
بسم الله الرحمن الرحيم

Rectal Cancer

Ashraf Hamed Hassouna, MD

Professor of Radiation Oncology

NCI, Cairo University

Contents

- Introduction
- Epidemiology
- Pathology
- Diagnosis
- Treatment
  - Algorithms
    - Early
    - Advanced
    - Metastatic
  - Modalities
    - Surgery
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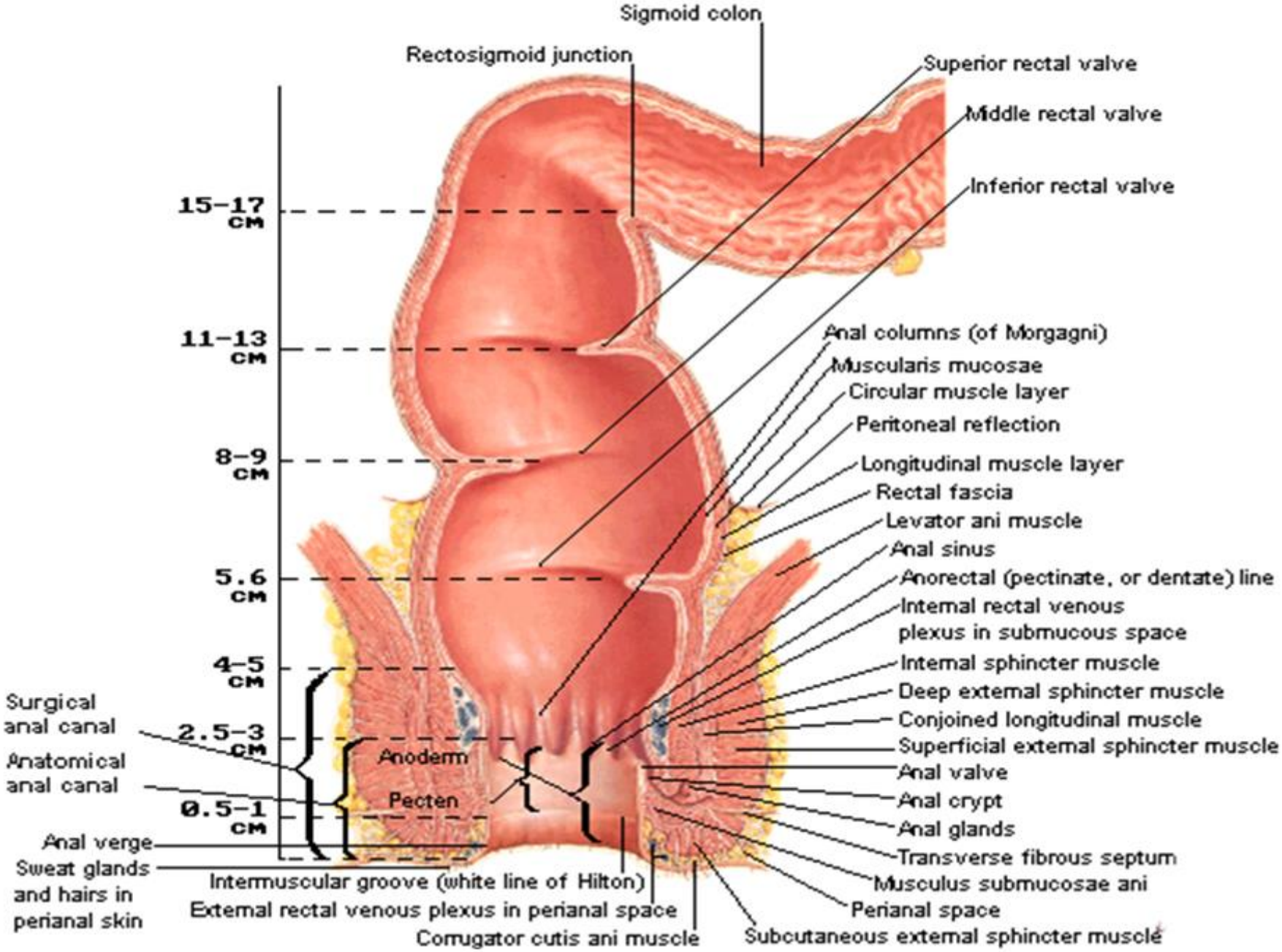
    - Chemotherapy

Rectum and Anal Canal



Incidence

- Colorectal cancer is the 3rd commonest cancer worldwide.
- 10% of all cancers.
- Colon : Rectum = 2:1.
- Incidence is declining in both genders but has risen sharply in young patients.

- 20-25% have metastatic disease at diagnosis.
- 30-40% will develop metastases later on.
- For this reason, strategies that deliver CT ± biological agents and reduce the burden of metastases are a priority for research.

Etiology

- Multifactorial (environmental and genetic factors).
- Most colorectal cancers arise from benign adenomatous polyps that grow to a large size (>2 cm), have a villous appearance, or contain dysplastic cells.

- Sporadic (75-85%)
- Hereditary (5-10%)
  - Hereditary non-polyposis colorectal cancer (HNPCC) (4-7%).
  - Familial adenomatous polyposis (FAP) (1%).
  - Inflammatory bowel disease, particularly ulcerative colitis (1%).
- Remainders
  - With 1st degree family relative affected by colorectal ca (RR 2)

HNPCC (lynch syndrome)

- Accounts for 5-10% of all colorectal cancer cases.
- Risk of colorectal cancer with HNPCC is 70-90%.
- Diagnosed with colorectal cancer at an average age of 45.
- Available genetic testing for the HNPCC genes.
- Measures can be taken to prevent cancer development.

FAP

- Accounts for 1% of colorectal cancer cases.
- Variants: Gardener's (sarcomas, osteomas, desmoid tumors) and Turcot's (GBM, medulloblastoma).
- Typically develop hundreds to thousands of colon polyps; initially benign, but there is nearly a 100% chance that the polyps will develop cancer if left untreated.
- Colorectal cancer usually occurs by age 40.
- Genetic testing is available. Yearly screening for polyps is recommended.

- A high-fat, low-fiber diet
- Red and processed meat (RR 1.65)
- Sedentary lifestyle
- Cigarette smoking
- Alcohol consumption

Prevention

- Higher-fiber, lower-fat diet
- Fish (RR 0.4)
- Increased physical activity
- Selenium
- Carotenoids
- Vitamins A, C, E, and folic acid
- Nonsteroidal anti-inflammatory drugs (aspirin, sulindac, or selective COX-2 inhibitors).

Screening & early detection

- Average-risk: begin at age 50 years, follow one of the following testing options:
  - Fecal occult blood testing every year
  - Double-contrast barium enema every 5 years.
  - Flexible sigmoidoscopy every 5 years
  - Colonoscopy every 10 years
- If polyps are found, colonoscopy should be performed every year until the patient is polyp free.
- Two promising but investigational approaches to screening: virtual colonoscopy and molecular stool testing.

High-risk population:

- Affected first-degree relative
- Family history of FAP or HNPCC
- Personal history of adenomatous polyps or colorectal ca
- Chronic inflammatory bowel disease

Screaning:

- Begin earlier (at age 40 years)
- Done more often than in average-risk

Pathology

>90% are adenocarcinoma

Staging AJCC 2017

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures

Nx	Regional nodes cannot be assessed
N0	No regional nodes
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in ≥4 regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in ≥7 regional lymph nodes

At least 12 pelvic nodes must be examined to obtain an accurate pN stage.

Tumors treated with preoperative CCRT are downstaged, however, and it is commonly not possible to evaluate 12 LNs for this purpose.

Prognostic factors

- TNM
- CRM, LVSI, Grade
- CEA (If >100: metastatic until proved otherwise. Preoperative CEA >5: inferior RFS and OS).
- Biologic markers: MSI, dMMR, KRAS, allelic loss of 18q, thymidylate synthase, thymidine phosphorylase, VEGF, EGFR, P21, P27, BCL2, BAX, and TP53.

