

When the Guidelines Can't Keep Up: Evidence-Based Management of Rectal Cancer

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Disclosures

- I have no relevant financial disclosures



Introduction

- The treatment of rectal cancer is evolving at rates that exceed recommendations from major organizations.
 - I authored my own society's most recent guidelines:
 - Finished 11/2022, already seemingly outdated as it preceded PROSPECT and 5-year RAPIDO results.
- It's becoming increasingly difficult to stay up-to-date on the best care for patients with rectal cancer.



Today's goals: Discuss current hot topics

- TNT
- Organ preservation/watch and wait
- Omission of radiation
- Immunotherapy for MMR deficient cancers
- I'm going to throw some stats around. If interested in a deep dive, the ASCRS CPG was just finally accepted
 - I should be able to share it soon.



Total Neoadjuvant Therapy



- Traditional NACRT → Surgery → adjuvant FOLFOX
 - Within RCTs, completion of adjuvant chemo occurs in 50-80%
 - Outside of RCTs, completion is 30-40%
 - Frailty, surgical complications, poor tolerance
- Adjuvant chemotherapy has been shown to improve DFS, even in the setting of a pathologic complete response (pCR)
- TNT arose from a desire to increase the number of patients who complete chemotherapy



TNT



- Consolidation total neoadjuvant therapy (TNT)
 - CRT→FOLFOX→Surgery
- Induction TNT
 - FOLFOX→CRT→Surgery
- Short-course and long-course radiation have both been used in these protocols.
- Here's the good news: With TNT, the rate of chemotherapy completion is 86-100%



Why TNT?

- Increased compliance/completion rates
- Increased pathologic complete response (pCR)
- ***Improved DFS and OS when compared to conventional NACRT***
- Decreased time with an ileostomy, which is very important to the patients.

JAMA Netw Open 2020;3:e2030097

Cancers 2020;12:3655

Ann Surg Oncol 2021;28:7476-86.



TNT side effects

- Compared to conventional NACRT, TNT is associated with similar toxicity, and similar functional outcomes.
- Regarding operative difficulty, the studies are mixed.
 - Long-term RAPIDO data suggests increases in “breached mesorectum” with SCRT-based consolidation TNT
 - TIMING trial suggested more fibrosis, but similar operative difficulty.
 - In reality, it’s harder, but it’s worth the struggle.

RAPIDO: Ann Surg. 2023 Jan 20 (epub ahead of print)

