Total Neoadjuvant therapy (TNT)in Rectal Cancer

1st September

Prof. Hesham Elghazaly
Professor of Clinical Oncology
Head of the Presidential Initiative of Woman's Health
Head Of Research Center (MASRI)
Faculty of Medicine,
Ain Shams University
BGICS President

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?
- Personalization.

Rectal Cancer …Incidence

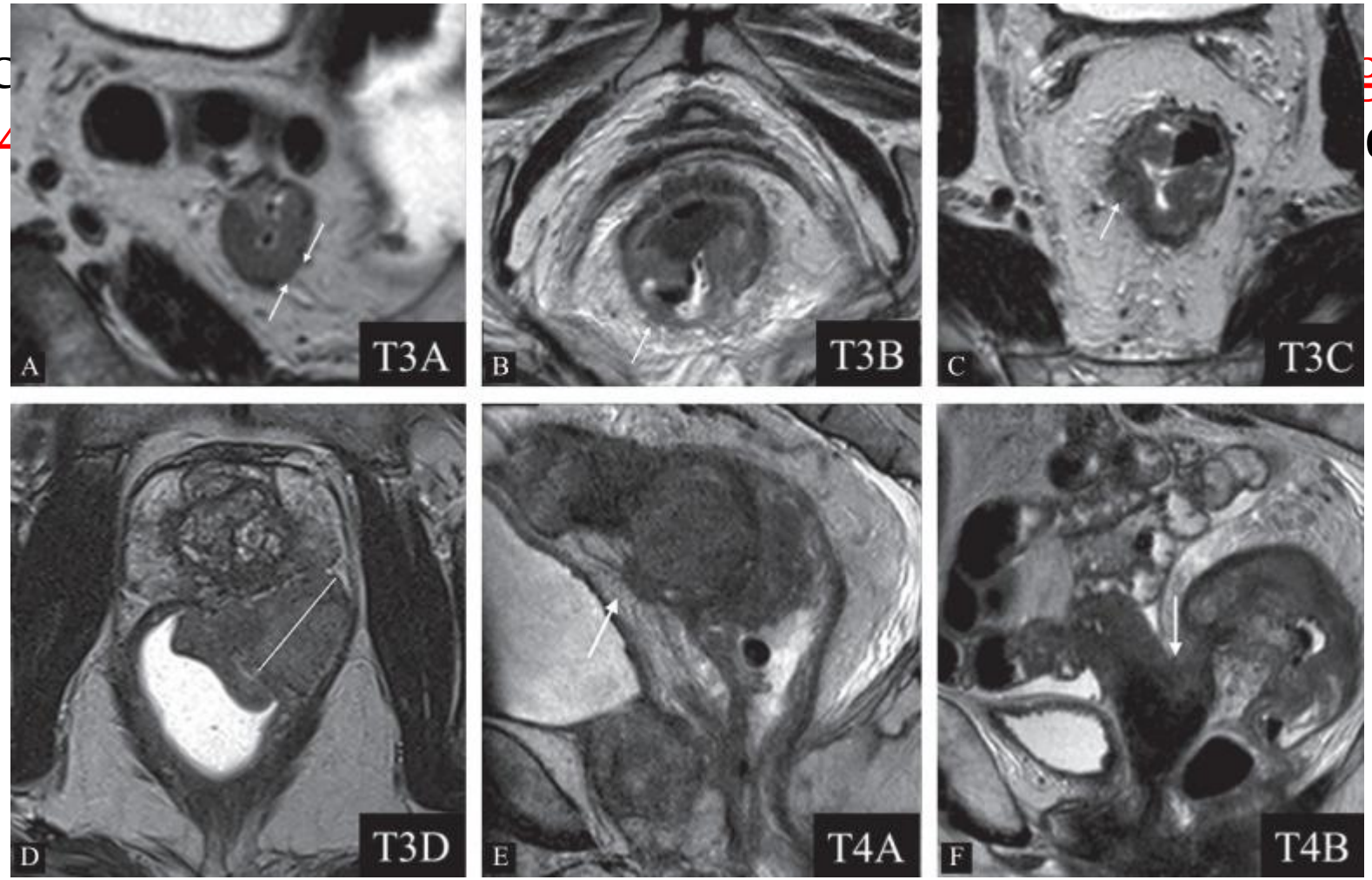
- Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cause of cancer-related death.*
- Within the next decade ,It is estimated that 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in adults younger than 50 years and mostly presented with advanced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

Locally Advanced Rectal Cancer

- Loc ge II or III
(T3-4 endoscopic



Total Neoadjuvant Therapy (TNT)in Rectal Cancer

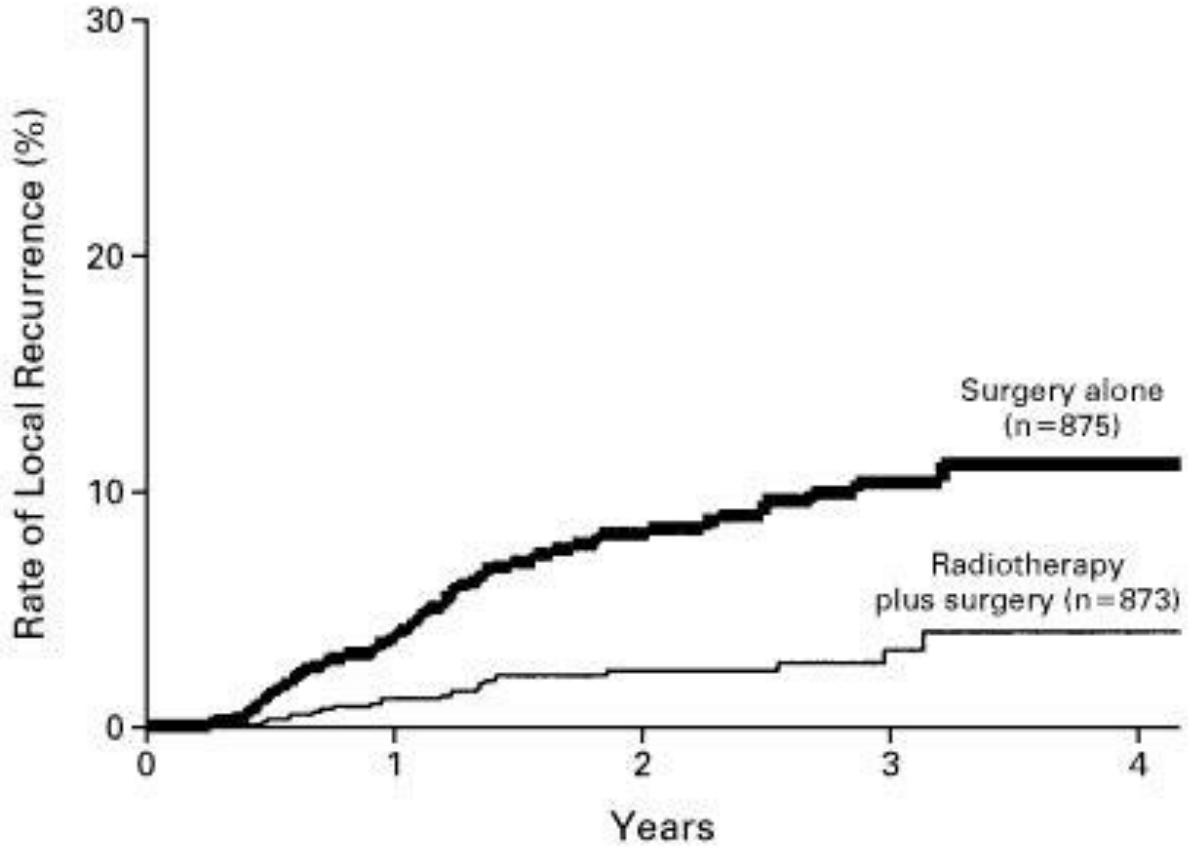
- Incidence, Early Onset & Definition
- **Multimodality Approach ..How did we start?**
- Total Neoadjuvant Therapy Rationale
- Total Neoadjuvant therapy outcomes… Evidence-based
- Watch &Wait approach …Hope or Hype?
- Personalization.

