Pergamon

European Journal of Cancer Vol. 31A, No. 12, pp. 1981–1986, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00426-2

Original Paper

Combined Intraperitoneal plus Intravenous Chemotherapy after Curative Resection for Colonic Adenocarcinoma

W. Scheithauer,[1] G. Kornek,[1] H. Rosen,[2] C. Sebesta,[2] A. Marcell,[3] W. Kwasny,[4] M. Karall[4] and D. Depisch[4]

[1]Division of Oncology, Department of Internal Medicine I, Vienna University Medical School, Waehringer Guertel 18–20, A-1090 Vienna; [2]Department of Surgery, Social Medical Center East, Langobardenstrasse 122, A-1220 Vienna; [3]Department of Surgery, Hunusch-Hospital, Heinrich-Collin-Strasse 30, A-1140 Vienna; and [4]Department of Surgery, Wr. Neustadt General Hospital, Corvinusring 3–5, A-2700 Wr. Neustadt, Austria

Patients who underwent potential curative surgery for colonic adenocarcinoma were enrolled in a prospectively randomised, controlled clinical trial of combined intraperitoneal (i.p.) plus systemic intravenous (i.v.) chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV). We investigated whether this adjuvant treatment approach, specifically addressing the risk of peritoneal and hepatic recurrence, could improve disease-free and overall survival. Between May 1988 and December 1990, 121 patients with resected stage III or high-risk stage II (T4N0M0) colon cancer were randomly assigned for observation (which was considered standard care until the NIH consensus conference) or adjuvant chemotherapy with LV (200 mg/m^2) plus 5-FU (350 mg/m^2), both given i.v. (days 1–4) and i.p. (days 1 and 3) every 4 weeks for a total of six courses. After a median follow-up time of 4.6 years, a comparative analysis between the two groups of patients suggested both an improvement in disease-free survival (75% versus 58%; $P = 0.06$) and a survival advantage (78% versus 63%; $P = 0.05$) in favour of adjuvant chemotherapy. The sites of recurrence were also different, i.e. local regional and intrahepatic tumour recurrences were observed in only 6/58 (10%) and 5/58 (9%) adjuvant treated patients as compared to 11/60 (18%) and 10/60 (17%) observed patients. The overall benefit of adjuvant therapy appeared to be greatest in patients with stage III colon cancer. Treatment-associated toxicity was infrequent and generally mild with only 5% experiencing severe (WHO grade 3) adverse reactions. Interim results of this adjuvant trial suggest that combined i.p. plus systemic i.v. chemotherapy with 5-FU and LV represents a potentially effective adjuvant regimen in stage II/III colon cancer.

Key words: colon cancer, adjuvant chemotherapy, 5-fluorouracil, leucovorin, biochemical modulation, intraperitoneal chemotherapy

Eur J Cancer, Vol. 31A, No. 12, pp. 1981–1986, 1995

INTRODUCTION

COLORECTAL ADENOCARCINOMA is the second most common type of cancer in the Western world and is responsible for approximately 4000 deaths a year in Austria [1, 2]. According to most patient series, approximately half the patients who undergo potential curative surgery will eventually die from recurrent disease. There is no established means of preventing colorectal cancer, nor a reliable and cost-effective means of screening to ensure early diagnosis, and until recently, controlled trials of adjuvant therapy using various treatment modalities have failed to demonstrate convincing and reproducible evidence of significant benefit [3]. Since 1990, based on the results of the Intergroup trial [4], combined 5-fluorouracil (5-FU) and levamisole has been recommended as standard adjuvant therapy for patients with stage III colon cancer [5]. Despite conclusive demonstration of a highly significant improvement in the recurrence rate and mortality rate with the use of 5-FU plus levamisole as compared to an untreated control, there is general agreement that the most favourable additive therapy for stage III and high-risk stage II colon carcinoma is not yet known. The adjuvant

Correspondence to W. Scheithauer.
Revised 22 Mar. 1995; accepted 26 Apr. 1995.

