Has TNT become the standard treatment modality? Did it meet the expectations?

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Total Neoadjuvant Therapy (TNT)in Rectal Cancer

- **Incidence, Early Onset & Definition**
- Multimodality Approach ..How did we start?
- Total Neoadjuvant Therapy Rationale
- Total Neoadjuvant therapy outcomes… Evidence-based
- Watch &Wait approach …Hope or Hype?
- What is Next?

Rectal Cancer …Incidence

- Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cause of cancer-related death.*
- Within the next decade ,It is estimated that 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in adults younger than 50 years and mostly presented with advanced stages.**

***Globocan 2020**

****(Increasing disparities in the age-related incidences of colon and rectal cancers in the United States)Bailey C.E.et al.,2015**

Definitions :

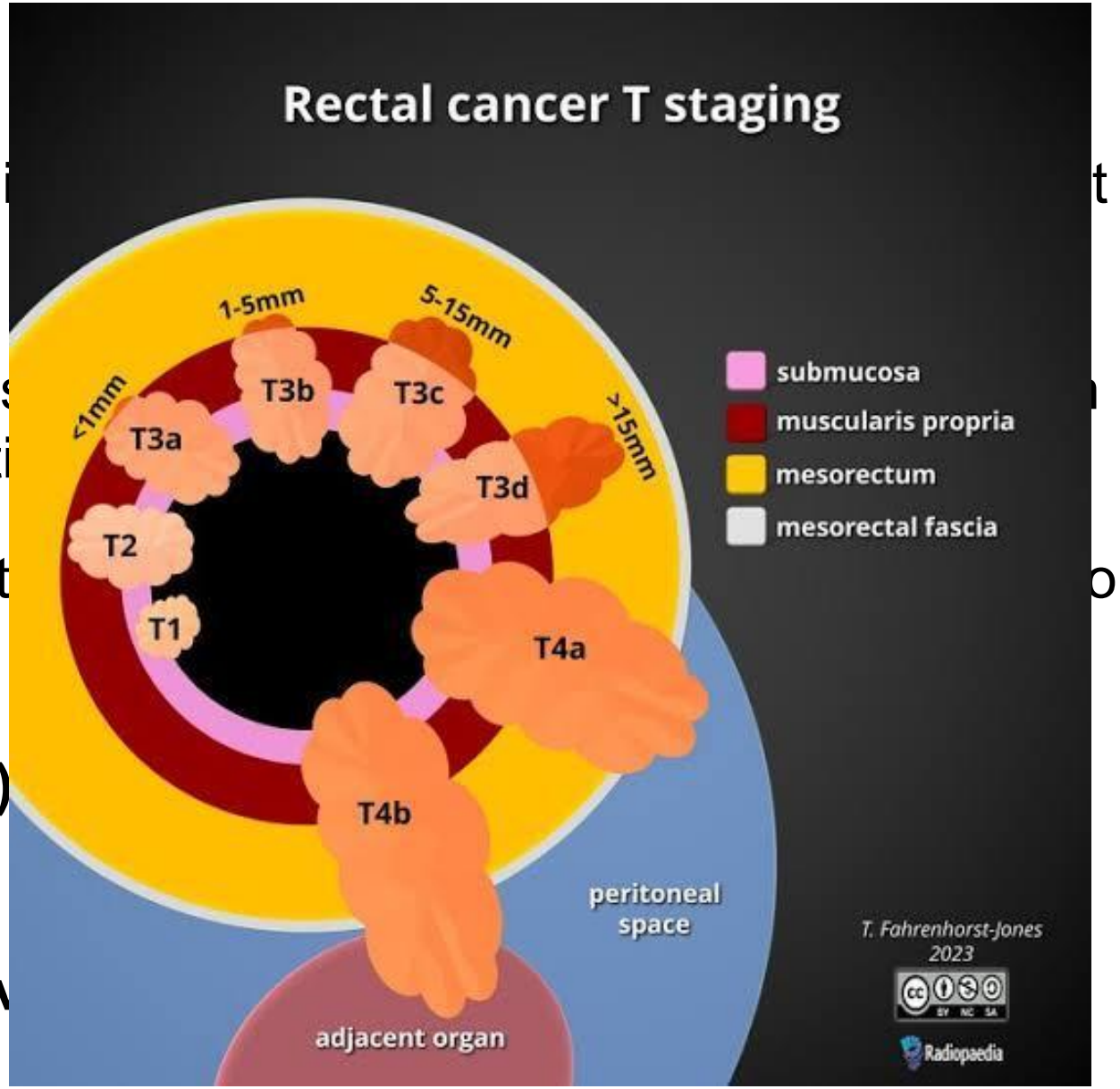
Locally advanced rectal cancer: as cli t metastasis

Total Neoadjuvant Therapy (TNT): Sys prior to surgical resection (or nonoperati

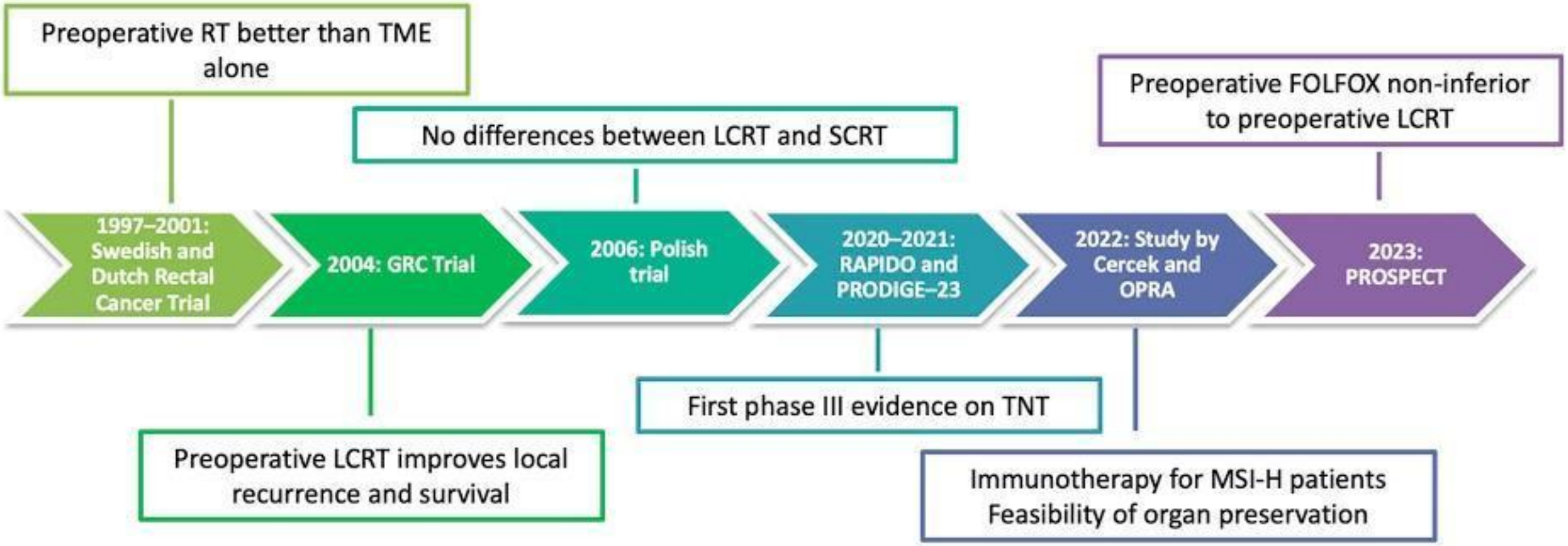
Induction Chemotherapy (INCT): Syst on in a TNT paradigm

