Best Neoadjuvant Approach in the Management of Rectal Cancer

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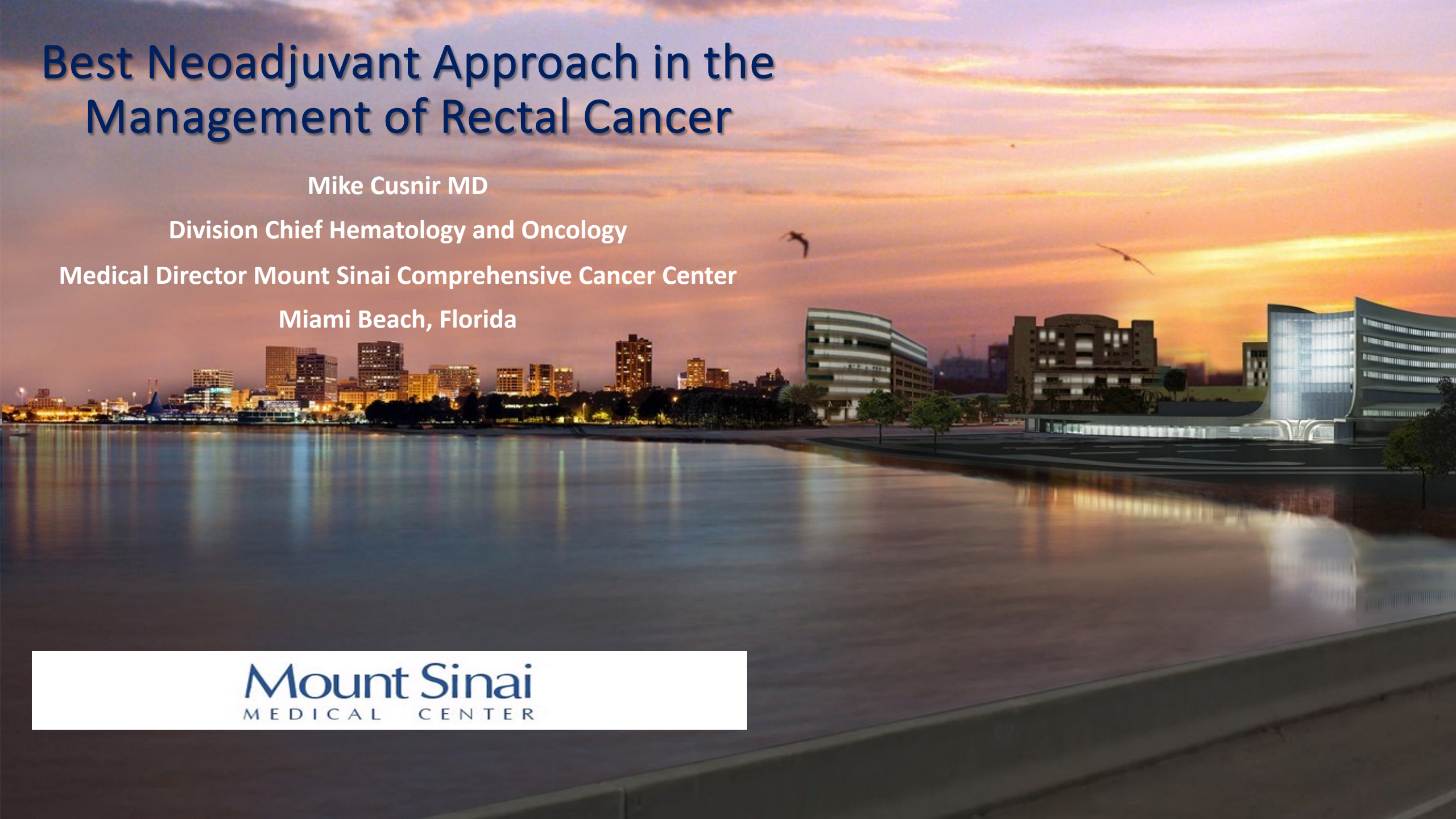


Mount Sinai
MEDICAL CENTER

EORTC 22921 (1011 patients)

Trial design

Randomisation

- Preop. Radiotherapy
  45 Gy → Local Recurr
- Preop. chemorad.
  45 Gy + 5-Fu/Lv → Survival

FFCD 9203

R

- RT: 45 Gy → OP
  5-FU: 350 mg/m²/d
  LV: 20 mg/m²/d
- 5-FU: 350 mg/m²/d
  LV: 20 mg/m²/d
  RT: 45 Gy → OP
  5-FU: 350 mg/m²/d
  LV: 20 mg/m²/d

Gérard JP et al, J Clin Oncol 2006

The NEW ENGLAND JOURNAL of MEDICINE
Volume 351:1731-1740 October 2004

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., et al. for the German Rectal Cancer Study Group

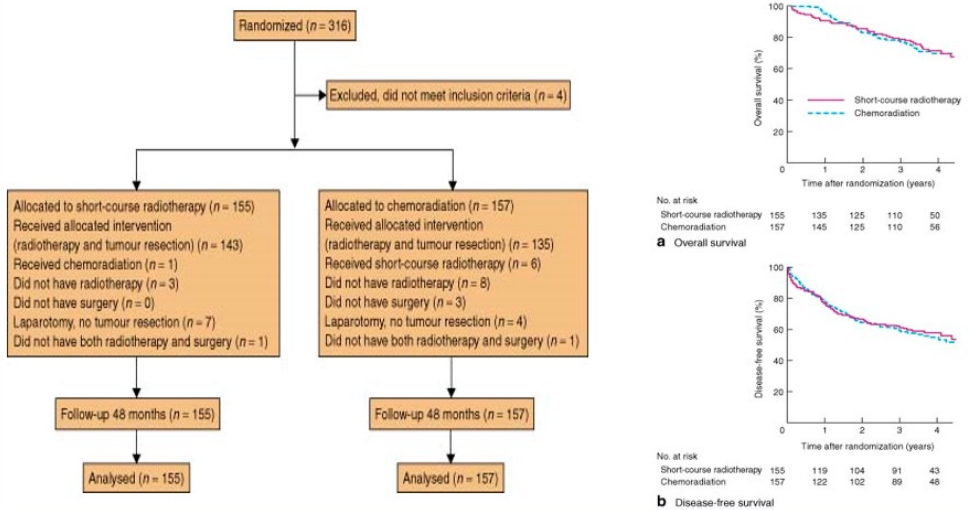
German Trial: CAO/ARO/AIO-94

R

- OP
  5-FU: 1 g/m²/d x 5
  RT: 50.4 Gy+5.4 Gy
  5-FU: 500 mg/m²/d
- 5-FU: 1 g/m²/d x 5
  RT: 50.4 Gy
  OP
  5-FU: 500 mg/m²/d

Sauer R et al., N Engl J Med 2004

Polish Study



Br J Surg, Volume 93, Issue 10, October 2006, Pages 1215–1223, https://doi.org/10.1002/bjs.5506

A little bit of History

- Can staging (pCR) be changed with neoadjuvant therapy?
- FFCD 9203: yes (11,4% TRC v. 3,6% RT; p<0,0001)
- Polish Study: yes (16,1% TRC v. 0,7% RT; p<0,001)
- EORTC 22921 : yes (13,7% TRC v. 5,3%; p<0,001)
- AIO 94: yes (8% Preop CRT v. 0% Postop CRT)

All showed ↑pCR with CRT

- ¿Neoadjuvant CRT ↑ Rate of Sphincter-Sparing Surgeries?
  - FFCD 9203: NO
  - Polish Study: NO
  - EORTC 22921: NO
  - AIO 94: NO (Preop vs Postop CRT)

No. But in the German study, patients who had been determined to need APR had more sphincter preservation with neoadjuvant therapy

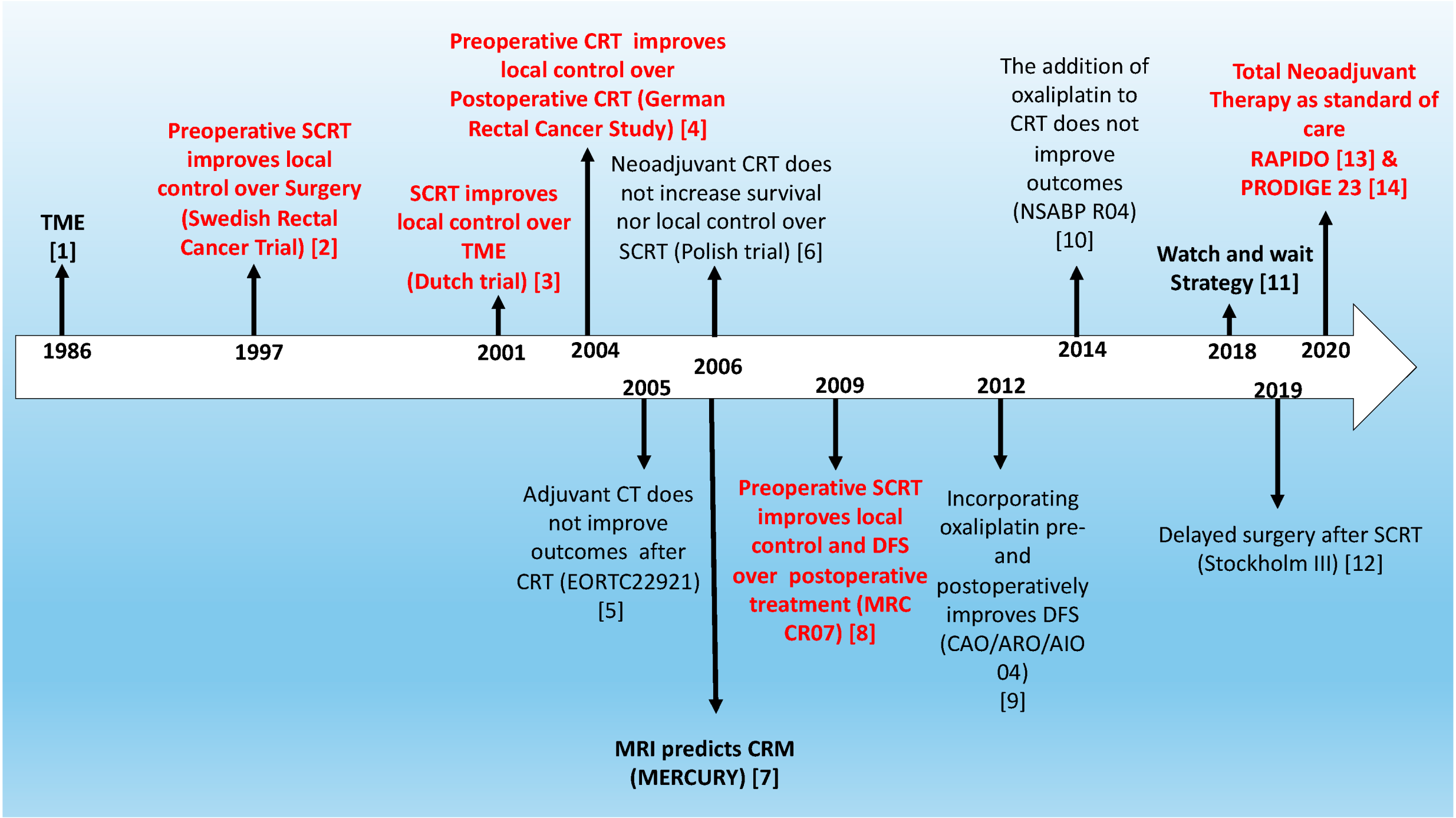
- ¿ Neoadyuvant CRT↑ OS o PFS?
  - FFCD 9203 : NO - 67,4% / 59,4% (5 years)
  - Polish Study: NO - 66,2% / 55,6% (4 years)
  - EORTC 22921 : NO - 64,8% / 56,1% (5 years)
  - German Study: NO - 76% / 68% (5 years)

