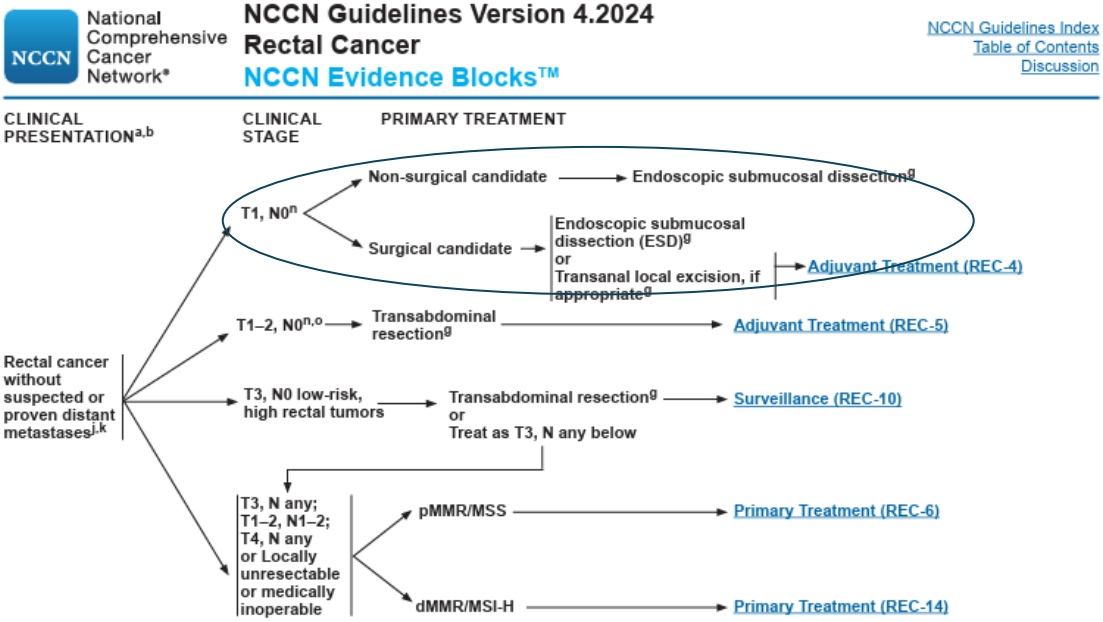
TOTAL NEOADJUVANT THERAPY FOR RECTAL CANCER: HOW DID WE GET HERE?

