Chemotherapy as an Adjuvant to Surgery for Colorectal Cancer

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A combined intraoperative and postoperative adjuvant program of 5 - Fluorouracil (5 FU) for patients undergoing "curative" resection for adenocarcinoma of the colon and rectum was initiated as a randomized clinical trial in January 1968. Patients at the Medical College of Virginia and the University of Virginia were randomly assigned to an intraluminal 5 FU or intraluminal control (Saline) group and were so treated at the time of surgical resection if findings at operation indicated that all gross neoplastic disease could be resected. Patients with operative findings denoting incurability were eliminated from the study after surgical exploration. Those patients receiving intraluminal 5 FU (30mg/kg) received intravenous 5 FU (10mg/kg) on each of the two first postoperative days and 5 subsequent postoperative courses of oral 5FU (90 mg/kg in each 18 day course) over a one year period. By December 31, 1973 (6 years) 156 patients undergoing "curative" resection were entered into the study. Survival curves and "disease free" curves for comparison of the group receiving adjuvant 5 FU therapy with the control or "No Treat" group reveal no significant benefit from this intensive adjuvant course of 5 FU thus far. Continued assessment of these patient groups and their subgroups will be required to develop confidence in these findings but the data thus far suggest no potential benefit from this particular adjuvant program.

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THE RATIONALE for combining chemotherapeutic agents with curative operative attempts for "solid tumors" has had great appeal as a potential means of improving end results of surgery for cancer. Despite a great deal of interest in this approach there have not yet been any clinical studies conclusively demonstrating benefit from surgical adjuvant chemotherapy for any of our common adult cancers. In January 1968 we initiated a cooperative two institution clinical trial designed to evaluate a combined intraoperative and long term postoperative adjuvant 5 fluorouracil program for cancer of the colon and rectum. This is a preliminary report of our findings

The surgical adjuvant studies for large bowel cancer reported thus far include trials of thiotepa,[7] 5 fluorouracil (5 FU),[6,8] and flurodeoxyridine (FUDR).[3] These trials have used either intraoperative chemotherapy,[4,8] chemotherapy immediately following the surgical resection,[6] or limited additional courses of chemotherapy later in the postoperative period.[3,6] Some studies have included only patients undergoing "curative" resection, while others have included separately identified groups undergoing palliative resection as well. The results have been well summarized by Carter and Friedman.[2]

The first major cooperative clinical trial for large bowel cancer, reported by Holden et al.,[7] was carried out with two different dosage levels of thiotepa due to increasing morbidity associated with the initial drug dosage chosen. Adjuvant therapy with this agent was limited to the immediate post-operative period. Later evaluation of this trial did show a trend toward benefit from adjuvant chemotherapy with thiotepa in the subgroup of females over 55 years of age who received the initial higher dosage schedule. Unfortunately this beneficial effect was balanced by the higher morbidity experienced at this high dose rate. The overall case for adjuvant therapy with alkylating agents was not made in this particular study, but this was only an immediate postoperative program with no effort to accomplish chronic treatment of minimal residual disease.

Interest then shifted to the fluorinated pyrimidines as

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possible adjuvants due to the demonstrated effectiveness of 5 fluorouracil in the management of advanced carcinoma of the colon and rectum. Rousselot and coworkers[8] initiated a trial of intraluminal 5 FU with immediate postoperative intravenous 5FU administration in a series of patients with cancer of the colon and rectum. There appeared to be a favorable trend in long term survival with adjuvant 5FU in comparison to prior surgical results, particularly with those patients who demonstrated lymph node metastasis. On this basis a multihospital cooperative project with double blind randomization of patients undergoing "curative" resection was initiated and this study is still in progress.[4] Meanwhile, two controlled trials, carried out by the Veterans Administration Surgical Adjuvant Cancer Chemotherapy Group, studied patients with carcinoma of the large bowel to determine the possible benefits of 5 FU[5] and of FUDR[3] as adjuvants to surgical resection. In both of these trials after "curative" resection, patients were given adjuvant therapy soon after surgery and again approximately 6 weeks following surgery. In neither of these studies could benefit from the adjuvant be demonstrated. In a more recent long range trial of intermittent postoperative systemic 5 FU by this Veterans Administration Surgical Adjuvant Group, there has been no evidence of survival benefit with intermittent courses carried out to the 19th month following operation. The followup period for this latter study is still quite short (2 years) and final conclusions cannot be drawn. However, it is fair to say that none of the adjuvant drug trials performed thus far have demonstrated convincing benefits from the adjuvant chemotherapy approach to surgery for colon and rectal cancer.