Consolidation Chemotherapy (CNCT) chemotherapy in a TNT paradigm

Watch and Wait (WW) or Nonoperativ preservation



Evolution of locally advanced rectal cancer treatment from surgery +adjuvant to TNT :



Daprà, V.; et al. Total Neoadjuvant Treatment for Locally Advanced Rectal Cancer Patients: Where Do We Stand? *Int. J. Mol. Sci.* **2023**, *24*, 12159

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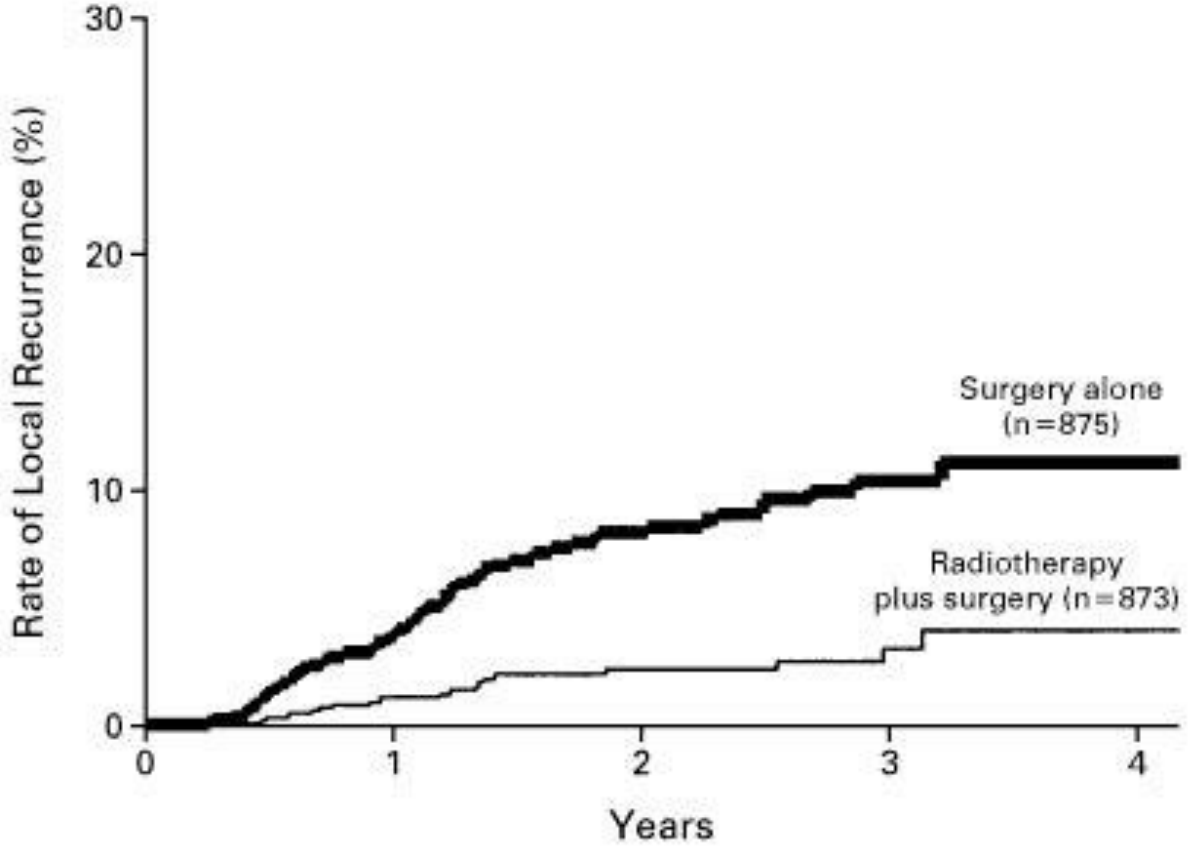
Multimodality A

- Around the 1970s ar

- Late Eighties → Radiotherapy versus co (LR).
- Late Nineties → **Du**

  TME alone had a higher preoperative radiothe difference in ov



No. at Risk					
Radiotherapy plus surgery	873	691	407	170	30
Surgery alone	875	688	406	173	37

***van Gijn W, et al. Preoperative radiotherap the multicentre, randomised controlled TME**

The Dutch Trial: Preoperative CRT Vs. Postoperative CRT : better local control , function preservation and less toxicity

Parameter	Preoperative chemoradiotherapy n=415	Postoperative chemoradiotherapy n=384	P-value
Local recurrence	6%	13%	0.006
Distant recurrence	36%%	38%	0.84
Toxicity			
Acute side-effects	27%	40%	0.001
Long-term side-effects	14%	24%	0.01
Sphincter-preserving surgery performed	45/116 (39%)	15/78 (19%)	0.004
Disease-free survival	68%	65%	0.32
Overall survival	74%	76%	0.80

Acute and long-term side effects were lower in the preoperative group, particularly with respect to acute and chronic diarrhea and the development of strictures at the anastomosis. Among 194patients with tumors determined prior to randomization to require an abdominoperitoneal resection, a statistically significantly higher rate of sphincter-preserving procedures was achieved in the preoperative group

Iv, A. A., Koprowski, M. A., Nabavizadeh, N., & Tsikitis, V. L. (2022). The evolution of rectal cancer treatment: the journey to total neoadjuvant therapy and organ preservation. *Annals of gastroenterology*, *35*(3), 226–233.

