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An Overview of Adjuvant Therapy for Colorectal Cancer

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Adjuvant therapy of colorectal cancer is one of the most active areas of clinical oncology research. Although the data for the benefits from early trials of adjuvant therapy were inconclusive, these trials suffered from inadequate sample sizes, poor staging, potentially suboptimal treatment regimens and ill-defined prognostic subgroups. More recently, larger trials of higher scientific quality have demonstrated that regimens of fluorouracil plus levamisole in stage III colon cancer and fluorouracil with postoperative radiation in stages II and III rectal cancer can reduce mortality. Such regimens have now become standard practice in settings in which treatment is believed to be both efficacious and tolerable, and when the overall impact of therapy is considered to be clinically relevant. More recent advances in adjuvant treatment of colorectal cancer further support the role of fluorouracil-based regimens. Peri-operative portal vein infusions of fluorouracil demonstrate improved relapse-free and overall survival, and infusional fluorouracil administered with radiation for rectal primaries appears superior to less intensive bolus fluorouracil regimens. Completed trials of fluorouracil plus leucovorin combinations are awaiting maturation, with expectations for superior adjuvant activity based on demonstrated improved response rates for biochemically modulated fluorouracil in advanced metastatic colorectal cancer. New systemic agents are also entering large-scale adjuvant trials, including monoclonal antibody 17-1a, given alone and in conjunction with standard fluorouracil regimens. Additional cytotoxic drugs, including CPT-11 and Tomudex, offer new opportunities for alternative adjuvant regimens for the large, heterogeneous population of patients with resected colorectal cancer.

Key words: adjuvant therapy, colon cancer, rectal cancer
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HISTORICAL PERSPECTIVE

TAKEN TOGETHER, tumours of the colon and rectum represent the second leading cause of cancer deaths in Western societies. Although many patients present with tumours that are surgically resectable, an unacceptably high absolute number of individuals die from recurrent disease after apparently curative surgery. Although a small number of people with recurrent disease may be cured by salvage resection of pulmonary or hepatic metastases, the majority of patients who present with tumours of the colon and rectum require tolerable, cost-effective adjuvant treatment programmes.

Controversy about the use of adjuvant treatment programmes in colorectal cancer has flourished for nearly two decades, since Li and Ross claimed a significant improvement in the 5-year cure rate of patients with stages II and III colorectal cancer with postoperative fluorouracil. This retrospective, non-controlled trial of 89 patients was greeted with much scepticism, particularly since earlier, randomised controlled trials failed to demonstrate significant benefit [1]. The stage was, therefore, set for ongoing disputes as to whether a fluorouracil-based adjuvant treatment programme could significantly benefit any subgroup of patients with resected colorectal cancer. Although these conflicting results seemed discouraging, two additional possibilities in the mid-1970s rekindled interest in postoperative adjuvant therapy. Firstly, the finding that methyl-CCNU (semustine) was a potentially independently active drug stimulated the initiation of a number of trials using combinations of this drug plus fluorouracil. Secondly, the emergence of peri-operative radiation for rectal primaries led to a number of controlled trials of postoperative radiation therapy alone and in combination with chemotherapy.

In 1988, one of the first meta-analyses of the effectiveness of adjuvant therapy of colorectal cancer was published, which included eight trials utilising radiotherapy in rectal cancer and 17 trials of various types of chemotherapy [2]. Nearly 10 000 patients in 25 randomised control trials were entered into this analysis. Overall, regimens that contained fluorouracil had a small benefit in terms of overall survival, with an odds ratio of 0.83 (95% CI, 0.70–0.98). The estimated benefit of such treatment varied depending upon the length of treatment, and whether any other drugs were administered in addition to fluorouracil. This analysis did not take into account the relative strength of each of the trials analysed, and the doses and schedules of fluorouracil either were not specified or were of low intensity by today's standards. The authors of this meta-analysis concluded that future trials of adjuvant therapy should be large enough to detect small, but clinically relevant, treatment effects in specific subgroups of patients.

The identification of a potentially active chemotherapy regi-

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men in advanced colorectal cancer, fluorouracil and semustine stimulated a number of appropriately large, randomised controlled trials of adjuvant therapy with this combination. NSABP C-01 compared a postoperative combination of fluorouracil, semustine and vincristine to surgery alone, with a modest improvement in overall survival of borderline statistical significance [3]. At least two other trials of fluorouracil plus semustine, however, failed to demonstrate a benefit for this combination when compared with surgery alone in stages II and III colon cancer [4, 5]. In retrospect, the toxicity of semustine and the necessity for decreasing the dosage of a potentially more active drug—fluorouracil—in this combination limited the future of this adjuvant programme. Indeed, two subsequent combined modality adjuvant trials in rectal cancer comparing fluorouracil alone to fluorouracil plus semustine have also failed to demonstrate any benefit from the addition of the latter drug [6, 7].

