THE ROLE OF SURGERY IN MSI-HIGH RECTAL CANCER

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EMORY
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Comprehensive Cancer Center

NCI
Designated
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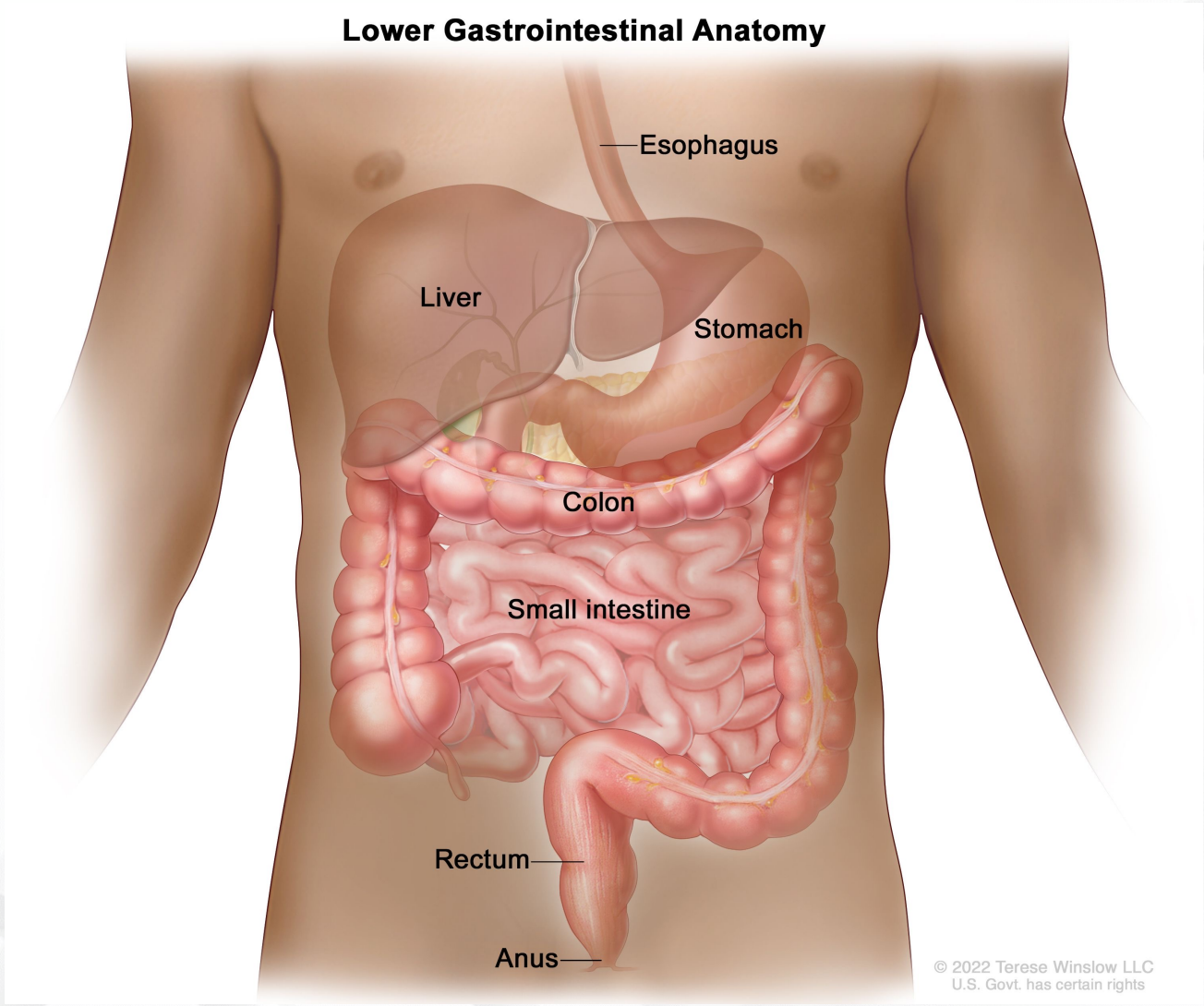
DISCLOSURES

