CANCER EDUCATION DAY

Rectal Cancer Management

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November 12, 2021

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Presenter Disclosure

- **Relationships with financial sponsors:**
  - **Grants/Research Support:** N/A
  - **Speakers Bureau/Honoraria:** N/A
  - **Consulting Fees:** N/A
  - **Patents**: N/A
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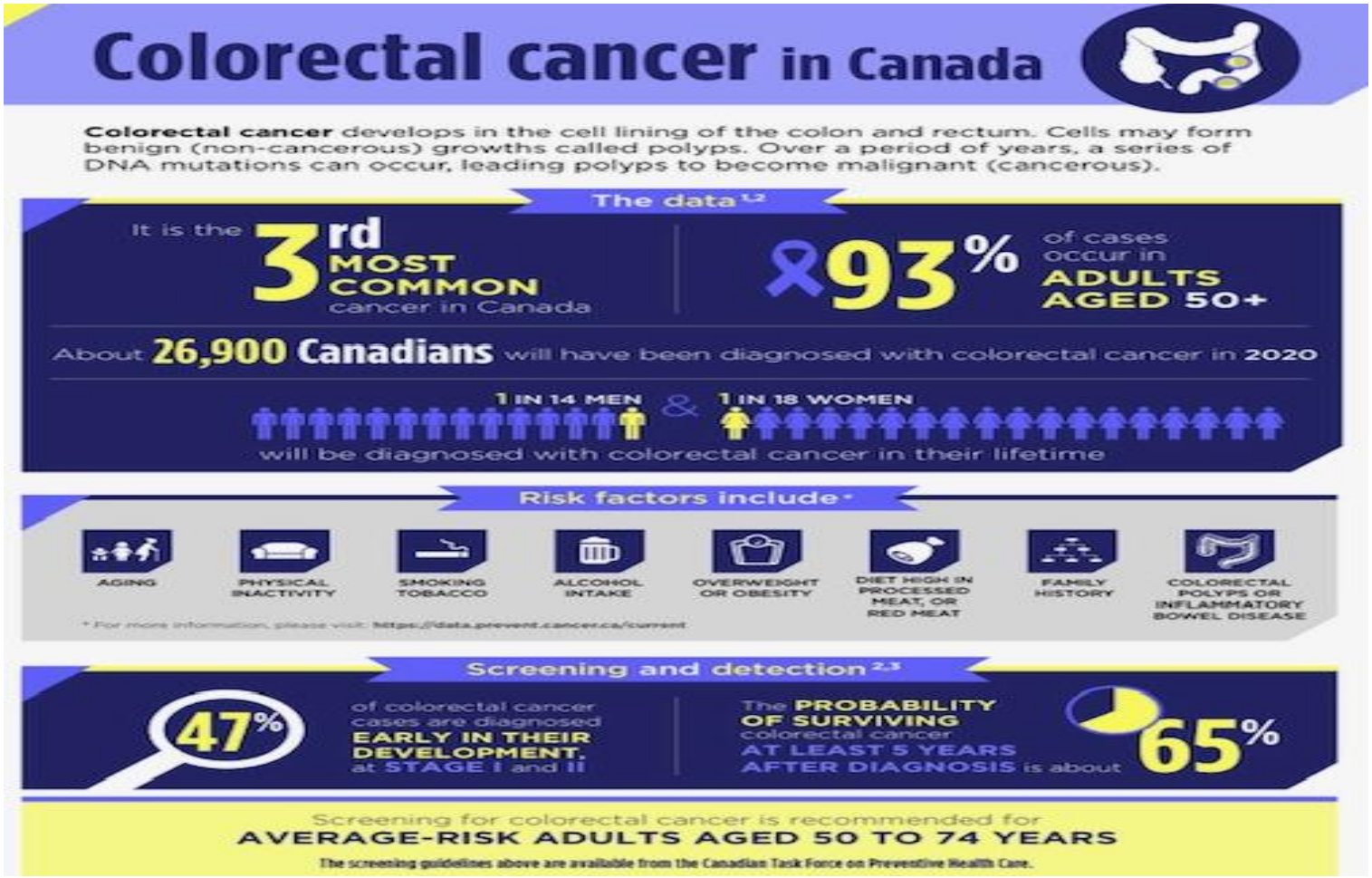
Colorectal cancer
Canadian Statistics