FLUOROURACIL PLUS LEVAMISOLE

With initial uncertainty as to the effectiveness of standard bolus fluorouracil treatment, other avenues of adjuvant treatments have been explored over the past 15 years. One of the most significant and controversial treatment programmes has included levamisole [8]. This drug, primarily in clinical use as an antihelminthic, has been available for nearly 30 years. Although a number of putative immunomodulatory effects of levamisole have been described, the relevance of these effects in human malignancies is unclear. Other biological and pharmacological effects of levamisole have been described, including the potential biochemical modulation of fluorouracil, although these effects have not been completely defined. Recent laboratory work has demonstrated that both fluorouracil and levamisole increase expression of HLA class I antigens, which may, in part, explain some of the synergistic effects of this combination demonstrated in clinical trials [9].

Interest in levamisole as an adjuvant treatment for colorectal cancer was spurred by a randomised trial in 82 patients with advanced disease, in which either fluorouracil or a combination of fluorouracil plus levamisole was administered [10]. The median survival for the combination was 15.5 months compared with 9.7 months for fluorouracil alone. Two subsequent trials, however, failed to suggest either an increase in overall response rate or median survival when levamisole was added to fluorouracil [11, 12]. In spite of these negative reports, continued interest in levamisole was stimulated by results from an adjuvant trial in resected large bowel cancer, in which a survival advantage was observed for patients assigned to receive levamisole [13].

In 1978, based on these preliminary results, the North Central Cancer Treatment Group/Mayo Clinic initiated a randomised trial comparing postoperative levamisole and a second, empirical regimen of fluorouracil plus levamisole to surgery alone in resected II and III colon cancer. The preliminary results of this trial were presented in abstract form in 1986, and the final report was issued in 1989, with a median follow-up of nearly 8 years [14]. Compared to surgery alone, there were improvements in recurrence-free survival for both treatment arms, which were borderline ($P = 0.05$) for levamisole alone but statistically significant for levamisole plus fluorouracil ($P = 0.003$). In subset analysis of stage C patients, the benefit for levamisole plus fluorouracil appeared more convincing, with a borderline survival advantage as well (one-sided $P = 0.03$) (Table 1).

In 1984, as the NCCTG data were maturing, the potential advantages of levamisole plus fluorouracil were intriguing, but clearly required confirmation in a larger population. Therefore, in 1984, the first Intergroup trial was initiated, in which two separate studies were performed. The larger study of 971 patients comprised the stage C population; these patients were randomised to the same treatments as the NCCTG trial. The second study, in stage II patients, compared surgery alone to levamisole plus fluorouracil. By September 1989, the 3-year recurrence and survival data mandated early reporting [15]. On the basis of the one-third reduction in recurrence and death with levamisole plus fluorouracil, the National Cancer Institute issued a clinical update in October 1989, concluding that "the therapeutic option of post-surgical observation ('no treatment' control groups) is no longer justifiable for NCI-sponsored adjuvant studies for Dukes' C patients" [16]. This announcement obviously had a great rippling effect throughout the oncological community, leading to the closure of a number of ongoing adjuvant trials with surgery-alone controls. More importantly, the announcement led to the acceptance of fluorouracil plus levamisole as standard therapy across the United States and in other countries. This abrupt change in standard practice led to controversies as yet unsettled.

Initial concerns that these early results of fluorouracil plus levamisole may have been transient have been put to rest by the recent publication of the final report of the Intergroup trial [17]. With a median follow-up of 6.5 years, fluorouracil plus levamisole continued to be associated with a significant benefit in recurrence-free and overall survival ($P = 0.0007$) (Figure 1). Although the original NCCTG trial had suggested some modest benefit from postoperative levamisole alone, the Intergroup trial demonstrated only non-significant reductions in recurrence of 2% and in death rate of 6%.

Fluorouracil plus levamisole substantially improves survival in patients with stage III colon cancer. In the United States, this treatment has been considered standard therapy for the past 5 years [18]. In other countries, the adoption of fluorouracil plus levamisole has been inconsistent. When the Intergroup trial was designed, a fluorouracil-alone treatment arm was considered, but many investigators did not think it reasonable to re-examine this issue. Therefore, the uncertain contribution of levamisole to the treatment programme has led some oncologists to reject the entire treatment programme. In spite of uncertainties concerning the mechanism of action of levamisole or its contribution to the efficacy of treatment, the early and late toxicity of levamisole appears to be small. Results of a levamisole adjuvant therapy trial in colorectal cancer from the 1970s have suggested increased non-cancer-related mortality in patients who received levamisole, and who survived for longer than 5 years. However, the total number of patients in this trial (78) was small, and the cumulative dose of levamisole was more than twice that administered in the standard fluorouracil plus levamisole programme. In addition, the Intergroup trial, with a much larger sample size, has shown no excess in all-cause mortality, with a median follow-up of 6.5 years. Neurological toxicity of levamisole has also been described, although its incidence is unclear; retrospective evaluations of neurotoxicity from larger, recent adjuvant trials are underway [19]. In addition, hepatic toxicity has been associated with fluorouracil plus levamisole adjuvant therapy [20]. This toxicity, primarily manifested as laboratory abnormalities or fatty infiltration by computed tomography (CT) scan, typically causes problems rather by false positive carcinoembryonic antigen (CEA) levels or radiographic suspicion of metastases, than by induction of significant disease. The hepatotoxicity associated with combination therapy appears to be unique to the combination, since the incidence of liver function

Table 1. Fluorouracil plus levamisole in stage C colon cancer

Study	No. of patients	Median follow-up	5-year disease-free survival			5-year overall survival		
			S	Lev	FU + Lev	S	Lev	FU + Lev
NCCTG	262	90 mo	38%	50%	50%	45%	50%	54%
			$P = 0.06$			$P = 0.06$		
			$P = 0.02$			$P = 0.03$		
INT-0035	929	78 mo	45%	45%	63%	54%	54%	65%
			$P = <0.0001$			$P = 0.0007$		

S, surgery alone; mo, month; Lev, levamisole; FU, fluorouracil.

