THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

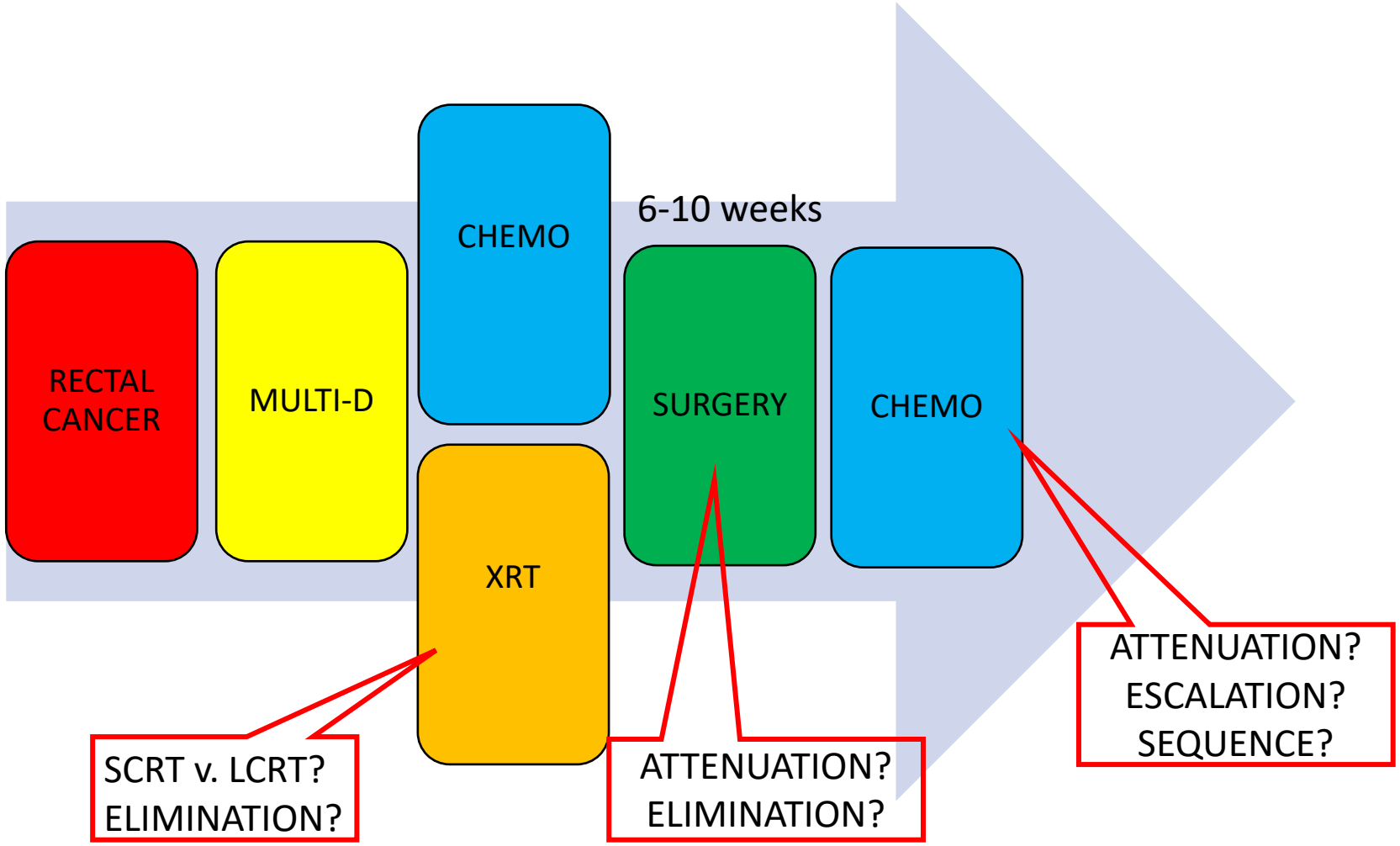
WATCH AND WAIT: PRINCIPLES OF NON-OPERATIVE MANAGEMENT OF RECTAL CANCER

David Shibata, MD, FACS, FSSO, FASCRS
UTHSC Department of Surgery

UTHSC Surgical Oncology Cancer Symposium
September 30, 2023

NO DISCLOSURES

STANDARD OF CARE FRAMEWORK 2004-2020



OVERVIEW

- Historical Perspective
- Assessing Clinical Response
  - How?
  - When?
- Surveillance for Complete Clinical Response
  - Consensus Schedule
  - Recurrence
  - Salvage
- Management of Near-Complete Clinical Response
  - Local Excision
- Concerns and Issues with Non-Operative Management

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‡*

- Conventional neoadjuvant chemoradiation (n=265)
  - Complete Clinical Response/Observation n=71 (26.8%)
    - 3 systemic recurrence
    - 2 local recurrence
  - Incomplete Response/Resection/pathCR n=22 (8.3%)
- 5-year OS
  - OBS 100% vs. RES 88%
- 5-year DFS
  - OBS 92% vs. RES 83%

Annals of Surgery • Volume 240, Number 4, October 2004

VOLUME 29 · NUMBER 35 · DECEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY

Wait-and-See Policy for Clinical Complete Responders After Chemoradiation for Rectal Cancer

Monique Maas, Regina G.H. Beets-Tan, Doenja M.J. Lambregts, Guido Lammering, Patty J. Nelemans, Sanne M.E. Engelen, Ronald M. van Dam, Rob L.H. Jansen, Meindert Sosef, Jeroen W.A. Leijtens, Karel W.E. Hulsewé, Jeroen Buijsen, and Geerard L. Beets

- ClinCR; N=21; 1 local recurrence
- Similar 2-yr OS, DFS to matched resected patients with pathCR

High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study

Ane L Appelt, John Pløen, Henrik Harling, Frank S Jensen, Lars H Jensen, Jens C R Jørgensen, Jan Lindebjerg, Søren R Rafaelsen, Anders Jakobsen

Lancet Oncol 2015; 16: 919–27

- Distal cancers potentially needing abdominoperineal resection
- Clin CR; N=40; 9 local recurrences (22.5%)

Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis

Andrew G Renehan, Lee Malcomson, Richard Emsley, Simon Gollins, Andrew Maw, Arthur Sun Myint, Paul S Rooney, Shabbir Susnerwala, Anthony Blower, Mark P Saunders, Malcolm S Wilson, Nigel Scott, Sarah T O'Dwyer

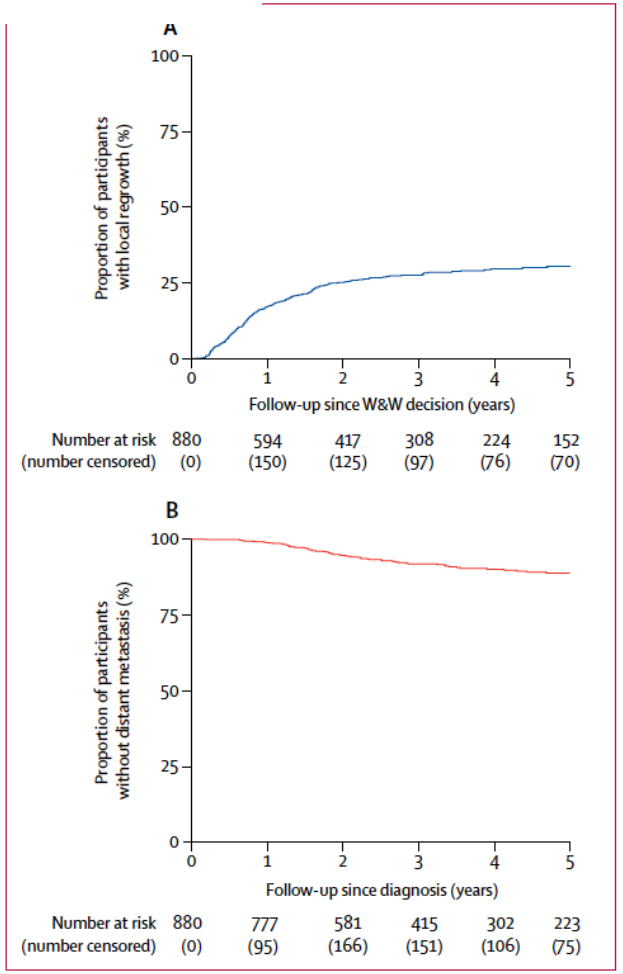
- Propensity-score matched cohort analysis
  - Locally advanced rectal cancer
  - Conventional chemoradiation
- Watch and wait (n=129)
  - 3-year local recurrence 38%
    - 88% salvaged with radical resection
- Matched analysis
  - 109 WW vs. 109 Resected
    - 3-year OS
      - 96% vs. 87% p=NS
    - 3-year colostomy-free survival
      - 74% vs. 47% p<0.0001

Lancet Oncol 2016; 17: 174–83

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

*Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium**

- International registry
- n=880 Clinical CR
  - 2-year local recurrence
    - 25.2%
  - Distant Metastases
    - 71(8%) of 880 patients
  - 5-year OS
    - 85%
  - 5-year DSS
    - 94%