Multi ve start?

- Arou rates varied between

- Late Ei without Radiotherapy versus c R).
- Late Ni

TM s who underwent preopera gnificant difference in rs.



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

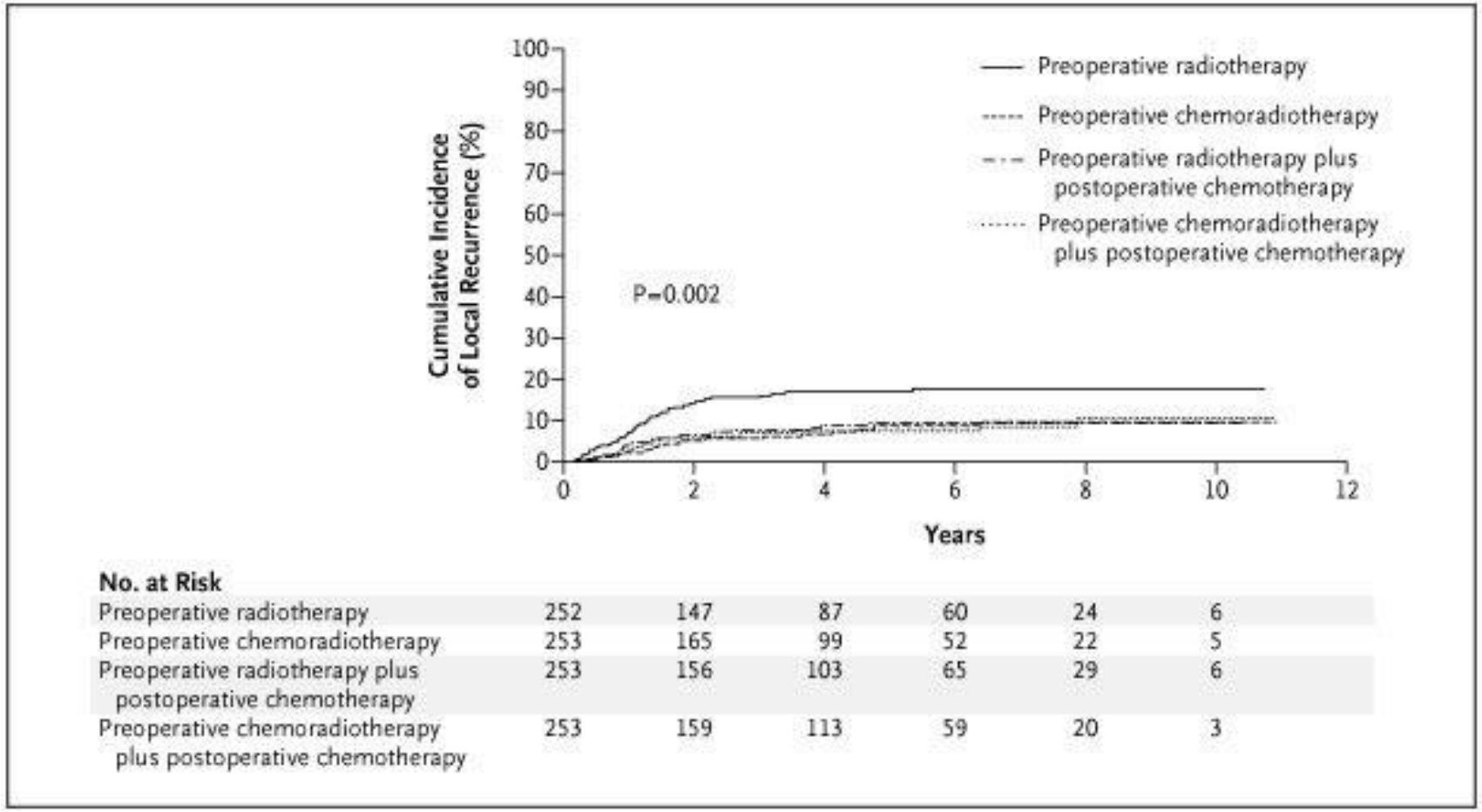
***van Gijn W, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011**

Mu[illegible]art?

- Ear[illegible]operative rad[illegible]T3-4,N0-2,M[illegible]

pelv[illegible]t did not recei[illegible]

with[illegible]etastasis (DM[illegible]



No. at Risk						
Preoperative radiotherapy	252	147	87	60	24	6
Preoperative chemoradiotherapy	253	165	99	52	22	5
Preoperative radiotherapy plus postoperative chemotherapy	253	156	103	65	29	6
Preoperative chemoradiotherapy plus postoperative chemotherapy	253	159	113	59	20	3

***Bosset JF, et al; EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006**

Multimodality Approach ..How did we start?