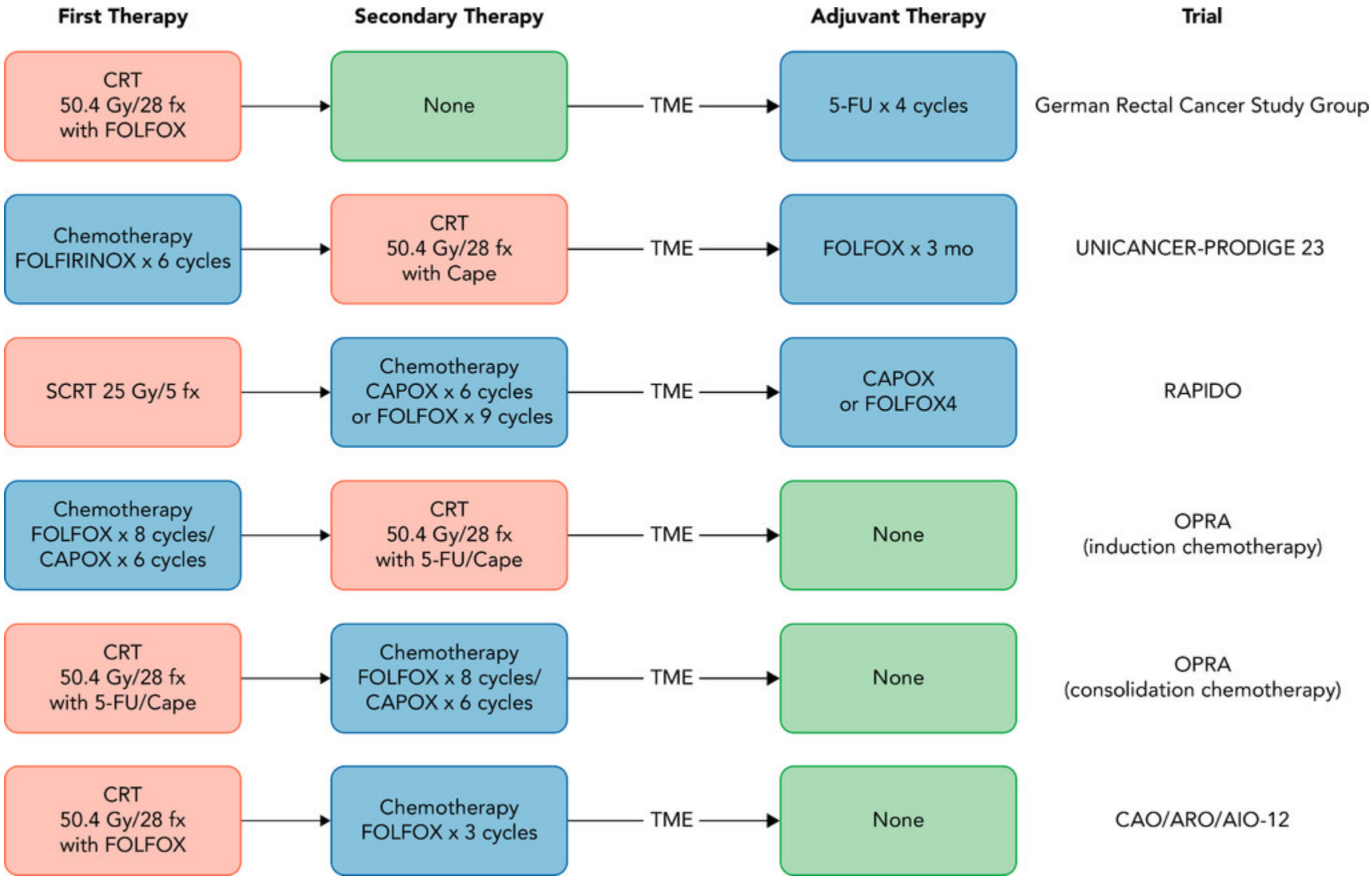
NO. But better OS/PFS
Seen in a German Studio

- ¿ neoadyuvante CRT↓Risk of local recurrence// Distant Recurrence?
  - FFCD 9203: SÍ (8,1% TRC v. 16,5% RT) // NO (36%)
  - Polish Study: NO (15,6% TRC v. 10,6% RT) // NO (34,6%)
  - EORTC 22921: SÍ (13,7% TRC v. 5,3%) // NO (34,4% todos los GRPS)
  - German Study: SÍ (6% Preop CRT v. 13% Postop CRT) // NO (36% Pre)
  -

YES, ↓risk of local recurrence.
NO ↓ risk of distant recurrence

- Patients to consider for neoadyuvant chemoradiotherapy:
- T3-4 y/o N+
- Low rectal injuries if sphincter-sparing procedures are considered
- TRUS better for assessing tumor depth; Best Imaging Modality to Assess Controversial LN Status (TRUS v MR)
- TME It is the preferred surgical procedure
- CRT neoadjuvant compared to RT:
  - There is no improvement in OS or PFS
  - Significant reduction in tumor staging and ↓ local recurrence
  - No ↑ in potty training procedures


TME [1]
1986
Preoperative SCRT improves local control over Surgery (Swedish Rectal Cancer Trial) [2]
1997
SCRT improves local control over TME (Dutch trial) [3]
2001
Preoperative CRT improves local control over Postoperative CRT (German Rectal Cancer Study) [4]
2004
Neoadjuvant CRT does not increase survival nor local control over SCRT (Polish trial) [6]
2006
Adjuvant CT does not improve outcomes after CRT (EORTC22921) [5]
2005
MRI predicts CRM (MERCURY) [7]
Preoperative SCRT improves local control and DFS over postoperative treatment (MRC CR07) [8]
2009
Incorporating oxaliplatin pre- and postoperatively improves DFS (CAO/ARO/AIO 04) [9]
2012
The addition of oxaliplatin to CRT does not improve outcomes (NSABP R04) [10]
2014
Watch and wait Strategy [11]
2018
Delayed surgery after SCRT (Stockholm III) [12]
2019
Total Neoadjuvant Therapy as standard of care RAPIDO [13] & PRODIGE 23 [14]
2020



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RAPIDO

MRI staging
At least one of:
cT4a, cT4b, EMVI+, N2, positive MRF, lat LN+

primary endpoint:
DrTF

R

Standard long-course CRT → *8 +/- 2 weeks* → TME → *6-8 weeks* → CAPOX/FOLFOX (optional)

5 1/2 weeks — *24 weeks*

SCRT → *11-18 days* → CAPOX/FOLFOX → *2-4 weeks* → TME

5 days — *18 weeks*

TOTAL NEOADJUVANT TREATMENT

PRODIGE 23

MRI staging
cT3 with isk of local recurrence or cT4,

primary endpoint:
DFS

R

Standard long-course CRT → *7 weeks* → TME → CAPOX/FOLFOX

5 1/2 weeks — *24 weeks*

mFOLFIRINOX (3 months) → Standard long-course CRT → *7 weeks* → TME → CAPOX/FOLFOX

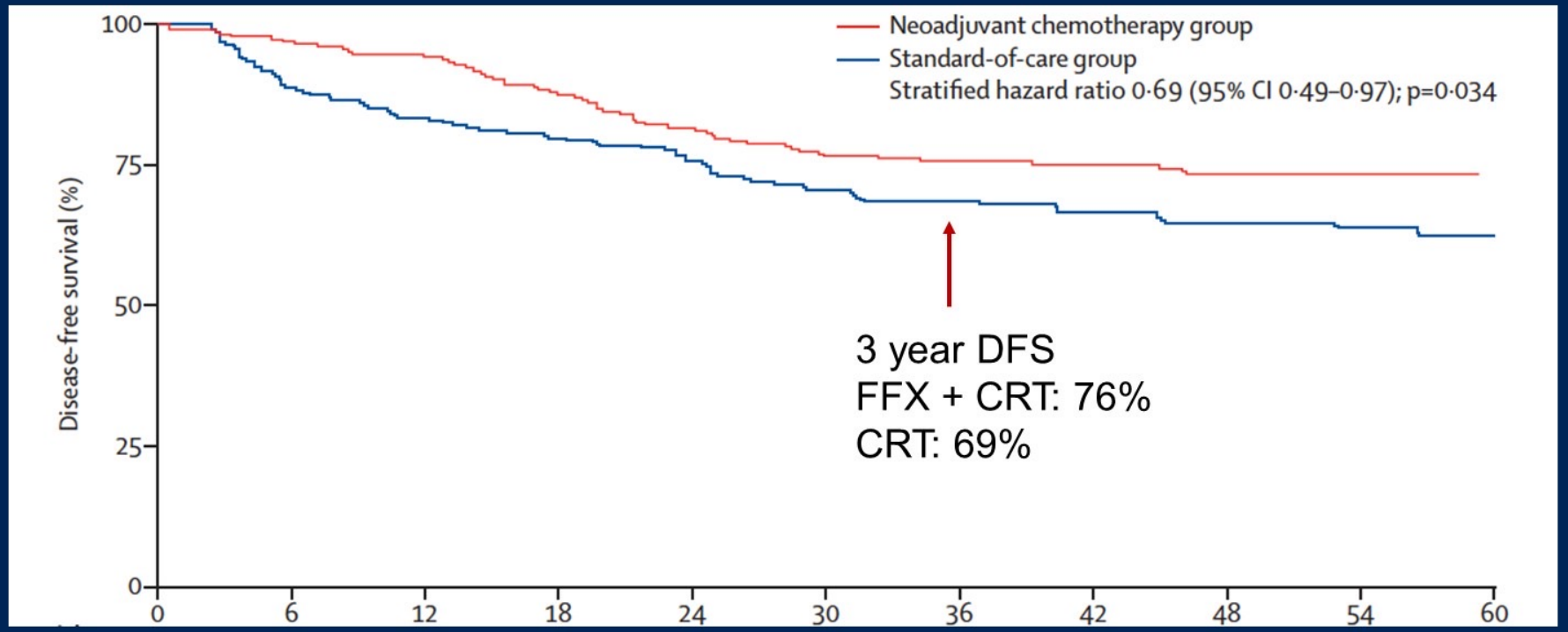
12 weeks — **5 1/2 weeks** — *8 weeks*

TOTAL NEOADJUVANT TREATMENT

Outcomes	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Median FU	4.6 yrs	3.8 yrs
Primary endpoint	3-year DrTF 23.7% vs. 30.4% (HR 0.75 [95% CI 0.60-0.96]; *P* = 0.019)	3-year DFS 75.7% vs. 68.5% (HR 0.69 95% [CI 0.49-0.97]; *P* = 0.034)
3-year MFS	80% vs. 73.2%	78.8% vs. 71.7%
pCR rate	28.4% vs. 14.3%	27.5% vs. 11.7%
Local relapse	8.7% vs. 5.4%	4.8% vs. 7%
3-year OS	89.1% vs. 88.8%	90.8% vs. 87.7%

FU: follow up; CRT: chemoradiotherapy; DrTF: disease-related treatment failure; DFS: disease-free survival; TNT: total neoadjuvant chemotherapy; pCR: pathological complete response; OS: overall survivsl; yrs: years.

UNICANCER-PRODIGE 23
Key Trial Results: DFS



Conroy T, et al. Lancet Oncol 2021; 22(5):702-715

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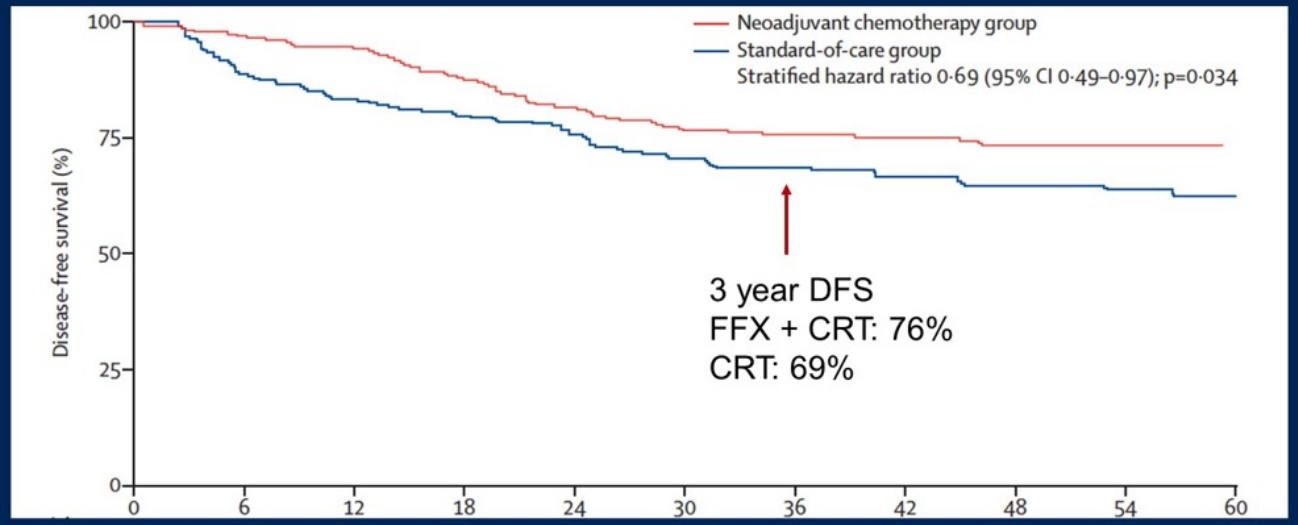
*UNICANCER-**PRODIGE 23***
Key Trial Results: DFS



Conroy T, et al. Lancet Oncol 2021; 22(5):702-715

Outcome	FFX + CRT	CRT	
DFS at 3 years	76%	69%	HR 0.69, .49-.97
OS at 3 years	91%	88%	HR 0.65, .4-1.05
Distant Met Free at 3 years	79%	72%	HR 0.64, .44-.93
Local Recur. At 3 years	4%	6%	HR 0.78, .34-1.8
pCR	28%	12%	p<0.0001
Clavien-Dindo grade IV-V operative complications	0.9%	4.6%	0.036

Conclusions

- PRODIGE 23 demonstrated feasibility of administering neoadjuvant mFOLFIRINOX in stage II/III rectal cancer
- Administering neoadjuvant mFOLFIRINOX prior to CRT and TME:
  - Increased probability of pCR
  - Decreased probability of surgery with noncurative intent (nontherapeutic laparotomy)
  - Improved DFS and MFS
- Investigators concluded that TNT with mFOLFIRINOX should now be considered a new standard of care for initial management of T3/T4 rectal cancer

Conroy. ASCO 2020. Abstr 4007.