Charles A. Ternent, MD
Methodist Physicians Clinic
Colon and Rectal Surgery

1



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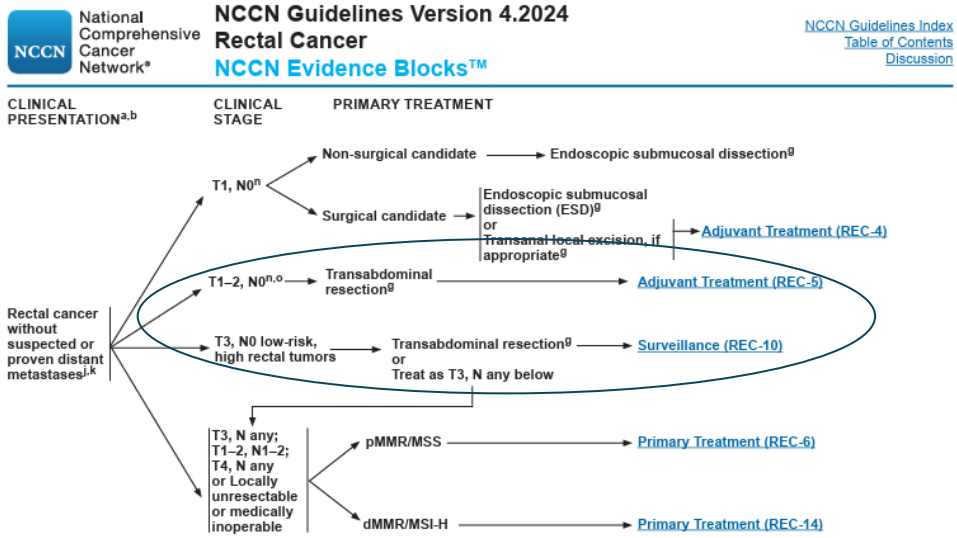
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Rectal Cancer
NCCN Evidence Blocks™
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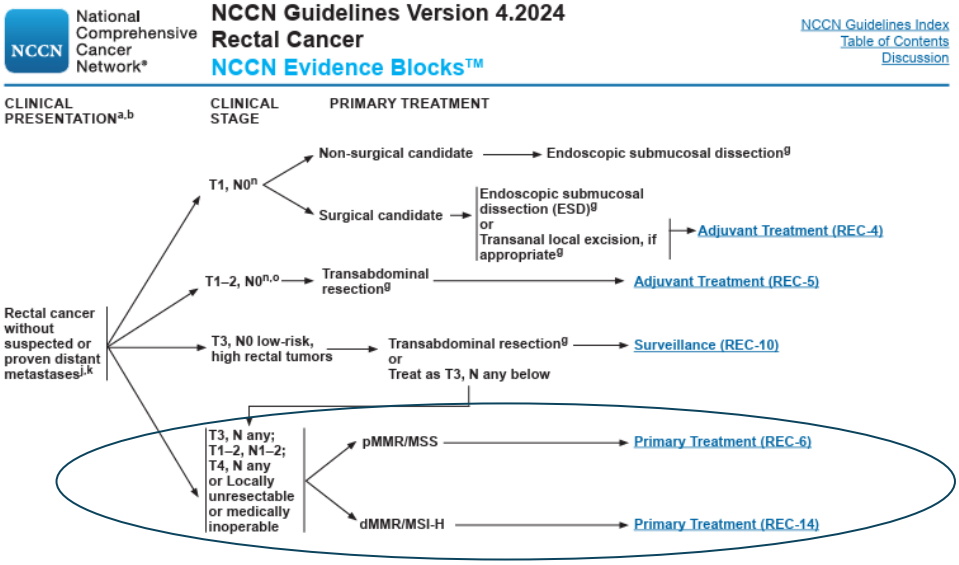
Discussion
CLINICAL PRESENTATION[a,b]
CLINICAL STAGE
PRIMARY TREATMENT
Rectal cancer without suspected or proven distant metastases[j,k]
T1, N0[n]
Non-surgical candidate
Endoscopic submucosal dissection[g]
Surgical candidate
Endoscopic submucosal dissection (ESD)[g] or Transanal local excision, if appropriate[g]
Adjuvant Treatment (REC-4)
T1–2, N0[n,o]
Transabdominal resection[g]
Adjuvant Treatment (REC-5)
T3, N0 low-risk, high rectal tumors
Transabdominal resection[g] or Treat as T3, N any below
Surveillance (REC-10)
T3, N any; T1–2, N1–2; T4, N any or Locally unresectable or medically inoperable
pMMR/MSS
Primary Treatment (REC-6)
dMMR/MSI-H
Primary Treatment (REC-14)

