Neoadjuvant Chemoradiotherapy for Rectal Cancer: Overrated

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Grand Rounds

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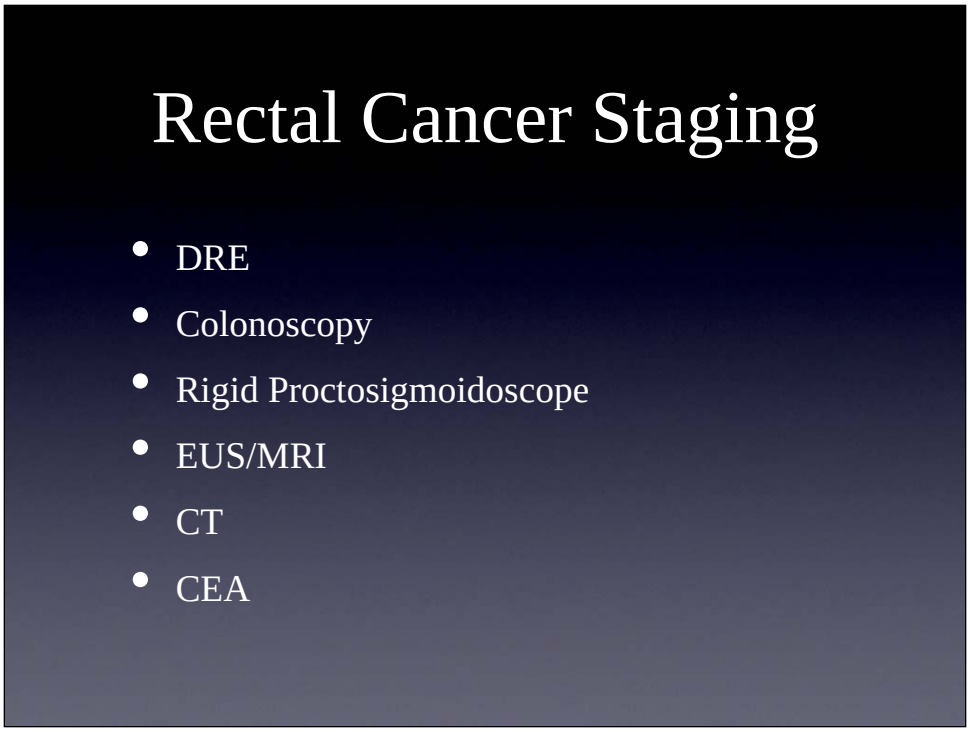


Digital-rectal examination and/or rectovaginal exam and rigid proctoscopy to determine if sphincter-saving surgery is possible.[7,18,19]

Complete colonoscopy to rule out cancers elsewhere in the bowel.[7]

Pan-body computed tomography (CT) scan to rule out metastatic disease.[7]

Magnetic resonance imaging (MRI) of the abdomen and pelvis to determine the depth of penetration and the potential for achieving negative circumferential (radial) margins, as well as to identify locoregional nodal metastases and distant metastatic disease.[18]

Endorectal ultrasound (ERUS) with a rigid probe or a flexible scope for stenotic lesions to determine the depth of penetration and identify locoregional nodal metastases.[19,21]

Positron emission tomography (PET) to image distant metastatic disease.[18]

Measurement of the serum carcinoembryonic antigen (CEA) level for prognostic assessment and the determination of response to therapy.[22,23]

Current Recommendations

- Neoadjuvant chemoradiation for stage II/III
  - Tumor regression, downstaging and improvement in resectability, and a higher rate of sphincter preservation and local control

NCI Recommendations

Standard of Care

- Neo-Adjuvant Therapy
  - Radiation
  - Chemotherapy: 5-FU, Leucovorin, Oxaliplatin
- Surgical Excision
  - Local Excision
  - Low Anterior Resection
  - Abdominal Perineal Resection

TNM Staging

Table 2. TNM Staging System for Colorectal Cancer. *

Stage	TNM Classification	Five-Year Survival
		%
I	T1–2, N0, M0	>90
IIA	T3, N0, M0	60–85
IIB	T4, N0, M0	
IIIA	T1–2, N1, M0	25–65
IIIB	T3–4, N1, M0	
IIIC	T (any), N2, M0	
IV	T (any), N (any), M1	5–7

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- Tis: Carcinoma in situ
- T1: Tumor invades submucosa
- T2: Tumor invades muscularis propria
- T3: Tumor penetrates muscularis propria and invades subserosa
- T4: Tumor directly invades other organs or structures or perforates visceral peritoneum