Lancet 2018; 391: 2537–45

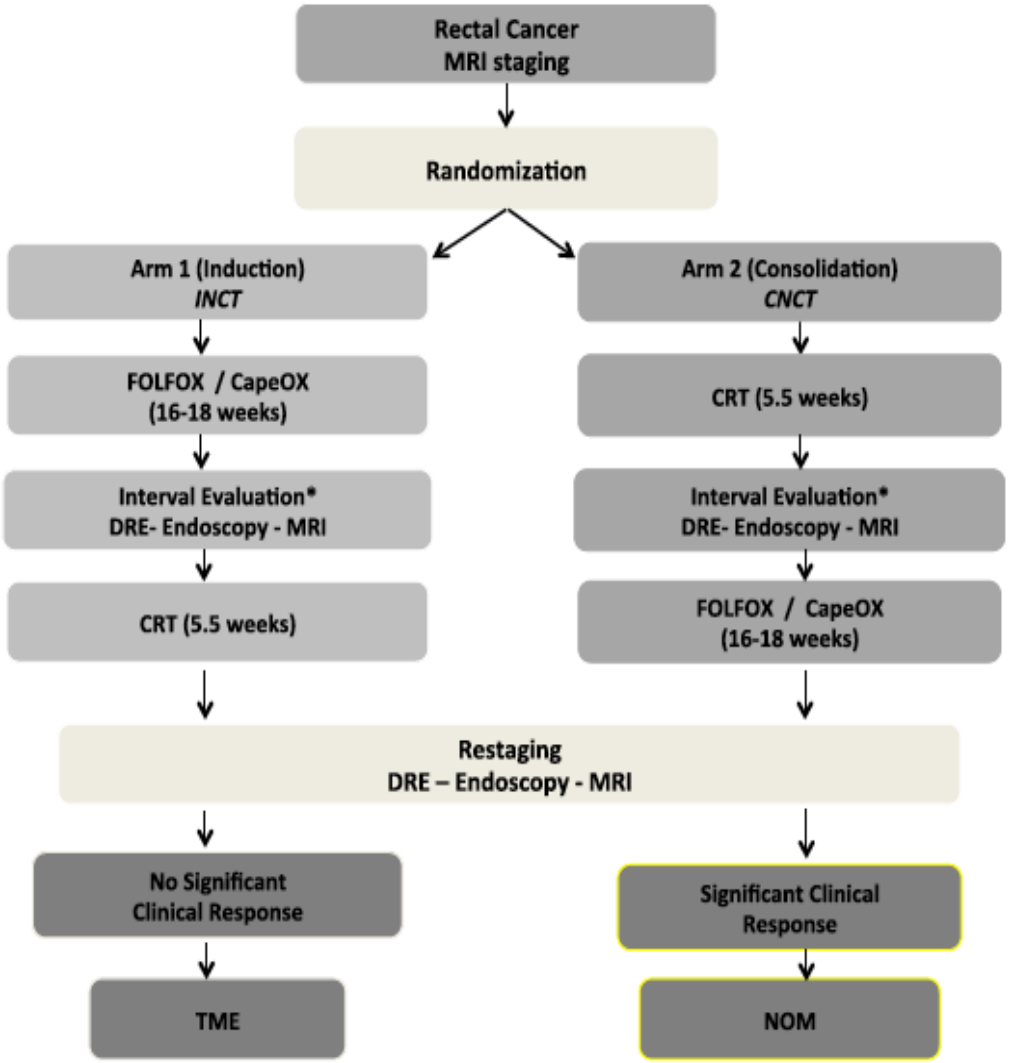
STUDY PROTOCOL Open Access

Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management

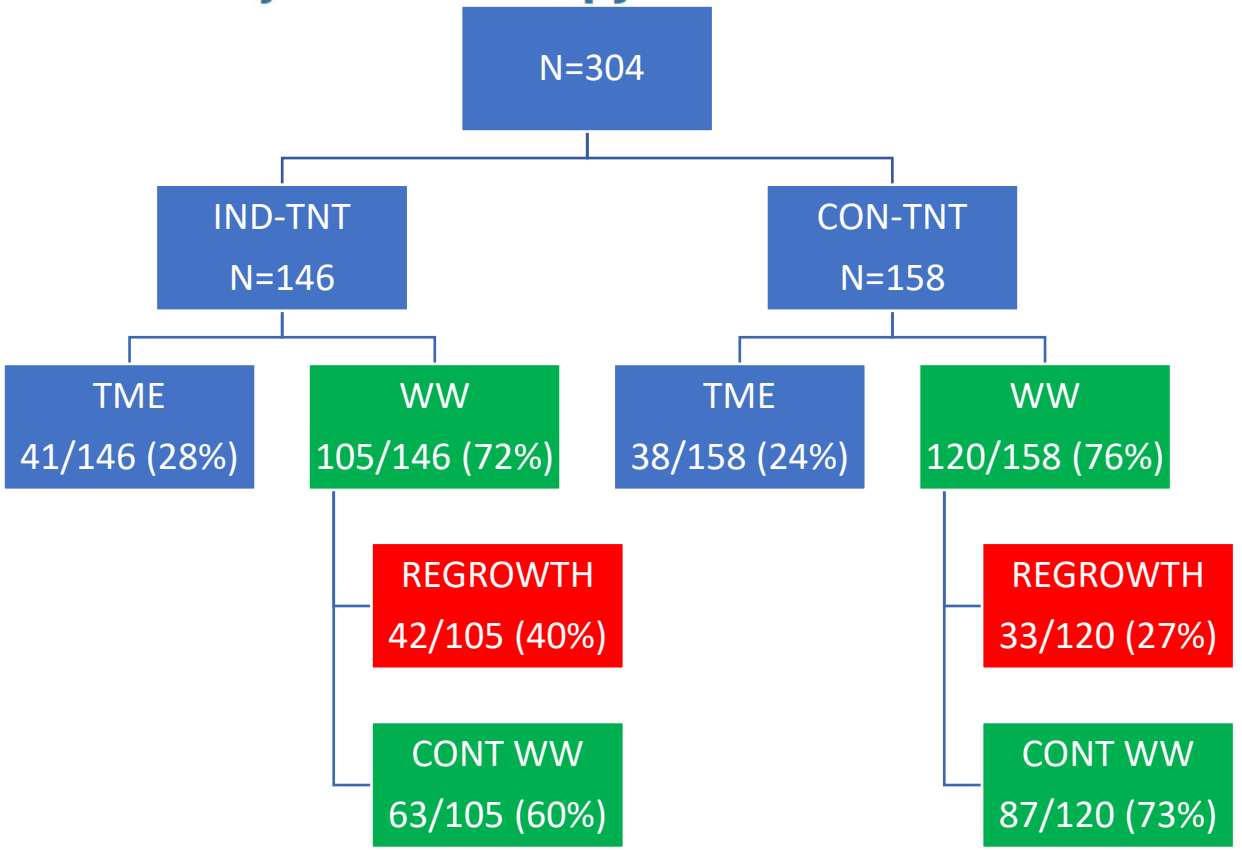
J. Joshua Smith[1], Oliver S. Chow[2], Marc J. Gollub[1], Garrett M. Nash[1], Larissa K. Temple[1], Martin R. Weiser[1], José G. Guillem[1], Philip B. Paty[1], Karin Avila[2], Julio Garcia-Aguilar[1*] and on behalf of the Rectal Cancer Consortium

- Examines issues of:

1. Induction chemo vs. consolidation chemo in TNT
2. Non-operative management (watch and wait)



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



P=0.03

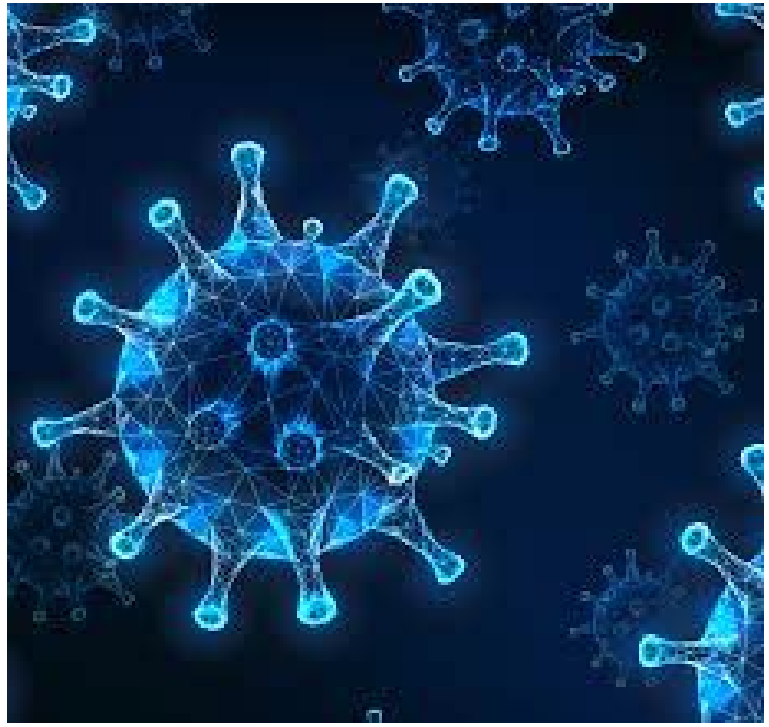
NO DIFFERENCE IN OUTCOME WITH THOSE GETTING TME IMMEDIATELY

3YR DFS	76%	75%	P=NS
3YR TME-FREE SURVIVAL	41%	53%	P=0.016

NO DIFFERENCES IN LOCAL RECURRENCE, DISTANT METASTASES OR OVERALL SURVIVAL

IMPACT OF COVID-19

- Total Neoadjuvant Therapy
  - With reduced surgical resources, accommodate delay in surgery
- Short Course Radiation
  - Reduced exposure of patient/staff in clinical environment
  - Less resource-intensive
- Watch and Wait
  - Reduced surgical resources
  - Avoidance of surgery altogether



ASSESSMENT OF CLINICAL RESPONSE

DRE

PROCTOSCOPY

MRI

Recommendations are for: CT Chest/Abdomen to rule out distant metastatic disease

COMPLETE CLINICAL RESPONSE AND DRE

- Digital Rectal Exam
  - Smooth and/or flat scar
  - No nodularity
- Inaccurate in predicting pathologic CR (21%)
  - No overestimation of response in 80/80 patients
- Remains an important component of re-assessment
- Perez et al. suggest avoidance of NOM in patients with tumors beyond reach of DRE.

Table 2. Influence of Pathologic Stage on Concordance Between DRE and Pathologically Based Assessment of Rectal Cancer Response to Preoperative CMT

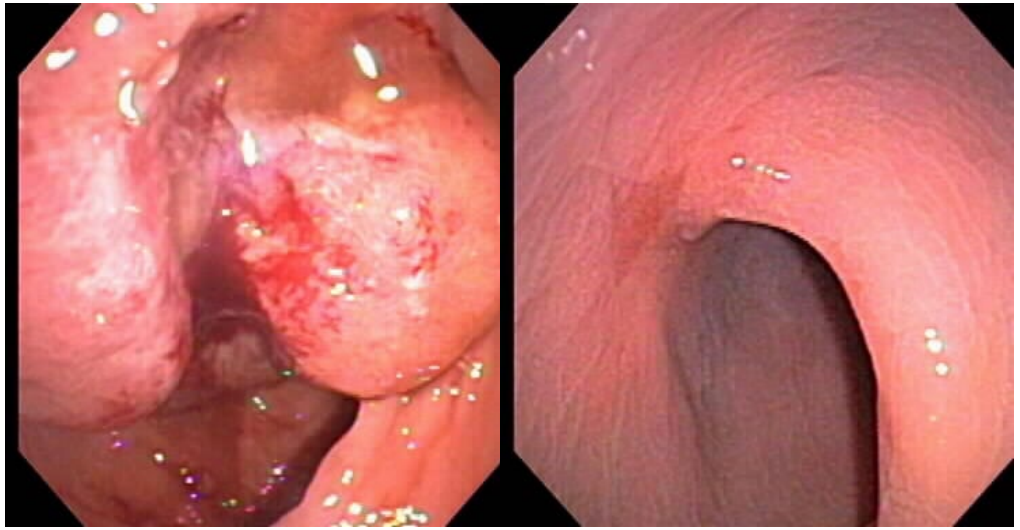
	Concordant		Discordant		
Pathologic Stage	No. of Patients	%	No. of Patients	%	*P*
pCR	3	21	11	79	.2
I	5	20	20	80	
II	7	35	13	65	
III	6	23	20	77	
IV	0	0	9	100	
Overall	21	22	73	78	

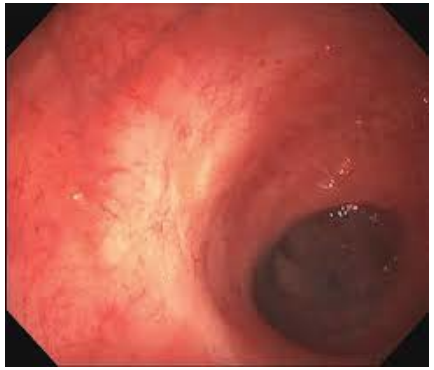
Abbreviations: DRE, digital rectal examination; CMT, combined modality therapy; pCR, pathologic complete response.

