

ANNUAL

**Advances and Innovations in Endoscopic Oncology
and Multidisciplinary Gastrointestinal Cancer Care**

Organ Preservation Options after TNT and Near complete response in Rectal Cancer

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Disclosures

- Consultant for Boston Scientific, Dilumen, and Intuitive Surgical

The presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed [Assembly Bill \(AB\) 1195](#), which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed [AB 241](#), which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

Outline

- What is the current rectal cancer treatment
- What are the paradigm shifts and TNT
- New endoluminal approaches and Robotics



Anal Cancer (SCC)



Who is Dr. Norman Nigro?



Dr. Norman D. Nigro
(1965-66)

Did You Know?

"...[Dr. Nigro] remains well known for the Nigro Protocol, a treatment for anal cancer that uses a combination of radiation and chemotherapy, avoiding a surgery that commonly resulted in a permanent colostomy." - J. Byron Gathright Jr., M.D., & Richard S. Bragaw, *From Matthews to the Millennium*, 1999

Combined Therapy for Cancer of the Anal Canal:
A Preliminary Report* 1974

NORMAN D. NIGRO, M.D.,† V. K. VAITKEVICIUS, M.D.,‡ BASIL CONSIDINE, JR., M.D.§

From Wayne State University, School of Medicine, Detroit, Michigan



First report of 3 cases

The lesions in all three patients
reported here disappeared following
the preoperative therapy:

- 25 mg/kg 5 FU daily for 5 days in the form of continuous infusion
 - Mitomycin C 0,5 mg/Kg in single bolus injection in day 1
- +
- Radiotherapy 3000 rads full pelvic dose

Anal Cancer-SCC

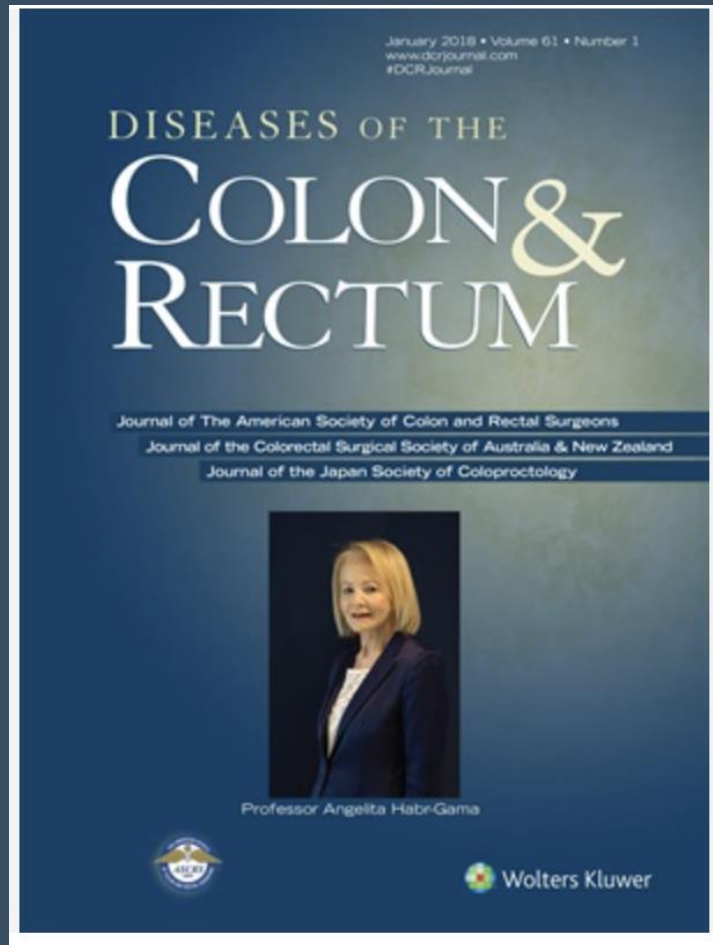


Nigro Protocol: RT combined with 5-FU and mitomycin-C

Can we accomplish the same with
rectal Adenocarcinoma?



Dr. Angelita Habr-Gama



Standard Locally Advanced Paradigm

(since ~2004)

Pre-op Chemo-XRT



Surgery



Adjuvant Chemotherapy



Rectal Cancer Paradigm Shift



What is the paradigm shift in
Rectal Cancer?



Paradigm Shift and TNT

Pre-op Chemo-XRT



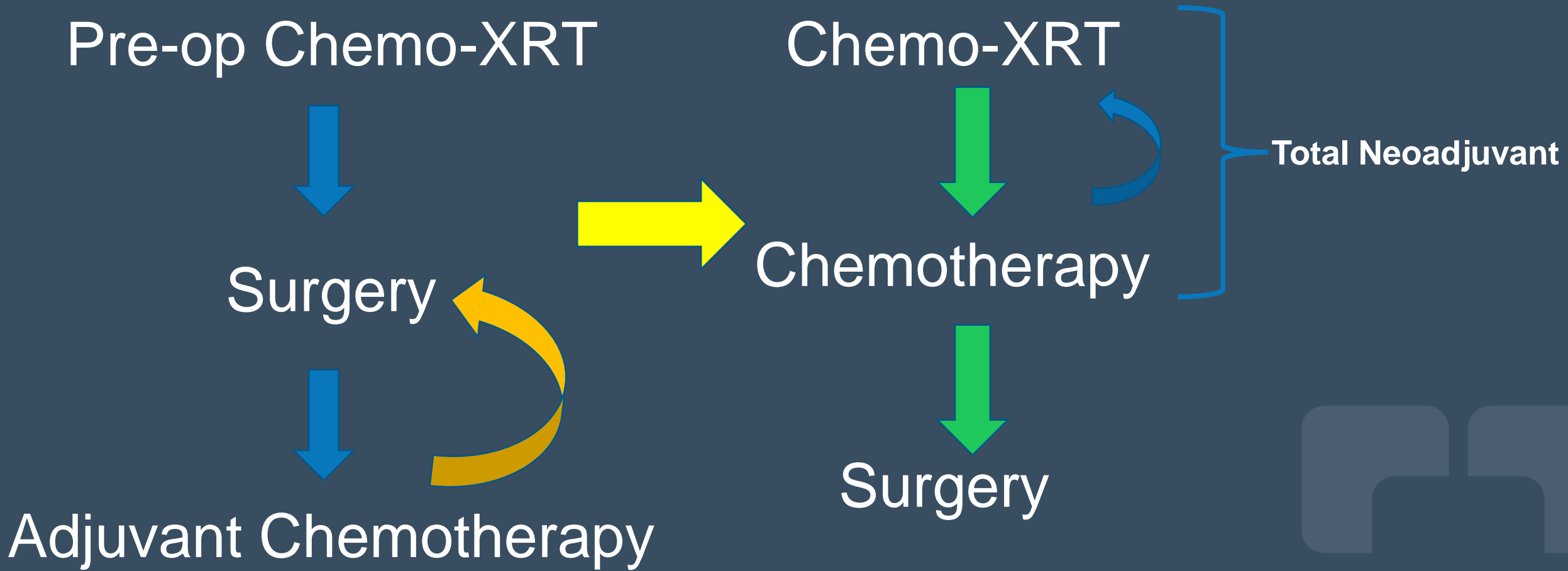
Surgery



Adjuvant Chemotherapy



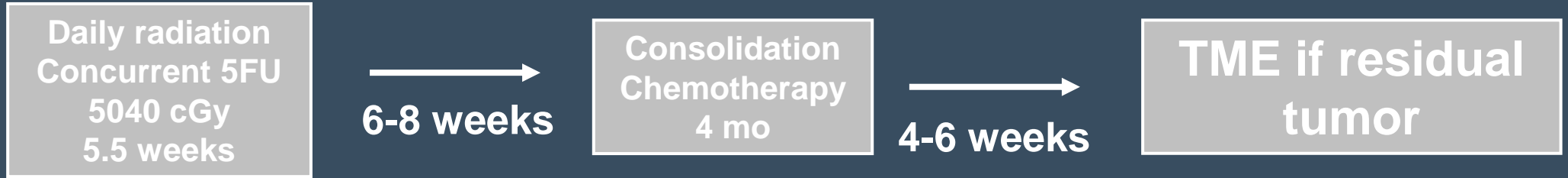
Paradigm Shift and TNT



What is the treatment of choice in locally advanced rectal cancer ?



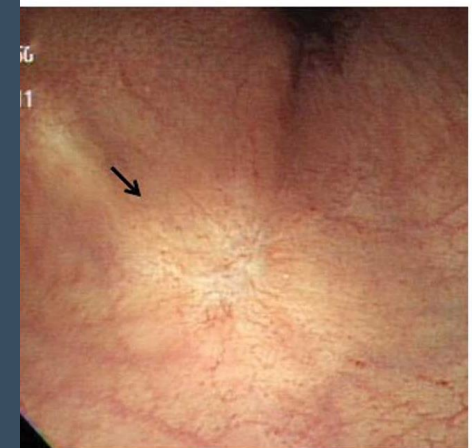
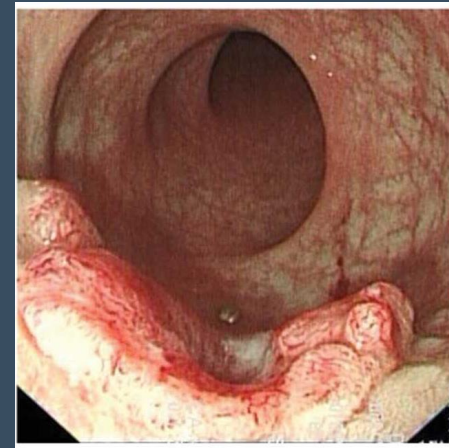
Current Rectal Cancer treatment



- Chemoradiation better tolerated in preoperative setting
- Decreased risk of positive surgical margins
- Greater likelihood of sphincter sparing surgery
- Better long-term function

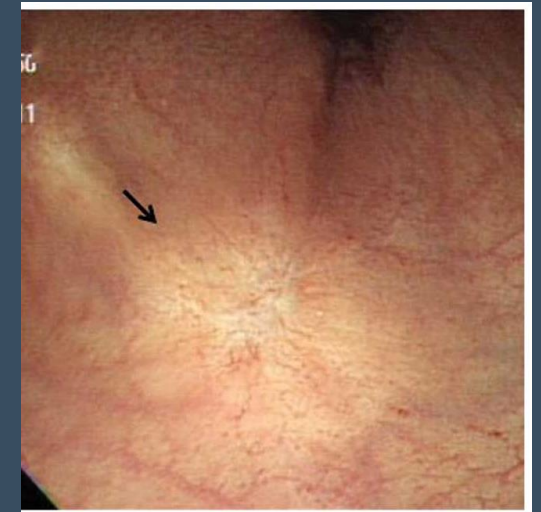
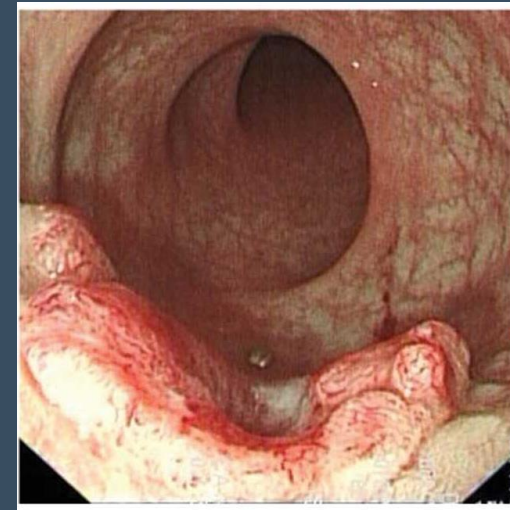
cCR and cPR

- Watch and Wait (W&W)
- Organ preservation
 - **Active surveillance**

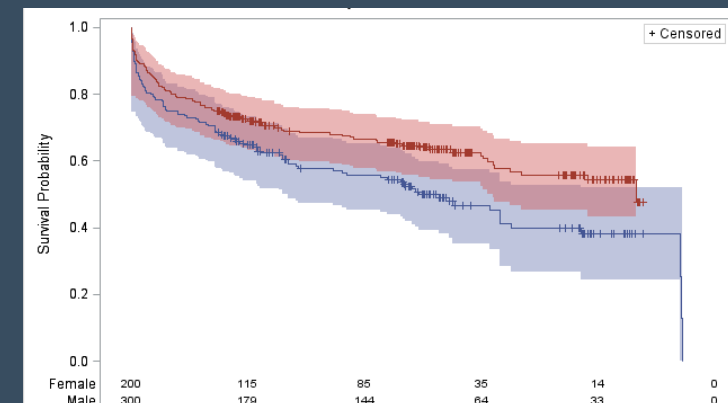


How do we accurately recognize cCR?

