Indications for and Results of Combined Modality Treatment of Colorectal Cancer

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Combined modality chemoirradiation is commonly used as a component of treatment in combination with maximum resection for both high-risk resectable and locally advanced primary or recurrent rectal cancers. With surgically resected but high-risk rectal cancers, postoperative chemoirradiation has been shown to improve both disease control (local and distant) and survival (disease-free and overall) and was recommended as standard adjuvant treatment at the 1990 National Institute of Health (NIH) Consensus Conference on Adjuvant treatment for patients with rectal and colon cancers. Subsequent intergroup trials are being conducted to help define optimal combinations of postoperative chemoirradiation for resected high-risk rectal cancers and to test sequencing issues of preoperative versus postoperative chemoirradiation.

With locally unresectable primary or recurrent colorectal cancers, standard therapy with surgery, external beam irradiation (EBRT) and chemotherapy is often unsuccessful. When intraoperative electron irradiation (IOERT) is combined with standard treatment, local control and survival appear to be improved in separate analyses from the Mayo Clinic and the Massachusetts General Hospital (MGH). However, routine use of systemic therapy is also needed as a component of treatment, in view of high rates of systemic failure.

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STAGING AND PATTERNS OF RELAPSE

Staging

Differences in or incorrect interpretations of staging systems may create difficulties when attempting to compare treatment results by series (1). Although both the original Dukes' system (A, B, C) and the current Tumor, Node, Metastasis (TNM) system (I, II, III) are useful in predicting general survival outcome after surgical resection, categories of patients within each stage have markedly different outcomes. A modification of the Astler-Coller rectal staging system (MAC) by Gunderson & Sosin (2) subdivided Astler-Coller stages B_2 and C_2 on the basis of degree of extrarectal or extracolonic tumor extension and operative or pathologic adherence to or invasion of surrounding organs or structures (B_3 or C_3; T_{4b} N_0, T_{4b} N_{1-2}). When the MAC system was used to analyze survival and patterns of release after potentially curative resection of either rectal or colon cancers, survival and local relapse rates differed in subsets of patients within both Dukes' B and C stages, and the rate of systemic metastasis differed within Dukes' C stage.

In the 1990 NIH Consensus Conference statement, it was noted that the MAC staging system was commonly used within the United States, but a plea was made for more standard use of the TNM system. The TNM system has a more precise definition of the degree of primary tumor extension for lesions confined to the bowel wall, and node involvement is defined by both number and location. The TNM system is confusing, however, with regard to the correct T stage for lesions with primary tumor adherence to other organs or structures since adherence is not defined within the TNM system. While adherent lesions are preferably substaged as T_{4b}, the most important factor in presentations and publications is a clear definition of disease extent with regard to both the primary lesion and nodes. If stage is defined only by TNM stages I–IV or Dukes' A–C, much valuable information is lost concerning differential survival and local relapse risks within TNM stages II and III (Dukes' B and C) and differential systemic risks within stage III (Dukes' C).

Patterns and rates of relapse after curative resection of primary rectal cancer

Patterns of relapse after curative resection of rectal cancer have been defined in clinical, reoperative (Fig. 1) and autopsy series (1, 2). Pelvic relapse is a function of both

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tumor bed and nodal relapse that occurs because of direct tumor extension or lymphatic spread. Distant metastases with low or mid-rectal cancers can occur in either the lung or liver (Fig. 1); with proximal rectal cancers the liver is primarily at risk.

The rate of local relapse after 'curative resection' of primary rectal cancers is related both to tumor extension beyond the rectal wall and to nodal spread (1). For patients with a single high-risk factor of either direct tumor extension beyond the rectal wall, nodes negative (T_3 or T_4, No; MAC B_2 or B_3) or involved nodes but primary tumor confined to the rectal wall, (T_{1-2}, N_{1-2}; MAC C_1) local relapse varies from 20 to 40%. For patients with both involved nodes and extension beyond the wall (T_3 or T_4 N_{1-2}; MAC C_2 or C_3), the risk of local relapse is nearly additive (40% to 65% in clinical series and 70% in a reoperative series). When lesions extend beyond the rectal wall, the amount of uninvolved tissue on microscopic review (circumferential or radial margin) may be as or more important than the degree of extrarectal extension in determining the risk of local relapse (3).

The rate of systemic metastases appears to be significantly higher in patients with both high-risk pathologic factors (extension beyond bowel wall and positive nodes; MAC C_2 and C_3) as opposed to those with only a single risk factor (MAC B_2, B_3, C_1). In published data from adjuvant rectal cancer patients irradiated at either the MGH or Mayo Clinic, the incidence of subsequent systemic relapse was approximately 20% with B_2, B_3, and C_1 lesions versus 40% to 60% with $C_2 \pm C_3$ lesions.

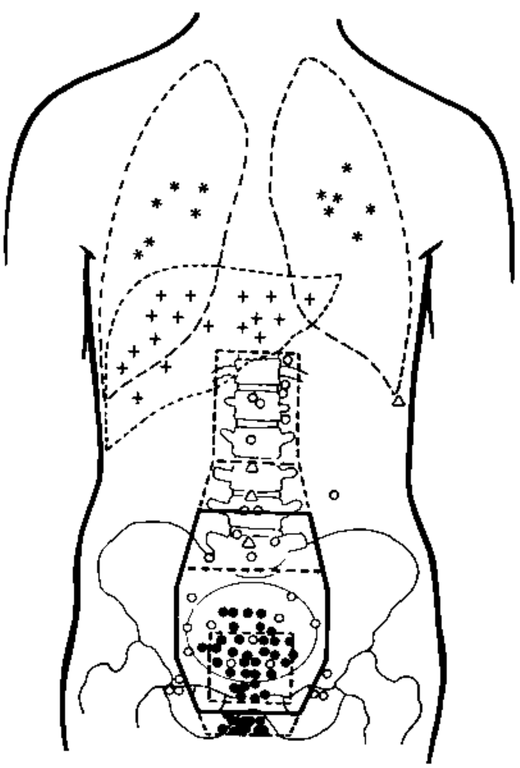

Fig. 1. Patterns of relapse in University of Minnesota rectal reoperation series (ref. 2—with permission).

ADJUVANT IRRADIATION ± CHEMOTHERAPY

Rationale

The rationale for using a combination of irradiation and chemotherapy as a component of adjuvant treatment in rectal cancer is based on the risks of relapse after surgery alone and evidence of radioresponsiveness in both preoperative and primary irradiation series for rectal cancers. With preoperative irradiation of clinically mobile lesions, pathologic complete response rates of 10% to 20% have been reported and with preoperative chemoirradiation, these rates have been as high as 30% to 35%.

Brierly et al. presented a series from the Princess Margaret Hospital (PMH) (4) in which primary irradiation was given to patients with tumour fixation (n = 77), partial fixation (n = 37), or clinically mobile lesions (n = 97). Patients in the last group were either medically inoperable or refused abdominoperineal resection. The most common irradiation dose was 45 to 50 Gy in 20 fractions over 4 weeks. In the 97 patients with mobile lesions, complete clinical regression was achieved in 48 patients (50%) but 18 relapsed locally for an ultimate local control rate of 31% (30 of 97). Five-year actuarial survival for those with mobile lesions was 48%. Surgical salvage was attempted in 25 patients with initially mobile lesions that persisted or relapsed and was successful in 18. Although the PMH results are not competitive with combined modality treatment that includes planned resection, they support the curative potential of irradiation as a single modality.

