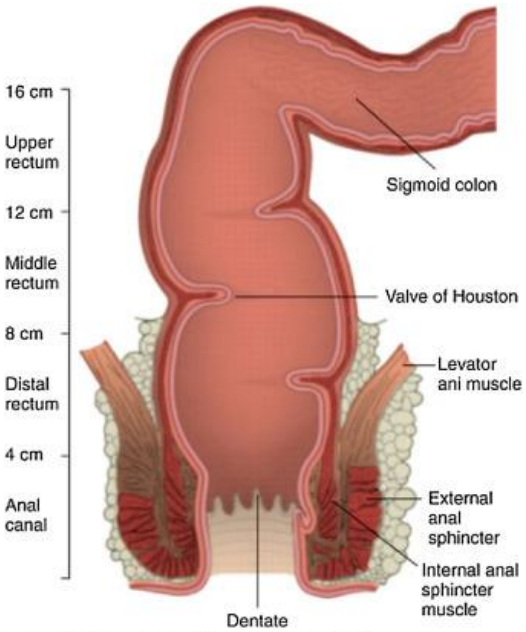
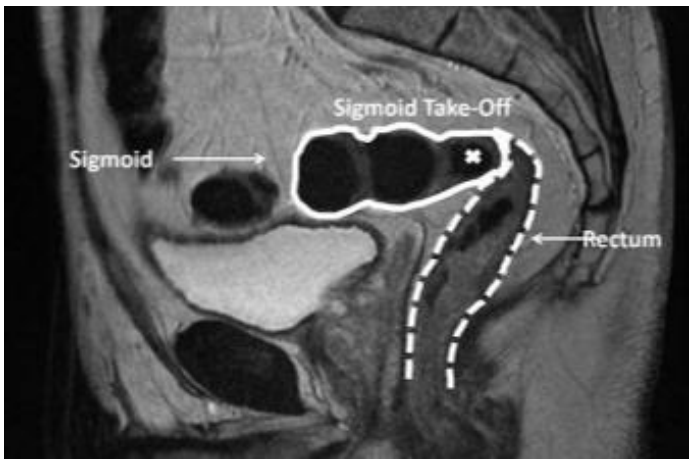
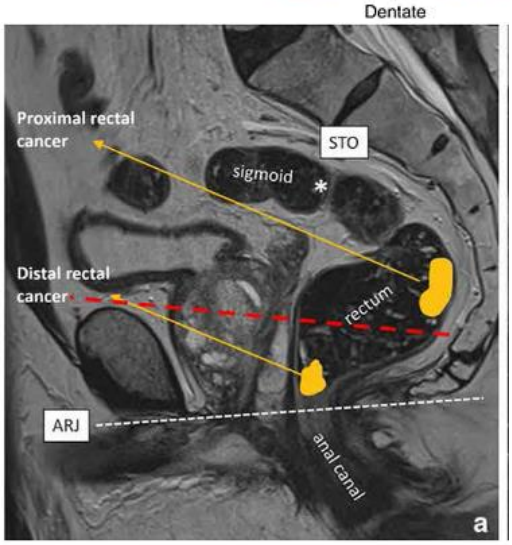
RECTAL CANCER

General Overview

- The optimal approach of treating rectal cancer depends on the location and disease extent
- Symptoms: bleeding, rectal mass, asymptomatic
- The upper margin of the rectum is located at the rectosigmoid junction (+/-15 cm from anal margin)
- Historically rectum is subdivided into proximal (10-15 cm), mid (5-10cm) and distal (<5cm).
- On MRI easier to distinguish between proximal and distal (line between upper margin of pubic bone anterior and insertion of the levator muscle to the coccygeal bone (see below figure from BJMO nov 2024)).







