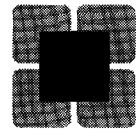

Adjuvant therapy for colorectal cancer

ANTHONY M. VERNAVA III, MD

■ The search for effective adjuvant therapy for colorectal cancer has been long and, until recently, largely unrewarding. Surgery alone is inadequate therapy in as many as 50% of patients. But recent studies demonstrate significant improvement in disease-free survival and overall survival for patients with advanced colon and rectal cancer who receive adjuvant therapy. Postoperative chemotherapy with fluorouracil and levamisole is the standard of care for patients with stage III colon cancer, and postoperative high-dose pelvic radiation combined with fluorouracil is the standard regimen for patients with stage II and III rectal cancer.

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THE SEARCH FOR an effective adjuvant therapy for colon and rectal cancer has been long and frustrating. Surgery alone has proved inadequate therapy for as many as 50% of patients, despite the fact that 75% of resections are labeled "curative." This represents a tremendous failure when one considers that 60,500 patients died from colorectal carcinoma in 1991.[1]

Thirty years of clinical trials failed to provide an effective adjuvant therapy for adenocarcinoma of the colon. Indeed, Buyse and colleagues,[2] in a meta-analysis of all randomized, controlled trials of adjuvant therapy for colorectal cancer up to December 1986 and involving 3,062 patients with rectal cancer and 6,791 patients with colon cancer, could demonstrate only a very small improvement in survival for patients treated with fluorouracil (5-FU)-containing regimens (mortality odds ratio of 0.83 in favor of adjuvant therapy).

From the Department of Surgery, The St. Louis (Missouri) University School of Medicine.
Address reprint requests to A.M.V., the Department of Surgery, St. Louis University School of Medicine, 3635 Vista Avenue/Grand Boulevard, St. Louis, MO 63110-0250.

However, in the 3 years since the publication of that excellent meta-analysis, the role of adjuvant therapy for colorectal cancer has changed significantly. A number of reports published recently demonstrate improved survival for patients with advanced colon cancer and rectal cancer who received postoperative adjuvant therapy.[3–5] This article examines these reports and the current status of adjuvant therapy for colorectal cancer.

PRINCIPLES OF EFFECTIVE ADJUVANT THERAPY

The goal of adjuvant therapy is to eliminate unresectable microscopic disease and thereby improve patient survival. Five basic principles of adjuvant therapy are outlined below.[6]

1. Occult, viable tumor cells may circulate intravascularly, intralymphatically, or intraperitoneally; microscopic foci of tumor cells may establish themselves at local or distant sites.
2. Therapy is most effective when the tumor burden is minimal and cell kinetics are optimal.
3. Agents with proven effectiveness against the tumor are available.

TABLE 1
THE TUMOR-NODE-METASTASIS (TNM) SYSTEM: AN OVERVIEW OF TUMOR CLASSIFICATION

TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Metastasis in one to three pericolic or perirectal lymph nodes
N2	Metastasis in four or more pericolic or perirectal lymph nodes
N3	Metastasis in any lymph node along the course of a named vascular trunk
MX	Presence of distant metastasis cannot be assessed
MO	No distant metastasis
MI	Distant metastasis

TABLE 2
PATHOLOGIC STAGING FOR COLORECTAL CANCER: TUMOR-NODE-METASTASIS (TNM) SYSTEM

Stage 0	Tis	NO	MO	Dukes	5-year survival % (21)
Stage I	T1	NO	MO	A	80-95%
	T2	NO	MO		
Stage II	T3	NO	MO	B	60-90%
	T4	NO	MO		
Stage III	Any T	N1	MO	C	30-55%
	Any T	N2, N3	MO		
Stage IV	Any T	Any N	MI		0-5%

4. Response to cytotoxic therapy is related to dose and therefore must be administered in the largest doses tolerated; moreover, the duration of therapy must be sufficient to eradicate all tumor cells.

5. The risk-to-benefit ratio for therapy must be favorable for individuals who may remain asymptomatic for their natural life expectancy after tumor resection.

Following the "curative" resection of colorectal cancer, liver metastasis occurs in 40% of patients, local recurrence occurs in 25% to 40%, and peritoneal metastases occur in 12% to 28%. However, patterns of surgical failure differ between colon cancer and rectal cancer, so the results of treatment of each disease should be evaluated separately. Colon cancer resection is known to fail primarily because of tumor cell metastasis, most commonly to the liver. An effective adjuvant therapy for colon cancer would therefore be directed at the prevention of systemic spread and hepatic metastasis. Local recurrence is less common than systemic spread. In contrast, local recurrence is very common following resection of rectal cancer, and systemic metastasis also occurs. Therefore, an effective adjuvant therapy for rectal cancer should prevent local or regional recurrence, as well as systemic metastasis.