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Staging

Tumor (T)	
TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae).
T1	Tumor invades submucosa (second layer of tissue in the colon or rectum) (through the muscularis mucosa [first layer of tissue in the colon or rectum] but not into the muscularis propria [third layer of tissue in the colon or rectum]).
T2	Tumor invades the muscularis propria (third layer of tissue in the colon or rectum).
T3	Tumor invades through the muscularis propria (third layer of tissue in the colon or rectum) into pericolorectal tissues (tissues around the colon or rectum).
T4 T4a T4b	Tumor invades the visceral peritoneum (outer lining of colon or rectum) or invades or adheres to adjacent organ or structure. Tumor invades through the visceral peritoneum (outer lining of colon or rectum) (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum). Tumor directly invades or adheres to adjacent organs or structures.
Node (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1 N1a N1b N1c	One to three regional lymph nodes are positive (tumor in lymph nodes measuring greater than or equal to 0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative. One regional lymph node is positive. Two or three regional lymph nodes are positive. No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery or nonperitonealized pericolic, or perirectal/mesorectal tissues (nearby tissues).
N2 N2a N2b	Four or more regional nodes are positive. Four to six regional lymph nodes are positive. Seven or more regional lymph nodes are positive.
Metastasis (M)	
M0	No distant metastasis by imaging, etc.: no evidence of tumor in distant sites or organs.
M1 M1a M1b M1c	Metastasis to one or more distant sites or organs or peritoneal (membrane that lines the abdominal cavity) metastasis is identified. Metastasis to one site or organ is identified without peritoneal (membrane that lines the abdominal cavity) metastasis. Metastasis to two or more sites or organs is identified without peritoneal (membrane that lines the abdominal cavity) metastasis. Metastasis to the peritoneal (membrane that lines the abdominal cavity) surface is identified alone or with other site or organ metastases.

Stage	T	N	M
0	Tis	N0	M0
I	T1 T2	N0 N0	M0 M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2 T1	N1/N1c N2a	M0 M0
IIIB	T3-T4a T2-T3 T1-T2	N1/N1c N2a N2b	M0 M0 M0
IIIC	T4a T3-T4a T4b	N2a N2b N1-N2	M0 M0 M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

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Signs &Symptoms

- A change in bowel habits
  -Frequent stools.
  -Diarrhea, constipation.
- Rectal bleeding.
- Narrow-pencil stool.
- Tenesmus.
- Incomplete rectal emptying.
- Abdominal pain, bloating, pelvic pain.
- Weight loss
- Anemia, weakness, fatigue
- Symptoms of locally advanced disease and distant mets.

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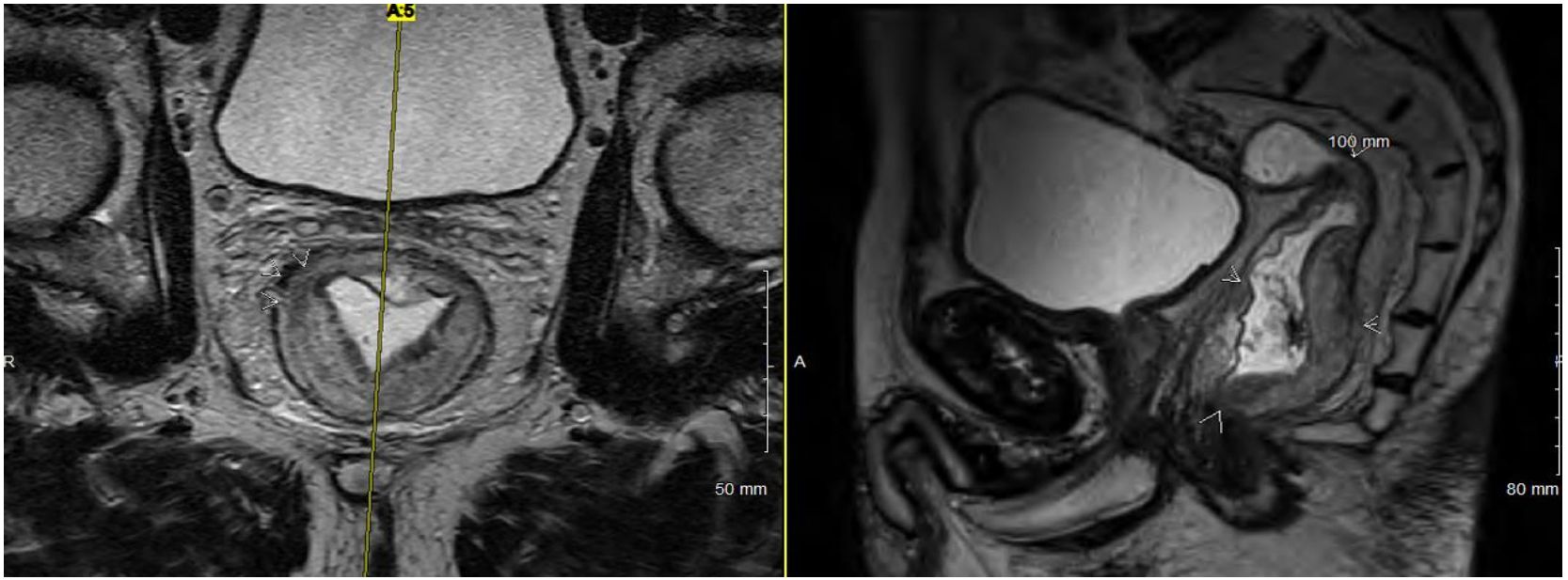
Investigations