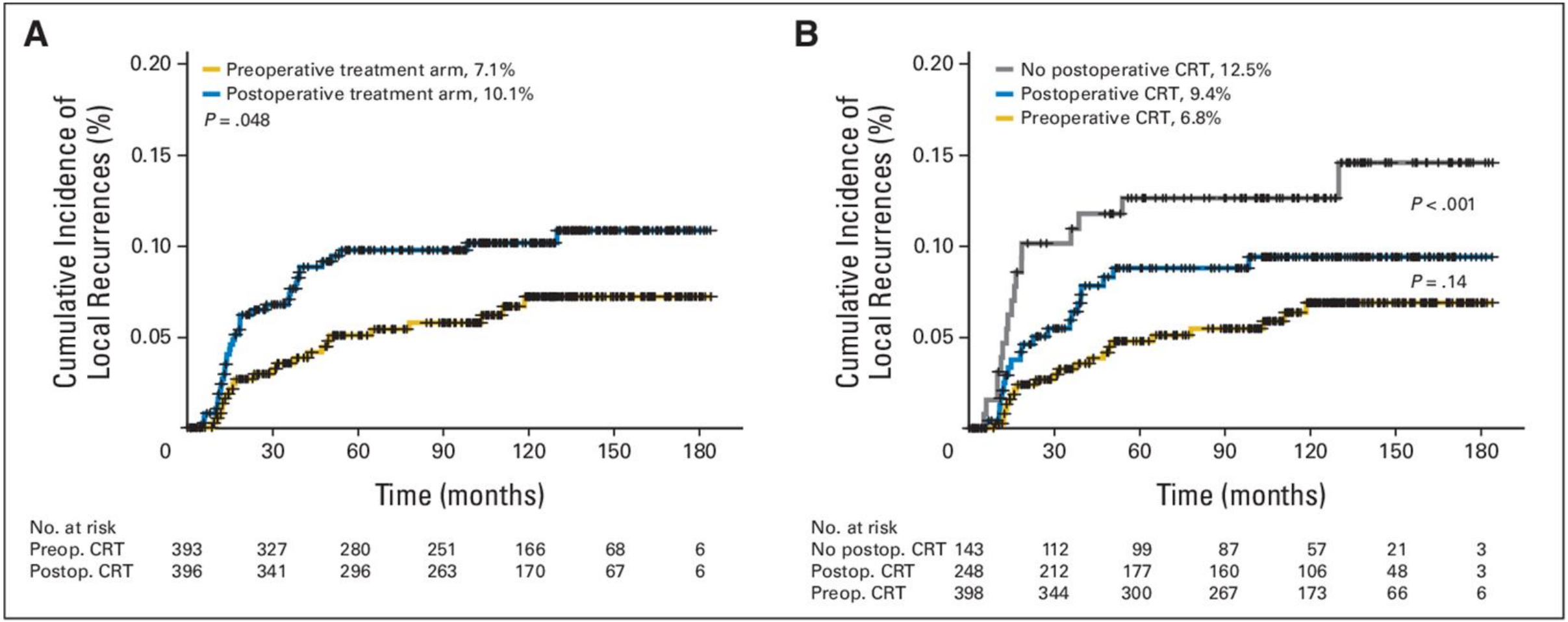
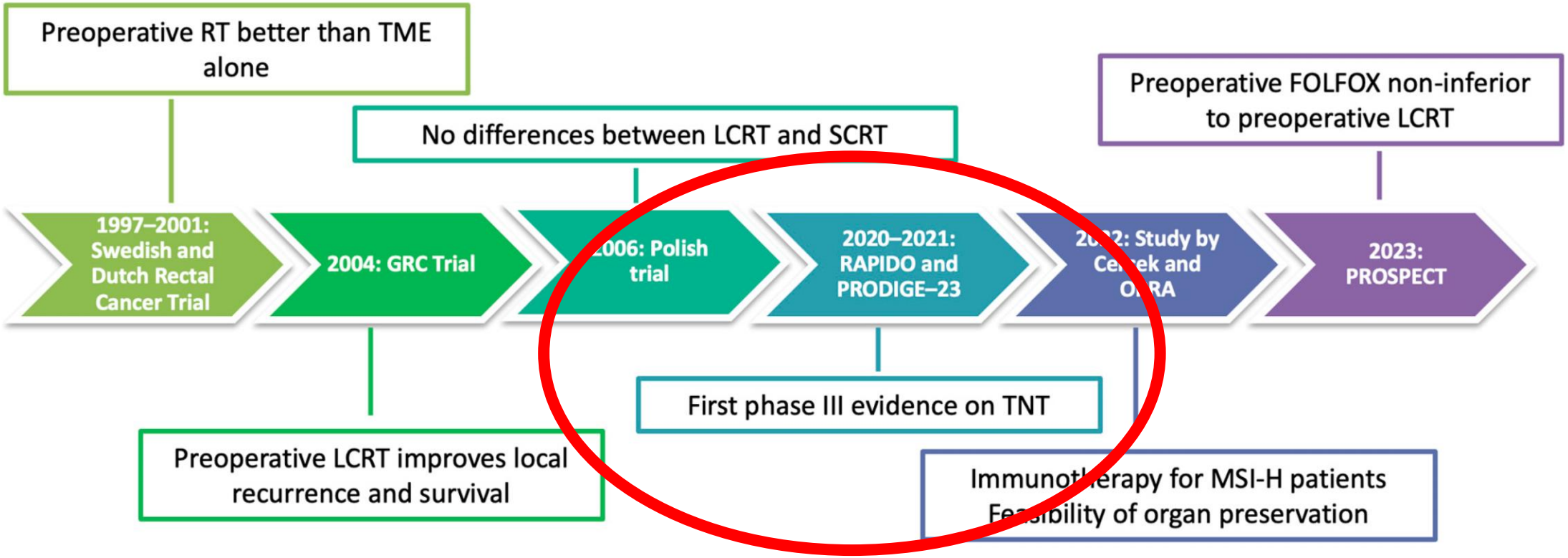


Fig 3. Cumulative incidence of local recurrences after macroscopically complete local tumor resection in the intention-to-treat population (A) and according to treatment received (B). CRT, chemoradiotherapy; preop, preoperative; postop, postoperative.

Total Neoadjuvant Therapy Era



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?
- Personalization.

