
# LOCALLY ADVANCED RECTAL CANCER

# TOTAL NEOADJUVANT THERAPY AND WATCH AND WAIT

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# DISCLOSURES

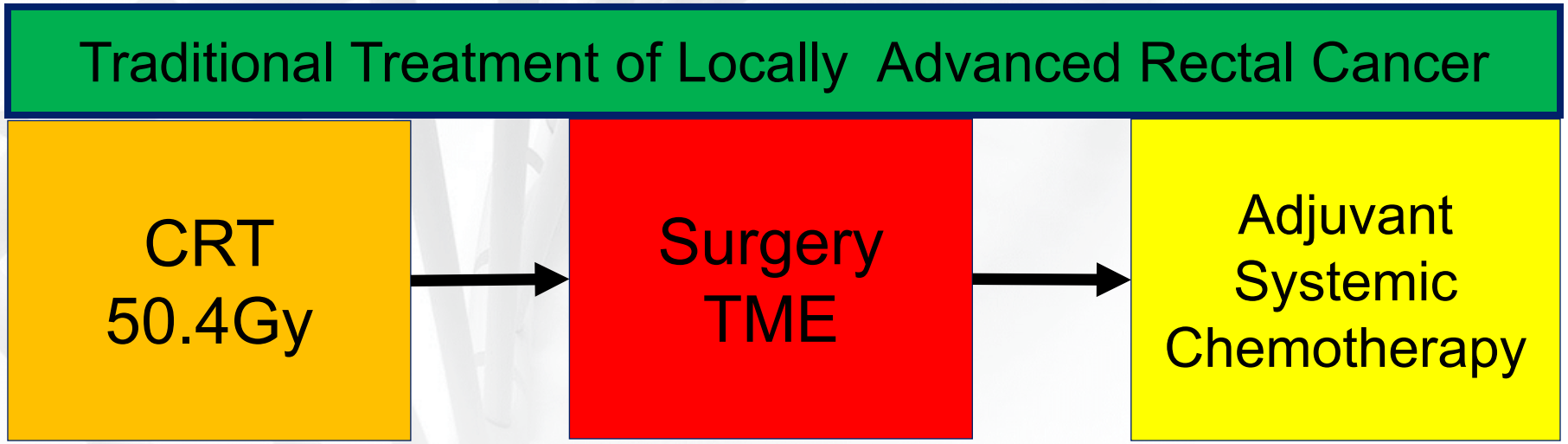
None

# OBJECTIVES

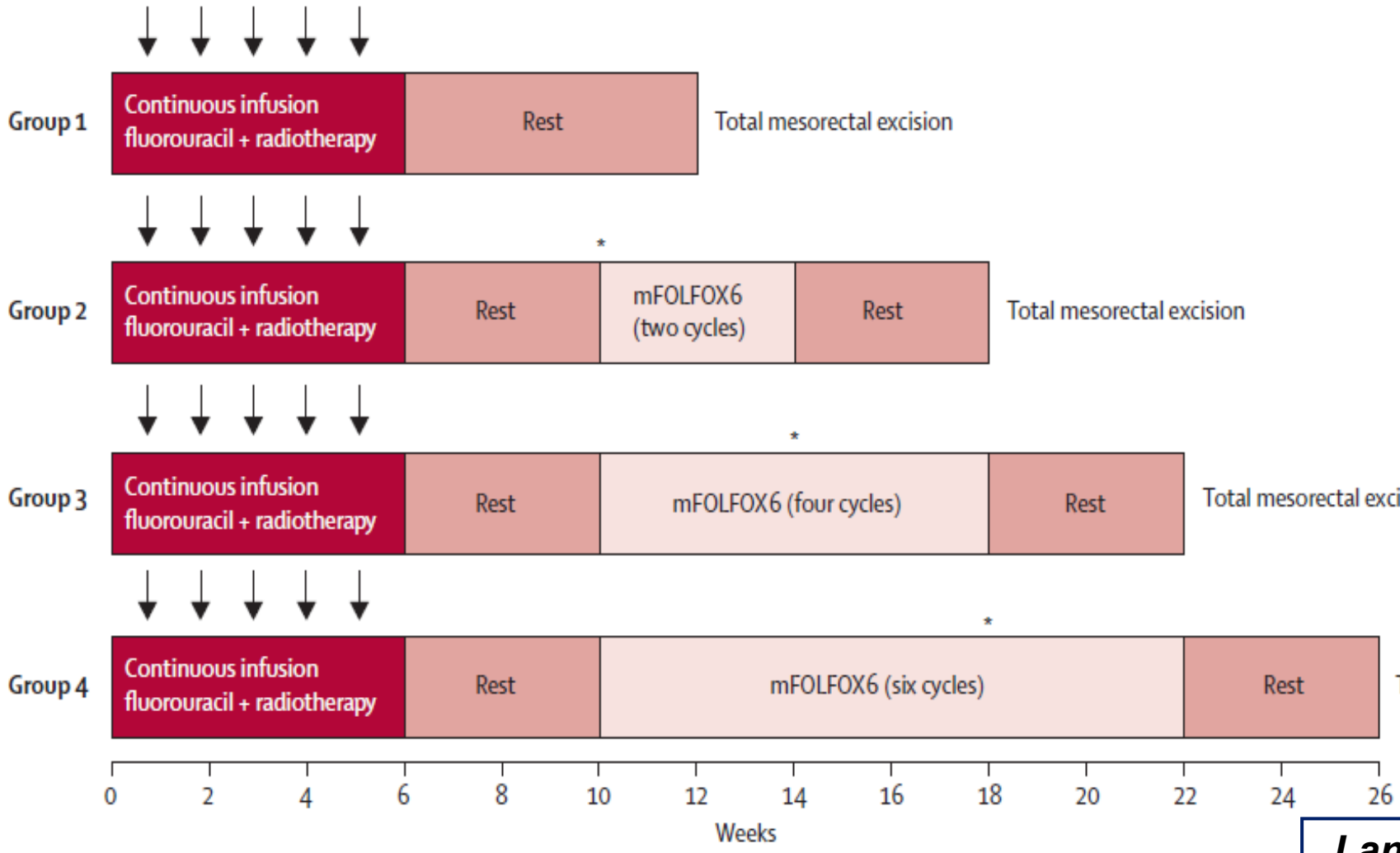
- Total Neoadjuvant Therapy (TNT) should be standard for locally advanced rectal cancer (LARC)
  - CRT -> chemotherapy (consolidation) preferred for organ preservation
  - Watch and Wait strategies are safe for complete clinical response (CCR)
- Mismatch Repair Deficient (MMRd) representing 5-10% of rectal cancers respond completely to immunotherapy

