Rectal cancer in 2023
What's new in Radio-Oncological Treatment?

Prof. Dr. W. Harms
Chefarzt Radioonkologie

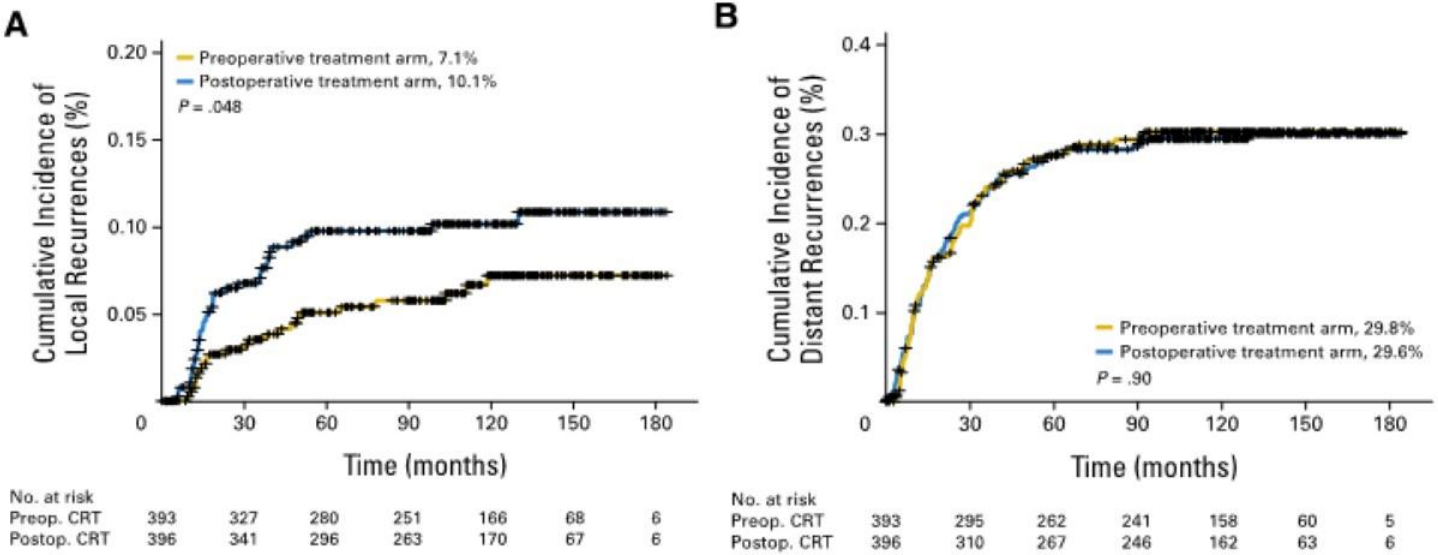
St Claraspital

New paradigms in the treatment of rectal cancer

TNT M1

W&W NOM (non operative management) with organ preservation

Why TNT?
Current standard: excellent local control, but in 30 % distant metastases (11J-data CAO/ARO/AIO-94)



Sauer et al. JCO 2012

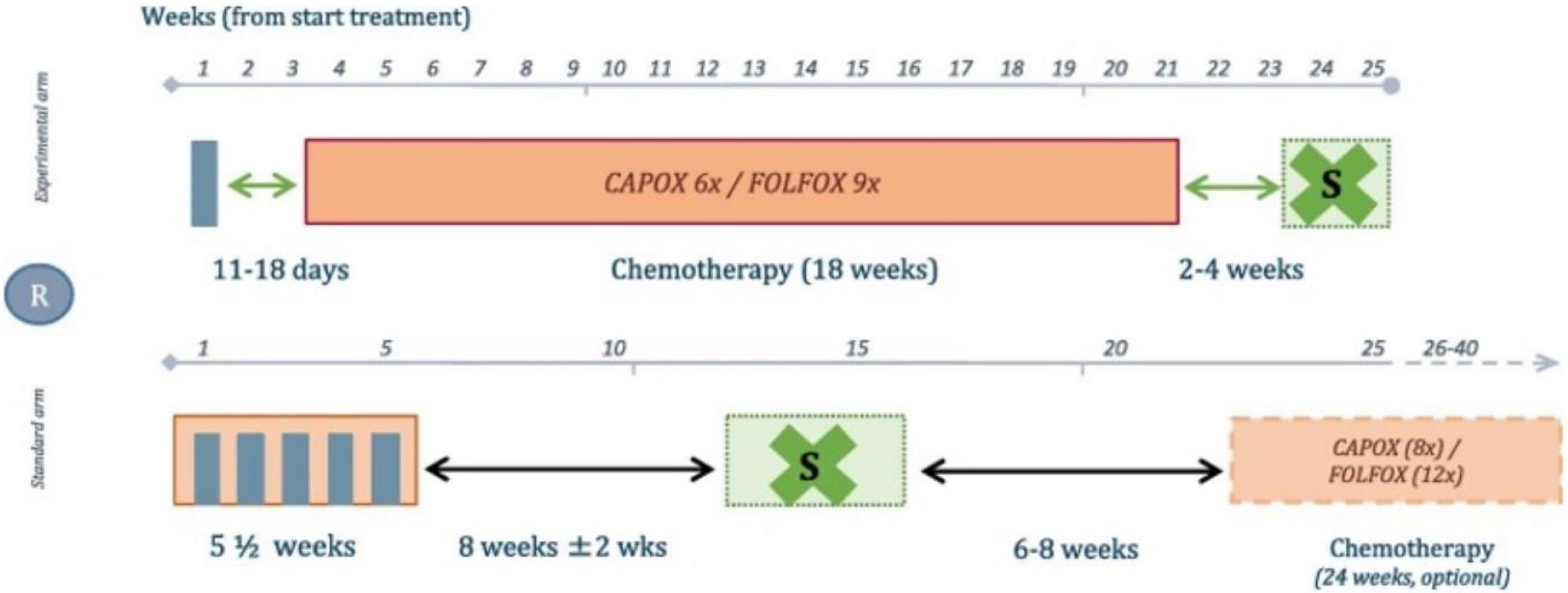
What is total neoadjuvant therapy (TNT) ?