2004 : Spanish GCR-3 phase II randomized trial

	Standard Tx N=52	TNT N=56	P-value
pCR	13%	14%	NS
R0	87%	88%	NS
G3/4 Toxicity during CRT	29%	23%	NS
G3/4 Toxicity during Chemo	54%	19%	0.0004
Compliance to Full Chemo	57%	94%	0.0001
Any Surgical Complications	45%	51%	NS

Given the lower acute toxicity and improved compliance with induction CT compared with adjuvant CT, integrating effective systemic therapy before CRT and surgery started to look like promising strategy

Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial. Fernandez-Martos, C. et al. Annals of Oncology, Volume 26, Issue 8, 1722 - 1728

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Why shifting to preoperative therapy? (TNT)

- Better local control
- Historically over 60% of patients didn't complete adjuvant chemotherapy
- Benefit of chemotherapy in the adjuvant setting is unclear
- Move systemic therapy upfront to address micrometastatic disease earlier, Particularly in high-risk patients- node positive disease— bulky primary tumors

+ Higher pCR rates in TNT create the possibility for organ preservation in select populations

Yoo RN, Kim HJ. Total neoadjuvant therapy in locally advanced rectal cancer: Role of systemic chemotherapy. Ann Gastroenterol Surg. 2019 Apr 29;3(4):356-367. doi: 10.1002/ags3.12253.