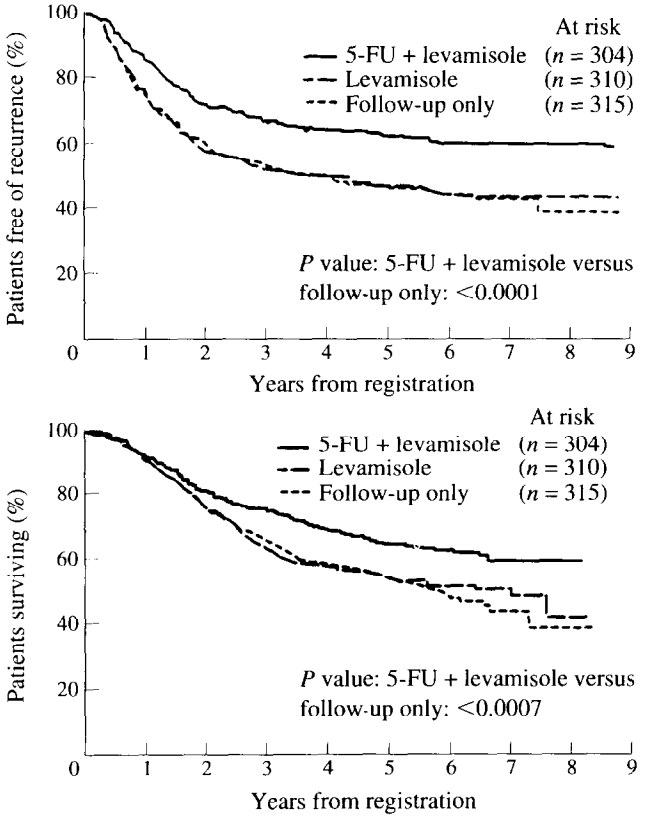

Figure 1. INT-0035 long-term results [17].

abnormalities in patients receiving levamisole alone is similar to that of untreated controls.

Apart from these concerns about the beneficial or toxic contributions of levamisole to adjuvant treatment, the other common cause of reticence in accepting fluorouracil plus levamisole therapy for stage C colon cancer rests in the relative risks, costs, and benefits of such treatment. This predicament is not unique to the adjuvant therapy of colon cancer. In most solid tumours, adjuvant therapy is associated with lack of benefit and excess treatment for many patients. For oncologists, for their patients and for society, the decision as to whether adjuvant treatment is clinically relevant or not depends on perceptions of costs and benefits identified in randomised, controlled trials. Using the results of the Intergroup study, fluorouracil plus levamisole therapy appears to be cost-effective, given a wide range of baseline assumptions and quality of life adjustments [21].

STAGE II COLON CANCER

Under the assumption that stage II patients may be biologically different from stage III patients, and with the intent to perform a prospective analysis, the Intergroup trial included a separate two-armed study for these patients. Subjects were randomised to surgery alone or to the combination of fluorouracil plus levamisole. With a median follow-up of 7 years, 318 patients are available for analysis for recurrence and survival (Table 2). Although fluorouracil plus levamisole reduced recurrence by 31%, this was not statistically significant ($P = 0.10$) (Daniel G. Haller, University of Pennsylvania, U.S.A.). Overall survival for each of the arms was virtually identical, with a higher rate of non-cancer related deaths on the treatment arm, and a higher proportion of patients who were rendered disease-free by salvage surgery on the observation arm. While this relative reduction in recurrence is similar to that observed in stage III patients, the absolute difference is less than 10% at 5 years. On the basis of these results, it is difficult to recommend fluorouracil plus levamisole as standard treatment for all patients with stage II disease. However, there are certain subgroups who may be at higher than average risk of recurrence (including those with completely obstructing, perforating or T4 tumours, or tumours that have abnormal DNA content) and who may benefit from adjuvant therapy. In addition, newer prognostic variables may be helpful in selecting and stratifying stage II patients for clinical research trials. Allelic loss of chromosome 18q has been identified as a poor prognostic variable in patients with stage II disease. In a retrospective study of 69 patients with stage II resected colon cancer, patients with no allelic loss had a 93% 5-year survival compared to 54% in those with allelic loss [22].