- Standard treatment in locally advanced rectal cancer

- TNT–Concept

stClaraspital

Short-course radiotherapy followed by chemotherapy before TME versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial



CTX n=187/450 (41.5%)

Bahadoer et al. Lancet Oncol 2021

RAPIDO Trial

„Ugly tumors“
n=920 patients

	Experimental group (n=462)	Standard of care group (n=450)
Sex		
Male	300 (65%)	312 (69%)
Female	162 (35%)	138 (31%)
Age at randomisation, years		
Median (IQR)	62 (55–68)	62 (55–68)
Range	31–83	23–84
Age category		
<65	280 (61%)	270 (60%)
≥65	182 (39%)	180 (40%)
Clinical T stage*†		
cT2	14 (3%)	14 (3%)
cT3	301 (65%)	299 (66%)
cT4	147 (32%)	137 (30%)
Clinical N stage*†		
cN0	42 (9%)	35 (8%)
cN1	118 (26%)	120 (27%)
cN2	302 (65%)	295 (66%)
Other high-risk criteria†		
Enlarged lateral nodes	66 (14%)	69 (15%)
Extramural vascular invasion positive	148 (32%)	125 (28%)
Mesorectal fascia positive	285 (62%)	271 (60%)

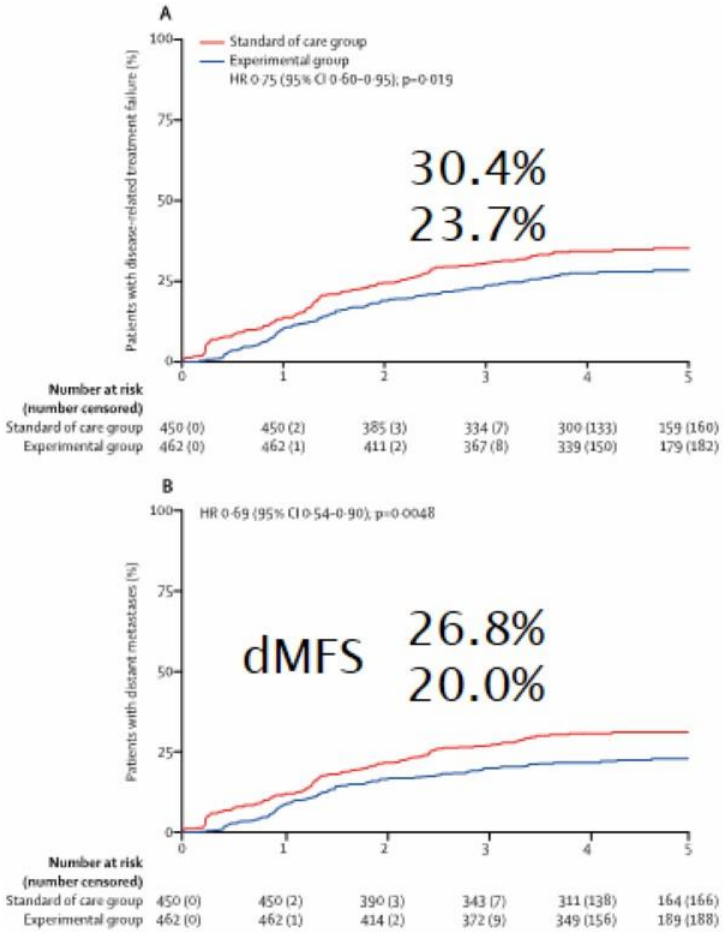
Bahadoer et al. Lancet Oncol 2021

RAPIDO:

Short course RTX followed by CTX (consolidation) and TME significantly reduced disease related treatment failures and **distant metastases**