Reminder comparison: RAPIDO Trial Results

n=920
Key Eligibility
cTt or N2 or <1mm MRF cM0
Extramural vasc invasion
MRI + lateral nodes
<16 cm
Treatment naive

Short course RT
25 Gy in 5 fx

CapeOx x 6 or
FOLFOX x 9

Long course CRT 50
Gy with capecitabine

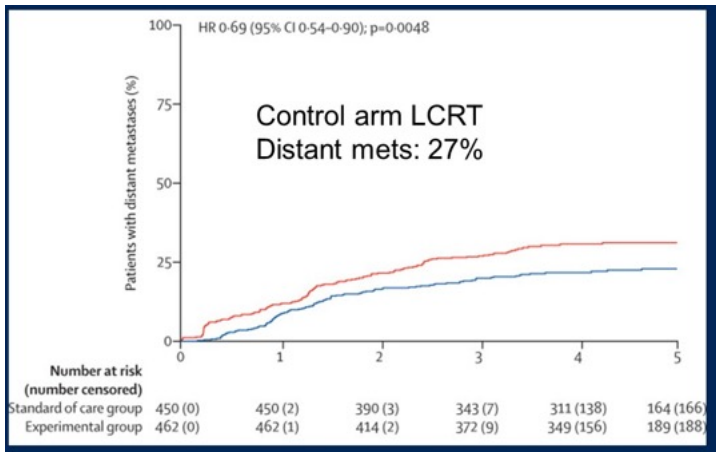
TME

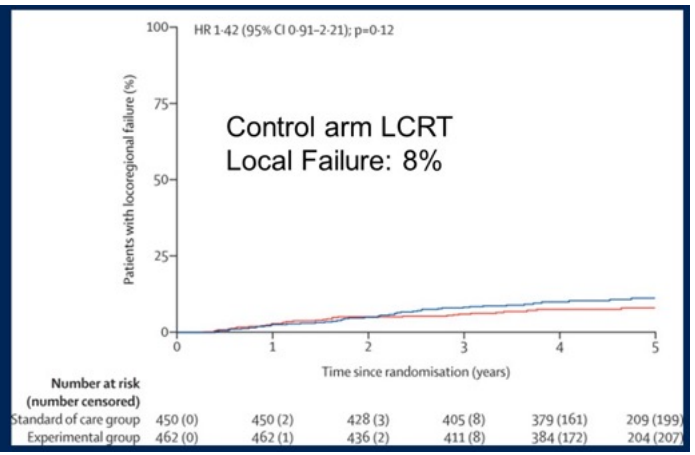
No additional
adjuvant

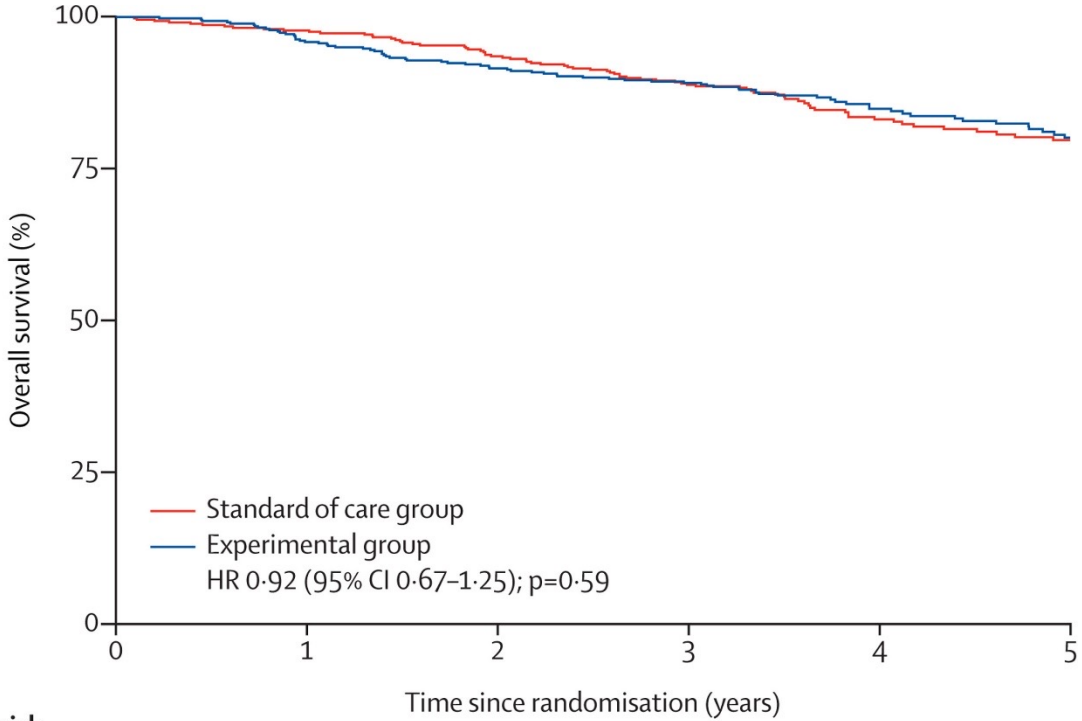
6 months adjuvant
per investigating
center (41% pts)

Outcome	SC + FOLFOX	Long Course CRT	
Disease related treatment failure at 3 years	24%	30%	HR 0.75, 0.6-0.95
OS at 3 years	89%	89%	HR 0.92, 0.67-1.25
Distant Mets at 3 years	20%	27%	HR 0.69, 0.54-0.9
Local Recur. At 3 years	8%	6%	HR 1.42, 0.9-2.21
pCR	28%	14%	p<0.0001

Bahadoer, et al Lancet Oncol 2021; 22: 29-42







Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	438 (3)	418 (8)	392 (169)	214 (208)
Experimental group	462 (0)	462 (1)	442 (2)	421 (9)	403 (181)	216 (217)

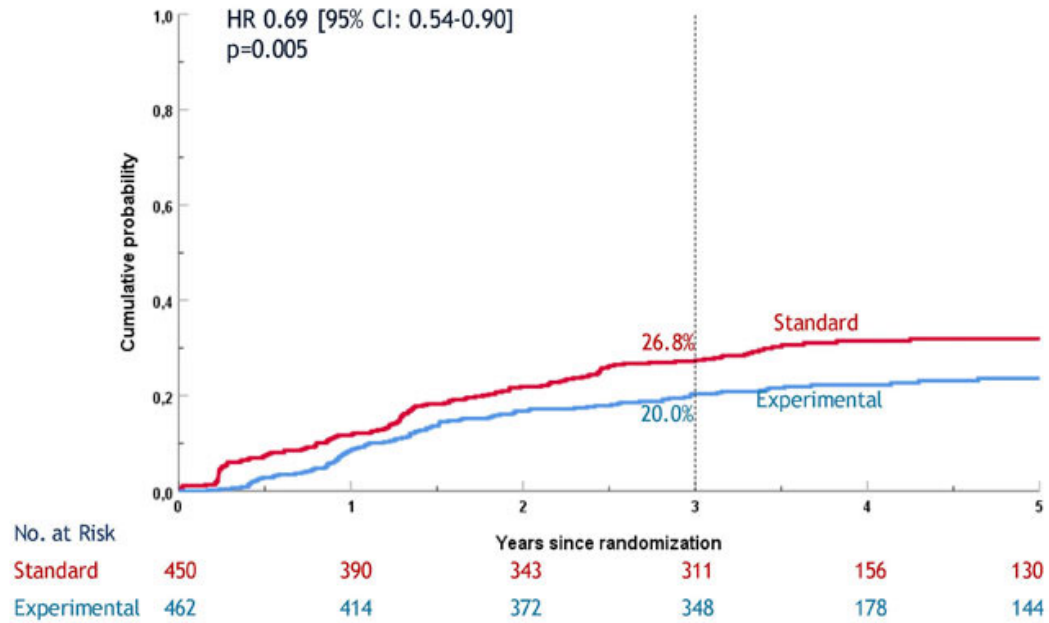


Table 2. Chemotherapy Dosing for Total Neoadjuvant Therapy Regimens

Trial	First Therapy	Second Therapy	Adjuvant Therapy
CAO/ARO/AIO-12[35]	Continuous infusion of 5-FU, 250 mg/m^2 on days 1–14 and 22–35 of RT and oxaliplatin, 50 mg/m^2 on days 1, 8, 22, and 29 of RT, concurrent with long-course RT	FOLFOX ×3 cycles (oxaliplatin, 100 mg/m^2 administered as a 2-h infusion, followed by a 2-h infusion of folinic acid, 400 mg/m^2, followed by a continuous 46-h infusion of 5-FU, 2,400 mg/m^2, repeated on day 15 for a total of 3 cycles)	None
UNICANCER-PRODIGE 23[25]	mFOLFIRINOX ×6 cycles (oxaliplatin, 85 mg/m^2; irinotecan, 180 mg/m^2; folinic acid, 400 mg/m^2; and 5-FU, 2,400 mg/m^2 continuous infusion every 14 days for 6 cycles)	Capecitabine, 800 mg/m^2 twice daily orally, concurrent with long-course RT	3 months of mFOLFOX (oxaliplatin, 85 mg/m^2; folinic acid, 400 mg/m^2; and 5-FU, 400 mg/m^2 bolus followed by 46-h continuous infusion at 2,400 mg/m^2 every 14 days) or capecitabine (1,250 mg/m^2 orally twice daily on days 1–14 every 21 days)
RAPIDO[26]	Short-course RT	CAPOX x6 cycles (capecitabine, 1,000 mg/m^2 orally twice daily on days 1–14; oxaliplatin, 130 mg/m^2 on day 1, every 21 days) or FOLFOX4 x9 cycles (oxaliplatin, 85 mg/m^2 on day 1; folinic acid, 200 mg/m^2 on days 1 and 2; followed by bolus 5-FU, 400 mg/m^2 and 5-FU, 600 mg/m^2 for 22 h on days 1 and 2, every 14 days)	CAPOX or FOLFOX4 per physician discretion hospital policy

Abbreviations: CAPOX, capecitabine/oxaliplatin; FOLFIRINOX, folinic acid/5-FU/irinotecan/oxaliplatin; FOLFOX, folinic acid/5-FU/oxaliplatin; mFOLFIRINOX, modified FOLFIRINOX; mFOLFOX, modified FOLFOX; RT, radiation therapy.

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Table 1. Review of Key Neoadjuvant Therapy in Rectal Cancer Trials and Outcomes

Trial	Year	Patients	Experimental	Control	Local Recurrence	Overall Survival
Swedish Rectal Cancer Trial[17]	1987–1990	1,168 Resectable	Preoperative SCRT	Surgery alone	5-y: 11% vs 27% $P<.0001$	5-y: 58% vs 48% $P=.004$
Dutch Colorectal Cancer Group study[19]	1996–1999	1,861 Resectable	Preoperative SCRT	Surgery alone	2-y: 2.4% vs 8.2% $P<.0001$	2-y: 82.0% vs 81.8% $P=.84$
German Rectal Cancer Study Group trial[10]	1995–2002	823 cT3–4/N+	Preoperative CRT	Postoperative CRT	5-y: 6% vs 13% $P=.006$	5-y: 76% vs 74% $P=.80$
TROG 01.04[20]	2001–2006	326 T3N0–2	Preoperative SCRT	Preoperative CRT	3-y: 7.5% vs 4.4% $P=.24$	5-y: 74% vs 70% $P=.62$
CAO/ARO/AIO-12[35]	2015–2018	311 Stage II–III	Induction chemotherapy then CRT	CRT then consolidation chemotherapy	3-y: 6% vs 5% $P=.67$	3-y: 92% vs 92% $P=.81$
Stockholm III[22]	1998–2013	840 Resectable	1. Preoperative SCRT 2. Preoperative SCRT with 4- to 8-wk delay of surgery	Preoperative CRT with 4- to 8-wk delay of surgery	Median time: 28.3 vs 22.1 vs 33.3 mo $P>.05$	5-y: 73% vs 76% vs 78% $P>.05$
UNICANCER-PRODIGE 23[25]	2012–2017	461 cT3–4M0	TNT FOLFIRINOX, CRT, TME, adjuvant FOLFOX ×6	Neoadjuvant CRT, TME, adjuvant FOLFOX ×9	(pCR) 3-y: 28% vs 12% $P<.0001$	3-y: 91% vs 88% $P=.0773$
RAPIDO[26]	2011–2016	920 cT4a/b, high-risk	Preoperative SCRT, CAPOX/FOLFOX4	Neoadjuvant LCRT with capecitabine, TME, adjuvant CAPOX/FOLFOX	3-y: 8.3% vs 6.0% $P=.12$	3-y: 89.1% vs 88.8% $P=.59$
Habr-Gama et al[32]	1991–2011	183 cT2–4N0–2 distal	Preoperative CRT then watchful waiting	—	5-y: 69% (94% after salvage)	5-y cancer-specific OS: 91%
OPRA[34]	2013–current	324 Stage II–III	Induction chemotherapy then CRT	CRT then consolidation chemotherapy	3-y: 78% vs 77% $P=.90$	—