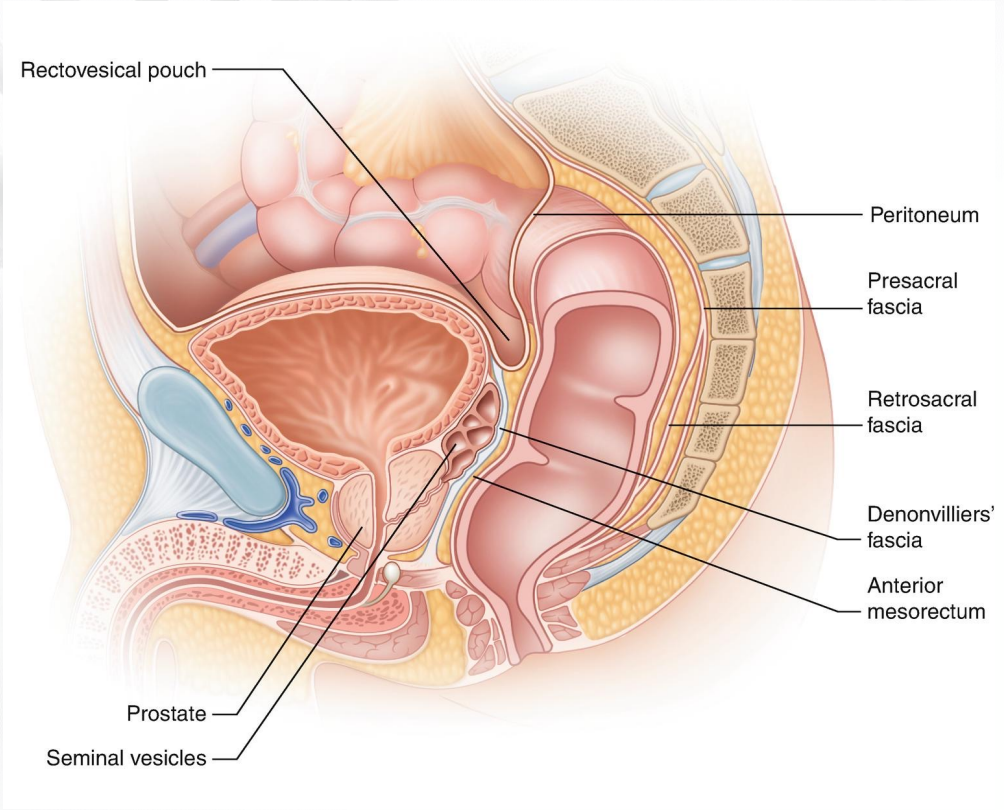
None

KEY CONCEPTS

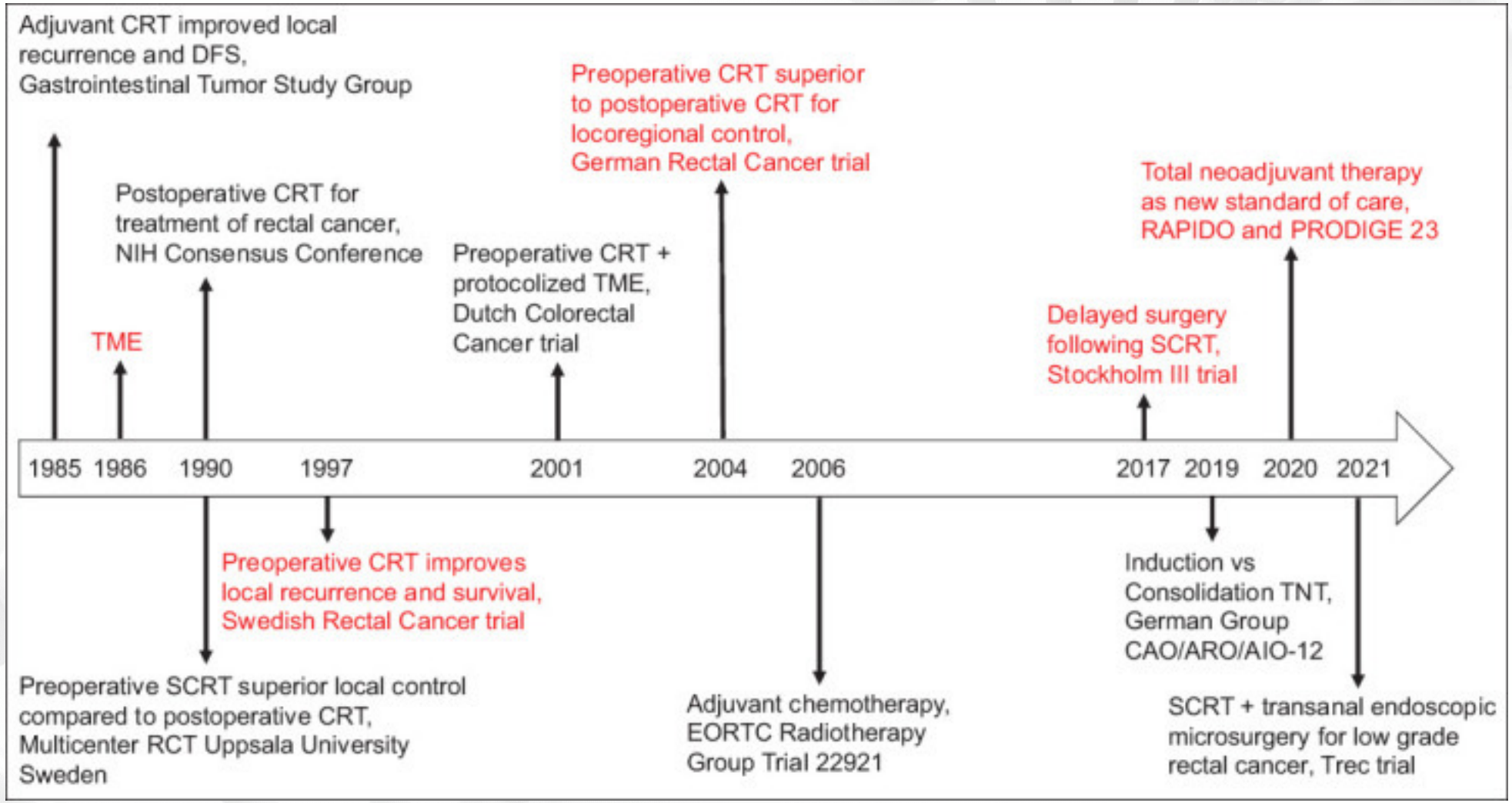
- MSI-H / MMRd rectal cancers represent 6-7% of rectal cancers (tiny numbers)
- Caution! No phase 3 data
- Incomplete responses to Immunotherapy reported
- Discordant endoscopy, radiology, and pathology response (can’t predict)
- Robotic surgical outcomes improved
- Impossible to tell with certainty a complete clinical response without resection

RECTUM ANATOMY





RECTAL CANCER TREATMENT OVER TIME



Iv AA et al.. *Ann Gastroenterol*. 2022;35(3)