5-FU/levamisole regimen has been defined empirically, the exact therapeutic role and mechanism of action of the antihelmintic drug levamisole is unknown, and in patients with metastatic disease this combination regimen does not show any advantage over 5-FU alone [6].

The most active chemotherapeutic regimen in patients with advanced colorectal cancer represents the biochemical modulation of 5-FU by leucovorin (LV). A number of prospective randomised trials have demonstrated its superior response activity compared to 5-FU monotherapy [7]. Preliminary data also suggest that 5-FU/LV is likely to play an important role in the adjuvant treatment setting [8–11].

In the present study, we randomised patients between adjuvant 5-FU plus LV administered, both by systemic intravenous (i.v.) infusion and intraperitoneally (i.p.) and no further therapy following surgery (observation), which was considered standard therapy until the NIH consensus meeting held in May 1990 [5]. The rational for the combined i.v. and i.p. mode of drug administration was to counteract tumour dissemination via haematogeneous/lymphogeneous spread as well as peri-operative implantation of tumour cells in the resection site and in peritoneal surfaces, which represent the most common site of colonic cancer recurrence [12]. Pharmacokinetic studies with i.p. 5-FU instilled in the (early) postoperative period have demonstrated that tumoricidal doses of the drug are present in the abdominal cavity for at least 8 h following instillation [12]. In addition, up to 10 times the level of drug is seen in the portal vein than is noted in the peripheral blood [13, 14], so i.p. 5-FU/LV could protect peritoneal surfaces and give additionally high levels of the drug for the adjuvant treatment of tumour cells in the liver. Despite the attractive rationale of this treatment approach [15, 16], clinical experience with adjuvant i.p. with or without i.v. chemotherapy in colorectal cancer is limited, with only its feasibility and tolerance so far demonstrated [17, 18].

PATIENTS AND METHODS

121 patients who had undergone potentially curative en bloc resection for colonic adenocarcinoma were entered in this prospective, randomised trial, initiated in May 1988. Patients had to have histopathological diagnosis of stage II with invasion extending at least to the serosa or pericolonic fat (Dukes' B2) or stage III (Dukes' C) disease. Additional eligibility criteria included age 75 years or younger, a World Health Organisation (WHO) performance status less than 2, a haematological profile that would enable patients to receive the protocol-specific adjuvant therapy within 35 days after the definitive tumour resection, and informed consent according to institutional regulations before registration in the study. Patients were ineligible if they had rectal carcinoma (defined by this protocol as any lesion that required the opening of the pelvic peritoneum in order to define the distal extent of the tumour), a history of any other malignancy within 5 years, except for superficial skin carcinoma or *in situ* carcinoma of the cervix, or if they had any other severe concomitant disease that would preclude a life expectancy of at least 5 years.

After informed consent was obtained, eligible patients were registered by telephone at the central statistical office. They were randomised either to observation or combined i.p. plus systemic i.v. chemotherapy. The treatment assignment was determined by blocked randomisation for centre, stage (II versus III with ≤ 4 or > 4 lymph nodes involved), sex and age (≤ 65 versus > 65 years).

Patients assigned to the control arm were observed after surgery with no planned treatment. During the first 2 years, they were evaluated every 3 months, thereafter every 6 months for a total of 5 years. These evaluations consisted of an interim history-taking and physical examination, haematological testing, and a blood chemistry panel including carcinoembryonic antigen. Chest radiography, liver sonography and examination of the entire colorectum (barium enema or endoscopy) was performed every 6 months and annually after the second year. Patients assigned to adjuvant chemotherapy had periodic evaluations at the same time as those who received no adjuvant therapy. Between 8 and 35 days after surgery, patients received 200 mg/m^2 LV followed by 350 mg/m^2 5-FU both administered by i.v. bolus injection daily for 4 consecutive days. On days 1 and 3 of each treatment cycle, LV and 5-FU, each drug diluted in 500 ml of saline, were also given i.p. in the same sequence and the same dosage. This was usually performed with a peripheral venous catheter under local anaesthesia, although 12 patients underwent surgical placement of an i.p. catheter attached to a subcutaneous reservoir permitting transdermal access to the catheter. Each 4-day course of adjuvant therapy was repeated every 28 days for a total of six cycles. This particular i.p./i.v. dose schedule was based on a small pilot study, indicating minimal toxicity despite use of a cumulative dose of the drugs comparable with that of most conventional i.v. 5-FU/LV regimens used in the palliative treatment setting. Toxicity was assessed according to WHO standard criteria [19]. The dose of i.v. 5-FU was reduced by 25% for myelosuppression or non-haematological side-effects exceeding WHO grade 2, but there was no dose attenuation for i.p. 5-FU. Complete blood cell counts, serum electrolytes, liver and kidney functional parameters were obtained at the start of each cycle and every 2 weeks thereafter.

