Total Neoadjuvant Therapy for pMMR Locally Advanced Rectal Cancer

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South Florida GI Cancer Symposium

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Outline

- Anatomy
- Historical trials
- Early data in TNT for rectal cancer
- Recent advances in TNT for rectal cancer

Rectal Cancer - Anatomy

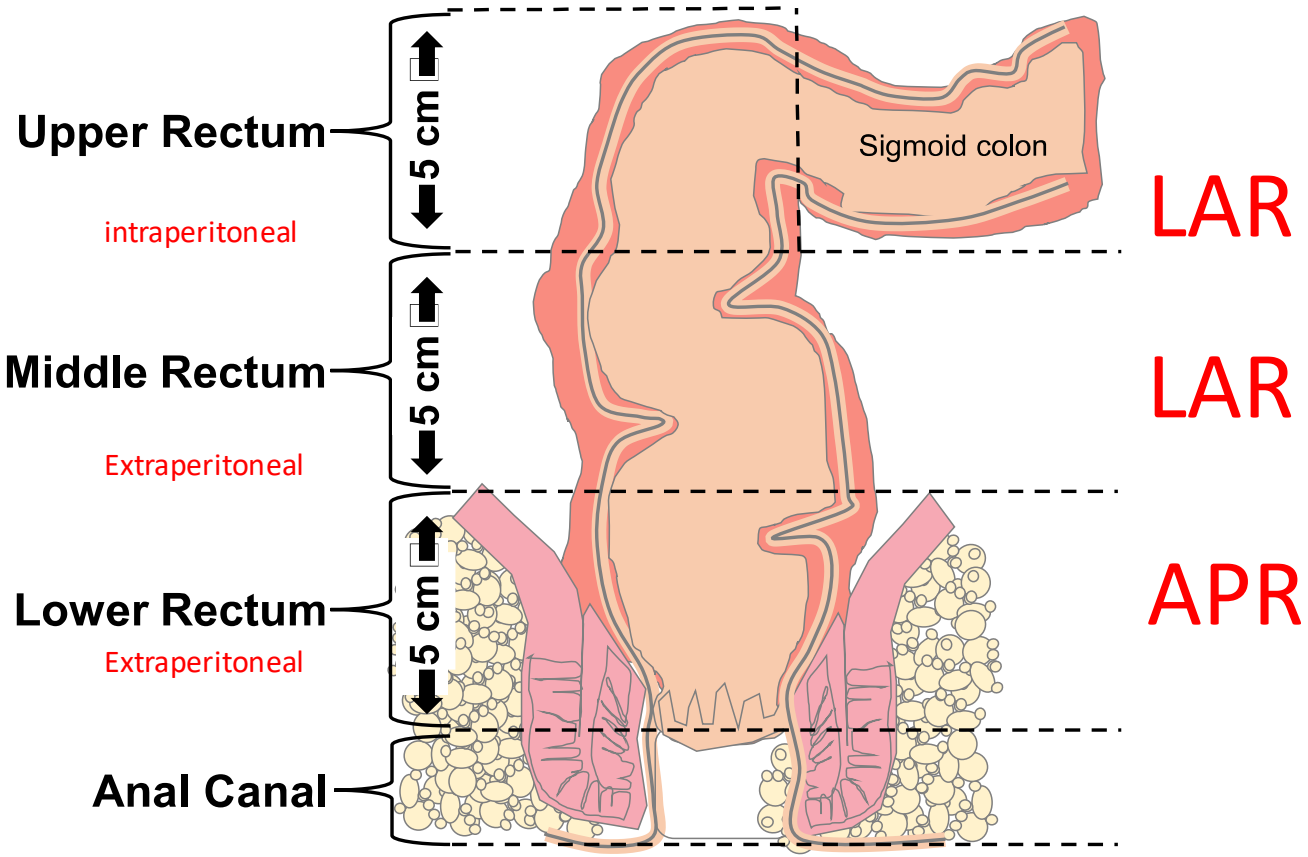


Fig. 2. The rectum is divided into 3 parts: lower, middle, and upper.

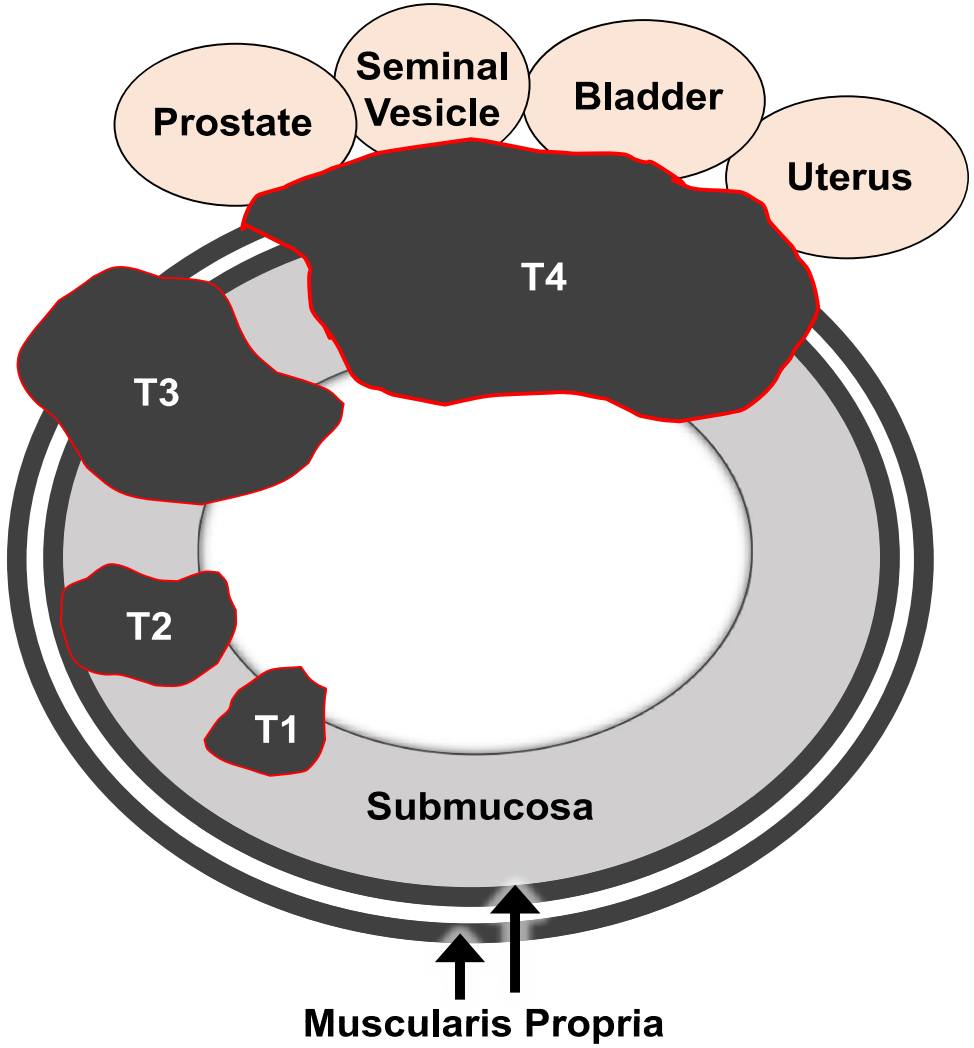


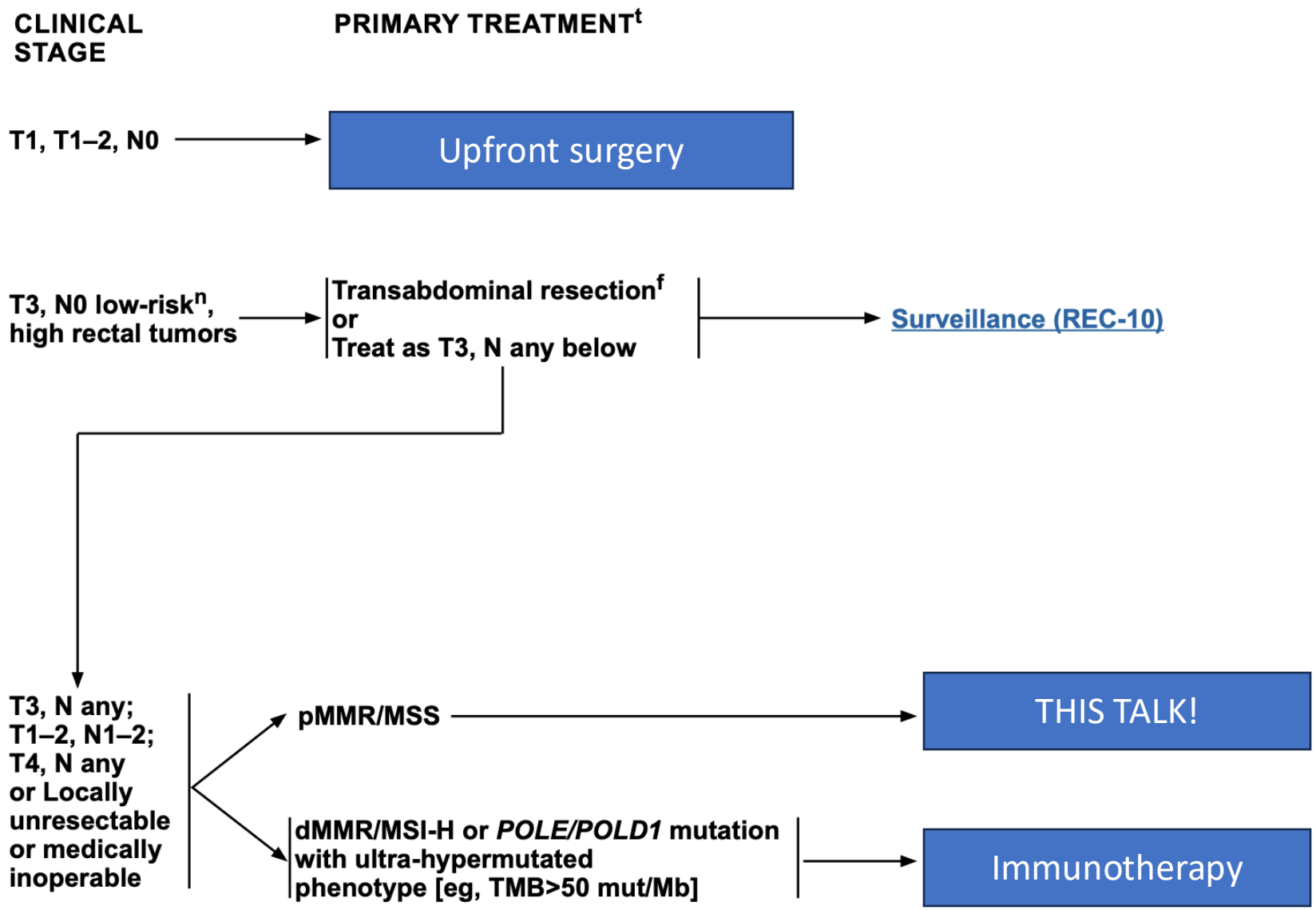
Fig. 3. Cartoon of tumor staging in rectal cancer.

Seminars in Oncology, 2020-02-01, Volume 47, Issue 1, Pages 85-92

American Joint Committee on Cancer (AJCC)
TNM Staging System for Rectal Cancer 8th ed., 2017

Table 2. **Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c



TME = Total Mesorectal Excision

- TME refers to the excision of the rectum and the tumor en bloc ***with its mesenteric blood and lymphatic supply*** (i.e.: mesenteric rectum or mesorectum along with its envelope, the mesenteric fascia)
- Complete resection of the tumor depends on noninvolvement of the mesorectal fascia.
- If the mesorectal fascia status is positive, downstaging of the tumor to facilitate complete removal is required

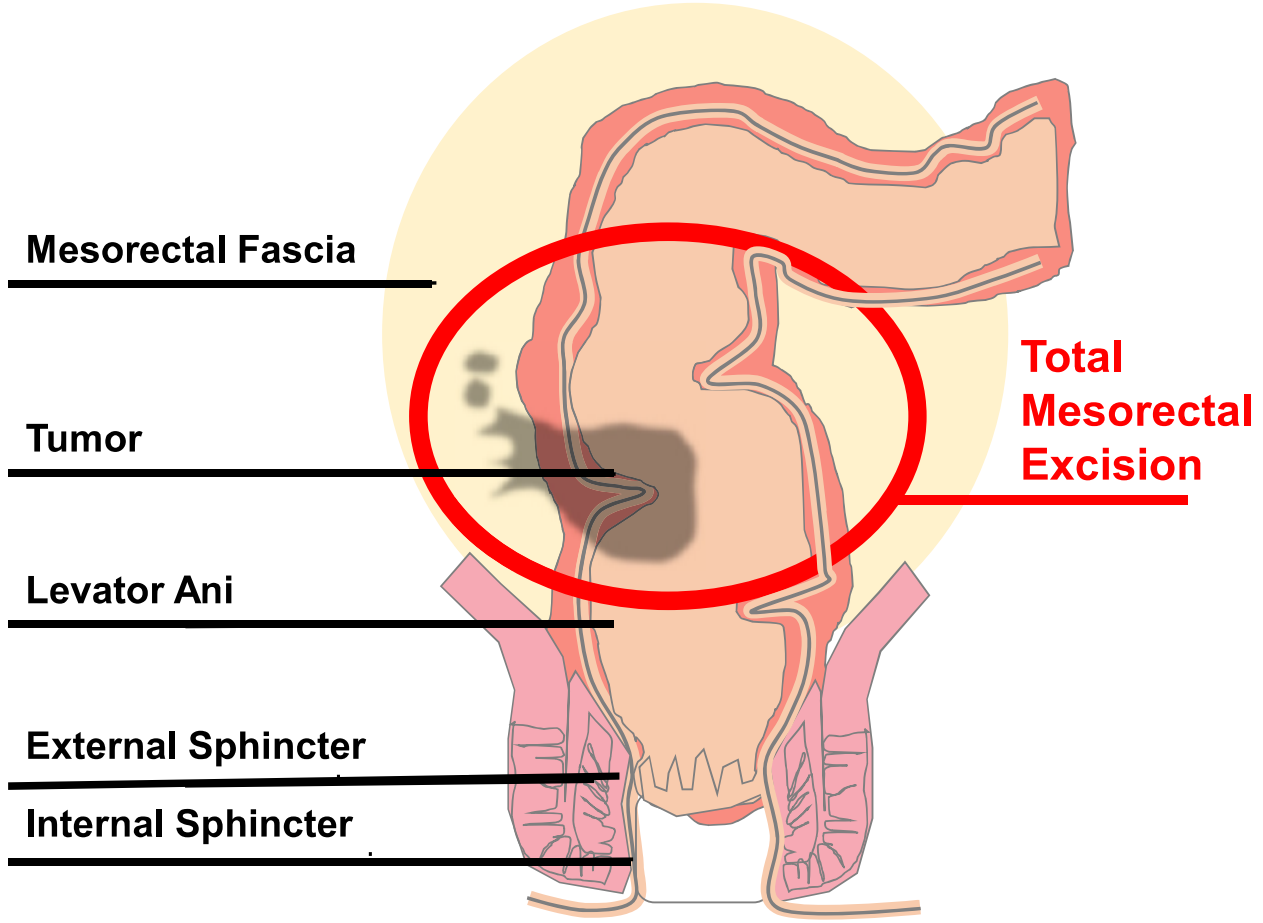
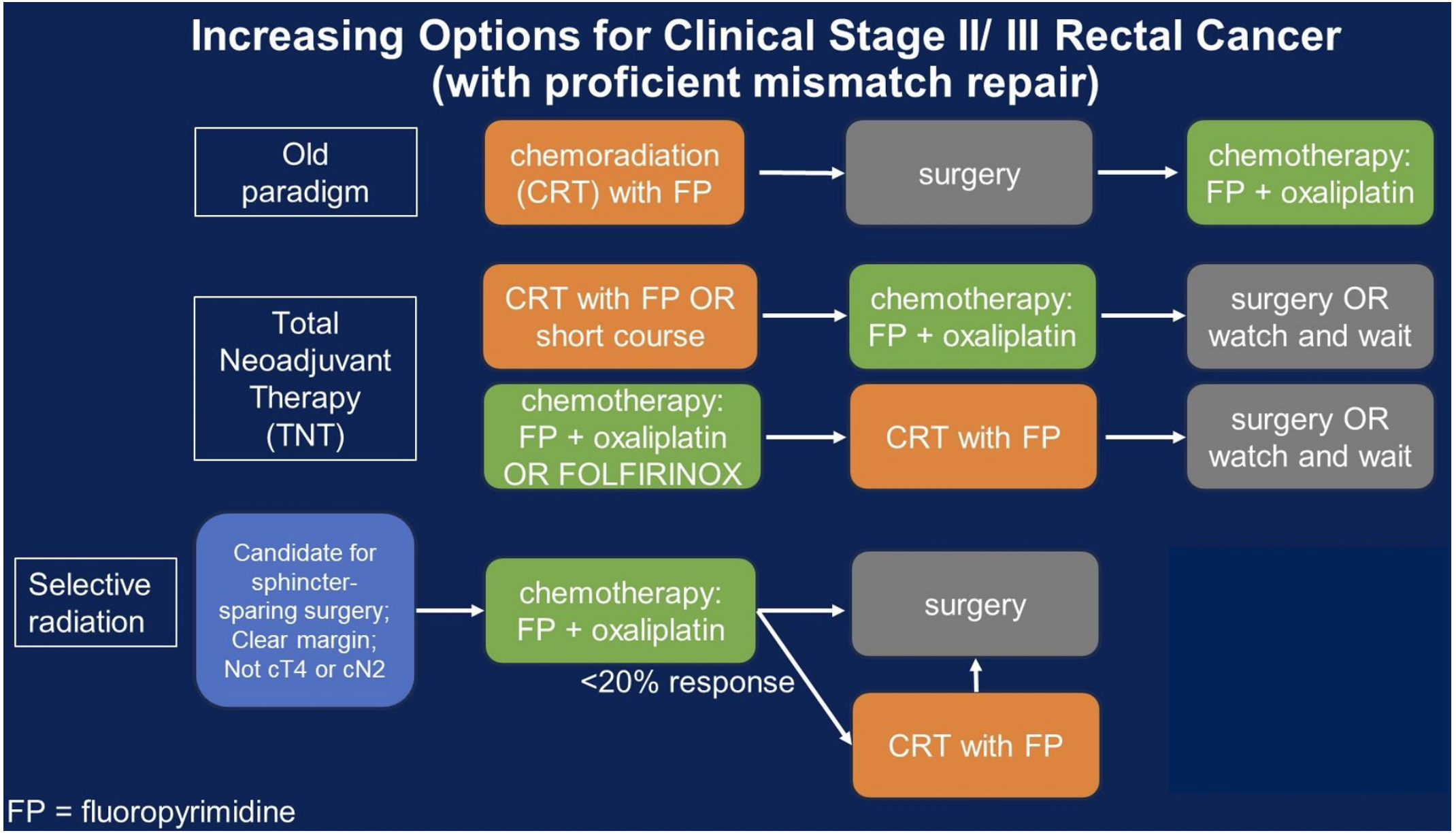