Guillem JG et al. JCO 2005;23:3475-9

ENDOSCOPY

- COMPLETE CLINICAL RESPONSE
  - Pale smooth scar with or without telangiectasia
  - No ulceration, nodularity, or mucosal irregularities
  - No stricture

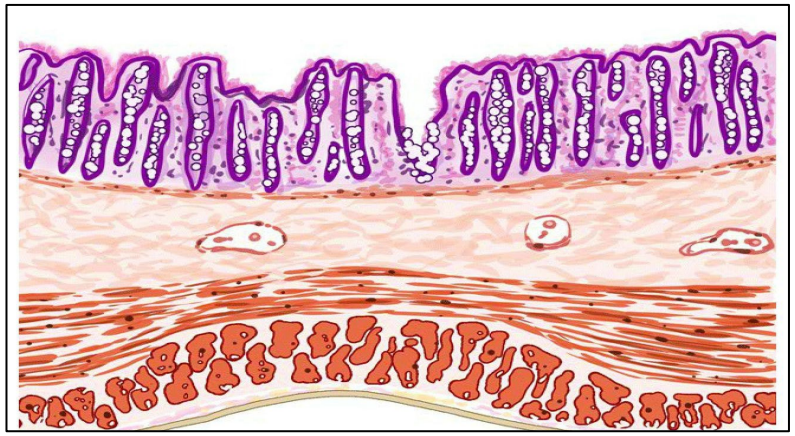


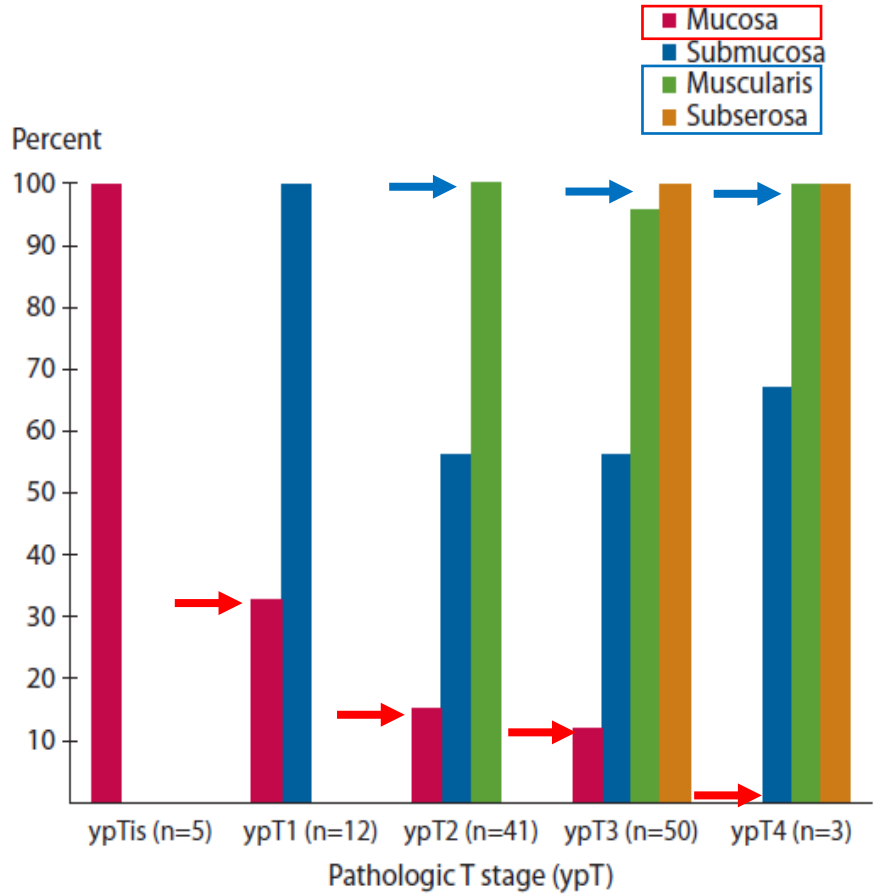


Distribution of Residual Cancer Cells in the Bowel Wall After Neoadjuvant Chemoradiation in Patients With Rectal Cancer

Distribution of RCCs	*Total* *n = 153*	CRT *n = 49*	CRT → FOLFOX x2 *n = 54*	CRT → FOLFOX x4 *n = 50*	*p*
No cancer cells (ypT0)	42 (27)	12 (24)	16 (30)	14 (28)	0.52
Mucosa	21 (14)	5 (10)	11 (20)	5 (10)	
Submucosa	65 (42)	21 (43)	25 (46)	19 (38)	
Muscularis propria	92 (60)	31 (63)	31 (57)	30 (60)	
Subserosa/perirectal fat	53 (35)	21 (43)	17 (32)	15 (30)	

Values stated are number of patients (%).
RCC = residual cancer cell; SG = study group; pCR = pathologic complete response; TRG = tumor regression grade.



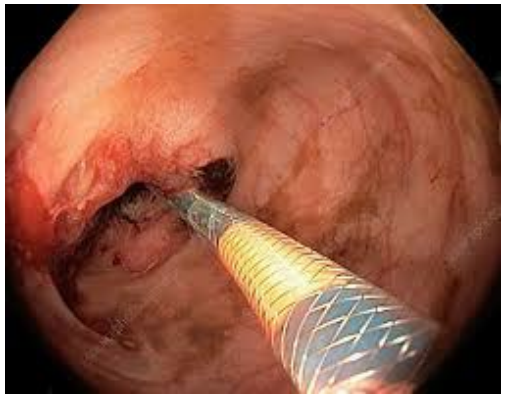


ROLE OF BIOPSY

International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer

Emmanouil Fokas[1,2,3,4,30]✉, Ane Appelt[5,30], Robert Glynne-Jones[6], Geerard Beets[7,8], Rodrigo Perez[9], Julio Garcia-Aguilar[10], Eric Rullier[11], J. Joshua Smith[10], Corrie Marijnen[12], Femke P. Peters[12], Maxine van der Valk[8], Regina Beets-Tan[7,13], Arthur S. Myint[14], Jean-Pierre Gerard[15], Simon P. Bach[16], Michael Ghadimi[17], Ralf D. Hofheinz[18], Krzysztof Bujko[19], Cihan Gani[20,21], Karin Haustermans[22], Bruce D. Minsky[23], Ethan Ludmir[23], Nicholas P. West[24], Maria A. Gambacorta[25], Vincenzo Valentini[25], Marc Buyse[26,27], Andrew G. Renehan[28,29], Alexandra Gilbert[5,30], David Sebag-Montefiore[5,30] and Claus Rödel[1,2,3,4,30]

Fokas E et al. Nat Rev Clin Oncol 2021; 18:805-815

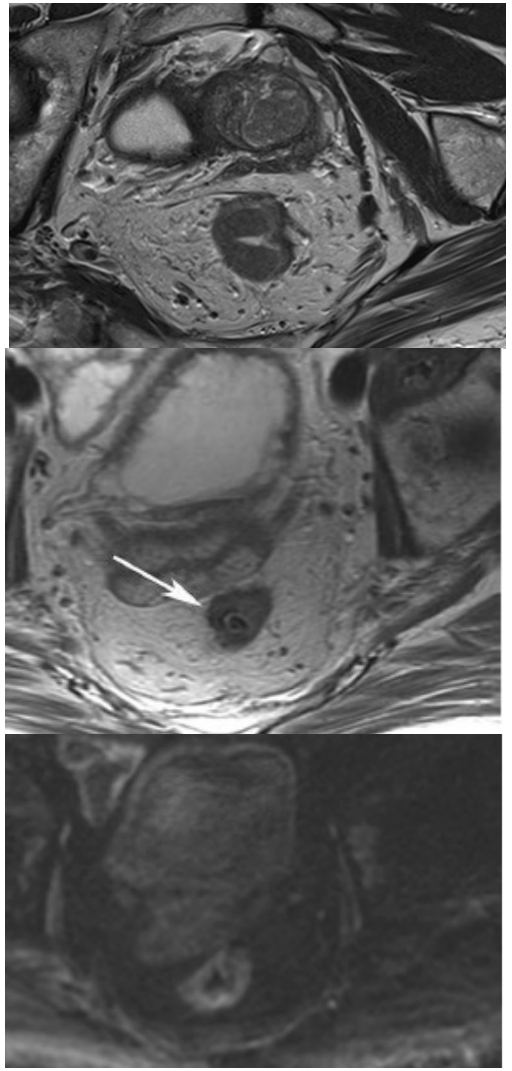


- Sampling errors are common
  - Limited value for ruling out residual cancer
  - Not mandatory to define complete or near complete clinical response
  - May lead to false negative results

Perez RO Colorectal Dis 2012:14:714-20

MAGNETIC RESONANCE IMAGING

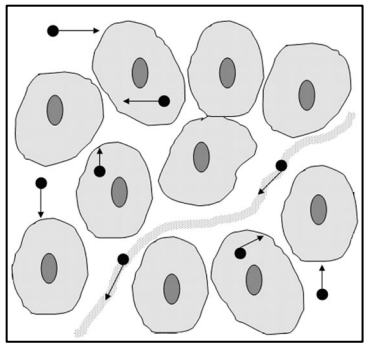
- COMPLETE CLINICAL RESPONSE
  - Substantial downsizing with no observable residual tumor
  - Or: Fibrotic/linear scar with low signal intensity on T2-weighted images
  - No suspicious lymph nodes
  - Diffusion-Weighted Imaging (DWI)
    - No diffusion restriction

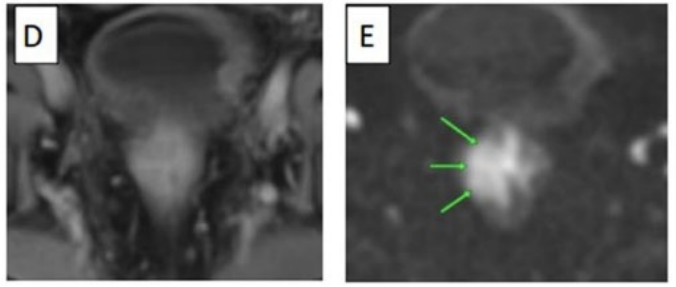


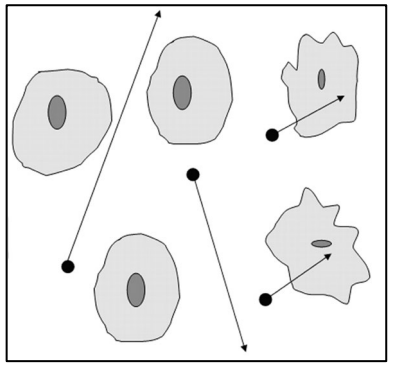
MRI DOS
Supine and comfortable position
1.5 T–3.0 T field strength
T2-weighted FSE without fat saturation
Small FOV OBL-AX SAG COR
Large FOV AX SAG

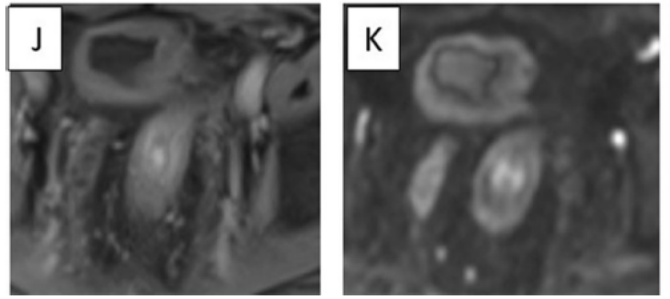
DIFFUSION-WEIGHTED IMAGING

- DWI measures water mobility within tissue at the cellular level
- High cellularity such as in tumors reduces movement or diffusion
  - =Restricted Diffusion
  - =High Signal on DWI
- Effective cancer treatment causes alterations to cellularity, cell membrane permeability and water homeostasis
  - =Less Restricted Diffusion
  - =Reduced Signal on DWI