Statistical analysis

Originally, it was planned that recruitment of patients would stop when 120 evaluable patients had been accrued in each arm of the study. Assuming a 5-year survival rate of 55% in the control group, it was expected that this level of recruitment would allow a 20% difference in outcome between the groups to be detected with 5% significance and a power of 90%. However, ethical concerns with regard to the untreated control (according to the NIH consensus statement in 1990) prompted early discontinuation of this trial.

The proportion of patients disease-free or surviving was calculated by the Kaplan–Meier method [20]. The statistical difference between the life-table distributions by treatment was determined by the log-rank test [21]. Differences in the characteristics of patients were analysed using the chi-squared test, and forward stepwise Cox regression [22] was used in the evaluation of possible prognostic factors influencing survival. All tests were two-sided.

RESULTS

From May 1988 to December 1990, a total of 121 patients were entered in this study. 3 patients were considered ineligible (2 assigned to adjuvant chemotherapy and 1 to the control group) because of inappropriate stage of disease. These patients were treated at the discretion of the participating investigator and were excluded from the analyses. Thus the study population consisted of 118 randomised patients, 58 eligible patients in the combined adjuvant i.p. and systemic i.v. chemotherapy arm and 60 who received no further therapy following the curative operation. The median follow-up time for this study is now 4.6

years (range 3–6.5). As shown in Table 1, patients' characteristics in the two treatment arms were essentially similar with respect to age, sex, location of primary tumour, pathological stage, and in patients with stage III, the number of positive regional lymph nodes. There was also no notable imbalance in terms of peri-operative complications such as intestinal obstruction or perforation (2 versus 3 and 4 versus 3 patients in the i.p./i.v. and control group).

Currently, 39 patients have had recurrences, 25 on the observation arm and 14 on the combined i.p./i.v. chemotherapy arm. At 55 months, 75% of the patients who received adjuvant chemotherapy, and 58% of the patients who received no further treatment are free of recurrence according to Kaplan–Meier estimates. Plots of recurrence-free intervals for all eligible patients are displayed in Figure 1, up to 62 months, at which point fewer than 20% could be followed up. Our data suggest that adjuvant treatment provides not only fewer recurrences, but also a delay in the observed recurrences. When patients were divided into subsets according to stage, the advantage for adjuvant chemotherapy was significant only in stage III ($P = 0.023$). Table 2 shows the effect of therapy on specific sites of initial recurrence. The rates of recurrence were reduced for both locoregional and distant sites. Only 5 of the patients in the chemotherapy arm had liver as the first site of treatment failure. There was one patient in the chemotherapy arm who experienced a second primary colonic cancer.