# TRADITIONAL TREATMENT OF RECTAL CANCER

- T1, N- : local excision, total mesorectal resection (TME)
- T2, N- : total mesorectal resection (TME)
  - CRT and local excision
- T2/3/4, N+, M0 Locally Advanced Rectal Cancer :



# EFFECT OF ADDING mFOLFOX6 AFTER CRT IN LOCALLY ADVANCED RECTAL CANCER

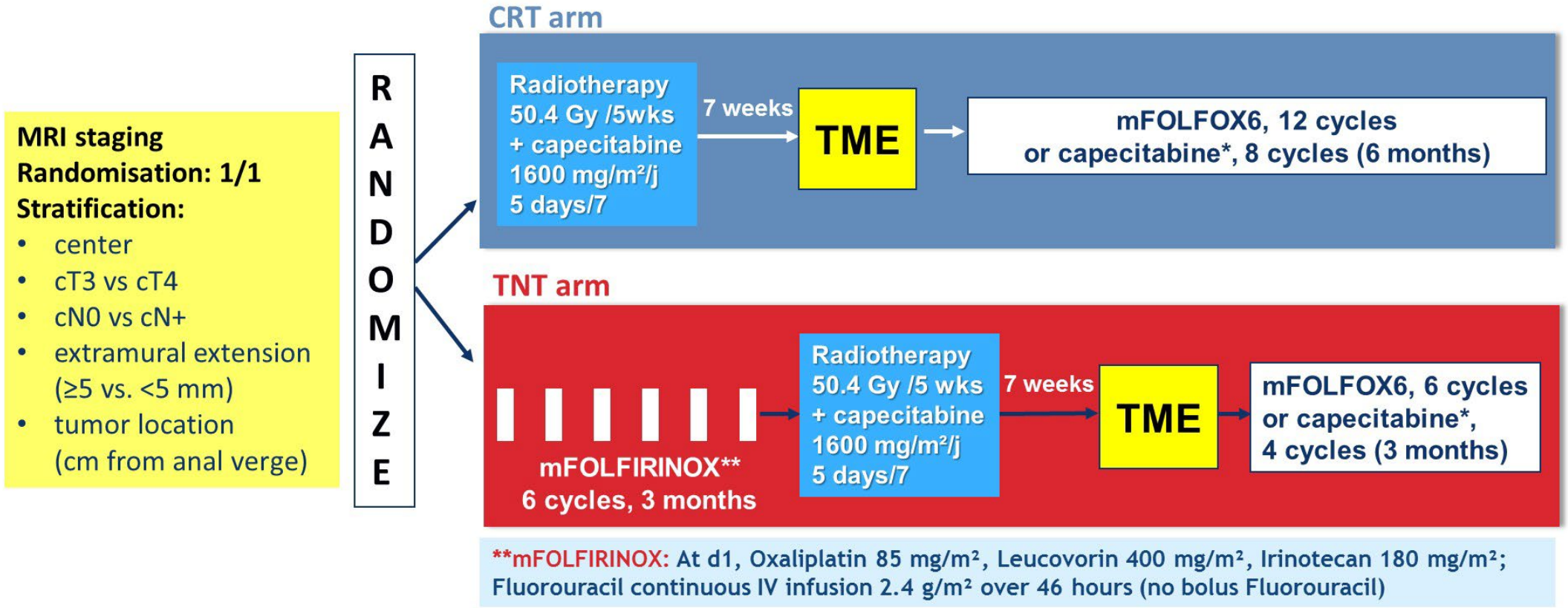



| Path Complete Response |
|---|
| 18% |
| 25% |
| 30% |
| 38% |

*Lancet Oncol* 2015; 16: 957–66

# PRODIGE 23 trial: study design

NCT 01804790; EudraCT 2011-004406-25




**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.

***Lancet Oncol* 2021**

# Neoadjuvant mFOLFIRINOX compliance and safety

**Compliance:**
6 cycles completion: 91.6% (207/226 patients)

**Grade 3-4 adverse events, % per patient (N=226)**

| | | | |
|---|---|---|---|
| Anemia | 0.9% | Fatigue | 7.1% |
| Neutropenia | 16.9% | Nausea | 6.2% |
| G-CSF use | 27.0% | Vomiting | 4.9% |
| Febrile neutropenia | 2.2% | Peripheral neuropathy | 2.2% |
| Thrombocytopenia | 1.3% | Thromboembolic event | 2.7% |
| Diarrhea | 11.1% | Sudden death | 0.4% |