3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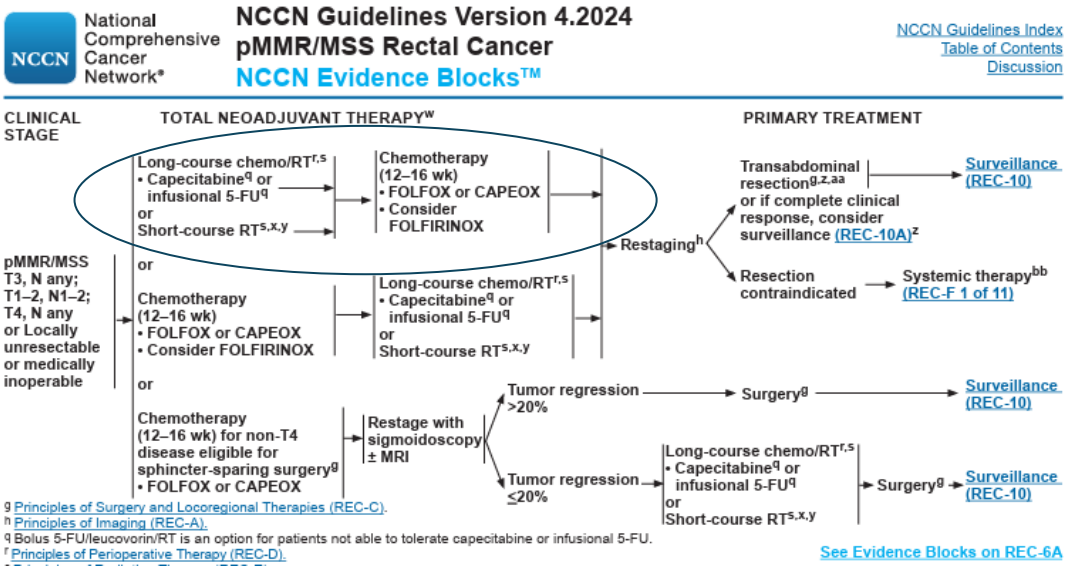
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Long-course chemo/RT[r,s] • Capecitabine[q] or infusional 5-FU[q] or Short-course RT[s,x,y]
Chemotherapy (12–16 wk) • FOLFOX or CAPEOX • Consider FOLFIRINOX
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Long-course chemo/RT[r,s] • Capecitabine[q] or infusional 5-FU[q] or Short-course RT[s,x,y]
Chemotherapy (12–16 wk) for non-T4 disease eligible for sphincter-sparing surgery[g] • FOLFOX or CAPEOX
Restage with sigmoidoscopy ± MRI
Tumor regression >20%
Tumor regression ≤20%
Long-course chemo/RT[r,s] • Capecitabine[q] or infusional 5-FU[q] or Short-course RT[s,x,y]
Restaging[h]
Transabdominal resection[g,z,aa] or if complete clinical response, consider surveillance (REC-10A)[z]
Resection contraindicated
Systemic therapy[bb] (REC-F 1 of 11)
Surgery[g]
Surveillance (REC-10)
[g] Principles of Surgery and Locoregional Therapies (REC-C).
[h] Principles of Imaging (REC-A).
[q] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[r] Principles of Perioperative Therapy (REC-D).
See Evidence Blocks on REC-6A

