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Treatment Trends in Rectal Cancer: Total Neoadjuvant Therapy (TNT) and Watch and Wait

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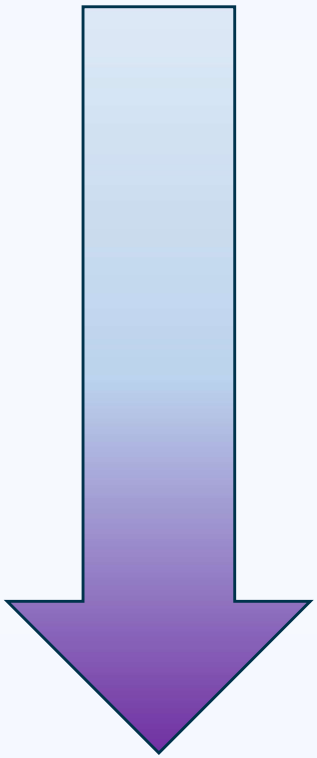
Evolution of Rectal Cancer Treatment



- Adjuvant chemoradiation therapy (GITSG)

- Total Mesorectal Excision and training (Heald)
- MDT approach (Europe)
- Neoadjuvant chemoradiation therapy (Swedish, Dutch, German Trials)

- Delayed surgery (Garcia-Aguilar, MSKCC)

ACS NAPRC National Accreditation Program for Rectal Cancer
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- Non-Operative Management/"Watch and Wait" (Habr-Gama)
- Total Neoadjuvant Therapy

Total Neoadjuvant Therapy (TNT)

Neoadjuvant Therapy

Radiation Therapy

↓

Surgery

↓

Systemic Chemotherapy

Total Neoadjuvant Therapy

Radiation Therapy

↓

Systemic Chemotherapy

↓

Surgery

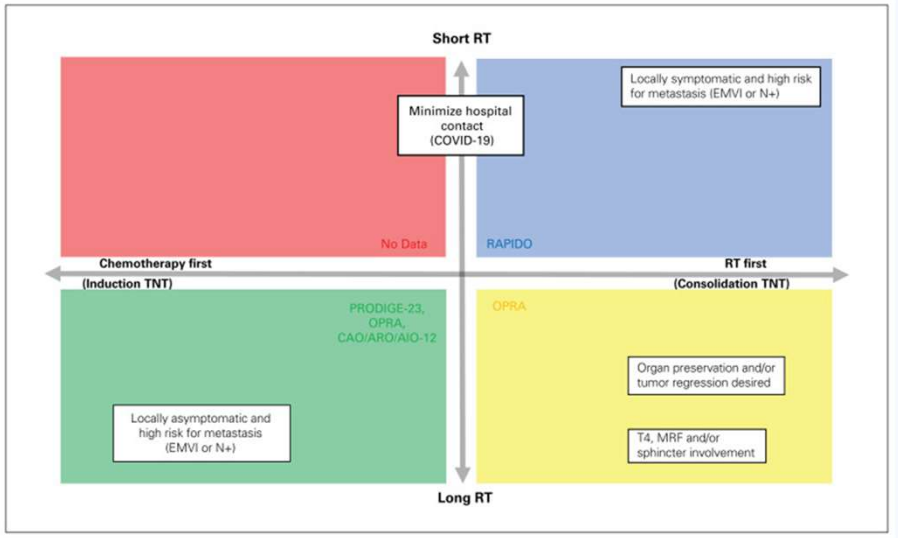
Total Neoadjvuant Therapy

- Varied regimens, but all ***systemic chemotherapy prior to surgery***
  - Improved disease-free survival (DFS) and local-recurrence
  - Higher pathologic complete response (pCR) rates
  - Better chemotherapy completion rates

- Trials (all locally-advanced rectal cancers)
  - Polish-II: SCRT + FOLFOX x3: improved pCR (16% vs. 12%)
  - RAPIDO: SCRT + more chemo: lower disease-related treatment failure (HR 0.75), lower distant metastatic disease (HR 0.69), better pCR 28% vs 14%, more patients completed chemo 85% vs 67% (*higher local failure)
  - PRODIGE: chemo + LC chemoRT + TME + chemo: similar outcomes (lower LR)

