Total Neoadjuvant Therapy in Rectal Cancer

A Radiation Oncology Perspective

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Agenda

1. Radiation in rectal cancer 1.0 (pre TNT): Who, why, when, how much?
2. TNT from a radiation perspective
3. Potential omission of surgery
4. Potential omission of radiation
5. Radiation in rectal cancer 2.0 (+TNT): Who, why, when, how much?

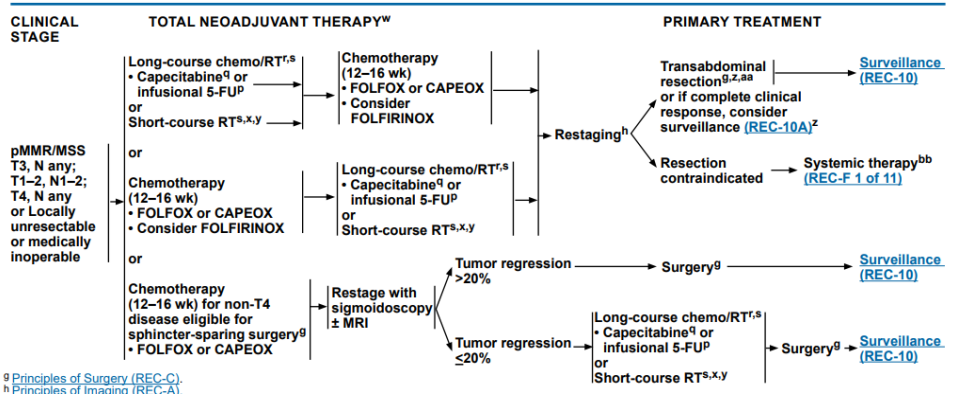
Radiation in rectal cancer 1.0 (pre TNT): Who, why, when, how much?

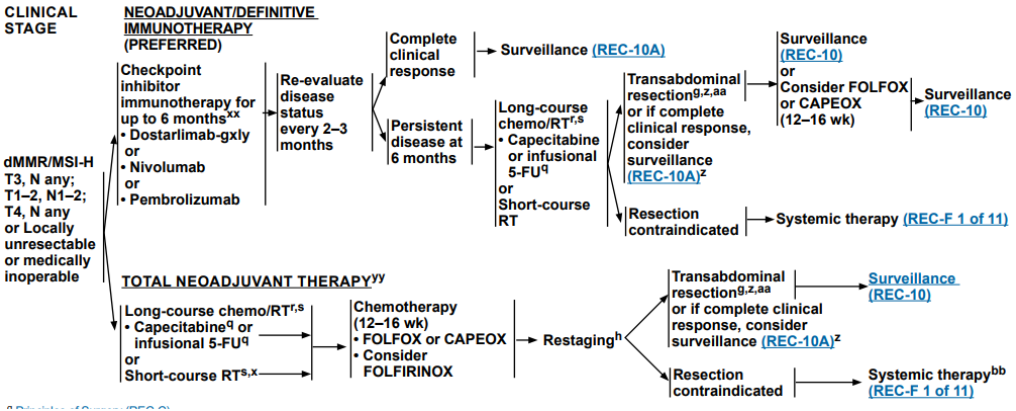
Radiation in rectal cancer

Indicated for T3+ and/or N1+

Current NCCN treatment paradigm listed on this slide…notice **TNT**

But radiation has been a part of rectal cancer long before TNT…



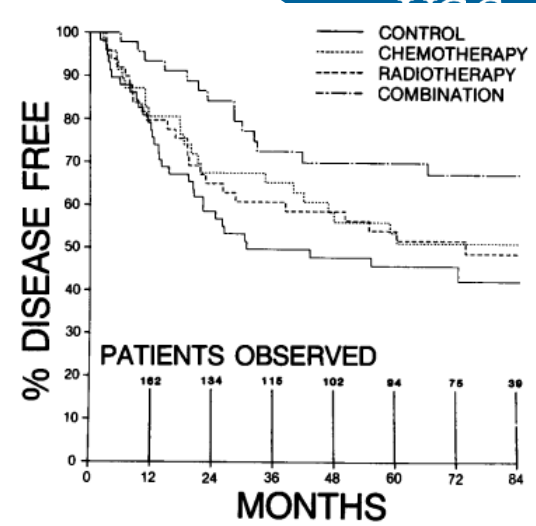


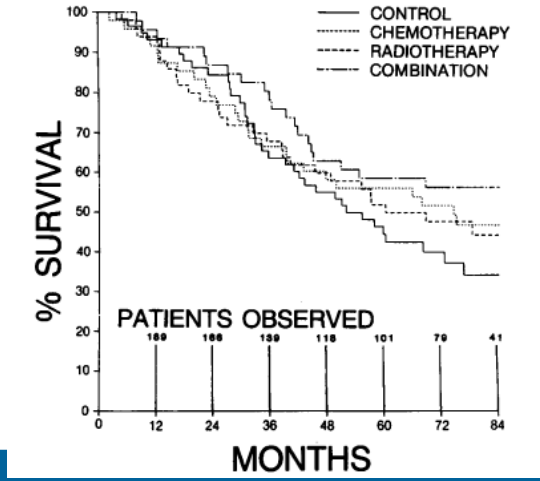
Why radiation?

GITSG7175

- 227 patients with stage pT3+ or N+ rectal cancer randomized to post-op observation vs chemo vs RT vs chemo RT

- 10 yr, surgery alone vs postop Chemo-RT
  - OS: 27% v 45%
  - LR: 55% v 33
  - LF Rate: 25% v 10%





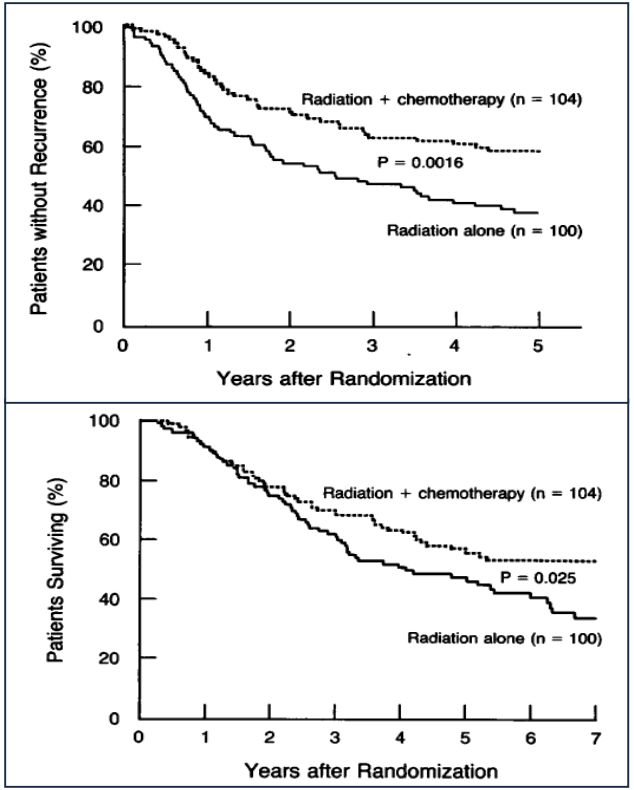
 Thomas PR et al. Radiother Oncol 1988

Why radiation?

NCCTG 79-47-51

- 204 patients with stage pT3+ or N+ rectal cancer randomized to post-op RT vs chemo RT

- 5-year overall recurrence: RT 63% vs. chemo-RT 41% (P = 0.0016)
  - LR 25% vs. 13% (P = 0.036)
  - DM 46% vs. 29% (P = 0.011)
  - 5-year OS ~40% vs. ~55% (P = 0.025)



NEJM 1991

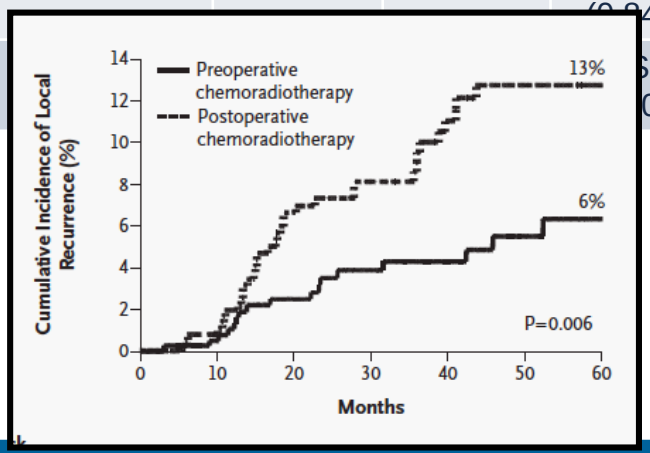
When radiation?

German Rectal Trial

- 823 patients with T3+ or N+ rectal cancer randomized to pre-op vs post-op chemo RT

- Conclusions:
  - No SS difference in incidence of DM, DFS, or OS
  - Recommended pre-op CRT for locally advanced disease:
    - Superior compliance
    - Improved LR control
    - Reduced Acute and Late Toxicity
    - Increased rate of sphincter-sparing surgeries

5yr f/u	PreOp(%)	Postop(%)	P-Value
Acute G3-4	27	40	0.001
Late G3-4	14	24	0.01
pCR	8	0	<0.001
LR	6	13	0.006
Sphincter preservation	39	19	0.004
DM	36	38	NS (0.84)
			0)



Sauer et al, NEJM 2004

Sauer et al, JCO 2012

How much radiation?

Long course chemoRT

- Daily M-F treatments given over ~5 weeks
- Smaller daily dose
- Higher net dose including higher biologically equivalent dose (BED)
- Concurrent chemo

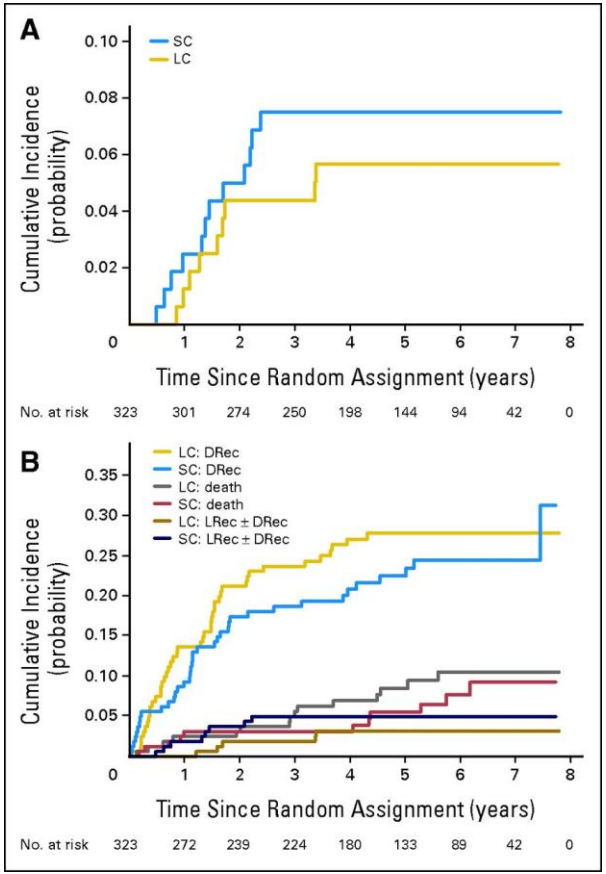
Short course RT alone

- Just 5 treatments typically delivered over 1 week
- Higher daily dose
- Lower net dose including lower biologically equivalent dose (BED)
- Radiation only, no concurrent chemo

How much radiation?

TROG 0104

- 326 pts randomized to short course (25/5) vs. std CRT (50.4/28 w. 5-FU)
  - Surgery 4-6 wks after long course CRT
  - No difference in 3 yr local control
    - 7.5 vs 4.4%
  - No difference in DFS or OS
  - More path downstaging w/ long course CRT (45 vs. 28% p= 0.002)
  - More pCR w/ LC-CRT (15 vs 1)
  - Distal tumors (< 5 cm): LR in 6 of 48 pts (short course) vs 1 of 31 (std CRT) (NS)



How much radiation

Experts Debate Short-Course Radiation for Rectal Cancer

continued from page 1

3 studies utilizing short-course radiation therapy for rectal cancer, and I conclude on these and many other studies that it is ready for prime time. Short-course radiation therapy has proven to be very effective."

