Pergamon

European Journal of Cancer Vol. 33, No. 8, pp. 1209–1215, 1997

Printed in Great Britain
0959-8049/97 $17.00 + 0.00

PII: S0959-8049(97)00052-X

Original Paper

Final Results of a Phase III Clinical Trial on Adjuvant Intraportal Infusion with Heparin and 5-Fluorouracil (5-FU) in Resectable Colon Cancer (EORTC GITCCG 1983–1987)

D. Nitti,[1] J. Wils,[2] T. Sahmoud,[3] D. Curran,[3] M.L. Couvreur,[3] M. Lise,[1] H. Rauschecker,[4] J. Guimaraes dos Santos,[5] W. Stremmel[6] and F. Roelofsen[7]

[1]Istituto di Clinica Chirurgica II, Università di Padova, Via Glustiniani 2, 35128 Padova, Italy; [2]S. Laurentius Ziekenhius, Roermond, The Netherlands; [3]European Organization for Research and Treatment of Cancer, Data Center, Bruxelles, Belgium; [4]Universitats Klinik Poliklinik of Gottingen, Germany; [5]Instituto Portuges de Oncologia, Porto, Portugal; [6]Evangelisches Krankenhaus, Duisburg, Germany; and [7]Bethesda Krankenhaus, Essen, Germany

In this phase III clinical trial conducted by the Gastrointestinal Tract Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (GITCCG-EORTC), we evaluated the effect of adjuvant intraportal infusion of heparin (HEP) and 5-fluorouracil (5-FU) on overall survival, disease-free survival and time to progression in patients with resectable colon cancer. From January 1983 to June 1987, 235 patients were randomised from 14 institutions in seven European countries: 79 patients made up the control group (control): 72 the portal vein infusion group given heparin alone (5000 IU daily × 7 consecutive days) (HEP); 84 the portal vein infusion group given heparin (5000 IU daily × 7 consecutive days) and 5-FU (500 mg/m^2 daily × 7 consecutive days) (HEP/5-FU); 34 patients were considered ineligible. The 199 patients considered eligible were well balanced for age, sex, Karnofsky index, tumour location, surgery, surgical procedure and Dukes' stage. Four patients (2 control, 1 HEP, 1 HEP/5-FU) died of surgical complications. No differences were observed between control group and treatment groups (HEP, HEP/5-FU) for postoperative complications and number of hospitalisation days. Severe toxicity (grade 3–4, WHO) was found in 12% of patients in the HEP group and 8% in the HEP/5-FU group. After a median follow-up of 9 years, disease progression was reported in 40% of patients in the control group, 40% in the HEP group and 29% in the HEP/5-FU group. Five-year survival, time to progression and disease-free survival were 69%, 58% and 56%, respectively, in the control arm, 61%, 58% and 56% in the HEP arm, and 71%, 69% and 65% in the HEP/5-FU arm. Based on all randomised patients, the effect of treatment was not statistically significant with respect to any of the endpoints. It is confirmed that intraportal 5-FU infusion is safe and has a tolerable toxicity, but cannot be considered standard treatment for patients with resectable colon cancer. © **1997 Published by Elsevier Science Ltd.**

Key words: colon cancer, adjuvant treatment, intraportal 5-FU infusion

Eur J Cancer, Vol. 33, No. 8, pp. 1209–1215, 1997

INTRODUCTION

IT IS widely accepted that hepatic metastases are the major cause of failure after surgery for colorectal cancer. Tumour invasion into the mesenteric vein, which causes the spread of malignant cells to the portal vein, may result in microscopic metastases [1]. It has, moreover, been suggested [2, 3] that during the early phases of growth the blood supply of metastatic lesions originates in the portal vein, whereas well-established liver metastases are supplied by the hepatic artery. It is therefore reasonable to assume that, in patients

Correspondence to D. Nitti.
Received 6 Aug. 1996; revised 19 Dec. 1996; accepted 20 Jan. 1997.

with subclinical disease, infusion of chemotherapy via the portal vein might more closely simulate the route of tumour emboli, thus reaching the small deposits.

Taylor and associates [4] were the first to suggest that 5-fluorouracil (5-FU) might be effective as adjuvant therapy if infused via the portal vein. In a trial on 244 patients, initiated in 1975, they reported, after a median follow-up of 50 months, a statistically significant improvement in survival ($P = 0.002$) in patients treated with 5-FU portal vein infusion (PVI) (1000 mg/day, with heparin infused continuously for the first 7 postoperative days) compared to patients receiving surgery alone.

