The Contemporary Management of Colorectal Cancer

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INTRODUCTION

Contemporary management of colorectal cancer requires a multidisciplinary approach that relies on careful pathologic staging and appropriate use of surgery, radiation therapy (XRT), and chemotherapy to produce the best possible survival and quality of life for patients with this disease. Overall, 50–60% of patients with newly diagnosed colorectal cancer will be cured with the best chance for long-term, disease-free survival occurring in those patients with tumors limited to the bowel wall.[1-4] For stage I tumors of the colon or rectum, the cure rate exceeds 90% following surgery alone and no further therapy is required.[5] Selected early stage distal rectal cancers can be treated successfully with trans-anal excision, thereby obviating the need for a colostomy and preserving normal sphincter function.[6] Stage II colon cancer is a biologically heterogeneous disease. Although the 5-year survival rate exceeds 75% following surgery, some patients have more biologically aggressive tumors and are at high risk for relapse and tumor dissemination.

A number of biological and molecular characteristics have been identified that may be of prognostic importance, although none have yet been validated in prospective clinical trials. Features such as S phase fraction,[7] *ras* gene mutation,[8] chromosome 18q deletion,[9] *DCC* gene deletion,[10] microsatellite instability,[11] and others have each been reported to impact the prognosis of patients with node-negative colon cancer, yet none are routinely employed in clinical decision making and risk assessment. Although pooled data from studies conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) suggests that postoperative chemotherapy provides benefits in patients with stage II colon cancer, no prospective, randomized clinical trial has yet been able to demonstrate improved survival for such patients following treatment with adjuvant chemotherapy; therefore, observation following surgery remains an acceptable standard of medical care. The situation is more straightforward in stage III colon cancer where many randomized trials have demonstrated a clear benefit for adjuvant chemotherapy and 6 months of treatment with an established 5-fluorouracil (5-FU) and leucovorin (LV) regimen has emerged as the current standard.[3] The potential contributions that irinotecan and oxaliplatin, a dachplatinum compound developed primarily in France, have to such a regimen are currently being investigated in prospective, randomized clinical trials (RCTs).

In the United States (US), adjuvant therapy for rectal cancer has traditionally included postoperative chemotherapy and pelvic XRT for both stages II and III. The use of continuous infusion of 5-FU during radiation has been proven superior to bolus administration of the drug with respect to both local and distant recurrence rates.[12] The recently reported NSABP R-02 study has raised a question as to the need for post-operative pelvic XRT when adjuvant chemotherapy is also given, particularly in patients with stage II disease.[13] European clinical trials have clearly shown that preoperative XRT alone is sufficient to improve the survival of patients with resectable rectal cancer.[10,14]

Patients with metastatic colorectal cancer confined to the liver should be considered for surgical resection of metastases. Up to 25% of selected patients are curable with this approach.[15] Postoperative administration of systemic chemotherapy has not been demonstrated to be beneficial in prolonging time to recurrence or survival in such patients. However, hepatic artery infusion (HAI) of floxuridine (FUDR) and dexamethasone along with systemic chemotherapy with 5-FU and LV has produced superior progression-free survival and overall survival at 2 years compared with systemic therapy alone.[15] Median overall survival is not improved with this approach however. Patients with unresectable metastases confined to the liver may benefit from HAI of chemotherapy with rapid relief of symptoms. Such an approach produces high rates of tumor regression but has not yet been proven to improve the overall survival of patients.[16-19]

The management of disseminated colorectal cancer is in evolution as new, effective drugs are introduced into clinical practice. Nearly 50 years after its introduction, 5-FU remains an important component of therapy for this disease. Despite a strong preclinical rationale, biochemical modulation strategies have failed to produce incremental improvements in survival of patients with advanced colorectal cancer. Indeed, continuous intravenous infusion of 5-FU (CIVI 5-FU) appears to be more effective and less toxic than any other way of administering

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the drug.[20] This observation has spawned the development of oral fluoropyrimidines as alternatives that can simulate CIVI 5-FU without the need for indwelling catheters and infusion pumps. Prospective randomized clinical trials have been completed comparing both capecitabine and the combination of uracil/ftorafur (UFT) and LV to standard regimens of bolus intravenous (IV) 5-FU and LV.[21–24] Studies of each agent appear to demonstrate equivalent efficacy to the IV regimen with a more favorable toxicity profile and capecitabine has recently received marketing approval from the Food and Drug Administration (FDA).