At present, 33 patients with recurrent disease have died, 22 on the observation arm and 11 who received adjuvant chemotherapy (including one peri-operative death during potential curative resection of a liver metastasis) ($\chi^2 = 7.03$; $P < 0.01$). The estimated reduction in the mortality rate by adjuvant chemotherapy treatment as compared with observation was 52% (95% confidence interval, 36–68%). The data of the 5 patients who died without evidence of recurrence (2 on the observation arm and 3 who received adjuvant chemotherapy)

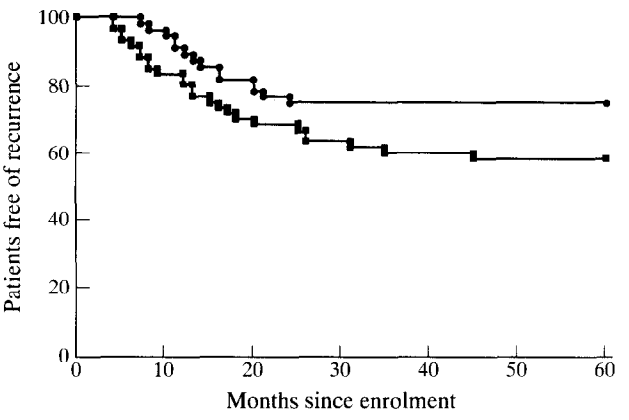

Figure 1. Comparison of disease-free survival between patients receiving adjuvant combined intraperitoneal (i.p.) and intravenous (i.v.) chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV) (•) and patients receiving no additional treatment following curative resection (■).

Table 1. Characteristics of eligible patients

Characteristic	Adjuvant chemotherapy ($n = 58$)	Observation ($n = 60$)
Age (years)		
Median	64	67
Range	31–75	35–75
Sex		
Male	32 (55)	27 (45)
Female	26 (45)	33 (55)
Site of primary tumour		
Caecum and right colon	9 (16)	13 (22)
Flexures and transverse colon	13 (22)	11 (18)
Left colon	4 (7)	6 (10)
Sigmoid and rectosigmoid	31 (53)	29 (48)
Multiple primaries	1 (2)	1 (2)
Depth of invasion		
pT1	1 (2)	2 (3)
pT2	6 (10)	9 (15)
pT3	19 (33)	16 (27)
pT4	32 (55)	33 (55)
Stage		
pT4pN0M0	29 (50)	31 (52)
pT1-4pN1M0	15 (26)	15 (25)
pT1-4pN2,3M0	14 (24)	14 (23)
Tumour differentiation		
Well	11 (19)	9 (15)
Moderate	41 (71)	42 (70)
Poor	3 (5)	4 (7)
Unclassified	3 (5)	5 (8)

Figures are number (per cent) of patients.

Table 2. Sites of first treatment failure following colonic resection

	Adjuvant chemotherapy (n = 58)	Observation (n = 60)
Liver*	5 (9)	10 (17)
Locoregional	6 (10)	11 (18)
Lung	2 (3)	1 (2)
Bone	—	1 (2)
Soft tissue	—	1 (2)
Second primary	1 (2)	—

* +/− Additional sites; figures are number (per cent) of patients.

were censored. There are 6 patients still alive who had documented recurrence, 3 on the observation arm, and 3 who received adjuvant chemotherapy. Survival among all eligible patients in the study is shown in Figure 2. The 5 year survival estimates were 63% for the observation arm and 78% for the combined i.p./i.v. chemotherapy arm (P = 0.05). Analysis of patients according to stage, again suggested that the treatment advantage was more distinct among stage III patients (P = 0.029) than in those with stage II (P = 0.25). Several potential prognostic factors, including sex, age, centre of surgery, stage, depth of invasion, nodal involvement and histological differentiation were analysed for their impact on survival. In this analysis, based on two-sided P values from a forward stepwise Cox regression model, only tumour stage and the number and location of metastatic lymph nodes (pN-classification) proved to be statistically significant prognostic factors for survival in this study, although adjustment for imbalances between the two treatment arms had no impact on our study results.

Of the 58 patients assigned to adjuvant chemotherapy, 46 (79%) completed the prescribed number of six treatment courses. Among the 12 patients in whom therapy was prematurely discontinued (after a median of three courses), the most common reason was negative compliance. Whereas 6 patients requested abbreviation of therapy for personal reasons, re-operation of colostomy resulting in a treatment delay of > 2 weeks in 4 patients, and documented drug toxicity in 2 patients were the principal reasons for premature discontinuation.