pCR 28% (TNT) vs. 14%

OS and LRR not improved

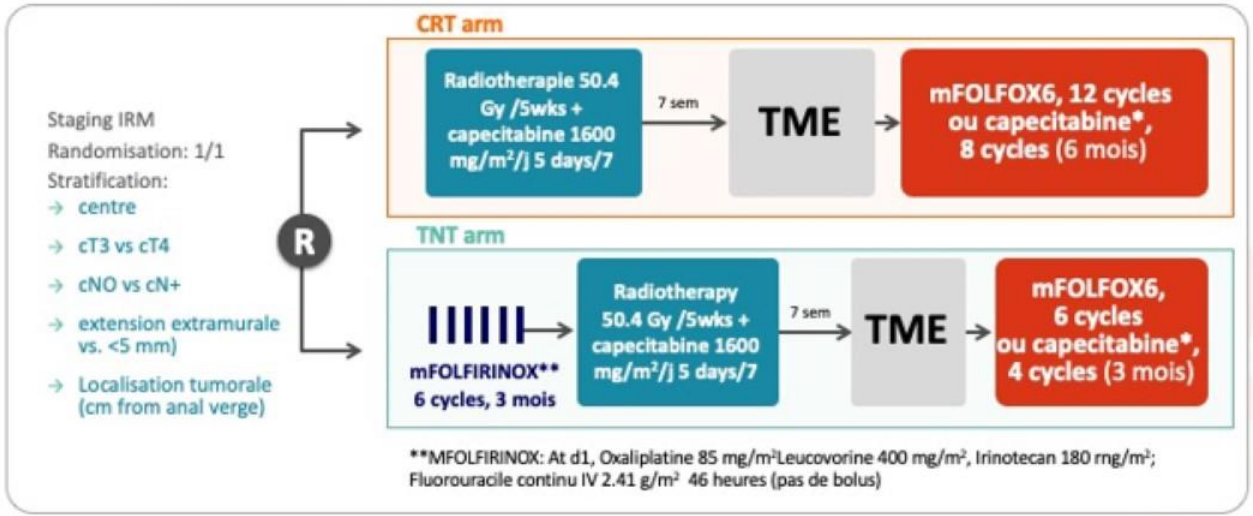


Bahadoer et al. Lancet Oncol 2021

Neoadjuvant CTX with FOLFIRINOX and preoperative RCT for patients with locally advanced rectal cancer (UNICANCER–PRODIGE 23):

Etude Prodige 23 : design de l'étude

- NCT 01804790; EudraCT 2011-004406-25



*according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM1 stage.

T. Conroy , et al., ASCO' 2020, Abs 4007

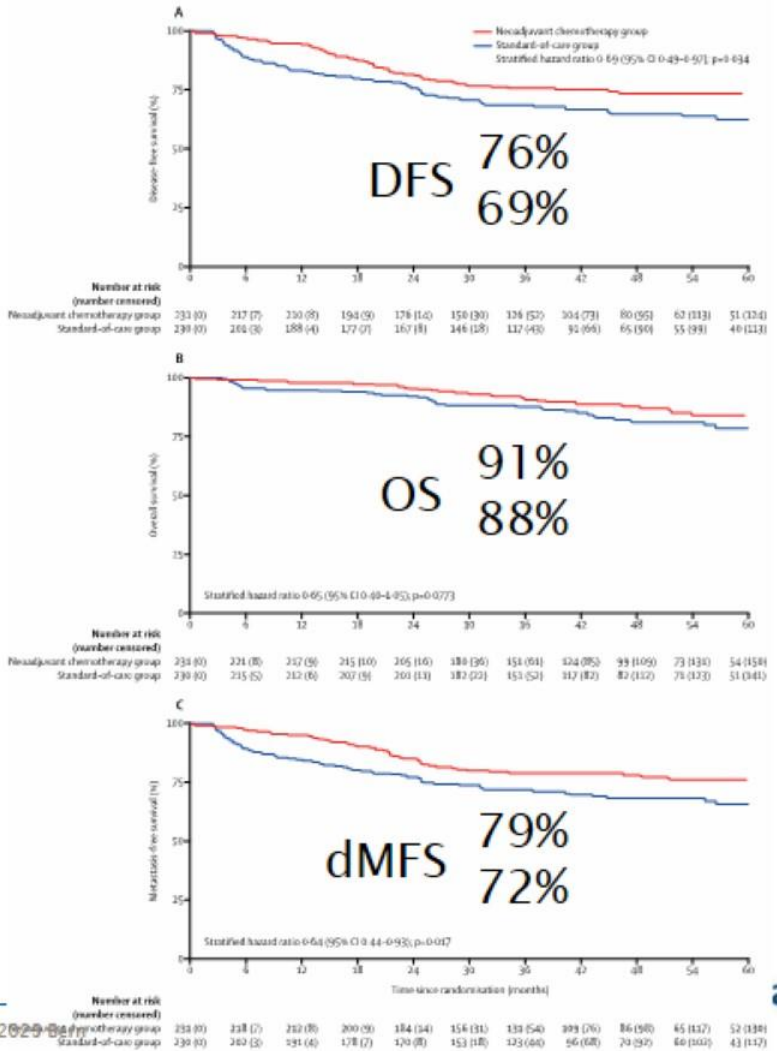
T. Conroy et al. Lancet Oncol 2021

Prodige23:

Induction CTX followed by RCT and TME significantly improved DFS and dMFS

pCR 28% (TNT) vs. 12%

OS and LRR not improved



T. Conroy et al. Lancet Oncol 2021

araspital

Toxicity (RAPIDO und Prodige23)

	RAPIDO			Prodige23	
	SAE			SAE	
TNT	Standard		TNT	Standard	
	+ adj. CTX	- adj. CTX			
38%	34%	34%	27%	22% (n.s.)	
Grade III/IV **neoadjuvant Tx**			Grade III/IV **adjuvant CTX**		
	TNT	Standard		TNT	Standard
Diarrhea	18%	9%	Lymphopenia	11%	27%
			Neutropenia	6%	18%
			Neuropathy	12%	21%

Is TNT ready for prime time?

pro

- Significant improvement: DFS, dMFS, pCR

contra

- No survival benefit
- Rather short median follow-up
  RAPIDO: mFu 4.6 J
  Prodige: mFu 3.87 J
  OPPRA: mFu 3 J

