Evidence Based Radiation Oncology Fact Sheets
Rectal Cancer 2023

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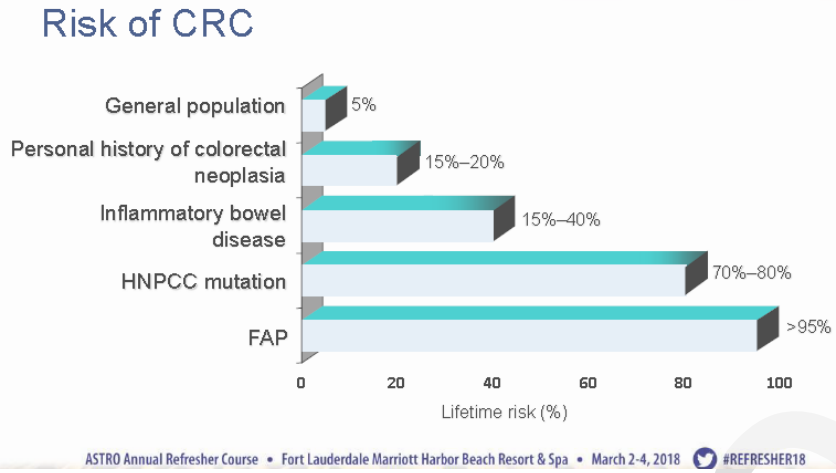
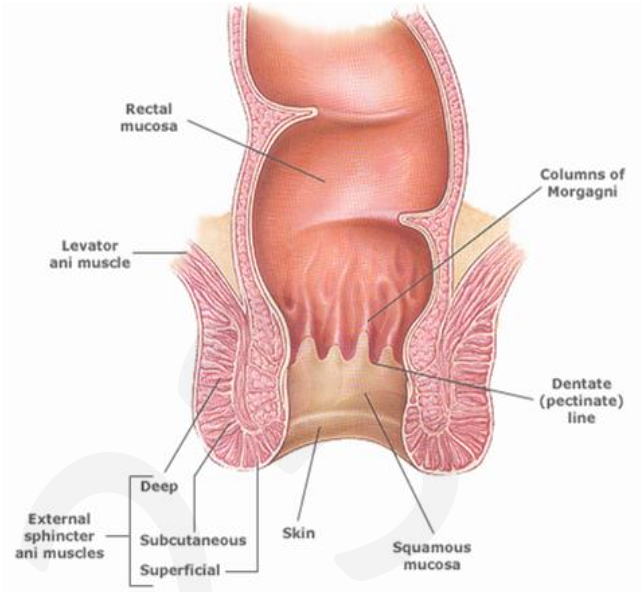
Overview:

- Epidemiology:
  - About 45,000 new cases of rectal cancer / year.[1]
  - About 105,000 new cases of colon cancer / year.





- Anatomy:
  - Extends from anal verge (palpable junction between hair-bearing and non-hair bearning squamous cells) and superiorly for about 12 (US) -15 (EUR) cm (to about sigmoid level).
    - **12 cm is middle transverse fold**.
    - **Superior margin: The PERITONEAL REFLECTION IS ACTUALLY ≈ 11 cm from anal verge aka also where the middle transverse fold is** (aka known as rectosigmoid junction)
  - **True surgical rectum begins at anorectal ring (just proximal to dentate line).**
    - Anorectal ring represents the most superior part of internal anal sphincter muscle.
      - Is lower limit for functional sphincter preservation surgery.
      - Marks the junction between the rectum and anus.
  - "True distance" requires RIGID proctoscope and not flexible (which can overestimate about 5 cm).
  - ↑ third draped with peritoneum anteriorly and on both sides (IMA → superior rectal artery)
  - ←→ Mid third only anterior surface covered by peritoneum (internal iliac → middle rectal artery)
  - ↓ third has no peritoneal covering and close to other pelvic structures (internal pudendal → inferior rectal artery)
    - Being more difficult to resect given the spatial confines, there is no natural barrier to block invasion of tumor.

  - Lymphatic Spread:
    - Tumors above anorectal ring – spread along middle rectal vessel distribution
      - Internal iliac LN
    - Tumors extending into anal canal spread via nodes along:
      - Inferior rectal and external iliac LN
    - Cancers arising in anal canal spread
      - Inferior rectal and external iliac pathways
      - To lungs rather than liver (common to true rectal cancers)

  - **Note**: True surgical rectum (prox to dentate line aka anorectal ring) also represents inferior limit for functional preservation surgery (defines lymphatic watershed for rectal cancer spread). ∴ Worse prognosis for distal lesions.
  - **Note**: Fixed tumors more difficult to resect. Distal tumors have more fixed tumors – due to confines of bony pelvis which inhibits surgeons from achieving adequate lateral/circumferential margins.

[1] https://www.cancer.org/cancer/types/colon-rectal-cancer/about/key-statistics.html

- Prognostic factors:
  - Cancer
    - Stage
    - Tumor location (distal worse than proximal)
    - Histology (signet cell poorer outcomes); tumor grade
    - Circumferential tumors or with near/total obstruction respond poorly
    - Circumferential margin
    - Mobile cancers more favorable than fixed
    - LVSI, PNI
    - Response to neoadjuvant tx
  - Lifestyle
    - Age, male, IBD (UC), high fat, low fiber, EtOH, tobacco, fam history, genetic (FAP, HNPCC), DM, red meat, cholecystectomy

- Protective:
  - NSAIDs, fiber, vitamin B6, COFFEE?!!?

Workup

- H & P
  - DRE (fixed -mobile -ulcerated –exophytic; distance from verge; anal tone; peri-rectal LAD; adjacent organ involvement)
- Chest X-ray (or CT chest) & abdominopelvicCT
- Full colonoscopy (synchronous disease in 5%)
- TRUS and/or **pelvic MRI for local staging**
- CBC (Hct), BUN/Cr, LFTs, CEA
  - **MUST GET A PSA to R/O prostate cancer.**
- Endorectal US:
  - 80-90% accurate in tumor staging
  - 70-75% accurate in mesorectal LN staging
  - Use limited to lesions <14 cm from anus
  - Also identify enlarged perirectal lymph nodes
  - Important for determining extension into the anal canal

- NOTE: NO PET/CT INDICATED for rectal cancers
  - BUT YES for anal.

TABLE 3
Summary Estimates of Sensitivity and Specificity for Endoluminal US, CT, and MR Imaging in the Staging of Rectal Cancer

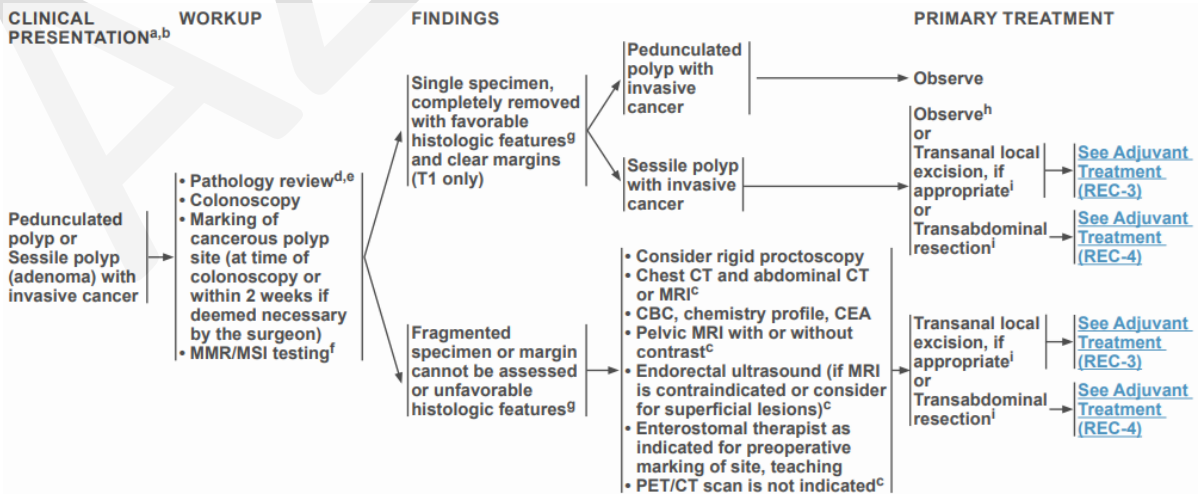
Stage	Imaging Modality	Sensitivity (%)	Specificity (%)
Muscularis propria invasion	EUS	94 (90, 97)	86 (80, 90)
	CT	NA	NA
	MR imaging	94 (89, 97)	69 (52, 82)*
Perirectal tissue invasion	EUS	90 (88, 92)	75 (69, 81)
	CT	79 (74, 84)*	78 (73, 83)
	MR imaging	82 (74, 87)*	76 (65, 84)
Adjacent organ invasion	EUS	70 (62, 77)	97 (96, 98)
	CT	72 (64, 79)	96 (95, 97)
	MR imaging	74 (63, 83)	96 (95, 97)
Lymph node involvement	EUS	67 (60, 73)	78 (71, 84)
	CT	55 (43, 67)	74 (67, 80)
	MR imaging	66 (54, 76)	76 (59, 87)

Note.—Numbers in parentheses are 95% CIs. EUS = endoluminal US, NA = not applicable.
* Significantly lower than EUS.

Clinical Presentation

- Hematochezia, diarrhea or constipation, reduced stool caliber, tenesmus, rectal urgency, inadequate emptying, urinary symptoms, perineal pain.
- Abdominal pain is more COLON cancer.

Imaging



Initial Workup/Staging

- Chest CT and abdominal CT or MRI
  - Evaluate local extent of tumor or infiltration into surrounding structures.
  - Assess for distant metastatic disease to lungs, thoracic and abdominal lymph nodes, liver, peritoneal cavity, and other organs.
  - CT performed with intravenous (IV) iodinated contrast and oral contrast material unless contraindicated.
  - IV contrast is not required for the chest CT (but usually given if performed with abdominal CT scan).
  - If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MR examination of the abdomen with IV gadolinium-based contrast agent (GBCA) can be obtained instead. In patients with chronic renal failure (glomerular filtration rate [GFR] <30 mL/min) who are not on dialysis, IV iodinated contrast material is also contraindicated, and IV GBCA can be administered in select cases using gadofosveset trisodium, gadoxetate disodium, gadobenate dimeglumine, or gadoteridol.
  - If iodinated and gadolinium contrast are both contraindicated due to significant allergy or chronic renal failure without dialysis, then consider MR without IV contrast or consider PET/CT imaging.
- Pelvic MRI with or without contrast or endorectal ultrasound (only if MRI is contraindicated [eg, pacemaker])
  [See Pelvic MRI Requirements (REC-A 3 of 4) and Reporting (REC-A 4 of 4)]
  - Assess T and N stage of the primary rectal tumor.
  - Pelvic MRI or CT can be used for workup of synchronous metastatic disease.
  - Pelvic MRI can be performed with or without IV gadolinium contrast per institutional preferences.
  - Pelvic MRI may not be required for local staging if tumor is known to be definite T1 or if patient is not a candidate for primary tumor resection (eg, widespread metastases, plan for permanent colonic diversion).
  - The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
- PET/CT is not routinely indicated.
  - PET/CT does not supplant a contrast-enhanced diagnostic CT or MR and should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MR scan or in patients with strong contraindications to IV contrast administration.
- Consider PET/CT (skull base to mid-thigh)
  - If potentially surgically curable M1 disease in selected cases.
  - In patients considered for image-guided liver-directed therapies for liver metastases (ie, ablation, radioembolization).[4-8]
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with IV routine extracellular or hepatobiliary GBCA is preferred over CT to assess exact number and distribution of metastatic foci for local treatment planning.

Pathology

- 90% are adenocarcinoma, of which 20% has excels colloid (no significance), but the 1% with signet ring do worse.
- Other: Small cell, carcinoid, leiomyosarcoma, lymphoma.

PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

Pathologic Stage

- The following parameters should be reported:
  - Grade of the cancer
  - Depth of penetration (pT), the pT stage, is based on viable tumor. Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.
  - Number of lymph nodes evaluated and number positive (N). Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.
  - Status of proximal, distal, circumferential (radial), and mesenteric margins.[11,12]
  - CRM[13-17]
  - Neoadjuvant treatment effect[15,16,18-20]
  - Lymphovascular invasion[15,16,21]
  - Perineural invasion (PNI)[22-24]
  - Tumor deposits[25,26]
- CRM - A positive CRM is defined as tumor ≤1 mm from the margin. This assessment includes both tumor within a lymph node as well as direct tumor extension. However, if CRM positivity is based solely on intranodal tumor, it should be stated in the pathology report. A positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy. A positive CRM secondary to lymph node metastasis in some studies has been associated with lower recurrence rates than by direct extension.[13-17]
- Neoadjuvant treatment effect - The most recent College of American Pathologists (CAP) Guidelines on examination specimens of the rectum and the AJCC Cancer Staging Manual, Eighth Edition require commenting on treatment effect after neoadjuvant therapy. The minimum requirement is:
  - Treatment effect present.
  - No definitive response identified.
- The system used to grade tumor response as recommended by the AJCC Cancer Staging Manual, Eighth Edition and the CAP Guidelines is that as modified from Ryan R, et al. Histopathology 2005;47:141-146 and Gavioli M, et al. Dis Colon Rectum 2005;48:1851-1857.
  - 0 - Complete response: No remaining viable cancer cells.
  - 1 - Moderate response: Only small clusters or single cancer cells remaining.
  - 2 - Minimal response: Residual cancer remaining, but with predominant fibrosis.
  - 3 - Poor response: Minimal or no tumor kill; extensive residual cancer.

  According to the College of American Pathologists, it is optional to grade the tumor response to treatment. However, the NCCN Rectal Cancer Guidelines Panel recommends grading tumor response. Other grading systems that are used are referenced.[15,16,18-20]

Pathologic Stage (continued)

- PNI - The presence of PNI is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer-specific, overall, and disease-free survival. For stage II rectal cancer, those with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82%; *P* = .0005). In stage III rectal cancer, those with PNI have a significantly worse prognosis.[21-26]
- Tumor deposits - Irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered to be tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular invasion or, more rarely, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.
- Tumor budding - In recent years, tumor budding has been identified as a new prognostic factor in colon cancer. Recently, there was an international consensus conference on tumor budding reporting.[27] A tumor bud is defined as a single cell or a cluster of ≤4 cells detected by hematoxylin and eosin (H&E) at the advancing edge of the invasive carcinoma. The total number of buds should be reported from a selected hot spot measuring 0.785 mm (20x ocular in most microscopes/via a conversion factor). Budding is separated into three tiers: low tier (0–4 buds), intermediate tier (5–9 buds), and high tier (10 or more buds). Two recent studies[28,29] using this scoring system have shown tumor budding to be an independent prognostic factor for stage II colon cancer. An ASCO guideline for stage II colon cancer designates tumor budding as an adverse (high-risk) factor.[30] Several studies have shown that high-tier tumor budding in pT1 colorectal carcinomas, including malignant polyps, is associated with an increased risk of lymph node metastasis; however, methodologies for assessing tumor budding and grade were not uniform.[31-35]

Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately stage rectal cancer.[11,12,36] Sampling of 12 lymph nodes may not be achievable in patients who received preoperative chemotherapy. The literature lacks consensus as to what is the minimum number of lymph nodes to accurately identify stage II cancer. The minimum number of nodes has been reported as >7, >9, >13, >20, and >30.[36-44] Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimum number to accurately identify stage II rectal cancer.[40,43] The number of lymph nodes retrieved can vary with patient age, gender, tumor grade, and tumor site.[37] For stage II (pN0) colon cancer, if fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs. 19, $P < .05$; 7 vs. 10, $P < .001$).[45,46] If 12 lymph nodes is considered the number needed to accurately stage stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.[46] To date, the number of lymph nodes needed to accurately stage neoadjuvant-treated cases is unknown. However, it is not known what the clinical significance of this is in the neoadjuvant setting, as postoperative therapy is indicated in all patients who receive preoperative therapy regardless of the surgical pathology results.

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry (IHC)

Examination of the lymph nodes (sentinel or routine) by intense histologic and/or immunohistochemical investigation helps to detect the presence of metastatic disease. The detection of single cells by IHC or by multiple H&E levels and/or clumps of tumor cells <0.2 mm are considered isolated tumor cells (pN0).[47] The Eighth Edition of the AJCC Cancer Staging Manual and Handbook[47] defines clumps of tumor cells ≥0.2 mm but ≤2 mm in diameter or clusters of 10 to 20 tumor cells as micrometastasis and recommends that these micrometastases be considered as standard positive lymph nodes (pN+).

- At the present time the use of sentinel lymph nodes and detection of isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[48-55] Some studies have shown that the detection of IHC cytokeratin-positive cells in stage II (N0) colon cancer (defined by H&E) has a worse prognosis, while others have failed to show this survival difference. In some of these studies, what are presently defined as isolated tumor cells were considered to be micrometastases.[51-55]

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).[56-58]

MRI Usage

MERCURY

Background: The prognostic relevance of preoperative high-resolution magnetic resonance imaging (MRI) assessment of circumferential resection margin (CRM) involvement is unknown.

Follow-up study 374 patients rectal cancer → protocol high-resolution pelvic MRI. Tumor distance to the mesorectal fascia of ≤ 1 mm was recorded as an MRI-involved CRM.

Taylor, JCO 2014 **62 months**

5-year OS was 62.2% MRI-clear CRM vs. 42.2% MRI-involved CRM (HR 1.97; P < .01).

5-year DFS was 67.2% MRI-clear CRM vs. 47.3% MRI-involved CRM (HR 1.65 P < .05).

Local recurrence HR for MRI-involved CRM was 3.50 (95% CI, 1.53 to 8.00; P < .05).

MRI-involved CRM was the only preoperative staging parameter that remained significant for OS, DFS, and LR on multivariate analysis.

Conclusion

High-resolution MRI preoperative assessment of CRM status is superior to AJCC TNM–based criteria for assessing risk of LR, DFS, and OS. Furthermore, MRI CRM involvement is significantly associated with distant metastatic disease; therefore, colorectal cancer teams could intensify treatment and follow-up accordingly to improve survival outcomes.

PRINCIPLES OF IMAGING
Pelvic MRI Requirements[3]

Patient Preparation

Rectal distension with gel	Not a requirement. There is controversy on the effect of rectal distension on accurately assessing the distance of tumor to mesorectal fascia (MRF)
Use of spasmolytic agents	Not a requirement. Can help decrease bowel movement-related artifacts if needed

MRI Hardware Requirement

Magnet strength	Minimum requirement 1.5 T 1.0 T magnets produce limited signal and should be avoided when possible
Coil	External surface body coil adequate and preferred to endorectal coils

MRI Sequences

2D high-resolution T2-weighted	• Slice thickness 1–3 mm (no more than 4 mm). 3D T2-weighted sequences are not adequate substitutes • Main sequences for T staging and detection of pathologic lymph nodes • Axial, sagittal, and coronal plane to assess extent and relationship to all surrounding structures • Axial and coronal slices should be angulated along the short (perpendicular) and long (parallel) axis of tumor for tumors in the middle and upper part of the rectum and along the anal canal for low rectal tumors
T1-weighted without contrast	Not a requirement for staging. May be helpful in assessing other pelvic organs and/or pathologies
Diffusion-weighted imaging (DWI)	Not a requirement for T staging or detection of pathologic lymph node. Helpful in assessing treatment response after neoadjuvant therapy (assessing the yT-stage)
T1-weighted with contrast	Not a requirement for staging[a]

At presentation (before neoadjuvant therapy)	• Distance from the anal verge or anorectal junction to the lower aspect of the tumor • Tumor length • T-stage of primary mass • Tumor deposits within the mesorectum • Involvement of the MRF and the smallest distance (mm) between the tumor and the MRF and its location[b] • N-stage • Presence/absence of suspicious extramesorectal lymph nodes • Additional findings that can be provided in synoptic report: ‣ The circumferential location of the tumor ‣ In T3 tumor, the extent (mm) of extramural growth or depth of invasion ‣ Number of suspicious lymph nodes ‣ Presence/absence of extramural vascular invasion (EMVI) ‣ Morphologic pattern of tumor growth (eg, annular, polypoid, mucinous, ulcerated, perforated)
After neoadjuvant therapy	• Distance from the anal verge or anorectal junction to the lower aspect of the remaining tumor • Tumor length • Presence/absence of a residual tumor (high signal on T2-weighted images) • Presence/absence of fibrosis (low signal on T2-weighted images) • yT-stage and any remaining tumor deposits within the mesorectum • yN-stage and number of remaining suspicious lymph nodes • Presence of any remaining suspicious extramesorectal lymph nodes • Persistent involvement/regression from the MRF[b] • The smallest distance (mm) between the remaining tumor and the MRF and its location • Additional findings that can be provided in synoptic report: ‣ The circumferential location of the remaining tumor within the wall ‣ In the case of a yT3 tumor, the extent (mm) of extramural growth ‣ The morphologic pattern of tumor growth ‣ Presence/absence of EMVI (no clear consensus on reporting this finding)

Screening

- Colonoscopy **at age 45 (USPSTF, 2021)** and q10 years if negative.
  - IF polyps, then repeat every 3-5 years depending on risk of polyp.
  - NOTE: 2023 study suggests that screening colonoscopies after age 75 are unlikely to detect cancers (0.2%).[2]
- HIGH RISK
  - 1st degree relative — Colonoscopy starts at age 40 or 10 years before first diagnosis in affected first degree relative. THEN q5 years.
  - IBD — Colonoscopy 8 years after first symptom. Depending on findings q 1-3 years afterwards.
  - HNPCC (Lynch MMR) — Starts age 20-25 then q1-2 years
  - FAP — Must do elective colectomy or proctolectomy after onset of polyposis.

US Nurses' Health Study II
Prospective 111,801 women aged 26-46 at enrollment.

Ma, JAMA Oncol 2022.
519 incident CRC cases were documented over 26 years. 2.5 M person-years of follow-up.
MVA endoscopy (vs. none) ↓↓ incident CRC for age at initiation **at ALL AGES.**
Before 45 years (HR, 0.37; SS), 45 to 49 years (HR, 0.43; SS), 50 to 54 years (HR, 0.47; SS), and ≥ 55 years (HR, 0.46; SS).
Absolute ↓ estimated cumulative incidence of CRC through 60 years of age was 72 per 100 000 persons for initiation of endoscopy at 45 to 49 years of age vs 50 to 54 years of age. Compared with no endoscopy, initiation of endoscopy before 50 years of age was also associated with a reduced risk of CRC diagnosed before 55 years of age (<45 years: HR, 0.45 [95% CI, 0.29-0.70]; 45-49 years: HR, 0.43 [95% CI, 0.24-0.76]).
Conclusions and Relevance: In this cohort study, compared with no endoscopy, initiation of endoscopy before 50 years of age was associated with a reduced risk of CRC, including CRC diagnosed before 55 years of age. Screening before 50 years of age was associated with greater absolute reduction in CRC risk compared with initiation of CRC screening at 50 years of age or later.

NordICC "Negative" Trial
←R→ 84,585 men and women 55-64 yo Poland, Norway, Sweden, and the Netherlands between 2009 and 2014.
1:2 ratio | 1. invitation to undergo a single screening colonoscopy (the invited group) | 2. no invitation or screening (the usual-care group) |.
1º risks of colorectal cancer and related death, and the secondary end point was death from any cause.

Bretthauer, NEJM 2022.
28,220 in the invited group, **11,843 of whom (42.0%) underwent screening**, and 56,365 in the usual-care group.
A total of 15 participants had major bleeding after polyp removal.
Median FU 10-years, 259 cases of colorectal cancer were diagnosed in the invited group as compared with 622 cases in the usual-care group.
Intention-to-screen analyses, 10-year risk of colorectal cancer 0.98% vs. 1.20% (RR 0.82; SS)
10-year risk of death from colorectal cancer 0.28% vs. 0.31% (RR 0.90; NS)
The number needed to invite to undergo screening to prevent one case of colorectal cancer was 455 (95% CI, 270 to 1429).
The risk of death from any cause was 11.03% vs. 11.04%.
CONCLUSIONS
In this randomized trial, the risk of colorectal cancer at 10 years was lower among participants who were invited to undergo screening colonoscopy than among those who were assigned to no screening.
Commentary: In a per-protocol analysis of patients who actually underwent screening, 31% RR ↓ in colorectal cancer risk (0.84% v 1.22%) and a 50% relative ↓ in colorectal cancer death (0.15% v 0.30%). AKA…screening works for those who actually go.

Age 49 → 50 Screening Study
RR → 170 434 cases of colorectal cancer were analyzed among 165 160 patients (92 247 men [55.9%]; mean [SD] age, 51.6 [6.7] years).
Data from the SEER 18 registries, representing 28% of the US population, were used to conduct a cross-sectional study of colorectal cancer incidence rates from January 1, 2000, to December 31, 2015, in 1-year age increments (ages 30-60 years).

Abualkhair, SEER 2020
Results ↑↑ incidence of colorectal cancer from 49 to 50 years of age (46.1% ↑).
Total of 8799 of the 9474 cases (92.9%) of colorectal cancer diagnosed among individuals aged 50 years **were invasive**.
Conclusions and Relevance :Steep incidence increases between 49 and 50 years of age are consistent with previously undetected colorectal cancers diagnosed via screening uptake at 50 years. These cancers are not reflected in observed rates of colorectal cancer in the SEER registries among individuals younger than 50 years. Hence, using observed incidence rates from 45 to 49 years of age alone to assess potential outcomes of earlier screening may underestimate cancer prevention benefits.

Genetics

- Li-Fraumeni — Autosomal dominant AD p53 STS
- Gardner — Subset of FAP APC gene.
- Cowden — Multiple Harmartoma syndrome PTEN mutation

[2] https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2803491

Prevention

CAPP2 Aspirin Study Lynch Syndrome
←R→ 861 international centers with Lynch syndrome | 1. 600 mg aspirin daily | 2. Placebo |.
1º Development of CRC.

Burn, Lancet 2020.
Mean 10 years = 8500 person-years.
10-year development of CRC 9% vs. 13% (HR 0·65, p=0·035).
Per-protocol analyses restricted to 509 who achieved 2 years' intervention gave an HR of 0·56 (0·34–0·91; p=0·019) and an incidence rate ratio of 0·50 (0·31–0·82; p=0·0057).
For all Lynch syndrome cancers combined, the intention-to-treat analysis did not reach significance but per-protocol analysis showed significantly reduced overall risk for the aspirin group (HR=0·63, 0·43–0·92; p=0·018). Adverse events during the intervention phase between aspirin and placebo groups were similar, and no significant difference in compliance between intervention groups was observed for participants with complete intervention phase data; details reported previously
Interpretation The case for prevention of colorectal cancer with aspirin in Lynch syndrome is supported by our results.

Aspirin Study
RR 2419 CRC from 1997-2008. FU 10.8 years.

Hua, JCO 2017.
Postdiagnostic aspirin-only users ↑ OS (HR, 0.75, SS) and ↑ CRC-specific survival (HR, 0.44, SS).
Association between any NSAID use after diagnosis and OS differed significantly by KRAS-mutation status (Pinteraction = .01). Use of any NSAID after diagnosis was associated with improved OS only among participants with KRAS wild-type tumors (HR, 0.60; 95% CI, 0.46 to 0.80) but not among those with KRAS-mutant tumors (HR, 1.24; 95% CI, 0.78 to 1.96).
Conclusion Among long-term CRC survivors, regular use of NSAIDs after CRC diagnosis was significantly associated with improved survival in individuals with KRAS wild-type tumors.

PRIMARY AND SECONDARY PREVENTION OF COLORECTAL CANCER

Certain lifestyle modifications are associated with a reduced risk of colorectal cancer (CRC) and can be an important adjunct to screening for CRC prevention. For risk assessment for average-risk individuals, see CSCR-1.

Lifestyle/dietary factors associated with reduced CRC risk/recurrence:
- **Physical activity: Regular physical activity (ie, occupational, recreational, transportation) has been associated with decreased CRC risk.[1]**
- **Fruits and vegetables: A diet high in fruits and vegetables has been associated with decreased CRC risk in some studies.[2,3]**
- **Dietary supplements: In general, nutrients should be obtained from natural food sources rather than solely from dietary supplements.[1]**
- **Smoking cessation: Smoking cessation counseling is strongly recommended. See NCCN Guidelines for Smoking Cessation.**

Aspirin:
- **There is substantial evidence about the protective effect of aspirin for CRC development when taken for at least 5–10 years.[4,5]**
  - ◊ **The U.S. Preventive Services Task Force endorses low-dose aspirin (81 mg) intake for individuals ages 45–59 with a ≥10% 10-year cardiovascular risk for the purposes of lowering both cardiovascular and CRC risk.**
  - ◊ **The decision to offer aspirin should take into consideration risk of bleeding, life expectancy, and long-term compliance.[6] The optimal dose has not been well established.**
  - ◊ **Regarding secondary prevention, aspirin use has been associated with improved CRC-specific survival and overall survival.[7]**

Lifestyle/dietary factors associated with increased CRC risk:
- **Smoking: Long-term cigarette smoking is associated with increased CRC incidence and mortality.[8,9] Risk reduction is seen with early smoking cessation.[9]**
- **Red meat and processed meat: Long-term consumption is associated with increased CRC risk.[1,10]**
- **Moderate to heavy alcohol consumption: This level of consumption is associated with increased CRC risk.[1,11,12]**
- **Obesity: Obesity is associated with an increased risk for CRC.[1,13,14,15]**
- **Vitamin D: Low levels of vitamin D have been associated with increased CRC risk.[16]**

Staging 8th EDITION

	Esophageal	Stomach	Rectum	Anal	Pancreas
T1a	Lamina propria, muscular mucosae		Tis = in situ = Stage 0s T1 = Submucosa	Tis = in situ = Stage 0 T1 < 2 cm (Breast!)	Tis = in situ (G3 PIN) T1a-c = **Breast!**
T1b	Submucosa				
T2	**Muscularis propria**			2-5 cm (Breast!)	2-4 cm
T3	Adventitia	Serosa	Pericolorectal soft tissue	> 5 cm (Breast!)	> 4 cm
T4a	Resectable*	Visceral peritoneum		Invade vagina, urethra, bladder	Involve CA, SMA, ComHep
T4b	Unresectable**	Adjacent organs			
M1	Distant Mets		M1a Just 1 single organ M1b ≥ 2 organs M1c Peritoneal Surface	Distant Mets	Distant Mets
N1	1-2		N1a 1 N1b 2-3 N1c only tumor deposits	N1a ing, meso, int N1b external iliac N1c (N1a+N1b)	1-3
N2	3-6		N2a 4-6 N2b ≥ 7		≥ 4
N3	≥ 7	N3a 7-15 N3b ≥ 16			

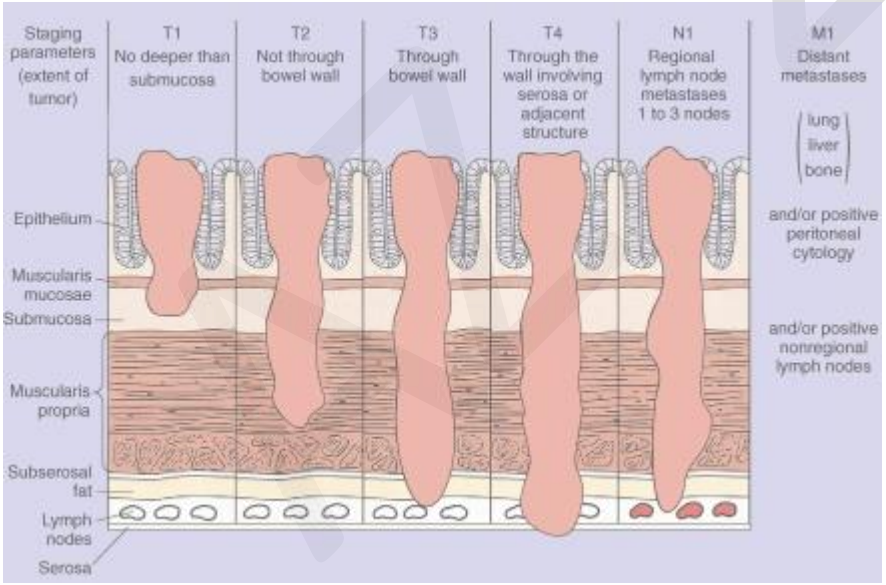
T4a - penetrates to the surface of the visceral peritoneum*

***Direct invasion of sphincter muscles does not count as T4**

T4b - directly invades or is adherent to other organs or structures

Layers: are the epithelium, basement membrane (defines intraepithelial), lamina propria (defines intramucosal) - contains capillaries and lymphatics (but little chance for mets), muscularis mucosae, submucosa (loose connective tissue), muscularis propria (circular and longitudinal layers), subserosa (single layer of cells).

Difference between rectum and colon is that most of the rectum lacks serosa. Thus, for the rectum, a T3 is invasion into perirectal fat; for colon, T3 is invasion of subserosa. Also for the rectum, T4 is only invasion of other organs, whereas for the colon T4 can also be perforation through serosa.



Regional Lymph Nodes:

N1 - 1 to 3 lymph nodes

N1a - 1 lymph node
N1b - 2-3 lymph nodes
N1c - tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis

N2 - 4 or more
N2a - 4-6 lymph nodes
N2b - 7 or more lymph nodes
Distant Metastasis:

M0 - none
M1 - yes
M1a - metastasis confined to one organ or site
M1b - metastasis in more than one organ/site
M1c - peritoneum

	N0	N1 a-c	N2a	N2b	N2c
T1	I	**IIIA**			
T2			**IIIB**		
T3	IIA				
T4a	IIB			**IIIC**	
T4b	IIC				
M1a	IVA				
M1b	IVB				
M1c	IVC				

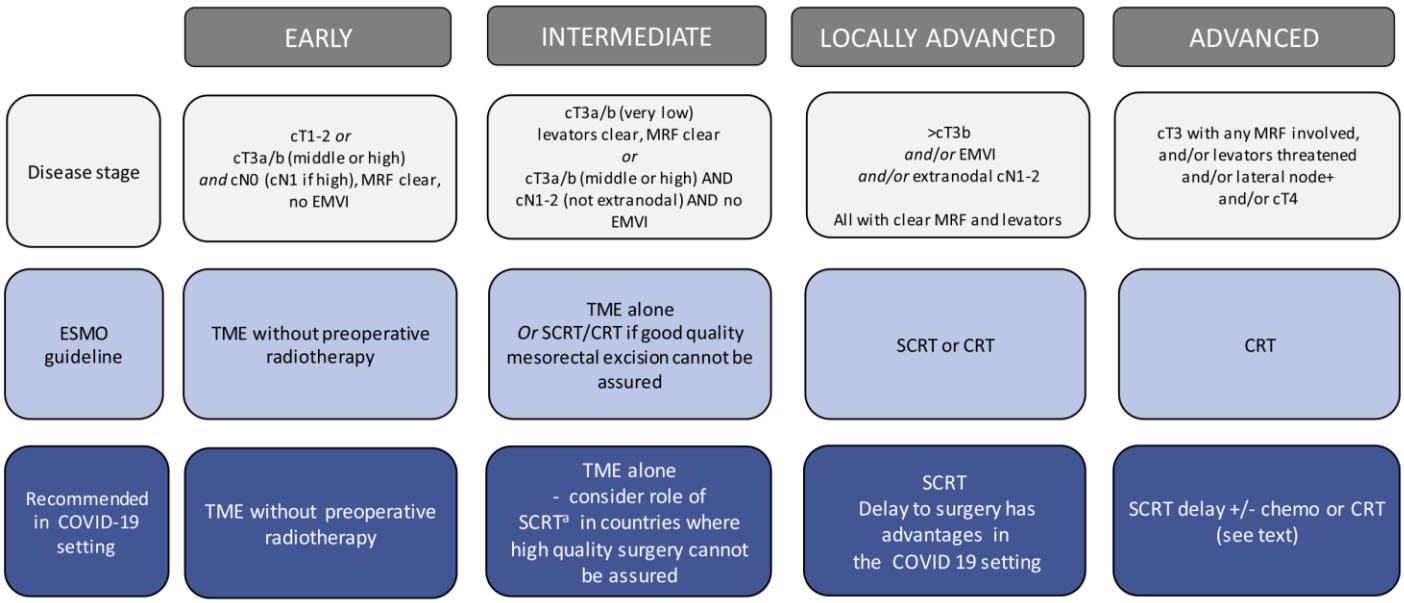
Overall Treatment Chart

Stage	Treatment	5 year LF	5 year OS
I **Early**	**TME** with APR (↓ lesions) or LAR (↑ lesions). If pT1-2N0, no adjuvant treatment. Possibly consider local excision for favorable tumor: < 3 cm size, < 30% circumf., within 8 cm of anal verge, well/mod diff, margin > 3mm, no LVSI/PNI). If local excision → *favorable T1 lesions = observe*, unfavorable T1 or T2 lesions → TME or 5-FU/RT.	< 5%	90%
II / III **Resectable**	**TNT (preferred options) vs. FOLFOX alone (PROSPECT Trial)** 1. FOLFOX / CAPEOX (12-16 wks) → SCRT or LCRT+5-FU→ Restaging → TME. 2. SCRT or LCRT+5-FU → FOLFOX / CAPEOX (12-16 wks) → Restaging → TME. 3. FOLFOX x 6c → Restaging → **1.** TME is 1^{O} response > 20% or **2.** CRT if 1^{O} response < 20% Consider upfront NACRT → restaging → TME → adj chemotherapy. Not recommended, but if upfront TME → FOLFOX / CAPEOX → SCRT or LCRT+5-FU	HISTORICAL II/III: T3N0 T1-2N1 5-10%, 80% T4N0 T3N1 10-15% 60% T4N1 T3-4N2 15-20% 40%	
III **(T4/unresectable)**	If obstructed, will need diverting colostomy or stent placed prior to definitive treatment. **TNT** (RT must for unresectable or non-sphincter sparing candidate). ~~(PROSPECT Trial)~~ 1. FOLFOX / CAPEOX (12-16 wks) → SCRT or LCRT+5-FU→ Restaging → TME. 2. SCRT or LCRT+5-FU → FOLFOX / CAPEOX (12-16 wks) → Restaging → TME. Consider FOLFIRINOX (for T4, N+).		
IV	If liver or long only mets → TNT → Restaging → TME + resection ± local therapy for mets. TNT ideally pathway 1. Chemo → SCRT. Consider Pembro/PDL1 for dMMR/MSI-H. At any time if the primary tumor becomes unresectable, options become individualized. Consider additional combination chemo, or chemo ± resection ± RT.		
Recurrent	Individualized options based on resectability and prior treatments.		

