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Review

Adjuvant treatment of colorectal cancer

Current status and concepts

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Summary. *Colorectal cancer is the second leading cause of cancer mortality in the United States, causing approximately 50,000 deaths per year. The overall prognosis and results of treatment have not changed impressively over the last three decades. Half of all the patients who undergo curative surgery finally succumb to locoregional or metastatic recurrence of their disease. Recent clinical research has been aimed at adjuvant therapeutic measures to improve survival after curative surgical resection.*

For rectal cancer, combined postoperative chemotherapy and radiation therapy have been shown to reduce the overall relapse rate and improve disease-free survival. Further studies of adjuvant treatment for rectal cancer are needed to evaluate the optimal radiation schedule and limit the side-effects of the treatment.

Adjuvant treatment of colon cancer must still be regarded as unsettled. Since liver metastases are the most common unfavorable outcome of colon cancer, ongoing trials using liver-directed treatment (perfusion, irradiation) should be followed with interest. The lack of proven efficacy and the side-effects of these treatments strongly favor the inclusion of an observation-only control group in trials for adjuvant treatment of colon cancer.

Unfortunately, there is as yet no proven significant benefit from immunotherapy as an adjuvant therapy for colorectal cancer, but further basic and clinical studies will be of great interest in this field.

Introduction

Colorectal cancer is the second leading cause of cancer death in the United States, with 40–50 individuals per 100,000 being affected each year [88]. Although there have been some advances in surgical technique and intensive care, reducing the perioperative morbidity and mortality, the overall picture and results of treatment of colorectal cancer have not changed impressively in the last 20 years [3, 4, 12, 23]. At least half of all the patients who have undergone curative surgery finally succumb to locoregional or distant recurrence of disease. In the last two decades, enormous efforts have been made to improve the results of treatment, either through earlier diagnosis by screening and recognition of high-risk patients or by adjuvant measures in surgically treated patients.

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Rationale and alternatives for adjuvant treatment

Any preoperative treatment that reduces the tumor volume and retards tumor cell dissemination may lead to a higher operability rate and improved radical surgery. Theoretically, recurrence after radical resection is caused either by micrometastases not visible during surgery [8] or by tumor cell dissemination through the surgical procedure itself [21]. Adjuvant treatment for colorectal cancer can apparently be appropriately administered immediately before, during, or immediately after the surgical resection, as early postoperative treatment at a time of lower tumor burden theoretically should be more efficient than later treatment [24, 71].

Radiotherapy, chemotherapy, immunotherapy, and anticoagulation/fibrinolysis have all been studied as adjuvant treatment modalities. Therapy has been applied pre-, intra-, and postoperatively. We will review here the pertinent adjuvant therapy trials and discuss the current status of surgical adjuvant therapy of large-bowel cancer.

Radiotherapy for rectal cancer

Preoperative radiotherapy

Because of locoregional recurrent rates of 30%–40% [65, 70, 73], adjuvant radiotherapy for rectal cancer has been the subject of study for 30 years. In 1959, Stearns et al. [78] reported the Memorial Hospital experience with preoperative radiation therapy using 1,000–2,000 rads in a series of 727 patients. In this retrospective, nonrandomized study, patients with Dukes' C lesions seemed to have an improved survival. Although a subsequent prospective randomized study at Memorial Hospital [79] did not confirm the initial results, this work led to a worldwide investigation of preoperative radiotherapy for rectal cancer. In 1964, the Veterans Administration Surgical Adjuvant Group initiated a prospective randomized trial with preoperative irradiation consisting of 2,000 rads and a perineal boost of 500 rads for lesions near the anal margin. Higgins et al. [35, 37] reported the results of this study in 700 patients. The most striking result was the reduction in incidence of Dukes' C lesions in the pretreated group to 27.8% compared with 41.2% in the control group, suggesting 'down-staging' of the irradiated patients. Pretreated patients with curative resection had a 5-year survival rate of