The rationale of this current study was based on the concept that intraluminal and intravenous chemotherapy at the time of operation might add some benefit (as suggested by the data of Rousslot et al.[8]) but long term postoperative administration of the chemotherapeutic agent might have supplementary benefit as well. Clinical trials prior to this study have been limited to relatively short term courses of therapy and it was conceivable that a useful margin of benefit could be detected by a more aggressive approach than had been employed up to the time this study was initiated. It was also considered worthwhile to give a maximum trial of 5 FU as the adjuvant since this agent had been shown to have a definite, albeit low, order of activity against measurable disease in patients with large bowel cancer (15-25% objective response rates).

Description of Study

This prospective surgical adjuvant study was initiated in January 1968 and the results to be reported include those patients entered January 1, 1968 through December 31, 1973 from the surgical services of the Medical College of Virginia Hospitals (Richmond) or the University of Virginia Hospital (Charlottesville). The random assignment of eligible patients with colon and rectal cancer to either a control or a 5 FU adjuvant group had been made prior to operation by calling a central point at each of the two institutions. Separate lists of random numbers for this purpose are maintained for cancer of the rectum (<15 cm from the anal verge) and cancers of the colon (>15 cm from the anal verge). Essentially equal groups of colon and rectal lesions are assigned to each group by this means.

Patient Eligibility. All patients with a clinical diagnosis of colon or rectal cancer and preoperative findings compatible with "curative" resection are eligible for this study except: 1). Patients considered "inoperable" for medical reasons or unsuitable for standard surgical resection for the same reasons; 2). Patients that have received prior irradiation, chemotherapy, or surgical resection for the current cancer other than preliminary colostomy for obstruction; 3). Patients with a primary cancer of another site (other than basal or squamous cell carcinoma of the skin); 4). Patients who are pregnant at the time of diagnosis; 5). Patients more than 80 years of age; 6). Patients who will require multiple organ resection, such as pelvic exenteration, due to extracolonic involvement of other organs (this observation may not be made until time of operation); 7). Patients with carcinoma of the colon who have free perforation of the cancer itself or the more proximal colon; 8). Patients who have a preoperative white blood cell count less than 4,000, or preoperative platelet count less than 150,000.

The fact that patient entry into this protocol occured prior to the time the operative procedure was actually accomplished led to a need for a system to eliminate patients found to be ineligible for a curative surgical procedure on the basis of operative findings. Some patients initially entered into the study were subsequently eliminated at the time of exploration if operative findings revealed factors that made the patient ineligible for the study as designed. These operative factors were either the presence of metastases, the direct involvement of extracolonic organs by the cancer itself, or the unexpected finding that the clinical diagnosis of colorectal cancer was incorrect. The preoperative assignment of patients to the 5 FU treatment or control groups prior to final pathologic classification also led to our inability to stratify the patients on the basis of various prognostic factors that may be found on pathologic study.

Intraoperative and Early Postoperative Management. After exploration to determine the presence or absence of metastases or extra colonic involvement by the neoplasm, the presence of the cancer is confirmed by gross examination. Early in the operation umbilical tapes are placed inside the proposed lines of resection and are so placed that they include the marginal vessels adjacent to

the bowel. For rectal lesions a purse string suture is placed around the anus prior to the exploratory surgery and only one tape is placed around the bowel on the proximal side.

After the bowel segment is isolated, 5 FU (30 mg/kg) diluted in 50 ml of physiologic saline, or 50 ml of saline without agent, is injected into the bowel lumen and the needle puncture site closed with a purse string suture. Although dissection for collectomy is begun, the blood supply to the colon is not ligated for a period of 30 minutes after intraluminal instillation. A standard radical colectomy is then performed using a "no touch" technique in so far as this is possible for the site of the particular primary lesion. This consists of a right hemicolectomy, left hemicolectomy, or abdominoperineal resection with the associated mesentery and blood vessels. For rectal lesions the operation includes ligation of the inferior mesenteric artery either at the aorta or just distal to the left colic branch of the inferior mesenteric artery.