Clinical manifestations

- Bleeding per rectum
- Change in bowel habits
- Urgency
- Inadequate rectal emptying
- Tenesmus
- Urinary symptoms
- Buttock, perineal, or Sciatic pain

Evaluation

- History & Physical examination.
- CBC, LFTs, KFTs, CEA.
- Proctoscopy, colonoscopy and biopsy.
- CT chest, abdomen, pelvis.
- MRI rectum with contrast is standard for clinical staging (rectal ultrasound if MRI not available).
- PET/CT is not routine, but is utilized in many practices.

PET/CT:

- Investigational for a routine preoperative metastatic workup in a patient who presents with primary disease.
- Should be considered strongly for patients with presumed locoregional relapse who are being considered for aggressive treatment approaches with curative intent.

Imaging after CCRT

Both diffusion-weighted MRI and PET/CT have been used to monitor therapy response and to predict the outcome following preoperative therapy.

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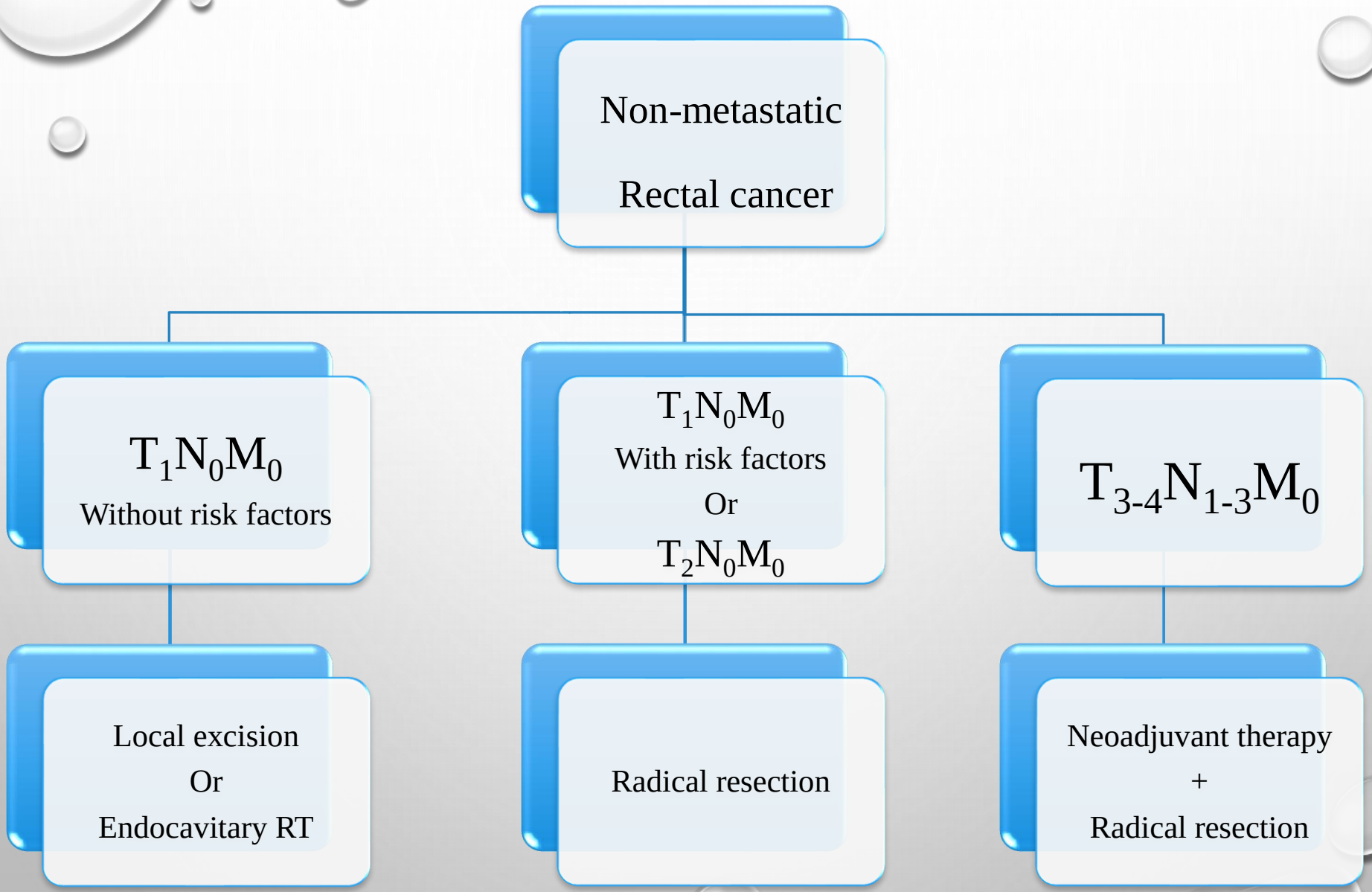
Non-metastatic
Rectal cancer
$T_1N_0M_0$
Without risk factors
$T_1N_0M_0$
With risk factors
Or
$T_2N_0M_0$
$T_{3-4}N_{1-3}M_0$
Local excision
Or
Endocavitary RT
Radical resection
Neoadjuvant therapy
+
Radical resection

T1N0M0

Early localized tumors (5% of rectal cancer) include:

- cT1N0M0
- Small (<3cm, <1/3 circumference)
- Exophytic
- < 8cm from dentate line (or below middle rectal valve)
- Without adverse pathologic factors (i.e., high grade, LVI, colloid histologic type)

adequately treated with a variety of local therapies such as local excision or endocavitary RT.

Oligo-Metastatic Disease

Short-course RT followed by CT

CT followed by RT (short or long course)

↓

Staged or synchronous resection (primary and metastasis)

↓

Adjuvant CT

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Surgical Options

- LAR - low anterior resection (including very low anterior resection with coloanal anastomosis)
  - sphincter preservation
- APR - abdomino-perineal resection
  - colostomy
- LE - local excision
  - sphincter preservation for low-lying tumors

