Colorectal Cancer Masterclass

Tuesday, August 30, 2022

Watch and wait post-neoadjuvant therapy

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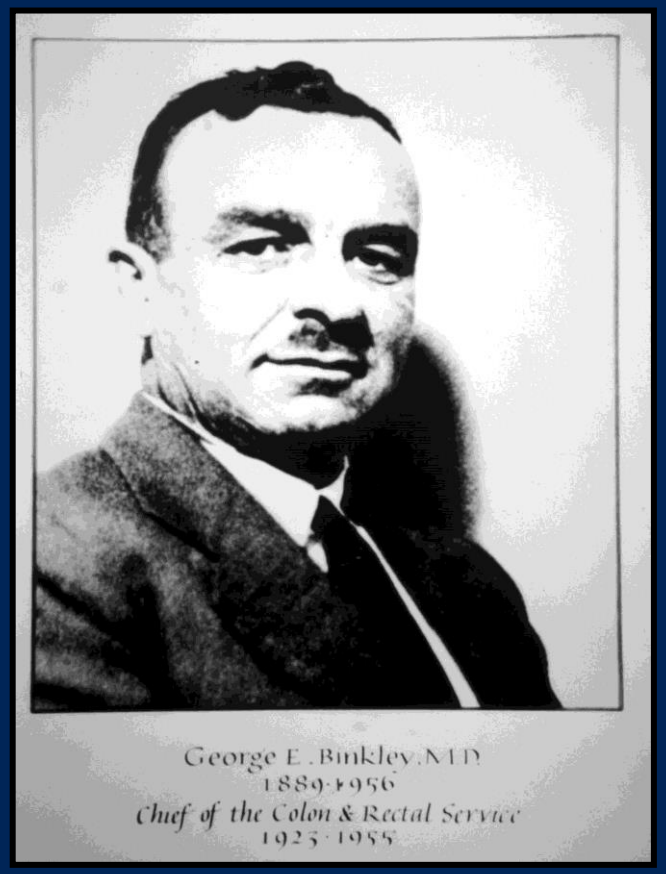
Tumor Response to Neoadyuvant Therapy

Will this patient benefit from TME?

RADIATION IN THE TREATMENT OF RECTAL CANCER

BY GEORGE E. BINKLEY, M.D.
OF NEW YORK, N. Y.
FROM THE SURGICAL SERVICE OF THE MEMORIAL HOSPITAL

Ann Surg. 1929 Dec; 90 (6): 1000-14



The most effectual methods for early cases are:

(I) Radiation therapy.

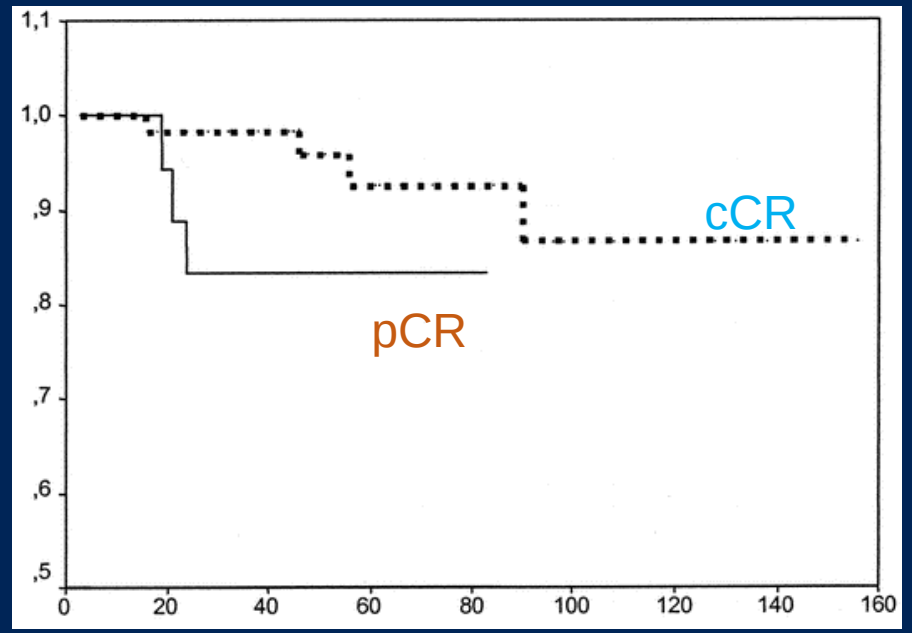
(II) The combined use of radium and surgery.

At Memorial Hospital we prefer to use radiation therapy as the principal factor of treatment of rectal cancer. We supplement this treatment with surgery in those cases in which surgical interference offers an additional advantage.

Operative vs. Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiotherapy

265 resectable rectal cancer patients treated with ChemoRT

- cCR → W&W (n = 71)
- non-cCR → Resection (n = 194; 22 had pCR)



Deferral of Surgery: Safe

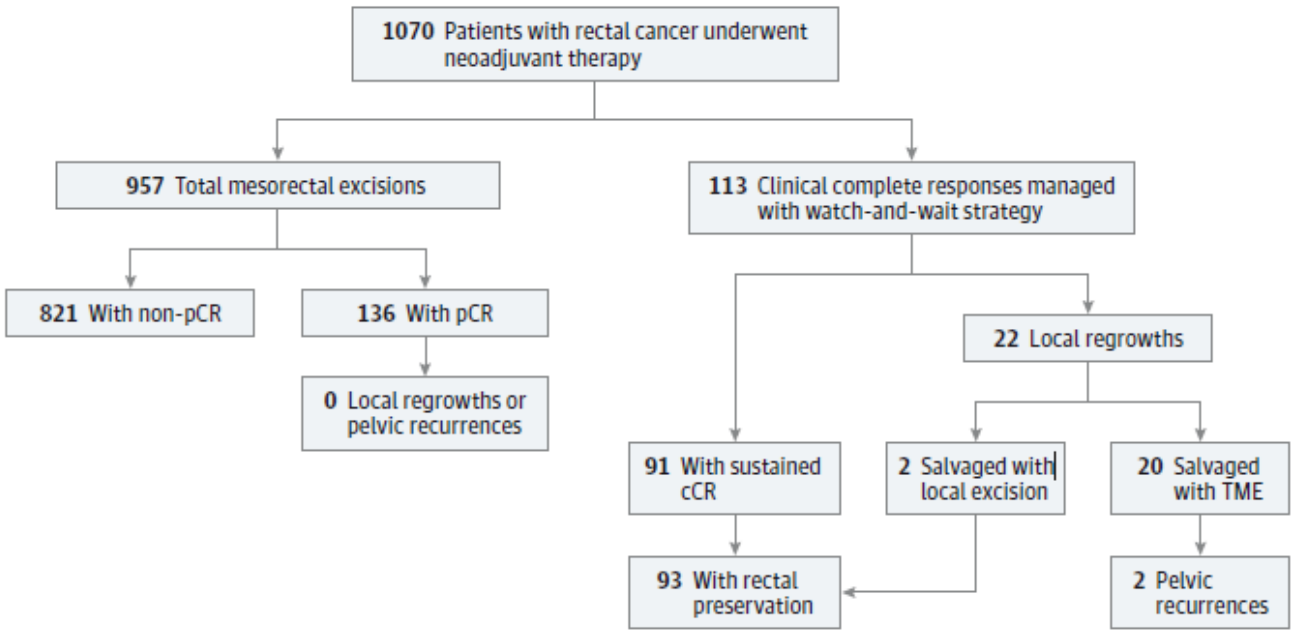
Surgical Salvage: Effective

Long-Term Survival: Possible

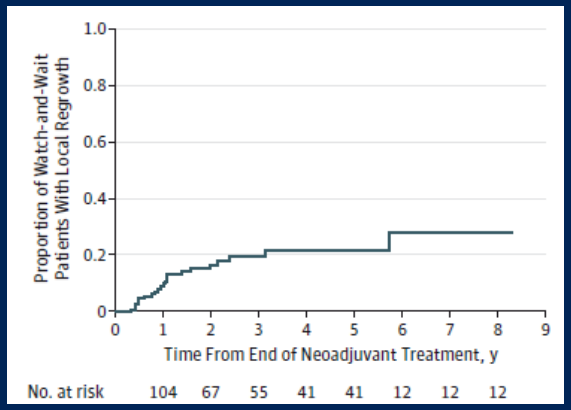
Habr-Gama A et al., *Ann Surg* 2004; 240:711-7

MSK results with W&W

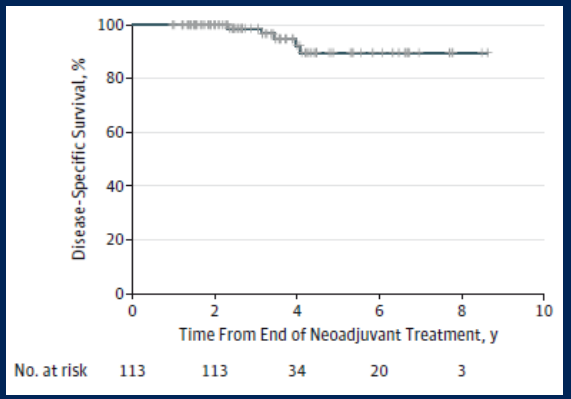
Figure 1. Selection of Patients Included in the Watch-and-Wait and Pathologic Complete Response (pCR) Groups



Tumor Regrowth



Disease Specific Survival



JJ Smith et al, JAMA Oncology 2019

Identifying true responders

- Critical for successful W&W
- Criteria for response
    - Too strict: we will miss many responders
    - Too loose: we will follow patients with residual tumor
- Currently use 3 modalities: DRE, Endoscopy, Imaging (MRI)