- Exam/Endoscopy
- Imaging
- Biopsies

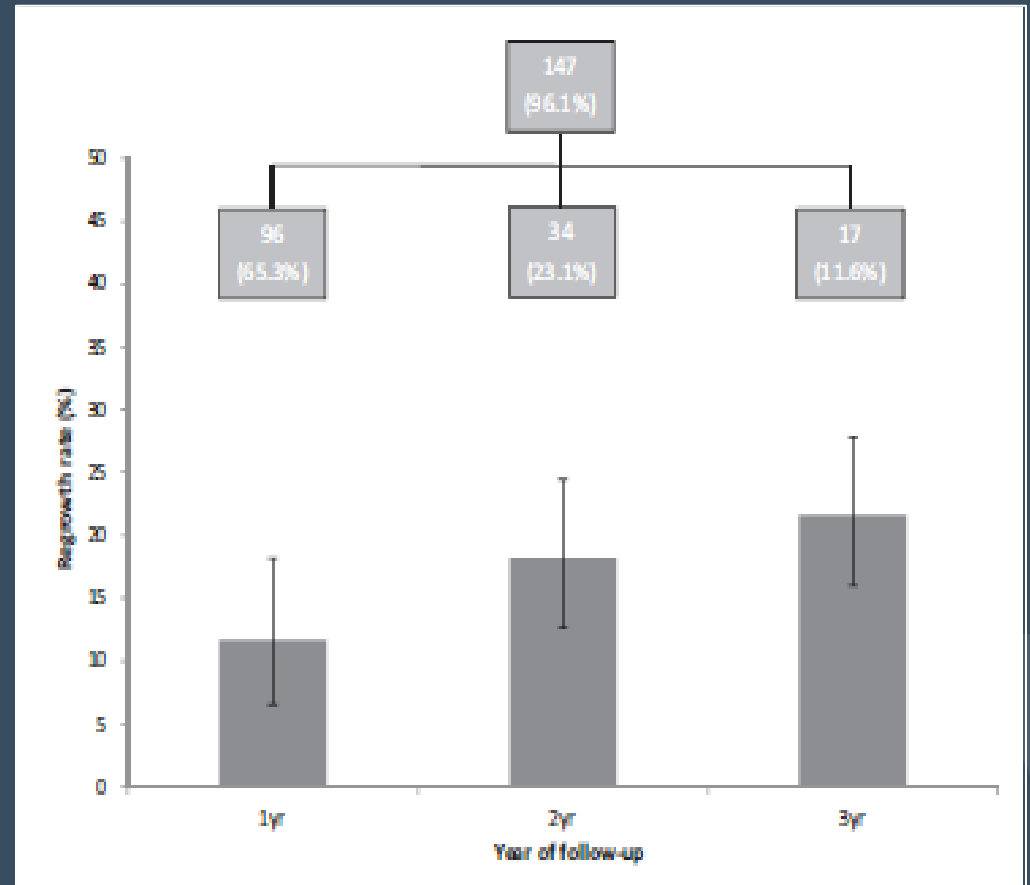


- *Surveillance Protocol*



Meta-Analysis “Regrowth”

- Majority of the re-growths occurred in the first year (96/157; %65.3)
- Emphasizes the need for aggressive surveillance



Watch & Wait

Rectal Cancer Active Surveillance

- Exam, DRE, CEA, and Flex Sig
 - Years 0-2 → every 3 mo
 - Years 3-4 → every 6 mo
 - Years 5-10 → yearly
- MRI Rectum
 - Years 0-4 → every 6 mo
 - Years 5-10 → yearly
- CT C/A/P
 - Year 0-2 → every 6 mo
 - Year 3-10 → yearly
- Colonoscopy
 - 1 year after treatment completion
 - Every 3 years following

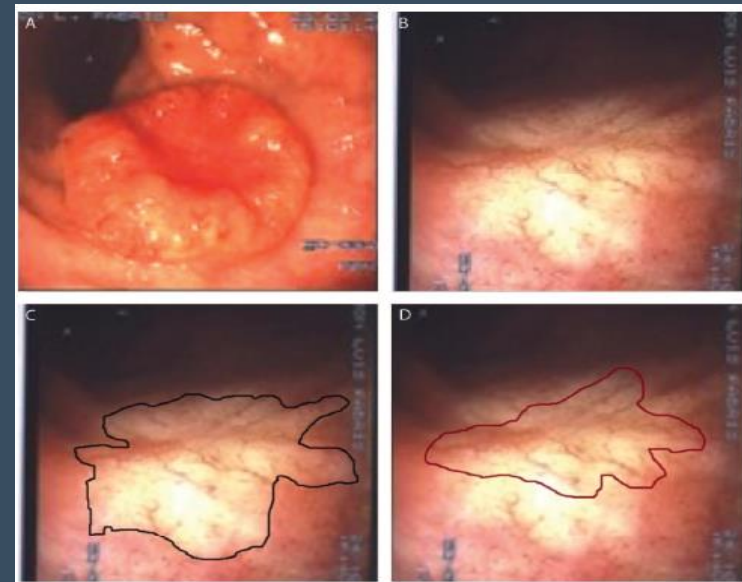
Watch & Wait

Rectal Cancer Active Surveillance

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 - Every 3 years following

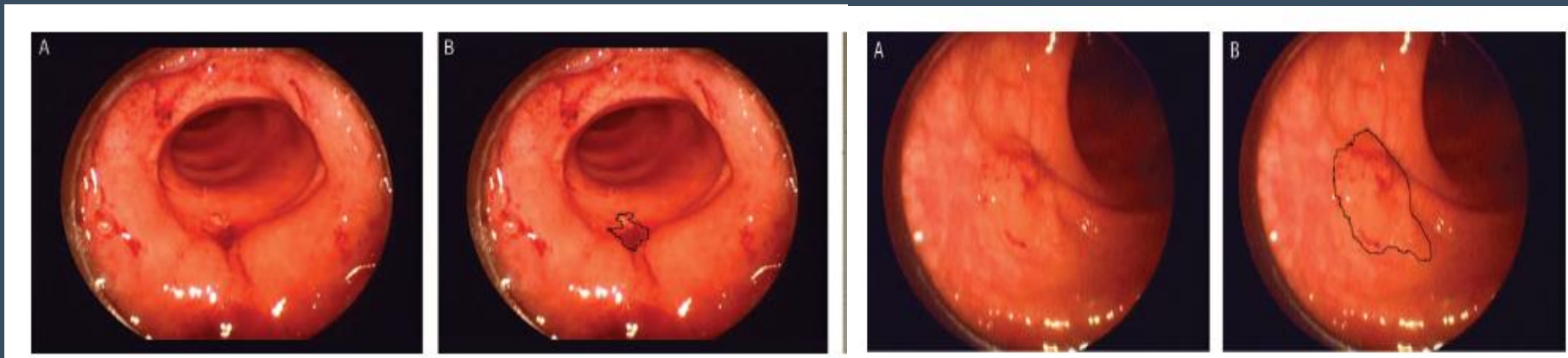
Assessment of Tumor Response

- DRE
 - Poor positive predictive value
 - Clinical assessment underestimated pathologic response in 78% of cases
 - Only identified 3 of 14 cases with a pCR
- Endoscopy
 - Whitening of mucosa, telangiectasia with mucosal integrity and subtle loss of pliability of the rectal wall

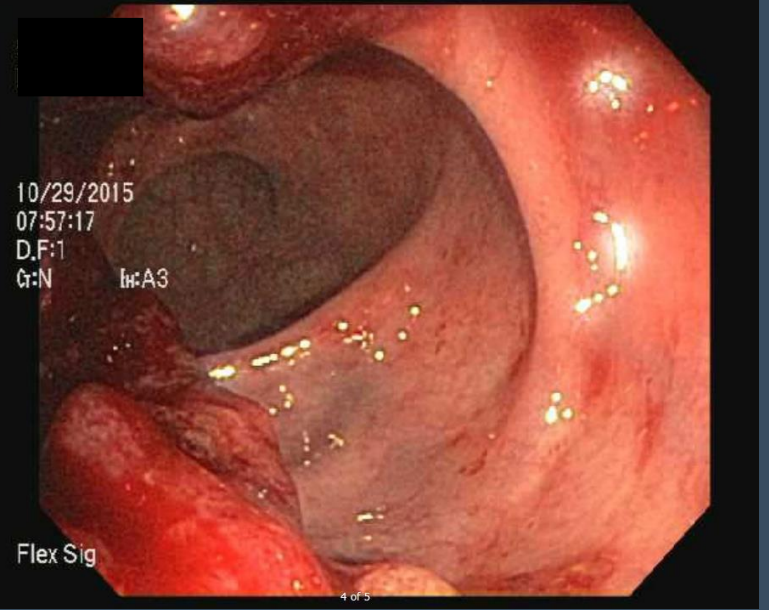
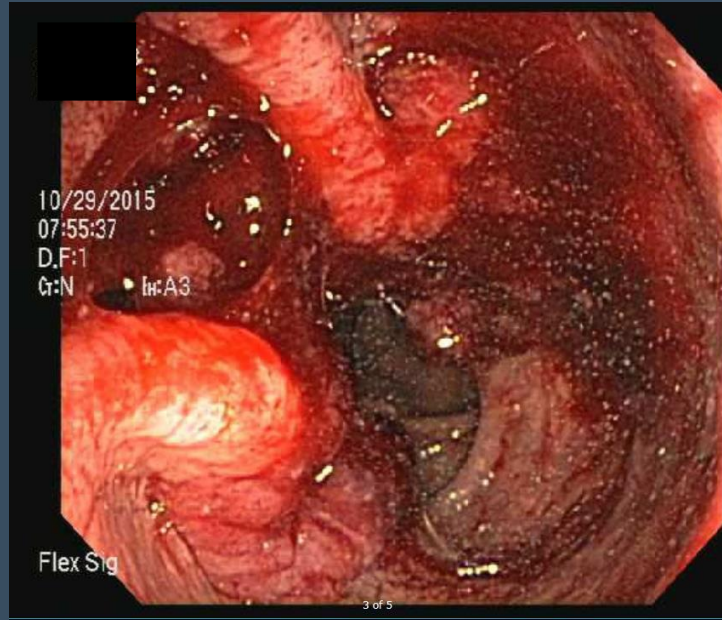