Total Neoadjuvant Therapy Rationale

TNT approach : The use of multi-agent chemotherapy followed by chemoradiation (usually long-course) and surgery

Aiming at:

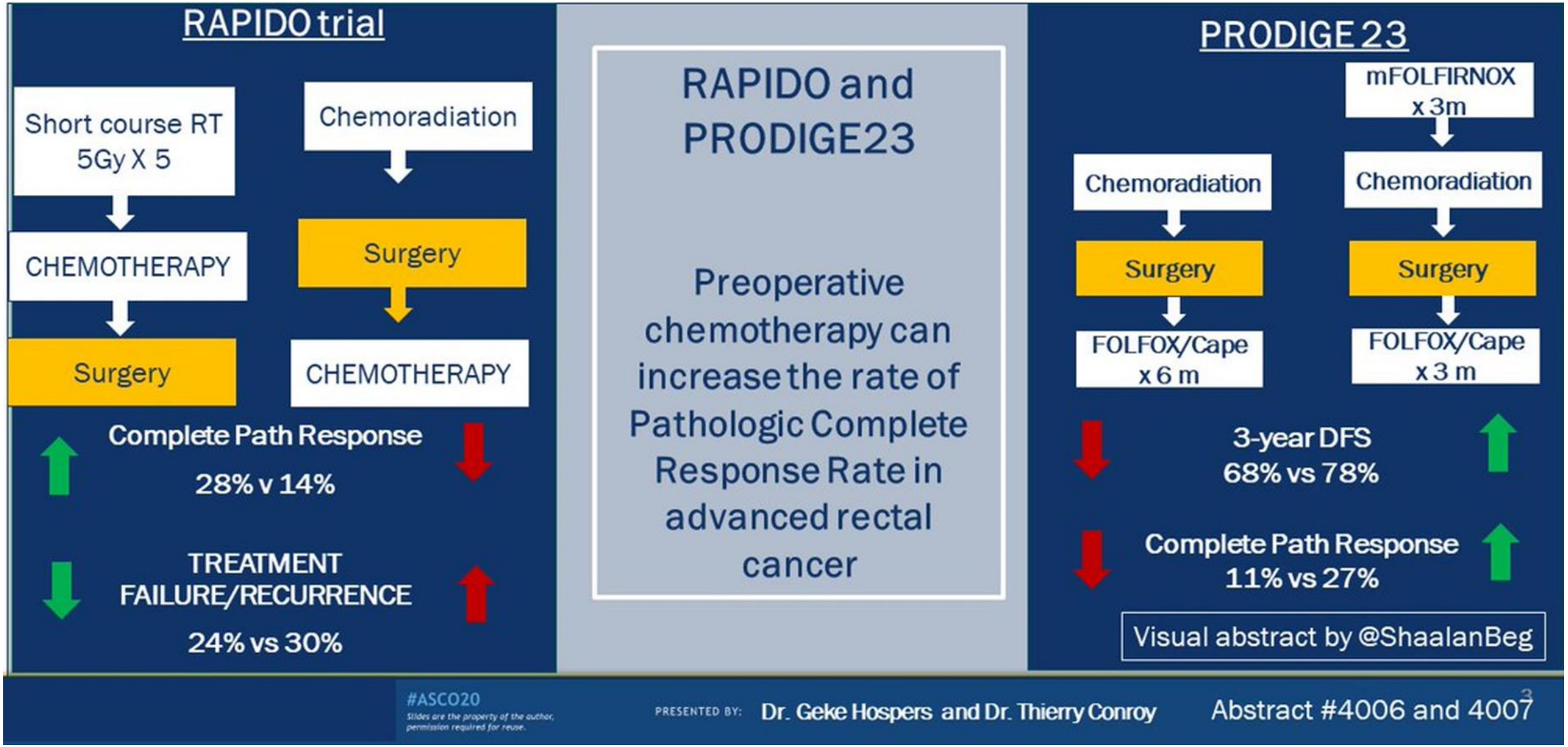
- ✓Tumor downsizing and possible pCR.
- ✓Improved local control, and the ability to consider nonoperative treatment (WW) if the patient declines surgery.
- ✓Increased possibility of sphincter preservation .
- ✓Increased compliance with chemotherapy (because of the greater tolerability in the preoperative as compared with the postoperative setting).
- ✓Decrease Distant metastasis by moving the systemic adjuvant chemotherapy to the interval between CCRT and TME, because of higher neoadjuvant compliance and the uncertain value of adjuvant chemotherapy.

***Jason Liu.,et al , Patterns of Care for Patients With Locally Advanced Rectal Cancer Treated with Total Neoadjuvant Therapy at Predominately Academic Centers between 2016-2020: An NCDB Analysis,2023.**

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?
- Personalization.

Total Neoadjuvant therapy outcomes…



Clinical Outcomes	RAPIDO (Exp vs. Std)	PRODIGE-23 (Exp vs. Std)	PROSPECT (Exp vs. Std)
Median follow-up	4.6 yrs	4.6 yrs	4.8 yrs
Primary endpoint	3-yrs DrTF	3-yrs DFS	5-yrs DFS
3-yrs Primary event (Δ%) *	23.7% vs. 30.4% (6.7%)	76% vs. 69% (7%)	n/a
5-yrs	27.8% vs. 34% (7%)	73.1% vs. 65.5% (7.6%)	80.8% vs. 78.6% (2.2%)
7-yrs	n/a	67.6% vs. 62.5% (5.1%)	n/a
* HR (95% CI); *p* value	0.75 [0.60–0.96]; $p = 0.019$	0.69 [0.49–0.97]; $p = 0.034$	0.92 [0.72–1.14]; $p = 0.005$ for noninferiority
3-yrs MFS	80% vs. 73.2%	79% vs. 72%	n/a
5-yrs	77% vs. 69.6%	77.6% vs. 67.7%	n/a
7-yrs	n/a	73.6% vs. 65.4%	n/a
pCR rate	28.4% vs. 14.3%	27.5% vs. 11.7%	21.9% vs. 24.3%
Local relapse rate	12% vs. 8% at 5 yrs	5.3% vs. 8.1% at 7 yrs	1.8% vs. 1.6% at 5 yrs
Distant relapse rate	23% vs. 30.4% at 5 yrs	20.7% vs. 27.7% at 7 yrs	n/a
3-yrs OS	89.1% vs. 88.8%	91% vs. 88%	n/a
5-yrs OS	81.7% vs. 80.2%	86.9% vs. 80%	89.5% vs. 90.2%
7-yrs OS	n/a	81.9% vs. 76.1%	n/a

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.