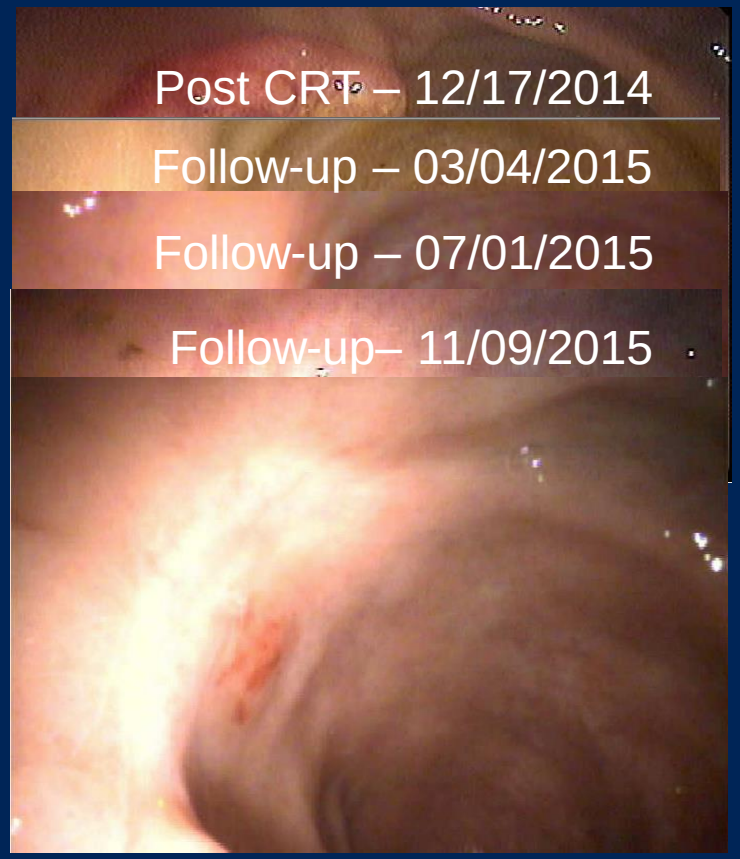
Salvage after tumor re-growth

	Patients W&W	Re-growth	Salvage after Re-growth	Distant Metastasis	Overall Survival	Disease-Free Survival
Habr-Gama 2014	90	**30 (31%)**	**28 (93%)**	8 (9%)	5-year 91%	5-year 68%
Renehan 2015	129	**44 (34%)**	**37 (84%)**	7 (5.5%)	3-year 96%	--
Martens 2016	100	**15 (15%)**	**13 (87%)**	5 (5%)	3-year 97%	3-year 81%
Smith 2018	113	**22 (19%)**	**20 (91%)**	9 (8%)	75% vs 94%*	73% vs 90%*

(*) patients with pCR after TME

75 y/o male rectal cancer, T2N1M0

Baseline 9/17/2014



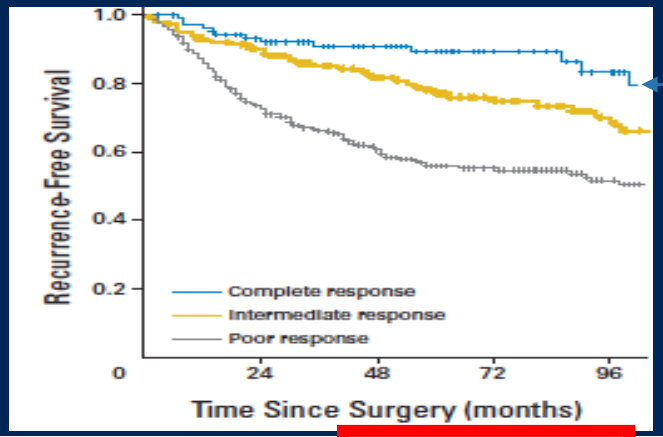
Biopsy: TVA with HGD → TME: ypT2N0

Distant metastasis during W&W

	Patients W&W	Re-growth	Salvage after Re-growth	Distant Metastasis	Overall Survival (%)	DFS (%)
Habr-Gama 2014	90	31%	28(93%)	**8 (9%)**	91%	68%
Renehan 2015	129	44 (34%)	37 (84%)	**7 (5.5%)**	96%**	--
Martens 2016	100	15 (15%)	13 (87%)	**5 (5%)**	97%**	81%**
Smith 2017	113	22 (19%)	20 (91%)	**9 (8%)**	75 vs 94%*	73 vs 90%*

(*) patients with pCR after TME; (**) 3-year data

Distant metastasis in patients with pCR



7% distant metastasis

Variable	Complete Response		Intermediate Response		Poor Response	
	No.	%	No.	%	No.	%
Total No. of patients	131		210		384	
Local recurrence only	0		3	1.4	17	4.4
Systemic recurrence only	8	6.21	19	9.0	87	22.7
Both local and systemic recurrence	1	0.8	2	1	16	4.2

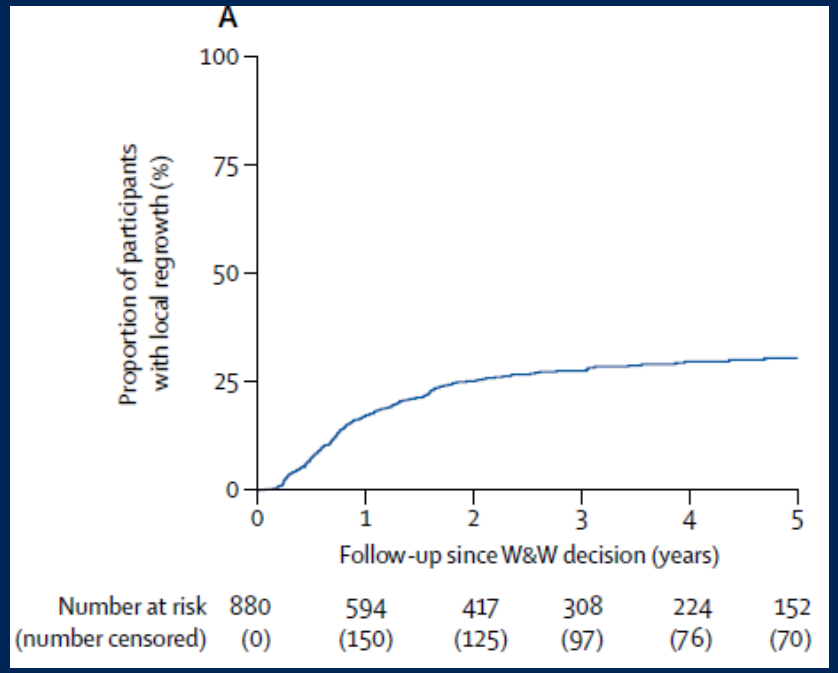
Cox regression model for risk of recurrence