On the first and second postoperative days patients randomized for adjuvant 5 FU receive intravenous 5 FU (10 mg/kg) in one liter of intravenous physiologic saline each day. All other details of postoperative management are standard and the same for both the control and the 5 FU treated patients. The overall procedure followed in the operative and immediate postoperative period is essentially the same as that described by Grossi, Nealon, and Rousselot.[4] The procedural addition in this study is the long term postoperative course of 5 FU.

Pathology Evaluation. Pathologic study has confirmed the diagnosis of adenocarcinoma in all patients remaining in the study and pathologic staging has been carried out at both institutions. A final pathologic diagnosis of a benign neoplasm or a malignant neoplasm other than adenocarcinoma has been a reason for elimination of the patient from the study. Microscopic proof of invasion of extracolonic organs has also been a reason for elimination of a patient from the study.

Postoperative Adjuvant Chemotherapy. Patients in the 5 FU treatment group receive 5 postoperative oral courses of 5 FU with the initial course being 30 days postoperative. Additional courses are begun each two months for a total of 5 complete 18-day courses. Oral 5 FU medication in fruit juice is administered each morning of treatment giving 12 mg/kg daily for 4 days and 6 mg/kg every other day for 7 doses (or less if leukopenia, thrombocytopenia, or signs of oral or gastrointestinal toxicity develop). Patient status and hematologic studies are monitored prior to each course of chemotherapy and at weekly intervals during these courses. Modification of drug dosage is dependent on both the clinical status and laboratory studies.

During the postoperative courses of treatment with 5 FU the drug is discontinued if the white blood cell count is less than 4,000 or the platelet count is less than 90,000. One half the dose outlined is given on the same schedule if the white blood cell count is between 4,000 and 5,000 or the platelet count between 90,000 and 125,000. Also if diarrhea develops, the drug is discontinued, but if the significance of this finding is questionable, and later followup substantiates the lack of toxicity, the drug is restarted.

Followup Observations. Patients on this study are followed monthly during the first year, every two months the second year, every 3 months the third year, and every 4 months the fourth and fifth years after surgery. Patients are subsequently followed every 6 months after the 5 year interval. Special forms outlining the patient's status are filled out at the time of each evaluation and these include details of the complete physical examination, protoscopic examinations at intervals to search for local recurrence or metastasis, and intermittent biochemical and x-ray evaluations. Patients in both the 5 FU adjuvant and control groups are followed at the same intervals. No placebo is used for patients in the control group as this study has not been performed in a "double blind" fashion.

Results

Of the 241 patients entered into this study by preoperative randomization January 1, 1968 through December 31, 1973, 85 patients have been eliminated following randomization. Two of these patients refused to participate in the study after initial randomization and 83 patients were subsequently found to be ineligible due primarily to findings at the time of operation or on later pathologic study (Table 1). The total number of patients eligible for analysis after this operation and pathologic evaluation is 156 patients (123 from Medical College of Virginia Hospitals and 33 from the University of Virginia Hospital). Of this total group 80 were randomized into the 5 FU adjuvant treatment group and 76 into the control group.

The patient profiles of the control and adjuvant therapy groups are shown in Table 2. The number of rectal cancer and colon cancer patients in each group are essentially equal in view of the stratification of patients into these categories at the time of randomization. The proportion of patients in each group with histologically involved

TABLE 1. *Reasons for Ineligibility for Clinical Trial After Initial Preoperative Randomization.*

Total patients entered-		241
Subsequent ineligibility:		
Intra-abdominal metastases	46	
Lesion not cancer	18	
Other malignant colon neoplasms	2	
Invasion extracolonic organs	9	
Multiple colorectal cancers	1	
Refused surgery after entry	2	
Other procedural problems	7	
Total	85	
Eligible patients retained in trial		156

TABLE 2. *Patient Profiles of Eligible Patients in the Control and 5 FU Groups (Clinical Trial of Adjuvant Chemotherapy After "Curative" Resection for Colorectal Cancer).*

	Adjuvant 5 FU	Control
Total cases	80	76
Sex (M:F)	40:40	36:40
Age—Mean	60.7	63.4
Range	33-80	24-85
Anatomic site		
Colon (> 15 cm)	49	49
Rectum (< 15 cm)	31	27
Pathologic stage		
Dukes' A or B	53	48
Dukes' C	27	28
Total cases	80	76

