts with follow-up and randomized to the Veliparib comparison is 14.5 mos at the time of analysis.

SELECTIVE USE OF RADIOTHERAPY : 'PROSPECT' TRIAL DESIGN

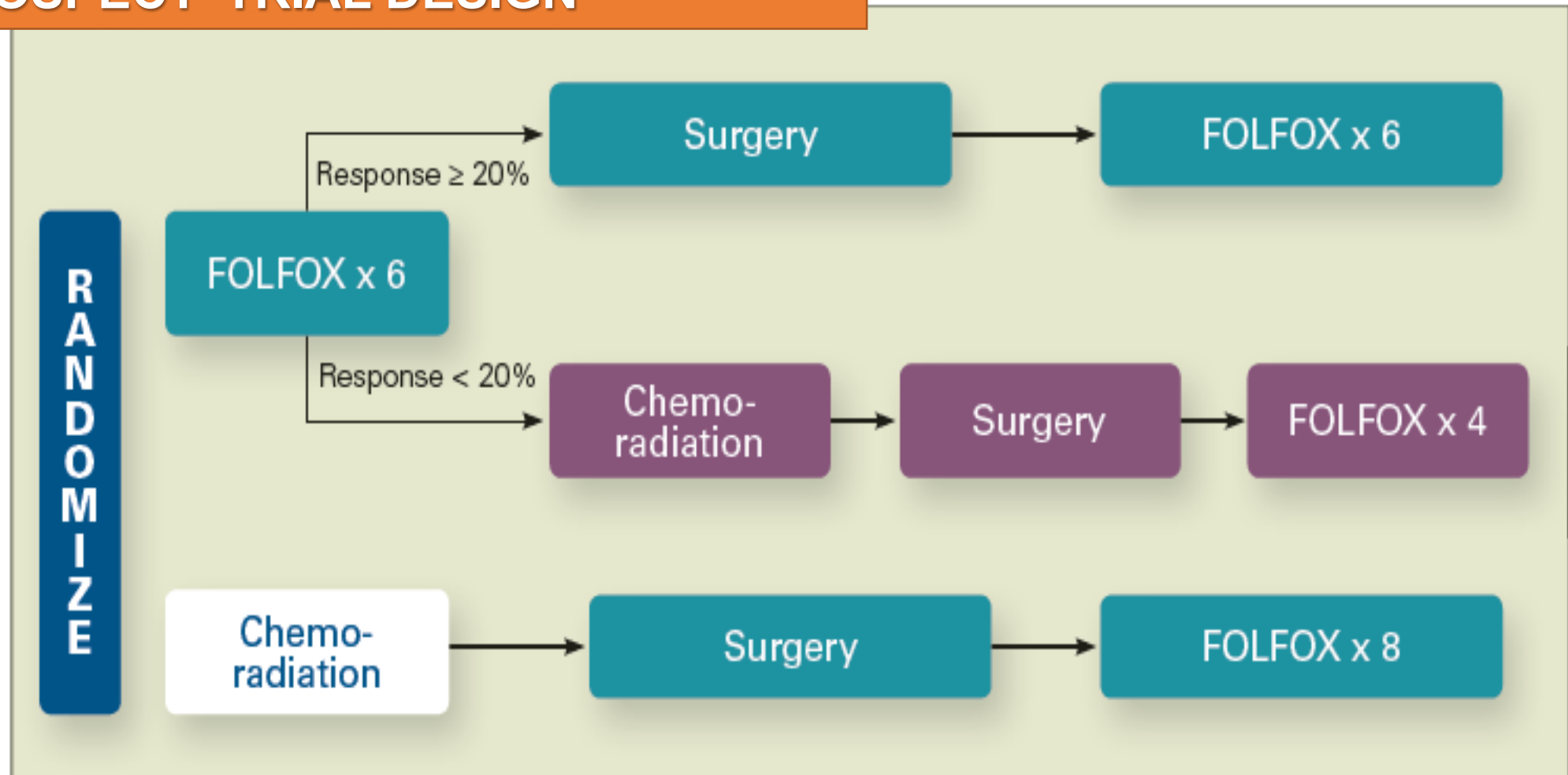


Figure 2. The PROSPECT Trial Design (ClinicalTrials.gov identifier: NCT01515787).

Avoidance of Radical Surgery for complete responders: NOM

Variables	OnCoRe (UK Study)	IWWD (multicenter registry)
Number of patients	cCR =109 Surgery = 109 (propensity score matched)	cCR : 880
Median Follow-up	33 months	3.3 years
Local Regrowth Rates	34%	25.2% (2-yr cumulative) (97% in bowel wall, 3% in lymph nodes)
Salvage surgery	88% TME	(data available for 148 of 225 (78% TME, 22% local excision
Survival	Non-regrowth DSS in 3-yr: 88% vs 77% (no significant difference) Colostomy-free survival 74% vs 47%	5 –yr DFS 94% ,5-yr OS 85%

CONCLUSIONS

- Total neoadjuvant therapy can be considered for locally advanced low-lying rectal tumors , cT3 with CRM (+) , bulky T4, N2 or locally unresectable tumors
- To date there is no phase III RCT comparing standart NACRT with TNAT and showing a survival benefit.
- Treatment compliance and pCR rates increase with TNAT.
- Ongoing phase II and III TNAT trials should provide long-term disease-related outcomes (rather than short-term pathologic end-points)

CONCLUSIONS

- Optimization of TNAT may facilitate greater number of patients who are potentially eligible for organ preservation.
- There is no single test to identify complete response following neoadj therapy
- Until further information is available from RCTs, NOM should be reserved for patients with cCR who are poor surgical candidates or decline transabdominal surgery.