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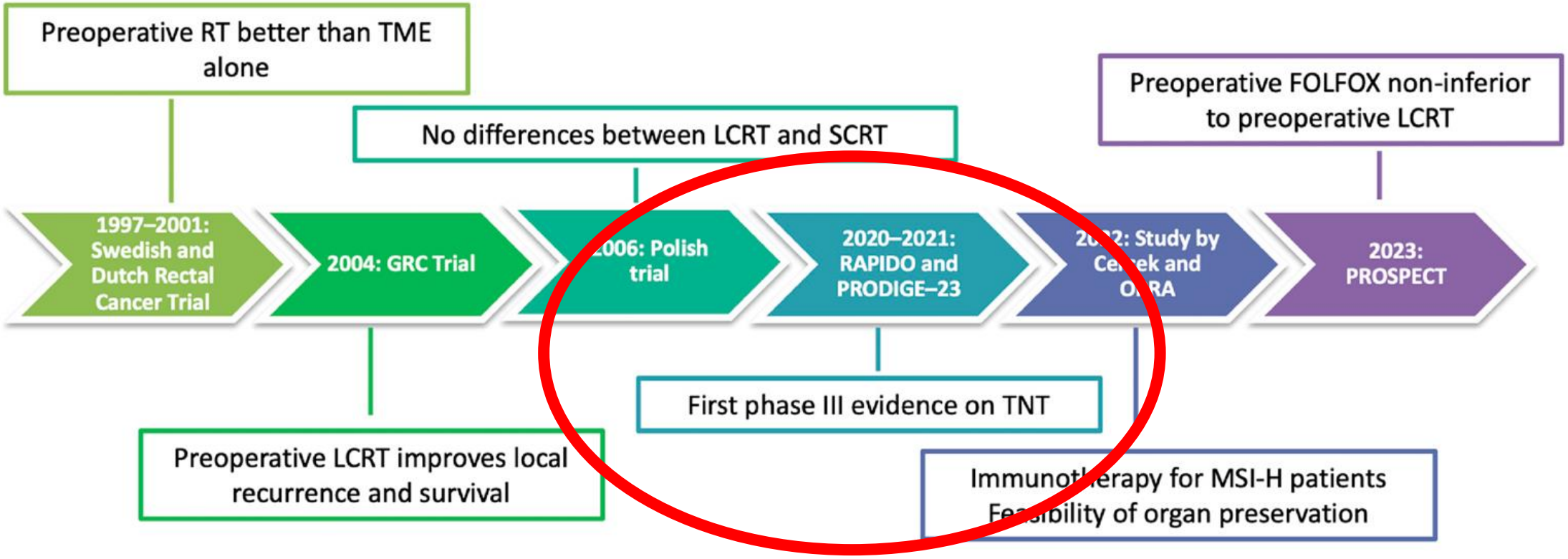
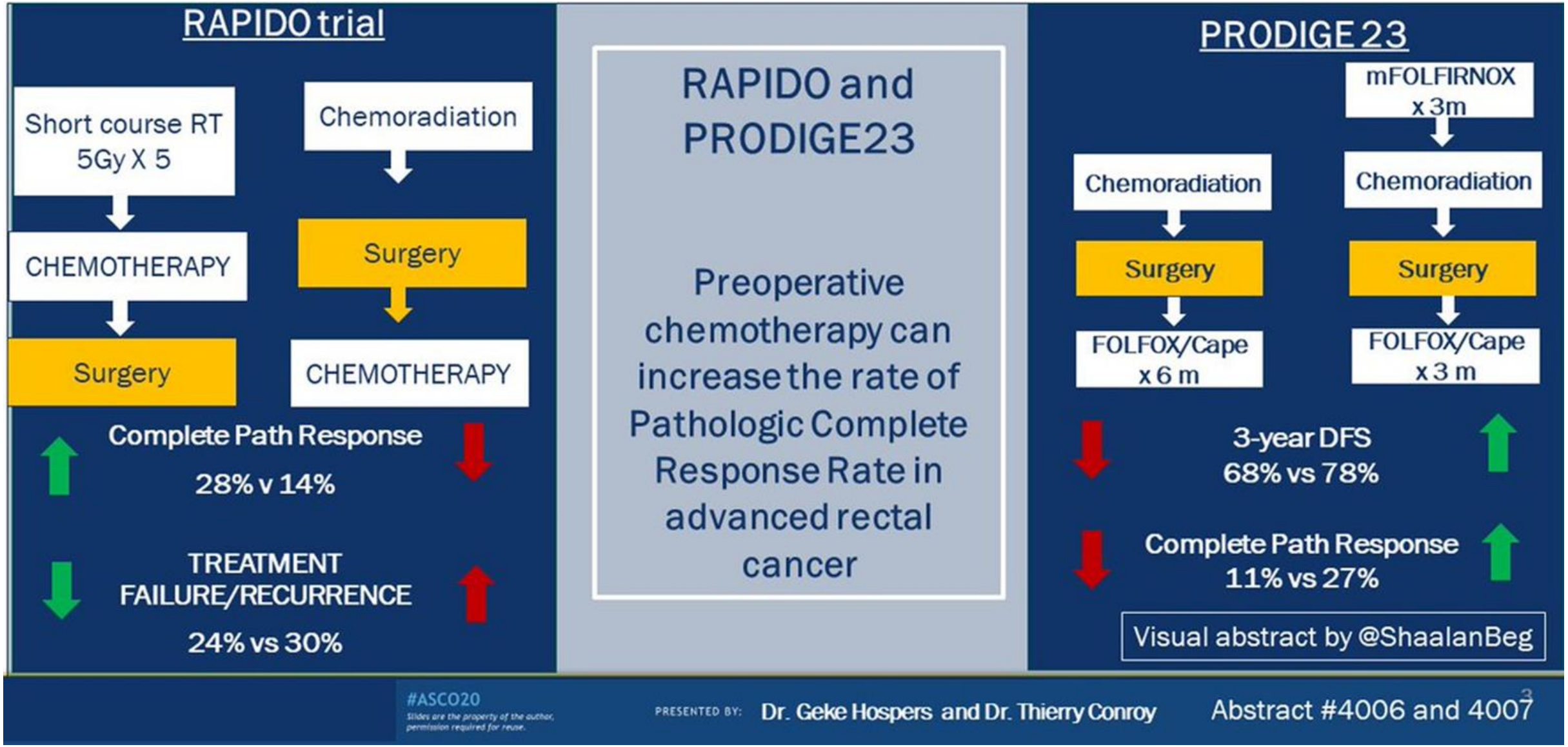
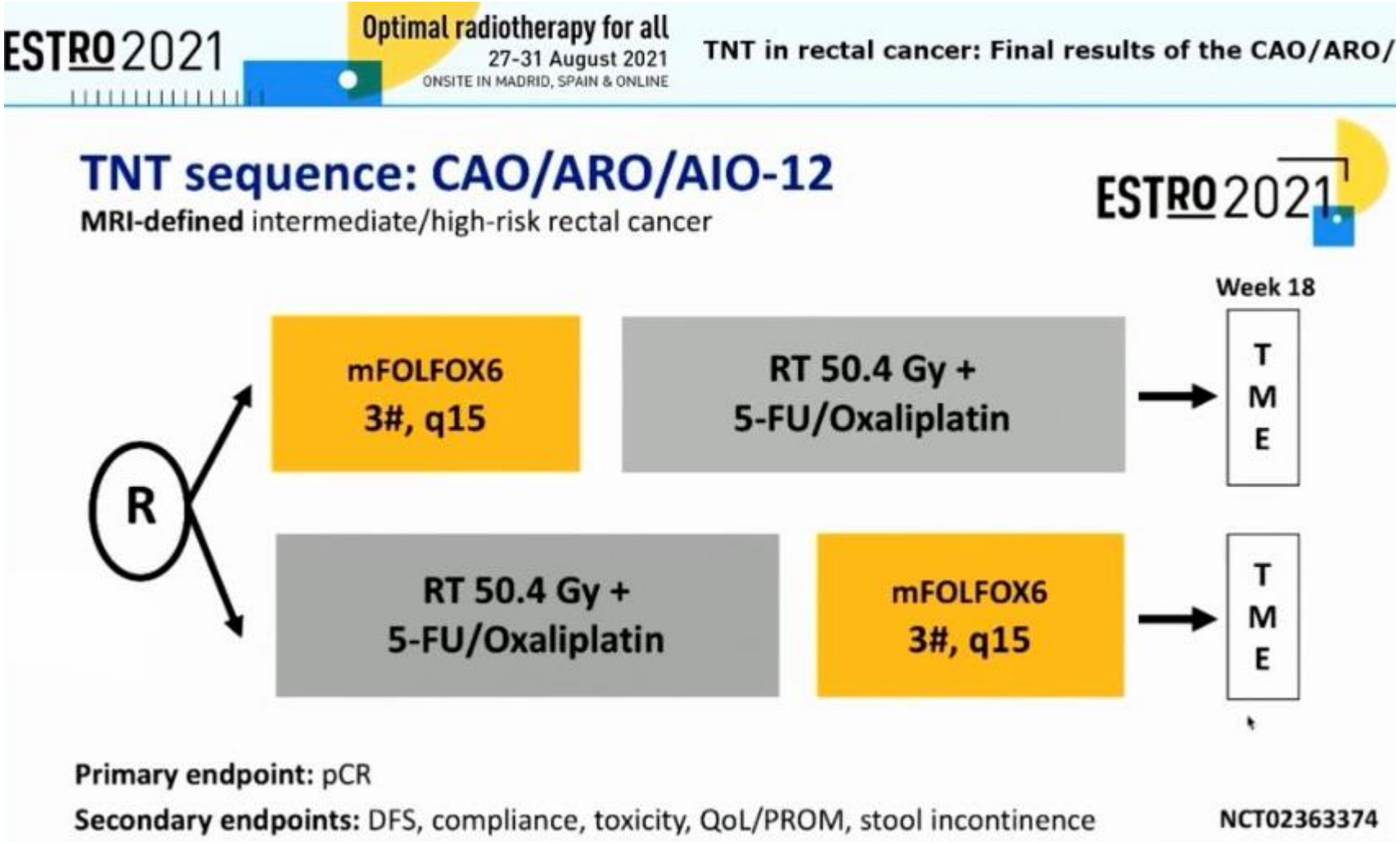
Total Neoadjuvant Therapy Era



Total Neoadjuvant therapy outcomes…



Chemotherapy first or CRT in TNT



CAO/ARO/AIO-12

	Induction CT Arm	Consolidation CT Arm	
Number of patients	156	150	
pCR	17%	25%	P < 0.001
3 yrs DFS	73%	73%	P 0.82
Locoregional recurrence	6%	5%	P 0.67
Distant Metastasis	18%	16%	P 0.52

CRT followed by chemotherapy resulted in higher pathological complete, and is thus proposed as the preferred TNT sequence if organ preservation is a priority.

Time to restaging and surgery?