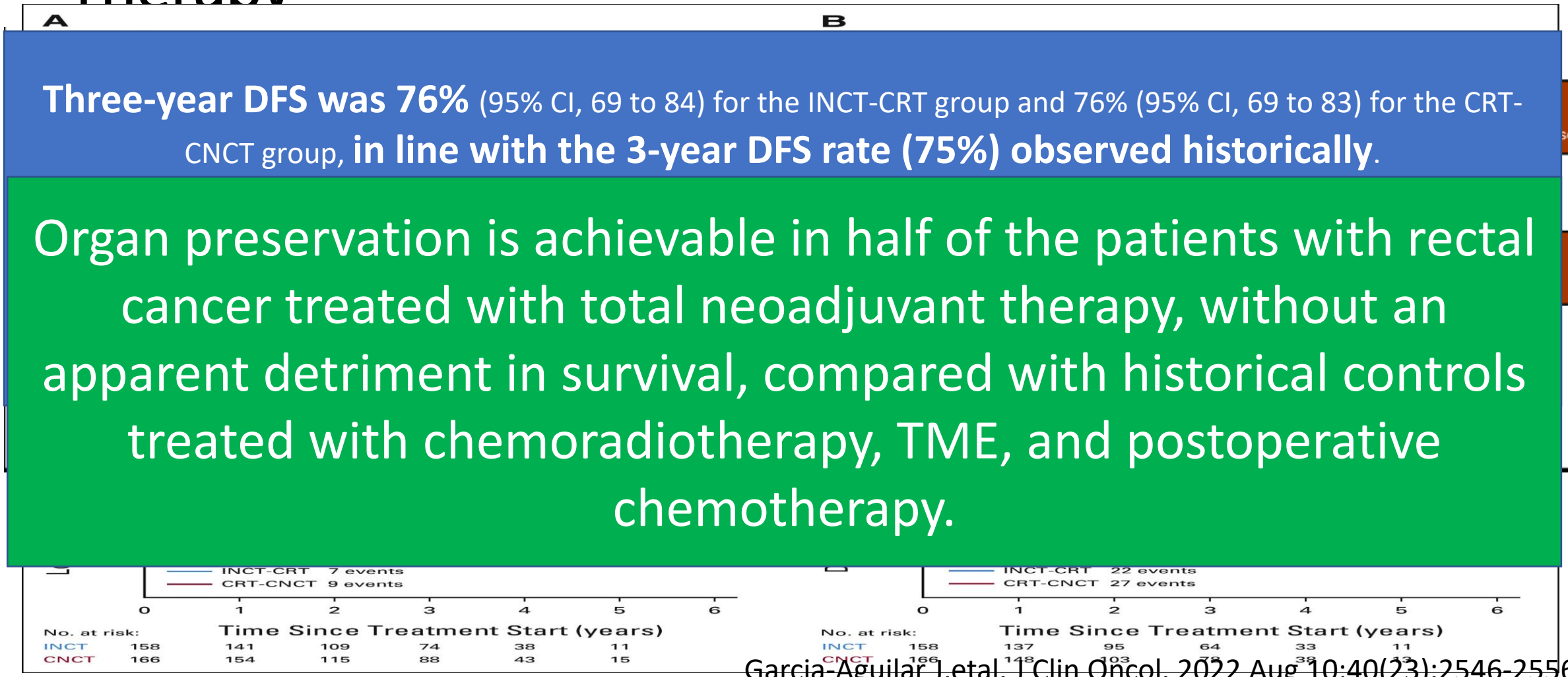
***Wouter H. Zwart.,et al ,The Multimodal Management of Locally Advanced Rectal Cancer: Making Sense of the New Data,2022.**

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?**
- Personalization.

Study, year	Analysis	Patients	Neoadjuvant therapy		Timing of assessment after neoadjuvant treatment	Outcomes[a]				
			Radiotherapy	Chemotherapy		Local regrowth	Salvage treatment after local regrowth	Distant metastasis	OS	DFS
Habr-Gama et al. [ ], 2004	Observational retrospective	71/265 (underwent WW)	50.4 Gy/28 fx	5-FU and leucovorin	8 weeks	2 (2.8%)	2/2 (100%) had transanal resection or brachytherapy	–	5-yr rate: 100%	5-yr rate: 92%
Appelt et al. [ ], 2015	Observational prospective	40/51 (underwent WW)	60 Gy/30 fx to tumor, 50 Gy/30 fx to elective lymph node volumes, and 5 Gy endorectal brachytherapy boost	Oral tegafur-uracil	6 weeks	9 (22.5%) 2-yr rate: 25.9%	9/9 (100%) had salvage surgery	3 (7.5%)	2-yr rate: 100% (in full population)	–
Renehan et al. [ ], 2016	Observational mixed prospective-retrospective	129 (underwent WW) 31/259 plus 98 from WW registry	45 Gy/25 fx	Fluoropyrimidine-based chemotherapy	8 weeks or more	44 (34%)	32/44 (72.7%) had salvage surgery	4 (3.1%)	3-yr rate: 96%	3-yr non-regrowth rate: 88%
Dossa et al. [ ], 2017	Meta-analysis	867 from 23 studies (underwent WW)	Various	Various	Various	2-yr rate: 15.7%	The pooled proportion of patients who had salvage therapy was 95.4%.	–	–	–
van der Valk et al. [ ], 2018	IWWD report Observational mixed prospective-retrospective	1,009 (underwent WW)	Various	Various	Various	213/880 2-yr rate: 25.2%	Of 148 patients with information, 46 (31%) had local excision and 115 (78%) had salvage TME.	71 (8%)	5-yr rate: 85%	5-yr rate: 94%
Garcia-Aguilar et al. [ ], 2022	OPRA trial Randomized phase II trial prospective	158 (underwent INCT-CRT, of which 105 underwent WW) 166 (underwent CRT-CNCT, of which 120 underwent WW)	45 Gy/25 fx to pelvic nodes and 50–56 Gy to primary tumor and involved nodes	Concurrent capecitabine or 5-FU with 8 cycles of FOLFOX or 5 cycles of CAPEOX before or after chemoradiation	8 ± 4 weeks	42/105 (40%): INCT-CRT 33/120 (27.5%): CRT-CNCT	All patients were recommended for TME.	3-yr distant metastasis-free survival rate: 84% (in full INCT-CRT group) and 82% (in full CRT-CNCT group)	–	3-yr rate: 76% (in full INCT-CRT population) and 75% (in full CRT-CNCT population)

Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy



Three-year DFS was 76% (95% CI, 69 to 84) for the INCT-CRT group and 76% (95% CI, 69 to 83) for the CRT-CNCT group, **in line with the 3-year DFS rate (75%) observed historically**.