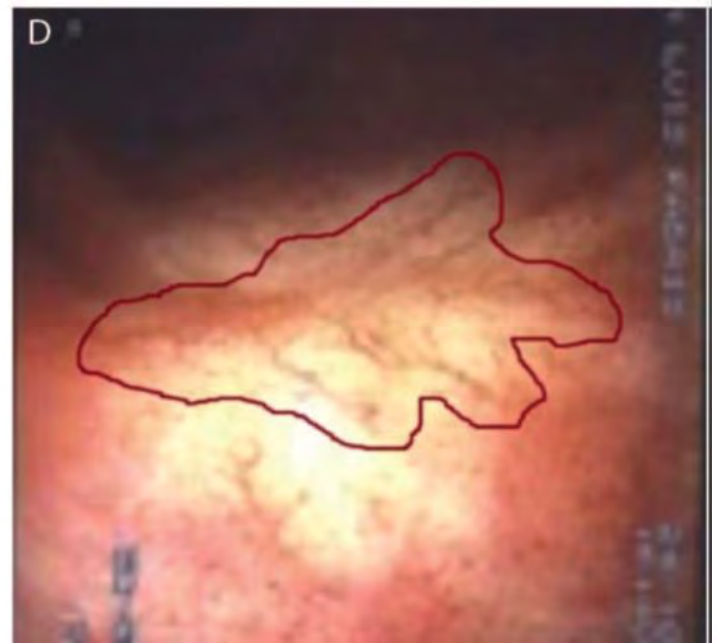
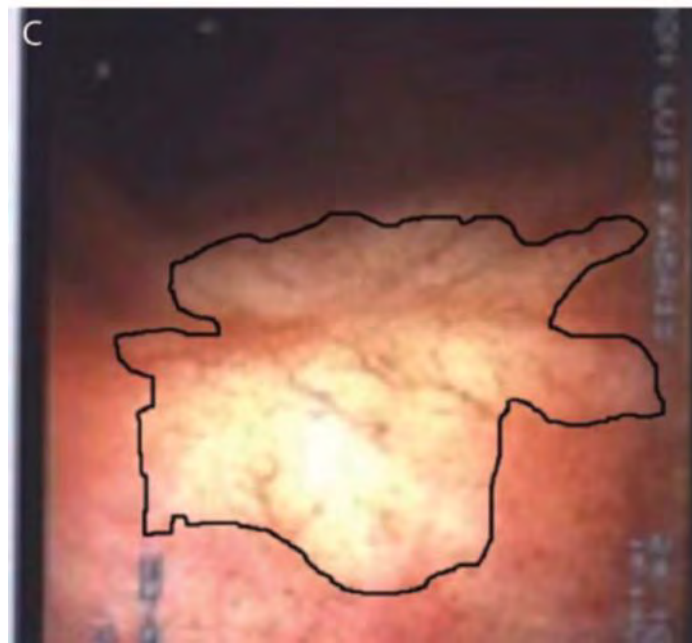
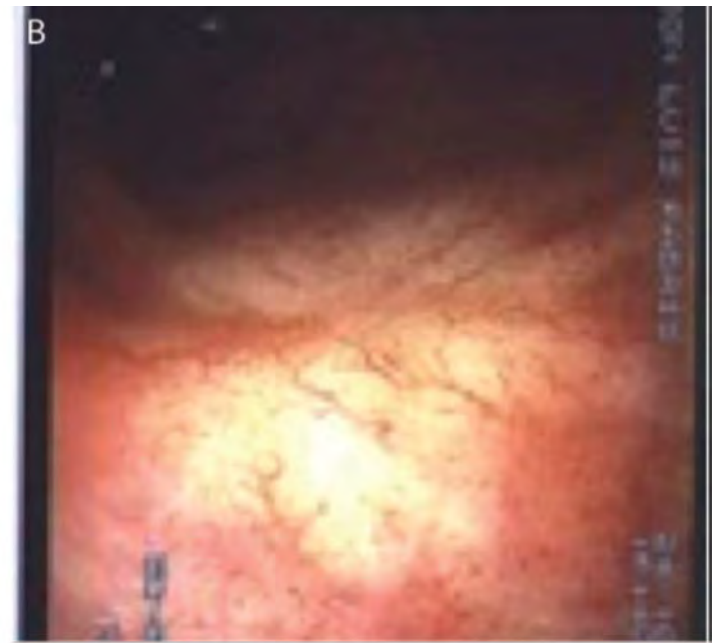
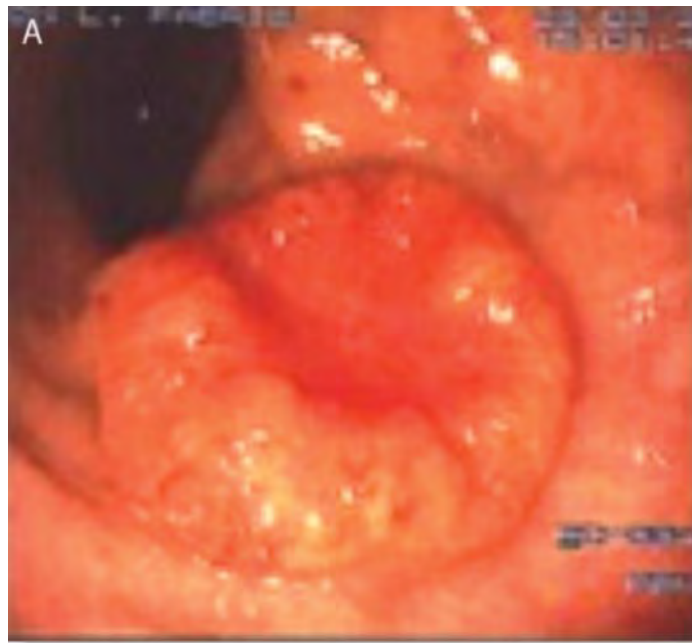
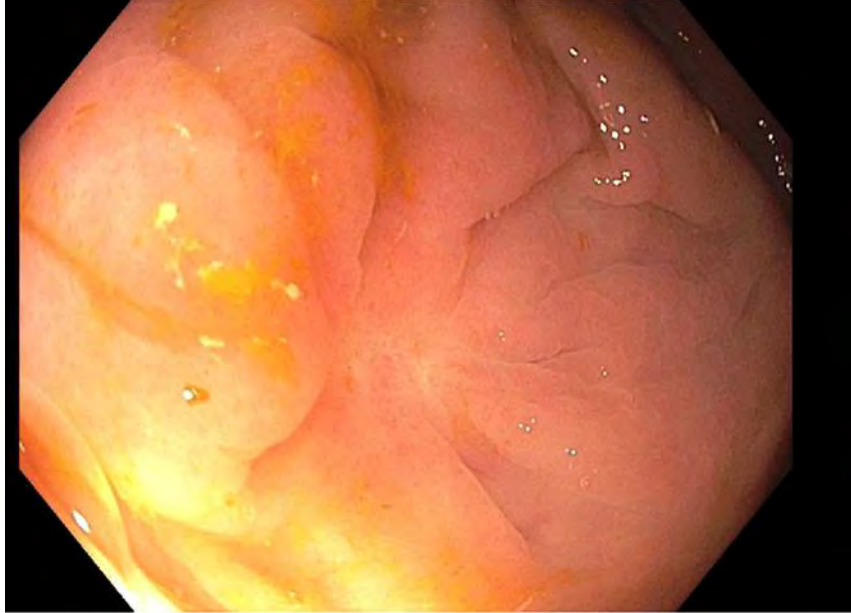
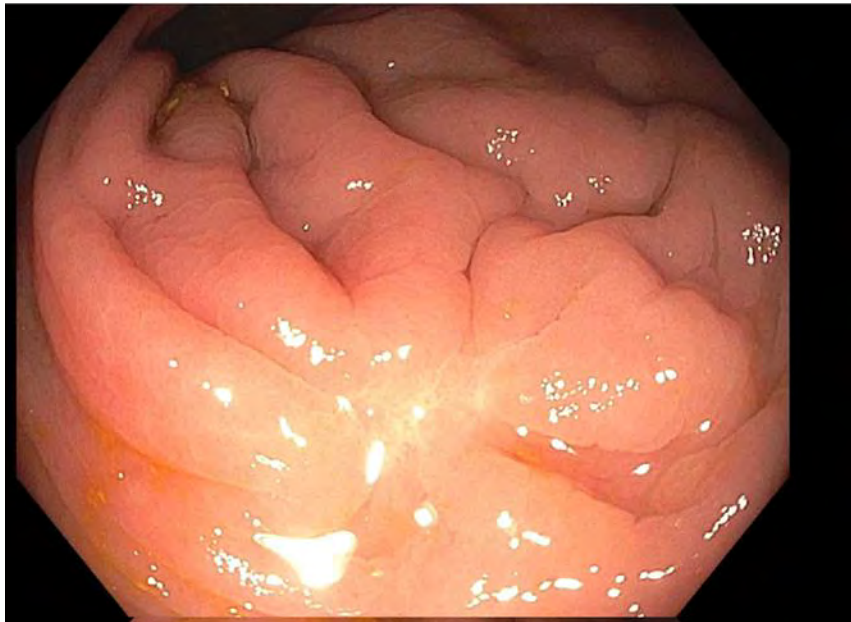
TIMING: Lancet Oncol 2015;16:957-66.