Fig. 1. Total mesorectal excision is the standard of care surgical procedure for rectal cancer that completely removes the rectum, surrounding mesorectal fat, perirectal lymph nodes and the thin sheath called the mesorectal fascia (MRF).

Seminars in Oncology, 2020-02-01, Volume 47, Issue 1, Pages 85-92



Slide: ASCO GI 2024, Dr. Krishnamurthi

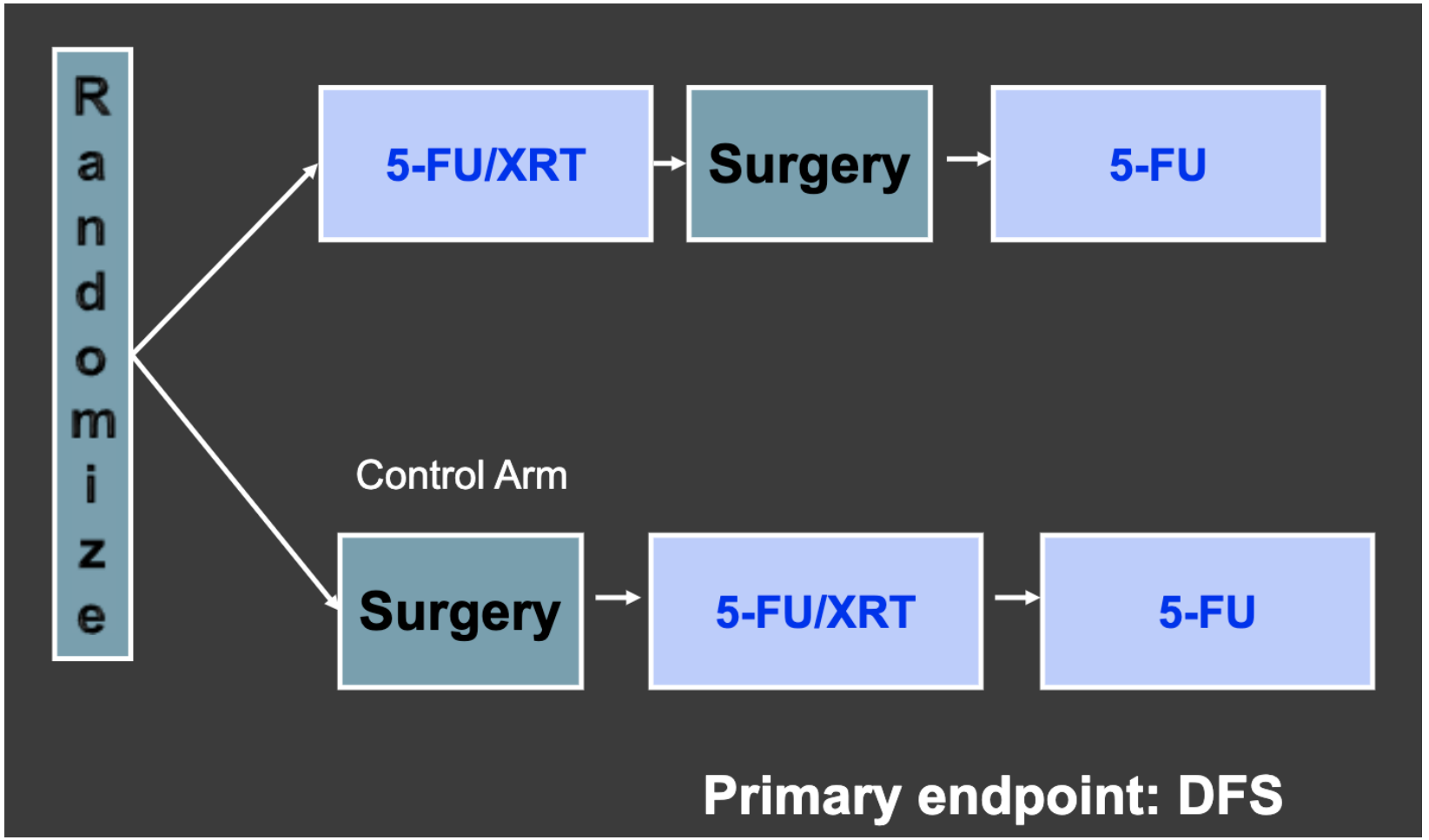
Pre-operative v post-operative RT: German Rectal Cancer Study CAO/ARO/AIO-94

Inclusion criteria:

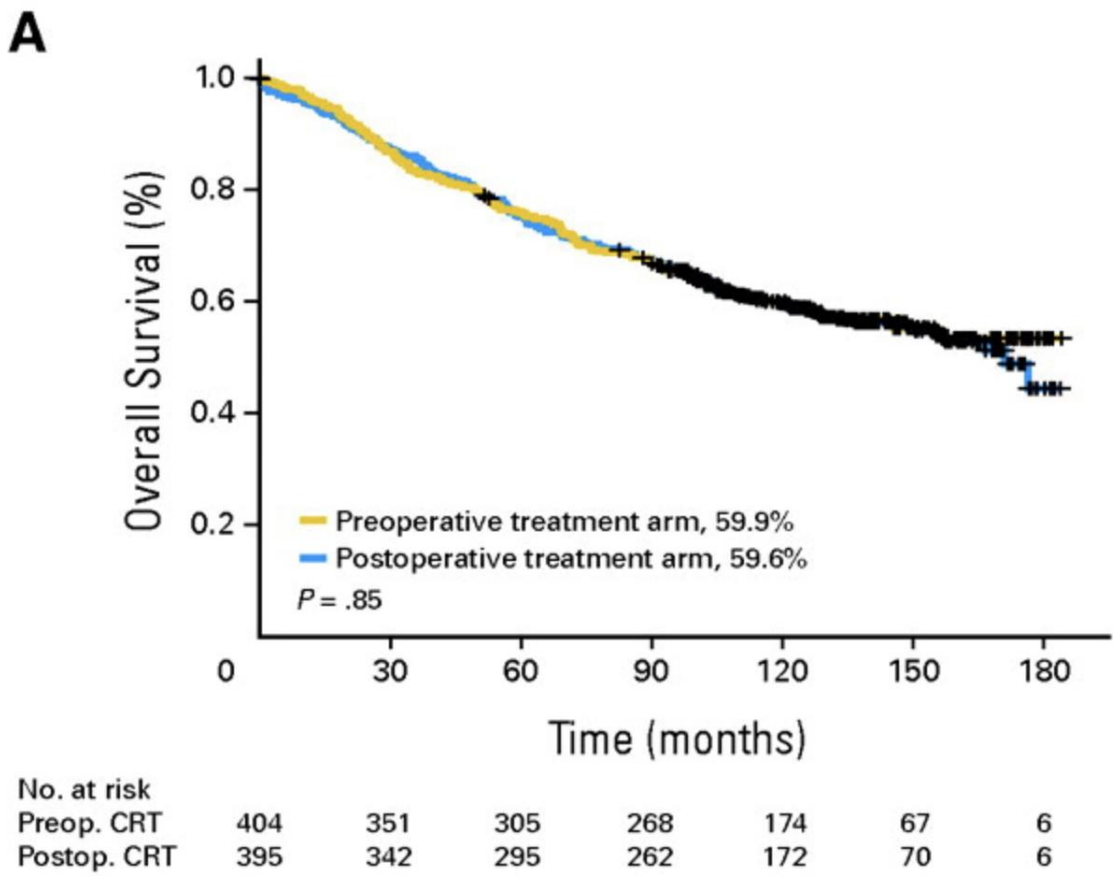
- 823 patients with cT3-4 or N+ rectal cancer
- 18-75 yrs old
- Feb 1995 - July 2002

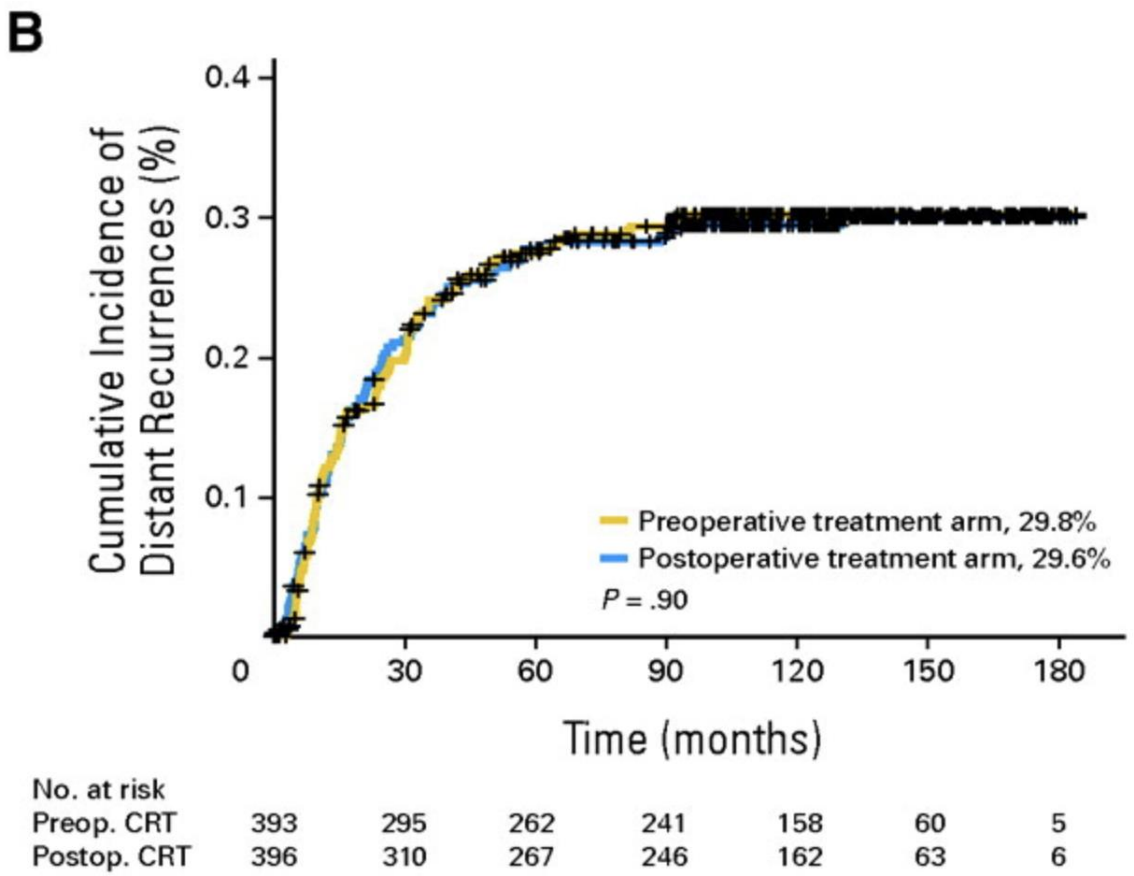
Methods:

- RT = 50.4 Gy in 28 fx with concurrent 5-FU
- TME 4-6 weeks after completion of CRT
- Adjuvant chemo (4C 5-FU) started 4 weeks after TME or CRT