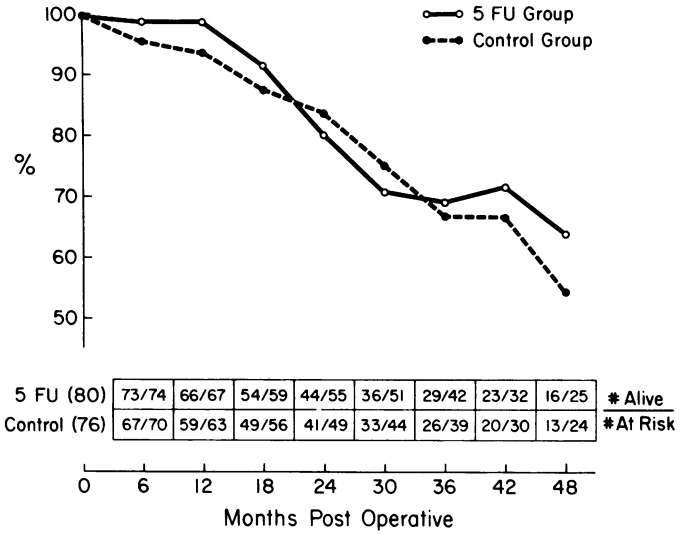

FIG. 1. Colorectal cancer. Survival after "curative" resection (all stages).

lymph nodes (Dukes' C) are quite comparable by virtue of the randomization process although this pathologic finding was unknown to the investigator at the time of the patient's entry into the protocol. Age and sex, other factors that might affect the subsequent treatment results, are also essentially similar in the two groups. The operative complication rates and mortalities are also similar for the control and adjuvant therapy groups (Table 3).

Drug Dosage Received. There have been no signs of hematologic or other toxicity in the early postoperative period in the adjuvant treatment group. The number of complete courses of chemotherapy and the total drug dose received in the first postoperative year is shown in Tables 4 and 5. In most instances incomplete drug dosage and incomplete numbers of postoperative courses were due to leukopenia, using the criteria for hematologic toxicity previously defined. Twenty-two patients in the 5 FU adjuvant group developed some degree of leukopenia and 8 patients developed signs of gastrointestinal toxicity which led to dosage reduction or discontinuation of 5 FU. The toxicity observed was evenly distributed between the colon and rectal groups (Table 6).

The total planned course of 5 FU has been successfully accomplished in 67% of the patients in the adjuvant therapy group. This, plus the fact that 23% of the adjuvant treatment group have received less than 40% of the total planned dosage, due primarily to hematologic toxicity, suggests that the dosage schedule chosen is in an effective range for the purpose of this study. Following the conservative guidelines outlined for dose restriction there have been no significant sequellae from chemotherapeutic treatment in the adjuvant group. Oral ulceration was not seen as a concomitant of 5 FU toxicity.

Survival Statistics. The results in the combined rectal and colon control and 5 FU adjuvant therapy groups thus far can be estimated from survival curves that have been constructed for each of these groups. The data shown at each 6 month interval after operation are based on the time "at risk" for each patient at the time of the survival calculation for this report (May 1, 1974). The three patients who died as a result of the operation are eliminated from this calculation. Also, those patients who clearly died from other causes, without evidence of recurrent or

TABLE 3. *Operative Complications and Mortality in Clinical Trial of Adjuvant 5 FU After "Curative" Resection for Colorectal Cancer*

	Total Patients	5 FU Group	Control Group
Number	156	80	76
Post-op Complications	38 (24%)	20 (25%)	18 (24%)
Operative Mortality (<30 Days)	3 (1.9%)	2 (2.5%)	1 (1.3%)

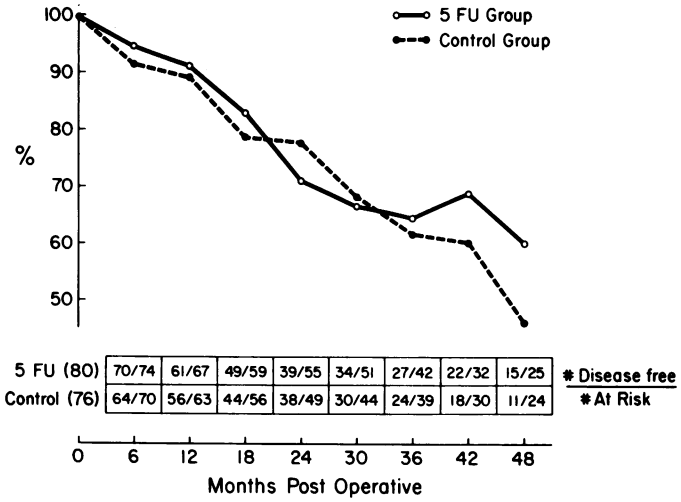

FIG. 2. Colorectal cancer. Survival free of recurrence after "curative" resection (all stages).