When both surgery and radiation are indicated in an adjuvant setting, there are differences of opinion regarding the preferred sequence of each modality. Potential advantages of preoperative irradiation (± concomitant and maintenance chemotherapy) include the damaging effect on cells that may be spread locally or distantly at the time of resection, and downstaging of lesions in an attempt to improve the rate of sphincter preservation. The main advantage of postoperative irradiation (± concomitant and maintenance chemotherapy) is that the only patients irradiated are those without metastases and at high risk for local recurrence on the basis of operative and pathologic findings.

Scientific endpoints

Trial design and results of pertinent randomized studies will be presented relative to the three independent scientific endpoints identified at the 1990 NIH Colorectal Consensus Conference (disease-free survival, overall survival and local control). Therapeutic gains achieved with combination adjuvant treatment programs might be offset by an unnecessary increase in complications unless physicians select

Table 1

*Adjuvant rectal–pre ± postoperative irradiation, impact on survival and disease control**

Sequence EBRT/Op'n			Advantage seen	Actuarial survival		Incidence local recurrence (%)			Incidence distant metastasis (%)		
				Disease-free % (p-value)	Overall % (p-value)	Op'n	EBRT	p	Op'n	EBRT	p
Preop (all stages)											
EORTC	–	Curative	Preop EBRT vs. Op'n alone	Not given	69 vs. 59, (0.08)	30	15	0.003	25	25	0.87
	–	Total	None	56 vs. 51, (0.54)	52 vs. 49, (0.69)	35	20	0.02	–	–	–
Rotterdam	–	T_3,T_4	Preop EBRT vs. Op'n alone	Not given	50 vs. 18, (0.001)	36	14	0.08	45	32	NS
	–	T_2	None	Not given	62 vs. 70, (NS)	18	0	NS	26	45	NS
Swedish	–		Total preop EBRT vs. Op alone	–	58 vs. 48 (0.04)	27	11	<0.001	–	–	–
			Curative preop EBRT	–	–	33	9	<0.001	24	23	NS
Preop vs. Postop (all stages)											
Swedish			Preop vs. postop	Not given for total group	43 vs. 37, (0.43)	–	13 vs. 22	0.02	–	28 vs. 37	0.30

Abbreviations: EBRT = external beam irradiation; Op'n = operation; CT = chemotherapy; PVI 5-FU = protracted venous infusion 5-FU; MAC = modified Astler-Coller; DM = distant metastases.
* All data are from controlled multi-institution randomized trials.

patients that have definite indications for treatment and work closely to optimize delivery of the combined modalities.

Preoperative irradiation

Low-dose preoperative irradiation (≤ 20 Gy in 1.8 to 2.0 Gy fractions) has had no significant impact on either tumor control (local or distant) or survival (disease-free, overall). This was demonstrated most definitively in the MRC trial, which compared a surgery alone control arm with treatment arms of 5 Gy in 1 fraction and 20 Gy in 10 fractions (5, 6).

Although moderate-dose preoperative irradiation has demonstrated improved local control in two randomized European trials, improved survival was demonstrated only in subset analyses (Table 1) (1, 7, 8). In both series, the dose delivered was 34.5 Gy in 15 fractions of 2.3 Gy over 19 days (equivalent to 39.6 to 44 Gy in standard fractionation). Subset analyses revealed suggestive survival advantages in irradiated T_3 and T_4 patients in the Rotterdam series ($p = 0.001$) and for patients with curative resection in the EORTC trial (5-year survival of 70% vs. 60%, $p = 0.08$). In the EORTC trial, no difference in distant metastasis rates was identified.

A large Swedish Trial has recently been published which demonstrated that a significant improvement in local control could translate into improved survival as well (Table 1, Fig. 2) (8). Patients were randomized to a surgery alone control arm (n = 557) or short-course, high-dose per fraction preoperative irradiation (25 Gy in 5 fractions) followed by resection in one week (n = 553). After a follow-up interval of 5 years the rate of local relapse was 27% with surgery alone vs. 11% with preoperative irradiation ($p < 0.001$). The 5-year overall survival rate was respectively 48% vs. 58% ($p = 0.004$). There was no impact

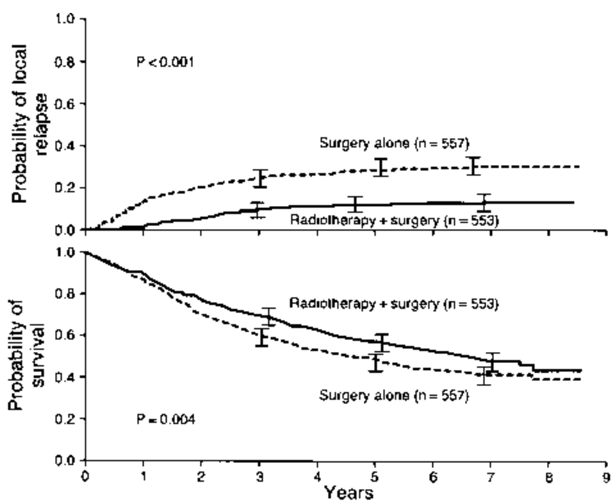

Fig. 2. Local control and overall survival curves from Swedish adjuvant rectal Phase 3 Trial comparing surgery ± short course, high dose per fraction preoperative irradiation (from ref. 8—with permission).

Table 2

Adjuvant postoperative randomized rectal trials, *US*, *and*

Group or institution	Treatment regimen	EBRT dose (Gy) schedule	Chemo
GITSG	Op'n alone	None	None
7175	EBRT	40 or 48/1.8 Gy Fx	None
	CT	None	5-FU + MeCCNU
	EBRT + CT	40 or 44	5-FU 500 mg/m^2 3 d wk 1 $\pm$ 5 EBRT 5-FU + MeCCNU
NSABP R01	Op'n alone	None	None
	EBRT	47/26 Fx	None
	CT	None	5-FU, MeCCNU, VCR
Norway	Op'n alone	None	None
	EBRT + 5-FU	46 Gy/2 Gy Fx	5-FU 500 or 750 mg 2 d wk 1, 3, 5 EBRT
Mayo/NCCTG	EBRT	50.4/28 Fx	None
79-47-51	EBRT + CT	Same	5-FU MeCCNU; 5-FU 500 mg/m^2 3 d wk 1 $\pm$ 5 EBRT; 5-FU MeCCNU
GTSG 7180	EBRT + CT (5-FU)	41.4/23 Fx	5-FU 500 mg/m^2 3 d wk 1 $\pm$ 5 EBRT; 5-FU
	EBRT + CT (5FU + MeCCNU)	Same	5-FU + EBRT (as in #1); (5-FU + MeCCNU)
NCCTG 864751 (intergroup)	EBRT + CT (bolus 5-FU MeCCNU)	50.4 to 54/ 28–30 Fx	Same as arm 2 79-47-51
	EBRT + CT (bolus 5-FU MeCCNU; CI5Fu)	Same	Bolus 5-FU MeCCNU; CI5FU 225 mg/m^2/d during EBRT

[1] Local control advantage to EBRT vs. no EBRT $p = 0.08$; [2] Distant control advantage to CT vs. no CT.
Abbreviations: MAC = modified Astler Coller Stage; Op'n = Operation; EBRT = external beam irradiation; Fx = fractions; CT = chemotherapy; CI5FU = continuous infusion 5-FU; LF = local failure; SR = survival; DFS = disease-free SR; Inc. = increased survival or tumor control but not statistically significant or marginally significant; Dec. = decreased; Yes = marginal or statistically significant improvement. (p values added for this category only).

of adjuvant irradiation on distant metastases with rates of 24% and 23%.