He said the first proof that short-course radiation works for rectal cancer comes from five years of follow-up from the Swedish Rectal Cancer Trial of patients younger than 80 years of age who had resectable rectal cancer (*N Engl J Med* 1997;336[14]:980-987). This trial compared surgery alone (n=557) with surgery and preoperative short-course radiation therapy with 25 Gy delivered in five fractions in one week (n=553). At five years, the researchers identified a gain of 10% in overall survival (58% vs. 48%; *P*=0.004) with short-course radiation therapy. Short-course radiotherapy also reduced the local recurrence rate from 27% to 11% (*P*<0.001) and increased cancer-specific survival from 65% to 74% (*P*=0.002).

The Polish I study compared long-course chemoradiotherapy (n=157) with short-course radiotherapy (n=135) in patients with T3 or T4 resectable primary tumors and no evidence of sphincter involvement on digital rectal examination (*Br J Surg* 2006;93[10]:1215-1221). The lower tumor margin had to be accessible by digital rectal examination. Patients receiving long-course chemoradiotherapy received 50.4 Gy in 28 fractions of 1.8 Gy, plus bolus 5-fluorouracil and leucovorin with surgery after four to six weeks. Patients receiving short-course radiotherapy received 25 Gy in five fractions of 5 Gy and surgery within seven days. At four years, there was no significant difference in overall survival, disease-free survival or local recurrence between groups.

> *'With the possibility of delayed surgery as a valid option in the treatment, a window of opportunity opens bringing forward chemotherapy after radiation therapy before surgery, treating micrometastases in these advanced rectal cancer patients.'*
>
> —Cornelius Van de Velde, MD, PhD

"The results indicated that radiation toxicity was significantly more after long-course radiation therapy, but all the other results were the same," Dr. Van de Velde said. Although severe late toxicities did not differ significantly, early radiation toxicity was greater with long-course radiation (18% vs. 3%; *P*<0.001).

The Tasman Radiation Oncology Group trial 01.04 compared long-course chemoradiotherapy (50.4 Gy, 1.8 Gy per fraction in 5.5 weeks plus fluorouracil 225 mg/m² per day; surgery in four to six weeks; four courses of adjuvant chemotherapy; n=163) with short-course radiotherapy (5×5 Gy in one week, early surgery, six courses of adjuvant chemotherapy; n=163) (*J Clin Oncol* 2012;30[31]:3827-3833). Patients had stage 3N0 to 2M0 rectal adenocarcinoma with 12 cm from the anal verge. The study indicated no significant differences between the two groups in terms of control of the tumor or toxicity.

The Stockholm III trial compared short-course radiotherapy with long-course radiotherapy and immediate versus delayed surgery. In the study, 840 patients with stage I to III rectal cancer were randomized to receive 5×5 Gy followed by direct surgery (less than one week), 5×5 Gy followed by delayed surgery (four to eight weeks), or 25×2 Gy followed by delayed surgery (four to eight weeks) (*Lancet Oncol* 2017;18[3]:336-346). The study concluded there were no significant differences among the three regimens in local or distant recurrence, recurrence-free survival, overall survival or surgical complications. There was a trend toward fewer postoperative complications with short-course and delayed surgery.

"With the possibility of delayed surgery as a valid option in the treatment, a window of opportunity opens bringing forward chemotherapy after radiation therapy before surgery, treating micrometastases in these advanced rectal cancer patients," Dr. Van de Velde said.

The RAPIDO trial included 920 patients with locally advanced rectal cancer randomized to standard chemoradiation therapy and then surgery after a delay of eight to 10 weeks, followed optionally by chemotherapy after six to eight weeks, or to

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Society of Surgical Oncology's 2021 International Conference on Surgical Cancer Care

Rectal Radiation

continued from page 3

the experimental arm of 5×5 Gy radiation therapy followed by CAPOX (capecitabine plus oxaliplatin) or FOLFOX (folinic acid, fluorouracil and oxaliplatin) for 18 weeks, and then surgery after two to four weeks (*Lancet Oncol* 2021;22[1]:29-42). The experimental arm was superior in terms of three-year, disease-related treatment failure (24% vs. 30%; *P*=0.019), three-year distant metastases (20% vs. 27%; *P*=0.005), and pathologic complete response (28% vs. 14%; *P*<0.001). There was no difference in postoperative complications or number of stomas.

Dr. Van de Velde said short-course radiation therapy has better patient compliance than long-course radiation therapy, and this was evident in the RAPIDO trial (100% vs. 93%) (*Radiother Oncol* 2020;147:75-83).

Another benefit of short-course radiation therapy is that it has a survival benefit in elderly patients with locally advanced rectal cancer, shown by results in 101 patients in the PRODIGE-42 study, presented at the American Society of Clinical Oncology's Gastrointestinal Cancers Symposium (abstract 4) last January. In this trial, arm A involved preoperative long-course chemoradiation (50 Gy, 2 Gy per fraction; five fractions plus capecitabine) and delayed surgery, while arm B involved preoperative short-course radiotherapy (25 Gy; 5 Gy per fraction, five fractions) and delayed surgery. The inclusion criteria were patients 75 years or older with T3/T4 rectal cancer tumors. The six-month mortality rate was higher with long-course radiation (10% vs. 3.92%), and the researchers concluded that short-course radiotherapy should be recommended as the new standard of care.

Dr. Van de Velde noted that short-course radiation therapy requires fewer visits to health care facilities, which is very important in the era of COVID-19.

"We also see in the Dutch M1 trial in metastatic rectal cancer patients and in the RAPIDO trial of locally advanced rectal cancer patients that there is a considerable pathologic complete response rate [with short-course radiation] which can be used to initiate a watch-and-wait strategy in selected patients," Dr. Van de Velde said.

"Short-course radiation therapy is here to stay," he said. "There are many reasons, especially now, to recommend short-course radiation therapy."

Con: Short-Course Is Not Ready for Prime Time

Philip Paty, MD, an attending surgeon in the Colorectal Surgery Service at Memorial Sloan Kettering Center, in New York City, offered a contrary opinion. "Is short-course radiation ready for prime time in rectal cancer? Absolutely not. The true story of short-course radiation is a sorrowful tale of burned bottoms, poor healing and smelly stomas. As we say in America, you get what you pay for."

To bolster his argument, Dr. Paty pointed to four randomized trials comparing short- and long-course neoadjuvant radiotherapy: the Polish I trial, Tasman Radiation Oncology Group trial 01.04, Polish II trial and Stockholm III trial (*Br J Surg* 2006;93[10]:1215-1221; *J Clin Oncol* 2012;30[31]:3827-3833; *Ann Oncol* 2016;27[5]:834-842; and *Lancet Oncol* 2017;18[3]:336-346). Dr. Paty pointed out that the three Northern European trials enrolled patients with resectable cancers and made adjuvant chemotherapy optional. The Polish II trial tested long-course oxaliplatin-based preoperative chemoradiation versus 5×5 Gy and consolidation chemotherapy for cT4 or fixed cT3 rectal cancer.

"There was no impact of radiation method across the board telling us that stage and surgery were the determinants of local recurrence. Survival end points were also no different," Dr. Paty said. "However, we can find one measure of radiotherapy efficacy that is different between the radiation methods: the rates of pathologic complete response, which were higher following long-course radiation. We learn that long-course radiation therapy is more effective in sterilizing primary tumors than is short-course radiotherapy. Of note, quality-of-life data may not be an accurate representation because data were reported only in underpowered subsets that excluded patients with adverse outcomes (tumor recurrence, ongoing treatment), thereby excluding many of the patients most likely to have problems."

Dr. Paty also said one clear outcome difference is found between short- and long-course radiotherapy: rates of permanent stoma. "The three trials with resectable cancers show the same trend of increased permanent stoma rates for short-course radiation." In the Polish I trial, the rates of permanent stoma were twice as high with short-course radiation, due to more patients requiring colostomy because of impaired healing (leak, stenosis, infection and fistula) or poor anorectal function. Dr. Paty pointed out that this outcome difference is supported by pooled data from the three randomized trials studying resectable rectal cancer, which show permanent colostomy rates are higher with short-course radiation (46% vs. 36%).

Finally, Dr. Paty shared a paper from England that evaluated bowel function in a population-based study of rectal cancer patients without stomas (*Int J Rad Onc Bio Phys* 2018;103:1132-1142). "Preoperative long-course radiation was bad for continence and for urgency. Short-course radiation was even worse, with 30% fewer patients achieving complete continence. Again, we learn that the large fraction sizes and hypofractionation of short-course radiotherapy damages sphincter muscles and anastomoses," Dr. Paty said.

Dr. Paty concluded that the four randomized trials directly comparing short- and long-course neoadjuvant radiotherapy show there is higher long-term morbidity and higher permanent stoma rates with short-course radiation. "So, if you get a rectal cancer, what do you want to buy?" he said. "You can go to Professor Van de Velde, save a few euros,

continued on page 22

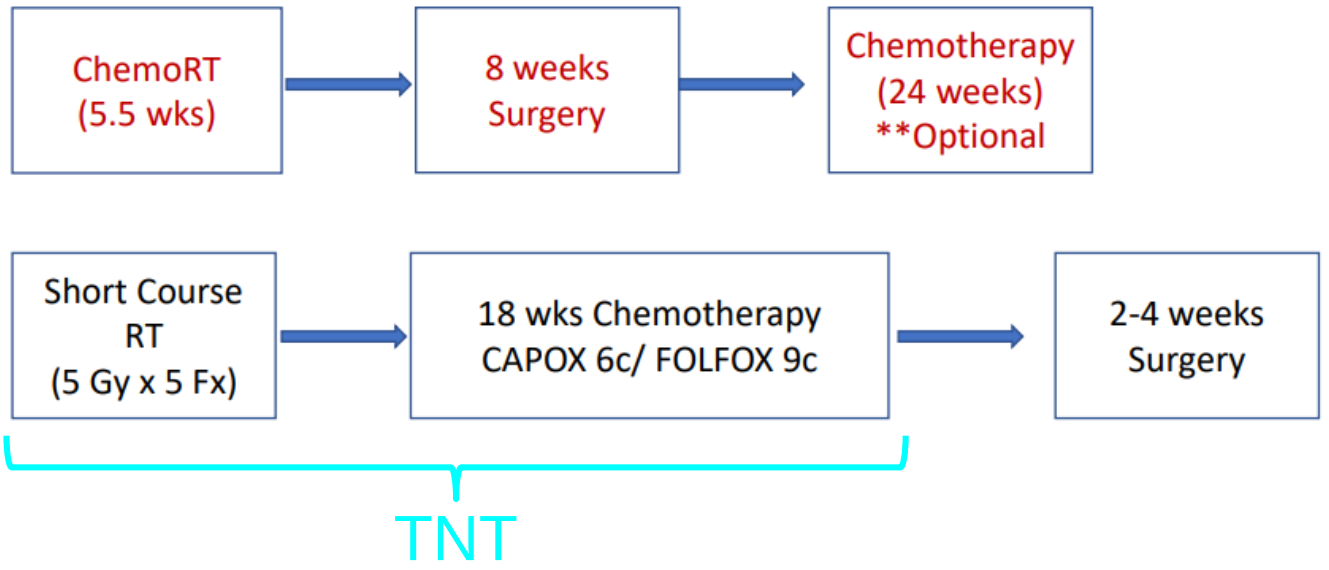
> *'So, if you get a rectal cancer, what do you want to buy? You can go to Professor Van de Velde, save a few euros, and live with a stoma or a diaper for the rest of your life, or you can spend a few dollars and go back to dignity and having fun.'*
>
> —Philip Paty, MD

TNT from a radiation perspective

RAPIDO Trial

912 patients with 1+ MRI high risk feature:

- T4a/b
- EMVI
- N2
- < 1mm MRF
- Lateral LN

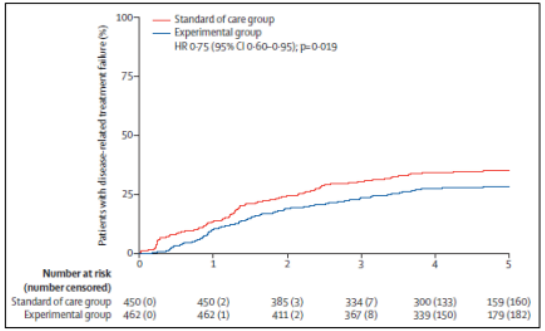


Dijkstra et al Annals Surg 2023 Bahadoer Lancet Oncol 2020

RAPIDO Trial

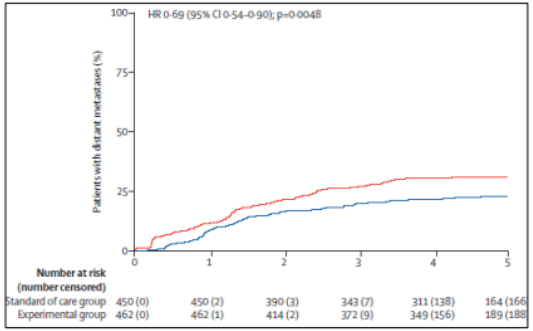
SS improvement in 3 & 5 year cure rates and distant mets with TNT, trend to improve local control