Incomplete Response

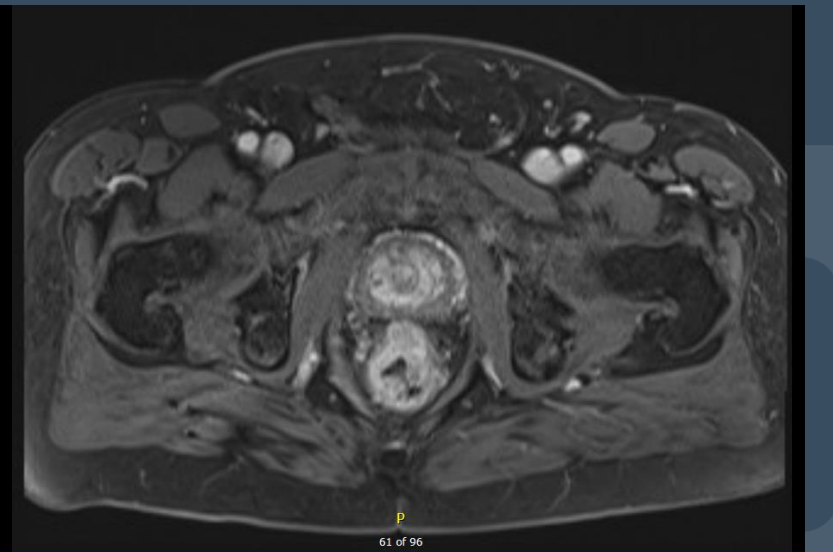
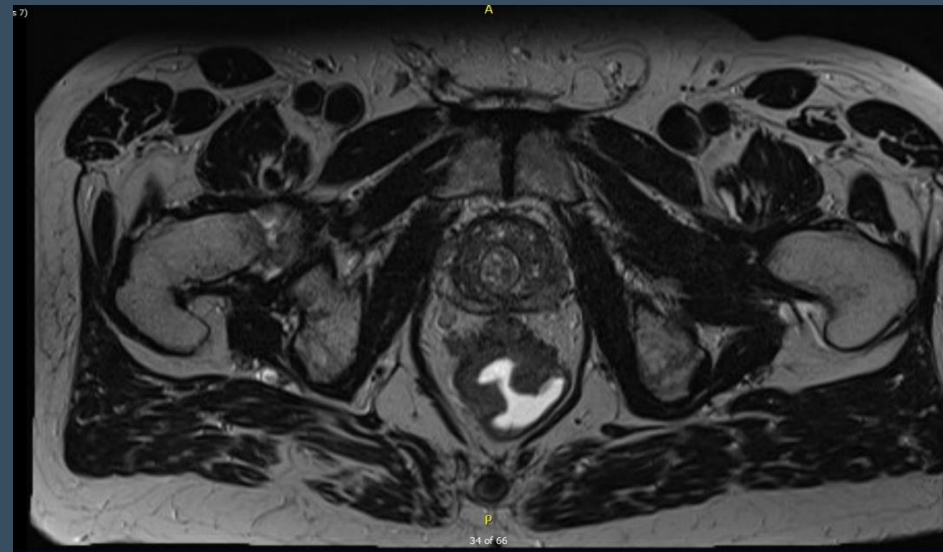
- Residual ulcer with or without necrotic center
- Superficial ulcer or irregularity
- Palpable nodule in rectal wall
- Significant stenosis impeding passage of scope



Assessing Response

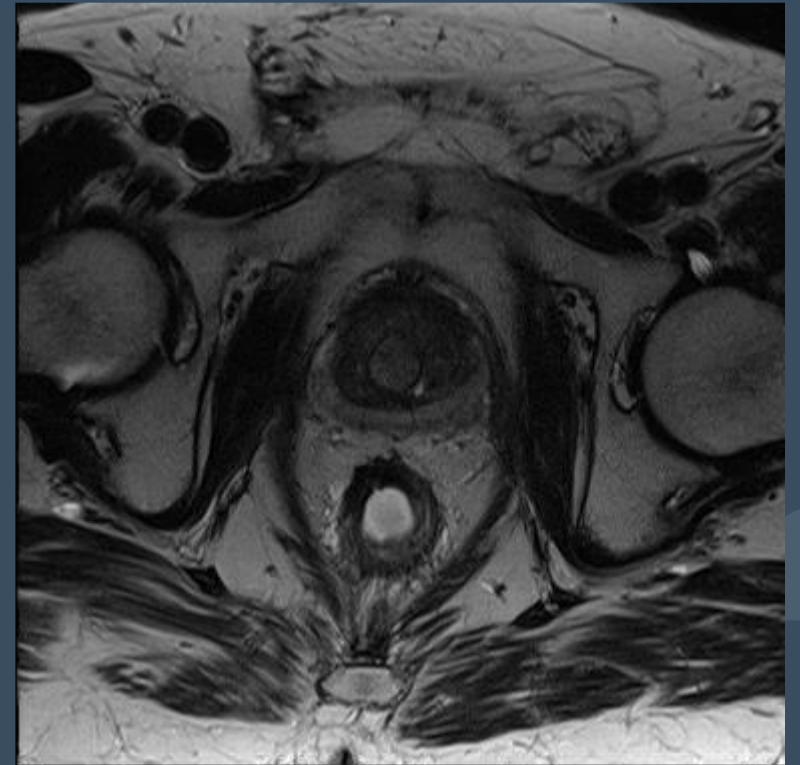
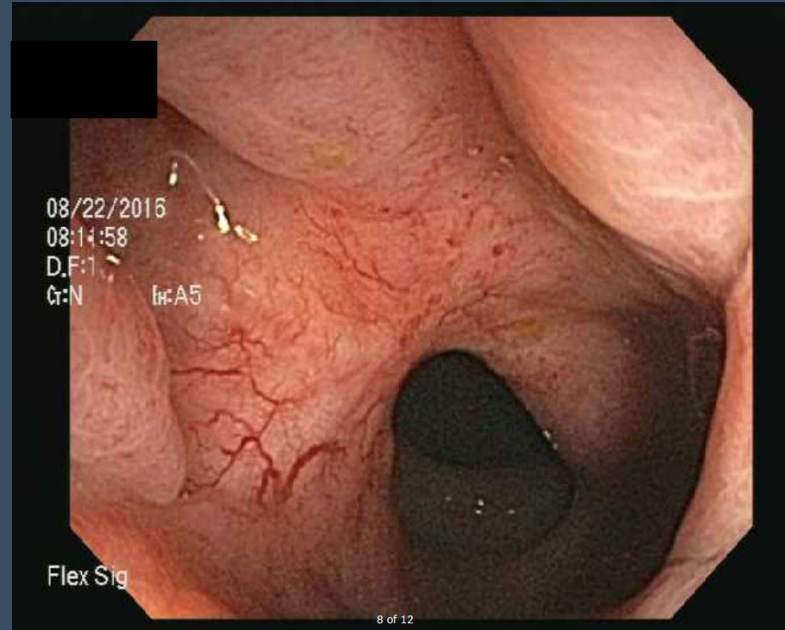


Diagnosis
cT3N1 top of anal canal
Abutting prostate



Assessing Response

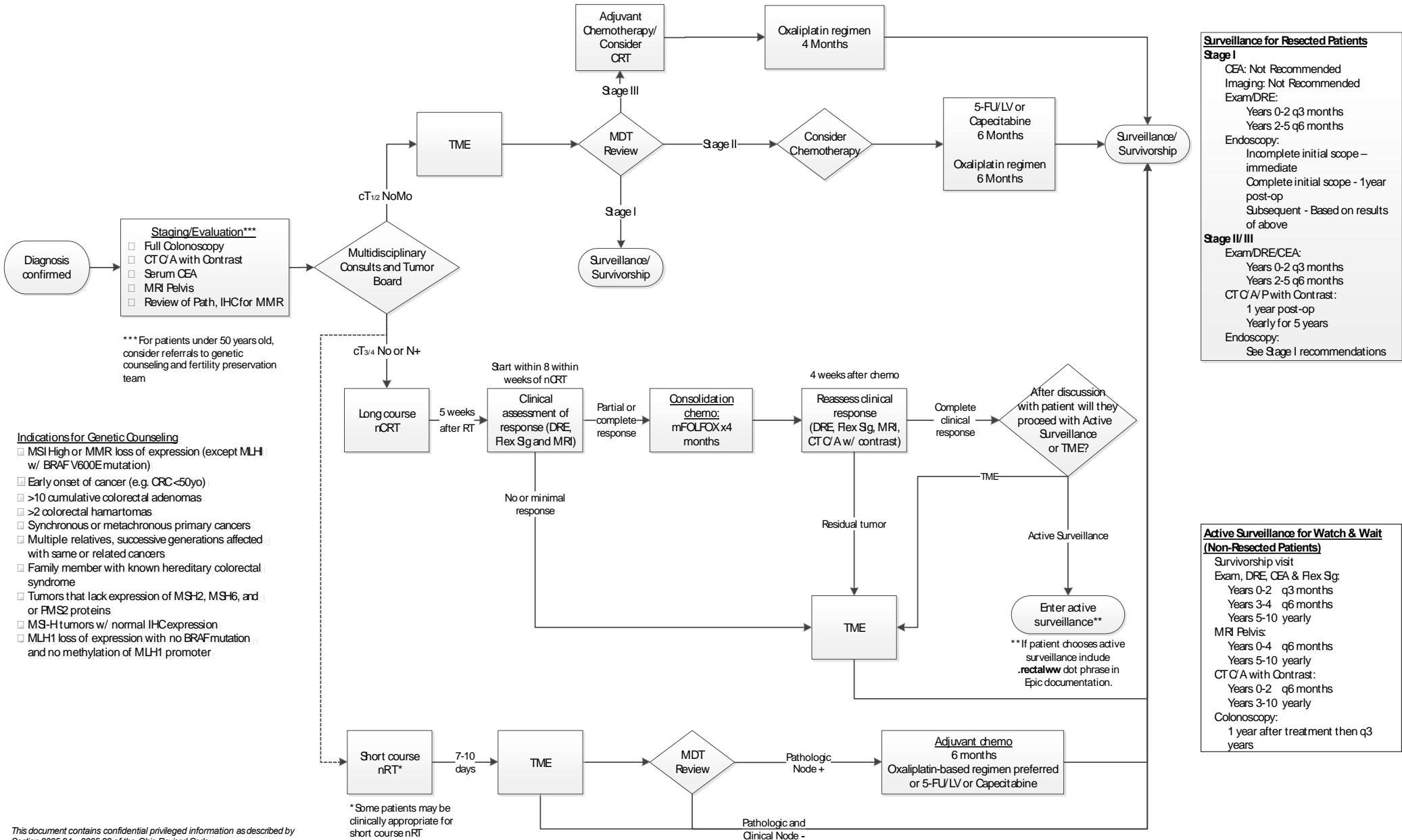
Completed TNT
cCR



Assessing Response

- MRI
 - mrTRG to allow for systematic and reproducible MR assessment of response

