Neoadjuvant Therapy for Rectal Cancer: OVERRATED

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General Surgery Grand Rounds
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American Joint Committee on Cancer (AJCC—7th Edition) Rectal Cancer TNM Staging

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria[1]
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into pericolorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneum[2]
- T4b Tumor directly invades or is adherent to other organs or structures[2,3]

Regional Lymph Nodes (N)*

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1–3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2–3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in 4 or more regional lymph nodes
- N2a Metastasis in 4–6 regional lymph nodes
- N2b Metastasis in 7 or more regional lymph nodes

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (for example, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

American Joint Committee on Cancer-- http://www.cancerstaging.org/staging/posters/colon8.5x11.pdf

Stage-Related Prognosis

Stage	Grouping	Five-Year Survival
I	T1-2, N0, M0	>90%
IIA	T3, N0, M0	60%–85%
IIB	T4, N0, M0	60%–85%
IIIA	T1-2, N1, M0	55%–60%
IIIB	T3-4, N1, M0	35%–42%
IIIC	T-1-4, N2, M0	25%–27%
IV	T1-4, N0-2, M1	5%–7%

Meredith KL, et al. Surg Clin North Am, 2009.

Treatment of Locally Advanced Rectal Cancer

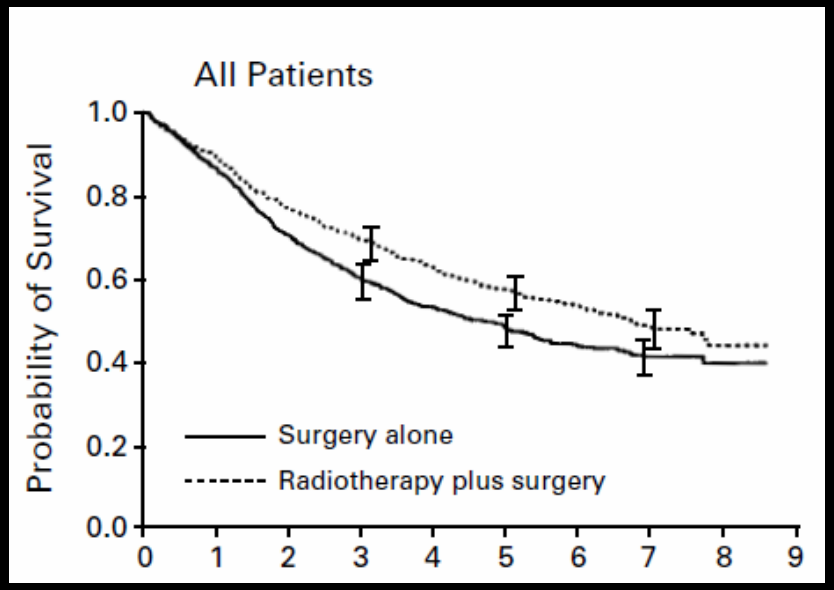
- **Surgical**
  - Low anterior resection (LAR)
  - Abdominoperineal resection (APR)
  - Total mesorectal excision (TME)
    - Gold standard for middle and lower third rectal cancer
- **Adjuvant Chemoradiotherapy**
  - Stage II and III rectal cancer

John L. Cameron. Current Surgical Therapy, 2008.
Sauer R, et. al. NEJM, 2004.