The recent introduction of irinotecan has resulted in modest but significant improvements in survival of patients with metastatic colorectal cancer. When administered in combination with 5-FU/LV, this drug produces about a 3-month improvement in median overall survival.[25] Similar benefits are seen when irinotecan is used as a single agent in the second-line setting following treatment with 5-FU/LV.[26] Oxaliplatin has significant single agent activity in the treatment of colorectal cancer, and has been shown to produce a higher response rate and better progression-free survival when given in combination with an infusional regimen of 5-FU/LV (deGramont regimen) than 5-FU/LV alone.[27] Unfortunately, the drug has not been shown to result in improved survival of patients and has not yet received marketing approval in the US.

New approaches to therapy of colorectal cancer are evolving in two directions. The first involves better methods of selection of patients for fluoropyrimidine-based therapy. Studies using human colorectal cancer specimens suggest that most cases of resistance to 5-FU-based therapy can be explained by overexpression of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD) or thymidine phosphorylase (TP) in the tumor.[20,28] Screening of tumor specimens for expression of these enzymes should allow selection of patients most likely to respond to 5-FU. Patients whose tumors overexpress TS might best be treated initially with irinotecan, while those whose tumors overexpress DPD might still benefit from therapy with one of the folate-based TS inhibitors in clinical development that are not DPD substrates. Tumors that overexpress TP should be uniquely sensitive to capecitabine, a drug which is selectively activated in tissues with high TP levels. The development of novel therapies for colorectal cancer will surely stem from a better understanding of the fundamental biological characteristics of this disease. Agents currently in development include monoclonal antibodies (MoAb) that target vascular endothelial growth factor (VEGF) and small molecules that target the tyrosine kinase activity of the VEGF receptor. Farnesyl transferase inhibitors may also find a role in this disease by interrupting *ras* signalling pathways and agents directed against the epidermal growth factor receptor have shown promise as well.

In the pages that follow, we summarize contemporary approaches to the management of colorectal cancer, and summarize the results of recent clinical trials that support these approaches. Better therapies are clearly needed for this common malignancy that affects men and women equally. New screening and prevention methods currently in development (eg, virtual colonography and selective cyclooxygenase II inhibitors) have even greater promise of reducing mortality from colorectal cancer in the years ahead.

TABLE 1. STAGING OF COLORECTAL CANCER
TNM Staging

	T	N	M	Dukes'
0	Tis	N0	M0	—
I	T1	N0	M0	A
	T2	N0	M0	A
II	T3	N0	M0	B
	T4	N0	M0	B
III	Any T	N1	M0	C
	Any T	N2	M0	C
IV	Any T	Any N	M1	D

PT	
PTX	Primary tumor cannot be assessed
PT0	No evidence of primary tumor
PTis	Carcinoma in situ; intraepithelial or invasion of lamina propria
PT1	Primary tumor invades submucosa
PT2	Primary tumor invades muscularis propria
PT3	Primary tumor invades through muscularis propria into subserosa or into nonperitonealized pericolic or perirectal tissues
PT4	Primary tumor directly invades other organs or structures, and/or perforates visceral peritoneum

RN	
RNX	Regional lymph nodes cannot be assessed
RN0	No regional lymph node metastasis
RN1	Metastasis into one to three regional lymph nodes
RN2	Metastasis in four or more regional lymph nodes

DM	
DMX	Distant metastasis cannot be assessed
DM0	No distant metastasis
DM1	Distant metastasis

T=tumor; N=lymph node; M=metastasis; Tis=tumor in situ; PT=primary tumor; RN=regional lymph nodes; DM=distant metastasis.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 2. ADJUVANT THERAPY FOR DUKES' B2 AND C COLON CANCER