Prognosis following resection of either colon cancer or rectal cancer is primarily determined by the pathologic stage. The more advanced the stage of colon cancer, the greater the likelihood of both systemic metastasis and local or regional recurrence. Similarly, the more advanced the stage of rectal cancer, the greater the chance of both local or regional recurrence and systemic metastasis. A number of pathologic staging systems have been employed for colorectal cancer, including the Dukes, Kirklin, Astler-Coller, and tumor-node-metastasis (TNM) systems. In an effort to standardize reporting, the most recent consensus statement by the National Institutes of Health (NIH) recommends that the TNM system (*Tables 1* and 2) replace all other staging systems and be used routinely.

ADJUVANT THERAPY FOR COLON CANCER

The single most active agent against colon cancer is 5-FU, a pyrimidine analogue that inhibits thymidylate synthetase and, hence, inhibits DNA synthesis. The response rate for 5-FU when given as a single agent to colon cancer patients is as high as 20% and depends on factors such as dose intensity and dose schedule. As mentioned above, a meta-analysis of over 6,000 patients involved in randomized, controlled studies could demonstrate only a slight improvement in survival for patients treated with 5-FU, which was not statistically significant.[2] Floxuridine (FUDR, 5-fluoro-2′-deoxyuridine), the conjugated analogue of 5-FU, contains a deoxyribose molecule which is readily removed by the enzyme thymidine phosphorylase. Ninety percent of FUDR is removed in the liver during its first pass. FUDR has response rates similar to 5-FU and no documented effect on survival when given alone.

Mitomycin C, semustine (methyl-CCNU), carmustine (BCNU), and lomustine (CCNU) have all been

used as single-agent adjuvants in colorectal cancer. Each of these agents has a clinical response rate between 10% and 20%, and none has demonstrated benefit with respect to survival.

Biologic response modifiers are agents that either enhance the immune response or produce direct cytotoxicity. Examples include the interferons (alpha, beta, gamma) and interleukin. Although these agents are currently undergoing investigation, preliminary evidence suggests that they have minimal activity against colorectal cancer when used alone. Widely variable results have been reported using combination chemotherapy (ie, 5-FU plus another agent). Agents that have been combined with 5-FU include semustine, vincristine, streptozocin, and cisplatin. With each of these combinations, no consistent improvement has been seen for either the response rate or survival. However, toxicity is greatly increased with these combination regimens. The combination of 5-FU and leucovorin (folinic acid) has been studied in patients with advanced carcinoma and is currently undergoing further evaluation as adjuvant therapy.[7] When used in patients with advanced colorectal cancer, 5-FU and leucovorin significantly improved tumor response rates, interval to tumor progression rates, and median survival when compared with 5-FU alone, 5-FU with methotrexate, and 5-FU with cisplatin.[7] The use of hepatic artery infusion and portal vein infusion as adjuvant therapy for colorectal cancer remains investigational. Studies evaluating these methods of therapy have failed to demonstrate either improved survival or a reduction in liver metastases.[8–10]

Over the past 2 years, two large trials—the North Central Cancer Treatment Group (NCCTG) trial and the Intergroup trial—have documented significant improvements in survival and recurrence rates for patients with advanced-stage colon cancer (TNM stage III) who received 5-FU and levamisole.[3,4] The NCCTG trial[3] evaluated patients with stage II and stage III colon cancer who underwent curative resection. A total of 401 patients were entered into the study. Patients were randomized to one of three different groups: no further treatment, levamisole alone, or 5-FU with levamisole. The levamisole dosage in both groups was 50 mg po every 8 hours for 3 days, repeated every 2 weeks for a year. The patients who received 5-FU started with a bolus injection of 450 mg/m^2/day for 5 consecutive days, followed by weekly injections of 5-FU, 450 mg/m^2. The median follow-up was 7 years and 9 months. Patients with stage III disease who received both 5-FU and levamisole experienced significant improvement in both overall survival (P=.02) and disease-free survival (P=.03) when compared with either the levamisole-alone group or the group receiving no further treatment. The 1989 report of the NCCTG trial was the first large, well-designed, randomized, controlled study to demonstrate a significant improvement in survival with adjuvant therapy in patients with advanced-stage colon cancer.