COVID-19 Recs

Dutch Expert Consensus
Radiotherapy Oncology, 2020

Descriptions next page →



Early subgroup
We strongly support the use of TME without pre-operative radiotherapy.

Intermediate subgroup
In countries where high quality surgery is performed, we strongly recommend TME alone. Careful discussion of the use of radiotherapy in this group is needed in the COVID 19 setting where the benefits of preoperative radiotherapy are likely to be small. If radiotherapy is to be used, SCRT should be the preferred option rather than CRT (see below).

Locally advanced subgroup
Two phase III trials have compared SCRT and CRT and demonstrate comparable outcomes for local recurrence, disease free survival (DFS), overall survival (OS) and late toxicity [2, 3]. Both approaches are widely used. In the COVID 19 setting there are some important factors to consider.

When the use of SCRT is compared with CRT there are many advantages of SCRT:- less acute toxicity; fewer radiotherapy treatment attendances; substantial reduction in travel and contact with other patients and staff; avoidance of any detrimental effect of concurrent chemotherapy on immune function; and thus significantly reduced risk of COVID 19 infection during treatment. The greater social distancing achieved with SCRT is a major advantage. An additional benefit is that the use of SCRT instead of CRT in this setting will have a substantial reduction in linear accelerator usage, will help avoid waiting time to start treatment and increase the ability of departments to treat all their patients in the setting of reduced staffing levels.
Timing of surgery after SCRT

The Dutch TME and MRC CR07 trials as well as the previous Swedish trials recommended that surgery should be performed within three to seven days of completion of SCRT [4, 5, 6]. The recently reported Stockholm III trial compared surgery performed within one week with 4–8 weeks after SCRT [[7]]. There was no difference in local recurrence, DFS and OS. A longer delay to surgery was associated with a reduction in post-operative and surgical morbidity but no difference in severe complications or re-operations. An admission rate of 6% was observed for the management of diarrhoea for patients who received SCRT and delay. 3D conformal radiotherapy techniques with a superior border of mid L5 were used. The use of SCRT and delay will result in approximately 10% of patients achieving a complete clinical response who may be offered an organ preservation strategy. If complete response is actively monitored, then further delay or even avoidance of surgery may be safely achieved (see below). Conversely, we note that this approach will delay the time to commencement of adjuvant chemotherapy, if considered indicated.

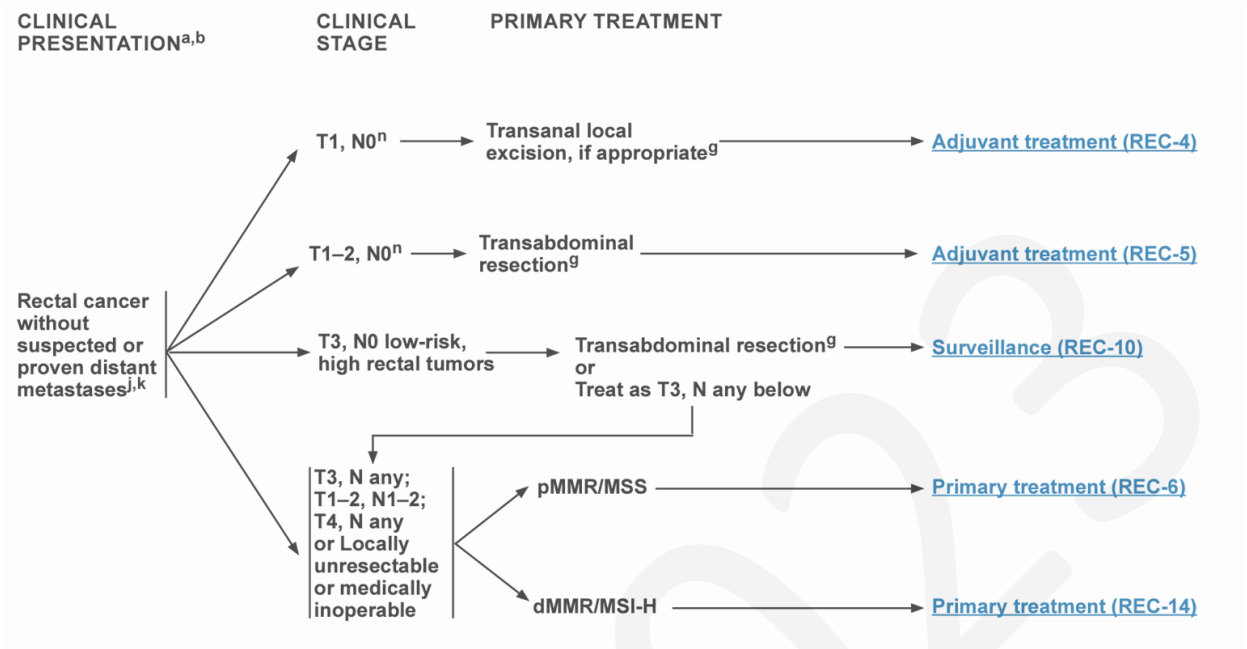
Advanced subgroup
Pre-operative CRT or SCRT followed by neo-adjuvant chemotherapy is recommended. CRT is given as a fluoropyrimidine (usually capecitabine) combined with radiotherapy, commonly 45–50.4 Gy given over 5–5.5 weeks. The role of adjuvant chemotherapy is then considered with wide international variation in its use. The Polish-2 randomized phase III trial comparing CRT with SCRT followed by three two-weekly cycles of neoadjuvant chemotherapy reported similar cancer outcomes for local recurrence, DFS and OS [[8]]. The results of the phase III RAPIDO trial that compared CRT with pre-operative SCRT and 18 weeks of capecitabine+oxaliplatin chemotherapy are awaited. In this trial, only patients with very high-risk criteria for recurrence were included. There is currently no published level I evidence that demonstrated improvements in DFS or OS using neoadjuvant chemotherapy.

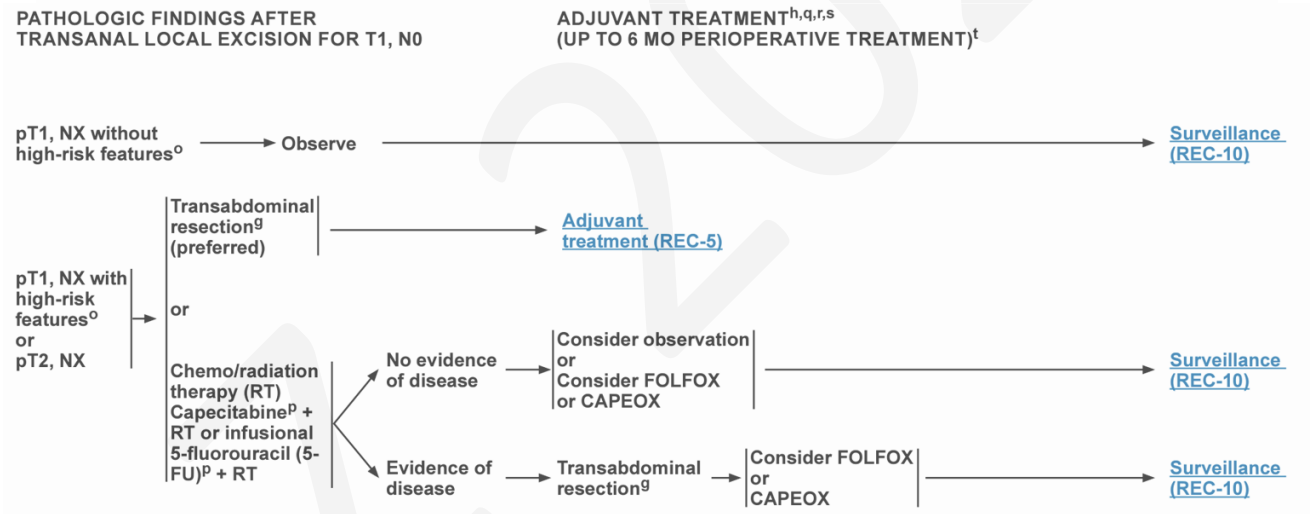
Recommendation: Based on the current evidence two options can be considered in the context of the COVID 19 pandemic:
1) Pre-op CRT – this is the most established standard of care and the duration of concurrent capecitabine chemotherapy is limited to 5–5.5 weeks. It involves the use of long course of radiotherapy.
2) SCRT +/− neoadjuvant chemotherapy – here the duration of radiotherapy is substantially less and the advantages of this approach when compared to CRT are described above.

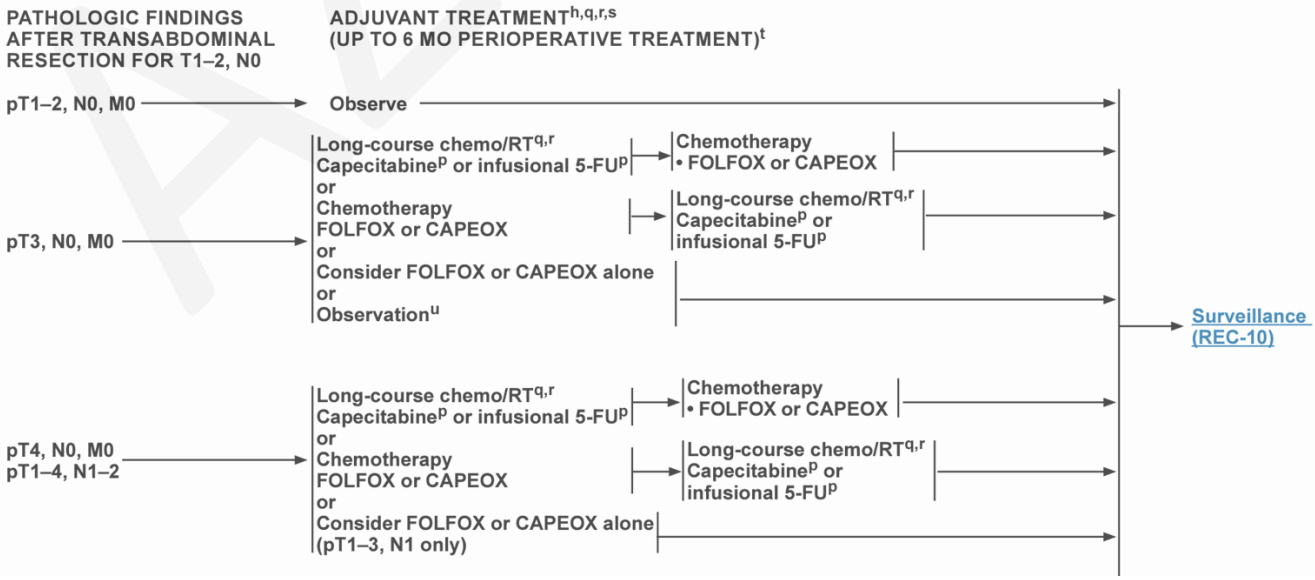
We consider both options to be acceptable but note the advantages of using SCRT in the COVID 19 setting. The decision to use neoadjuvant chemotherapy in option 2 will reflect the attitudes to neoadjuvant and adjuvant chemotherapy in each country, the assessment of the risk–benefit ratio, considering the risk factors for COVID 19 increased mortality, and the capacity and prioritisation of chemotherapy delivery. The choice of chemotherapy regimen and duration is outside the scope of this document but should broadly align with the Polish trial with a preference for capecitabine-based chemotherapy.

In elderly patients, patients with poorer performance status, or patients not fit for chemotherapy or standard CRT, SCRT with a delay is strongly recommended.

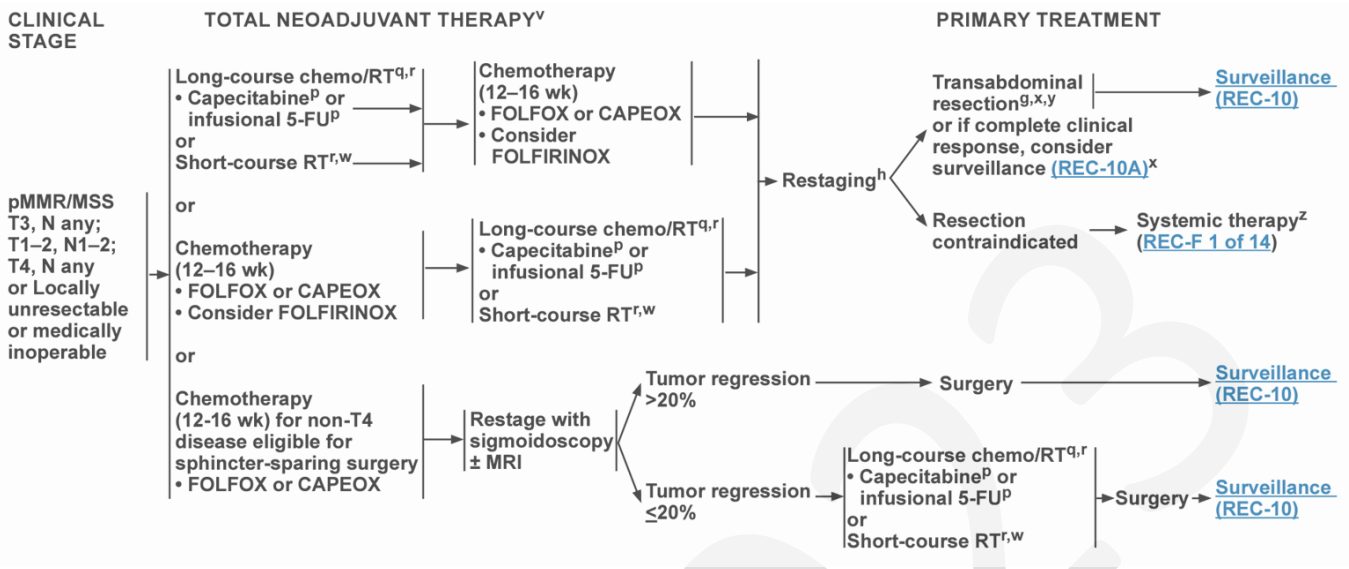
Organ preservation
The use of an organ preserving strategy is increasingly considered when a complete clinical response is observed following CRT or SCRT and delay [[9]].
In some countries, radiotherapy is used in early-stage disease to avoid the need for radical surgery. However, there is limited evidence for this approach, and it is not recommended outside clinical trials in several countries. In the context of COVID 19, if radiotherapy is used, we consider SCRT a preferred option rather than CRT for the reasons described above. This option should be considered in the context of surgical and radiotherapy capacity, and where possible in clinical studies.
An organ preservation approach may be considered during the COVID-19 period providing that resources for an adequate surveillance including imaging and endoscopy are available to detect local failures that require salvage surgery.







HIGH RISK FEATURES = + SM, LVSI, ↓ 1/3 submucosal level, poorly differentiated tumors.


CLINICAL STAGE
TOTAL NEOADJUVANT THERAPY[v]
PRIMARY TREATMENT
pMMR/MSS T3, N any; T1–2, N1–2; T4, N any or Locally unresectable or medically inoperable
Long-course chemo/RT[q,r]
• Capecitabine[p] or infusional 5-FU[p]
or
Short-course RT[r,w]
Chemotherapy (12–16 wk)
• FOLFOX or CAPEOX
• Consider FOLFIRINOX
or
Chemotherapy (12–16 wk)
• FOLFOX or CAPEOX
• Consider FOLFIRINOX
Long-course chemo/RT[q,r]
• Capecitabine[p] or infusional 5-FU[p]
or
Short-course RT[r,w]
or
Chemotherapy (12-16 wk) for non-T4 disease eligible for sphincter-sparing surgery
• FOLFOX or CAPEOX
Restage with sigmoidoscopy ± MRI
Restaging[h]
Transabdominal resection[g,x,y]
or if complete clinical response, consider surveillance (REC-10A)[x]
Surveillance (REC-10)
Resection contraindicated
Systemic therapy[z] (REC-F 1 of 14)
Tumor regression >20%
Surgery
Surveillance (REC-10)
Tumor regression ≤20%
Long-course chemo/RT[q,r]
• Capecitabine[p] or infusional 5-FU[p]
or
Short-course RT[r,w]
Surgery
Surveillance (REC-10)

ASTRO 2020 Consensus

https://www.practicalradonc.org/cms/10.1016/j.prro.2020.08.004/attachment/e1261b8a-30c1-425b-848d-11752c949c9a/mmc1.pdf

Indications for Neoadjuvant Radiation Therapy (NA-RT)	Rec Strength	Evidence
1. Pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.	Strong	Moderate
2. For patients with stage II-III rectal cancer, neoadjuvant RT is recommended.	Strong	High
3. For patients with stage II rectal cancer at lower risk* of locoregional recurrence, omission of neoadjuvant RT is conditionally recommended after discussion with a multidisciplinary team.	Conditional	Moderate
4. For cT1-2N0 rectal cancer who may need an APR, neoadjuvant chemoradiation is conditionally recommended to improve the chance of sphincter preservation	Conditional	Expert Opinion
5. Where radiation is indicated, RT should be performed preoperatively rather than postoperatively.	Strong	High

*** Implementation remark: Lower risk is defined as a cT3a/b N0 tumor that is >10 cm from the anal verge** and with mrCRM ≥2 mm and no mrEMVI.**
**** cT3a/b = 1 to 5 mm extramural tumor spread; tumor height should be surgeon defined.**
Abbreviations: APR = abdominoperineal resection; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; MRI = magnetic resonance imaging; RT = radiation therapy.

Neoadjuvant (NA) Regimens	Rec Strength	Evidence
1. If NA-CRT, 5000-5040 cGy in 25-28 fractions with concurrent chemotherapy is recommended.	Strong	High
2. If NA-SCRT, 2500 cGy in 5 fractions without concurrent chemotherapy isrecommended.	Strong	High
3. If NA-CRT, only concurrent 5-fluorouracil or capecitabine is recommended with RT for radiosensitization.	Strong	High
4. If recommendation for NA Tx, chemotherapy alone (FOLFOX or CAPOX) is conditionally recommended only in the context of a clinical trial or multiinstitutional registry.	Conditional	Low
5. If NA Tx without tumor factors that portend increased recurrence risk,* (1) chemoradiation or (2) short-course RT are recommended.	Strong	High
6. If NA Tx without tumor factors that portend increased recurrence risk,* addition of multiagent (FOLFOX or CAPOX) chemotherapy (1) before or after chemoradiation or (2) after short-course RT is conditionally recommended.	Conditional	Low
7. If NA Tx **with** tumor factors that portend increased recurrence risk, addition of multiagent (FOLFOX or CAPOX) chemotherapy (1) before or after chemoradiation or (2) after short-course RT is conditionally recommended.	Conditional	Moderate
8. In NAC as part of TNT, 3-4 months of either FOLFOX or CAPOX (without additional agents, targeted therapy or immunotherapy) is recommended.	Strong	Moderate
9. If NA-CRT with no further neoadjuvant chemotherapy planned, an interval of 6-11 weeks from the end of chemoradiation to surgery is recommended.	Strong	High (≥ 6 weeks) Moderate (6-11)
10. NA-SCRT with no further neoadjuvant chemotherapy planned, an interval of either ≤3 days or 4-8 weeks from the end of RT to surgery is recommended. *Implementation remark: An interval of 4-8 weeks is preferred for patients who may benefit from tumor downstaging before resection.*	Strong	Moderate

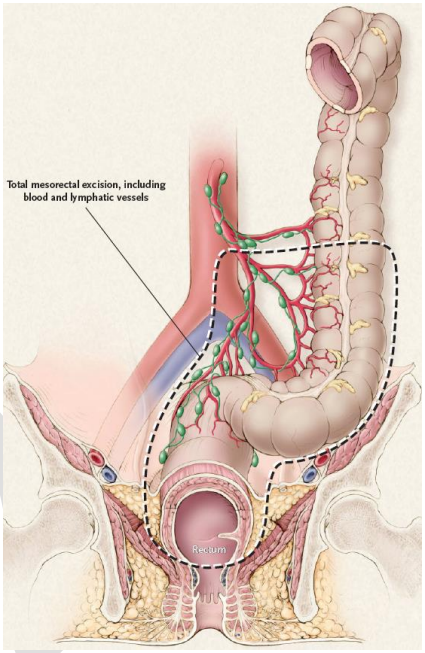
*** Risk factors for increased recurrence include cT3 tumors ≤5 cm from the anal verge or mrCRM <2 mm; cT4 tumor or cN2 disease, presence of mrEMVI.**
Abbreviations: NA-CRT = Neoadjuvant chemoradiation therapy; CA-SCRT = Neoadjuvant short course radiation therapy; NA Tx = Neoadjuvant Therapy; NAC = Neoadjuvant Chemotherapy; CAPOX = capecitabine and oxaliplatin; FOLFOX = folinic acid, 5-Fluorouracil, and oxaliplatin; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion.

LE and Non-Operative Management (NOM)	Rec Strength	Evidence
1. NOM conditionally rec after multidisciplinary discussion if a cCR is achieved after NA-Tx in patients: a. would have a permanent colostomy or inadequate bowel continence after TME AND b. decline TME AND c. agree to close follow-up by a multidisciplinary team.	Conditional	Moderate
2. Organ preservation through NA-CRT → LE is conditionally recommended after multidisciplinary discussion for patients with cT2 N0 who: a. would have a permanent colostomy or inadequate bowel continence after TME AND b. decline TME AND c. are found to have ≤ypT1 disease and R0 margins upon LE AND d. agree to close follow-up by a multidisciplinary team	Conditional	Moderate
3. If considering NOM or LE after RT, concurrent CRT is recommended. Conventional fractionation from 5000-5400 cGy in 25-30 fractions.	Strong	Moderate
4. If considering NOM, concurrent CRT ± induction or consolidation chemotherapy is conditionally recommended.	Conditional	Moderate
5. If considering NOM, assessment for response is recommended with rectal protocol MRI, CT abdomen/pelvis, and proctoscopy/sigmoidoscopy with DRE 2-3 months after completion of treatment.	Strong	Moderate
6. If undergoing NOM or LE, surveillance is recommended with: • proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6-12 months thereafter, • rectal protocol MRI every 3-6 months for the first 2 years, then every 6-12 months thereafter, and • cross-sectional imaging of the chest, abdomen and pelvis every 6-12 months for the first 2 years, then every 12 months thereafter. Implementation remark: Follow-up should continue for a minimum of 5 years.	Strong	Moderate

RT Volumes, Doses, and Constraints	Rec Strength	Evidence
1. For cT3-4 and/or cN +, inclusion of the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the CTV is recommended.	Strong	High
2. For invasion of an anterior organ or structure (eg, prostate, seminal vesicles, cervix, vagina, and/or bladder), **inclusion of the external iliac nodes** in the CTV is conditionally recommended in addition to **1.**	Conditional	Low
3. If involving the anal canal, **inclusion of inguinal and external iliac nodes** in the CTV is conditionally recommended in addition to **1.**	Conditional	Expert Opinion
4. If treated with RT, an IMRT/VMAT technique is conditionally recommended. Implementation remark: IMRT/VMAT may be beneficial when the external iliac nodes and/or the inguinal nodes require treatment or when 3-D conformal techniques may confer a higher risk for toxicity.	Conditional	Low
5. If IMRT/VMAT, daily image guidance to verify localization is conditionally recommended.	Conditional	Expert Opinion
6. When CTV does not include the inguinal nodes, simulation prone with a belly board is conditionally recommended.	Conditional	Low

Surgery

- **The cornerstone of treatment**.
- **Total Mesorectal excision (TME)** either via the **low anterior approach (LAR)** or **abdomino-perineal approach (APR)** is the gold standard.
    - Sharp dissection along presacral fascia + the mesorectum with entire fascia propria should be excised en bloc with the rectum
    - Reduces radial positive margin
    - Non-randomized trials:
        - 5-10% local recurrence rate vs 15-45% of blunt dissection
        - Upper rectal tumors-resect 4-5cm below distal edge of tumor
        - Distal rectal tumors <5cm from verge: 1-2 cm margin may be acceptable
- BENEFITS:
    - LRC - https://www.ncbi.nlm.nih.gov/pubmed/19269520 https://www.ncbi.nlm.nih.gov/pubmed/21298350
    - OS - https://www.ncbi.nlm.nih.gov/pubmed/12190680 https://www.ncbi.nlm.nih.gov/pubmed/11736973
    - Pelvic autonomic function -https://www.ncbi.nlm.nih.gov/pubmed/17235719 https://www.ncbi.nlm.nih.gov/pubmed/11683749 https://www.ncbi.nlm.nih.gov/pubmed/15486739
- Note:
    - Previously, an APR or LAR consisted of a blunt dissection of the perirectal soft tissue.
        - But, failed to remove all tumor in the mesorectum. **∴ recurrence rate 15-45%**.



Posteriorly, the mesorectal dissection is carried out along the presacral fascia.

Anteriorly, the dissection follows the posterior vaginal wall in females or Denonvilliers' fascia in males, both of which may be resected in the presence of an anterior wall rectal cancer. Reported rates of local recurrence following TME for rectal cancer have generally been < 10%.

Distal margins: Controversial. The status of the distal and radial resection margins is an important determinant of surgical outcome. Although the first line of rectal cancer spread is upward along the lymphatics, tumors below the peritoneal reflection can spread distally via intramural or extramural lymphovascular routes.

- The use of the APR for low rectal cancers has traditionally been based upon the need for a 5 cm distal margin of normal tissue.
    - However, in retrospective studies, margins as short as 1 cm have **NOT** been associated with an ↑ risk of local recurrence.
    - Distal intramural spread is usually limited to within 2.0 cm of the tumor, unless the lesion is poorly differentiated or widely metastatic.
        - In one series, only 12 of 50 APR specimens with distal margins >5 cm had distal intramural spread beyond the confines of the tumor edge (seven spread within 1 cm and five beyond 1 cm), 10 of whom had node-positive cancer.
        - Because only three patients (6 percent) had distal intramural spread beyond 2 cm, the authors concluded that a "wet" (or prefixation) margin of 2.5 cm was adequate in 94% of cases.
        - Furthermore, all five patients with intramural tumor spread beyond a 1.5 cm wet margin had poorly differentiated, node positive cancers, and mortality was attributable to distant rather than local recurrence.
        - There was no difference in survival or recurrence rates between patients with a distal resection margin of 5 cm or <5 cm.
        - Others have also concluded that extramural retrograde lymphatic spread beyond 1.5 cm represents a poor prognostic sign, and that more radical operations are not advantageous.
- Further data from a randomized prospective National Surgical Adjuvant Breast and Bowel Project (NSABP) trial demonstrated no significant differences in survival or local recurrence when comparing distal rectal margins of <2 cm, 2 to 2.9 cm, and >3 cm [49]. **As a result, a 2 cm distal margin has become acceptable, although a 5 cm proximal margin is still recommended** [59]. The radial margin is more critical for local control.

Radial margins — In addition to the traditional concerns of achieving adequate distal margins, the importance of obtaining adequate circumferential (radial) margins has been more recently delineated. Besides spreading distally within the mucosa or within the muscularis propria, there is a zone of downward spread within the mesorectum, the peritoneal investment of the ↑ rectum.

In fact, one rationale for total mesorectal excision (TME, see below) is to remove this zone of potential downward spread.

A positive radial margin is an independent predictor of both local recurrence and survival [60-65].

Abdominoperineal resection (APR):

- Abdominal & perineal incisions
- Resection of entire rectum, distal sigmoid, ***anal sphincter and canal*** and mesocolon with its regional lymphatics
- Permanent colostomy
- Indicated
    - **Tumors of distal rectum (Traditionally < 5 cm…but now can-do LAR if at least 2 cm)**
    - Incompetent anal sphincter
    - Bulky size
    - Close proximity to the anorectal ring sphincter musculature
    - Inability to achieve a cancer free margin
- Ideal distal margin disputed-2cm
- Worse QOL relate to body image, and deprsssion
- Higher risk of positive margins as mesorectal is very thin in the distal segment of the rectum and lateral margins are restricted by the close presence of the prostate in the male and vagina in females

Low Anterior Resection (LAR)

- Tumors of mid and upper rectum
- Needs at least 2 cm margin from anorectal ring.
- Sphincter Preservation
- Dissection and anastomosis below the peritoneal reflection, with ligation of the superior and middle hemorrhoidal arteries.
- Extended LAR: mobilization of the rectum down to the pelvic floor to the tip of the coccyx & between the anterior rectal wall and the vagina or prostate
- Factors
    - body habitus
    - Patients ability to care for stoma
    - adequacy of the anal sphincter
    - encroachment of the tumor on the anal sphincters
    - adequacy of the distal margin (“at least 2 cm”)

Transanal Excision

- 5-yr LC rates – 82-97%; 5 yr survival >90% in T1 lesions
- Per NCCN 2020:
    - (T1 only, < 30% circumference, < 3 cm size, SM > 3 mm, Mobile (non-fixed), within 8 cm of anal verge, no LVI+ or PNI+, no Grade 3.
- If found to have high risk features (e.g. T2, SM+, LVI+, Grade 3), need to do full transabdominal resection.
- If further high risk features (e.g. T3, N+) then adjuvant chemo-RT.

Transanal Local Excision[1]

- **Criteria**
    - **<30% circumference of bowel**
    - **<3 cm in size**
    - **Margin clear (>3 mm)**
    - **Mobile, nonfixed**
    - **Within 8 cm of anal verge**
    - **T1 only**
    - **Endoscopically removed polyp with cancer or indeterminate pathology**
    - **No lymphovascular invasion or PNI**
    - **Well to moderately differentiated**
    - **No evidence of lymphadenopathy on pretreatment imaging**
    - **Full-thickness excision must be feasible**
- **When the lesion can be adequately localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal microscopic surgery or transanal minimally invasive surgery (TAMIS).**

Canadian “Tranasanal TME” Study

Objective: To assess the association of transanal TME with the incidence of local recurrence (LR) of cancer and the probability of remaining free of LR during follow-up.

Caycedo-Marulanda, JAMA NET 2018

N = 608, 423 (69.6%) were male, the median age was 63 years.
Local recurrence was identified in 22 patients (3.6%) after a median follow-up of 27 months (IQR, 18-38 months).
Median time to LR was 13 months (IQR, 9-19 months).
Sixteen of the 22 patients with LR (72.7%) were male, 14 (63.6%) received neoadjuvant chemoradiation, and 12 (54.5%) had American Joint Committee on Cancer stage III disease.
Of those with LR, 16 (72.7%) had a negative circumferential radial margin and 20 (90.9%) had a negative distal resection margin, 2 (9.1%) experienced conversion to open surgery, and 15 (68.2%) also developed SR.
3-year LR-FS 96%.
Conclusions and relevance: In this cohort study, transanal TME performed by experienced surgeons was associated with an incidence of LR and SR that is in line with the published literature on open and laparoscopic TME, suggesting that transanal TME may be an acceptable approach for management of rectal cancer.

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Workup

- Independent evaluation by the treating surgeon with either proctosigmoidoscopy or flexible sigmoidoscopy is recommended for all rectal tumors. Critical characteristics to be documented, in conjunction with digital rectal examination (DRE), include tumor size, distances from the anal verge and the anorectal ring, orientation within the rectal lumen (eg, anterior-posterior, laterality) and/or degree of circumferential involvement, extent of obstruction, extent of fixation to the rectal wall, degree of sphincter involvement, and sphincter tone.

Transanal Local Excision[1]

- Criteria
  - <30% circumference of bowel; <3 cm in size; margin clear (>3 mm); mobile, nonfixed; within 8 cm of anal verge; T1 only; endoscopically removed polyp with cancer or indeterminate pathology; no lymphovascular invasion or PNI; well to moderately differentiated; no evidence of lymphadenopathy on pretreatment imaging; full-thickness excision must be feasible
- When the lesion can be adequately localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS).

Transabdominal Resection: Abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision (TME)

- Management principles
  - The treating surgeon should be experienced in rectal cancer surgery, and specifically with TME. For patients with predicted positive margins based on preoperative imaging, or lateral pelvic lymph node involvement, the surgeon should be experienced in extended resections beyond the TME plane and have a multidisciplinary team available if necessary.[2]
  - The treating surgeon should assess the distal margin before initiating treatment by DRE ± rigid or flexible endoscopy, particularly for non-palpable lesions.
  - Anticipated circumferential margins should be assessed by MRI (see Principles of Imaging, REC-A) prior to any required neoadjuvant therapy, and again considered prior to surgery. If margins are involved, assessment for feasibility of resection beyond the TME plane is required. Such an extended resection (± reconstruction) should involve careful preoperative planning and may require a multidisciplinary team.
  - For adequately staged, low-risk, upper-rectal T3, N0 tumors, surgery alone is an appropriate treatment option.
  - Remove primary tumor with adequate circumferential and distal margins.
  - Treat draining lymphatics by TME.
  - Sphincter preservation and restoration of organ integrity should be achieved without compromise of oncologic resection and consideration of anticipated patient functional outcome and quality of life.
- TME is a standard component of radical rectal cancer surgery. TME reduces the positive radial margin and local recurrence rates.
  - Extend 4 to 5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, <5 cm from anal verge), negative distal bowel wall margin of 1 to 2 cm may be acceptable.
  - Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.
  - Some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,[3] whereas other studies have shown that laparoscopy is associated with higher rates of circumferential margin positivity and incomplete TME.[4,5] Therefore, minimally invasive resection may be considered based on the following principles:
    - ◊ The surgeon should have experience performing minimally invasive proctectomy with TME.
    - ◊ It is not indicated for locally advanced disease with a threatened or high-risk circumferential margin based on staging. For these high-risk tumors, open surgery is preferred.
    - ◊ It is not generally indicated for acute bowel obstruction or perforation from cancer.
    - ◊ Thorough abdominal exploration is required.
- Lymph node dissection[6,7]
  - Clinically suspicious nodes beyond the field of resection should be biopsied and/or removed, if possible. Extensive resection of M1 lymph nodes is not indicated.
  - Extended lymph node resection is not indicated in the absence of clinically suspected nodes.

Chemotherapy

- TNT and Concurrent
  - **5-FU PVI** (protracted venous infusion) with RT improves LC, DFS, and OS (see the old trials under **Surgery ± CRT**)
    - Concurrent: 225 mg/m^2 throughout RT (7 days/week)
    - > 30%: **N/V, Diarrhea**, mouth sore, ↓ appetite, photophobia, metallic changes in mouth, **↓ blood counts**.
    - 10-30%: **skin** dry/hyperpigmentation/radiation recall, hair thinning, **nail changes**, **hand-foot mouth**.
  - **Capecitabine** (Xeloda, 5-FU prodrug). NONINFERIOR oral drug to 5-FU PVI. (see R-04)
    - Concurrent: 825 mg/m^2 BID, 5 days per week.
    - Cape w/o RT: 1000-1250 mg/m^2 BID, days 1-14, q3 week cycle.
    - **MORE hand-foot-mouth**, fatigue, proctitis **LESS blood counts.**
  - **Oxaliplatin**.
    - Not for adjuvant setting. No benefit despite increased toxicity.
    - YES for Total Neoadjuvant therapy.
  - **Irinotecan and bevacizumab**.
    - Multiple phase 2 trials show good tolerability in combo with Cape as part of long-course RT.
    - Investigational.

PRINCIPLES OF PERIOPERATIVE THERAPY

Not every patient with rectal cancer requires trimodality treatment – trials with adaptive designs have demonstrated some patients will have favorable outcomes with selective usage of radiation or selective usage of surgery, based on reassessment of response during therapy.[1,2] The regimens used in patients who will undergo or have undergone surgery include both concurrent chemotherapy/RT and chemotherapy alone. Perioperative treatment is recommended for up to a total of 3 to 6 months.

Perioperative Chemotherapy:

- **mFOLFOX 6[3,4,5]**
  Oxaliplatin 85 mg/m² IV, day 1,[a] leucovorin 400 mg/m² IV day 1,[b] 5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
- **CAPEOX[6,7]**
  Oxaliplatin 130 mg/m² IV day 1.[a] Capecitabine 1000 mg/m² PO twice daily for 14 days every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.
- **FOLFIRINOX[8,c]**
  Oxaliplatin 85 mg/m² IV on day 1,[a] leucovorin 400 mg/m² IV over 2 hours on day 1,[b] irinotecan 180 mg/m² IV over 30–90 minutes on day 1, 5-FU 400 mg/m² IV push day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks.
- **Modified FOLFIRINOX[9,c]**
  Oxaliplatin 85 mg/m² IV on day 1,[a] leucovorin 400 mg/m² IV over 2 hours on day 1,[b] irinotecan 150 mg/m² IV over 30–90 minutes on day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks.

Dosing Schedules for Concurrent Chemotherapy/RT:

- **RT + continuous infusion 5-FU[10]**
  5-FU 225 mg/m² IV over 24 hours daily on days 1–5 or days 1–7 for 5 weeks with RT
- **RT + capecitabine[11,12]**
  Capecitabine 825 mg/m² PO BID, Monday–Friday, on each day that RT is given throughout the duration of RT (typically 28–30 treatment days depending on stage)
- **RT + 5-FU/leucovorin[13,d]**
  5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during week 1 and 5 of RT

[a] Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
[b] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[c] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of 5-FU (3,200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with 5-FU. The dose of 5-FU (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[d] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

Radiation

General Principles

- Chemotherapy with a fluoropyrimidine in oral or continuous venous infusion form should be delivered concurrently with conventionally fractionated radiation therapy.
- In patients with a limited number of liver or lung metastases, ablative radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT).