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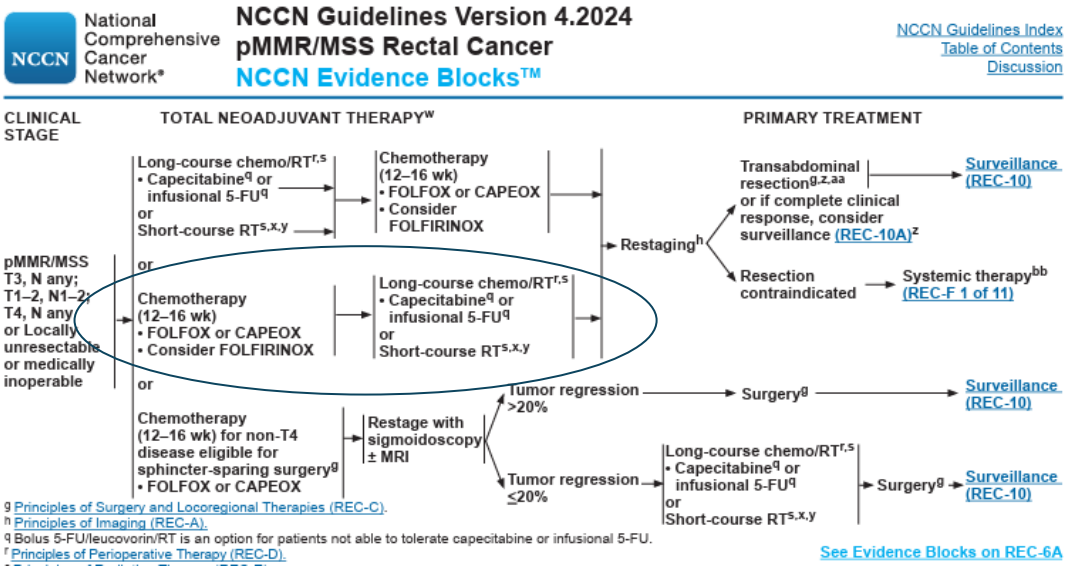
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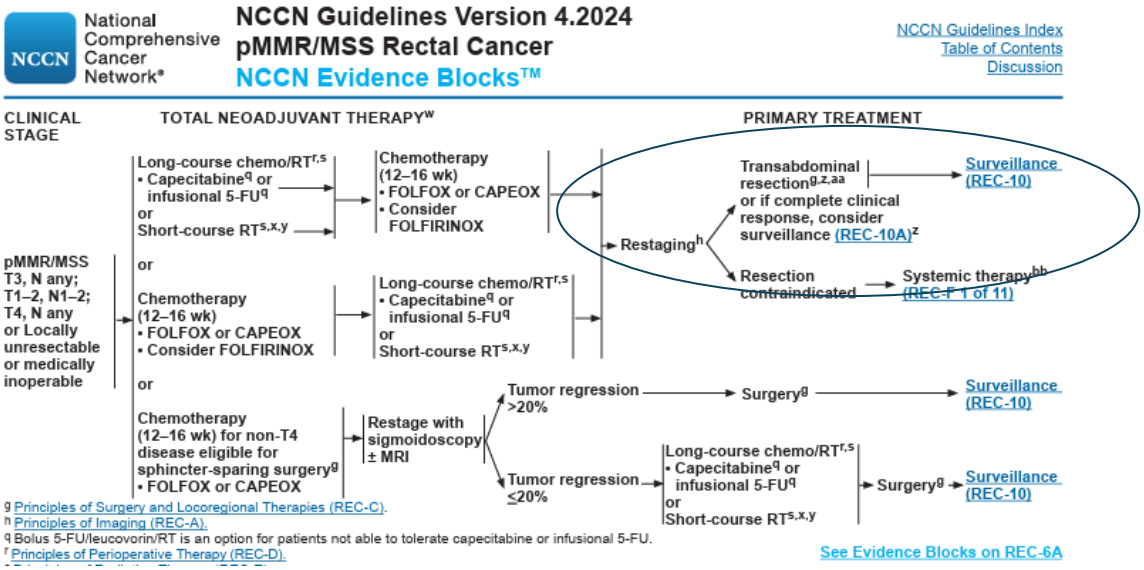

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What Is Total Neoadjuvant Therapy?

- **Total = Chemotherapy (5FU based Chemotherapy) and External Beam Radiation Therapy Combination For Locally Advanced Rectal Cancer**
- **Neoadjuvant = Initial Therapy Before Surgery**
  - **Induction Chemotherapy Followed by Radiation Therapy or**
  - **Radiation Therapy followed by Consolidation Chemotherapy**
- **Which One is Better?**

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Why Use Total Neoadjuvant Therapy?

- **Are Chemo and Radiation Therapy Tolerated Better Before or After Surgery?**
- **Is There a Downstaging effect on Locally Advanced Rectal Cancers?**
- **Does it Increase Complete Clinical Response and Complete Pathologic Response?**
- **Does it Affect Rectal Organ Preservation?**
- **Downside?**

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Why Do Some Rectal Cancers Need Chemotherapy / Radiation Therapy?