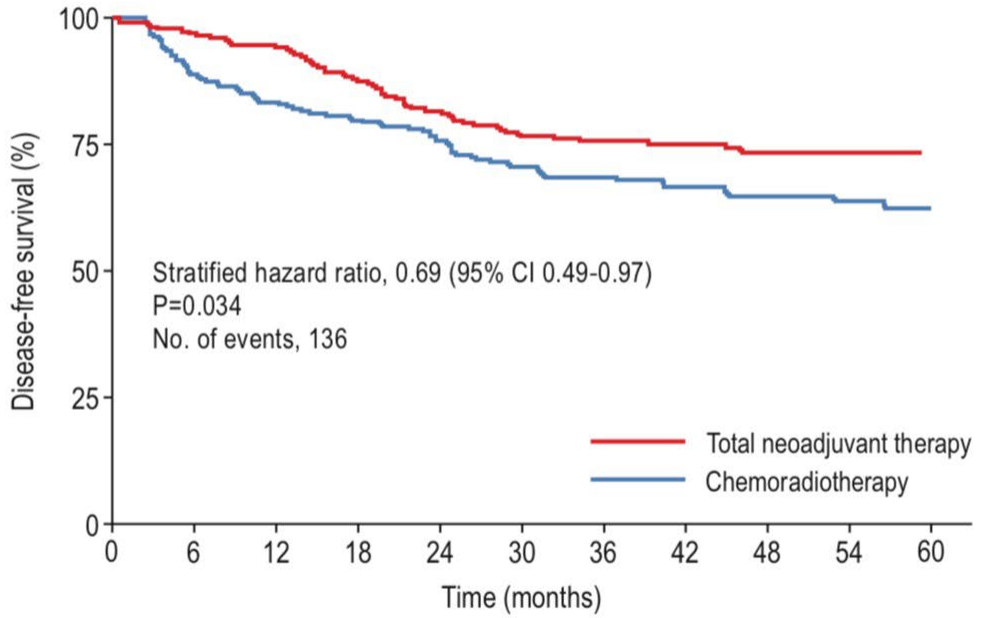
# Safety: adjuvant chemotherapy

| Adjuvant CT duration: | TNT group 3 months N=163 | CRT group 6 months N=158 | p |
|---|---|---|---|
| **Grade 3-4 AEs:** | 44.4% | 74.1% | <0.001 |
| Neutropenia | 5.6% | 18.1% | <0.001 |
| Lymphopenia | 11.2% | 27.1% | <0.001 |
| Peripheral neuropathy | 11.7% | 20.7% | 0.033 |

**Significant increase of all grade toxicities in the CRT arm:**

- At 6 months: for neutropenia, thrombocytopenia, lymphopenia, fatigue, diarrhea, anorexia, peripheral neuropathy, weight loss, mucositis, and thromboembolic events.
- **For the same duration of chemotherapy, the perioperative approach is better tolerated than the adjuvant chemotherapy**

# Disease-Free Survival




| Number at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Total neoadjuvant therapy | 231 | 217 | 210 | 194 | 176 | 150 | 126 | 104 | 80 | 62 | 51 |
| Chemoradiotherapy | 230 | 201 | 188 | 177 | 167 | 146 | 117 | 91 | 65 | 55 | 40 |

**3-yrs DFS rate:**

- **75.7% [95%CI: 69.4-80.8] for the TNT group**
- **68.5% [95%CI: 61.9-74.2] for the CRT group**

**HR: 0.69; p=0.034**

# Pathology findings

| Parameter: | TNT N=213 | CRT N=218 | P |
|---|---|---|---|
| Grade 1 modified Dworak's* tumor regression: | 47.6% | 31.8% | 0.003 |
| ypT0 | 28.3% | 12.6% | <0.001 |
| ypN0 | 82.6% | 67.4% | <0.001 |
| ypT0N0 | 27.8% | 12.1% | <0.001 |

All data except tumor regression were assessed by independent central review

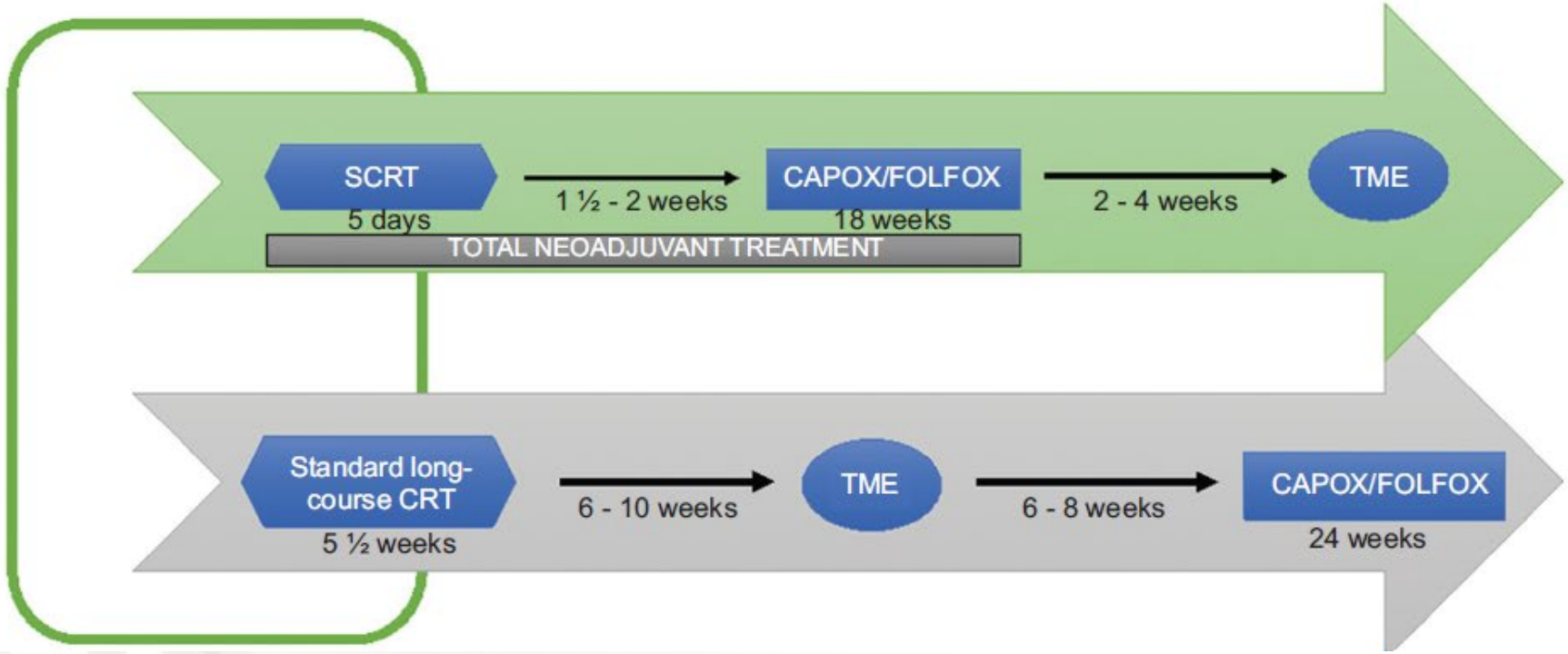
* **Grade 1:** complete or near-complete response (Washington MK, *et al.* 2009)