- Colonoscopy+Biopsy(path).
- MRI Rectum: TN stage
- CT chest/abdomen/pelvis: M stage.



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Treatment

- **Stage I:** Surgery
- **Stage II & III:**

-Neoadjuvant chemotherapy-Pelvic irradiation(long course 6 weeks),followed by Surgery(TME)in 6-10 weeks, followed by adjuvant chemotherapy.

or

-Neoadjuvant Short course pelvic irradiation over 1 week followed by Surgery(TME)in 7-10 days followed by adjuvant chemotherapy.

or(new)

-Total Neoadjuvant therapy(TNT):Chemotherapy+Chemoradiation or short course radiation followed by TME

. **Stage IV:** Palliative intent: Systemic therapy,+/- surgery +/- Radiation for selected cases.

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Swedish Rectal Cancer Trial
NEJM 1997

-1168 patients, Dukes A,B,C

-Short course RT>Surgery 1 week later vs Surgery.

-Surgery: Not TME

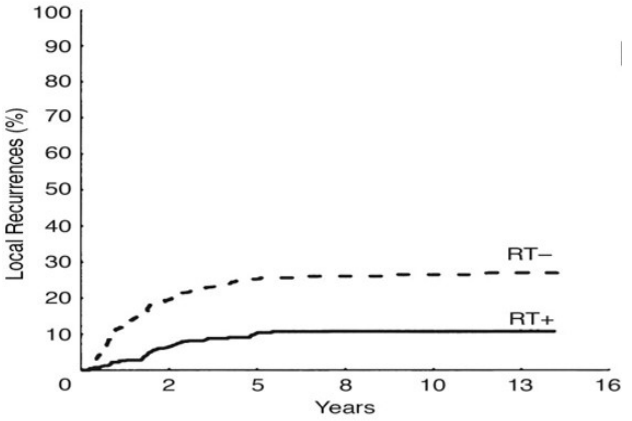
-Local recurrence is less 11% vs 27% at 5 years.

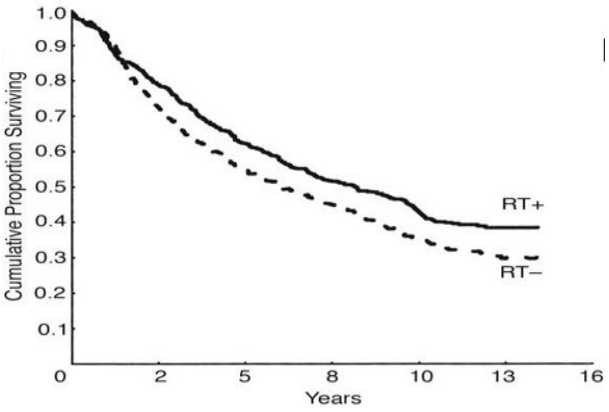
-Overall survival at 5 years improved from 48%

(surgery alone) to 58% %(Preop RT and surgery)

-Benefit sustained after 10 years

Folkesson et al JCO 2005,23:5644-50.