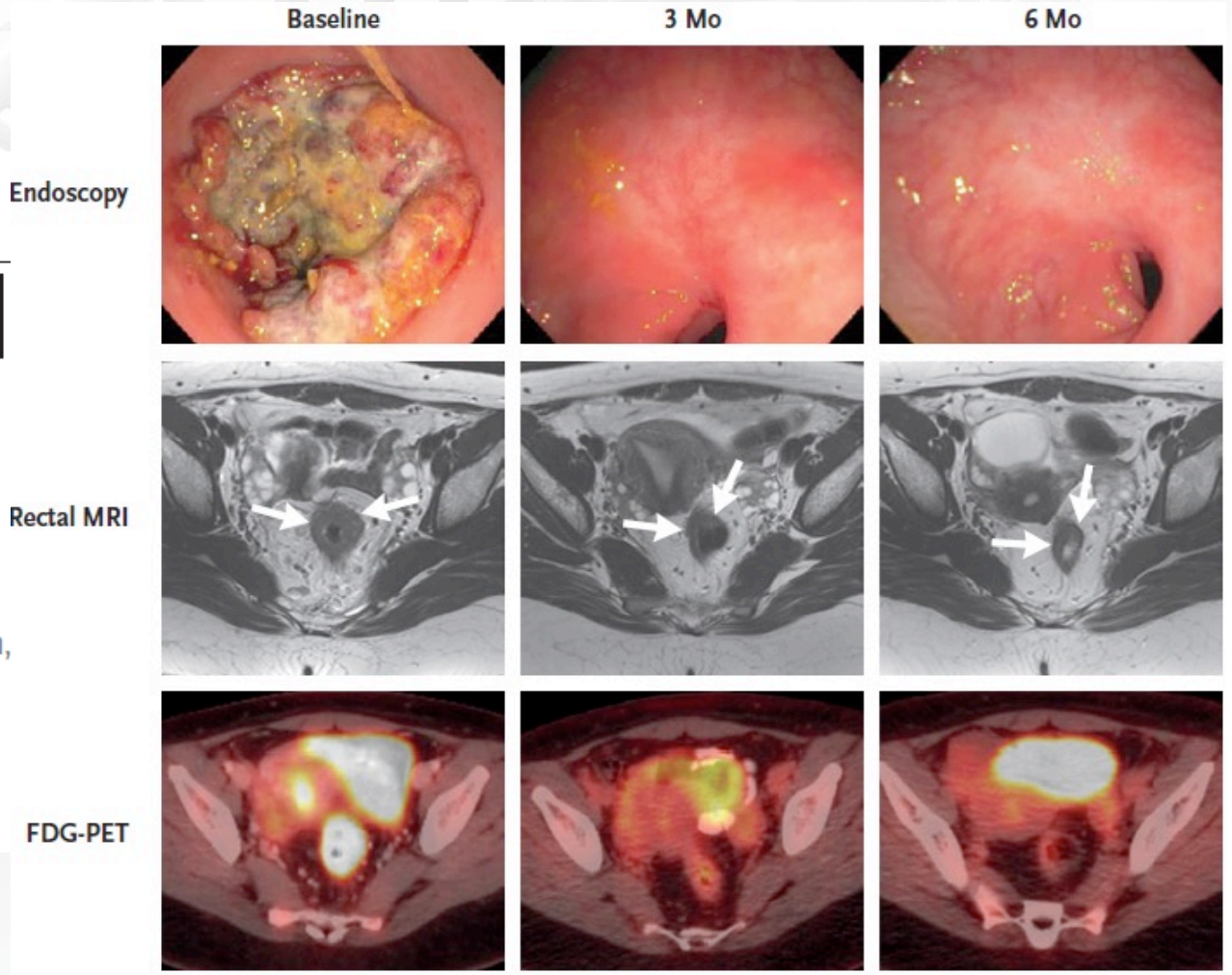
IMMUNOTHERAPY TREATMENT
MISMATCH REPAIR DEFICIENT RECTAL CANCER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.



IMMUNOTHERAPY TRIALS FOR MMR-D RECTAL CANCER

Study & Design	Population (Number of Patients)	Treatment Regimen	Outcomes
Cercek et al., Phase 2 (2022, 2025)	Stage II/III dMMR rectal cancer (12 in 2022; 49 in 2025)	Dostarlimab 500 mg IV q3wks × 6 months; nonoperative if cCR	100% cCR;
Wang et al., Multicenter cohort (2022)	Stage I–III dMMR rectal cancer (19)	Anti-PD-1 (various agents); nonoperative if cCR	100% 2-yr local RFS
Emiloju & Sinicrope, Review (2023)	dMMR rectal cancer Pembrolizumab: 8 Toripalimab: 6 Nivolumab: 5	Pembrolizumab toripalimab nivolumab	Pembrolizumab: 2/8 cCR, 2/8 surgery (1 pCR), ypT4N0 Toripalimab: 4/6 pCR Nivolumab: 3/5 pCR

Discordant endoscopy, radiology, and pathology response

NOT ALL THAT GLITTERS IS GOLD!

1. **High-Dose Chemotherapy with Autologous Bone Marrow Transplant (HDC+ABMT) for Breast Cancer**

Early promise: In the 1980s–1990s, it was believed that escalating chemotherapy doses followed by bone marrow rescue could cure advanced breast cancer

2. **Tecemotide (L-BLP25) Vaccine in Non–Small Cell Lung Cancer (NSCLC)**

Early promise: A MUC1-targeted therapeutic cancer vaccine showed encouraging results in a subgroup of patients post-chemoradiation

