Whole Abdominal Radiotherapy and Concomitant 5-Fluorouracil as Adjuvant Therapy in Advanced Colon Cancer

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PURPOSE: This analysis was undertaken to assess whole abdomen radiation therapy and concurrent 5-fluorouracil for toxicity and patterns of failure in high-risk colon cancer patients after curative surgical resection. METHODS: Eighteen patients were treated adjuvantly after curative resection. Four patients (22 percent) had Stage B and 14 (78 percent) had Stage C disease. Histology was poorly differentiated in 4 (22 percent) and moderately differentiated in 14 (78 percent) patients. Four patients received whole abdominal radiation only, 30 Gy at 1 Gy/day. Fourteen patients had an additional locoregional boost of 9.6 to 16 Gy at 1.6 Gy/day. The liver received 19.8 Gy at 0.67 Gy/day. 5-Fluorouracil was given as a continuous infusion during therapy. RESULTS: With a median follow-up of three years, 6 of 18 (33 percent) patients have relapsed. Failure occurred locally in 3 of 18 (17 percent) and distantly in 4 of 18 patients (22 percent). Four of six (67 percent) failures occurred in the liver. The five-year actuarial survival and disease-free survival were 78 percent and 66 percent, respectively. Median elapsed time on radiotherapy was 73 days, with 5 of 18 patients (28 percent) requiring two or more weeks of unplanned treatment breaks. Acute Grade 3 to 4 toxicity (diarrhea, leukopenia) occurred in 3 of 18 patients (17 percent), with late complications (bowel obstruction) occurring in 2 of 18 patients (11 percent). CONCLUSIONS: Whole abdominal radiotherapy with concomitant 5-fluorouracil appears to improve local control but not to prevent liver metastases. Significant toxicity resulted in frequent interruption of therapy and protracted its course. Whether this adjuvant regimen impacts on survival or offers an advantage over locoregional irradiation remains to be studied. [Key words: Whole abdomen radiotherapy; Colon cancer; Adjuvant therapy; Combined modality]

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Local recurrence of carcinoma of the colon after curative resection is a frequent occurrence. Subset of patients at particularly high risk include those with tumors extending through the bowel wall with adherence or invasion of adjoining structures or lymph node involvement. As many as 31 percent of modified Astler-Coller Stage B3 and 53 percent of Stage C3 patients fail within the tumor bed, in adjacent organs (by direct extension), or in regional lymph node groups.[1, 2] Distant metastases develop in 27 to 45 percent of these patients, predominantly in the abdomen.[1, 2]

Because disease recurrence is almost invariably fatal, various adjuvant treatment programs have been studied. A survival benefit with 5-fluorouracil (5-FU) plus levamisole has been recently demonstrated for node-positive patients in the Mayo/North Central Cancer Treatment Group trial[3] and confirmed by a larger intergroup trial.[4] Adjuvant radiation therapy for colon cancer above the peritoneal reflection has not been studied in a prospective randomized fashion. Several retrospective studies, however, suggest a decrease in local failure for patients with modified Astler-Coller Stages B3, C2, and C3 and an improvement in the five-year disease-free survival rate for patients with Stages B3 and C3.[5–9] Whole abdomen radiation (WAR) therapy has been used as adjuvant treatment by several groups[10–12] with inconclusive results. The combination of WAR and concomitant continuous infusion of 5-FU was pioneered at the University of Kansas[13] and has been in use at our institution since 1986. This retrospective study was undertaken to evaluate the toxicity of this regimen and its potential to reduce intra-abdominal recurrence rate.

METHODS

Patient Characteristics

During the period from 1986 to 1991, 22 patients were treated with WAR and continuous infusion of 5-FU following curative resection of an advanced colon cancer above the peritoneal reflection. Eighteen of these patients were treated adjuvantly; four were treated for peritoneal metastasis and will not be discussed further. Pretreatment extent of disease evalu-

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ation consisted of physical examination, complete blood count, chest x-ray, and CT scan of abdomen and pelvis. Staging was according to the modified Astler-Coller system. All patients were ambulatory and capable of self care.

Patient's ages ranged from 33 to 76 (median, 63) years. Other pertinent characteristics are summarized in Table 1.