- **No International consensus on the optimal interval between TNT and surgery**, both European and U.S. guidelines recommend an interval between 6 and 12 weeks.*

- RAPIDO Trial recommending restaging time 8 weeks after radiotherapy to assess poor responders to neoadjuvant with high risk for distant metastasis.

***Wouter H. Zwart.,et al ,The Multimodal Management of Locally Advanced Rectal Cancer: Making Sense of the New Data,2022.**

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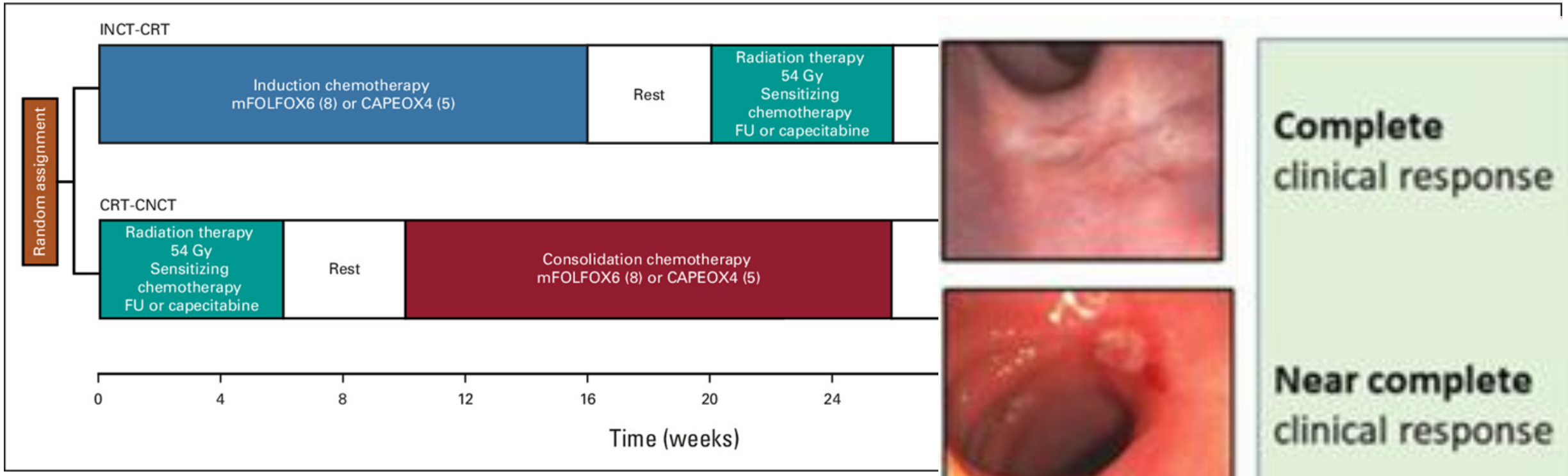
The better treatment response with the TNT strategy has lead to new goal : do patients who have achieved a clinical complete response after TNT require surgery ?

Watch and wait (WW) is an organ preservation strategy for selected patients that experience a cCR, defined as the absence of detectable macroscopic tumor by clinical means after NAT, and is used interchangeably with Non operative management (NOM)

OPRA trial:



Inclusion : Resectable rectal adenocarcinoma at diagnosis

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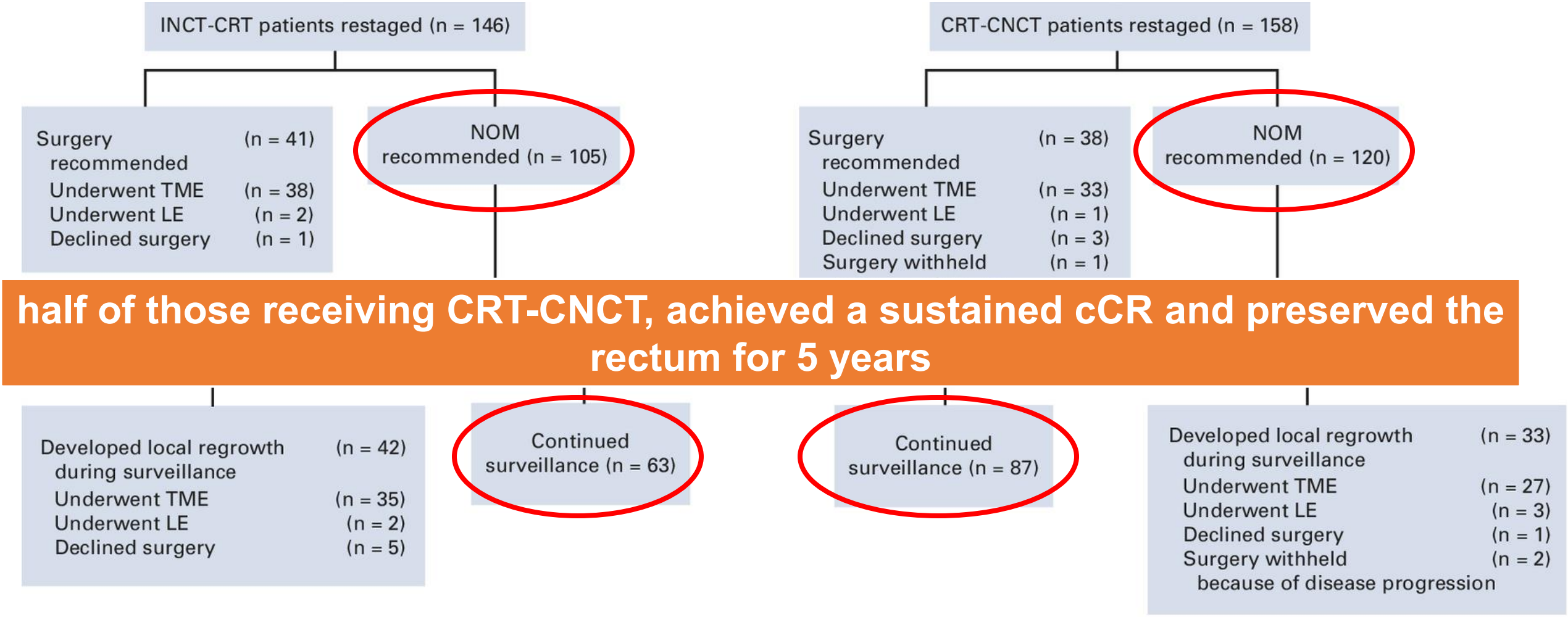
Julio Garcia-Aguilar et al. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. JCO 40, 2546-2556(2022).