Organ preservation is achievable in half of the patients with rectal cancer treated with total neoadjuvant therapy, without an apparent detriment in survival, compared with historical controls treated with chemoradiotherapy, TME, and postoperative chemotherapy.

Garcia-Aguilar J,etal. J Clin Oncol. 2022 Aug 10;40(23):2546-2556.

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?
- **Personalization.**

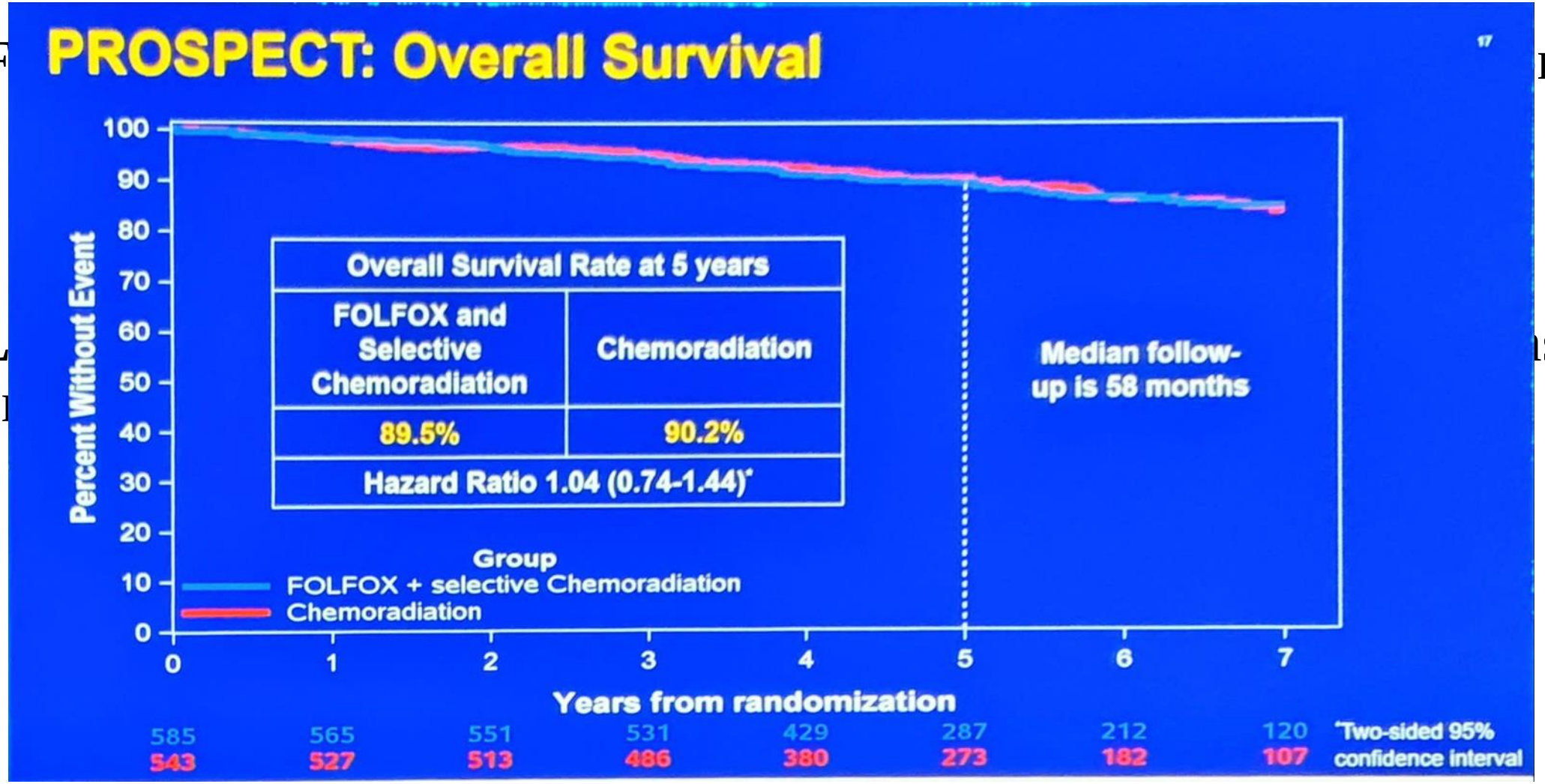
Personalization and possible TTT Algorithm

Rationale:

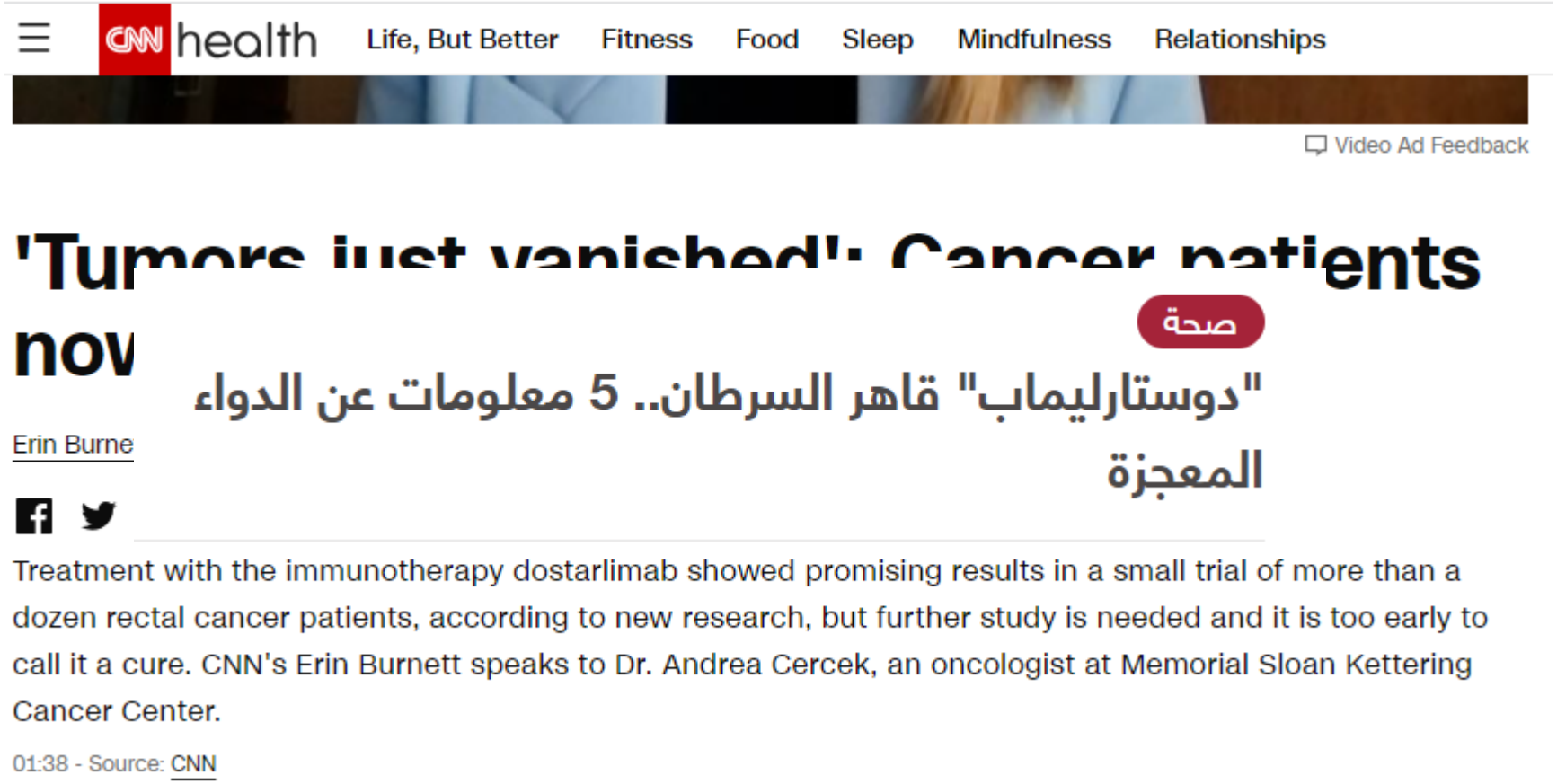
Selective Individualized therapy based on biomarkers and tumor response to minimize treatment related toxicity ,long term morbidity ,preserve lines of treatment in case of recurrence & improve QOL especially in early onset cases.