Treatment Protocol

Patients started radiation therapy a median of 43 days following surgical resection. Radiation was delivered with megavoltage photons of 10 MV or 15 MV. Seven patients received only WAR; 12 patients completed an additional boost to the primary tumor bed and regional lymph nodes. WAR was administered through parallel opposed anteroposterior and posteroanterior fields at 1 Gy/day fractions to a planned total dose of 30 Gy. During WAR the dose to the liver was reduced by partial transmission blocks to 0.67 Gy/day. Median whole liver dose was 19.8 Gy. Kidneys were shielded by five half-value layer blocks for the posteroanterior field, thus limiting whole kidney dose to a median of 14.4 Gy. Locoregional boost consisted of 9.6 to 16 Gy (1.6 Gy/fraction) delivered with two to four field arrangements. A planned treatment interruption of one to two weeks was incorporated into the radiation treatment regimen.

Table 1.
Patients Characteristics

	No. of Patients	% of Total
Sex		
Male	10	55
Female	8	45
Stage*		
B2	3	17
B3	1	5
C1	2	11
C2	11	61
C3	2	5
Grade†		
2	13	72
3	5	28
Site		
Sigmoid	5	28
Ascending	3	17
Cecum	4	22
Transverse	5	28
Descending	1	5

* Modified Astler-Coller system.

† 2 = moderately differentiated; 3 = poorly differentiated.

Chemotherapy was started between two and eight weeks following surgery. 5-Fluorouracil began as a continuous infusion of 200 mg/M^2/day, seven days per week during radiotherapy.

Statistics

Actuarial survival and disease-free survival were calculated using the life-table method.

RESULTS

With a median follow-up of 36 months, six (33 percent) patients have relapsed. No patient was lost to follow-up. Table 2 illustrates the treatment outcome for patients treated adjuvantly. Table 3 reveals the patterns of failure. Local failures were seen in the pelvis and retroperitoneum (one at each site). Distant metastases were seen predominantly in the liver and accounted for four of six (67 percent) failures. Actuarial survival is illustrated in Figure 1. Disease-free survival is illustrated in Figure 2. Five-year actuarial survival was 78 percent. Median survival has not yet been reached.

Radiation therapy was administered for 43 to 110 (median elapsed time, 73) days. This included one to two weeks of planned treatment interruption. Unplanned treatment break lasted up to 48 (median, 5) days, with 5 of 18 (28 percent) requiring more than two weeks. Acute Grades 3 to 4 toxicity occurred in 3 of 18 (17 percent) patients (diarrhea in two, leukopenia in one). Late toxicity was manifested as three episodes of small bowel obstruction in two patients; one required surgery.

DISCUSSION

The combination of chemoradiotherapy we used has been designed with the intent of reducing intraabdominal recurrence in patients with transmural and node-positive colon cancer. After a gross total resection this adjuvant regiment was expected to address possible microscopic residual disease. The radiation dose prescribed was lower than the dose traditionally considered effective in controlling microscopic disease.[14] However, it was based on the observation that ineffective doses of either radiation or 5-FU, when used in combination, were curative for certain rodent tumors.[15, 16] The mechanism underlying this synergism is assumed to be depletion by 5-FU of tumor cells in the relatively radioresistant S-phase, thereby rendering the surviving tumor cell population sensitive to subsequent irradiation. In addition, 5-FU also

Table 2.
Treatment Outcome

Patient	Sex	Stage	Site	Dose*	Status	Follow-Up†
1	F	C2	Cecum	46	DOD	9.7
2	M	C2	Ascending	46	AWD	13.7
3	M	C1	Sigmoid	30	DOD	15.9
4	M	C3	Transverse	39.6	DOD	18.9
5	M	C2	Transverse	46	NED	19.9
6	F	B2	Ascending	42	NED	21.9
7	M	C2	Descending	46	NED	27.1
8	F	C2	Sigmoid	46	NED	37.2
9	F	C2	Ascending	46	NED	40.9
10	M	C2	Transverse	46	NED	41.1
11	F	C2	Sigmoid	46	AWD	42.4
12	M	B2	Cecum	46	NED	46.8
13	M	B3	Sigmoid	30	AWD	51.8
14	M	C1	Transverse	46	NED	53.6
15	M	B2	Cecum	46	NED	59.7
16	F	C2	Sigmoid	46	NED	68.3
17	F	C2	Cecum	30	NED	74.5
18	F	C2	Transverse	30	NED	76.7

AWD = alive with disease; NED = no evidence of disease; DOD = dead of disease.
* Dose to primary site specified in Gy.
† Length of follow-up from surgery specified in months.