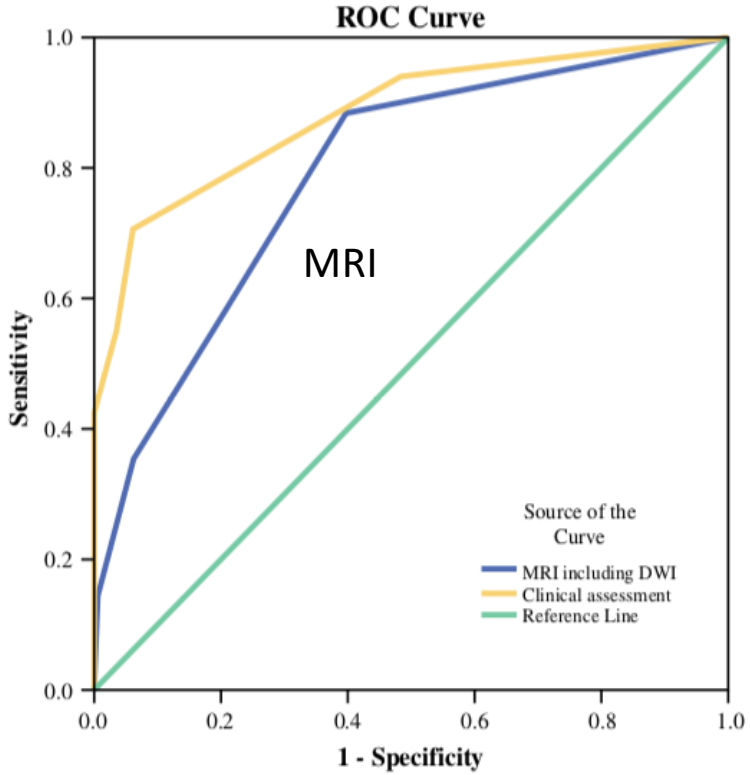
ASSESSMENT OF CLINICAL RESPONSE

DRE

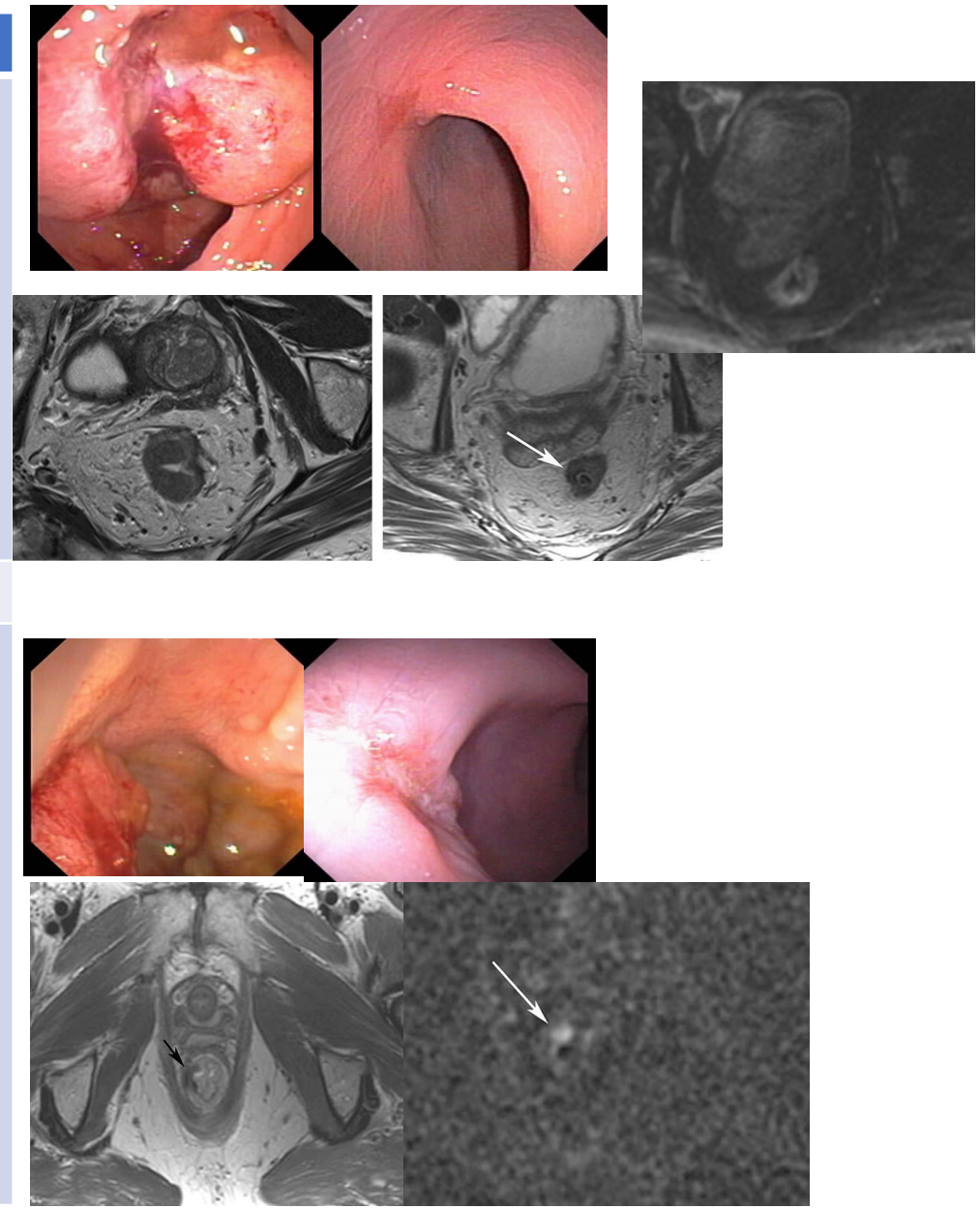
PROCTOSCOPY

MRI

- AUC
  - 0.88 for clinical assessment
  - 0.79 for MRI
- Combination 98% post-test probability of correctly predicting CR (either by pathology or 1-year non-regrowth)
- 15% false negative rate when combined modalities suggesting residual tumor



	DRE	PROCTOSCOPY	MRI
COMPLETE CR	Smooth and/or flat scar with no nodularity	Pale, smooth scar with or without telangietasia No ulceration, nodularity, mucosal irregularities or stricturing	Substantial downsizing with no residual tumor Or residual fibrosis No diffusion restriction by DWI No suspicious LN
NEAR-COMPLETE CR	Small but smooth irregularities including residual ulcer, nodules	Visible small ulcers, nodules or mucosal abnormalities	Obvious downstaging but with residual fibrosis and heterogeneous or irregular aspects Complete or near-complete LN regression Minimal restricted diffusion



OTHER

- PET-CT Scan
  - Not currently recommended for routine surveillance of CRC or for NOM for patients with rectal cancer
  - Not part of routine pre-treatment staging
  - Compared to MRI
    - Additional radiation
    - Lower resolution
- Circulating Tumor DNA
  - No proven role in the non-operative management of patients with rectal cancer

TIMING OF ASSESSMENT FOR CLINICAL RESPONSE

- Determining the optimal timing for initial assessment is complex and influenced by:
  - Initial tumor stage
  - Treatment regimen
  - Treatment duration
  - Treatment intensity
  - Tumor biology
  - Assessment methodology

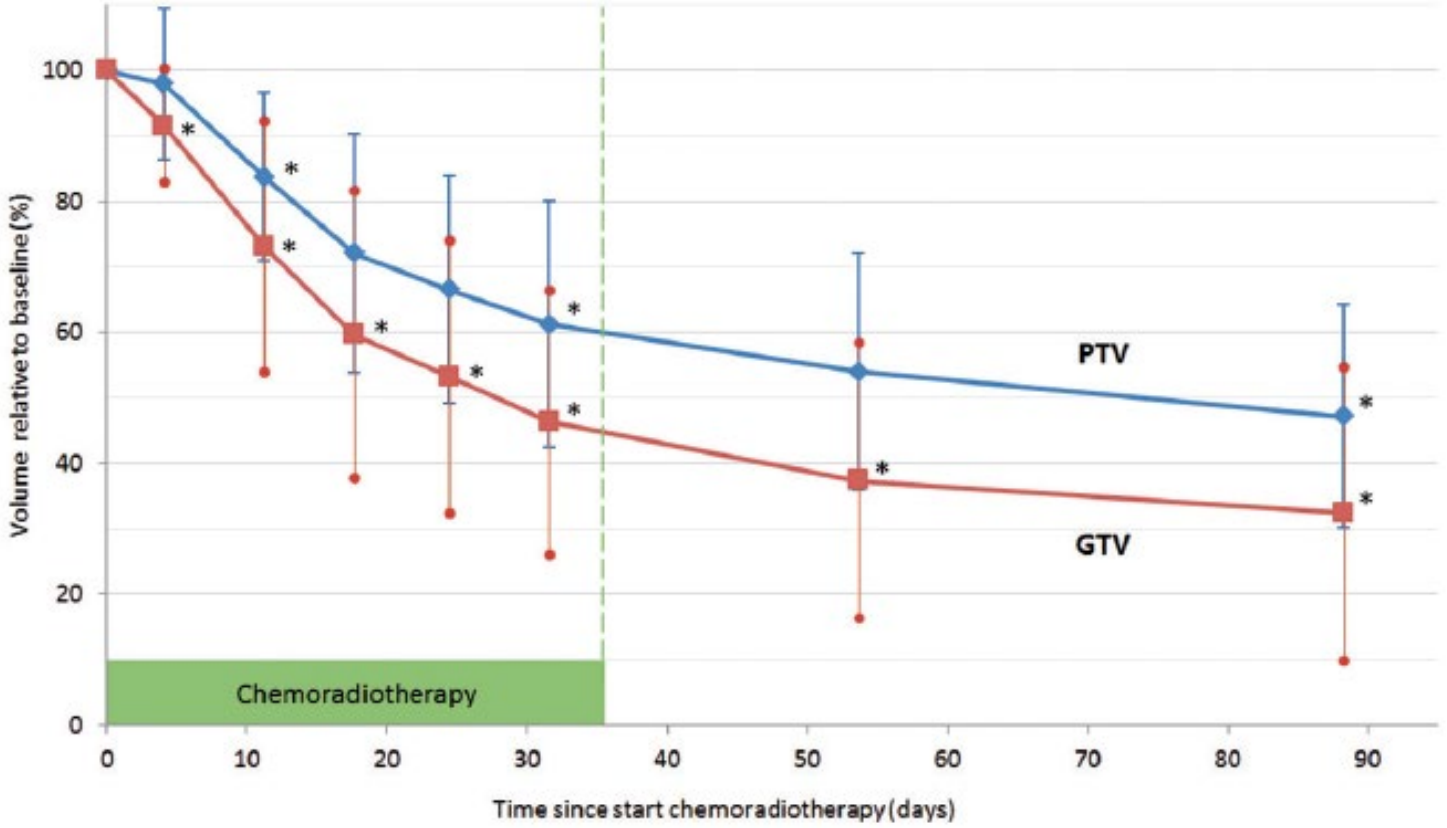
CONSENSUS PANEL

Box 2 | Consensus recommendations on the optimal RA time points for cCR determination

- Standard short-course radiotherapy (duration of 5 days) or chemoradiotherapy (CRT; duration of about 6 weeks) for patients with early-stage tumours.
  - A two-step approach is recommended, involving initial measurement at 12 weeks from the start of treatment and then, in patients with a near clinical complete response (ncCR) at initial assessment, a repeat assessment at 16–20 weeks should be used to determine cCR, as performed in the STAR-TREC trial (NCT02945566).
- CRT followed by brachytherapy (duration of 12 weeks).
  - cCR should be determined at 14 weeks after start of treatment and should be repeated at 20–24 weeks in patients with a ncCR at initial assessment, as performed in the OPERA trial (NCT02505750).
- Total neoadjuvant treatment with CRT and either induction or consolidation chemotherapy (duration of 16–20 weeks).
  - cCR should be determined at 24 weeks after start of treatment, as performed in the GRECCAR12 (NCT02514278) and ACO/ARO/AIO-18.1 (NCT04246684) trials.
- Total neoadjuvant treatment with standard short-course radiotherapy or CRT followed by prolonged consolidation chemotherapy (duration of 26–34 weeks).
  - cCR should be determined at 34–38 weeks after start of treatment, as performed in the OPRA[22] and TRIGGER trials[33].