Disease Related Treatment Failure



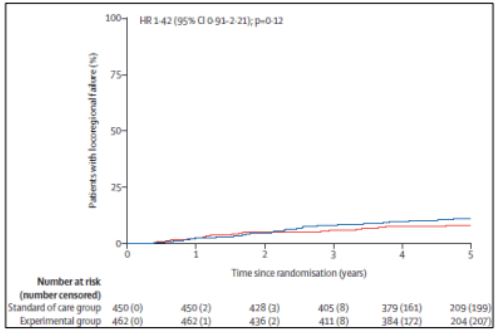
	SC-RT-> FOLFOX	Standard Arm
3 Year	23.7%	30.4% (p=0.019)
5 Year	27.8%	34.0% (p=0.048)

Distant Metastases



	SC-RT-> FOLFOX	Standard Arm
3 Year	20.0%	26.8% (p=0.0048)
5 Year	23.0%	30.4% (p=0.011)

Local Failure

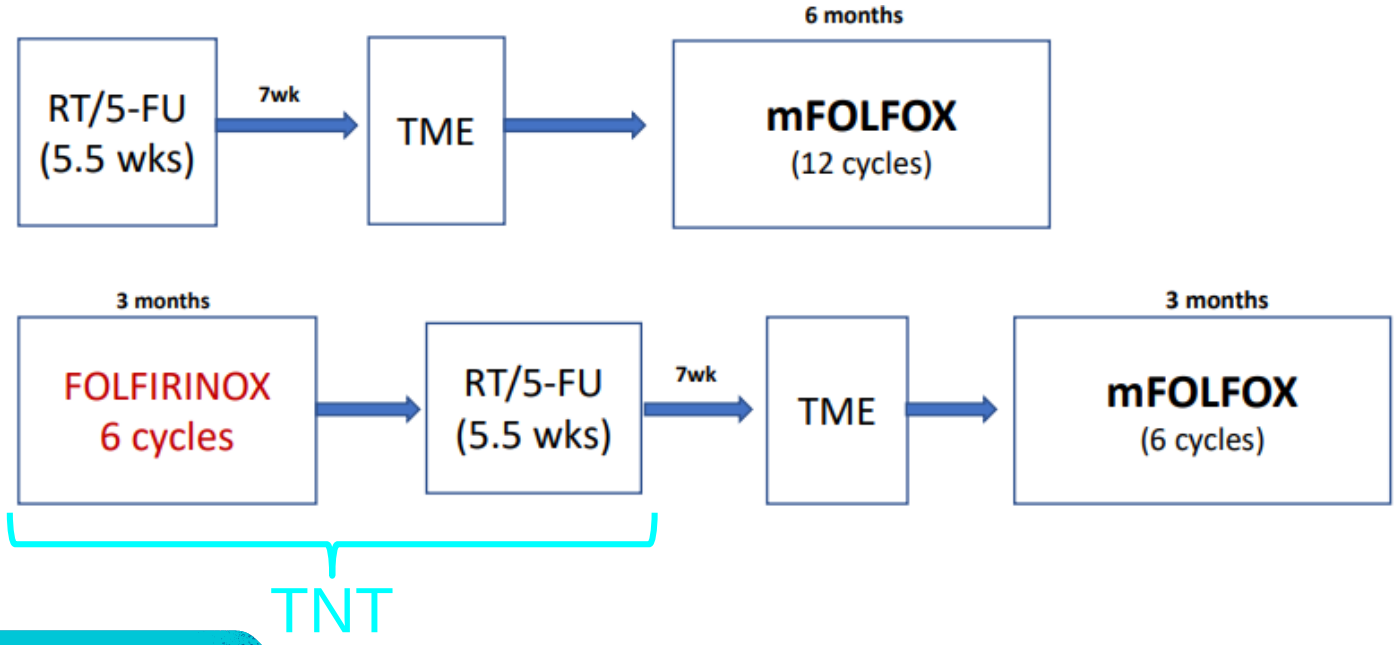


	SC-RT-> FOLFOX	Standard Arm
3 Year	8.7%	6.0% (p=0.12)
5 Year	12%	8.0% (p=0.07)

Dijkstra et al Annals Surg
2023 Bahadoer Lancet Oncol
2020

PRODIGE 23 Trial

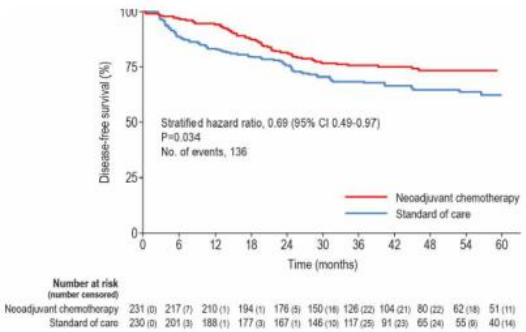
461 patients with traditional chemoRT criteria: T3+ or N1+



PRODIGE 23 Trial

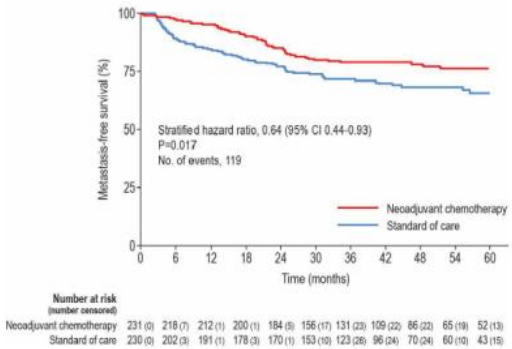
SS improvement in 3-yr cure rates and distant mets, trend to improve OS with TNT

Disease-Free Survival



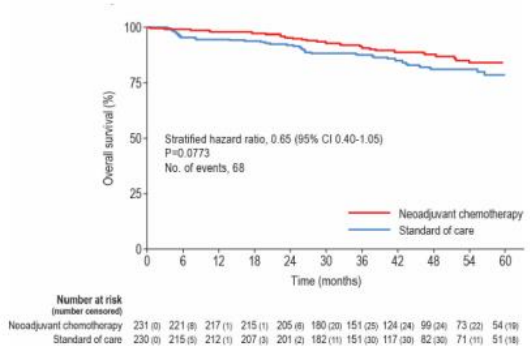
	Neoadjuvant FOLFIRINOX	Standard Arm
3 Year	76%	69%

Distant Metastases-Free Survival



	Neoadjuvant FOLFIRINOX	Standard Arm
3 Year	79%	72%

Overall Survival



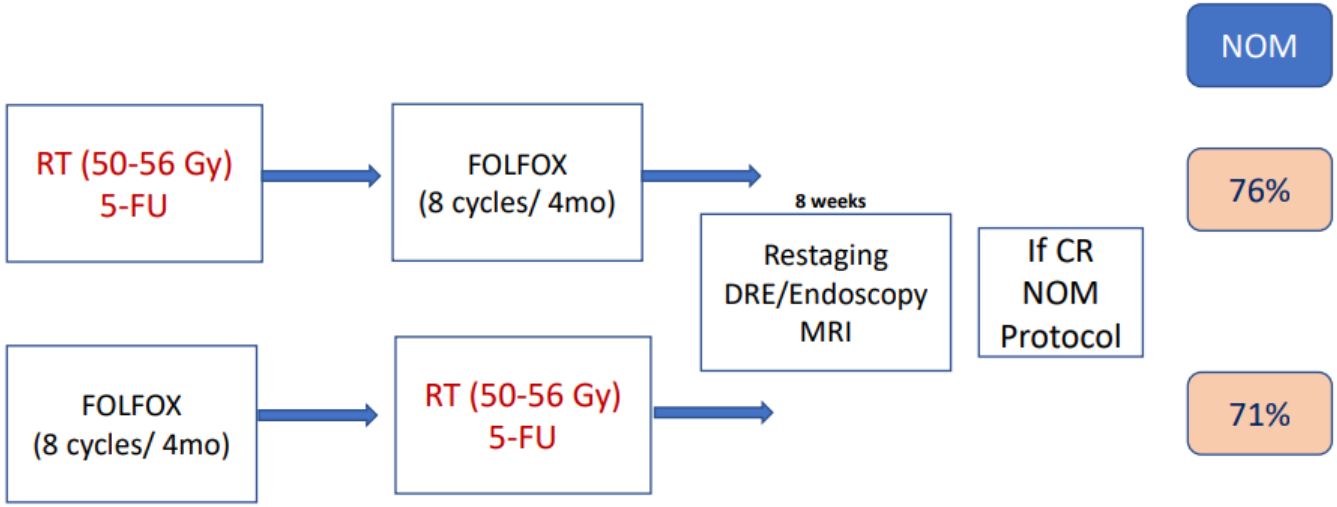
	Neoadjuvant FOLFIRINOX	Standard Arm
3 Year	91%	88%

Conroy Lancet Onc 2021

Potential omission of surgery

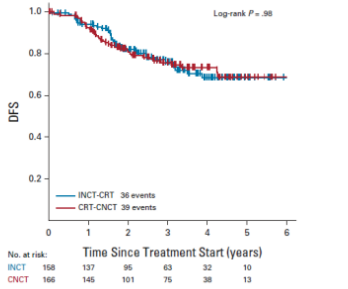
OPRA Trial

324 patients with Stage II or III distal rectal cancer requiring APR



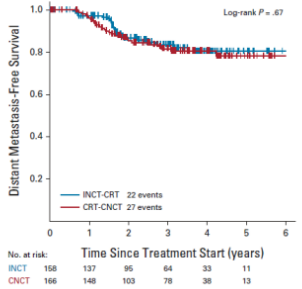
OPRA Trial

Disease-Free Survival



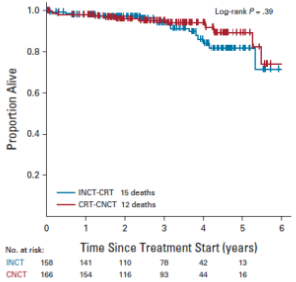
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	76%	76%

Distant Metastases-Free Survival



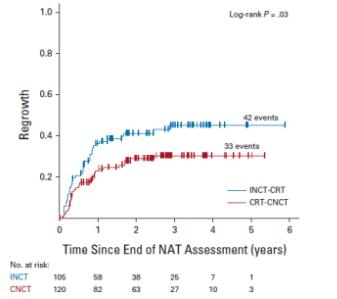
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	84%	82%

Overall Survival



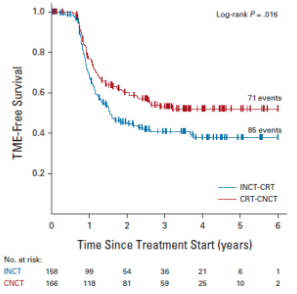
Disease outcomes in line with historical norms

Regrowth



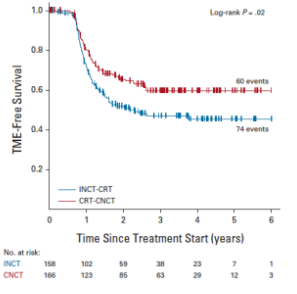
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	40% (42/105)	27% (33/120)

TME-Free Survival (IIT)



	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	41%	53%

TME Free Survival (actual TME)

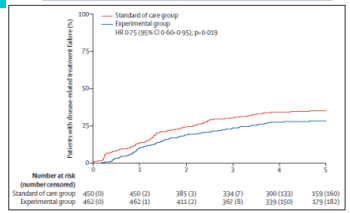


	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	47%	60%

Comparing TNT approaches

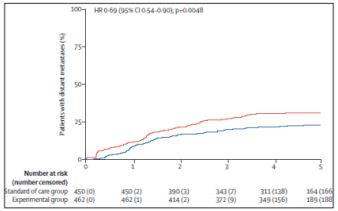
RAPIDO

Disease Related Treatment Failure



	SC-RT-> FOLFOX	Standard Arm
3 Year	23.7%	30.4% (p=0.019)
5 Year	27.8%	34.0% (p=0.048)

Distant Metastases



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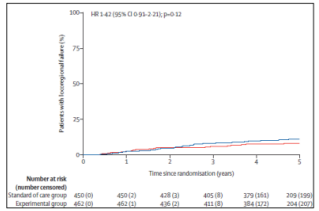

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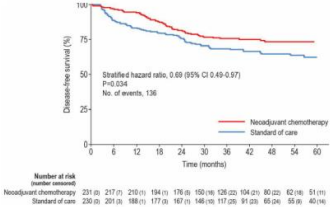
PRODIGE 23