The encouraging results of this trial [5] prompted different institutions and cooperative groups to conduct confirmatory randomised clinical trials. In January 1983, the Gastro-Intestinal Tract Cancer Cooperative Group (GITCCG) of the European Organization for Research and Treatment of Cancer (EORTC) initiated a randomised clinical trial on adjuvant intraportal infusion for resectable colon cancer (protocol No. 40812). In June 1987, due to low accrual of patients and in view of the feasibility of adjuvant intraportal infusion, the EORTC GITCCG closed the trial to patient entry, and designed a new large-scale clinical trial (protocol No. 40871) to include patients with rectal cancer.

Here we present the results of the first study (No. 40812), and discuss them in the light of those obtained in other studies in the literature.

PATIENTS AND METHODS

The criteria for eligibility were: (1) age less than 75 years; (2) Karnofsky performance status of 60 or more; (3) histologically confirmed and surgically excised colon adenocarcinoma; (4) no evidence of distant metastases or residual tumour following surgical resection (Dukes' A, B and C); (5) no evidence of acute or chronic liver disease, portal thrombosis, infection, diabetes, leucopenia (<4000 mm^3) or thrombocytopenia (<50 000 mm^3); (6) no serious intraoperative complications; (7) no pre-existing or concomitant malignant neoplasms or pre-operative chemo and/or radiotherapy; (8) treatment to be started immediately after tumour resection and continued for the following 7 days.

Treatment

Before surgery the patients were randomised into three arms (Figure 1).

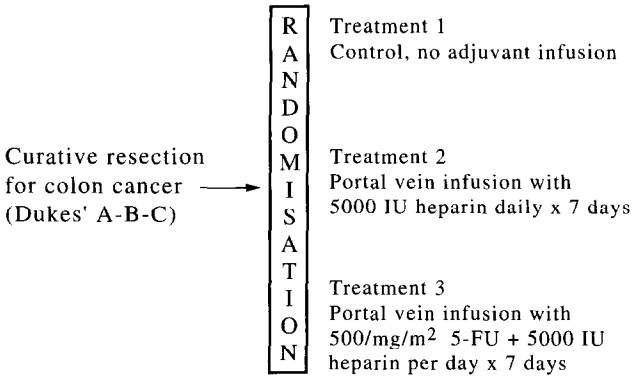

Figure 1. Schema of the EORTC study No. 40812.

Control group. These patients did not receive postoperative chemotherapy, and the catheter was not inserted into the portal vein.

Heparin group (HEP group). In these patients, a catheter was inserted into the portal vein through the umbilical vein or portal vein tributaries (ileocolic, colic, inferior mesenteric or gastroepiploic vein). The tip of the catheter (a sterile paediatric finding tube) was checked by peri-operative radiography or by fluorescein injections to ensure that infusion of the two hepatic lobes had been achieved. A 24-h infusion of 1000 ml 5% dextrose plus 5000 IU heparin was started, using an infusion pump, and continued for a total of 7 consecutive days.

5-FU group (HEP/5-FU group). Catheter placement and infusion were the same as in the HEP group, but 500 mg 5-FU per m^2 per 24 h were added to the infusate, for a total of 7 consecutive days.

Patients were seen by the investigators every day during the period of infusion, which was discontinued if any of the following reactions were observed: (1) stomatitis; (2) diarrhoea (five loose stools a day or more); (3) dermatitis; (4) leucopenia (less than 3000/mm^3); (5) thrombocytopenia (less than 100 000 mm^3); (6) raised SGOT-SGPT (serum glutamic-oxalacetic transaminase/pyruvic transaminase) more than 3-fold normal values); (7) evidence of sepsis from catheter; (8) severe postoperative complications. All cases of toxicity and side-effects were reported according to the WHO scale.

Follow-up

The patients were evaluated every 6 months until the end of the second year and yearly thereafter. Follow-up examinations included an evaluation of the patients' general condition, liver function tests, CEA (carcinoembryonic antigen) liver US (ultrasound) or CT scans, chest X-ray (yearly) and colonoscopy (yearly). During follow-up, documentation of recurrence was made by tissue diagnosis whenever possible. Typical metastatic nodules at US, CT scans, or chest X-ray were not confirmed histologically if they showed a definite change with respect to baseline studies. Changes in liver function or raised CEA levels prompted a search for disease progression, but on their own did not constitute evidence of recurrence.