RECTAL CANCER

It is not within the scope of this review to provide a complete historical perspective on the development of adjuvant treatment for rectal cancer. It is, however, appropriate to explore recent trends in adjuvant therapy for this subset of patients with colorectal cancer, to provide additional documentation for the overall efficacy of adjuvant fluorouracil-based chemotherapy. Patients with rectal primaries are typically considered separately from patients with colon primaries, primarily upon anatomical differences [23]. Tumours below the peritoneal reflection do not have a serosal covering, and anatomical relationships within the pelvis limit wide circumferential margins. Associated with these factors is an increased risk of locoregional failure for rectal

Table 2. INT-0035: fluorouracil plus levamisole in stage II colon cancer

	No. of patients	7-year DFS		7-year survival		No. of deaths from cancer	Non-cancer deaths
Surgery alone	159	71%	$P = 0.10$	73%	P = NS	36	7
Fluorouracil plus levamisole	159	79%		73%		29	15

DFS, disease-free survival; NS, not significant.

primaries, compared to similarly staged tumours of the extrapelvic colon. Historically, this observation has led to the use of both pre- and postoperative radiation therapy for resected rectal cancer. Although it is generally conceded that radiation therapy alone may reduce locoregional failure, the impact on overall survival has been minimal in most randomised trials, with meta-analysis suggesting no overall survival benefit [2].

Randomised trials were begun in the 1970s to assess the roles of chemotherapy and radiation therapy in the adjuvant treatment of rectal cancer. The theoretical underpinning of combined modality therapy is based on two mechanisms: the first is radio-enhancement by fluorouracil, and the second is independent anatomical activity ("spatial co-operation") of radiation and of chemotherapy. The importance of this latter theoretical advantage of combined modality treatment is strengthened by observations from colon adjuvant trials which have suggested that distant sites of metastases are preferentially reduced by systemic therapy, whereas locoregional failure appears to be less affected [17, 24].

In 1975, the Gastrointestinal Tumor Study Group initiated a study comparing surgery alone to postoperative radiotherapy, chemotherapy or combined chemoradiotherapy in patients with stages II and III rectal cancer [25]. Radiation doses ranged from 4000 to 4800 cGy; chemotherapy was a combination of fluorouracil plus semustine, with fluorouracil alone given during radiation therapy in the combined treatment arm. A statistically significant recurrence-free survival advantage for the combined modality treatment compared to surgery alone was observed [25]. Further follow-up also confirmed a survival advantage for combined modality treatment [26]. Because of the small number of patients and the potentially suboptimal radiation programme in the GITSG study, a second trial of combined modality adjuvant treatment was instituted by the Mayo Clinic/NCCTG in 1980. Patients were randomly assigned to receive postoperative radiation alone (total dose 5040 cGy) or a combined chemoradiotherapy treatment that included fluorouracil plus semustine—both before and after pelvic radiation therapy—and fluorouracil alone on the first and last three days of radiation. This trial demonstrated both recurrence-free and overall survival advantage for chemoradiotherapy compared to postoperative radiation alone [27]. Combined therapy reduced recurrence by 34% ($P = 0.0016$), with both local and distant recurrences significantly reduced, and was associated with a 29% reduction in the overall death rate (Table 3). In 1991, the National Cancer Institute issued a clinical announcement recommending that all patients with resected stages II and III rectal cancer receive postoperative combined modality treatment [28]. Although both the GITSG and the Mayo/NCCTG trial included semustine as part of the treatment programme, two subsequent randomised trials have demonstrated that this drug is not an essential component of postoperative combined modality treatment for rectal cancer [6, 7].

The optimal combined modality adjuvant programme for rectal cancer has not been determined. Most recently, data from the first Intergroup trial in rectal cancer have shown that a protracted infusion of fluorouracil during pelvic radiation significantly reduces both locoregional failure and distant failure, and produces a 10% improvement in overall tumour-free survival and mortality, compared with a standard programme of bolus fluorouracil [7]. This observation provides further evidence that fluorouracil is an effective adjuvant treatment for resected colorectal cancer. However, individual and societal determinations concerning the cost-effectiveness of such combined modality adjuvant regimens for rectal cancer must guide patient selection, given substantial short and long-term toxicities of treatment [29].

Although these data strongly suggest that chemotherapy significantly adds to the effectiveness of postoperative radiation therapy, there are few data concerning the exact contribution of pelvic radiation to systemic adjuvant chemotherapy in patients with resected rectal tumours. One of the few trials to address this issue is NSABP R-02 [30]. In this trial, 741 patients were randomised to receive either postoperative chemotherapy alone or postoperative chemoradiotherapy. Depending upon gender, chemotherapy consisted of either semustine, vincristine plus fluorouracil or leucovorin plus fluorouracil. With 3.5 years of follow-up, there was no significant difference in disease-free or overall survival, although there was reduction in local recurrence as a site of first treatment failure. These preliminary data will require further follow-up.