# RAPIDO TRIAL: SHORT-COURSE RADIOTHERAPY FOLLOWED BY CHEMOTHERAPY BEFORE TME VS. PREOP CRT, TME, AND OPTIONAL ADJUVANT

RAPIDO

MRI Staging
At least one:
cT4a, cT4b, EMVI, cN2, or mesorectal fascia involvement

Primary endpoint:
DrTFat 3 years

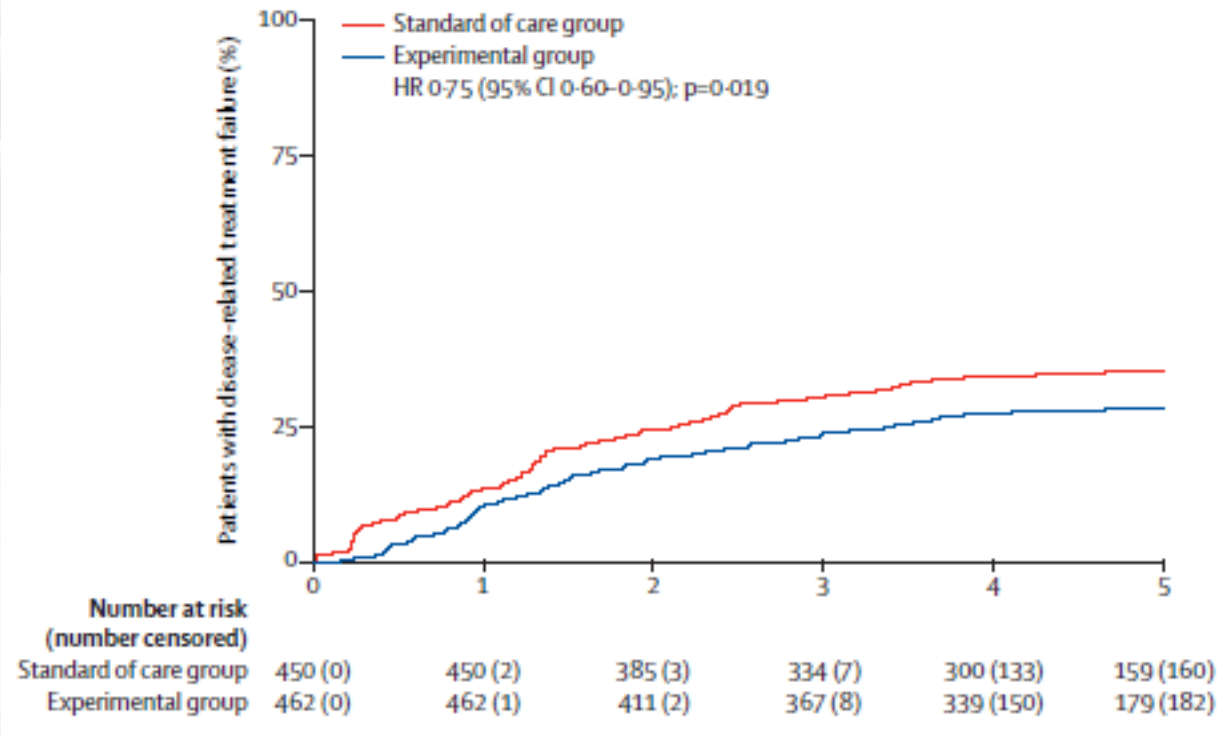



***Lancet Oncol* 2021; 22: 29–42**

# RAPIDO TRIAL: SHORT COURSE TNT VS. STANDARD

- **Disease Related Treatment Failure**
  - TNT: 23.7%; Control: 30.4% (p=0.019)
- **Pathologic Complete Response**
  - TNT: 28%; Control: 14% (p=<0.001)
- **Local Recurrence**
  - TNT: 8.3%; Control: 6% (p=0.12)
- **Distant Metastasis**
  - TNT: 20%; Control: 27% (p=0.005)

## 3 Year Disease-Related Treatment Failure

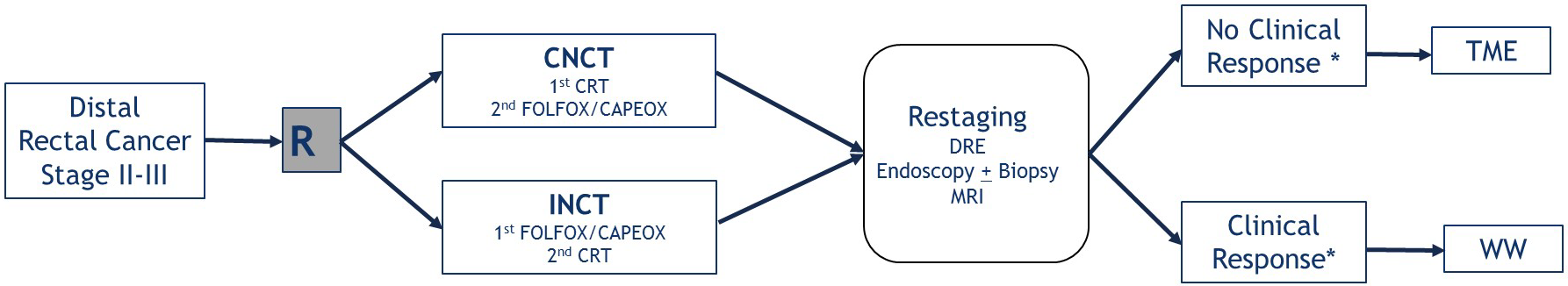


# INDUCTION VS. CONSOLIDATION CHEMOTHERAPY IN TNT WHICH IS BETTER?

## Protocol Schema

NCI trial registration: NCT02008656
NIH-funded (R01): 1R01CA182551-01

### Investigational Arm



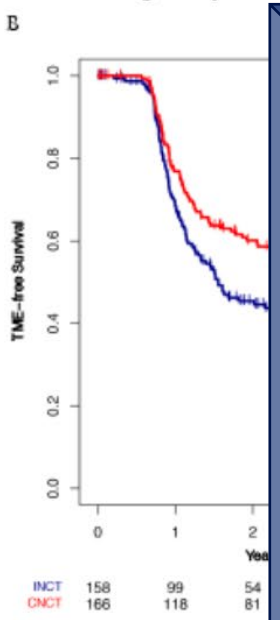

(*) Smith J et al, BMC Cancer 2015;15:767.