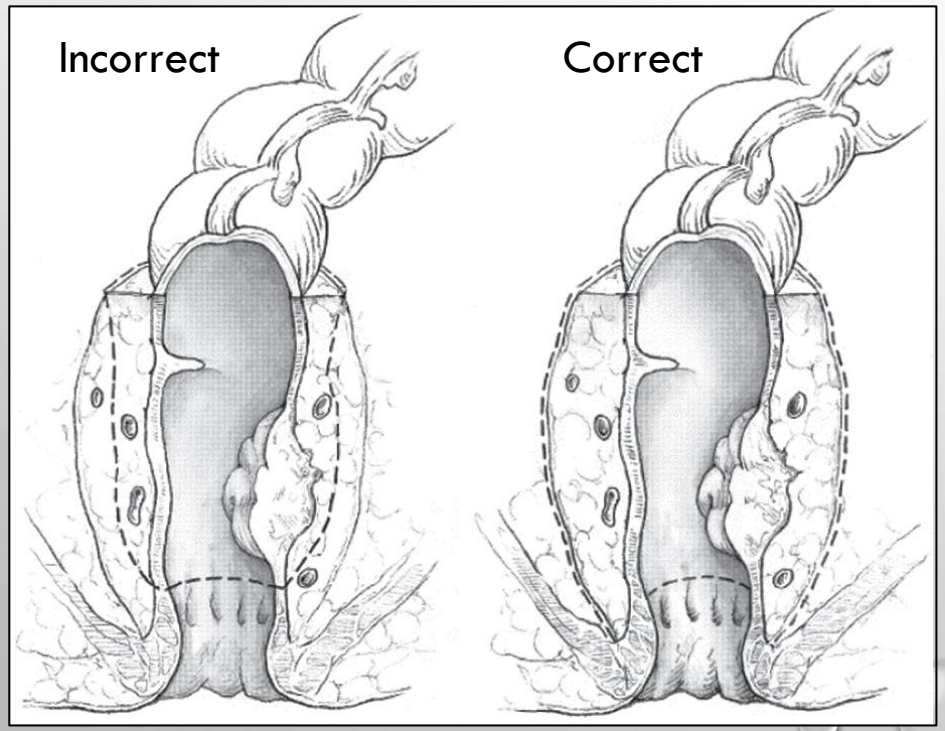
Local excision

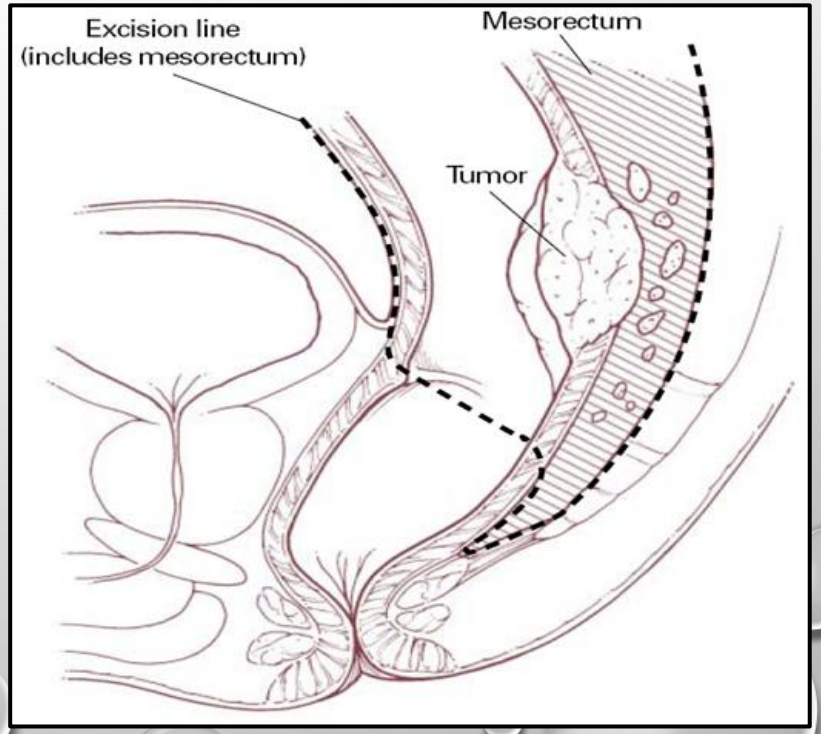
- Local excision alone (1 cm circumferential margin, without LN sampling or excision) is done only for selected pT1.
- It should be: full thickness, nonfragmented, –ve margins.
- Varieties: trans-anal local excision, posterior proctotomy, and trans-sphincteric excision.
- Trans-anal endoscopic microsurgery (TEM) is a new option either alone for T1 tumors or combined with RT for T2-3.

- The CALGB performed a phase II trial of local excision and selective postoperative CCRT.
- A total of 91% underwent a full-thickness local excision. Patients with pT1 disease were observed, and pT2 patients received postoperative treatment with 54 Gy plus concurrent 5-FU.
- With a median follow-up of 4 years, LR in 59 patients with pT1 was 5% and with pT2 was 14%.

Total Mesorectal Excision (TME)

Sharp en-bloc removal of mesorectum including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia.





- Changed dramatically LRC.
- Surgeon became major prognostic factor.
- Designed to spare autonomic nerves (impotence, retrograde ejaculation, and urinary incontinence)
- Higher rate of anastomotic leaks.
- Local recurence in pT3-4N1-2 still 15-21%.

Sphincter sparing & Stoma

- Where the sphincter cannot be saved a permanent colostomy is the best option.
- Total anorectal reconstruction (TAR) is an experimental option for patients who refuse a stoma.
- Retrograde irrigation system: common technique to make stoma care more convenient. Patients empty the bowel every 2nd or 3rd day using an enema. So, only a pad is needed to cover the soma instead of a stoma bag.

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Endocavitary RT

Papillion technique

- Before delivery, the anus is dilated and a 4-cm proctoscope is introduced.
- A low-energy x-ray unit is placed through the scope almost against the tumor.
- Generally, 50 kV x-rays are delivered at 30 Gy/F in 3-4 fractions over 1 month.

EBRT techniques

- Locoregional failures occurred in the soft tissue of the pelvis or the anastomotic site in 69%, pelvic lymph nodes in 42%, and perineum in 25%.
- External iliac LNs: at risk with anterior tumor extension and adjacent organ involvement.
- Inguinal LNs: at risk if lesion extends to the anal canal or the lower third of the vagina.

GTV-P: all gross disease on physical examination, endoscopy.

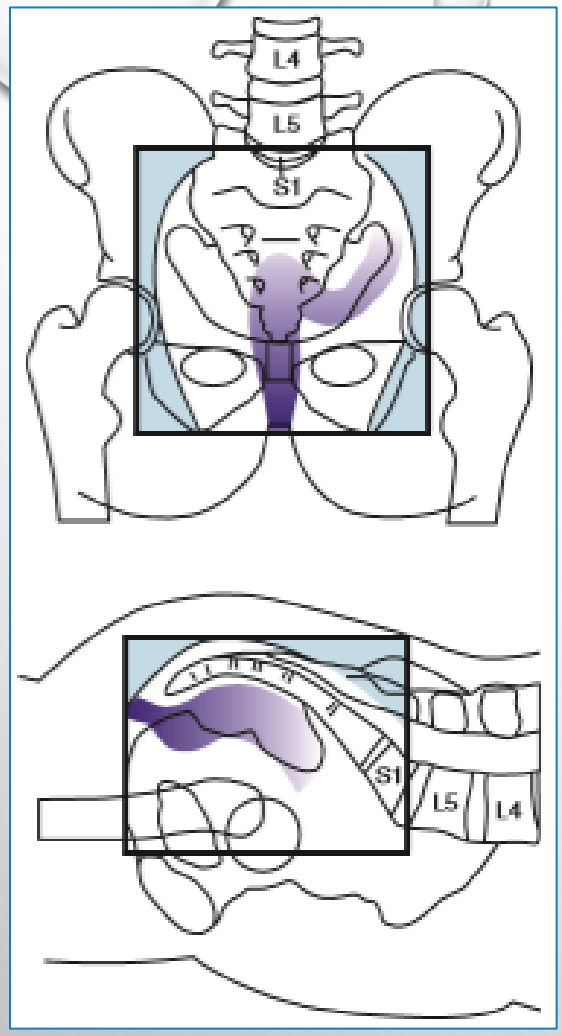
GTV-N: all involved nodes.

CTV 50: GTV-P with 1.5-2 cm margin superiorly and inferiorly + the entire rectum, mesorectum, and presacral space in the transverse plane at these levels + GTV-N with 1-1.5 cm margin.

CTV 45: CTV50 + entire rectum and mesorectum (from L5-S1 to pelvic floor) + bilateral internal iliac lymph nodes + margin of 1 cm into bladder.

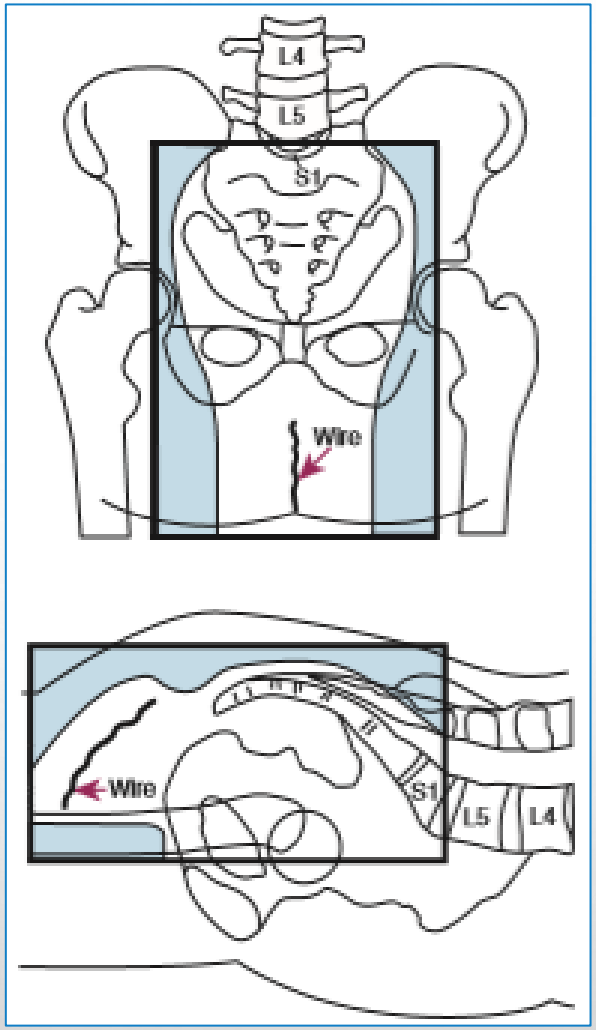
PTV: Each CTV + 0.5-1 cm

- Dose: 45-50.4 Gy in 5-6 weeks.
- A boost of 5.4 Gy to the primary tumor or tumor bed may be delivered if the small bowel is excluded from the high-dose field.
- It is not clear that dose > 50 Gy improve LC.
- Postoperatively, R1 or R2 resection requires doses > 60 Gy.
- EBRT is limited by normal tissue tolerance, and results for patients with residual disease who received postoperative EBRT alone are disappointing.
- IORT may help to overcome this problem by direct visualization and irradiation of the persistent tumor.