PROSPECT Trial

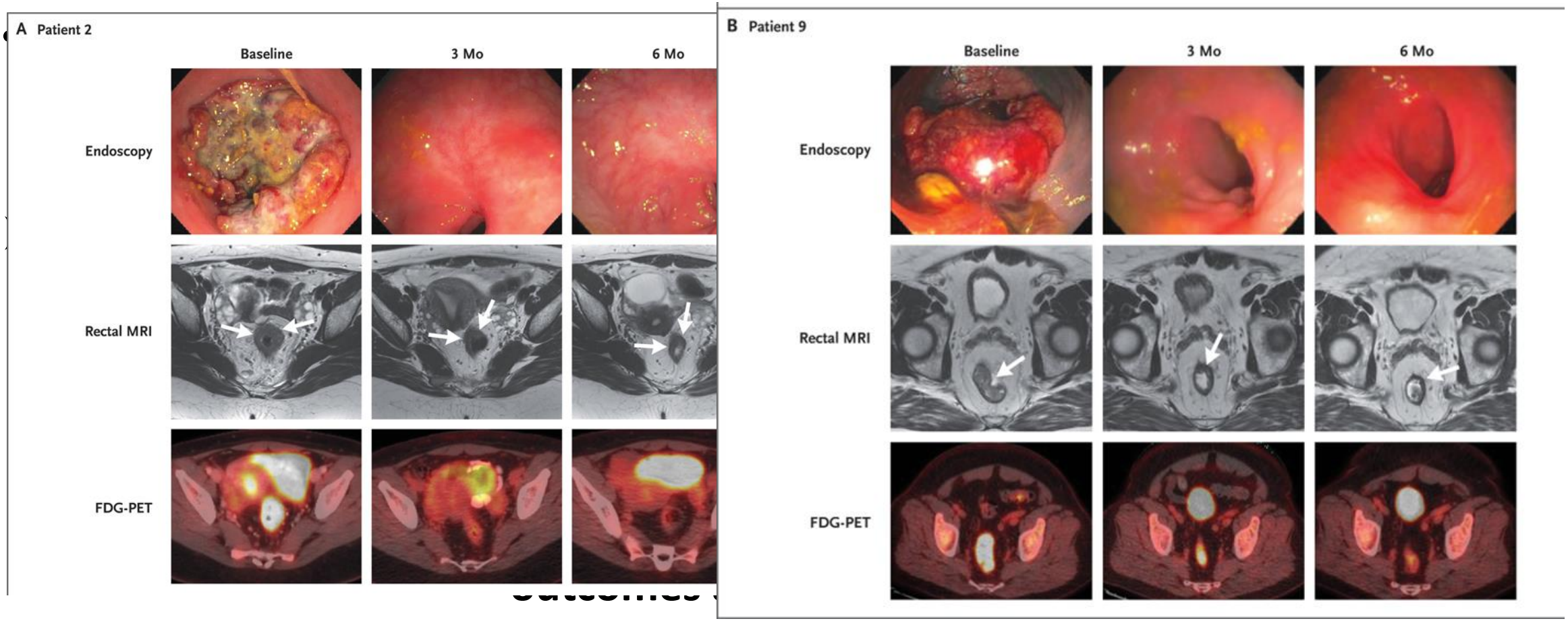
- F r
- **L** s
  o



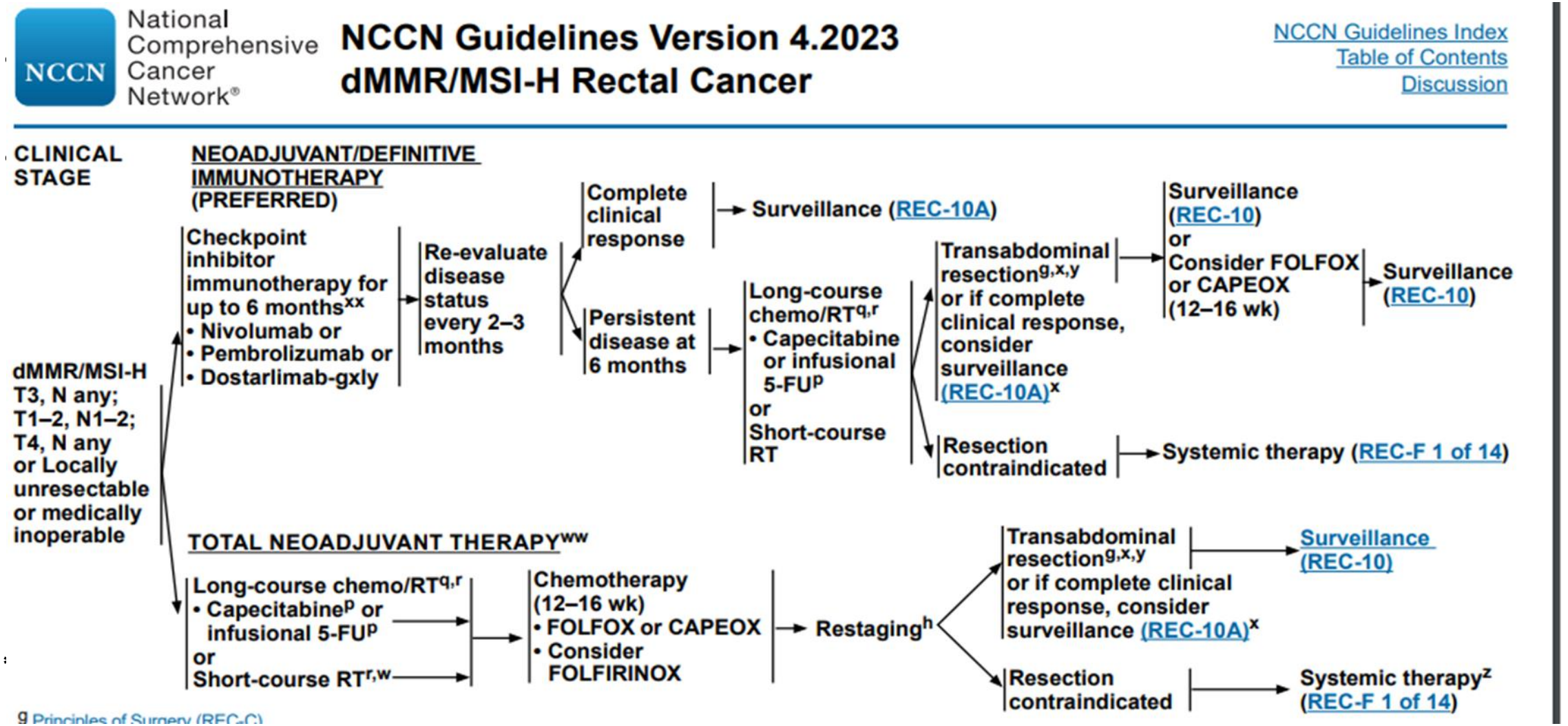
Immunotherapy..



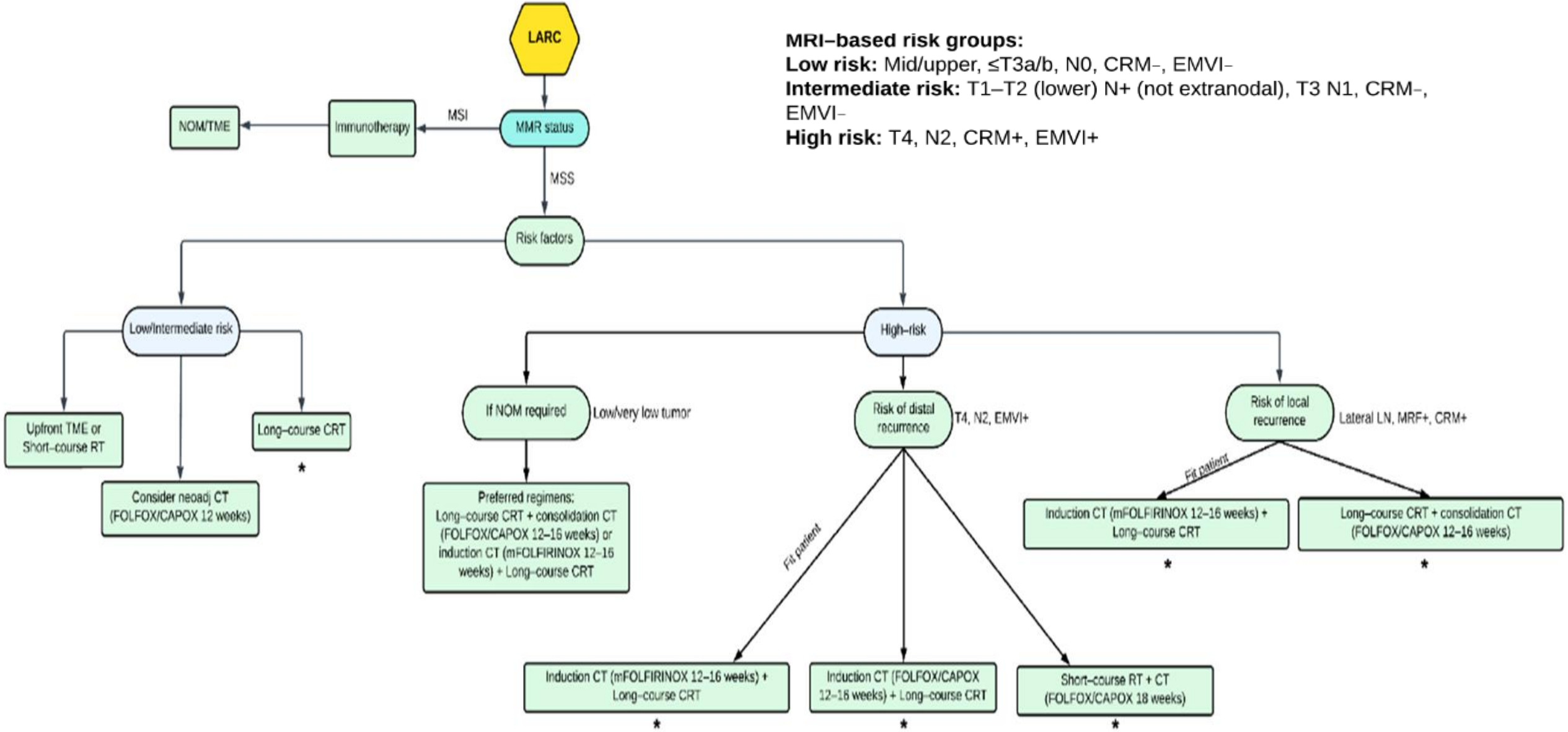
Dostarilimab as Neoadjuvant



Neoadjuvant Immunotherapy for d MMR Rectal Cancer:



Suggested TTT Algorithm



Take Home Message….

- Multidisciplinary Team is the main pillar for best management of rectal cancer.
- Rising incidence for early onset rectal cancer showed the need to maximize the survival benefit in alignment with keeping better QOL and least long term morbidity.
- Personalized Treatment became main approach even in local treatment of rectal cancer .

Thank You!