Nodal status (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No metastases in regional lymph nodes
- N1: Metastases in one to three regional lymph nodes
- N2: Metastases in four or more regional lymph nodes

Distant metastases (M)

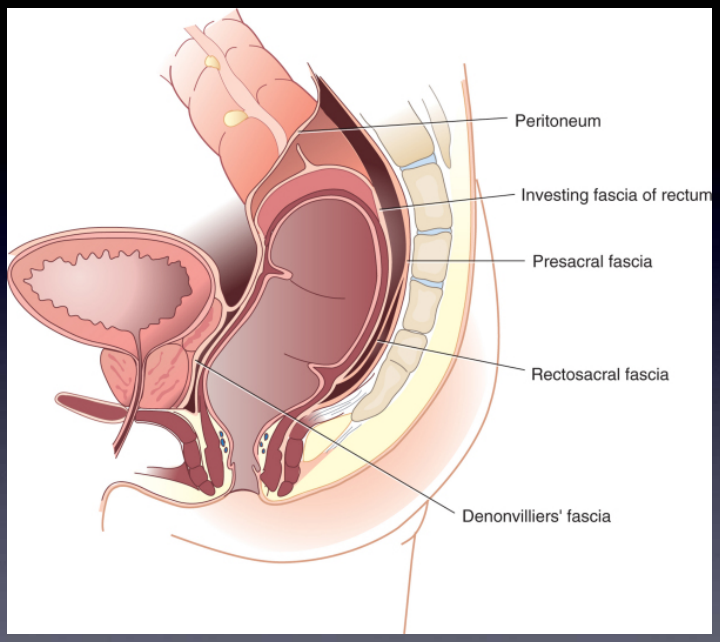
- MX: Presence or absence of distant metastases cannot be determined
- M0: No distant metastases detected
- M1: Distant metastases detected

* The information is from Greene et al.[7]

Dukes Staging

TNM Classification (American Joint Commission on Cancer)				Dukes' Classification
Stages	T	N	M	Stages
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	B1
Stage II	T3	N0	M0	B2
	T4	N0	M0	B2
Stage III	T1, T2	N1 or N2	M0	C1
	T3, T4	N1 or N2	M0	C2
Stage IV	Any T	Any N	M1	D

Dukes' classificationA: Limited to the bowel wall
B: Through the bowel wall. B1: tumors invade into the muscularis propria B2: tumors completely penetrate the smooth muscle layer into the serosa
C: Regional lymph nodes metastasis: C1: tumors invade the muscularis propria with fewer than four positive nodes. C2: tumors invade the muscularis propria with more than four positive nodes
D: Distant mets


Peritoneum
Investing fascia of rectum
Presacral fascia
Rectosacral fascia
Denonvilliers' fascia

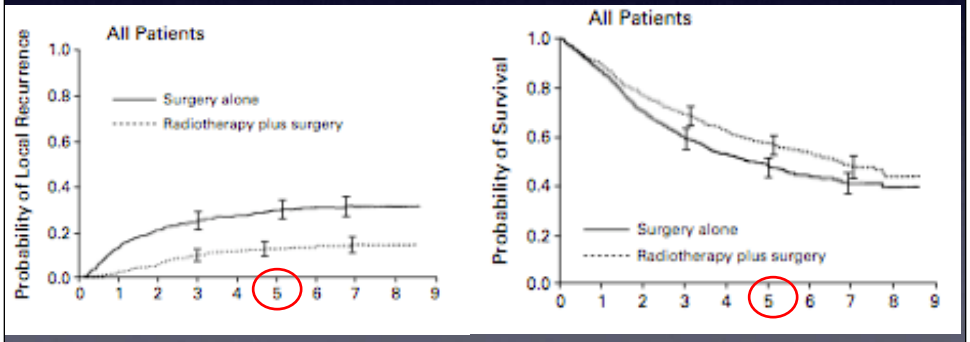
Major Studies

- Swedish Rectal Cancer Trial - 1997
- Heald TME Paper – 1998
- German Rectal Cancer Study Group - 2004
- Dutch Colorectal Cancer Group - 2007