OPRA trial:



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What is Next…?Selective Therapy

Rationale:

Selective Individualized therapy based on biomarkers and tumor response to minimize treatment related toxicity ,long term morbidity ,preserve lines of treatment in case of recurrence & improve QOL especially in early onset cases.

MSI-H/MMRd Rectal adenocarcinoma :

100%

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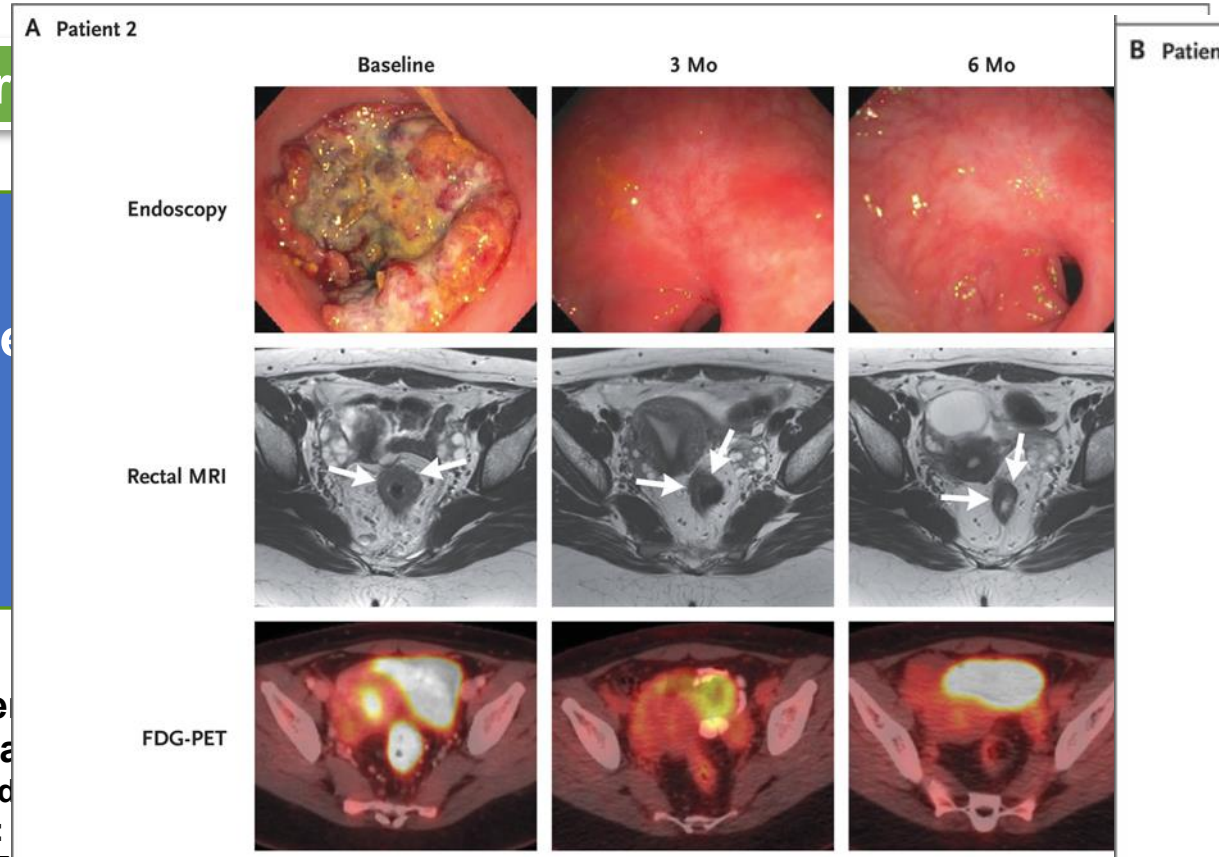
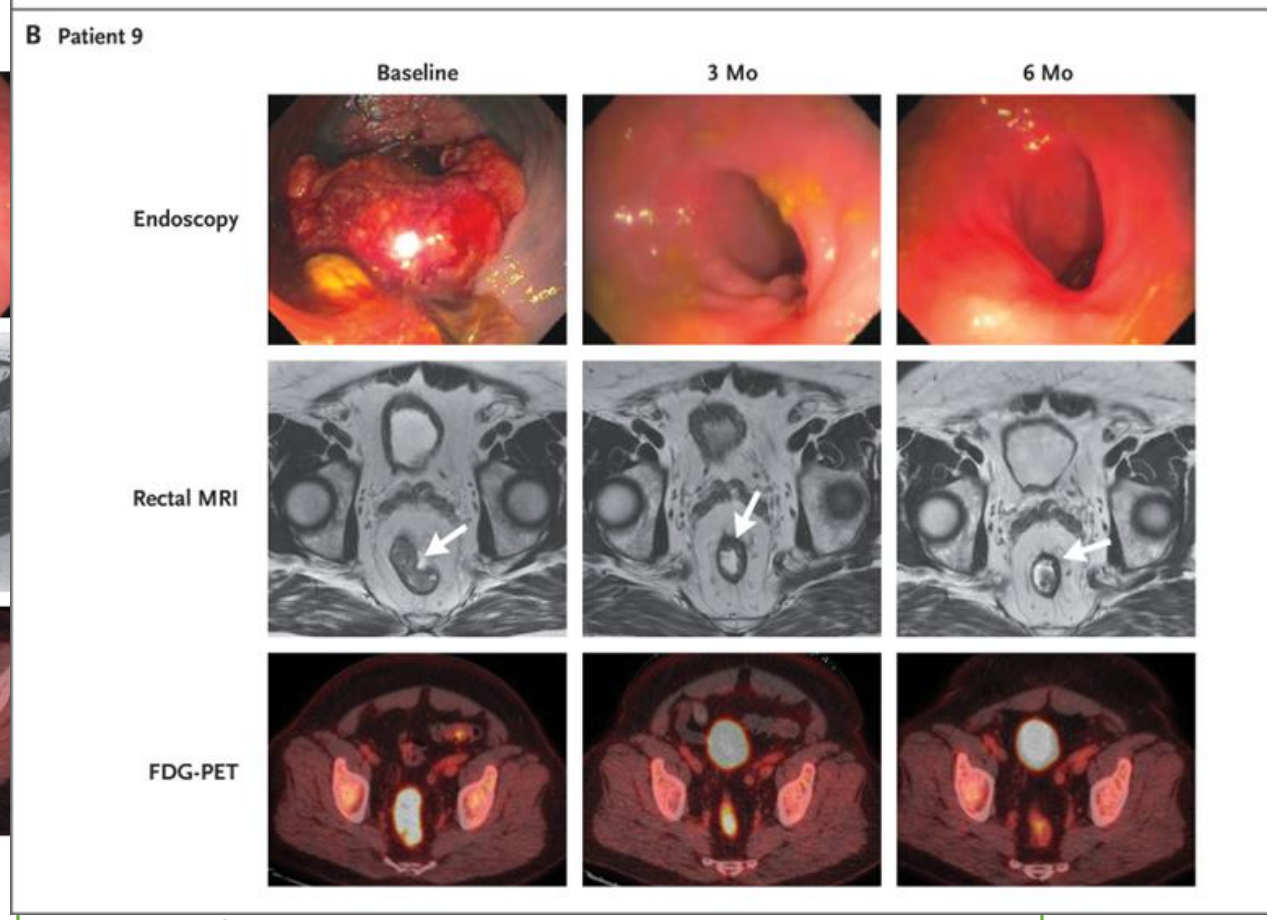
1ry e
overa
MMRd
cCR :
CCRTH : Concurrent chemoradiotherapy
TME : Total mesorectal excision