FUTURE DIRECTIONS IN ADJUVANT THERAPY FOR COLON CANCER

The establishment of standard adjuvant treatment programmes for patients with resected high-risk colon and rectal cancers has led to a number of new directions in clinical research. The first comes from the laboratory, in which experimental studies have demonstrated that the cytotoxic activity of fluorouracil may be modulated and potentiated by reduced folates. Early phase I and II trials of combinations of fluorouracil plus leucovorin suggested increased activity in patients with metastatic colorectal cancer, and phase III trials have also confirmed evidence of improved therapeutic efficacy [31]. A meta-analysis of nine randomised clinical trials which compared fluorouracil alone to fluorouracil plus leucovorin in advanced colorectal cancer showed a highly significant benefit for the

Table 3. Adjuvant therapy of rectal cancer

Study	Regimen	Local relapse	DFS	Survival	
*GITSG [26] (202 pts)	S	24%	45%	32%	
	versus				
	S + CT	27%	54%	48%	
	versus				$P = 0.005$
	S + XRT	20%	52%	45%	
	versus				
	S + XRT + CT	11%	67%	57%	
*NCCTG [27] (204 pts)	S + XRT	25%	38%	38%	
	versus				$P = 0.025$
	S + XRT + CT	14%	58%	53%	
†Intergroup [7] (660 pts)	S + XRT + bolus FU		53%	60%	
	versus	NS			$P = 0.01$
	S + XRT + PVI FU		63%	70%	

* 7-year follow-up; † 4-year follow-up; S, surgery; CT, fluorouracil plus semustine; XRT, pelvic radiation; FU, fluorouracil; PVI, protracted venous infusion; DFS, disease-free survival.

combination in tumour response (23% versus 11%) [32]. This improvement in response did not translate into an overall survival benefit for patients with metastatic disease. However, the doubling of the response rate suggests that fluorouracil plus leucovorin may be a more effective systemic adjuvant programme than fluorouracil alone or fluorouracil plus levamisole.

In the mid-1980s, a number of colon adjuvant treatment programmes were initiated which utilised fluorouracil plus leucovorin (Table 4). NSABP C-03 was among the first of these trials; it compared a regimen of fluorouracil plus high-dose leucovorin to fluorouracil, vincristine plus semustine (MOF) [33]. This trial accrued 1081 patients with Dukes' stages II and III colon cancer, and was completed in 1989 prior to the NCI announcement concerning the efficacy of fluorouracil plus levamisole. At 3 years, the disease-free survival rate was 73% for fluorouracil plus leucovorin compared with 64% for MOF. Survival was also improved, with a 32% reduction in mortality risk. Other trials of fluorouracil plus leucovorin adjuvant therapy were also begun in North America and Europe, but were prematurely terminated when the fluorouracil plus levamisole results were reported. The data from these trials have been combined, and pooled analysis suggests that both event-free and overall survival are superior in patients treated with fluorouracil plus leucovorin compared to surgery alone [34]. In nearly 1500 eligible patients (55% with stage II disease), the survival at 3 years was 78% for the control group and 83% for the adjuvant chemotherapy group ($P = 0.03$).

Although these potential benefits of biochemically modulated fluorouracil are encouraging, it is difficult to compare these directly to those from fluorouracil plus levamisole (Table 5). To address this issue, the second Intergroup study (INT-0089) was initiated in 1989. Patients were assigned to receive standard fluorouracil plus levamisole, fluorouracil plus high-dose leucovorin, fluorouracil plus low-dose leucovorin, or a triple combination of fluorouracil, low-dose leucovorin and levamisole. The fluorouracil plus leucovorin regimens were chosen from two previously reported protocols in advanced colorectal cancer, with similar response rates but different toxicity profiles [35]. INT-0089 accrued more than 3500 patients. With a median follow-up of approximately 3.5 years, it is expected that preliminary data may be available in late 1995. Other North American trials of biochemically modulated fluorouracil regimens have also been completed, and are at varying stages of follow-up: NSABP C-04 compared a standard regimen of fluorouracil plus levamisole to fluorouracil plus high-dose leucovorin and to fluorouracil, high-dose leucovorin plus levamisole. Taken together, NSABP C-04 and INT-0089 may further explain the role of levamisole in adjuvant treatment. The NSABP has also completed protocol C-05, which compared a standard regimen of fluorouracil plus leucovorin to a doubly modulated regimen of fluorouracil, leucovorin, and alpha-interferon.

Table 4. Adjuvant therapy of colon cancer: fluorouracil plus leucovorin

Study	Median follow-up	Regimen	DFS	Survival	
NSABP C-03 [33] (1081 patients)	48 months	MOF	64%	77%	
		versus			$P = 0.003$
		FU + LV	73%	84%	
Pooled analysis [34] (1493 patients)	37 months	S	63%	78%	
		versus			$P = 0.03$
		FU = LV	72%	83%	

S, surgery alone control; MOF, fluorouracil, vincristine, semustine; FU, fluorouracil; LV, leucovorin; DFS, disease-free survival.

Table 5. Adjuvant therapy of colon cancer: recently completed North American trials

Study	Regimens	Analysis due
INT-0089	FU + Lev versus FU + HDwLV versus FU + LDLV versus FU + LDLV + Lev	1995
NSABP C-04	FU + Lev versus FU + HDwLV versus FU + HDwLV + Lev	1995
NSABP C-05	FU + HDLV versus FU + HDLV + IFN α	1996–1997

FU, fluorouracil; HDwLV, weekly, high-dose leucovorin; LDLV, 5 day, low-dose leucovorin; HDLV, 5 day, high-dose leucovorin; IFN α, interferon alpha 2a.