5-FU/LV vs Surgery Alone

IMPACT (N=1526)[1]

Treatment	3-Year Disease-Free Survival (%)	3-Year Overall Survival (%)
5-FU/LV	71 (*P*=.001)	83 (*P*=.018)
Surgery Alone	62	78

IMPACT for Dukes' B2 Points Only (N=1016)[2]

Treatment	5-Year Event-Free Survival (%)	5-Year Overall Survival (%)
5-FU/LV	76 (*P*=.061)	82 (*P*=.057)
Surgery Alone	73	80

Comparison of Adjuvant Therapy Regimens

NSABP C-04 for Patients With Dukes' B2 and C Colon Cancer (N=2152)[3]

Treatment	5-Year Disease-Free Survival (%)	5-Year Overall Survival (%)
5-FU/LV	65 (*P*=.04, .67)*	74 (*P*=.07, .99)*
5-FU/levamisole	60	70
5-FU/LV/levamisole	64	73

**P* values listed are for pair-wise comparison with 5-FU/levamisole arm and 5-FU/LV/levamisole arm, respectively.

Intergroup 0089 for Patients With Dukes' B2 and C Colon Cancer (N=3759)[4]

Treatment	5-Year Disease-Free Survival (%)	5-Year Overall Survival (%)
5-FU/levamisole x 12 months	56	63
5-FU/HDLV x 6 months	59	65
5-FU/LDLV x 6 months	59	66
5-FU/LDLV/levamisole	60	67

No statistical difference among the arms except for 5-FU/LDLV/levamisole which was superior to 5-FU/levamisole in 5-year disease free survival (*P*=.04).

Conclusions:

5-FU with LV results in significantly improved disease-free survival and overall survival in Dukes' C colon cancer when compared with surgery alone. 5-FU with LV does not significantly improve disease-free survival and overall survival in Dukes' B2 colon cancer when compared with surgery alone. The addition of levamisole to 5-FU/LV does not improve outcome. The outcome is the same for both HDLV and LDLV regimens.

Standard Adjuvant Therapy Regimens and Frequency of Toxicities

5-FU/LV (Machover regimen)

LV 200 mg/m² IV
5-FU 370 mg/m² IV push
Days 1–5 every 28 days
Repeated for 6 cycles

Frequency of Toxicities[29]

Toxicity	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Nausea/Vomiting	11	3	1
Stomatitis	14	9	2
Diarrhea	17	7	1
Leukopenia	7	1	1
Thrombocytopenia	1	1	1

5-FU/LDLV (Mayo Clinic regimen)

LV 20 mg/m² IV
5-FU 425 mg/m² IV push
Days 1–5 every 28 days
Repeated for 6 cycles

Frequency of Toxicities[30]

Toxicity	Grade 3 (%)	Grade 4 (%)
Nausea/Vomiting	7	0
Stomatitis	33	3
Diarrhea	20	4
Leukopenia	14	0

5-FU/HDLV (Roswell Park regimen)

LV 500 mg/m² IV over 2 hours
5-FU 500 mg/m² IV push after 1 hour of the LV infusion
Weekly for 6 weeks followed by a 2 week break
Repeated for 6 cycles

Frequency of Toxicities[31]

Toxicity	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Nausea/Vomiting	18	4.3	1.3
Stomatitis	7.9	0.6	0
Diarrhea	16	41.2	27.6
Leukopenia	3.2	0.6	0.2
Thrombocytopenia	0.4	0	0

5-FU=5-fluorouracil; LV=leucovorin; IMPACT=International Multicentre Pooled Analysis of Colon Cancer Trials; NSABP=National Surgery Adjuvant Breast and Bowel Project; HDLV=high-dose leucovorin; LDLV=low-dose leucovorin; IV=intravenous.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 3. ONGOING AND RECENTLY COMPLETED CLINICAL TRIALS:

Figure 1: CALGB 9581

Phase III Randomized Study of Adjuvant Immunotherapy With MoAb 17-1A vs No Adjuvant Therapy Following Resection for Stage II (Modified Astler-Coller B2) Adenocarcinoma of the Colon