48.5%, as against 38.8% in the control group. This difference was not statistically significant, ($0.05 < P < 0.1$). However, patients with abdominoperineal resection had a significantly improved 5-year survival of 40.8%, compared with 28.4% for the controls ($P < 0.02$), suggesting that patients with lower lesions profit from preoperative irradiation. Kligerman [47] has reported that preoperative irradiation (4,500 rads in 25 doses) results in Dukes' C lesions among only 28% of patients, whereas Dukes' C lesions were found in 69% of patients in an unirradiated control group. The overall 7-year survival rate was 41% for the pretreated versus 25% for the control group. However, the number of randomized patients was too small for statistical evaluation, possibly also indicating the very high portion of Dukes' C lesions in the untreated control group.

In 1977, Rider et al. [74] reported a double-blind Canadian trial treating 125 patients with 500 rads as a single dose immediately before the surgical procedure. Neither the surgeon nor the patient knew whether irradiation had been performed or not. In this study only patients with Dukes' C lesions had a significantly improved survival , i.e., 34% versus 18% for the control group ($P = 0.014$). Stevens et al. [80] reported a 5-year survival rate of 53% for rectosigmoidal cancer after preoperative irradiation with 5,000–6,000 rads. None of their patients developed local recurrence, suggesting that radiotherapy can achieve local tumor control. Of 40 inoperable patients, 20 were rendered operable and nine patients showed no evidence of tumor at the time of surgery. Unfortunately this study was not randomized, and compared radiotherapy with a historical control group. Nevertheless, preoperative radiation therapy has a demonstrated effect in down-staging of the disease, in rendering some inoperable cases operable, and finally, in local tumor control.

In currently ongoing or recently closed trials radiation dosages ranging between 3,000 and 4,000 rads are being evaluated to determine the rate of local surgical complications. Whereas in the Veterans Administration Group study no increased morbidity or mortality was experienced among the irradiated patients [75], Stevens et al. [81] reported higher incidence rates of anastomotic leaks and intestinal obstruction when 5,000 rads was given as preoperative radiation therapy. Preoperative irradiation has one disadvantage due to the impossibility of exact pretreatment staging. Thus, some patients are given radiotherapy when they have Dukes' A lesions or undetectable distant disease. Both these groups are unlikely to profit from preoperative irradiation but are burdened with the possible complications. Another potential problem with preoperative irradiation is the possible influence on the surgeon's selection of the resection procedure. For these reasons the current emphasis is on postoperative radiation therapy.

Intraoperative radiotherapy

Papillon, in France, treated 133 patients with early rectal cancers by endocavitary contact radiotherapy with or without subsequent interstitial curie-therapy and obtained a 5-year survival rate of 78% [67, 68]. Similar results in a smaller number of patients have been reported by others [42, 43], suggesting that local tumor control can be achieved by localized radiation therapy alone. Despite these results, intraoperative radiotherapy has never been evaluated in a prospective randomized manner for adjuvant treatment. These localized procedures are limited by the damage of surrounding tissue and, finally, by the technical difficulties in performing intraoperative radiotherapy.

Postoperative radiotherapy

Several retrospective studies have reported that postoperative radiotherapy has a positive effect on the incidence of local recurrence [28, 56, 72, 86, 89]. Radiation doses ranged between 4,500 and 5,000 rads. In a recently closed trial of the Gastrointestinal Tumor Study Group (GITSG, no. 7175) 227 patients were randomized after curative resection to (1) no further treatment, (2) postoperative radiotherapy with 4,000–4,800 rads, (3) postoperative chemotherapy with 5-fluorouracil and methyl-CCNU, or (4) the combination of radiotherapy and chemotherapy. Among the 192 completely evaluable patients, interim statistical analyses indicate a significantly better disease-free survival for patients assigned to the combined therapy arm compared with the control group ($P < 0.03$). No definitive comparison of overall survival is possible at this time. Since neither the radiotherapy nor the chemotherapy arm differs from the control arm in a statistically significant manner, no analysis can as yet be made of the contribution of these two modalities to the favorable result of combination therapy [58]. Recently, a new approach has been tried with the so-called sandwich technique combining pre- and postoperative radiotherapy for rectal cancer [13, 63]. It is not yet clear whether this approach will be more effective than high-dose postoperative treatment alone. Thus, postoperative radiation therapy has the advantage of selecting patients at high risk for local recurrence, but is still aimed at local disease only and leaves distant micrometastases untreated.