Disease-Free Survival



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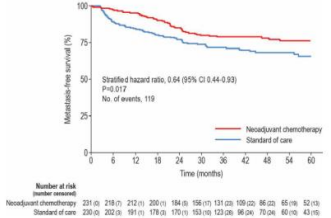
Distant Metastases-Free Survival



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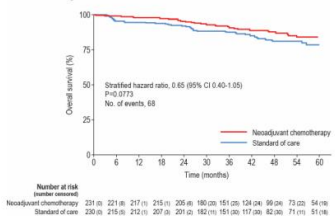
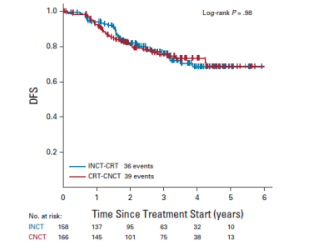


	Neoadjuvant FOLFIRINOX	Standard Arm
3 Year	91%	88%

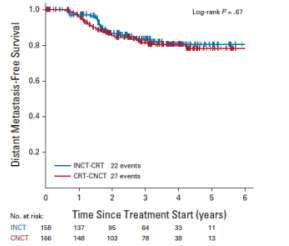
OPRA (includes NOM)

Disease-Free Survival



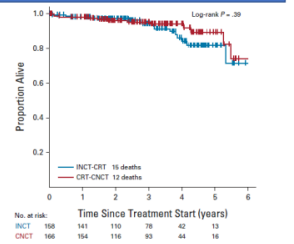
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	76%	76%

Distant Metastases-Free Survival



	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	84%	82%

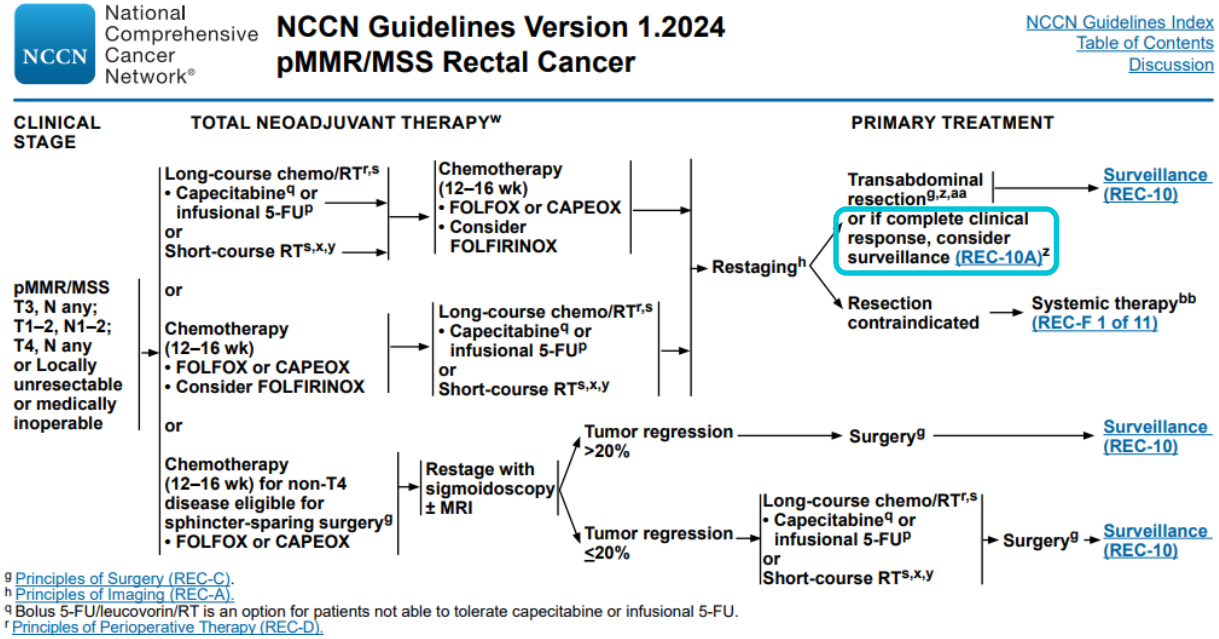
Overall Survival



ASTRO 2021 Guidelines

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. NOM is conditionally recommended after multidisciplinary discussion if a cCR is achieved after neoadjuvant treatment in patients with rectal cancer who: **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[50, 51, 52, 53]

NCCN 2024 Guidelines



[g] Principles of Surgery (REC-C).
[h] Principles of Imaging (REC-A).
[q] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[r] Principles of Perioperative Therapy (REC-D).

NCCN 2024 Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Rectal Cancer

NCCN G
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SURVEILLANCE FOLLOWING NONOPERATIVE MANAGEMENT

- History and physical examination every 3–6 months for 2 years and then every 6 months for a total of 5 years
- CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years
- DRE and proctoscopy or flexible sigmoidoscopy every 3–4 months for 2 years, then every 6 months for a total of 5 years
- MRI rectum every 6 months for up to 3 years
- CT chest/abdomen every 6–12 months for a total of 5 years, CT pelvis to be included once no longer doing MRI
- Colonoscopy at 1 year following completion of therapy
  - If advanced adenoma, repeat in 1 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years
- Principles of Nonoperative Management (REC-H)

NCCN 2024 Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2024
Rectal Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF NONOPERATIVE MANAGEMENT

To provide nonoperative management (NOM) for patients with rectal cancer, the multidisciplinary team's diagnostic skills are crucial. They must accurately assess clinical, radiologic, and pathologic findings, determining patient eligibility for NOM and closely monitoring progress. The team's expertise extends to tracking treatment responses, identifying surgical needs promptly, and adjusting the management plan as necessary. Additionally, the team should maintain a comprehensive understanding of the watchful waiting literature and surveillance methodology, adeptly treating patients with complete or near-complete clinical responses and regularly monitoring for potential tumor recurrence or progression. Given this, NOM is recommended only at centers with experienced multidisciplinary teams and for patients committed to intensive surveillance.

Criteria for Complete Clinical Response

- High-definition flexible endoscopy[1]
  - Pale smooth scar with or without telangiectasia
  - No ulceration, nodularity, or mucosal irregularities
  - No stricture
- DRE[1]
  - Smooth, flat scar
  - No nodularity
- Diffusion-weighted MRI[2]
  - Fibrotic, linear scar with low signal intensity on T2-weighted images
  - No diffusion restriction
  - No suspicious lymph nodes
- All of the criteria must be satisfied in order to define a complete clinical response
- Biopsy offers no added diagnostic value if the criteria are met[3,4]
- Circulating tumor DNA (ctDNA) has no proven role in the NOM of patients

Timing of Assessment for Complete Clinical Response

- For patients treated with chemotherapy first followed by radiation (induction chemotherapy), assessment should be performed no earlier than 8 weeks after completion of radiotherapy to allow time for delayed response to radiation.[5]
- For patients treated with radiation first followed by chemotherapy (consolidation chemotherapy), assessment should be completed within a month of completion of chemotherapy.

Near Complete Response[6,7]

- If the patient has had a near complete response and wishes to avoid surgery, then an additional 8 weeks of observation followed by reassessment can be considered.
  - An nCR is defined by:
    - ◊ Smooth induration or superficial minor mucosal irregularity on DRE
    - ◊ Endoscopic appearance with irregular small mucosal nodules, superficial ulceration, or mild persistent erythema
    - ◊ T2-weighted MRI with downstaging with or without residual fibrosis, small area of residual signal, and complete or partial regression of lymph nodes
    - ◊ Diffusion-weighted MRI with small area of residual high signal intensity

Indications for Surgery

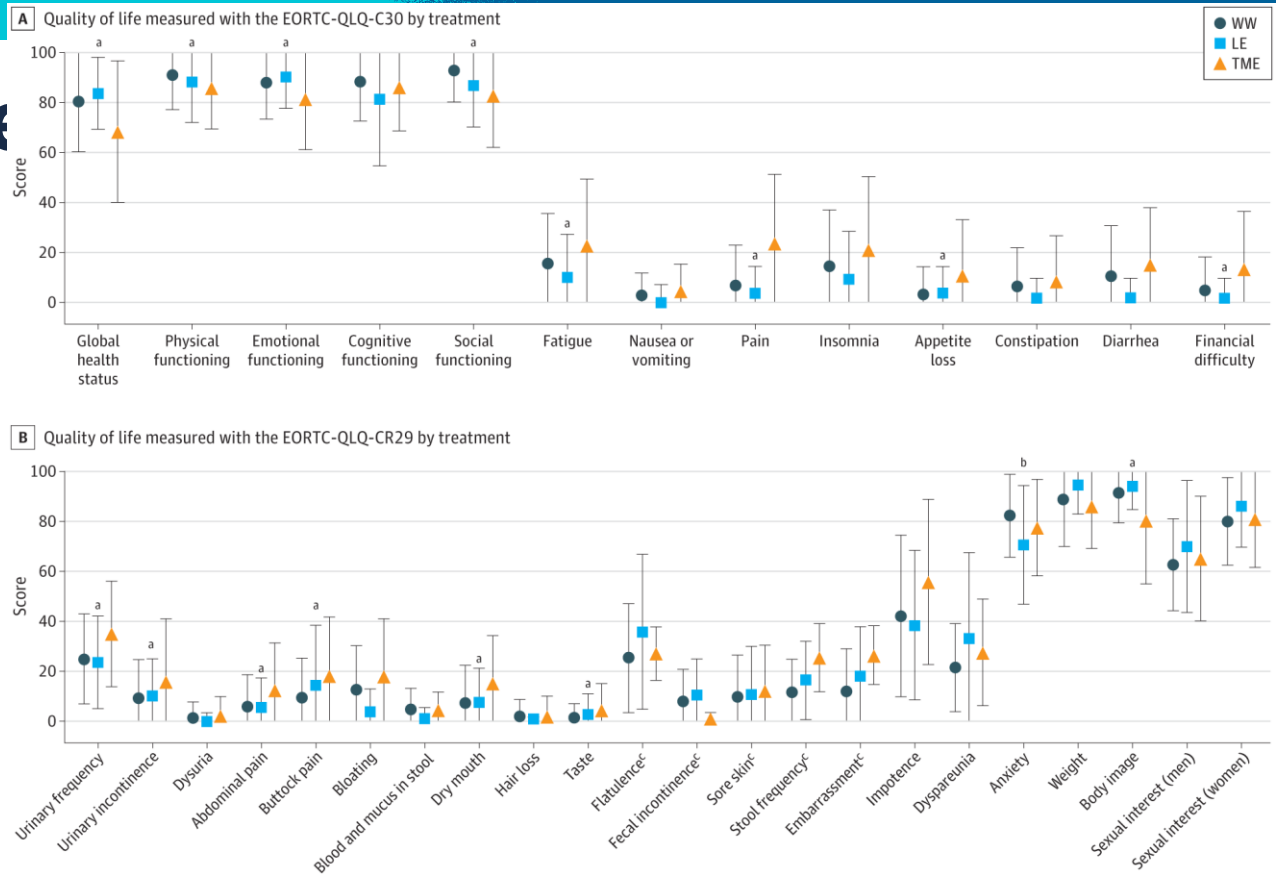
- Radical surgery is indicated for patients who do not ultimately achieve a complete clinical response based on the above criteria or patients who have tumor regrowth after a clinical response.
- If residual tumor or regrowth is suspected at the time of assessment, it is not necessary to perform biopsies. False-negative biopsies are common in this scenario and a high degree of suspicion for tumor is sufficient as an indication for surgery.[8]

Quality of life

278 patients

Dutch prospective cohort

Treated with NOM



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.