Clinical complete response

- Occurs in 40-65% of patients undergoing TNT
- No evidence of tumor on:
 - DRE
 - Flexible sigmoidoscopy
 - MRI pelvis
- NOT the same as a pCR
 - Only a microscope can determine a pCR





Organ preservation, aka “Watch and wait”

- First described in 1998
 - 30 patients from Brazil with a cCR after conventional NACRT were observed, and none of them had local regrowth at a median f/u of 36 months.
- The same Brazilian group (Habr-Gama, Perez, et al) spent 20 years perfecting their treatment and surveillance strategies so that we didn't have to.
- We now have RCTs and international databases that are supportive of OP/WW as a treatment strategy for rectal cancers that experience a cCR.



Organ Preservation, aka “watch and wait”

- Local regrowth occurs in 25-33% of patients
 - Majority of these patients (88-95%) can undergo salvage LAR or APR
 - R0 rates of 90-95% (same as for LAR for primary rectal cancer)
- Distant metastasis occurs in 8-18% of patients
 - Same as for TME
 - Believe it or not, OP/WW is oncologically equivalent to TME
- **OPRA Trial**: cCR higher and local regrowth lower for consolidation TNT compared to induction TNT



Detection of local regrowth

- Q3-4 month office exam and CEA
- Q6 month MRI and flex sig
- Local recurrence drops off dramatically after 3 years.