### Control Arm (Historical Controls)


Journal of Clinical Oncology, 2022

# Relevant data from OPRA: Organ preservation (OP) & survival endpoints

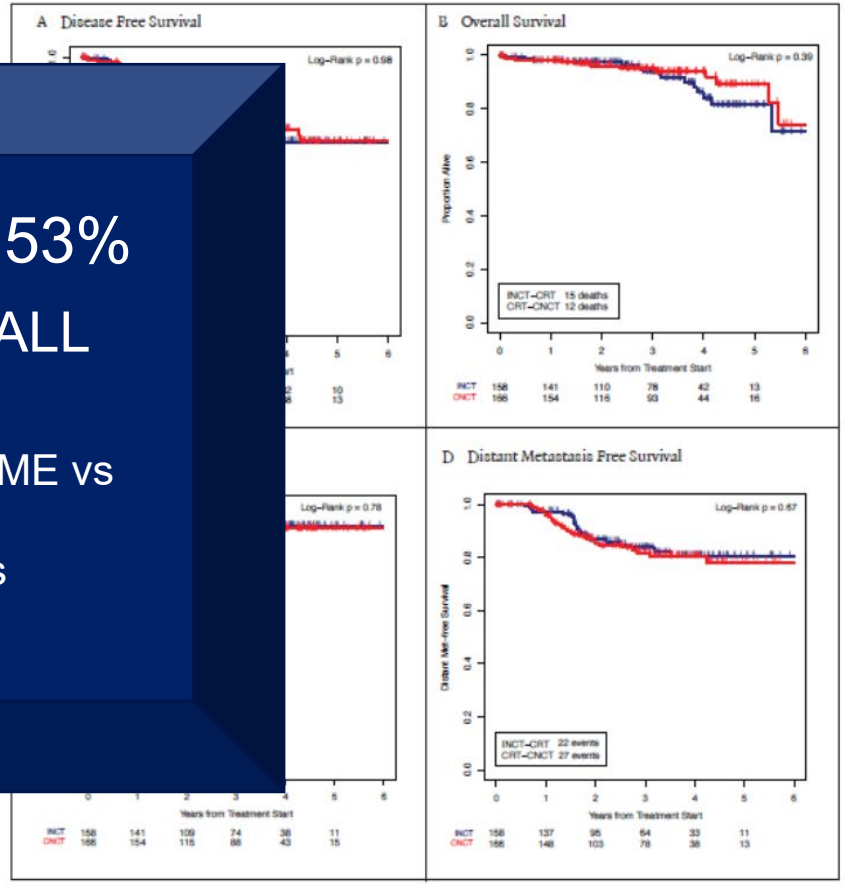
## Organ preservation rates




- 3 yr OP rate in CNCT= 53%
- If regrowth (27%) then ALL salvaged with TME
  - DFS similar in immediate TME vs salvage TME for regrowth
  - Most recurrences w/in 3 yrs

**3-year OP rates:**
CNCT= 53%
INCT = 41%

CNCT: long
INCT: FOLFOX x 8 then LCRT

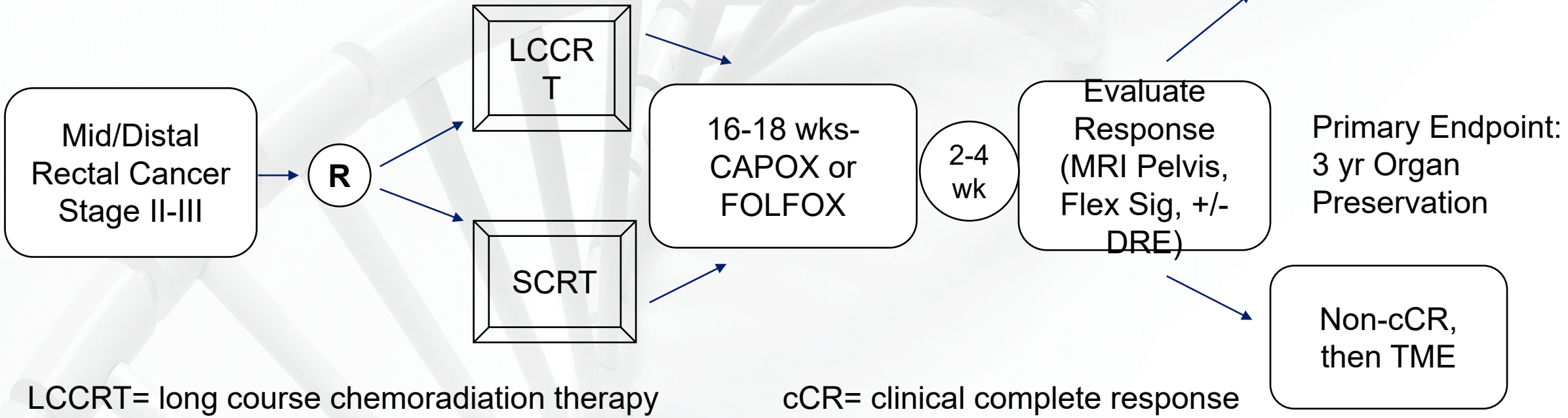



Garcia-Aguilar J, et al. submitted 2021
In press, *J Clin Oncol* 2022

# "SOLO" TRIAL:
# PHASE III RCT OF TNT W/ SC VS LC RADIATION FOR RECTAL CANCER

Design by G.C. Balch, MD

- Radiation Intervention
- Surgical Outcome: Operative vs Nonoperative management