TABLE 4. *Total Courses of Oral 5 FU Received in Adjuvant Chemotherapy Group in First Postoperative Year of Clinical Trial**

No. of Postop Courses	Total Group	Colon Cancer	Rectal Cancer	Colon & Rectal Cancer	
				Dukes' A & B	Dukes' C
All 5 Courses	50/75 (67%)	29/46 (63%)	21/29 (72%)	34/50 (68%)	16/25 (64%)
< 2 Courses	17/75 (23%)	11/46 (24%)	6/29 (21%)	12/50 (24%)	5/25 (20%)

* 75 patients >1 year postop

metastatic cancer, were considered free of cancer at the calculated 6 month interval prior to death, but were eliminated from the calculation in the next period "at risk." The actual data and the visual graph of these results reveals no detectable difference in survival between the two groups (Fig. 1). The 95% confidence limit at three years indicates that, on the basis of current figures, the survival rate for the 5 FU group will not exceed the control group by more than 19%. Looking at the data for three year survival in another way, the probability of finding a statistically significant difference ($P<.05$) is 0.7 if there was a 20% difference actually present. Longer followup observations on patients already entered into this protocol will naturally increase our confidence in this "negative" result.

Data from these same groups using the time of recurrence or metastasis, rather than death as the end point of treatment failure, are presented in Figure 2. Again no difference between the 5 FU adjuvant treatment group and control group is apparent.

The survival data from those patients with rectal cancer (less than 15 cm from the anal verge) are graphed separately in Figure 3. The total number of patients with rectal lesions appears too small for a reliable comparison of the 5 FU adjuvant treatment and control groups, but it is noteworthy that the constructed survival curves are similar to those calculated for the combined groups of colon and rectal lesions. Another selected subgroup of the whole, the Dukes' C lesions, was examined separately despite the small numbers of patients concerned. Again, there was no suggestion of benefit from adjuvant therapy noted (Table 7).

Discussion

It must be stressed that these results comparing "curative" surgery for colorectal cancer with and without adjuvant 5 FU therapy must be considered preliminary. There has been no demonstrated benefit for the group subjected to this lengthy adjuvant program following surgical resection, but the number of patients and the length of followup are both inadequate to clearly establish the fact that any possible difference is "contained" in a range that is of negligible ultimate benefit.

In view of the fact that there is good rationale for therapeutic value from adjuvant chemotherapy following "curative" surgery for cancer, it is prudent to consider possible factors that may have lead to our failure to demonstrate adjuvant benefit with this particular program of 5 FU. These factors include the choice of the chemotherapeutic agent itself, the total dosage administered in the postoperative interval, the actual schedule or method of drug administration, as well as other aspects of the conduct of the study. It is also conceivable that a subgroup of patients from the total study may have demonstrated benefit from this approach but that this has been obscured by consolidation of all subgroups into the two major categories. These concerns will be discussed separately.

The choice of the chemotherapeutic agent for an adjuvant chemotherapy program is dependent on the current information on tumor-drug relationships available to us from the use of chemotherapeutic agents in patients with advanced cancer. Although the response rate of advanced colorectal cancer to 5 FU is low (in the 20% range), there is no single agent with proven benefits for

TABLE 5. *Total Oral Dosage Received by Adjuvant Chemotherapy Group in First Postoperative Year of Clinical Trial**

Total Oral Dosage	Total Group	Colon Cancer	Rectal Cancer	Colon & Rectal Cancer	
				Dukes' A & B	Dukes' C
> 80%	44/75 (59%)	26/46 (57%)	18/29 (62%)	30/50 (60%)	14/25 (56%)
> 60%	54/75 (72%)	34/46 (78%)	20/29 (69%)	36/50 (72%)	18/25 (72%)
> 40%	58/75 (77%)	35/46 (76%)	23/29 (79%)	38/50 (76%)	20/25 (80%)
< 40%	17/75 (23%)	11/46 (23%)	6/29 (21%)	12/50 (24%)	5/25 (20%)

* 75 patients >1 year postop.