Preoperative vs. postoperative irradiation

A Swedish trial compared single adjuvant, high dose per fraction preoperative irradiation (25.5 Gy in 5 fractions over 1 week) to postoperative irradiation (60 Gy in 30 fractions over 8 weeks with planned 2-week split) (9, 10). The local relapse rate in patients with curative resection was less in the preoperative patients at 13% vs. 22% ($p = 0.02$) (10). No significant difference was seen in survival (9, 10) or distant metastasis rates (9) (Table 1).

Postoperative irradiation $\pm$ *chemotherapy*

A summary of results in six published randomized adjuvant trials for resected high-risk rectal cancers is presented in Tables 2 and 3. Results are reported as a function of treatment impact on patterns of relapse (local, distant) and survival (disease-free, overall). Positive survival results were reported in five of the trials.

US trials. The National Surgical Adjuvant Breast and Bowel Program three-arm trial (NSABP R01) compared surgery alone with postoperative irradiation and postoperative chemotherapy as single adjuvants (11). An advantage in disease-free survival was demonstrated with adjuvant chemotherapy versus surgery alone ($p = 0.006$), but neither local relapse nor distant metastasis was significantly altered with the addition of chemotherapy. In patients randomized to receive irradiation, there was a significant decrease in local relapse from 25% to 16% when compared with surgery alone ($p = 0.06$), but overall survival was equal (14% of patients randomized to the irradiation arm did not receive such).

Norway—irradiation & chemotherapy (MAC B_2, B_3, C_1, C_2, C_3)

No. pts.	Advantage in tumor control		Survial advantage	
	Local	Distant	Disease-free	Overall
58	–	–	–	–
50	Yes[1]	No	Inc.	Inc.
48	No	Yes[2]	Inc.	Inc.
46	Yes[1] p = 0.08	Yes[2]	Yes p = 0.009	Yes p = 0.005
173	–	–	–	–
177	Yes (p = 0.06)	Dec.	Equal	Equal
178	Inc.	Equal	Yes p = 0.006	Yes p = 0.05
70	–	–	–	–
66	Yes (p = 0.01)	No (p = 0.52)	Yes (p = 0.05)	Yes (p = 0.01)
101	–	–	–	–
103	Yes p = 0.04	Yes p = 0.01	Yes p = 0.002	Yes p = 0.025
104	Equal	Yes p = 0.05	Inc.	Inc.
95	Equal	–	–	–
332	–	–	–	–
328	Inc. p = 0.11	Yes p = 0.03	Yes p = 0.01	Yes p = 0.005

Two randomized postoperative trials from the United States (US) (Gastrointestinal Tumor Study Group [GTSG 7175] (12, 13) Mayo/North Central Cancer Treatment Group [NCCTG 79-47-51]) (14), and a recent trial from Norway (15) documented a decrease in local relapse and improvement in both disease-free and overall survival with combined postoperative chemoirradiation for resected high-risk patients (Dukes' B or C lesions; TNM stages II, III; MAC B_2, B_3, C_1, C_2, C_3). In both of the US trials (12–14), bolus 5-FU was given for three days on weeks one and five of irradiation, and patients received 5-FU and MeCCNU as systemic treatment either after (GTSG 7175) or before and after irradiation plus 5-FU (NCCTG 79-47-51) (Table 2). In the Norwegian Trial (15), bolus 5-FU was given for two consecutive days on weeks one, three, five of irradiation as an IV bolus 30 min before irradiation (500 mg/day for patient surface area [SA] < 1.75 m^2, 750 mg IV for SA > 1.75 m^2). No maintenance 5-FU was given in the Norwegian Trial.

In the GTSG 7175 trial, patients were randomized to a surgery-alone control arm and adjuvant arms of postoperative irradiation, postoperative chemotherapy, or a combination thereof (12, 13). The statistically significant advantages in disease-free and overall survival with the chemoirradiation arm were achieved in a comparison with the surgery-alone control arm ($p = 0.009$ and 0.005). Local relapse, as an initial pattern of relapse, was significantly decreased with irradiation versus no irradiation ($p = 0.08$). The local control was achieved with combined chemoirradiation (local relapse rate of 11% vs. 20% with irradiation alone). No impact on local control was seen with chemotherapy as a single adjuvant (local relapse rate of 27% vs. 24% with surgery alone). Although distant metastases rates were less in the two arms that contained chemotherapy when compared with the two arms without chemotherapy, no single arm had a significant impact on the rate of distant metastases (Table 3). The survival advantage achieved with combined chemoirradiation appeared to relate primarily to the marked reduction in local relapse.

In the initial Mayo Clinic NCCTG trial (79-47-51) (14), the minimum irradiation dose within the boost field in both the irradiation and radiochemotherapy arms was higher than in the GTSG 7175 trial (50.4 Gy vs. 40–48 Gy). The chemoirradiation arm achieved statistically improved results with regard to both disease control and

Table 3

Adjuvant rectal postoperation irradiation ± chemo-

Sequence EBRT/Op'n	Advantage seen	Actuarial survival		Incidence local re-	
		Disease-free %, (p-value)	Overall %, (p-value)	Op'n	CT
Postop† (5-yr actuarial data and 2-tail p-values unless specified)					
GTSG 7175	EBRT CT vs. Op'n	70 vs. 46 (0.009)	58 vs. 45 (0.005, 1-tail)	24	27
NSABP RO1	CT vs. Op'n	41 vs. 30 (0.006)	53 vs. 43 (0.05)	25	21
Norwegian	EBRT 5-FU vs. Op'n	64 vs. 46 (0.01)	64 vs. 50 (0.05)	30	–
NCCTC/Mayo 794751	EBRT CT vs. EBRT	59 vs. 37 (0.002)	58 vs. 48 (0.025)**	–	–
GTSG 7180 (3-yr data)	EBRT 5-FU ± MeCCNU	69 vs. 54 (0.20)	75 vs. 66 (0.58)	–	–
NCCTG 864751 (4-yr data)	EBRT PVI 5-FU vs. EBRT bolus 5-FU	63 vs. 53 (0.01)	70 vs. 60 (0.005)	–	–
Preop vs. Postop (all stages)					
Swedish	Preop vs. postop	Not given for total group	43 vs. 37 (0.43)	–	–