TRG scale	mrTRG (low no.=more regression)
1	No/minimal fibrosis visible (tiny linear scar) and no tumour signal
2	Dense fibrotic scar (low signal intensity) but no macroscopic tumour signal (<i>indicates no or microscopic tumour</i>)
3	Fibrosis predominates but obvious measureable areas of tumour signal visible
4	Tumour signal predominates with little/minimal fibrosis
5	Tumour signal only: no fibrosis, includes progression of tumour



Staging/Evaluation***

- Full Colonoscopy
- CT/A with Contrast
- Serum CEA
- MRI Pelvis
- Review of Path, IHC for MMR

***For patients under 50 years old, consider referrals to genetic counseling and fertility preservation team

Indications for Genetic Counseling

- MSI High or MMR loss of expression (except MLH1 w/ BRAF V600E mutation)
- Early onset of cancer (e.g. CRC <50yo)
- >10 cumulative colorectal adenomas
- >2 colorectal hamartomas
- Synchronous or metachronous primary cancers
- Multiple relatives, successive generations affected with same or related cancers
- Family member with known hereditary colorectal syndrome
- Tumors that lack expression of MSH2, MSH6, and/or FMS2 proteins
- MS-H tumors w/ normal IHC expression
- MLH1 loss of expression with no BRAF mutation and no methylation of MLH1 promoter

*Some patients may be clinically appropriate for short course nRT

**If patient chooses active surveillance include .rectalww dot phrase in Epic documentation.

Surveillance for Resected Patients

Stage I

CEA: Not Recommended
Imaging: Not Recommended
Exam/DRE:
Years 0-2 q3 months
Years 2-5 q6 months

Endoscopy:
Incomplete initial scope – immediate
Complete initial scope - 1 year post-op
Subsequent - Based on results of above

Stage II/III

Exam/DRE/CEA:
Years 0-2 q3 months
Years 2-5 q6 months

CT/A/P with Contrast:
1 year post-op
Yearly for 5 years

Endoscopy:
See Stage I recommendations

Active Surveillance for Watch & Wait (Non-Resected Patients)

Survivorship visit
Exam, DRE, CEA & Flex Sg:
Years 0-2 q3 months
Years 3-4 q6 months
Years 5-10 yearly

MRI Pelvis:
Years 0-4 q6 months
Years 5-10 yearly

CT/A with Contrast:
Years 0-2 q6 months
Years 3-10 yearly

Colonoscopy:
1 year after treatment then q3 years

TNT Cleveland Clinic Experience

- January 2015 December 2021
- 119 patients

Predictors of complete response:

- Tumors located lower:
OR 2.6 (95% CI:1.1-5.9), $p = 0.02$
- Lack of extramural vascular invasion (EMVI)
OR 5.4 (95% CI:1.2-25.1), $p = 0.01$

ORIGINAL CONTRIBUTION

What Predicts Complete Response to Total Neoadjuvant Therapy in Locally Advanced Rectal Cancer?

Running Head: Predictors of complete response to TNT

Sumeyye Yilmaz, M.D.¹ • David Liska, M.D.¹ • Madison Conces, M.D.² • Naz Tursun, M.D.¹ • Doua Elamin, M.D.¹ • Ilker Ozgur, M.D.¹ • Marianna Maspero, M.D.¹ • David Rosen, M.D.¹ • Alok Khorana, M.D.² • Ehsan Balagamwala, M.D.³ • Sudha Amarnath, M.D.³ • Michael Valente, D.O.¹ • Scott R. Steele, M.D., M.B.A.¹ • Smitha Krishnamurthi, M.D.² • Emre Gorgun, M.D., M.B.A.¹

Total Neoadjuvant Therapy

	Number of Patients	Complete Response (%)
Surgical Group (pathological CR)	88	22.7%
Watch-and-Wait Group (clinical CR)	31	77.4%
Overall Complete Response Rate	119	37%

Diagnostic Tool	Sensitivity (%)	Specificity (%)
Sigmoidoscopy	76.0%	72.5%
MRI	62.5%	69.2%
Combined (Sigmoidoscopy + MRI)	N/A	82.5%



Takeaways

Complete response following TNT
37%

**Complete response stage 1 following TNT
Stage 100%



Absence of extramural vascular invasion, low tumor location are predictors of complete response

Endoscopy is more accurate than MRI in detecting incomplete response

Growing Cleveland Clinic Experience

Original Article

Evaluating complete response rates and predictors in total neoadjuvant therapy for rectal cancer

Kamil Erozkán^a, Doua Elamin^a, Muhammed Enes Tasci^a, David Liska^a, Michael A. Valente^a,
Ali Alipouriani^a, Lukas Schabl^a, Olga Lavryk^a, Brogan Catalano^a, Smitha Krishnamurthi^b,
Jacob A. Miller^c, Andrei S. Purysko^d, Scott R. Steele^a, Emre Gorgun^a  

Predictors of complete response:

- Low tumors
- Lack of EMVI
- Lack of MRF involvement

Growing Cleveland Clinic Experience

	Number of Patients	Complete Response (%)
Clinical Complete Response (cCR)	57	27.4%
Sustained cCR after 1 year	166	80.0%
Pathologic Complete Response (pCR)	42	-
Final Complete Response Rate	208	42.3%

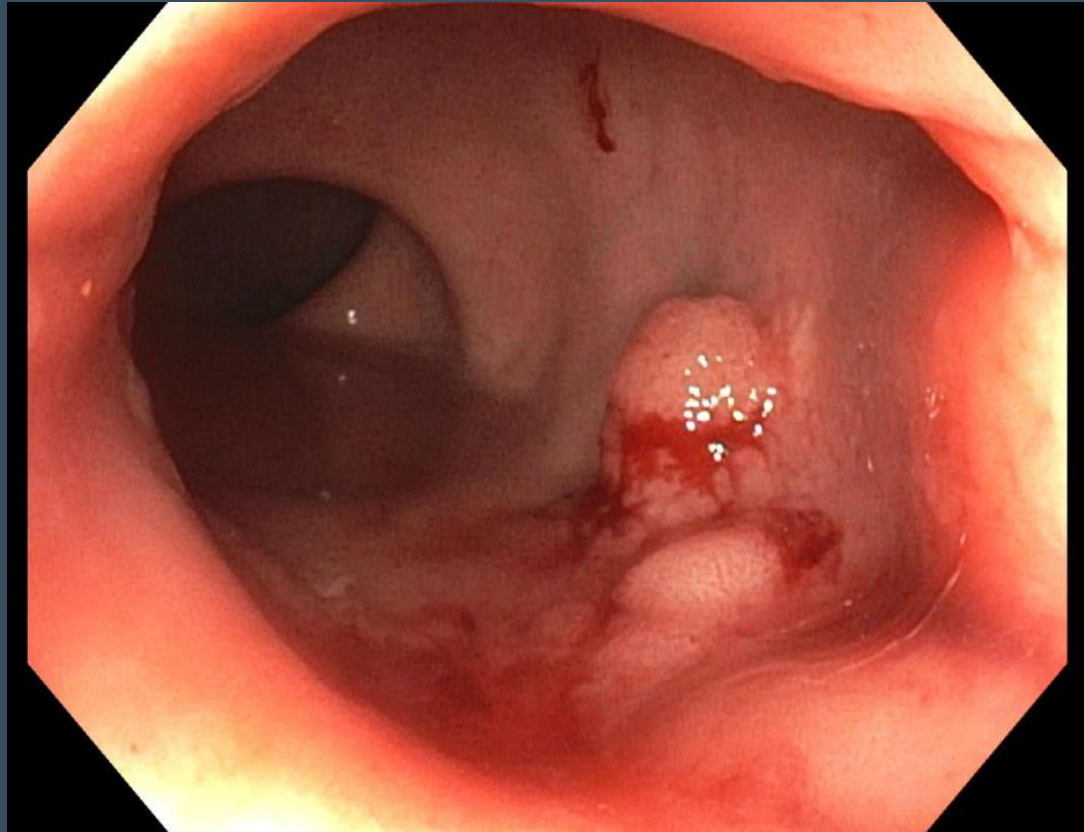
Outcome	CR Group (%)	Incomplete Response Group (%)	P-value
Disease-Free Survival	91.3%	71.0%	< .01
Overall Survival	98.8%	90.2%	.03

Growing Cleveland Clinic Experience

	Number of Patients	Complete Response (%)
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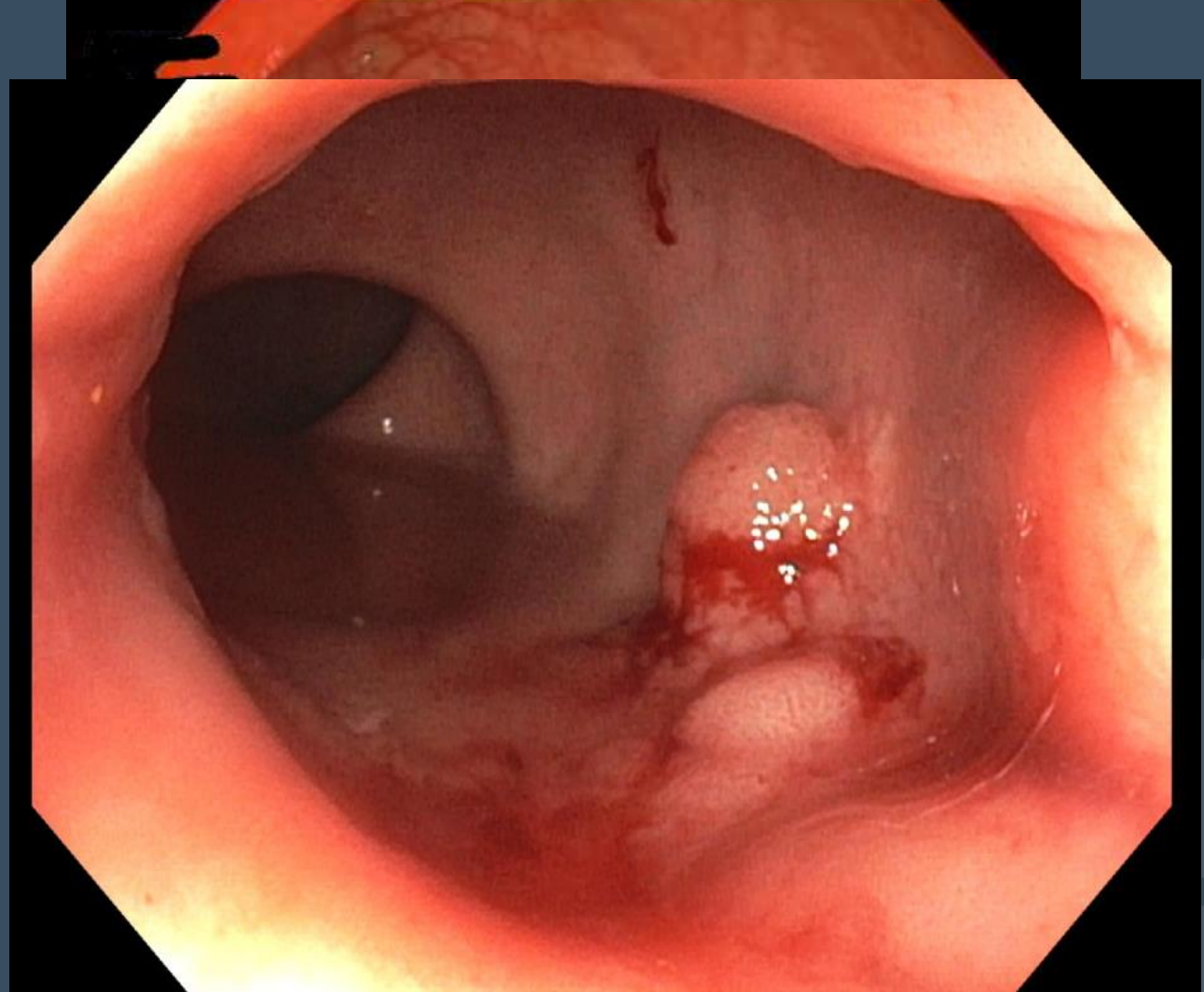
Outcome	CR Group (%)	Incomplete Response Group (%)	P-value
Disease-Free Survival	91.3%	71.0%	< .01
Overall Survival	98.8%	90.2%	.03

What if there is a minimal residual disease or regrowth?