Primary Endpoint: 3 yr Organ Preservation

LCCRT= long course chemoradiation therapy
WW=Watch & Wait
SCRT= short course chemoradiation

cCR= clinical complete response

TME= Total mesorectal excision

# WATCH AND WAIT FOR COMPLETE CLINICAL RESPONSE

## Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy

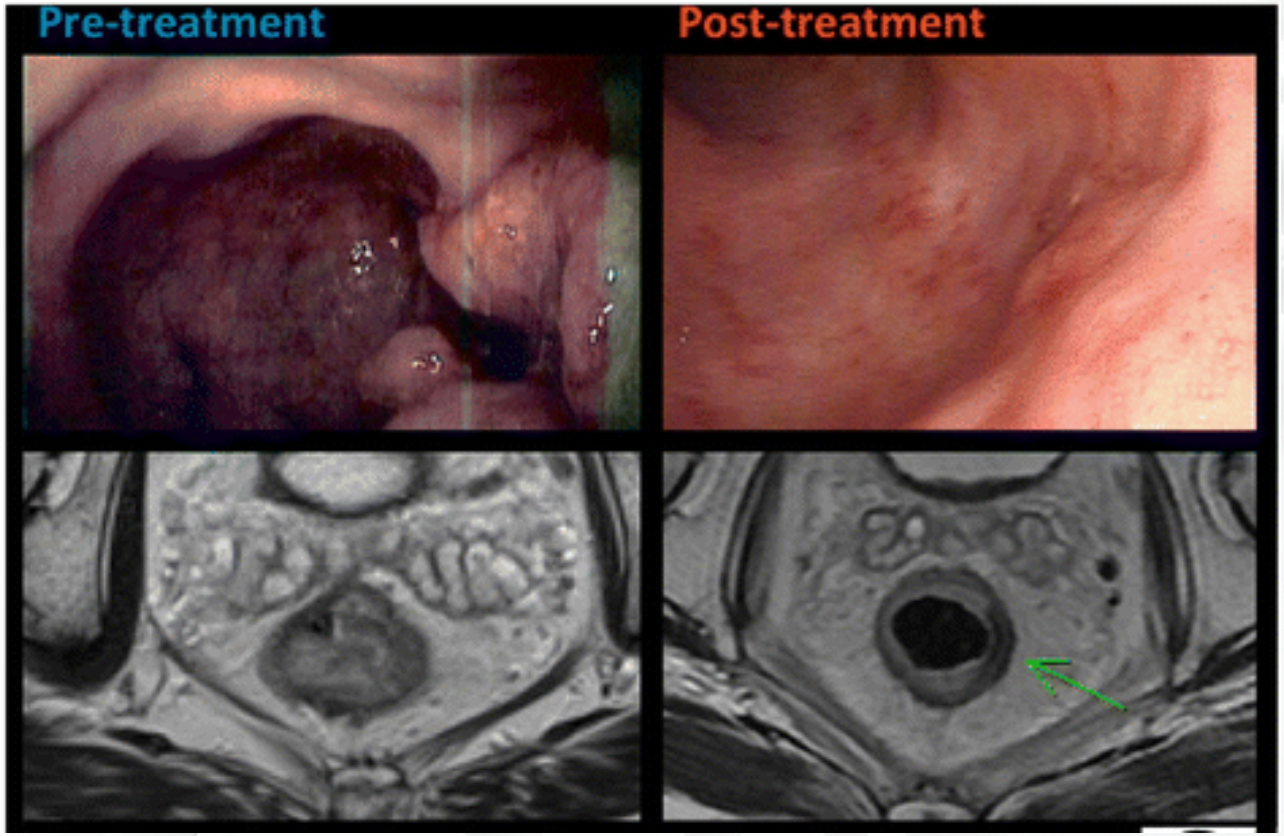
### *Long-term Results*

*Angelita Habr-Gama, MD,* Rodrigo Oliva Perez, MD,* Wladimir Nadalin, MD,†*
*Jorge Sabbaga, MD,† Ulysses Ribeiro Jr, MD,‡ Afonso Henrique Silva e Sousa Jr, MD,**
*Fábio Guilherme Campos, MD,* Desidério Roberto Kiss, MD,* and Joaquim Gama-Rodrigues, MD‡*

- Compared 71 pts with complete clinical response (CCR) sustained for 12 months vs. 22 pts. with complete pathologic response (CPR)
- All patients received combination long course chemo radiotherapy
- No adjuvant chemotherapy given

Habr-Gama, Ann Surg 2004

# COMPLETE CLINICAL RESPONSE – WATCH AND WAIT




| | Complete Response |
|---|---|
| Endoscopy | Flat, white scar<br>Telangiectasia<br>No ulcer<br>No nodularity |
| Digital Rectal Exam | Normal |
| MRI-T2W | Only dark T2 signal, no intermediate T2 signal<br>AND<br>No visible lymph nodes |
| MRI-DW | No visible tumor on B800-B1000 signal<br>AND/OR<br>Lack of or low signal on ADC map<br>Uniform, linear signal in wall above tumor is ok |

# WATCH AND WAIT RESULTS

71 patients with sustained 1 yr CCR

7% recurrence rate

- 2.8% endoluminal recurrence
- 4.2% distant metastasis
- 0% pelvic recurrence

0 cancer related deaths at 10-yr f/u

22 patients resected with PCR

- 9 APR (41%)
- 7 LAR with DLI (32%)
- 6 LAR w/o DLI (27%)