Indications for TNT

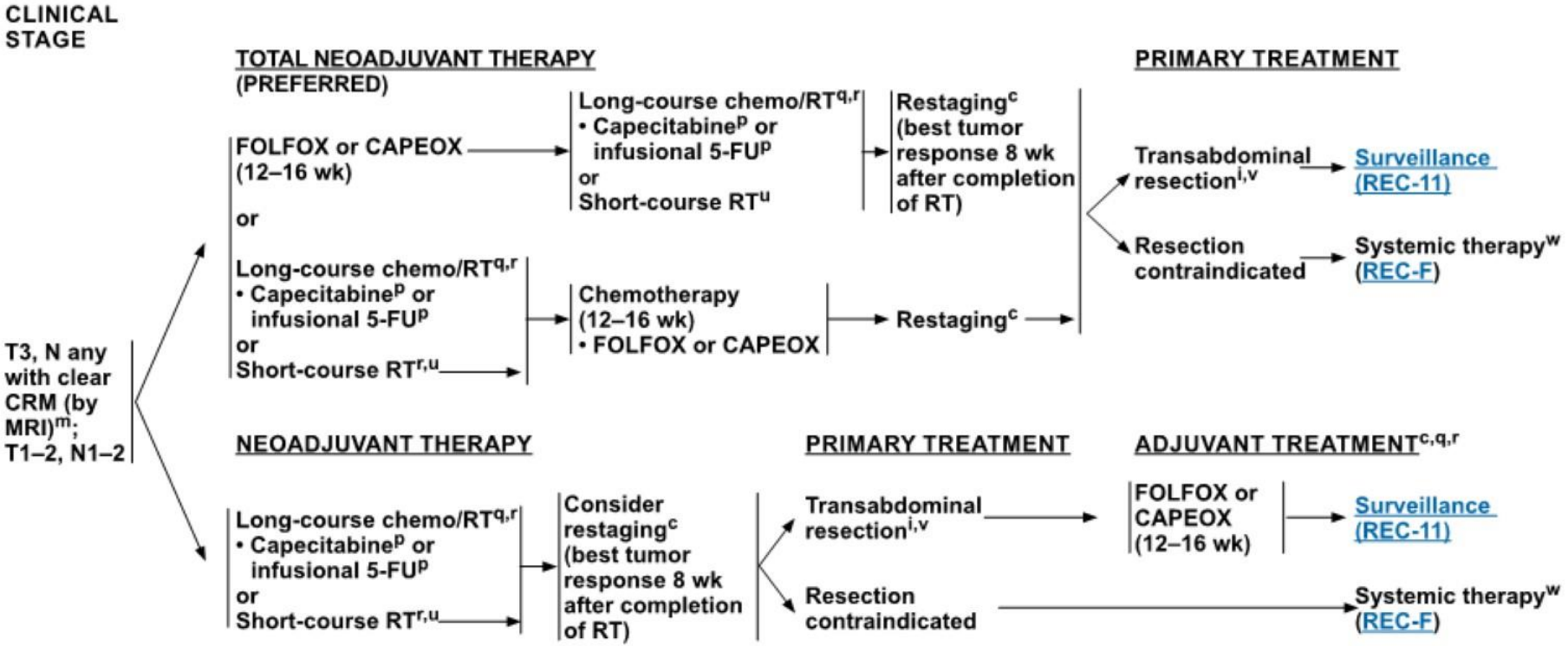
	RAPIDO**	Prodige23
Tumor localisation	0-15 cm (upper 1/3: 32-34%)	0-15 cm (upper 1/3: 13%)
T-Stage	T4 a/b	T3/4*
N-Stage	N2	N+ (90%)
M-Stage	M0	M0
Risk factors	EMVI, Infiltration mesorectal fascia	

*Inclusion crit. Prodige23: T3/4 with indication for neoadjuvant radiochemotherapy

** Inclusion crit. RAPIDO: Risk factors as listed

NCCN Guidelines Version 3.2022
Rectal Cancer

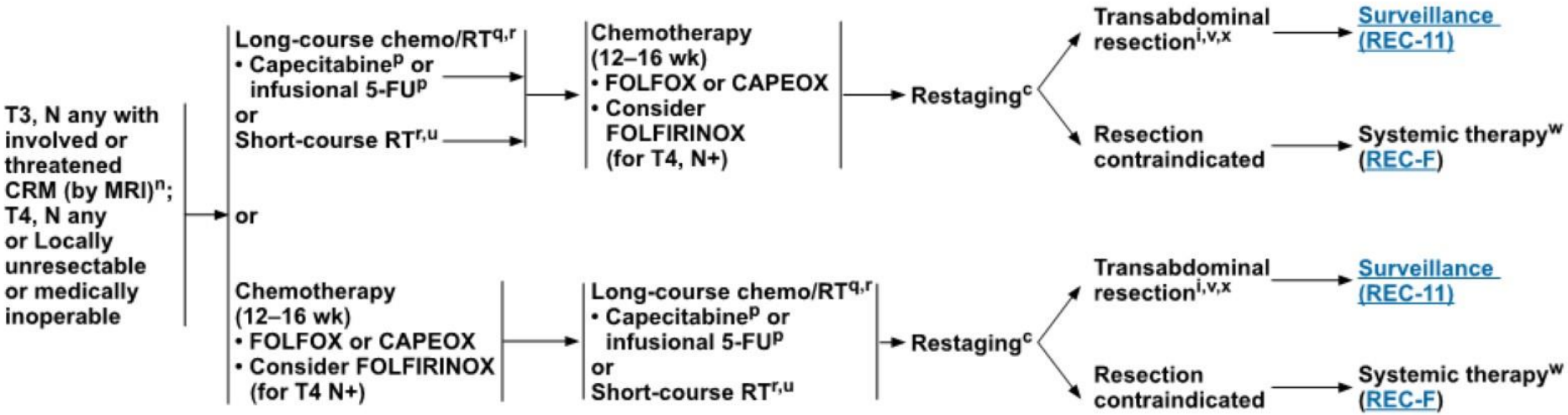
NCCN Guidelines Index
Table of Contents
Discussion