CAO/ARO/AIO-94: Pre-operative v post-operative RT

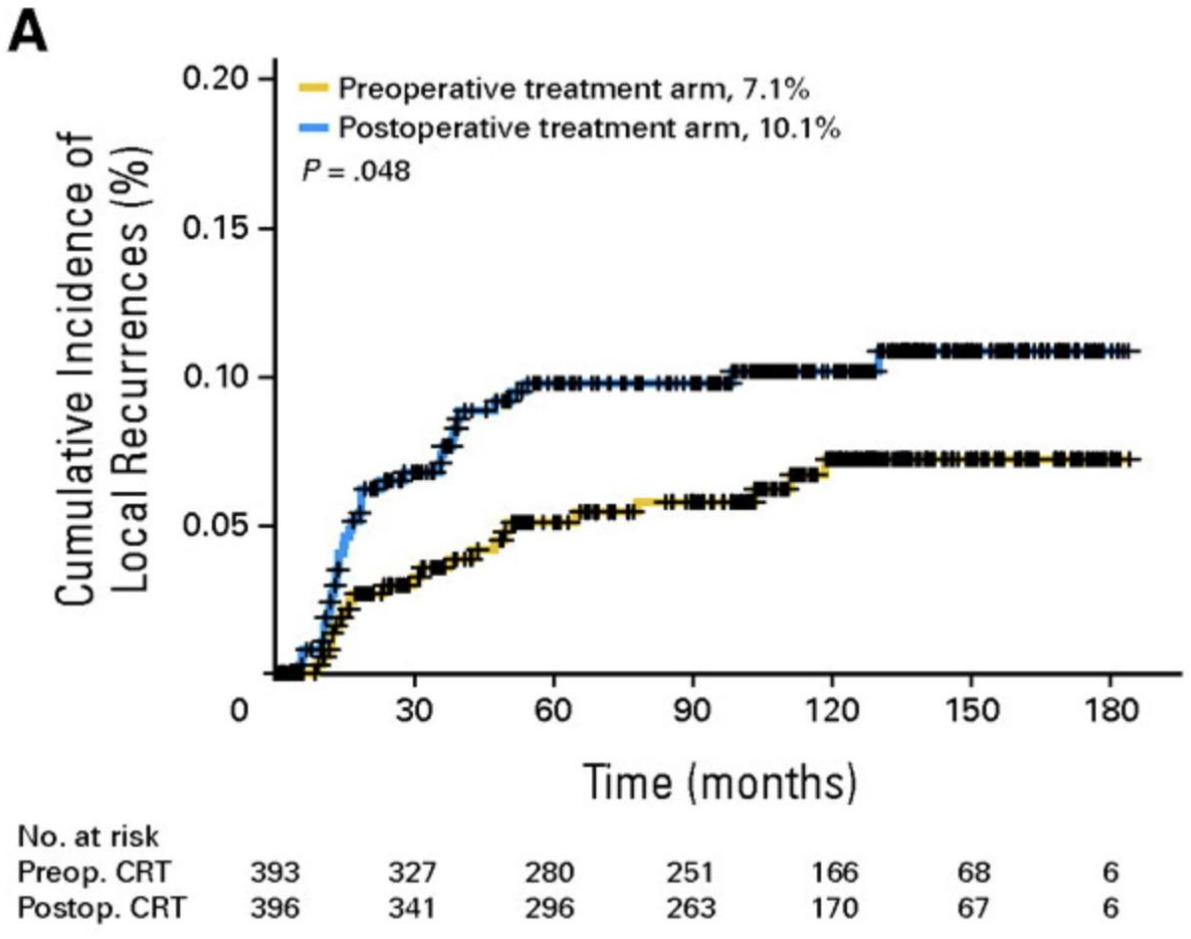




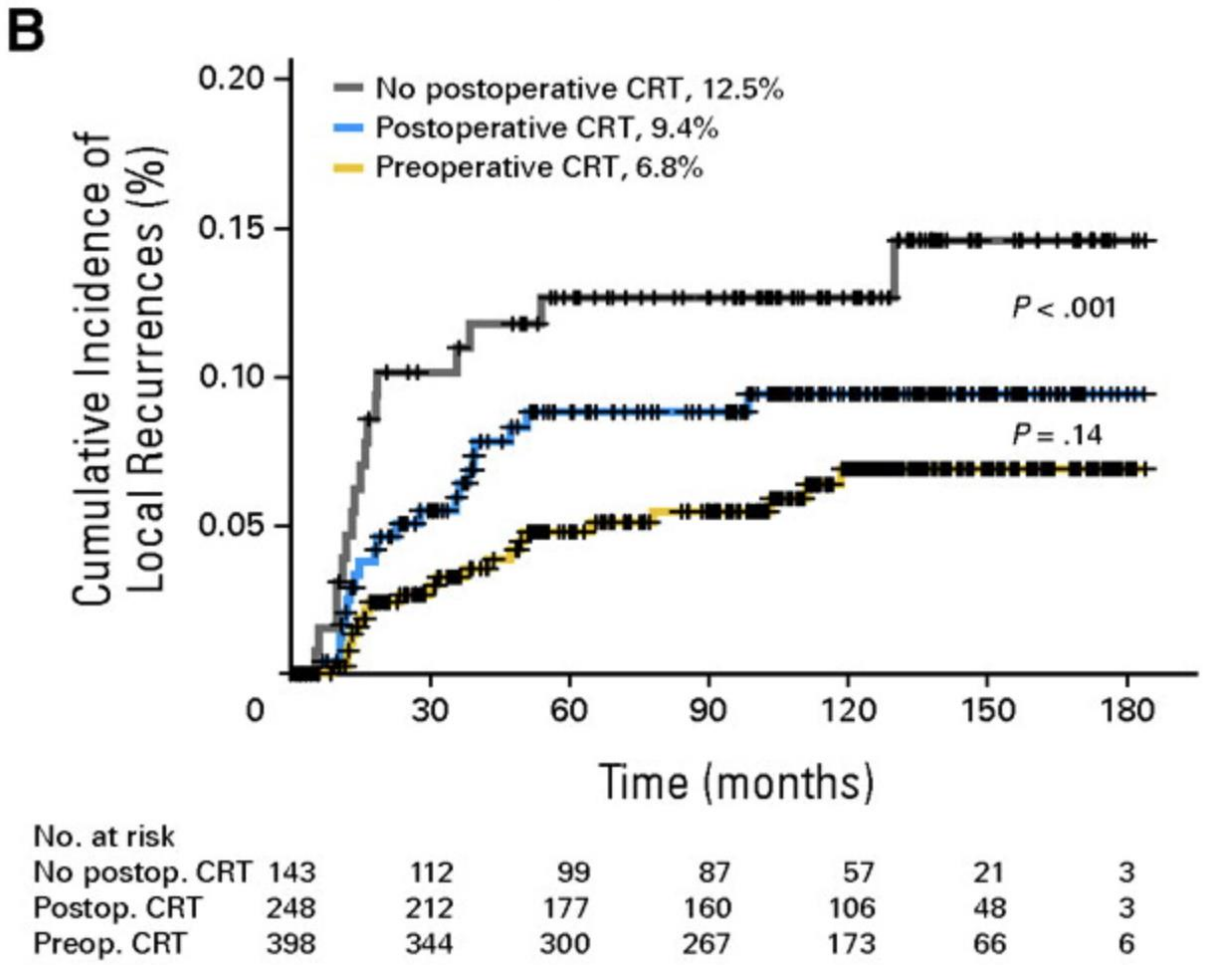
Journal of clinical oncology 2012
Volume 30, Issue 16, p. 1926

CAO/ARO/AIO-94: Pre-operative v post-operative RT

Intention to treat



By treatment received



pCR rate in the pre-operative group was 8%

Journal of clinical oncology 2012
Volume 30, Issue 16, p. 1926

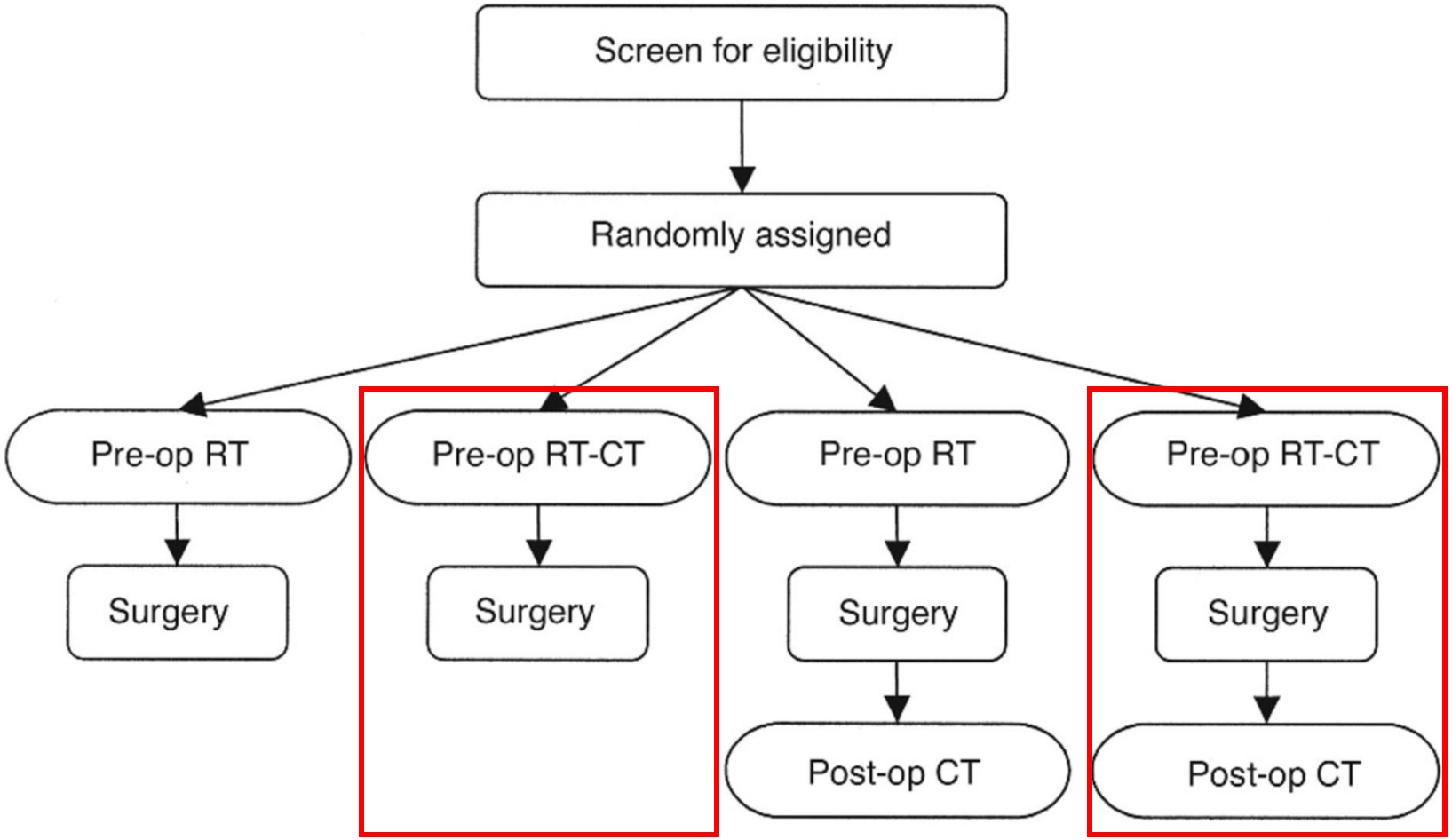
Role of chemotherapy? EORTIC 22921

Inclusion criteria:

- 1011 patients with T3-4, Nx, M0 rectal ca
- Age < 80 yrs
- April 1993 - March 2003

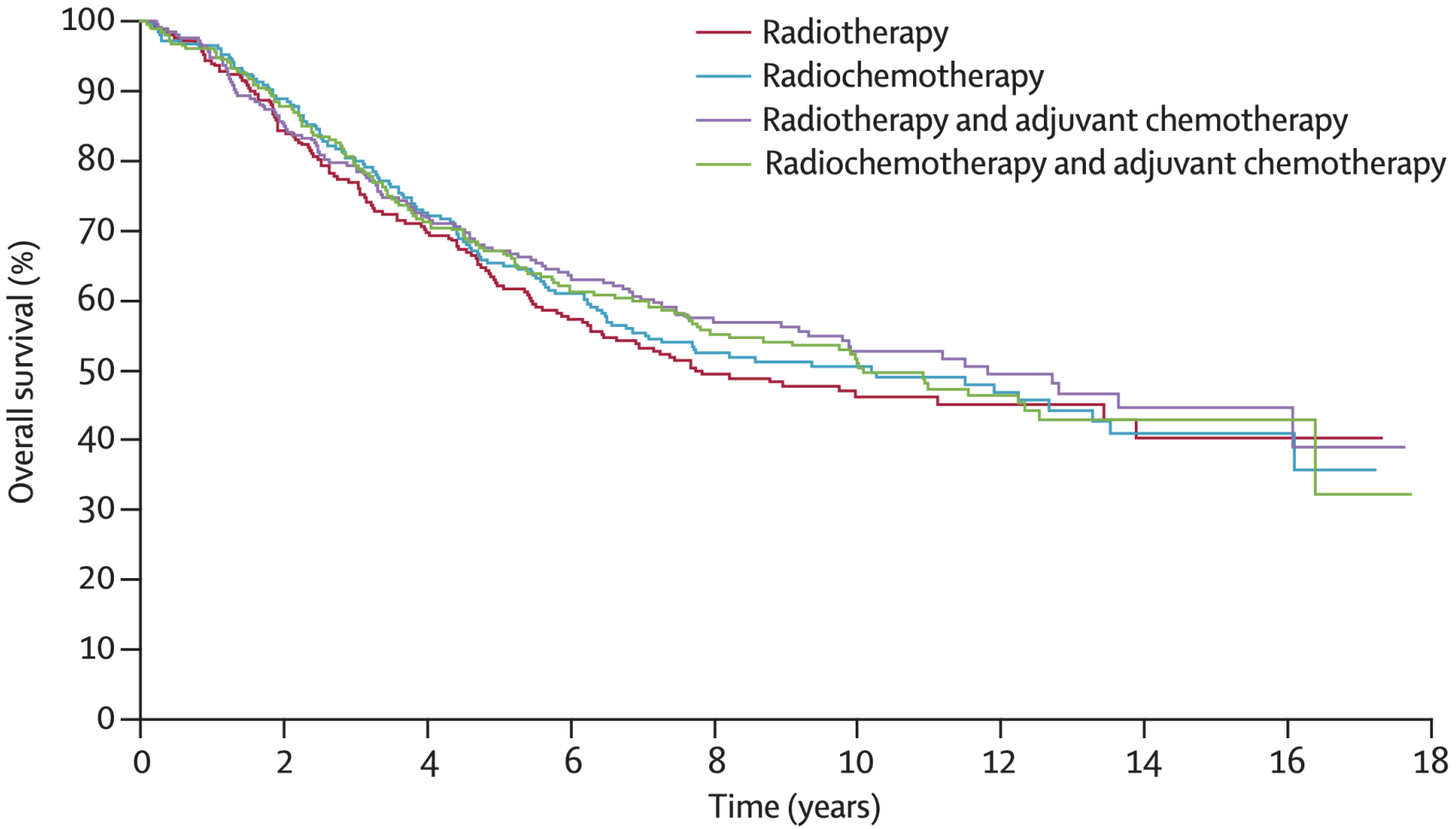
Methods:

- RT with 45 Gy in 25 fractions over 5
- Concurrent chemotherapy with 5FU during week 1 and 5
- Surgery 3-10 weeks after the end of RT.
- Adjuvant chemotherapy arms: 5FU/LV x4 cycles



The Lancet Oncology
Volume 15, Issue 2, February 2014, Pages 184-190

EORTIC 22921



	Surveillance	Adjuvant chemotherapy	Pre-op RT	Pre-op CRT
10-year OS	48·4% (43·6–53·0)	51·8% (95% CI 47·0–56·4)	49·4% (95% CI 44·6–54·1)	50·7% (45·9–55·2)
	HR 0·91 (95% CI 0·77–1·09) p=0·32		HR 0·99 (95% CI 0·83–1·18) p=0·91	

The Lancet Oncology
Volume 15, Issue 2, February 2014, Pages 184-190

EORTIC 22921

	No adjuvant chemotherapy		Adjuvant chemotherapy	
	Radiotherapy (N=252)	Chemoradiotherapy (N=253)	Radiotherapy (N=253)	Chemoradiotherapy (N=253)
Local relapse				
At 5 years	21·9% (16·7–27·1)	10·9% (7·0–14·8)	13·7% (9·4–17·9)	10·7% (6·914·5)
At 10 years	22·4% (17·1–27·6)	11·8% (7·8–15·8)	14·5% (10·1–18·9)	11·7% (7·7–15·6)
Distant metastases				
At 5 years	36·9% (30·9–42·9)	32·1% (26·3–37·9)	33·5% (27·6–39·3)	29·8% (24·1–35·4)
At 10 years	39·6% (33·5–45·8)	33·4% (27·5–39·3)	35·9% (29·9–41·9)	34·1% (28·2–40·1)

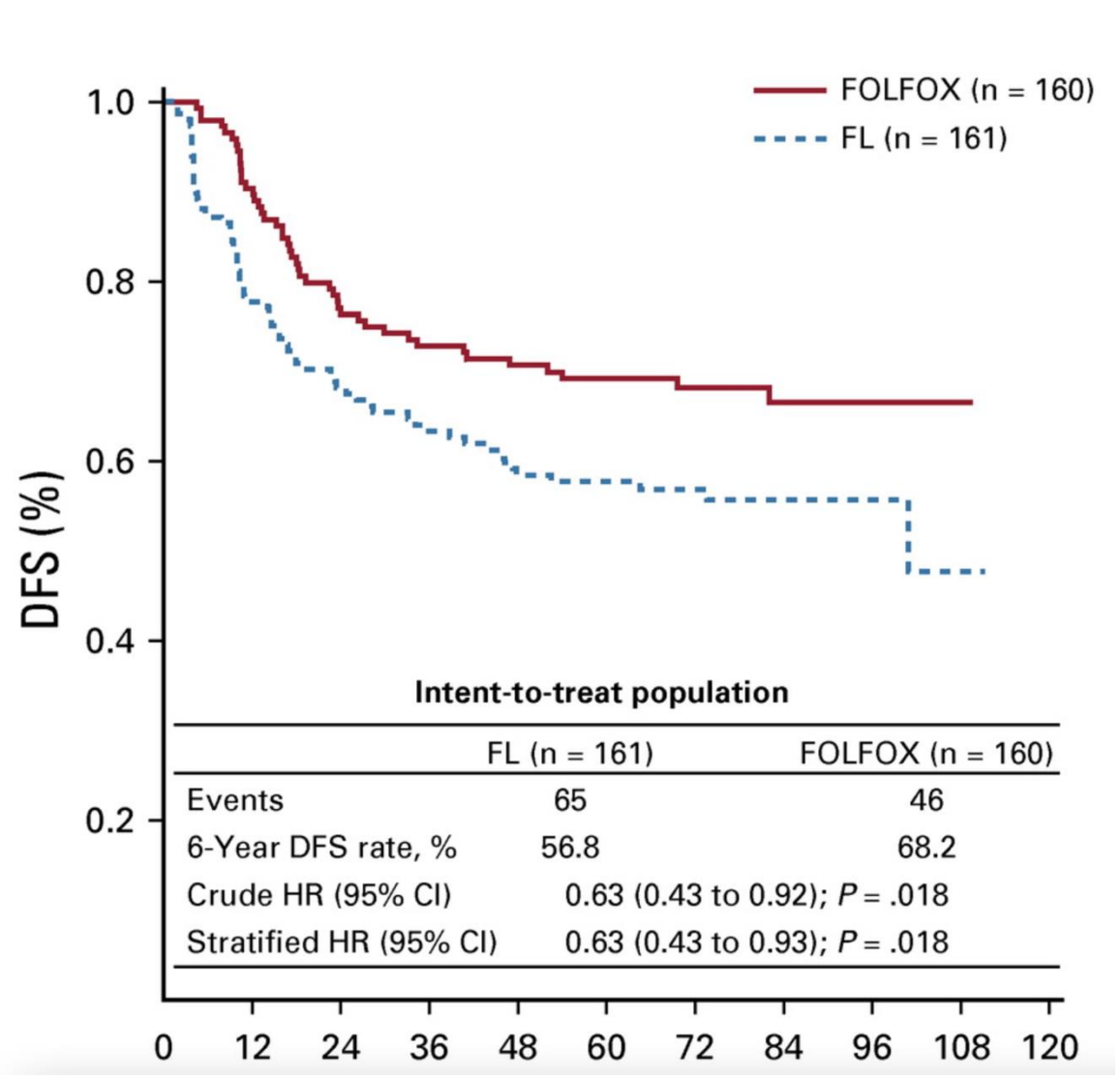
Data are % (95% CI).