Treatment Information

- Image-guided radiation therapy (IGRT) with kilovoltage (kV) imaging or cone-beam CT imaging should be routinely used during the course of treatment with IMRT and SBRT.
- IMRT is preferred for reirradiation of previously treated patients with recurrent disease, patients treated postoperatively due to increased acute or later toxicity[1] or in unique anatomical situations (eg, coverage of external iliac or inguinal lymph nodes or avoidance of small bowel).
- In patients with locally recurrent disease after prior pelvic radiation therapy, consider use of hyperfractionated pelvic re-irradiation if re-treatment is planned.[2]
- Intraoperative radiation therapy (IORT), if available, may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers.
- Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

CT simulation

A Standard Approach:

Prone
Belly Board placement cavity junction at pubis symphysis.
Full Bladder + Empty Rectum
Oral (SB follow through) ± IV Contrast
Anal Marker
2.5 - 3mm Slice Thickness
wire on perineal scar if s/p APR

Consider Slight Trendelenburg.
Consider Vaginal Marker.
Consider contrast-soaked tampon in vagina.
Consider IMRT for Select Cases (small bowel issues, T4, inguinal LN / anal canal involvement).

Target Delineation

FOR IMRT → See Anal Cancer Chapter.

3D-CRT

CTV: Elective nodal regions
- Standard: Peri-rectal, internal iliac, and superior hemorrhoidal (7 mm around vessels), presacral
- For T4 tumors extending anteriorly: include external iliac
- For tumors invading anal canal: external iliac
- For tumor invading anal canal below puborectalis sling: inguinal.

PTV: 5-7 mm around CTV if perform daily IGRT; 1 cm if not

- **Target Volumes**
  - **Radiation therapy fields should include the tumor or tumor bed, with a 2- to 5-cm margin, the mesorectum, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.**
  - **Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields is encouraged.**
  - **For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.**

Initial Lateral fields 45 Gy	Initial AP/PA fields 45 Gy	Boost 5.4 cGy OPPOSED LATs	Notes:
Superior L5/S1	same	GTV + 2 cm field edge.	
Anterior 3cm anterior to sacral promontory / behind pubis symphysis.	Lateral 2 cm pelvic inlet	ALL OF PRESACRAL SPACE + mesorectum	
Posterior 1 cm posterior to sacrum			
Inferior 3-5 cm ↓ GTV or inferior obturator foramen	same		

Note: Rectal Cancer-RT Fields RTOG R-0012

Posterior: 1cm behind sacrum T4, 2 cm posterior to presacrum T3 T4 CANNOT SPLIT SACRUM **GITSG GI-7175 LR 12% Pre-Sacrum.**

Anterior: T3 tumor: posterior pubic symphysis T4 tumor or anterior rectal wall invasion: **anterior to pubic** if anterior invasion
After APR cover scar with 1.5 cm margin

Boost: 3 field or opposed laterals to GTV/bed +2-3 cm or any lymph nodes → 1.5 cm to 50.4Gy

Post-op: Final Boost to 55.8Gy

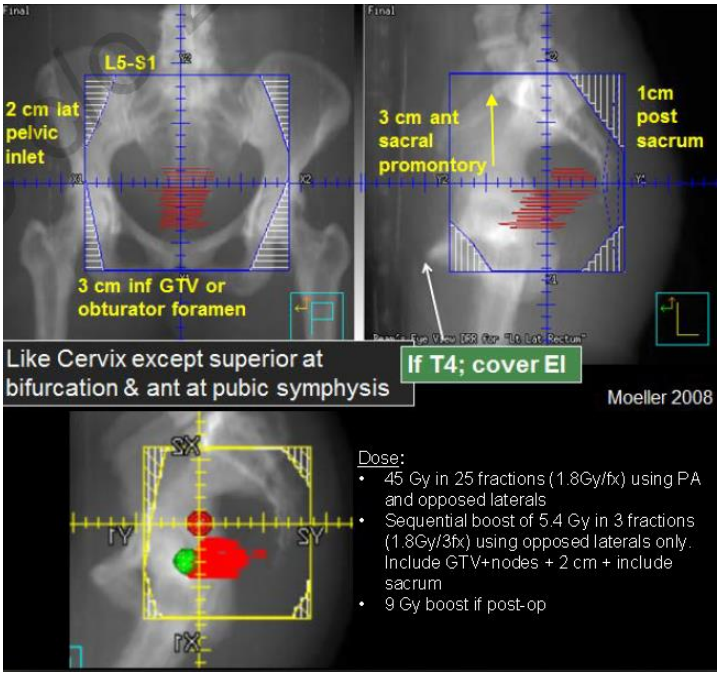
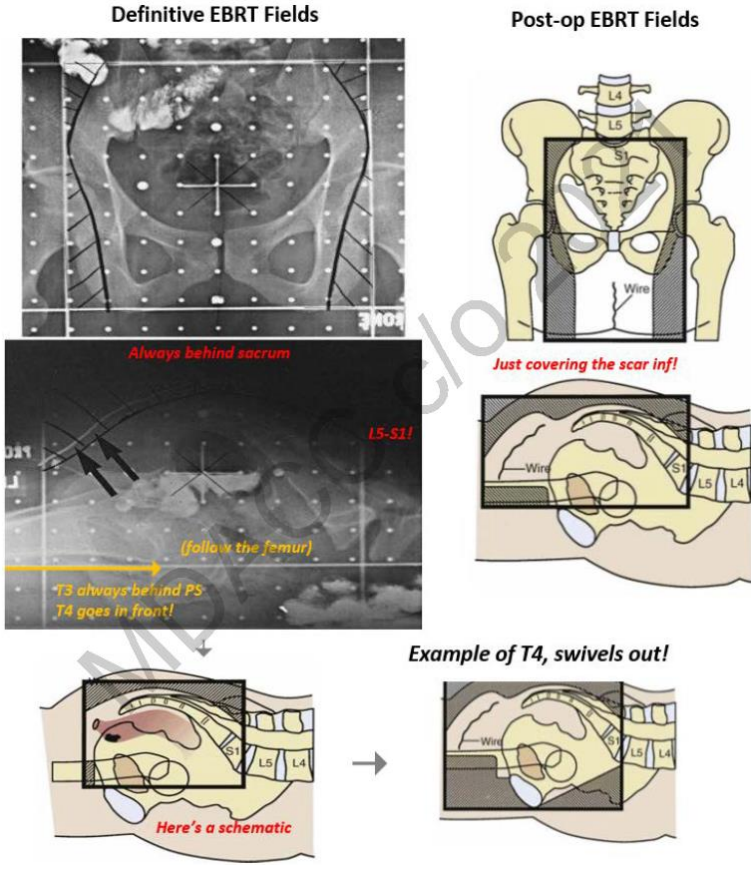
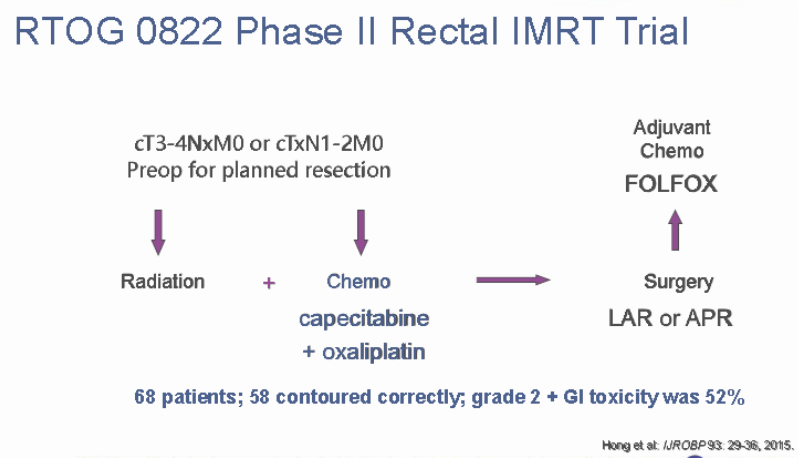


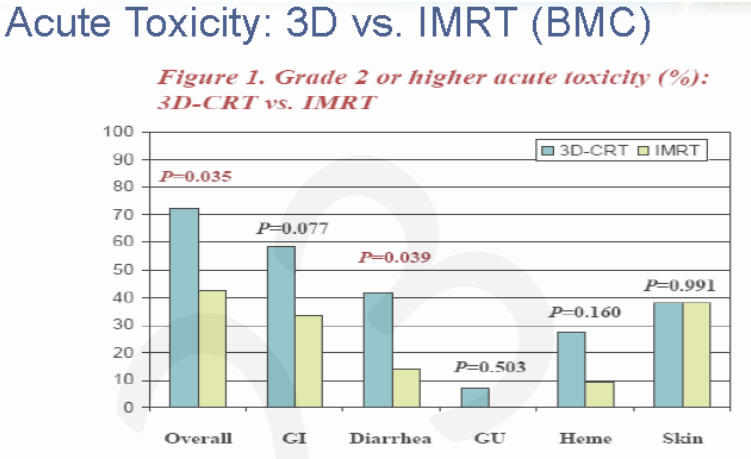
DIAGRAM FROM MD ANDERSON



Considerations for SC-RT (25 Gy in 5 fractions).
- IMRT dose painting 5 Gy x5 to the gross disease / boost volume + 4 Gy x 5 to the elective nodal volume.
  - https://pubmed.ncbi.nlm.nih.gov/24606849/ WashU Experience.
- Of note, possible significant diarrhea 1-2 weeks after treatment.

NOTES Section:





Phase II ENI Omission.
52 patients T2 (low lying) or T3, N0-1, without disease in lateral lymph nodes.
All received NA-CRT (5040 cGy RT reduced treatment volumes – excluded pelvic nodal irradiation) with concurrent 5-FU based C.
CTV Primary tumor and the mesorectum with vascular supply containing the perirectal and presacral nodes.
Upper border S2/S3 interspace.
1^{o} ↓ GI toxicity.

Fiore, PRO 2020. Median FU 72.9 months (2.5 – 127.6 months).
Acute G3 GI toxicity 7.6%. No cases of grade 4 toxicity.
Local Recurrences 5.7%. **No relapse occurred in the lateral lymph nodes**.
5-year LC 96.1%.
3-year OS 89.4%.
5-year OS 87%.
Conclusions De-escalation of radiation therapy target volume reduces GI side effects without compromising efficacy in patients with rectal cancer. These results cannot be clearly extended to high-risk disease and need further evaluation in future randomized trials.

NCCN Principles

PRINCIPLES OF RADIATION THERAPY

Treatment Information

- Target Volumes
  - Target volume definition should be performed per ICRU 50 recommendations.
  - Gross tumor volume (GTV) should include all primary tumor and involved lymph nodes, using information from physical examination, endoscopic findings, diagnostic imaging, and the simulation planning study for delineation. Clinical target volume (CTV) should include the GTV plus areas at risk for microscopic spread from the primary tumor and at-risk nodal areas. A consensus atlas may be helpful to review when defining elective nodal CTVs.[3]
  - At-risk nodal regions include mesorectal, presacral, and internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
  - Fusion of the pelvic MRI is strongly recommended to optimally define gross disease.
  - If using 3D conformal radiation, multiple RT fields should be used (generally a 3- or 4-field technique). Prone positioning, full bladder, and other techniques to minimize the volume of small bowel in the fields are encouraged.
  - For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- RT Dosing
  - 45–54 Gy in 25–30 fractions to the pelvis.
    - ◊ For resectable cancers, after 45 Gy a tumor bed boost with a 2-cm margin of 5.4 to 9.0 Gy in 3 to 5 fractions could be considered for preoperative radiation.
    - ◊ Small bowel max point dose should be limited to 50 Gy, V45Gy should be <195 cc for a bowel bag avoidance, or V15 should be <120 cc for individual small bowel loops.
    - ◊ For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
  - Short-course RT (25 Gy in 5 fractions) can also be considered for patients for preoperative radiation.
    - ◊ For high-risk rectal cancer (clinical tumor stage cT4a or cT4b, EMVI, clinical nodal stage cN2, involved MRF, [tumor or lymph node 1 mm or less from the MRF] or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional failure rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (7%) of chemoRT → surgery → adjuvant chemotherapy.[4]

Supportive Care

- Patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
- Patients of childbearing potential should be counseled about the effects of premature menopause and consideration should be given to referral for discussion of hormone replacement strategies.
- Patients of childbearing potential should be counseled that an irradiated uterus cannot carry a fetus to term.
- Patients should be counseled on sexual dysfunction, potential for future low testosterone levels, and infertility risks and given information regarding sperm banking or oocyte, egg, or ovarian tissue banking, as appropriate, prior to treatment.

Dose and Constraints

Of interest: A History of Rectal Dose Escalation: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5674246/pdf/jgo-08-05-902.pdf

3D Plan –Final Tumor Dose 50.4 Gyin 28 Fractions

- 45 Gy to pelvis in 25 fractions
- Standard –3-field if prone
- External iliac coverage for T4 –4-field may be needed
- 5.4 Gy to boost tumor/mesorectum in 3 fractions –lats or 3-field
- Femoral heads, small bowel <45 Gy; small bit sb50.4 Gy

IMRT Plan –Final Tumor Dose of 50 Gyin 25 Fractions (Dose Painted)

- 5-field static plan or 270 VMAT
- 45 Gyto PTV45 for elective pelvis
- 50 Gyto PTV rectal tumor and adjacent positive nodes

Organ at risk	Constraints
Small bowel	**QUANTEC** V15Gy < 120 cc (individual loops) V45Gy < 195 cc (entire potential space within peritoneal cavity) **RTOG 0822** V35Gy < 180 cc V40Gy < 100 cc V45 Gy < 65 cc Dmax < 50 Gy
Bladder	**QUANTEC** Dmax < 65 Gy V65Gy < 50 % **RTOG 0822** V40Gy < 40 % V45Gy < 15 % Dmax < 50 Gy
Femoral heads	**RTOG 0822** V40Gy < 40 % V45Gy < 25 % Dmax < 50 Gy

Table 5 Suggested dose and fractionation methods for rectal cancer

	PTV-HR	PTV-SR
Preoperative T3 or T1-2 N+	50.4 Gy at 1.8 Gy/fx, OR 50 Gy at 2 Gy/fx (SIB)	45 Gy at 1.8 Gy/fx, OR 45 Gy at 1.8 Gy/fx (SIB)
Preoperative T4 any N	54–55.8 Gy at 1.8 Gy/fx, OR 54 Gy at 2 Gy/fx (SIB)	45 Gy at 1.8 Gy/fx, OR 45.9 Gy at 1.7 Gy/fx (SIB)
Preoperative (short course) T3-4 or N+		25 Gy at 5 Gy/fx
Postoperative (negative margins)	54–55.8 Gy at 1.8 Gy/fx, OR 54 Gy at 2 Gy/fx (SB)	45 Gy at 1.8 Gy/fx 45.9 Gy at 1.7 Gy/fx (SIB)
Postoperative (gross disease or positive margin)	54–59.4 Gy at 1.8 Gy/fx, OR 54–60 Gy at 2 Gy/fx (SIB)	45 Gy at 1.8 Gy/fx, OR 45.9 Gy at 1.7 Gy/fx (SIB)

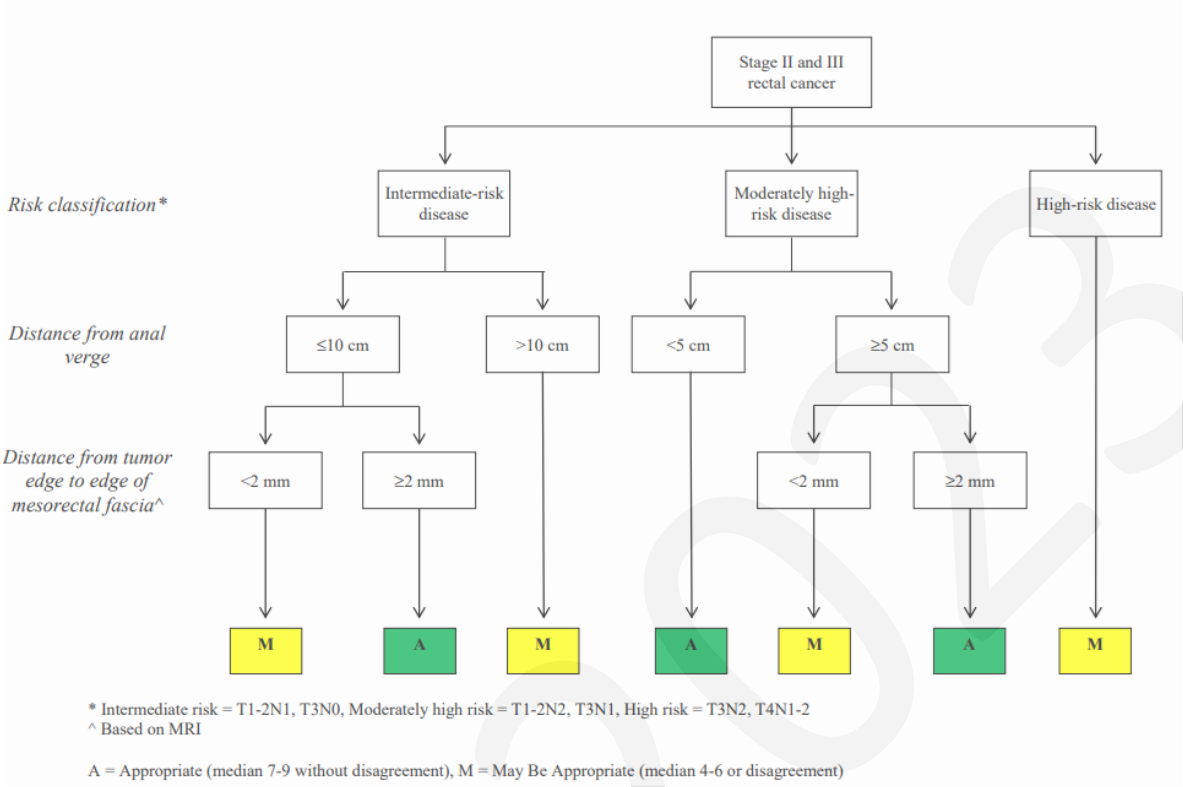
Of note: V30Gy < 100cc and V30 < 200cc are predicts of late G2 and G3 toxicity < 5%, respectively when *small bowel loops* contoured (excluding large bowel). Abraham, PRO 2020.

Toxicity

- Acute Diarrhea, Acute proctitis, Decreased blood counts, Dysuria/cystitis, Fatigue, Skin redness/desquamation
- Delayed Persistent diarrhea, Proctitis, Fistula, SB obstruction/adhesions, Perineal and scrotal tenderness, Delayed wound healing, Urinary incontinence, Bladder atrophy/bleeding, Sexual dysfunction, Secondary Malignancy.

NA+Adj. CRT Criteria

GOODMAN KA Practical Rad Oncol 2016. Appropriateness of criteria of Adjuvant and Neoadjuvant Tx. **Follows German study TX (see above!)**



- **NEOADJUVANT CRT → adjuvant 4 mo chemo** **ALWAYS APPROPRIATE**
  - German Trial 45 Gy pelvis + CD exclude small bowel to 50.4 Gy with concurrent infusional 5-FU or capecitabine.
- NEOADJUVANT **SHORT COURSE RADIATION (the graph above describes this).**
  - You want CLOSE to anal verge and FAR from edge of fascia.
  - **Short-course RT is 25 Gy in 5 fraction**
- NEOADJUVANT Chemo alone or NO Adjuvant Tx:
  - High — NEVER.
  - ModHigh — Never, unless ≥ 5 cm from anal AND ≥ 2 mm distance from edge of mesorectal fascia.
  - Int — See ↑
  - **Neoadjuvant chemo is FOLFOX** (leucovorin calcium aka folinic acid, fluorouracil and oxaliplatin).
- Adjuvant CRT → adjuvant ≥ 4 mo chemo
  - HIGHEST (aka positive Margin) ALWAYS
  - High — ALWAYS
  - ModHigh — ALWAYS
  - Int — ALWAYS, unless ≥ 10 cm from anal
  - **German Trial 50.4 Gy + 5.4 Gy boost with concurrent infusional 5-FU or capecitabine.**
- Adjuvant C alone
  - HIGHEST (aka positive Margin) Maybe
  - High — Maybe
  - ModHigh — ALWAYS IF > 10 cm from anal **(this is from the METAANALYSIS OF Adj Chemo)**
  - Int — Maybe
  - **C alone is adjuvant FOLF** (leucovorin and 5-FU)**, FOLFOX, capecitabine, or CapeOx.**
- Definitive CRT + brachy or Definitive Brachy alone (medically inoperable)
  - Only Maybe (rest is NEVER) if distance from anal verge is ≤ 10 cm (≤ 5 cm is best)
  - Local symptoms present or absence is not as important as anal verge distance.
  - **Brachy is 26 Gy in 4 fractions with I-192.**

Local / Transanal Excision

T1 vs. T2

RTOG 89-02 (Russell, IJROBP 2000).
←R→ 65 patients to 1 of 3 arms. Phase II study assigned to local excision.
1. Negative Margin, no adverse prognostic features = **observation**. 2. Negative margin + 1 adverse feature = **concurrent 5-FU and RT 50-56 Gy**.
3. Positive margin = **concurrent 5-FU and RT 59.4 – 65 Gy**.
Inclusion: < 4 cm in diameter, involve ≤ 40% of the rectal circumference, and be below the peritoneal reflection (middle or lower rectum).
Outcome: **LF** (after surgery + adapted chemo-RT) by T-stage: **T1** 0%, **T2** 20%, **T3** 23%.
Loco-regional failure 12%. By T-stage: **T1** 4%, **T2** 16%, **T3** 23%. By circumference: <20% 6%, 20-40% 18%.
Distant metastasis 12%. By T Stage: **T1** 4%, **T2** 12%, **T3** 31%). 5-year pelvic control 88%.
Conclusion: Conservative sphincter-sparing therapy is feasible, but relatively **high local failure rate for T2 and T3 lesions**

CALGB 8984. (Greenberg, Dis Colon Rectum 2008).
Phase II. 110 patients with rectal lesions < 10 cm from dentate line, < 4 cm diameter, < 40% rectal circumference, and negative margins were included (Note no EUS or MRI). **1.** 59 patients found with T1 lesions were treated with local excision alone.
2. 51 Pts found with T2 → local excision plus adjuvant radiation (54Gy) + 5-FU (500 mg/m2 intravenously Days 1–3, Days 29–31).
Outcome: **Ten-year rates of OS 84% vs 66% (T1 vs T2).** DFS 75% vs 64%. LR 8% vs 18%.
Conclusion: Conservative sphincter-sparing therapy is feasible for well selected T1 lesions, but T2 lesions have high LR even with adjuvant ChemoXRT.

T2(3ab)N0

T3N0 TAU-TEM

Background: Standard treatment of T2-T3ab,N0,M0 rectal cancers is TME due to the high recurrence rates recorded with local excision.
Initial reports of the pre-operative chemoradiotherapy (CRT) and transanal endoscopic microsurgery (TEM) have shown ↓ in local recurrence.
←R→ 173 rectal adenocarcinoma T2-T3ab,N0,M0 | 1. CRT-TEM | 2. TME |.

Inclusion: T2N0 (69.8%) or T3a/bN0 (≤5mm invasion through the muscularis) (30.2%)
Well to moderately differentiated, ≤4cm, and within 10cm of the anal verge.

Serra-Aracil, Ann Oncol 2022

The CRT-related morbidity rate was 29.6% (24/81).
Post-operative morbidity 20.7% vs. 50.6% (P < 0.001, SS). Length of hospital stay 3.7 vs 10.6 days.
Temp Ostomy 4.9% vs. 76.8%.

pCR in the CRT-TEM group was 44.3% (35/79).
In the TME group, pN1 were found in 17/81 (21%).
4.9% were understaged with T3c/d disease
12.3% were overstaged with T1 disease

Conclusion CRT-TEM treatment obtains high pathological complete response rates (44.3%) and a high CRT compliance rate (98.8%). Post-operative complications and hospitalisation rates were significantly lower than those in the TME group. We await the results of the follow-up regarding cancer outcomes and quality of life.

ACOSOG Z6041.

Single Arm Prospective. 72 patients **cT2N0** neoadjuvant CRT. Staged via endorectal ultrasound or endorectal coil MRI.
< 4 cm, < 40% circumference, < 8 cm of anal verge.
Recall Transanal resection T1N0 is rules of THREE. < 30% circumferential, > 3mm margin, also < 8cm anal verge.

C: CAPEOX capecitabine (original dose 825 mg/m ^{2} twice daily on days 1–14 and 22–35), oxaliplatin (50 mg/m ^{2} on weeks 1, 2, 4, and 5)
RT: 45→54 45 Gy in 1·8 Gy per day for 5 weeks → boost of 9 Gy = total dose of 54 Gy.
CRT is followed by local excision.
NOTE: Adverse events during CRT, the dose of capecitabine ↓ 725 mg/m ^{2} twice daily, 5 days per week, for 5 weeks, boost RT ↓ 5·4 Gy.
1^O 3-year DFS.

Garcia-Aguilar, Lancet 2015.

3-year DFS intention to treat group 88.2% vs. per protocol 86.9%.
34 (47%) patients achieved pCR 49 patients (64%) downstage to ypT0-1
33 patients (39%) of 84 pts developed CRT grade ≥3 complications
72 (91%) of 79 patients receiving neoadjuvant chemoradiotherapy had rectal preservation.

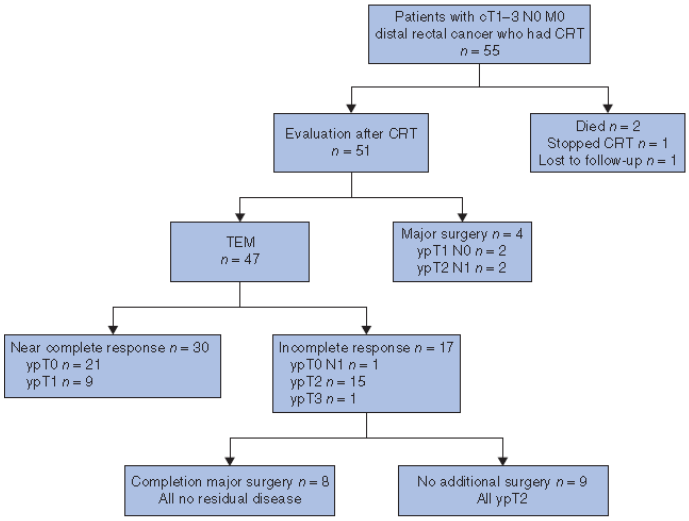
****Unacceptably high toxicity even at decreased dosing**

Interpretation
3-year DFS is not as high as expected, but CRT → local excision OK in carefully selected patients T2N0 who refuse or are not TME candidates.

	Original dose group (n=53)			Revised dose group (n=26)			Overall (n=79)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Gastrointestinal	4 (8%)	18 (34%)	0	18 (69%)	5 (19%)	0	22 (28%)	23 (29%)	0
Pain	2 (4%)	9 (17%)	1 (2%)	16 (62%)	2 (8%)	0	18 (23%)	11 (14%)	1 (1%)
Dermatological	2 (4%)	7 (13%)	0	7 (27%)	2 (8%)	0	9 (11%)	9 (11%)	0
Haematological	1 (2%)	4 (8%)	1 (2%)	11 (42%)	6 (23%)	1 (4%)	12 (15%)	10 (13%)	2 (3%)
Infectious or febrile neutropenia	0	3 (6%)	1 (2%)	2 (8%)	0	0	2 (3%)	3 (4%)	1 (1%)
Constitutional symptoms	5 (9%)	3 (6%)	0	17 (65%)	1 (4%)	0	22 (28%)	4 (5%)	0
Metabolic or laboratory	1 (2%)	2 (4%)	1 (2%)	9 (35%)	2 (8%)	1 (4%)	10 (13%)	4 (5%)	2 (3%)
Cardiovascular	0	2 (4%)	1 (2%)	6 (23%)	0	0	6 (8%)	2 (3%)	1 (1%)
Haemorrhage	0	1 (2%)	1 (2%)	4 (15%)	1 (4%)	0	4 (5%)	2 (3%)	1 (1%)
Lymphatic	0	1 (2%)	0	2 (8%)	0	0	2 (3%)	1 (1%)	0
Neurological	3 (6%)	1 (2%)	0	8 (31%)	0	0	11 (14%)	1 (1%)	0
Coagulation	0	0	0	1 (4%)	1 (4%)	0	1 (1%)	1 (1%)	0
Musculoskeletal	1 (2%)	0	0	0	1 (4%)	0	1 (1%)	1 (1%)	0
Renal or genitourinary	1 (2%)	0	0	12 (46%)	0	0	13 (16%)	0	0
Hepatic	0	0	0	8 (31%)	0	0	8 (10%)	0	0

Table 2: **Adverse events during neoadjuvant chemoradiotherapy**

CARTS TRIAL **cT1-T3 patients cap/RT to 50-50.4 Gy. TEM 8-10 weeks later if cCR if yp T2, then completion TME surgery.**
Prospective multicentre study was performed to quantify the number of patients with minimal residual disease (ypT0-1) after neoadjuvant chemoradiotherapy and transanal endoscopic microsurgery (TEM) for rectal cancer.
cT1-3 N0 distal rectal cancer received long-course CRT. Clinical response was evaluated 6-8 weeks later and TEM performed.
Total mesorectal excision was advocated in patients with residual disease (ypT2 or more).
cT1 N0 in n=10 cT2 N0 in n=29 cT3 N0 in n=16.



Verseveld, Br J Surg 2015.
Of 47 patients who had TEM, 2/3 "near complete response" 1/3 "incomplete"
ypT0 n=21 ypT1 n=9 ypT0 N1 n=1 ypT2 n=15 ypT3 n=1.
If you DECLINED further surgery, LR developed in 3 of 9 of patients ypT2… ONLY 33%...
Postoperative complications grade I-IIIb occurred in 13 of 47 patients after TEM and in five of 12 after (completion) surgery.
If you followed through everything with 1.5 year f/u (17 mo), **4 LR overall (8%)**.
ypT2 n=3 (20%), ypT1 n=1..
CRT complications ≥ G3 was 23 of 55 patients (42%), (with two deaths toxicity).
CONCLUSION:
TEM after chemoradiotherapy enabled organ preservation in **one-half** of the patients with rectal cancer.

Table 2 Adverse events during chemoradiotherapy

	Grade 3	Grade 4	Grade 5
Cardiac (arrhythmia)	2	0	0
Constitutional	6	0	0
Dermatological	1	0	0
Gastrointestinal	19	1	1
Genitourinary	2	0	0
Infectious	1	0	1
Pain	5	0	0
Total	36	1	2

A total of 39 grade 3–5 complications were experienced by 23 patients.

GRECCAR 2 trial. No SUPERIORITY was NOT SHOWN FOR LOCAL EXCISION OVER TME. Rullier, Lancet 2017.
←r→ 186 enrolled → 148 good responders → **145 analyzed**. Age ≥ 18 years stage T2T3 lower rectal carcinoma, ≤ 4 cm, "good clinical response" to neoadjuvant chemoradiotherapy (residual tumour ≤2 cm). 1. local excision 2. total mesorectal excision surgery.
In the local excision group, a completion total mesorectal excision was required if tumour stage was ypT2–3.

Rullier, Lancet 2017.
In the local excision group, 26 patients had a completion total mesorectal excision.
≥ 1 events from **composite primary outcome** 56% in the local excision vs. 48% in TME (p=0·43).
In the modified ITT analysis, there was no difference between the groups in all components of the composite outcome, and superiority was not shown for local excision over total mesorectal excision.
Interpretation
We failed to show superiority of local excision over total mesorectal excision, because many patients in the local excision group received a completion total mesorectal excision that probably increased morbidity and side-effects, and compromised the potential advantages of local excision. Better patient selection to avoid unnecessary completion total mesorectal excision could improve the strategy.

TNT: Total Neoadjuvant Therapy

Summary

TNT has tremendous benefits, but with some caveats in terms of radiation technique and treatment.

- **French PRODIGE-23** showed that 3-year DFS was better for the modified/split-course TNT by 76% vs. 69% (HR 0·69; p=0·034).
  - Updated 2023 ASCO reporting = 5-year TNT ↑ on **ALL ENDPOINTS** DFS Δ ↑ 7.6%, **OS ↑ 6.9% ,** DMFS ↑ 9.9%, CSS ↑ 5.7%.
- But, **RAPIDO** showed TNT w/ SC-RT 5x5 (vs. standard CRT → Surg → Adj C) 3-year treatment failures ↓ 23·7% vs. 30·4%.
  - While pCR rate at TME were halved with TNT at 28% vs 14% (SS)… LRF 8.3% vs 6% (NS) and all survival endpoints were NS.
  - However, 5-year data shows TNT SC-RT EXP = LRR ↑ 10% vs. 6% (SS) **AND** LRR + breached mesorectum ↑ 21% vs. 4% (SS).
- **PROSPECT** suggested that for **resectable (spincter sparing surg candidate)** L.A. rectal CA, FOLFOX alone ("no RT") is non-inferior to TNT.
  - FOLFOX alone ↑ preop ≥ G3 tox (FOLFOX 41% vs. TNT 22.8%).
    ↓ postop ≥ G3 tox (FOLFOX 25.6% vs. TNT 39.0%).
- Similarly, the **Chinese FOWARC Trial** showed that mFOLFOX ± RT had no difference in 3- or 10-year DFS and OS.

- **STELLAR** suggested in terms of "survival endpoints" (e.g. OS, DFS, etc.), TNT SC-RT 5x5 could offer some benefit vs. standard CRT.
  - 3-year OS 86.5% vs. 75.1%; P = .033.
  - However, more patients of the SC-RT arm finished adjuvant chemotherapy than the standard arm (60% vs. 48%).
  - **BUT**… there are certain subsets that could have true benefits (distance to anal verge ≤ 5 cm, bulky cT4).
- **Polish II** (bulky cT4 + fixed cT3) showed 3-year OS benefit with TNT SC-RT 5x5, although was SS weak (p=0.046)
  - SS disappeared at 8-year follow-up.
- **GI-002 abstract** suggested that adding pembrolizumab to CRT after FOLFOX did not improve neoadjuvant rectal score vs post-FOLFOX CRT alone in patients with locally advanced rectal cancer.

- **OPRA Phase II** suggests that CRT → C is better than C → CRT in terms of…
  - 3-year TME-FS 53% vs. 41% (SS).
  - 5-year TME-FS 54% vs. 39% (SS).
  - Decreased tumor regrowth 27% vs. 40%.

TABLE 3. Summary of Randomized Controlled Trials Comparing TNT and CRT Followed by Surgery in Patients With Locally Advanced Rectal Cancer

			Stage		TNT					Surgery	Postoperative	3-Year	3-Year	3-Year	3-Year
Study	Eligibility (total number)	Treatment Schedules	cT4, %	N+, %	RT	CRT	Regimen	Completion, %	≥ 3 Toxicity, %	% of ITT	Chemotherapy	DFS, %	OS, %	DM, %	LRR, %
STELLAR	cT3-4 or N+ (n = 599)	TNT: 298	15.9	84.8	5 Gy × 5f	—	4 CAPOX	82.6	26.5	77.8	2 CAPOX	64.5	86.5[a]	22.8	8.4
		CRT: 293	12.8	83.5	50 Gy/25f	CAP	—	95.2	12.6	77.4	6 CAPOX	62.3	75.1[a]	24.7	11.0
RAPIDO[16]	cT4 or N2/+	TNT: 462	32	91	5 Gy × 5f	—	8 CAPOX/12 FOLFOX	84.6	47.6	92	—	23.7[b]	89.1	20.0[a]	8.3
	EMVI/MRF+ (n = 912)	CRT: 450	30	92	50 Gy/25f	CAP	—	90.0	24.7	89	8 CAPOX/12 FOLFOX	30.4[b]	88.8	26.8[a]	6.0
Polish II[15]	Fixed cT3, cT4 (n = 515)	TNT: 256	63	–	5 Gy × 5f	—	3 FOLFOX	72	24.2	84	—	53	73[a]	30	22
		CRT: 259	64		50 Gy/25f	CAPOX	—	64	23.5	81	—	52	65[a]	27	21
PRODIGE 23[14]	cT3-4 or N+ (n = 461)	TNT: 231	18	90	50 Gy/25f	CAP	6 FOLFIRINOX	89.6	46.9	92	6 mFOLFOX6/4 CAP	76[a]	91	17[a]	4
		CRT: 230	16	90	50 Gy/25f	CAP	—	98.7	35.6	95	12 mFOLFOX6/8 CAP	69[a]	88	25[a]	6

Major Studies

French PRODIGE-23 **"Split-Course TNT" – 3 months (half of chemo) prior and 3 months (half of chemo) after TME.**
←R→ 461 L.A. rectal AC cT3 or cT4, M0 <15 cm anal verge, age 18-75 years, and WHO PS ≤1 to| A. SOC | B. TNT-LCRT |.
ARM A. SOC = CRT → TME → Adj C.
ARM B. TNT-LCRT = FOLFIRINOX → CRT 50 Gy + CAPE → TME → Adj FOLFOX6 or CAPE.
1^{O} DFS 3 years.
Treatment Details:
FOLFIRINOX (oxaliplatin 85 mg/m2, irinotecan 180 mg/m2, leucovorin 400 mg/m2, and fluorouracil 2400 mg/m2 intravenously every 14 days for 6 cycles), chemoradiotherapy (50 Gy during 5 weeks and 800 mg/m2 concurrent oral capecitabine twice daily for 5 days per week), total mesorectal excision, and adjuvant chemotherapy (3 months of modified FOLFOX6 [intravenous oxaliplatin 85 mg/m2 and leucovorin 400 mg/m2, followed by intravenous 400 mg/m2 fluorouracil bolus and then continuous infusion at a dose of 2400 mg/m2 over 46 h every 14 days for six cycles] or capecitabine [1250 mg/m2 orally twice daily on days 1–14 every 21 days]).