Statistical considerations

The main endpoint of the study was survival. The trial was initially designed to detect a 30% increase in the median survival in a pairwise comparison of the treatment and control arms. With a power of 80% and a one-sided significance level of 5%, 180 patients followed until death were required in each of the three treatments arms [6]. No correction for multiple comparisons was taken into account.

Randomisation was made using the minimisation technique [7], patients being stratified according to their institution, and by tumour location i.e. colon: ascending versus transverse versus descending versus sigmoid.

Duration of survival and disease-free survival curves, estimated using the Kaplan–Meier technique [8], were compared using the Cox proportional hazards regression model [9]. The Cox model was also used to adjust for any prognostic factors.

The main analysis was performed on all randomised patients according to the 'intent-to-treat' principle. Analysis

of toxicity was based on the treatment the patient actually received.

RESULTS

From January 1983 to June 1987, 235 patients were randomised from 14 institutions in seven European countries: 79 patients in the control group, 72 in the portal vein infusion group with heparin alone (HEP), and 84 in the portal vein infusion group with heparin and 5-FU (HEP/5-FU). In December 1986, the Clinical Trial Committee closed entry into the heparin group, but continued to randomise patients into the remaining two arms.

Two patients were excluded from the analysis because no case report forms were received for them. 34 patients (14%) were considered ineligible for the following reasons: the pre-randomisation examination was incomplete (4 patients), disease stage was inadmissible (Dukes' D; 26 patients); physical condition was poor (2 patients); lesions benign (2 patients). The relatively high percentage of patients found to be ineligible was mainly due to the randomisation procedure occurring before surgery.

The present analysis is therefore based on 199 eligible patients (72 in the control group, 57 in the HEP group, and 70 in the HEP/5-FU group). Table 1 shows the patients' characteristics at entry by treatment arm, and Table 2 the tumour location and pathology data by treatment arm, according to Dukes' classification.

Postoperative complications

Postoperative complications (control versus HEP versus HEP/5-FU) occurred in 7% versus 13% versus 5% patients, respectively. 4 patients (2%) died of surgical complications: 2 in the control group, of myocardial infarction; 1 in the HEP group, of septic shock following perforating gastroduodenal ulcer; 1 in the HEP/5-FU group, following recurrent small bowel occlusion.

The numbers of patients hospitalised for less than 10 days, or more than 20 days were respectively: 14(19%) and 10 (14%) in the control group; 6(11%) and 7 (12%) in the HEP group; 9 (13%) and 11 (16%) in the HEP/5-FU group.

Compliance to treatment and toxicity

Of the 127 patients randomised to adjuvant therapy arms (HEP or HEP/5-FU), 15 did not receive treatment: 6/57 in the HEP arm (2 because it was technically impossible to insert the catheter, 2 patients refused treatment, and 2 for reasons unknown) and 9/70 in the HEP/5-FU arm (7 because it was technically impossible to insert the catheter, and 2 for reasons unknown). In the HEP group, 51 patients were started on treatment and in 1 of these (2%) the heparin dosage was reduced because of catheter displacement. In the HEP/5-FU group, 61 started treatment and in 6 of these (10%) the HEP/5-FU dosage was reduced (because of catheter displacement in 1, complications due to the catheter in 1, gastrointestinal toxicity in 1, haemorrhage in 1, and nausea and vomiting in 2). In 2 of 61 patients (3%), treatment was delayed because of gastrointestinal toxicity in 1 and moderate haemorrhage in 1. Severe toxicity (grade 3–4 WHO scale) was reported in 5 out of 51 patients (10%) in the HEP group (haemoglobin depletion, 4; increase in SGOT-GPT, 1); and in 5 out of the 61 (8%) in the HEP/5-FU group (haemoglobin depletion, 2; nausea and vomiting, 2; cardiac complications, 1).