- **+ Circumferential Radial Margin (CRM) Predictor of Survival and Local Recurrence**
- **Locally Advanced Rectal Cancer Has Increased Risk of +CRM with upfront Surgery**
- **Chemoradiation Decrease the Rate of Stoma in Locally Advanced Rectal Cancer**

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A Method of Performing Abdomino-Perineal Excision for Carcinoma of the Rectum and of the Terminal Portion of the Pelvic Colon (1908)*

W. Ernest Miles, F.R.C.S., L.R.C.P.

- **Combined abdominal and perineal rectal cancer resection Czerny 1884**
- **Perineal proctectomy only failed in addressing zone of upward spread**
- **Up until 1906 perineal resections 54/57 recurrences at 6 months – 3 years (Miles)**
- **1908 N=12 Patients abdominoperineal resection with over 50% mortality**

Lancet Volume 172, Issue 4451p1812-1813December 19, 1908

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Clinical Trial › J Clin Oncol. 2005 Aug 20;23(24):5644-50. doi: 10.1200/JCO.2005.08.144.

Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate

Joakim Folkesson [1], Helgi Birgisson, Lars Pahlman, Bjorn Cedermark, Bengt Glimelius, Ulf Gunnarsson

- **Curative rectal cancer resection +/- preop short course radiation**
- **N=1,168**
- **Median follow-up 13 years**
- **Overall survival 38% radiated group / 30% non-irradiated (p=0.008)**
- **Cancer specific survival radiated group 72% / 62% non-irradiated (p=0.03)**
- **Local recurrence rate 9% vs 26%**

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ORIGINAL ARTICLE

Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Authors: Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D., Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D., Peter Martus, Ph.D., +7, for the German Rectal Cancer Study Group* Author Info & Affiliations

Published October 21, 2004 | N Engl J Med 2004;351:1731-1740 | DOI: 10.1056/NEJMoa040694 | VOL. 351 NO. 17

- **Initiated 1994 RCT T3-4 or N+**
- **Long course preop chemoradiation 5040 cGy + 5FU then surgery after 6 weeks (N=421) or Surgery followed by chemoradiation (N=402)**
- **Main outcome Overall Survival 76% vs 74% (p=NS)**
- **5-year DFS 68% vs 65% (p=NS)**
- **5-year local recurrence 6% vs 13% (p=0.006)**
- **Grade 3-4 toxicities 27% vs 40% (p=0.001)**
- **In low cancers rate sphincter saving surgery doubled**

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Comparative Study > Ann Surg. 2004 Oct;240(4):711-7; discussion 717-8.

doi: 10.1097/01.sla.0000141194.27992.32.

Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results

Angelita Habr-Gama [1], Rodrigo Oliva Perez, Wladimir Nadalin, Jorge Sabbaga, Ulysses Ribeiro Jr, Afonso Henrique Silva e Sousa Jr, Fábio Guilherme Campos, Desidério Roberto Kiss, Joaquim Gama-Rodrigues

Stage 0 rectal cancer disease is associated with excellent long-term results irrespective of treatment strategy. Surgical resection may not lead to improved outcome in this situation and may be associated with high rates of temporary or permanent stoma, operative and unnecessary morbidity and mortality rates.

- **N=265 resectable distal rectal adenocarcinomas**
- **Neoadjuvant chemoradiation (Long course)**
  - **Group A Incomplete response proceeded to surgery**
  - **Group B Complete clinical response proceeded to nonoperative management**
- **Group A pT0N0cM0 compared to Group B Nonop Management**
- **5-year OS and DFS 88% and 83% (Group A) and 100% and 92% (Group B)**

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Comparative Study > Ann Surg. 2004 Oct;240(4):711-7; discussion 717-8.
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- **Conclusions:**
  - **Stage 0 rectal cancer disease is associated with excellent long-term results irrespective of treatment strategy**
  - **Surgical resection may not lead to improved outcome in this situation and may be associated with high rates of temporary or definitive stoma construction and unnecessary morbidity and mortality rates.**

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Clinical Trial > Lancet Oncol. 2015 Aug;16(8):957-66. doi: 10.1016/S1470-2045(15)00004-2.
Epub 2015 Jul 14.