The overall toxicity attributed to combined i.p./i.v. chemotherapy was, in general, mild. Ten per cent of the patients experienced grade 1 or 2, and 2% had grade 3 haematological toxicities. Nausea was reported in 24% of the treated patients (compared with 2% in the observed control group). Other treatment-related adverse reactions, such as diarrhoea, stomatitis and abdominal pain during or shortly after i.p. drug instillation were uncommon, generally mild and easily managed (Table 3).

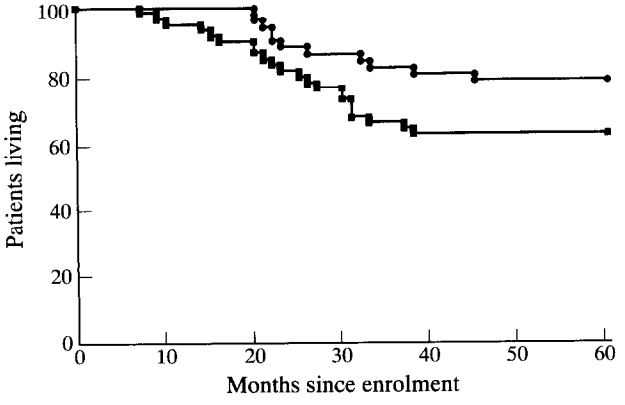

Figure 2. Comparison of overall survival between patients receiving adjuvant combined intraperitoneal (i.p.) and intravenous (i.v.) chemotherapy with 5-fluorouracil (5-FU) and leucovorin (LV) (•) and patients receiving no additional treatment following curative resection (■).

DISCUSSION

The results of this study indicate that combined i.p. and systemic i.v. chemotherapy with 5-FU/LV reduces recurrence rates in patients with surgically treated stage III colon carcinoma. There is also evidence that this adjuvant regimen significantly reduces the overall mortality rate in these patients, at least during the first 4.5 years after surgery. Despite suggestion of a similar advantage of adjuvant treatment in patients with high-risk stage II (T4N0M0), the difference between the two treatment groups did not reach the level of statistical significance. It seems clear that a much larger trial would have been necessary to elucidate such an effect or firmly establish the overall effectiveness of adjuvant i.p./i.v. chemotherapy with 5-FU/LV; however, ethical concerns with regard to the (untreated) control arm prompted early discontinuation of this trial. A similar problem had also been encountered by other co-operative study groups [9, 10].

Table 3. Toxic effects in the adjuvant chemotherapy arm (n = 58)

Toxicity	No. (%) of patients
Gastrointestinal	
Nausea/vomiting	
Mild to moderate	12 (21)
Severe	2 (3)
Diarrhoea	
Mild to moderate	4 (7)
Severe	1 (2)
Stomatitis	
Mild to moderate	3 (5)
Severe	—
Haematologic	
Leucopenia	
< 4000–> 2000/mm³	6 (10)
< 2000/mm³	1 (2)
Thrombocytopenia	
< 100,000–> 50,000/mm³	2 (3)
< 50,000/m³	—
Other	
Alopecia	
Mild to moderate	5 (9)
Severe	—
Peripheral neuropathy	
Mild to moderate	1 (2)
Severe	—
Abdominal pain	
Mild to moderate	4 (7)
Severe	—
Infection	
Mild to moderate	3 (5)
Severe	—

A major drawback of this study was its weakened statistical strength by early termination. The fact, however, that despite the small number of patients, a superior disease-free and overall survival could be demonstrated for patients who received adjuvant chemotherapy, supports the therapeutic potential of this novel adjuvant treatment approach. The site-of-recurrence-oriented adjuvant therapy with 5-FU/LV, currently representing the most active drug combination for treatment of patients with advanced colorectal cancer, resulted in both locoregional and intrahepatic tumour recurrences being reduced to half that which occurred in the observation alone group. The lower incidence of liver metastases in patients receiving adjuvant i.p./i.v. chemotherapy seems to contrast with the disappointing results of controlled adjuvant trials with portal vein drug administration [23–28]. This could be explained by (1) use of a more effective drug regimen utilising biochemical modulation of 5-FU, (2) the additive effects of systemic intravenous and intraperitoneal drug administration, and (3) the much longer duration of treatment, i.e. 180 rather than 7 days as generally used in trials of adjuvant portal vein cytotoxic perfusion. Nevertheless, the relative importance of instillation of chemotherapeutic drugs into the peritoneal cavity as performed in the present trial remains to be established by a randomised controlled study of this method versus simple i.v. administration of 5-FU/LV.