TABLE 6. *Incidence of Toxicity From Postoperative Oral 5 FU in Adjuvant Chemotherapy Group of Clinical Trial*

		No. with Toxicity/ Total (%)	
Intraluminal and Immediate Postop IV 5 FU		0/80	
Oral 5 FU			
Colon cancer cases		18/49	(37%)
Rectal cancer cases		11/31	(35%)
Total		29/80	(36%)
Nature of toxicity:			
Leukopenia only -	21		
G I Only -	7		
Leukopenia and G I -	1		
Total	29		

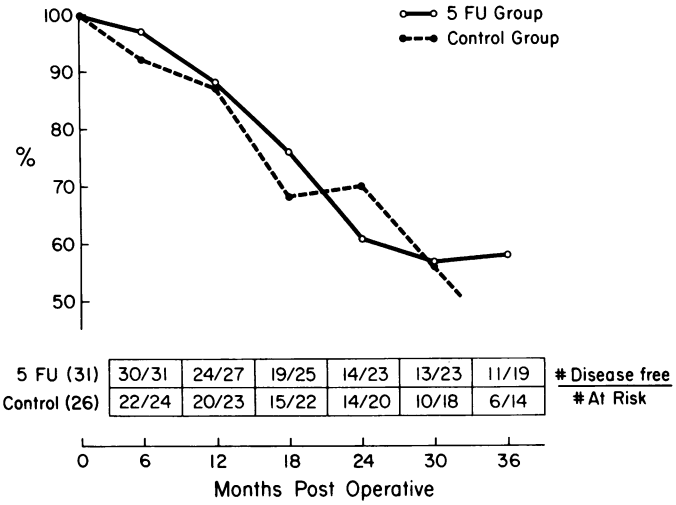

FIG. 3. Rectal cancer. Survival free of recurrence after "curative" resection (all stages).

colorectal cancer that is superior to 5 FU at present. It is also quite possible that the responsiveness of minimal residual (*i.e.* microscopic) disease is greater than the response rate for gross recurrent disease.

Using the dosage schedule and total dosage of 5 FU used in this study, the majority of patients, though not all, have tolerated this dose level given by intermittent courses. The toxicity observed gives some degree of confidence as to the adequacy of drug dosage for this adjuvant trial, even though the guidelines for toxicity and dose reduction are admittedly conservative in contrast to the levels of toxicity used for protocols that are applicable to established or advanced disease. It is generally agreed, however, that life endangering toxicity from adjuvant chemotherapy is not justified in patients with a reasonable chance for permanent control for their cancer.

Another possible objection to this program is the use of the oral route of drug administration rather than the more commonly used intravenous medication. Studies on plasma concentrations of 5 FU after peroral administration show that peak plasma levels occur rapidly but are generally lower than seen after intravenous administration of comparable doses. There is also more variability in absorption than with intravenous administration but responses of established disease do occur and the toxicity observed is similar with both routes of administration.[1]

The actual dosage schedule used in this study is an intermittent one rather than continuous weekly administration of agent at a lower dose level. The latter approach has not been shown to be better than the more commonly accepted loading dose technique but it is virtually impossible to assess the importance of variations in dose scheduling at this time. The ongoing long term postoperative adjuvant trial of 5 FU by the Central Oncology Group uses the chronic weekly administration of 5 FU and the results in this study may eventually provide an answer to this question. The COG Study appears to suggest some improvement in survival statistics in the 5

TABLE 7. *Survival and Recurrence Free Survival Data for Patients with Dukes' C Lesions in 5 FU Adjuvant Trial*

		Followup Period (Mos.) 6	12	18	24	30	36	42	48
5 FU Group	Proportion Surviving	25/25 (100%)	22/23 (96%)	17/20 (85%)	12/19 (63%)	10/19 (53%)	8/16 (50%)	6/12 (50%)	6/11 (55%)
	Proportion Free of Disease	22/25 (88%)	17/23 (74%)	12/20 (60%)	8/19 (42%)	8/19 (42%)	6/16 (38%)	5/12 (42%)	5/11 (45%)
Control Group	Proportion Surviving	27/28 (96%)	24/27 (89%)	22/26 (85%)	19/24 (79%)	16/23 (70%)	10/18 (56%)	6/13 (46%)	4/12 (33%)
	Proportion Free of Disease	26/28 (93%)	22/27 (81%)	21/26 (81%)	18/24 (75%)	14/23 (61%)	10/18 (56%)	6/13 (46%)	4/12 (33%)

FU adjuvant arm of this particular protocol, but the difference between the adjuvant and control groups is not statistically significant at this time (See addendum).