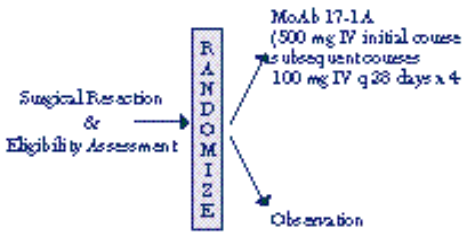


Figure 2: NSABP C-06

A Clinical Trial Comparing Oral UFT Plus LV With 5-FU Plus LV in the Treatment of Patients With Stages II and III Carcinoma of the Colon

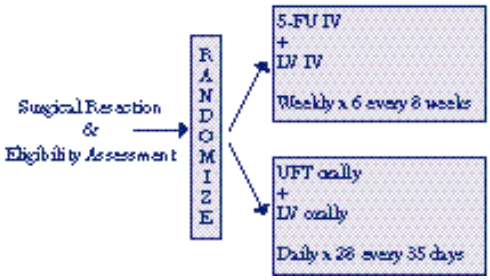


Figure 3: CALGB 89803

Phase III Intergroup Trial of Irinotecan Plus 5-FU/LV vs 5-FU/LV Alone After Curative Resection for Patients With Stage III Colon Cancer

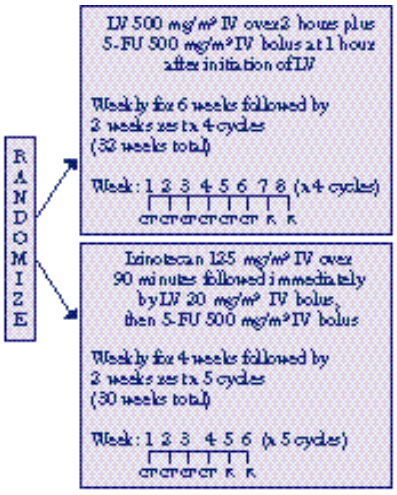
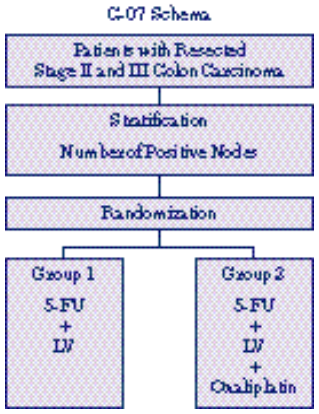


Figure 4: NSABP C-07



CALGB=Cancer and Leukemia Group B; MoAb=monoclonal antibody; IV=intravenous; NSABP=National Surgery Adjuvant Breast and Bowel Project; UFT=uracil and ftorafur; LV=leucovorin; 5-FU=5-fluorouracil; CT=chemotherapy; R=rest.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 4. RECTAL CANCER

Predictors of Outcome

Local Recurrence Rates in Rectal Cancer According to Stage (Results of Recent Large Series)

Series	Number of Patients	Stage I (%)	Stage II (%)	Stage III (%)
Braun, 1992[32]	534	6	20	39
Zirngibl,[33] 1990	1,062	9	17	30
Tumorregistrar Erlangen,[32] 1974–95	1,581	10	20	30
Swedish Rectal Cancer Trial,[34] 1997	454	12	21	36

Multivariate Analysis of Local Recurrence Rates in a Prospective Series of 596 Patients Followed for at Least 5 Years Following Curative Resection of Rectal Cancer (N=596)[11]

Variable		5-Year Local Recurrence Rate (%)	*P* Value
Distal Margin (cm)	>1 cm	9.9	.01
	<1 cm	27.2	
Macroscopic Type	Nonulcerating	5.8	.01
	Ulcerating	12.9	
Grade	High	9.7	<.01
	Low	23.3	
Venous Invasion	No	9.1	.01
	Yes	20.3	
Stage	A	2.5	A+B vs
	B	6.5	C<.01
	C	22.6	

Conclusion:

The involvement of lymph nodes is the most significant variable in determining the rate of local recurrence.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 5. SPHINCTER SPARING SURGERY FOR EARLY STAGE RECTAL CANCER

Survival Statistics Following Sphincter Sparing Surgery by Stage[6]

	T1(%)	T2*(%)	Overall(%)
Survival (6 years)	87	85	85
Failure-Free Survival (6 years)	83	71	78

*Patients with T2 lesions received adjuvant radiation (5,400 cGy/30 fractions) and 5-FU (500 mg/m^2 d1–3 and d29–31).