An important advantage of the adjuvant regimen used in this study represents the minimal treatment-associated toxicity and the resultant excellent patient compliance. The cumulative dose of 5-FU per treatment cycle used in this regimen (2100 mg/m^2) is comparable with that of most 5-FU/LV regimens used in the palliative treatment setting (1850–2000 mg/m^2 in case of monthly administration, 2400 mg/m^2 in case of weekly administration of 5-FU/LV) [7]. Yet, severe side-effects (WHO grade 3) were noted in only 5%. In fact, most of our patients did not experience any adverse reaction, suggesting an improved therapeutic index if chemotherapy (or at least one third of the drug dosage) is given i.p. [14]. Patient compliance was remarkable, with 80% completing the prescribed number of six adjuvant treatment cycles. In contrast, the proportion of patients prematurely discontinuing adjuvant therapy with 5-FU/levamisole due to toxicity, was reported to be 30% after a median of 5 months in the 5-FU/levamisole arm of the Intergroup study [4]. Since, in the large majority of patients, i.p. drug administration was performed on an ambulatory basis without use of a port-a-cath system, the costs of therapy were also acceptable.

Despite its statistical shortfalls, the promising results of this adjuvant trial prompted us to follow this lead and initiate a successor trial in 1991 comparing i.p. plus i.v. 5-FU/LV versus 5-FU/levamisole in the control group, as recommended by the NIH consensus conference in patients with stage III colon cancer. Should postoperative i.v. chemotherapy with 5-FU/LV be judged at least equal to 5-FU plus levamisole, a controlled trial to clarify the potential role of adjuvant i.p. drug (co-)administration should be considered. Clinical phase I studies in patients with refractory cancer [29], and toxicity data from the present drug regimen suggest that a dose escalation of 5-FU/LV could be safely undertaken in patients with a particularly increased risk of disease recurrence.