A subsequent study, the Intergroup trial,[4] confirmed the positive results obtained with 5-FU and levamisole in the NCCTG trial. This study entered 1,296 patients with stage II and stage III disease and randomized them postoperatively to either observation alone or treatment for 1 year with levamisole and 5-FU. Some stage II patients were also randomized to levamisole alone. The dosages of levamisole and 5-FU in the Intergroup study were the same as in the NCCTG trial, except that treatment with 5-FU was continued for 48 weeks instead of 1 year. The results of treatment in patients with stage III disease were striking and significant. To summarize, treatment with levamisole and 5-FU reduced the risk of cancer recurrence by 41% (P=.001) and decreased the death rate by 33% (P=.006). Levamisole alone had no significant effect. Patients with stage II disease did not significantly benefit from any adjuvant therapy in the study at a median follow-up of 3 years. The authors of the Intergroup trial anticipate the need to follow these patients an additional 2 years prior to making any conclusions regarding the efficacy of 5-FU and levamisole in stage II disease.

NIH CONSENSUS STATEMENT

Based on the results of the NCCTG and Intergroup trials, the NIH has strongly recommended that all patients with stage III colon cancer be treated postoperatively with 5-FU and levamisole, or that they be enrolled in a clinical study.[6] The NIH further stated that, in view of the documented efficacy of 5-FU and levamisole for stage III disease, treatment with these drugs should serve as the control arm in any future studies of postoperative adjuvant therapy. A no-treatment arm in future clinical studies of stage III colon cancer has been ruled out as unethical. Therapy for patients with stage II disease has not been proven efficacious, so routine treatment is not recommended. Patients with stage II colon cancer should be entered into clinical trials to obtain an answer. The precise mechanism of action of levamisole when combined with 5-FU is unknown and is the subject of current investigation.

CURRENT ADJUVANT THERAPY FOR RECTAL CANCER

The pattern of clinical failure of rectal cancer after surgical resection differs from that of colon cancer in that local recurrence is significantly more common. The reasons for this increased risk of local recurrence for rectal cancer are not difficult to understand and are primarily related to the anatomic constraints of the human pelvis and the surrounding structures. Tumor cells reside in the unresected pararectal tissue and result in locally recurrent disease. The risk of local recurrence is directly related to the pathologic stage: stage I, 5% to 10%; stage II, 25% to 30%; stage III, 50%. Systemic metastasis also can occur following "curative" resection of rectal cancer, the liver being the most common site. Therefore, an effective adjuvant therapy for rectal cancer would achieve two goals: first, decrease the risk of local recurrence; and second, diminish the incidence of systemic spread and improve survival.

A number of studies have documented a reduction in local recurrence with adjuvant radiation therapy, but none has demonstrated a significant improvement in survival.[11,12] Completed prospective randomized trials of preoperative radiotherapy for rectal cancer include the Veteran's Administration Surgical Adjuvant Group (VASAG) study I,[11] VASAG II,[13] Yale-New Haven Hospital study,[14] Princess Margaret Hospital study,[15] and the European Organization for Research and Treatment of Cancer (EORTC) study.[16] Several of these studies demonstrated improved survival for patients who received adjuvant preoperative radiation therapy, but the improvement in each study was not statistically significant. The EORTC study demonstrated a significant decrease in local recurrence in patients who received preoperative radiotherapy.[16]

Trials employing postoperative radiation therapy alone have not demonstrated an improvement in survival, but some have noted a significant decrease in local recurrence.[12,17] A trial at the M.D. Anderson Hospital[17] and the National Surgical Adjuvant Breast and Bowel Project Protocol R-01[12] both demonstrated a decrease in local recurrence without a significant impact on survival.

Two studies have now demonstrated that a combination of chemotherapy and postoperative radiation therapy results in both a decrease in local recurrence and an improvement in survival. The Gastrointestinal Tumor Study Group initially reported a significant improvement in survival for patients with advanced-stage rectal cancer who received 5-FU with radiation, followed by 5-FU and semustine for 1.5 years (P=.005).[18,19] Radiation dosage in this trial was 4,000 to 4,400 cGy. Despite the publication of these results in 1985, combination chemotherapy-radiotherapy failed to gain widespread acceptance.

In 1991, Krook et al[5] reported a trial of postoperative 5-FU with semustine and high-dose pelvic radiation (4,500 to 5,040 cGy) for patients with advanced-stage rectal cancer (stage II and stage III). The study assumed a treatment benefit for radiation therapy alone, so a no-treatment arm was not used. The recurrence rates in this study were very high (62.7% in the group receiving only radiation therapy, and 41.5% in the group receiving combination therapy). Interestingly, the group receiving combination therapy had significantly fewer local recurrences (13.5% vs 25%, P=.036), as well as fewer distant metastases (28.8% vs 46%, P=.011). Perhaps, most importantly, combination therapy resulted in a significant improvement in survival compared with radiation therapy alone, and the mortality rate was reduced by 29% (P=.043).