Table 3.
Pattern of Failure

Patient	Site of Failure	Time to Failure*
1	Liver, lung	4.1
2	Liver, retroperitoneum	7.2
4	Liver	7.5
3	Pelvic	10.1
11	Liver, lung	22.6
13	Retroperitoneum	39.8

* Months from completion of radiotherapy.

inhibits sublethal damage repair, and optimal radiosensitization, therefore, requires the presence of the drug both before and after irradiation.

The local failure rate of 28 percent (5/18) observed in this study compares favorably with the rate of 40 to 60 percent expected after surgery only[1, 2] and is similar to what has been reported with postoperative local abdominal irradiation.[5–9] Five-year local failure rates reported by Willett *et al.*[9] were 10, 8, 21, and 31 percent for Stages B2, B3, C2, and C3, respectively. Wong *et al.*[5] reported local relapses in 9 of 28 (32 percent) Stage C patients and 3 of 20 (15 percent) Stage B2 patients. These results were obtained with doses of 45 to 54 Gy. Total dose to tumor bed in our study ranged from 30 to 46 (median, 46) Gy. Although a statistically valid dose-response analysis was not performed because of the small number of patients, it is interesting to note that two of three local failures occurred after doses of 30 Gy. Disease recurred in 60 percent (3/5) and 23 percent (3/13) of patients receiving less than 40 Gy or 40 Gy and more, respectively. Liver metastases occurred in 4 of 18 (22 percent) patients. The liver was the predominant site of failure accounting for four of six (67 percent) failures. This failure rate is not unlike that observed with no adjuvant treatment[1, 2] or with prophylactic liver irradiation.[17] The Gastrointestinal Tumor Study Group (GITSG), in a prospectively randomized study, noted no benefits (in terms of liver recurrences or survival) from adjuvant 5-FU and hepatic irradiation.[17]

It is important to note, though, that the dose of radiation delivered to the liver, both in our study (19.8 Gy) and by GITSG (21 Gy), was relatively low. Colon cancer cells are generally considered moderately radioresistant,[18, 19] and higher doses of radiation might prove more effective. Ingold *et al.*[20] suggested that the whole liver could tolerate 25 to 30 Gy conventionally fractionated, in the absence of chemotherapy. Rotman *et al.*[21] reviewed their experience with concomitant infusion of 5-FU and radiotherapy for colorectal hepatic metastasis and advocated not to exceed 27 Gy in 1.8-Gy fractions given for five weeks. Although the whole liver radiation tolerance dose is not accurately established, it seems that further dose escalation is still feasible.

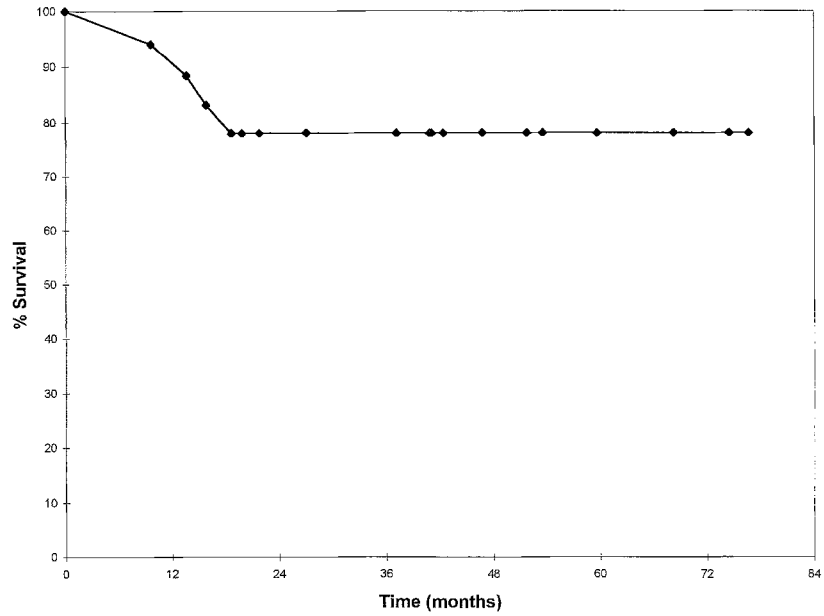

Figure 1. Overall survival.