TABLE 1: PRODIGE 23 Outcomes With mFOLFIRINOX Neoadjuvant Chemotherapy vs Standard Chemoradiotherapy

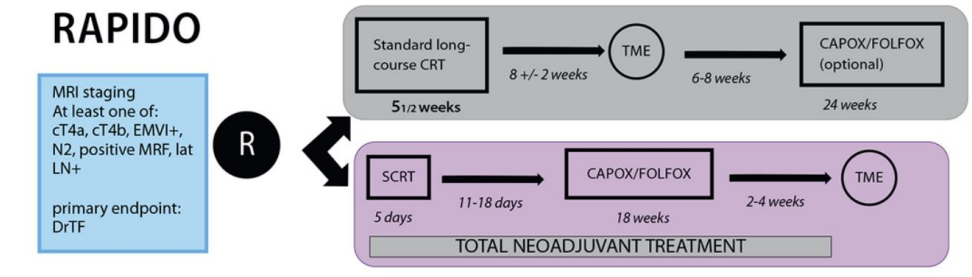
Endpoint	Modified FOLFIRINOX Followed by Chemoradiotherapy	Chemoradiotherapy	Hazard Ratio; *P* Value
3-year disease-free survival	75.7%	68.5%	0.69; *P* = .034
3-year metastasis-free survival	78.8%	71.7%	0.64; *P* = .017
Noncurative surgery	0%	3.7%	*P* = .007
Pathologic complete response (ypTONO)	27.8%	12.1%	*P* < .001
Grade 3 or 4 adverse events with adjuvant chemotherapy	44.4% (3 months of chemotherapy)	52.5% (first 3 months of chemotherapy)	*P* = .03
		74.1% (total 6 months of chemotherapy)	*P* < .001

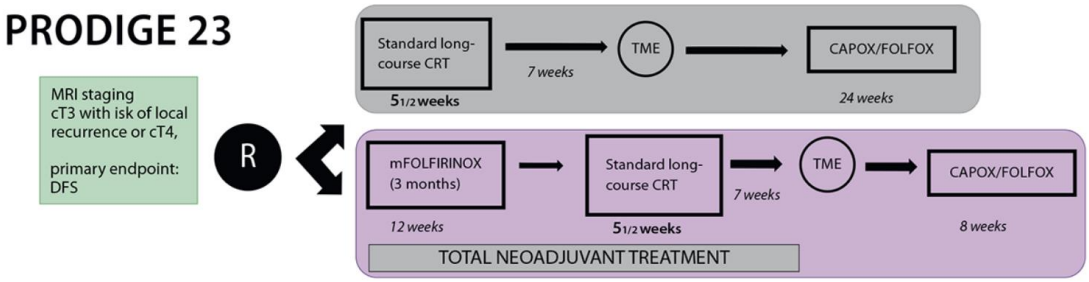
Conroy, Lancet 2021. Median 46·5 months.
3-year DFS 76% vs. 69% (HR 0·69; p=0·034).
mTNT reduced the rate of distant metastasis (25→ 17%) while maintaining a similar rate of locoregional failure (4% vs 6%). The proportion of patients who received planned chemoradiation was lower in the TNT arm (95% vs 99%), however there was no difference in the proportion of patients who proceeded to surgery. The pCR rate was also significantly higher with TNT (12→ 28%). There was no difference in 3-year overall survival.
Interpretation
Intensification of chemotherapy using FOLFIRINOX before preoperative chemoradiotherapy significantly improved outcomes compared with preoperative chemoradiotherapy in patients with cT3 or cT4 M0 rectal cancer. The significantly improved disease-free survival in the neoadjuvant chemotherapy group and the decreased neurotoxicity indicates that the perioperative approach is more efficient and better tolerated than adjuvant chemotherapy. Therefore, the PRODIGE 23 results might change clinical practice.

Conroy, ASCO 2023 Median F/U of 82.2 mos
All survival endpoints Arm A << Arm B.
5-year DFS Δ ↑ 7.6%, OS ↑ 6.9% , DMFS ↑ 9.9%, CSS ↑ 5.7%.
7-year LRR 8.1% vs. 5.3% (NS).
Conclusions: NACT with mFOLFIRINOX followed by CRT, surgery, and ACT significantly improved all outcomes, including OS in pts with LARC vs those who received standard CRT, surgery, and ACT.

	Arm A: CRT 7-year est [95% CI]	Arm B: mFOLFIRINOX + CRT 7-year est [95% CI]	Stratified HR [95%CI] (Cox Model)	Δ RMST in mos (Arm B - Arm A) [95%CI]	p-value (Difference RMST test)
DFS	62.5% [55.6-68.6]	67.6% [60.7-73.6]	0.80 [0.58-1.11]		
RMST*	60.4 mos [56.2-64.7]	66.2 mos [62.4-69.9]		5.7 [0.05-11.4]	0.048
MFS	65.4% [58.7-71.3]	73.6% [67.0-79.2]	0.73 [0.51-1.02]		
RMST*	62.1 mos [57.9-66.3]	69.3 mos [65.7-72.8]		7.1 [1.7-12.6]	0.011
OS	76.1% [69.8-81.3]	81.9% [75.8-86.7]	0.73 [0.48-1.09]		
RMST*	71.9 mos [68.8-75.1]	76.3 mos [73.8-78.8]		4.3 [0.4-8.4]	0.033
CSS	79.6% [73.5-84.4]	84.9% [79.1-89.2]	0.66 [0.42-1.05]		
RMST*	73.4 mos [70.3-76.4]	77.2 mos [74.8-79.6]		3.8 [-0.02-7.7]	0.051

* restricted mean survival time (RMST)





RAPIDO **TNT 5x5**

←R→ 920 LA rectal AC with MRI high risk (cT4a or cT4b, extramural vascular invasion, cN2, involved mesorectal fascia, or enlarged lateral LNs).

| **1.** SC-RT → 6c CAPOX or 9c FOLFOX 4 → TME |
| **2.** CRT → TME → adj 8c CAPOX or 12c FOLFOX4 |

Outcomes	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Median FU	4.6 yrs	3.8 yrs
Primary endpoint	3-year DrTF	3-year DFS
	23.7% vs. 30.4% (HR 0.75 [95% CI 0.60-0.96]; *P* = 0.019)	75.7% vs. 68.5% (HR 0.69 95% [CI 0.49-0.97]; *P* = 0.034)
3-year MFS	80% vs. 73.2%	78.8% vs. 71.7%
pCR rate	28.4% vs. 14.3%	27.5% vs. 11.7%
Local relapse	8.7% vs. 5.4%	4.8% vs. 7%
3-year OS	89.1% vs. 88.8%	90.8% vs. 87.7%

FU: follow up; CRT: chemoradiotherapy; DrTF: disease-related treatment failure; DFS: disease-free survival; TNT: total neoadjuvant chemotherapy; pCR: pathological complete response; OS: overall survivsl; yrs: years.

SC-RT = short-course radiotherapy (5 × 5 Gy over a maximum of 8 days).
CRT = 5040 cGy in 180 cGy or 5000 cGy in 200 cGy + BID oral capecitabine 825 mg/m2.
CAPOX (capecitabine 1000 mg/m2 orally BID on days 1–14, oxaliplatin 130 mg/m2 IV on day 1, and a chemotherapy-free interval between days 15–21)./
FOLFOX4 (oxaliplatin 85 mg/m2 IV on day 1, leucovorin [folinic acid] 200 mg/m2 IV on days 1 and 2, followed by bolus fluorouracil 400 mg/m2 IV and fluorouracil 600 mg/m2 IV for 22 h on days 1 and 2, and a chemotherapy-free interval between days 3–14).
Choice of 5040/5000 cGy and CAPOX/FOLFOX4 were per physician discretion or hospital policy.
1^{O} 3-year DFS. **NOTE: DrTF = Disease Related Treatment Failure**

NOTE: EXP patients were more often treated with 3 dimensional-conformed radiotherapy (P=0.029).
NOTE: Difference in Treatment time BEFORE surgery = 40 wk in EXP group vs. ~25 wk in STD group.

	Experimental group	Standard of care group	p value
All eligible patients			
Surgery with curative intent within 6 months after the end of preoperative treatment			
Yes	426/462 (92%)	400/450 (89%)	0·086*
No	36/462 (8%)	50/450 (11%)	..
Disease-related treatment failure, first occurring	128 (23·7%)†	152 (30·4%)†	0·019†
Locoregional failure			
Local progression, unresectable tumour	1/128 (1%)	1/152 (1%)	..
R2 resection	0	0	..
Local recurrence	22/128 (17%)	13/152 (10%)	..
Locoregional failure and distant metastasis‡			
Local progression, unresectable tumour	4/128 (3%)	2/152 (1%)	..
R2 resection	1/128 (1%)	0	..
Local recurrence	7/128 (5%)	4/152 (3%)	..
Distant metastasis	86/128 (67%)	123/152 (81%)	..
New primary colorectal tumour	3/128 (2%)	5/152 (3%)	..
Treatment-related death	4/128 (3%)	4/152 (3%)	..
Patients with a resection within 6 months after the end of preoperative treatment			
Residual tumour classification			
R0 >1 mm	382/423 (90%)	360/398 (90%)	0·87*
R1 ≤1 mm	38/423 (9%)	37/398 (9%)	..
R2	3/423 (1%)	1/398 (<1%)	..
Circumferential resection margin			
>1 mm	385/423 (91%)	363/398 (91%)	0·92*
≤1 mm	38/423 (9%)	35/398 (9%)	..
Differentiation grade during pathological assessment			
Well differentiated	62/423 (15%)	82/398 (21%)	0·09*§
Moderately differentiated	167/423 (39%)	189/398 (47%)	..
Poorly differentiated	44/423 (10%)	35/398 (9%)	..
No tumour	129/423 (30%)	69/398 (17%)	..
Not assessed	21/423 (5%)	23/398 (6%)	..
Pathological complete response			
Yes	120/423 (28%)	57/398 (14%)	<0·0001*
No	303/423 (72%)	341/398 (86%)	..
Pathological T stage¶			
ypT0	129/423 (30%)	69/398 (17%)	<0·0001*
ypTis	2/423 (<1%)	1/398 (<1%)	..
ypT1	17/423 (4%)	17/398 (4%)	..
ypT2	82/423 (19%)	96/398 (24%)	..
ypT3	157/423 (37%)	190/398 (48%)	..
ypT4	36/423 (9%)	25/398 (6%)	..
Pathological N stage¶			
ypN0	317/423 (75%)	273/398 (69%)	0·017*
ypN1	75/423 (18%)	78/398 (20%)	..
ypN2	31/423 (7%)	47/398 (12%)	..
Postoperative M stage¶			
ypM0	420/423 (99%)	396/398 (99%)	0·70*
ypM1	3/423 (1%)	2/398 (1%)	..

Bahadoer, Lancet 2021 Median follow-up was 4·6 years (IQR 3·5–5·5).
3-year disease-related treatment failure **23·7%** vs. 30·4% (HR 0·75, p=0·019).
3-year distant failure 20% vs 26.8% (SS).
pCR rate at TME 28% vs 14% (SS). LRF 8.3% vs 6% (NS).
No survival endpoints were different.
Neoadjuvant ≥ G3 both groups was diarrhoea (18% vs. 9%)
Adjuvant neurological toxicity in CRT group (9%).

Serious adverse events occurred in 177 (38%) vs. of 460 participants in the experimental group and, in the standard of care group, in 87 (34%) of 254 patients without adjuvant chemotherapy and in 64 (34%) of 187 with adjuvant chemotherapy. Treatment-related deaths occurred in four participants in the experimental group (one cardiac arrest, one pulmonary embolism, two infectious complications) and in four participants in the standard of care group (one pulmonary embolism, one neutropenic sepsis, one aspiration, one suicide due to severe depression).

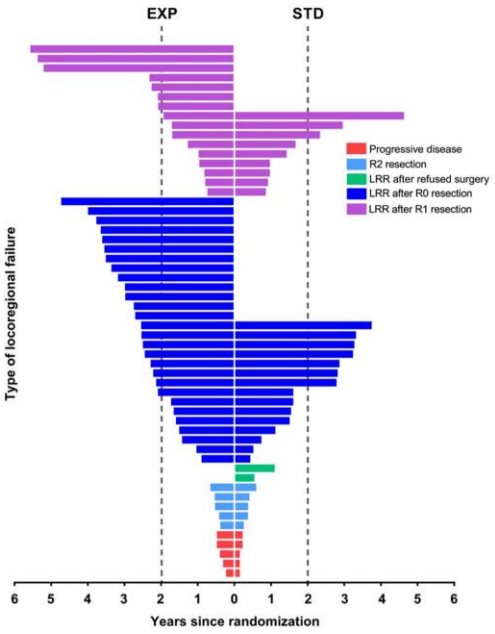
Interpretation
The observed decreased probability of disease-related treatment failure in the experimental group is probably indicative of the increased efficacy of preoperative chemotherapy as opposed to adjuvant chemotherapy in this setting. ~~**Therefore, the experimental treatment can be considered as a new standard of care in high-risk locally advanced rectal cancer.**~~
→ **See 5-year FU below**
Note: eContour here, RAPIDO protocol here.

Commentary:
NOTE1: Polish II trial **3-year** LRR similar rates (22% vs 21%), but ↑ 3-year OS (73% vs 65%; HR 0·73, p=0·046). Difference could be → some RAPIDO trial patients were non-responders or poor responders to radiotherapy but still had a delayed surgery at 26 weeks per protocol after the entire course of consolidation chemotherapy, which offset the anticipated benefit in terms of locoregional failure and overall survival in the experimental group.

How to overcome? As suggested by Bahadoer, an interim restaging MRI scan after 3c of chemotherapy can potentially identify non-responders to preoperative treatment, thus → promp earlier surgery than planned. This potentially can ↑ overall survival outcomes.

NOTE2: That OS benefit disappeared anyways at **8-year follow-up**.

NOTE3: GRECCAR-6 did not find any benefit in rates of pathological complete response beyond 7 weeks after radiotherapy. The increase in pathological complete response observed in the RAPIDO protocol isprobably due to the effect of additional chemotherapy after initial radiotherapy.



Dijkstra, Ann Surg 2023 **5.6-year**

5-year LRF EXP 54/460 (12%) vs. STD 36/446 (8%), respectively (P=0.07).

In EXP group, LRR was detected more often 10% vs. 6% (SS)

LRR + breached mesorectum 21% vs. 4% (SS).

The EXP treatment, enlarged lateral lymph nodes, positive circumferential resection margin, tumor deposits, and node positivity at pathology were the significant predictors for developing LRR. Location of the LRRs was similar between groups.

5-year DrTF 27.8% vs. 34.0% (HR: 0.79, P=0.0480).

5-year DM 23.0% vs. 30.4% (HR: 0.73, P=0.011).

5-year OS 81.7% vs. 80.2% (NS).

Conclusions:

The EXP treatment was associated with an increased risk of LRR, whereas the reduction in disease-related treatment failure and distant metastases remained after 5 years. Further refinement of the TNT in rectal cancer is mandated.

Comment: The failure timeline is **DELAYED +** ↑ with the EXP arm (vs. Std arm).

PROSPECT **Non-inferiority "TNT is SoC, but can we just use FOLFOX without RT?"**

←R→ 1194 patients cT2 node-positive, cT3 node-negative, or cT3 node-positive + candidates for sphincter-sparing surgery.

15% were ≤5 cm anal verge.

| 1. FOLFOX no RT | 2. TNT |.

TNT = 50.4 Gy in 28 fractions with concurrent 5-FU or CAPE.

FOLFOX = FOLFOX x 6C → if Primary Tumor Response ↓ < 20% = additional neoadjuvant CRT (9%).

→ if Primary Tumor Response ↑ > 20% = Straight to TME.

The proportion of participants with clinical node-positive tumors at assignment was 60.3% in the experimental group and 63.5% in the control group.

1^{o} DFS.

Outcomes	FOLFOX with selective 5-FU CRT (585 patients)	5-FU CRT, (543 patients)
5-year disease-free survival, % (90.2% CI)	80.8 [77.9, 83.7]	78.6 [75.4, 81.8]
	HR 0.92 [0.74, 1.14] stratified noninferiority *P* = .0051	
5-year overall survival, % (95% CI)	89.5 [87.0, 92.2]	90.2 ([87.6, 92.9]
	HR 1.04 [0.74, 1.44]	
5-year local recurrence-free survival, % (95% CI)	9 events	7 events
	98.2 [97.1, 99.4]	98.4 [97.3, 99.6]
	HR 1.18 [0.44, 3.16]	
Surgical and pathological endpoints		
Number completing surgery	535	510
Complete (R0) rectal resection	98.9%	97.1%
Pathologic complete response	21.9%	24.3%
Low anterior resection rate	97.6%	98.0%
Positive radial margin	1.2%	1.5%

Schrag, NEJM 2023 **58 months**

5-year DFS FOLFOX 80.8% vs. TNT 78.6%.

5-year LR ~1.6-1.8% both.

The groups were similar with respect to overall survival (hazard ratio for death, 1.04; 95% CI, 0.74 to 1.44) and local recurrence (hazard ratio, 1.18; 95% CI, 0.44 to 3.16). In the FOLFOX group, 53 patients (9.1%) received preoperative chemoradiotherapy and 8 (1.4%) received postoperative chemoradiotherapy.

Preop side effect ≥ G3 FOLFOX 41% vs. TNT 22.8%.

Postop side effect ≥ G3 FOLFOX 25.6% vs. TNT 39.0%.

CONCLUSIONS In patients with locally advanced rectal cancer who were eligible for sphincter-sparing surgery, preoperative FOLFOX was noninferior to preoperative chemoradiotherapy with respect to disease-free survival.

NOTE: "Patients with very high–risk tumors that are touching on the pelvic wall—those patients need radiation." ← not included in study.

Chinese FOWARC Trial **1:1:1**

Purpose: In the multicenter, open-label, phase III FOWARC trial, modified infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus radiotherapy resulted in a higher pathologic complete response rate than fluorouracil plus radiotherapy in Chinese patients with locally advanced rectal cancer. Here, we report the final results.

←R→ 495 patients 18 to 75 years stage II/III rectal cancer | 1. 5c IV 5-FU + RT → surgery → 7c IV 5-FU |
| 2. mFOLFOX + RT → surgery → mFOLFOX |
| 3. 4-6c mFOLFOX → surgery → 6-8c mFOLFOX | **± "add. of RT before or after surgery at physician's discretion"**

IV 5-FU = leucovorin 400 mg/m2, fluorouracil 400 mg/m2, and fluorouracil 2.4 g/m2 over 48 hours
RT = 46.0 to 50.4 Gy delivered in 23 to 25 fractions during cycles 2 to 4
IV Ox = IV oxaliplatin 85 mg/m2 on day 1 of each cycle (mFOLFOX6)
1^{O} 3-year DFS.

TABLE 1. Baseline Demographic and Clinical Characteristics (intention-to-treat population)

Characteristic	Fluorouracil Plus Radiotherapy No. (%)	mFOLFOX6 Plus Radiotherapy No. (%)	mFOLFOX6 No. (%)
No. of patients	165	165	165
Mean age, years (SD)	54.0 (11.9)	52.2 (11.8)	54.1 (12.1)
Male sex	103 (62.4)	114 (69.1)	108 (65.5)
Clinical T category			
cT4b	14 (8.5)	14 (8.5)	5 (3.0)
cT4a	43 (26.1)	42 (25.5)	45 (27.3)
cT3	100 (60.6)	106 (64.2)	114 (69.1)
cT2	8 (4.8)	3 (1.8)	1 (0.6)
Clinical N category			
cN2a	36 (21.8)	33 (20.0)	35 (21.2)
cN2b	8 (4.8)	14 (8.5)	8 (4.8)
cN1	84 (50.9)	88 (53.3)	76 (46.1)
Clinical stage III	128 (77.6)	135 (81.8)	119 (72.1)
Mean tumor length, cm (SD)	4.3 (1.8)	4.3 (1.5)	4.3 (1.6)
Distance from anal verge, cm			
> 10	5 (3.0)	7 (4.2)	9 (5.5)
5-10	70 (42.4)	75 (45.5)	86 (52.1)
< 5	90 (54.5)	83 (50.3)	70 (42.4)
Mean distance, cm (SD)	5.3 (2.3)	5.4 (2.5)	6.0 (2.6)
Mesorectal fascia involvement	32 of 101 (31.7)	38 of 107 (35.5)	33 of 105 (31.4)

Zhang, ASCO 2023 **9.5 years**
10-year DFS 55.5% vs. 63.0% vs. 62.8% (NS)
10-year OS 66.2% vs. 73.2% vs. 73.0% (NS)
Conclusions: With long-term follow up, no significant difference in was found in survival outcome between mFOLFOX6, with and without radiation. Comparing with fluorouracil plus radiation, mFOLFOX6 plus radiation also failed to improve long-term survival

Deng, JCO 2019 45.2 months.
3-year DFS 72.9%, 77.2%, and 73.5% (NS)
3-year LR (R0/1 resection) 8.0%, 7.0%, and 8.3% (P = .873 by the log-rank test)
3-year OS 91.3%, 89.1%, and 90.7% (P = .971 by log-rank test), respectively.

Conclusion: mFOLFOX6, with or without radiation, did not significantly improve 3-year DFS versus fluorouracil with radiation in patients with locally advanced rectal cancer. No significant difference in outcomes was found between mFOLFOX6 without radiotherapy and fluorouracil with radiotherapy, which requires additional investigation of the role of radiotherapy in these regimens.

TABLE 2. Anal Function Findings in Patients With No Stoma at Last Follow-Up

Finding	Fluorouracil Plus Radiotherapy	mFOLFOX Plus Radiotherapy	mFOLFOX	*P**
No. of patients	61	70	89	
Stool frequency, per day				.000
0-3	24 (39.3)	26 (37.1)	64 (71.9)	
4-5	17 (27.9)	20 (58.6)	10 (11.2)	
6-9	12 (19.7)	21 (30.0)	14 (15.7)	
≥ 10	8 (13.1)	3 (4.3)	1 (1.1)	
Wexner score > 8	25 (41)	25 (35.7)	16 (18)	.005
Solid incontinence	18 (29.5)	14 (20.0)	6 (6.7)	.001
Liquid incontinence	20 (32.8)	11 (15.7)	7 (7.9)	.000
Gas incontinence	10 (16.4)	5 (7.1)	2 (2.2)	.006
Day incontinence	24 (39.3)	24 (34.3)	20 (22.5)	.068
Night incontinence	20 (32.8)	19 (27.1)	8 (9.0)	.001
Anal blood loss	2 (3.3)	6 (8.6)	3 (3.4)	.252
Use of pads	19 (31.1)	18 (25.7)	8 (9.0)	.002

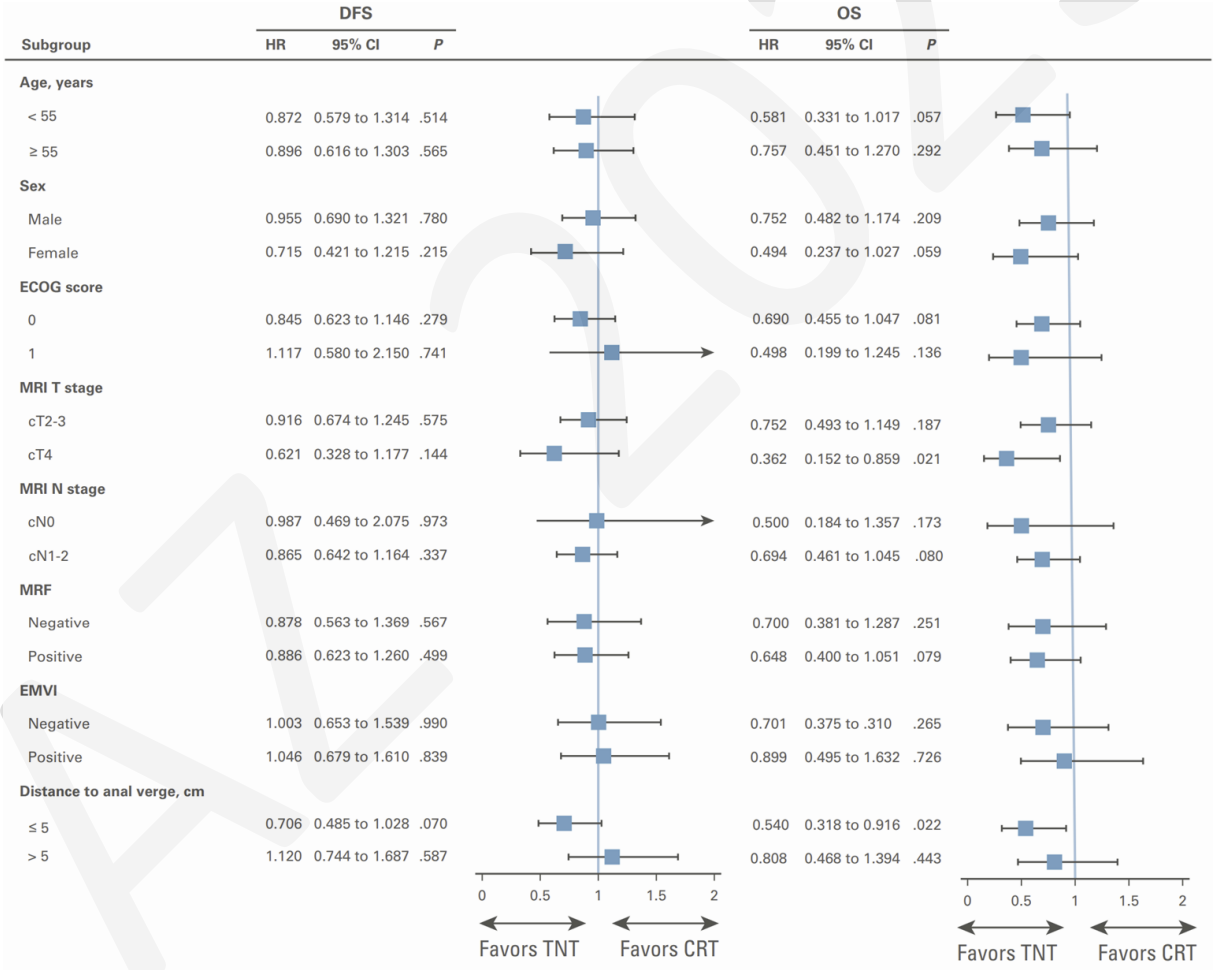
STELLAR non-inferiority Trial

←R→ 599 patients distal or middle 1/3 rectal cancer cT3-4 and/or LN+ | 1. SC-RT 5x5 over 1 weeks → 4x C | 2. CRT 50 Gy over 5 weeks + Cape |.
All patients received TME 6-8 weeks afterwards → 2x CAPOX (if arm 1) or 6x CAPOX (if arm 2).
1^{O} 3-year DFS.

TABLE A2. Recurrences and DM of 599 ITT patients

Recurrence and Distant Metastasis	TNT Group, No./Total No. (%)	CRT Group, No./Total No. (%)
Total No. of patients (ITT)	302	297
Deaths	47/302 (15.6)	63/297 (21.2)
DM	65/302 (21.5)	67/297 (22.6)
LRR in entire cohort	20/302 (6.6)	23/297 (7.7)
LRR only	13/302 (4.3)	15/297 (5.0)
LRR with DM	7/302 (2.3)	8/297 (2.7)
LRR in special situation		
Unresected persistent primary tumors	4/28 (14.3)	5/50 (10.0)
R1 resections	6/20 (30.0)	4/28 (14.3)
R0 resections and CRM (–)	8/215 (3.7)	13/202 (6.4)
cCR	2/28 (7.1)	1/10 (10.0)

Jin, JCO 2022.
3-year DFS 64.5% vs. 62.3% (HR 0.883; P < .001 for noninferiority).
3-year MFS 77.1% vs. 75.3% (NS)
3-year OS 86.5% vs. 75.1%; P = .033.
cCR 11.1% vs. 4.4% R0 resection both arms similar.
pCR 50% vs. 48.3%.
About 25% of ALL patients on both arms did NOT receive adjuvant therapy (23% vs. 26%).
NOTE: % completing adjuvant therapy (60% vs. 48.3%).
Acute grade III-V toxicities 26.5% vs. 12.6% (P < .001).
Conclusion: Short-term radiotherapy with preoperative chemotherapy followed by surgery was efficacious with acceptable toxicity and could be used as an alternative to CRT for locally advanced rectal cancer.



EMVI =extramural vascular venous invasion
MRF = mesorectal fascia.

OPRA Phase II **TNT Order**
←R→ 324 Stage II/III rectal AC | 1. C → CRT | 2. CRT → C |. 8-12 month after TNT reassess. If pCR → WW. If < pCR → TME.
C = 4 months of infusional fluorouracil-leucovorin-oxaliplatin or capecitabine-oxaliplatin
CRT = 5,000 to 5,600 cGy RT + either IV 5-FU or Cape.
1^{O} DFS.

Verheij, ASCO 2023. 5-year Follow-up

	3-year, %	5-year, %	3-year, %	5-year, %	P
DFS	77 (70-84)	72 (65-80)	76 (70-83)	71 (63-78)	0.60
TME-free survival	41 (34-50)	39 (32-48)	55 (48-63)	54 (47-63)	0.01
LRFS	95 (91-99)	94 (90-98)	94 (90-98)	90 (85-95)	0.27
DMFS	83 (78-90)	82 (75-89)	83 (77-89)	79 (72-86)	0.66
OS	95 (92-99)	88 (82-94)	94 (91-98)	88 (82-94)	0.73

Regrowth in WW population: 80 of 225 (36%). Regrowth 94% occurred within 2 years and 99% occurred within 3 years.
Conclusion: In patients with rectal cancer treated with TNT and WW, the majority of tumor regrowths occur in the first 2 years, and regrowth after 3 years is vanishingly rare. Salvage TME for tumor regrowth during WW appears to offer similar outcome to immediate TME after incomplete response to TNT. Distant metastases remain the most frequent cause of treatment failure, with similar rates in the two treatment groups.

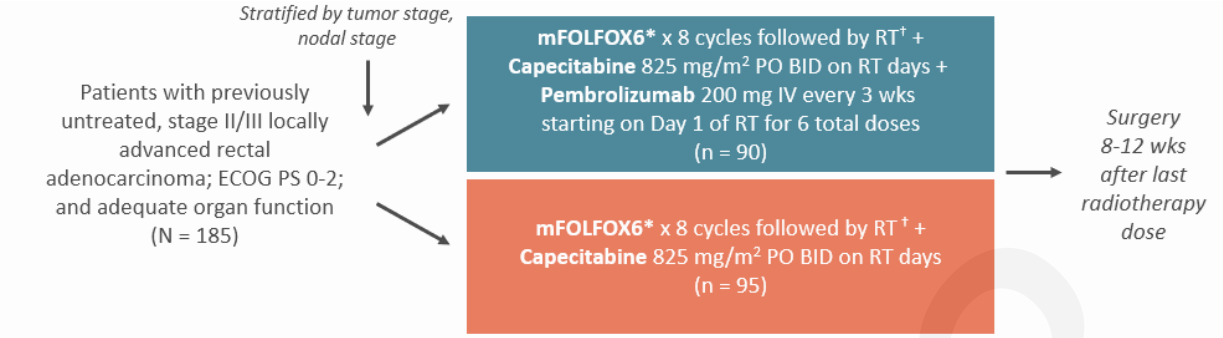
Garcia-Aguilar, JCO 2022 **3-year Follow-up**
3-year DFS 76% both arms. In line with the 3-year DFS rate (75%) observed historically.
Total 74% of patients went on to WW without initial surgery. Tumor regrow 40% vs. **27%**.
3-year TME-FS 41% vs. **53%**.

3-year LRFS, DMFS, OS are all NS.
Patients who underwent TME after restaging and patients who underwent TME after regrowth had similar DFS rates.
CONCLUSION 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.
Note: You should do CRT first.

Polish II **TNT 5x5 for "Locally Advanced"**
←R→ 515 patients cT4 or fixed cT3 | 1. SC-RT 5x5 → 3c FOLFOX 4 | 2. CRT 50.4 Gy + 5-FU, Leucovorin, Oxaliplatin |.
NOTE: The protocol was amended in 2012 to allow oxaliplatin to be then foregone in both groups.
1^{O} R0 resection rates.

Bujko, Ann Oncol 2016
Preoperative treatment acute toxicity 75% vs. 83% (SS). Grade III-IV 23% versus 21% and toxic deaths 1% versus 3%.
R0 resection rates 77% vs. 71% (SS). pCR 16% vs. 12%, (NS).
3-year OS 73% vs. 65%, p=0.046. 3-year DFS 53% vs. 52%, (NS).
3-year LF 22% vs. 21% (NS) 3-year DM 30% vs. 27% (NS).
Postoperative and late complications rates in group A and group B were, respectively, 29% versus 25%, P = 0.18, and 20% versus 22%, P = 0.54.
Conclusions: No differences were observed in local efficacy between 5 × 5 Gy with consolidation chemotherapy and long-course chemoradiation. Nevertheless, an improved overall survival and lower acute toxicity favours the 5 × 5 Gy schedule with consolidation chemotherapy.

Cisel, Ann Oncol 2019 The median follow-up was 7.0 years.
8-year OS 49% in both groups. 8-year DFS 43% vs. 41% (NS).
8-year LF 35% vs. 32% (NS) 8-year DM 36% vs. 34% (NS).
Rate of late complications was similar (P = 0.66), grade 3+ being 11% versus 9% in the short-course/CCT group versus the chemoradiation group, respectively.
Conclusion: The superiority of preoperative short-course/CCT over chemoradiation was not demonstrated.



*Modified FOLFOX regimen: oxaliplatin 85 mg/m² IV Day 1 + leucovorin 400 mg/m² IV bolus followed by 5-FU 2400 mg/m² continuous infusion over 46 hours every 2 weeks x 8 cycles.
†RT began 3-4 wks after last dose of mFOLFOX6: 4500 cGy in 25 fractions over 5 wks + 540 cGy boost in 3 fractions.

Rahma. ASCO GI 2021. Abstr 8.
1^{O} Endpoint = neoadjuvant rectal score.
Only 46% of patients completed all 6 pembrolizumab doses
26% completed 5 doses, 26% completed 1-4 doses
NS Δ in exposure to C or RT between study arms (mFOLFOX: 84.4% pembrolizumab, 83.2% control; CRT 83.3% pembrolizumab, 74.7% control)

	Pembrolizumab	Control	*P* Value
Mean NAR score (95% CI)	11.53 (8.54-14.51)	14.08 (10.74-17.43)	.26
pCR, %	31.9	29.4	.75
cCR, %	13.9	13.6	.95
Margin-negative resection %	94.0	89.4	.36
Sphincter preservation %	59.4	71.0	.15

Conclusions: Adding pembrolizumab to CRT after FOLFOX did not improve neoadjuvant rectal score vs post-FOLFOX CRT alone in patients with locally advanced rectal cancer.

Other Studies

OCUM Trial

1099 patients rectal cancer (cT2-4, any cN, cM0) were classified according to the minimal distance between MESORECTAL FASCIAL (mrMRF) vs. the tumor, suspicious lymph nodes or tumor deposits.
If distance >1 mm → up-front TME (low-risk). If distance ≤1 mm and/or cT4 and cT3 tumors in the lower rectal third → nCRT → TME (high Risk)
80% treated according to protocol. 60% had upfront TME. 40% had nCRT → surgery.
Adjuvant Therapy Usage (mostly chemo) = LR 35.7% vs. HR 77%.
1^{O} primary end point was 5-year LR rate.

Ruppert, JCO 2023

5-year LR 4.1% if treated per protocol 5-year LR 2.9% after up-front surgery 5.7% after nCRT followed by surgery.
pCR HR group = 12%

5-year DM 15.9% after up-front surgery 30.5% after nCRT followed by surgery.

In a subgroup analysis **of 570 patients with lower and middle rectal third** cII and cIII tumors, 257 (45.1%) were at low-risk.
5-year LR rate in this group was 3.8%.
5-year LR HR (involved mrMRF and/or cT4) = 5.9%. 5-year DM HR 34.5%.
CONCLUSION
The findings support the avoidance of nCRT in low-risk patients and suggest that in high-risk patients, neoadjuvant therapy should be intensified to improve prognosis.

German TNT CAO/ARO/AIO-12

←R→ 311 patients cT3-4 and/or LN+ | 1. 3c C → CRT | 2. CRT → C |. TME scheduled 123 days after the START of TNT.
C = FOLFOX RT = 5040 cGy.

Fokas, JAMA Oncol. 2022. FU 43 months.
3-year DFS 73% in both groups. 3-year CI LRR 6% vs 5%. 3-year DM 18% vs 16%.
3-year Chronic Toxicity G3-4 11.8% vs. 9.9%.
The GHS/QoL score decreased after total mesorectal excision but returned to pretreatment levels 1 year after randomization with no difference between the groups. Stool incontinence deteriorated 1 year after randomization in both groups and only improved slightly at 3 years, but never reached baseline levels.
Conclusions and relevance: This secondary analysis of a randomized clinical trial showed that CRT followed by chemotherapy resulted in higher pathological complete response without compromising disease-free survival, toxicity, QoL, or stool incontinence and is thus proposed as the preferred total neoadjuvant therapy sequence if organ preservation is a priority.

Fokas, JCO 2019.
CRT-related G 3 or 4 toxicity 37% v 27%. CRT compliance was higher was CRT 80 → 90%.
The longer interval between completion of CRT and surgery in group B (median 90 v 45 days in group A) did not increase surgical morbidity.
pCR 17% vs. 25%.
Thus, only group B (P < .001), but not group A (P = .210), fulfilled the predefined statistical hypothesis.
CONCLUSION Up-front CRT followed by chemotherapy resulted in better compliance with CRT but worse compliance with chemotherapy compared with group A. Long-term follow-up will assess whether improved pCR in group B translates to better oncologic outcome.

Diefenhardt, Radiother Oncol 2022 Secondary Analysis
Patients from both AIO-04 and AIO-12

RR	607 patients treated with	AIO-04	(Conventional Trimodality) 5-FU/Ox neoadjuvant CRT → surg → adjuvant CT
	306 patients treated with	AIO-12	TNT.

pCR 25.3% (TNT : CRT → consolidation CT) vs. 17.3% (AIO-04 EXP), P = 0.04.
Post-surgical complications were less common in the CAO/ARO/AIO-12 trial.
Median follow-up of 46 months, clinical outcome did not differ significantly in the overall cohort, in any subgroup or after propensity score matching. In multivariate analysis, disease-free survival (DFS) was similar between the experimental arm of the CAO/ARO/AIO-04 trial and treatments arms of the CAO/ARO/AIO-12 trial (vs arm A: HR 0.92 [95 % CI 0.62–1.37], P = 0.69; vs arm B: HR 1.06 [95 % CI 0.72–1.58], P = 0.76).
Interpretation
Notwithstanding the limitations of intertrial comparison, TNT did not improve long term oncological outcome in our study compared to the intensified neoadjuvant CRT and adjuvant CT treatment in the CAO/ARO/AIO-04 trial. Improved response rates after TNT offers an attractive option to explore organ preservation in selective patients with locally advanced rectal cancer.