Abbreviations: EBRT = external beam irradiation; Op'n = operation; CT = chemotherapy; PVI 5-FU = protracted venous infusion 5-FU; MAC = modified Astler Coller; DM = distant metastases.
* AII data are from controlled multi-institution randomized trials.
† Postop–MAC stages B_2, B_3, C_1, C_2, C_3 (TNM stage II, III, or T_{3-4} N_0, T_{is-4} $N_{1,2}$).
+ GTSG advantage to chemotherapy vs. no chemotherapy at 20% vs. 30% (DM only), 27% vs. 32% (any DM).
** Mayo alone series 5-yr overall SR 70% vs. 57% postop EBRT CT vs. EBRT (p = 0.01) and distant metastasis rate of 33% vs. 52%. (Schild et al. reference 22).
†† EBRT vs. no EBRT.
++ Advantage EBRT 5-FU vs. EBRT 5-FU MeCCNU.
††† Advantage to EBRT CI5FU vs. EBRT bolus 5-FU.

survival. Local relapse, as an initial pattern of failure, was reduced from 25% to 13.5% (p = 0.04), and distant metastases were decreased from 46% to 29% (p = 0.01). Both disease-free survival (DFS) and overall survival (OS) were also statistically improved (DFS—59% vs. 37% at five years, p = 0.002; OS—58% vs. 48% at five years, p = 0.025). This was the first randomized trial in which a course of full-dose chemotherapy was given before as well as after combined chemoirradiation in an attempt to decrease the incidence of distant metastases (one dose of MeCCNU, two cycles of 5-FU in both the pre- and post-chemoirradiation arms). This was also the first trial in which both local relapse and distant metastases were reduced significantly by the experimental treatment arm.

Two subsequent randomized postoperative trials, GTSG 7180 (16) and the intergroup 86-47-51 trial coordinated by NCCTG (17), demonstrated that methyl CCNU did not produce an additive benefit to irradiation plus 5-FU. The intergroup trial NCCTG 86-47-51 also tested the best method of giving 5-FU concomitantly with irradiation (interrupted bolus 5-FU 500 mg/m^2 for 3 days, weeks 1 and 5 of EBRT vs. protracted low-dose infusion 5-FU 225 mg/m^2 per 24 h, 7 days per week or until intolerance) with a 2 × 2 randomization design in 664 patients (17). A planned interim analysis of disease control (initial patterns of relapse) and time to relapse indicated a significant advantage for patients who received protracted venous infusion 5-FU during irradiation (local relapse 8% vs. 12%; distant metastases 31% vs. 40%, p = 0.03; disease-free survival at four years 63% vs. 53%, p = 0.01). The analysis also revealed a significant improvement in overall survival (four-year 70% vs. 60%, p = 0.005).

As a result of no additive benefit from MeCCNU, the control arm in the subsequent US intergroup rectal adjuvant (INT 0114) was postoperative irradiation plus bolus 5-FU (18) (INT 0114 tested four different systemic regimens before and after irradiation plus bolus 5-FU ± leucovorin: 5-FU alone, 5-FU and levamisole, 5-FU plus low-dose leucovorin and all three drugs). Accrual to INT 0114 was initiated in 1990 and completed in late 1992, before results from 86-47-51 were available concerning the advantage of infusion 5-FU over bolus 5-FU when given as single drugs during irradiation. An initial analysis, reported at ASCO in 1996, showed no statistical benefit for any treatment arm versus another with regard to either disease control or survival (17).

Norway trial. The trial conducted by the Norwegian Adjuvant Rectal Cancer Project Group (15) was initiated in 1986–1987 when only the GTSG 7175 trial had demonstrated both a local control and a survival benefit for combined postoperative chemoirradiation. Therefore, the investigators chose to conduct a two-arm trial of surgery alone (n = 70 patients) ± postoperative chemoirradiation (n = 66 patients). The combined adjuvant arm differed from the GTSG 7175 and subsequent trials in that the adjuvant 5-FU was given only concomitantly with adjuvant EBRT (46 Gy/2 Gy fractions/4 1/2 to 5 weeks) and no maintenance chemotherapy was given. With a minimum follow-up of four *therapy. Impact on survival and disease control*

currence (%)			Incidence distant metastasis (%)				
EBRT	EBRT/CT	P	Op'n	CT	EBRT	EBRT/CT	p
20	11	0.08[††]	34	27[†]	30	26[+]	–
16	–	0.06	26	24	31	–	NS
–	12	0.01	–	–	–	–	–
25	13.5	0.04	–	–	46	29	0.01**
–	17 vs. 16	NS	–	–	–	26 vs. 40	0.05[++]
–	8 vs. 12	0.11[†††]	–	–	–	31 vs. 40	0.03[†††]
13 vs. 22	–	0.02	–	–	28 vs. 37	–	0.30

years, an improvement in local control was demonstrated in the chemoirradiation arm. Local relapse rates were 30% with surgery alone vs. 12% with adjuvant chemoirradiation ($p = 0.01$). No significant impact on distant metastases was achieved (39% with surgery alone, 33% with chemo EBRT; $p = 0.52$). The improvement in local control translated into improvements in both disease-free survival (DFS) and overall survival (OS) at 46% vs. 64% DFS ($p = 0.05$) and 50% vs. 64% OS ($p = 0.01$) (Fig. 3).

Complications and therapeutic ratio

An optimal therapeutic ratio between local control and complications is achieved only with close interaction between the surgeon and the radiation oncologist and the use of sophisticated radiation techniques (19). In the MGH postoperative rectal adjuvant series which used shaped multiple-field irradiation techniques, bladder distention, etc., the incidence of small-bowel obstruction requiring operative intervention was the same in patients receiving adjuvant postoperative irradiation ($\pm$ chemotherapy) and those with surgery alone at 6% vs. 5%, respectively (20). In the Mayo/NCCTG 79-47-51 adjuvant rectal trial using multiple-field irradiation techniques, the incidence of acute enteritis was higher in the patients with irradiation plus 5-FU vs. irradiation alone at 20% vs. 5% (Table 4) (14). This did not translate into increased chronic intolerance; the incidence of severe small-bowel problems was $\leq 6\%$ with either adjuvant irradiation alone or adjuvant radiochemotherapy.

In the subsequent 86-47-51 trial, acute GI intolerance was higher with protracted venous infusion (PVI) 5-FU vs. bolus 5-FU during irradiation with severe diarrhea in 24% vs. 14% of patients ($p < 0.01$) (Table 4) (17). Severe hematologic intolerance was lower with PVI 5-FU vs. bolus 5-FU with the WBC < 2000 in 2% vs. 11% of patients ($p < 0.01$).