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Dutch Study:
Kapiteijn et al NEJM 345,9,2001
Willem Van Gijn et al Lancet Oncology,12,2011

-1861 patients,Resectable rectal ca stages I,II,III

-Preop Short course RT>TME in 1 week vs TME alone

-Overall Cumulative local recurrence at 10 years:

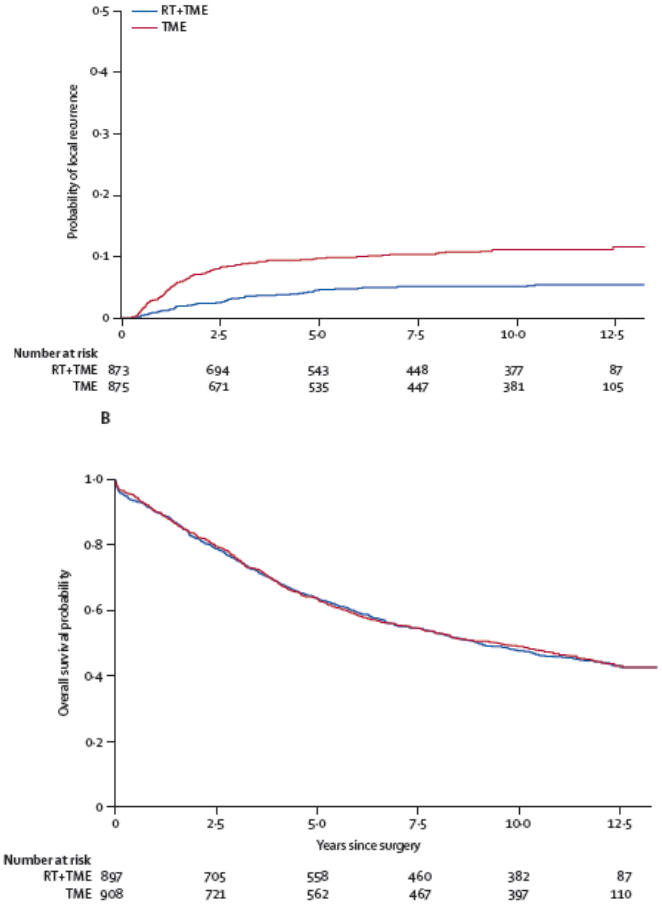
Preop RT>TME=3% vs 9% TME (P<0.001).

-No Overall Survival difference,Preop RT>TME: 48% vs TME: 49% (p=0.86).

-Distal tumors behave aggressively(should not consider short course)

-Stage III with negative margin: Overall Survival advantage with Preop RT>TME 50% vs TME 40%(p=0.032).

-Higher GI toxicity(fecal urgency 79% vs 61% and fecal leakage requiring pads 58% vs 35%) and sexual dysfunction on long Term Analysis at 14 years-Health Related QOL Questionnaires among patients-*Wiltink et al Eur J Cancer 2014,50(14)*



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Stockholm III study: Optimal fractionation of preop RT and timing to surgery

Erlandsson et al Lancet Onc 2017

- Multicenter randomised phase 3 non inferiority trial
- Resectable Rectal cancer,840 patients

  -Arm-1:Short course RT>TME in 1 week

  -Arm-2:Short course RT>TME 4-8 weeks

  -Arm-3:Long course chemoradiation>TME 4-8 weeks
- No difference in outcome between the 3 arms
- Higher surgical complications in Arm-1, no difference in surgical complications between arms 2 and 3.
- Short course radiation with a delay 4-8 weeks to TME is a useful alternative to long course chemoradiation, waiting 4-8 weeks did not have any negative impact on disease outcome and has less surgical morbidity compared to immediate surgery within 1 week.

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MRC/NCIC
Sebag-Montefiore et al Lancet 373,2009

-1350 patients, stages II and III.

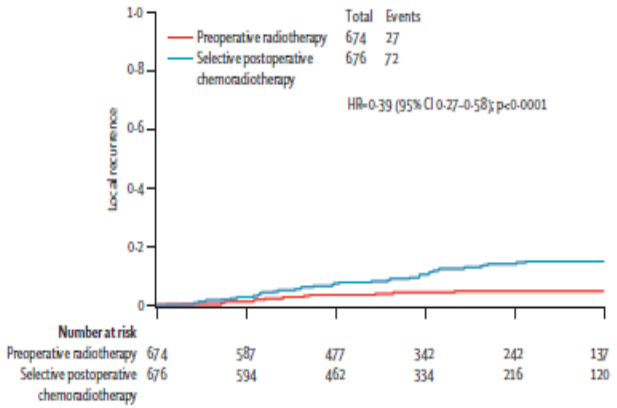
-Preop short course RT>TME vs Postop chemoRT for selected group with positive margin.