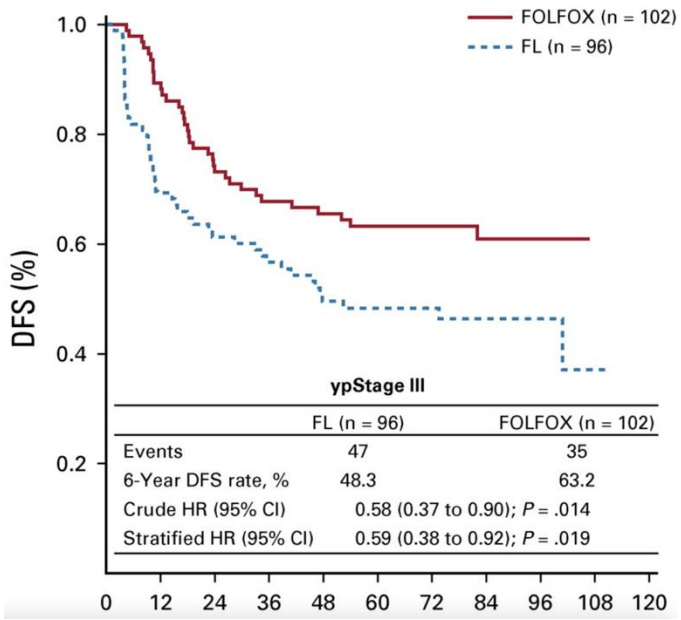
***Table 2*: Cumulative incidence of local relapse and distant metastases**

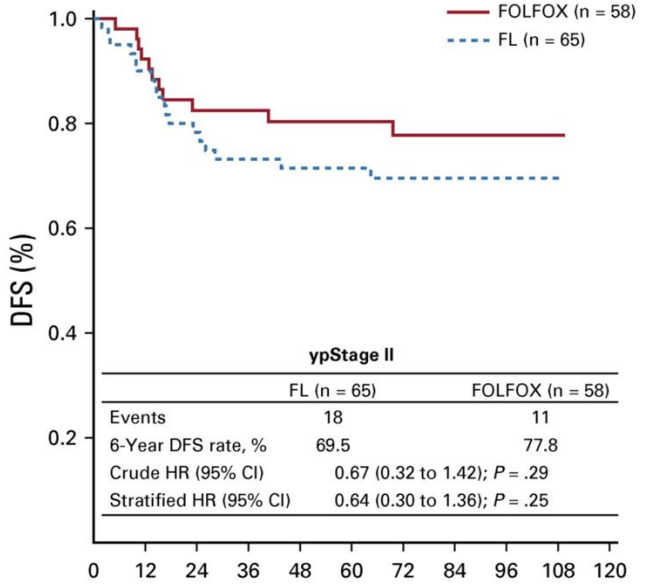
What is the role of adjuvant chemotherapy?

EORTC 22921	1011 patients who received neoadjuvant chemoRT with 5FU or RT, patients randomized to 4 cycles of adjuvant 5-FU or observation	No difference in 10-year OS (51.8% vs 48.4%; *P* = .32)
I-CNR-RT	655 patients who underwent chemoRT with 5FU, randomized to 6 cycles of adjuvant 5-FU or observation	No difference in 5-year OS (70% vs 69%; *P*=.772) or distant failure (20% in both arms)
German CAO/ARO/AIO-04 trial	1,236 patients randomized to either standard chemoRT with 5-FU followed by adjuvant 5-FU, or to chemoRT with 5-FU and oxaliplatin followed by adjuvant 5-FU and oxaliplatin	3-year DFS 76% vs 71%; ***P* = .03** 3-year OS 88·7% vs 88·0% 3-year local recurrence 2.9% vs 4.6% 3-year distant recurrence 18.5% vs 22.4%
ADORE trial	Randomized 321 patients to either adjuvant 5-FU or FOLFOX	3-year DFS rate improved in oxaliplatin arm (72% vs 63%; ***P* = .047**) 6-year OS 78.1% vs 76.4% (*P* = 0.21).
PETACC-6	Randomized 1094 patients to chemoRT with capecitabine and adjuvant capecitabine or to chemoRT with CAPEOX and adjuvant CAPEOX	3-year DFS difference was not observed (76.5% vs 75.4%; *P* = .744) No difference in 3- and 7- year OS

ADORE trial: adjuvant oxaliplatin in Rectal Ca







Journal of Clinical Oncology
November 20, 2019 , Volume 37 (33), p 3111 – 3123

What about total neoadjuvant therapy (TNT)?

Earlier introduction of chemotherapy is hypothesized to improve:

(1) chemotherapy delivery overall (without compromising SCRT, CRT or surgical morbidity)

(2) tumor regression and downstaging

(3) R0 resection rates

(4) sphincter and rectal preservation rates

(5) local and distant relapse rates

(6) disease-free and OS

PRODIGE 23 trial: study design

NCT 01804790; EudraCT 2011-004406-25

35 centers in France
June 2012 - June 2017
461 patients

MRI staging
Randomisation: 1/1
Stratification:
- center
- cT3 vs cT4
- cN0 vs cN+
- extramural extension (≥5 vs. <5 mm)
- tumor location (cm from anal verge)

RANDOMIZE

CRT arm

Radiotherapy 50.4 Gy /5wks + capecitabine 1600 mg/m²/j 5 days/7 → 7 weeks → **TME** → mFOLFOX6, 12 cycles or capecitabine*, 8 cycles (6 months)

TNT arm

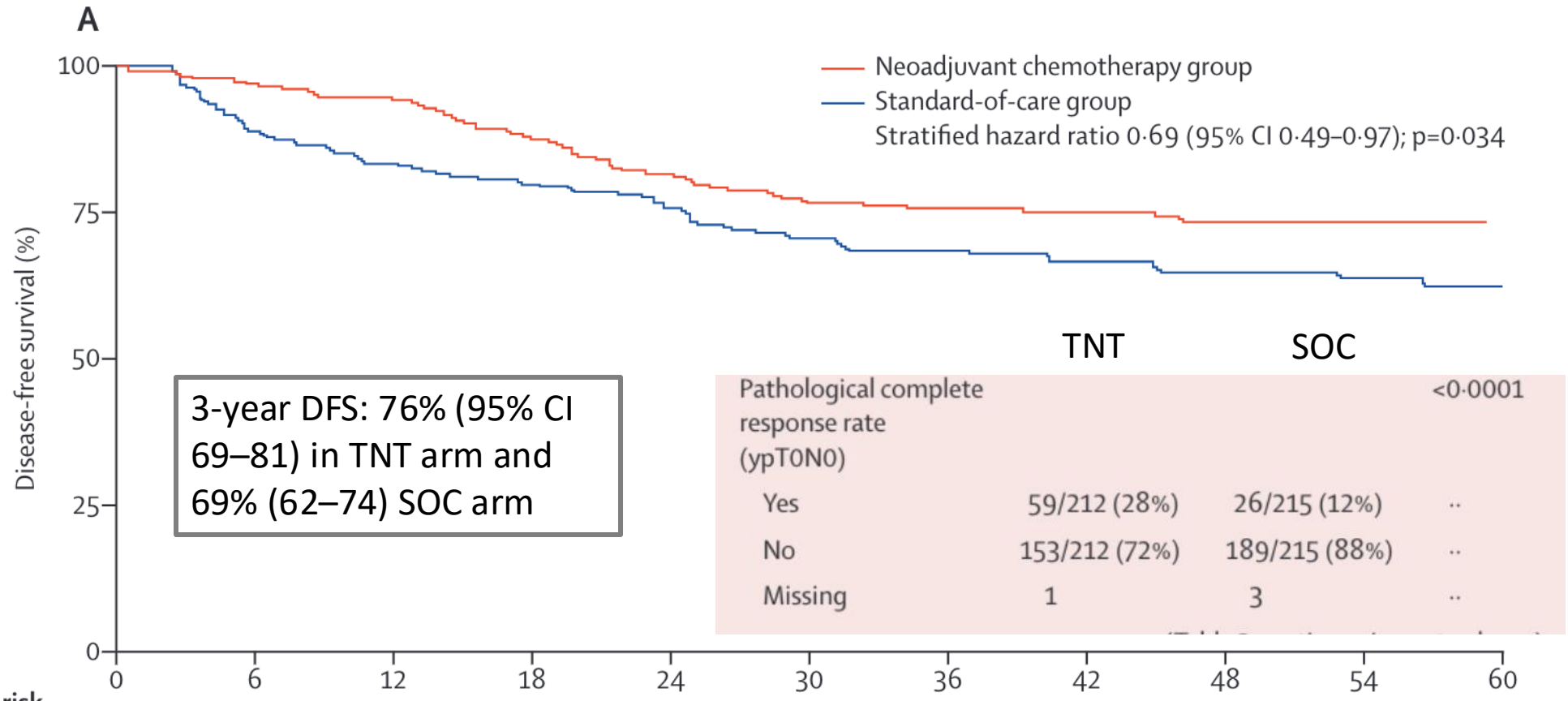
mFOLFIRINOX** 6 cycles, 3 months → Radiotherapy 50.4 Gy /5 wks + capecitabine 1600 mg/m²/j 5 days/7 → 7 weeks → **TME** → mFOLFOX6, 6 cycles or capecitabine*, 4 cycles (3 months)

**mFOLFIRINOX: At d1, Oxaliplatin 85 mg/m², Leucovorin 400 mg/m², Irinotecan 180 mg/m²; Fluorouracil continuous IV infusion 2.4 g/m² over 46 hours (no bolus Fluorouracil)

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

The Lancet Oncology
Volume 22, Issue 5, May 2021, Pages 702-715

PRODIGE 23: TNT vs SOC



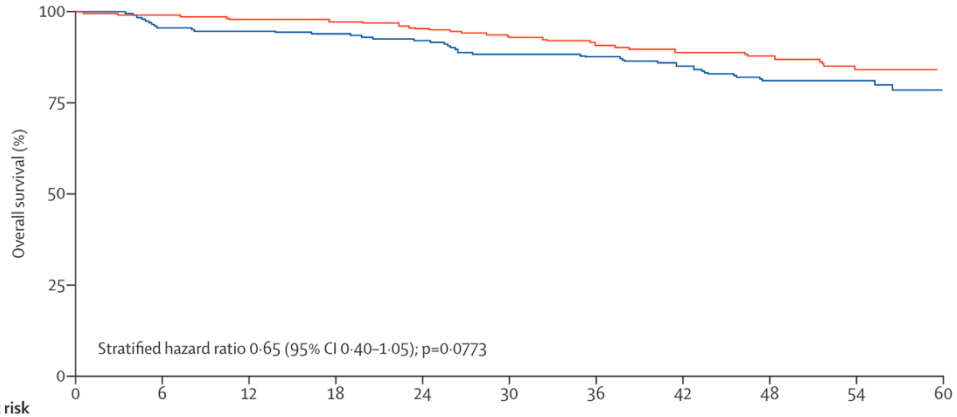
3-year DFS: 76% (95% CI 69–81) in TNT arm and 69% (62–74) SOC arm

	TNT	SOC	
Pathological complete response rate (ypT0N0)			<0·0001
Yes	59/212 (28%)	26/215 (12%)	..
No	153/212 (72%)	189/215 (88%)	..
Missing	1	3	..

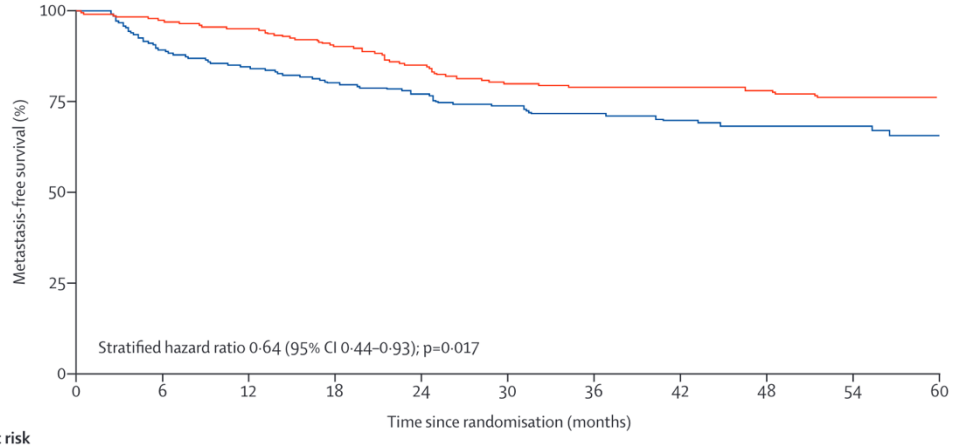
Number at risk (number censored)											
Neoadjuvant chemotherapy group	231 (0)	217 (7)	210 (8)	194 (9)	176 (14)	150 (30)	126 (52)	104 (73)	80 (95)	62 (113)	51 (124)
Standard-of-care group	230 (0)	201 (3)	188 (4)	177 (7)	167 (8)	146 (18)	117 (43)	91 (66)	65 (90)	55 (99)	40 (113)

The Lancet Oncology
Volume 22, Issue 5, May 2021, Pages 702-715

PRODIGE 23: TNT vs SOC



Number at risk (number censored)											
Neoadjuvant chemotherapy group	231 (0)	221 (8)	217 (9)	215 (10)	205 (16)	180 (36)	151 (61)	124 (85)	99 (109)	73 (131)	54 (150)
Standard-of-care group	230 (0)	215 (5)	212 (6)	207 (9)	201 (11)	182 (22)	151 (52)	117 (82)	82 (112)	71 (123)	51 (141)