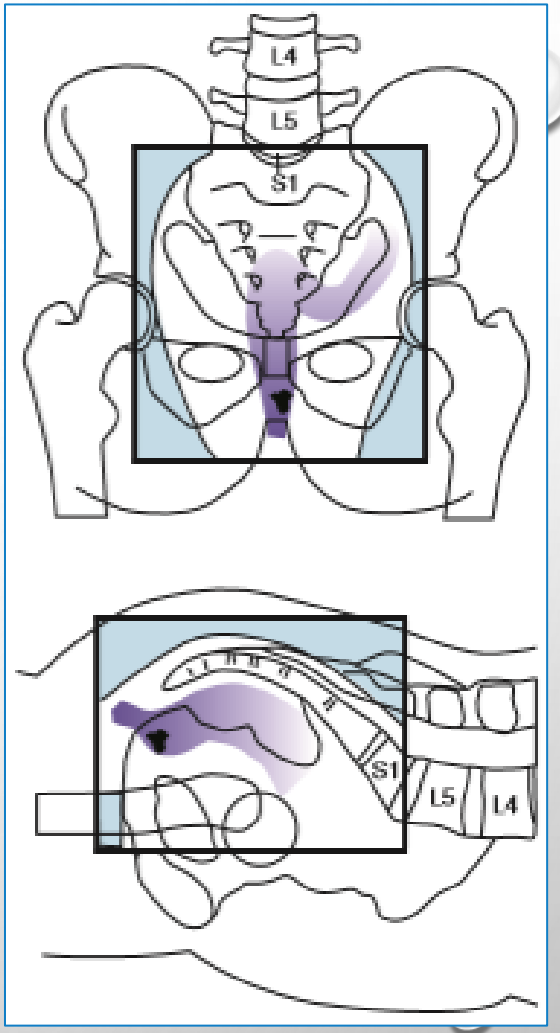
After LAR for a T3N1

at 8 cm from the anal verge



After APR for a T3N1

at 2 cm from the anal verge



Preoperative for a low-lying T3Nx

(or after LAR for a T3N1)

3D CRT vs IMRT

RT side effects

- Acute: diarrhea, tenesmus, acute proctitis, and dysuria.

- Delayed: persistent diarrhea, proctitis, anastomotic site strictures, small bowel obstruction, perineal/scrotal tenderness, delayed perineal wound healing, urinary incontinence, and bladder atrophy and bleeding.

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Standard and novel systemic therapy

- The NCCTG 85-47-51 postoperative adjuvant rectal trial revealed a 10% survival benefit for patients who received concurrent PVI *vs* bolus 5-FU. Therefore, when 5-FU is combined with RT, either preoperatively or postoperatively, it should be delivered as a continuous infusion (CI).
- FOLFOX has replaced CI 5-FU as a standard postoperative CT based on the efficacy demonstrated in stage III colon ca.

- Based on the X-ACT trial, which reported equivalence with the Mayo Clinic regimen in patients with stage II and III colon cancer, it is reasonable to substitute capecitabine for 5-FU. However, capecitabine has not been directly compared with CI 5-FU.
- Other agents: tegafur-uracil (UFT), raltitrexed, oxaliplatin, irinotecan, gefitinib, tegafur-oteracil-gimeracil, bevacizumab, and cetuximab.

Immune checkpoint inhibitors (ICIs)

- Immunotherapy agents designed to target specific regulatory proteins involved in modulating immune responses, such as programmed death 1 (PD1), programmed death-ligand 1 (PDL1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4).
- By blocking these checkpoints, these inhibitors unleash the immune system's ability to recognize and attack cancer cells, thereby enhancing anti-tumor immune responses.

- Marked antitumour effects of checkpoint inhibitors in microsatellite instable (MSI) CRC.
- Overall, about 15-20% of CRC are MSI, but most of them are right-sided. In rectal cancer, only a few per cent are MSI. However, in small patient series, remarkable effects have been noted in LARC with CCR or pCR.
- Other recently developed drugs against KRAS G12C mutated tumours could also potentially be included in the armamentarium in primary rectal cancer.

ICI	Study Title/ Reference	Patients (N°)	Induction	Radio Therapy	Consolidation	pCR
dMMR/MSI						
Dostarlimab	NCT04165772	12	Dostarlimab	LCRT	None	100%
Sintilimab	NCT04304209	17	Sintilimab	None	None	75%
Tislelizumab, Sintilimab, Pembrolizumab	Zhang X.	32	None	Not Specified	None	100%
Tislelizumab, Sintilimab, Pembrolizumab	Yang R.	20	None	None	None	90%
Pembrolizumab, Nivolumab +/− CT	Kothari A.	9	None	None	None	89%
Pembrolizumab, Nivolumab +/− CT	Demisse R.	3	None	Not Specified	None	100%
MSS						
Nivolumab	VOLTAGE-A	37	Nivolumab	LCRT	None	30%
Camrelizumab	NCT04231552	26	None	SCRT	CAPOX + Camrelizumab (2 × 21 days cycles)	46.2%
Durvalumab	PANDORA	46	None	LCRT	Durvalumab	34.5%
Avelumab	AVERECTAL	26	None	SCRT	FOLFOX + Avelumab	37%
Avelumab	AVANA	38	None	LCRT	Avelumab	23%

Follow up

Recommended	Not Recommended
Coordinating physician visits	CBC
Risk assessment	LFT
CEA testing	FOBT
CT scans	Chest X-ray
Colonoscopy	Molecular or cellular markers
Flexible proctosigmoidoscopy	

ASCO

Laboratory Tests
2005 Recommendations

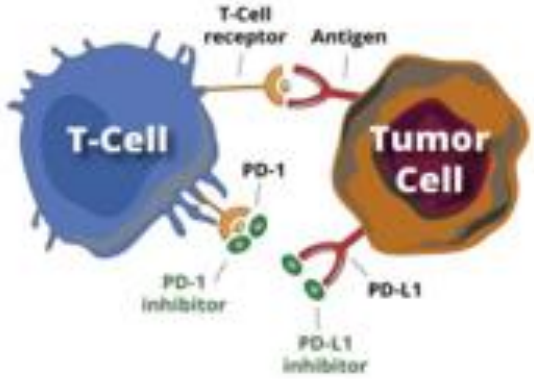
Carcinoembryonic Antigen

- *Every 3 months for at least 3 years after diagnosis*
  - *If the patient is a candidate for surgery or systemic therapy*

- *Caution: 5-FU-based therapy may falsely increase CEA values – wait until adjuvant treatment is finished before initiating surveillance*