Abbreviations: CAPOX, capecitabine/oxaliplatin; CRT, chemoradiation; FOLFIRINOX, folinic acid/5-FU/irinotecan/oxaliplatin; FOLFOX, folinic acid/5-FU/oxaliplatin; LCRT, long-course radiation therapy; pCR, pathologic complete response; SCRT, short-course radiation therapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

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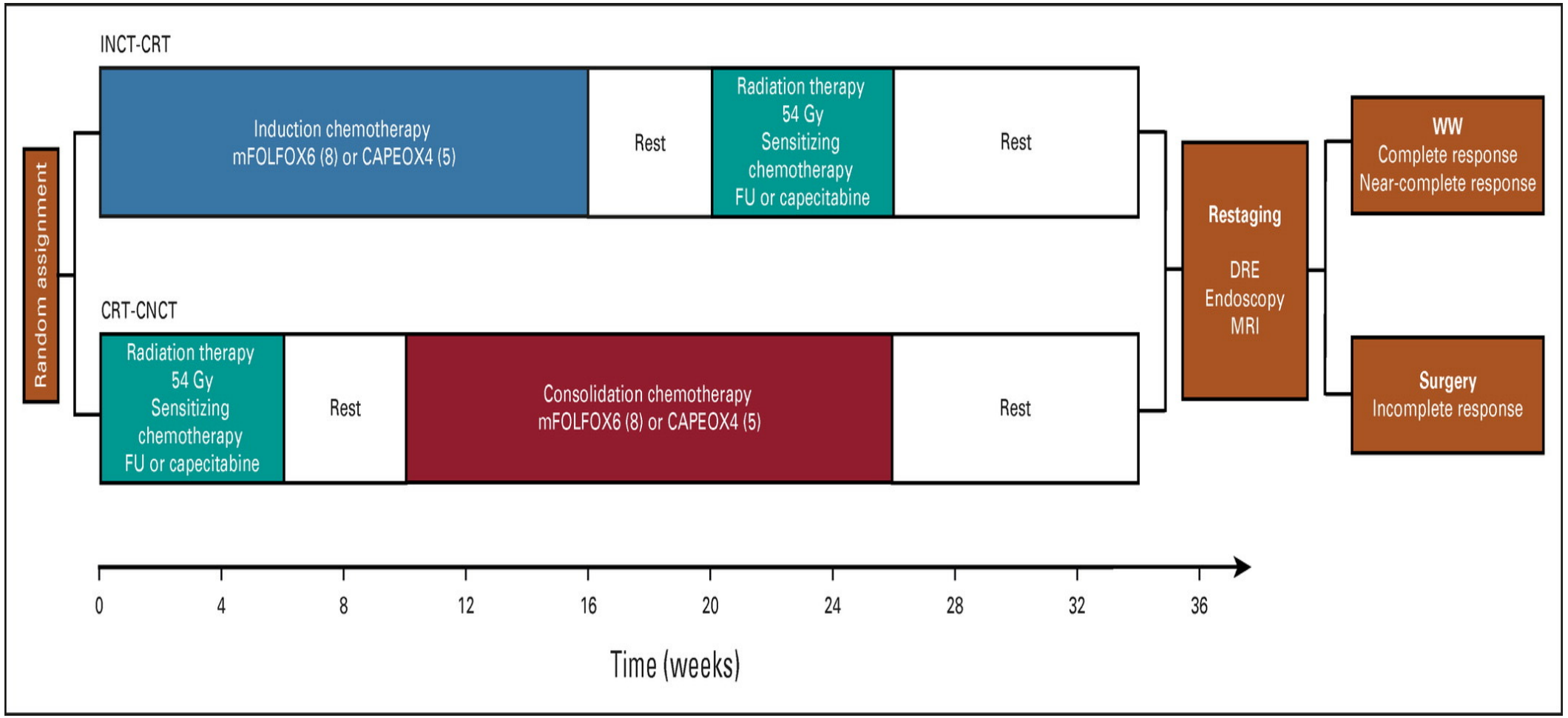

FIG A1. Trial schema. CAPEOX, capecitabine and oxaliplatin; CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; DRE, digital rectal exam; FU, fluorouracil; Gy, gray; INCT-CRT, induction chemotherapy followed by chemoradiotherapy; mFOLFOX, modified infusional fluorouracil, leucovorin, and oxaliplatin; MRI, magnetic resonance imaging; WW, watch-and-wait.

Published in: Julio Garcia-Aguilar; Sujata Patil; Marc J. Gollub; Jin K. Kim; Jonathan B. Yuval; Hannah M. Thompson; Floris S. Verheij; Dana M. Omer; Meghan Lee; Richard F. Dunne; Jorge Marcet; Peter Cataldo; Blase Polite; Daniel O. Herzig; David Liska; Samuel Oommen; Charles M. Friel; Charles Ternent; Andrew L. Coveler; Steven Hunt; Anita Gregory; Madhulika G. Varma; Brian L. Bello; Joseph C. Carmichael; John Krauss; Ana Gleisner; Philip B. Paty; Martin R. Weiser; Garrett M. Nash; Emmanouil Pappou; José G. Guillem; Larissa Temple; Iris H. Wei; Maria Widmar; Sabrina Lin; Neil H. Segal; Andrea Cercek; Rona Yaeger; J. Joshua Smith; Karyn A. Goodman; Abraham J. Wu; Leonard B. Saltz; *Journal of Clinical Oncology* 2022 402546-2556.
DOI: 10.1200/JCO.22.00032

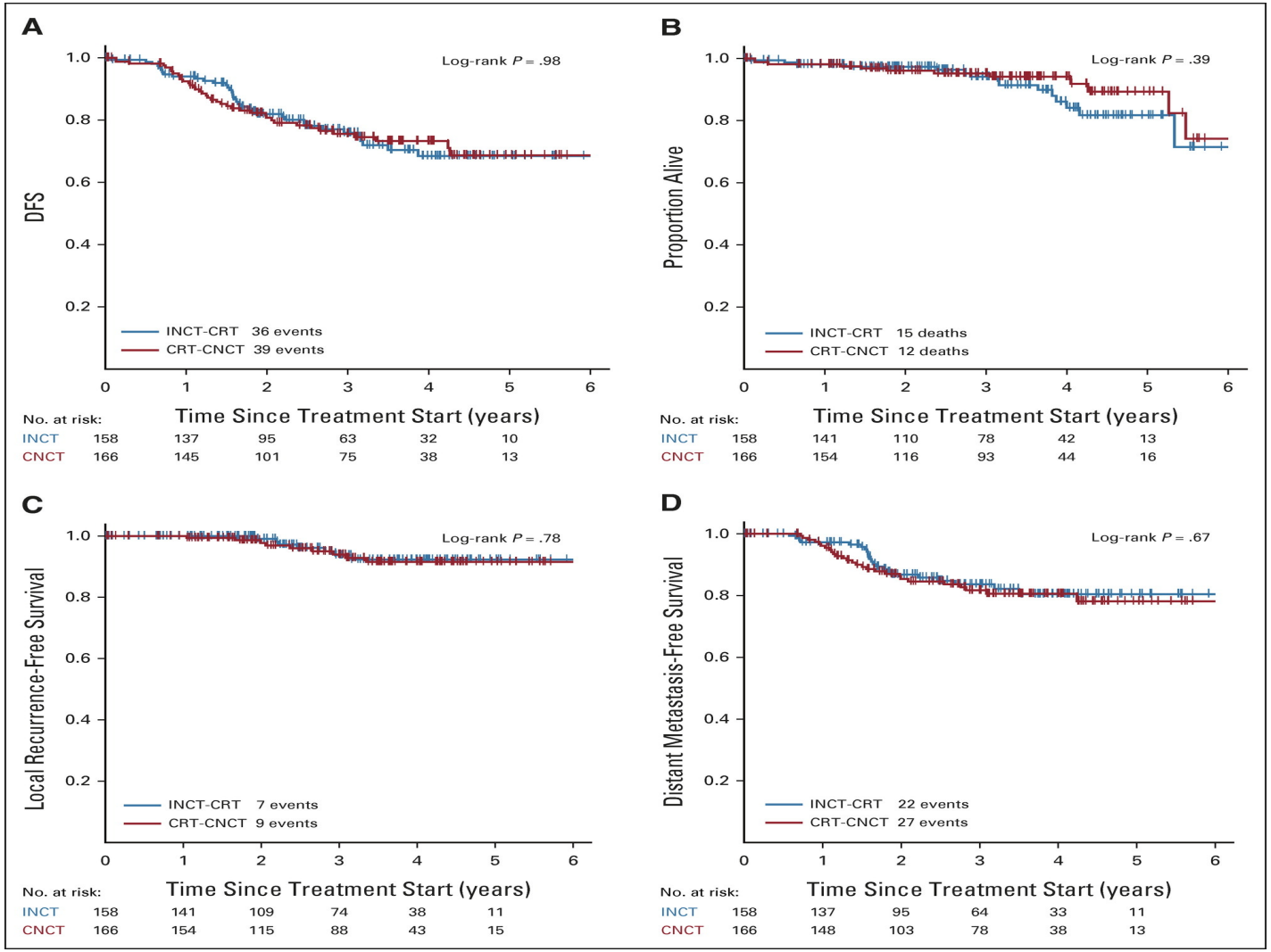

FIG 2. Kaplan-Meier estimates of (A) DFS, (B) overall survival, (C) local recurrence-free survival, and (D) distant metastasis-free survival in the intention-to-treat population by study group. CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; DFS, disease-free survival; INCT-CRT, induction chemotherapy followed by chemoradiotherapy.

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DOI: 10.1200/JCO.22.00032

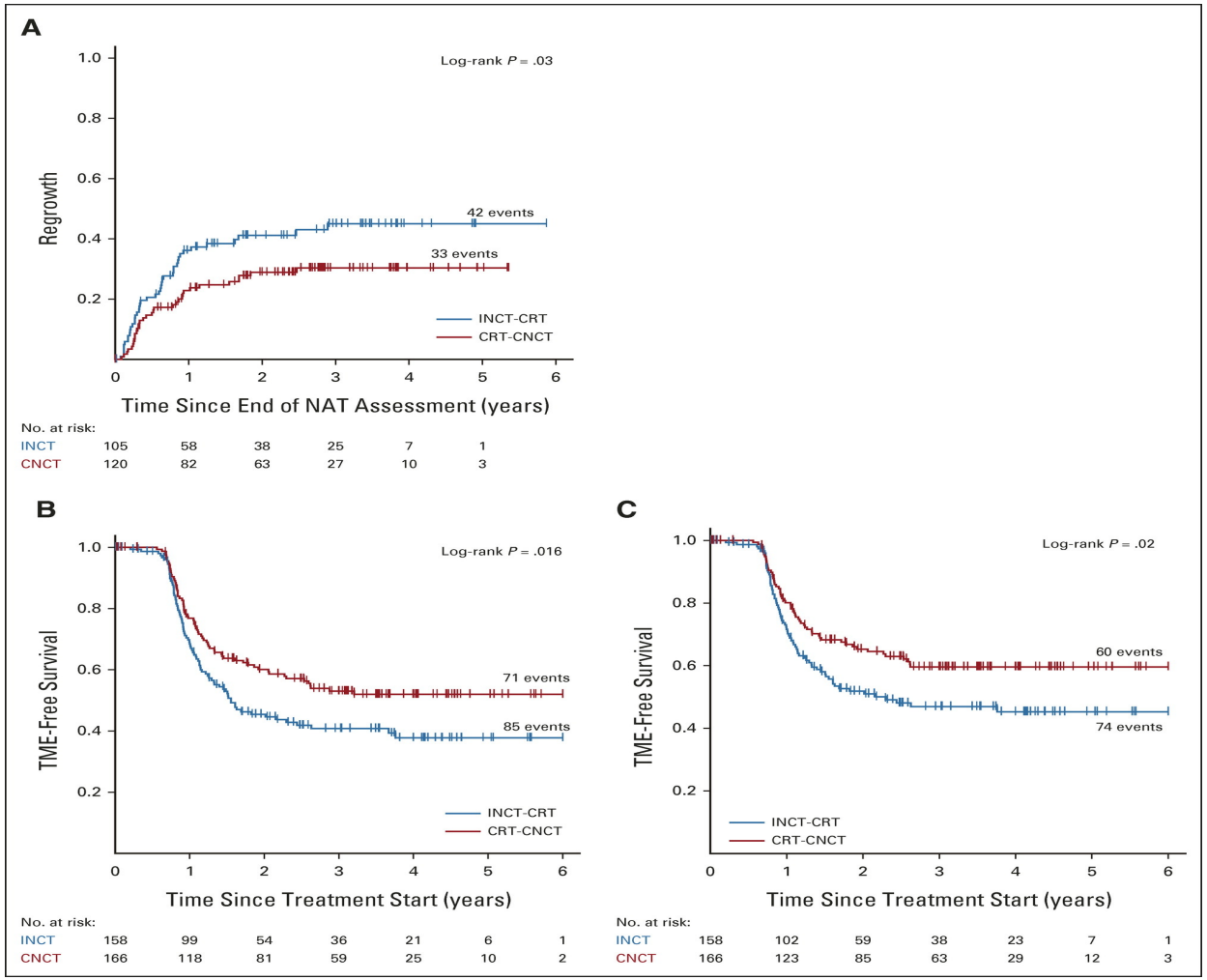

FIG 3. Kaplan-Meier estimates of (A) time to regrowth in watch-and-wait patients, (B) TME-free survival by intention to treat, and (C) for patients who underwent TME. CRT-CNCT, chemoradiotherapy followed by consolidation chemotherapy; INCT-CRT, induction chemotherapy followed by chemoradiotherapy; NAT, neoadjuvant therapy; TME, total mesorectal excision.