National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2022
Rectal Cancer

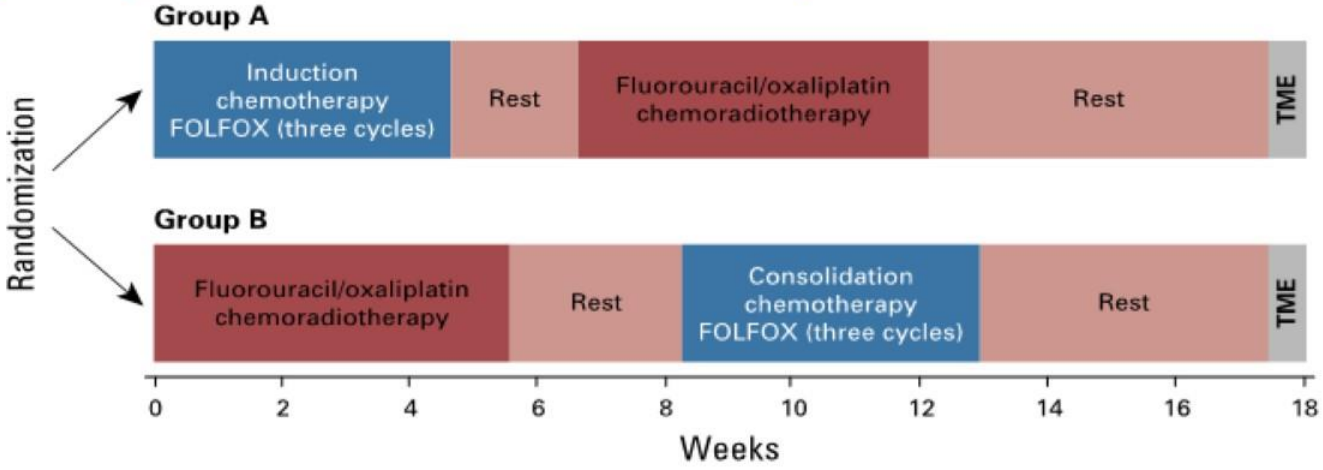
NCCN Guidelines Index
Table of Contents
Discussion



Perfect timing: Induction or consolidation chemotherapy?

dailynewsdig.com

CAO/ARO/AIO-12: Consolidation-CTX resulted in higher pCR and lower toxicity



	N=	pCR	Tox. III/IV	Interval CRT to surgery	Clavien-Dindo (Grad 3/4)
Induction (A)	156	17%	37%	45d	18%
Consolidation (B)	150	25%	27%	90d	18%

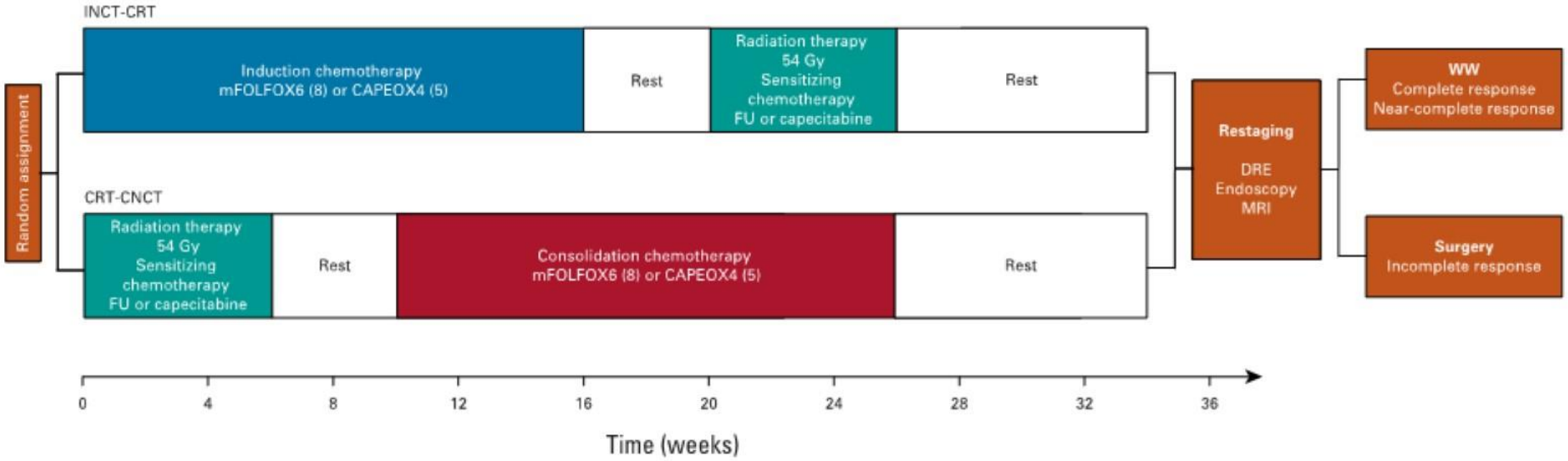
Fokas et al. JCO 2019

New paradigms in the treatment of rectal cancer

W&W NOM (non operative management) with organ preservation

OPRA–the organ preservation of rectal adenocarcinoma trial

Randomized phase II trial, UICC stage II/III, n= 324 pts., distal RC (requiring APR or coloanal anastomosis)