MSKCC protocol

Surveillance Protocol for WW Patients

Years	Year 1	Year 2	Year 3	Year 4	Year 5
Digital Rectal Exam	q 4 months	q 4 months	q 6 months	q 6 months	q 6 months
Flexible Sigmoidoscopy					
CEA					
MRI (T2W and DWI)	q 6 months	q 6 months	q 12 months	q 12 months	q 12 months
CT CAP	X1	X1	X1	X1	X1
Colonoscopy	X1				X1

TME patients were monitored according to NCCN guidelines



Sure, this is a radiation oncology conference, but do all locally advanced rectal cancers need radiation?

- As you all know well, pelvic radiation has side effects.
 - Anastomotic leak
 - GI, sexual, and urinary function
- Multiple small phase II trials omitted radiation from neoadjuvant therapy, and demonstrated acceptable R0 rates.

J Clin Oncol 2014;32:513-518.

Ann Surg Oncol 2017;24:3587-3595



PROSPECT Trial (epub 6/4/23)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Treatment of Locally Advanced Rectal Cancer

Deborah Schrag, M.D., M.P.H., Qian Shi, Ph.D., Martin R. Weiser, M.D., Marc J. Gollub, M.D., Leonard B. Saltz, M.D., Benjamin L. Musher, M.D., Joel Goldberg, M.D., Tareq Al Baghdadi, M.D., Karyn A. Goodman, M.D., Robert R. McWilliams, M.D., Jeffrey M. Farma, M.D., Thomas J. George, M.D., Hagen F. Kennecke, M.D., Ardaman Shergill, M.D., Michael Montemurro, M.D., Garth D. Nelson, M.S., Brian Colgrove, B.S., Vallerie Gordon, M.D., Alan P. Venook, M.D., Eileen M. O'Reilly, M.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Amylou C. Dueck, Ph.D., Ethan Basch, M.D., George J. Chang, M.D., and Harvey J. Mamon, M.D., Ph.D.

N Engl J Med 2023; 389:322-334

- Multicenter, unblinded, noninferiority, randomized trial of 1,128 patients with locally-advanced rectal cancer
- Randomized to conventional NACRT vs 6 cycles of FOLFOX-only followed by restaging
 - If <20% tumor shrinkage → CRT → Surgery
 - If 20+% shrinkage → surgery
- Primary endpoint: DFS



PROSPECT Trial

- Groups were well-matched (demographics, tumor stage/location)
- Overall, 6.5% of patients in the FOLFOX arm had <20% shrinkage and required radiation.
- Median f/u 58 months
- No significant difference in:
 - DFS
 - OS
 - pCR
 - Local recurrence
 - Receipt of adjuvant chemotherapy
 - R0 resections



PROSPECT Trial conclusion

- Regarding DFS, preoperative FOLFOX is non-inferior to conventional NACRT.
- Ok great, so now what?



Confused? We haven't even talked about immunotherapy yet.

- The previous innovations have led to the greatest changes in rectal cancer care.
- But they were NOT the most talked-about.





'Tumors just vanished': Cancer patients now in remission after drug trial

Erin Burnett Out Front



Immunotherapy trial for rectal cancer offers hope for future



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<https://www.marca.com> › us-news › 2022/06/09

Dostarlimab, the miracle drug that has been shown to cure ...

Jun 9, 2022 — Dostarlimab, the **miracle drug** that has been shown to cure **colon cancer** ... The results of a recently disclosed cancer study were "unprecedented" ...



NPR
<https://www.npr.org> › 2022/06/07 › cancer-drug-experi...

An experimental cancer drug had a 100% success rate

Jun 7, 2022 — A small trial using the **drug** dostarlimab yielded an unprecedented success rate in eliminating **tumors**.



TODAY.com
<https://www.today.com> › health › new-drug-appears-cur...

New drug appears to cure rectal cancer in 100 ...

Jun 9, 2022 — 100% of **rectal cancer** patients treated with an experimental immunotherapy **drug** went into full remission in a small study, researchers said.



