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Special Paper

Gastrointestinal Tract Cancer Liaison Office: an Attempt to Organise Clinical Research in Europe

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The Gastrointestinal Tract Cancer Liaison Office (GITCLO) was developed in an attempt to organise the increasing body of clinical research in gastrointestinal tumours in Europe. This paper represents an analysis, by tumour localisation, of the trials collected for the second edition of the GITCLO booklet. The list of co-operative groups, chairmen and study co-ordinators is given with their respective telephone and telefax numbers. A total of 84 trials were collected, conducted by 46 co-operative groups in 14 countries. For each organ and stage of disease, a summary of concepts investigated is given with the references of the study co-ordinator. Obviously, too many questions are raised at the same time. In colorectal cancer, for example, a total of 41 trials exploring 22 concepts are currently open for patients' registration. We hope that the present attempt to clarify the situation of clinical research in the field of gastrointestinal cancers in Europe will speed up therapeutic progress in the best interest of the patients. © **1997 Elsevier Science Ltd.**

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INTRODUCTION

FOR MANY years clinical research was a prerogative of only a few research groups with heavy computer systems and the support of well-trained biostatisticians that gave them the capability of launching well-designed studies and properly interpreting the results. The Gastrointestinal Tract Cancer Co-operative Group (GITCCG) of the European Organisation for Research and Treatment of Cancer (EORTC) was created in 1972 with the support of the National Cancer Institute of the U.S.A. Then, most of the so-called large series did not exceed 200–300 patients and the accrual rate was generally rather slow. The idea of randomising a patient in a study was, by itself, considered unethical by most of the European physicians. Contrarily to standard practice in the U.S., the patients were barely told the truth regarding their diagnosis and prognosis, particularly if they had potentially lethal disseminated cancer.

Then, only a few agents were used for treating gastrointestinal tract (GIT) cancers, mainly 5-fluorouracil (5-FU), semustin (methyl-CCNU) and vincristine in colorectal cancer; 5FU, doxorubicin (DOX) and mitomycin C (MMC) for gastric cancer; and streptozotocin for pancreatic cancers. The results were poor. GIT cancers were generally considered resistant to chemotherapy and most of the medical oncologists were reluctant to investigate this group of patients.

The first EORTC studies mainly focused on radiotherapy in rectal cancer [1], in gastric cancer [2] and in oesophageal cancer [3]. During the late 1980s, together with better results

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obtained in colon and gastric cancers [4–6], computer systems became more powerful and cheaper. These two facts, combined with the advent of a new generation of well-trained biostatisticians, stimulated the efflorescence of national or even regional co-operative groups embarking on studies including an increasing number of patients.

The Gastrointestinal Tract Cancer Liaison Office (GITCLO) was developed in an attempt to organise the increasing body of clinical research in gastrointestinal tumours in Europe. Our first objective was to identify all the clinical trials on cancers of the digestive system handled by multicentre co-operative groups. The second objective, more ambitious, was to promote and facilitate interactions between researchers, help them to improve their research and stimulate intergroup studies.

The first edition of the GITCLO booklet was published in 1994 [7]. It included 79 trials conducted by 26 co-operative groups in 12 European countries. This paper represents an analysis, by tumour localisation, of the trials collected for the second edition of the GITCLO.

Collection of data

In most European countries, there is no centralised structure able to identify all the groups which, in their country, are involved in multicentric studies. If national structures do exist, they may ignore regional groups undertaking high-quality studies. Moreover, medical oncologists, surgeons or radiotherapists may run trials unknown to each other, making their identification difficult.

The present list has been collected by asking persons known to be involved in clinical research if they are aware of other groups working in the field of gastrointestinal tract cancer. In each country one person was nominated to verify with the co-ordinator of the GITCLO that all the groups in his country had been properly identified. However, considering this type of approach, it cannot be excluded that some groups remain unnoticed. Canadian investigators through the CNCI CTG have some collaboration with the EORTC and some of their studies that we considered of interest for the European investigators have been included in the current list. A standardised clinical descriptive form was sent to all the chairpersons or study co-ordinators regarding their co-operative group: full name, address, telephone and fax numbers of the responsible officers, denomination, aim, design, summary and present status of the trial. The list of the study co-ordinators with their telephone and fax numbers is given in Appendix 1. The co-operative groups, with the chairperson's name and telephone and fax numbers, are given in Appendix 2. Published papers are listed in the reference list. In the next chapter the name of the study co-ordinator identifies an ongoing project.