Potential omission of radiation

PROSPECT Trial

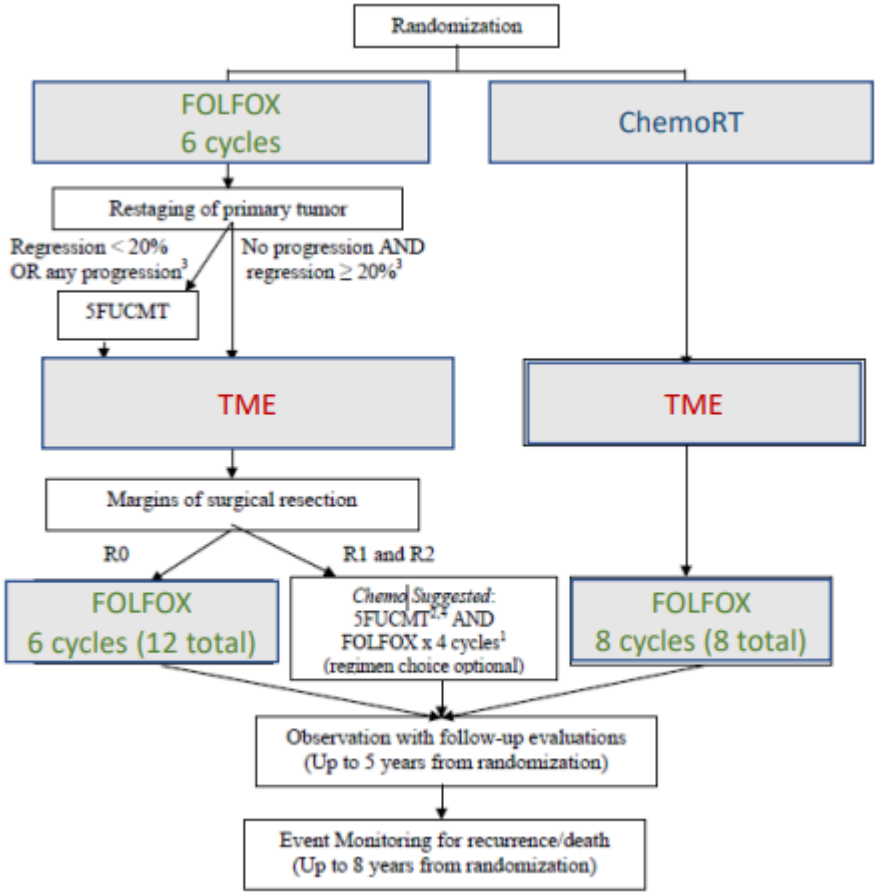
1194 patients with T2N1, T3N0 or T3N1

No distal tumors (>5cm from anal verge)

No N2

No T4

>3mm from MRF



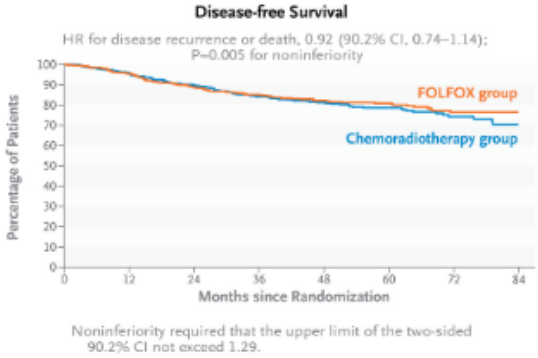
PROSPECT Trial

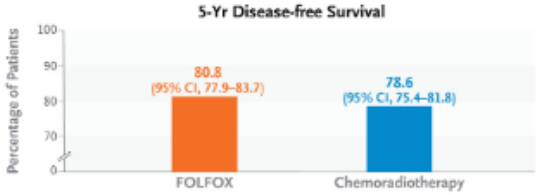
9.1% of patient in FOLFOX group received pre-op chemoRT, and 1.4% received post-op

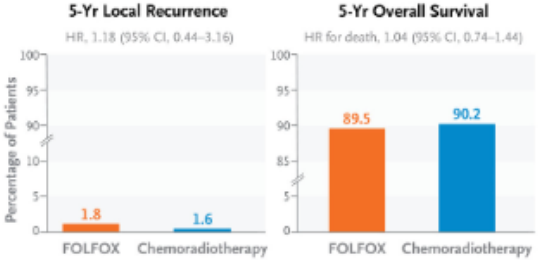
Criticisms:

-No TNT for chemoRT arm

-15% of patients not staged with MRI







OCUM Study

Avoidance of Overtreatment of Rectal Cancer by Selective Chemoradiotherapy: Results of the Optimized Surgery and MRI-Based Multimodal Therapy Trial

Definition of high risk: involved mesorectal fascia (mrMRF ≤1mm) or cT3 lower third or cT4

Prospective multicenter study with 1093 patients

878 patients treated per protocol
- nCRT avoided in 60 %
- low local recurrence rate

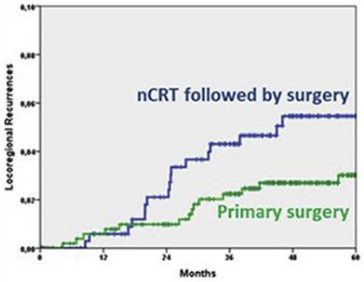


Fig. 1 Local recurrences in 526 patients with primary surgery compared to 352 patients with nCRT followed by surgery

604 patients with clinical stage II and III
- nCRT avoided in > 40%
- low local recurrence rate

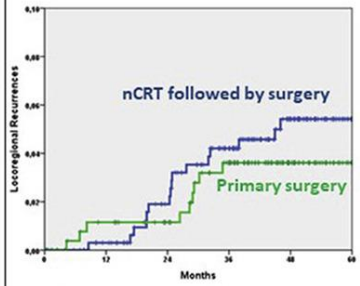


Fig. 2 Local recurrences in 267 patients with primary surgery compared to 337 patients with nCRT followed by surgery

27.3% had pathological stage I
- Overtreatment avoided

The results justify restriction of nCRT to high-risk patients.

This requires high quality of
- MRI diagnosis
- TME surgery
- Histopathology

nCRT neoadjuvnt chemoradiation; TME total mesorectal excision; MRI magnetic resonance imaging, mrMRF mesorectal fascia in MRI

Ruppert et al. J Am Coll Surg, October 2020

JACS

MMR deficient/MSI high

RESEARCH SUMMARY

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Cercek A et al. DOI: 10.1056/NEJMoa2201445

CLINICAL PROBLEM

Standard treatment for locally advanced rectal cancer includes neoadjuvant chemotherapy and radiation, followed by surgical resection of the rectum. This approach, however, is associated with substantial complications and toxic effects. Research suggests that immune checkpoint blockade alone is highly effective in patients with mismatch repair–deficient metastatic colorectal cancer; whether this strategy is effective in mismatch repair–deficient, locally advanced rectal cancer is unknown.

CLINICAL TRIAL

Design: A prospective, phase 2, single-group study examined the efficacy and safety of neoadjuvant therapy with the programmed death 1 (PD-1) inhibitor dostarlimab in patients with mismatch repair–deficient stage II or III rectal adenocarcinoma.

Intervention: Adult patients received intravenous dostarlimab every 3 weeks for 6 months, to be followed by chemoradiotherapy and total mesorectal excision. Patients with a clinical complete response to dostarlimab could forgo chemoradiotherapy and surgery. A key primary end point was overall response to dostarlimab alone or to dostarlimab plus chemoradiotherapy, determined on the basis of rectal magnetic resonance imaging, endoscopic visualization, and digital rectal examination.

RESULTS

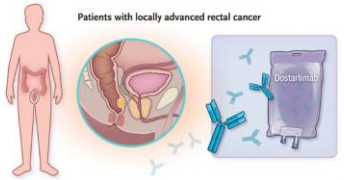
Efficacy: 12 of 16 enrolled patients have already completed 6 months of dostarlimab. All 12 had a clinical complete response, with no evidence of tumor on any diagnostic test. During a median follow-up of 12 months, no patient received chemoradiotherapy or underwent surgery, and none had disease progression or recurrence.

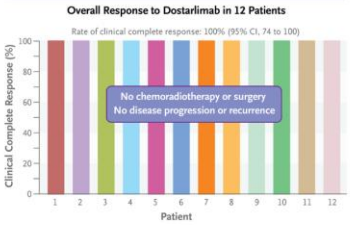
Safety: No adverse events of grade 3 or higher have occurred. The most common adverse events of grade 1 or 2 included rash or dermatitis, pruritus, fatigue, and nausea.

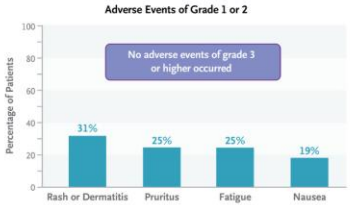
LIMITATIONS AND REMAINING QUESTIONS

- The study was small and limited to a single institution, and most of the patients were White.
- Longer-term follow-up is needed to evaluate the duration of response.

Links: Full Article | NEJM Quick Take | Editorial

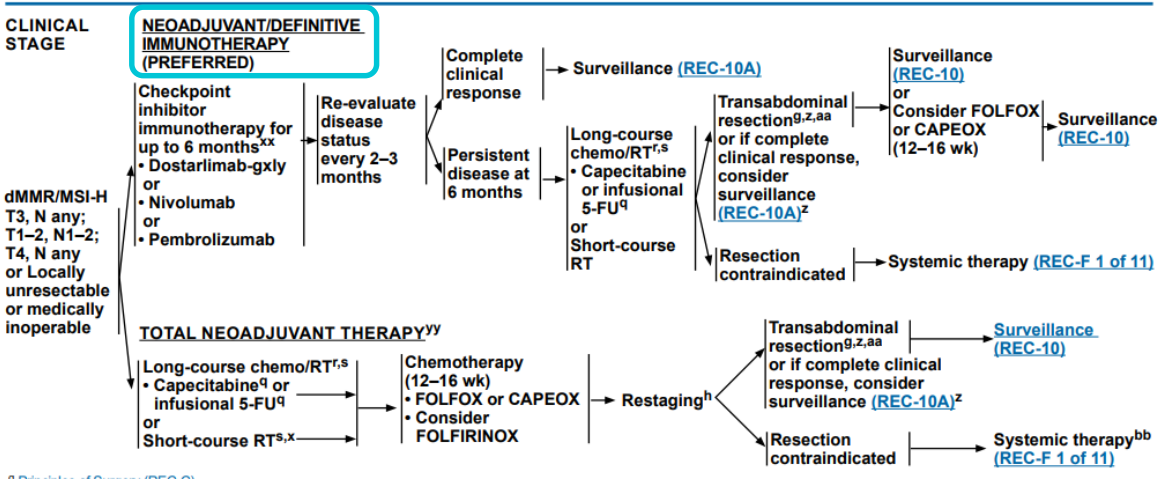






CONCLUSIONS

All patients with mismatch repair–deficient, locally advanced rectal cancer who were treated with the PD-1 inhibitor dostarlimab alone for 6 months had a clinical complete response, although longer follow-up is warranted.



Radiation in rectal cancer 2.0 (+TNT): Who, why, when, how much?

Who 2.0

Definitely

- Involving/abutting sphincter
- Threatened MRF
- T4
- Extra-pelvic LNs
- No/minimal response to chemo
- Patient motivated for NOM

Probably

- Mid-rectum
- N+
- Approaching MRF
- Bulky

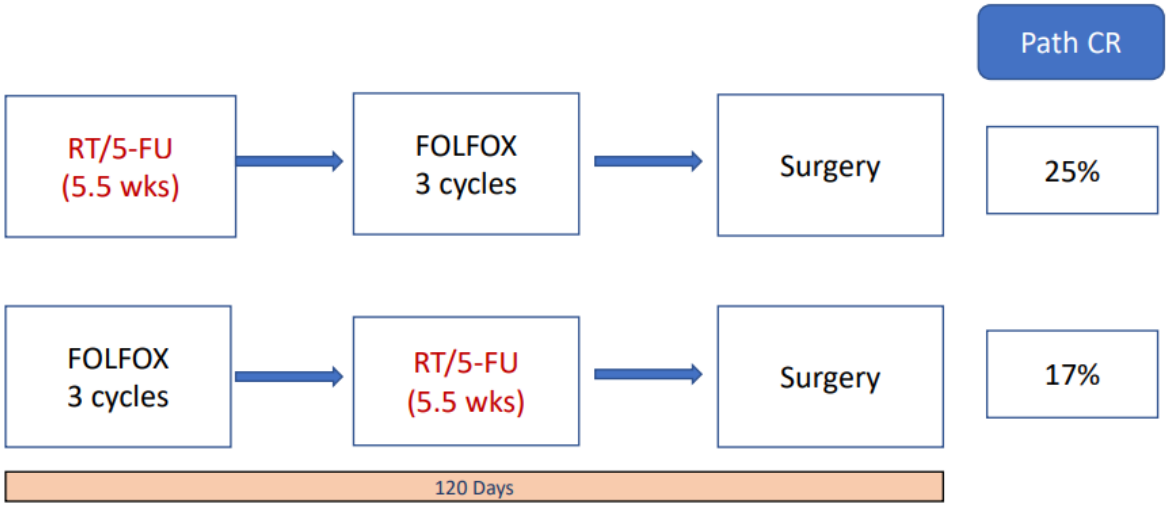
Consider omission

- T3 N0 High rectum far from sphincter
- MMR deficient/MSI high
- Meets criteria for PROSPECT trial
- Not motivated for NOM