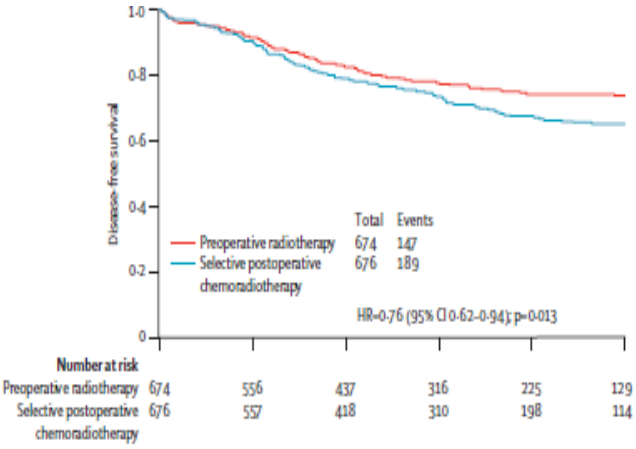
-61% Reduction in local recurrence at 3 years (4.4% vs 10.6%,6.2% absolute difference<0.0001).

-Relative improvement in DFS 24% in favor of Preop arm(77.5% vs 71.5%,p=0.013) .

-No Overall Survival difference.

-QOL Questionnaires from MRC/NCIC C016-3 years follow up: Mild unintentional release of stools (64% vs 38%)-*Stephens RJ et al JCO 2010:28(27)*





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German study

Sauer et al NEJM 351,17,2004
Sauer et al JCO,30,June 2012

-823 patients,T3-4,N1-2 with any T

-Preop chemoRT vs Postop chemoRT(long courses)

-Local recurrence:Preop chemoRT:7.1% vs Postop chemoRT:10.1%(P=0.048)

-No difference in overall survival 59.6% vs59.9%(p=0.85).

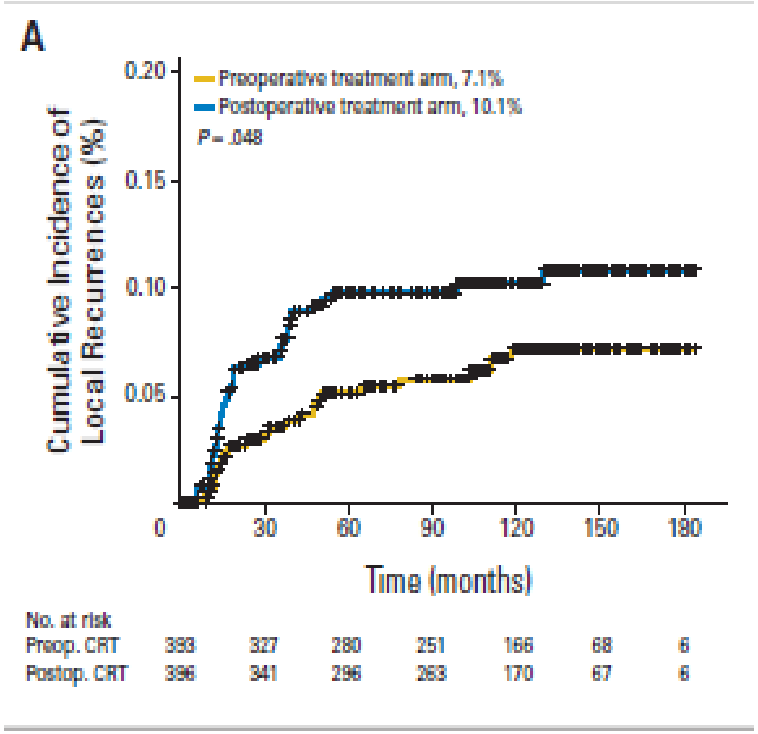
-No difference in Distant Metastases:29.8% vs 29.6%(p=0.9).

-More sphincter preservation with Preop arm(39% vs 19%).

-Less acute Grade 3 and 4 toxicity.

-3x less likely to develop chronic anastomotic strictures in preop arm.

Long course preop chemoradiation is the standard of care.