After TNT (02/2020)

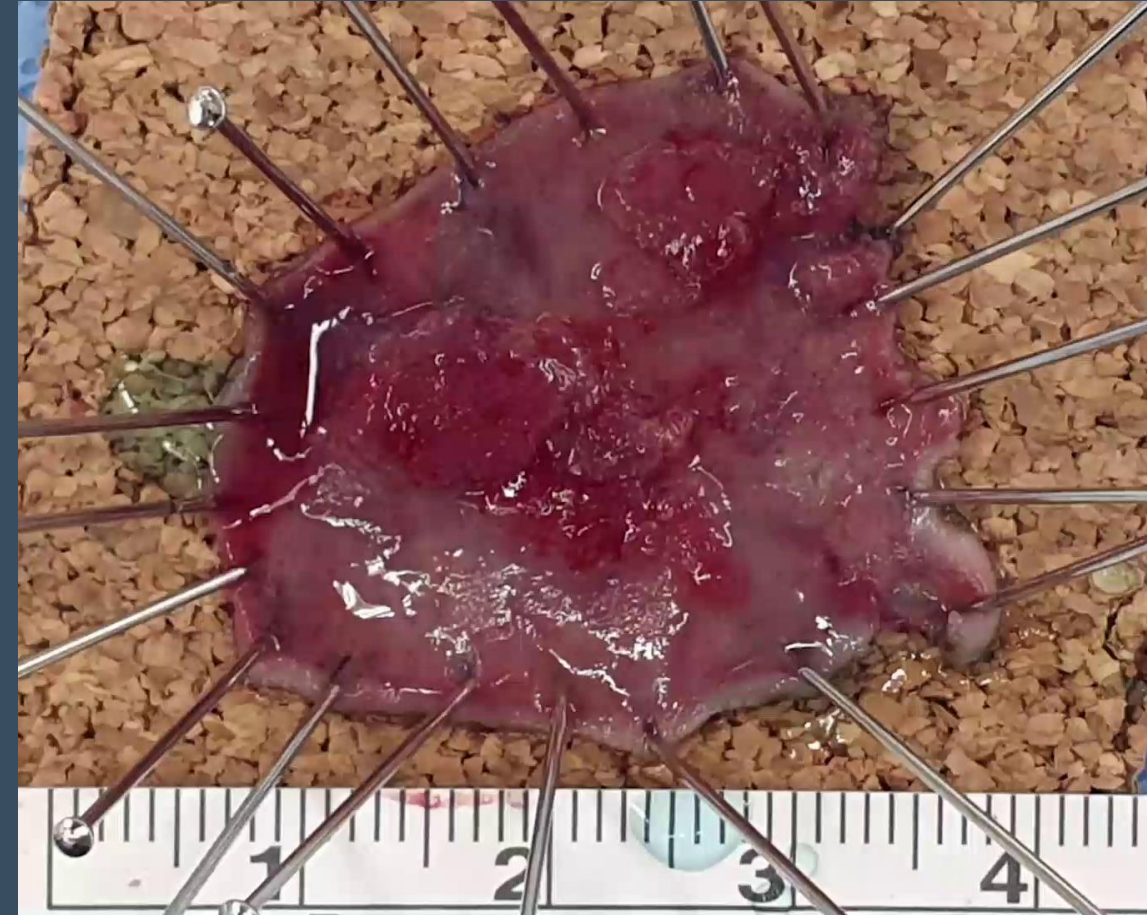
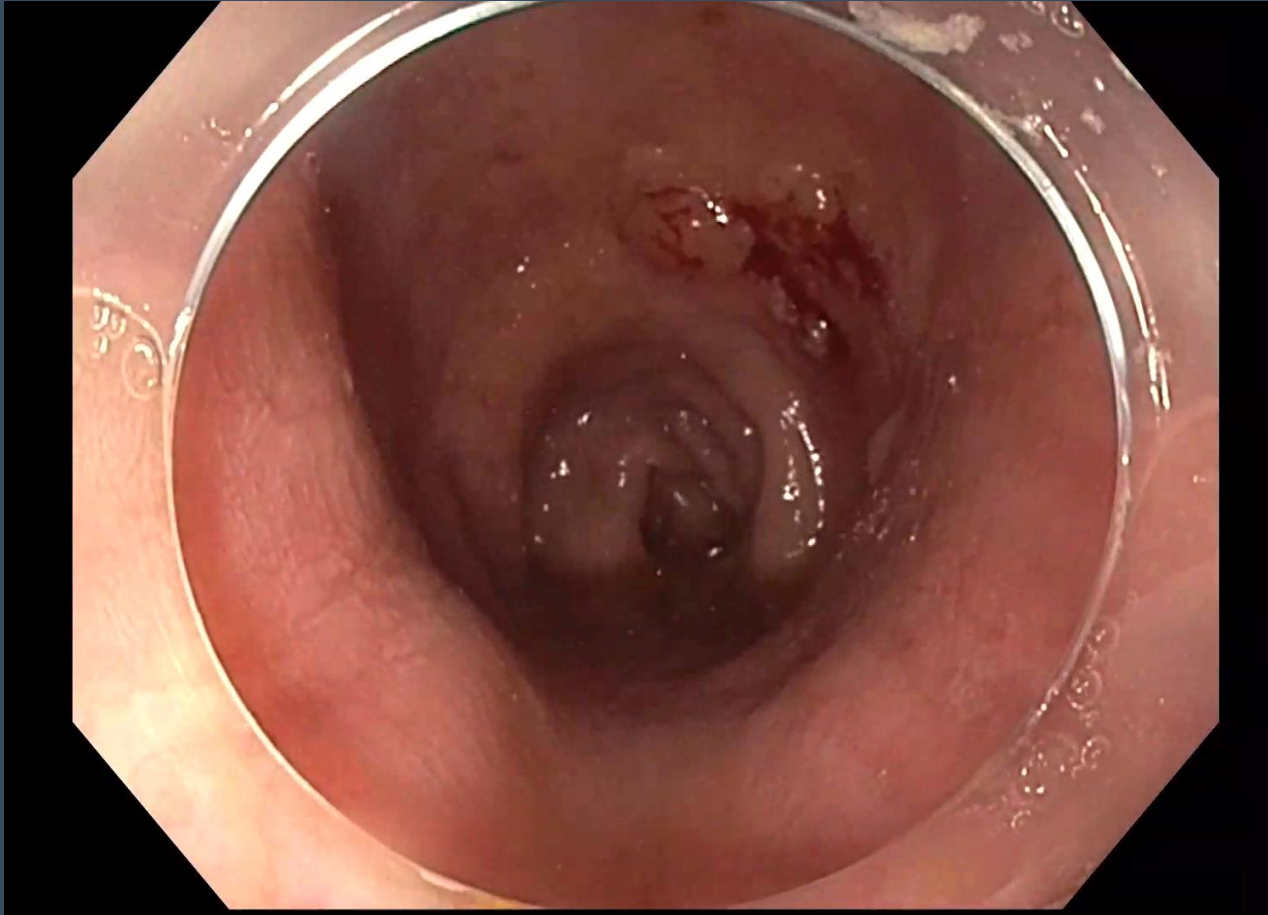
- 25 mm polypoid lesion in distal rectum
- Bx: high grade adenomatous dysplasia
- CEA:0.8 ng/ml



- The role of Endoluminal Surgery and ESD (Endoscopic Submucosal Dissection) for "Mucosal regrowth"



ESD (5/2020)