In addition to modulating the activity of fluorouracil by agents such as leucovorin and alpha-interferon, the pharmacology of fluorouracil may be altered by prolonged infusional therapy. There have been phase III trials demonstrating improved response rates for this technique compared to standard bolus therapy in advanced colorectal cancer [36]. Although somewhat cumbersome and expensive, protracted venous infusion fluorouracil therapy results in response rates similar to biochemically modulated fluorouracil plus leucovorin. In the adjuvant setting, protracted venous infusion of fluorouracil during radiation therapy for rectal cancer reduces recurrence and prolongs survival [7]. To further explore the potential benefits of protracted venous infusions of fluorouracil, two new Intergroup trials have been initiated within the past year (Table 6). INT-0153, for high-risk colon cancer, randomly assigns patients to a control treatment of bolus fluorouracil, leucovorin and levamisole (as administered in INT-0089) or an experimental treatment arm of infusional fluorouracil plus levamisole. The second trial of protracted venous infusion fluorouracil, INT-0144, has been designed as a postoperative treatment programme for patients with rectal cancer, and will be described further in the concluding section on the future of adjuvant therapy for rectal cancer.

A trend currently under investigation in the adjuvant treatment of colorectal cancer is portal vein fluorouracil. The theoretical advantages of hepatic-directed adjuvant therapy are that many patients with colon cancer will develop hepatic metastases, and infusional fluoropyrimidine therapy may provide higher dose intensity for micrometastases within the liver. The first randomised trial of adjuvant portal vein perfusion was performed by Taylor and associates [37]. Patients without obvious liver metastases were randomised intra-operatively to either surgery alone or to immediate portal vein infusion of fluorouracil at 1 g per day for 7 days. A total of 244 patients was available for analysis, and the overall results suggested a reduction in liver metastases in the group receiving portal vein infusion therapy, as well as an improvement in overall survival. In subset analysis, the survival advantage appeared to be restricted to Dukes' B patients with colon primaries. Encouraged by these preliminary data, further portal vein trials were initiated. One of the first, and the largest study is NSABP C-02, in which 1158 patients with Dukes' A, B and C carcinoma of the colon were randomly assigned to receive no further treatment after curative resection or postoperative fluorouracil at a dose of 600 mg/M^2 per day for 7 postoperative days. With 42 months of follow-up, there was a 10% improvement in 4-year disease-free survival ($P = 0.02$) and an 8% 4-year survival advantage ($P = 0.07$) in the chemotherapy-treated population [38]. There was, however, no apparent decrease in the incidence of hepatic metastases as the first site of treatment failure. These results were recently updated, with an average time on study of more than 7 years [38]. Patients randomised to peri-operative portal vein infusion of fluorouracil continue to demonstrate significant improvement in disease-free survival (68% versus 60%) and overall survival (76% versus 71%).

Nine randomised trials of adjuvant portal vein infusion therapy have been performed, involving more than 4000 patients. A recently reported meta-analysis of these trials has confirmed a significantly lower mortality for patients treated with portal vein infusion (13% risk reduction; $P = 0.02$) [39]. Among these studies, there is an inconsistent trend toward reduction in liver metastases, raising the question as to whether the beneficial effects of portal vein infusion therapy are based primarily on the hepatic-directed nature of the treatment, or on the systemic effects of immediate, peri-operative fluorouracil adjuvant treatment. In 1982, a randomised trial was begun in Australia and New Zealand in which patients were randomised to receive either no postoperative chemotherapy, systemic continuous infusion fluorouracil for 7 postoperative days, or postoperative intraportal fluorouracil, exactly as administered in NSABP C-02. Although this trial did not accrue sufficient numbers of patients to assess the efficacy of peri-operative systemic fluorouracil, it did establish that such treatment was tolerable. Therefore, to evaluate the role of peri-operative systemic fluorouracil in a larger population of patients, INT-0136 was begun in 1993 (Table 6). This trial pre-operatively randomises patients to receive either no peri-operative chemotherapy or fluorouracil 600 mg/M^2/day for 7 days by continuous i.v. infusion beginning within 24 h of surgery. Patients who are found to have Dukes' stage A, B1 or D tumours are taken off study at the time of pathological documentation. Patients with stage II disease receive no further therapy after the 7 day peri-operative infusion. For those patients with stage II and III tumours, standard fluorouracil plus levamisole is administered postoperatively.