Tumor volume regression during preoperative chemoradiotherapy for rectal cancer: a prospective observational study with weekly MRI

Robbe Van den Begin, Jean-Paul Kleijnen, Benedikt Engels, Marielle Philippens, Bram van Asselen, Bas Raaymakers, Onne Reerink, Mark De Ridder & Martijn Intven



- 46.3% of tumor shrinkage occurs during chemoradiation therapy
- Rate of shrinkage declines but continues 8-12 weeks after completion of chemoradiation

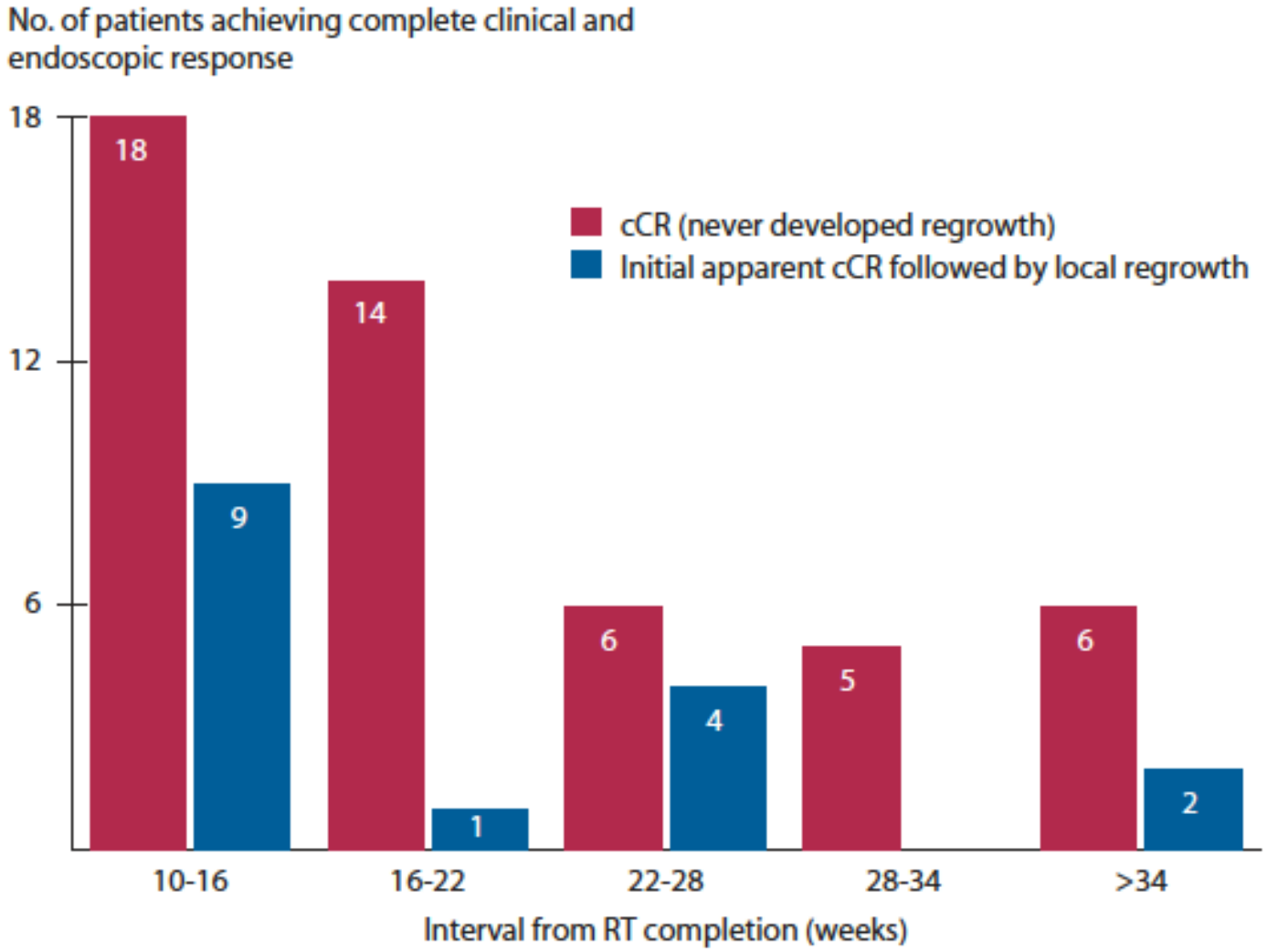
ACTA ONCOLOGICA
2018, VOL. 57, NO. 6, 723–727

Achieving a Complete Clinical Response After Neoadjuvant Chemoradiation That Does Not Require Surgical Resection: It May Take Longer Than You Think!

Angelita Habr-Gama, M.D., Ph.D.[1,2] • Guilherme P. São Julião, M.D.[1]
Laura M. Fernandez, M.D.[1] • Bruna B. Vailati, M.D.[1] • Andres Andrade, M.D.[1]
Sérgio E. A. Araújo, M.D.[2] • Joaquim Gama-Rodrigues, M.D., Ph.D.[1,2]
Rodrigo O. Perez, M.D., Ph.D.[1–3]

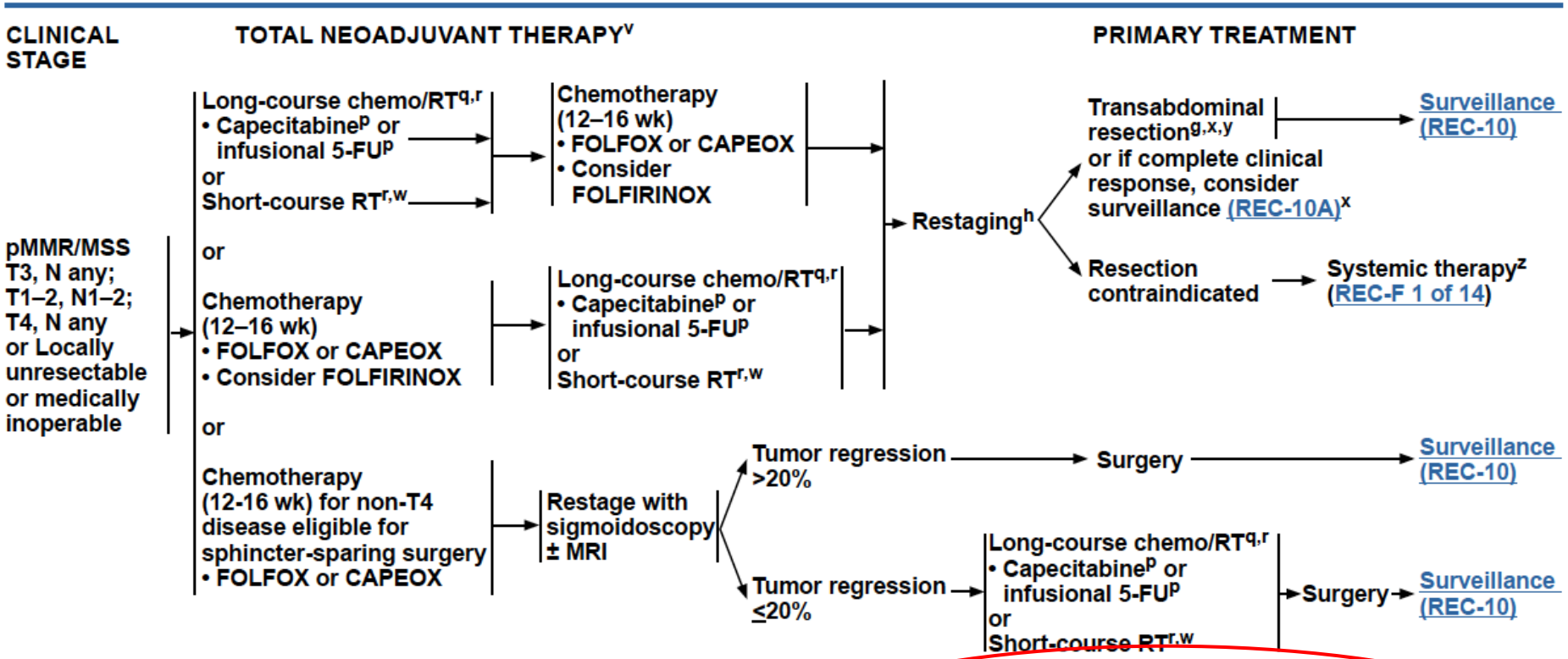
Dis Colon Rectum 2019; 62: 802–808

- CRT + 4 cycles of 5-FU-based consolidation chemo (TNT)
  - Only 38% had cCR from week 10-16
  - 62% required >16 weeks
- T2/T3a: 19.5 +/- 8.4 weeks
- T3b-d/T4: 26.4 +/-10.3 weeks
- Most cCR are achieved within 6 months from completion of radiation
  - If still incomplete, surgery recommended



NCCN

- Induction chemotherapy TNT (Chemo first followed by radiation)
  - Initial assessment no less than 8 weeks after completion of radiotherapy to allow time for delayed response to radiation
- Consolidation chemotherapy TNT (Radiation first followed by chemo)
  - Initial assessment within ~4 weeks of completion of chemotherapy.
- If the patient has had a near-complete response and wishes to avoid surgery, then re-assessment in an additional ~8 weeks
- Not specified: However, general recommendation is if response remains incomplete at 24-26 weeks proceed with TME surgery



[g] Principles of Surgery (REC-C).
[h] Principles of Imaging (REC-A).
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] Principles of Perioperative Therapy (REC-D).
[r] Principles of Radiation Therapy (REC-E).
[v] In select cases (eg, a patient who is not a candidate for intensive therapy) neoadjuvant therapy with chemo/RT or RT alone may be considered prior to surgery.
[w] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.