Park I J et al. *J Clin Oncol* 2012;30:1770-1776

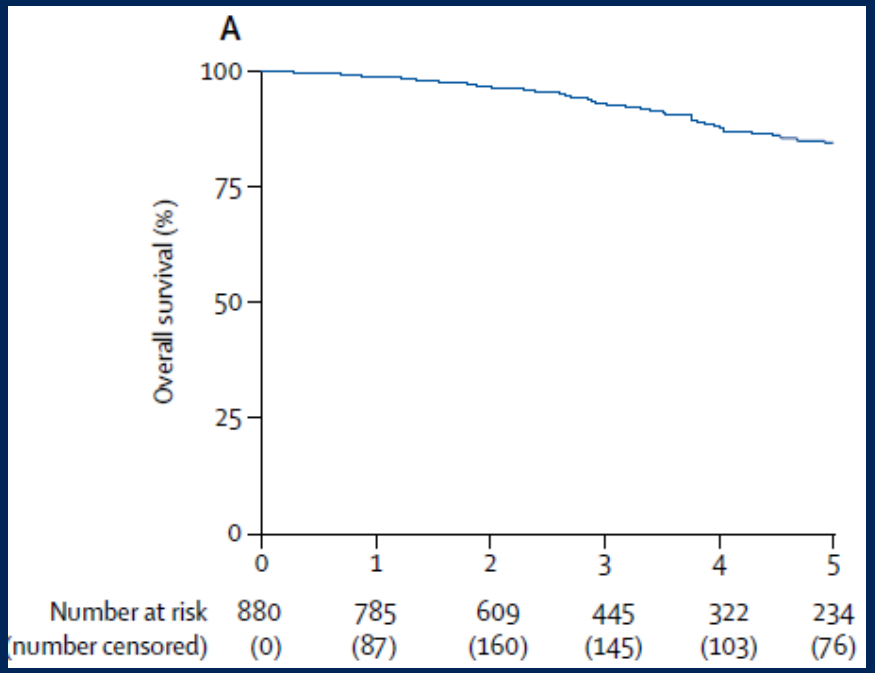
International Watch & Wait Registry

- 880 patients
- 47 centers
- 25 countries
- 1991-2017

Tumor Regrowth



Overall Survival



van der Valk et al, The Lancet 2018;391:2537-45

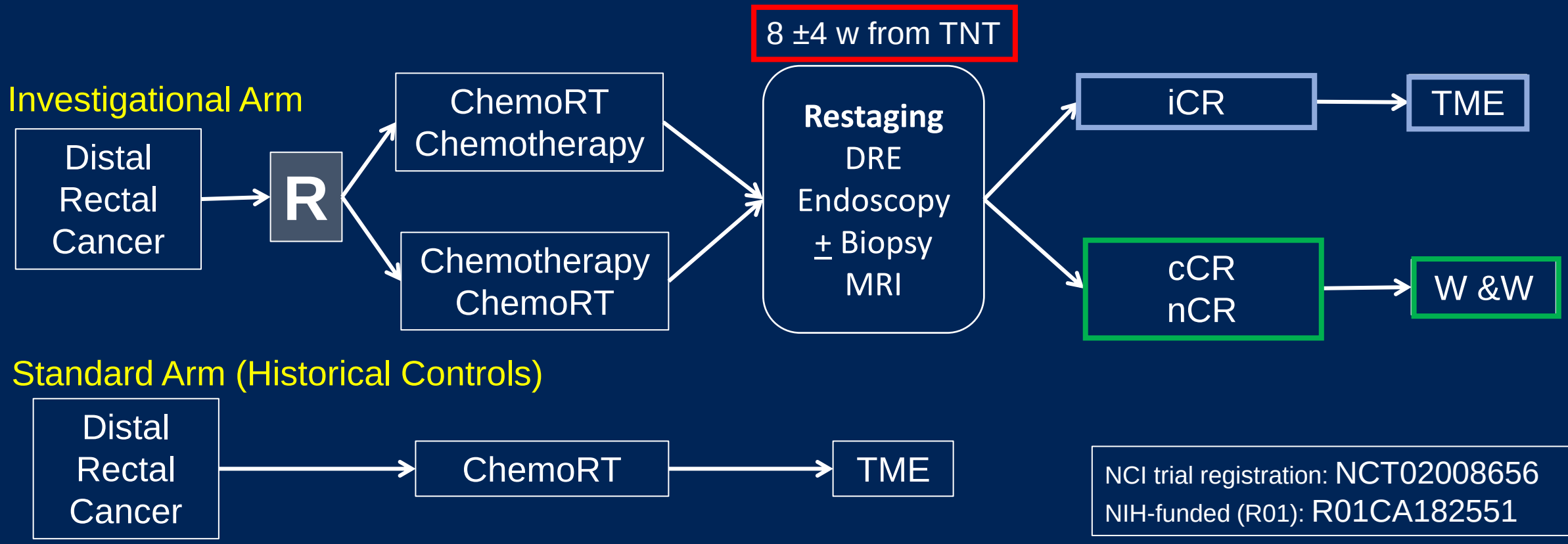
International Watch & Wait Registry: Limitations

- Denominator unknown
- No uniform criteria for inclusion
- Variable neoadjuvant regimens
- No information on timing of response assessment
- No defined criteria for clinical response
- Endoscopy and MRI done only in 64% of patients
- Variable surveillance protocols
- No pathological proof of tumor regrowth
- Variable salvage interventions for patients with regrowth

Controversies in Watch & Wait

- How many patients can benefit from organ preservation?
- How best to select patients for watch and wait?
- Should we attempt organ preservation in patients in patients with near complete response?
- What are the results of salvage surgery in patients with tumor regrowth?

Feasible Design – The OPRA trial



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

Hypothesis: A treatment approach that incorporates TNT and selective WW for patients with a complete response will result in better 3-year DFS compared to patients treated with CRT, TME and adjuvant chemotherapy (historical controls)

Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

OPRA Trial: Endpoints

Primary endpoint

- Compare 3-year disease-free survival between patients treated with TNT and either WW or TME to historical controls (patients treated with CRT, TME, and adjuvant CXT)

Secondary endpoints

- Compare outcomes in patients treated with CNCT vs. INCT with respect to organ preservation, treatment compliance, and adverse events

- Measure patient-reported functional outcomes and QoL, comparing TME and NOM patients

Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

OPRA Trial: Inclusion Criteria

- Age 18 years or older
- Histologic diagnosis of rectal adenocarcinoma
- Clinical stage II or III by rectal MRI
- Distal rectal cancer (requiring TME with APR or coloanal anastomosis at baseline)

Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

OPRA Trial: Treatment Plan

- Systemic chemotherapy (CNCT or INCT)

  mFOLFOX6 or CapeOX, for 4 months

- Radiation therapy

  5000 cGy in 25 fractions of 200 cGy

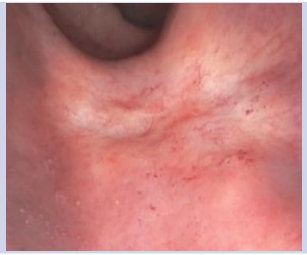
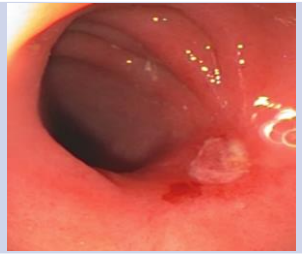
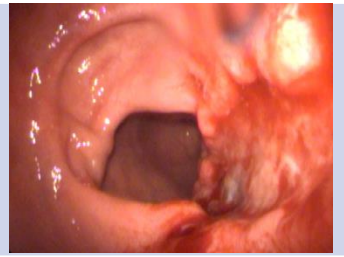
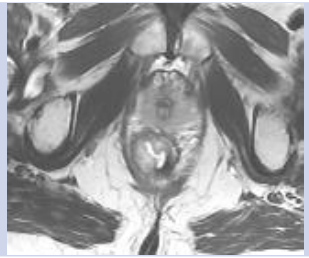
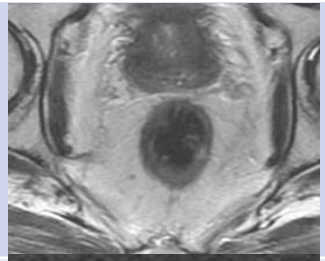
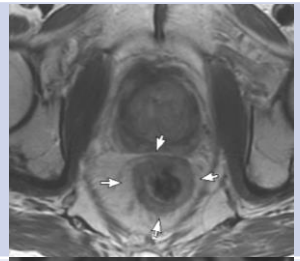
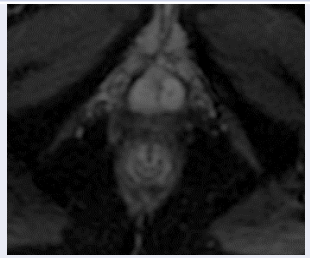
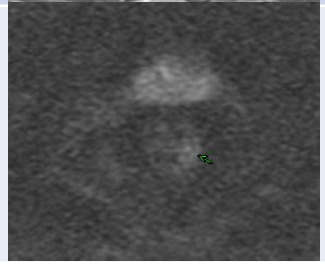
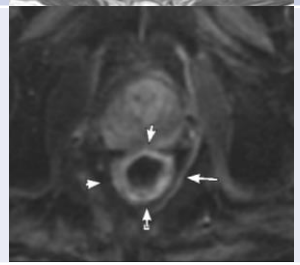
  Optional PTV boost of 400-600 cGy for a total dose of 5400-5600 cGy

- Sensitizing chemotherapy

  CI 5-FU (225 mg/m^2/day) or oral capecitabine (825 mg/m^2 bid)

Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

MSK Rectal Cancer Regression Schema

	Clinical Complete Response (cCR)	Near Complete Clinical Response (nCR)	Incomplete Clinical Response (iCR)
Endoscopy			
Digital Rectal Exam	Normal	Smooth induration	Palpable tumor
MRI - T2W			
MRI - DWI			

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

Surveillance Protocol for WW Patients

Years	Year 1	Year 2	Year 3	Year 4	Year 5
Digital Rectal Exam	q 4 months	q 4 months	q 6 months	q 6 months	q 6 months
Flexible Sigmoidoscopy					
CEA					
MRI (T2W and DWI)	q 6 months	q 6 months	q 12 months	q 12 months	q 12 months
CT CAP	X1	X1	X1	X1	X1
Colonoscopy	X1				X1

TME patients were monitored according to NCCN guidelines

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

Patient Characteristics

Characteristic		INCT-CRT (n=158)	CRT-CNCT (n=166)
Age (IQR), years		59 (51-68)	56 (49-67)
Female – no. (%)		55 (35%)	64 (39%)
cT classification no. (%)	cT1-2	7 (4%)	11 (7%)
	cT3	124 (78%)	126 (76%)
	cT4	23 (15%)	19 (11%)
cN classification no. (%)	cN-negative	47 (30%)	47 (28%)
	cN-positive	111 (70%)	119 (72%)
Distance from anal verge (IQR), cm		4.3 (3.0-6.3)	4.45 (3.0-6.5)
High-grade tumor – no. (%)		7 (4%)	8 (5%)

Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

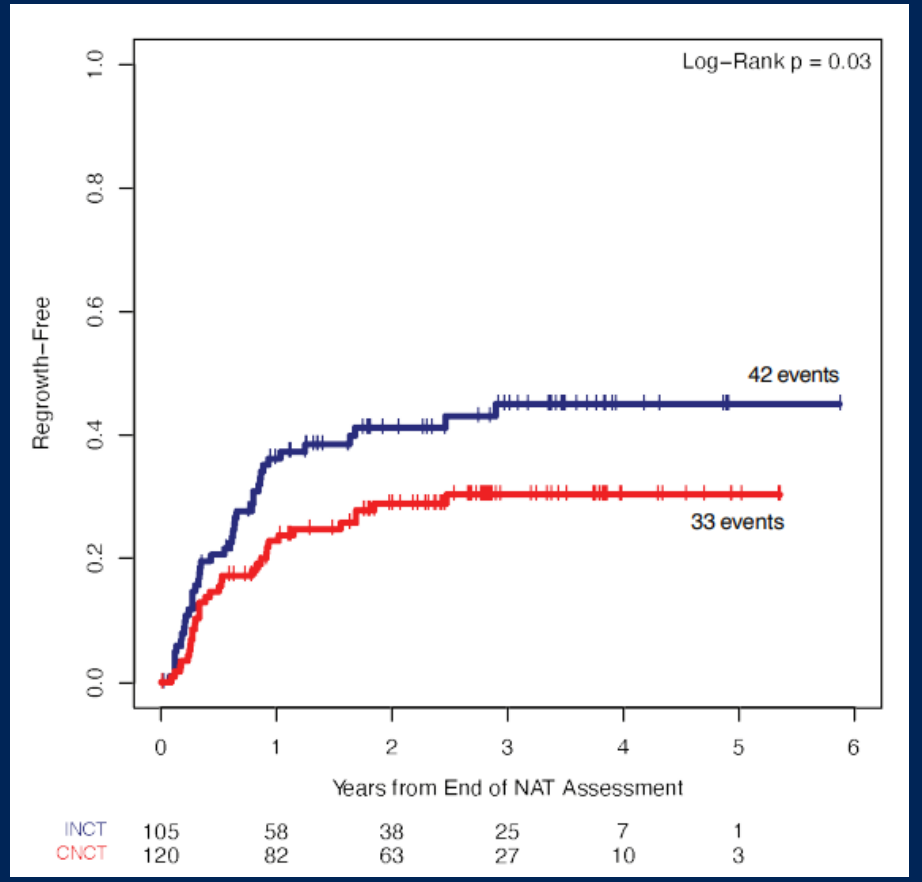
Initial Response and Tumor Regrowth

Treatment recommended at restaging

	INCT n=146	CNCT n=158
Recommended TME	41 (28%)	38 (24%)
Recommended WW	105 (72%)	120 (76%)