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Julio Garcia-Aguilar [1], Oliver S Chow [2], David D Smith [3], Jorge E Marcet [4], Peter A Cataldo [5], Madhulika G Varma [6], Anjali S Kumar [7], Samuel Oommen [8], Theodore Coutsoftides [9], Steven R Hunt [10], Michael J Stamos [11], Charles A Ternent [12], Daniel O Herzig [13], Alessandro Fichera [14], Blase N Polite [15], David W Dietz [16], Sujata Patil [17], Karin Avila [2]; Timing of Rectal Cancer Response to Chemoradiation Consortium

- **2004-2012 N=259**
- **Four sequential study groups Stage II-III Rectal Cancer**
- **Long course chemoradiation followed by**
  - **Group 1 – Surgery in 6-8 weeks**
  - **Group 2 – add 2 cycles mFOLFOX6 then Surgery**
  - **Group 3 – add 4 cycles mFOLFOX6 then Surgery**
  - **Group 4 – add 6 cycles mFOLFOX6 then Surgery**

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Clinical Trial > Lancet Oncol. 2015 Aug;16(8):957-66. doi: 10.1016/S1470-2045(15)00004-2. Epub 2015 Jul 14.

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- **Pathologic Complete Response**
  - **18%, 25%, 30%, 38% Groups 1-4 (p=0.0036)**
- **Conclusions:**
  - **mFOLFOX6 after chemoradiation and before total mesorectal excision has the potential to increase the proportion of patients eligible for less invasive treatment strategies**
  - **This strategy is being tested in phase 3 clinical trials.**

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PARTIAL ACCESS | CLINICAL TRIAL UPDATES | October 26, 2023

Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial

Authors: Floris S. Verheij, BSc, Dana M. Omer, MD, Hannah Williams, MD, Sabrina T. Lin, MSc, Li-Xuan Qin, PhD, James T. Buckley, BSc, Hannah M. Thompson, MD, ... SHOW ALL ..., and Julio Garcia-Aguilar, MD, PhD AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 5 • https://doi.org/10.1200/JCO.23.01208

- **Stage II/III rectal cancer randomly assigned to induction chemotherapy followed by chemoradiation (INCT-CRT) or chemoradiation followed by consolidation chemotherapy (CRT-CNCT).**
- **Patients who achieved a complete or near-complete response after finishing treatment were offered watch-and-wait (WW).**
- **Total mesorectal excision (TME) was recommended for those who achieved an incomplete response.**
- **The primary end point was disease-free survival (DFS). The secondary end point was TME-free survival.**
- **324 patients randomly assigned (INCT-CRT, n = 158; CRT-CNCT, n = 166).**
- **Median follow-up was 5.1 years.**

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Publication: Journal of Clinical Oncology • Volume 42, Number 5 • https://doi.org/10.1200/JCO.23.01208

- **5-year DFS rates were 71% (95% CI, 64 to 79) and 69% (95% CI, 62 to 77) for INCT-CRT and CRT-CNCT, respectively (*P* = .68).**
- **TME-free survival was 39% (95% CI, 32 to 48) in the INCT-CRT group and 54% (95% CI, 46 to 62) in the CRT-CNCT group (*P* = .012).**
- **81 patients (25%) with regrowth, 94% occurred within 2 years and 99% occurred within 3 years.**
- **DFS was similar for patients who underwent TME after restaging (64% [95% CI, 53 to 78]) and patients in WW who underwent TME after regrowth (64% [95% CI, 53 to 78]; *P* = .94).**
- **Updated analysis continues to show long-term organ preservation in half of the patients with rectal cancer treated with total neoadjuvant therapy. In patients who enter WW, most cases of tumor regrowth occur in the first 2 years.**

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Future?

- **De-escalation of treatment**
- **ctDNA for surveillance in WW after TNT**
- **AI for assessment of clinical, endoscopic and imaging response of rectal cancer to TNT for Watch and Wait patients**

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Conclusions: TNT

- **Allows better exposure to chemotherapy**
- **Opens up possibility of Watch and Wait**
- **50% Rate of Long Term Organ Preservation After TNT on Watch Wait**
- **99% of Recurrences On Watch and Wait after TNT Occur Within the First 3 Years (99%)**

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