[x] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination (DRE), 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. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of their risk tolerance. Principles of Nonoperative Management (REC-H).
[y] For select patients who may be candidates for intraoperative RT (IORT), see Principles of Radiation Therapy (REC-E).
[z] FOLFIRINOX is not recommended in this setting.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF FOLLOW UP

Table 1
Summary of important WW studies for patients with locally advanced rectal cancer treated with neoadjuvant therapy

Study	n	NAT strategy	Regrowth, n (%)	Salvage therapy, n (%)	Overall survival (%)
Habr-Gama et al [38], 2004	71	LCRT	2 (3%)	2 (100%)	OS: 100%, DFS: 92%
Smith et al [65], 2012	32	LCRT	6 (18.8%)	6 (100%)	OS: 96% DFS: 88%
Habr-Gama et al [23]2014	90	LCRT	28 (31%)	26 (92.8%)	OS: 91% DFS: 68%
Appelt et al [66], 2015	40	LCRT	10 (25.9%)	9 (90%)	OS: 100%DFS: 70%
Lai et al [67], 2016	18	LCRT	2(11%)	2 (100%)	OS: 100%
Martens et al [68], 2016	100	LRCT: 95%SCRT: 5%	15(15%)	13 (87%)	OS: 96.6% DFS: 80.6%
OnCore Project [69], 2016	129	45 Gy w/5-FU	44(34%)	36 (81.8%)	OS: 96% DFS:88%
IWWD Consortium [70], 2018	880	LCRT: 91%	222 (25.2%)	141 (69%)	OS: 85% DFS: 94%
Smith et al [59], 2019	113	LCRT: 31(27%)Induction: 47(42%)Consolidation: 33 (29%)Chemotherapy alone: 2(2%)	22 (19.5%)	22 (100%)	OS: 85% DFS: 94%
Jimenez-Rodriguez et al [60], 2021	33	Induction TNT (FOLFOX)	2 (6%)	2(100%)	OS:97%, DFS:94%
GarciaAguilar et al [54] (OPRA Trial), 2022	225Induction group: 105/146Consolidation group: 120/158	TNTInduction Chemotherapy + LCRT: 146LCRT + consolidation chemotherapy: 158	75Induction: 42/105Consolidation: 33/120	62/75	DFS: 78% (Induction) vs 77% (Consolidation)

- Systematic reviews (Dossa 2017, Martin 2012, Socha 2023)
  - Local Regrowth Rates: 15.7-34%
  - Successful Surgical Salvage: 93-95.4%
  - Most regrowths occur within 2 years and virtually all within 3 years

Quezada-Diaz et al. Adv Surgery 2023;57:141-154

SURVEILLANCE SCHEMA

Table 2 | **Consensus follow-up methods and intervals for organ preservation strategies**

Year	Serum carcino-embryonic antigen	DRE	Endoscopy	Pelvic MRI	Chest and/or abdominal CT
1	3 months	3–4 months	3–4 months	3–4 months	6–12 months
2	3 months	3–4 months	3–4 months	3–4 months	Annually
3	3 months	6 months	6 months	6 months	Annually
4	6 months	6 months	6 months	6 months	Annually
5	6 months	6 months	6 months	6 months	Annually

First follow-up assessments typically occur at 6–8 weeks following completion of preoperative or definitive treatment. DRE, digital rectal examination.

Fokas E et al. Nat Rev Clin Oncol 2021; 18:805-815

CONCERNS/ISSUES

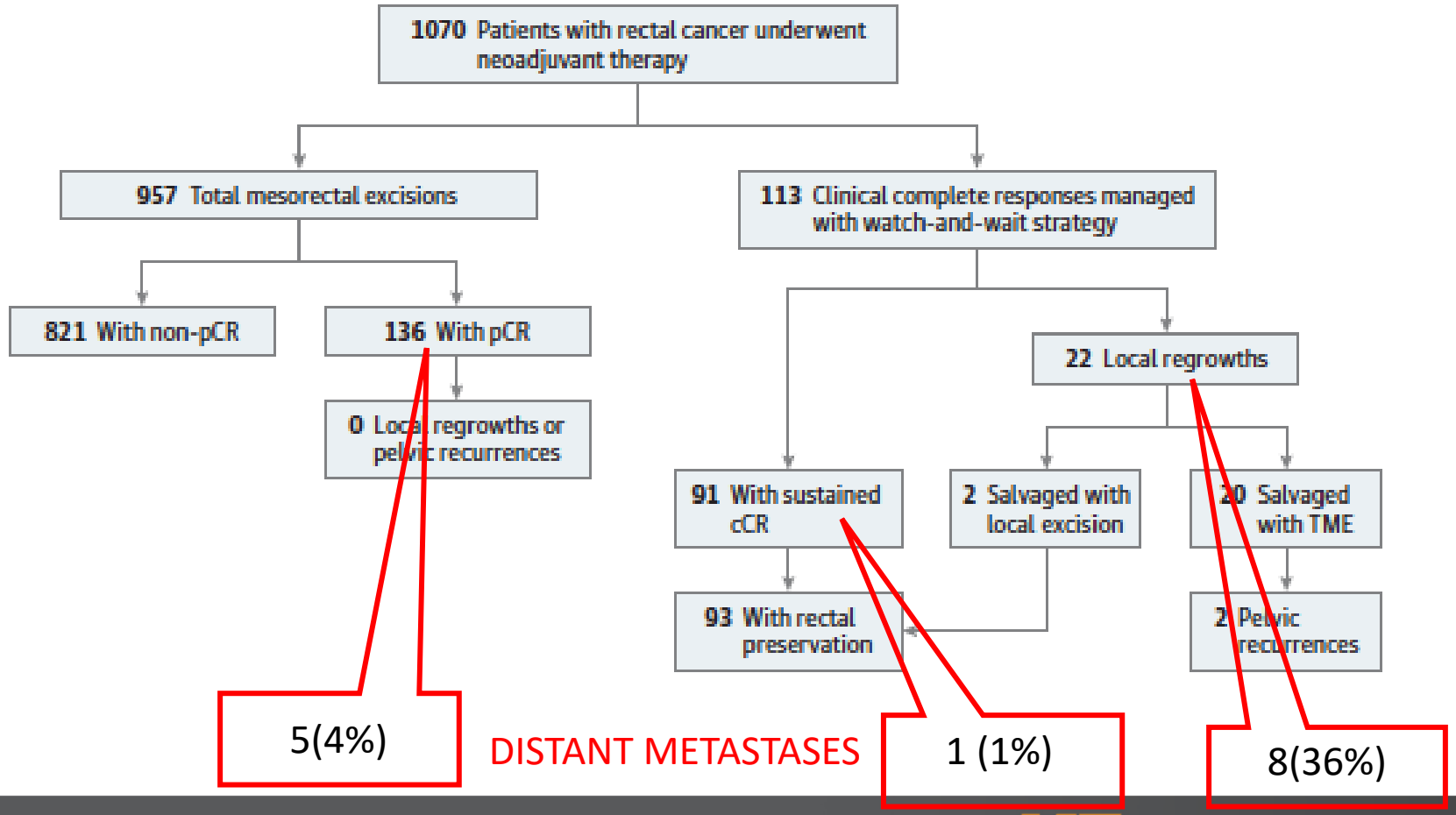
- Distant metastases with local regrowth
- Worse outcomes with delayed surgery
  - Waiting too long with poor response patients
  - Technical/Morbidity
  - Oncologic
- How about local excision for near-complete response?

LOCAL REGROWTH AND DISTANT METASTASES

JAMA Oncology | Original Investigation

Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy

J. Joshua Smith, MD, PhD; Paul Strombom, MD; Oliver S. Chow, MD; Campbell S. Roxburgh, MD, PhD; Patricio Lynn, MD; Anne Eaton, MS; Maria Widmar, MD; Karuna Ganesh, MD, PhD; Rona Yaeger, MD; Andrea Cercek, MD; Martin R. Weiser, MD; Garrett M. Nash, MD, MPH; Jose G. Guillem, MD, MPH; Larissa K. F. Temple, MD, MSc; Sree B. Chalasani, MD; James L. Fuqua, MD; Iva Petkovska, MD; Abraham J. Wu, MD; Marsha Reyngold, MD, PhD; Efsevia Vakiani, MD, PhD; Jinru Shia, MD; Neil H. Segal, MD, PhD; James D. Smith, MD, PhD; Christopher Crane, MD; Marc J. Gollub, MD; Mithat Gonen, PhD; Leonard B. Saltz, MD; Julio Garcia-Aguilar, MD, PhD; Philip B. Paty, MD

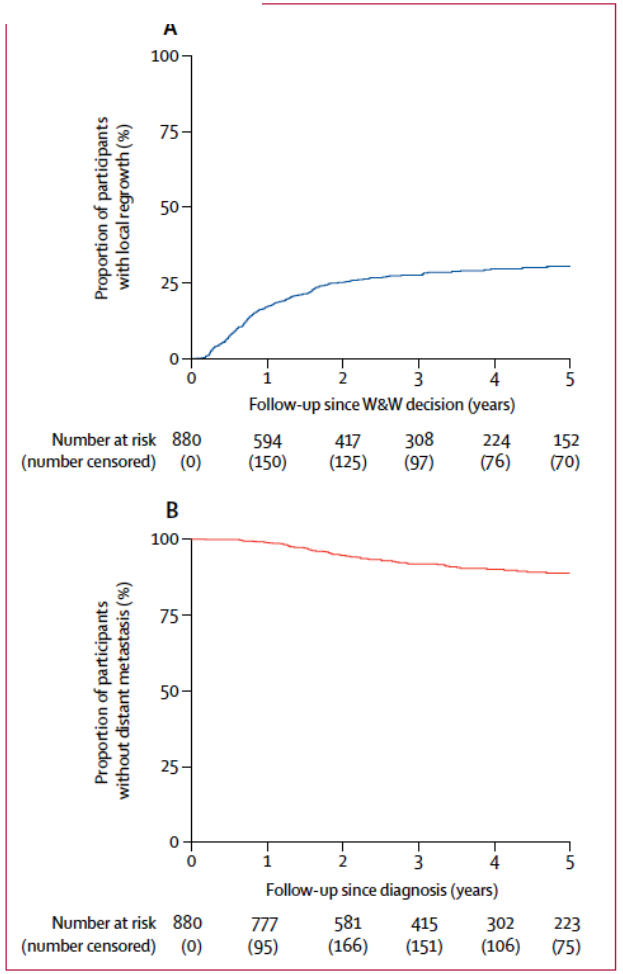


Smith JJ et al. JAMA Oncol 2019

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

*Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium**

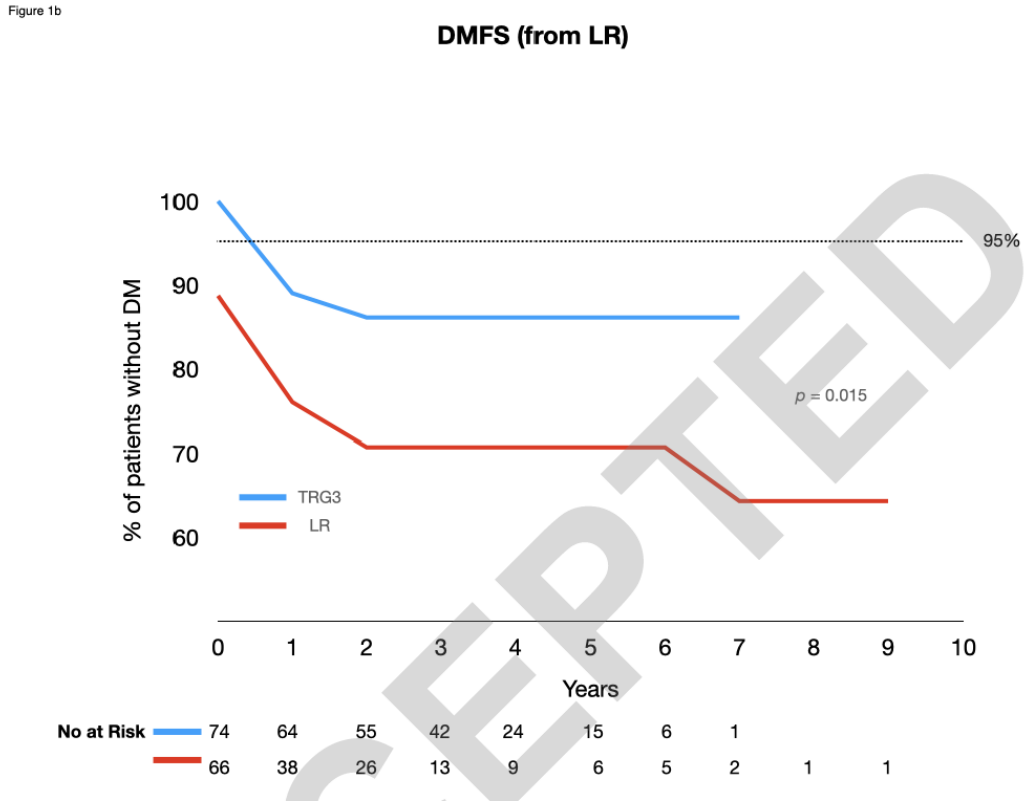
- International registry
- n=880 Clinical CR
  - 2-year local recurrence
    - 25.2%
  - Local Regrowth
    - n=213
    - Distant metastases 38/213 (18%)
  - Sustained cCR
    - N=634
    - Distant metastases 33/634 (5%)