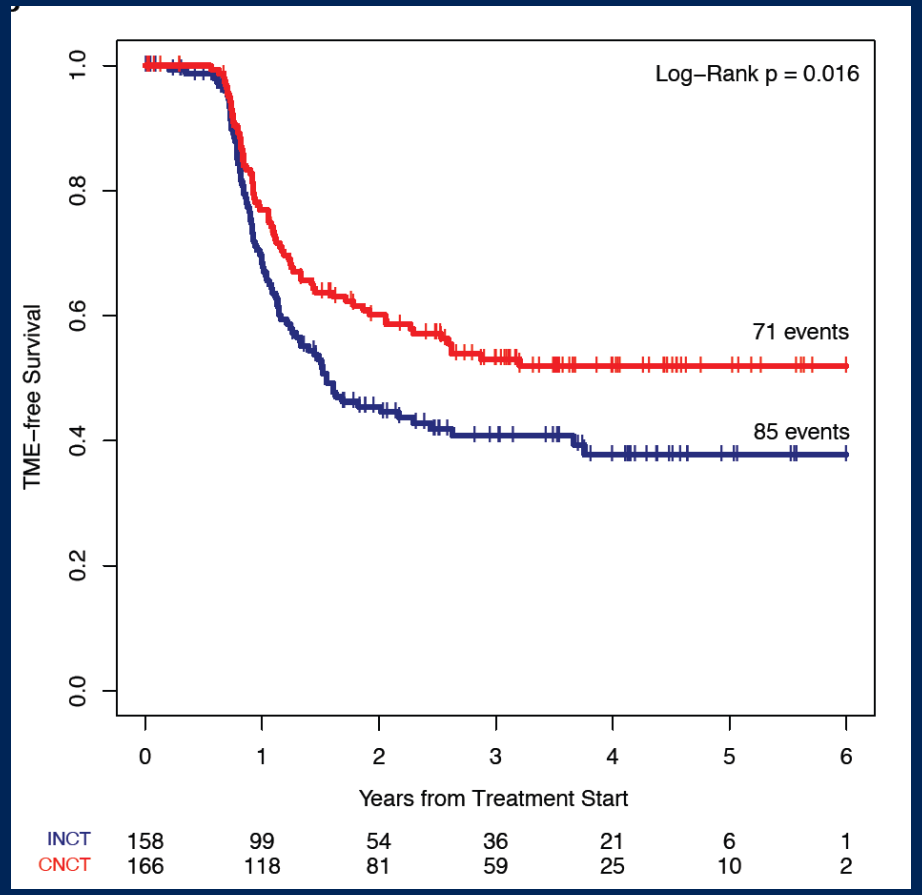
Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

Regrowth rates for patients in WW

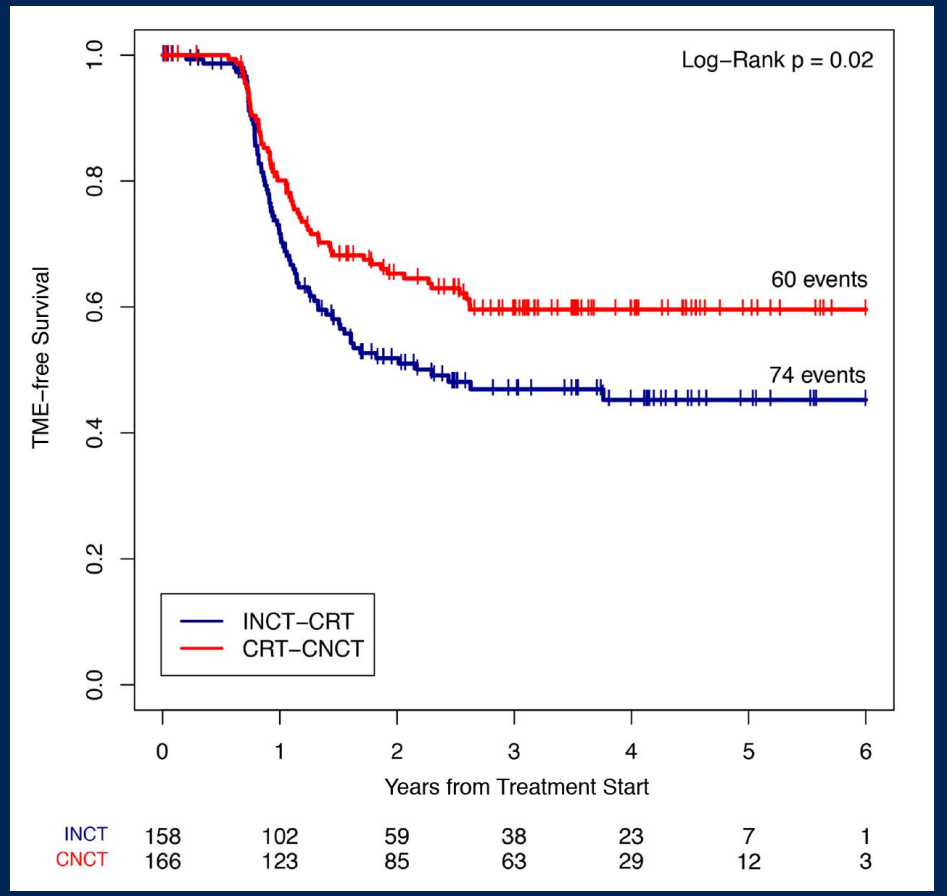


TME-Free Survival: Organ Preservation over Time

Recommended TME
(intention to treat)