Combined Phase II.
Background: Fluorouracil-based neoadjuvant chemoradiotherapy (CRT) is still the standard of treatment for locally advanced rectal cancer, but it delays administration of systemic chemotherapy, leading to high incidence of distant metastases.
180 patients 2 prospective database.
TNT = mFOLFOX6 x1c → CRT (mFOLFOX6 x 3c) → mFOLFOX x 4c → TME.
CRT = CRT (five 2-week cycles of inf 5-FU + RT).

Zhang, JCO 2018.
TOTAL pCR 21.7%. pCR rate of TNT group and CRT group was 34.2% vs. 15.2%, respectively ($p < 0.005$).
Tumor downstaging rate was 60.8% vs. 35.4%, respectively ($p = 0.001$).
Grade3/4 neutropenia was the more common in TNT group, which was 30.4% vs. 8.9% ($P = 0.0007$).
Grade 3/4 Leukopenia (21.5% vs. 12.7%, $p = 0.14$) and thrombocytopenia (5.1% vs. 11.4%, $p = 0.15$) was similar between the two groups.
Conclusions: TNT showed higher pCR rate and tumor downstaging rate than that of CRT, which was a promising strategy for improving outcome of rectal cancer, although the grade 3-4 adverse events were a little bit higher in TNT group. But this finding requires further analysis from long-term survival data. The phase III study comparing TNT with CRT is ongoing.

MSK Total Neoadjuvant RR.
RR 628 patients LARC (T3/4 or node-positive) were identified.
320 traditional CRT → surgery → planned adjuvant C. 308 received TNT (Induction 5-FU/Ox → CRT).

Cercek, JAMA Oncol 2018.
RESULTS: Age 56.7 years.
Patients in the TNT cohort received greater percentages of the planned oxaliplatin and fluorouracil prescribed dose than those in the chemoRT with planned adjuvant chemotherapy cohort.
Rate of response (CR+PR) in those who underwent surgery and sustained clinical CR (cCR) for at least 12 months posttreatment in those who did not undergo surgery = 21% traditional vs. TNT 36%.

CONCLUSIONS AND RELEVANCE: Our findings provide additional support for the National Comprehensive Cancer Network (NCCN) guidelines that categorize TNT as a viable treatment strategy for rectal cancer. Our data suggest that TNT facilitates delivery of planned systemic therapy. Long-term follow-up will determine if this finding translates into improved survival. In addition, given its high CR rate, TNT may facilitate nonoperative treatment strategies aimed at organ preservation.

Treatment Group	All Patients, No.	All Patients, Sustained cCR, No. (%)	Surgery Within 12 Months, No.	Surgery Within 12 Months, pCR, No. (%)	pCR and Sustained cCR at 12 Months, No. (%)
ChemoRT with planned Adj. Chemo					
Stage II	94	9 (9.6)	82	14 (17.1)	23 (24.5)
Stage III	226	10 (4.4)	214	35 (16.4)	45 (19.9)
Total	320	19 (5.9)	296	49 (16.6)	68 (21.3)
TNT					
Stage II	43	23 (53.5)	20	0	23 (53.5)
Stage III	265	44 (16.6)	215	43 (20.0)	87 (32.8)
Total	308	67 (21.8)	235	43 (18.3)	110 (35.7)

TNT w/ SC-RT 5x5 Cost Effectiveness vs. LC-CRT
All patients either received SC-RT 5 Gy x 5 fractions or LC-CRT all → TME.
Data collected from 11/15/2020 – 4/25/2021.
Effectiveness was defined as quality-adjusted life-years (QALYs).

Chin, JAMA Network Open 2022.
Both costs and QALYs were discounted at 3% annually. Willingness-to-pay threshold was set at $50 000/QALY.
5-year total cost / QALY $41,355 / 2.21 vs.$54,827 / 2.12.
The net monetary benefit was $69 300 for SCRT-TNT and $51 060 for LCCRT.
Sensitivity analyses using willingness to pay at $100 000/QALY and $150 000/QALY demonstrated the same conclusion.
Conclusions and Relevance These findings suggest that SCRT-TNT followed by TME incurs lower cost and improved QALYs compared with conventional LCCRT followed by TME and adjuvant chemotherapy. These data offer further rationale to support SCRT-TNT as a novel cost-saving treatment paradigm in the management of locally advanced rectal cancer.

Non-OPERATIVE Regimens

- There will always be a subset of patients who do well with surgery alone, as suggested by the MRI vs. NICE Criteria trial.
- How should we approach follow-up and risk evaluation for these patient with no surgery? → Perhaps Immunoscore.

MRI vs. NICE Criteria (Re: Surg Alone)
Retrospective 378 patients 66-month FU. All undergoing 1^{O} resectional surgery for rectal cancer, without preoperative radiotherapy.
MRI High-Risk n=248 (66%) MRI-detected Extramural venous invasion, tumour deposits, and circumferential resection margin involvement.
NICE High-Risk n=121 (32%) MRI-detected T3+ or MRI-detected N+ status.

Lord, Lancet 2022.
LR 22 (6%) of 378 patients, Distant Failures 68 (18%) of 378 patients.
5-year DFS 76% NICE HR vs. 87% NICE LR (HR 1·91, SS)
66% MRI HR vs. 88% MRI LR (HR 3.01, SS)
5-year OS 80% NICE HR vs. 88% NICE LR (NS, trend p=0.077).
71% MRI HR vs. 89% MRI LR (HR 2.59, SS).
MVA, NICE risk assessment NS either DFS or OS.
MVA, MRI risk assessment predicted DFS (HR 2·74, SS) and OS (HR 2·44, SS).
Note: 139 NICE high-risk patients were defined as MRI low-risk based had similar DFS as 118 NICE low-risk patients
Δ, 37% (139 of 378) of patients in this study cohort would have been overtreated with NICE 2020 guidelines.
Of the 130 patients defined as low-risk by NICE guidelines, 12 (9.2%) were defined as high-risk on MRI risk stratification and would have potentially been missed for treatment.
Interpretation
Compared to previous guidelines, implementation of the 2020 NICE guidelines will result in significantly more patients receiving preoperative radiotherapy. High-quality MRI selects patients with good outcomes (particularly low local recurrence) without radiotherapy, with little margin for improvement. Overuse of radiotherapy could occur with this unselective approach. The high-risk group, with the most chance of benefiting from preoperative radiotherapy, is not well selected on the basis of NICE 2020 criteria and is better identified with proven MRI prognostic factors (extramural venous invasion, tumour deposits, and circumferential resection margin).

ONGOING: NOM-ERA (Non-Operative Management Early Risk Assessment)
https://clinicaltrials.gov/ct2/show/NCT03904043

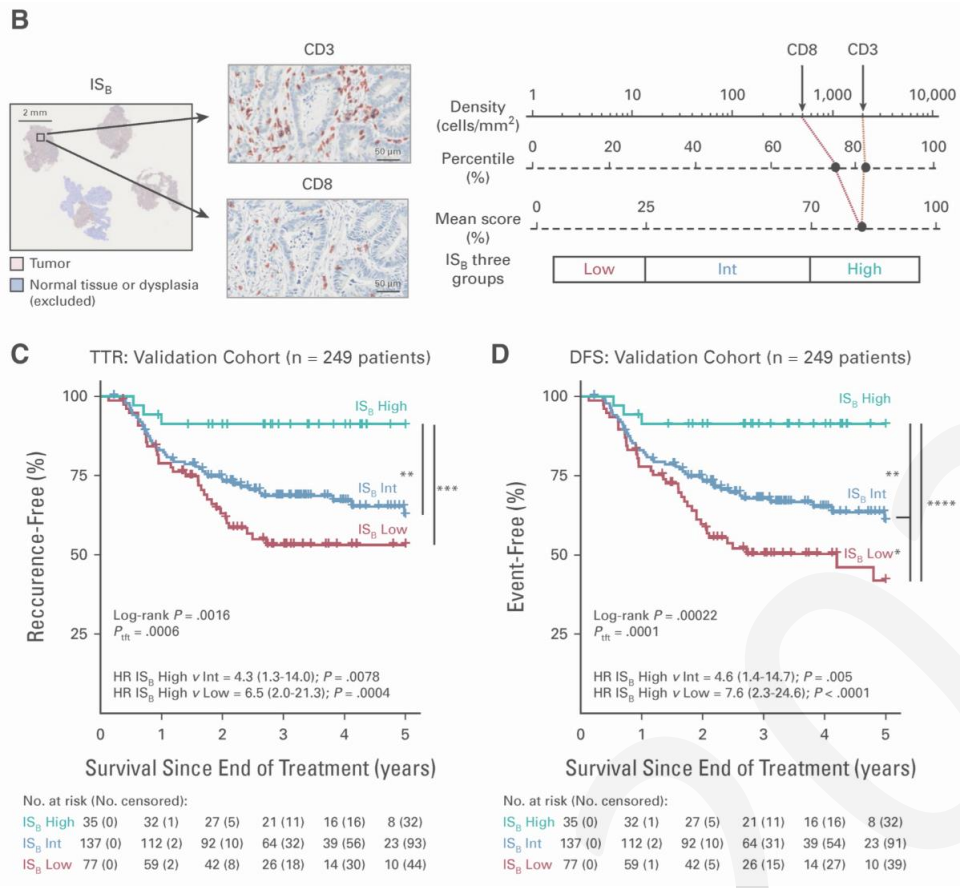
NORMAL-R **N**on-**O**perative **R**adiation **M**anagement of **A**denocarcinoma of the **L**ower **R**ectum
19 patients 5 Gy x 5 → FOLFOX ×8 or CAPOX ×5 cycles. If cCR → nonoperative surveillance.
21% stage I, 32% stage II, and 47% stage III disease.
1^{O} cCR 1 year.

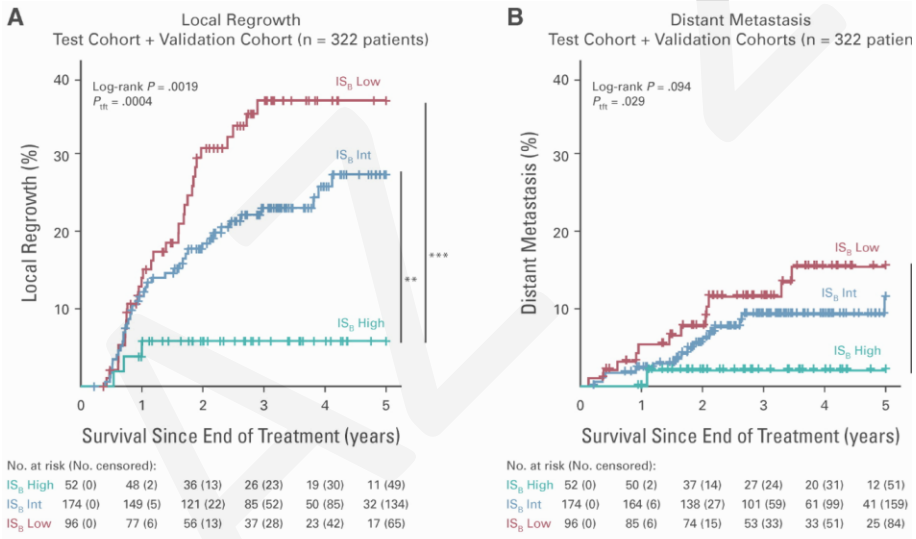
Kim, Clin Colorectal Cancer 2021. Median FU 27.7 months.
1-year cCR rate 68%. 18 of 19 patients are alive without evidence of disease.
Patients with cCR versus without had ↑ 2-year DFS (93% vs 67%; P = .006), ↑ DMFS (100% vs 67%; P = .03), and ↑ OS (100% vs 67%; P = .03).
cCR influenced by Involved versus uninvolved circumferential resection margin on MRI (40% vs 93%; P = .04).
Anorectal function by Functional Assessment of Cancer Therapy-Colorectal cancer score at 1 year was not different than baseline.
There were no severe late effects.
Conclusions: Treatment with SCRT and chemotherapy resulted in high cCR rate, intact anorectal function, and no severe late effects.
NCT02641691.

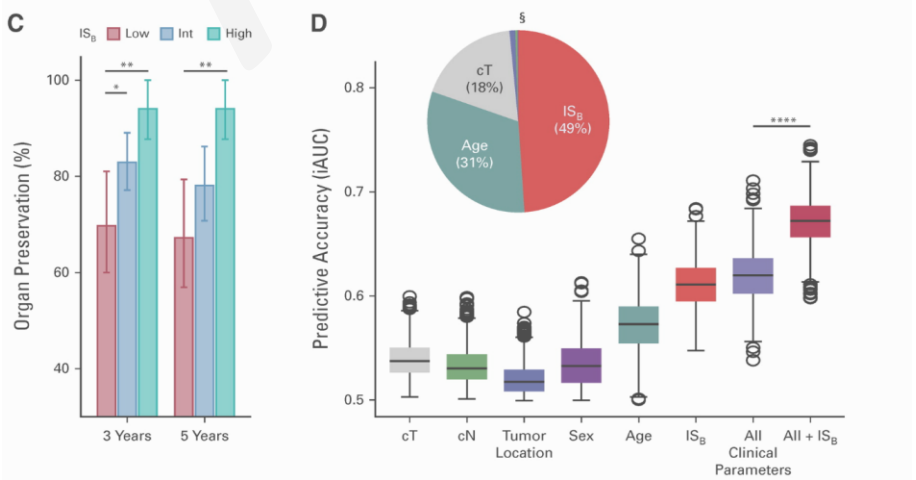
Habr-Gama, Ann Surg 2004.
Retrospective. 265 patients cT2-4, 24% LN+. All treated with neoadjuvant 5040 cGy with **FOLF**. If incomplete CR → radical surgical resection.
Therefore, we are comparing cCR vs. pT0 (those who had incomplete CR and was actually pT0 on surgery).
cCR was 71/265 (26.8%). Additional 8.3% were pT0 on resection.
5-year OS was 100% (if cCR), and 88% (if pT0). 5-year DFS was 92% vs. 83%.

Habr-Gama, Seminars Radiation Oncology 2011.
Retrospective. 173 patients ≤ 7cm from anal verge. All received neoadjuvant 5040 – 5400 cGy with concurrent 5-FU (1st and last 3 days of RT).
Staging initial studies: stage I disease (cT2N0M0) in 16% stage II (cT3-4N0M0) in 63%, stage III (cTxN1-2M0) in 21%
Results: cCR = 67 (39%) and did NOT undergo immediate radical surgery. Of cCR, 9 (13%) had excisional biopsy of residual scar as *diagnostic* procedure.
Remaining patients 58 (87%) managed WITHOUT any surgical procedure.
5-year OS 96% and DFS 72%.
5-year all recurrences 15 (21%). **Of these, 8 (11%) local endorectal**, 7 (10%) distant none (0%) extrarectal pelvic recurrence.
Of the 8 local recurrences, 7 salvaged successfully.

Immunoscore Trial







Background: No biomarker capable of improving selection and monitoring of patients with rectal cancer managed by watch-and-wait (W&W) strategy is currently available. Prognostic performance of the **Immunoscore biopsy (ISB)** was recently suggested in a preliminary study.
International validation study → 249 patients with cCR managed by W&W strategy.
Intratumoral CD3+ and CD8+ T cells were quantified on pretreatment rectal biopsies by digital pathology and converted to **ISB**.
1^{O} time to recurrence (TTR); the time from the end of neoadjuvant treatment to the date of local regrowth or distant metastasis).

El Sissy, JCO 2023
5-year RFS **ISB ↑** 91.3%, **ISB int** 62.5%, **ISB ↓** 53.1% (HR ↓ vs ↑, 6.51; P = .0004).

ISB was also significantly associated with disease-free survival (log-rank P = .0002), and predicted both local regrowth and distant metastasis.

MVA, ISB was independent of patient age, sex, tumor location, cT stage (T, primary tumor; c, clinical), cN stage (N, regional lymph node; c, clinical), **and was the strongest predictor for TTR** (HR [ISB High v Low], 6.93; 95% CI, 2.08 to 23.15; P = .0017).

The addition of ISB to a clinical-based model significantly improved the prediction of recurrence.

Finally, B-cell proliferation and memory in draining lymph nodes was evidenced in the draining lymph nodes of patients with cCR.

CONCLUSION
The ISB is validated as a biomarker to predict both local regrowth and distant metastasis, with a gradual scaling of the risk of pejorative outcome.

Applet, Lancet 2015.
Retrospective. 55 with T2 or T3, N0–N1 AC ≤ 6 cm from anal verge. Neoadjuvant CRT.
RT: 60 Gy to GTV 50 Gy in 30 fx to elective nodes 5 Gy endorectal boost
C: Oral tegafur-uracil (similar class to capecitabine…aka 5-FU prodrug) 300 mg/m^2.
If cCR (complete clinical tumour regression, negative tumour site biopsies, and no nodal or distant metastases on CT and MRI 6 weeks after TX) → **Obs**.
1^O local tumour recurrence 1 year after allocation to the observation group.
Results:
cCR = 40/51 (78%).
Side effects: GI G3 diarrhea 8%.
Sphincter function "excellent" 72% and 69% at 2 years with no fecal incontinence.
Interpretation
High-dose chemoradiotherapy and watchful waiting might be a safe alternative to abdominoperineal resection for patients with distal rectal cancer.

OnCoRe project.
Propensity Matched Cohort Study of neoadjuvant CRT (45 Gy in 25 fx + 5-FU based chemotherapy).
If cCR then → watch-and-wait approach. If incomplete response → surgical resection if eligible.
Of 259 patients included, 31 had cCR. They also added another 98 patients via national registry for total of 129 patients managed by wait and watch.

Renehan, Lancet 2016.
LR = 44/129 (34%). DFS 88% watch and wait vs. 78% immediate surgery (p=0.04) 3-year OS 96% vs. 87%, (p = 0.02).
3-year colostomy-free survival 74% vs. 47%, (p<0·0001), with a 26% absolute Δ in patients who avoided permanent colostomy at 3 years.
Note: the paper states that there is "no difference" in DFS and OS despite p < 0.05.
INTERPRETATION: A substantial proportion of patients with rectal cancer managed by watch and wait avoided major surgery and averted permanent colostomy without loss of oncological safety at 3 years. These findings should inform decision making at the outset of chemoradiotherapy.

QoL WW Approach Study
Importance A watch-and-wait approach for patients with rectal cancer and a clinical complete response after neoadjuvant chemoradiotherapy or radiotherapy is associated with better quality of life and functional outcome. Nevertheless, prospective data on both parameters are scarce.
Objective To prospectively evaluate quality of life and functional outcome, including bowel, urinary, and sexual function, of patients following a watch-and-wait approach.
RR 278 patients rectal cancer + cCR **or** near-CR after NAC or RT (included in 2 prospective cohort studies)
Patients were observed by a watch-and-wait approach.
Additional local excision or total mesorectal excision was performed for residual disease or regrowth.
67% female.

Custers, JAMA Surgery 2023
In the first 24 months, 221 patients (80%) were observed by a watch-and-wait approach without requiring surgery
→ 18 patients (6%) underwent additional local excision
→ 39 patients (14%) underwent total mesorectal excision.
In general, patients observed by a watch-and-wait approach reported good quality of life, with limited variation over time.
Major bowel dysfunction @ 3 months 25.3%, 12 months 24.0%, 24 months 24.9%.
Erectile Dysfunction 24 months 31.8% males.
Patients who underwent local excision reported more major bowel dysfunction (10 of 18 patients [55.6%]) compared with those without additional surgery. Quality-of-life scores, however, were comparable. After total mesorectal excision, patients scored significantly worse on several quality-of-life subscales.

Conclusions and Relevance Results of this study suggest that patients with rectal cancer who were observed by a watch-and-wait approach had good quality of life, with some patients reporting bowel and sexual dysfunction. Quality of life and functional outcome deteriorated when patients required surgery. These data will be useful in daily care to counsel patients on what to expect from a watch-and-wait approach.

Historical Studies

Surgery ± Adjuvant Tx

- Local recurrence after surgery alone for Dukes T3-T4 or N+ is >50% and can be symptomatically devastating.
- Most adjuvant trials were done in patients with Dukes B and C (T3-4N0 or N+)
- Outcomes with adjuvant chemotherapy alone have been disappointing.
- 8 prospective randomized trials evaluated surgery alone vs. post-op RT.
  - RT alone improves local control, but not survival.
- Combined RT + 5-FU improved local control, distant control, as well as survival in two randomized trials.
  - RT plus continued infusion of 5-FU ↑ survival over bolus 5-FU.

- **Advantages for adjuvant therapy**: Pathologic staging available.
- **Disadvantages for adjuvant therapy**: Increased small bowel in treatment filed, potentially hypoxic post-surgical bed, if APR → RT scar.
- **Modern TNT** overrides the adjuvant treatment paradigm (surg → adj Tx) for locally advanced rectal cancers.

Trial	Patients	Randomization/Adjuvant Tx	Outcome
NSABP R-01 (JNCI, 1988)	555 pts w/stage II-III treated by curative resection	1. Observation 2. Postop 8c 5-FU, CCNU, vincristine (MOF) 3. XRT alone (46-47 gy)	**Chemo improved DFS, OS.** **XRT ↓ LRR from 26% to 16% (p=0.06), no effect on DFS/OS**
NSABP R-02 (JNCI, 2000)	694 pts w/stage II-III treated with resection	1. Females -> LV **± RT** (50.4 gy) MOF not effective in females 2. Males -> 5c MOF vs 6c 5-FU/LV **± RT (50.4 gy)**	Addition of RT ↓ 5 yr LRR relapse from 13% to 8% (p=.02) No benefit of RT on DFS or OS
GITSG 7175 (NEJM, 1985-1986)	227 pts w/stage II-III with R0 resection	1. Observation 2. Bolus 5-FU amd M-CCNU 3. RT 40-48 gy **4. ChemoRT** (40-44 gy w/bolus 5-FU) → 5-FU/M-CCNU	Postop chemoRT ↑ OS to 55% vs 30% w/observation; ↓ LRR (25% vs 10%), distant (35% vs. 25%) , and any recurrence rate (55% vs. 33%) **Diff btw chemRT vs RT alone vs chemo alone NS**
Mayo-NCCTG 79-47-51 (NEJM, 1991)	204 pts with T3-4 or N+ treated with surgery and all received 1 cycle of 5-Fu and M-CCNU	1. RT alone (50.4 gy) **2. ChemoRT** (50.4 Gy) with 5-FU, followed by 2 more cycles of 5-FU/M-CCNU	ChemoRT ↓ LR (25% vs. 14%), DM (46% vs. 29%), and significantly increased OS (55% vs. 45%) vs RT alone Increased dose 50.4 vs 45 ↓ LR from 24% to 18% but did not improve recurrences overall.

Summary of this table:

NSABP R-01: Adj C ↑ DFS and OS. Adj RT ↑ LC benefit.		Can't just do obs. Need either C (OS!) or RT (LC!).
NSABP R-02: Adj CRT is better than adj C alone due to ↓ LR benefit.		Yea, C gives you OS benefit, but C+RT also gives you LR.
GITSIG:	Essentially R-01 + another CRT arm, which ↑ everything vs. **Obs.**	BUT the difference between CRT vs RT vs C alone NS.
Mayo:	Essentially R-02 REVERSED, which CRT ↑ everything vs. **RT alone**	When you increase dose from 45 Gy to **50.4** it has ↓ LR benefit! Therefore, German study chose 50.4 cGy.

Quirke, Lancet 2009. **Plane of surgery.**
Prospective study. Negative CRM and good surgical plane associated with low LR.
3-yr LR 6% vs 17% for negative vs positive resection margin. LR 4% (mesorectal plane), 7% (intramesorectal), and 13% (muscularis propria).
Pts with mesorectal excision who had pre-op RT had only a 1% LR.
Conclusion: plane of surgery is an important prognostic indicator for local recurrence. Short-course pre-op RT ↓ the rate of LR in all groups.

Pooled ←R→ Surgery and Adjuvant Tx RELAPSE STUDY

3,791 eligible patients enrolled onto North Central Cancer Treatment Group (NCCTG) 79-47-51, NCCTG 86-47-51, US Gastrointestinal Intergroup 0114, Five-year follow-up was available in 94% of surviving patients, and 8-year follow-up, in 62%.

Gunderson, JCO 2004

Different treatment strategies may be indicated for intermediate-risk versus moderately high- or high-risk patients based on differential survival rates and rates of relapse. Use of trimodality treatment for all patients with intermediate-risk lesions may be excessive, since S plus CT resulted in 5-year OS of approximately 85%; however, 5-year disease-free survival rates with S plus CT were 78% (T1-2/N1) and 69%(T3/N0), indicating room for improvement.

Table 1. Adjuvant Rectal Cancer Pooled Analysis: Patient Group and Treatment Method by Trial

Treatment Method	No. of Patients					
	NCCTG		Intergroup	NSABP		
	794751	864751	0114*	R01	R02	Total
Surgery	—	—	—	179	—	179
Surgery + radiation	99	—	—	182	—	281
Surgery + radiation + bolus chemotherapy†	101	331	—	—	347	779
Surgery + radiation + PVI chemotherapy	—	325	—	—	—	325
Surgery + radiation + bolus chemotherapy‡	—	—	1,695	—	—	1,695
Surgery + chemotherapy	—	—	—	183	349	532
Total assessable patients	200	656	1,695	544	696	3,791§

Abbreviations: NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PVI, protracted venous infusion; FU, fluorouracil; MOF, methoxy flurane; MeCCNU, semustine, oncovin, FU.
*US Gastrointestinal Intergroup trial coordinated by Cancer and Leukemia Group B.
†Concurrent bolus FU during radiation therapy; FU alone or plus semustine as maintenance in 794751 and 864751; in R02, maintenance chemotherapy was either FU, leucovorin, or MOF.
‡Concurrent bolus FU or FU leucovorin with radiation; maintenance FU alone or plus leucovorin and levamisole.
§T stage known in 3,784, N stage in 3,751, and TN stage in 3,745.

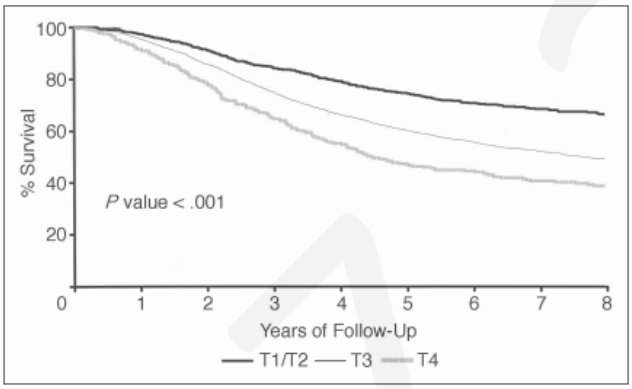


Fig 1. Impact of T stage on overall survival in the rectal cancer pooled analysis. *P* value reflects pair-wise comparisons between the adjacent T stages of patients.

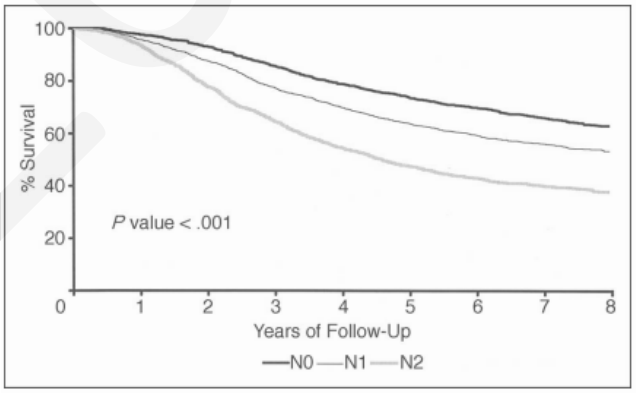
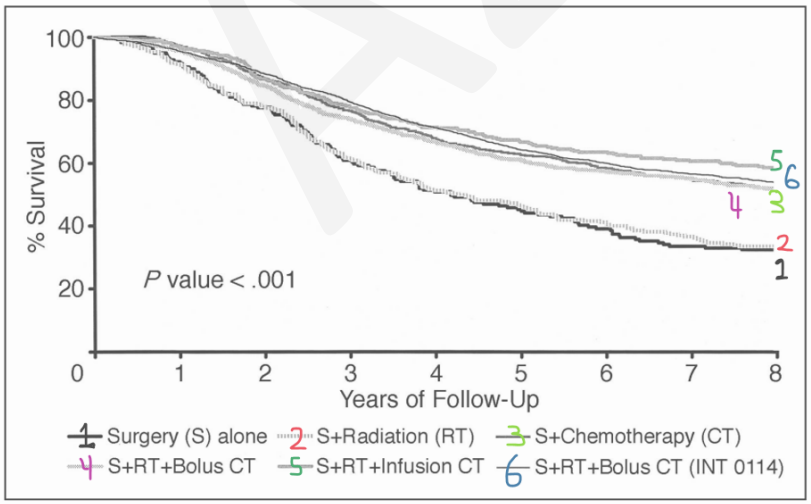


Fig 2. Impact of N stage on overall survival in the rectal cancer pooled analysis. *P* value reflects pair-wise comparisons between the adjacent N stages of patients.



Stage II: T3/T4, Node-negative

Stage III: Node-positive

AJCC Stage	TNM Stage	5-yr LR	5-yr OS
I	T1N0M0 T2N0M0	<5%	90%
IIA IIB IIC	T3N0M0 T4aN0M0 T4bN0M0	5-10% 10-15%	80% 60%
IIIA IIIB IIIC	T1-2N1 / T1N2a T3-4aN1 / T2-3N2a / T1-2N2b T4aN2a / T3-4aN2b / T4bN1-2	5-10% 10-15% 15-20%	80% 60% 40%
IVA IVB	M1a M1b		

Table 2. Pooled Rectal Analysis: Impact of T Stage and TN Stage on Survival and Relapse

Stage	Overall Survival* No. of Patients	Overall Survival* 5-Year (%)	Overall Survival* P	Disease-Free Survival* No. of Patients	Disease-Free Survival* 5-Year (%)	Disease-Free Survival* P	Local Recurrence† 5-Year (%)	Local Recurrence† P	Distant Metastases† 5-Year (%)	Distant Metastases† P
T										
T1-T2	588	75		588	67		7		22	
T3	2,909	60	< .001	2,895	50	< .001	12	< .001	34	< .001
T4	286	47		286	39		16		41	
TN										
T1-2/N1	355	79		355	73		7		15	
T1-2/N2	226	67	.001‡	226	58	< .001	8	.3	31	< .001
T3/N0	1,060	75		1,058	65		9		20	
T3/N1	887	60	< .001	881	48	< .001	12	.002	37	< .001
T3/N2	935	44		929	36		14		47	
T4/N0	111	65		111	54		13		28	
T4/N1	62	35	< .001	62	30	< .001	23	.25	39	.002
T4/N2	108	37		108	30		17		53	

Table 11. Rectal Pooled Analysis: 5-Year Survival by Risk Group and Treatment Method

Risk Group/TN Stage	% S	S + RT	S + CT	RT + bolus CT*	RT + PVI CT	RT + bolus CT†
Overall survival						
Intermediate risk						
T1-2/N1 (n = 355)	41	67	85	83	78	82
T3/N0 (n = 1,060)	65	62	84	76	80	74
Moderately high						
T1-2/N2 (n = 226)	20 (5)	60	43	55	44	77
T3/N1 (n = 887)	40	50	52	61	73	63
T4/N0 (n = 111)	0 (2)	33 (3)	70 (10)	58	80	67
High risk						
T3/N2 (n = 935)	24	22	45	42	46	50
T4/N1 (n = 62)	50 (4)	40 (5)	29 (7)	57	0 (1)	31
T4/N2 (n = 108)	—	0 (9)	25 (4)	29	53	44
Disease-free survival						
Intermediate risk						
T1-2/N1 (n = 355)	29	61	78	78	76	75
T3/N0 (n = 1,058)	51	50	69	63	75	66
Moderately high						
T1-2/N2 (n = 226)	20 (5)	60	36	48	39	66
T3/N1 (n = 881)	24	33	43	51	63	51
T4/N0 (n = 111)	0 (2)	33 (3)	50 (10)	55	70	55
High risk						
T3/N2 (n = 929)	16	18	36	34	30	42
T4/N1 (n = 62)	50 (4)	40 (5)	14 (7)	57	0 (1)	26
T4/N2 (n = 108)	—	0 (9)	25 (4)	26	47	31

Table 12. Rectal Pooled Analysis: 5-Year Relapse Rates by Risk Group and Treatment Method

Risk Group/TN Stage	% S	S + RT	S + CT	RT + bolus CT*	RT + PVI CT	RT + bolus CT†
Local relapse						
Intermediate risk						
T1-2/N1 (n = 355)	12	7	5	6	5	6
T3/N0 (n = 1,058)	14	12	11	10	5	8
Moderately high						
T1-2/N2 (n = 226)	40 (5)	10	0	13	11	9
T3/N1 (n = 881)	11	13	17	12	9	10
T4/N0 (n = 111)	NA (2)‡	33 (3)	20 (10)	18	10	11
High risk						
T3/N2 (n = 929)	24	11	15	17	11	15
T4/N1 (n = 62)	50 (4)	0 (5)	43 (7)	0	18	22
T4/N2 (n = 108)	—	NA (9)§	0 (4)	22	33	16
Distant						
Intermediate risk						
T1-2/N1 (n = 355)	41	25	16	14	15	14
T3/N0 (n = 1,058)	34	31	18	20	13	18
Moderately high						
T1-2/N2 (n = 226)	40 (5)	30	57	40	61	28
T3/N1 (n = 881)	60	53	37	35	30	33
T4/N0 (n = 111)	NA (2)‡	67 (3)	20 (10)	27	59	25
High risk						
T3/N2 (n = 929)	59	70	46	53	30	41
T4/N1 (n = 62)	50 (4)	80 (5)	43 (7)	40	36	34
T4/N2 (n = 108)	—	78 (9)	75 (4)	78	22	53

Surgery → Chemo ± RT.

Meta-analysis. 22 randomized trials. Colorectal Cancer Collaborative Group (Lancet, 2001).
5-year OS: observation 58.6% vs. RT 57.5% (NS). Annual death rate 4.6% lower with RT.
5-year risk of any recurrence: observation 54% vs. RT 50% (NS)
5-year risk of isolated local recurrence: observation 23% vs. RT 15% (SS). This was driven by 2 trials (UK MRC 3 and NSABP R-01).
Few recurrences > 5 years out.
No subgroup benefit

NSABP R-02. — "Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum"
←R→ 694 pts. Dukes' B and C after curative resection. **1.** adjuvant chemotherapy alone **2.** chemotherapy plus RT. All females received 5-FU/LV, whereas males were randomized to MOF vs 5-FU/LV. Median f/u 93 months.
Wolmark, J Natl Cancer Inst. 200.
Results: Post-op RT resulted in ↓ LR (13% vs 8%) but did not ↑ DFS or OS. For male, 5-FU/LV resulted in ↑ DFS ↑ OS.
Conclusion: No role for post-op RT, although benefit with local control.

Question: Does a different fractionation schedule and interval to surgery changes outcomes?

French Lyon 90-01 trial
201 pts with T2-T3 NX rectal cancer randomized to RT (39 Gy/13 fx) delivered:
1) short interval to surgery, mandated as surgery within 2 weeks after RT completed
2) long interval, mandated as surgery within 6 - 8 weeks

Longer interval group with improved tumor response rates (72% vs 53%, p=0.007) and pathological downstaging (26% vs 10%, p=0.005)
No differences with respect to sphincter preservation rate, morbidity, local relapse, or short term survival

Surgery → CRT.

GITSG GI-7175 2x2 Study (1975-1980) -- surgery alone ± postop C ± postop RT
←R→, 4 arms. *Terminated early due to significant benefit of chemo-RT arm*. 227/520 patients. Dukes B and C (T3-4 or N+), distal edge within 12 cm from anal verge. Only R0 resection allowed. **1.** Surgery alone, **2.** post-op Chemo (bolus IV 5-FU/M-CCNU), **3.** post-op RT 40 or 48 Gy standard fx, **4.** post-op Chemo-RT 40 or 44 Gy standard fraction + 5-FU 500 mg/m2 followed by adjuvant 5-FU/M-CCNU as in chemo alone arm.
RT AP/PA, ↑ border L4/L5, ↓ border included perineum; major deviations in 39%. Consolidative chemo given x1.5 years or disease progression.

GI Tumor Study Group, NEJM 1985. 7-years.
Outcome: Recurrence surgery 55% vs. chemo 46% vs. RT 48% vs. chemo-RT 33% (SS). Benefit of chemo-RT (p=0.009) due to both RT (better LRC p=0.06) and chemo (better DM p=0.06) components. Initial LRR overall 21%; by arm 24% vs. 27% vs. 20% vs. 11%; initial DM overall 25%.
LR in perineum 21%, vagina/uterus 17%, anastomosis 12%, **sacrum/coccyx 12%**, bladder/prostate 12%. Actuarial OS 36% vs. 46% vs. 46% vs. 56% (p=0.07).
Toxicity: Severe nonhematological chemo 15% vs. RT 16% vs. chemo-RT 35%
Conclusion: Postoperative chemo-RT significantly better for disease-free survival, with trend to overall survival benefit.