In a single institution retrospective analysis of rectal function following adjuvant treatment, Kollmorgen et al. (21) suggested that rectal function was unfavorably altered by postoperative irradiation $\pm$ chemotherapy for high-risk lesions when compared with surgery alone for low-risk lesions. This was manifest primarily as increased frequency of bowel movements, occasional stool incontinence, and the need for periodic antidiarrheal agents. *Flaws in the analysis* included the non-random selection of treatment, early stage versus late stage disease in the surgery alone versus adjuvant treatment groups, retrospective nature of the analysis and non-blinding of the interviewer with regard to treatment method. Nonetheless, it is not surprising that postoperative irradiation $\pm$ chemotherapy may reduce compliance of the reconstructed stool reservoir and result in some dysfunction. Such dysfunction can usually be prevented in social settings by the use of antidiarrheal agents. The incidence of severe treatment-related dysfunction was judged to be low, and this risk must be placed in proper perspective by considering the severe morbidity and dysfunction of pelvic relapse. Prospective quality of life studies needed to be performed to determine both the actual level of dysfunction with pre- versus postoperative adjuvant chemoirradiation and

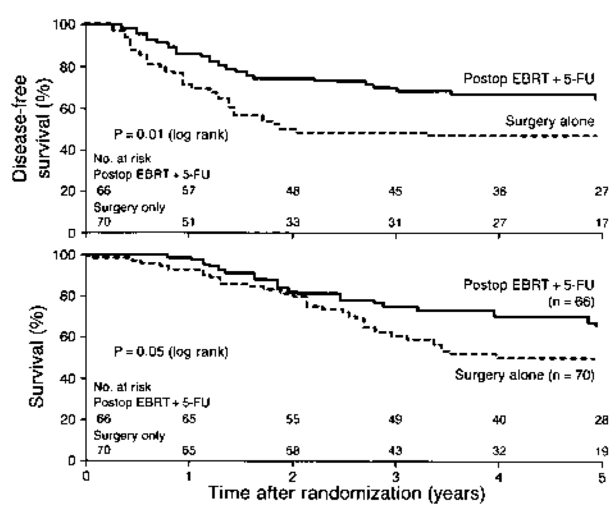

Fig. 3. Disease-free and overall survival curves from Norwegian Phase 3 postoperative rectal adjuvant rectal trial comparing surgery $\pm$ postoperative irradiation plus concomitant 5-FU (from ref. 15—with permission).

Table 4

Acute and chronic severe or life-threatening treatment-related side effects in postoperative adjuvant rectal Mayo NCCTG protocols 79-47-51 and 86-47-51

	Incidence (%) 79-47-51[9]				Incidence (%) 86-47-51[11]			
	*CT	EBRT + CT	EBRT		EBRT + bolus 5-FU	EBRT + PVI 5-FU	5-FU	5-FU + MeCCNU
Acute intolerance (severe)	(n = 101)	(n = 96)	(n = 99)		(n = 314)	(n = 297)	(n = 218)	(n = 226)
Nausea	10	2	0		1	1	1	4
Vomiting	6	2	0		1	1	0	3
Diarrhea	21	20	5		14	24^Δ	12^Δ	5
Stomatitis	1	1	0		0	1	7^Δ	1
Leukopenia < 2 000	15	18	0		11^Δ	2	30^Δ	14
Thrombocytopenia < 25 000	4	0	0	< 50 000	1	0	0	15^Δ
Dermatitis	0	5	0		33	1	0	0
Chronic intolerance (severe)								
Small bowel[†]	–	6	4		–	–	–	–
Rectal perforation	–	0	1		–	–	–	
Sigmoid obstruction	–	1	0		–	–	–	
Pelvic fibrosis	–	1	1		–	–	–	–

* Alopecia in 16%, severe 1%.
[†]Total 10 patients–9 obstruction, 1 hemorrhage (6 EBRT + CT, 4 EBRT).
^Δ $p < 0.01$ for the comparison with the other group in this category (i.e., diarrhea 14 vs. 24%, etc.).
Abbreviations: CT = chemotherapy (before or after combined irradiation plus 5-fluorouracil, 5-FU); EBRT = external beam irradiation; EBRT + CT = external irradiation plus concomitant chemotherapy with 5-FU; PVI = protracted venous infusion.

whether treatment-related effects can be modified or prevented with agents such as somatostatin and sucralfate.

Summary and future directions for adjuvant therapy

The impact of pre- and postoperative irradiation ± chemotherapy on both disease control and survival in major randomized adjuvant rectal cancer trials is summarized in Tables 1 and 3.

Single modality rectal adjuvants. Neither irradiation nor chemotherapy as single adjuvants achieve all the suggested criteria of efficacy, with the exception of the large Swedish preoperative irradiation trial (8). Adjuvant irradiation reduces the rate of local relapse in both prospective non-randomized as well as randomized preoperative and postoperative trials, but this has not translated into an improvement in overall survival in most series, because of a lack of impact on distant metastases. The only published trial in which single adjuvant treatment improved both local control and survival was the large Swedish trial of over 1 100 patients testing surgery ± preoperative irradiation (8). The adjuvant irradiation did not reduce distant metastases. Adjuvant chemotherapy produced a significant improvement in disease-free survival and marginal improvement in overall survival in the NSABP-R-01 trial (11). However, no significant improvement in local control has been seen with adjuvant chemotherapy in any randomized study (incidence of 21% in NSABP-R-01 and 27% in GTSG 7175 as initial pattern of relapse).

In a Swedish trial comparing high-dose per fraction preoperative irradiation with postoperative irradiation as single adjuvants, the local relapse rate in patients with curative resection was less in the preoperative patients at 13% vs. 22% ($p = 0.02$) (10). No significant difference was seen in survival or distant metastases rates (9, 10).

Combined modality rectal adjuvants. Only combined modality postoperative adjuvant treatment has consistently demonstrated efficacy in all scientific endpoints, as noted in two prospectively randomized US trials (GTSG 7175 (12, 13) and Mayo/NCCTG 79-47-51 (14)) and a third trial from Norway (15)). In both of the US studies, bolus 5-FU was given during irradiation, and patients received additional chemotherapy either after irradiation plus 5-FU (GTSG) or both before and after (Mayo/NCCTG). In the Norwegian study, patients received 5-FU only during irradiation. Subsequent randomized trials by both US groups (GTSG 7180 and NCCTG 86-47-51) have determined that MeCCNU does not produce additive benefits to bolus 5-FU as the systemic component of treatment for adjuvant rectal combined modality regimens (16, 17). However, in the intergroup trial NCCTG 86-47-51, the use of PVI 5-FU during irradiation produced a reduction in both local relapse and distant metastases and improvements in both disease-free and overall survival (17).

Despite the advantages found with combined-modality treatment, there is a need to further improve both local control and systemic control of disease. Although the reported intergroup trial NCCTG 86-47-51 suggested a decrease in local relapse with the use of PVI vs. bolus 5-FU during irradiation (8% vs. 12% as initial relapse), the true incidence of local relapse as a component of failure at any time in follow-up is probably 10% to 12.5%, even with combinations of irradiation and PVI 5-FU chemotherapy (possibly higher for the highest risk C_2 and C_3 patients; T_3–T_{4b}, N_1–$_2$). This inference is based on the single institution Mayo analysis by Schild et al. which demonstrated that use of initial failure data to predict local relapse risks underestimates the total risk of local relapse by $\sim 33\%$ (22). To accomplish further improvements in local control, it may be necessary to institute the best local and systemic adjuvants simultaneously instead of delaying postoperative irradiation for two cycles of chemotherapy. Alternatively, preoperative chemoirradiation may be more effective than postoperative chemoirradiation.

Systemic metastases, as an initial pattern of relapse, existed in 26% to 29% of patients despite combined chemoirradiation in both GTSG 7175 and NCCTG 79-47-51. In the intergroup NCCTG study 86-47-51, distant metastases were decreased with PVI 5-FU vs. bolus 5-FU at 40% vs. 31%, but the magnitude of the problem is still significant. There is a need to evaluate the delivery of the most effective systemic therapy during as well as before and after irradiation to avoid delays of 2.5 to 3 months between sequences of the most effective systemic therapy. As systemic control of disease is optimized, more aggressive drug combinations may be needed with C_2 and C_3 lesions (T_3, T_{4a}, N_{1-2}; T_{4b} N_{1-2}) as opposed to B_2 (T_3 N_0), B_3 ($T_{4b}N_0$) and C_1 (Tis-2 $N_{1,2}$) lesions (all C_1 versus those with < 4 positive nodes).