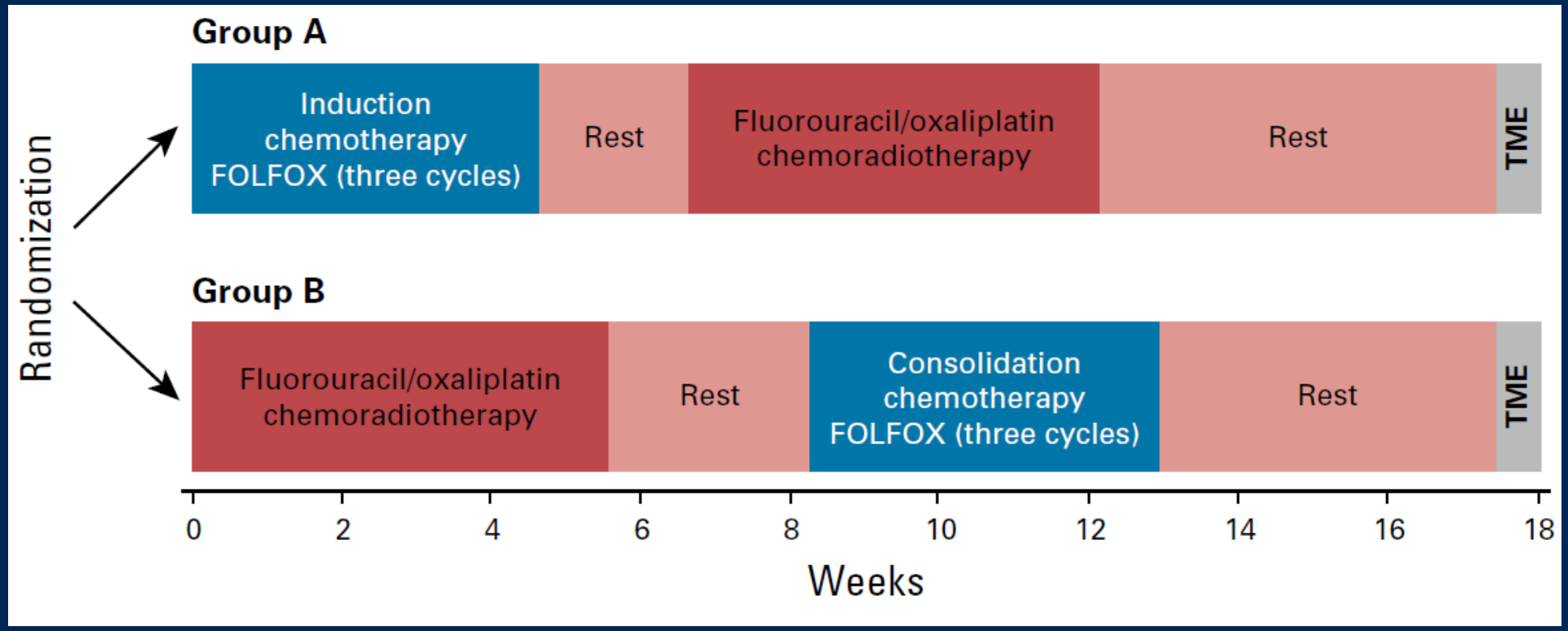


Had TME



Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

INCT vs. CNCT in Patients Treated with ChemoRT and TME: The CAO/ARO/AIO-12 Trial

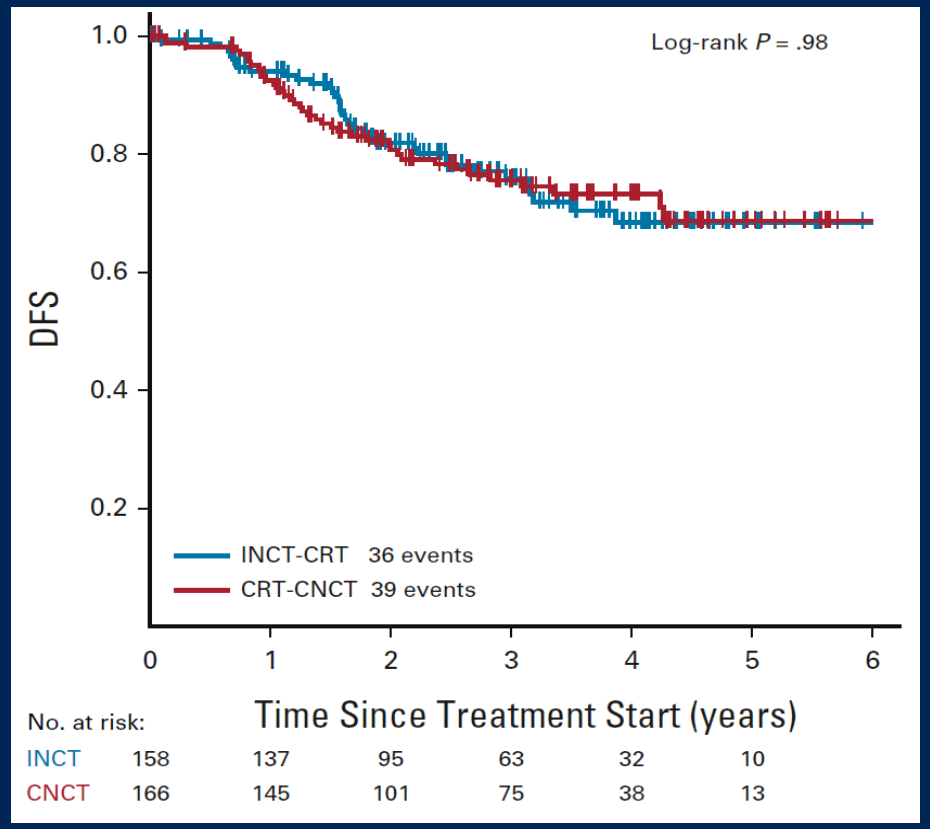


17% pCR

25% pCR

Fokas et al, J Clin Oncol 2019;37:3212-3222

Disease-Free Survival: OPRA vs. Other Trials



Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

Study	Control Arm	Experimental Arm
OPRA	**76%**	**76%**
NSABP R-04*	64%	69%
ACCORD 12	68%	73%
PETACC 6	76%	76%
CA0/ARO/AIO-4	71%	76%
Spanish GCR3*	64%	62%
PRODIGE 23	69%	76%
CA0/ARO/AIO-12	73%	73%

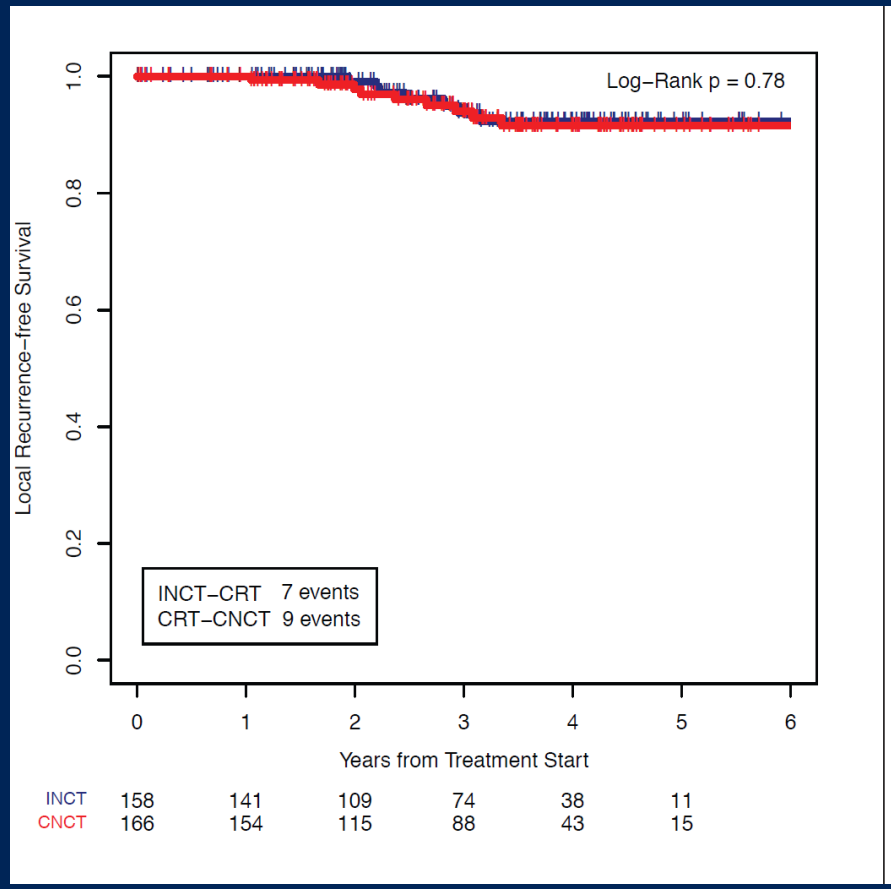
(*) 5-y DFS

Allegra et al, J Nat Cancer Inst 2015;107:1-8
Rodel et al, Lancet Oncol 2015; 16: 979-89
Conroy et al, Lancet Oncol 2021; 22:702-15
Gerard et al, 2012 Dec 20;30(36):4558-65

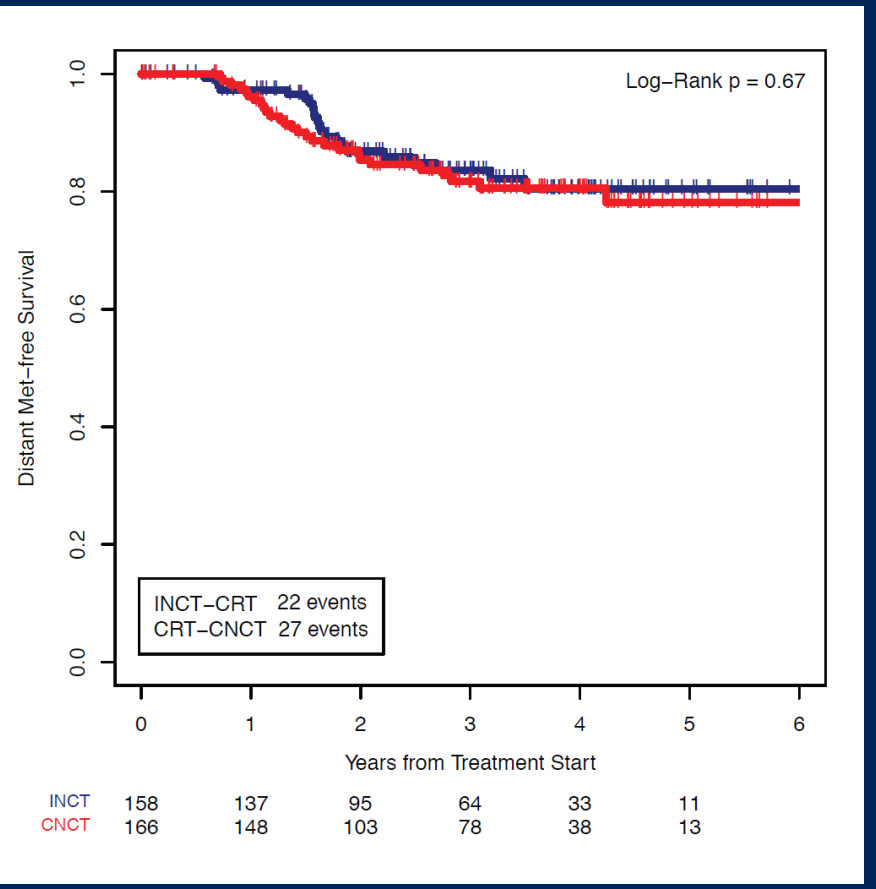
Schmoll et al, J Clin Oncol 2020; 39:17-29
Fernandez-Martos et al, Ann Oncol 2015; 26:1722-1728
Focas et al, JAMA Oncology 2021; 8(1):e215445.