T=tumor; cGy=centgray; 5-FU=5-fluorouracil.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 6. TREATMENT OF STAGES II–III:

Surgery Followed by Adjuvant XRT Along With 5-FU Followed by Adjuvant Chemotherapy

Results of NCCTG 86-47-51: Randomized study of postoperative radiation with or without semustine and comparing bolus 5-FU with protracted continuous infusion 5-FU during radiotherapy.[12]

Treatment	Overall Relapse Rate (%)	Rate of DM (%)	Relapse Free at 4 Years (%)	Survival at 4 Years (%)
Bolus 5-FU	47	40	53	60
CIVI 5-FU	37 (*P*=.01)	31 (*P*=.03)	63 (*P*=.02)	70 (*P*=.01)

Incidence of Toxicities on NCCTG 86-47-51

Toxicity	CIVI 5-FU (N=297)	Bolus 5-FU (N=314)
Diarrhea	24 (*P*<0.01)	14
Stomatitis	1	0
Nausea	1	1
Vomiting	1	1
Leukopenia (<2,000/mm^3)	2	11 (*P*<0.01)
Thrombocytopenia (<50,000/mm^3)	0	1
Dermatitis	3	3

Conclusions:

The addition of semustine did not significantly improve patient outcome. The use of protracted CIVI 5-FU during adjuvant radiotherapy decreased the rate of local recurrence and improved overall survival. There was an increased rate of diarrhea associated with the use of continuous 5-FU therapy but less leukopenia in this setting.

XRT=radiation therapy; 5-FU=5-fluorouracil; NCCTG=North Central Cancer Treatment Group; DM=distant metastasis; CIVI=continuous intravenous infusion.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 7. ROLE OF POSTOPERATIVE ADJUVANT RADIOTHERAPY IN PATIENTS TREATED WITH POSTOPERATIVE ADJUVANT CHEMOTHERAPY FOR STAGE II–III RECTAL CANCER

Results of NSABP R-02 Trial: A Randomized Trial of Postoperative Adjuvant Chemotherapy With or Without Radiotherapy for Stage II–III Rectal Cancer[13]

Treatment Comparison	Relapse-Free Survival (5 Year %)	Disease-Free Survival (5 Year %)	Overall Survival (%)
XRT vs no XRT	Equivalent (*P*=.38)	Equivalent (*P*=.90)	Equivalent (*P*=.89)
MOF vs 5-FU/LV*	5-FU/LV=61 MOF=55 (*P*=.046)	5-FU=55 MOF=47 (*P*=.009)	5-FU=65 MOF=62 (*P*=.17)

*Males only.

MOF
Semustine 130 mg/m² day 1
5-FU 325 mg/m² IV bolus days 1–5 and days 36–40 of each cycle
Vincristine 1 mg/m² day 1 and day 36
Repeated every 10 weeks x 5

5-FU/LV
LV 500 mg/m² IV over 2 hours
5-FU 500 mg/m² IV push after 1 hour of the LV infusion
Weekly for 6 weeks followed by a 2-week break
Repeated for 6 cycles

Conclusions:

The addition of XRT did not impact on relapse-free survival, disease-free survival or overall survival. At 5 years however, there was a 5% absolute decrease in the rate of locoregional recurrence from 13% without adjuvant radiotherapy to 8% with adjuvant radiotherapy (*P*=.02). 5-FU/LV chemotherapy was superior to MOF chemotherapy.