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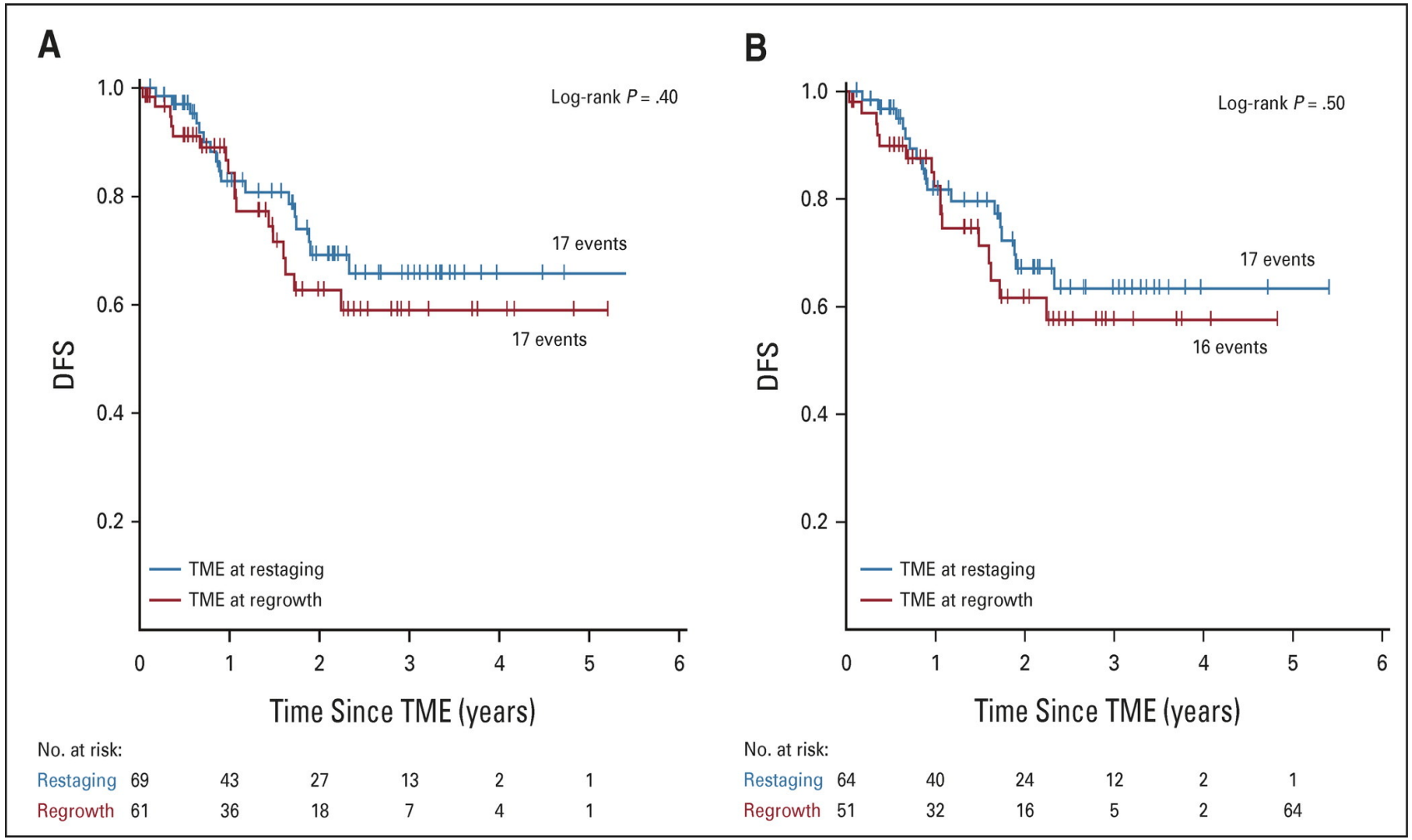

FIG 4. Kaplan-Meier estimates of DFS for (A) patients recommended TME after restaging and after tumor regrowth by intention to treat and (B) patients who actually underwent TME. Patients who developed distant metastasis before TME was recommended (three at restaging and six at regrowth) and patients in whom TME was not performed because of disease progression found at surgery (one at restaging and two at regrowth) are not included in the analysis. Six patients in each group have not reached the first follow-up clinical assessment after TME. DFS, disease-free survival; TME, total mesorectal excision.

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DOI: 10.1200/JCO.22.00032

What about sphincter and function preservation?

- APR + low anastomoses are permanently life-altering
- Current paradigms under study pathologic complete responses ~15-40%
- pCR rates are improved by total neoadjuvant therapy

…But minimal difference between rates of APR

→**Is the only way to alter the rates of life changing surgery to skip the surgery?**

Example Trials	APR Rate
Prodige 23	
- LC CRT	14%
- FFX-CRT	14%
RAPIDO	
- LC CRT	40%
- SC RT--FOLFOX	35%
CAO/ARO/AIO-04	
- CRT with 5FU	24%
- CRT with ox + 5FU	25%

Bahadoer, et al Lancet Oncol 2021; 22: 29-42
Conroy T, et al. Lancet Oncol 2021; 22(5):702-715
Garcia-Aguilar et al. Lancet Oncol 2015; 15: 957-66
Rodel C, et al. Lancet Oncol 2012; 13: 679-87
Kasi A, et al. JAMA Netw Open 2020; 3(12): e203009

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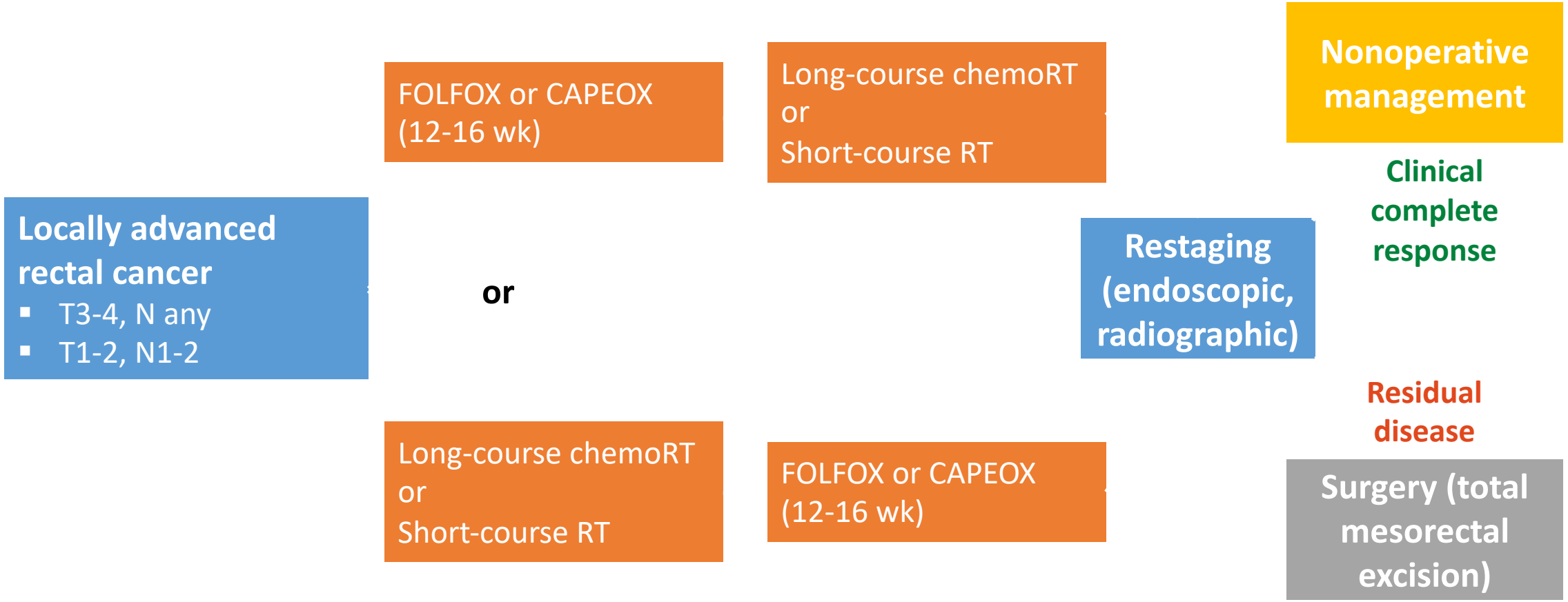
Example Trials	APR Rate
Prodige 23	
- LC CRT	14%
- FFX-CRT	14%
RAPIDO	
- LC CRT	40%
- SC RT--FOLFOX	35%
CAO/ARO/AIO-04	
- CRT with 5FU	24%
- CRT with ox + 5FU	25%

Organ Preservation Trials

	Inclusion	Treatment regimen	Results
OPERA	cT2-T3b N0-N1 ≲10cm AV	45Gy CRT → 9Gy/5 CRT → CXB (90Gy/3)	3yr OP rate 60% vs 81%
OPRA	cT3-T4 N0-N+ ≲6cm AV	CRT → chemo Chemo → CRT	3yr TME-FS 53% vs 41%
STAR-TREC	cT1-T3b N0 ≲10cm AV	SCRT CRT	Phase II- 1yr OP 60%
GRECCAR12	cT2-T3 N0-N1 ≲10cm AV	CRT Chemo → CRT	Closed, no results
WW3	cT1-T3b N0 ≲10cm AV	CRT CRT + SIB (62Gy)	Still accruing
AIO-18.1	cT3-T4 N0-N+ ≲12cm AV	SCRT → chemo CRT → chemo	Still accruing