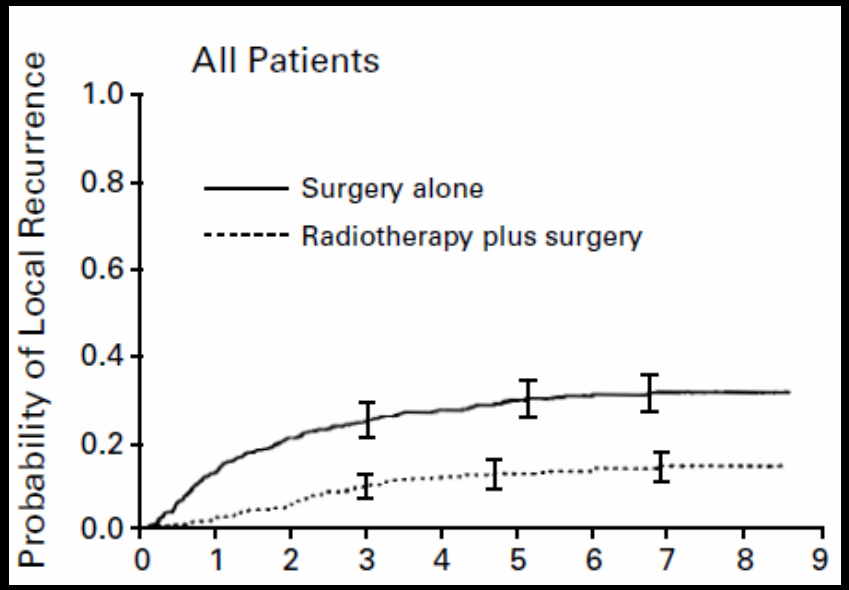
Swedish Rectal Cancer Trial

- RCT
- 1168 patients total—5 year follow-up
  - 583 pre-op radiotherapy vs. 585 surgery alone

Increased 5-year overall survival
58% vs. 48% (p=0.004)



Decreased local recurrence
11% vs. 27% (p<0.001)



Swedish Rectal Cancer Trial. NEJM, 1997.

Swedish Rectal Cancer Trial—Study Limitations

- No TME performed
- No post-operative adjuvant therapy
- Irradiated group
  - Increased bowel movements
  - Incontinence
  - Urgency
  - Soiling

Swedish Rectal Cancer Trial. NEJM, 1997.

Meta-Analysis—14 RCTs

- 6426 patients total
- Neoadjuvant radiotherapy vs. surgery alone
- Increased 5-year overall survival (OR, 0.84, P-0.03)
- Decreased local recurrence (OR, 0.49, p<0.001)
- Significantly increased post-operative complications (57.4% vs. 42.3%, p<0.001)
  - Sepsis, anastomotic leak, and intestinal obstruction

Cammà, et. al. JAMA, 2000.

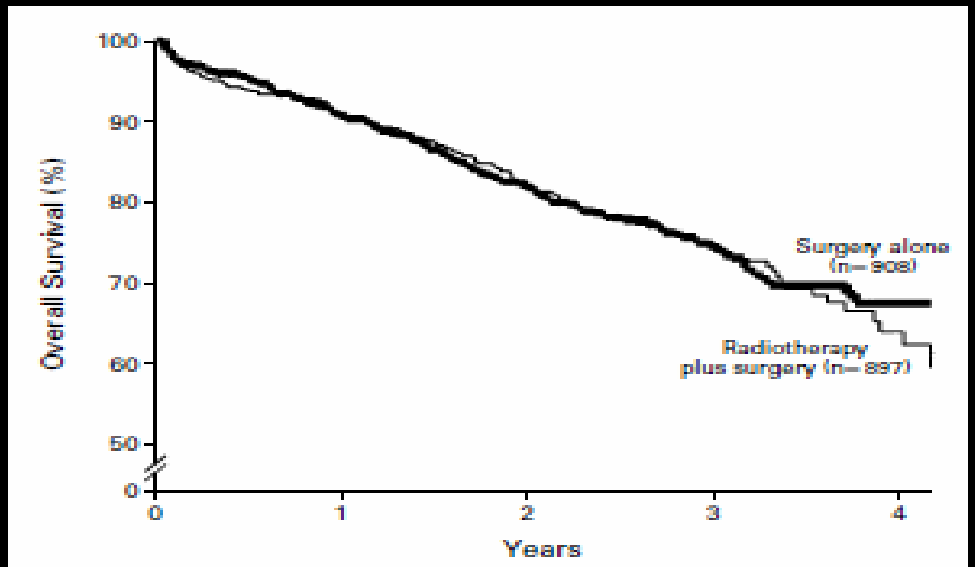
Meta-Analysis—14 RCTs Study Limitations

- Differences in the baseline severity of disease
- Variations in irradiation techniques and doses
- Substantial variability between surgical procedures
- “magnitude of the overall effect is small but clinically relevant”

Cammà, et. al. JAMA, 2000.