NSABP=National Surgery Adjuvant Breast and Bowel Project; XRT=radiation therapy; MOF=semustine/5-fluorouracil/vincristine; 5-FU=5-fluorouracil; LV=leucovorin.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 8. NEOADJUVANT XRT WITH 5-FU CHEMOTHERAPY FOLLOWED BY SURGERY AND THEN ADJUVANT CHEMOTHERAPY

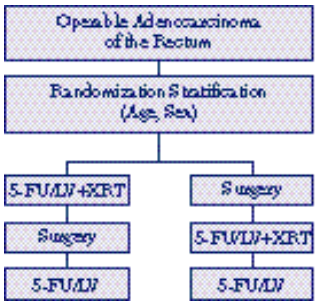
Results of European Randomized Trials Comparing Preoperative Radiotherapy With Surgery Alone[14]

Trial	Decreased Local Recurrence Rate	Increased Overall Survival
Norway (Low Dose XRT)	No	No
EORTC	Yes (*P*=0.003)	No
Medical Research Council	Yes (*P*=0.02)	No

XRT=radiation therapy; 5-FU=5-fluorouracil; EORTC=European Organization for Research and Treatment of Cancer.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 9. ONGOING CLINICAL TRIAL: NSABP R-03



NSABP=National Surgical Adjuvant Breast and Bowel Project; 5-FU/LV=5-Fluorouracil/Leucovorin; XRT=radiation therapy.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 10. ADVANCED COLON CANCER-ORGAN CONFINED RESECTABLE

Randomized Trial of 5-FU/LV With or Without HAI With FUDR and Dexamethasone in Patients With Resected Hepatic Metastases (Kemeny et al)[15]

Treatment	Median Overall Survival (months)	Median Survival-Free of Hepatic Progression (months)	Median Progression Survival (months)
Systemic Therapy Only	59.3	42.7	17.2
Systemic and Intrahepatic Therapy	72.2 (*P*=0.11)	Not reached with median 5-FU of 62.7 (*P*<.001)	37.4 (*P*=.01)

Frequency of Grade 3 and 4 Toxicities:

Toxicity	HAI and Systemic Therapy (N=74)		Systemic therapy (N=82)		
	Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)	*P* Value
Neutropenia	10	8	12	9	0.62
Diarrhea	22	7	11	4	0.03
Vomiting	6	4	4	1	0.26
Stomatitis	11	0	7	3	0.83
Nausea	8	4	4	0	0.07

Conclusions:

Locoregional therapy improves hepatic progression and progression-free survival when combined with systemic therapy compared with systemic therapy alone in patients who have undergone resection of hepatic metastases. However, this therapy does not significantly impact overall survival.

5-FU=5-fluorouracil; LV=leucovorin; HAI=hepatic arterial infusion; FUDR=floxuridine.

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TABLE 11. ADVANCED COLON CANCER-ORGAN CONFINED UNRESECTABLE

Randomized Studies of HAI vs Systemic Chemotherapy

Study	Arm	Response Rate (%)	Time to Hepatic Progression	Median Survival
MSKCC[16] (n=99)	HAI of FUDR	53 (*P*=.001)	—	17 months (*P*=.42)
	FUDR IV	21	—	12 months
NCOG[17] (n=117)	HAI	42 (*P*<.001)	401 days (*P*=.0010)	503 days
	Systemic Therapy	10	201 days	484 days
NCI[18] (n=64)	HAI	62 (*P*<.003)	—	20 months
	Systemic Therapy	17	—	18 months
NCCTG[20] (n=69)	HAI	48 (*P*=.02)	15.7 months (*P*=.001)	12.6 months
	Systemic Therapy	21	7 months	10.5 months

Conclusions:

HAI therapy increases the response rate in patients with organ confined unresectable advanced colorectal cancer. The majority of randomized clinical trials completed to date do not demonstrate a survival benefit. Interpretation of these trials may be limited by their small numbers and crossover designs.