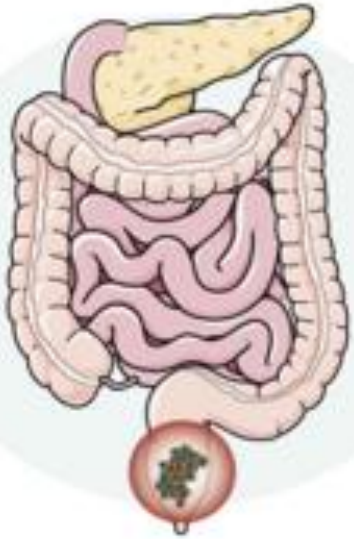
ASCO

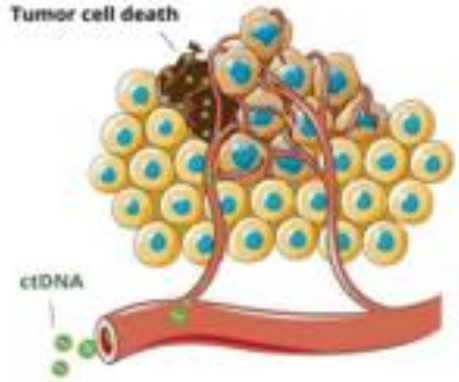
Recent Advances



Immunochekpoint Inhibitors (ICIs)

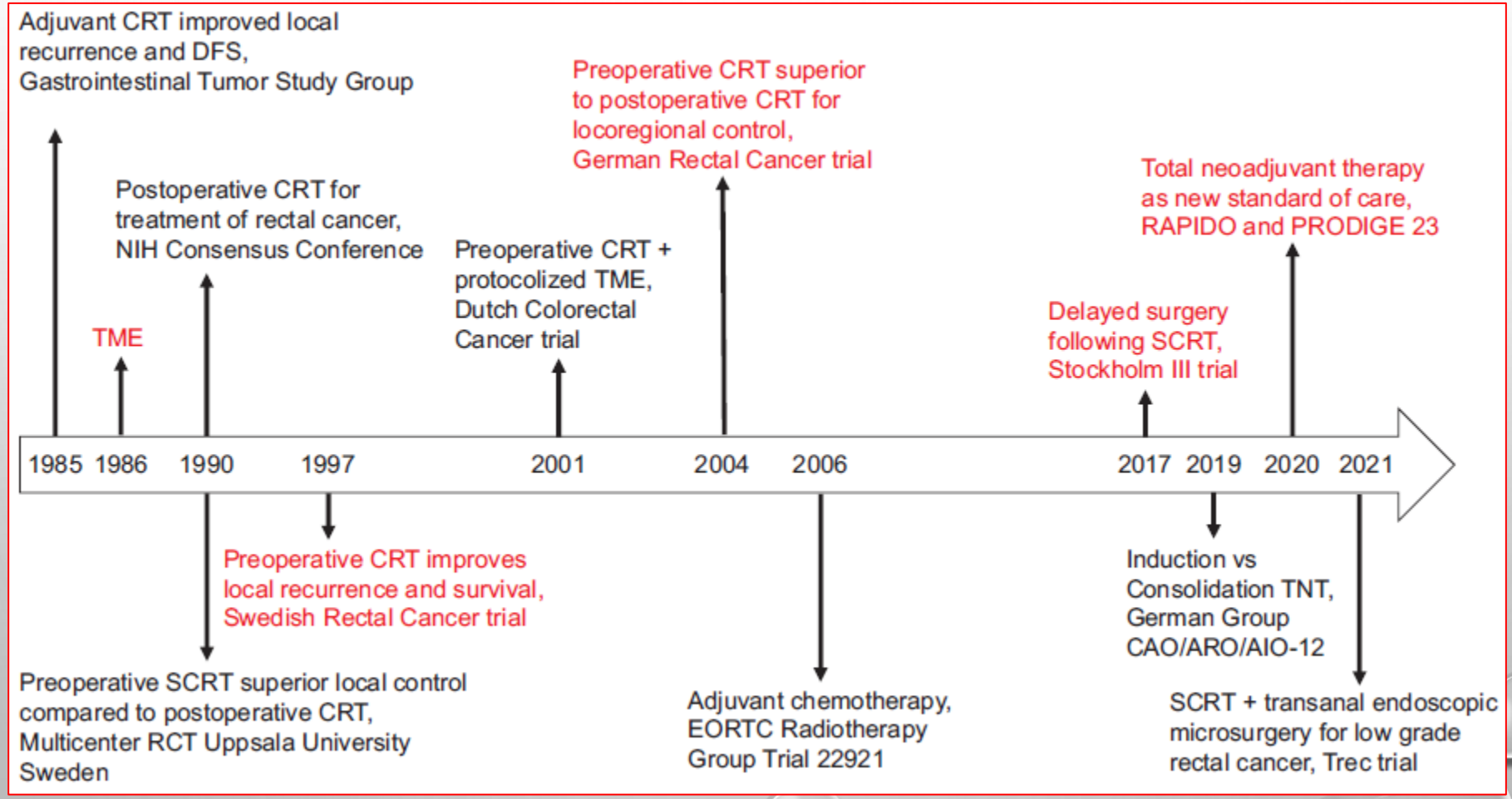
Total Neoadjuvant Therapy (TNT)





Circulating Tumor DNA (CTDNA)

Non Operative Management (NOM)


Adjuvant CRT improved local recurrence and DFS, Gastrointestinal Tumor Study Group
Postoperative CRT for treatment of rectal cancer, NIH Consensus Conference
TME
Preoperative CRT + protocolized TME, Dutch Colorectal Cancer trial
Preoperative CRT superior to postoperative CRT for locoregional control, German Rectal Cancer trial
Delayed surgery following SCRT, Stockholm III trial
Total neoadjuvant therapy as new standard of care, RAPIDO and PRODIGE 23
1985
1986
1990
1997
2001
2004
2006
2017
2019
2020
2021
Preoperative SCRT superior local control compared to postoperative CRT, Multicenter RCT Uppsala University Sweden
Preoperative CRT improves local recurrence and survival, Swedish Rectal Cancer trial
Adjuvant chemotherapy, EORTC Radiotherapy Group Trial 22921
Induction vs Consolidation TNT, German Group CAO/ARO/AIO-12
SCRT + transanal endoscopic microsurgery for low grade rectal cancer, Trec trial

Adjuvant, Neoadjuvant, TNT, WW

Adjuvant Radiation for Stage II, III Cancer

- **22 Randomized Trials**
  - **Postoperative: 2157 patients in 8 trials**
  - **Preoperative: 6350 patients in 14 trials**
- **Local Recurrence**
  - **37% decrease in postoperative trials**
  - **46% decrease in preoperative trials**
- **Survival – No Significant Improvement**

Colorectal Cancer Collaborative Group. Lancet 358:1291-1304, 2001.

Postoperative RT

- Advantage: pathologic staging and avoiding over treatment.
- Five randomized trials examined PORT without CT in pT3 and/or N+ve rectal cancer.
  - Two reveal a decrease in LR; NSABP R-01 trial (16% *vs* 25%; p = .06) and MRC trial (21% *vs* 34%; p = .001).
  - None have shown an improvement in OS.

Preoperative RT

Advantage: sphincter preservation and down staging

Swedish Rectal Cancer Trial: cT1-3 randomized to 25 Gy/5F/1W followed by surgery 1 week later *vs* surgery alone.

Parameter	Radiotherapy plus surgery n=553	Surgery alone n=557	P-value
Local recurrence, n (%)	63 (11)	150 (27)	0.001
Distant metastases, n (%)	84 (19)	65 (14)	-
Both local and distant recurrence, n (%)	19 (4)	47 (10)	-
5-year overall survival (%)	58	48	0.004

Radiotherapy shown to reduce local recurrence and improve 5-year survival

Dutch CKVO 95-04 randomized trial: cT1-3, TME ± short-course preoperative RT.

Parameter	Radiotherapy plus surgery n=897	Surgery alone n=908	P-value
Local recurrence rate (%)	2.4	8.2	0.001
Distant metastases rate (%)	14.8	16.8	0.87
Both local and distant recurrence (%)	16.1	20.8	0.09
2-year overall survival (%)	82	81.8	0.84

Further reduction in local recurrence with standardized total mesorectal excision protocol

Pre-op Short-course
Vs
Pre-op Long-course CCRT

- Although 3 randomized trials failed to show a significant difference, these trials had modest sample sizes.
- Decision depended on geography (Short-course in northern Europe and long-course in north America and central Europe).
- Long-course remains favored (ability to give concurrent CT, improved sphincter preservation, and tumor regression).