Lancet 2018; 391: 2537–45

LOCAL REGROWTH AND RISK OF DISTANT METASTASES

- Multi-institutional Study
- Watch and Wait
  - 79 patients experiencing local regrowth
    - Distant Mets 21/79 (26.5%)
- Standard TME Surgery
  - 74 patients with near complete pathologic response
    - Distant Mets 10/74 (13.5%)
      - P=0.01



SURGERY AND OUTCOMES FOLLOWING EXTENDED DELAY

JOURNAL OF CLINICAL ONCOLOGY

Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6)

Jérémie H. Lefevre, Laurent Mineur, Salma Kotti, Eric Rullier, Philippe Rouanet, Cécile de Chaisemartin, Bernard Meunier, Jafari Mehrdad, Eddy Cotte, Jérome Desrame, Mehdi Karoui, Stéphane Benoist, Sylvain Kirzin, Anne Berger, Yves Panis, Guillaume Piessen, Alain Saudemont, Michel Prudhomme, Frédérique Peschaud, Anne Dubois, Jérome Loriau, Jean-Jacques Tuech, Guillaume Meurette, Renato Lupinacci, Nicolas Goasgen, Yann Parc, Tabassome Simon, and Emmanuel Tiret

- Locally advanced rectal cancer
  - Conventional chemoradiation
  - Interval to surgery- 7 vs 11 weeks
- Primary endpoint (pathCR)
  - 7 weeks (20/133; 15.0%)
  - 11 weeks (23/132; 17.4%) p=NS
- Morbidity
  - 11 weeks: Higher- 44.5% vs. 32%; p=0.0404
- Complete TME rate
  - 11 weeks: Lower- 78.7% vs. 90%; p=0.0156

J Clin Oncol 34:3773-3780.

Time Interval Between the End of Neoadjuvant Therapy and Elective Resection of Locally Advanced Rectal Cancer in the CRONOS Study

Yoelimar Guzmán, MD; José Ríos, MSc, PhD; Jesús Paredes, MD, PhD; Paula Domínguez, MD; Joan Maurel, MD, PhD; Carolina González-Abós, MD; Ana Otero-Piñeiro, MD, PhD; Raúl Almenara, MD, PhD; María Ladra, MD, PhD; Borja Prada, MD; Marta Pascual, MD, PhD; María Alejandra Guerrero, MD; Álvaro García-Granero, MD, PhD; Laura Fernández, MD; Aina Ochogavía-Seguí, MD; Margarita Gamundí-Cuesta, MD; Francesc Xavier González-Argente, MD, PhD; Lorenzo Viso Pons, MD, PhD; Ana Centeno, MD; Ángela Arrayás, MD; Andrea de Miguel, MD; Elena Gil-Gómez, MD, PhD; Beatriz Gómez, MD, PhD; José Gil Martínez, MD; Antonio M. Lacy, MD, PhD; F. Borja de Lacy, MD, PhD

JAMA Surg. doi:10.1001/jamasurg.2023.2521
Published online July 12, 2023.

- Neoadjuvant Therapy followed by TME Surgery
  - N=908
  - Interval to Surgery
    - <=8 weeks
    - 8-12 weeks
    - >12 weeks
      - Lower risk of poor response
      - Lower risk of systemic recurrence
      - Increased risk of postoperative complications
      - Increased risk of incomplete mesorectum

JAMA Surgery | Original Investigation

Association of Delayed Surgery With Oncologic Long-term Outcomes in Patients With Locally Advanced Rectal Cancer Not Responding to Preoperative Chemoradiation

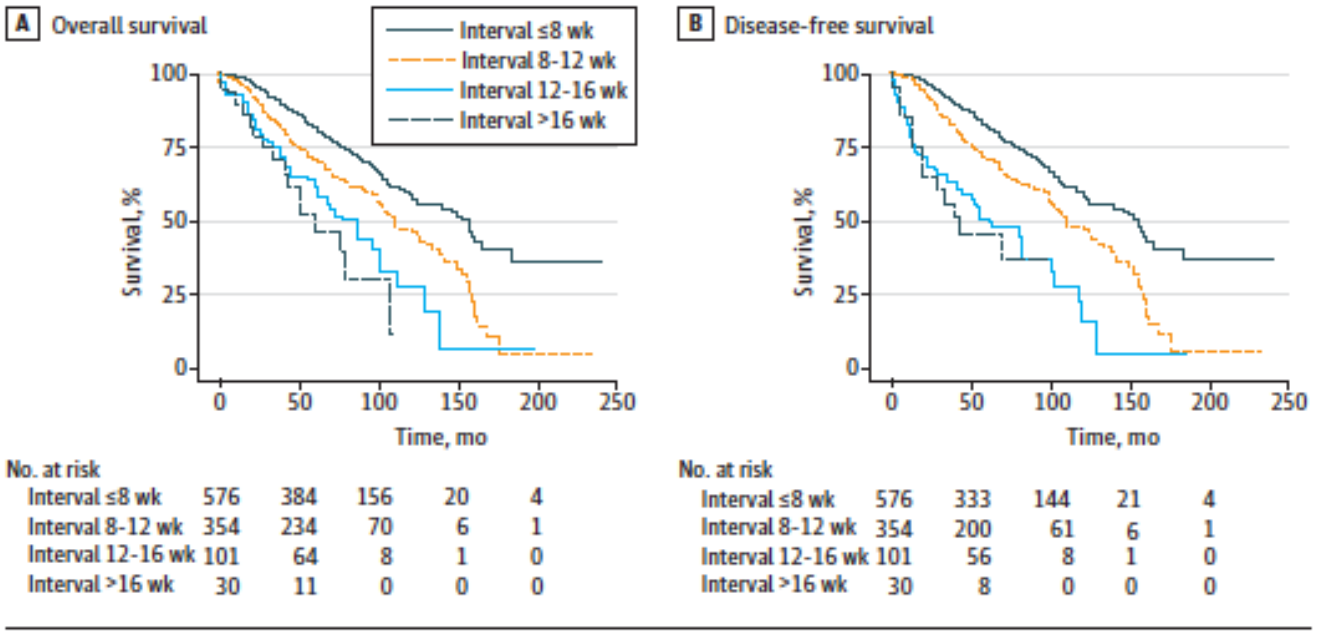
Simona Deidda, MD; Ugo Elmore, MD; Riccardo Rosati, MD; Paola De Nardi, MD; Andrea Vignali, MD; Francesco Puccetti, MD; Gaya Spolverato, MD; Giulia Capelli, MD; Matteo Zuin, MD; Andrea Muratore, MD; Riccardo Danna, MD; Marcello Calabrò, MD; Mario Guerrieri, MD; Monica Ortenzi, MD; Roberto Ghiselli, MD; Stefano Scabini, MD; Alessandra Aprile, MD; Davide Pertile, MD; Giuseppe Sammarco, MD; Gaetano Gallo, MD; Giuseppe Sena, MD; Claudio Coco, MD; Gianluca Rizzo, MD; Donato Paolo Pafundi, MD; Claudio Belluco, MD; Roberto Innocente, MD; Maurizio Degiuli, MD; Rossella Reddavid, MD; Lucia Puca, MD; Paolo Delrio, MD; Daniela Rega, MD; Pietro Conti, MD; Alessandro Pastorino, MD; Luigi Zorcolo, MD; Salvatore Pucciarelli, MD; Carlo Aschele, MD; Angelo Restivo, MD

- Stage II and III LARC
- Surgical Delay:
  - <=8 weeks vs >8 weeks

Table 1. Patient and Treatment Details

Characteristic	No. (%)			P value
		Wait time		
	Total (N = 1064)	≤8 wk (n = 579)	>8 wk (n = 485)	
30-d Morbidity				
Yes	181 (17.1)	86 (14.8)	95 (19.6)	.04
No	883 (82.9)	493 (85.2)	390 (80.4)	
Surgical complications				
Yes	131 (12.3)	58 (10.0)	73 (15.1)	.01
No	933 (87.7)	521 (90.0)	412 (84.9)	
CRM				
Positive	12 (1.3)	3 (0.5)	9 (1.9)	.04
Negative	1052 (98.9)	576 (99.5)	476 (98.1)	

Figure 3. Survival Curve of Patients Stratified for Every Additional Month of Waiting After 8 Weeks



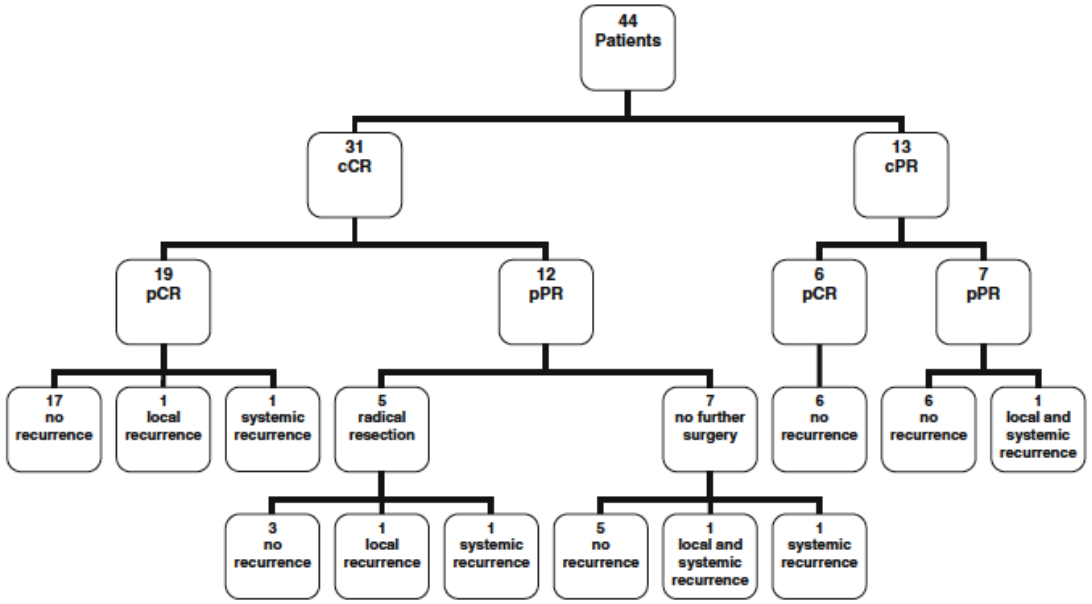
JAMA Surg. 2021;156(12):1141-1149. doi:10.1001/jamasurg.2021.4566