3. **Olaratumab in Soft Tissue Sarcoma**

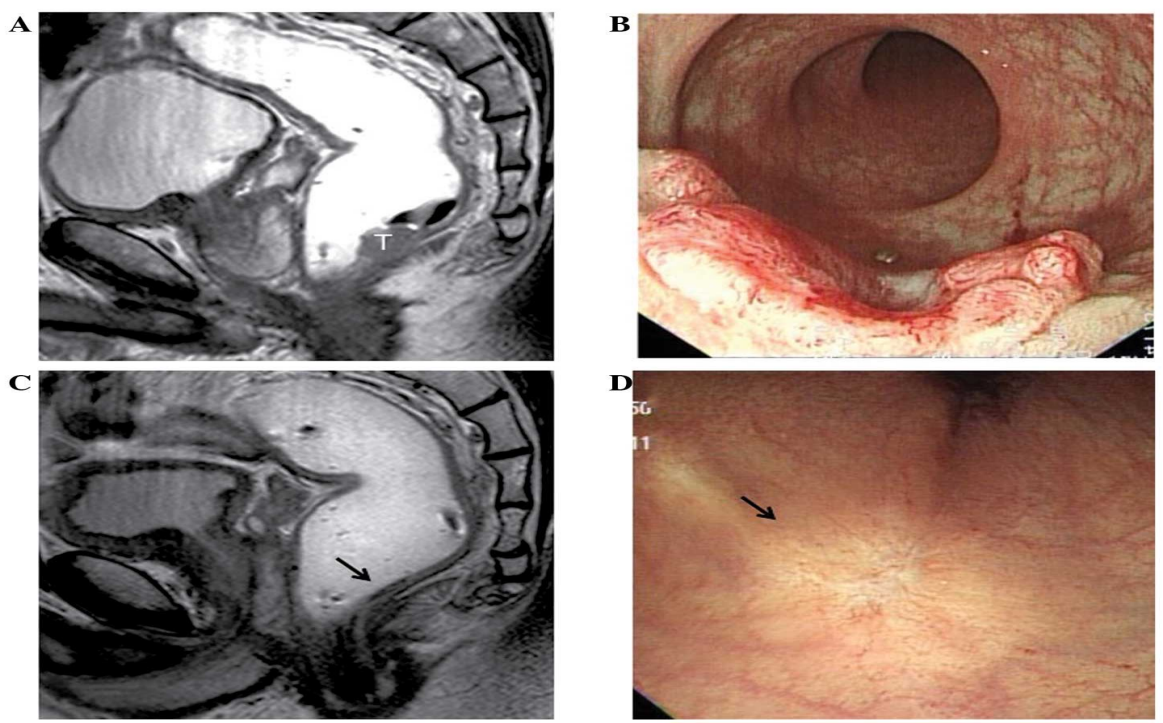
Early promise: This PDGFRα-targeting monoclonal antibody showed a surprising survival benefit in a Phase II trial when combined with doxorubicin

IMMUNOTHERAPY ADVERSE EVENTS

Event	Cohorts 1 and 2 (N = 124)	
	Grade 1 or 2†	Grade 3 or 4
	number of patients (percent)	
Dermatologic		
Rash or dermatitis	26 (21)	0
Flushing	2 (2)	0
Pruritus	24 (19)	0
Dry skin	5 (4)	0
Gastrointestinal		
Colitis	2 (2)	0
Constipation	4 (3)	0
Diarrhea	11 (9)	0
Nausea	8 (6)	0
Dry mouth	8 (6)	0
Constitutional		
Fatigue	28 (23)	0
Chills	4 (3)	0
Fever	3 (2)	0
Myalgia	3 (2)	0
Hot flashes	2 (2)	0
Arthralgia	9 (7)	0
Arthritis	2 (2)	0
Neurologic		
Headache	4 (3)	0
Encephalitis	0	1 (1)
Endocrine		
Diabetes	0	1 (1)
Hyperthyroidism	4 (3)	0
Hypothyroidism	16 (13)	1 (1)