Primary endpoint: **3–yr DFS**: 85% compared to historical 75%
Secondary endpoint: **3–yr NOM** 35% to 20%

J. Garcia-Aguilar et al. JCO 2022

St Claraspital

OPRA Trial – Toxicity/Adherence

	Induction Chemo - Chemoradiation n=158	Chemoradiation - Consolidation Chemo n=166
Started radiotherapy (%)	93	98
Median RT dose (Gy)	54 (50.4-54)	54 (50.4-54)
Started chemotherapy (%)	99	94
Received 8 cycles or 5 cycles of CAPOX (%)	86/85	84/88
Grade 3/4/5 Toxicity	34/11/1	31/7/2
Median time from treatment start to restaging	35 (33-37) wks	34 (32-37) wks

J. Garcia-Aguilar et al. JCO 2022

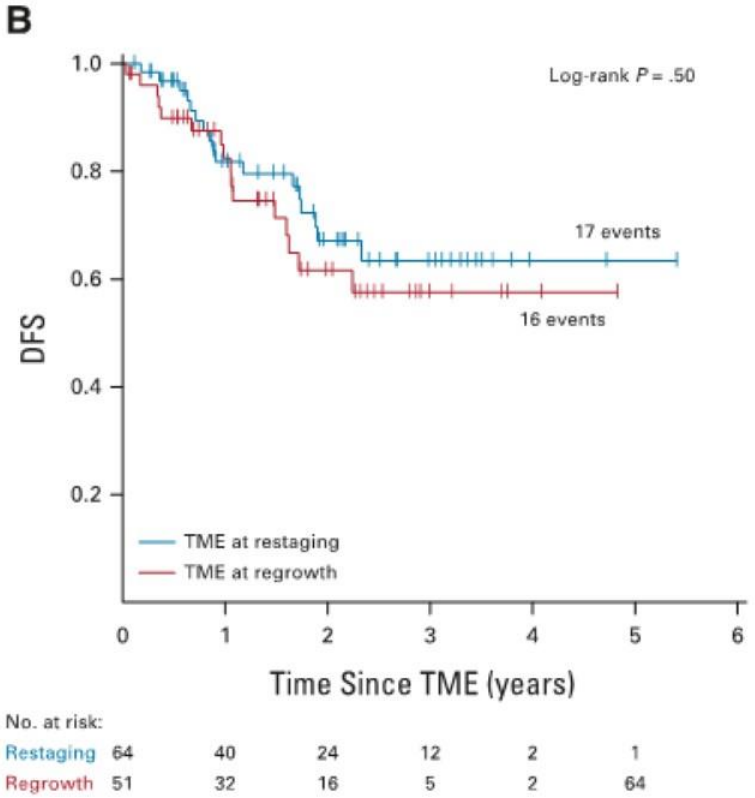
OPRA Trial – Oncologic Results (median F/u: 3 years)

	Induction Chemo - Chemoradiation n=158	Chemoradiation - Consolidation Chemo n=166	p
3-y DFS	76%	76%	0.63*
W+W at restaging	105 (71%)	120 (76%)	
Developed local regrowth	42/105 (40%)	**33/120 (27%)**	0.03
3y-TME-free survival	41%	**53%**	0.01

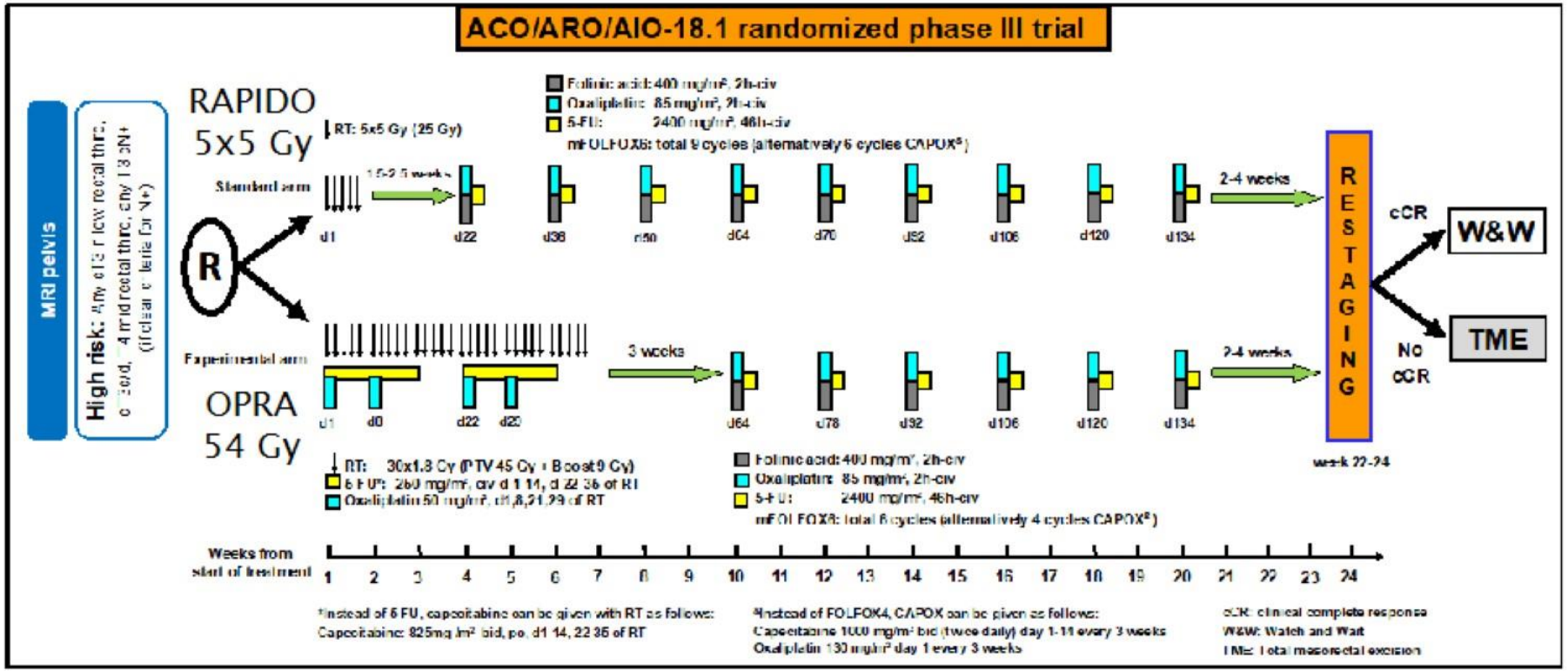
*primary endpoint negative: DFS in comparison to historical controls is not significantly improved