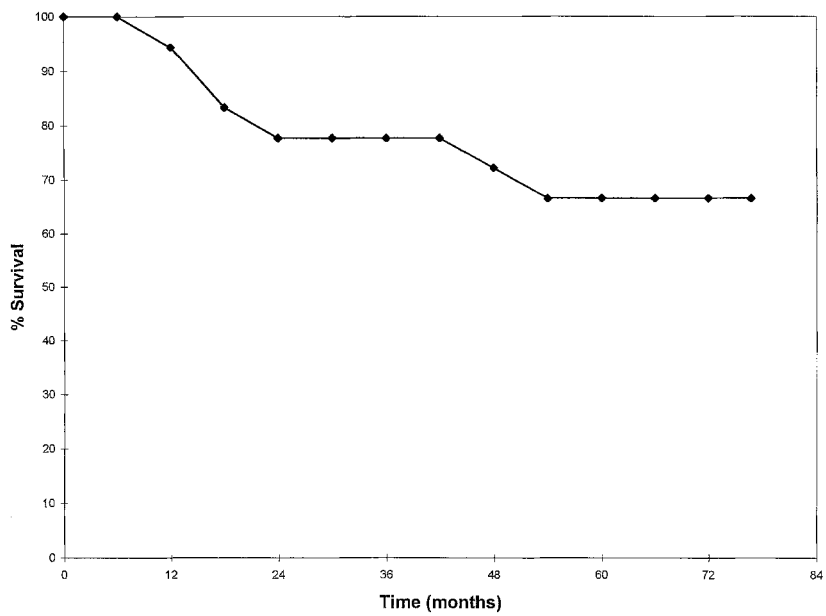

Figure 2. Disease-free survival.

The five-year actuarial survival and disease-free survival in our series are 78 and 66 percent, respectively. These rates are remarkably similar to those reported by Fabian *et al.*[13] (81 percent survival at 32 months). They compare favorably to results reported by Willett *et al.*[9] for similar high-risk patients treated with surgery (58 percent 5-year survival) or surgery and local field radiotherapy (62 percent 5-year survival). Survival rate also compares favorably with that reported for patients observed (59 percent) or treated with prophylactic liver irradiation (60 percent) on GITSG study[17] or that reported by Wong *et al.*[5] for patients treated with adjuvant local abdominal irradiation (67 percent). However, given the small number of patients and limitations of a retrospective analysis, no conclusion can be drawn regarding the impact of this type of treatment on survival.

Toxicity of the treatment was considerable but not significantly different than what has been previously described with WAR. Acute Grades 3 to 4 toxicity occurred in 3 of 18 (17 percent) patients. Late complications occurred in 2 of 18 (11 percent) patients.

Unplanned treatment breaks were needed in the majority of patients and lasted up to 48 (median, 5) days. This was in addition to the one to two weeks of planned interruption that was incorporated into the treatment plan. This protraction may have contributed to a decrease in efficacy, by allowing tumor cells to repopulate during treatment. If WAR should be further explored as adjuvant treatment, ways must be found to reduce its toxicity to allow completion of treatment without undue delays. Attractive solutions to this problem include hyperfractionation[22, 23] and systemic administration of radioprotectors.

CONCLUSIONS

The combined chemoradiotherapy described appears to achieve superior local control to that achieved with surgery alone and is similar to that achieved with adjuvant local field irradiation. Morbidity was substantial and caused treatment protraction, which might have reduced efficacy. This treatment regimen does not appear to prevent development of liver metastasis, and its impact on survival has yet to be studied.

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