With the exception of some of the earliest trials of adjuvant therapy, most drug programmes to date have been almost entirely based on fluorouracil regimens. A growing interest in the oncological community in immunological treatments of malignancy, and the lack of other useful cytotoxic drugs, has led to the development of both specific and nonspecific immunotherapy adjuvant trials. One of the first large studies was NSABP C-01, in which patients with stages II or III colon cancer were randomised to receive no postoperative therapy, postoperative chemotherapy with MOF, or BCG by intradermal injection [41]. At 5 years of follow-up, the BCG-treated group demonstrated a slight survival advantage compared to surgery alone, although there was no statistically significant difference in cancer-free survival. The authors concluded that the lack of specific benefit in preventing tumour recurrence and the excess of cardiovascular deaths in the untreated control group negated further interest in the use of BCG as a nonspecific immunotherapy agent for the adjuvant treatment of colon cancer. Further

Table 6. Adjuvant therapy of colorectal cancer: current North American trials

Study	Schema
Colon cancer	
INT-0136	Peri-operative FU versus surgery alone → FU + Lev (stages II/III)
INT-0153	FU + LDLV + Lev versus CIFU + Lev
Rectal cancer (postoperative)	
INT-0114*	FU → XRT + FU → FU versus FU + LDLV → XRT + FU + LDLV → FU + LDLV versus FU + Lev → XRT + FU → FU + Lev versus FU + LDLV + Lev → XRT FU + LDLV → FU + LDLV + Lev
INT-0144	FU → XRT + PVI FU → FU versus PVI FU → XRT + PVI FU → PVI FU versus FU + LDLV + Lev → XRT + FU + LDLV → FU + LDLV + Lev
Rectal cancer (pre-operative/postoperative)	
NSABP R-03	FU + HDLV → XRT + FU + LDLV → S → FU + HDLV versus S → FU + HDLV → XRT + FU + LDLV → FU + HDLV
INT/RTOG 9401	XRT + FU + LDLV → S → FU + LDLV versus S → XRT + FU + LDLV → FU + LDLV

* Terminated; FU, fluorouracil; Lev, levamisole; LDLV, low-dose leucovorin; PVI, protracted venous infusion FU; S, surgery; XRT, pelvic radiation; HDLV, weekly high-dose leucovorin.

efforts in adjuvant immunotherapy of colorectal cancer have focused primarily on more specific mechanisms, including autologous tumour vaccines to elicit a specific immune response, otherwise known as active specific immunotherapy (ASI). One trial randomised 98 patients with high-risk colon or rectal primaries to receive either ASI or surgery alone [42]. This rather small study, with a heterogeneous population of patients, suggested an improvement in disease-free and overall survival at a median follow-up of 93 months; these benefits were restricted to the patients with colon primaries. The size of this trial, and the heterogeneity of the patient population, led to much scepticism concerning the activity of ASI in the adjuvant setting [43]. In 1986, the Eastern Cooperative Oncology Group began a larger randomised trial of ASI in patients with high-risk stages II and III colon cancer. Although this original trial compared ASI to a surgery-alone control arm, the publication of the fluorouracil plus levamisole data in 1989 led to premature termination, with a total of 156 Dukes' B and 118 Dukes' C patients entered. In 1990, this trial was revised, so that patients with stage C disease were randomly assigned to receive either standard postoperative fluorouracil plus levamisole therapy or ASI given in conjunction with fluorouracil plus levamisole.

In addition to the introduction of active specific immunotherapy into the adjuvant treatment of colorectal cancer, one of the most exciting new areas of investigation is in the use of monoclonal antibodies. Specifically, the murine monoclonal antibody 17-1A, while demonstrating only anecdotal responses in patients with metastatic disease, has shown intriguing activity in micrometastases as demonstrated in a recently reported adjuvant trial [24]. In this study, 189 patients with stage III colon and rectal primaries were randomly assigned to observation alone after surgery, or to postoperative treatment with 17-1A. With a median follow-up of 5 years, the antibody treatment was associated with an overall reduction in mortality of 30%, with a similar decrease in recurrence. Unlike fluorouracil-based regimens, the antibody treatment was associated with few toxicities. The results of this well-performed study should be confirmed, as the small sample size results in some statistical uncertainty as to the size of the treatment benefit; the 95% confidence interval for the 30% reduction in mortality ranges from 1 to 53%. If correct, this one-third reduction in mortality is similar to that seen with fluorouracil plus levamisole. However, the original Mayo Clinic/NCCTG trial also suggested potential benefit for levamisole alone, which was not confirmed in the larger Intergroup study. The entry of both colon and rectal primaries into the 17-1A trial is also a potential source of bias. The direction of further study of monoclonal antibody 17-1A varies according to the acceptance of fluorouracil-based regimens as standard treatment for stage III colon cancer. A number of potential investigations have already been considered, including

a larger confirmatory trial of 17-1A versus surgery alone in locations where fluorouracil plus levamisole is not considered to be standard. Where fluorouracil-based adjuvant therapy is considered standard, oncologists and immunologists are devising ways in which 17-1A may be given with chemotherapy, so that the combined immunochemotherapy programme may be compared with a standard fluorouracil-based adjuvant treatment.