A partial list of the ongoing adjuvant studies in colorectal cancer, most of which are evaluating combined modality therapies, is shown in Table 1.

Chemotherapy

The difficulty in finding an effective adjuvant chemotherapy lies in the lack of drugs that are highly active in advanced disease. 5-Fluorouracil, after over 20 years of evaluation [32], still remains the most active drug, with an overall response rate of 21% [10]. Despite extensive testing of single agents, there have been few drugs with any degree of therapeutic activity (Table 2). Although there were some suggestions of improved survival for responders to 5-FU compared with nonresponders and historical controls [60], it can be safely said that single-agent chemotherapy has done little to affect the overall survival of this patient population as a whole.

The first drug combination reported to have activity superior to single agents was that of Falkson et al. [20], which consisted of BCNU plus 5-FU plus vincristine plus DTIC. They reported a 43% objective response rate for the combination, compared with 25% for 5-FU alone ($P = 0.26$). Using a combination of 5-FU with methyl-CCNU and vincristine, the same group obtained a 37% objective response rate [19], which seemed to be confirmed by Moertel et al. [62], who reported a 43% response rate for the same combination. Nevertheless, further follow-up of this trial failed to demonstrate an improvement in duration of response and survival for the combination. There have been several attempts to confirm the activity of this drug combination, but the largest comparative study in 848 previously untreated patients showed that none of these combination regimens was significantly more active than oral or IV 5-FU with respect to survival or objective tumor

Table 1. Adjuvant treatment of colorectal cancer. Ongoing trials

Tumor site and investigators	Tumor stage	Treatment arms
A. Colon		
Gastrointestinal Tumor Study Group	B_2, C	5-FU + 2,100 rad to the liver vs control
M.D. Anderson Hospital	C, D_1	FUDR + Mito (HAI + PAI), BCG + RT vs FUDR + Mito (HAI), BCG vs FUDR + Mito (HAI), RT, then HAI + PAI, BCG vs FUDR + Mito (HAI, 5 courses), BCG
North Central Cancer Therapy Group	B_2, C	5-FU + levamisole vs levamisole vs control
Ann Arbor, Michigan	B_2, C	BCG PO and SC vs 5-FU + MeCCNU vs 5-FU + MeCCNU + BCG vs control
National Surgical Adjuvant Breast and Bowel Project	B, C	5-FU + MeCCNU + vincristine vs BCG scarification vs control
Vetrerans Administration Surgical Oncology Group	B_2, C	Hydroxyurea + 5-FU vs 5-FU vs control
European Organization for Research on Treatment of Cancer	C	Levamisole vs control
B. Rectum		
Gastrointestinal Tumor Study Group	B_2, C	RT + 5-FU/MeCCNU postoperativ vs RT + 5-FU alone postoperativ
North Central Cancer Therapy Group	B_2, C	4,500 rad postoperativ vs same RT + 5-FU + MeCCNU
National Surgical Adjuvant Breast Project	B, C	4,000 rad postoperativ vs 5-FU + MeCCNU + vincristine vs control
Veterans Administration Surgical Oncology Group	All	3,150 rad preoperativ vs control
European Organization for Research on Treatment of Cancer	B_2, C	4,500 rad postoperativ vs control
C. Both colon and rectum		
National Cancer Institute	C	IV 5-FU vs IP 5-FU