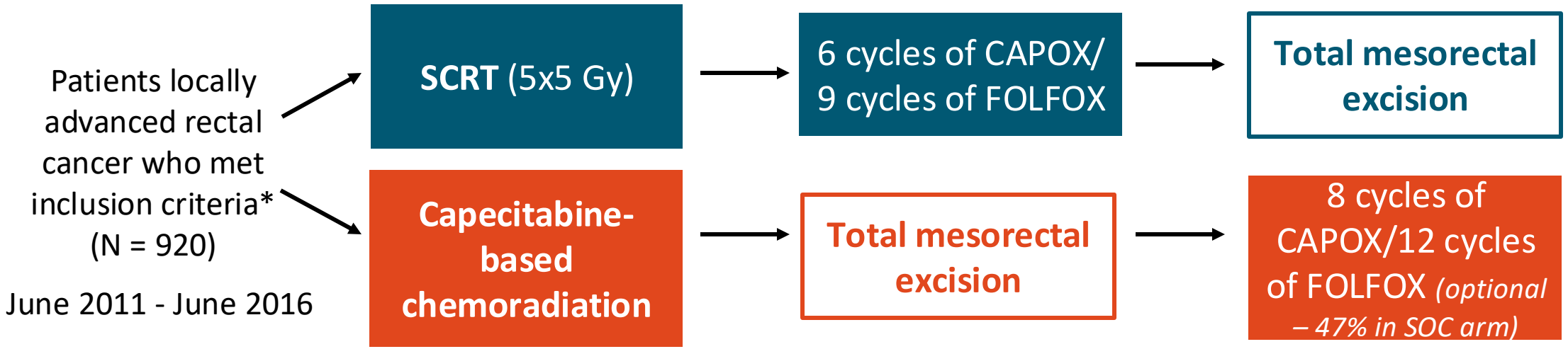


Number at risk (number censored)											
Neoadjuvant chemotherapy group	231 (0)	218 (7)	212 (8)	200 (9)	184 (14)	156 (31)	131 (54)	109 (76)	86 (98)	65 (117)	52 (130)
Standard-of-care group	230 (0)	202 (3)	191 (4)	178 (7)	170 (8)	153 (18)	123 (44)	96 (68)	70 (92)	60 (102)	43 (117)

	Neoadjuvant chemotherapy group (n=163)				Standard-of-care group (n=158)				p value
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	
Any adverse event	89/162 (55%)	68 (42%)	5 (3%)	0	38 (24%)	103 (65%)	14 (9%)	3 (2%)*	<0·0001

RAPIDO: Preoperative Short-Course Radiotherapy and Chemotherapy for Locally Advanced Rectal Cancer

- Randomized, international, multicenter phase III trial



*Inclusion criteria: biopsy-proven primary adenocarcinoma of the rectum, 18 years or older, absence of distant metastases, MRI with high-risk features (T4a/b, extramural vascular invasion +N2, mesorectal fascia + enlarged lymph nodes).

- Primary endpoints: disease-related treatment failure
- Secondary endpoints: OS, R0 rate, pCR, toxicity, surgical complications, QoL at 3 yrs

Bahadoer. ASCO 2020. Abstr 4006.

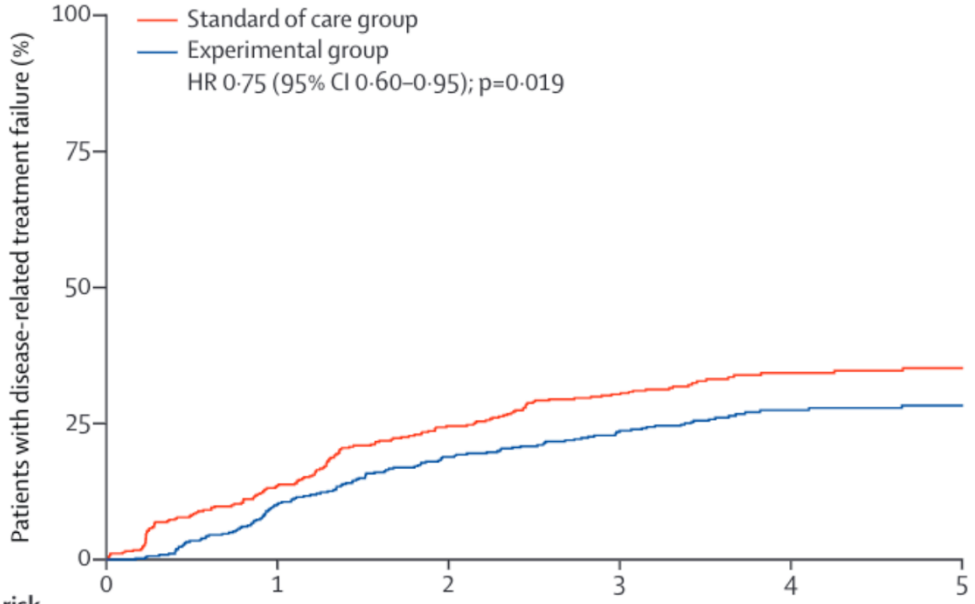
Slide credit: clinicaloptions.com

The Lancet Oncology
Volume 22, Issue 1, January 2021, Pages 29-42

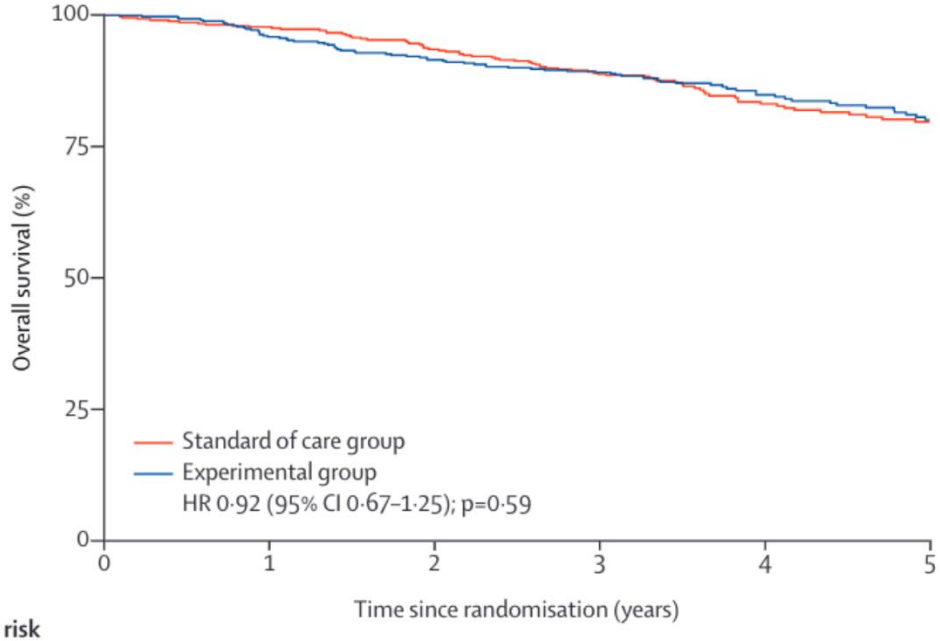
RAPIDO: SCRT and TNT vs SOC

3-year disease-related treatment failure:

- 23·7% (95% CI 19·8–27·6) in the SCRT/TNT
- 30·4% (2 6·1–34·6) in the SOC arm



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	385 (3)	334 (7)	300 (133)	159 (160)
Experimental group	462 (0)	462 (1)	411 (2)	367 (8)	339 (150)	179 (182)



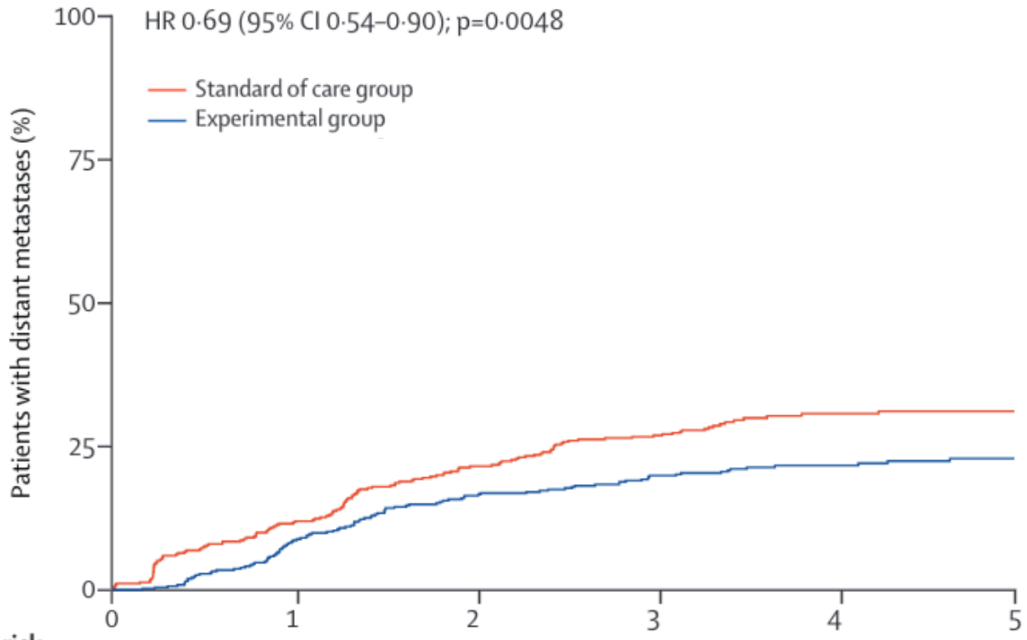
Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	438 (3)	418 (8)	392 (169)	214 (208)
Experimental group	462 (0)	462 (1)	442 (2)	421 (9)	403 (181)	216 (217)

The Lancet Oncology
Volume 22, Issue 1, January 2021, Pages 29-42

RAPIDO: SCRT and TNT vs SOC

3-year cumulative probability of distant metastases:

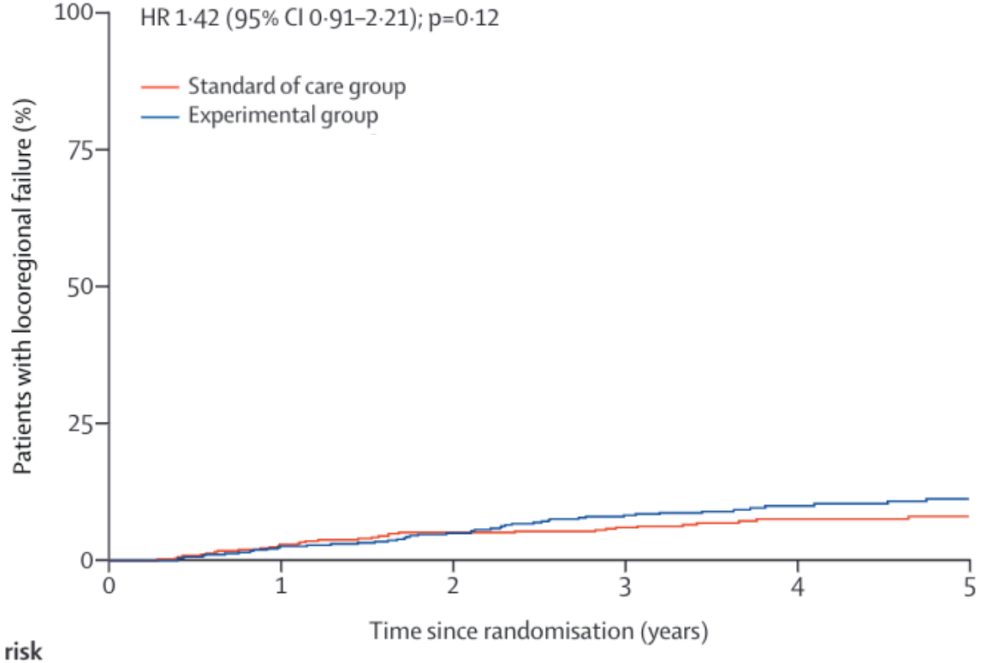
- 20·0% (95% CI 16·4–23·7) in SCRT/TNT arm
- 26·8% (22·7–30·9) in SOC arm



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	390 (3)	343 (7)	311 (138)	164 (166)
Experimental group	462 (0)	462 (1)	414 (2)	372 (9)	349 (156)	189 (188)

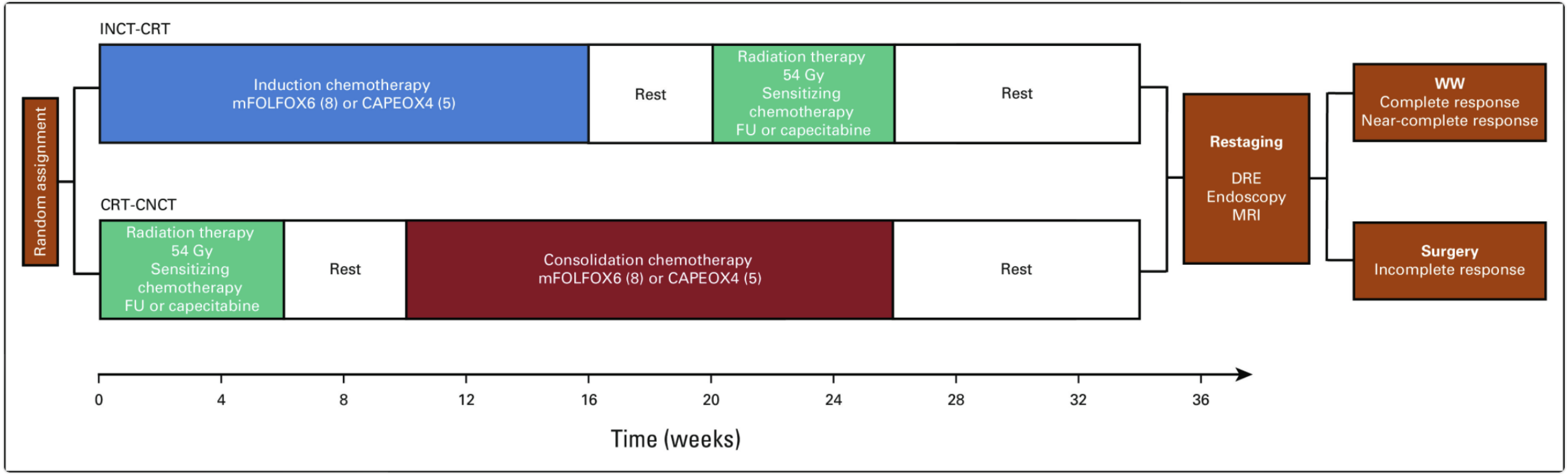
3-year cumulative probability of locoregional failure:

- 8·3% (9 5% CI 5·8–10·8) in the SCRT/TNT arm
- 6·0% (3 ·8–8·2) in the SOC arm



Number at risk (number censored)						
Standard of care group	450 (0)	450 (2)	428 (3)	405 (8)	379 (161)	209 (199)
Experimental group	462 (0)	462 (1)	436 (2)	411 (8)	384 (172)	204 (207)