The remaining concern regarding this trial of adjuvant 5 FU for colorectal cancer is the possibility of "burying" an advantage from this approach in the subgroup of the whole by focusing on a comparative analysis of the total colorectal group with and without the adjuvant. The rectal and colon lesions were actually randomized separately to allow homogeneity and this fact will be used at a later date to conduct separate analyses by site when the numbers of patients involved are larger, and the followup period longer. Although the rectal lesions in the ongoing multihospital study in New York have somewhat better results in the adjuvant 5 FU group (as opposed to no difference with colon lesions) this difference is far from statistical significance.[4] It is of interest that the small groups of rectal cancers in our study have grossly identical survival curves thus far despite a more prolonged course of adjuvant 5 FU therapy than used in the New York Study.

The initial studies of Rousselot and coworkers[7] using historical controls seemed to indicate benefit from adjuvant 5 FU with colorectal lesions in patients in a higher risk category (Dukes' C). However, the current prospective clinical trial from this same group fails to even suggest this difference and our data are in agreement with this latter finding. One might conclude from all of these incomplete data that any real differnce between adjuvant and control groups in a subcategory of the whole must be relatively small, or it would have been more apparent in the data that have been presented.

Conclusions

From our findings to date, we do not believe that the benefit of prolonged adjuvant therapy with 5 FU for patients undergoing "curative" surgery for colorectal cancer is adequate to justify its' general use. In time, minor degrees of benefit from this approach might become evident for all patients, or for patients in selected subgroups, but further evaluation to substantiate this must be accomplished before this approach can be recommended. Future trials of adjuvant chemotherapy for colorectal cancer may be more justified with a combination of chemotherapeutic agents or hopeful new agents, or immuno-adjuvants that are found to be effective for recurrent large bowel cancer.

Addendum

Since submission of this manuscript the results showing benefit from adjuvant 5 FU in the COG study have become statistically significant (Grage, T. E.; personal communication). It is of interest that the COG study differs from ours both in route of drug administration (intravenous) and scheduling of maintenance 5 FU (single weekly dose).

Acknowledgments

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Discussion

(Note: Some of the discussants' remarks relate to both this paper and the following one by Dr. George Higgins. Such discussions follow both articles in this volume.)

Dr. Murray M. Copeland (Houston, Texas): The results of the study by Dr. Lawrence and his colleagues are in keeping with the results of other studies using 5-FU as an adjuvant to curative resection for colorectal cancer. The important difference between this study and a well-known study by the VA group which Dr. Higgins has been considerably involved in is that more intensive and longer duration of 5-FU was used in Dr. Lawrence's study. Nevertheless, on the basis of these studies it seems reasonable to conclude that 5-FU, given by itself, is probably not beneficial in prolonging the disease-free interval for patients who have had curative resections for colorectal cancer.

A study presently being conducted by Dr. Mavligit and Dr. Freireich at our institution is one in which BCG, therapy as an adjuvant to curative resection for colorectal cancer is being used. Although it is too early to draw significant conclusions or to compare this study with that of Dr. Lawrence, there is a suggestion that early recurrence is less frequent with the use of BCG therapy. Thus, it is exciting to consider the possibility that immunotherapy or combinations of immunotherapy and chemotherapy might have significant advantages as adjuvants to curative surgical resection of colorectal cancer.

The findings in the report by Dr. Higgins and his group are of interest, and strongly suggest that preoperative radiation is worthwhile in patients who have rectal and low sigmoid primary lesions. It is important to emphasize that Dr. Higgins' results, as reflected in the survival curves for patients who have had curative resections, may be more significant than indicated. This is because patients who had curative resections following radiotherapy could have a worse prognosis than patients who had curative resections in the control group. Thus the difference in the survival curves might be more significant, taking this into account.

The major concern is that the sites and extent of recurrences, I don't believe, are discussed, Dr. Higgins. Perhaps I'm wrong about that. I