Table 1 (continued)

Tumor site and investigators	Tumor stage	Treatment arms
National Cancer Institute Canada	B_2, C	Levamisole vs levamisole + 5-FU vs control
Swiss Group for Clinical Cancer Research	All	Intraportal 5-FU + Mito c vs control
United Kingdom, Liverpool, Royal Liverpool Hospital	All	Intraportal 5-FU vs control
United Kingdom, Hammersmith Hospital	B, C	Urokinase intraoperativ vs urokinase + warfarin 2 years vs control

Table 2. Single drugs with therapeutic activity in colorectal cancer

Agent	Response rate	References
5-Fluorouracil	19.5%–22%	11, 19, 62
FUDR	23%	11
ThioTepa	22%	11
Cyclophosphamide	19%	11
Chlorozotocin	18%	40
Triazinate	18%	55
Mitomycin C	12%–16%	11, 15, 59
Methyl-CCNU	15%–18%	11, 49, 59
BCNU	10%–14.5%	11, 59
Nitrogen mustard	15.5%	11
Mithramycin	14%	11
ICRF 159	12%	52
Hexamethylmelamine	11.5%	11
DTIC	11%	11
Hydroxyurea	11%	11
Methyl-GAG	15%	64

Table 3. Eastern Cooperative Oncology Group: Advanced colorectal cancer trial. (Adapted from Lavin et al. [49])

Protocol	Treatment program	No. of patients	Response rate (%)	Median survival time (weeks)
No prior chemotherapy (848 patients)				
E 4273	IV 5-FU	39	15	30
	Oral 5-FU	28	18	33
	5-FU + cytoxan	87	5	29
	5-FU + 6-TG	78	10	32
	Methyl-CCNU	87	15	27
E 4275	5-FU + methyl-CCNU	112	9	27
	5-FU + methyl-CCNU + VCR	103	11	29
	5-FU + methyl-CCNU + DTIC	114	16	40
	5-FU + hydroxyurea	94	21	35
	5-FU + MeCCNU + DTIC + VCR	99	11	29

Table 4. Adjuvant chemotherapy of colorectal cancer. Closed trials

Reference	Trial design	No. of patients	Result
Dwight et al. [16]	FUDR 6 weeks vs control	704	NS difference
Lawrence et al. [50]	5-FU 12 months vs control	156	NS difference
Higgins et al. [38]	5-FU 12–18 months vs control	522	NS difference
Grage et al. [25]	5-FU 12 months vs control	189	NS difference
Killen et al. [46]	5-FU + MeCCNU vs MER BCG vs 5-FU + MeCCNU + MER BCG vs control	621	NS difference
Panettiere et al. [66]	5-FU + MeCCNU vs 5-FU + MeCCNU + oral BCG vs control	626	NS difference
Mittelman et al. [58]	5-FU + MeCCNU vs 4,000–4,800 rad postoperativ vs CT + RT vs control (prefinally closed)	245	Significantly prolonged disease-free survival for combined CT + RT treatment arm ($P < 0.03$)
Mavligit et al. [53, 54]	BCG scarification vs BCG oral 5-FU	121	NS difference

response [49]. The results of this trial are shown in Table 3.

The one apparent hope for nitrosourea + 5-FU combinations comes from Memorial Hospital with a report of a 32% response rate with the combination of methyl-CCNU, 5-FU, vincristine and streptozotocin (MOF-Strept) [44]. In a randomized trial comparing MOF versus the MOF-Strept regimen, these same investigators have now reported CR and PR rates of 7% and 36% respectively, ($P = 0.011$), with initial evidence of superior survivorship for patients receiving MOF-Strept [45].

