

ADJUVANT AND NEOADJUVANT THERAPY FOR RECTAL CANCER

Main Components of Adjuvant Therapy:

1. Radiation Therapy (RT) to the pelvis.
2. 5-FU-based Chemotherapy (CT).

Goals of CT:

1. Increase tumor radiation sensitivity.
2. Decrease the incidence of distal metastases.

Goals of RT:

1. Improve local control.
2. Increase margin-negative resection rates - in the preoperative setting.
3. Increase sphincter preservation - in the preoperative setting.

Primary tumor (T)	
T1	Invades submucosa
T2	Invades muscularis propria
T3-T4	
Serosa	
T3	Invades into subserosa, but not through serosa
T4	Invades through serosa into free peritoneal cavity or into contiguous organ
No Serosa	
T3	Invades through muscularis propria
T4	Invades contiguous organs
Regional lymph nodes (N)	
N0	No lymph node metastasis
N1	Lymph node metastasis in 1-3 nodes
N2	Lymph node metastasis in 4 or more nodes
N3	Lymph node metastasis in central nodes
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastases present

I. Preoperative Radiation +/- Chemotherapy

Several theoretical advantages to the use of preoperative RT have led to its use in recent trials:

1. Reduction in size of tumor increases the potential for sphincter preservation.
2. Decreased risk of local failure and distant metastases from cells shed at operation.
3. Decreased risk of late radiation enteritis because the small bowel can be more readily excluded from the radiation field in the preoperative setting.
4. Some tumors considered unresectable may become resectable with therapy.
5. Tumor cells are well oxygenated when treated preoperatively because there has been no surgical manipulation of the blood supply to the tumor.

6. No delay of therapy as in some cases of postoperative therapy due to operative morbidity.
7. Systemic therapy is initiated earlier than in postoperative therapy.
8. Preoperative RT maybe more dose efficient then postoperative RT secondary to the tumor cells being better oxygenated.

Studies Evaluating the Preoperative RT:

10 randomized trials:

Table 7 Five-Year Survival in Rectal Cancer After Single-Modality Radiation Therapy

TRIAL/ YEAR	PATIENTS (n)	GROUPS	OVERALL SURVIVAL (%)			RECURRENCE (%)	
			LOCAL	DISTANT	LOCAL	DISTANT	
PREOPERATIVE RADIATION THERAPY							
Norway, 1990	300	Surgery	58		23	17	
		Preoperative 31.5 Gy	57		15	18	
EORTC, 1988	466	Surgery	49		30†	22†	
		Preoperative 34.5 Gy	52		15†	23†	
Stockholm, 1990	849	Surgery	41		30†	22†	
		Preoperative 25 Gy	45		18†	16†	

- 5 reports on decreased local recurrence and increased sphincter-preservation rates with acceptable toxicities.
- Only 1 report of a survival advantage (Swedish Rectal Cancer Trial, 1997)
 - Delivered 25 Gy in 5 fractions (1 week) to RT group vs. resection alone.
 - Local recurrence rate and 9-year disease specific survival was 11% and 74% for the RT group versus 27% and 65% for the control group.

Many nonrandomized trials demonstrating decreased local recurrence rates and increased sphincter-preservation rates

- 3/4 of patients initially declared to need an APR have been found in some trials to be able to receive sphincter preservation.

Studies on Preoperative RT + CT - Several Nonrandomized Trials:

Table 8 Five-Year Survival in Rectal Cancer with Multimodality Radiation Plus Chemotherapy

TRIAL/ YEAR	PATIENTS (n)	GROUPS	SURVIVAL (%)		RECURRENCE (%)		
			OVERALL	DISEASE FREE	LOCAL	DISTANT	
PREOPERATIVE RADIATION THERAPY							
EORTC, 1984	247	Surgery, XRT	59	60	15	—	
		Surgery, XRT, 5-FU	46	65	15	—	

1. MDACC trial - Chemoradiotherapy (5-FU-based) for resectable T2 and T3 lesions resulted in improved local recurrence (4-5%) and 5-year survival (93%).

2. Memorial Sloan-Kettering Study - Grann et al - 1997 - Leucovorin + 5-FU + RT: 85% sphincter-preservation rate in patients initially thought to require an APR, no local failure (median f/u of 22 months), and 60% 3-year disease-free survival.

3. Pending trial:

NSABP preoperative RT + 5-FU + leucovorin vs. postoperative RT + 5-FU + leucovorin.

II. Postoperative Radiation

- 3 randomized studies have been performed comparing surgery alone with surgery + postoperative RT for T3 or N1 to N2 rectal cancer.