9% parastomal hernias

13.6% recurrence rate

Habr-Gama, Ann Surg 2004

# OVERALL SURVIVAL AND DISEASE FREE SURVIVAL

5 year Overall Survival

5 year Disease Free Survival

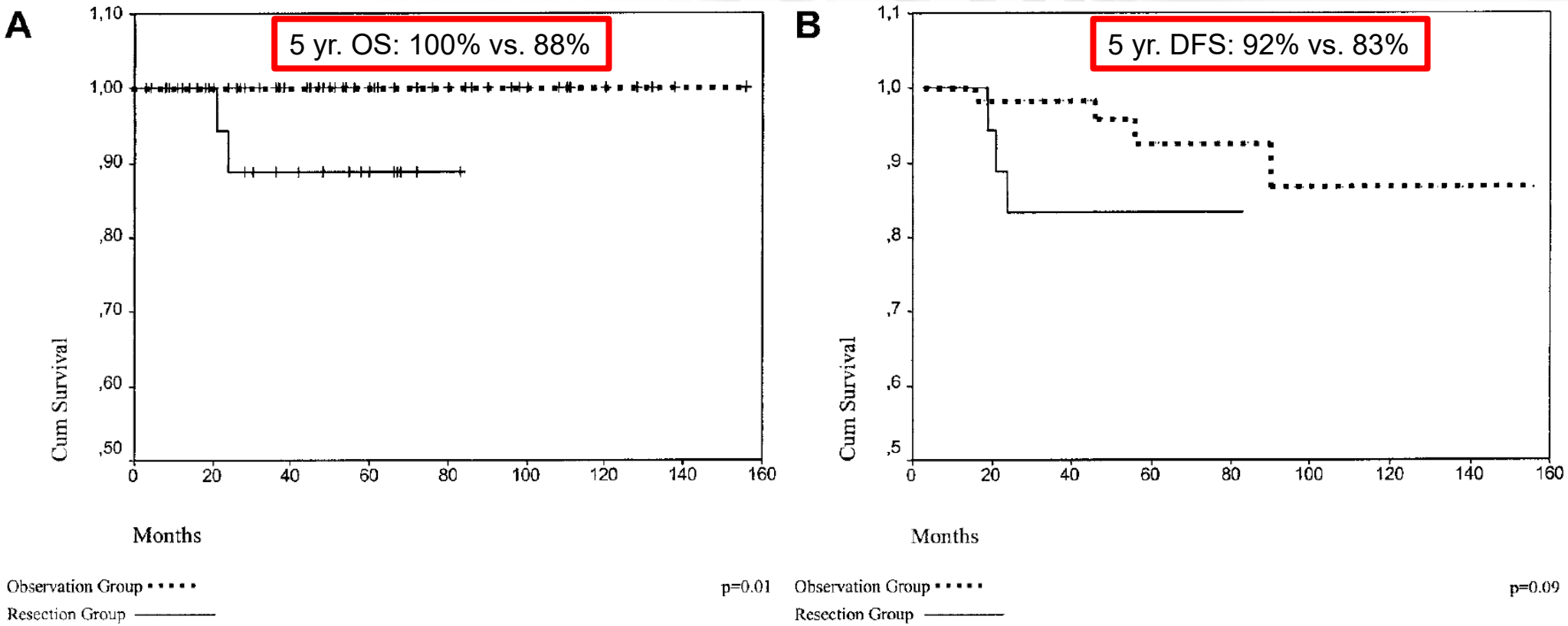



**FIGURE 1.** A, Overall survival. B, Disease-free survival.

Habr-Gama, Ann Surg 2004

# CURRENT NCCN

National Comprehensive Cancer Network®

## NCCN Guidelines Version 1.2022
## Rectal Cancer

NCCN Guidelines Index
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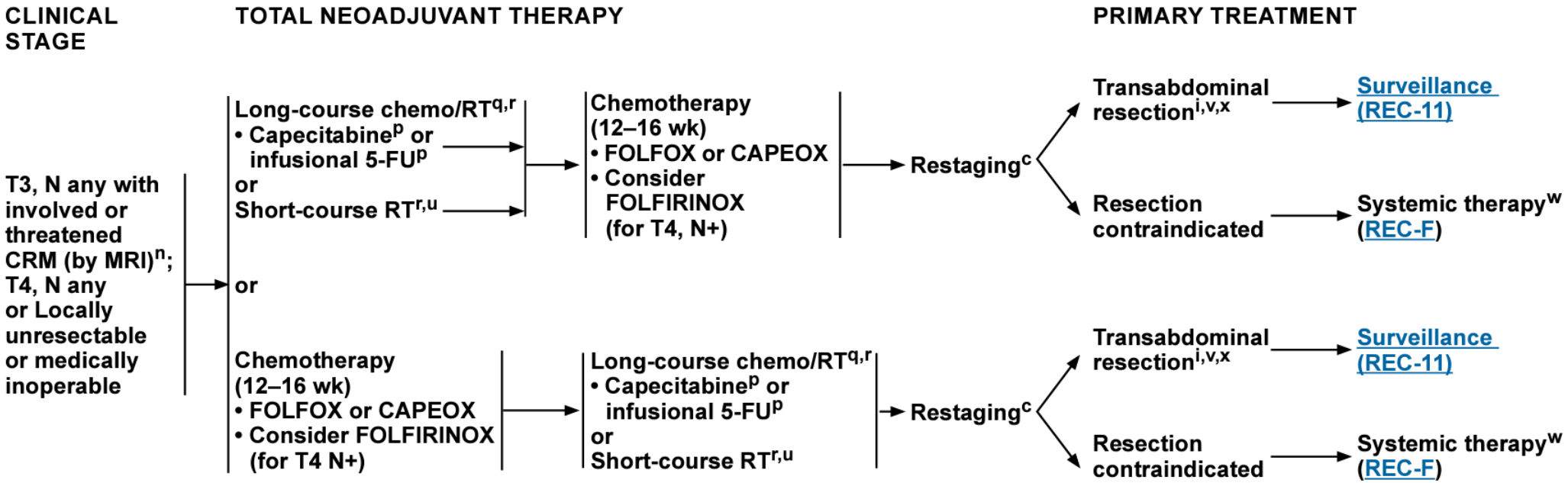



[v] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams.