1. Boring CC, Squires TS, Tong T. Cancer statistics, 1993. *Cancer J Clin* 1993, **43**, 7–26.
2. Friedl HP. Die Häufigkeit der Krebserkrankungen in Österreich. In Steindorfer P, ed. *Manual der Chirurgischen Krebstherapie*. Springer, Wien, 1991, 1–3.
3. Metzger U. Adjuvant therapy for colorectal carcinoma. *World J Surg* 1991, **15**, 576–582.
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**, 352–358.
5. NIH Consensus Conference on Adjuvant Therapy for Patients with Colon and Rectal Cancer. *JAMA* 1990, **264**, 1444–1450.
6. Buroker TR, Moertel CG, Fleming TR, *et al.* A controlled evaluation of recent approaches to biochemical modulation or enhancement of 5-fluorouracil therapy in colorectal carcinoma. *J Clin Oncol* 1985, **3**, 1624–1631.
7. Advanced Colorectal Cancer Meta-Analysis Project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992, **10**, 896–903.
8. Wolmark N, Rockette H, Fisher B, *et al.* The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Project protocol C-03. *J Clin Oncol* 1993, **11**, 1879–1887.
9. Zaniboni A, Erlichman C, Seitz JF, *et al.* FUFA increases disease-free survival (DFS) in resected B2C colon cancer (CC): results of a prospective pooled analysis of 3 randomised trials (RCTs). *Proc Am Soc Clin Oncol* 1993, **12**, 191 (abstract).
10. O'Connell M, Mailliard J, Macdonald J, Haller D, Mayer R, Wieand H. An Intergroup trial of intensive course 5FU and low dose leucovorin as surgical adjuvant therapy for high risk colon cancer. *Proc Am Soc Clin Oncol* 1993, **12**, 190 (abstract).
11. Francini G, Petrioli R, Lorenzini L, *et al.* Folinic acid and 5-fluorouracil as adjuvant chemotherapy in colon cancer. *Gastroenterology* 1994, **106**, 899–906.
12. Cunliffe WJ, Sugarbaker PH. Gastrointestinal malignancy: rationale for adjuvant therapy using early postoperative intraperitoneal chemotherapy. *Br J Surg* 1989, **76**, 1082–1090.
13. Sugarbaker PH, Graves T, de Bruijn EA, *et al.* Rationale for early postoperative intraperitoneal chemotherapy (EPIC) in patients with advanced gastrointestinal cancer. *Cancer Res* 1990, **50**, 5790–5794.
14. Speyer LS. The rationale behind intraperitoneal chemotherapy in gastrointestinal malignancies. *Semin Oncol* 1985, **12**, 23–28.
15. Köhne-Wömpner CH, Schoeffski P, Schmoll HJ. Adjuvant therapy for colon adenocarcinoma: current status of clinical investigation. *Ann Oncol* 1994, **5** (Suppl. 3), 97–104.
16. Rougier P, Nordlinger B. Large scale trial for adjuvant treatment in high risk resected colorectal cancers: rationale to test the combination of loco-regional and systemic chemotherapy and to compare l-leucovorin + 5-FU to levamisole + 5-FU. *Ann Oncol* 1993, **4** (Suppl. 2), 21–28.
17. Sugarbaker PH, Gianola FJ, Speyer JC, Wesley R, Barofsky I, Meyers CE. Prospective randomized trial of intravenous versus intraperitoneal 5-fluorouracil in patients with advanced primary colon or rectal cancer. *Surgery* 1985, **98**, 414–421.
18. Nordlinger B, Bouteloup PY, Favre JP. Early post-operative intraperitoneal chemotherapy if feasible and well tolerated in colon cancer. A prospective randomized study. *J Cancer Res* 1990, **116**, 686 (abstract).
19. Miller AB, Hoogstraten B, Staquet M. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
20. Kaplan LK, Meier P. Nonparametric estimation from incomplete observations. *Am J Stat Assoc* 1958, **53**, 457–481.
21. Mantel H, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959, **22**, 719–748.
22. Cox DR. Regression models and life-tables. *J R Stat Soc (B)* 1972, **34**, 187–220.
23. Taylor I, Machin D, Mullee M, Trotter G, Cooke T, West C. A randomized controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985, **72**, 359–363.
24. Wereldsma JC, Bruggink EDM, Meijer WS, Roukema JA, van Putten WLJ. Adjuvant portal liver infusion in colorectal cancer with 5-fluorouracil plus heparin versus urokinase versus control. *Cancer* 1990, **65**, 425–432.
25. Wolmark N, Rockette H, Wickerham D, Fisher B, Redmond C, Fisher ER, *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.

26. Metzger U, Laffer U, Aeberhard P, *et al.* Randomized multicenter trial of adjuvant intraportal chemotherapy for colorectal cancer SAKK 40/81: an interim report. *Acta Chir Scand* 1990, **156**, 467–472.
27. Fielding P, Hittinger R, Grace HR, Fry JS. Randomized controlled trial of adjuvant chemotherapy by portal vein perfusion after curative resection for colorectal adenocarcinoma. *Lancet* 1992, **340**, 502–506.
28. Ryan J, Weiden P, Crowley J, Bloch K. Adjuvant portal vein infusion for colorectal cancer: a 3-arm randomized trial. *Proc Am Soc Clin Oncol* 1988, **7**, 95 (abstract).
29. Reichman B, Markman M, Hakes T, *et al.* Phase I trial of concurrent intraperitoneal and continuous intravenous infusion of fluorouracil in patients with refractory cancer. *J Clin Oncol* 1988, **6**, 158–162.