Rectal Cancer Disappears After Experimental Use of Immunotherapy

The NEW ENGLAND
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

JUNE 23, 2022

VOL. 386 NO. 25

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

A. Cercek, M. Lumish, J. Sinopoli, J. Weiss, J. Shia, M. Lamendola-Essel, I.H. El Dika, N. Segal, M. Shcherba, R. Sugarman, Z. Stadler, R. Yaeger, J.J. Smith, B. Rousseau, G. Argiles, M. Patel, A. Desai, L.B. Saltz, M. Widmar, K. Iyer, J. Zhang, N. Gianino, C. Crane, P.B. Romesser, E.P. Pappou, P. Paty, J. Garcia-Aguilar, M. Gonen, M. Gollub, M.R. Weiser, K.A. Schalper, and L.A. Diaz, Jr.

- 5-10% of rectal cancers are MMR-deficient/MSI-high
 - These tend to respond poorly to chemoradiation
- Stage IV MMR-deficient CRC has already been shown to be very responsive to immune checkpoint inhibitors
- Phase II study of 12 patients with MMR-deficient LARC who received dostarlimab with a minimum of 6 months follow-up
 - 100% of patients experienced a cCR and did not require surgery

N Engl J Med 2022;386:2363-76



Sometimes the guidelines DO keep up



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Rectal Cancer

Version 4.2023 — July 25, 2023

NCCN.org





National
Comprehensive
Cancer
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NCCN Guidelines Version 4.2023

pMMR/MSS Rectal Cancer

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CLINICAL
STAGE

TOTAL NEOADJUVANT THERAPY^v

PRIMARY TREATMENT

pMMR/MSS
T3, N any;
T1-2, N1-2;
T4, N any
or Locally
unresectable
or medically
inoperable

Long-course chemo/RT^{q,r}
• Capecitabine^p or
infusional 5-FU^p
or
Short-course RT^{r,w}

Chemotherapy
(12-16 wk)
• FOLFOX or CAPEOX
• Consider
FOLFIRINOX

or
Chemotherapy
(12-16 wk)
• FOLFOX or CAPEOX
• Consider FOLFIRINOX

Long-course chemo/RT^{q,r}
• Capecitabine^p or
infusional 5-FU^p
or
Short-course RT^{r,w}

or
Chemotherapy
(12-16 wk) for non-T4
disease eligible for
sphincter-sparing surgery
• FOLFOX or CAPEOX

Restage with
sigmoidoscopy
± MRI

Tumor regression
>20%

Tumor regression
≤20%

Restaging^h

Transabdominal
resection^{g,x,y}

or if complete clinical
response, consider
surveillance (REC-10A)^x

Resection
contraindicated

Surveillance
(REC-10)

Systemic therapy^z
(REC-F 1 of 14)

Surgery

Surveillance
(REC-10)

Long-course chemo/RT^{q,r}
• Capecitabine^p or
infusional 5-FU^p
or
Short-course RT^{r,w}

Surgery

Surveillance
(REC-10)





CLINICAL STAGE

NEOADJUVANT/DEFINITIVE IMMUNOTHERAPY (PREFERRED)

dMMR/MSI-H
T3, N any;
T1-2, N1-2;
T4, N any
or Locally unresectable
or medically inoperable

Checkpoint inhibitor immunotherapy for up to 6 months^{xx}
• Nivolumab or
• Pembrolizumab or
• Dostarlimab-gxly

Re-evaluate disease status every 2-3 months

Complete clinical response

Surveillance ([REC-10A](#))

Persistent disease at 6 months

Long-course chemo/RT^{q,r}
• Capecitabine or infusional 5-FU^p
or
Short-course RT

Transabdominal resection^{g,x,y} or if complete clinical response, consider surveillance ([REC-10A](#))^x

Surveillance ([REC-10](#))

or
Consider FOLFOX or CAPEOX (12-16 wk)

Surveillance ([REC-10](#))

Resection contraindicated

Systemic therapy ([REC-F 1 of 14](#))

TOTAL NEOADJUVANT THERAPY^{ww}

Long-course chemo/RT^{q,r}
• Capecitabine^p or infusional 5-FU^p
or
Short-course RT^{r,w}

Chemotherapy (12-16 wk)
• FOLFOX or CAPEOX
• Consider FOLFIRINOX

Restaging^h

Transabdominal resection^{g,x,y} or if complete clinical response, consider surveillance ([REC-10A](#))^x

Surveillance ([REC-10](#))

Resection contraindicated

Systemic therapy^z ([REC-F 1 of 14](#))

^g Principles of Surgery ([REC-C](#)).

^h Principles of Imaging ([REC-A](#)).