Douglass, NEJM, 1986. 8-years.
Outcome: No new recurrences. Now overall survival benefit for chemo-RT over surgery alone (SS)
Conclusion: Postoperative chemo-RT improves overall survival over surgery alone in T3-4 or N+ patients

MAYO NCCTG 79-47-51 (1980-1986) -- postop RT vs postop chemo-RT.
←R→ 204 patients, rectal CA T3-4 or N+, within 12 cm of anal verge. **1.** post-op RT **2.** post-op chemo-RT.
RT: 45/25 + 5.4/3 Gy boost to tumor bed and adjacent LN. **Chemo:** bolus 5-FU bolus + semustine x1 month, then bolus 5-FU 500 mg/m2 concurrent with RT, then 2 months consolidative 5-FU/semustine. Major deviations 9%.
Krook, NEJM 1991. 7-years f/u.
Outcome: 5-year recurrence RT 63% vs. chemo-RT 41% (decreased by 34%, SS). LR 25% vs. 13% (decreased by 47%, SS), DM 46% vs. 29% (SS). 5-year OS ~40% vs. ~55% (decreased by 29%, SS). Reduction in death rate highly significant for LAR (52%), not significant for APR (10%)
Toxicity: SBO 5%, median time-to-complication 10 months; overall severe late toxicity 7% (comparable between 45 and 50.4 Gy)
Conclusion: Adjuvant chemo-RT superior to RT alone; confirms prior GITSG 7175 results
Comment: CRT generally well tolerated, unlike GITSG GI-7175. Adjuvant chemo 1 month first, consolidaation 2 months vs 1.5 years in GITSG. On the basis of this study and GITSG 7175, NIH consensus conference recommended chemo-RT as standard of care for T3-T4 or N+ patients

If giving adjuvant therapy, the addition of radiation to chemo is SOC. Δ cannot omit RT.

Δ Historical Chemo

Some History:

- Semustine (Methyl-CCNU) was a component of both trials demonstrating benefit, but is known to increase risk of leukemia (4% cumulative risk at 6 years). GITSG 7180 and NCCTG 86-47-51 demonstrated that semustine is not a necessary component of chemo-RT
- In the setting of metastatic CRC, **continuous infusion 5-FU is superior to bolus 5-FU** (86-47-51). Synergistic effects of 5-FU and RT are greatest when there is a continuous exposure to 5-FU for 24-48 hours after RT (PMID 6818194).
- INT 86-47-51 demonstrated improved OS with infusional 5-FU (70% vs. 60% at 4 years).
  - The improvement was due to increased control of distant mets, with no impact on local control.
- INT 0144 trial evaluated infusion 5-FU vs. bolus 5-FU sandwich around infusion 5-FU/RT.
  - Results at 5 years suggest comparable outcomes.

INT/NCCTG 86-47-51 "Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery."
←R→ 660 pts. Stage II-III. 2x2 randomization | 1. 5-FU + Semustine vs. 5-FU | 2. 5-FU bolus vs. 5-FU continuous infusion |.
Treated with 9 weeks of systemic chemotherapy -> RT with 5-FU -> 2nd cycle of chemotherapy.
Higher dose of 5-FU used when given alone than with semustine.
RT dose 45 Gy to the pelvis + boost 5.4 - 9 Gy, total 50.4 - 54 Gy.
Bolus 5-FU was 500 mg/m2 days 1-3, weeks 1+5 of RT.
C.I. 5-FU was 225 mg/m2 daily during RT.

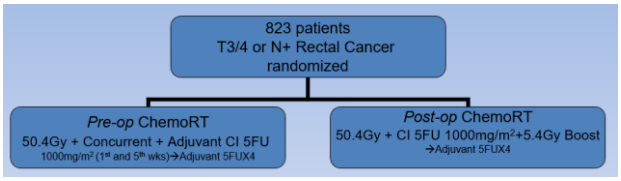
O'Connell, NEJM 1994.
Outcome: Median f/u 46 mo. For C.I., less tumor relapse (37% vs 47%), distant mets (31% vs 40%), time to relapse, and overall survival compared to bolus 5-FU. Decreased tumor relapse by 27%, death by 31%. 4-yr relapse-free survival 63% vs 53%, OS 70% vs 60%. No difference in LR. Increased rate of severe diarrhea for C.I.; higher rate of leukopenia for bolus. No benefit seen for semustine.
Conclusion: **C.I. 5-FU is superior to bolus 5-FU IN OVERALL SURVIVAL**. Improves DM (extra-pelvic disease) but not LC. Much higher doses of 5-FU were given by continuous infusion than by bolus. **No benefit to semustine in addition to 5-FU**.

Intergroup INT-0144 (1994-2000) - bolus vs modulated bolus vs CI 5-FU
←R→ 1917 pts. T3-4 or N+. Follow-on to INT 864751.
1. bolus 5-FU → CI 5-FU/RT → bolus 5-FU
2. CI 5-FU → CI 5-FU/RT → CI 5-FU,
3. bolus 5-FU + LV + levimasole → CI 5-FU/RT → bolus 5-FU + LV + levimasole. RT given 45 Gy to field including presacral and internal illiac LN + 5.4 Gy boost with 2cm margin + optional 3.6 Gy boost to tumor bed if no small bowel in-field.

Smalley, JCO 2006. Phase III trial. Median F/U 5.7 years.
Outcomes: 5-year survival: no DFS difference (57-62%), no OS difference (68-71%).
LR failure (tumor bed, anastomosis, regional LNs) at first relapse 8% vs. 5% vs. 7%. LR failure in non-T4 patients 5% vs. 3% vs. 5%, and primary surgical treatment without neoadjuvant can be appropriate
Toxicity: GI Grade 3/4 41-44%; hematologic Grade 3/4 bolus arm 49-55% vs. CI arm 4%
Conclusion: similar survival in all arms, different toxicity profiles and central catheter requirements. LAR reasonable initial resection, since local failure rates only 5% at first failure.

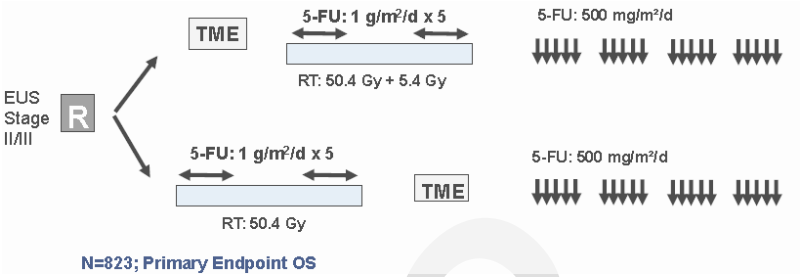
Smalley, Proc Am Soc Clin Oncol 2003.
Median f/u 4.6 yrs. No difference in RFS or OS. 5-year estimated OS 72% CI vs. 67% bolus
Similar toxicity profiles; less GI toxicity in bolus group, less hematologic toxicity in CI group

Preop CRT



Preop CRT vs Postop CRT

German CAO/ARO/AIO-94 (1995-2002)
←R→ 823. Clinical stage T3-4, N+. 1° endpoint = OS.
≤ 75 yo, ≤ 16 cm from anal verge.
Background. Swedish trial showed us that preop RT is better than surgery alone. It is also known that adjuvant CRT > adjuvant RT alone.
Q: Therefore, what about PREOP CRT vs POSTOP CRT?



| 1. Preop 5040 (180 cGy/fx) + 5-FU (120 hour continuous infusion 1000 mg/m², 1st/5th weeks of RT → 6 weeks later = **surgery**
→ 1 month later **Adjuvant:** 4x five day cycles of 5-FU (500 mg/m² per day) |
| 2. **Surgery** → 5040 (180 cGy/fx) + 5-FU (120 hour continuous infusion 1000 mg/m², 1st/5th weeks of RT + 540 cGy boost → **Adjuvant.**
RT: 3 or 4 field box technique. **TME performed in ALL patients.**

Table 2. Compliance with the Protocol and Protocol Violations.*

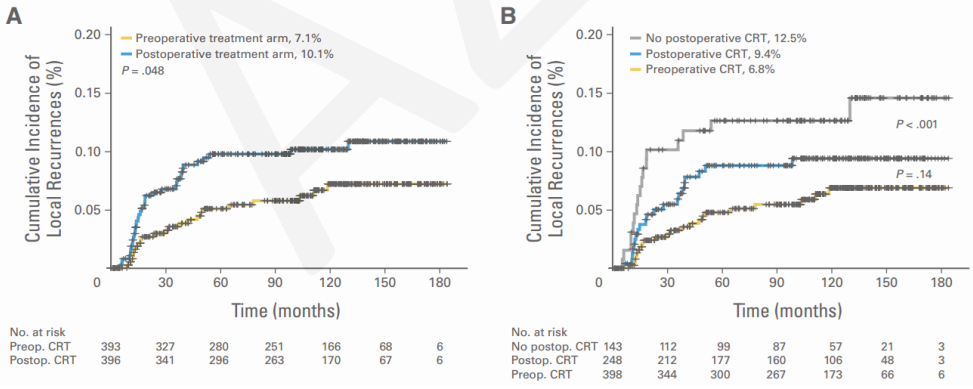
Variable	Preoperative Chemoradiotherapy	Postoperative Chemoradiotherapy	P Value
Randomly assigned — no.	421	402	
Included in full analysis population — no.	405	394	0.12
Requested change in treatment group — no.	9	19	0.05
Included in treated population — no.	415	384	
Received full dose of radiotherapy — no. (%)	380 (92)	206 (54)	<0.001
Received full dose of chemotherapy — no. (%)	369 (89)	193 (50)	<0.001
Did not receive chemoradiotherapy — no. (%)			
Stage I disease	NA	71 (18)	<0.001
Other reason†	1 (<1)	39 (10)	<0.001
Received radiotherapy with modification — no. (%)‡	19 (5)	31 (8)	0.04
Received chemotherapy with modification — no. (%)‡	23 (6)	26 (7)	0.47
Protocol violations — no. (%)§			
Radiotherapy	13 (3)	33 (9)	0.001
Chemotherapy	15 (4)	49 (13)	<0.001
Missing data — no. (%)			
Radiotherapy	2 (<1)	4 (1)	0.36
Chemotherapy	7 (2)	6 (2)	0.89

* NA denotes not applicable.
† Other protocol-specified reasons for not receiving postoperative chemoradiotherapy included intraoperative detection of distant disease and postoperative complications or death.
‡ Modifications included dose reductions because of toxicity or alterations in treatment because of distant disease detected during treatment.
§ The protocol was considered violated when patients declined or erroneously did not receive radiotherapy or chemotherapy or did receive non–protocol-specified radiotherapy or chemotherapy.

Sauer, NEJM 2004. f/u 4 years.
Results: 5-year OS preop 76% vs postop 74% (NS); 5-year DFS 68% vs. 65% (NS); **LR 6% vs. 13% (SS)**; DM 36% vs. 38% (NS).
Preop downstaging: pCR 8%. In favor of pre-op 25% vs 40% were LN+ (stage III). TNM Stage I disease found in 18% of post-op group (vs. 25% in pre-op).
Note: Sphincter preservation rate in 194 patients with low-lying tumors declared by the surgeon prior to randomization to require an APR:
Preop: 39% (43/109)
Postop: 19% (17/85) (P = 0.004)
But overall rates of sphincter pres. same 69% vs 71%.
Grades 3 or 4 Toxicity: Fewer acute (27% vs 40%) and late toxicities (14% vs 24%) in preoperative-treatment group.

Conclusion: Preop chemo-RT improved local control and improved toxicity, but did not impact overall survival.

Critique: only 54% of adjuvant patients vs. 92% of neoadjuvant patients received full RT dose.
But perhaps this goes to say that RT is much better tolerated preop, while postop is that much more difficult.



Sauer, NEJM 2012.
10-yr OS preop 59.6% vs postop 59.9% (NS).
LR: 7.1% vs 10.1% (SS). DM: 29.8% vs 29.6% (NS). DFS: NS.
Conclusion: "There is a persisting significant improvement of pre- versus postoperative CRT on local control; however, there was no effect on overall survival."

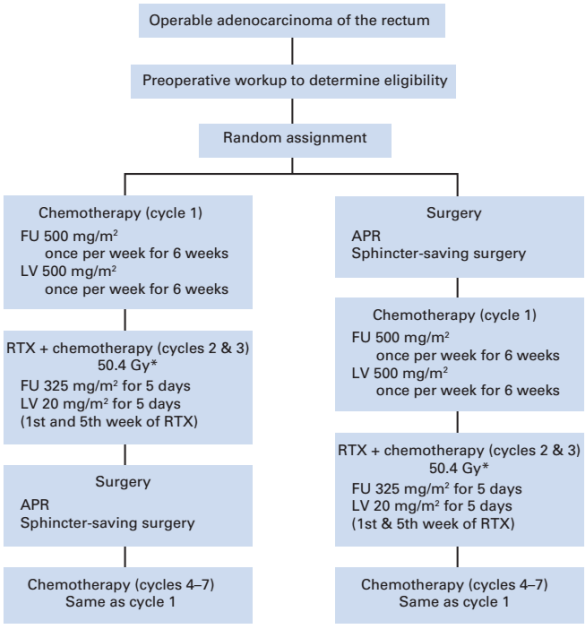
LR RISK BY DISTANCE FROM ANAL VERGE (NO RT)
High rectal tumors 10.4%
Mid-rectal 18.7%
0-5cm form anal verge 4.5%

CONCLUSION: Pre-op CRT improved:
5 yr local recurrence 6% vs. 13% (p=0.006). Rates of pathologic LN involvement (25% vs. 40%).
↑ sphincter preservation 39% vs. 19% p=0.004
↓ grade 3-4 acute toxicity 27 % vs. 40% (p=0.001)
↓ grade 3-4 long term toxic effects 14 and 24% (p=0.01)
No difference in survival (76 vs. 74% p=0.8).

- Potential for Overtreating with Preop CRT:
  - pT1-2 N0 Disease Was Found in 18% of Postop Patients
- Difficult to Administer Postop Therapy:

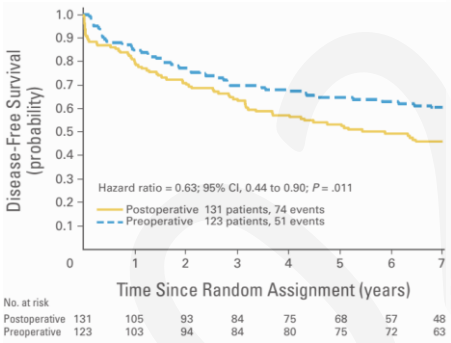
	Preop (%)	Postop (%)	P-Value
Completed RT	**92**	**54**	**<0.001**
Completed CT	**89**	**50**	**<0.001**

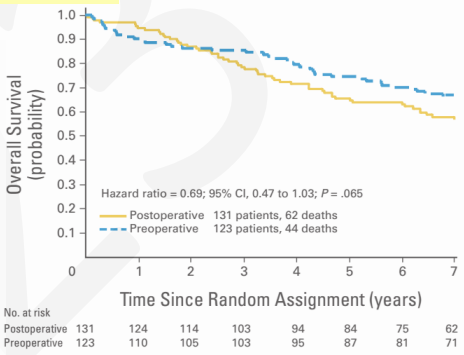
NSABP R-03. Preoperative or postoperative CRT. **Strange trial in that ONLY DFS was better (not LC or OS).**
←R→ 267 of 900 expected patients. *Trial closed prematurely **@ 30%** due to poor accrual.* Clinical T3-T4 or N+ rectal cancer. **(Same population as Sauer)**
70% male, 80% palpable tumor. ≤ 15 cm from anal verge.
Surgery APR, LAR, or local excision; TME not mandated.
1. Preop chemo-RT 50.4/28 + 5-FU 500 mg/m2 and leucovorin 500 mg/m2 **2.** Postop chemo-RT (same as preop).
Both groups adjuvant 3 cycles of 5-FU/leucovorin



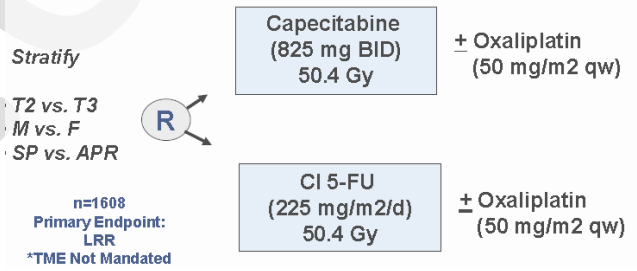
Roh, JCO 2009. Surviving patients followed for 8.4 years.
Results: 5 yr DFS pre vs post: 64.7% vs. 53.4% (SS). OS 74.5% vs 65.6% (NS). LRR 11% vs 11% (NS). Significant reduction in N+ (67% vs. 52%, SS). **pCR** Complete pathologic response achieved in 15% of preop patients (none of these 15% had a recurrence).
Toxicity: Grade 4 diarrhea preop 24% vs. postop 13%; Grade 5 toxicity 5% vs 3%.

Conclusions: Preoperative CRT, compared with postoperative CRT, SS ↑ DFS and showed a trended ↑ OS.
To REITERATE: NO PATIENT WITH A pCR RECURRED!!!!





NSABP R-04: pre-operative chemo/RT. T3-4N0 or T1-4N+.
1608 clinical stage II or III rectal cancer undergoing preoperative RT (4,500cGy in 25 fractions over 5 wks + boost of 540cGy-1080cGy in 3-6 daily fractions). 2x2 trial.
Primary Endpoint: 3-year LRC with 3 years of minimum follow-up.
Secondary Endpoints: **pCR**, # sphincter saving surg, DFS, OS, QoL, Tox.



Allegra, J Nat Cancer Inst, 2015.
Results: July 2004 to August 2010
LRC, OS, DFS (NS). pCR reported in that paper of 17.8 to 20.7%
+ Ox = ↑↑↑ 3-4 diarrhea (p<0.0001). Analysis of the primary endpoint showed 3-yr rates of L-R tumor control ranged from 87.4%-88.2%.
LRR (3 yr) with R0 resection: **2-4 % stage II pts, 4-11% stage III.**
Distant mets (5 yr): **16% of stage II, 26% of stage III pts**.
Chemo compliance: 84% to 97% pts received >80% chemo.
Conclusions: CVI 5-FU or oral Cape + RT = similar outcomes and toxicity.
Oral Cape avoids central venous catheters. New STD of care.
Ox just adds toxicity and no benefit.

Toxicity (Grade)	5-FU	Capecitabine	5-FU + Oxaliplatin	Capecitabine + Oxaliplatin
Overall (3+)	26.5	30.1	39.9	42.2
**Diarrhea (3/4)	7	7	16	16
Death (5)	0.3	1.3	0.3	1.6

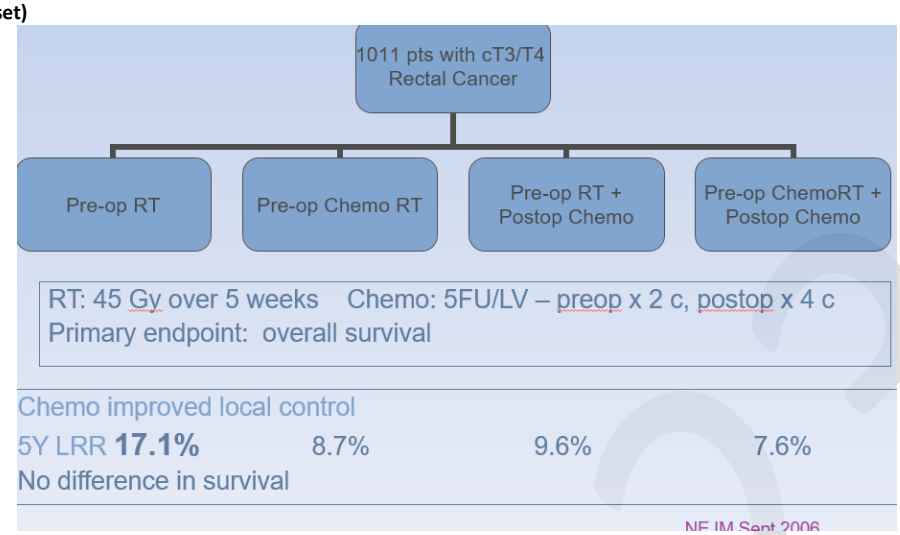
Russell, Ann Surg, 2015. Patient reported QOL between APR and SP.
This trial did NOT show worse QOL at 1 year between APR compared to SP surgery, but profiles were DIFFERENT.
Results: 987/1608 had data for planned analyses; 62% underwent SSS; 38% underwent APR.
APR worse: body image (70.3 vs 77.0, P = 0.0005), micturition symptoms (26.9 vs 21.5, P = 0.03), MALES only worse sexual enjoy (43.7 vs 54.7, P = 0.02)
SSS worse: GI symptoms (18.9 vs 15.2, P < 0.0001), weight loss (10.1 vs 6.0, P = 0.002). Conclusions:

ACCORD 12 / PRODIGE 2
PURPOSE: The ACCORD 12 trial investigated the value of two different preoperative chemoradiotherapy (CT-RT) regimens in T3-4 Nx M0 resectable rectal cancer. Clinical results are reported after follow-up of 3 years.
←R→ 598 preoperative CRT with | 1. CAP45 | 2. CAPOX50 |
CAP45 = 45-Gy RT for 5 weeks with concurrent capecitabine CAPOX50 = 50-Gy RT for 5 weeks with concurrent capecitabine and oxaliplatin.
Total mesorectal excision was planned 6 weeks after CT-RT. 1^{O} CR "sterilization of operative specimen"

Gerard, JCO 2012.
CR: 13.9% vs. 19.2% (ALL NS).
LR 5%, OS 88%, DFS 70% (ALL NS).
All toxicity NS.
CONCLUSION: At 3 years, no significant difference in clinical outcome was achieved with the intensified CAPOX regimen. When compared with other recent randomized trials, these results indicate that concurrent administration of oxaliplatin and RT is not recommended.

Preop CRT vs Preop ±C±RT

EORTC 22921 (Bosset)



EORTC 22921
←R→ 2x2 design. 1011 patients with T3 or T4 resectable rectal CA. 1) Preop RT, 2) Preop CRT, 3) Preop RT + postop CT, or 4) Preop CRT + postop CT. RT given 45/25 to posterior pelvis. 5-FU given 350 mg/m2/day

Bosset, NEJM 2006.
5-year OS: overall 65% (no difference among the 4 groups)
5-year LR: preop RT 17% vs. CRT 9% (preop CRT 9% vs. preop RT + postop CT 10% vs. preop CRT + postop CT 8%)
Adherence: 82% for preop CT vs. 43% for postop CT

Bosset, JCO 2005.
Tumors after preop CRT vs RT alone: smaller, lower pT, lower pN, fewer examined nodes, less LVN, increase in mucinous tumors
Conclusion: Significant downstaging with CRT over RT alone

French FFCD 9203 (1993-2003)
←R→ 733 pts. Resectable T3-T4, Nx. 1) Preop 45 Gy RT vs 2) Preop CRT → Surgery → 4 cycles of adjuvant 5-FU/Leucovorin
C: concurrent **bolus** 5-FU (350 mg/m2) + leucovorin on days 1-5, weeks 1,5.

Gerard, JCO 2006.
5-year OS (primary endpoint): no difference. Sphincter preservation: no difference
5-year LR: CRT 8% vs. 16% RT alone (SS)
Grade 3+ toxicity: CRT 15% vs. 3% RT alone (SS)
Conclusion: chemoradiation recommended for improved local control

Criticism. 5fu bolus and not continuous infusion. TME not standardized in trial. Done over long period of time.

Cochrane Meta-analysis "Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer."
Laura De Caluwé et al.Cochrane Database Syst Rev. 2013 Feb 28;2.
Five trials were identified and included in the meta-analysis. From one of the included trials only preliminary data are reported.
Outcome:
Response rate: CRT significantly increased the rate of complete pathological response (OR 2.12-5.84, P < 0.00001)
Sphincter Preservation: did not translate into a higher sphincter preservation rate (OR 0.92-1.30, P = 0.32)
Post-op Morbidity: marginally affected postoperative overall morbidity (OR 0.67-1.00, P = 0.05)
Anastomotic leak: No differences were observed in anastomotic leak rate
Post-op Mortality: No differences were observed in postoperative mortality
Local recurrence: at five years was significantly lower in the CRT group compared to RT alone (OR 0.39-0.72, P < 0.001).
Survival: No statistically significant differences in DFS (OR 0.92-1.34, P = 0.27) or OS (OR 0.79-1.14,P = 0.58) at five years.
Toxicity: increased grade III and IV acute toxicity (OR 1.68-10, P = 0.002)
Conclusion: No benefit to chemo-RT compared with short-course RT alone. **BUT INCREASED pCR.**

Preop 5x5 vs. Surg alone

Swedish Cancer Trial. **ONLY TRIAL TO SHOW SURVIVAL ADVANTAGE WITH RT ALONE**
←R→. 1168 patients, 908 curative intent (included 316 patients from Stockholm II).
| 1**.** preop RT 25/5 → surgery within 1 week | **2.** surgery alone |. RT given as AP/PA, 3-field, or 4-field; superior border at L4.
Non-TME trial.

Pahlman, NEJM 1997. LR at 5 years: RT 11% vs surgery alone 27% (SS). OS: RT 58% vs 48% (SS).

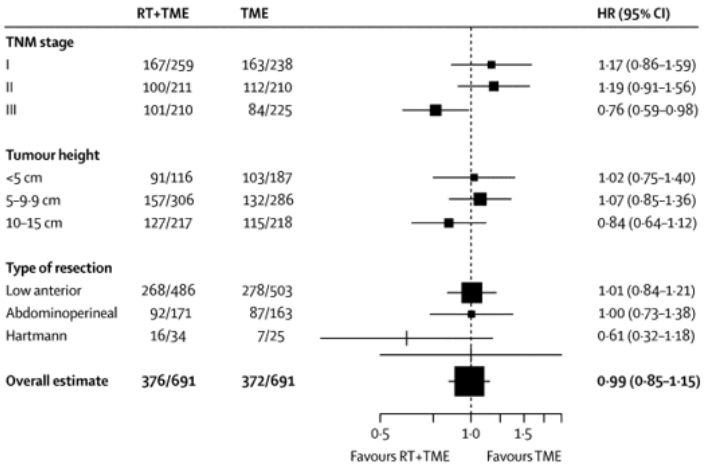
Dahlberg IJROBP, 2002. Cost-effectiveness study. 8 year F/U. 98/1168 randomly selected patients from main trial from single region.
Total costs: RT USD 35,300 vs. surgery alone USD 30,000
Survival benefit 21 months - cost of year saved USD 3,654. Sensitivity analysis worst case USD 15,228.

Folkesson, JCO 2005. 13-years. Overall survival: RT 38% vs. surgery alone 30% (SS)
Cancer-specific: RT 72% vs. surgery alone 62% (SS) Local recurrence: RT 9% vs. surgery alone 26% (SS)

Birgisson, JCO 2005. Long term side effects.
Side effects: RT group more likely to be admitted < 6 months after treatment (mostly GI related); no difference > 6 months out.
Bowel obstruction: more common long term in RT patients.

Birgisson, Br J Surg. 2008. Late GI side effects.
Outcome: RT increased risk of SBO (RR 2.5), surgically managed SBO (RR 7.4).
Difference seen after 7-8 years for conservatively managed SBO, after 1-2 years for surgically managed SBO. No impact of RT technique
Conclusion: Small bowel obstruction more common in preop RT.

Dutch TME: Question: Do you need radiation if you use TME? And the answer is YES! Benefit of LR **("NO" SURVIVAL BENEFIT, but CAVEAT)**
←R→ 1805 patients treated with | 1. preop RT 25/5 → surgery within 1 week | 2. surgery alone |.
If surgery-only patients had SM+ (≤ 1mm), mandatory post-op RT. **ALL patients received TME :D.**



Kapiteijn, NEJM 2001.
2-year OS: RT 82% vs. TME alone 82%
2-year LR: RT 2.4% vs. TME alone 8.2% (SS)
Conclusion: Short-term preop RT reduces risk of LR with TME

Marinjen, IJROBP 2003. 120 patients in surgery-only group with SM+; 47% received post-op RT; LR: Post-op RT 17% vs. surgery only 16% (NS)
LR as a function of surgical margins:
Wide SM: preop RT 1% vs. 6% (SS)
Narrow SM: preop RT 0% vs. 15% (SS)
Positive SM: preop RT 9% vs. 16% (NS) … RT cannot compensate + margins.
Conclusion: Preop RT beneficial with wide or narrow SM, but not in positive SM.

Peeters, Ann Surg 2007. Median F/U 6.1 years.
Outcome: 5-year LR TME 11% vs. RT + TME 6% (SS); OS 63% vs. 64% (NS)
Subgroup benefit: N+, tumors 5-10 cm from anal verge, negative margins
Conclusion: **Preop short-term RT improves local control; no effect on survival**

Kusters, Eur J Surg Onc. 2010. Local Failure Patterns.
Outcome: 5-year LR rate RT+ 5% vs RT- 11%. Most common LR: presacral (43% and 33%). RT SS ↓ anastomotic LR (from 2.7% to 0.7%).
Conclusion: RT reduces LR in all subsites, and is especially effective in preventing anastomotic LR after LAR

	10-year local recurrence					10-year overall survival				
	n	RT+TME (%)	TME (%)	p	Interaction	n	RT+TME (%)	TME (%)	p	Interactic
All eligible patients					p=0·312					p=0·262
TNM I	507	<1%	3%	0·027	..	507	65%	72%	0·321	..
TNM II	491	5%	8%	0·212	..	496	50%	55%	0·242	..
TNM III	622	9%	19%	<0·0001	..	624	39%	37%	0·526	..
Patients with a negative CRM					p=0·15					p=0·027
TNM I	497	<1%	3%	0·027	..	497	65%	72%	0·293	..
TNM II	421	4%	7%	0·355	..	421	51%	57%	0·213	..
TNM III	435	5%	17%	<0·0001	..	435	50%	40%	0·032	..

van Gijn, Lancet 2011. 12 year f/u (See the LEFT 2 Graphs)
Note: The effect of radiotherapy became stronger as the distance from the anal verge ↑. However, +SM patients were excluded, the relation between distance from the anal verge and the effect of radiotherapy disappeared.
Results: 10-yr incidence of LR 5% RT+ vs 11% RT-.
If negative margin, RT effect was **irrespective** of the distance from the anal verge and led to an ↑ CSS.
However ←→ OS since there was an ↑ in other causes of death.
… But if stage III w/ negative circumferential resection margin, 10-year survival was 50% vs. 40% (surg alone) p=0·032.
Conclusion: LR reduced by more than 50% with RT compared to TME alone.

Comments: Stage I patients had ↓↓ LR, but only absolute reduction of 2·6%.
∴ 38 patients RT tx to --| 1 LR.
Stage III patients, < 10 pts RT tx --| 1 LR/ local recurrence AND exactly 10 patients RT tx --| 1 death.

TROG 01.04. Short Course Neoadjuvant XRT vs. Long Course in T3 patients. **RT 5x5 v PRE-OP CRT.**
←R→ 326 patients T3N0-2M0 rectal cancer within 12 cm of anal verge randomized
| 1. 25 Gy x 5 Gy/fx in 1 week → surg within 3-7 DAYS → 6 courses of chemo
| 2. 50.4 Gy x 1.8 Gy/fx in 5.5 weeks + inf 5-FU → surg within 4-6 weeks → 4 courses of chemo.
Inf 5-FU 225 mg / m^2. SC border: ↑ Sacral promontory. Mesorectum, pelvic side wall, presacral space, Elective LN (internal iliac perirectal nodes).

Ngan, JCO 2012. Med FU 5.9 years.

3 yr LR	7.5% vs. 4.4% (NS).	For distal tumors (< 5 cm) 6 pts vs 1 pt had LF. So in DISTAL tumors, it is UNCLEAR if NS.
5 yr Distant Failure	27% vs. 30% (NS).	
5 yr OS	74% vs. 70% (NS).	
Late toxicities G3-4	6% vs. 8% (NS).	

∴ No Short course for low lying tumors.

Polish Study. **RT 5x5 v PRE-OP CRT.** **TME NOT MANDATED**
←R→ 312 patients to receive either
| **1.** Preoperative 25 Gy | 5 fx + surgery within 7 days
| 2. CRT (50.4 Gy in 28 fractions of 1.8 Gy, bolus 5-fluorouracil and leucovorin) and surgery 4-6 weeks later. → Adjuvant Chemo NOT STANDARD.
The median follow-up of living patients was 48 (range 31-69) months.

Bujko, Br J Surg. 2006 Oct;93(10):1215-23
RESULTS:
Early RT tox: 5x5 3.2% vs. CRT 18.2% (P < 0.001).
severe late toxicity was 10.1 versus 7.1 per cent (NS) respectively.
4-year OS 67.2% vs. 66.2% (NS). 4-year DFS 58.4% vs. 55.6% (NS) Crude incidence of LR 9.0% vs. 14.2% (NS).
*****The rate of pathologic complete response was significantly higher WITH LONG COURSE!!!!! (16.1% vs. 0.7%).**
CONCLUSION:
Neoadjuvant chemoradiation did not increase survival, local control or late toxicity compared with short-course radiotherapy alone.
There was a higher risk of margin positivity with 5 x 5 than CRT. So maybe with larger cancers you need CRT rather than 5 x 5.

Criticism. Short follow-up unable to assess late toxicity. Short course had more post op chemotherapy. Not powered to detect less than 15%. Staging was ONLY clinical (no US or MRI). TME NOT MANDATED Adjuvant Chemo NOT STANDARD.

Pietrzak, Annals of Oncology 2019.
FU 7 years. Long term follow-up.
OS HR 0.90 (NS). However, the difference in early OS favouring short-course/CCT previously reported was observed again, being 9% at 3 years (95% CI 0.5% to 17%). This difference disappeared later; at 8 years OS was 49% in both groups.
DFS HR 0.95 (NS) at 8 years 43% versus 41% (NS).
Local failure (35% vs 32%) and distant metastases (36% vs 34%).
Late complications grade 3+ 11% versus 9% (NS).
Conclusion
The superiority of preoperative short-course/CCT over chemoradiation was not demonstrated.

Preop 5x5 vs. POSTop CRT

UK MRC CR07 and NCIC C016 (1998-2005). Preop RT 25/5 | selective **postop** chemo-RT 45/25.

Background: At the start of the trial, the standard of care in most of the UK was considered to be preoperative RT.

Q: Is post-op CRT non-inferior to preoperative RT? **Note**: LR for preop RT = 10% at 2 years.

←R→ 1350. Operable carcinoma of rectum (< 15 cm from anal verge), TME encouraged but not mandated (done in 93%).

| 1. Preop-RT 25/5 **± adj chemo** | 2. Surgery + selective postop chemo-RT → **if SM + ≤ 1mm** (RT 45/25 + concur 5-FU and leucovorin) **± adj chemo**|.

Concurrent Chemo: either continuous (infusion 5-FU 200 mg/m² per day + leucovorin) **or** weekly bolus (5-FU 300 mg/m² + leucovorin 20 mg/m²).

Adj Chemo: Either monthly (5-FU 370–425 mg/m² on days 1–5 + 20 mg/m² leucovorin) **or** weekly (5-FU 370–425mg/m² + 20 mg/m² leucovorin).

When do you need adjuvant chemo?

Circumferential resection margin + and **LN status +**, which was to be applied to both treatment groups.

If both postoperative CRT and adjuvant chemo were required, postoperative CRT was to be given first.

RT fields: sacral promontory superiorly, 3–5 cm below the inferior tumor extent, 2–3 cm anterior to the sacral promontory, 1 cm posterior to the anterior sacrum, and 1 cm lateral to the most lateral aspect of the bony true pelvis.

1^{O} outcome: LR. **2^{O} outcome**: OS, DFS, LRFS, time to appearance of DM, post-op morbidity, QoL, LT complications.

Note: In postop arm, SM+ was in 12% as trigger for postop CRT vs 10% in preop group. Adj chemo in 40% of preop arm and 45% of postop arm.

Sebag-Montefiore, Lancet 2009. F/U median 4 years.

Results: Preop RT vs postop CRT: **LR** ↓ 61% RR of LR, HR 0.39, p < 0.001. **Absolute difference of 6.2% at 3 years (4.4% vs 10.6%).**

DFS ↑ 24% RR of DFS, HR 0.76, p = 0.013. Absolute difference of 6% at 3 years (77.5% vs 71.5%).

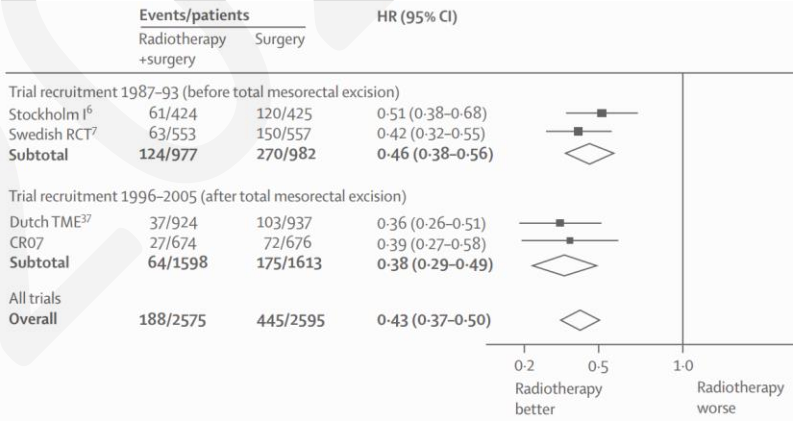
	Preoperative radiotherapy (n=674)	Selective postoperative chemoradiotherapy (n=676)	HR (95% CI)
Kaplan-Meier results*			
Local recurrence	..	..	0·39 (0·27–0·58); p<0·0001
2 year	3·4%	8·3%	..
3 year	4·4%	10·6%	..
5 year	4·7%	11·5%	..
Disease-free survival	..	..	0·76 (0·62–0·94); p=0·013
2 year	82·5%	77·6%	..
3 year	77·5%	71·5%	..
5 year	73·6%	66·7%	..
Overall survival	..	..	0·91 (0·73–1·13); p=0·40
2 year	86·1%	84·8%	..
3 year	80·3%	78·6%	..
5 year	70·3%	67·9%	..

Conclusions: Preop RT effective treatment for operable rectal cancer.

Post-operative radiation therapy cannot compensate for a positive CRM.

Overall negativity rate for circumferential resection margin was 89%.

Dutch trial showed similar results with 77%.