When radiation 2.0

German CAO/ARO/AIO-12 trial

326 patients with T3+ or N+

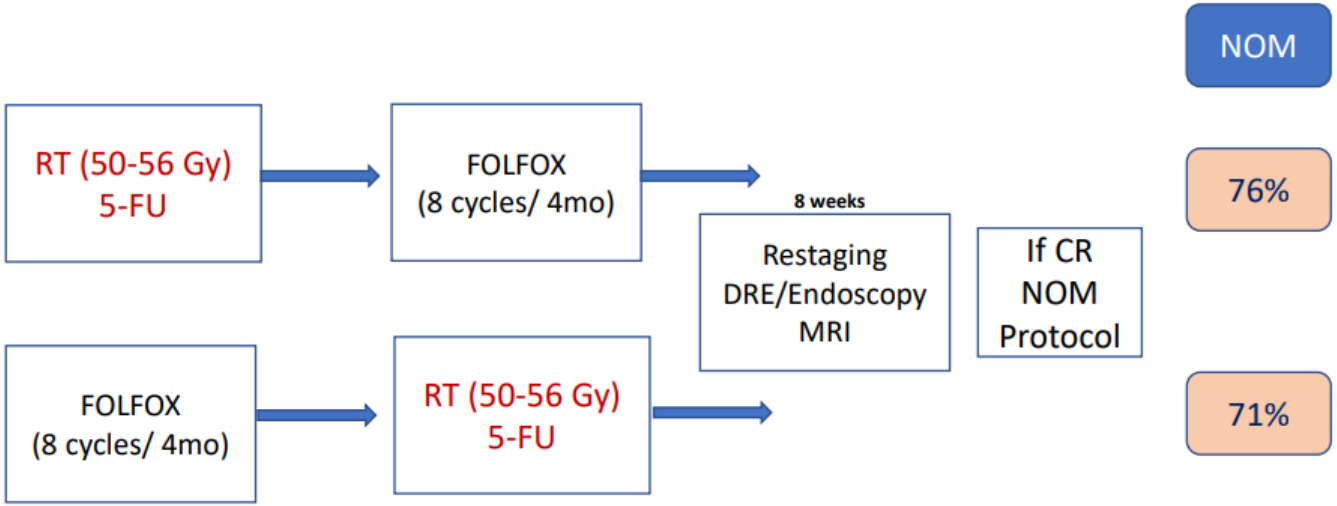


Fokas, JCO 2019

When radiation 2.0

OPRA Trial

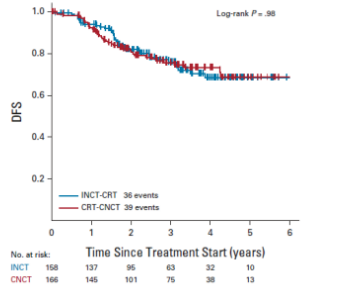
324 patients with Stage II or III distal rectal cancer requiring APR



Fokas, JCO 2019

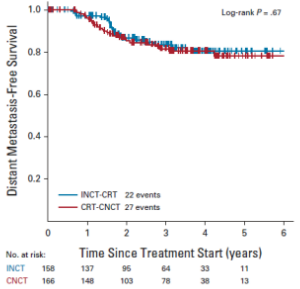
When radiation 2.0

Disease-Free Survival



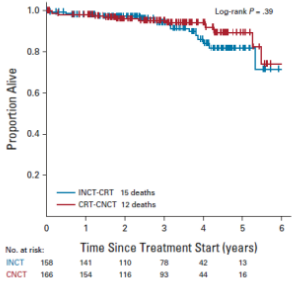
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	76%	76%

Distant Metastases-Free Survival

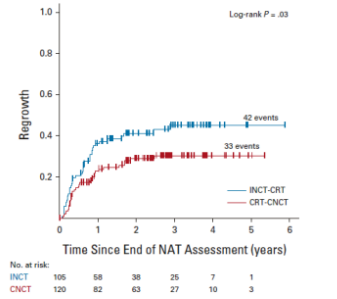


	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	84%	82%

Overall Survival

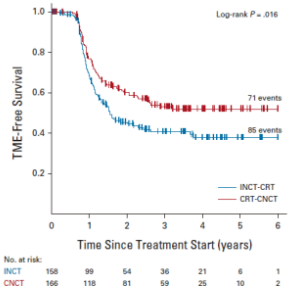


Regrowth



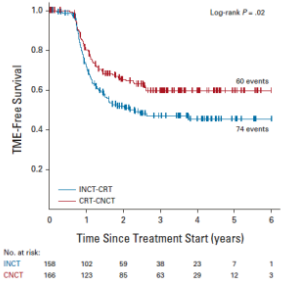
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	40% (42/105)	27% (33/120)

TME-Free Survival (IIT)



	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	41%	53%

TME Free Survival (actual TME)

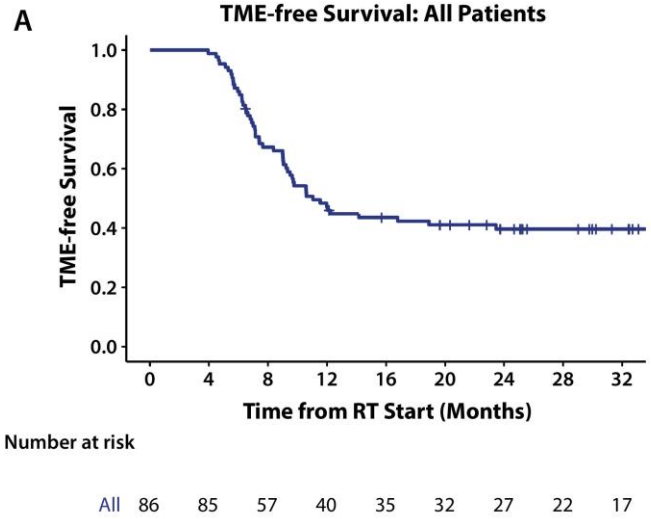


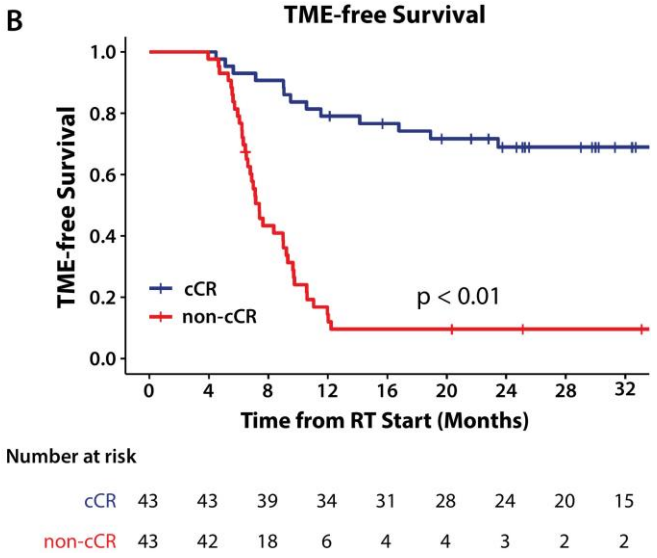
	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	47%	60%

How much 2.0

Wash U. Phase II trial 90 patients with Stage I-III rectal cancer treated with short course radiation followed by chemo

- 50% had CR and underwent NOM
- At 30.1m 79% had persistent CR

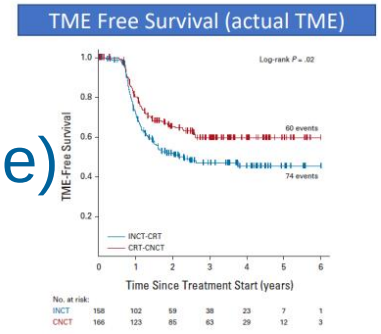




Chin et al, IJROBP 2021

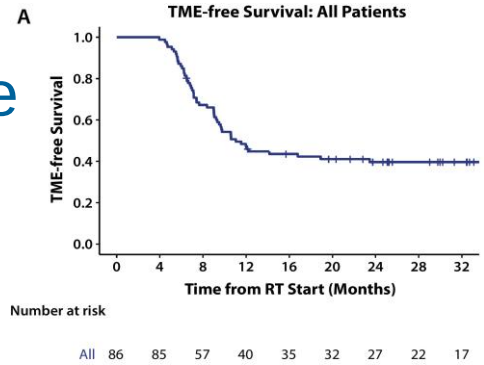
How much 2.0

OPRA
(Long course)
47-60%



	INCT-CRT (FOLFOX first)	CRT-CNCT (ChemoRT first)
3 Year	47%	60%

Wash U.
Short course
~40%



How much 2.0

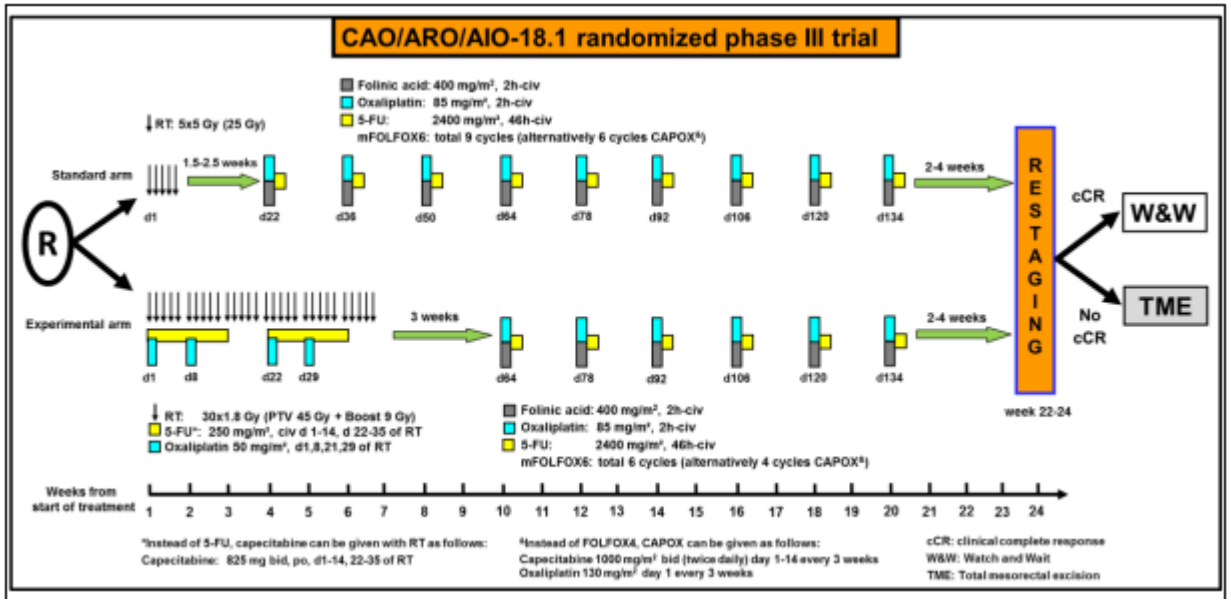
ASTRO 2021 guidelines

Table 4 Recommendations for nonoperative or LE approaches

follow-up by a multidisciplinary team.		
3. For patients with rectal cancer considering NOM or LE after RT, conventional fractionation from 5000-5400 cGy in 25-30 fractions with concurrent chemotherapy is recommended.	Strong	Moderate[50,54, 55, 56]

How much 2.0

Ongoing GERMAN TNT Trial CAO/ARO/AIO-18.1



How much 2.0

Ongoing STAR-TREC UK Trial

The Phase II component of STAR-TREC (now completed) was a randomised, three arm (1:1:1) study using the following arms:

1. Standard TME surgery (control)
2. Organ saving treatments using:
    1. Long course concurrent chemoradiation:
        - Capecitabine: 825 mg/m² orally, b.d., on radiotherapy days
        - Radiotherapy: A dose of 50 Gy applied to the primary tumour and surrounding mesorectum in 25 fractions of 2 Gy, 5 days a week.
    2. Short course radiotherapy:
        - A dose of 25 Gy applied to the primary tumour and surrounding mesorectum in 5 fractions of 5 Gy, 5 days a week.

The phase III component of STAR_TREC is now open and has a partially randomised patient preference design where patients choose between organ saving treatment or standard surgery.