Swedish Rectal Cancer Trial

Surgery: 27%
XRT + Surgery: 11%

Surgery: 48%
XRT + Surgery: 58%



NEJM 1997; 336: 980-7

1168 Patients younter than 80. 25 Gy – 5 fractions in one week followed by surgery in 1 week vs surgery alone.

Rectal Cancer: The Basingstoke Experience of TME

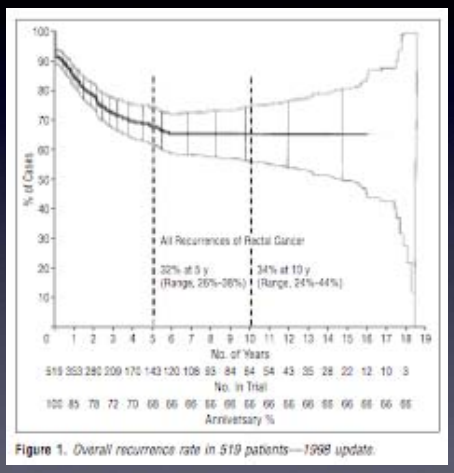


Figure 1. *Overall recurrence rate in 519 patients—1998 update.*

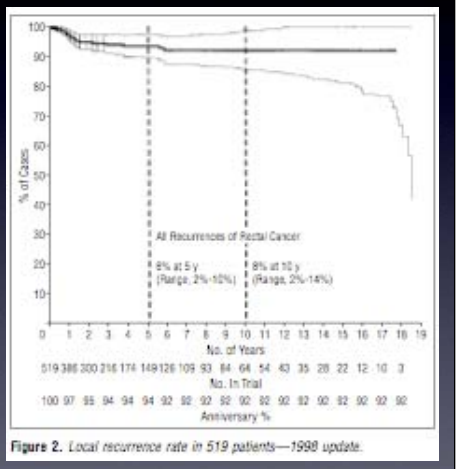


Figure 2. *Local recurrence rate in 519 patients—1998 update.*

Heald, RJ, Arch Surg 1998; 133:894-9

All Recurrence: 32% at 5y and 34% at 10y
Local Recurrence: 6% at 5y and 8% at 10y
Disease Free Survival: 80% at 5y and 78% at 10y

Dutch Colorectal Cancer Group: TME Trial

	Local Recurrence 5 Year	Overall Survival 5 Year
TME	10.9%	64.2%
XRT + TME	5.6%	63.5%

Ann Surg 2007;246:693-701

1861 randomized to TME vs. 25 Gy in 5 fractions over 5-7 days followed by TME NO chemo

Subgroup analysis suggests XRT most beneficial in pts with nodal involvement and tumor distance 5-10 cm from anal verge

Preoperative vs. Postoperative Chemoradiotherapy for Rectal Cancer: German Rectal Cancer Study Group

- Preoperative Chemoradiotherapy
  - Decreased local recurrence
  - Increase sphincter preservation
  - Less acute and late toxicity
  - Same overall survival

Sauer NEJM 2004;351:1731-40

Chemo: 5-FU

Sauer NEJM 2004;351: 1731-40

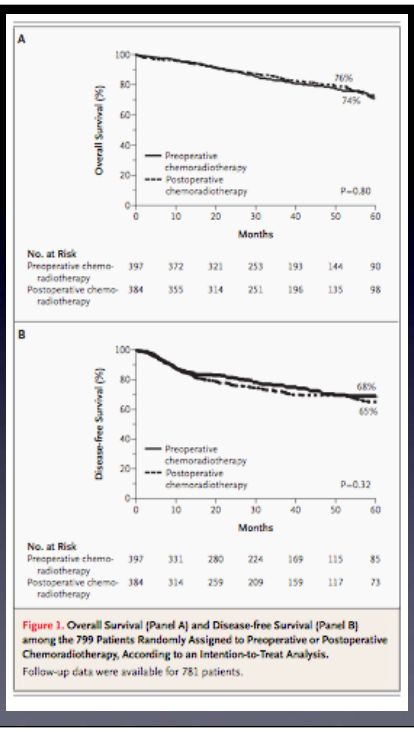


Figure 1. Overall Survival (Panel A) and Disease-free Survival (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.

Follow-up data were available for 781 patients.

Sauer NEJM 2004;351: 1731-40

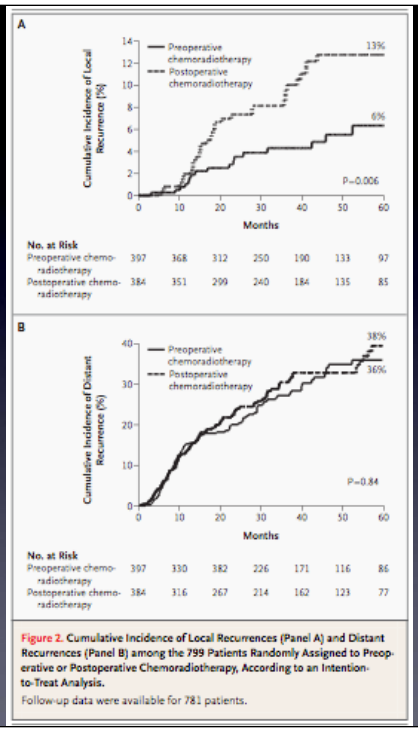


Figure 2. Cumulative Incidence of Local Recurrences (Panel A) and Distant Recurrences (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.