Table 1. Patients' characteristics at entry by treatment arm

	Control (72 pts)		HEP (57 pts)		HEP + 5-FU (70 pts)	
	n	(%)	*n*	(%)	*n*	(%)
Age (years)						
Median (range)	62	(31–74)	58	(22–74)	61	(30–74)
Sex						
Male	33	(46)	32	(56)	35	(50)
Female	39	(54)	25	(44)	35	(50)
Karnofsky index						
80	5	(7)	4	(7)	5	(7)
90	29	(40)	21	(37)	29	(41)
100	37	(51)	31	(54)	33	(47)
Unknown	1		1		3	

Table 2. Pathology data by treatment arm

	Control (72 pts)		HEP (57 pts)		HEP + 5-FU (70 pts)	
	n	(%)	*n*	(%)	*n*	(%)
Ascending colon	22	(31)	14	(25)	16	(23)
Transverse colon	5	(7)	5	(9)	7	(10)
Descending colon	7	(10)	11	(19)	9	(13)
Sigmoid colon	36	(50)	27	(47)	38	(54)
Unknown	2	(3)	0	(0)	0	(0)
Dukes' stage						
A	6	(8)	5	(9)	8	(11)
B	41	(57)	32	(56)	42	(60)
C	23	(32)	19	(33)	19	(27)
Unknown	2	(3)	1	(2)	1	(1)

Progression of disease and survival

After a median follow-up of 9 years, no disease progression was observed in 29 (40%) patients in the control group, 23 (40%) in the HEP group, and 20 (29%) in the HEP/5-FU group. The type and site of disease progression per treatment arm are detailed in Table 3. The liver was found to be the most common site of distant metastases.

At analysis, a total of 73 deaths were reported: 32 (44%) in the control arm, 20 (35%) in the HEP group, and 21 (30%) in the HEP/5-FU group. The cause of death was malignant disease in most patients (25, 19 and 16 in the

Table 3. Site of disease progression by treatment arm

	Control (72 pts)		HEP (57 pts)		HEP + 5-FU (70 pts)	
	n	(%)	*n*	(%)	*n*	(%)
No progression documented	43	(60)	34	(60)	50	(71)
Progression	29	(40)	23	(40)	20	(29)
Locoregional only	9		5		3	
Distant only	12		14		13	
Local and distant	7		4		3	
Unknown	1		0		1	
Site of distant metastases						
Liver only	7		11		7	
Lung only	2		0		4	
Liver + other	4		2		1	
Other	4		2		3	
Unknown	2		3		1	

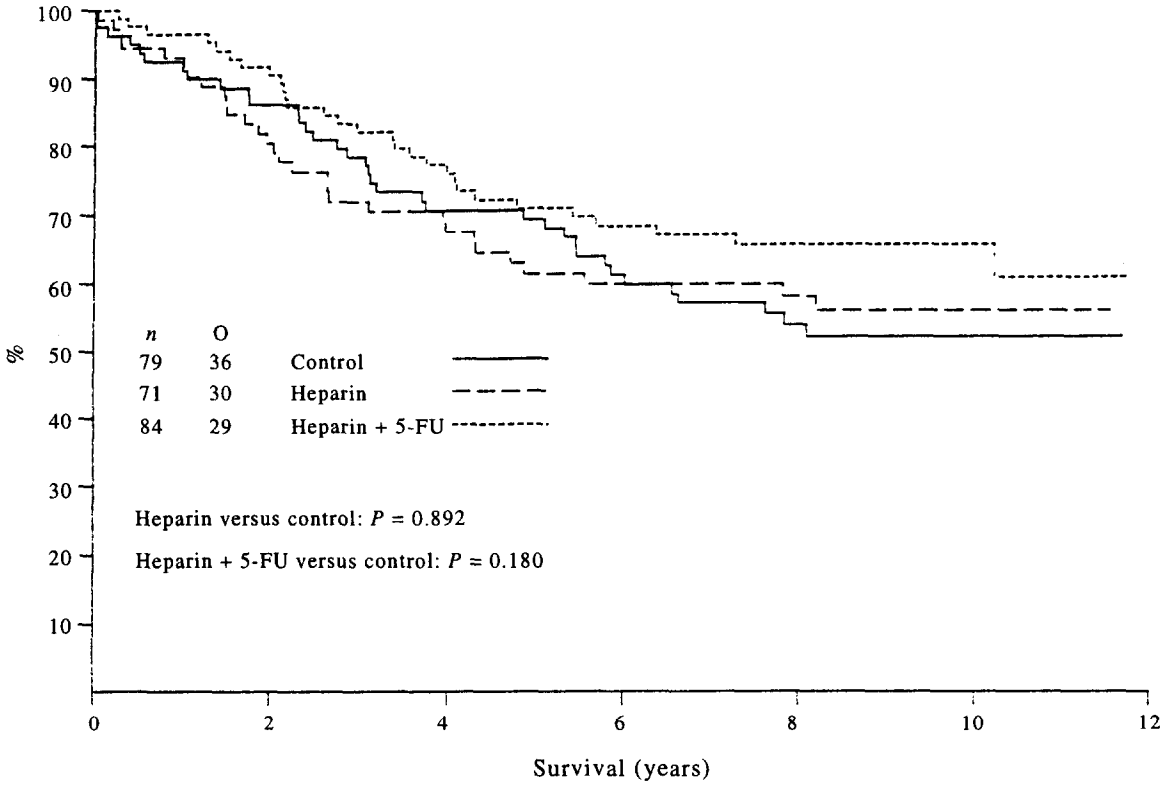

Figure 2. Duration of survival by treatment arm (*n*, number of patients; O, observed number of events).