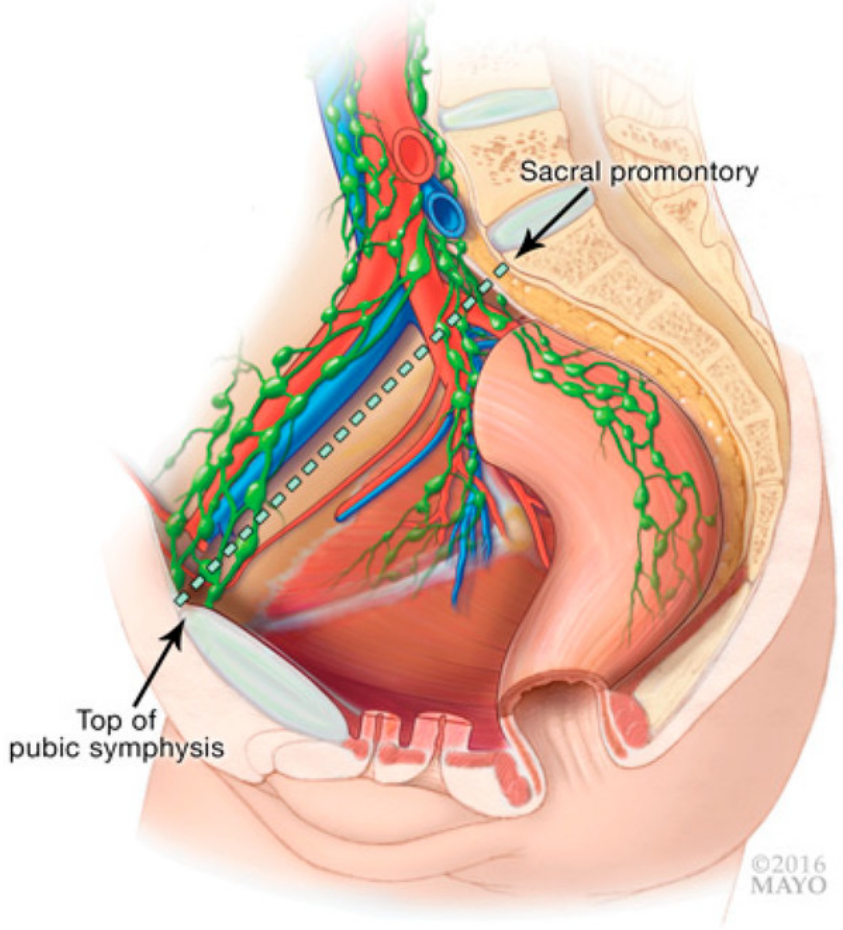
Cercek et al., NEJM 2022

ARE YOU SURE THERE IS NO REMAINING DISEASE?



Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC
MRI	36–72	43–90	36–55	77–89	0.55–0.79
Endoscopy	72–94	61–85	63–78	80–92	0.80–0.84
Combined*	91	75	—	91	0.84

UPPER RECTAL VS. SIGMOID CANCER



Location	LR Rate (%)	5-year OS (%)	3-year DFS (%)
Upper Rectal Cancer	2–4	~80–85	~73–77
Colon Cancer	2–4	~80–85	~75–80
Mid/Low Rectal CA	6–12	~75–80	~70–75

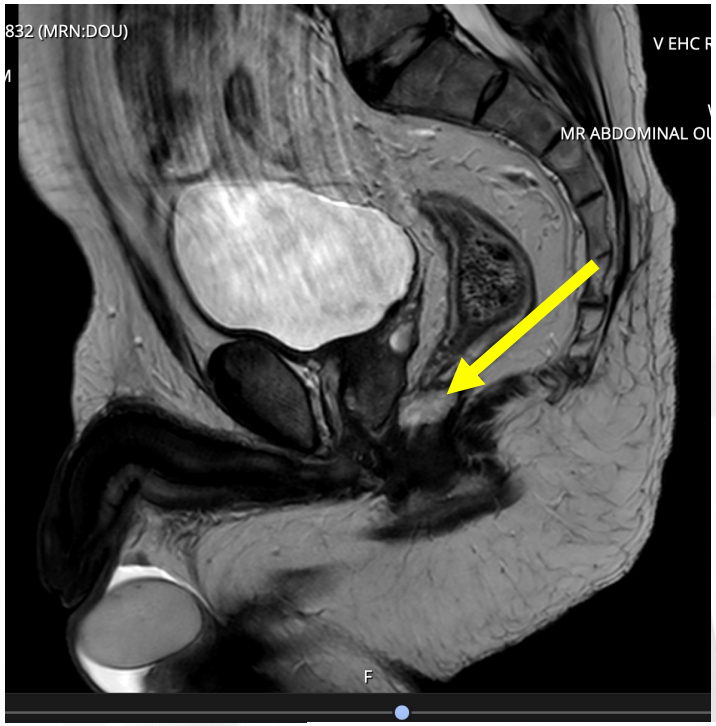
ROBOTIC PROCTECTOMY FOR RECTAL CANCER OUTCOMES IMPROVED

Era/Approach	Major Complication Rate (%)	30-day Mortality (%)	3-year OS (%)
Open (2005–2010)	22–28	1.5–2.0	78–85
Laparoscopic (2010–2016)	19–25	1.0–1.5	78–93
Robotic (2011–2016)	13–19	0.4–1.2	86–95
Modern Robotic (2017–2025)	12–16	0.4–1.0	93–95