Future trials need to continue to define optimal combinations of chemoirradiation (which drugs, route and timing of delivery, sequencing of irradiation and chemotherapy, etc.) and to determine whether some patients can be spared the most aggressive treatment combinations (i.e., limited B_2 and C_1 lesions). There is a need to evaluate which drug(s) and methods should be used during irradiation to enhance its effect and which drugs are necessary to alter systemic patterns of failure.

The replacement US intergroup rectal adjuvant study, coordinated by SWOG (INT 0144), was developed to further pursue optimal combinations of postoperative irradiation and chemotherapy. The control arm is the positive arm of intergroup study 86-47-51 wherein systemic treatment consists of two cycles of bolus 5-FU before and after irradiation plus PVI 5-FU. One investigative arm was taken from intergroup trial 0114 (systemic treatment with bolus 5-FU plus low-dose leucovorin before, during and after irradiation). The third arm tests PVI 5-FU as both systemic treatment and in combination with irradiation to determine whether the systemic benefit of PVI 5-FU during irradiation in NCCTG 86-47-51 can be enhanced by using it for all courses of chemotherapy.

Separate trials were developed by both NSABP and the intergroup mechanism to randomly compare full-dose preoperative chemoirradiation with postoperative chemoirradiation for potentially resectable T_3 and tethered T_4 rectal cancers. Both trials were designed to test quality of life issues in addition to disease control and survival (disease control and survival may be equivalent but preoperative treatment may yield improved bowel function, since an unirradiated limb of large bowel will form the proximal portion of the reservoir for stool). The intergroup trial was closed prematurely due to poor accrual, but the NSABP trial continues to accrue patients. The NSABP study will randomly test some of the conclusions raised about rectal function in the retrospective Mayo analysis by Kollmorgen et al. (21).

Table 5

Locally recurrent or primary colorectal cancer survival and disease relapse with EBRT ± IOERT, various series

Disease category and treatment	Ref. No.	No. pts	Overall survival (%)				Local relapse (EBRT)		Distant relapse	
			Median (mo)	2 yr	3 yr	5 yr	No.	%	No.	%
Recurrent + primary–EBRT										
Mayo Clinic—Moertel	36	65								
EBRT alone	–	–	10.5	24	9	–				
EBRT + 5-FU	–	–	16	38	19	5				
Recurrent—EBRT										
Netherlands—Lybeert et al.	37	76	14	25	13	5	43/63	(68)	26/63	(41)
EBRT < 50 GY	–	–	12	20	6	0	–		–	
EBRT ≥ 50 Gy	–	–	20	40	18	10	–		–	
Australian—EBRT	38	135	15	–	–	–	–		–	
Low-dose palliative	–	16	9	13	6	–	–	(94)	–	
High-dose palliative[Δ]	–	80	15	26	12	4	–	(94)	–	(38)[†]
Radical (50–60 Gy/2 Gy Fx)	–	39	18	31	28	≤9	–	(82)	–	(49)[†]

[Δ]High-dose palliative patients had 45 Gy/3 Gy Fx with 1-week treatment break after 30 Gy in 10 Fx.

[†] Incidence of metastasis underestimated as patients were investigated as warranted by symptoms.

Table 6

Colorecteral IOERT—tumor failure in IOERT (CF) or EBRT field (LF) vs. amount of residual

Series	Ref. No.	No. pts.	CF or LF (%)		Residual vs. CF or LF (%)		
			1°	Rec	None	Res (m) or none	Unresect or Res (g)
MGH (5-year actuarial)							
Primary	40	42	23	–	12	31	50
Recurrent	45	41	–	70	–	53	79
Rush Presbyterian	48						
Primary		9	33	–	–	14	100
Recurrent		35	–	54	–	39	64
RTOG—recurrent	49	37	–	62	–	33	89
Pamplona—recurrent	50	27	–	74	–	50	84

Abbreviations: CF = central failure (IOERT field); LF = local failure (external field); Res (m) (g) = microscopic and gross residual; unresect = unresectable.

ADJUVANT COLON

Patterns of relapse

Significant data has been accumulated in autopsy, clinical and reoperative series to indicate that local-regional relapse in the tumor bed or regional nodes is a significant risk after resection of selected stages of colonic as well as rectal lesions (23–25). The risk of local regional relapse is felt to be $\geq 30\%$ with surgery alone for MAC stages B_3, C_3, and C_2 (TNM T_{4b}, N_0, T_{4b}, N_{1-2}, $T_{3,4a}$, N_{1-2}).

Adjuvant postoperative irradiation ± chemotherapy

Results from a large MGH pilot study using adjuvant tumor-bed nodal irradiation for patients with high-risk colon cancers were compared with those achieved by surgery alone (26, 27). Patients defined as at high risk for local relapse included those with a MAC B_3 or C_3 lesion or C_2 lesions except for mid-transverse or mid-sigmoid. Patients with B_2 lesions were included only if the surgeon felt the radial margins (usually posterior) were narrow. EBRT doses of 45–50 Gy in 1.8 Gy fractions were given to tumor bed plus 3–5 cm margins ± regional nodes. In a 1993 publication of 169 adjuvant colon cancer patients irradiated at MGH (52 with simultaneous 5-FU with EBRT), 5-year actuarial local control and survival appeared to be better in irradiated B_3 and C_3 patients. Those differences may have been due in part to patient selection, since this was not a controlled randomized trial. Simultaneous 5-FU during EBRT produced a trend for improved local control and disease-free survival, as found in randomized rectal adjuvant studies.

Estes, Giri and Fabian compared patterns of relapse for MAC C_2 patients in SWOG 8591 (28) (arms of surgery alone or surgery plus 5-FU Levamisole) SWOG 8572 (29) (whole abdomen irradiation [WART] plus tumor-bed EBRT and infusion 5-FU) and the surgery alone arm from the Willet MGH analysis (27). In SWOG 8591, although lung relapse was decreased from 34% to 21% with the addition of 5-FU Levamisole to surgical resection, the chemotherapy adjuvant had no impact on the rate of local-regional relapse (surgery alone—20%, 5-FU Levamisole—27%) which was equivalent to the 32% incidence with surgery alone in the MGH analysis. Patients who received chemoirradiation (WART + tumor-bed EBRT + infusion 5-FU) in SWOG 8592 had only a 12% tumor-bed nodal relapse rate along with a reduction in liver and peritoneal relapse rates (liver relapse rate of 22% with chemoirradiation vs. 54% and 57% in the two arms of SWOG 8591; peritoneal relapse rates of 15% in SWOG 8572 vs. 37% and 40% in SWOG 8591).