Pre-op Radiotherapy with TME- The Dutch Colorectal Cancer Group

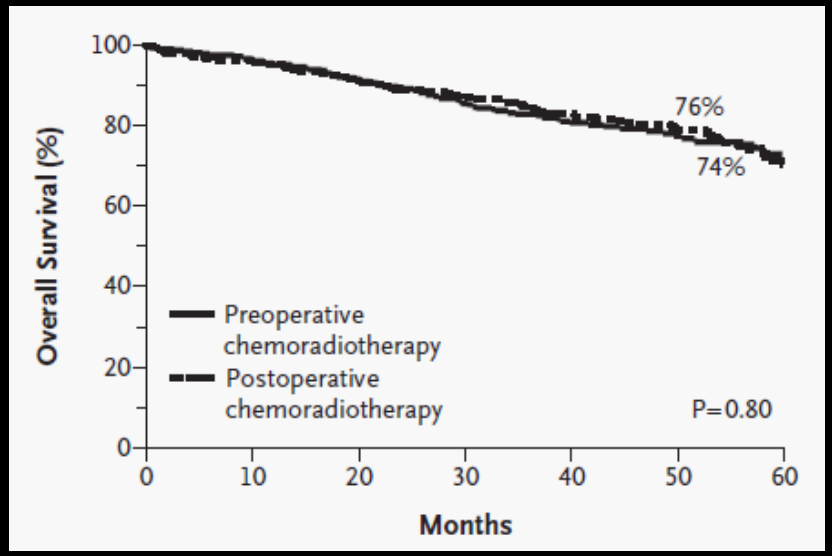
- Multicenter, RCT—1861 pts., 2-yr follow-up
  - Pre-op Radiotherapy and TME vs. TME alone
- No overall survival benefit (82% vs. 81.8%, p=0.84)
- No difference in distant and overall recurrence rates
- Increased blood loss (1000mL vs. 900mL, p<0.001) and perineal wound complications (26% vs. 18%, p=0.05)

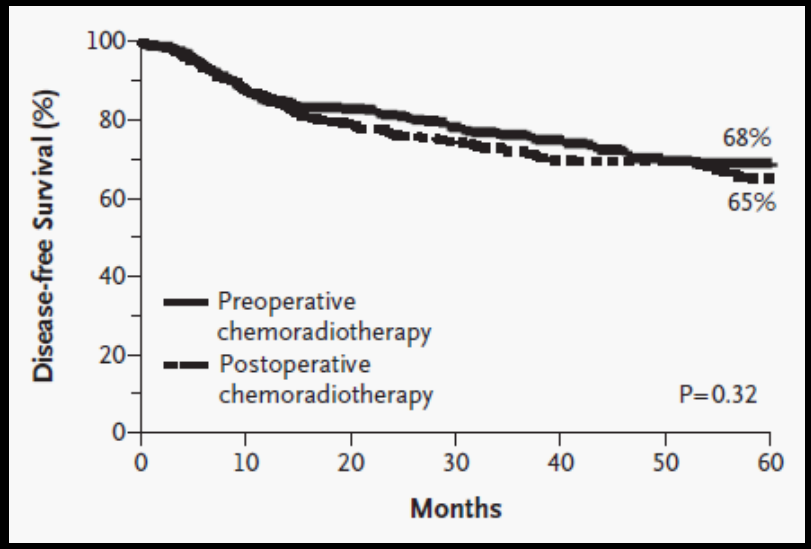


Kapiteijn, et. al. NEJM, 2001.