- Despite randomized studies indicating comparable survival, local control, and late toxicity outcomes between LCRT and SCRT, the latter is associated with a clear reduction in pCR, along with an increase in circumferential margin infiltration and LR.
- Therefore, while acknowledging the advantages of SCRT in terms of economic health and QoL, the preference for LCRT prevails in cases where achieving a pCR is of utmost importance.

Polish (Bujko, Br J Surg 2006; Pietrzak, Radiother Oncol 2007)

Phase III, 312 T3/4 resectable rectal ca randomized to pre-op RT (25 Gy/5fx) + surgery vs pre-op CCRT (50.4 Gy with bolus 5-FU and leucovorin) + surgery.

	4-Yr LR	4-Yr DFS	5-Yr OS	Grades 3–4 Early Toxicity	Grades 3–4 Late Toxicity	Positive CRM
Pre-op chemoRT	15.5%	55.6%	66%	18%	7%	4.4%
Pre-op short-course RT	10.6%	58.4%	67%	3%	10%	12.9%
***p* value**	.2	NS	NS	<.001	.36	.017

TROG 01.04 (Ngan, JCO 2012)

Phase III, 326 patients with T3N0-2 low rectal ca randomized between short course RT vs long-course CCRT. All patients received adjuvant CT.

TROG 01.04	3-Yr LR	5-Yr DR	5-Yr OS	Late Grades 3–4 Toxicity
Long course	4.4%	30%	70%	8.2%
Short course	7.5%	27%	74%	5.8%
p value	.24	.92	.62	NS

Stockholm III (Pettersson, BJS 2010 & 2015)

- Phase III, 303 patients randomized to short-course RT (25 Gy/5 f) and early surgery (within 1 week), short-course and delayed surgery (after 4-8 weeks), and long-course RT (50 Gy/25 f).
- Among patients receiving short-course, patients in the delayed surgery arm had lower ypT stages, higher pCR (11.8% vs 1.7%), and higher tumor regression (10.1% vs 1.7%).

Polish (Bujko, Ann Onc 2016)

- Phase III, 515 patients randomized to pre-op sequential short-course RT (25 Gy/5 F) + FOLFOX4 vs pre-op long-course CCRT (50.4 Gy/28 F with 5-FU).
- Short-course has: lower acute toxicity (75% vs 83%), higher R0 resection (77% vs 71%, p = 0.07), higher pCR (16% vs 12%, p = 0.17), higher 3-year OS (73% vs 65%, p = 0.046).
- No difference in DFS, LR, DM, post-op and late complications.

Preoperative vs postoperative CCRT

The German trial randomized 823 patients with T3-4 and/or LN+ve rectal cancer <16 cm from anal verge to preoperative *vs* postoperative CCRT.

- Local failure (6% vs. 13%; p = .006)
- Acute toxicity (27% vs. 40%; p = .001)
- Chronic toxicity (14% vs. 24%; p = .012)
- Sphincter preservation (39% vs. 20%; p = .004) in 194 cases judged by the surgeon before treatment to require APR
- No difference in 5-year OS (74% vs. 76%).

CAO/ARO/AIO-94 5-Year Outcomes

Outcome	Preop (%)	Postop (%)	P-Value
Gd 3-4 acute toxicity	27	40	0.001
Gd 3-4 late toxicity	14	24	0.01
Pathologic CR	8	0	<0.001
N+ (Downstaging)	25	40	0.001
Pelvic recurrence	6	13	0.006

Sauer et al., N Engl J Med 351:1731-1740, 2004.

Confirmed at 11 years median FU. J Clin Oncol 2012

CAO/ARO/AIO-94 Survival

Preop vs. Postop:

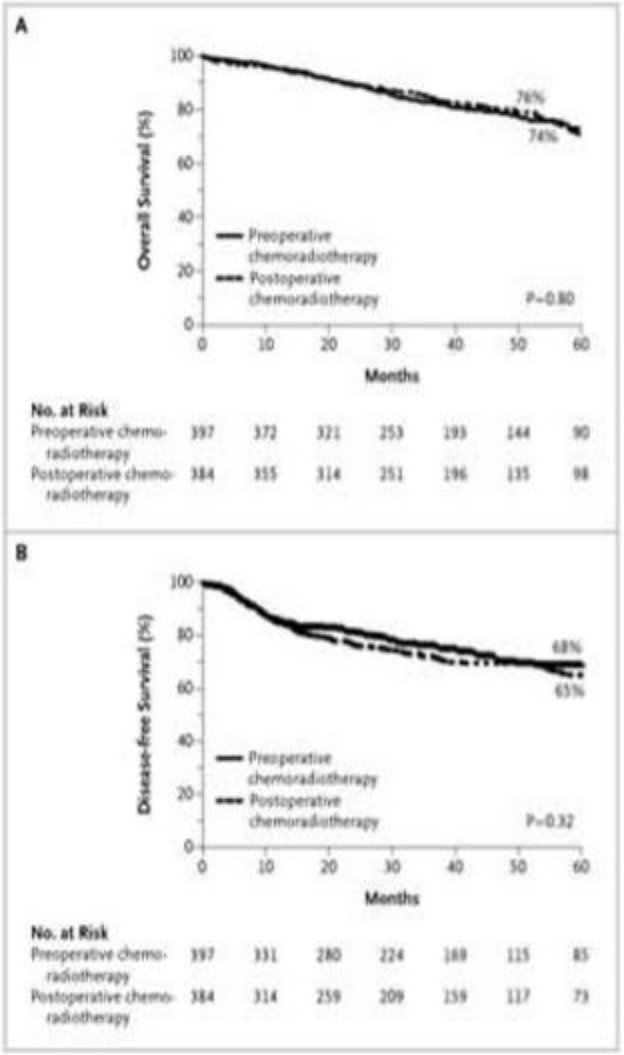
- **Overall Survival**

  76% vs. 74%, ns

- **Disease-free Survival**

  68% vs. 65%, ns

N Engl J Med 351:1731-1740, 2004.



Confirmed at 11 years median FU. J Clin Oncol 2012

Increased RT toxicity with postoperative RT ?

- Amount of small bowel in RT field.
- Potentially more radio-resistant hypoxic post-surgical bed needs more dose.
- RT field should include the perineal scar after APR.

Over-treatment ?

- In the German trial, 18% of cT3N0 and underwent surgery without preoperative therapy had pT1-2N0 disease.
- Therefore, those patients would have been over-treated if they had received preoperative therapy.
- Although not ideal, this is preferred to performing surgery first because 20-40% will have pLN+ and require postoperative CCRT, which has inferior results.

Organ Preservation

(NOM or WW)

- Limited clinical series report favorable results with non-operative management among select patients who achieve cCR with CCRT.
- LR after CCRT without surgery was 26-38%. Many, but not all, patients can be salvaged with subsequent surgery.
- Additional clinical trials are ongoing.

W&W

- Widely accepted and practiced worldwide. International registration is performed (international watch & wait database, IWWD) and regularly updated.
- With many thousands of patients presently registered from multiple centres, it can be concluded that outcomes in those who respond with cCR at an evaluation about 12 weeks after RT/CRT are favorable. Regrowth rates in the bowel are 25%, but most of the regrowth can be salvaged by surgery.

- No consensus on the FU protocol.
- NCCN recommend digital rectal examination and proctoscopy every 3-4 months for the initial 2 years, followed by semiannual evaluations for 3 years, alongside pelvic MRI every 6 months for at least 3 years.

W&W: two different situations

Intentionally

- More CT
- More RT
- Earlier stages (T2N0)

If-it-happens

- Give the standard treatment

Sao Paulo (Habr-Gama, IJROBP 2014)

- Retrospectively, 183 patients with cT2-4 or N+ were treated with neoadjuvant CCRT (50.4-54 Gy + 5-FU), with planned response assessment at 8 weeks. Patients with < cCR underwent TME; those with cCR were kept on FU.
- 90 (49%) patients achieved cCR. Of these, the 5-year LRFS was 69% and salvage therapy was possible in 93% of failures.