ROLE OF TRANSNAL EXCISION FOR NEAR COMPLETE REPONSE

Long-Term Results of Transanal Excision After Neoadjuvant Chemoradiation for T2 and T3 Adenocarcinomas of the Rectum

Rajesh M. Nair · Erin M. Siegel · Dung-Tsa Chen · William J. Fulp · Timothy J. Yeatman · Mokenge P. Malafa · Jorge Marcet · David Shibata

- n=44
  - Recurrence
    - Local Recurrence only (n=2)
    - Local and Systemic (n=2)
    - Systemic only (n=3)
  - 5-year OS
    - T2/T3N0 84%
    - T2/T3N1 81%



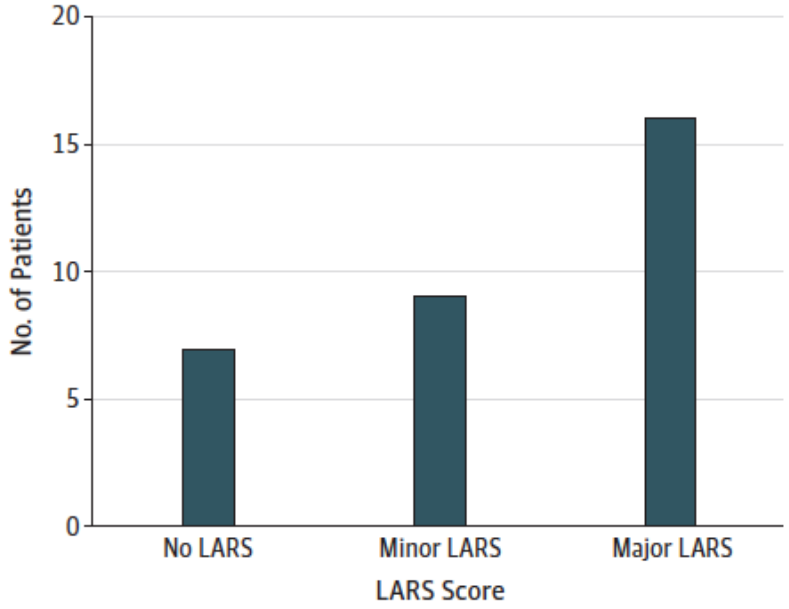
J Gastrointest Surg (2008) 12:1797–1806

JAMA Surgery | Original Investigation

Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer
The CARTS Study

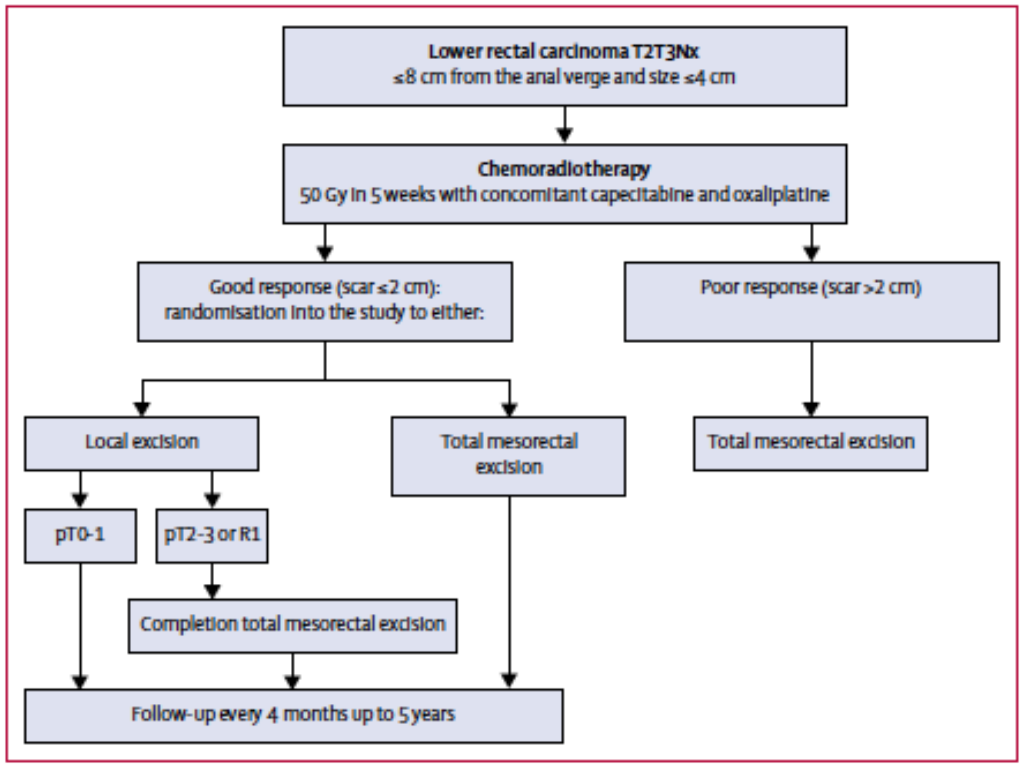
Rutger C. H. Stijns, MD; Eelco J. R. de Graaf, MD, PhD; Cornelis J. A. Punt, MD, PhD; Iris D. Nagtegaal, MD, PhD; Joost J. M. E. Nuyttens, MD, PhD; Esther van Meerten, MD, PhD; Pieter J. Tanis, MD, PhD; Ignace H. J. T. de Hingh, MD, PhD; George P. van der Schelling, MD, PhD; Yair Acherman, MD; Jeroen W. A. Leijtens, MD; Andreas J. A. Bremers, MD, PhD; Geerard L. Beets, MD, PhD; Christiaan Hoff, MD, PhD; Cornelis Verhoef, MD, PhD; Corrie A. M. Marijnen, MD, PhD; Johannes H. W. de Wilt, MD, PhD; for the CARTS Study Group

- cT1-T3 rectal cancer (n=55)
  - Neoadjuvant conventional chemoradiation
  - ycT0-T2 (n=47;85%)
    - Treated with TEM
      - 35 (74%) TEM alone
      - LR rate 7.7%
      - 5-year DFS 81.6%
      - 5-year OS 82.8%
    - Bowel Function
      - ?larger tumors



Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial

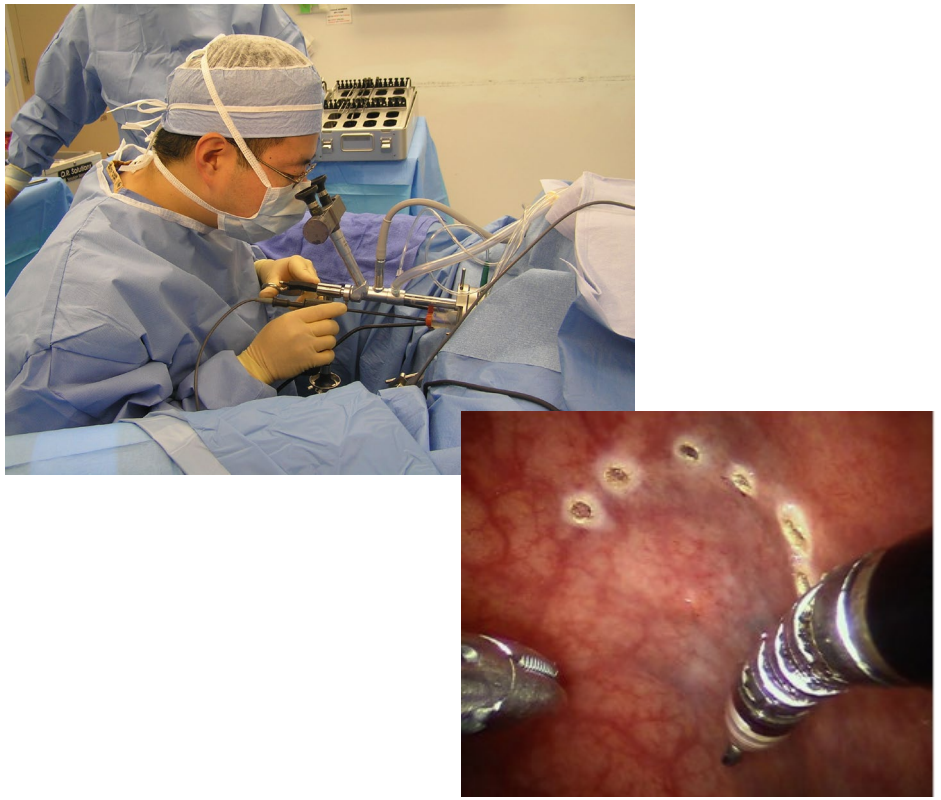
Eric Rullier, Philippe Rouanet, Jean-Jacques Tuech, Alain Valverde, Bernard Lelong, Michel Rivoire, Jean-Luc Faucheron, Mehrdad Jafari, Guillaume Portier, Bernard Meunier, Igor Sieznieff, Michel Prudhomme, Frédéric Marchal, Marc Pocard, Denis Pezet, Anne Rullier, Véronique Vendrely, Quentin Denost, Julien Asselineau, Adélaïde Doussau



- n=186
  - Intent to Treat analysis
    - Composite outcome of death, recurrence, morbidity and side-effects at 2 years
  - 145 Good responders
    - 74 TAE/TEM
      - 26 COMPLETION TME
    - 71 TME
  - Composite Component
    - 56% vs. 48% p=NS
- Failed to show superiority of local excision
  - High proportion of LE receiving TME
  - Better selection criteria needed

LOCAL EXCISION SUMMARY

- Local excision following neoadjuvant chemoradiation
  - Near-complete clinical response
- Potential option for non-candidates for watch and wait approach
- Poor radical surgery candidates
- Patients refusing APR
- Careful patient selection



NCCN STATEMENT ON NOM

PRINCIPLES OF NONOPERATIVE MANAGEMENT

To provide nonoperative management (NOM) for rectal cancer patients, the multidisciplinary team's diagnostic skills are crucial. They must accurately assess clinical, radiological, and pathological findings, determining patient eligibility for NOM and closely monitoring progress. The team's expertise extends to tracking treatment responses, identifying surgical needs promptly, and adjusting the management plan as necessary. Additionally, the team should maintain a comprehensive understanding of the watchful waiting literature and surveillance methodology, adeptly managing patients with complete or near-complete clinical responses and regularly monitoring for potential tumor recurrence or progression. Given this, NOM is recommended only at centers with experienced multidisciplinary teams and for patients committed to intensive surveillance.

CONCLUSIONS

- Locally advanced rectal cancer
  - Substantial growth in management options
  - Multidisciplinary collaboration is critical
- Increasing opportunity for personalization of treatment
  - Maximizing treatment vs. selective modulation/omission
  - Harmonize with patient toxicity, quality of life, function
- Opportunities/Future Directions in NOM
  - Patient selection
  - Improved imaging (e.g. determining degree of response, TRIGGER trial)
  - More aggressive TNT (PRODIGE 23, BRAZIL TNT, JANUS)
  - Less aggressive (PROSPECT, Sao Paolo: FOLFOX v. 5FU)
  - Molecular biomarkers (e.g. predicting degree of response)
  - Immunotherapy and MSI-H
  - Quality of Life
  - Cost

Every nail does not need a hammer…..


UNIVERSITY OF TENNESSEE