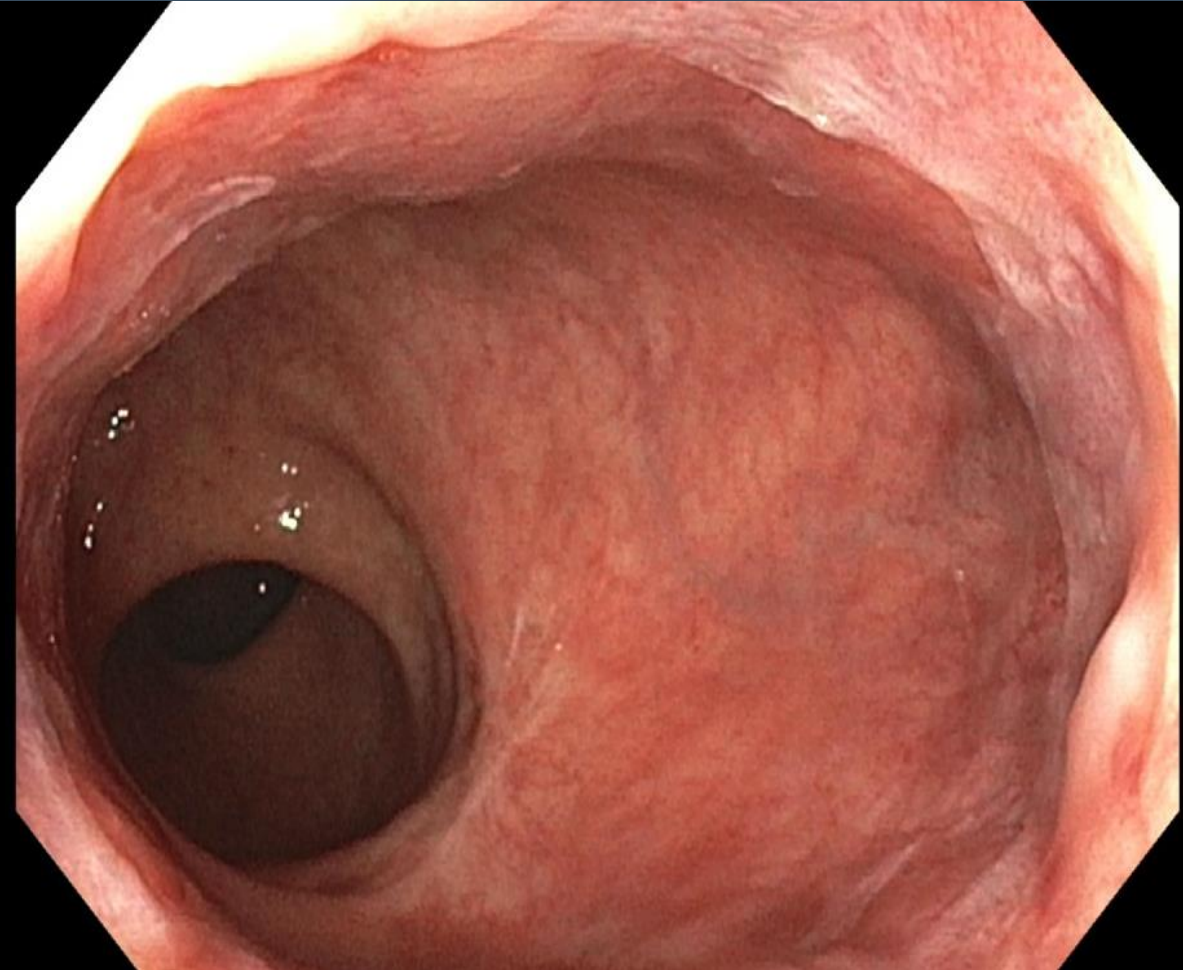
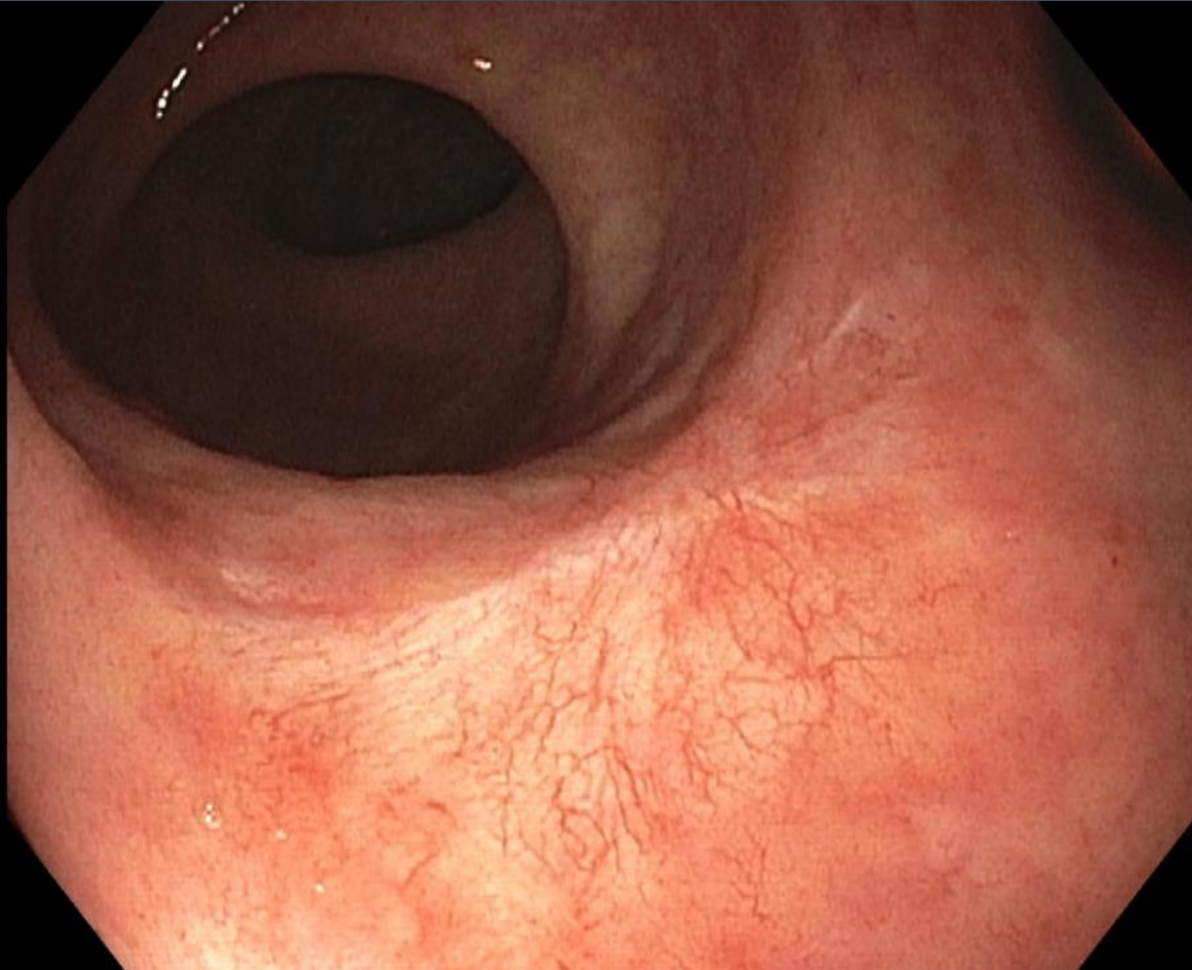


ESD (5/2020)

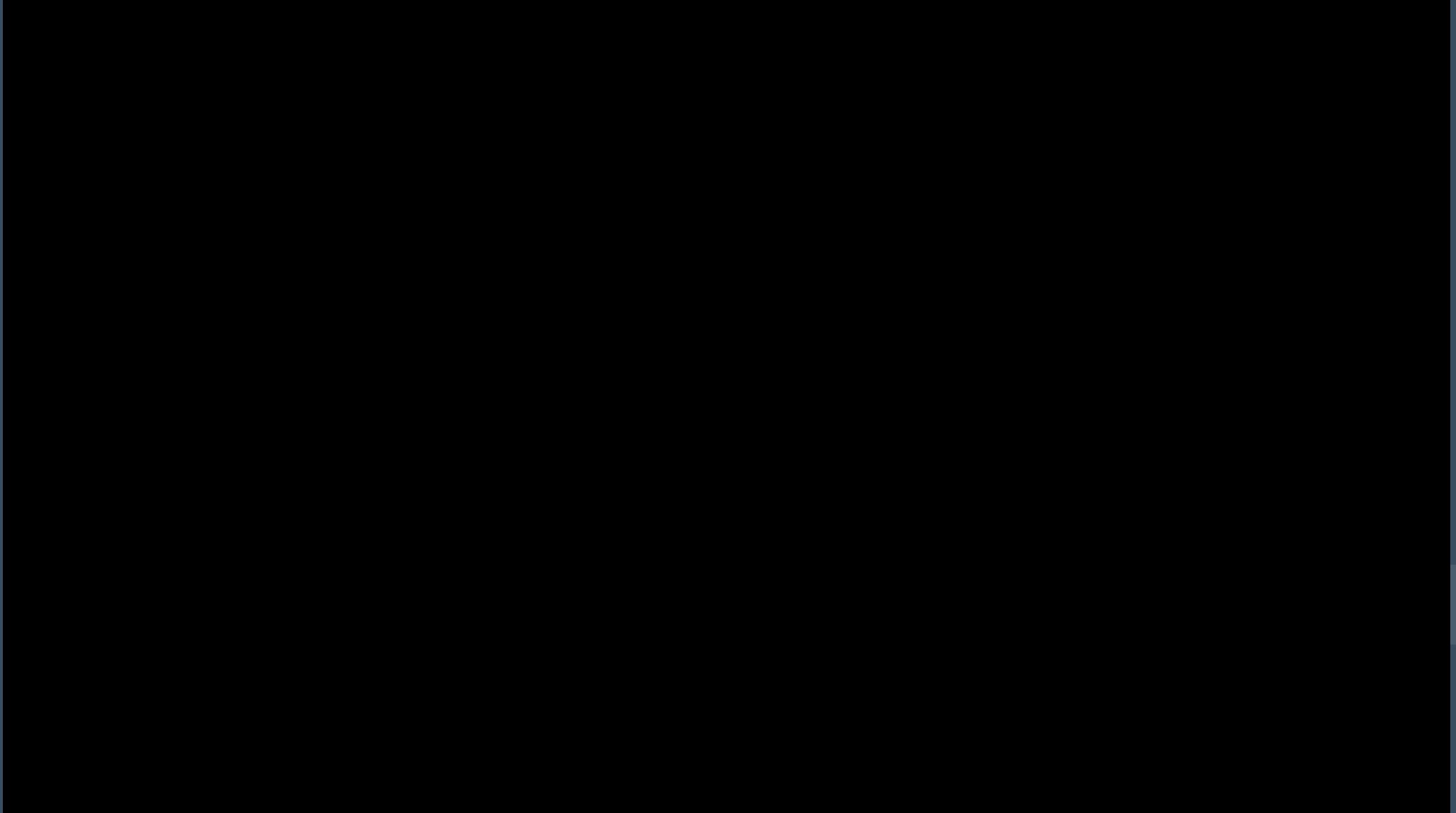
- Tubulovillous adenoma
- Focal HGD
- FU every 6 months