control, HEP and HEP/5-FU groups, respectively). 3 patients (1 on HEP, and 2 on HEP/5-FU) died of infection, 4 died of cardiovascular disease (2 in the control and 2 in the HEP/5-FU group), 4 died of other cancers (3 in the control and 1 in the HEP/5-FU group), whereas the cause of death was unknown for 2 patients in the control arm. The survival, time to progression and disease-free survival curves are shown in Figures 2–4. The analysis, made on all

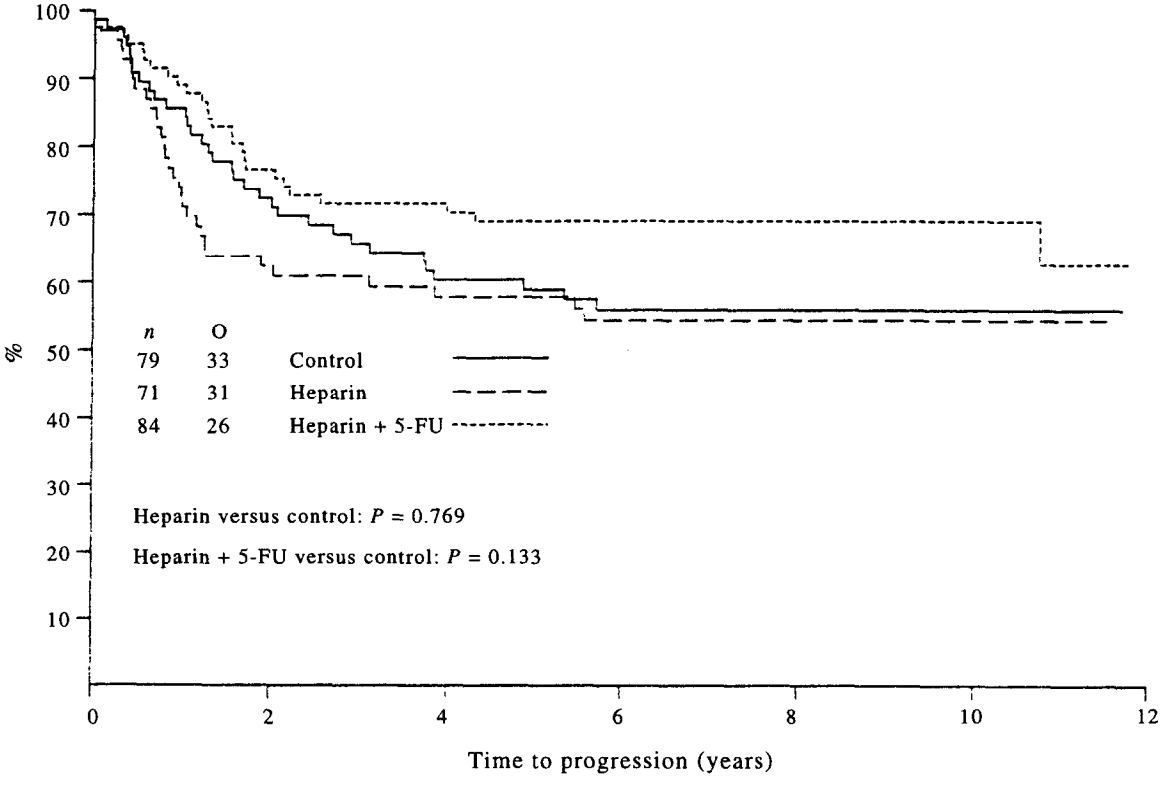

Figure 3. Time to progression by treatment arm (*n*, number of patients; O observed number of events).