Adjuvant chemotherapy of colorectal cancer

Table 4 lists some of the closed and published randomized colorectal trials. Some of these studies were focused on colon cancer, but most addressed both colon and rectal tumors. Some of the trials also included an immunotherapy or a chemoimmunotherapy arm. The first adjuvant trial was reported by Dwight et al. [16] in 1973 for the Veterans Administration Surgical Adjuvant Group. Using FUDR single-durg therapy as adjuvant to curative colorectal surgery, they reported a 5-year survival rate of 50% compared with 47.1% for the control group. The difference was not significant.

Other trials conducted by the VASAG have been reported by Higgins et al. [38]. With short-term 5-FU they observed a 5-year survival rate of 58.5%, versus 49.4% for the untreated patients. With a prolonged intermittent 5-FU regimen the 5-year survival rate was 48.9%, against 44.2% for the controls. Among the patients with abdominoperineal resection the difference was more pronounced, 43.3% for the 5-FU group as against 33.7% for the control group, suggesting that patients with lesions near the anal margin may obtain more benefit from adjuvant treatment. However, despite a large number of patients entered in these trials, none of the survival differences were statistically significant.

Using intraluminal 5-FU and oral 5-FU postoperatively for 12 months, Lawrence et al. [50] reported 4-year disease-free survival rates of 33% for surgery alone and 45% for surgery + 5-FU. These figures and the survival data were not significantly different. In a study of the Central Oncology Group, Grage et al. [25] reported a slightly longer disease-free interval for patients with Dukes' C lesions with long-term 5-FU added to curative surgery than with surgery alone ($P = 0.06$). However, survival curves did not differ significantly for the Dukes' C group or for all patients. Summarizing all these 5-FU trials, Higgins suggested that there may be a definitive benefit from adjuvant 5-FU therapy [36]. However, statistical analysis of these studies fails to support this hypothesis.

Following these single-agent trials, a considerable number of studies of combination chemotherapy with or without immunotherapy were designed. Some of these are still ongoing (see Table 1), while others have recently been closed (see Table 4). In a study conducted by the Southwest Oncology Group, 626 patients were randomized to (1) 5-FU + methyl-CCNU, (2) 5-FU + methyl-CCNU + oral BCG or (3) no further treatment. Preliminary analysis shows no significant differences between the treatment arms, but prolonged follow-up is certainly needed for definitive conclusions [6]. The GITSG conducted a similar trial which included only colon cancer patients, comparing 5-FU + methyl-CCNU vs MER BCG vs the combination of chemotherapy + immunotherapy vs untreated controls. Initial results indicate no differences between the treatment arms. The overall recurrence rate after a median follow-up of more than 3 years was 27% [46]. This is markedly lower than was predicted at the time the study was designed, emphasizing the necessity of a surgery-alone control arm in trials for adjuvant treatment of colon cancer.

Since the liver is the most common metastatic site after curative resection of large-bowel cancer, several attempts have recently been made to reduce the incidence of liver metastases. Liver perfusion has been studied in metastatic disease via the portal [5, 83] and arterial routes [2, 69, 84], with objective response rates up to 50%. Taylor et al. [85] reported a randomized trial with 5-FU perfusion through the dissected and cannulated umbilical vein immediately after the curative resection of colorectal cancer. Among 80 evaluable patients in each treatment arm, they observed only two liver recurrences in the perfusion group, whereas 13 patients in the control group had liver metastases. Preliminary results also indicate superior survivorship for the patients receiving adjuvant liver perfusion (I. Taylor, personal communication). Similar results within a smaller group of patients have recently been reported by Campos et al. [9] using adjuvant perfusion with 5-FU + mitomycin C + vincristine via the arterial route.

Another approach to intraperitoneal and hepatic tumor involvement has been made by peritoneal dialysis with high-dose 5-FU [77]. This achieves high drug concentrations in the peritoneal fluid and a concentration in the portal vein similar to that achieved by direct portal perfusion. An adjuvant trial comparing this 'belly bath' technique with systemic 5-FU for Dukes' C lesions is now ongoing. Grossi et al. [26] reported a study with intraluminal 5-FU lavage and short-term postoperative 5-FU therapy. Patients with Dukes' C rectal cancer had a 5-year disease-free survival of 35%, compared with 23% for the control group. However, the difference was not significant and further overall survival data are not available.