Randomized trial—postoperative chemotherapy ± irradiation

In view of the high local relapse risks in selected subsets of colon cancer patients, encouraging pilot study results with postoperative irradiation ± 5-FU for such patients at MGH, and the positive results of 5-FU and Levamisole in high-risk adjuvant colon cancer (30, 31), an Intergroup randomized trial was conducted comparing 5-FU and Levamisole with 5-FU and Levamisole plus irradiation (tumor bed ± regional nodes). Eligible patients, felt to be at high risk for local relapse following surgical resection, included modified Astler-Coller stage B_3, C_3 and retroperitoneal C_2 lesions; TNM T_{4b}, N_0, T_{4b} $N_{1,2}$, $T_{3,4a}$, $N_{1,2}$. This protocol did not reach planned accrual objectives, since six months of adjuvant 5-FU Leucovorin has become the standard of adjuvant chemotherapy for high-risk colon cancer patients (32, 33). Approximately 200 of a planned 400 patients were accrued prior to closure and will be followed for disease control, survival and tolerance analyses.

Table 7

Locally advanced primary and recurrent colorectal—EBRT ± IOERT, Mayo

Treatment	Ref.	Patients at risk (no.)	Median (mo)	Survival %			Local failure (LF)			Distant failure (DF)		
				2-yr	2-yr	5-yr	No.	(%)	Act. 3-yr	No.	(%)	Act. 3-yr
Primary disease												
External (EBRT)*	47	17	18	35	24	24	13	(76)	76	10	(59)	59
EBRT + IOERT	43	56	40	70	55	46	7	(13)	16	27	(48)	49
Localized recurrence												
a) Suzuki et al.	46											
No IOERT	–	64	17	26	18	7	54	(84)	93	29	(45)	54
IOERT ± EBRT	–	42	30	62	43	19	16	(38)	40	24	(57)	60
b) IOERT ± EBRT												
No prior EBRT	47	123	28	62	39	20	24	(20)	25	65	(53)	64
Prior EBRT	51	51	23	48	28	12	14	(26)	49	26	(49)	71

* All deaths within 30 mo. LF range 3–15 mo. DF range 3–17 mo.

LOCALLY ADVANCED COLORECTAL CANCER

Results of external irradiation (± resection, chemotherapy)

External beam irradiation (EBRT) has been combined with surgical resection, chemotherapy, or immunotherapy for locally advanced cancers (34). In separate series from the Princess Margaret Hospital (4) and Mayo Clinic using EBRT alone or with immunotherapy (35), local persistence or relapse was ≥ 90% in evaluable patients. As seen in Table 5, attempts to control locally recurrent disease with EBRT ± resection are primarily palliative (34–39). A recent Australian publication by Guiney et al. discussed results in 135 patients with pelvic relapse of rectal cancer who had no evidence of extrapelvic metastases. A select group of 39 patients were treated with radical intent; re-resection in 54% and EBRT doses of 50 to 60 Gy in all 39. Median survival was 18 months and 5-year survival was ≤ 9%.

Local relapse has been reduced with locally advanced lesions by combining irradiation with surgical resection ± chemotherapy (34). External irradiation has been given either after subtotal resection of locally advanced lesions (45 to 70 Gy in 1.8 to 2.0 Gy fractions) or before an attempt at resection for disease that is initially unresectable for cure (45 to 60 Gy in 5 to 6.5 weeks preoperatively followed by resection in 3 to 5 weeks). Long-term local control and survival can be obtained in a minority of patients, but the risk of local recurrence is still too high at 30% to 70%.

IOERT ± external irradiation

Primary lesions. When intraoperative irradiation with electrons (IOERT) is combined with conventional treatment for locally advanced primary cancers, separate analyses from the MGH and the Mayo Clinic suggest an improvement in both local control and survival (39–43). In an early MGH series, disease relapse within irradiation fields was 43% vs. 0% for 17 non-IOERT vs. 16 IOERT patients, and 1- and 2-year survival rates were statistically better with IOERT (39). An updated MGH analysis by Willett and colleagues reports actuarial 5-year survival of 43% in 42 IOERT patients (40). In the MGH analysis, patients with gross total resection prior to IOERT did better with regard to local control and survival than those with gross residual disease (Table 6).

In a Mayo comparison of 17 non-IOERT (25) and 56 IOERT + EBRT patients with locally advanced primary rectal ± colon cancers, local control was 24% vs. 87% median survival was 18 vs. 40 months and the 3-year survival was 24% vs. 55% (Table 7) (42, 43). Prognostic factors that had a statistically positive impact on disease control and survival in IOERT patients included EBRT + 5-FU vs. EBRT alone, treatment sequence of preoperative EBRT + 5-FU vs. postoperative EBRT + 5-FU, ≤ microscopic residual after maximal resection and colon vs. rectal primary (Table 8).

A separate Mayo analysis was carried out to assess the use of EBRT ± IOERT as a supplement to maximal resection for 103 patients with locally advanced colon cancers (44). The 5-year actuarial local relapse rate was 10% for patients with no residual disease, 54% for patients with microscopic residual disease, and 79% for patients with gross residual disease ($p < 0.0001$). For patients with residual disease, local relapse occurred in 11% of patients receiving IOERT compared with 82% of patients receiving only EBRT ($p = 0.02$). The 5-year actuarial survival rate was 66% for patients with no residual disease, 47% for patients with microscopic residual and 23% for patients with gross residual disease ($p = 0.0009$). The 5-year survival rate in patients with residual disease was 76% for patients receiving IOERT and 26% for patients receiving EBRT alone ($p = 0.04$).

Locally recurrent cancers. For locally recurrent colorectal cancers, standard treatment with EBRT with or

Table 8

Primary colorectal IOERT—disease relapse and overall survival by prognostic factor, Mayo

Prognostic factor	No. at risk	Local (EBRT)			Distant (%)			Overall survival (%)				
		No. (%)	3-yr	p*	No. (%)	3-yr	p	Median (mo)	2-yr	3-yr	5-yr	p
EBRT ± 5-FU (n = 56)												
EBRT	17	3 (18)	24	–	13 (77)	66	–	40	64	58	35	–
EBRT + 5-FU$^{\Delta}$	39	4 (10)	11	0.5-4	14 (36)	35	0.013	81	72	53	53	0.39
Treatment sequence (n = 38)												
Preop EBRT + 5-FU	29	4 (14)	14	–	10 (35)	32	0.18	81	77	62	62	0.003
Postop EBRT + 5-FU	9	0	0	0.37	4 (44)	53	–	25	52	17	17	–
Amount of residual (n = 56)												
Gross	16‡	4 (25)	27	–	12 (75)	66	0.008‡	22	49	28	21	–
≤ Microscopic	39‡	2 (5)	9	0.01‡	15 (39)	37	0.008‡	67	80	69	59	0.005
No resection†	1	1	–	–	0	–	–	–	0	9	0	–
Site of Primary (n = 56)§												
Colon	18	1 (6)	6	0.20	5 (28)	29	0.03	81	77	63	63	0.10
Rectum	38	6 (16)	21	–	22 (58)	53	–	37	65	51	38	–
Grade (n = 56)§												
1, 2	27	2 (7)	4	0.09	15 (56)	43	0.83	67	73	60	54	0.28
3, 4	29	5 (17)	32	–	12 (41)	45	–	37	68	51	36	–
Nodal Status (n = 51, Unk = 5)												
Negative	24	1 (4)	4	0.11	12 (50)	50	0.95	45	79	67	47	0.34
Positive	27	5(19)	23	–	14 (52)	48	–	28	59	46	41	–
Total Group	56	7 (13)	16	–	27 (48)	45	–	40	70	55	46	–

* Logrank p-value modified from ref. 43.