Table 7 Five-Year Survival in Rectal Cancer After Single-Modality Radiation Therapy

TRIAL/ YEAR	PATIENTS (n)	GROUPS	OVERALL SURVIVAL (%)	RECURRENCE (%)	
				LOCAL	DISTANT
POSTOPERATIVE RADIATION THERAPY					
GITSG, 1985	108	Surgery	46	24	34
		Postoperative 40-48 Gy	52	20	30
NSABP R-01, 1988	368	Surgery	43	25	26
		Postoperative 46-51 Gy	40	16	31
Netherlands, 1991	172	Surgery	57	33	27
		Postoperative 50 Gy	45	24	39

- The only trial to demonstrate a decrease in local recurrence rate was the NSABP trial.
 - Local recurrence was decreased from 25% in the surgical arm to 16% in the postoperative RT arm (p=0.06).
 - Several nonrandomized trials have shown a decrease in local recurrence rates to 6-8%.
 - The differences in these trials may reflect RT dosing and patient selection. Higher RT dosing was associated with a higher control rate.
 - Despite the performance of several large prospective trials, survival, local pelvic control, and extrapelvic recurrence rates have not been improved consistently by RT doses of 45 to 50 Gy.
 - This prompted the addition of CT to RT in the postoperative period.

III. Postoperative Radiation + Chemotherapy

- Increase success of RT + CT versus RT alone postoperatively.
- Several studies have not only shown a reduction in local recurrence but increase in survival by 10-15%.

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TRIAL/ YEAR	PATIENTS (n)	GROUPS	SURVIVAL (%)		RECURRENCE (%)	
			OVERALL	DISEASE FREE	LOCAL	DISTANT
POSTOPERATIVE RADIATION THERAPY						
Norway, 1995	144	Surgery	49*	46*	30*	—
		Surgery, XRT, 5-FU	64*	61*	12*	—
GITSG, 1985	202	Surgery	46†	45*	24	34
		Surgery, XRT	52	52	20	30
		Surgery, 5-FU/MeCCNU	56	54	27	27
		Surgery, XRT, 5-FU/MeCCNU	58†	67*	11	26
ECOG, 1991	237	Surgery, XRT	46	40	—	—
		Surgery, 5-FU/MeCCNU	47	45	—	—
		Surgery, XRT, 5-FU/MeCCNU	50	46	—	—
NCCTG, 1991	204	Surgery, XRT	47†	37*	25*	46*
		Surgery, XRT, 5-FU/MeCCNU	58†	58*	14*	29*

- 2 large studies by the Gastrointestinal Tumor Study Group (GITSG) and NCCTG showed that there was a significant improvement in local control and prevention of metastases.
- GITSG: Improved local control: 11% vs. 24% for surgery alone
Improved survival by 10-15%.
- NCCTG: Significant decrease in pelvic recurrence (14% vs. 25% for surgery + RT only) and a significant decrease in cancer-related deaths for patients treated with resection + RT + CT.
- Has led to the NCI Consensus recommending adjuvant therapy for patients with Dukes B and C rectal CA (T3, T4, N0 as well as T3, T4, N1-N3)
- Consists of 6 cycles of 5-FU along with concurrent RT to the pelvis (usually given as 55Gy of radiation delivered to the pelvis in 1.8 to 2.0 Gy fractions (6-week treatment).
- This is the standard by which all adjuvant therapy protocols are compared.

IV. Intraoperative Radiation Therapy

- Used for recurrent and locally advanced rectal cancer, areas with positive microscopic (15 Gy) margins or gross residual disease after resection (17 Gy).
- Advantages:
 1. Increased local control in high-risk cancers.
 2. Accurate treatment of focal areas at risk.
 3. Ability to adjust the depth of the radiation beam.
 4. Ability to shield sensitive structures.
- Few studies evaluating the efficacy of IORT.

V. M.D. Anderson Recommendations

- For T3 to T4 (Dukes B), or any T with N1 or greater (Dukes C) rectal cancer, preoperative RT + 5-FU.
- Surgery is performed 6-8 weeks after completion of therapy.

Recent paper published by M.D. Anderson:

- T3:
 - 61% had either a complete response or only microscopic disease remaining before surgery.
 - 66% underwent sphincter-preserving procedures.
 - Negative margins in 99%.
 - Grade 3 or 4 toxicity seen in 3-4%.
 - 3 year survival: 88%.
- For fixed T3 or T4:
 - Same regimen with intraoperative RT for positive or close margins
 - Local control rate: 97%.
 - 5-Year survival: 82%.

VI: FUTURE TRENDS/RESEARCH IN MULTIMODALITY TREATMENT

- Comparing continuous versus bolus RT to investigate whether there is a difference in efficacy.
- Comparing 5-FU alone, 5-FU + leucovorin, and 5-FU + levamisole.
- Evaluating lower doses of preoperative RT for shorter periods of time to evaluate if similar results regarding decreased local recurrence can be obtained.
- Further investigation of the role of intraoperative RT.
- Elucidation of molecular markers that can aid in the identification of patients who will benefit from treatment

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