Total Neoadjuvant Therapy: treatment sequence

- "Induction" = systemic chemotherapy first
- "Consolidation"= systemic chemotherapy after radiation therapy
- Trials
  - CAO/ARO/AIO-12: differences in treatment tolerance
  - OPRA: no difference in outcomes except ***higher organ preservation in consolidation group*** (58% vs 43%)
  - Longer interval between completion of radiation and surgery in "consolidation" approach ***has not translated into worse pathologic or surgical outcomes***



OLD: RT → (6-8 wks) **Surgery**

NEW RT → (30+ wks) **Surgery**

New RneoRT Quality Measure

RneoRT – Rectum Measure: For patients with surgically treated clinical T4NanyM0 or TanyN2M0 rectal cancer, neoadjuvant radiation therapy is initiated within 9 months prior to resection or recommended.

- Recognizes move of radiation therapy from after surgery (adjuvant) to before surgery (neoadjuvant)
- Recognizes that systemic chemotherapy moved prior to surgery in higher risk patients
- Recognizes that some lower risk patients can be spared radiation therapy

Non-Operative Management

- AKA “Watch and Wait”, “Wait and Watch”, “Watchful Waiting”, etc

- Patients with complete clinical response to neoadjuvant therapy skip surgery and are closely observed for recurrence of disease
- Option for nearly half of all newly-diagnosed rectal cancer patients
- Has reached mainstream in last 5 years and since inception of NAPRC
- Applications are broadening and require careful scrutiny
  - Safety, adverse-effects, risk:benefit ratio, cost

Habr-Gama

- 265 patients treated with NCRT, median f/u 4+ yrs
- 71 patients (27%) achieved complete clinical response (CCR) and were observed without surgery
- 22 patients (8%) had incomplete clinical response but were ypT0N0 after surgery
- 3 systemic recurrences in each group, 2 luminal recurrences (3%) in the observation group
- Five-year OS and DFS rates were 88% and 83% (surgery) and 100% and 92% (observation)

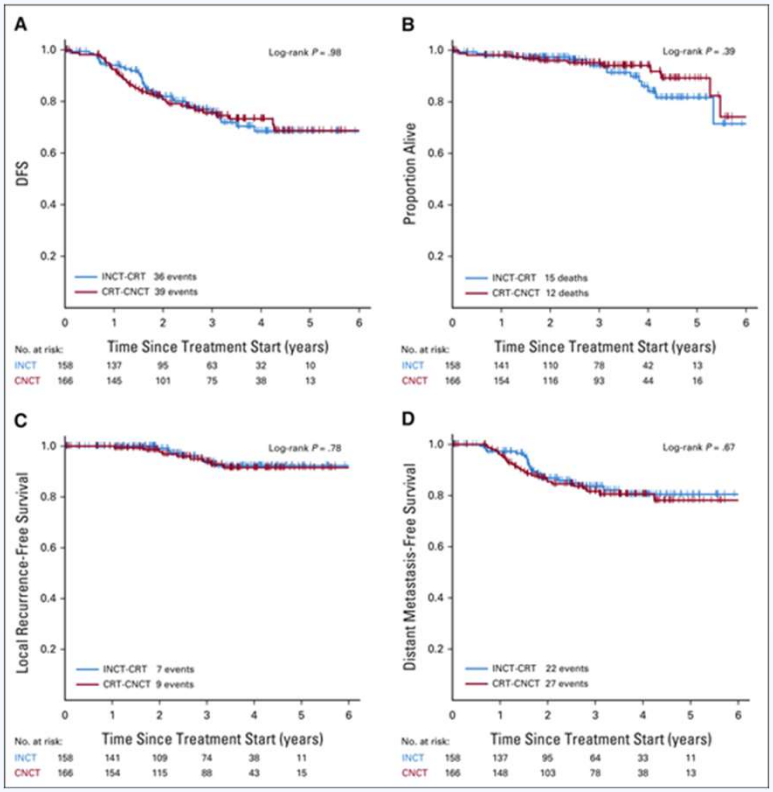
CONCLUSIONS: Stage 0 rectal cancer disease is associated with excellent long-term results irrespective of treatment strategy. Surgical resection may not lead to improved outcome in this situation and may be associated with high rates of temporary or definitive stoma construction and unnecessary morbidity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