Danish (Appelt, Lancet Oncol 2015)

- Phase I/II trial, 55 patients treated with CCRT (60Gy/30f to tumor, 50Gy/30f to elective nodes, 5 Gy Endorectal brachytherapy boost + oral tegafur-uracil).
- Forty patients achieved cCR at 6-week assessment and were allocated watchful waiting, the remainder underwent surgery.
- 2-year LR was 25.9% (9 patients), and all underwent successful salvage surgery with clear margins.

UK (Renehan, Lancet Oncol 2016)

- 129 patients treated with pre-op CCRT 45 Gy with 5FU-based CT had cCR and were observed.
- 3-year LR 38%.
- 88% of nonmetastatic local failures were salvaged.
- Compared to matched cohort who had surgical resection, a greater portion of patients watched after CR after CCRT were colostomy free at 3 years (74% vs 47%).

Smith, MSKCC (JAMA Oncol 2019)

- Retrospective, 113 patients, stage II/III, achieved cCR after neoadjuvant CCRT, were followed by W&W, compared with patients who underwent neoadjuvant therapy followed by TME found to have pCR.
- 22 LR occurred in W&W, 5-year OS 73% vs. 94%, DFS 75% vs. 92%. Rate of DM 36% in W&W with LR vs. 1% in W&W without LR ($p<.001$).
- Conclusion: Excellent rectal preservation with W&W, but with worse OS and higher risk of DM in those with LR.

Total Neoadjuvant Therapy (TNT)

- administering all CT upfront, either prior to, or after, CCRT/short course RT, but prior to surgery.
- Investigated with both long and short-course RT with the goals of obtaining higher pCR and greater CT compliance with lower toxicity.

- Advantages include introduction of the best systemic therapy as early as possible, thus maximally addressing concerns over distant micrometastases and enabling the rapid initiation of CT to obtain symptomatic relief.
- Patients who are treated with CT as a first-line approach have a high likelihood of receiving all planned CT, which is less often the case when CT is planned postoperatively.
- Furthermore, diverting ostomies can be closed substantially earlier when no postoperative CT is required.

RAPIDO trial (Lancet Oncol 2020)

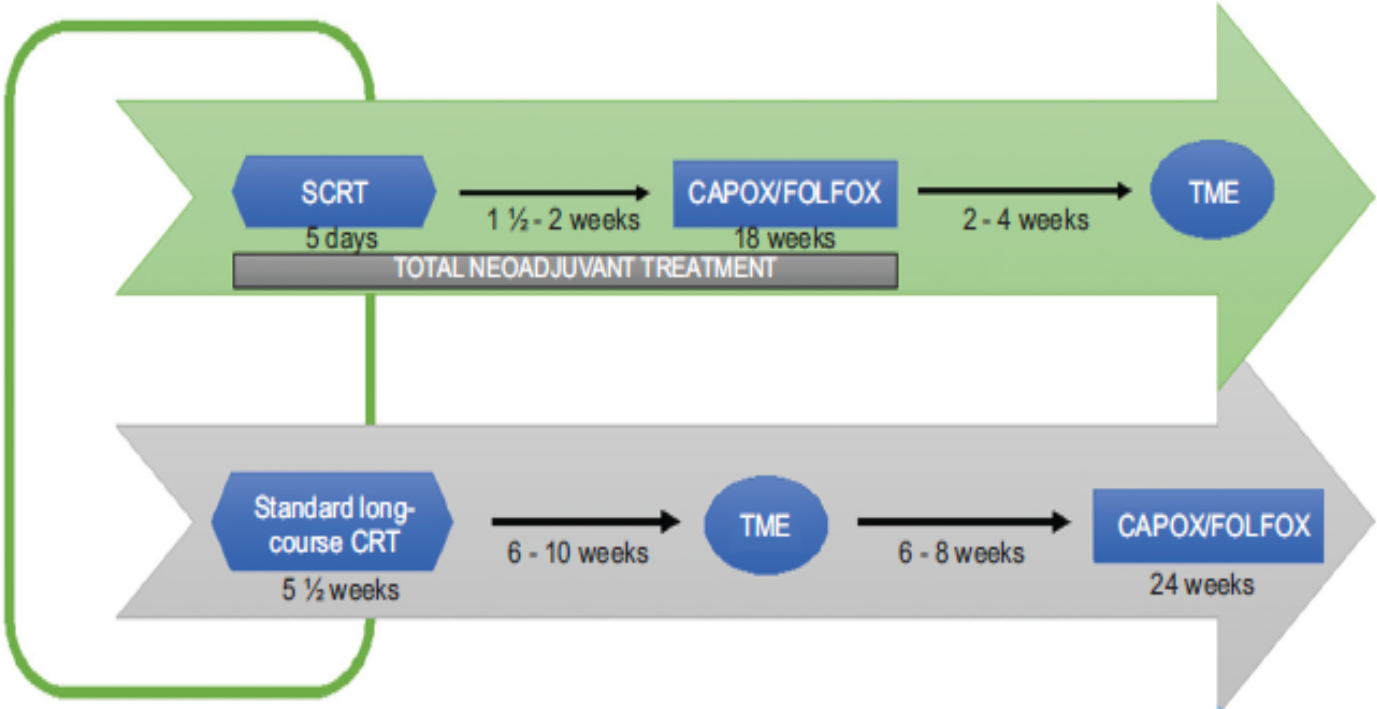
- Phase III RCT, 912 patients, locally advanced rectal cancer with high-risk features on MRI. MFU 4.6 years.
- Randomized to TNT vs. standard therapy.
- TNT: short course RT (25 Gy/5 fx) followed by 6 x CAPOX or 9 x FOLFOX4, followed by TME.
- Standard arm: CCRT, 50 to 50.4 Gy/25 to 28 fx, with capecitabine, followed by TME and adjuvant CT.

- A recent update with longer FU showed a significantly increased LR rate in the TNT arm, compared with the standard-of-care group (12% vs. 8% respectively, p=0.007).
- This finding suggests that, in patients with high-risk features, consolidation CT cannot compensate for a suboptimal RT strategy in terms of LC.

RAPIDO

MRI Staging
At least one:
cT4a, cT4b, EMVI, cN2, or mesorectal fascia involvement