PRESENTED BY: Emma Holliday @DrEmmaHolliday

Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer

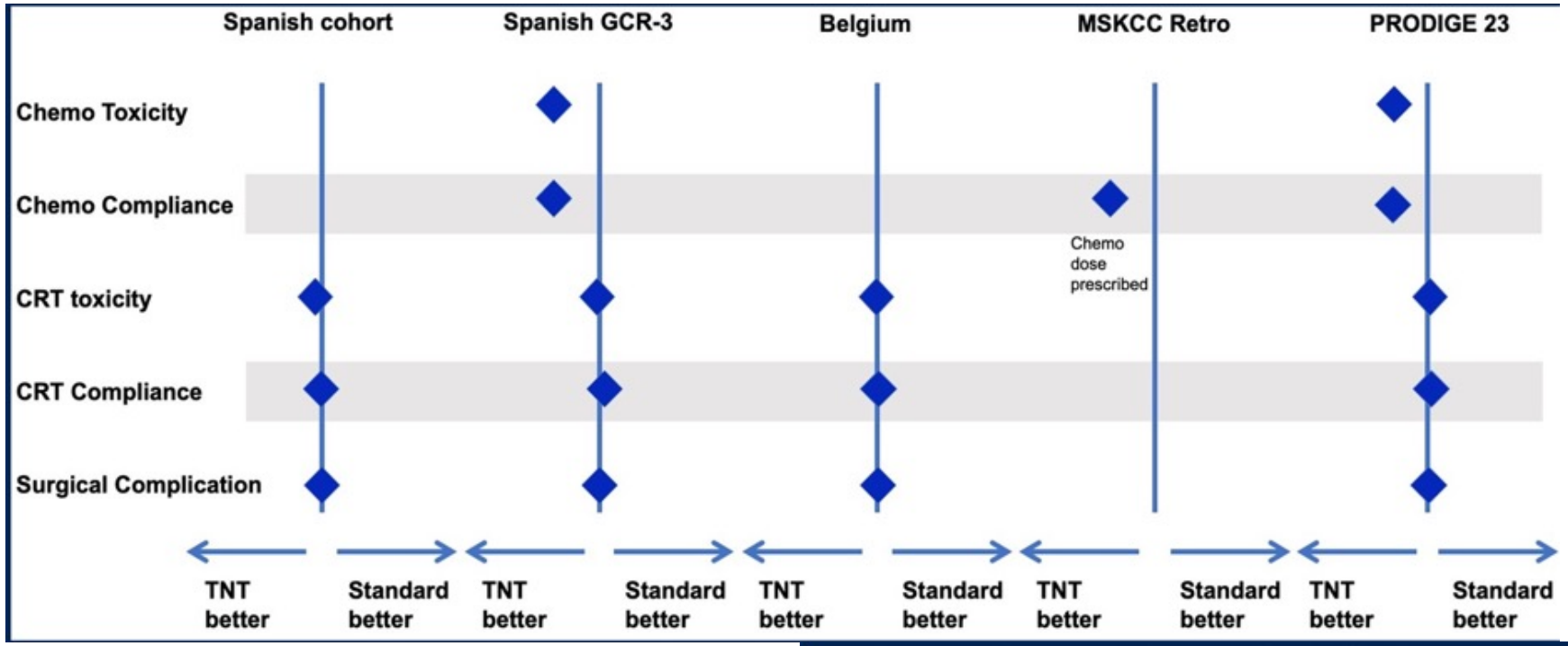


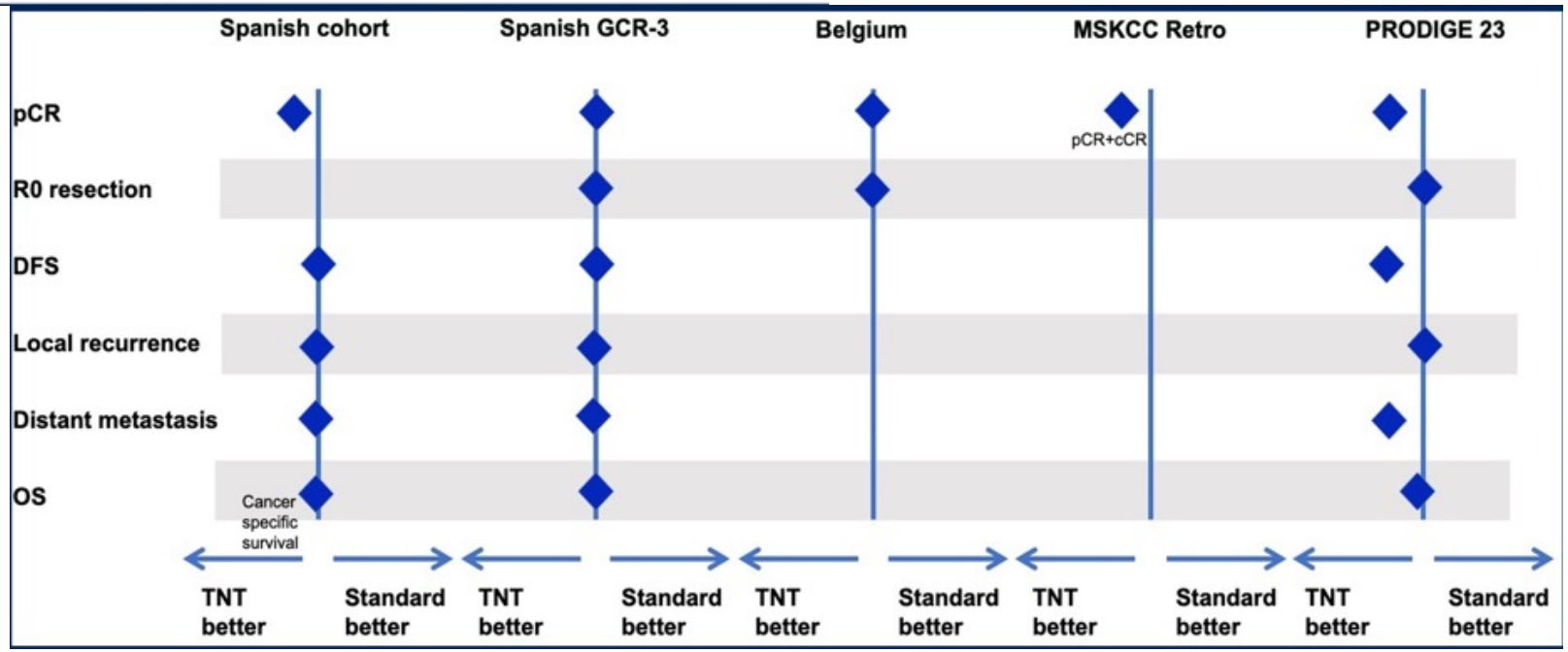
Lumish. ASCO GI 2022. Abstr 16. NCCN. Clinical practice guidelines in oncology: rectal cancer. v.1.2022. nccn.org.

Order of Factor

- Chemotherapy first
  - Upfront systemic disease control
  - Selective use of XRT

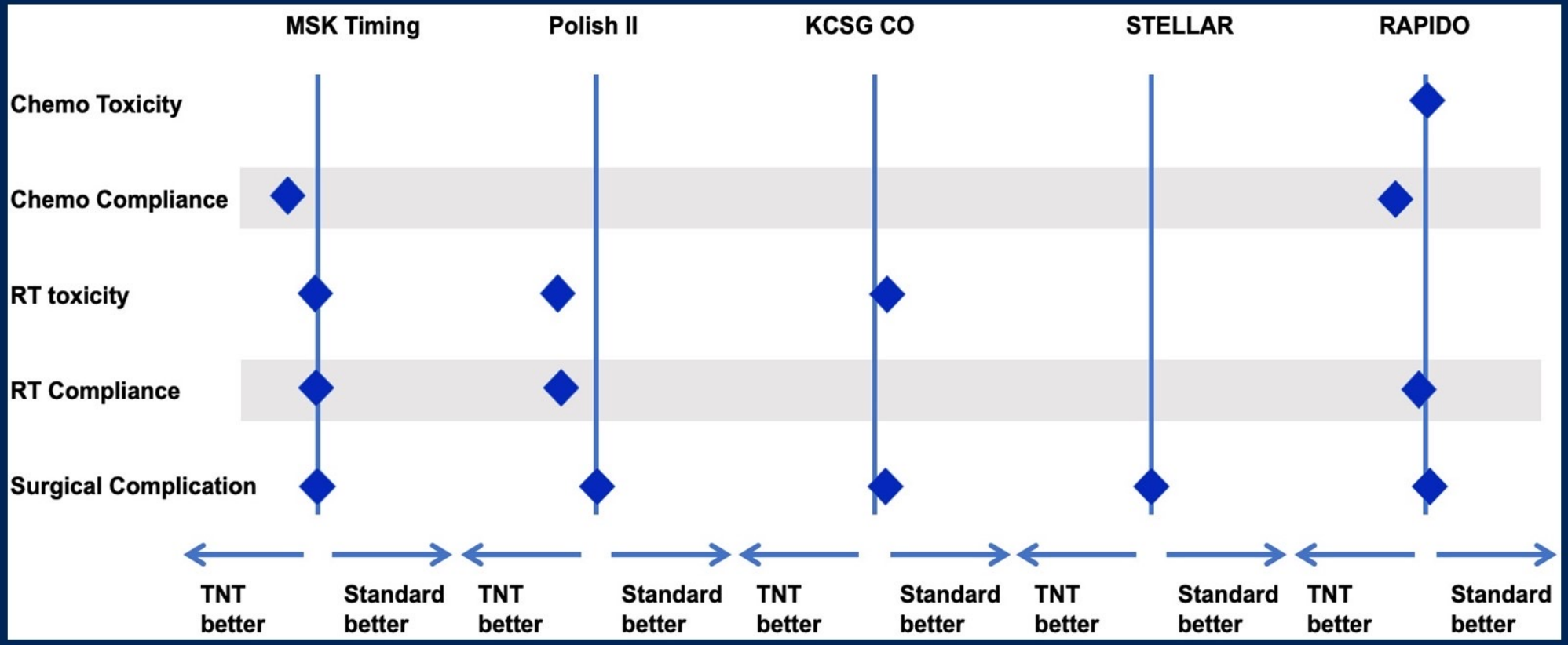
- XRT first
  - Faster local symptom control
  - More tumor regression after interval from XRT


Spanish cohort
Spanish GCR-3
Belgium
MSKCC Retro
PRODIGE 23
Chemo Toxicity
Chemo Compliance
Chemo dose prescribed
CRT toxicity
CRT Compliance
Surgical Complication
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better


Spanish cohort
Spanish GCR-3
Belgium
MSKCC Retro
PRODIGE 23
pCR
pCR+cCR
R0 resection
DFS
Local recurrence
Distant metastasis
OS
Cancer specific survival
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better

Chemotherapy second (Consolidation chemo TNT) *vs* Standard

Toxicities and Complications



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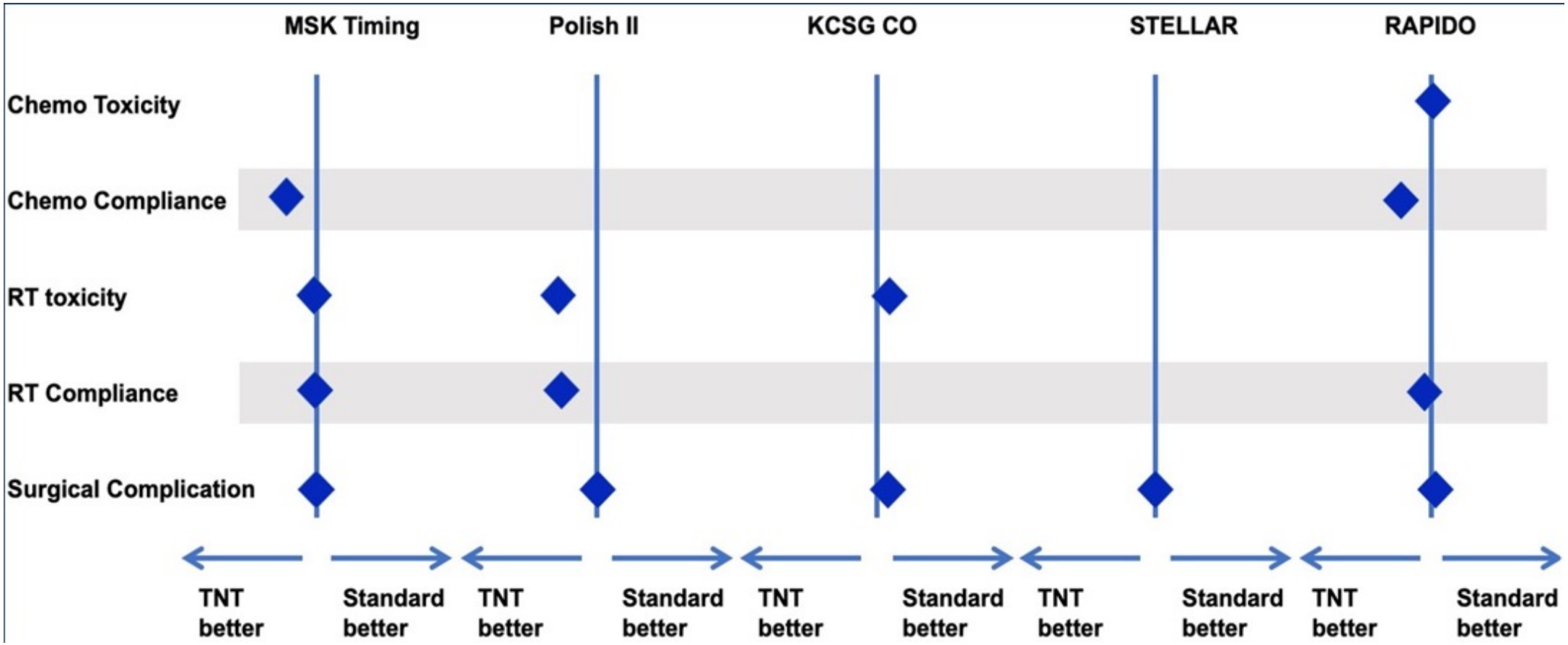

MSK Timing
Polish II
KCSG CO
STELLAR
RAPIDO
Chemo Toxicity
Chemo Compliance
RT toxicity
RT Compliance
Surgical Complication
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better
TNT better
Standard better

From: **Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Patients With Locally Advanced Rectal Cancer: Long-term Results of the CAO/ARO/AIO-12 Randomized Clinical Trial**
JAMA Oncol. 2022;8(1):e215445. doi:10.1001/jamaoncol.2021.5445

Efficacy	INCT arm (A) "chemotherapy first" N=142	CNCT arm (B) "chemotherapy second" N=142
Complete TME	85%	82%
R0 resection	92%	90%
Sphincter-preserving surgery	68%	72%
CRM ≤ 1 mm	10%	7%
pCR	17%	25%
pCR + cCR	21%	28%