OPRA Trial: Local Recurrence and Distant Metastasis

LR-Free Survival



DM-Free Survival



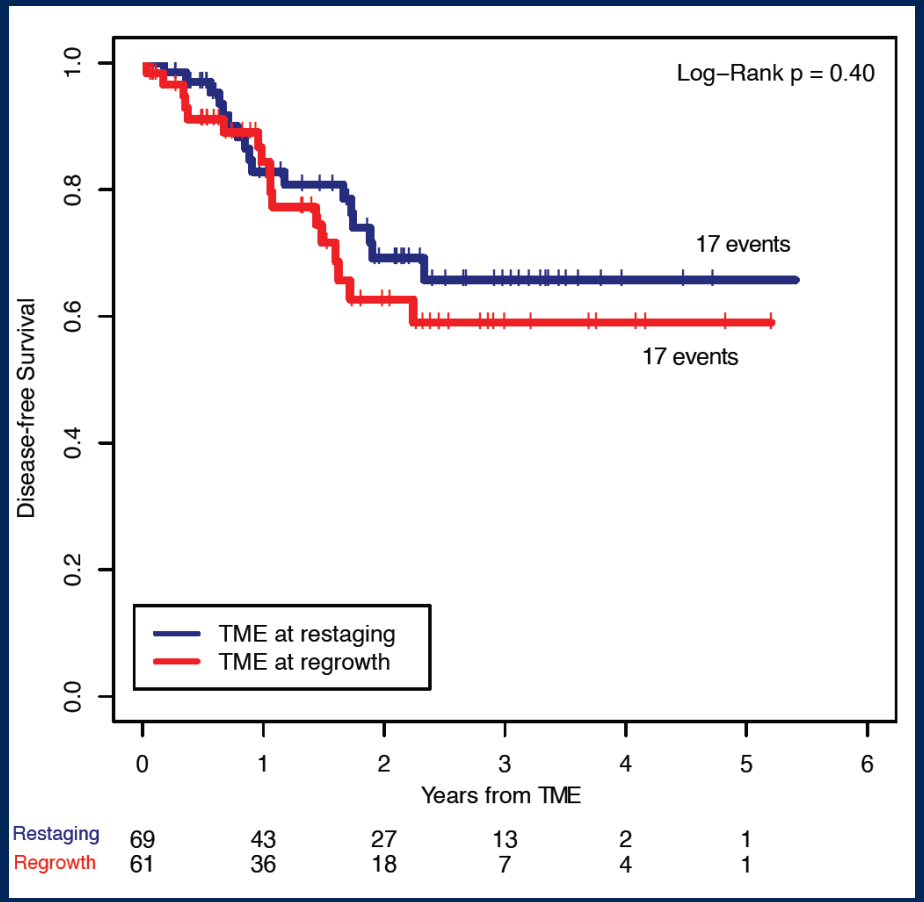
Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

Surgery and Pathology

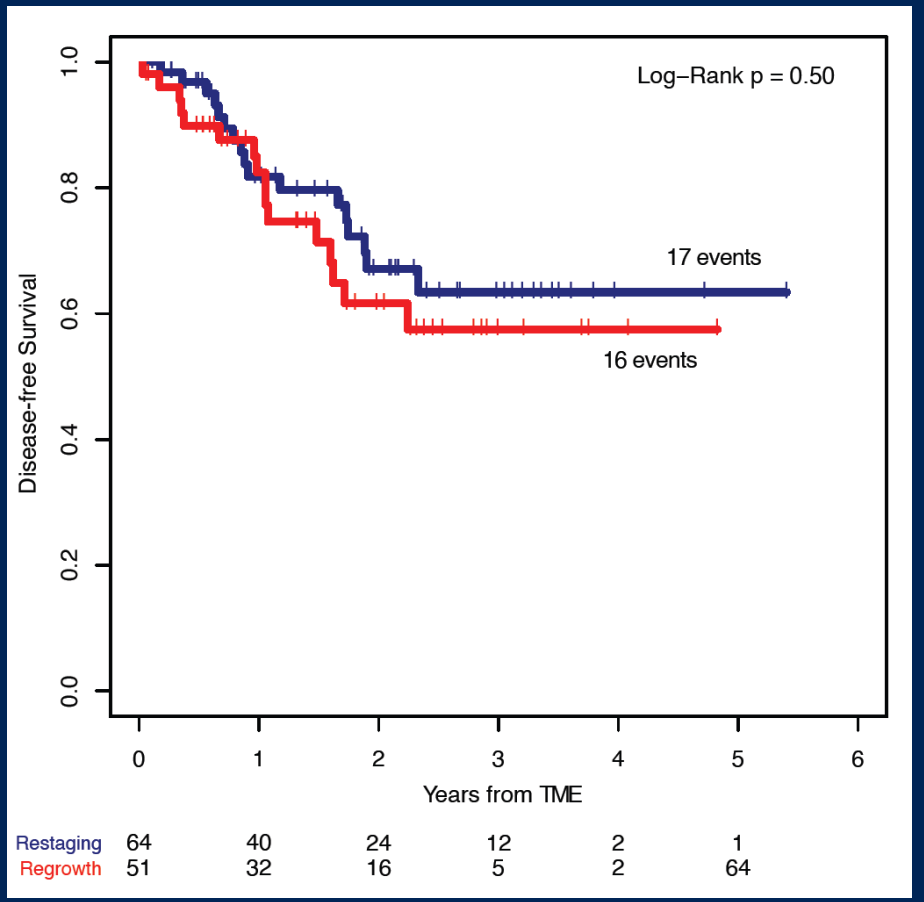
	INCT-CRT group (n = 158)	CRT-CNCT group (n = 166)
Surgery performed – n (%)	78 (49)	64 (37)
TME	74 (95)	60 (94)
TAE	4 (5)	4 (6)
ypT classification – n (%)		
T0	6 (8)	6 (9)
Tis	3 (4)	3 (5)
T1	9 (12)	2 (3)
T2	26 (33)	19 (30)
T3	30 (38)	31 (48)
T4	4 (5)	3 (5)
ypN classification – n (%)		
N-negative	63 (85)	40 (73)
N-positive	11 (15)	16 (27)
Surgical margin status – n (%)		
R0	67 (91)	53 (88)
R1	7 (9)	7 (12)

DFS for Patients Who Had TME at Restaging or after Regrowth

Recommended TME (Intention to Treat)



Had TME



Garcia Aguialr et al, J Clin Oncol. 2022 Apr 28:JCO2200032.

Outcomes for TME at Restaging and TME after Regrowth

		TME at Restaging, n=71	TME after Local Regrowth, n=62
Recurrence	Local, n=16	7 (10%)	9 (15%)
	Distant, n=32	15 (21%)	11 (17%)
	Both, n=9	3 (4%)	6 (10%)
Surgery	APR, n=67	32 (45%)	35 (56%)
	LAR, n=66	39 (55%)	27 (44%)

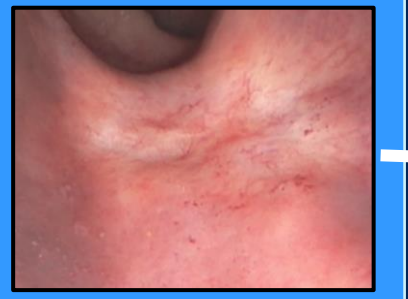
OPRA Trial: Clinical Response at Restaging

Rectal Adenocarcinoma Stage II-III

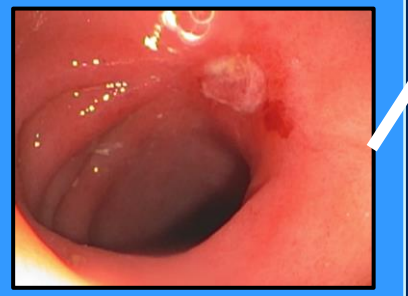
CRT-CNCT or INCT-CRT

8 (±4) weeks

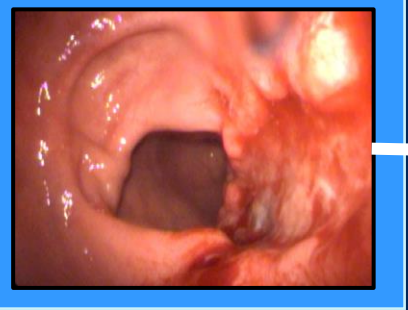
cCR



nCR



iCR



Recommend WW

Recommend TME

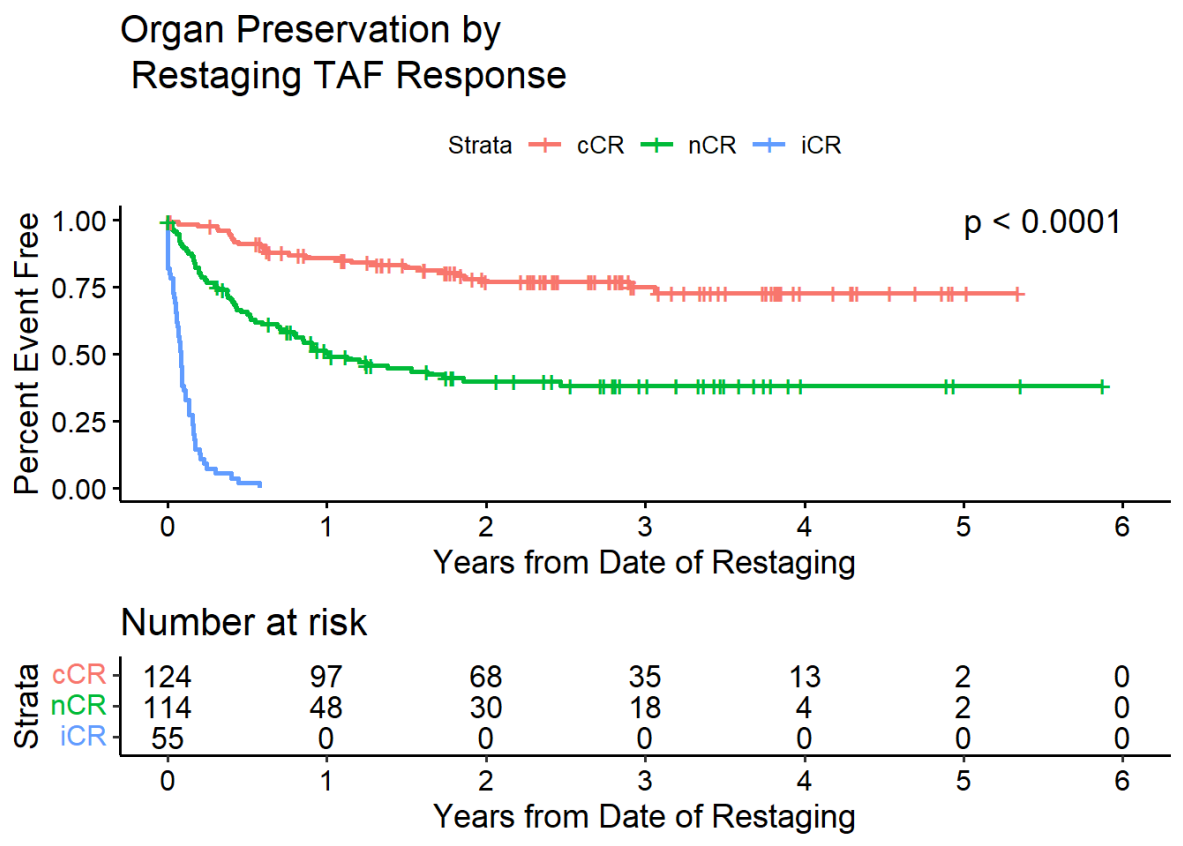
Thompson et al, ASCO 2021, abstract 3509