HAI=hepatic arterial infusion; MSKCC=Memorial Sloan-Kettering Cancer Center; FUDR=floxuridine; IV=intravenous; NCOG=Northern California Oncology Group; NCI=National Cancer Institute; NCCTG=North Central Cancer Treatment Group.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 12. ADVANCED COLORECTAL CANCER-CHEMOTHERAPY

First-Line Therapies

Phase III Trial of Irinotecan With 5-FU and LV vs 5-FU and LV vs Irinotecan Alone[25]

End Point	Irinotecan/ 5-FU/LV	5-FU/LV	*P* Value*	Irinotecan alone
Median Progression-Free Survival (months)	7.0	4.3	.004	4.2
Objective Response Rate (%)	50	28	<.001	29
Confirmed Objective Response (%)	39	21	<.001	18
Median Response Duration (months)	9.2	8.7	0.37	9.0
Median Overall Survival (months)	14.8	12.6	.04	12.0

*5-FU/LV vs CPT-11/5-FU/LV.

5-FU/LV

LV 20 mg/m² IV bolus
5-FU 425 mg/m² as an IV bolus given daily for 5 days repeated every 4 weeks

5-FU/LV/Irinotecan

LV 20 mg/m² IV bolus
5-FU 500 mg/m² IV bolus
Irinotecan 125 mg/m² IV over 90 minutes
Weekly for 4 weeks, repeated every 6 weeks

Irinotecan Alone

Irinotecan 125 mg/m² IV over 90 minutes
Weekly for 4 weeks, repeated every 6 weeks

Frequency of Toxicities (Grade 3 and 4)

Adverse Event	5-FU/LV/ Irinotecan (%)	5-FU/LV (%)	Irinotecan (%)
Diarrhea	22.7	13.2	31
Vomiting	9.7	4.1	12.1
Mucositis	2.2	16.9	2.2
Neutropenia	53.8	66.2	31.4
Neutropenic Fever	7.1	14.6	5.8
Drug-Related Death	0.9	1.4	0.9

Conclusion:

The addition of irinotecan to 5-FU and LV therapy significantly increases the response rate and results in improved overall survival.

5-FU=5-fluorouracil; LV=leucovorin; CPT-11=oxaliplatin; IV=intravenous.

Grinblatt DL, Schilsky RL. *Oncology Spectrums.* Vol 2. No 7. 2001.

TABLE 13. PHASE III TRIALS OF OXALIPLATIN WITH 5-FU AND LV VS 5-FU AND LV ALONE (DE GRAMONT AND CHRONOTHERAPY REGIMENS)[27]

	de Gramont 5-FU/LV	de Gramont 5-FU/LV + Oxaliplatin	*P* Value
Overall Response Rate (%)	21.9	50	0.001
Complete Response (%)	0.5	1.4	—
Partial Response (%)	21.4	48.6	—
Stable Disease (%)	51	31.9	—
Progression-Free Survival (months)	6.1	8.7	0.001
Overall Survival (months)	14.7	16.2	0.1

5-FU and LV (de Gramont regimen)

LV 200 mg/m² IV over 2 hours followed by 5-FU 400 mg/m² bolus followed by 600 mg/m² given over 22 hours with the LV and 5-FU repeated on day 2

Cycles are repeated every 2 weeks

5-FU, LV, and Oxaliplatin (de Gramont regimen)

Oxaliplatin 85 mg/m² IV on day 1 followed by LV 200 mg/m² IV over 2 hours followed by 5-FU 400 mg/m² bolus followed by 600 mg/m² given over 22 hours with the LV and 5-FU repeated on day 2

Cycles are repeated every 2 weeks

	Chronotherapy 5-FU/LV	Chronotherapy 5-FU/LV + Oxaliplatin[35]	*P* Value[36]
Overall Response Rate (%)	16	53	<0.001
Progression-Free Survival (median, months)	6.1	8.7	0.048
Overall Survival (months)	19.4	19.9	NS

5-FU and LV (Chronotherapy regimen)

LV 300 mg/m²/day CIVI x 5 days

5-FU 700 mg/m² CIVI x 5 days

Cycles are repeated every 4 weeks

5-FU, LV, and Oxaliplatin (Chronotherapy regimen)

Oxaliplatin 125mg/m² IV over 6 hours on day 1

LV 300 mg/m²/day CIVI x 5 days

5-FU 700 mg/m² CIVI x 5 days

Cycles are repeated every 4 weeks

Conclusions:

The addition of oxaliplatin to 5-FU and LV therapy significantly increases the response rate and median progression-free survival when used as initial therapy for advanced colorectal cancer. Overall survival was not improved in these trials which allowed crossover to oxaliplatin at the time of progression.