Outcomes after rectal surgery

- **Volume matters**
 - Hospital volume (and use of MDT)
 - Surgeon volume

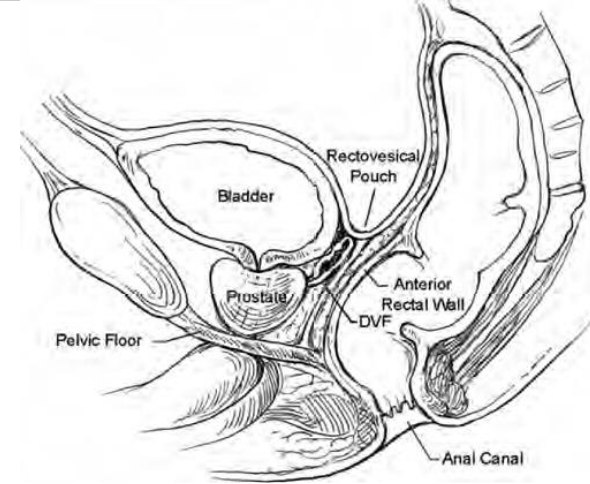
- **Specialization matters**
 - Only 20% of proctectomies in US performed by colorectal surgeons.
 - Outcomes clearly better:
 - **short and long-term morbidity (anastomotic leak, lap vs. open)**
 - **disease-free survival, rates of local recurrence**
 - **Rate of permanent stoma**
 - **Sexual and urinary function**
 - **Rates of fecal incontinence**
 - **Quality of Life**

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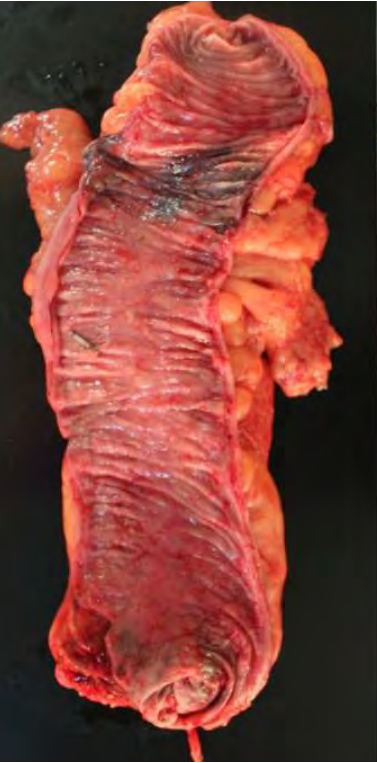
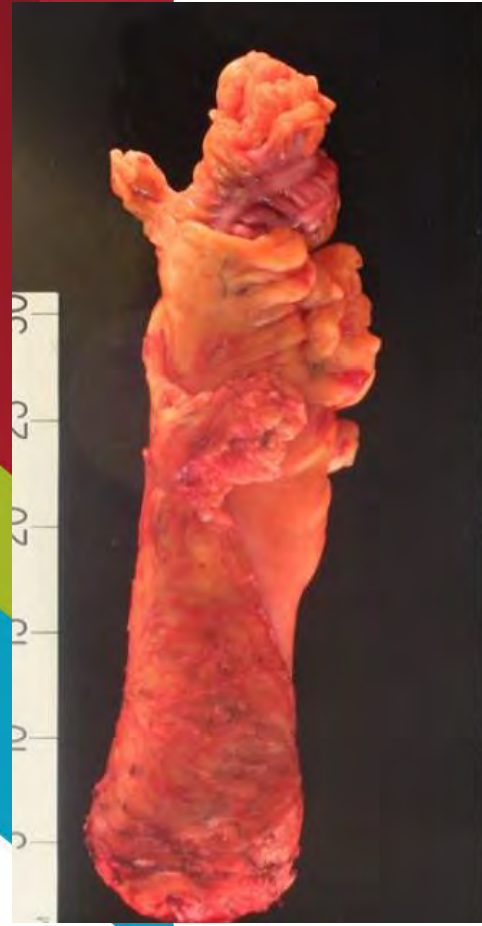