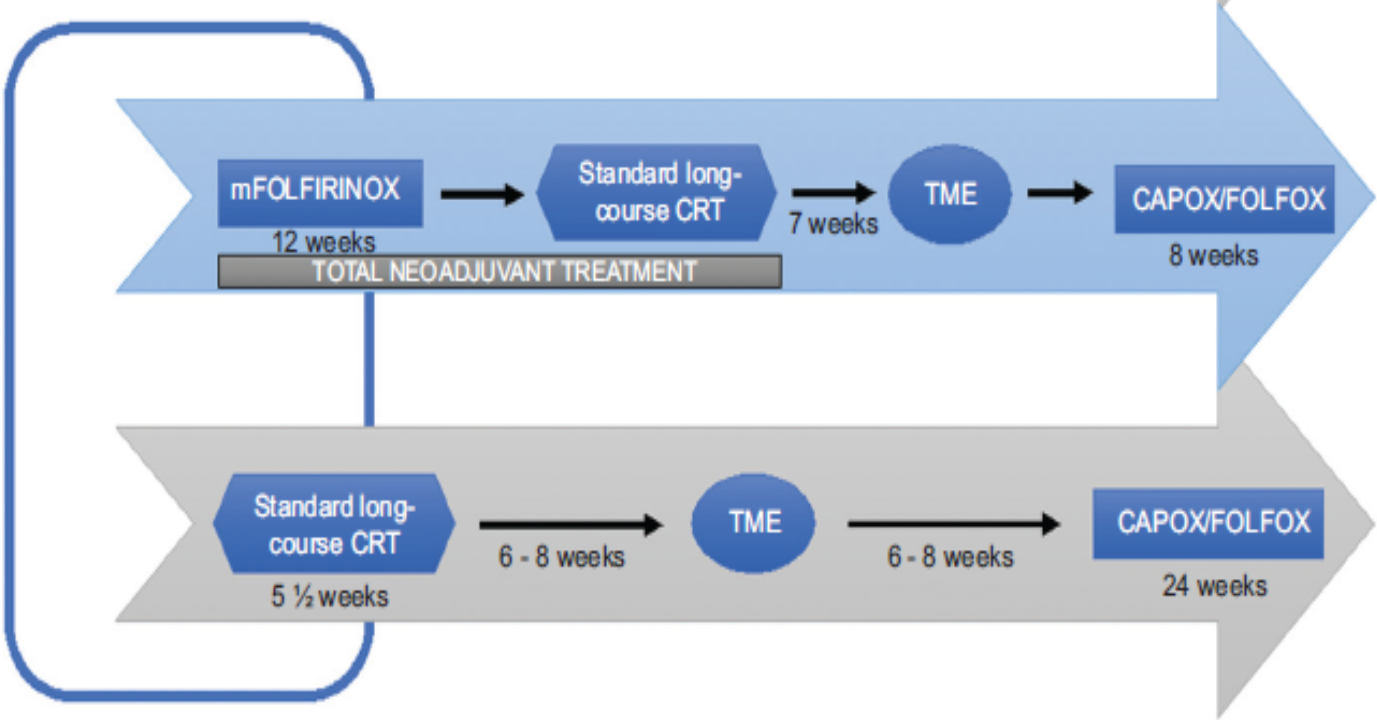
Primary endpoint:
DrTFat 3 years



PRODIGE 23

MRI Staging
cT3 with high risk features or cT4

Primary endpoint:
DFS at 3 years



Outcomes from RADIPO and PRODIGE

Outcome	RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
Primary endpoint	3-year DrTF 23.7% vs. 30.4%	3-year DFS 75% vs. 68.5%
pCR rate	28.4% vs. 14.3% P<0.001	27.8% vs. 12.1% P<0.001
Locoregional failure (at 3 years)	8.3% vs. 6.0% P=0.12	NR
Distant metastasis (at 3 years)	Cumulative probability 20.0% vs. 26.8%	Metastasis-free survival 78.8% vs. 71.7%
OS (at 3 years)	89.1% vs. 88.8% P=0.59	90.8% vs. 87.7% P=0.07

TNT: Summary

Randomized trials have shown that compliance to the treatment has become better, more tumors have disappeared (increased pCR) and fewer systemic recurrences are seen but none showed any OS benefit.

A recent meta-analysis (3579 patients from 15 trials): TNT was associated with 22.7% pCR vs 13.6% in the standard treatment ($p<0.0001$).

Zhang X., et al; PLoS ONE 2022

TNT - WW

OPRA trial

- Stage II or III rectal cancer were randomized to either FOLFOX followed by long-course CRT or long-course CRT followed by FOLFOX. They subsequently underwent either non-operative management or TME based on tumor response.
- Preliminary 3-year DFS did not significantly differ between the 2 groups (78% vs. 77%), nor did distant metastasis free survival (81% vs. 83%). Consolidation CT, however, was associated with increased rates of organ preservation at 3 years (58% vs. 43%) with decreased rates of local regrowth once a cCR was achieved (27% vs. 40%).

TNT regimens and current pattern of utilization

Clinical trial	Regimen description	Advantages	Disadvantages	Target patient at MDACC
PRODIGE-23	FOLFOXIRI followed by long-course chemoradiation	• Improved disease-free and overall survival • Decreased rates of developing distant metastases	• High rate of grade 3–4 adverse events • No specific data on use as part of non-operative management strategy • Radiation after chemotherapy allows less time for tumor shrinkage	• Aggressive tumors at high risk for systemic failure (i.e. EMVI, multiple lateral pelvic lymph nodes)
RAPIDO	Short-course radiation followed by FOLFOX	• Well-tolerated • Convenience of short-course radiation	• Higher rates of locoregional recurrence compared to standard therapy • No specific data on use as part of non-operative management strategy	• Synchronous metastatic disease who require pelvic radiation • Unable to receive long-course chemoradiation
OPRA	Long-course chemoradiation followed by FOLFOX	• Well-tolerated • Radiation prior to chemotherapy allows maximal time for tumor shrinkage • Excellent rates of organ preservation	• No treatment intensification for patients at high risk of distant metastases	• Mid- or low-lying tumors who would like to attempt organ preservation or tumors with positive/threatened CRM, without significant risk for systemic failure in whom triplet chemotherapy is unnecessary.

Omission of Radiotherapy

RT toxic effects, particularly concerning bowel and sexual function, together with improvements in systemic CT, have recently called its role into question.

Study title	Study		Stage	Chemiotherapy	Radiotherapy
FOWARC	Prospective phase III	495	cT3-4 or N+	mFOLFOX6	None
PROSPECT	Prospective phase III	1128	cT2-3 or N+	FOLFOX	CTRT in selected cases **

FOWARC: lack of a significant difference in outcomes between mFOLFOX6 without RT and 5-FU+RT

PROSPECT trial

- Phase III non-inferiority, 1128 patients, rectal cancer staged as T2N+, T3N0, or T3N+.
- Randomized to standard preoperative LCRT or experimental neoadjuvant CT (FOLFOX for 6 cycles) with LCRT given only if the primary tumor decreased in size by <20% or if FOLFOX was discontinued because of side effects.
- Postoperative CT was suggested in both arms.

- Median FU 5 years, neoadjuvant FOLFOX was non-inferior to LCRT for DFS and OS.
- 9% of patients enrolled in the FOLFOX arm received LCRT.
- pCR: 21.9% in the FOLFOX and 24.3% in the LCRT group.
- Patients assigned to FOLFOX reported significantly lower rates of fatigue and neuropathy and better sexual function.
- Omission of RT may represent a safe and viable option in a subset of patients, who are willing to avoid some long-term RT toxicities (e.g., young patients aiming for fertility preservation).

Recurrence & Palliation

Locally advanced disease and palliation

- With the exception of the uncommon suture line-only recurrence, patients with locally unresectable primary or recurrent disease should receive preoperative CCRT.
- Extended surgery to obtain -ve margins is still recommended even if there is a favorable response to preoperative therapy.
- Given the limitation of the total EBRT dose that can be delivered to the bulky tumor in the pelvis and the frequent problem of LR, the surgeon should be aggressive.

IORT

- Delivered by electron beam or brachytherapy.
- Brachytherapy is delivered by the HDR technique, and the dose rate is similar to that used for electron beam IORT.
- 10-20 Gy IORT depending on the volume of residual disease.
- For example, at the Mayo Clinic, patients with locally unresectable primary cancers receive 7.5-10 Gy after R0 resection with narrow margins, 10-12.5 Gy after R1 resection, and 15-20 Gy after R2 resection

Locally recurrent disease

- Pain, hemorrhage, pelvic infection, and obstructive symptoms.
- Unfavorable prognosis with median survival 1-2 years.
- In contrast to patients who have R0 or R1, it is unclear if those with R2 resection, benefit from aggressive therapy in view of differing results by series.
- Although the Oslo study reported no long-term survivors with R2 resection, US IORT series report 10-16% 5 year OS.
- Re-RT with 30 Gy (and if the small bowel can be excluded from the field, 40 Gy) can be used for limited volumes.

Systematic review of re-RT (Guren, Radiother Oncol 2014)

- Median initial dose was 50.4 Gy.
- Most studies used 1.2 Gy BID or 1.8 Gy daily with + 5-FU.
- Median total dose was 30:40 Gy to GTV + 2:4 cm margin.
- Among patients who could be resected, MS was 39 to 60 months and 12 to 16 months for unresectable patients.
- Good symptomatic relief in 82:100%. Acute diarrhea reported in 9:20%; however, late toxicity was insufficiently reported.

- Resectable: preoperative CCRT → resection ± IORT
- Unresectable: CT ± RT
- If prior pelvic RT, consider BID re-RT. May also consider SBRT in the unresectable setting.


Thank You

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Ashraf Hamed Mohamed Hassouna

Professor of Radiation Oncology

(email)

CAIRO UNIVERSITY

Bio

Biography | *Curriculum Vitae*

M.D.
in Radiation Oncology

NCI, Cairo University,

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