J. Garcia-Aguilar et al. JCO 2022

Similar DFS after TME for regrowth in comparison to TME after restaging



Rectal Cancer Study ACO/ARO/AIO 18.1 Prof. C. Rödel, Frankfurt am Main, St. Claraspital open (primary endpoint: organ preservation)



AIO Study: Definition of cCR, near cCR and poor/no response

Modality	cCR	Near cCR	Poor response/ no response
DRE	No palpable tumor	Small and smooth mucosal irregularity	Palpable tumor mass
Rectoscopy	Flat, white scar with or without telangiectasia No ulcer No nodules (biopsy not mandatory)	Residual ulcer or Small mucosal nodules or minor mucosal abnormalities. Mild persisting erythema of the scar	Visible macroscopic tumor.
Pelvic MRI	No residual suspicious lymph nodes (s. SOP MRI)	Regression of lymph nodes with no malignant enhancement features but size > 5mm. (s. SOP MRI)	No regression of suspicious lymph nodes. (s. SOP MRI)

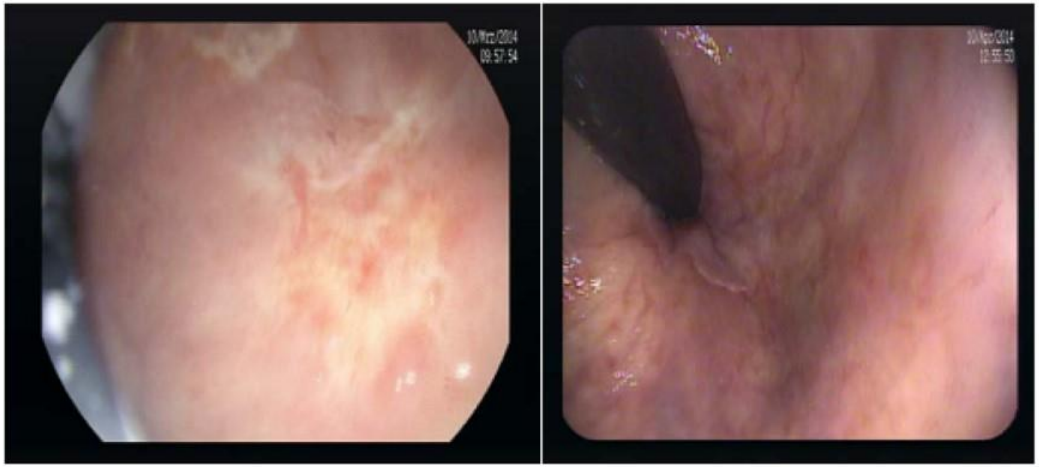


Figure 1. Examples for a clinical complete response on endoscopy.