FUTURE DIRECTIONS IN ADJUVANT THERAPY FOR RECTAL CANCER

On the basis of results of postoperative adjuvant trials from the GITSG, the NCCTG, and the first Intergroup study, combined fluorouracil plus radiation appears to comprise standard adjuvant therapy for high-risk resected rectal cancer patients. However, the optimal adjuvant treatment regimen has not yet been determined. After the fluorouracil plus levamisole data were published for stage III colon cancer, the question was raised as to whether levamisole may also have a role in the treatment of rectal cancer. In addition, the mounting evidence that biochemically modulated fluorouracil was more effective than fluorouracil alone also suggested the need to incorporate fluorouracil plus leucovorin regimens into rectal adjuvant trials. In 1990, INT-0114 was begun, which compared a standard regimen of fluorouracil plus radiation to three experimental treatment arms including either levamisole, leucovorin or both drugs. This trial is similar to the design of INT-0089 in colon cancer. INT-0114 is currently in follow-up, with preliminary results likely to be available in 1996.

The first Intergroup rectal adjuvant study suggested that protracted venous infusion (PVI) fluorouracil was superior to bolus fluorouracil given on the first and last three days of radiation. Recently, the third Intergroup rectal adjuvant trial was initiated, in which the standard treatment arm is PVI fluorouracil given during pelvic radiation. The first experimental treatment arm comprises PVI fluorouracil given for 2 months before and after pelvic radiation therapy, as well as during pelvic radiation. The second experimental arm is identical to the combination treatment given in INT-0114, in which bolus fluorouracil, leucovorin plus levamisole are administered during chemotherapy-alone months, and fluorouracil plus leucovorin given during pelvic radiation therapy. One goal of this study, therefore, is to determine whether the relatively less expensive and less cumbersome fluorouracil plus leucovorin chemotherapy, given during radiation therapy, may be as effective as PVI fluorouracil. This study has only recently been activated; it is anticipated that a total of 2400 patients will be required for completion.

Recently, there has also been a great deal of interest in pre-operative combined modality adjuvant treatment for rectal tumours. The potential advantages of pre-operative treatment include downstaging and improved resectability rates, lack of delay in initiating systemic therapy, and improved sphincter preservation [44]. Recent advances in staging, including MRI and endorectal ultrasound, have allowed for better selection of patients, with the reduced likelihood that patients with early stage disease will be overtreated. Single institution pilot trials of pre-operative radiation therapy, and at least one randomised trial of pre-operative versus postoperative radiation therapy alone, support ongoing research into the optimal timing of combined modality adjuvant therapy for high-risk rectal cancers [44]. In North America, two randomised trials are currently underway comparing pre-operative versus postoperative combined modality therapy. The first trial, NSABP R-03, compares a standard programme of postoperative fluorouracil plus leucovorin during radiation therapy with adjuvant fluorouracil plus high-dose leucovorin chemotherapy, to a programme consisting of an induction phase of fluorouracil plus high-dose leucovorin followed by chemosensitised pre-operative radiation. Patients will also receive postoperative fluorouracil plus leucovorin. The second North American trial, R9401, will also randomise patients between pre-operative combined modality therapy and postoperative treatment.

There are two additional subsets of patients with colorectal cancer in whom combined modality treatment is currently being considered. The first protocol, C8984, is an Intergroup trial of conservative treatment of adenocarcinoma of the distal rectum. In the design of this study, it was not felt practical to perform a randomised trial comparing conservative surgery to abdominoperineal resection. Therefore, the study is primarily a registry trial, in which patients with T1 and T2 lesions will be treated with limited sphincter-sparing surgery and results compared to historical controls treated with radical surgery. Patients with T3 tumours will receive a standard postoperative chemoradiation programme, with those results also compared to historical controls. Locoregional recurrence and salvage rates with abdominoperineal resection will also be evaluated.

A second group of patients who may benefit from combined modality therapy are those patients with extrapelvic colonic carcinomas at high risk for locoregional failure. Combined series suggest that certain subgroups of patients with extrapelvic colon cancers may be at high risk for locoregional failure, including those patients with stages B3, C2, and C3 tumours (i.e., those patients with positive lymph nodes and transmural invasion, or any patient with tumour adherence or invasion of adjacent organs) [45]. To evaluate the role of combined modality therapy in extrapelvic colon cancers in a phase III trial, INT-0130 was initiated in 1992. In this study, these high-risk, completely resected colon cancer patients are randomised to receive either standard fluorouracil plus levamisole or a combined programme of fluorouracil plus levamisole and radiation.

CONCLUSION

This review has briefly addressed the evolving role of adjuvant treatment in colorectal cancers, chiefly represented by North American trials. There are expanding research efforts worldwide, which will serve to amplify and further define the efficacy of adjuvant treatment for the large and diverse population of patients with tumours of the colon and rectum. Studies to date have clearly demonstrated that adjuvant therapy is effective and tolerable for a substantial population of patients, but it will be the goal of future trials to determine the optimal treatment for specific subgroups of patients. In addition to expanding upon traditional fluorouracil-based regimens, exciting new opportunities have also arisen, including the potential role for monoclonal antibody therapy and the recent development of new cytotoxic drugs. For example, CPT-11 and Tomudex represent alternative drugs that may make treatment either more efficacious or more tolerable [46, 47]. The continued worldwide interest in expanding our therapeutic armamentarium, and in developing newer biological techniques for patient selection, will no doubt enhance our ability to offer optimal adjuvant therapy to individual patients with resected colorectal cancer in the future.

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