$^{\Delta}$1 of 39 had chemotherapy prior to but not concomitant with EBRT.

† Central failure in IOERT field occurred in only 1 patient (preoperative EBRT + 5-FU, rectal, no resection).

‡ p-value for comparison of two major variables (gross ≤ microscopic); when all 5 variables are included (gross; ≤ microscopic–margin (+), margin (–), no tumor; no resection) p < 0.0001 for local control, 0.04 for distant control, 0.001 for overall survival and 0.008 for disease-free survival.

§ Time to relapse by grade;. Gr 2 LF range 1.0–5.5 yr, DF range 0.5–5.5 yr; Gr 3—all LF by 3 yr DF by 1.5 yr; Gr 4—all LF by 2 yr, DF by 1.5 yr.

EBRT = external beam irradiation; IOERT = intraoperative electron irradiation; LF = local failure in EBRT field; DF = distant failure; 5-FU = 5-fluorouracil; Unk = unknown.

without chemotherapy results in excellent short-term palliation (usually less than one year), median survival or 10 to 18 months, but rare long-term survival (0% to 7% at 5 years) (Table 7). With the addition of IOERT supplements to standard treatment, 5-year survivals of ~20% have been achieved in series from both MGH and Mayo (45–50).

In a Mayo analysis of 106 locally recurrent rectal cancer patients with palliative resection and no extrapelvic disease, 42 received IOERT (46). Overall survival with IOERT versus no IOERT was 3 years—43% vs. 18% and 5 years—19% vs. 7% (p = 0.0006) (Table 7). The 3-year survival differences favoring IOERT also persisted when subset analyses were done which evaluated results in patients who presented with pain or had gross residual disease remaining after maximal resection (overall 3-year survival 43% vs. 19% and 44% vs. 15%, respectively; disease-free survival 25% vs. 8% and 29% vs. 6%, respectively).

In an updated Mayo analysis, 123 previously unirradiated patients with local regional relapse of colorectal cancer received IOERT as a component of treatment (47). Disease control and survival were similar to that reported by Suzuki in the smaller group of 42 IOERT patients (Table 7) (6). The only progonostic factor which had a trend for improved overall and disease-free survival was EBRT + 5FU vs. EBRT alone.

Sequencing of modalities

The preferred sequencing of modalities in IOERT-containing regimens is usually preoperative external irradiation plus chemotherapy followed by maximal resection and IOERT. Several analyses including those of the MGH (Table 6) have shown the advantage of achieving a gross total resection whenever this is safe and feasible for both primary and recurrent lesions even when IOERT is a component of treatment (40, 45, 48–51). In recent Mayo IOERT analyses, the advantage of gross total resection

Table 9

Colorectal IOERT—locally recurrent, no prior EBRT disease relapse and overall survival by prognostic factor, Mayo (9/95 analysis)

Prognostic factor	No. at risk	Local (EBRT) (%)			Distant (%)			Overall survival % p-value				
		No. (%)	3yr	p*	No. (%)	3yr	p*	Median (mo)	2-yr	3-yr	5-yr	
EBRT ± 5-FU												
EBRT	32	5 (16)	16	0.46	20 (63)	69	–	25	55	29	16	–
EBRT + 5-FU	91	19 (21)	29	–	45 (50)	63	0.32	31	65	43	22	0.14
Treatment sequence												
PreopEBRT + 5-PU	78[†]	17 (22)	31	–	36 (46)	61	0.36	31	66	44	19	0.91
Postop EBRT + 5-FU	13[†]	2 (15)	17	0.43	9 (69)	71	–	28	56	38	28[ˆ]	–
Site of primary												
Colon	43	6 (14)	20	0.51	24 (56)	76	–	27	59	26	21	–
Rectum	80	18 (23)	26	–	41 (51)	60	0.19	31	64	43	20	0.60
Amount of residual												
Gross	65	16 (25)	32	–	37 (57)	64	–	27	60	36	18	–
≤ Microscopic	57	8 (14)	16	0.30	27 (47)	64	0.84	29	64	41	24	0.56
No resection	1	0	–	–	1	–	–	–	1/1	–	–	–
Grade (n = 121, unk-2)												
1, 2	69	15 (22)	24	0.81	41 (59)	66	0.98	29	65	39	19	0.65
3, 4	52	9 (17)	28	–	24 (46)	63	–	27	56	38	22	–
Total group	123	24 (20)	25	–	65 (53)	64	–	28	62	39	20	–

Abbreviations: IOERT = intraoperative electron irradiation; EBRT = external beam irradiation; 5-FU = 5-fluorouracil.
* Logrank p-value modified from ref. 47.
[†] 1 patient each group with EBRT dose < 40 Gy.
[ˆ] Survival decreased to 19% at 5.5yr.

with regard to local control and survival was demonstrated in the 56 IOERT patients who presented with locally advanced primary lesions (43) (Table 8). In the 123 IOERT patients who presented at IOERT, the time of local relapse without prior EBRT (47), however, the 5-year survival in the 65 patients with gross residual was 18% vs. 24% for those with ≤ microresidual (Table 9).

The risk of systemic failure is ≥ 50% in patients with locally advanced colorectal cancers, which provides the rationale for the routine addition of maintenance chemotherapy to concomitant radiochemotherapy and resection. Pilot trials have demonstrated that either the two-drug bolus combination of 5-FU plus leucovorin (52) or protracted venous infusion 5-FU (17) can be combined with external irradiation with acceptable tolerance, thus starting effective local and systemic treatment simultaneously. Therefore, it is reasonable to have patients receive both concomitant and maintenance 5-FU-based chemotherapy.

Future directions

When IOERT-containing trials are compared with standard treatment approaches in separate analyses from MGH and the Mayo Clinic, encouraging trends are seen with regard to improvement in local control and possibly the survival of patients with locally advanced primary and recurrent colorectal lesions. However, the incidence of systemic failure is ≥ 50%, and local failures within the IOERT and EBRT fields still occur especially when a gross total resection is not surgically feasible. In an attempt to improve local control, it seems reasonable to consistently add protracted or infusion 5-FU or bolus 5-FU + leucovorin or other enhancing or additive agents during EBRT and to evaluate the use of dose modifiers in conjunction with IOERT (sensitizers, hyperthermia, etc.). In view of the high systemic failure rates, clinical trials should evaluate the use of more aggressive chemotherapy during and after external irradiation. Since survival advantages with 5-FU plus leucovorin versus 5-FU alone have been demonstrated in randomized trials for metastatic disease, this regimen is currently being employed as the maintenance systemic component of treatment. Protracted venous infusion 5-FU as systemic treatment and during EBRT is also reasonable to evaluate in locally advanced primary or recurrent disease, in view of results in the adjuvant setting.

While it would be of scientific interest to randomly compare standard treatment with or without an IORT electron or brachytherapy boost, such trials were attempted in the US and could not be completed. Many patients are referred to institutions with IORT or brachytherapy expertise with the expectation of receiving the specialized boost technique and will not consent to randomization. Trials which will be easier to complete in the US are those in which surgical, external beam, and intraoperative irradiation options with electrons or brachytherapy are standard and the randomization tests optimal chemotherapy during as well as after external irradiation and test the presence or absence of radiation sensitizers or dose modifiers during IORT.

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