OPRA trial: Organ Preservation in Rectal Ca

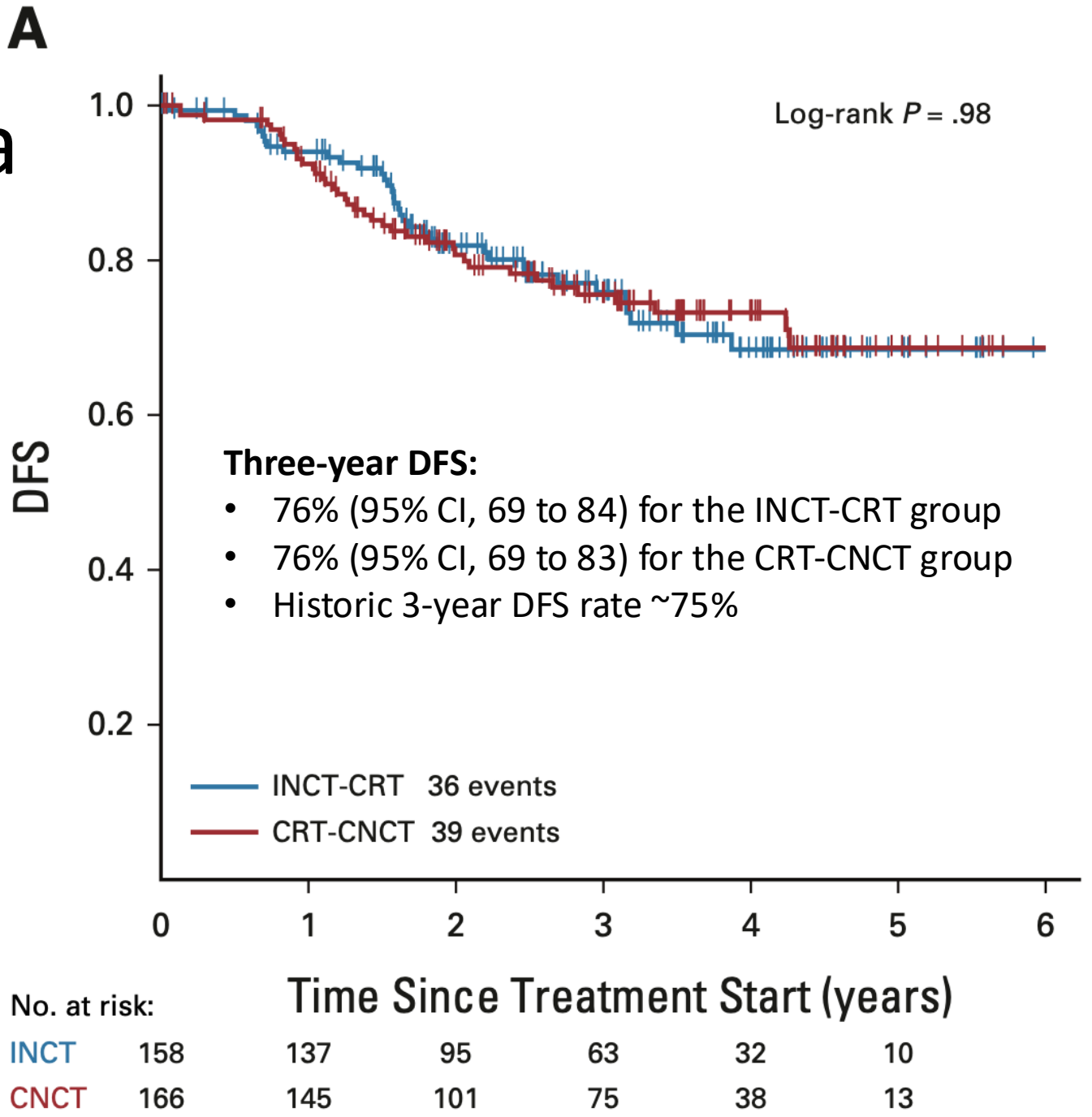


- 324 patients with stage II or III rectal adenocarcinoma
- April 2014 to March 2020
- MSKCC, UCSF, UW, U of Colorado, OHSU, U of Vermont

OPRA trial: Organ Preservation in Rectal Ca

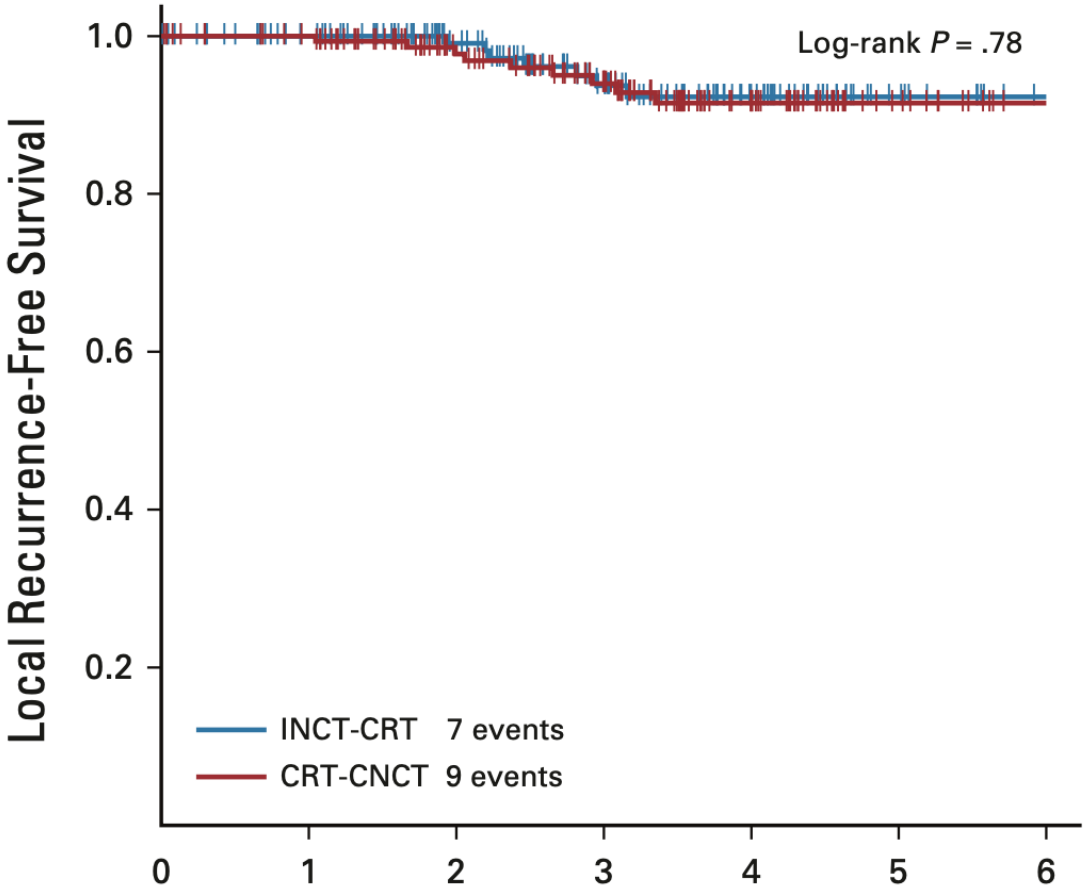
Baseline Characteristics:

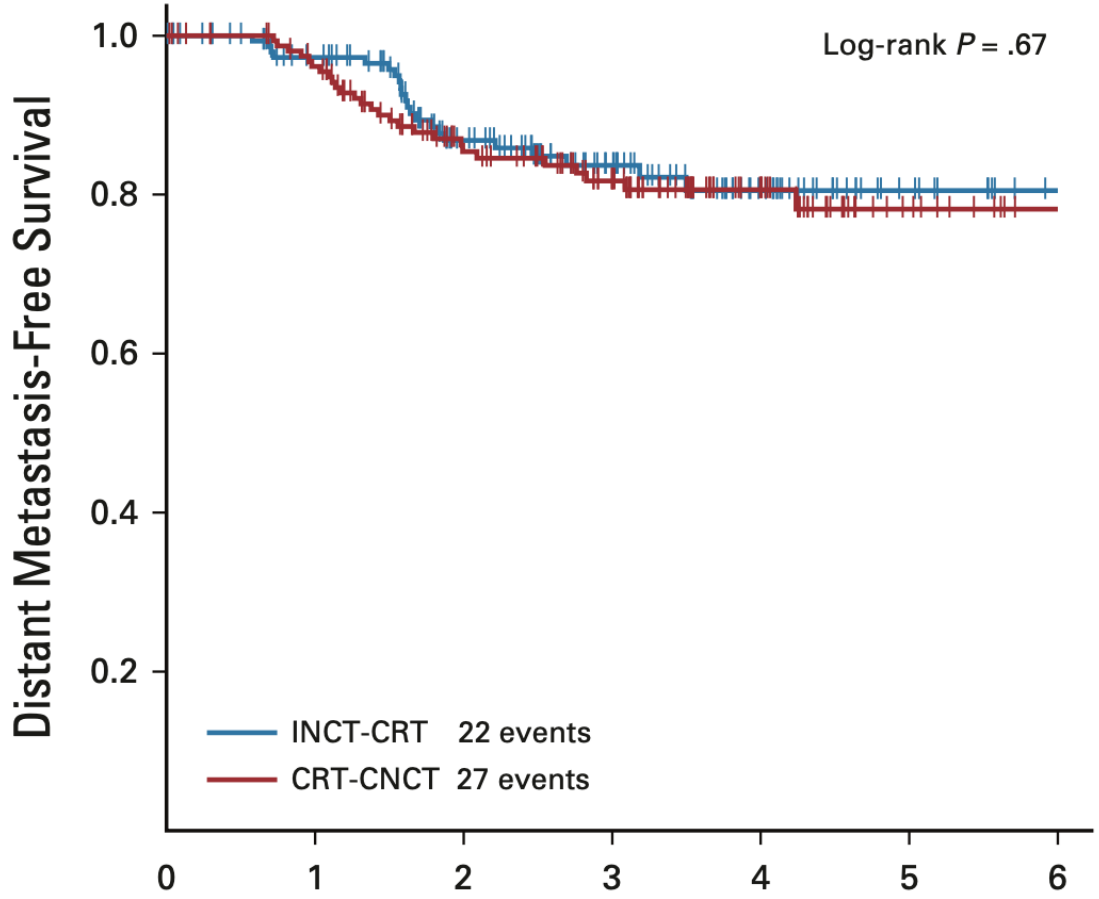
- 37% female
- Age range: 51-67 years
- 90% T3 or higher
- 71% node positive
- Distance from anal verge 3.0-6.5 cm



Journal of Clinical Oncology
February 10, 2024 , Volume 42 (5), p 500 – 506

OPRA trial: organ preservation in rectal ca





No differences were found between groups in local recurrence-free survival or distant metastasis-free survival

Journal of Clinical Oncology
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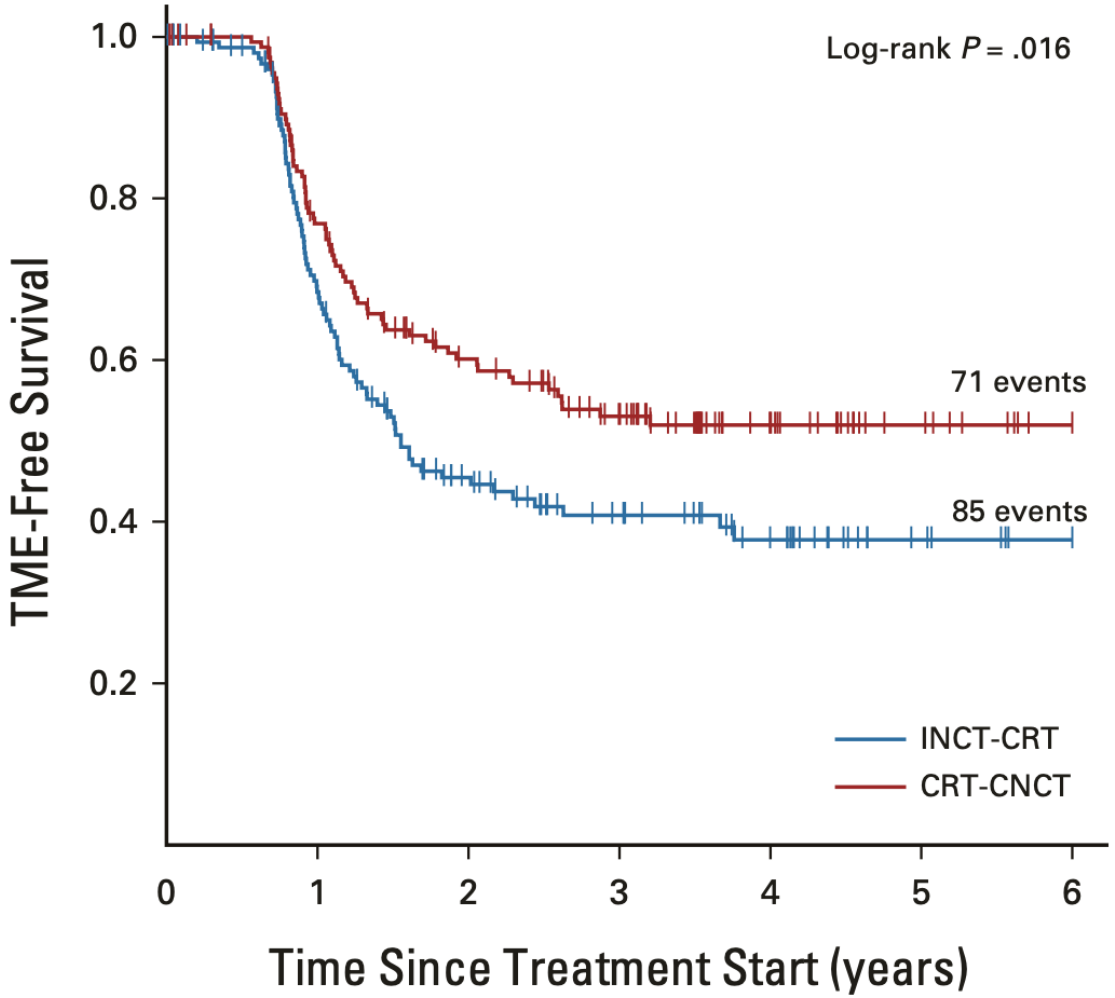
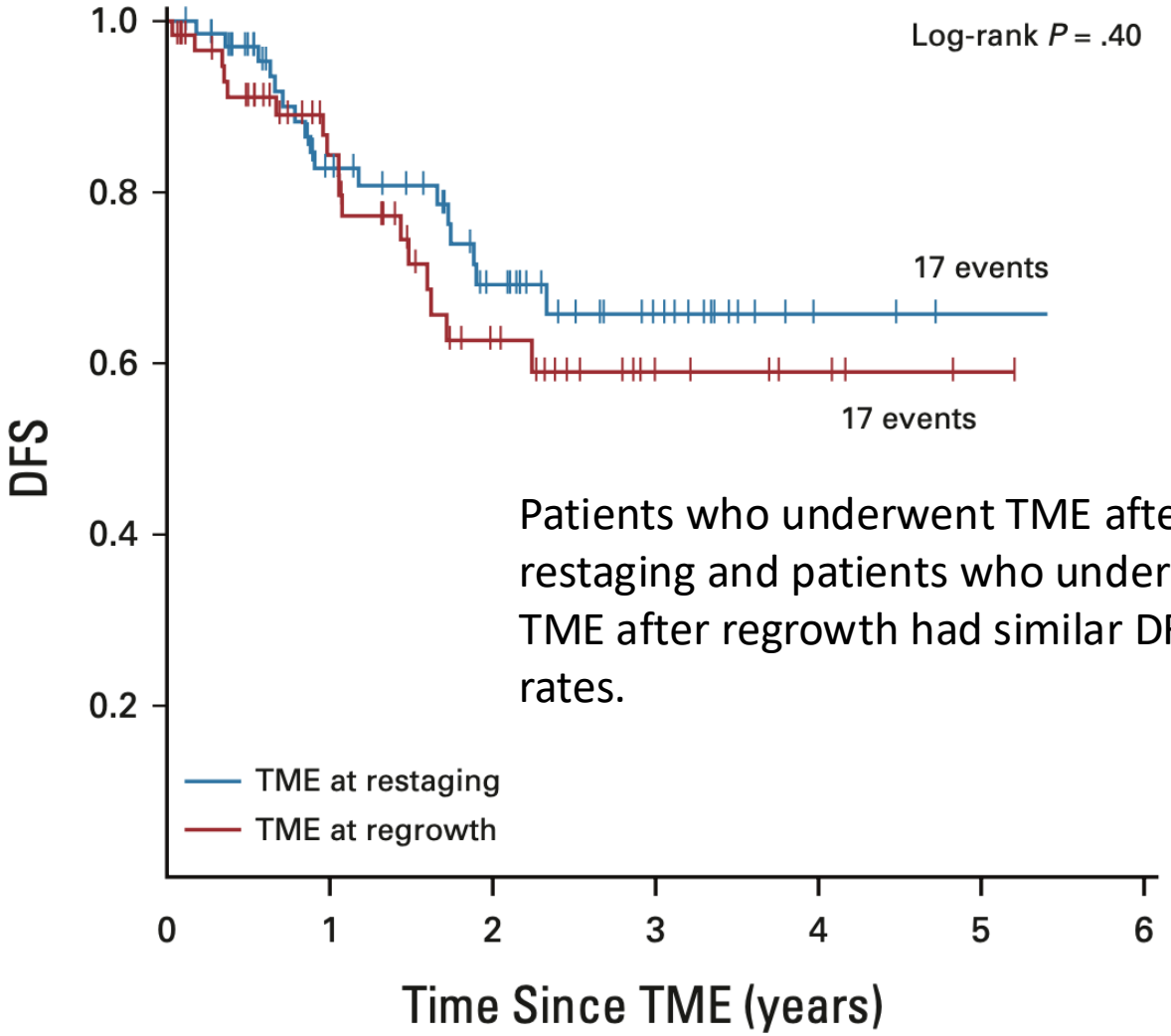
OPRA trial: organ preservation in rectal ca



3-year TME-free survival:

- 41% (95% CI, 33 to 50) in the INCT-CRT
- 53% (95% CI, 45 to 62) in the CRT-CNCT



Patients who underwent TME after restaging and patients who underwent TME after regrowth had similar DFS rates.