Patient Characteristics by Response Grade

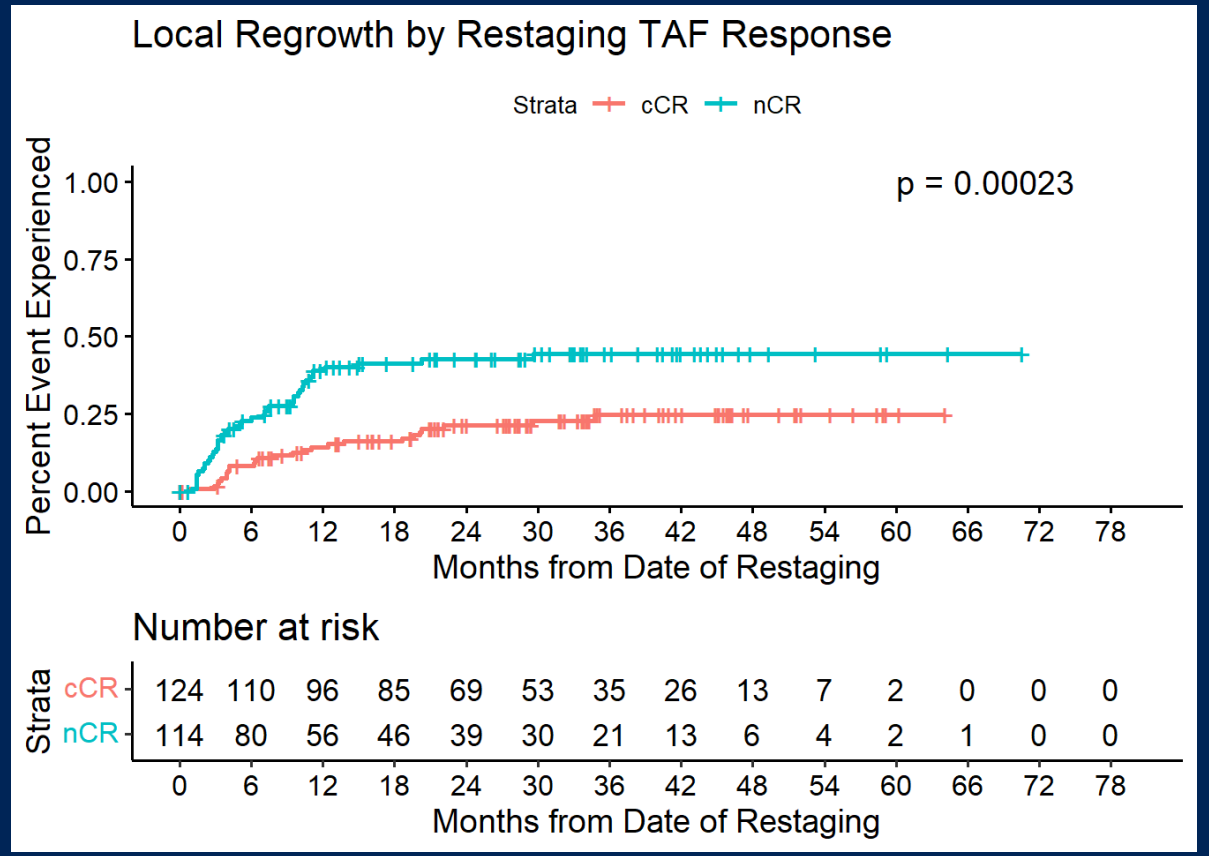
Characteristic	cCR, N = 124	nCR, N = 114	iCR, N = 55	p-value
Age	60.1 (50.3, 67.9)	57.6 (49.1, 67.9)	55.2 (47.3, 64.1)	0.086
Sex				0.290
Male	75 (60.5%)	80 (70.2%)	37 (67.3%)	
Female	49 (39.5%)	34 (29.8%)	18 (32.7%)	
Arm				0.339
Induction	54 (43.5%)	60 (52.6%)	28 (50.9%)	
Consolidation	70 (56.5%)	54 (47.4%)	27 (49.1%)	
Clinical T Stage				0.782
T1 or T2	16 (12.9%)	11 (9.6%)	4 (7.3%)	
T3	94 (75.8%)	87 (76.3%)	45 (81.8%)	
T4	14 (11.3%)	16 (14.0%)	6 (10.9%)	
Clinical N Stage				0.094
N0	45 (36.3%)	28 (24.6%)	13 (23.6%)	
N+	79 (63.7%)	86 (75.4%)	42 (76.4%)	
Distance from Anal Verge	4.5 (3.3, 7.0)	4.0 (3.0, 5.9)	4.5 (3.0, 6.2)	0.274