https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1461

# WATCH AND WAIT

# Rectal Cancer – Complete Clinical Response (cCR)
# Watch and Wait Surveillance Protocol

| Labs/Test/Appointments | 3 mths | 6 mths | 9 mths | 1 yr | 15 mths | 18ths | 21 mths | 2 yrs | 2 1/2 yrs | 3 yrs | 3 1/2 yrs | 4 yrs | 4 1/2 yrs | 5 yrs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| History and Physical | x | X | x | X | x | X | x | X | X | X | X | X | X | X |
| Lab - CEA | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Colonoscopy / flex sig | FS DRE | FS DRE | FS DRE | Full COLON Scope | FS DRE | FS DRE | FS DRE | FS DRE | FS DRE | FS DRE | FS DRE | Full COLON Scope | FS DRE | FS DRE |
| Imaging | | MRI rectal | | MRI rectal CT C/A | | MRI rectal | | MRI Rectal CT C/A | | MRI Rectal CT C/A | | MRI Rectal CT C/A | | MRI Rectal CT C/A |

**FS – flexible sigmoidoscopy**

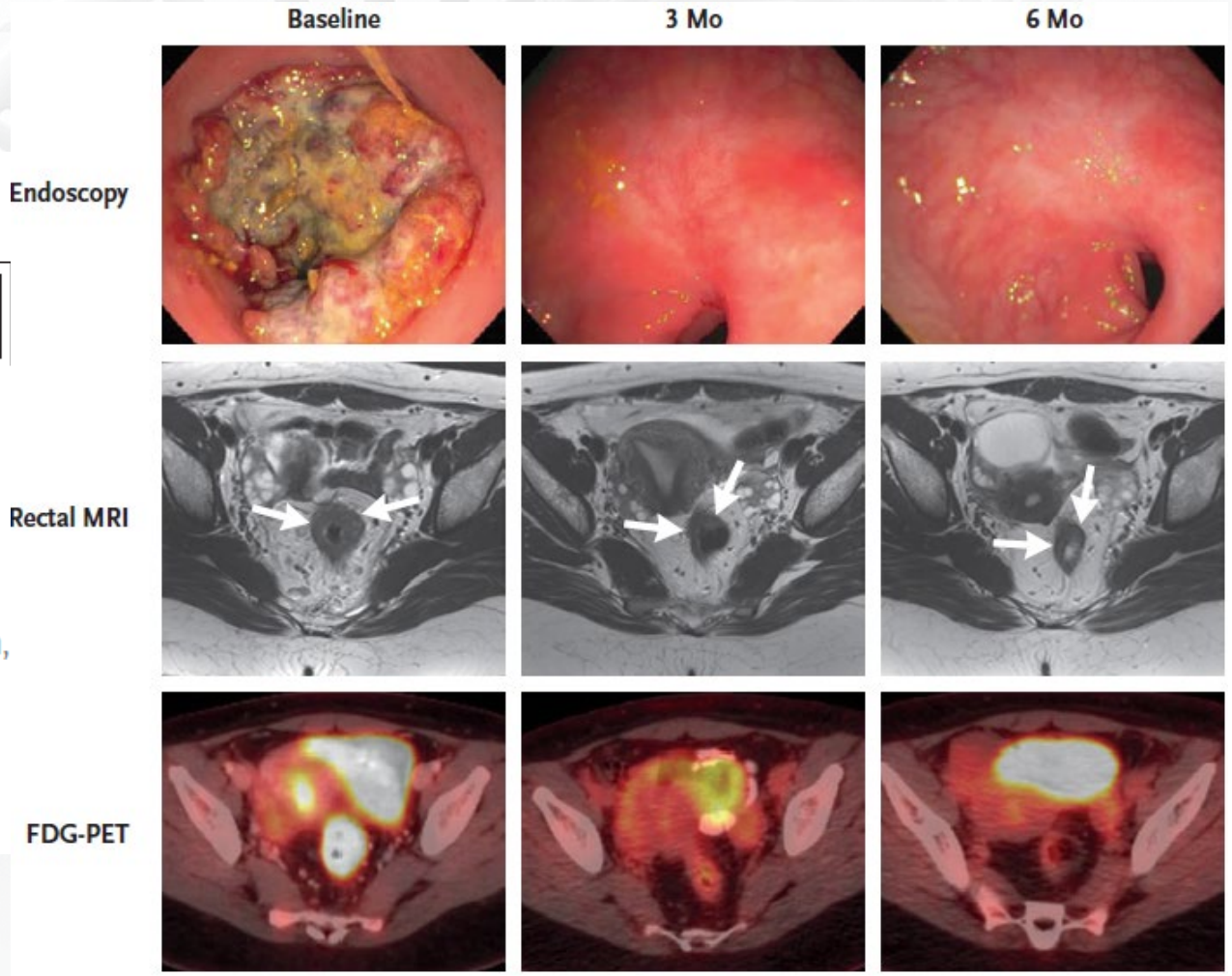
# IMMUNOTHERAPY TREATMENT
# MISMATCH REPAIR DEFICIENT RECTAL CANCER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.



# PERSONALIZED CARE FOR RECTAL CANCER PATIENTS

- Multidisciplinary Approach – Team Approach
  - Colorectal surgeons, Medical oncology, radiation oncology, radiology, pathology, genetic councilors, dieticians, social workers, rectal cancer coordinators
  - American College of Surgeons – National Accreditation Program for Rectal Cancer (NAPRC)
- Reflexive mismatch repair testing
- Patient values – organ preservation

# LOCALLY ADVANCED RECTAL CANCER (LARC)

- 58 y/o M presenting with rectal bleeding without obstructive symptoms
  - Colonoscopy – 3cm lesion, 3cm from the anal verge
  - Pathology – moderately differentiated adenocarcinoma, **microsatellite stable (MSS)**
  - Clinical Staging
    - MRI A/P Rectal Cancer Protocol, CT chest
    - T3, N1, M0
  - **<u>Motivated to Avoid a Stoma</u>**

What would be the next best steps?

A. Surgical  Resection
B. CRT -> surgery -> chemo
C. Immunotherapy -> assess response -> watch and wait or surgery
D. CRT -> Chemo (consolidation) -> assessment -> surgery vs. WW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# KEY STAT OR MESSAGE CALLOUT BOXES

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Add photo here

1 **Insert name**

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