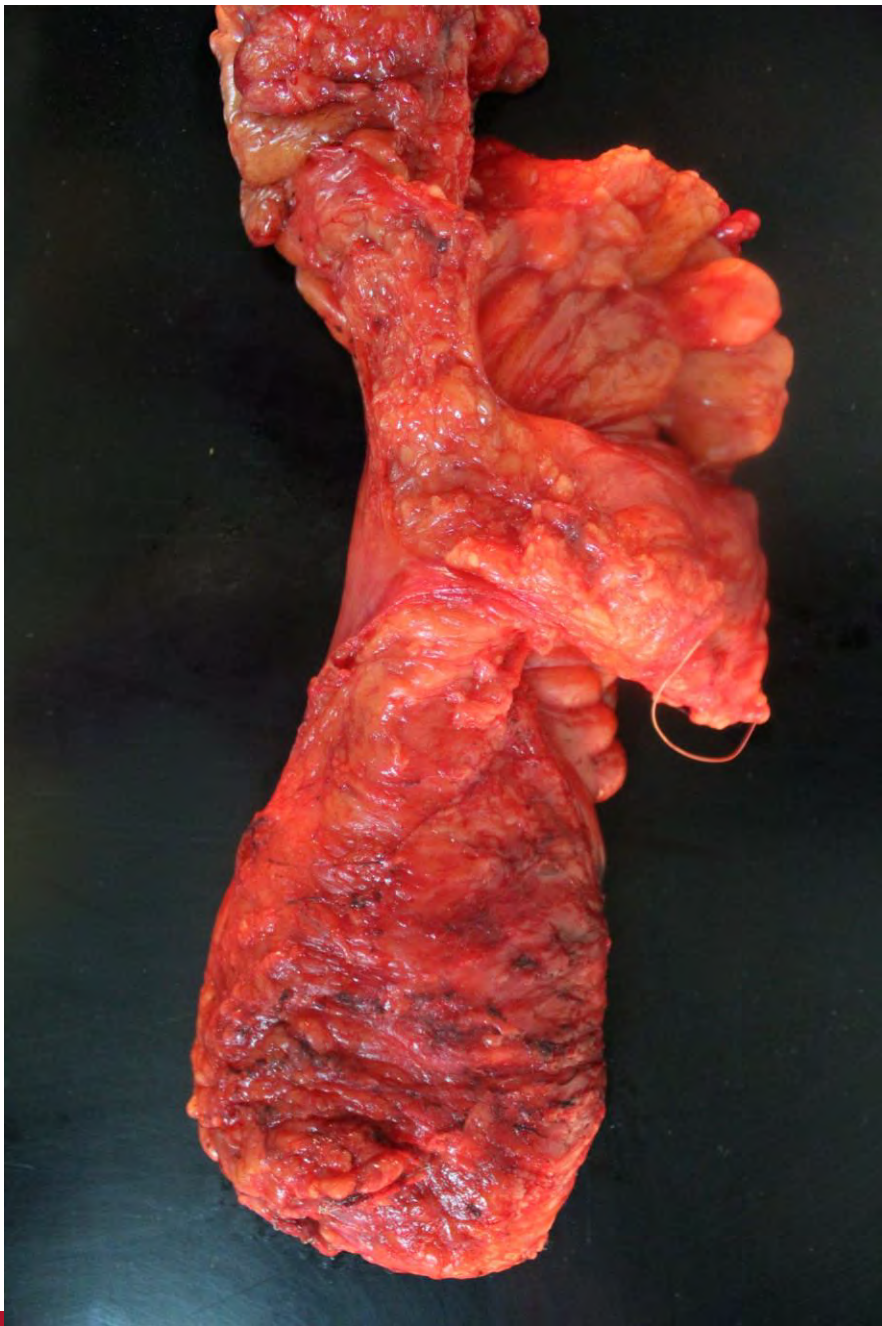
Rectal surgery is hard!

- Confines of the bony pelvis
 - Operating in a glass tube
- Proximity to adjacent organs
 - **Too far outside** → massive bleeding, RVF, urethral injury, sexual and urinary dysfunction
 - **Too close** → Recurrence and death 😞
- Poor visualization
- Radiated field with fibrosis/edema/friability
- Poor functional outcome and higher rates of leak and sepsis when compared to colon surgery.











IT'S A FISSURE!

Dr Rooster, my hemorrhoids are really hurting, I need prepar--



Conclusions

- TNT has become the standard of care for MMR-proficient rectal cancer
- Organ preservation/watch-and-wait is oncologically appropriate, but requires tight surveillance.
- As the treatment of rectal cancer continues to evolve, it has become evident that a ***tailored approach to care***, taking into consideration patient and tumor factors, is the most appropriate treatment strategy.





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