Those who prefer organ preservation will undergo randomisation 1:1 between:

1. Long course concurrent chemoradiation (as described above)
2. Short course radiotherapy (as described above)

How much 2.0

OPERA Trial

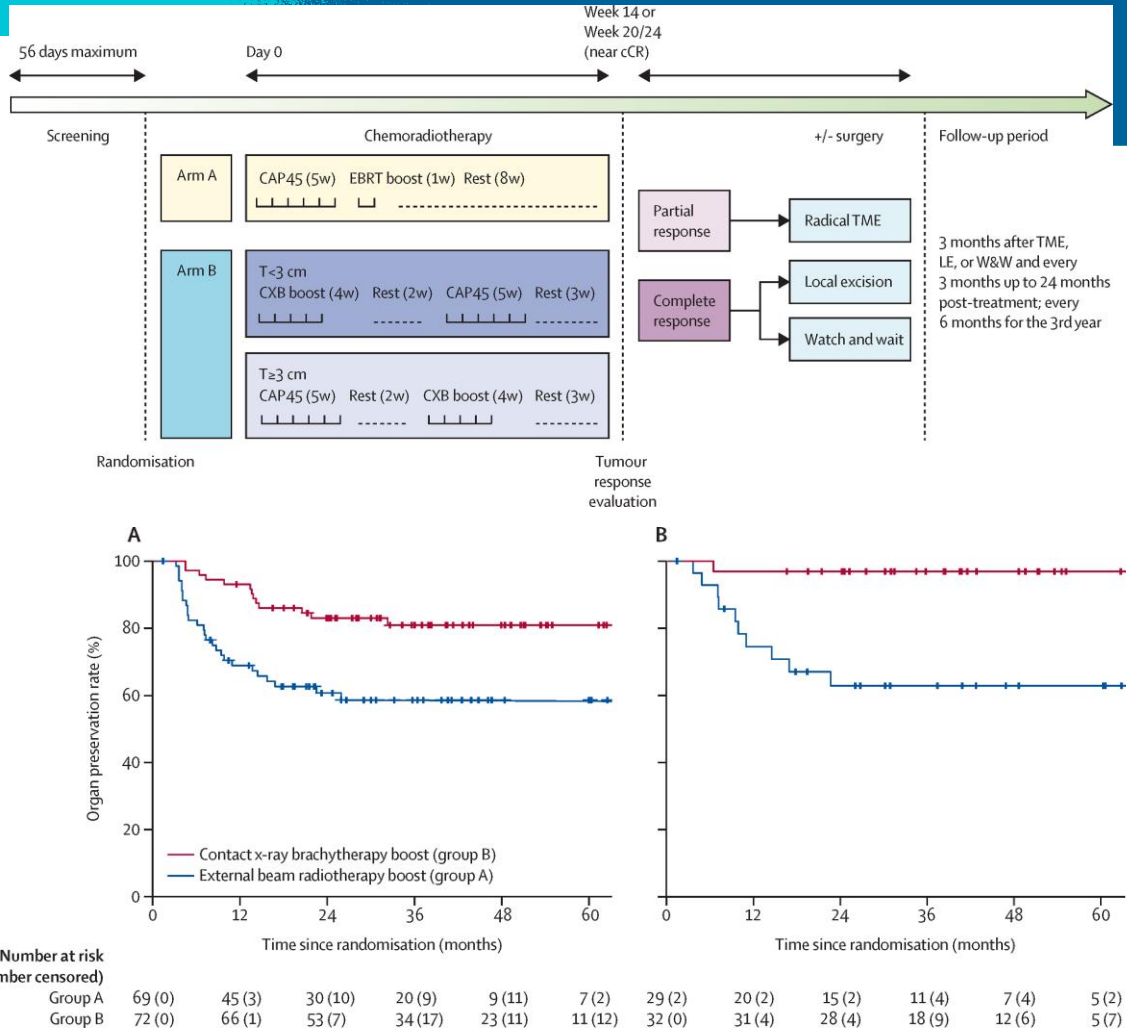
T2 or T3, N0 or N1

Tumors <5cm in diameters

All patients got 45Gy chemoRT

Arm A got 9Gy in 5 fx external beam boost

Arm B got 90Gy 3 fx contact internal brachy boost



How much 2.0

Table 3Adverse events

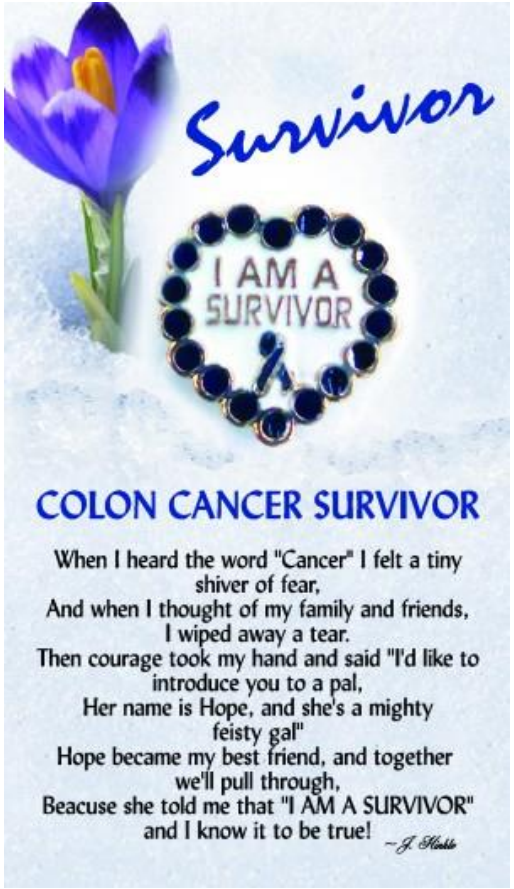
	Group A (n=69)				Group B (n=72)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
Blood disorders	0	0	0	0	1 (1%)	2 (3%)	0	0
Neutropenia	0	0	0	0	0	1 (1%)	0	0
Lymphopenia	0	0	0	0	0	1 (1%)	0	0
Venous thromboembolism	0	0	0	0	1 (1%)	0	0	0
Gastrointestinal	4 (6%)	0	0	0	10 (14%)	5 (7%)	0	0
Proctitis	4 (6%)	0	0	0	7 (10%)	2 (3%)	0	0
Diarrhoea	0	0	0	0	3 (4%)	3 (4%)	0	0
General disorders and administration site conditions	0	1 (1%)	0	0	0	4 (6%)	0	0
Asthenia	0	0	0	0	2 (3%)	0	0	0
Coronary artery spams	0	1 (1%)	0	0	0	0	0	0
Anorexia	0	0	0	0	1 (1%)	0	0	0
Erectile dysfunction	0	0	0	0	1 (1%)	0	0	0
Renal and urinary disorders	2 (3%)	3 (4%)	0	0	4 (6%)	0	0	0
Urinary infection	0	2 (3%)	0	0	0	0	0	0
Dysuria	2 (3%)	1 (1%)	0	0	4 (6%)	0	0	0
Skin disorders	7 (10%)	0	0	0	2 (3%)	0	0	0
Radiation dermatitis	7 (10%)	0	0	0	2 (3%)	0	0	0
Other	4 (6%)	0	0	0	2 (3%)	0	0	0
Rectal bleeding	2 (3%)	0	0	0	0	0	0	0
Chest pain	0	0	0	0	2 (3%)	0	0	0
Oral candidiasis	1 (1%)	0	0	0	0	0	0	0
Palmar-plantar erythrodysesthesia	1 (1%)	0	0	0	0	0	0	0

The highest-grade adverse event for each patient is reported.

How much 2.0

No late adverse event of grade 3 or higher occurred. The most common late side-effect was mild rectal bleeding (grade 1–2), which was analysed in the 102 patients who did not undergo total mesorectal excision. Mild rectal bleeding was more frequent in group B (37 [63%] of 59) than in group A (five [12%] of 43; p<0·0001). Argon coagulation was needed to control bleeding in six patients (one in group A, five in group B; appendix p 36). Rectal bleeding was due to telangiectasia, which on average appeared 6 months after treatment, increased in incidence between 1 year and 2 years, and subsided after 3 years (appendix p 14).

Why 2.0


Survivor
I AM A SURVIVOR
COLON CANCER SURVIVOR
When I heard the word "Cancer" I felt a tiny shiver of fear,
And when I thought of my family and friends, I wiped away a tear.
Then courage took my hand and said "I'd like to introduce you to a pal,
Her name is Hope, and she's a mighty feisty gal"
Hope became my best friend, and together we'll pull through,
Beacuse she told me that "I AM A SURVIVOR" and I know it to be true!
~J. Hobbs

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Thank you

Annex

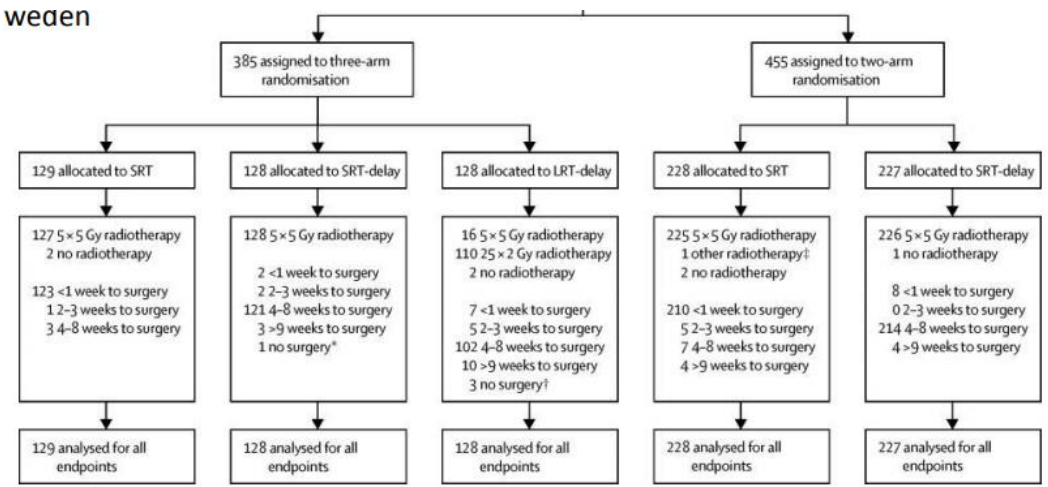
When surgery?

- Stockholm III

Phase III non inferiority study

- Randomized patients
  - 5 x 5 Gy and surgery w/in 1 wk
  - 5 x 5 Gy and surgery in 4-8 wks
  - 25 x 2 Gy and surgery in 4-8 wks
- Had to addend protocol because not enough centers wanted to enroll in 25x2 Gy arm
- No difference in 3 arm comparison with oncologic outcomes including OS, LR, DFS or toxicity
- In 2 arm comparison no difference in oncologic outcomes but increased toxicity w/ complications

	SRT (n=357)	SRT-delay (n=355)	p value
Complications			
Any postoperative complication	188 (53%)	144 (41%)	..
OR (95% CI)	1·00 (ref)	0·61 (0·45–0·83)	0·001†
Any surgical complication	128 (36%)	100 (28%)	..
OR (95% CI)	1·00 (ref)	0·70 (0·51–0·96)	0·03†
Reoperation	43 (15%)	37 (14%)	..
OR (95% CI)	1·00 (ref)	0·88 (0·55–1·41)	0·59†



When surgery

- GRECCAR-6: French phase III study cT3/4 or N+ treated with CRT w/ 5-FU or Capecitabine
  - Randomized to 7 or 11 wk break
  - 265 pts
  - No difference in pCR 15 vs. 17.4%
  - Morbidity was significantly increased in the 11 wk group
    - 44.5 vs. 32% p= 0.04
  - Worse quality of the resections (less with complete en bloc resection)
    - 78.7 vs. 90% p= 0.016