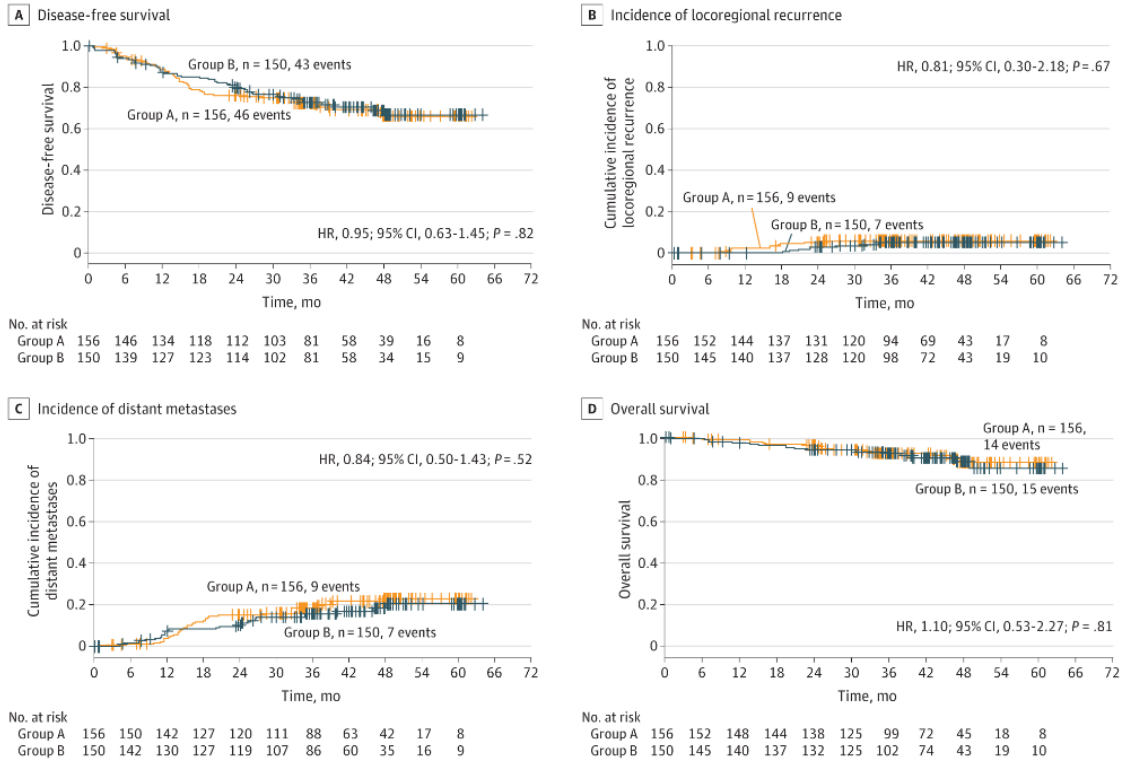
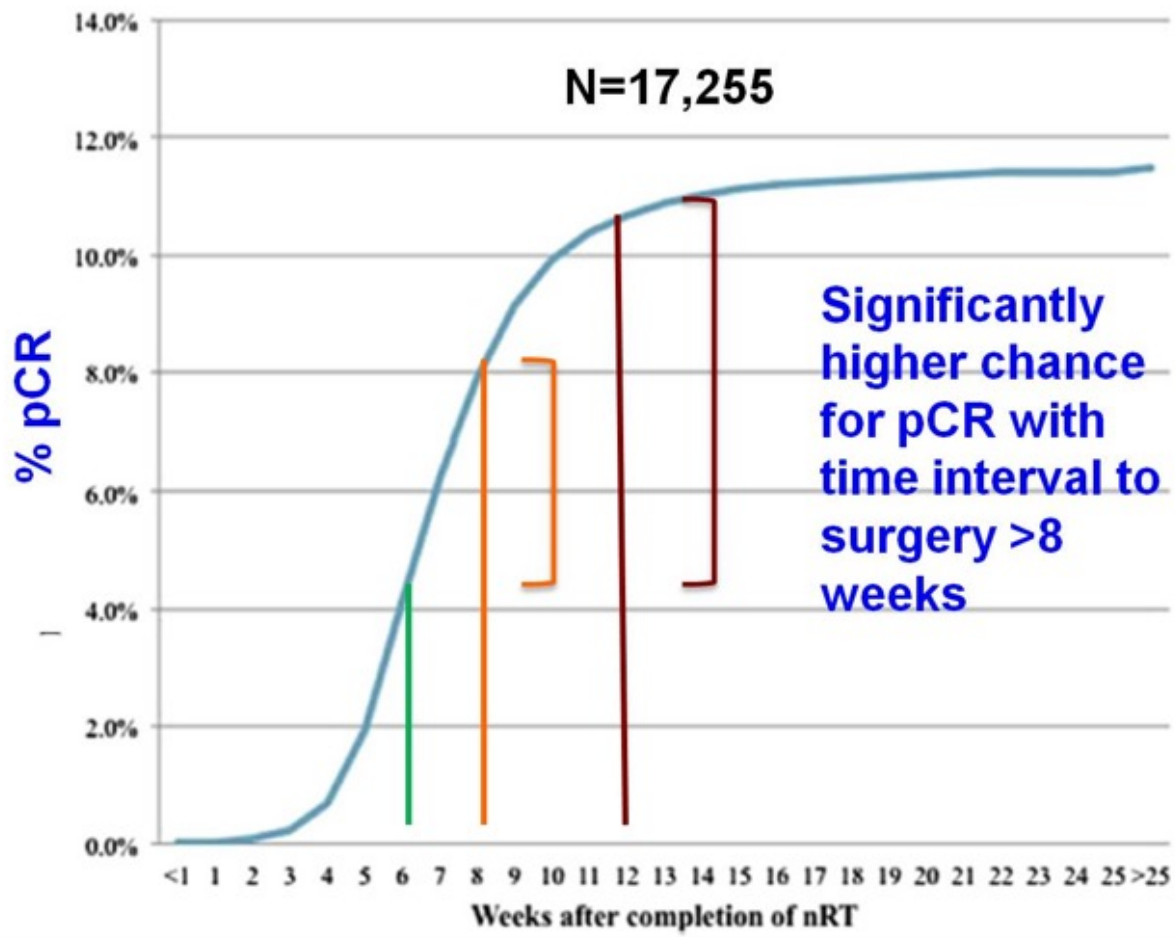


Figure Legend:

Long-term Oncologic OutcomesA, Disease-free survival; B, cumulative incidence of locoregional recurrence after R0-1 resection; C, cumulative incidence of distant metastases; D, overall survival. HR indicates hazard ratio.



OSTRICh Consortium JACS Vol 221:2 August

TABLE 3. Pretreatment Clinical Characteristics

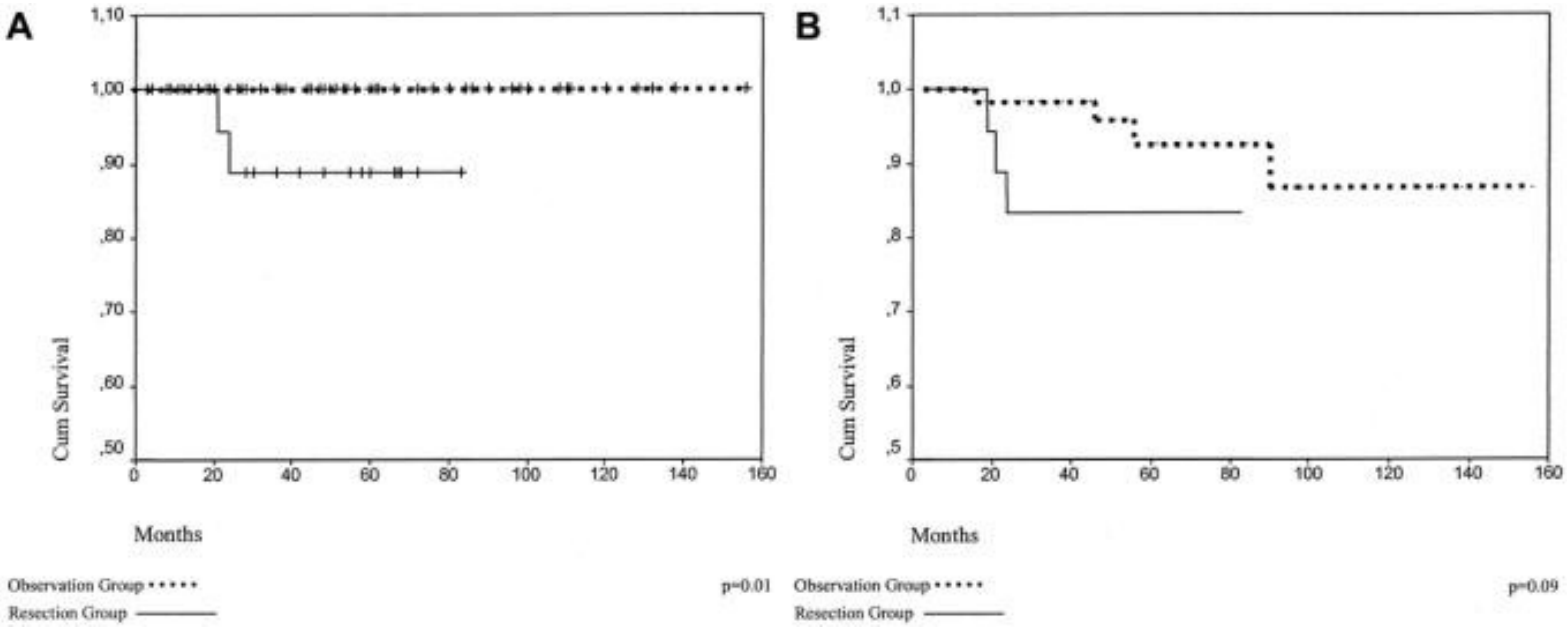
	(OB) Observation Group	(R) Resection Group	*P*
Gender (M:F)	1.05	1.2	ns
Mean age	58.1 (35–92)	53.6 (25–73)	ns
Pre-CRT tumor size (mean)	3.6 cm (1–7)	4.2cm (2.5–7)	ns
Distance from AV (cm)	3.6 (0–7)	3.8 (2–7)	ns
T2	14 (19.7%)	1 (4.5%)	ns
T3	49 (69%)	19 (86.5%)	ns
T4	8 (11.3%)	2 (9%)	ns
N+	16 (22.5%)	6 (27.2%)	ns
Total	71	22	

AV, anal verge; F, female; M, male; ns, not significant.

TABLE 4. Follow-up at Yearly Intervals

Follow-up, mo	(OB) Observation Group No. (%)	(R) Resection Group No. (%)
12	71 (100)	22 (100)
24	60 (84.5)	18 (81.8)
36	48 (67.6)	14 (63.6)
48	40 (56.3)	10 (45.4)
60	28 (39.4)	6 (27.3)
72	23 (32.3)	2 (9)
84	18 (25.3)	—
96	15 (21.1)	—
108	10 (14)	—
120	6 (8.5)	—

- Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy
- Ann Surg. 2004 Oct; 240(4): 711–718.
- Angelita Habr-Gama, MD et al



Time Period	Source	No.	cCR Rate: Initial/Sustained, %	Local/Pelvic Failures, %	Salvage Rate, n/N (%)	Systemic Recurrence, %	Survival, %
1991-2002a	Habr-Gama 2004[52]	265	NR/27	3	2/2 (100)	4	100 (5-y OS)
1991-2005a	Habr-Gama 2006[53]	361	34/27	6	5/5 (100)	8	93 (5-y OS)
1991-2011b	Habr-Gama 2014[54]	183	49/40	31	26/28 (93)	14	91 (5-y CSS)