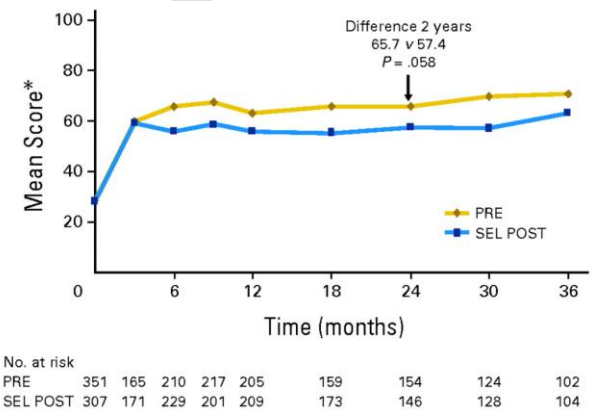


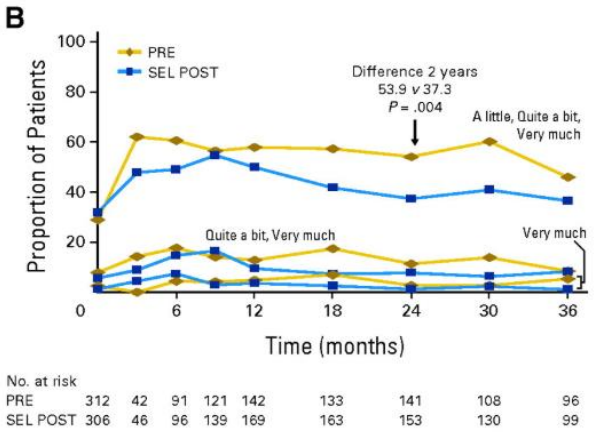
Stephens, JCO 2010. QoL Study.

Conclusion These results from a large randomized trial using validated patient-completed questionnaires show that, for males, the main adverse effect was sexual dysfunction, and the main cause of this was surgery, but that **PRE 5x5** also affected sexual and some aspects of bowel functioning.

(LEFT) Male Sexual Dyfunction. MSD was negatively affected by surgery (mean score at baseline, 28.4; at 3 months, 59.3; P < .001 for difference) with no difference between treatment arms. Thus, the impact of surgery (> 30 percentage points) represents a major clinical impact, whereas PRE (8 to 10 percentage points) had only a small impact.

(RIGHT B) GI. Proportion of patients reporting unintentional release of stools ("A little," "Quite a bit," or "Very much") by treatment. PRE, preoperative radiotherapy; SEL POST, selective postoperative chemoradiotherapy. (*) High score indicates worse quality of life.





Time from 5x5 → Surg?

STOCKHOLM III.
←R→ 840 rectal AC, M0. Surgical candidate to
1. 5 × 5 Gy → surgery within 1 week **2.** 5 x 5 Gy → surgery after 4–8 weeks **3. Long Course** 25 × 2 Gy → after 4–8 weeks.
After a protocol amendment, ←R→ could include all three arms or just the 2 short-course RT arms per hospital preference. 1^{O} time to LR.

Erlandsson, Lancet 2017.
Median time to LR 33.4 mo vs. 19.3 mo. vs. 33.3 mo. HR arm1vs2 1·44 [95% CI 0·41–5·11]; HR 1vs3 2·24 [0·71–7·10]; p=0·48; NS both.
Side effects: Acute radiation-induced toxicity was recorded in one patient (<1%) of 357 after short-course radiotherapy, 23 (7%) of 355 after short-course radiotherapy with delay, and six (5%) of 128 patients after long-course radiotherapy with delay.
Postoperative complications similar all arms 50% vs. 38% vs. 39%. [OR] 1vs3, 0·59 [95% CI 0·36–0·97], 1vs3 0·63 [0·38–1·04], p=0·075.
Pooled analysis 1 vs 2. risk of postoperative complications SS ↓ with delay, 53% vs. 41% (OR 0·61, SS).
Conclusion: Based on these findings, we suggest that **short-course radiotherapy with delay** to surgery is a useful alternative to conventional short-course radiotherapy with immediate surgery.
Criticism: no C in the long course arm. Very few people got adj C, too. Use of neoadjuvant C was NOT reported. Therefore, cannot interpret this well.

Erlandsson, Radiother Oncol 2020
318, 285, and 94 patients were included in the SRT, SRT-delay and LRT-delay groups. Median follow up was 5.7 years. There were significantly lower tumour stages after SRT-delay. pCR was seen in 1 (0.3%), 29 (10.4%) and 2 (2.2%) patients in SRT, SRT-delay and LRT-delay, respectively. The pCR and Dworak grade 4 were associated with superior survival. pCR vs no-pCR Hazard Ratio (95% Confidence Interval) OS: 0.51 (0.26–0.99) p = 0.046, TTR: 0.27 (0.09–0.86) p = 0.027.
Conclusion
SRT-delay induces pCR in about 10% of the patients and is in this aspect superior to 25 × 2 Gy. A complete tumour response, TRG 4 using the Dworak system, or a pCR, is associated with superior OS and TTR.

Polish Randomized 5x5
←R→ 154 patients all received 5x5 preop RT | 1. Surgery after 7-10 days | 2. Surgery after 4-5 weeks |.

Pach, Langenbecks Arch Surg 2012.
5-year survival rate 63% vs. 73% (NS).
5-year survival rate 90% (downstaging after RT) vs. 60% (without response), p = 0.004.
Recurrence was diagnosed in 13.2% of patients.
Systemic recurrence 12.3% vs. 2.8% (p = 0.035).
No differences in local recurrence rates were observed in both subgroups of irradiated patients (p = 0.119).
Higher downstaging rate 13% vs. 44.2%, p = 0.0001.
But NS rate of sphincter-saving procedures (p = 0.627) or curative resections (p = 0.132).
Conclusions: 1. Improved 5-year survival rate is observed only in patients with downstaging after preoperative irradiation dose of 25 Gy. 2. Longer time interval after preoperative radiotherapy 25 Gy does not improve the rate of sphincter-saving procedures and curative resections (R0) despite higher downstaging rate observed in this regimen.

Note: In certain circumstances when for a rectal cancer with questionable T3 or questionable N+ by MRI 5x5 short course radiation → immediate surgery can still lead to reasonable pathology interpretation as a guide for adjuvant chemotherapy.

Trimodality → Adjuvant Chemo

History: Many centers used to do after extrapolating from colon studies:
Adjuvant 5FU/levamisole ↓ mortality rate among patients with stage III colon cancer by 33%.
This prompted several trials which established 6 months treatment with 5FU and leucovorin as standard adjuvant chemo for stage III colon cancer.

Either 5-FU for 6 months or FOLFOX for 6 months.

Adj FOLFOX

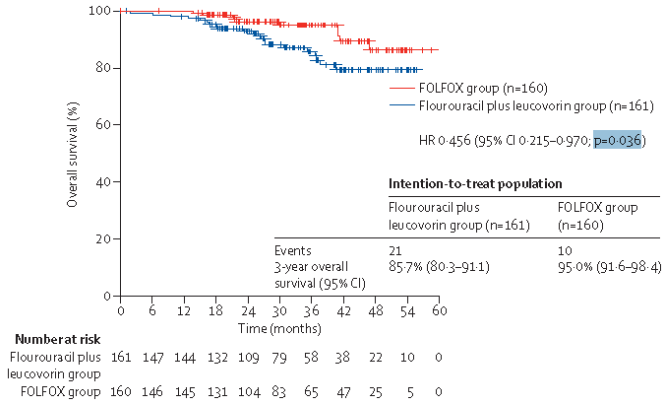
PENDING: RTOG 08-22
CRT → 4-8 weeks surgery → 4-8 weeks FOLFOX.
CRT = Pelvic IMRT: 45 Gy in 25 fx 3D-CRT + boost: 5.4 Gy in 3 fx to total dose of 50.4 Gy in 28 fx
Concurrent Capecitabine, Oxaliplatin

COLON CANCER "IDEA" Noninferiority Timing Trial
BACKGROUND Since 2004, 6 months of FOLFOX is great in patients with stage III colon cancer. However, since oxaliplatin is associated with cumulative neurotoxicity, a shorter duration of therapy could spare toxic effects and health expenditures.
Noninferiority TRIAL: Prospective, preplanned, pooled analysis of six randomized, phase 3 trials that were conducted concurrently to evaluate the noninferiority of adjuvant therapy with either FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) administered for 3 months, as compared with 6 months. 1^{O} DFS at 4 years.

Grothey, NEJM 2008.
Overall: The noninferiority of 3 months vs. 6 months **was not confirmed** in the overall study population (HR, 1.07, CI, 1.00 - 1.15).
CAPOX Subset: Noninferiority **was seen** (HR, 0.95; 95% CI, 0.85 to 1.06).
FOLFOX Subset: Non inferiority was not (HR, 1.16; 95% CI, 1.06 to 1.26).
Exploratory Subset: T4, N2, or both, DFS 6-month > 3 months (64.4% vs. 62.7%) FOR SUPERIORITY (SS).
CONCLUSIONS Among patients with stage III colon cancer receiving adjuvant therapy with FOLFOX or CAPOX, noninferiority of 3 months of therapy, as compared with 6 months, was not confirmed in the overall population. However, in patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in the lower-risk subgroup. (Funded by the National Cancer Institute and others.)

ADORE Korean Trial
←R→ 321 patients AC rectum (≤ less than 12 cm from anal verge or below peritoneal reflection). Preop CRT (with 5-FU monotherapy) → TME.
pStage II/III (ypT3–4N0 or ypTanyN1–2), all RO, with no microscopic residual (IE, all three resection margins—proximal, distal, and radial)
THEN Randomized Adjuvant 1. 4 x cycles **FOLF** 5-FU 380 mg/m², leucovorin 20 mg/m² on days 1–5, every 4 weeks
2. 8 x cycles **FOLFOX** 5-FU bolus 400 mg/m², leucovorin 200 mg/m², oxaliplatin 85 mg/m² on day 1
+ 5-FU infusion 2400 mg/m² for 46 h, every 2 weeks).
Radiation was 50.4.

Hong, Lancet 2014.
Results: 95-97% patients completed treatment.
Dose modification: FOLFOX 60% vs. FOLF 32%, p<0.0001
Cycles with reduced doses: FOLFOX 35% vs FOLF 18%, p<0.0001
3-year DFS: **FOLFOX 71·6%** vs. **FOLF** 62·9%, p=0·047.
3-year OS: **FOLFOX 95%** vs. **FOLF** 85.7%, p=0·036



	Fluorouracil plus leucovorin group (n=149)					FOLFOX group (n=146)				
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Haematological										
Leucopenia	33 (22%)	6 (4%)	19 (13%)	8 (5%)	0	47 (32%)	10 (7%)	25 (17%)	12 (8%)	0
Neutropenia*	68 (46%)	0	30 (20%)	33 (22%)	5 (3%)	102 (70%)	1 (<1%)	49 (34%)	36 (25%)	16 (11%)
Febrile neutropenia	4 (3%)	..	..	2 (1%)	2 (1%)	1 (<1%)	..	..	1 (<1%)	0
Thrombocytopenia*	3 (2%)	3 (2%)	0	0	0	38 (26%)	17 (12%)	20 (14%)	1 (<1%)	0
Anaemia	3 (2%)	0	2 (1%)	1 (<1%)	0	3 (2%)	1 (<1%)	2 (1%)	0	0
Non-haematological										
Fatigue*	26 (17%)	22 (15%)	4 (3%)	0	0	41 (28%)	33 (23%)	8 (5%)	0	0
Alopecia	28 (19%)	26 (17%)	2 (1%)	0	0	18 (12%)	18 (12%)	0	0	0
Nausea*	56 (38%)	47 (32%)	8 (5%)	1 (<1%)	0	78 (53%)	70 (48%)	6 (4%)	2 (1%)	0
Vomiting	17 (11%)	11 (7%)	5 (3%)	1 (<1%)	0	19 (13%)	16 (11%)	2 (1%)	1 (<1%)	0
Stomatitis	63 (42%)	49 (33%)	12 (8%)	1 (<1%)	1 (<1%)	47 (32%)	43 (29%)	4 (3%)	0	0
Diarrhoea	38 (26%)	27 (18%)	7 (5%)	4 (3%)	0	49 (34%)	33 (23%)	14 (10%)	2 (1%)	0
Allergic reaction	1 (<1%)	1 (<1%)	0	0	0	3 (2%)	3 (2%)	0	0	0
Sensory neuropathy*	8 (5%)	7 (5%)	1 (<1%)	0	0	103 (71%)	98 (67%)	4 (3%)	1 (<1%)	0

	Fluorouracil plus leucovorin group (n=161)	FOLFOX group (n=160)
Any event	53 (33%)	39 (24%)
Local recurrence	12 (7%)	5 (3%)
Distant metastasis	44 (27%)	35 (22%)
Lung	29 (18%)	24 (15%)
Liver	15 (9%)	8 (5%)
Lymph node	10 (6%)	6 (4%)
Bone	4 (2%)	2 (1%)
Peritoneum	1 (<1%)	1 (<1%)
Other*	2 (1%)	2 (1%)

Data are number of patients (%). FOLFOX=fluorouracil, leucovorin, and oxaliplatin. *Other site of metastasis were brain (one) and ovary (one) in the FOLFOX group, and bladder (one) and pleura (one) in the fluorouracil plus leucovorin group.

Table 3: Patterns of recurrence

"German 2" CAO/ARO/AIO-4. 1^{O} = DFS
←R→ 1236 cT3–4 or +cN
1. STD preop RT 50·4 Gy in 28 fx + IV 5-FU (1000 mg/m² d 1–5, 29–33) → surgery → 4c bolus 5-FU (500 mg/m² d 1–5, 29) for 4 months.
2. EXP preop RT 50·4 Gy in 28 fx + IV **FOX** → surgery → 8c **bolus FOLFOX** for total 4 months.
Concurrent **FOX** 5-FU (250 mg/m² on days 1–14, 22–35), **oxaliplatin** (50 mg/m² on days 1, 8, 22, and 29),
Adjuvant **FOLFOX** **leucovorin 2h** (400 mg/m² d 1, 15), **IV 5-FU 46h** (2400 mg/m², d 1–2 and 15–16), **oxaliplatin 2h** (100 mg/m² d 1, 15),

Rodel, JCO 2015. FAVOR EXP GROUP
3-year DFS EXP 75·9% vs. STD 71.2%, p=0.03.
3-year OS EXP 88.7% vs. STD 88.0%, NS

CONCLUSION: EXP significantly improved disease-free survival of patients with clinically staged cT3–4 or cN1–2 rectal cancer compared with our former fluorouracil-based combined modality regimen (based on CAO/ARO/AIO-94). The regimen established by CAO/ARO/AIO-04 can be deemed a new treatment option for patients with locally advanced rectal cancer.

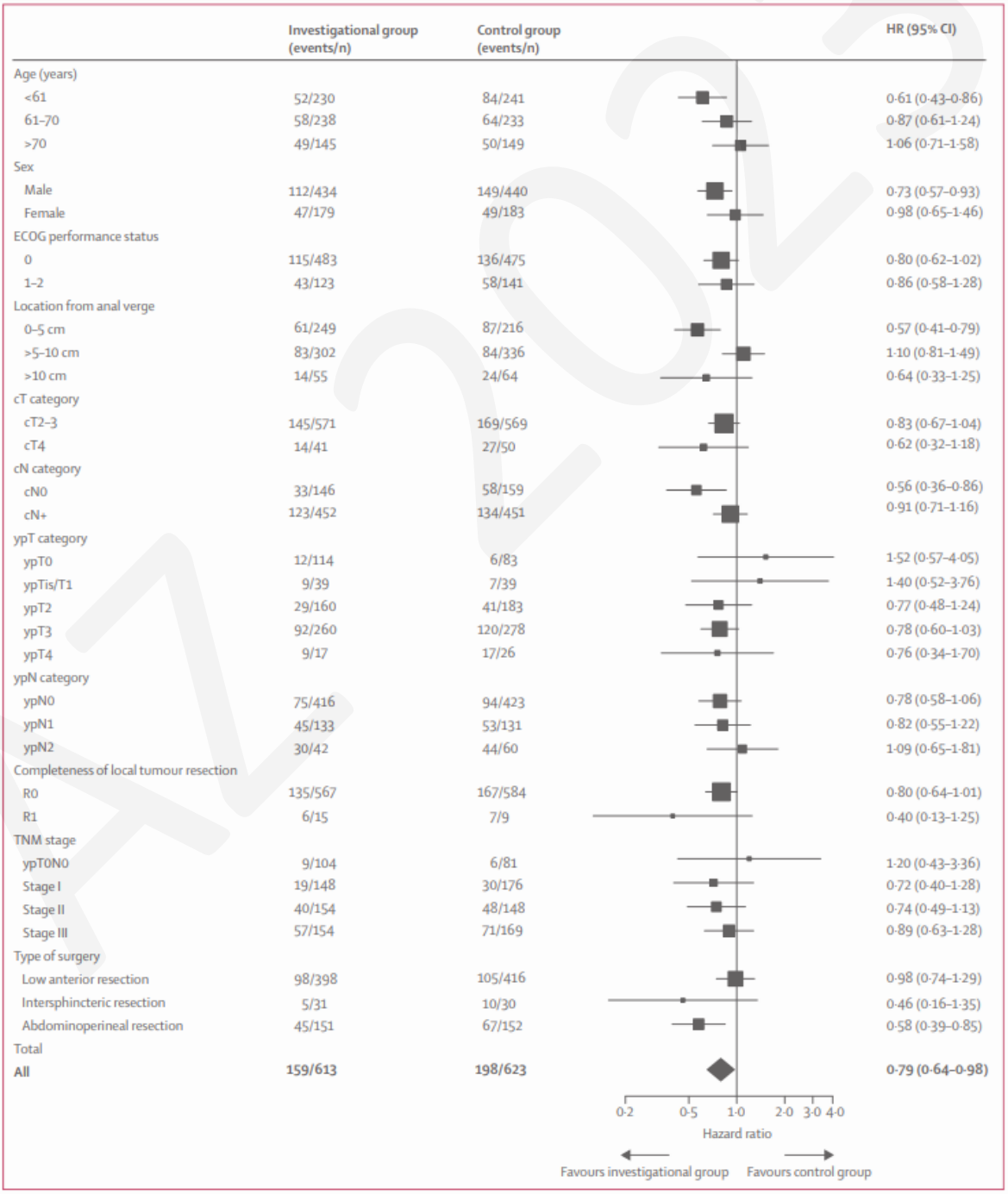


Figure 4: Disease-free survival in the intention-to-treat population by patient subgroups according to pretreatment and surgical or pathological factors after preoperative chemoradiotherapy

METAANALYSIS:

4 eligible trials, 1196 patients with (y)pTNM stage II or III disease, who had an R0 resection, LAR or APR, and had a tumor within 15 cm of the anal verge.

Breugom, Lancet Oncol. 2015.

No significant differences in OS between patients of 1. adjuvant chemotherapy vs 2. observation (hazard ratio [HR] 0·97, 95% CI 0·81–1·17; p=0·775); there were no significant differences in overall survival in subgroup analyses. No DFS (HR 0·91, 95% CI 0·77–1·07; p=0·230) or distant recurrences (0·94, 0·78–1·14; p=0·523) compared with observation. However, in subgroup analyses, patients with a tumour 10–15 cm from the anal verge had improved disease-free survival (0·59, 0·40–0·85; p=0·005, p=0·107) and fewer distant recurrences (0·61, 0·40–0·94; p=0·025, p=0·126) when treated with adjuvant chemotherapy compared with patients undergoing observation.

CONCLUSION: Adjuvant fluorouracil-based chemotherapy NO BENEFIT in OS, DFS, or distant recurrence. However, adjuvant chemotherapy might benefit patients with a tumor 10–15 cm from the anal verge in terms of DFS and distant recurrence. Further studies of preoperative and postoperative treatment for this subgroup of patients are warranted.

Sainato, Radiother Oncol, 2014.

←R→ locally advanced rectal cancer. 655 patients treated preoperative CRT → surg → RANDOMIZED. 1. Post-operative 6 c x leucovorin and 5FU 2. Obs.
Results: No difference in recurrence rate or OS 5 year (69 vs 70% with and without). Even when restricted to patients who had node-positive disease (ypN+), OS no difference (52% vs 51%).

Dutch Colorectal PROCTOR/SCRIPT.

221npTNM stage II–III rectal cancer patients treated with neoadjuvant radiotherapy and TME surgery, ←R→ 1. adjuvant chemotherapy or 2. observation. Radiotherapy consisted of 5 × 5 Gy. Chemoradiotherapy consisted of 25 × 1.8-2 Gy combined with 5-FU-based chemotherapy. Adjuvant chemotherapy consisted of 5-FU/LV (PROCTOR) or eight courses capecitabine (SCRIPT).
Of 470 enrolled patients, 437 were eligible. The trial closed prematurely because of slow patient accrual.

Breugom, Ann Oncol 2015.

Patients were randomly assigned to observation (n = 221) or adjuvant chemotherapy (n = 216). After a median follow-up of 5.0 years, 5-year overall survival was 79.2% in the observation group and 80.4% in the chemotherapy group [hazard ratio (HR) 0.93, 95% confidence interval (CI) 0.62-1.39; P = 0.73]. The HR for disease-free survival was 0.80 (95% CI 0.60-1.07; P = 0.13). Five-year cumulative incidence for locoregional recurrences was 7.8% in both groups. Five-year cumulative incidence for distant recurrences was 38.5% and 34.7%, respectively (P = 0.39).

Swets, Eur J Cancer 2018.

Lymphatic invasion, PNI, extramural venous invasion, intramural venous invasion and tumour budding were determined in standard tissue slides.

Results: The presence of PNI (HR 3.36; 95% CI 1.82–6.21), extramural vascular invasion (HR 1.93; 95% CI 1.17–3.19) and tumour budding (HR 1.83, 95% CI 1.11–3.03) was associated with a significant worse overall survival. The presence of ≥2 adverse biomarkers resulted in a stronger prediction of adverse outcome in terms of overall survival (HR 2.82; 95% CI 1.66–4.79), disease-free survival (HR 2.27; 95% CI 1.47–3.48), and distant recurrence (HR 2.51; 95% CI 1.56–4.02). None of these markers alone or combined predicted a beneficial effect of adjuvant chemotherapy.

Discussion

We confirmed that several stage-independent biomarkers were significantly associated with a decreased outcome in rectal cancer patients. More importantly, these markers did not have predictive value and are thus not useful to select for adjuvant therapy in rectal cancer.

UK Chronicle Trial

Background: In stage III colon cancer, oxaliplatin/5-fluorouracil (5-FU)-based adjuvant chemotherapy (FOLFOX) improves disease-free survival (DFS) and overall survival (OS). In rectal adenocarcinoma following neoadjuvant chemoradiation (CRT), we examined the benefit of postoperative adjuvant capecitabine and oxaliplatin (XELOX) chemotherapy.
←R→ 113. CLOSED PREMATURELY. Fluoropyrimidine-based CRT and curative resection → 1. observation or 2. six cycles of XELOX. The primary end point was DFS; secondary end points were acute toxicity and OS. 390 patients were required in each arm, to detect an improvement in 3-year DFS from 40% to 50.5%, with 85% power and two-sided 5% significance level.

Glynne-Jones, Ann Oncol 2014.

Compliance was poor, 93% allocated chemotherapy started and 48% completed six cycles. Protocolised dose reductions in XELOX were 39%, and levels of G3/G4 toxicity 40%. After a median follow-up of 44.8 months, 16 patients (27%) in the observation arm had relapsed or died compared with 12 patients (22%) in XELOX.
3yr DFS for XELOX and observation were 78% and 71%, respectively (HR for DFS = 0.80; 95% CI 0.38-1.69; P = 0.56).
3ur OS for XELOX and observation were 89% and 88%, respectively (HR for OS = 1.18; 95% CI 0.43-3.26; P = 0.75).

How to ↑ pCR?

Δ RT (Boost?)

Phase II RECTAL-BOOST Trial CRT → "immediate intervention" → planned surgery 12 weeks after.
←R→ 128 patients locally advanced (50% were ≤ 3cm anal verge, 95% cT3-4, 70% ≤ 1mm distance to mesorectal fascia, ~90% N+, ~5% oligomets).
Patients in the intervention group were "offered intervention" aka they can choose to accept or not.
Patients in the control group were not offered the choice for the intervention.
Control = 50 Gy in 25 fractions (2 Gy / fx) + concurrent Cape.
Intervention = RT boost 15 Gy in 3 fractions (5 Gy / fx) without C.
1^{o} pCR.

Table 1 Baseline characteristics by allocated treatment

Baseline characteristics	Boost group (n = 64)	Control group (n = 64)
Age, y	64.5 (55.0-69.0)	62.0 (56.0-71.0)
Sex		
Male	48 (75.0)	47 (73.4)
Female	16 (25.0)	17 (26.6)
Comorbidities		
None	30 (46.9)	26 (40.6)
1 or more	34 (53.1)	38 (59.4)
Tumor distance*		
≤3.0cm	29 (45.3)	36 (56.3)
3.1-5.0 cm	12 (18.8)	8 (12.5)
5.1-10.0cm	23 (35.9)	20 (31.2)
Tumor stage		
cT2	2 (3.1)	5 (7.8)
cT3	51 (79.7)	39 (60.9)
cT4	11 (17.2)	20 (31.3)
Distance to the mesorectal fascia†		
≤1 mm	42 (65.6)	46 (71.9)
>1 mm	22 (34.4)	18 (28.1)
Nodal stage		
cN0	5 (7.8)	9 (14.1)
cN1	14 (21.9)	17 (26.6)
cN2	45 (70.3)	38 (59.4)
Oligometastatic disease		
No	61 (95.3)	62 (96.9)
Yes	3 (4.7)	2 (3.1)
Capecitabine prescribed dose, mg/d	3300 (3000-3600)	3300 (3000-3300)
Interval to MRI, wk‡	9.0 (8.0-9.0)	9.0 (8.0-9.0)
Interval to surgery, wk	12.0 (12.0-14.0)	12.0 (11.0-13.0)

Table 2 Treatment course by allocated treatment

Treatment characteristics	Boost group (n = 64)	Control group (n = 64)
Mean PTV_{tumor} dose, Gy*	66.8 (60.1-69.8)	50.0 (49.9-50.2)
Minimum PTV_{tumor} dose, Gy†	58.9 (50.5-64.3)	48.6 (48.3-48.8)
Maximum PTV_{tumor} dose, Gy†	74.0 (65.6-75.1)	51.4 (51.2-51.8)
Radiation therapy fractions completed	60 (93.8)	63 (98.4)
Prescribed capecitabine dose completed	60 (93.8)	61 (95.3)
Planned surgery		
Low anterior resection	28 (43.8)	19 (29.7)
Abdominoperineal resection	18 (28.1)	32 (50.0)
Hartmann resection	2 (3.1)	2 (3.1)
Local excision	1 (1.6)	0
Delayed/salvage surgery‡		
Low anterior resection	1 (1.6)	2 (3.1)
Abdominoperineal resection	1 (1.6)	2 (3.1)
Local excision	2 (3.1)	0
2-y watch-and-wait	9 (14.1)	5 (7.8)
Palliative systemic treatment	2 (3.1)	2 (3.1)

Couwenberg, IJROBP 2020.
51 of the 64 (79.7%) patients in the intervention group accepted and received a boost.
pCR = 23 of 64 (35.9%) intervention vs. 24 of 64 (37.5%) control.

Near-complete or complete tumor regression 34 of 49 (69.4%) intervention vs. 24 of 53; (45.3%).
Grade ≥3 acute toxicity was comparable: 6 of 64 (9.4%) in the intervention group versus 5 of 64 (7.8%) in the control group (OR = 1.22; 95% CI, 0.35-4.22).

Conclusions
Dose escalation with an external radiation therapy boost to the tumor before neoadjuvant chemoradiation did not increase the pathologic or sustained clinical complete tumor response rate in LARC.

NOTE: Similar findings were seen in INTERACT Trial cT2 (distal) – cT3.
Valentini, Radiother Oncol 2019.

Table 3 Primary outcome and secondary outcomes by allocated treatment

Outcomes	Boost group (n = 64)	Control group (n = 64)	OR or MD (95% CI) boost vs control	*P* value*
pCR or 2-y cCR	23 of 64 (35.9)	24 of 64 (37.5)	0.94 (0.46-1.92)	.86
ycT0(near)ycN0 at response MRI†	18 of 64 (28.1)	12 of 64 (18.8)	1.73 (0.75-3.98)	.21
Sphincter preservation	36 of 64 (56.3)	22 of 64 (34.4)	2.46 (1.20-5.01)	.01
Mandard TRG 1-2‡	34 of 49 (69.4)	24 of 53 (45.3)	2.74 (1.21-6.18)	.02
CTCAE grade ≥3	6 of 64 (9.4)	5 of 64 (7.8)	1.22 (0.35-4.22)	.75
Clavien–Dindo grade ≥3	14 of 53 (26.4)	11 of 57 (19.3)	1.50 (0.61-3.68)	.50
QoL summary score§				
Baseline	87.7 (1.6)	86.3 (1.6)	1.31 (−5.81 to 3.18)	.57
3 mo	80.8 (1.6)	88.4 (1.7)	−7.54 (−12.09 to −2.99)	.001
6 mo	78.5 (1.7)	82.2 (1.7)	−3.64 (−8.28 to 1.00)	.12
12 mo	87.0 (1.8)	87.5 (1.8)	−0.57 (−5.56 to 4.42)	.82

OPERA Contact X-ray Boost

Background

Organ preservation after reaching clinical complete response on neoadjuvant therapy is gaining interest for rectal cancers, although the role of radiation dose escalation is still not known. We aimed to determine whether a contact x-ray brachytherapy boost, following or preceding neoadjuvant chemoradiotherapy, increases the probability of 3-year organ preservation for patients with early rectal cancers.

←R→ 148 operable rectal CA patients, aged ≥ 18, cT2, cT3a, or cT3b AC low-mid rectum, ≤ 5 cm, cN0 or cN1 < 8 mm.

NA-CRT → |1. EBRT Boost 9 Gy in 5 Fx | 2. Contact X-ray Brachy 90 Gy in 3 fractions |.

CRT = 45 Gy external beam radiotherapy in 25 fractions over 5 weeks with concurrent oral capecitabine (825 mg/m2 twice a day).

Brachy = contact x-ray boost preceded pelvic radiation when the tumor was <3 cm and followed it when ≥3 cm.

No adjuvant Chemotherapy.

Gerard, Lancet Gastro & Hepato 2023	38·2 months	
3-year organ preservation rate	ALL	59% vs. 81% (HR 0·36, p=0·0026).
	tumor < 3 cm	63% vs. 97% (HR 0·07, p=0·012).
	tumor > 3 cm	55% vs. 68% (HR 0·54, NS).
Early G2-3 adverse event		30% vs. 42% (NS)

The most common early grade 2–3 adverse events were proctitis (four [6%] in group A, nine [13%] in group B) and radiation dermatitis (seven [10%] in group A, two [3%] in group B). The main late side-effect was grade 1–2 rectal bleeding due to telangiectasia, which was more frequent in group B (37 [63%] of 59) than in group A (five [12%] of 43; p<0·0001) and subsided after 3 years.

Interpretation

Neoadjuvant chemoradiotherapy with a contact x-ray brachytherapy boost significantly improved the 3-year organ preservation rate, particularly for patients with tumours smaller than 3 cm who were treated with contact x-ray brachytherapy first, compared with neoadjuvant chemoradiotherapy with a boost via external beam radiotherapy. This approach could be discussed and offered to operable patients with early cT2–cT3 disease who are keen to avoid surgery and seek organ preservation.

Surgical Timing?

CRONOS Study

Importance The treatment for extraperitoneal locally advanced rectal cancer (LARC) is neoadjuvant therapy (NAT) followed by total mesorectal excision (TME). Robust evidence on the optimal time interval between NAT completion and surgery is lacking.

Objective To assess the association of time interval between NAT completion and TME with short- and long-term outcomes. It was hypothesized that longer intervals increase the pathologic complete response (pCR) rate without increasing perioperative morbidity.

Cohort Study 1506 patients LARC from 6 referral centers. All completed NAT TME 2005 - 2020.

Time interval between NAT completion → surgery: short (≤8 weeks) n=34%, intermediate (>8 and ≤12 weeks) n=53%, and long (>12 weeks) n=13%.

908 were male (60.3%), and the median (IQR) age was 68.8 (59.4-76.5) years.

Guzman, JAMA Surgery 2023 Follow-up duration was 33 months.

Overall pCR was 17.2%.

pCR comparison NS between INT and short or INT and long.

The long-interval group was significantly associated with **↓ risk of bad response** (tumor regression grade [TRG] 2-3; OR, 0.47; 95% CI, 0.24-0.91), systemic recurrence (hazard ratio, 0.59; 95% CI, 0.36-0.96), higher conversion risk (OR, 3.14; 95% CI, 1.62-6.07), minor postoperative complications (OR, 1.43; 95% CI, 1.04-1.97), and incomplete mesorectum (OR, 1.89; 95% CI, 1.02-3.50) when compared with the intermediate-interval group.

Conclusions and Relevance Time intervals longer than 12 weeks were associated with improved TRG and systemic recurrence but may increase surgical complexity and minor morbidity.

Large Pooled Analysis pCR from ←R→ Trial

3085 patients all age ≥ 18, cT3–T4 and cN0–2, no clinical evidence of distant metastasis at diagnosis, NAdj-CRT → Surgery.

1^{O} best surgical interval (SI) to achieve ↑ pCR.

2^{O} effect on survival outcomes according to the surgical intervention.

Gambacorta, Radiother Oncol 2020.

Overall, pCR 14% if SI at 6 weeks.

Cumulative pCR ↑ when SI lengthened, with **95% of pCR events** within **10 weeks** from Nad-CRT.

At UVA and MVA, lengthening of SI (p< 0.01), radiotherapy dose (p< 0.01), and the addition of oxaliplatin to Nad-CRT (p< 0.01) had a favorable impact on pCR. Furthermore, lengthening of SI was not impactful on local recurrences, distance metastases, and overall survival.

Conclusion This pooled analysis suggests that the best time to achieve pCR in LARC is at 10 weeks, considering that the lengthening of SI is not detrimental concerning survival outcomes.

GRECCAR-6.

←R→ 265 patients. cT3/T4 or Tx N+ tumors of the mid or lower rectum. Neoadjuvant RCT (45 to 50 Gy with fluorouracil or capecitabine) were included.

1. wait 7-week until surgery 2. Wait 11-week (11w). Primary end point was the pCR rate defined as a ypT0N0 specimen (NCT01648894).

Lefevre, JCO 2016

Most of the tumors were cT3 (82%). After RCT, surgery was not performed in nine patients (3.4%) because of the occurrence of distant metastasis (n = 5) or other reasons. Two patients underwent local resection of the tumor scar. A total of 47 (18.6%) specimens were classified as ypT0 (four had invaded lymph nodes [8.5%]).

1^{O} endpoint no different. 7 weeks: 20 of 133, **15.0%** vs 11w: 23 of 132, **17.4%**.

Morbidity SS ↑ in the 11w group (44.5% v 32%; P = .0404) as a result of increased medical complications (32.8% v 19.2%; P = .0137).

The 11w group had a ↓ SS quality of mesorectal resection (complete mesorectum [I] 78.7% v 90%; P = .0156).

Conclusion: Waiting 11 weeks after RCT did not increase the rate of pCR after surgical resection. A longer waiting period may be associated with higher morbidity and more difficult surgical resection.

Induction Chemo?

Phase 2 Non-Randomized.
292 patients registered, 259 analyzable. Stage II–III locally advanced rectal cancer at 17 institutions in the USA and Canada.
All patients received CRT (fluorouracil 225 mg/m ^{2} per day by continuous infusion throughout radiotherapy, and 45·0 Gy in 25 fractions, 5 days per week for 5 weeks, followed by a minimum boost of 5·4 Gy).
Group 1. Patients in group 1 had total mesorectal excision 6–8 weeks after chemoradiation.
Groups 2-4. Patients in groups 2–4 received two, four, or six cycles of mFOLFOX6, respectively, between CRT and total mesorectal excision.
Each cycle of mFOLFOX6 consisted of racemic leucovorin 200 mg/m ^{2} or 400 mg/m ^{2}, according to the discretion of the treating investigator, oxaliplatin 85 mg/m ^{2} in a 2-h infusion, bolus fluorouracil 400 mg/m ^{2} on day 1, and a 46-h infusion of fluorouracil 2400 mg/m ^{2}.
The primary endpoint was the proportion of patients who achieved a pathological complete response, analysed by intention to treat.

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Pathological complete response	11 (18%)	17 (25%)	20 (30%)	25 (38%)	0·0036
Partial response	44 (73%)	50 (75%)	46 (69%)	39 (60%)	..
Stable disease	5 (8%)	0	1 (1%)	1 (2%)	..

Data are number (%). p value tests the null hypothesis of equal proportions across study groups.

Table 3: **Pathological tumour response**

Garcia-Aguilar, Lancet 2015.
pCR Group 1: 18% Group 2: 25% Group 3: 30% Group 4: 38% p=0·0036.
Hematologic G3-4 Group 3 8% Group 4 28% (SS).

Interpretation
Delivery of 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.

THIS TRIAL IS THE BASIS FOR GI-002 and PROSPECT Trials.

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Time from start of chemoradiation to surgery (weeks)	14·2 (4·3)	17·1 (2·9)	21·0 (2·7)	25·2 (4·0)	0·0001
Time from end of chemoradiation to surgery (weeks)	8·5 (4·2)	11·1 (2·9)	15·4 (2·6)	19·3 (4·2)	0·0001
Sphincter-saving surgery	46 (77%)	50 (75%)	50 (75%)	44 (68%)	0·68
Ileostomy	38/46 (83%)	43/50 (86%)	47/50 (94%)	38/43 (88%)*	0·33
Resection with negative margins	59 (98%)	67 (100%)	64 (96%)	64 (100%)†	0·089
Number of nodes examined	12 (2–31)	14 (2–30)	13 (2–30)	11 (1–47)	0·20
Pelvic fibrosis‡	2·4 (1·7)	3·9 (2·6)	4·4 (2·4)	3·9 (2·4)	0·0001
Technical difficulty§	4·6 (2·7)	4·9 (2·8)	5·1 (2·5)	4·8 (2·4)	0·80
Estimated blood loss (mL)	200 (50–1200)	225 (25–1500)	200 (50–1000)	150 (0–1000)	0·62

Data are mean (SD), number (%), n/N (%), or median (range). p values test the null hypothesis of equal means or proportions across study groups. *Information on whether an ileostomy was created or not was not available for one patient. †Data missing for one patient. ‡Scale ranges from 1 (none) to 10 (maximum). §Scale ranges from 1 (easy) to 10 (difficult).