Based on these studies, the NIH has recommended routine postoperative adjuvant therapy for patients with stage II and stage III rectal cancer. Therapy should consist of intravenous 5-FU and high-dose pelvic radiation (4,500 to 5,040 cGy).[6] The addition of semustine to the regimen is not recommended because it can cause leukemia and because fluorouracil plus radiotherapy has now been demonstrated to be equivalent to fluorouracil plus semustine plus radiotherapy.[20]

CONCLUSION

Significant improvement in disease-free survival and overall survival has been demonstrated for patients with advanced colon and rectal cancer who received adjuvant therapy. Postoperative chemotherapy consisting of 5-FU and levamisole for patients with stage III colon cancer is now the standard of care: all patients with stage III disease should be so treated or referred to a clinical trial. High-dose pelvic radiation combined with 5-FU postoperatively is now the standard therapy for patients with stage II and stage III rectal cancer. Clinical trials are in progress to further evaluate the mechanism of action of levamisole when used with 5-FU, as well as the role of 5-FU and levamisole or leucovorin in combination with radiation for rectal cancer.

REFERENCES

1. Boring CC, Squires TS, Tong T. Cancer statistics. Cancer 1991; **41:**19–51.
2. Buyse M, Zeleniuch-Jadquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer: why we still don't know. JAMA 1988; **259:**3571–3578.
3. Laurie JA, Moertel CG, Fleming TR, et al. Surgical adjuvant therapy of large-bowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. J Clin Oncol 1989; **7:**1447–1456.
4. Moertel CG, Fleming TR, MacDonald JS, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990; **322(6):**352–358.
5. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high risk rectal carcinoma. N Engl J Med 1991; **324:**709–715.
6. Consensus Statement. NIH Consensus Development Conference, 1990 April 16-18; **8:**1–25.
7. Poon MA, O'Connell MJ, Moertel CG, et al. Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 1989; **7:**1407–1417.
8. Wolmark N, Rockette H, Wickerham DL, et al. Adjuvant therapy of Dukes' A, B and C adenocarcinoma of the colon with portal-vein fluorouracil hepatic infusion: preliminary results of national surgical adjuvant breast and bowel project protocol, C-02. J Clin Oncol 1990; **8:**1466–1475.
9. Beart RW, Moertel CG, Wieand HS, et al. Adjuvant therapy for resectable colorectal carcinoma with fluorouracil administered by portal vein infusion: a study of the Mayo Clinic and the North Central Cancer Treatment Group. Arch Surg 1990; **125:**897–901.
10. Taylor I, Machin D, Mullee M, Trotter G, Coke T, West C. A randomized, controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. Br J Surg 1985; **72:**359–363.
11. Roswit B, Higgins G, Keehn R. Preoperative irradiation for carcinoma of the rectum and rectosigmoid colon: report of a National Veterans Administration randomized study. Cancer 1975; **35:**1597–1602.
12. Fisher B, Wolmark N, Rockette H, et al. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP Protocol R-01. J Natl Cancer Inst 1988; **80:**21–29.
13. Higgins GA, Humphrey EW, Dwight RW, et al. Preoperative radiation and surgery for cancer of the rectum. Veterans Administration Surgical Oncology Group Trial II. Cancer 1986; **58:**352–359.
14. Kligerman MM, Vraaneta-Lafee N, Knowlton A, et al. Preoperative irradiation of rectosigmoid carcinoma including its regional lymph nodes. Am J Roentgenol Radium Ther Nucl Med 1972; **114:**498–503.
15. Rider WD, Palmer JA, Mahoney LJ, et al. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. Can J Surg 1977; **20:**335–338.
16. Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer: final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 1988; **208:**606–614.
17. Withers HR, Romsdahl M. Postoperative radiotherapy for adenocarcinoma of the rectum and rectosigmoid. Int J Radiat Oncol Biol Phys 1977; **2:**1069–1074.
18. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. N Engl J Med 1985; **312:**1465–1472.
19. Douglass HO, Moertel CG, Mayer RJ, et al. Survival after postoperative combination treatment of rectal cancer. N Engl J Med 1986; **315:**1294–1295.
20. Boice JD Jr, Greene MH, Killen JY Jr, et al. Leukemia and preleukemia after adjuvant treatment of gastrointestinal cancer with semustine (methyl-CCNU). N Engl J Med 1983; **309:**1079–1084.