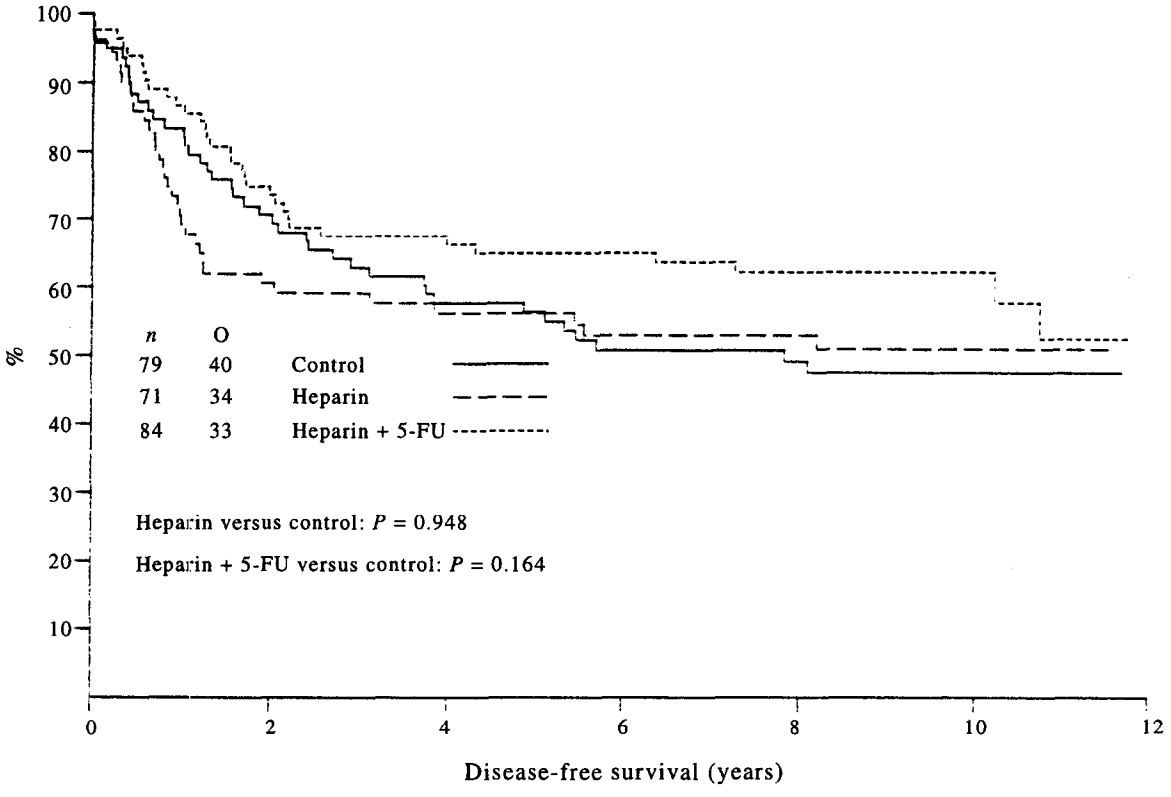

Figure 4. Disease-free survival by treatment arm (*n*, number of patients; O, observed number of events).

randomised patients, showed that the effect of treatment was not statistically significant with respect to any of the endpoints.

A multivariate model for survival was used to ascertain the effect of treatment after adjustment for possible prognostic factors. The following factors were tested: age (≤55 versus 56–60 versus 61–65 versus ≥66 years), sex, Karnofsky index (100 versus 50–90), CEA (≤5 versus >5 ng/ml), tumour location (sigmoid versus other sites), Dukes' stage (A and B versus C), length of resected margin (<10 ≥ 10 cm) and tumour diameter (<5 versus ≥5 cm). Only age and Dukes' stage were retained in the final multivariate model at a 5% level of significance. Older patients were at a higher risk than younger patients ($P = 0.042$, a test for linear trend), and stage C patients had a relative risk (RR) of 2.34 with respect to stage A or B patients (95% CI 1.45–3.77, $P < 0.001$). After adjustment for these two factors, the effect of treatment was still not significant.

DISCUSSION

Our findings confirm that intraportal adjuvant therapy with heparin and 5-FU following radical surgery for colon cancer is safe, and has a tolerable toxicity. During hospitalisation, the postoperative complications and toxicity observed in patients on portal infusion were comparable to those in patients who underwent surgery alone. The higher number of cases of anastomotic leakage found in patients on heparin alone (8/57) was not related to treatment because this complication occurred in only 1 of the 70 patients on heparin and 5-FU. Moreover, patients' characteristics at entry, the tumour location and stage, and the surgical procedures were similar in the two groups. In 9 out of 127 patients (7%), catheter insertion was not possible for technical reasons. These failures are acceptable in view of the fact that they occurred in two institutions at the beginning of their experience.