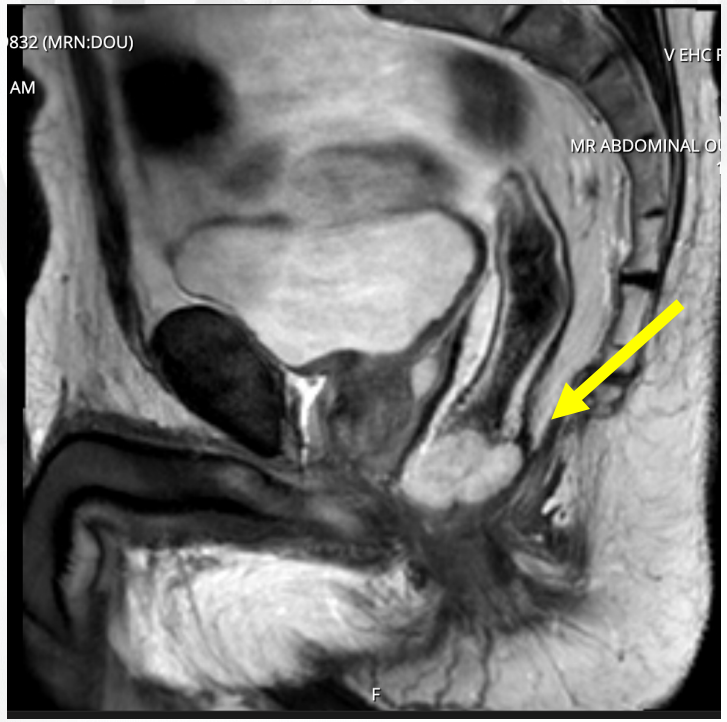
COST AND COMPLICATIONS OF TREATMENT

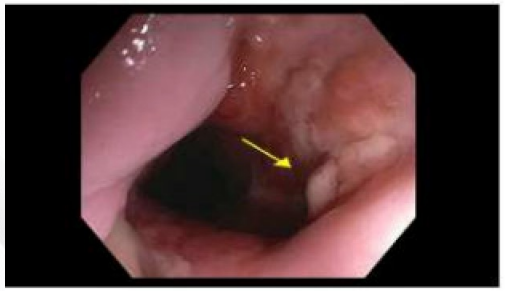
Treatment Strategy	Estimated 6-Month Drug Cost (USD)	Major Grade ≥3 Side Effects (%)	Most Common Side Effects (≥10%)	Severe Long-term Toxicity
Immunotherapy (PD-1 inhibitor, 6 month)	$70,000–$90,000	0–10%	Fatigue, pruritus, diarrhea, hypothyroid	Rare (endocrinopathy, colitis)
Neoadjuvant Chemoradiotherapy	$2,000–$10,000	15–25%	Diarrhea, proctitis, fatigue, cytopenia	Bowel, sexual, urinary dysfunction
Upfront Surgery (TME)	$15,000–$30,000	10–20% (surgical complications)	Wound infection, anastomotic leak, ileus	Low (stoma, bowel dysfunction)

BEWARE OF IMMUNOTHERAPY IN SETTING OF INFLAMMATORY BOWEL DISEASE

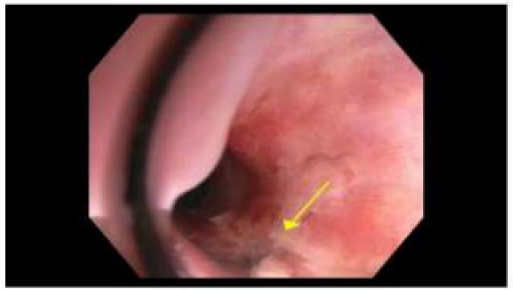


4 Months Pembrolizumab





4 Anus slight ulceration anterior



5 Anus with slight ulceration anterior

6 Anus slight ulceration anterior

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