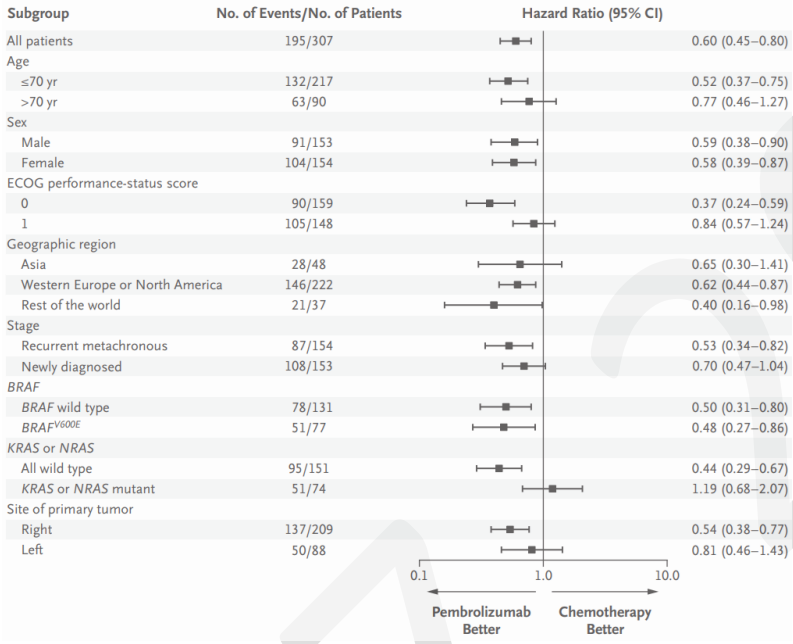
Table 2: **Surgical results**

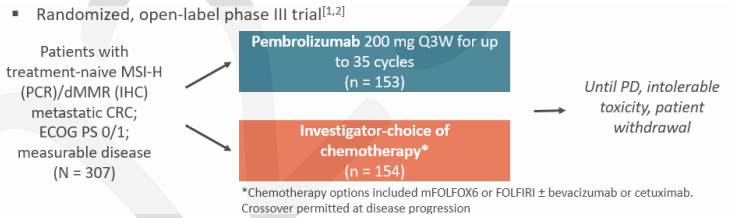
Immuno and Δ Systemics

Phase II Dostarlimab (PD-1 inhibitor for **dMMR**- mismatch repair deficient patients)
12 patients with stage II or III rectal adenocarcinoma + dMMR (rare in general population 5-10%).
All → 6 months of dostarlimab → CRT → Surgery.

Cercek, NEJM 2022
100% with 6 months of follow-up have cCR (no evidence on MRI, PET, endoscopy, DRE, or biopsy).
No patients received surgery yet.
CONCLUSIONS Mismatch repair–deficient, locally advanced rectal cancer was highly sensitive to single-agent PD-1 blockade. Longer follow-up is needed to assess the duration of response.

Keynote- 177 **MSI-High** Pembrolizumab
←R→ 307 metastatic MSI-H–dMMR colorectal cancer treatment naïve | 1. pembrolizumab | 2. Chemotherapy ± bevacizumab |.
Pembro = 200 mg every 3 weeks Chemo = 5-fluorouracil–based therapy with or without bevacizumab or cetuximab every 2 weeks.
Patients receiving chemotherapy could cross over to pembrolizumab therapy after disease progression.
1^{O} PFS and OS co-endpoints.





Andre, NEJM 2020 32.4 month follow-up.
Mean PFS 16.5 months vs. 8.2 months (HR 0.6, SS).
Estimated restricted mean survival after 24 months of follow-up was 13.7 months vs. 10.8 months.
Data on overall survival were still evolving (66% of required events had occurred) and remain blinded until the final analysis.
Response (complete or partial) 43.8% vs. 33.1%.
Among patients with overall response, DURABLE response of 24 months = 83% vs. 35%.

Crossover from CT to pembro after PD in **56/154 patients (36%)**.
In ITT population, effective crossover rate was 59%.
35 additional patients received anti–PD-L1 tx outside of trial.

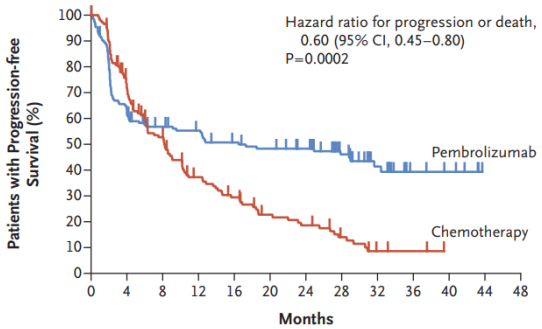
Treatment-related adverse events of grade 3 or higher occurred in 22% of the patients in the pembrolizumab group, as compared with 66% (including one patient who died) in the chemotherapy group.

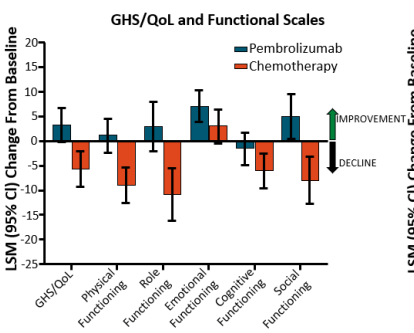
Δ in EORTC QLQ-C30 Scores From Baseline to Wk 18 (BELOW) ↓

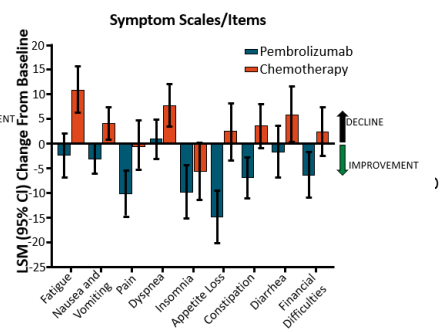
CONCLUSIONS
Pembrolizumab led to significantly longer progression-free survival than chemotherapy when received as first-line therapy for MSI-H–dMMR metastatic colorectal cancer, with fewer treatment-related adverse events

Table 2. Antitumor Activity in the Intention-to-Treat Population.

Variable	Pembrolizumab (N=153)	Chemotherapy (N=154)
Overall response*		
No. of patients	67	51
% (95% CI)	43.8 (35.8 to 52.0)	33.1 (25.8 to 41.1)
Best response — no. (%)†		
Complete response	17 (11.1)	6 (3.9)
Partial response	50 (32.7)	45 (29.2)
Stable disease	32 (20.9)	65 (42.2)
Progressive disease	45 (29.4)	19 (12.3)
Could not be evaluated or no assessment made‡	9 (5.9)	19 (12.3)
Median time to response (range) — mo	2.2 (1.8 to 18.8)	2.1 (1.7 to 24.9)
Median duration of response (range) — mo§	NR (2.3+ to 41.4+)	10.6 (2.8 to 37.5+)
Response duration of ≥24 months — %§	82.6	35.3







Galunisertib TGT-β Phase II

Background: TGF-β is an immunosuppressive cytokine that is upregulated in colorectal cancer.
TGF-β blockade ↑ response to CRT in preclinical models of colorectal adenocarcinoma.
Hypothesis: Adding the TGF-β type I receptor kinase inhibitor galunisertib to neoadjuvant CRT could ↑ pCR in LA Rectal Cancer.
Single Arm n=38 Phase II Locally advanced, rectal adenocarcinoma, stage IIA–IIIC or IV.

Treatment: Two 14-day courses of PO galunisertib 150 mg BID, before and during 5-FU based CRT
C = IV fluorouracil 225 mg/m2 over 24 h daily 7 days per week **or** PO Cape 825 mg/m2 twice per day 5 days per week.
RT = 50·4–54·0 Gy in 28–30 fractions. Concurrent with above chemo.
5–9 weeks later, patients underwent response assessment.
If CR → opt for non-operative management aka chemo.
Chemo → modified FOLFOX6 (IV leucovorin 400 mg/m2 on day 1, IV fluorouracil 400 mg/m2 on day 1 then 2400 mg/m2 over 46 h, and IV oxaliplatin 85 mg/m2 on day 1 delivered every 2 weeks for eight cycles) or CAPEOX (IV oxaliplatin 130 mg/m2 on day 1 and PO Cape 1000 mg/m2 twice daily for 14 days every 3 weeks for four cycles).
If < CR → surgical resection.

1^{O} CR rate = composite pCR (at surgery) and cCR maintained at 1 year after last therapy in patients with non-operative management.

Yamakazi, Lancet 2022.
Of the 35 patients who completed CRT → 25 (71%) proceeded to TME.
Of the 25, five (20%) had pCR.
Ten (29%) patients had non-operative management, three (30%) of whom ultimately chose to have TME → 2/3 (66%) = pCR.
Of the remaining 7 in the non-operative management group, five (71%) had cCR at 1 year after their last modified FOLFOX6 infusion.
In total, 12 (32%) of 38 patients had a complete response.
Common grade 3 adverse events during treatment included diarrhoea in six (16%) of 38 patients, and haematological toxicity in seven (18%) patients. Two (5%) patients had grade 4 adverse events, one related to chemoradiotherapy-induced diarrhoea and dehydration, and the other an intraoperative ischaemic event. No treatment-related deaths occurred.
Interpretation The addition of galunisertib to neoadjuvant chemoradiotherapy in patients with locally advanced rectal cancer improved the complete response rate to 32%, was well tolerated, and warrants further assessment in randomised trials.

Chinese Irinotecan UGT1A1 Genotype **CRT → S → XELOX**

Background: Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) genotype is associated with better irinotecan tolerance. Could pCR be ↑?
←R→ 360 patients cT3-4 and/or N+ rectal adenocarcinoma, UGT1A1 genotype *1*1 or *1*28
| 1. pelvic RT of 50 Gy/25 + concurrent Cape → CapeOx | 2. RT + Cape + weekly irinotecan → irinotecan + Cape |
Irinotecan 80 mg/m2 for patients with UGT1A1*1*1 (75%) or 65 mg/m2 for patients with UGT1A1*1*28 (25%).
TME Surgery was performed in 88% all patients, 8 weeks after end of CRT.
All patients after surgery regardless of path results received 5x XELOX.
The primary end point was pCR.

Zhu, JCO 2022
pCR rates 15% (n = 27 of 178) vs. 30% (n = 53 of 178), RR 1.96; SS.
CCR n=4 vs n=6
Grade 3-4 toxicities 11 (6%) vs. 68 (38%), SS. Mostly Heme Toxicities.
The commonest grade 3-4 toxicities were leukopenia, neutropenia, and diarrhea.
Overall surgical complication rate was not significantly different between the two groups "(11% v 15%; P < .001)." [SIC}.
CONCLUSION Adding irinotecan guided by UGT1A1 genotype to capecitabine-based neoadjuvant chemoradiotherapy significantly increased complete tumor response in Chinese patients.

RTOG 02-47 Irinotecan and pCR CRT → S → C

←R→ 146 T3 or T4 rectal cancer < 12 cm from the anal verge Preop RT (50.4 Gy in 1.8 Gy) + concurrent | 1. Cape and irinotecan | 2. CapeOx |.
Surgery was performed 4–8 weeks after chemoRT, and adjuvant chemotherapy 4–6 weeks after surgery.
Arm 1 Chemo = Capecitabine (1200 mg/m2/d M-F) and Irinotecan (50 mg/m2 weekly × 4 doses)
Arm 2 Chemo = Capecitabine (1650 mg/m2/d M-F) and oxaliplatin (50 mg/m2 weekly × 5 doses)
The primary endpoint was pCR rate, requiring 48 evaluable patients per arm.

Wong, IJROBP 2011
. Protocol chemotherapy was modified due to excessive GI toxicity after treatment of 35 patients.
96 were assessed for the primary endpoint—final regimen described above.
Tumor downstaging was 52% vs. 60% Nodal downstaging (excluding N0 patients) was 46% vs. 40%.
pCR rate 10% vs. 21%.
Preop chemoRT grade 3/4 hematologic toxicity was 9% vs. 4%, Grade 3/4 non-hematologic toxicity was 26% vs. 27%.
Conclusions Preoperative chemoRT with capecitabine plus oxaliplatin for distal rectal cancer has significant clinical activity (10/48 pCRs) and acceptable toxicity. This regimen is "currently" being evaluated in a phase III randomized trial (NSABP R04).

Metastatic

Systemic Options

TASCO1 First-line Trifluridine/Tipiracil + Bevacizumab vs Capecitabine + Bevacizumab in Unresectable mCRC

Van Cutsem. Ann Oncol. 2020;31:1160. Van Cutsem. ASCO GI 2021. Abstr 14
Treatment effect on OS was significantly in favor of the TT-B group for women, patients with BRAF Δ, and patients w/o surgical resection.

- Open-label, noncomparative phase II study[1,2]

Stratified by RAS status, ECOG PS, and Region

Patients with unresectable metastatic CRC naive to systemic therapy; not eligible for intensive therapy* per investigator's discretion (N = 153)

Trifluridine/Tipiracil 35 mg/m² BID orally Days 1-5, 8-12 Q4W + **Bevacizumab** 7.5 mg/kg IV Day 1 Q3W (n = 77)

Capecitabine 1250 or 1000 mg/m² BID orally Days 1-14 Q3W + **Bevacizumab** 7.5 mg/kg IV Day 1 Q3W (n = 76)

Until PD, intolerant toxicity, or investigator/ patient decision

*eg, elderly, low tumor burden, high ECOG PS, comorbidities

Characteristic	TT-B (n = 77)	C-B (n = 76)
Median age, yrs (range)	73 (43-83)	75.5 (33-91)
Male, %	51.9	61.8
ECOG PS, %		
▪ 0	33.8	34.2
▪ 1	49.3	51.3
▪ 2	16.9	14.5
Location of primary, %		
▪ Right colon	39.0	25.0
▪ Left colon	61.0	75.0
Prior adjuvant treatment, %	27.3	19.7
Mutant *RAS*, %	57.1	56.6
Mutant *BRAF*, %*	10.4	9.2

*22.1% and 19.7% of patients in the TT-B and C-B arms, respectively, did not have available BRAF mutation results.

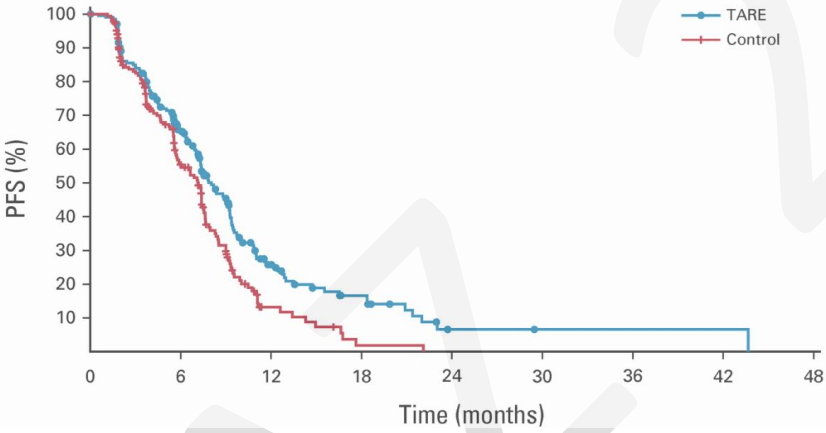
Characteristic	TT-B (n = 77)	C-B (n = 76)
Reason ineligible for intensive chemotherapy, n (%)		
▪ Elderly	28 (36.4)	42 (55.3)
▪ Low tumor burden	15 (19.5)	14 (18.4)
▪ ECOG PS	14 (18.2)	2 (2.6)
▪ Comorbidities	7 (9.1)	3 (3.9)
▪ Other	13 (16.9)	15 (19.7)

Survival Endpoint,[1] mos (95% CI)	TT-B (n = 77)	C-B (n = 76)
Median OS	22.31 (18.00-23.69)	17.67 (12.58-19.81)
Survival probability		
▪ 6	0.85 (0.75-0.92)	0.83 (0.72-0.90)
▪ 12	0.76 (0.65-0.84)	0.67 (0.55-0.76)
▪ 18	0.62 (0.50-0.72)	0.47 (0.35-0.57)
▪ 24	0.38 (0.27-0.49)	0.34 (0.24-0.45)

Korean Retrospective 2011 – 2020.
RR 4157 patients mCRC with metastasis-directed radiotherapy (MRT) for oligoprogressive or oligopersistent disease in patients receiving systemic Tx.
Only 91 (2%) received MRT to limited lesion sites (55 oligoprogressive and 36 oligopersistent) during systemic Tx following a period of Tx response.
1^{O} time to change to systemic therapy.

Lee, Clinical Colorectal Cancer 2021
Median time to change to next-line systemic therapy was doubled! **Overall cohort 5 months** vs. **MRT group 9.5 months**.
Overall cohort measured from the current chemotherapy session.
MRT group measured from the MRT session.
No severe toxicity or systemic treatment interruption was observed following MRT.
1-year LC 69%. 1-year OS 99%.
Conclusion In patients with oligoprogressive or oligopersistent mCRC, MRT may be performed safely in conjunction with systemic treatment to maximize the benefit of systemic therapy and to prolong the time to change to systemic therapy. Further prospective studies should confirm these findings.

"Second line Chemo+SIRT" EPOCH TRIAL
←R→ 428 patients with colorectal liver metastases (CLM) who progressed on oxaliplatin- or irinotecan-based first-line therapy.
| 1. second-line chemotherapy | 2. Second-line chemo + TARE |.
TARE = radioembolization using Yttrium-90 (TheraSphere).
TARE delivered prior to 2nd line chemo, although 1 cycle was allowed during treatment planning.
Bilobar disease (82%, majority) and ¾ (76%) received TX to both lobes on the same day.
Also ¾ (74%) of patients with unilobar disease received unilobar treatment
Exclusion: confirmed extrahepatic disease. However, 49% had "indeterminate" extrahepatic lesions.
1^{O} co-endpoints PFS and hepatic PFS (hPFS).



Mulcahy, JCO 2021.
Median PFS 7.2 months vs. 8.0 months (HR 0.69, SS).
Median hPFS 7.2 months vs. 9.1 months (HR 0.59, SS).
Objective response 21.1% vs. 34.0% (SS).

Median OS 14 months (NS).

Grade 3 adverse events were reported more frequently with TARE (68.4% v 49.3%). Both groups received full chemotherapy dose intensity.
Grade 3 toxicity was higher with chemo alone (49%) vs. TARE (68%).
CONCLUSION
The addition of TARE to systemic therapy for second-line CLM led to longer PFS and hPFS. Further subset analyses are needed to better define the ideal patient population that would benefit from TARE.

"First line Chemo+SIRT" Combined Randomized Phase III **TARE TRIAL**
3 ←R→ Trials (FOXFIRE, SIRFLOX, and FOXFIRE-Global) with Chemo-naive mCRC + liver mets **not suitable for curative resection or ablation.**
| 1. FOLFOX-based| 2. FOLFOX-based + single treatment SIRT concurrent with cycle 1 or 2 of chemotherapy |.

SIRT	Selective internal radiotherapy Y90.	
"FOLFOX-based"	FOXFIRE	OxMdG (oxaliplatin modified de Gramont chemotherapy; 85 mg/m2 oxaliplatin infusion over 2 h, L-leucovorin 175 mg or D,L-leucovorin 350 mg infusion over 2 h, and 400 mg/m2 bolus fluorouracil followed by a 2400 mg/m2 continuous fluorouracil infusion over 46 h).
	SIRFLOX/FOXFIRE-G	mFOLFOX6 (85 mg/m2 oxaliplatin infusion over 2 h, 200 mg leucovorin, and 400 mg/m2 bolus fluorouracil followed by a 2400 mg/m2 continuous fluorouracil infusion over 46 h).

1^{O} OS. All three trials have completed 2 years of follow-up.

Wasan, Lancet 2017.
Median survival time 23 months both arms.
Interpretation Addition of SIRT (Y90) to first-line FOLFOX chemotherapy for patients with liver-only and liver-dominant metastatic colorectal cancer did not improve overall survival compared with that for FOLFOX alone. Therefore, early use of SIRT in combination with chemotherapy in unselected patients with metastatic colorectal cancer cannot be recommended. To further define the role of SIRT in metastatic colorectal cancer, careful patient selection and studies investigating the role of SIRT as consolidation therapy after chemotherapy are needed.

BECOME Bevacizumab Trial RAS Δ unresectable liver mets
←R→ 241 RAS Δ unresectable liver-limited metastases from CRC
| 1. mFOLFOX6 + bevacizumab | 2. mFOLFOX6 alone |.
1^{O} actual rate of patients converted to R0 resection for liver metastases.

TABLE 2. Efficacy (ITT population)

Characteristic	mFOLFOX6 Plus Bevacizumab (n = 121)	mFOLFOX6 Alone (n = 120)	P
Overall response			
CR	1 (0.8)	1 (0.8)	
PR	65 (53.7)	43 (35.8)	
SD	38 (31.4)	34 (28.3)	
PD	16 (13.2)	41 (34.2)	
Not assessable[a]	1 (0.8)	1 (0.8)	
ORR (CR plus PR)	66 (54.5)	44 (36.7)	< .001
DCR (CR plus PR plus SD)	104 (86.0)	78 (65.0)	< .001
PFS, years			< .001
Median (95% CI)	9.5 (8.6 to 10.4)	5.6 (5.1 to 6.1)	
OS, years			.031
Median (95% CI)	25.7 (20.0 to 31.4)	20.5 (17.1 to 23.9)	
1	94.1	75.6	
2	53.0	40.4	
3	26.5	20.5	
Surgery for liver metastases			
Resection rate from MDT	28 (23.1)	8 (6.7)	< .001
Actual R0 resection rate	27 (22.3)	7 (5.8)	< .001

TABLE 3. Subgroup Analysis

		LM R0 Resection		ORR		PFS (months)		OS (months)	
Subgroup	No. of Patients	%	P	%	P	Median	P	Median	P
Right sided			.054		.112		.004		.053
CT + Bev	45	22.0		51.1		9.7		20.3	
CT	41	7.3		34.1		5.6		16.2	
Left sided			.002		.020		.001		.116
CT + Bev	76	22.4		56.6		9.5		28.0	
CT	79	5.1		38.0		5.7		23.0	
Interaction analysis			.660		.495		.736		.752
Colectomy			.024		.003		.006		.222
CT + Bev	59	16.9		50.8		9.4		30.5	
CT	55	7.3		30.9		5.4		24.0	
Noncolectomy			.001		.014		.001		.068
CT + Bev	62	27.4		58.1		9.7		23.7	
CT	65	4.6		41.5		6.0		20.0	
Interaction analysis			.225		.945		.441		.771

TABLE 4. Toxicity (ITT population)

Adverse Event	mFOLFOX6 Plus Bevacizumab (n = 121)	mFOLFOX6 Alone (n = 120)	P
Total patients with ≥ grade 3	48 (39.7)	32 (26.7)	.032
Anemia	4 (3.3)	4 (3.3)	1.0
Leukopenia/neutropenia	17 (14.1)	15 (12.5)	.723
Thrombocytopenia	8 (6.6)	6 (5.0)	.593
Nausea/vomiting	5 (4.1)	7 (5.8)	.544
Peripheral neuropathy	6 (5.0)	7 (5.8)	.764
Hemorrhage	4 (3.3)	2 (1.7)	.684
Hypertension	10 (8.3)	3 (2.5)	.048
Proteinuria	12 (9.9)	4 (3.3)	.040
Thrombosis	4 (3.3)	0 (0)	.122

Tang, JCO 2020. Follow-up 37 months.
R0 resection rates for liver metastases were 22.3% vs. 5.8% (SS).
OR rates 54.5% vs. 36.7% (SS).
Median PFS 9.5 vs 5.6 months (SS).
Median OS 25.7 v 20.5 months (P = .03)
Bevacizumab was associated with ↑ frequent proteinuria (9.9% v 3.3%; P = .04) and hypertension (8.3% v 2.5%; P < .05).

CONCLUSION For patients with initially unresectable RAS mutant colorectal liver metastases, bevacizumab combined with mFOLFOX6 increased the resectability of liver metastases and improved response rates and survival compared with mFOLFOX6 alone.

Other Questions

High Rectosigmoid Tumors

Some Helpful Notes:

- High rectosigmoid tumors (generally 12-15+ cm) require a rigid proctoscopy as flexible ones can overestimate the distance from anal verge.
- A general reflection on whether to offer neoadjuvant CRT is if the tumor originates in (or part of the tumor extends into) the true pelvis as defined by the peritoneal reflection on MRI.
- RT should be highly considered bulky tumors T3-4 and LN+ tumors.
- RT can be discussed and avoided in younger women of childbearing age.
- It is always preferable to give pre-op rather than post-op RT.
- Regarding RT volumes, recall that the LN drainage from the upper rectum is through the mesenteric drainage.
  - The iliac nodal drainage only happens if there is gross bladder invasion, etc.
- Local failures are generally lower with higher rectosigmoid tumors.

Japanese Proton Beam
Prospective 23 patients PBT-treated patients with locally-recurrent rectal Ca (LRRC) between December 2008 and December 2019.
RT plan ideally = >70 Gy in >2.2 Gy/fx per bowel tolerance to GTV + with 0.5 cm-CTV and 0.5 cm-PTV margins.

Takagawa, Adv Rad Onc 2023
11 with CR or complete metabolic response (CMR)
8 with PR or PMR
2 with stable disease or stable metabolic response
2 with progressive disease or progressive metabolic disease.
3-year OS 72.1% PFS 37.9% LC 55%
5-year OS 44.6% PFS 38.9% LC 47.2
SUV MAX PET/CT before PBT (cutoff value, 10) showed significant differences in OS (P = .03), PFS (P = .027), and LC (P = .012).
CR or CMR after PBT had SS ↑ LC (vs. non-CR or non-CMR) HR 4.49; P = .021.
Older patients (aged ≥65 years) had significantly higher LC and PFS rates.
Patients with pain before PBT and larger tumors (≥30 mm) also had significantly lower PFS.
Of 23 patients, 12 (52%) experienced further local recurrence after PBT. One patient developed grade 2 acute radiation dermatitis. Regarding late toxicity, grade 4 late gastrointestinal toxic effects were recorded in 3 patients, in 2 of whom reirradiation was associated with further local recurrence after PBT.
Conclusions
The results showed that PBT may have potential to be a good treatment option for LRRC. 18F-FDG-PET/CT before and after PBT may be useful for assessing tumor response and predicting outcomes.

Acupuncture Trial
Importance Despite the adoption of the optimized Enhanced Recovery After Surgery (ERAS) protocol, postoperative ileus (POI) severely impairs recovery after colorectal resection and increases the burden on the health care system.
Objective To assess the efficacy of electroacupuncture (EA) in reducing the duration of POI with the ERAS protocol.
←R→ 249 patients | 1. 4 sessions of EA | 2. sham electroacupuncture (SA) |. after surgery.
1^{O} time to first defecation.

Wang, JAMA Surgery 2023
Median (IQR) time to first defecation 76.4 hours vs. 90.0 hours (P = .003).
first flatus 44.3 hours vs. 58.9 hours (P < .001)
tolerability of semiliquid diet 105.8 hours vs. 116.5 hours (P = .01)
solid food 181.8 hours vs. 190.3 hours (P = .01)
Prolonged post-op ilius (POI) 10% vs. 20% (RR 0.51; P = .03).
Other secondary outcomes were not different between groups. There were no severe adverse events.

Conclusions and Relevance Results of this randomized clinical trial demonstrated that in patients undergoing laparoscopic surgery for colorectal cancer with the ERAS protocol, EA shortened the duration of POI and decreased the risk for prolonged POI compared with SA. EA may be considered as an adjunct to the ERAS protocol to promote gastrointestinal function recovery and prevent prolonged POI after surgery.

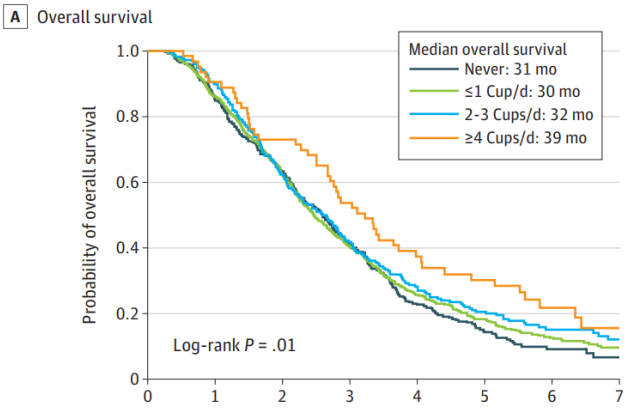
Differences Men and Women during TX → **CAO/ARO/AIO-94** and **CAO/ARO/AIO-04** Phase 3
Intro: The risk of toxic effects from chemotherapy is greater in women than in men, as shown in lung and colon cancer, sarcoma, Hodgkin lymphoma, and glioblastoma, which can be explained by different pharmacokinetics and pharmacodynamics.
Few studies have demonstrated better clinical outcome in women with melanoma, lymphoma, glioblastoma, sarcoma, lung cancer, gastric cancer, and anal cancer compared with men, but large confirmatory analyses are lacking. Intriguingly, despite the large number of phase 3 multimodal randomized clinical trials published to date for rectal cancer, the association of sex with treatment-related factors and clinical outcome remains largely unexplored for this disease site.

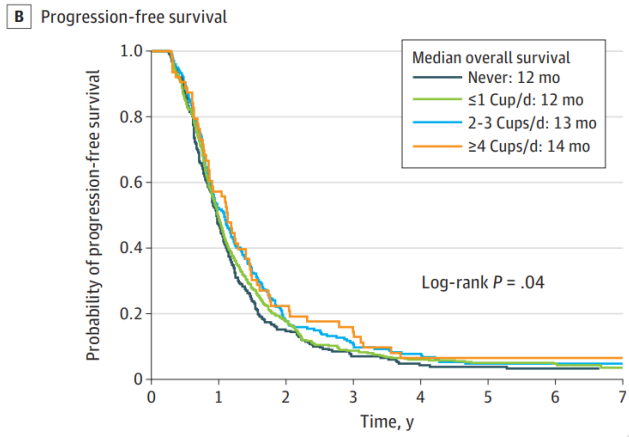
Methods Cohort of 1016 patients with cT3, cT4, or LN+ rectal cancer treated by CRT (5-FU based) → surgery → 4 cycles of adjuvant fluorouracil.
See experimental arm of the CAO/ARO/AIO-94 and the control arm CAO/ARO/AIO-04.
Mean age 62 yo.
291 (28.6%) were female.

Diefenhardt, JAMA Oncol 2019
Results Pretreatment clinical and postchemoradiotherapy pathologic factors did not differ significantly between men and women
Women underwent sphincter-sparing surgery more often than men and experienced fewer postoperative complications (Table 1).
We observed higher rates of chemoradiotherapy-induced diarrhea and leukopenia in women.
However, treatment adherence during neoadjuvant chemoradiotherapy and adjuvant chemotherapy was similar for the 2 groups (Table 2).
After a median (interquartile range) follow-up of 59 (39-111) months, sex was not associated with DFS, overall survival, local recurrence, or distant metastasis (Table 2).

PREHAB Trial
Importance Colorectal surgery is associated with substantial morbidity rates and a lowered functional capacity. Optimization of the patient's condition in the weeks prior to surgery may attenuate these unfavorable sequelae.
Objective To determine whether multimodal prehabilitation before colorectal cancer surgery can reduce postoperative complications and enhance functional recovery.
←R→ 251 patients planned for colorectal cancer | 1. 4-week in-hospital supervised multimodal prehabilitation program consisted of a high-intensity exercise program 3 times per week, a nutritional intervention, psychological support, and a smoking cessation program when needed | 2. None.
206 (82%) had tumors located in the colon and 234 (93%) underwent laparoscopic- or robotic-assisted surgery.

Molenaar, JAMA Surgery 2023
Severe complications (CCI score >20) 17.1% vs. 29.7% (OR 0.47, P = .02).
Medical complications (eg, respiratory) 15.4% vs. 27.3% (OR 0.48, P = .02).
Four weeks after surgery, 6-minute walking distance did not differ significantly between groups when compared with baseline (mean difference prehabilitation vs standard care 15.6 m [95% CI, −1.4 to 32.6]; P = .07). Secondary parameters of functional capacity in the postoperative period generally favored prehabilitation compared with standard care.
Conclusions and Relevance This PREHAB trial demonstrates the benefit of a multimodal prehabilitation program before colorectal cancer surgery as reflected by fewer severe and medical complications postoperatively and an optimized postoperative recovery compared with standard care.





Coffee Cohort Trial

1171 patients prospective previously untreated locally advanced or metastatic colorectal cancer who were enrolled in Cancer and Leukemia Group B (Alliance)/SWOG 80405, a completed phase 3 clinical trial comparing the addition of cetuximab and/or bevacizumab to standard chemotherapy.

Patients reported dietary intake using a semiquantitative food frequency questionnaire at the time of enrollment.

Data were collected from October 27, 2005, to January 18, 2018, and analyzed from May 1 to August 31, 2018.

Exposures Consumption of total, decaffeinated, and caffeinated coffee in cups per day.

1^{O} OS and PFS.

Mackintosh, JAMA Oncology 2020. Median FU 5.4 years.

A total of 1092 patients (93%) had died or had disease progression.

↑ consumption of coffee ↓ risk of cancer progression (HR for 1-cup/d increment, 0.95; 95% CI, 0.91-1.00; P = .04 for trend).

↓ risk of death (HR for 1-cup/d increment, 0.93; 95% CI, 0.89-0.98; P = .004 for trend).

MVA (2-3 cups coffee / day vs. NO COFFEE) **HR** OS of 0.82 (95% CI, 0.67-1.00)
PFS of 0.82 (95% CI, 0.68-0.99).

MVA (≥ 4 cups of coffee / day vs. NO COFFEE) **HR** OS 0.64 (95% CI, 0.46-0.87)
PFS of 0.78 (95% CI, 0.59-1.05).

Significant associations were noted for both caffeinated and decaffeinated coffee.

Conclusions and Relevance Coffee consumption may be associated with reduced risk of disease progression and death in patients with advanced or metastatic colorectal cancer. Further research is warranted to elucidate underlying biological mechanisms.

Table. Associations of Total, Caffeinated, and Decaffeinated Coffee Consumption With Overall and Progression-Free Survival

Variable	Frequency of consumption					1-Cup/d increment	*P* value for trend[a]
	Never	<1 Cup/d	1 Cup/d	2-3 Cups/d	≥4 Cups/d		
Total coffee consumption							
Overall survival							
No. of events/ No. of patients	246/280	248/301	253/298	191/229	49/63	NA	NA
Adjusted HR (95% CI)[b]	1 [Reference]	0.88 (0.74-1.06)	0.89 (0.74-1.07)	0.82 (0.67-0.99)	0.64 (0.47-0.88)	0.93 (0.89-0.98)	.004
Multivariable HR (95% CI)[c]	1 [Reference]	0.89 (0.75-1.07)	0.91 (0.76-1.09)	0.82 (0.67-1.00)	0.64 (0.46-0.87)	0.93 (0.89-0.98)	.004
Progression-free survival							
No. of events/ No. of patients	266/280	274/301	281/298	212/229	59/63	NA	NA
Adjusted HR (95% CI)[b]	1 [Reference]	0.85 (0.72-1.01)	0.95 (0.80-1.12)	0.81 (0.68-0.98)	0.78 (0.58-1.04)	0.95 (0.91-1.00)	.04
Multivariable HR (95% CI)[c]	1 [Reference]	0.86 (0.72-1.02)	0.96 (0.81-1.14)	0.82 (0.68-0.99)	0.78 (0.59-1.05)	0.95 (0.91-1.00)	.04
Caffeinated coffee consumption							
Overall survival							
No. of events/ No. of patients	326/381	303/361	151/179	169/200	38/50	NA	NA
Adjusted HR (95% CI)[b]	1 [Reference]	0.98 (0.84-1.15)	1.05 (0.86-1.27)	0.92 (0.76-1.11)	0.68 (0.49-0.96)	0.95 (0.90-1.00)	.04
Multivariable HR (95% CI)[c]	1 [Reference]	0.98 (0.84-1.15)	1.09 (0.89-1.33)	0.93 (0.77-1.12)	0.66 (0.47-0.94)	0.95 (0.90-1.00)	.04
Progression-free survival							
No. of events/ No. of patients	355/381	335/361	168/179	187/200	47/50	NA	NA
Adjusted HR (95% CI)[b]	1 [Reference]	0.95 (0.82-1.11)	1.07 (0.89-1.28)	0.86 (0.72-1.03)	0.86 (0.63-1.17)	0.96 (0.92-1.01)	.14
Multivariable HR (95% CI)[c]	1 [Reference]	0.95 (0.82-1.11)	1.09 (0.91-1.32)	0.87 (0.72-1.04)	0.85 (0.62-1.17)	0.96 (0.92-1.01)	.15
Decaffeinated coffee consumption[d]							
Overall survival							
No. of events/ No. of patients	700/828	226/265	35/44	26/34		NA	NA
Adjusted HR (95% CI)[b]	1 [Reference]	0.99 (0.85-1.16)	0.69 (0.49-0.98)	0.63 (0.42-0.93)		0.81 (0.71-0.93)	.002
Multivariable HR (95% CI)[c]	1 [Reference]	0.97 (0.83-1.13)	0.68 (0.48-0.96)	0.64 (0.43-0.95)		0.81 (0.71-0.93)	.003
Progression-free survival							
No. of events/ No. of patients	775/828	250/265	38/44	29/34		NA	NA
Adjusted HR (95% CI)[b]	1 [Reference]	1.01 (0.88-1.17)	0.85 (0.61-1.19)	0.74 (0.51-1.08)		0.88 (0.78-1.00)	.05
Multivariable HR (95% CI)[c]	1 [Reference]	1.02 (0.88-1.18)	0.85 (0.61-1.19)	0.75 (0.52-1.09)		0.88 (0.78-1.00)	.05