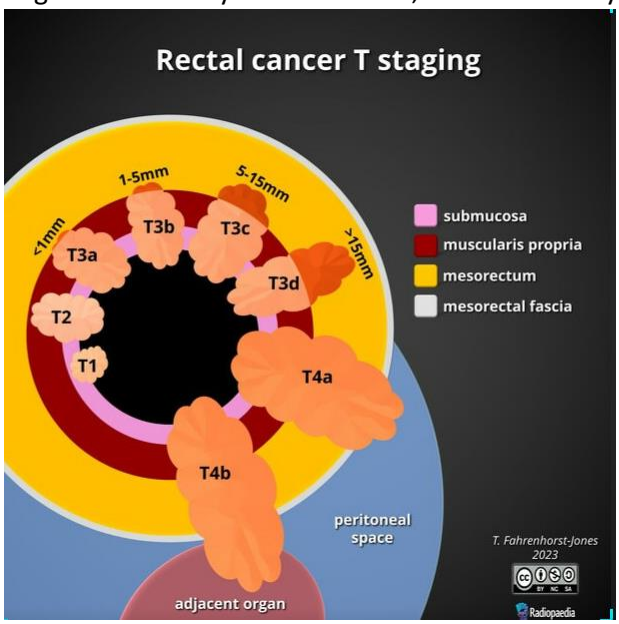
Staging (AJCC Version 8)

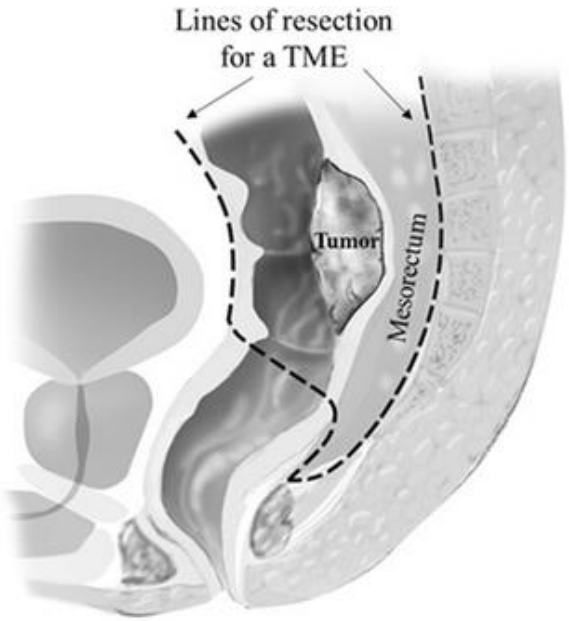
- MRI rectum (!), digital rectal examination, endoscopy, CT thorax/Abdomen, (ERUS)

Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastasis (M)
Tx: Primary tumor cannot be assessed **T0:** No evidence of primary tumor **Tis:** carcinoma in situ **T1:** Tumor invades submucosa **T2:** Tumor invades muscularis propria **T3:** Tumor invades subserosa (*fig) **T4:** Tumor invades other organs or structures (4b) and/or perforates visceral peritoneum (4a).	**Nx**: LN cannot be assessed **N0**: no regional LN **N1**: metastasis in 1-3 LN **N1a**: 1 regional LN **N1b**: 2-3 regional LN **N1c**: tumor deposits in subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional LN M+ **N2**: ≥ 4 (N2a: 4-6 ; N2b ≥7)	**M0**: no distant M+ **M1**: distant M+ **M1a**: 1 organ without peritoneal M+ **M1b**: more than 1 organ **M1c**: peritoneum with or without organ involvement

Update: December 2024

*fig T3a <1mm beyond muscularis, T3b 1-5 mm beyond muscularis, T3c 5-15mm, T3d 15 mm beyond





- Anatomic Stage
  - Stage I: T1-2N0M0
  - Stage IIA: T3N0M0
  - Stage IIB: T4aN0M0
  - Stage IIC: T4bN0MO
  - Stage IIIA: T1-2N1M0 or T1N2aM0
  - Stage IIIB: T1-2N2bM0 or T2-3N2aM0 or T3-4aN1M0
  - Stage IIIC: T3-4aN2bM0 or T4aN2aM0 or T4bN1-2M0