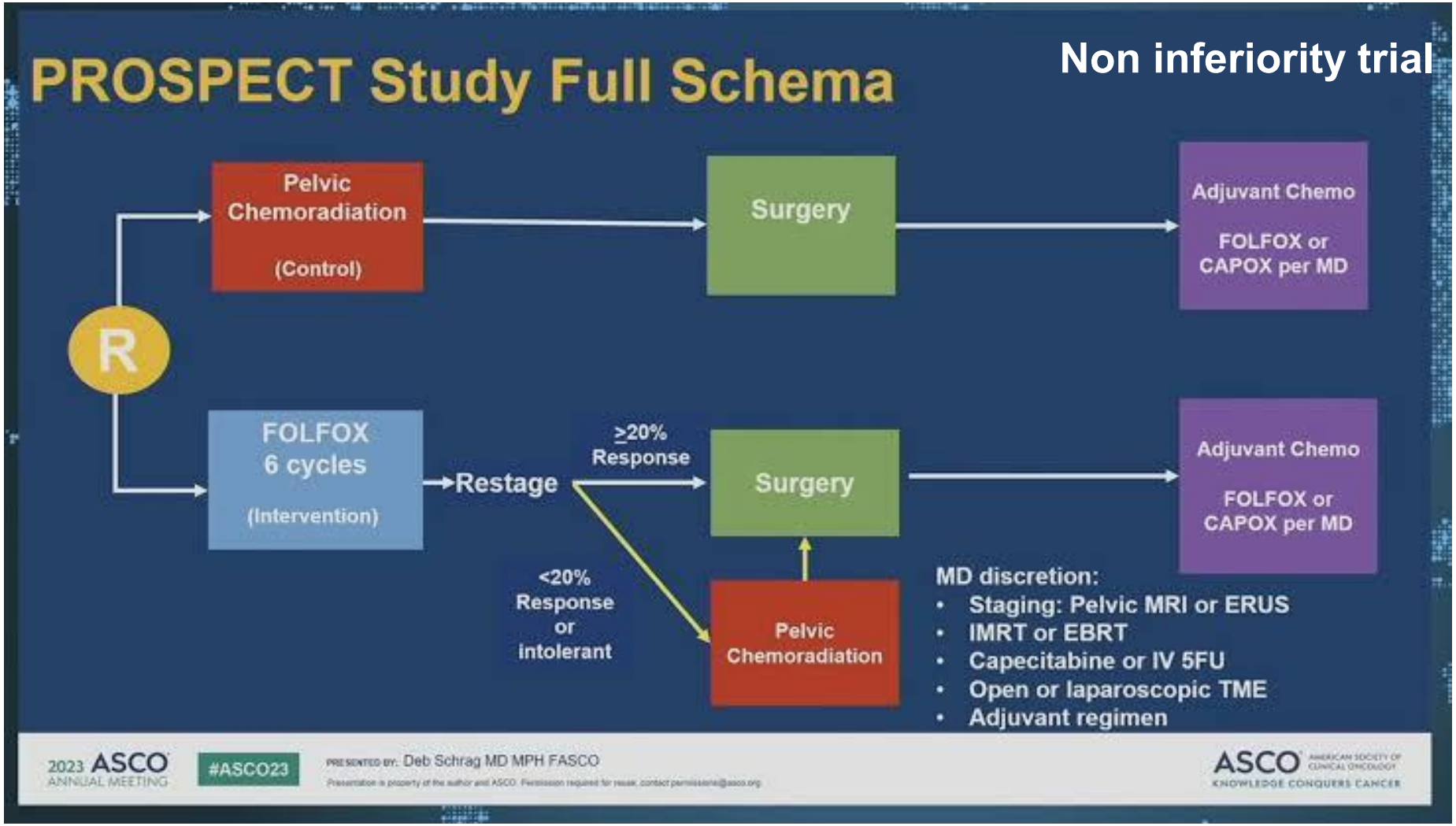




trials for dostarlimab neoadjuvant in colon and rectal cancers to confirm results

Immunotherapy..

Omitting radiotherapy



National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
pMMR/MSS Rectal Cancer