5-FU=5-fluorouracil; LV=leucovorin; IV=intravenous; NS=not significant; CIVI=continuous intravenous infusion.

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TABLE 14. PHASE III TRIALS OF CAPECITABINE VS 5-FU/LV (MAYO REGIMEN)

Capecitabine 2,500 mg/m²/day x 14 Days Every 3 Weeks vs 5-FU 450 mg/m² and LV 20 mg/m² Days 1–5 Repeated Every 4 Weeks

	Trial #1 (Cox et al)[21]		Trial #2 (Twelves et al)[22]	
	5-FU/LV	Capecitabine	5-FU/LV	Capecitabine
Overall Response Rate (%)	15.5	23.2 (*P*=.02)	17.9	26.6 (*P*=.013)
Duration of Response (months)	9.7	9.1	9.6	7.3
Progression-Free Survival (months)	5.1	4.4	4.8	5.3
Median Overall Survival (months)	13.9	12.9	13.0	13.7

Conclusions:

Capecitabine resulted in an increased rate of response and equivalent progression-free and overall survival. There were more serious grade 3–4 toxicities in the 5-FU/LV arm especially with respect to neutropenia.

5-FU=5-fluorouracil; LV=leucovorin.

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TABLE 15. PHASE III TRIAL OF ORAL UFT PLUS LV VS PARENTERAL 5-FU PLUS LV IN PATIENTS WITH ADVANCED COLORECTAL CANCER

	Trial #1 (Carmichael et al)[23]		Trial #2 (Pazdur et al)[24]	
	5-FU/LV	UFT/LV	5-FU/LV	UFT/LV
Overall Response Rate (%)	9	11	15	12
Time to Progression (median, months)	3.3	3.4	—	—
Median Survival (months)	11.9	12.2	—	—

Frequency of Grade 3–4 Toxicities for Trial 1/Trial 2

Toxicity	UFT/LV (% Trial 1/2)	5-FU/LV (% Trial 1/2)	P Value (Trial 1/2)
Diarrhea	18/21	11/16	NS/NS
Nausea/ Vomiting	9/13	9/10	NS/NS
Mucositis	2/1	16/20	<.001/.001
Neutropenia	3/1	31/56	<.001/.001
Thrombo-cytopenia	1/0	2/2	NS/.003
Anemia	5/3	4/7	NS/.032

UFT/LV

UFT 300 mg/m²/day
LV 90 mg/day
Administered for 28 days repeated every 35 days

5-FU/LDLV

LV 20 mg/m² IV
5-FU 425 mg/m² IV push
Days 1–5 every 35 days

Conclusions:

Oral uracil and tegafur with LV have equivalent activity to IV 5-FU and LV in patients with advanced colorectal cancer. Toxicities such as mucositis and neutropenia occur less frequently with the oral combination when compared to the Mayo Clinic monthly 5-FU/LV regimen.

UFT=uracil/ftorafur; LV=leucovorin; 5-FU=5-fluorouracil; NS=not significant; LDLV=low-dose leucovorin; IV=intravenous.

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TABLE 16. SECOND-LINE THERAPIES

Irinotecan Alone (For Patients Who Have Previously Failed 5-FU/LV Alone)

	Study 1		Study 2	
	Irinotecan	Supportive Care	Irinotecan	Infusional 5-FU
Number of Patients	189	90	127	129
Duration of Study Treatment (median, months)	4.1	—	4.2 (*P*=0.02)	2.8
Median Survival (months)	9.2 (*P*=0.0001)	6.5	10.8 (*P*=0.035)	8.5

5-FU=5-fluorouracil; LV=leucovorin.

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