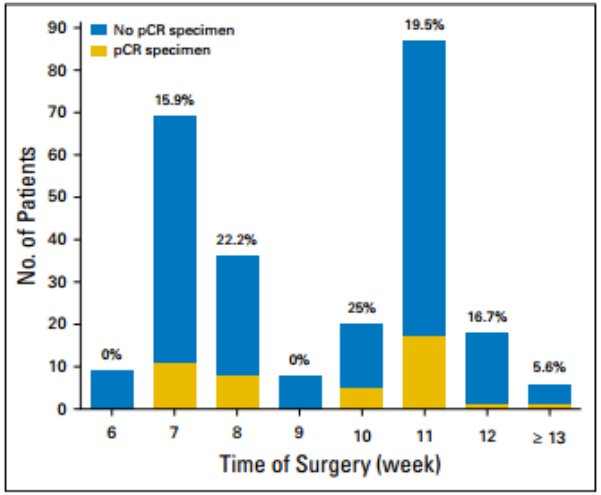
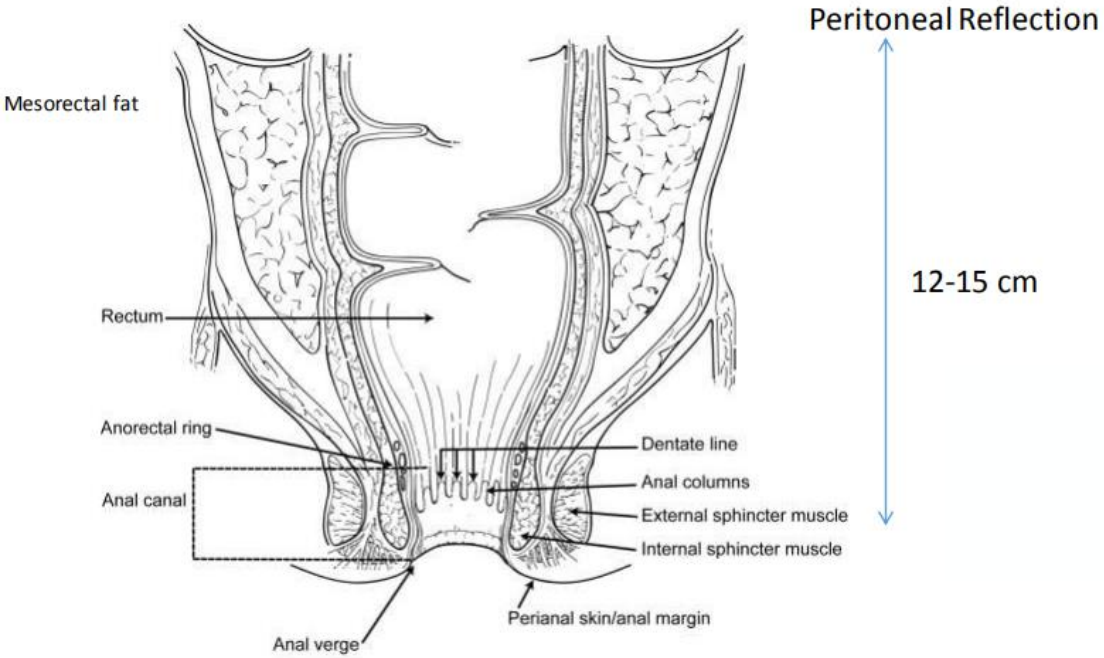


Fig 2. Effect of time of surgery on the complete pathologic response rate. pCR, pathologic complete response.

Anatomy



- Above dentate line to below the peritoneal reflection

Peritoneum:

- Upper 1/3 of rectum: covered by peritoneal reflection anteriorly and laterally
- Middle 1/3 of rectum: covered by peritoneum anteriorly only
- Lower 1/3 of rectum: no peritoneal coverage

Anatomy: LN Drainage

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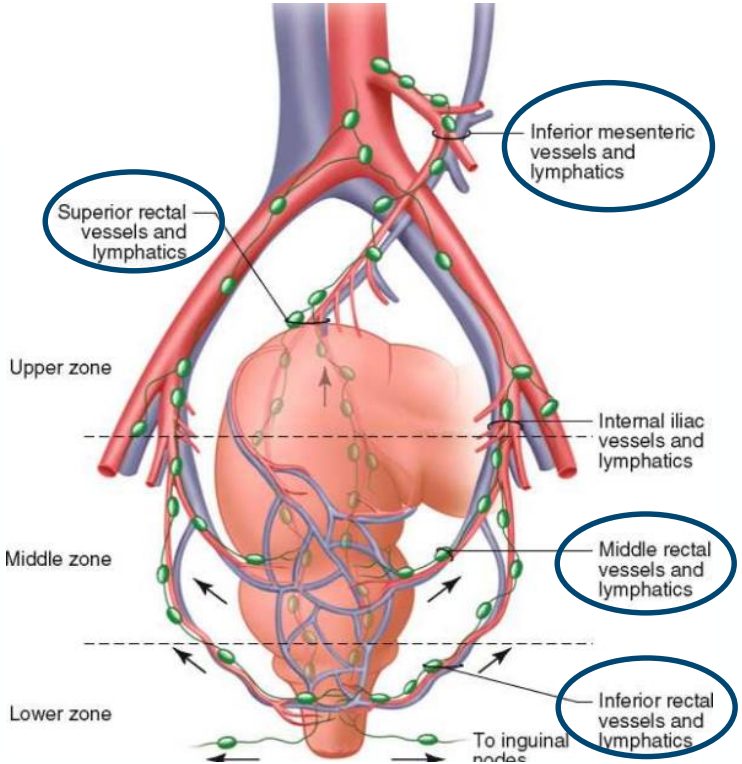
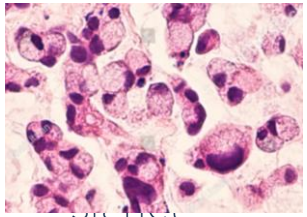
Lymph Node Drainage

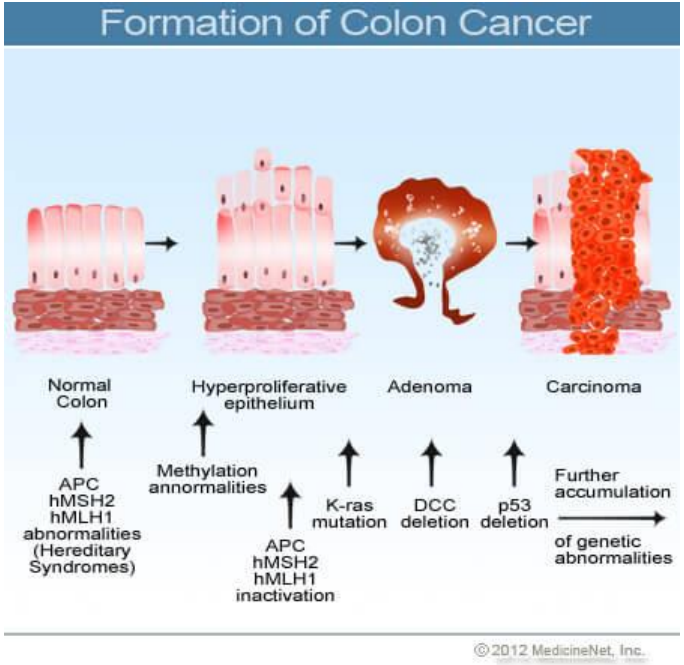
- Upper and middle third:
  - Superior rectal (hemorrhoidal) artery (SRA) to IMA
- Distal third: Dual drainage
  - SRA to IMA
  - Middle & inferior hemorrhoidal vessels to IVC via Internal iliacs
- Extension to anus
  - Inguinal nodes



Pathology

- >90% are adenocarcinomas
  - 15-20% have extracellular (colloid) – not prognostic
  - 1-2% have intracellular mucin, ring' – poorer prognosis





- Additional types include squamous cell, melanoma, small cell, carcinoid, sarcoma, and lymphoma
- Less likely to spread longitudinally like esophageal tumors

Epidemiology

- 44,000 new cases of rectal cancer annually. Slight male predominance (60:40), more common in AA population
- Incidence rising in younger patients
- Colorectal cancer is #2 leading cause of cancer death among men and #3 among women
- US lifetime risk of CRC is 5%
- Genetic and environmental factors affect risk

Risk factors

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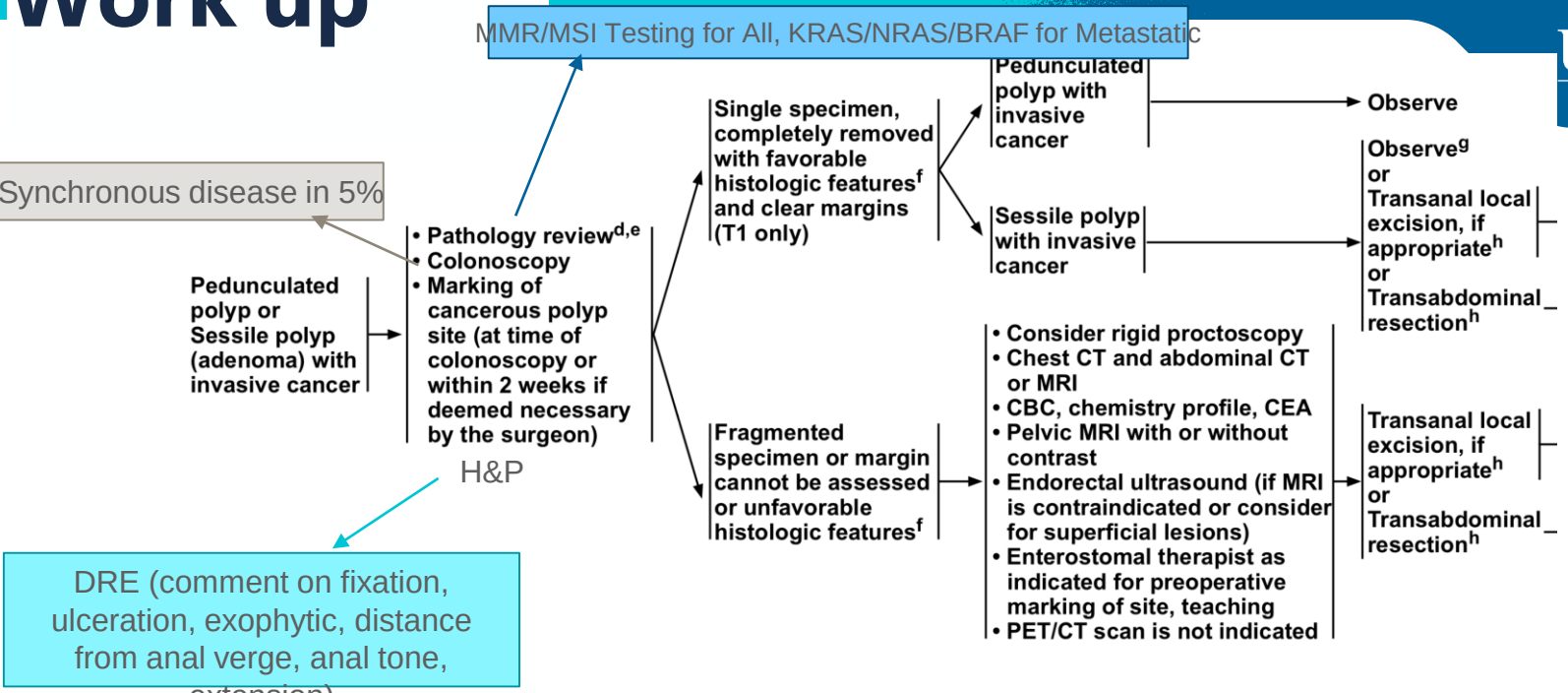
- Hereditary syndromes
  - FAP
  - Lynch syndrome (HNPCC)
  - MUTYH-associated polyposis
- Increasing age
- Male sex
- Family history
- IBD
- Increasing height
- Increasing BMI
- Consumption of processed meat, refined grains, starches, sugars
- Excessive alcohol intake
- Smoking
- Low folate consumption
- Cholecystectomy

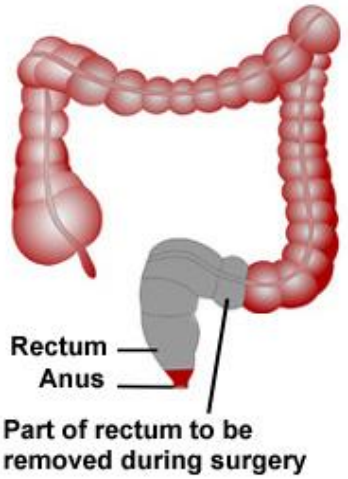
Work up

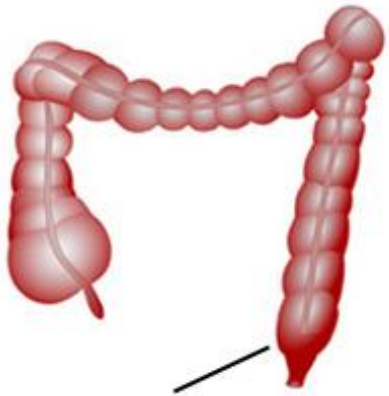


- Chest imaging for lower 1/3 rectal lesions as more likely to have lung mets (caval>portal drainage)
- Sensitivity for CEA for CRC is 46%
  - Elevated in benign conditions including COPD, DM, diverticulitis, PUD, any acute or inflammatory state
  - Can be helpful in relapse setting

Low Anterior Resection (LAR)

- Sphincter-sparing
- Colo-anal anastamosis
- Need circumferential margin
- Ideally 2 cm distal margin
- Similar recurrence rates to APR if adequate margin





Abdominoperineal resection (APR)

- Sacrifice sphincter
- Permanent Ostomy