Treatment

- Sparing surgery is only feasible in the absence of invasion of the intersfincteric space.
- At Least 12 regional LN should be examined. Pathological examination should include a photographic record of the specimen and assessment of TME (total mesorectal excision) quality
- Involved CRM (circumferential resection margin) is associated with higher rates of recurrence and poor prognosis.
- Prognostic factors: EMVI, tumor deposits (N1c)
- **Very early rectal cancer** (cT1, sm1, cN0)
  - TEM or ESD if pT1 and no adverse features
  - TME if adverse features (sm ≥2, G3, V1, L1)
  - Local RT may be used as alternative to local surgery
- **Early proximal rectal cancer** (cT1-3a/b,N0-1, no EMVI, no LN, MRF clear):
  - primary surgery (PME or TME)
- **Early distal rectal cancer** (cT1-3a/b, N0-1, no EMVI, no LN, MRF clear)
  - Primary surgery or chemoRT long course followed by watch and wait or surgery

Update: December 2024

- Watch and wait approach should preferentially be done within a clinical trial.
  - Close follow-up of these patients for 12 to 16 weeks before decision to rescue surgery
  - Organ preservation study: Garcia-Aguilar J et al. JCO Aug 2022
- **Locally advanced proximal rectal cancer** (T3/4, N2, MRF +, EMVI/TD + or lateral pelvic LN)
  - Neoadjuvant chemo (6 cycles mFOLFOX or 4 cycles CAPOX)
  - Alternative: primary surgery followed by chemo according to pTNM
  - Based on findings in the PROSPECT trial:
    - Locally advanced rectal cancer (T2N+, T3N- or T3N+)
    - Neo-adj chemoRT vs neoadj chemo
    - 5y DFS 80.8% (exp) vs 78.6% (control); 5y OS 89.5% vs 90.2; recur 5y 1.8 vs 1.6 %
- **Locally advanced distal rectal cancer** (≥cT3c, N1-2, MRF +, EMVI/TD + or lateral pelvic LN)
  - Total neoadjuvant treatment based on PRODIGE and RAPIDO trial (both phase 3)
  - PRODIGE23
    - ARM1 (exp): 6 x mFOLFIRINOX, preop chemoRT, surgery, 3m adj chemo
    - ARM2 (control): preop chemoRT (+capecitabine), surgery, 6m adj chemo
    - cT3,cT4 rectal cancer
    - 3y DFS 76% (exp) vs 69%; 3y OS 91% vs 88%; no diff in locoregional recurrence
  - RAPIDO:
    - ARM1 (exp): 5x5Gy RT followed by 6 x CAPOX or 9 x FOLFOX followed by TME
    - ARM2: long course chemoRT with capecitabine 825 mg/m2 2/d followed by TME; adjuvant chemo with 8x CAPOX or 12x FOLFOX based on hospital policy
    - High risk rectal cancer: cT4 or EMVI or cN2 or involved MRF or LN+
    - Distant M+ at 3y 20% (exp) vs 26.8%; locoregional failure 8.3% vs 6.0%
    - At long time follow-up higher local relapse (10 vs 6%). Possible explanation is prolonged interval to surgery in the exp arm leading to fibrosis potentially affecting quality of the TME.
  - OPRA phase 2 trial (organ preservation) investigated with TNT schedule induces the most optimal local control (clinical complete response)
    - cT3-4N0 or anyTN+ based on MRI.
    - 4 months of doublet chemo followed by long course chemoRT vs reversed
    - No diff in DFS (76% 3y) but LCRT followed by chemo had better local control with a 3y TME free survival of 53% vs 41%

References

1) PROSPECT trial: Schrag D et al. NEJM 2023;389:322-334
2) PRODIGE trial: Conroy T et al Lancet oncol 2021 and Ann Oncol 2024 oct
3) RAPDIO trial: Bahadoer RR et al. Lancet Oncol 2021
4) OPRA trial: Garcia-Aguillar J et al. JCO 2022 and Verheij et al JCO feb 2024

What's new ?

- Role of checkpoint inhibitors as neoadjuvant treatment in dMMR/MSI-H rectal cancer:
  - Andrea Cercek et al. NEJM 2022
  - +/- 2.7% of rectal cancers ; CR and organsparing approach in almost all patients

Update: December 2024

- OPERA study : neoadj chemoRT with RT dose escalation with brachy boost or EB RT for organ preservation in early cT2-cT3 rectal adenoca (Lancet gastroenterol hepatol 2023, Gerard et al)