Neoadjuvant Vs. Adjuvant Chemoradiotherapy- German Rectal Cancer Study Group

- RCT—823 patients
  - 421 pre-op vs. 402 post-op chemoradiotherapy
  - 5-FU and identical irradiation
  - TME performed in all patients
- No significant overall or disease-free survival

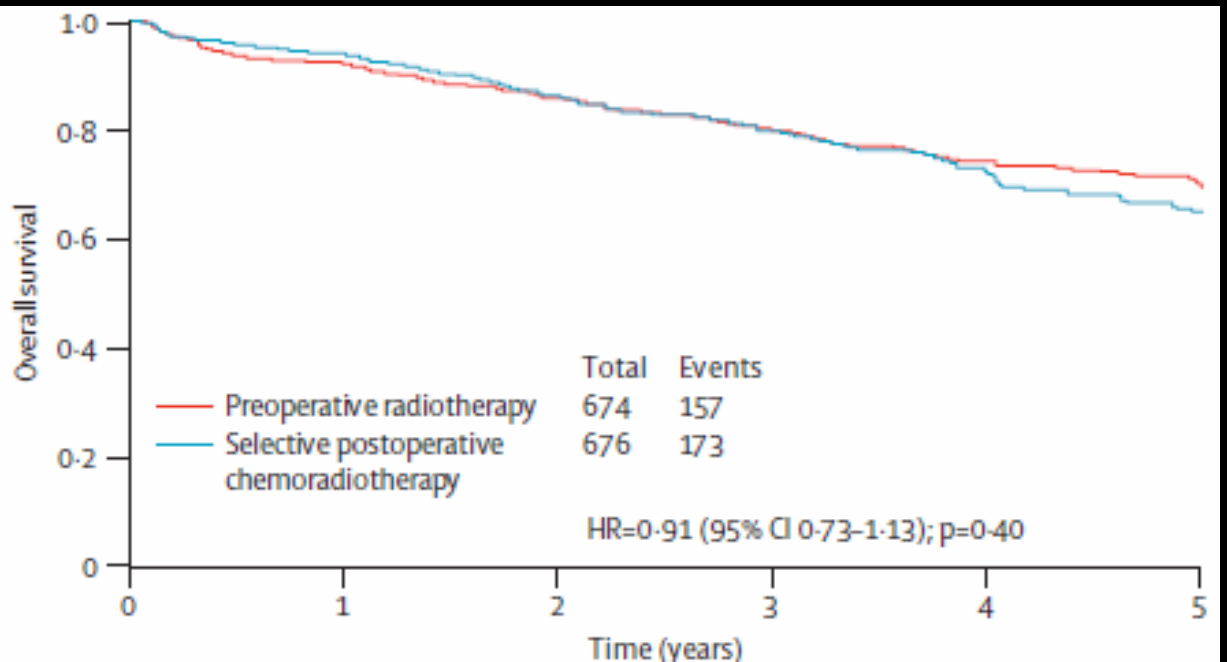




Sauer, et. al. NEJM, 2004.

Preop vs. Selective Post-op Chemoradiotherapy- Multicenter, RCT

- 80 centers, 4 countries—1350 patients
  - Post-op chemoradiotherapy for pts. with surgically positive margins
  - TME in 92% of cases



- No overall survival benefit

Sebag-Montefiore D, et. al. Lancet, 2009.

Preop vs. Post-op Chemoradiotherapy-Multicenter, RCT

- RCT—267 patients, T3-T4 or node +
  - Leucovorin and 5-FU
- No 5-year overall survival benefit (74.5% vs. 65.6%, p=0.693)
- No difference in locoregional recurrence (10.7% for both arms, p=0.693)
- Increased grade 4 diarrhea (24% vs. 13%)

Roh MS, et. al. J Clin Oncol, 2009.

CONCLUSIONS

- No benefit of neoadjuvant therapy in 5-year overall survival
- Increased complications from neoadjuvant radiotherapy
- Should perform TME with locally advanced rectal cancer

Neoadjuvant therapy is overrated!!!