While the combination of chemotherapy with postoperative radiotherapy may have a role in reducing the relapse rate of rectal cancer, adjuvant treatment for colon cancer must still be regarded as unsettled. The lack of proven efficacy and the side-effects of these treatments strongly favor the inclusion of observation-only control groups in studies of surgical adjuvant colon treatment.

Immunotherapy

In 1893, Coley [14] treated ten patients with repeated intratumoral inoculations of erysipelas, and opened the large field of basic and clinical studies of immunology of cancer. The rationale of cancer immunotherapy is based on possible immune deficiencies in patients with colorectal cancer [6, 7, 76]. Current treatment modalities are likely to diminish the immune response of cancer patients [7, 31, 82]. Despite some remarkable advances in basic immunology of colorectal cancer – inhibition of leucocyte migration [27], leukocyte adherence inhibition [30], cell-mediated cytotoxicity against tumor cells [33, 34] – the clinical studies performed have not shown clinical usefulness. Neither BCG by the oral [18], intradermal [53], or intraperitoneal route [17], nor the systemic route for the methanol extraction residue fraction of BCG [61] has affected the natural course of this disease in a manner that could recommend its routine adjuvant use. Trials with toxins of *Corynebacterium parvum* [29] and with levamisole [87] have shown no significant improvement of survival. Inoculation with

irradiated tumor cells modifies the immunologic response of cancer patients but does not influence patient survival [41].

In the above-cited large studies of GITSG and SWOG [46, 66], neither MER BCG nor oral BCG showed statistically significant advantages versus the other treatment arms, but the median follow-up may be too short for definitive conclusions. In a randomized trial at M.D. Anderson Hospital, the combination of BCG plus 5-FU was not superior to 5-FU alone [53, 54]. Unfortunately, there was no control group in this study.

In conclusion, there is as yet no proven significant benefit of immunotherapy as an adjuvant to surgery in colorectal cancer. Future studies will probably utilize more specific immune modifiers, such as monoclonal antibodies.

Fibrinolysis and anticoagulants

Michaels reported in 1964 a reduced incidence of cancer among patients receiving long-term anticoagulation therapy for thromboembolic disorders compared with the estimated cancer risk for a pairwise matched normal population group [57]. Agostino et al. [1], Koike [48], Hilgard et al. [39], and Malone et al. [51] have pointed out the importance of coagulation and the fibrinolytic system in the lodging of tumor cells and the growth of metastasis. The clinical confirmation of these animal research data has been established for small cell lung cancer and other metastatic diseases [22, 90]. An adjuvant trial for colorectal cancer using peroperative fibrinolysis and postoperative anticoagulation is now ongoing in the United Kingdom.

Conclusions

In rectal cancer, there is an apparent benefit from combined chemotherapy and radiation therapy as an adjuvant to curative surgery that reduces the overall relapse rate. A strong trend favoring the combined-modality approach also exists for survivorship, and further follow-up and statistical analysis is awaited with great interest. Further studies of adjuvant treatment for rectal cancer are needed to evaluate the optimal radiation schedule and to limit the side-effects of both local and systemic treatment.

Since liver metastases are the most common unfavorable sequelae of colon cancer, liver-directed therapeutic trials using perfusion or irradiation are being followed with great interest. For systemic treatment, there is a definite need of more potent cytotoxic compounds and future efforts should be directed towards identification of new active drugs since progress in combining known active agents has been limited at best.

Unfortunately, there is as yet no proven significant benfit from immunotherapy as an adjuvant to colorectal cancer, but further basic and clinical studies will be of great interest in this field.

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