The results obtained by Taylor and associates [4] suggested that the anticoagulative effect of heparin might have a role in preventing the settling of micrometastases in the liver. An additional arm with heparin alone was therefore included in our trial. Two studies using heparin [10, 11] and one using urokinase [12] failed to show a statistically significant difference between the survival of patients treated with anticoagulants or fibrinolytics alone and that of patients who received no postoperative infusion. Our findings confirm that when used alone, intraportal heparin infusion neither prevents liver metastases nor prolongs survival.

The specific aim of adjuvant portal infusion is to prevent liver metastases as a first recurrence by achieving higher 5-FU concentrations in the liver. This goal was fulfilled in the first trial, which was performed in Liverpool [4], and in another two studies [11, 12], but not by us or by other authors in four different "confirmatory" trials [10, 13–15]. Some [15, 16] have suggested that intraportal infusion might prolong survival without reducing the incidence of liver metastases because of the systemic effect of intraportally administered 5-FU. Moreover, the timing of 5-FU infusion in the immediate postoperative period might control the 'in transit' cells more effectively.

Taylor [4], like other authors [13, 15], observed that intraportal 5-FU infusion has a positive effect on survival. An improvement in survival was also observed in a subgroup of patients (Dukes' C) [11]. These positive results, however, were not confirmed by our findings or by those in other studies [10, 12, 14].

It is important to consider whether the 5-FU dose (500 mg/m^2 × 7 days) in our trial was optimal. In Taylor's study [4, 5] a fixed dose of 1000 mg was given, which is approximately 600 mg/m^2 for the average patient. Other trials have utilised 600 mg/m^2 5-FU daily for 7 days [11, 13]. In another two trials, mitomycin C was added to 5-FU [10, 15]. Positive effects on survival have not been observed with respect to controls when the 5-FU dosage has been increased to 600 mg/m^2 [11, 12] or mitomycin C added to 5-FU [10]. Differences in treatment for recurrences may have an impact on survival. No data on treatment given after recurrence were recorded on the case report forms. It is, however, unlikely that different treatments would have been given by different institutions, whether or not patients had received adjuvant PVI. A bias in disease-free survival may have been caused by systemic adjuvant chemotherapy, but this type of treatment was not widely used in the early 1980s. Moreover, when it was used, it is unlikely to have been administered to the three groups using different modalities.

A meta-analysis based on individual data was conducted in nine randomised trials, including the study presented here, for a total of 3824 patients [17]. The risk of death was significantly lower in the liver infusion arm (risk reduction: 13% ± 6%, $P = 0.02$) after a median follow-up of 5 years. Benefit from liver infusion was more evident in terms of disease-free survival (risk reduction: 14% ± 5%, $P = 0.007$) and time to metastases (risk reduction: 27% ± 8%, $P = 0.0008$).

This meta-analysis confirms the need for large-scale clinical trials in which adjuvant treatments are tested. A 5% increase in the 5-year survival would mean thousands of lives saved every year in a disease as common as colorectal cancer. In order to detect the small benefits that can reasonably be expected from adjuvant therapy, large numbers of patients should be accrued for new studies [18, 19].

In a successive large-scale clinical trial (No. 40871), conducted by the EORTC GITCCG in 1987–1993, 1235 patients were accrued and randomised to receive either PVI or no further therapy after curative surgery. After a median follow-up of 63 months, no differences were found in the main endpoints [20]. If these data are included in the meta-analysis [17], the benefit will probably become less significant.

In conclusion, intraportal 5-FU infusion cannot be considered a standard treatment for patients with resectable colon cancer, especially in view of the positive results obtained recently with systemic adjuvant chemotherapy using 5-FU + levamisole [21, 22] or 5-FU + leucovorin [23].

The question under investigation by the current multicentric trial (No. 40911) of the Gastrointestinal Tract Cancer Cooperative Group of the EORTC is whether intraportal infusion and systemic chemotherapy together could have an additive effect.