Maastricht Univ Experience

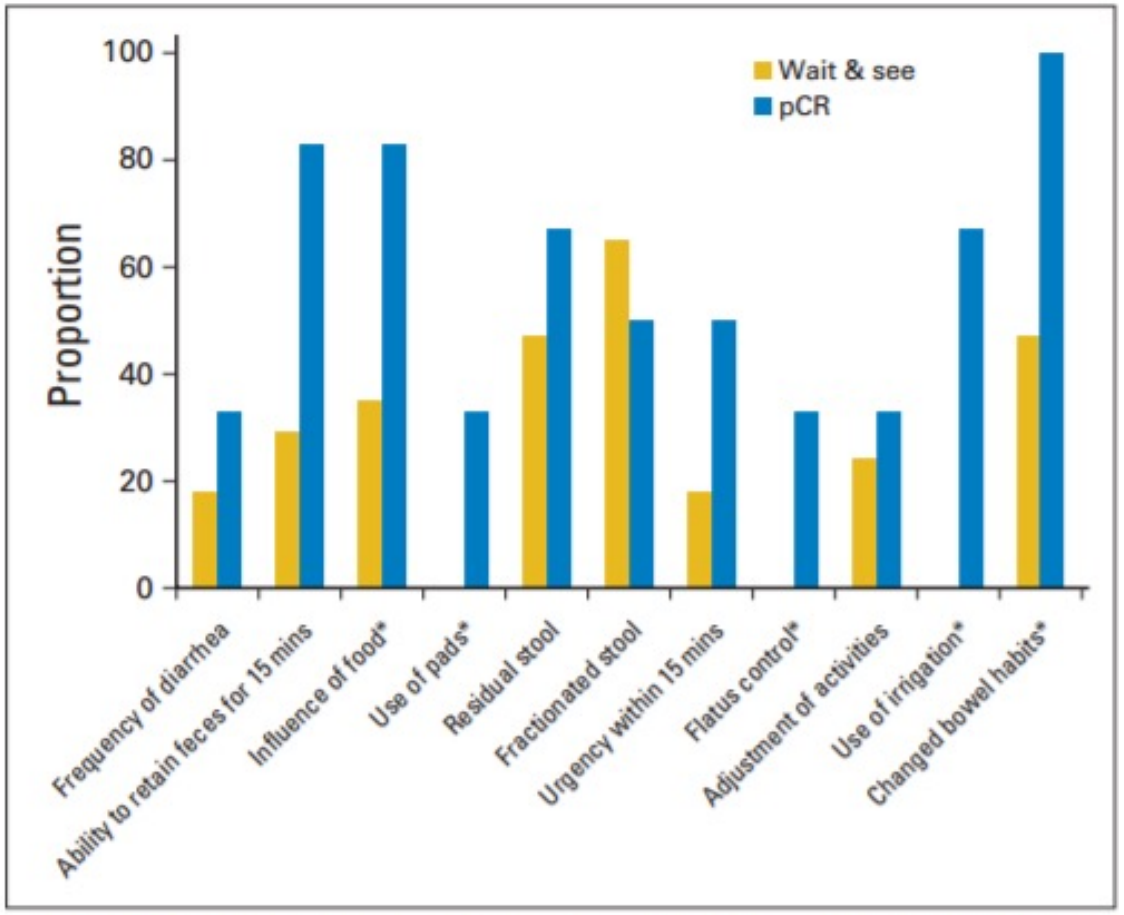
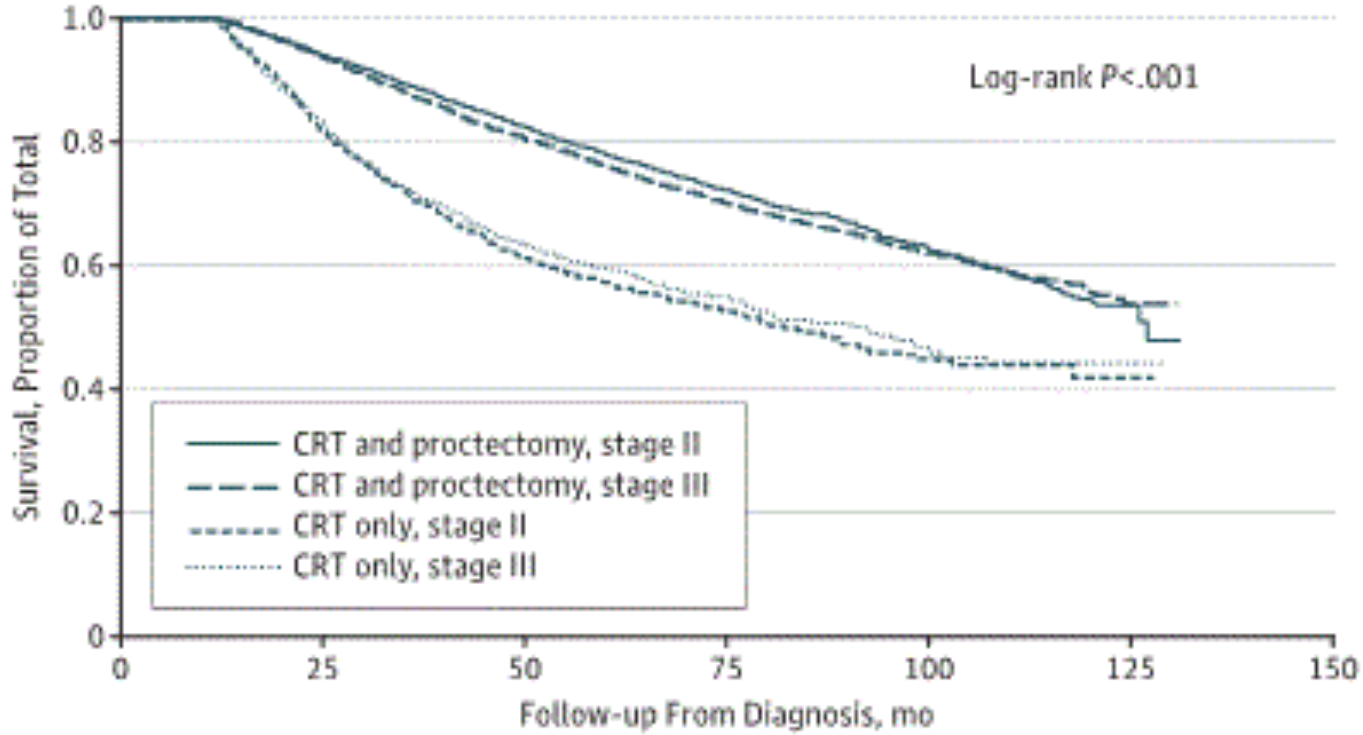


Fig 3. Bowel function on the basis of several items from the Memorial Sloan-Kettering Cancer Center bowel function questionnaire and the Wexner incontinence score for patients with a clinical complete response following wait-and-see policy and patients with a pathologic complete response (pCR) after total mesorectal excision. (*) Indicates that the difference was statistically significant.

Assessment of complete response	Initial assessment	First year	Second year	Third year and after
DRE	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
CEA	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
Endoscopic assessment	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
MRI	10 wk	If 1st assessment normal with cCR, then every 6 mo	Every 6 mo	Every 6 mo

Figure. Unadjusted Overall Survival of Patients With Rectal Cancer by Treatment Type and Stage of Disease



No. at risk						
CRT and proctectomy, stage II	6971	6385	5361	3266	1099	42
CRT and proctectomy, stage III	7192	6570	5363	3153	1019	43
CRT only, stage II	967	754	541	320	92	3
CRT only, stage III	680	535	375	222	65	3

Jama Oncology online epub

RESEARCH SUMMARY

Preoperative Treatment of Locally Advanced Rectal Cancer

Schrag D et al. DOI: 10.1056/NEJMoa2303269

CLINICAL PROBLEM

Pelvic chemoradiotherapy for locally advanced rectal cancer markedly reduces the risk of disease recurrence and has been standard care in North America for decades. However, it carries risk of short- and long-term toxic effects. Whether preoperative chemotherapy with the FOLFOX regimen (fluorouracil, leucovorin, and oxaliplatin) would allow patients to avoid chemoradiotherapy without increasing the risk of disease recurrence is unclear.

CLINICAL TRIAL

Design: A multicenter, unblinded, randomized, noninferiority trial compared neoadjuvant FOLFOX (with selective use of chemoradiotherapy) with chemoradiotherapy in adults with locally advanced rectal cancer amenable to sphincter-sparing surgery.

Intervention: 1194 patients with previously untreated rectal cancer clinically staged as T2 node-positive, T3 node-negative, or T3 node-positive were assigned to neoadjuvant FOLFOX (six cycles) or chemoradiotherapy. Patients in the FOLFOX group whose tumors decreased in size by <20% or who discontinued treatment because of side effects were given chemoradiotherapy. The primary end point was disease-free survival. Secondary outcomes included overall survival and local recurrence.

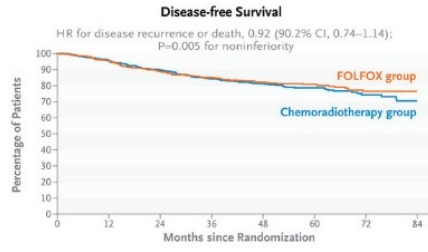
RESULTS

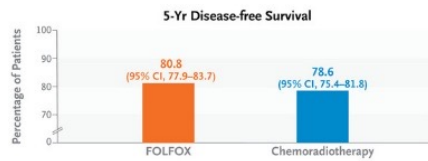
Among the 1128 patients who began treatment, neoadjuvant FOLFOX with selective use of chemoradiotherapy was noninferior to chemoradiotherapy with respect to disease-free survival over a median follow-up of 58 months. In the FOLFOX group, 9.1% of patients received preoperative chemoradiotherapy and 1.4% received postoperative chemoradiotherapy.

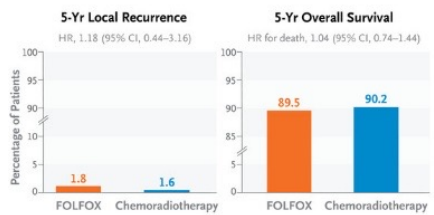
LIMITATIONS AND REMAINING QUESTIONS

- Because of the eligibility criteria used in the trial, the generalizability of the findings to high-risk patients may be limited.
- Further research is needed to determine whether distinctive molecular features predict responsiveness to chemotherapy as compared with radiation.
- Longer follow-up is required to evaluate the magnitude of late effects of pelvic radiation.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

In patients with locally advanced rectal cancer amenable to sphincter-sparing surgery, neoadjuvant FOLFOX chemotherapy with selective use of chemoradiotherapy was noninferior to neoadjuvant chemoradiotherapy for disease-free survival, and nearly 90% of patients in the FOLFOX group were able to avoid chemoradiotherapy.

1194 Patients with T2 node-positive, T3 node-negative, or T3 node-positive locally advanced rectal adenocarcinoma were enrolled in the trial

1194 Underwent randomization

597 Were assigned to receive FOLFOX followed by selective use of chemoradiotherapy
585 Received intervention as assigned
6 Withdrew
6 Were deemed ineligible

597 Were assigned to receive chemoradiotherapy alone
543 Received intervention as assigned
46 Withdrew
6 Were deemed ineligible
1 Had disease progression
1 Decided not to receive intervention

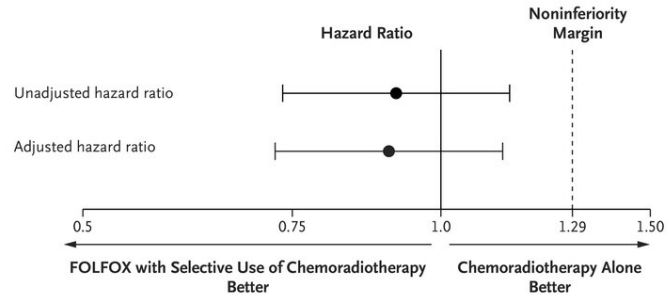
55 Discontinued therapy
16 Withdrew
11 Were deemed ineligible
7 Had adverse events
6 Underwent alternative therapy
4 Had tumor progression or more extensive tumor
3 Died
1 Opted to watch and wait
1 Decided to discontinue therapy
1 Was lost to follow-up
5 Had other reason

40 Discontinued therapy
16 Withdrew
5 Were deemed ineligible
5 Had adverse events
1 Underwent alternative therapy
3 Had tumor progression or more extensive tumor
1 Died
2 Opted to watch and wait
2 Decided to discontinue therapy
1 Was lost to follow-up
4 Had other reason

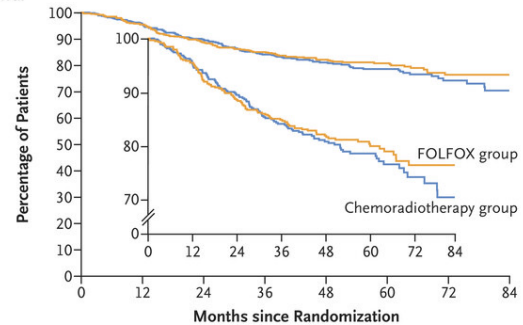
585 Were included in the primary analysis

543 Were included in the primary analysis

A Analysis of Noninferiority for Disease-free Survival



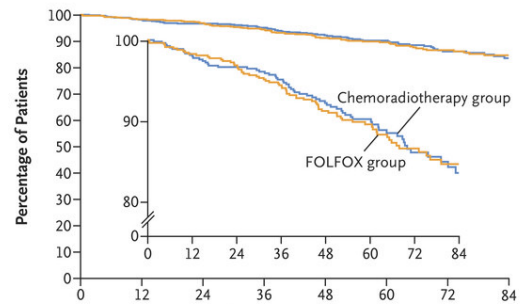
B Disease-free Survival



No. at Risk								
FOLFOX group	585	543	489	443	342	200	97	42
Chemoradiotherapy group	543	500	456	395	295	181	80	37

Group	No. of Events/ Total No.	Hazard Ratio (90.2% CI)	5-Year Estimate	Stratified P Value for NI
			percent	
FOLFOX group	114/585	0.92 (0.74–1.14)	80.8 (77.9–83.7)	0.005
Chemoradiotherapy group	113/543	Reference	78.6 (75.4–81.8)	—

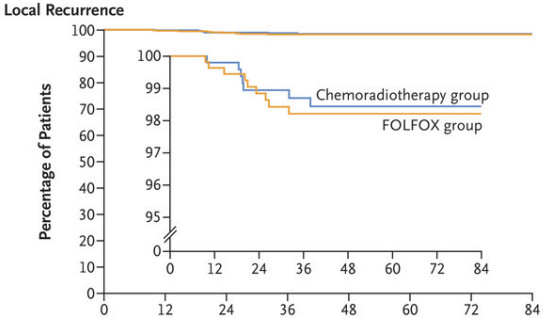
C Overall Survival



No. at Risk								
FOLFOX group	585	565	551	531	429	287	212	120
Chemoradiotherapy group	543	527	513	486	380	273	182	107

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate
			percent
FOLFOX group	74/585	1.04 (0.74–1.44)	89.5 (87.0–92.2)
Chemoradiotherapy group	67/543	Reference	90.2 (87.6–92.9)

D Freedom from Local Recurrence



No. at Risk								
FOLFOX group	585	542	483	438	339	195	95	39
Chemoradiotherapy group	543	499	455	389	289	175	78	36

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate
			percent
FOLFOX group	9/585	1.18 (0.44–3.16)	98.2 (97.1–99.4)
Chemoradiotherapy group	7/543	Reference	98.4 (97.3–99.6)

The Janus Rectal Cancer Study: A Randomized Phase II Trial

NCT05610163

A022104 → An Alliance, NRG & SWOG Study

N=113