Journal of Clinical Oncology
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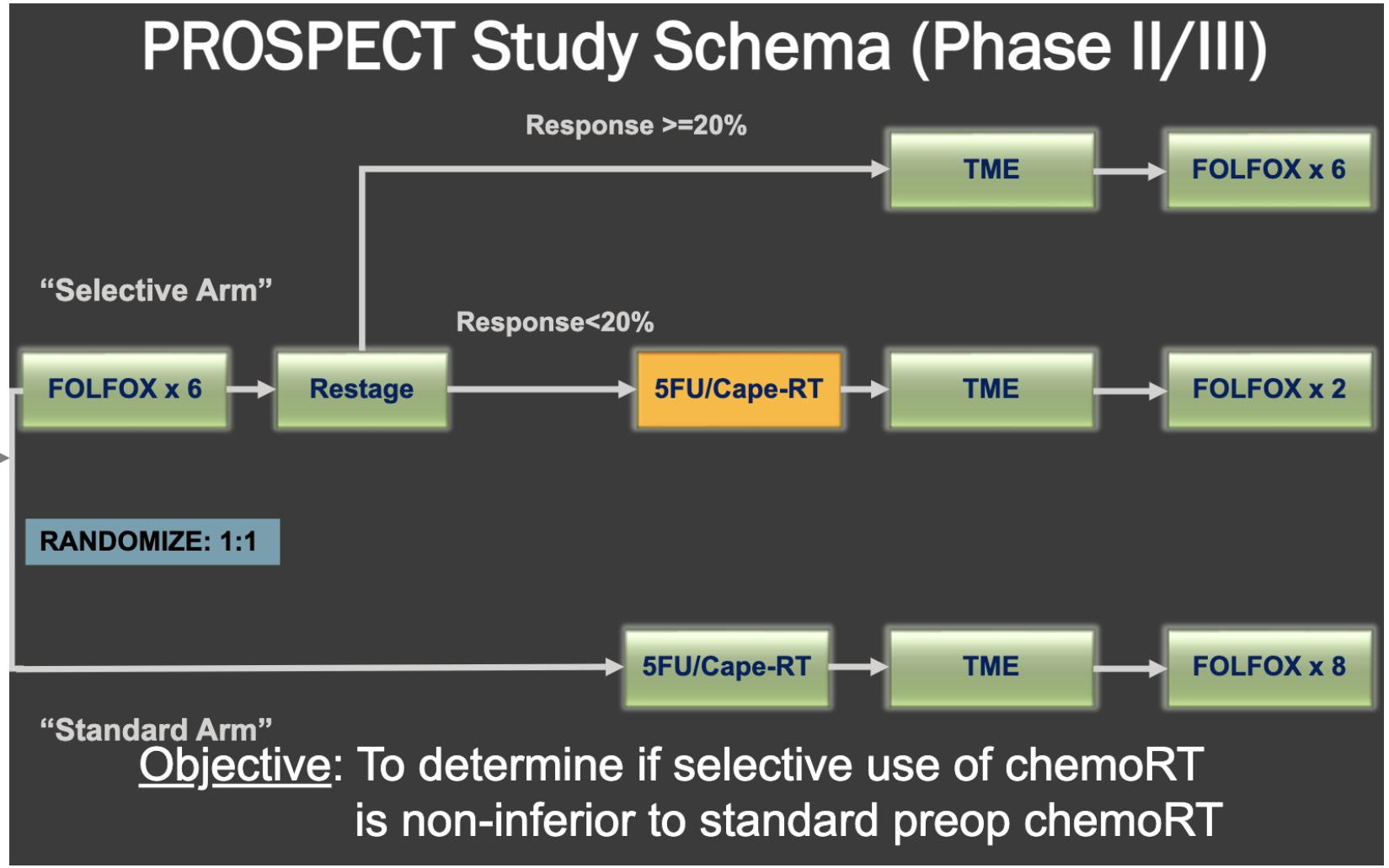
Watch and wait

- Sustained clinical complete response is equivalent to pathologic complete response
- Response evolves over time
- Vast majority of regrowth occurs within 2 years
- Regrowth develops over time
- Patients can be salvaged with delayed surgery
- Regrowth does not impact survival

Treatment de-escalation: NCCTG N1048/Alliance

Intermediate-risk LARC (T1/2N1, T3N0, T3N1) without involvement of the circumferential resection margin (candidates for sphincter sparing surgery)



Exclusion:

- Clinical/radiographic T4, N2
- Threatened radial margins [≤ 3 mm]
- Expectation that APR would be required

Treatment de-escalation: NCCTG N1048/Alliance

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Per-Protocol Population).*

Characteristic	FOLFOX Group (N=585)	Chemoradiotherapy Group (N=543)
Rectal tumor location — cm from anal verge		
No. of patients with data	585	542
Mean	8.6±2.9	8.5±2.8
Median (range)	8 (2–25)	8 (2–18)
Rectal tumor location — no. (%)		
≤5 cm from anal verge	83 (14.2)	90 (16.6)
>5 to ≤10 cm from anal verge	375 (64.1)	344 (63.4)
>10 cm from anal verge	127 (21.7)	109 (20.1)
Clinical stage — no./total no. (%)		
T2 node positive	63/584 (10.8)	38/543 (7.0)
T3 node negative	232/584 (39.7)	198/543 (36.5)
T3 node positive	289/584 (49.5)	307/543 (56.5)

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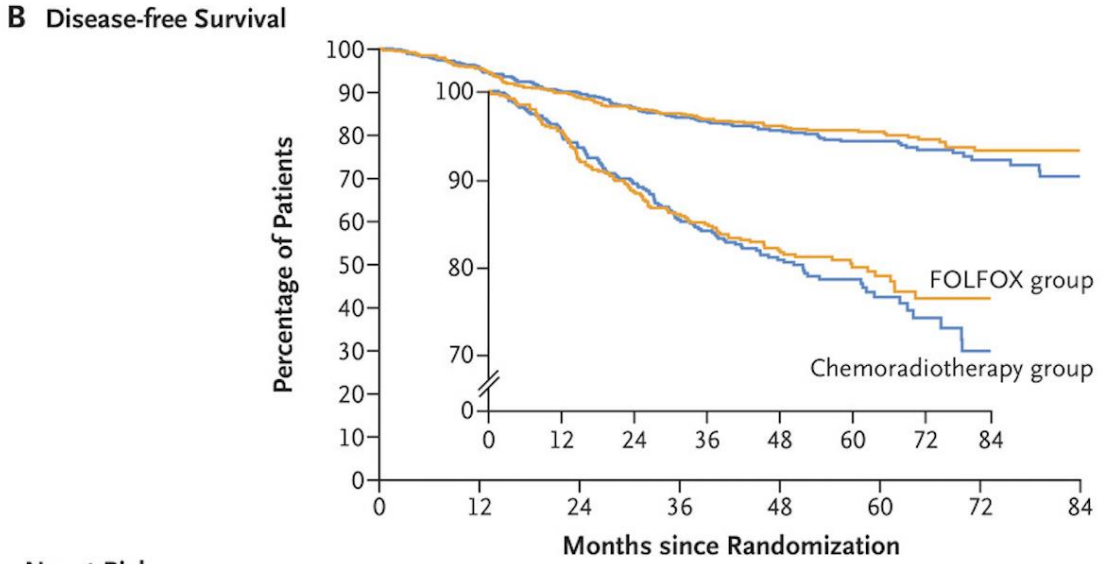
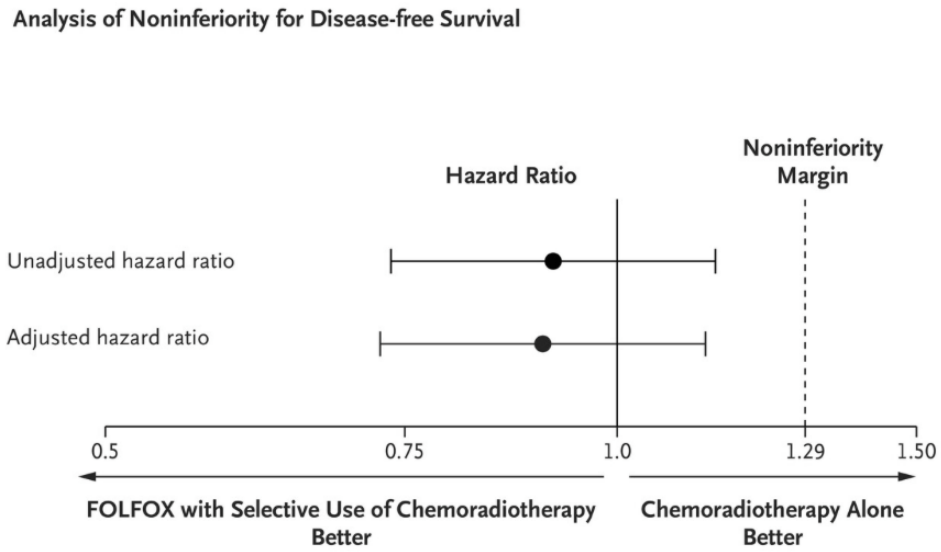
Treatment de-escalation: NCCTG N1048/Alliance



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 *percent*	Stratified P Value for NI
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)	—



- 89.6% of patients assigned to neoadjuvant FOLFOX avoided CRT
- Pathological complete response rates were similar in the two groups (21.9% in the FOLFOX group and 24.3% in the CRT group)

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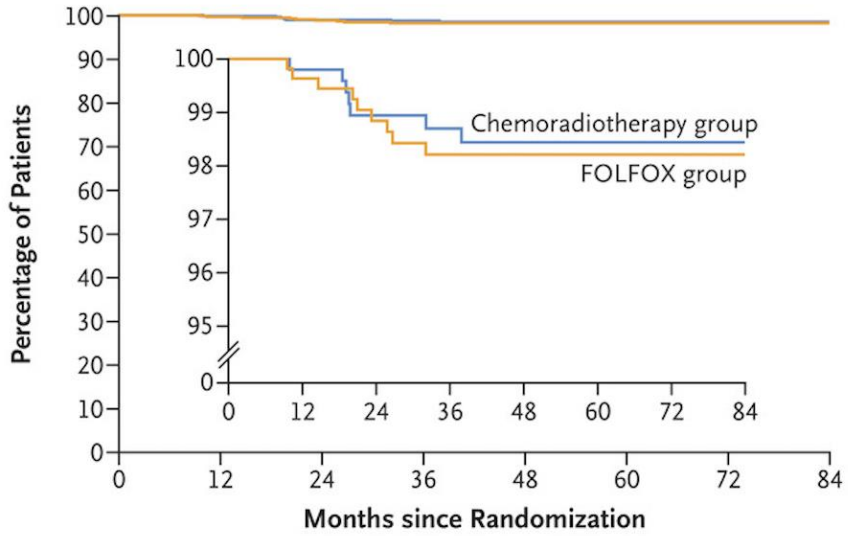
Treatment de-escalation: NCCTG N1048/Alliance

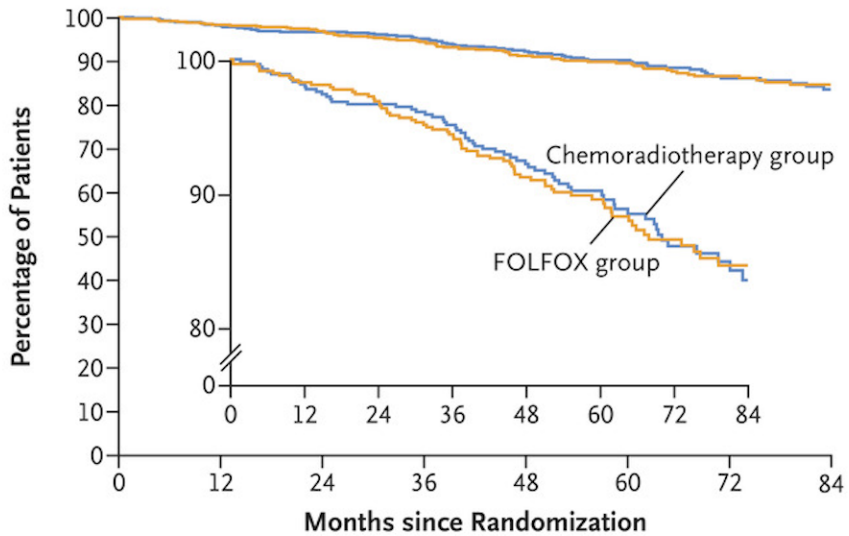
D Freedom from Local Recurrence



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)

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)