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Short course Neoadjuvant Radiation vs Long course Neoadjuvant Radiation+Chemotherapy

- 2 Randomised studies(stages II,III)

-Polish Study(*Bujko et al BJS,93,2006).*

-Australian TROG 01.04(*Ngan et al JCO,30,2012).*

- ***More acute toxicity but no differences in late toxicity.***
- ***No differences in local control or survival***
- ***Higher clinical and pathological response with the long course due longer interval time between radiation completion and surgery(6-10 weeks vs 1 week)***
- ***If sphincter preservation is desired, or if bulky tumors or threatened margins, use the long course.***

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Neoadjuvant long course chemoradiation or short course radiation

- Neoadjuvant ChemoRdaiation is superior to Adjuvant ChemoRadiation in local control, toxicity profile, sphincter preservation, but no difference in survival and remains standard for T3-4N0,or N1-2 any T.
- Neoadjuvant Short course Radiation is similar to long course ChemoRadiation in local control and survival, and better acute toxicity profile, more convenient, but no enough time for down staging, or sphincter preservation,unless surgery is delayed, longer follow up is needed to assess the impact of severe late toxicity.
- Despite excellent Local control(95% or more)the rates of distant metastases remain high exceeding 25%.
- Many patients do not get adjuvant chemotherapy due to prolonged postop complications and poor healing, or they don't finish all chemotherapy.

Total Neoadjuvant Therapy(TNT)
3 RCT's ASCO 2020

	OPRA	PRODIGE 23	RAPIDO
Treatment Arms	CRT followed by chemotherapy (A) vs. chemotherapy followed by CRT (B)	Chemotherapy → CRT → TME → chemotherapy (A) vs. CRT → TME → chemotherapy (B)	Short-course RT → chemotherapy → TME (A) vs. CRT→TME→chemotherapy (B)
Radiation Used	50 Gy in 25 fractions with optional 4-6 GY boost	50.4 Gy in 28 fractions	25 Gy in 5 fractions
Chemotherapy Used	4 months of FOLFOX/CAPOX; continuous infusion 5-FU or capecitabine with radiation	Capecitabine with radiation; 6 cycles of mFOLFIRINOX before TME and 6 cycles of mFOLFOX6 or 4 cycles of CAPOX after TME (A); 12 cycles of mFOLFOX6 or 8 cycles of CAPOX (B)	Capecitabine with radiation; 6 cycles of CAPOX or 9 cycles of FOLFOX (A); 8 cycles of CAPOX or 12 cycles of FOLFOX (B)
Number of Enrolled Patients	324	461	920
Inclusion Criteria	Stage II or III rectal adenocarcinoma	cT3 at risk of local recurrence or cT4 rectal adenocarcinoma	Rectal adenocarcinoma with at least one high-risk feature (T4a/b, extramural vascular invasion, N2, +mesorectal fascia, enlarged lateral lymph nodes)
Primary Outcome	3-year DFS 78% (A) vs. 77% (B)	3-year DFS 75.7% (A) vs. 68.5% (B)*	3-year disease-related treatment failure 23.7% (A) vs. 30.4% (B)*
Additional Outcomes	3-year DMFS 84% (A) vs. 82% (B)	3-year DMFS 78.8% (A) vs. 71.7% (B)*	3-year distant metastases rate 20.0% (A) vs. 26.8% (B)* pCR 28.4% (A) vs. 14.3% (B)*
	3-year organ preservation rates 59% (A) vs. 43% (B)*	pCR 27.8% (A) vs. 12.1% (B)*	pCR 28.4% (A) vs. 14.3% (B)*

*P<0.05

Abbreviations: CRT, chemoradiation; DFS, disease-free survival; DMFS, distant-metastasis free survival; TME, total mesorectal excision; pCR, pathologic complete response; vs, versus.

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Total Neoadjuvant therapy(TNT)

- A promising treatment.
- Allows earlier introduction of chemotherapy to treat micro metastatic disease.
- No impact on outcome despite the delay in TME from last radiation(beyond 10 weeks).There is even improvement in DFS and DMFS.
- Higher rates of down staging and pCR, which will likely improve organ preservation rates and avoid TME,therefore may move the approach of watch-and-wait into the mainstream.
- Awaiting long term data on toxicity.

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Conclusions

- Management of rectal cancer today involves navigating the complex balance between loco regional and distant disease control and patient's quality of life.
- The management seems to be shifting towards giving all oncological treatments prior to surgery and preliminary data suggests improvement in disease outcomes, organ preservation due to improvement in response rates and better down staging, which may lead to avoidance of radical surgery in complete responders.
- TNT is likely to be the new standard of care treatment for stages II and III rectal cancers.

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Thank you