Follow-up data were available for 781 patients.

Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.

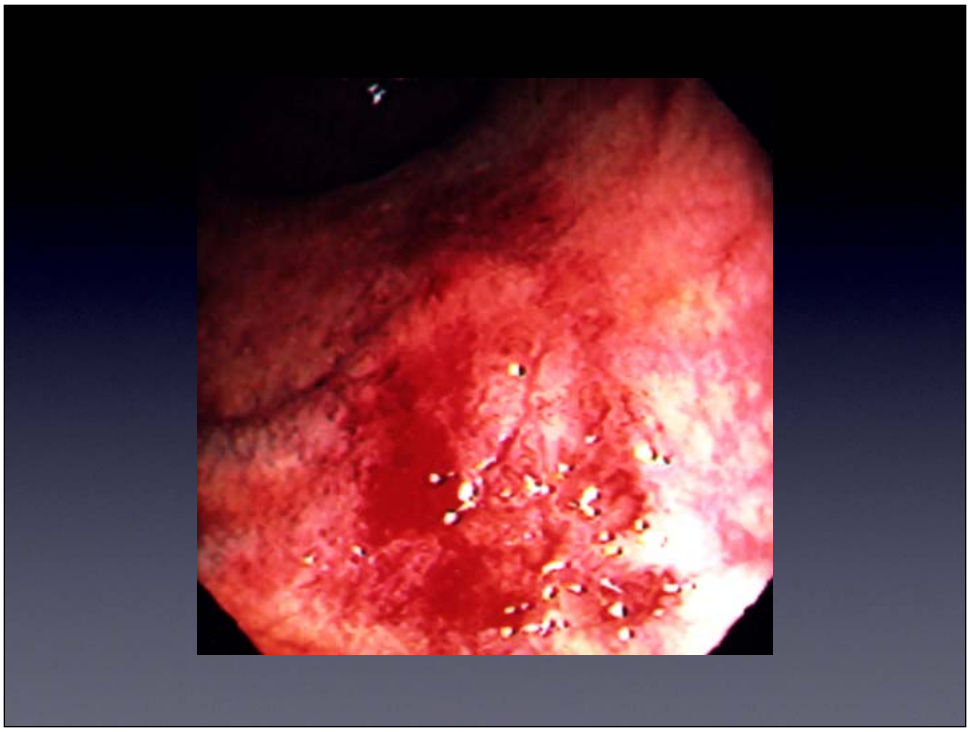
Variable	Preoperative Chemoradiotherapy (N=415)	Postoperative Chemoradiotherapy (N=384)	P Value
Abdominoperineal resection deemed necessary — no. (%)	116 (28)	78 (20)	
Sphincter-preserving surgery performed — no./total no. (%)	45/116 (39)	15/78 (19)	0.004

Sauer NEJM 2004;351: 1731-40

Table 5. Grade 3 or 4 Toxic Effects of Chemoradiotherapy, According to Actual Treatment Given.*

Type of Toxic Effect	Preoperative Chemoradiotherapy (N=399)	Postoperative Chemoradiotherapy (N=237)	P Value
	% of patients		
Acute			
Diarrhea	12	18	0.04
Hematologic effects	6	8	0.27
Dermatologic effects	11	15	0.09
Any grade 3 or 4 toxic effect	27	40	0.001
Long-term			
Gastrointestinal effects†	9	15	0.07
Strictures at anastomotic site	4	12	0.003
Bladder problems	2	4	0.21
Any grade 3 or 4 toxic effect	14	24	0.01

Sauer NEJM 2004;351:1731-40



Timing of Surgery

- Group A: 28-41 days (4-6 weeks) b/w CRT and surgery
- Group B: 42-56 days (6-8 weeks) b/w CRT and surgery
  - Does not improve CRT response
  - Does not improve sphincter preservation
  - Does not decrease morbidity or local reccurrence

Lim Annals of Surg 2008;248:243-51

Summary of Chemoradiotherapy

- Advantages
  - Decrease Local Recurrence
  - Improved Sphincter Preservation
- Disadvantages
  - Diarrhea
  - Wound Healing Complications
  - Sexual/Bladder/Sphincter Dysfunction
  - Radiation Enteritis
  - Intestinal Obstruction
  - Acute/Chronic Toxicity
  - No significant overall survival difference


THIS IS MY
SHIRT