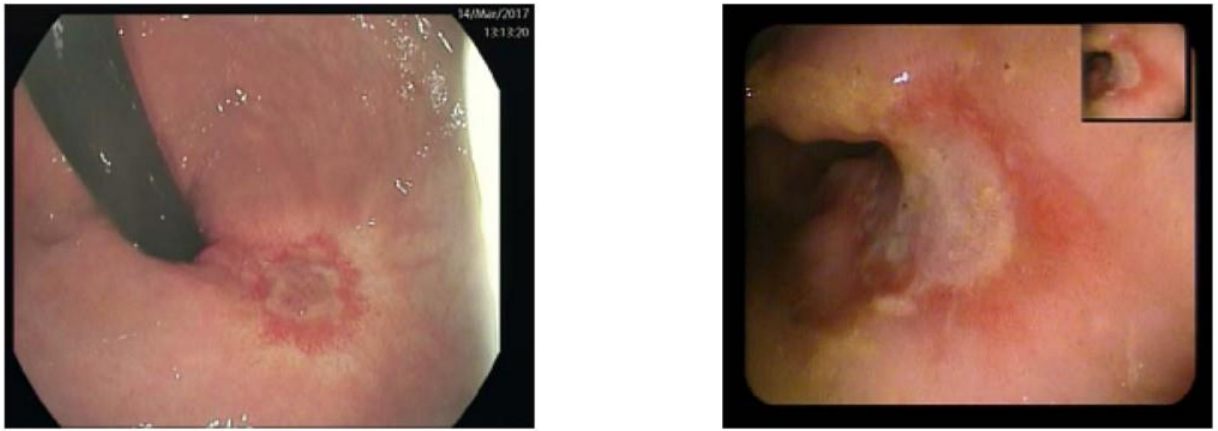


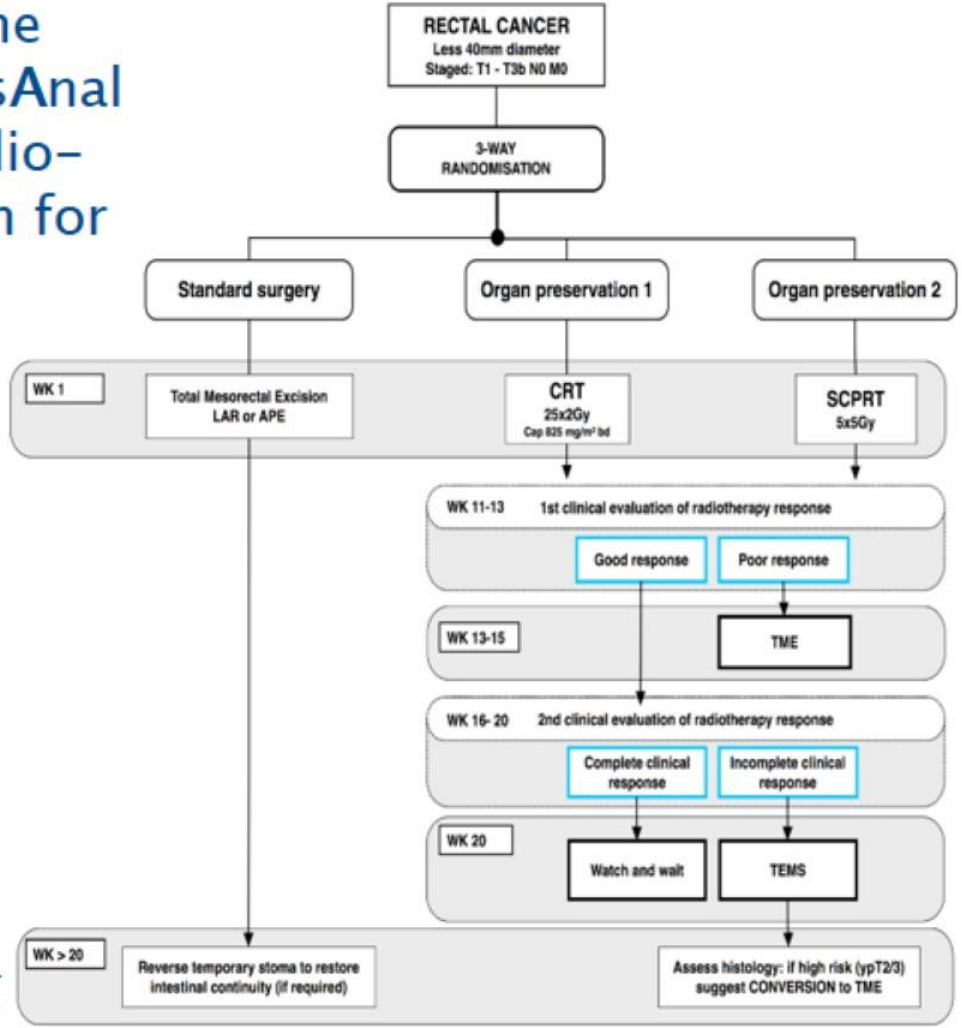
Figure 2. Examples for a near clinical complete response on endoscopy

Rectal Cancer Study ACO/ARO/AIO 18.1
Intense follow-up schedule after W&W

Months after Watch and Wait	3	6	9	12	15	18	21	24	30	36	48	60
Physical examination, tumor marker CEA	X	X	X	X	X	X	X	X	X	X	X	X
Colonoscopy*		X*										X
Abdomen sonography		X		X		X		X		X	X	X
Rectoscopy	X	X	X	X	X	X	X	X	X	X	X	X
Pelvic MRI	X	X	X	X		X		X		X	X	X
Chest X-ray				X				X		X	X	X

* if a colonoscopy was not performed before surgery; next colonoscopy in 5 years in cases of normal findings (lack of adenoma or carcinoma).

STAR-TREC phase 3: Can we Save the rectum by Watchful waiting or TransAnal microsurgery following (chemo) Radio-therapy vs Total mesorectal excision for early Rectal Cancer?



Rectal cancer 2023: New standards and paradigms

- TNT is new standard for intermediate and high risk rectal cancer (RAPIDO, Prodige23)
  - Improved 3J-DFS (ca. 75% vs. 69%), pCR (28% vs. 12-14%), dMFS
  - Consolidation is superior to induction chemotherapy

- NOM (non operative management)/W&W in prospective trials (OPRA, AIO 18.1):
  - In approximately 50% possible
  - Intense after care program
  - Sign. lower tumor regrowth after consolidation CTX (27% versus 40%)
  - Ongoing trial: Organ preservation in early rectal cancer cT1-3b N0 M0: STAR-TREK Trial