Habr-Gama A, et al. Ann Surg. 2004 Oct;240(4):711-7

OPRA II

- 5-year DFS rates were 71% vs 69% for INCT-CRT and CRT-CNCT
- TME-free survival was 39% in the INCT-CRT group and 54% in the CRT-CNCT group (P = .012)
- Of 81 patients with regrowth, 94% occurred within 2 years and 99% occurred within 3 years.
- DFS was similar for patients who underwent TME after restaging 64% vs patients in WW who underwent TME after regrowth 64%

In conclusion, TNT for rectal cancer patients resulted in long-term organ preservation in half of the patients. Local tumor regrowth occurs mostly within the first 2 years. While the order of TNT did not result in a difference in survival, CRT-CNCT resulted in higher organ preservation at 5 years compared to INCT-CRT. Future research should focus on more effective and less toxic neoadjuvant treatment regimens to further drive up cCR rates.



Floris, et al. JCO 42, 500-506(2024)

International Watch and Wait Registry

- 1009 patients from 47 participating institutes (15 countries) between 2015-2018.
- 880 patients (87%) with a cCR were included.
- Median follow-up time was 3·4 years
- Two-year local regrowth rate was 25%
- 88%of all local regrowth was diagnosed in the first two years and was located in the bowel wall in 97%
- 5-year overall survival was 85%
- 5-year disease-specific survival was 94%

CONCLUSIONS: This is the largest series of patients with rectal cancer treated with a W&W approach, consisting of approximately 50% data from previous cohort series and 50% unpublished data. Local regrowth occurs mostly in the first two years and in the bowel wall, emphasizing the importance of endoscopic surveillance to ensure the option of deferred curative surgery. Local unsalvageable disease after W&W was rare. It is our hypothesis that the majority of the 6% rectal cancer-specific death was more related to tumour biology rather than to omission of surgery.

Protocol

	Y 1	Y 2	Y 3-5	>Y 5
Endoscopy	q 4 mo	q 4 mo	q 6 mo	q 12 mo
DRE	q 4 mo	q 4 mo	q 6 mo	q 12 mo
MRI	q 6 mo	q 6 mo	q 12 mo	NA
CT imaging	q 12 mo	q 12 mo	q 12 mo	q 12 mo
CEA	q 4 mo	q 4 mo	q 6-12 mo	q 12 mo

Table 1 Follow-up schedule of patients who achieved cCR who were enrolled on a wait-and-see policy by Maas *et al.* (14)

Year 1
Every 3 months: CEA, DRE, endoscopy, MRI
Every 6 months: CT for distant staging
Year 2-3
Every 3 months: CEA
Every 6 months: DRE, endoscopy, MRI
Every 12 months: CT for distant staging
Year 4-5
Every 6 months: CEA, DRE, endoscopy, MRI
Every 12 months: CT for distant staging

cCR, clinical complete response; CEA, carcinoembryonic antigen; DRE, digital rectal exam; MRI, magnetic resonance imaging; CT, computed tomography.

- Highest intensity in first 2 years of surveillance (approx. 90% of recurrences)
- Trading cost/inconvenience/anxiety for less stomas and bowel dysfunction (LARS)

New NAPRC Standard (2026)

5.13 Watch and Wait Protocol

- A protocol is in place for managing patients under watch and wait surveillance, including eligibility criteria and contraindications for watch and wait surveillance, and patient presentation and approval for watch and wait surveillance by the RC-MDT

- Post-treatment endoscopy images are presented and discussed by the RC-MDT for a minimum of fifty percent (50%) of watch and wait candidates

- Patients under watch and wait surveillance receive necessary follow-up care, including any required follow-up imaging, review of discordant imaging results, and representation for discussion by the RC-MDT in the event of a significant clinical finding

Summary

- Evolution of rectal cancer care has accelerated over past 2 decades
- Total Neoadjuvant Therapy (TNT) has improved systemic chemotherapy completion rates, disease-free survival rates, local-recurrence rates, and complete clinical response rates
- Non-Operative Management may allow up to 30-40% of patients to avoid proctectomy
- **TNT + NOM + MDT-approach + TME = improved patient outcomes**