Tumor Regrowth and Organ Preservation by Response

TME-Free Survival

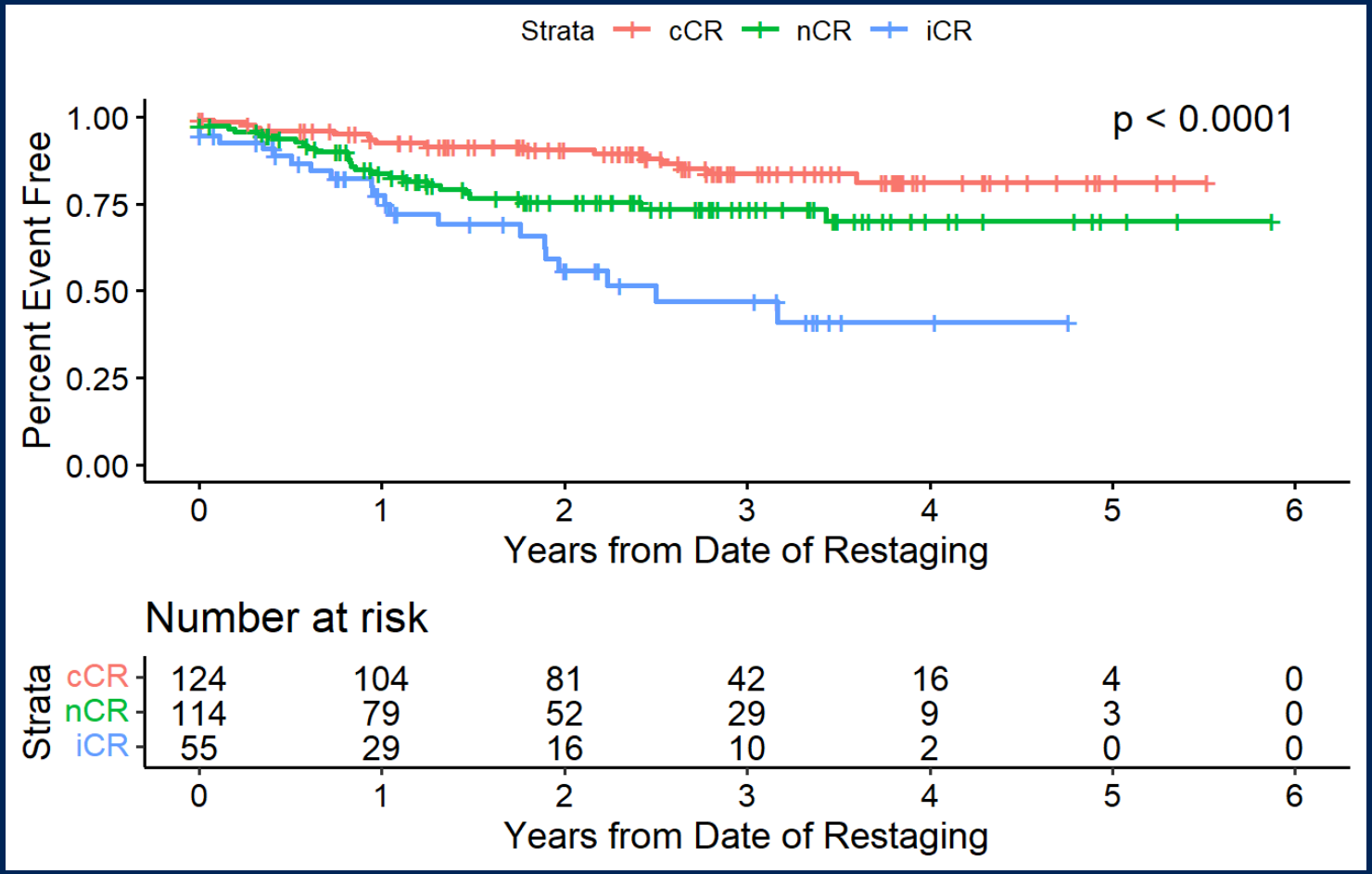


Regrowth



Thompson et al, ASCO 2021, abstract 3509

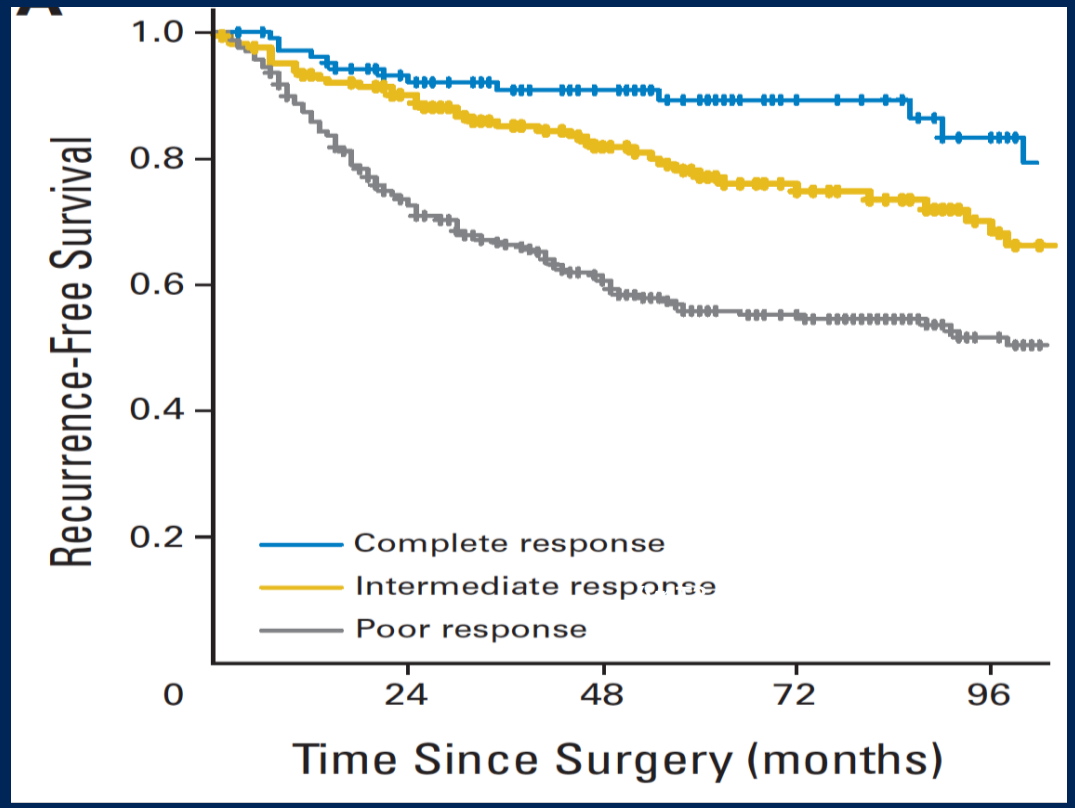
DFS by Clinical Response at Restaging



Thompson et al, ASCO 2021, abstract 3509

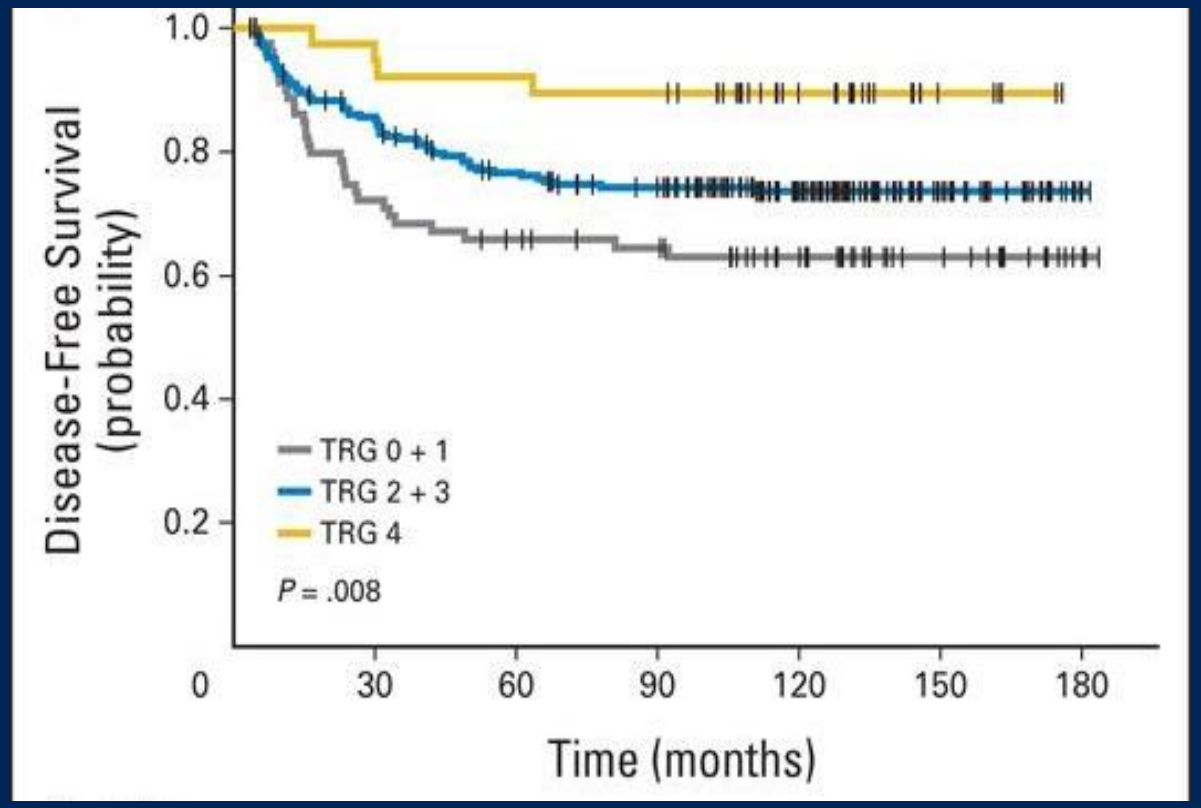
DFS by Pathological Response after ChemoRT

MD Anderson (ypTN)



Park et al; J Clin Oncol 2012; 30:1770-1776.

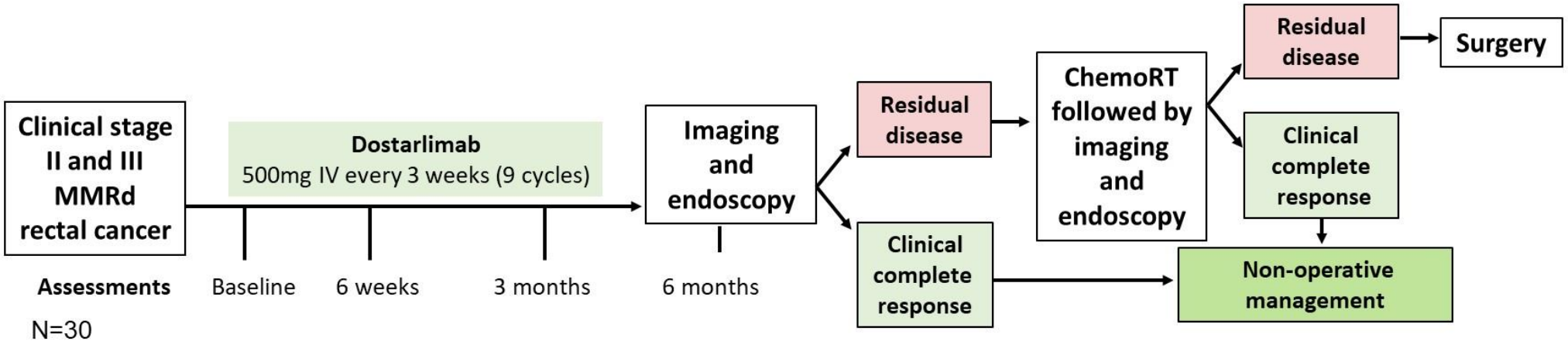
CAO/ARO/AIO-94 Trial (TRG)



Fokas et al; J Clin Oncol 2014; 32:1554-1562.

Neoadjuvant PD-1 blockade for stage II/III MMRd rectal cancer

NCT 04165772



N=30

Simon's two stage minimax

Primary Objectives:

- Overall response rate (ORR) of PD-1 blockade
- The clinical complete response (cCR) rate at 12 months after completion of PD-1 blockade or pathologic complete response (pCR) with or without chemoradiation

Secondary Objectives:

- Safety and tolerability

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Lessons Learned: Rate of Organ Preservation

- The rate of rectal cancer response to neoadjuvant therapy is much higher than previously thought
- Rectal cancer response takes time
- Delivering chemoRT before chemotherapy seems to result in higher rates of response and organ preservation

Lessons Learned: identifying Responders

- A predefined three-tier response criteria correlates with organ preservation and survival
- We continue underestimating (8-9% pCR) and overestimating (>25% tumor regrowth) tumor response

Lessons Learned: near-Complete Responders

- The majority of patients with a complete clinical response preserve the rectum
- Almost half of the patients with a near complete response can preserve the rectum if given enough time to respond
- The oncologic outcomes for patients with near complete response are intermediate between patients with complete response and patients with incomplete response

Lessons Learned: Salvage Surgery

- Salvage surgery for patients with tumor regrowth seems to provide equivalent survival compared to surgery for persistent tumor, however the sample size is too small to draw definitive conclusions
- Resistance to TNT (persistence or regrowth) should be considered a high-risk feature for local and distant metastasis
- Outcomes of the 50% of patients with tumor resistant to TME (persistent or regrowth) probably have worse outcomes compared to patients treated in trials not offering TME
- The role of local excision was not addressed in this trial but considering the results with salvage TME surgery in patients with resistant tumors, the role of local excision in these patients is at least debatable.

Lessons Learned: Survival

- The OPRA trial was designed to improve survival in stage II and III rectal cancer patients treated with TNT and selective WW compared to historical controls treated with CRT and TME
- Disease-free survival was on the range of other recent clinical trials treating stage II and III rectal cancer patients with neoadjuvant therapy and TME
- Offering WW to patients with a clinical complete response to TNT seems to result in no oncologic disadvantage to the patients

Conclusion

- A treatment strategy that includes TNT and selective WW allows organ preservation in more than half of rectal cancer patients, without apparent detriment to oncologic outcomes
- WW is acceptable to most rectal cancer patients and already demanded by some; it should be part of the treatment discussion
- Successful WW requires well informed patients willing to comply with an intensive surveillance protocol

Many Thanks