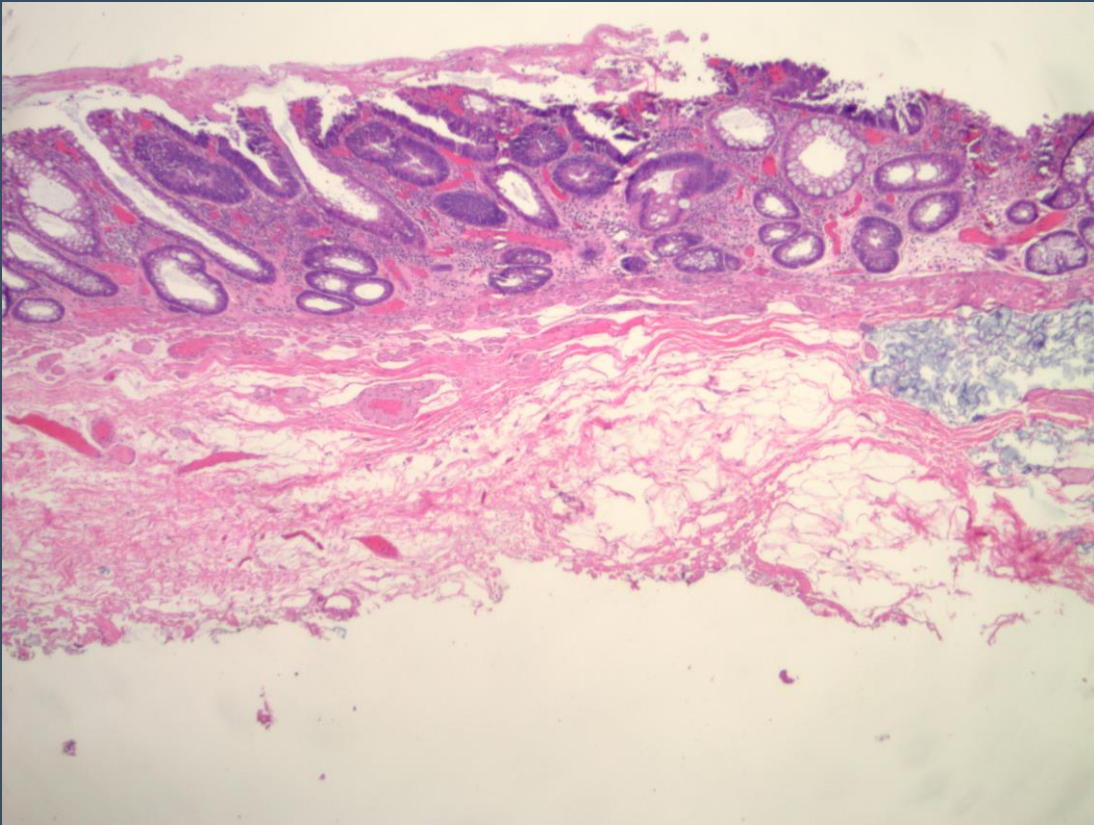
Sigmoidoscopy last f/u



ESD after TNT

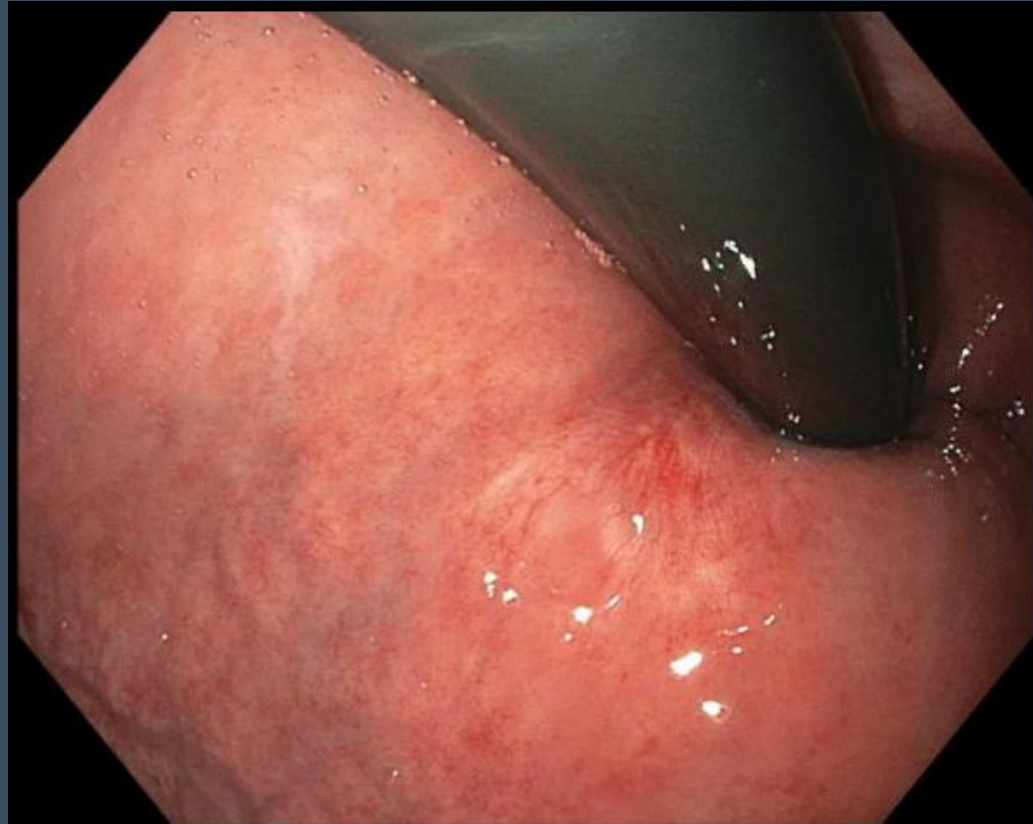


Pathology: ESD specimen



- Tubular adenoma with focal high-grade dysplasia
- Free deep and radial margins

Follow Up Flex Sigmoidoscopy



ESD AFTER TNT

VIDEO VIGNETTE

Endoscopic Submucosal Dissection in the Management of an Adenoma Within the Area of Rectal Cancer After Complete Clinical Response

Cihad Tatar, M.D. • Kristen T. Crowell, M.D. • Ipek Sapci, M.D. • I. Emre Gorgun, M.D.

Department of Colorectal Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, Ohio

Robotic SP technology



Single Port Endorobotic Surgery

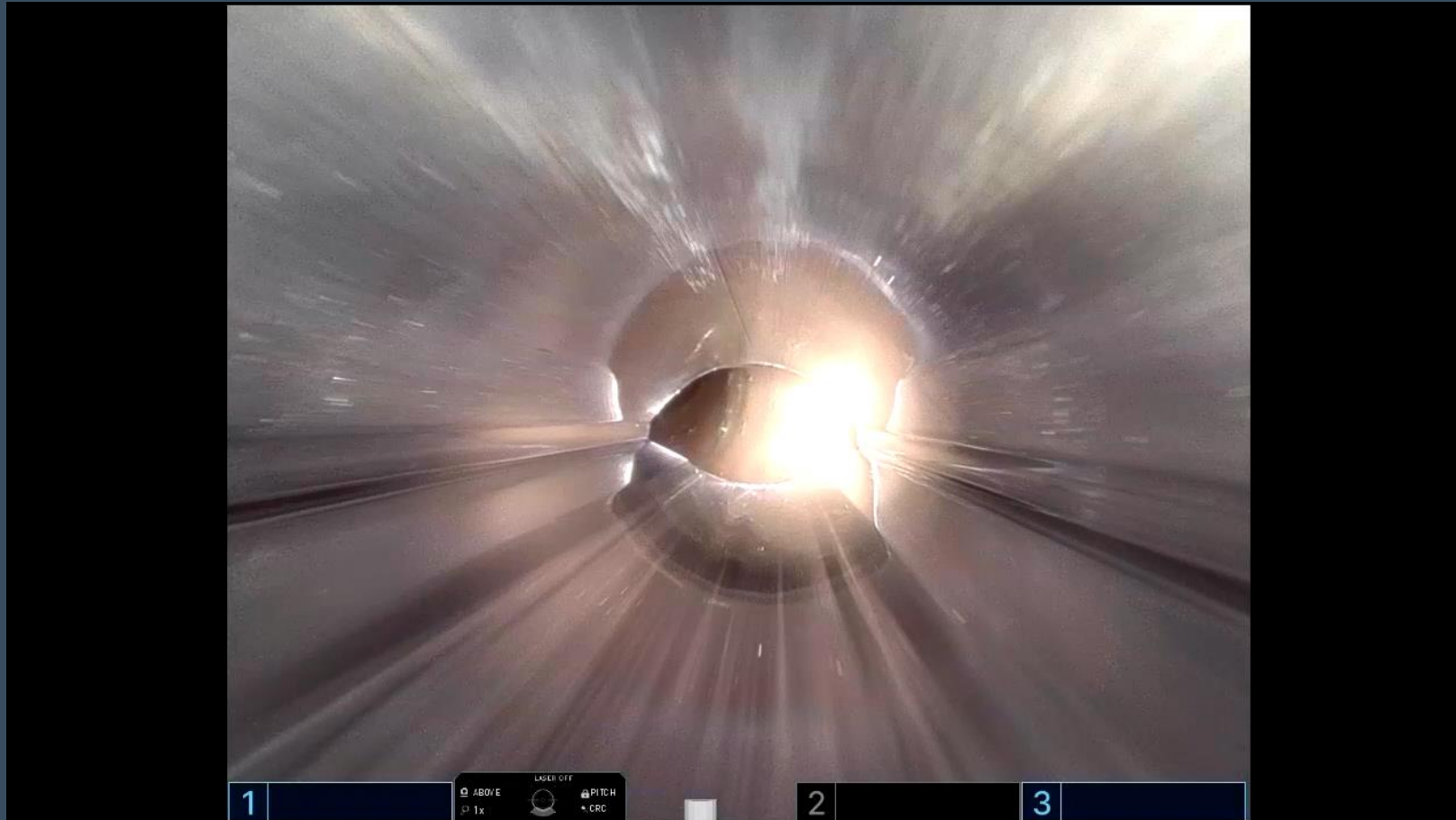
- New approach
- Similar principles to ESD
- Improved dexterity and visualization







ERSD after TNT



Endorobotic Surgery-ERSD

> [Ann Surg.](#) 2024 May 17. doi: 10.1097/SLA.00000000000006346. Online ahead of print.

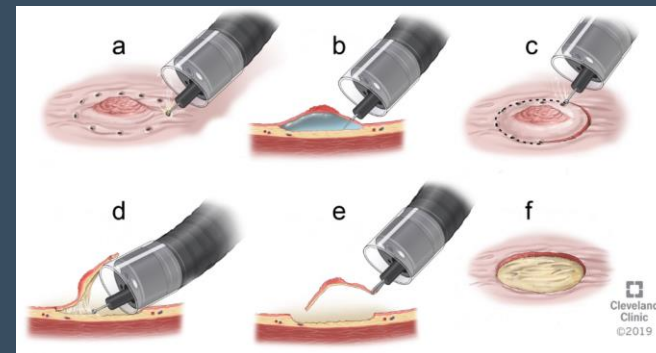
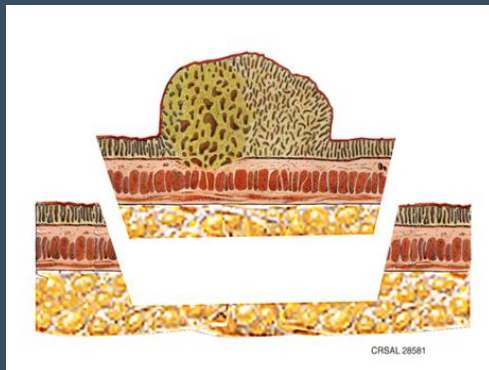
Early Experience with EndoRobotic Submucosal Dissection (ERSD): Pathologic and Short-term Outcomes in the First 28 Patients

Ali Alipouriani ¹, Ilker Ozgur ¹, Amit Bhatt ², Scott R Steele ¹, Joshua Sommovilla ¹,
Emre Gorgun ¹

- SP ERSD is safe and feasible at our institution
- Enhanced visualization and precision enables complex resections not possible with standard TAMIS

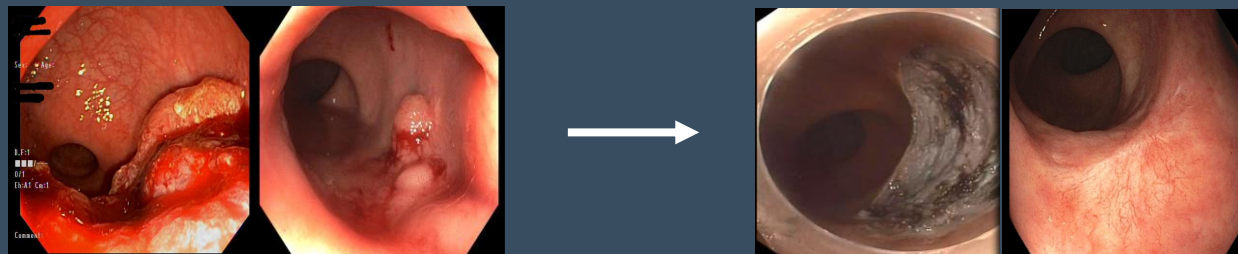
Advantages of **ESD** over Full Thickness Excision

- ESD allows plans to be intact for reconstructive organ resection
- ESD provides fast healing of the site and excellent “**re-epithelialization**”
 - may yield to low complication rates
 - superior functional outcomes compared to other full thickness LE techniques