1. Fisher ER, Turnbull RB. The cytological demonstration and significance of tumor cells in the mesenteric blood in patients with colorectal cancer. *Surg Gynecol Obstet* 1955, **100**, 102–107.
2. Ariel FM. Intra-arterial chemotherapy for cancer metastatic to the liver. *Arch Surg* 1965, **91**, 851–862.
3. Storer EH, Akin TJ. Chemotherapy of hepatic neoplasm on the umbilical portal vein. *Am J Surg* 1966, **111**, 56–58.
4. Taylor I, Machin D, Mullee M, *et al.* A randomized controlled trail of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985, 72, 359–363.
5. Taylor I, Rowling J, West C. Adjuvant cytotoxic liver perfusion for colorectal cancer. *Br J Surg* 1979, **66**, 833–837.
6. George SL, Desu MM. Planning the size and duration of a clinical trial studying the time to some critical event. *J Chron Dis* 1974, 27, 15–24.
7. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975, **31**, 103–115.
8. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
9. Cox DR. Regression models and life-tables. *J R Stat Soc B* 1972, **34**, 187–202.
10. Ryan J, Weiden P, Crowley J, Bloch K. Adjuvant portal vein infusion for colorectal cancer: a 3-arm randomized trial. *Proc ASCO* 1988, 7, 95 (abstract **361**).
11. Fielding LP, Hittinger R, Grace RH, Fry JS. Randomized controlled trial of adjuvant chemotherapy by portal-vein infusion after curative resection for colorectal adenocaracinoma. *Lancet* 1992, **340**, 502–506.
12. Wereldsma JCJ, Bruggink EDM, Meijer WS, *et al.* Adjuvant portal liver infusion in colorectal cancer with 5- fluorouracil/heparin versus urokinase versus control. *Cancer* 1990, **65**, 425–432.
13. 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.
14. Beart RW, Moertel CG, Wieand HS, *et al.* Adjuvant therapy for resectable colorectal carcinoma with fluorouracil administered by portal vein infusion. *Arch Surg* 1990, **125**, 897–901.
15. Swiss Group for Clinical Cancer research (SAKK). Long-term results of single course of adjuvant intraportal chemotherapy for colorectal cancer. *Lancet* 1995, **345**, 349–353.
16. Metzger U, Gross TH, Honneger HP. Adjuvant treatment for colorectal cancer: 'State of the Art'— messages from recent trials. *Eur J Surg Oncol* 1995, 21, 341–352.
17. Piedbois P Buyse M Gray R Clarke M *et al.* for the Liver Infusion Meta Analysis Project.. Portal vein infusion is an effective adjuvant treatment for patients with colorectal cancer. *Proc ASCO* 1995, **14**, 192 (abstract 444).
18. George SL. The required sample size and length of a phase III clinical trial. In Buyse M, Staquet M, Sylvester E eds. *Cancer Clinical Trials: Methods and Practice.* Oxford, Oxford University Press, 1984, 287–310.
19. Sahmoud T, Rougier P, Nitti D, *et al.* Adjuvant portal vein infusion of 5-FU and heparin (PVI) in colorectal cancer: An EORTC–GIVIO Intergroup phase III trial. *Ann Oncol* (S5) 1996, 7, 33.
20. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. *Stat Med* 1982, **1**, 121–129.
21. 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. *J Clin Oncol* 1989, 7, 1447–1456.
22. Moertel CG, Fleming TR, Macdonald JS, *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon cancer. *N Engl J Med* 1990, **322**, 352–358.
23. International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995, **345**, 939–944.

Acknowledgements—The authors wish to thank Sara Pearcey for her editorial assistance. This publication was supported in part by grant numbers 5R 10-CA11488-12 through 2U10-CA11488-25 from the National Cancer Institute (Bethesda, Maryland, U.S.A.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

APPENDIX

The following centres and their investigators participated in this study, with the randomisation of at least 10 patients. St. Laurentius Ziekenhuis, Roermond, The Netherlands (J. Wils, C. Nuyens, R. Estorique); Universitats Klinik Poliklinic, Gottingen, Germany (H. Rauschecker); Clinica Chirurgica II, Universitàdi Padova, Italy (M. Lise, D. Nitti); Evangelisches Krankenhaus, Duisburg, Germany (W. Stremmel); Instituto Portuges de Oncologia, Porto, Portugal (J. Guimaraes dos Santos); Bethesda Krankenhaus, Essen, Germany (F. Roelofsen); Universitats Klinik Johannes Gutenberg, Mainz, Germany (W. Bruchner); Universitaetsspital, Zurich, Switzerland, (U. Metzger); Clinica Chirugica, Università di Genova, Italy (D. Civalleri); Institut J. Bordet, Bruxelles, Belgium (J.C. Pector).