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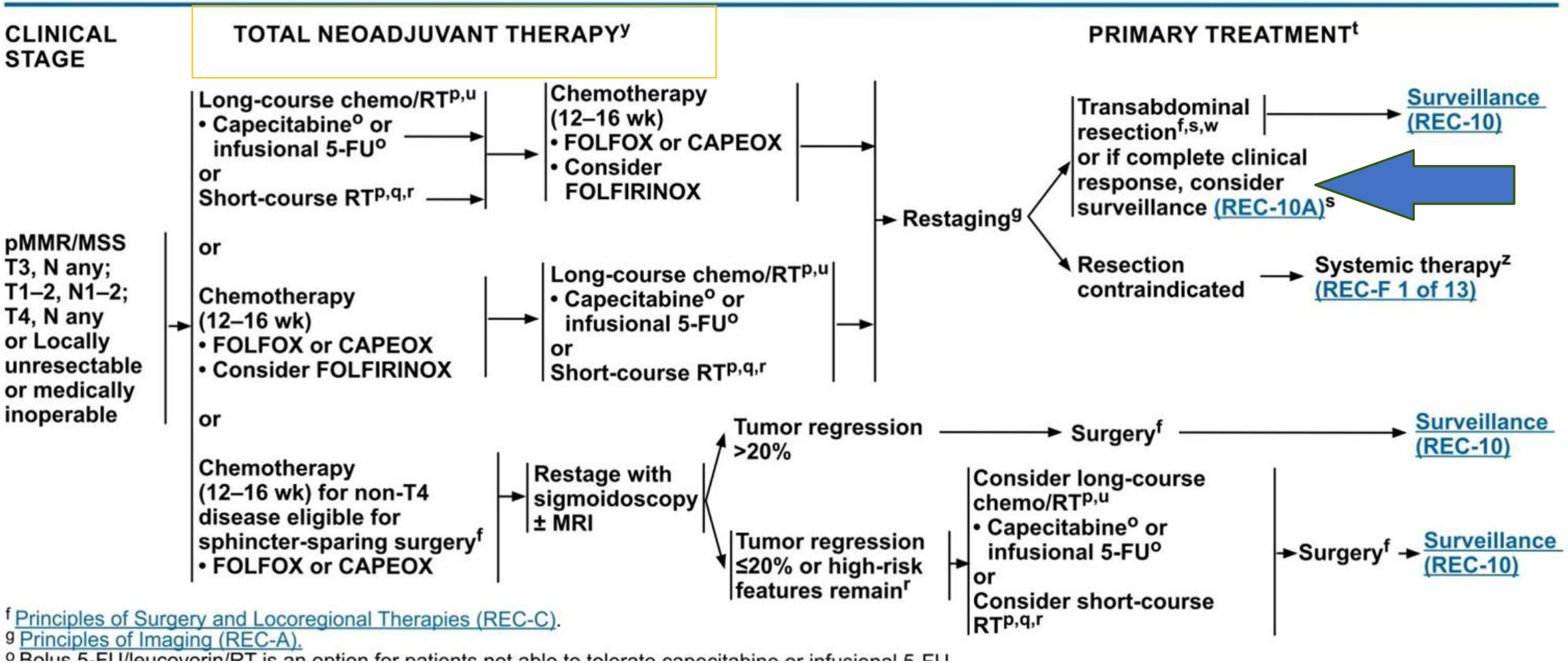

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

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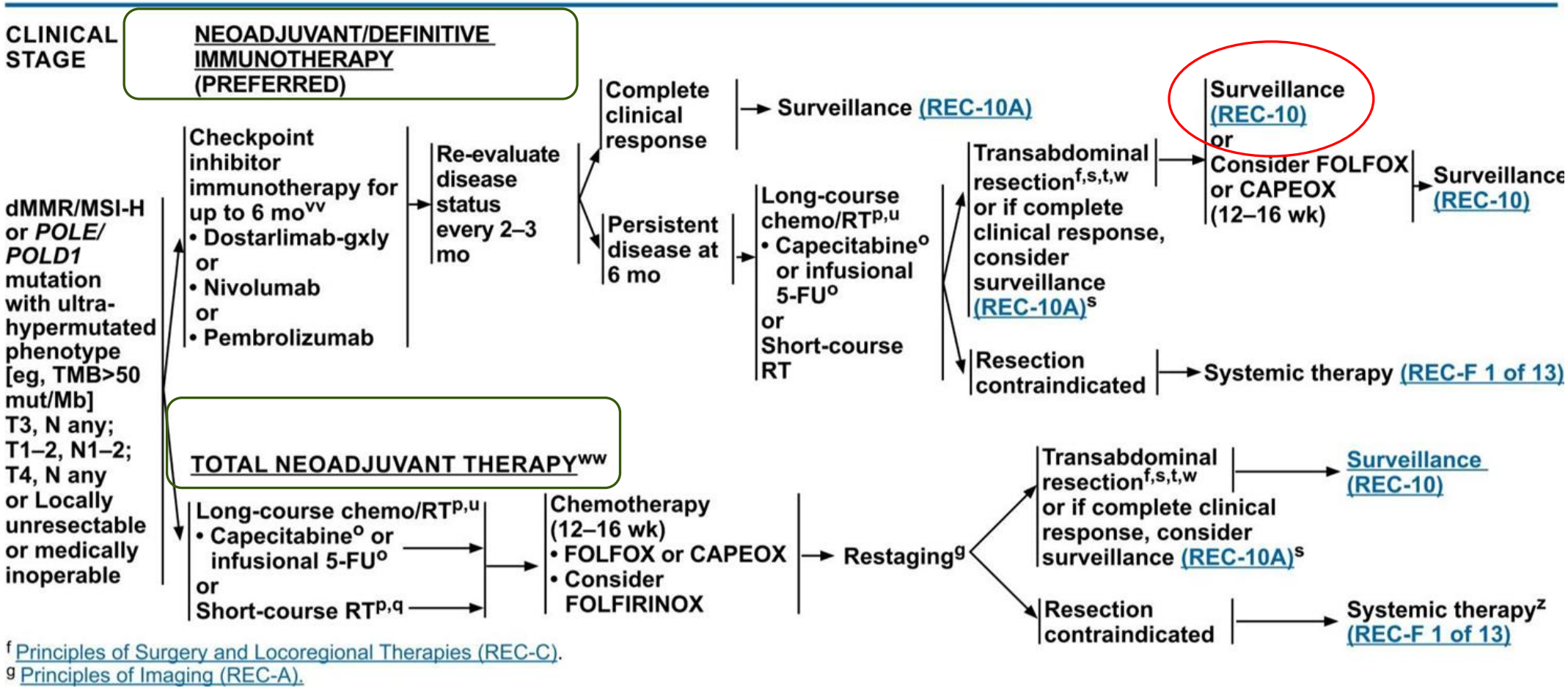

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).

Take home messages:

- Total Neoadjuvant Therapy has demonstrated superior pathological response rates, reduced chronic toxicities, and improved treatment compliance compared with conventional approaches, positioning it as a preferred therapeutic strategy in locally advanced rectal cancer.

- **MSI/MMR testing at time of diagnosis for possibility of neoadjuvant immunotherapy.**

- **TNT has facilitated opportunities for organ preservation and improved quality of life.**

Thank You!