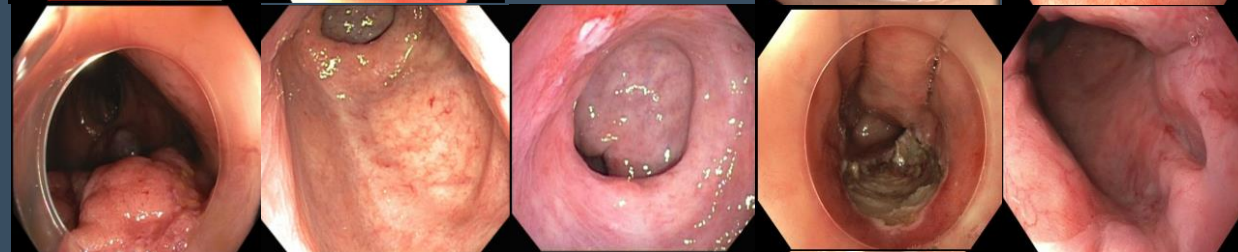


Diagnosis After TNT Regrowth After ESD Follow-up

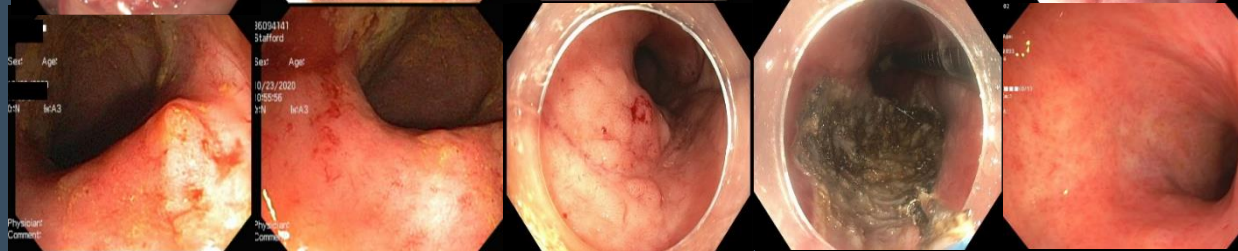
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2



3



4

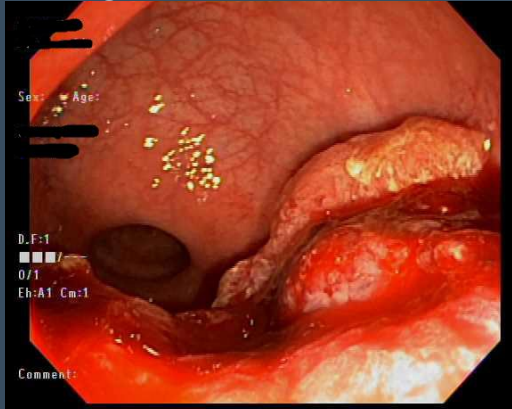


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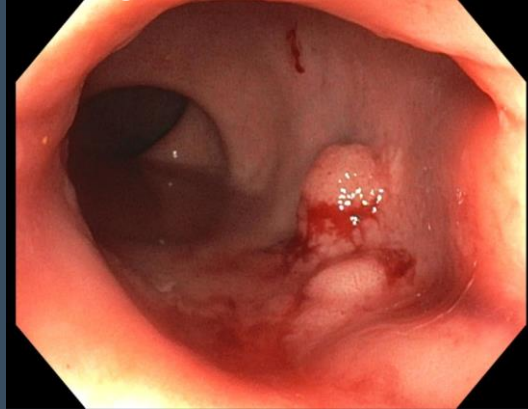


Diagnosis

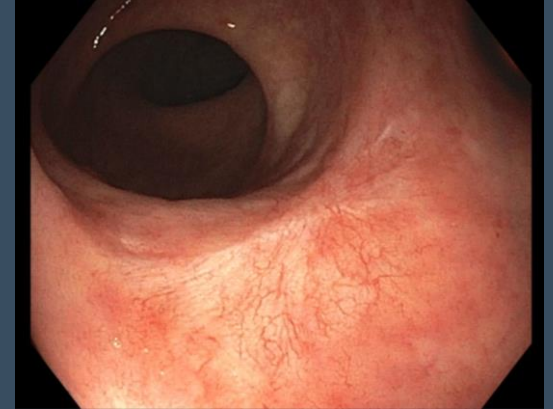
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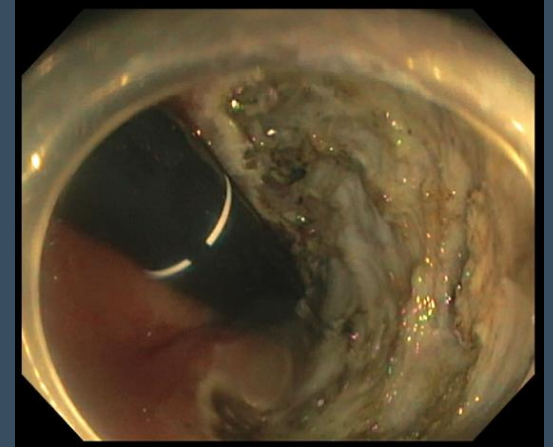
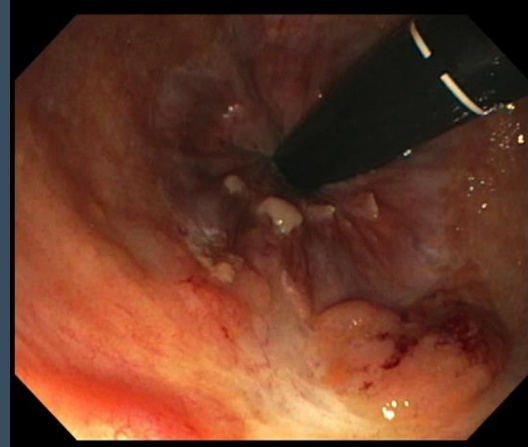
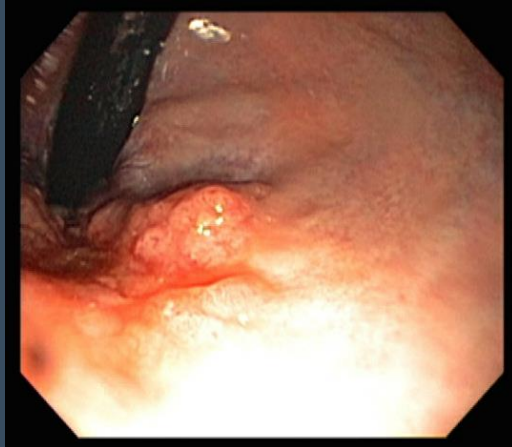
Regrowth After TNT



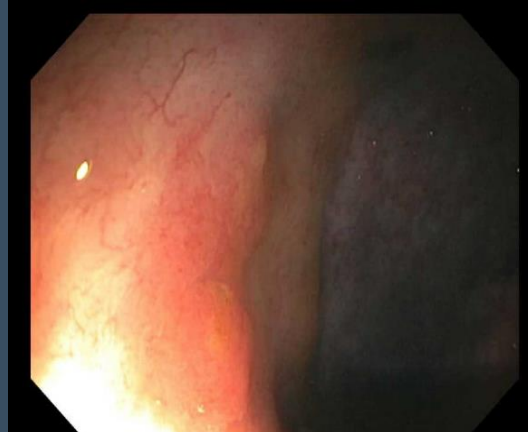
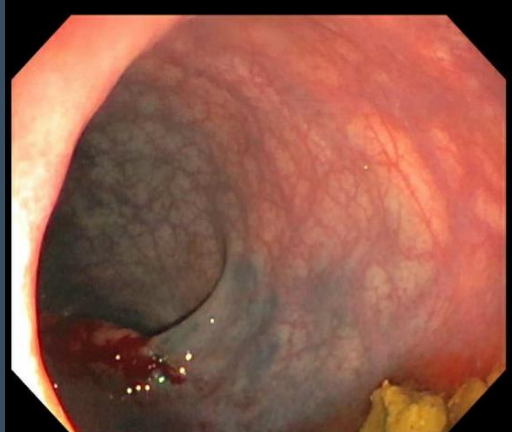
After ESD



#2



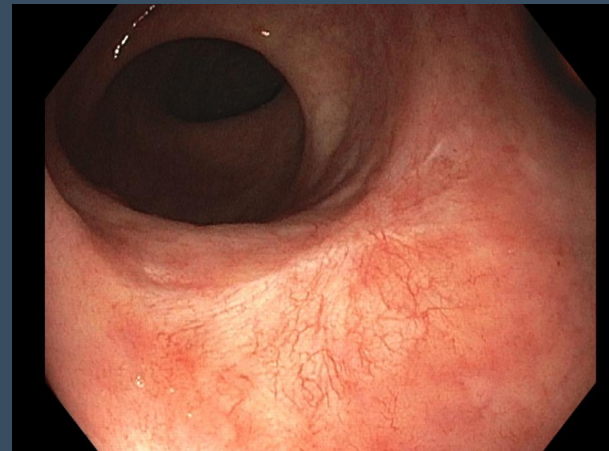
#3



<i>Pt #</i>	<i>Age</i>	<i>Gender</i>	<i>Stage</i>	<i>ESD reason</i>	<i>Time to regrowth</i>	<i>Histopathology</i>	<i>Margins</i>	<i>WW time</i>	<i>Disease Recurrence</i>	<i>Action</i>
1	72	F	T2N1b	near-CR	n/a	Tubulovillous adenoma with HGD	negative	61	no	WW
2	51	M	T3N1b	regrowth	15	T2 adenocarcinoma (2.5 mm)	<1mm	56	no	refused surgery
3	47	M	T1/2N1b	regrowth	25	Tubular adenoma with HGD	negative	49	no	WW
4	42	F	T2/3aN0	regrowth	11	Tubular adenoma with LGD	negative	16	yes	LAR (T3N0)
5	49	F	T3N2a	regrowth	22	Tubular adenoma with HGD	negative	44	no	WW
6	67	M	T3N1a	near-CR	n/a	T1 adenocarcinoma (0.5 mm)	negative	n/a	no	APR (T0N1)
7	66	M	T2N0	near-CR	n/a	Tubular adenoma	focally extends	27	no	WW
8	51	F	T3N0	near-CR	n/a	Colonic Mucosa	negative	16	no	WW
9	71	F	T3N0	regrowth	9	Tubular adenoma	negative	23	no	WW
10	83	M	T3N1a	regrowth	20	Tubulovillous adenoma with HGD	focally extends	52	no	WW
11	66	M	T3bN1a	near-CR	n/a	Tubular adenoma with HGD	negative	17	no	WW
12	53	F	T3bN1a	near-CR	n/a	Tubular adenoma with HGD	negative	10	no	WW
13	51	F	T3bN0	near-CR	n/a	Colonic Mucosa	negative	11	no	WW
14	41	M	T3N2	regrowth	12	T2 adenocarcinoma (8 mm)	<0.5mm	12	no	LAR (T0N0)
15	61	M	T3N0	Near-CR	n/a	T2 adenocarcinoma (foci)	<1mm	7	no	APR (T2N0)
16	40	M	T3aN2	Near-CR	n/a	Tubular Adenoma	negative	5	no	WW
17	55	Male	T3bN1	regrowth	3	Tubular Adenoma	negative	10	no	WW
18	67	F	T3N1	regrowth	10	T2 adenocarcinoma (10 mm)	positive	16	yes	LAR (T2N0)
19	80	M	T3N1	near-CR	n/a	Tubulovillous adenoma with HGD	negative	3	no	WW
20	74	M	T4bN0	regrowth	13	Adenocarcinoma	N/A	16	yes	APR (T2N0)

ESD after TNT

- pCR: 1 out of 6 (16.6%)
- cCR: 14 (70%)
- Combined complete Response: 15 (75%)



Conclusions

- TNT and W&W is a safe treatment strategy with good oncologic outcomes in appropriately selected and surveyed rectal cancer patients
- ESD and ERSD has the potential to expand the opportunity for organ-preservation after TNT
- Larger prospective trials with longer f/u are needed

Thank you!