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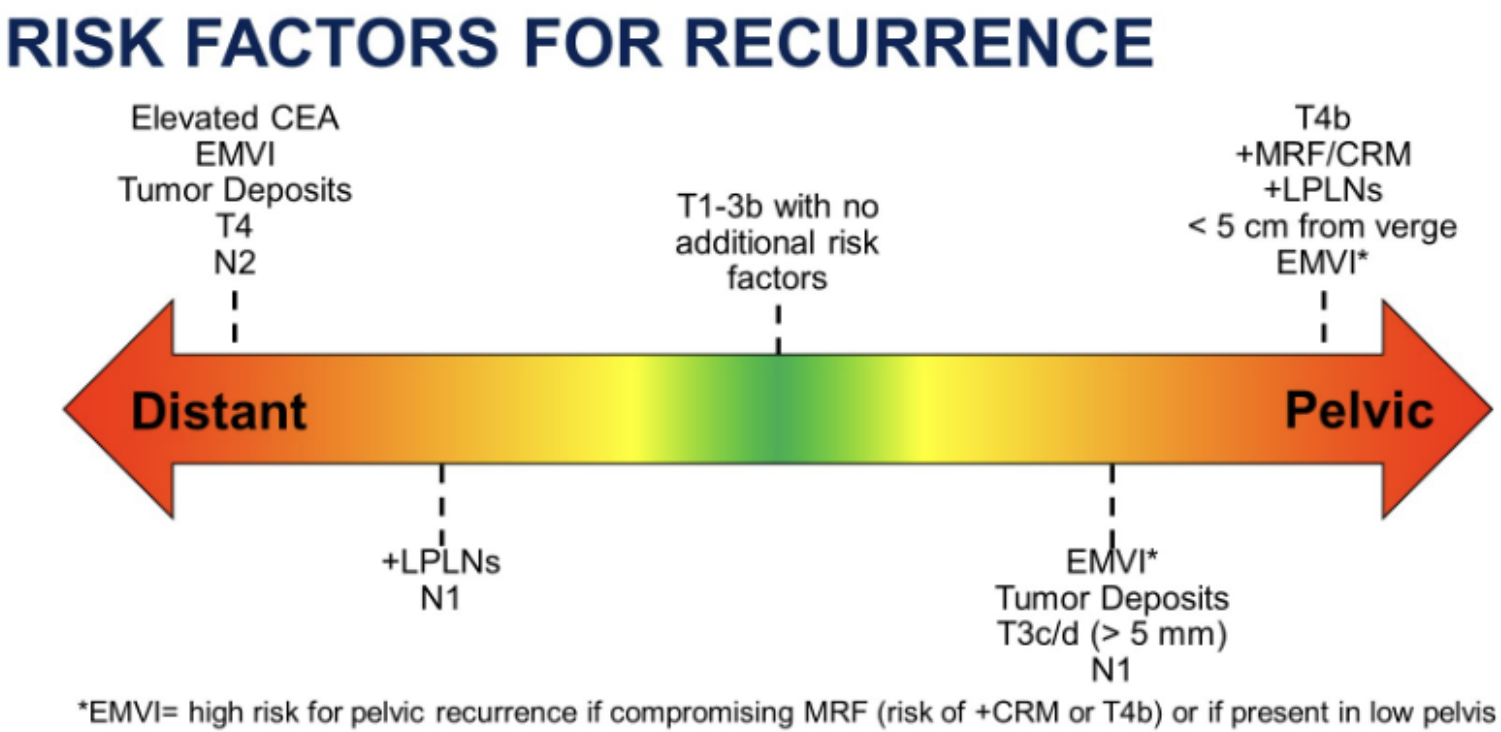
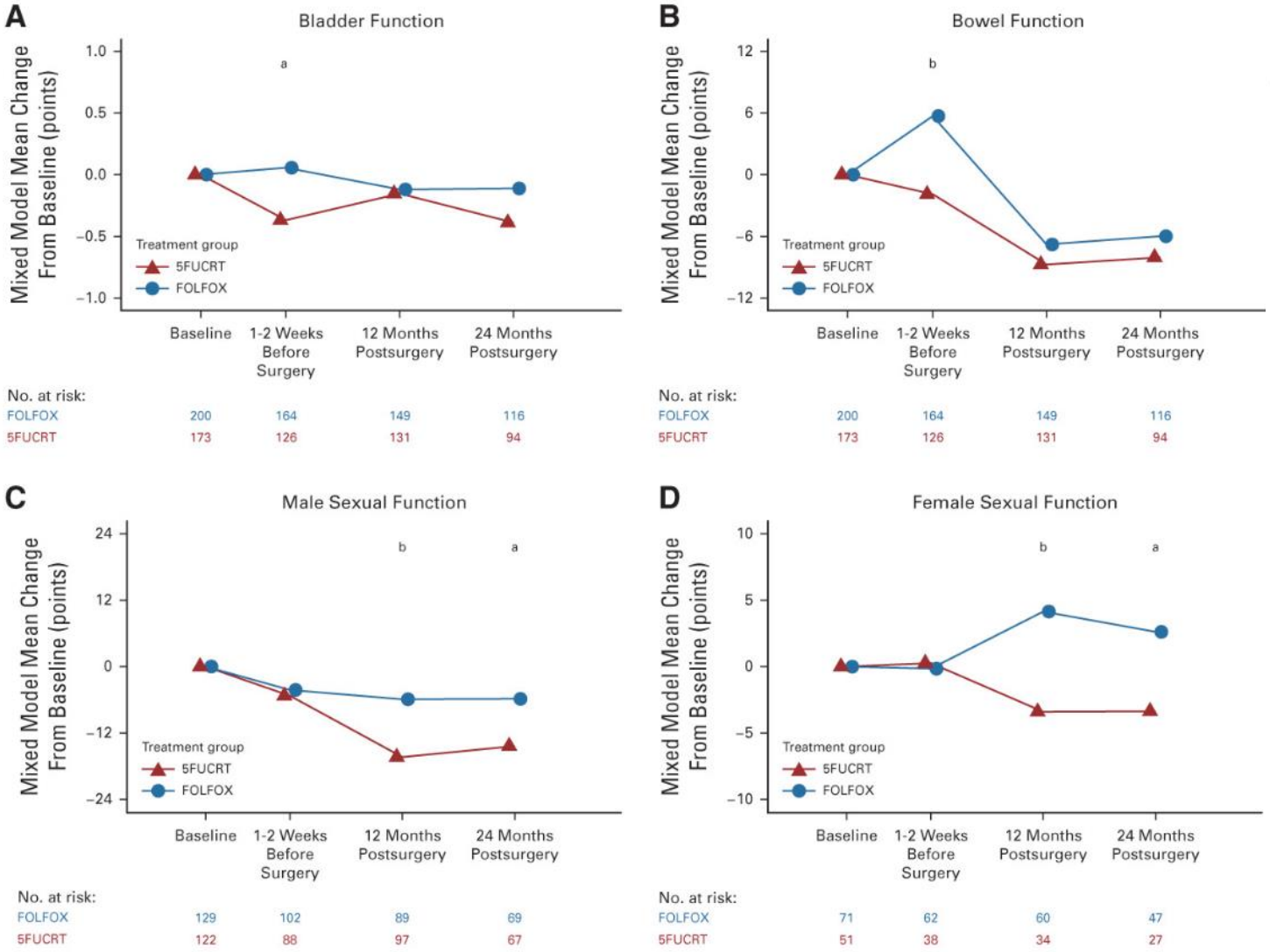
Should patients avoid surgery or pelvic RT in LARC?

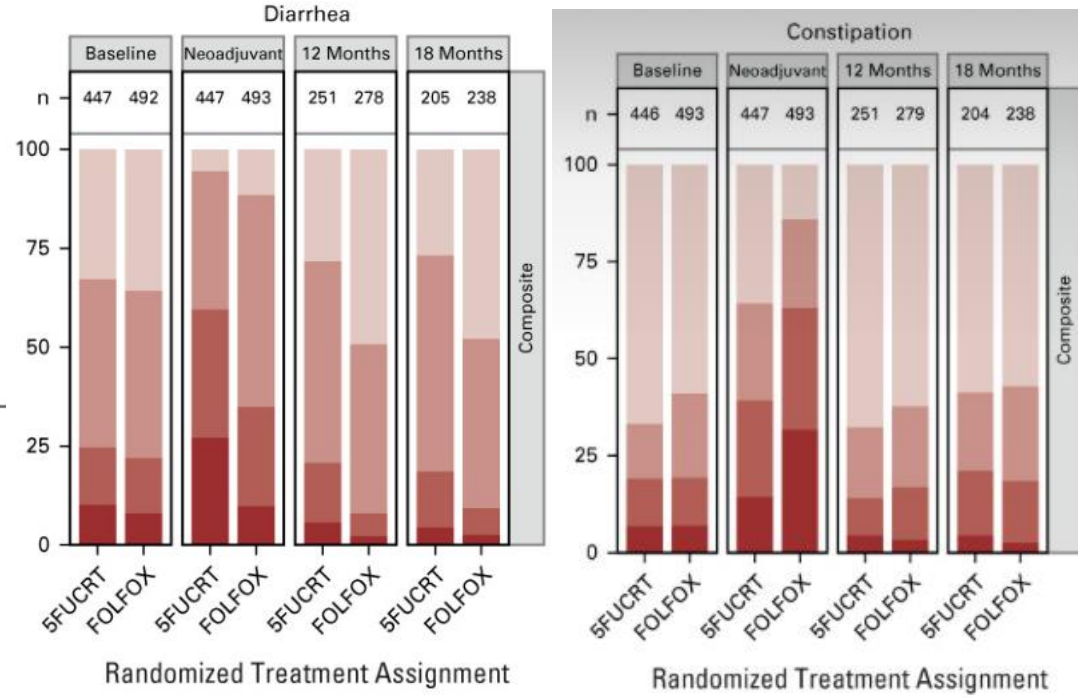
- Functional outcomes after treatment for rectal cancer :
  - Bowel, urinary, and sexual function
- Fertility preservation, prior treatment (prior pelvic radiation), ability to comply with surveillance
- Surgery candidacy



ASCO GI 2024, Dr. Jethwa

Functional Outcomes: PROSPECT trial





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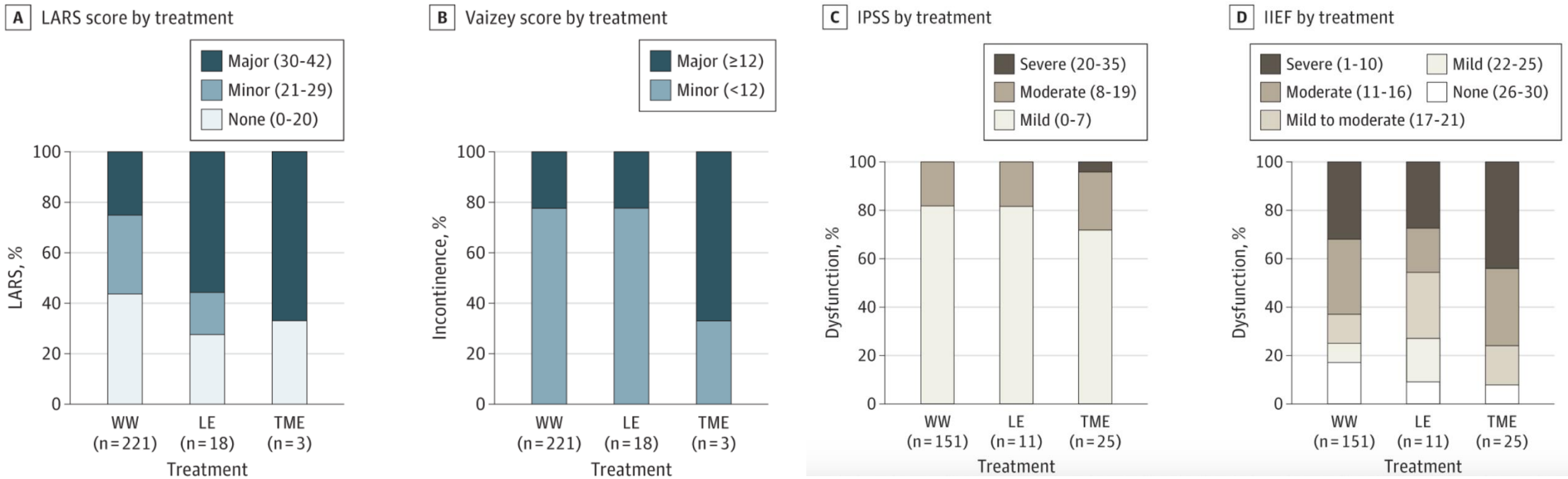
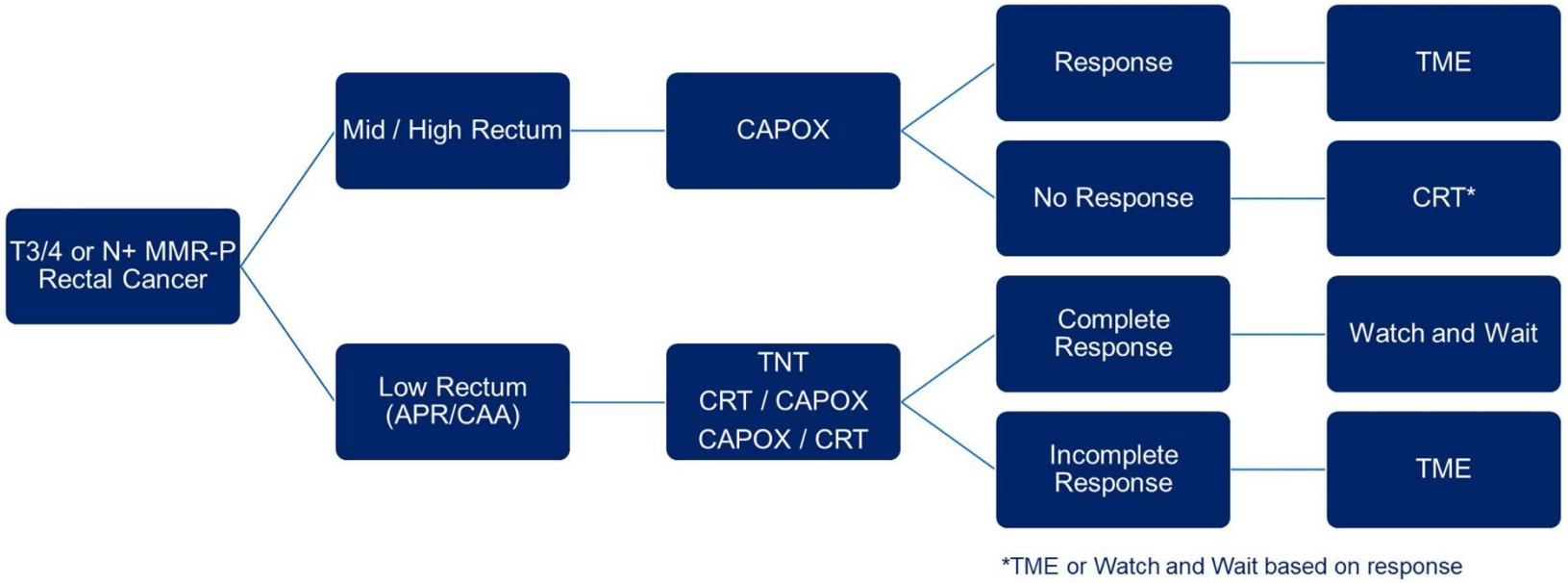
Quality of Life measures in patients undergoing WW for LARC (Dutch WW registry)



JAMA Surg. 2023;158(5):e230146

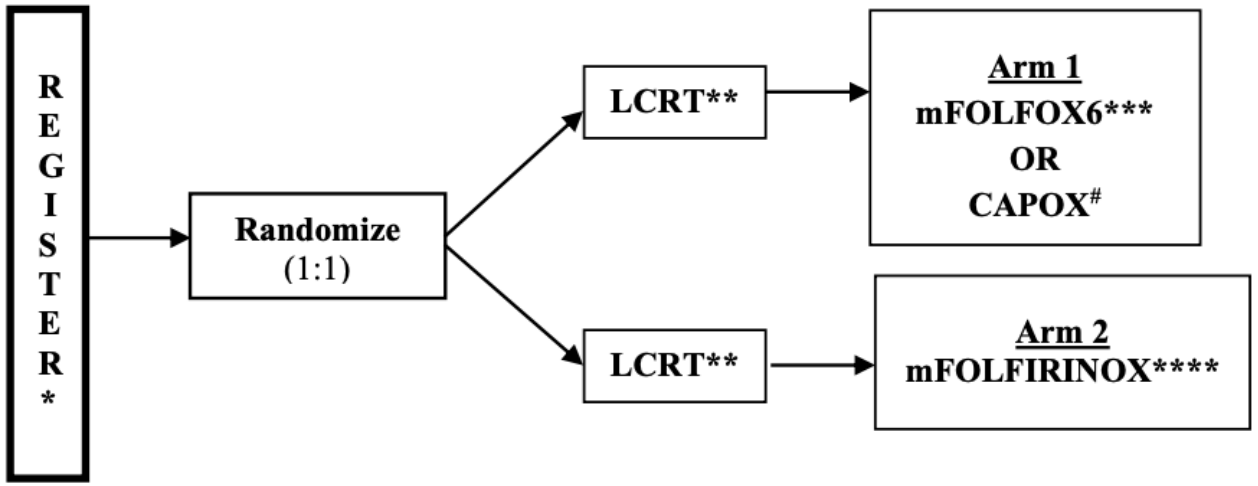
Should patients avoid surgery or pelvic RT in LARC?

- TNT affects bowel, bladder and sexual function
- LARS is worse when pelvic RT is combined with surgery
- Radiation impacts fertility and has a small but real risk of secondary malignancies



JANUS trial

Schema



* Patients with locally advanced rectal cancer: <=12cm, T4N0 OR anyT, N1 OR T3N0 that would require APR or coloanal anastomosis

** LCRT = long-course chemoradiation (5 weeks)

***mFOLFOX6 = 8 cycles (1 cycle = 2 weeks)

****mFOLFIRINOX = 8 cycles (1 cycle = 2 weeks)

\# CAPOX = 5 cycles (1 cycle = 3 weeks)

Eligibility Criteria (see Section 3.2)

- Clinical stage II or III rectal adenocarcinoma defined as T4N0, or any T with node positive disease (any T, N+); also T3N0 requiring APR or coloanal anastomosis
- No prior systemic chemotherapy, targeted therapy, or immunotherapy; or radiation therapy administered as treatment for colorectal cancer within the past 5 years
- Not pregnant and not nursing
- Age ≥ 18 years
- ECOG Performance Status 0-1
- No upper rectal tumors (distal margin of tumor > 12 cm from the anal verge)
- No recurrent rectal cancer; prior transanal excision, prior distal sigmoid cancer with a low anastomosis
- No known mismatch repair deficient rectal adenocarcinoma

Conclusions/Take-Aways

- Treatment for LARC can be personalized to minimize toxicity without compromising long-term oncologic outcomes
- Upfront surgery may be appropriate for low-risk T3N0 rectal cancer
- Neoadjuvant RT can be avoided in patients with MRI-defined favorable risk mid-upper rectal cancers, who are not interested in organ preservation (cT1-3b N0-1)
  - This strategy may be preferred for young patients wishing to preserve fertility
- TNT is the preferred approach for patients with high-risk LARC
  - Long course RT + chemotherapy first is preferred if organ preservation is the goal
- Ongoing investigation:
  - Intensification of neoadjuvant systemic therapy
  - RT dose intensification