REVIEW BY TUMOUR TYPE

Oesophagus

Neoadjuvant. In operable oesophageal cancer, the benefit for survival of pre-operative radiotherapy with or without chemotherapy remains questionable [8]. The Fondation Française de Cancérologie Digestive (FFCD) and the EORTC Gastrointestinal Tract Cancer Co-operative Group (GITCCTG) have investigated the combination of split course pre-operative radiotherapy (2×20 Gy) with cisplatin (CDDP) 80 mg/m^2 before each course of radiotherapy. No survival benefit over surgery alone could be demonstrated so far (data not published). The place of preoperative therapy versus surgery alone is being further investigated in two studies: (a) chemotherapy alone: two 4-day courses of cisplatin and 5-FU, at a 3-week interval (D.J. Girling); (b) Chemoradiotherapy with two cycles of CDDP/VP16 concomitant to radiotherapy and two additional cycles before surgery in case of response (T. Kok).

Adjuvant. The place of postoperative treatment has not been properly investigated. The French Association for Surgical Research is investigating the role of a split-course radiotherapy (20 Gy and 24 Gy at a 4-week interval) and 5-FU 1000 mg/m^2 with CDDP 20 mg/m^2/day, for 5 consecutive days every 42 days for 4 cycles, to be started not beyond 45 days following curative surgery, versus surgery alone (A. Fingerhut).

Locally advanced. In patients with locally advanced T3 N0-1 M0 oesophageal cancer, various questions are raised and some trials are proposed:

(1) What is the role of surgery? A trial is comparing radiochemotherapy (5-FU/CDDP) with surgery to intensified radiochemotherapy alone (L. Bedenne).
(2) Which type of radiotherapy should be used? A trial is comparing split-course (2×20 Gy) to prolonged (50 Gy/25 fractions) radiotherapy both combined to 5-FU and CDDP (J.F. Seitz).
(3) What is the most effective chemotherapy treatment to be combined with radiotherapy? A phase I study is comparing protracted venous infusion of 5-FU and daily CDDP with traditional external beam radiation (J.F. Bosset).
(4) Which is the best prosthesis to relief tumour obstruction? A trial is comparing celestin tube to wallstent prosthesis (P.D. Siersema).

Advanced. Disseminated oesophageal cancer has been poorly investigated mainly due to the poor performance status of these patients. The GITCCG has performed a comparison of 5-FU/CDDP versus CDDP alone showing the poor tolerance of these patients to an aggressive treatment [9]. In a previous phase II study, navelbine 25 mg/m^2 D1 and 8 every 3 weeks disclosed a 25% response rate with a good tolerance [10].

Only two phase II trials are currently investigating advanced stage.

(a) The combination of navelbine (25 mg/m^2 d1 and 8 every 3 weeks) and CDDP (80 mg/m^2 d1 every 3 weeks) is under investigation by the EORTC-GITCCG (T. Conroy).
(b) The randomised phase II of FP (5-FU 800 mg/m^2 ci d1–5, CDDP 100 mg/m^2 d1 or 2) versus FLP (5-FU 350 mg/m^2 i.v. bolus d1–5, folinic acid 100 mg/m^2 d1–5, CDDP 100 mg/m^2 d1 or 2) run by the FFCD (M. Ychou).

Gastric cancer

Adjuvant and neoadjuvant. Adjuvant treatment of gastric cancer after curative surgery is not established. Although many studies have been performed, the small number of patients included and the lack of an adequate methodology do not allow any conclusion to be drawn [11].

Four current trials question the role of chemotherapy after curative surgery for tumours of any stage.

(a) FAMTX (methotrexate, MTX, 1.5 g/m^2 d1, 5-FU 1.5 g/m^{2}d1, doxorubicin, DOX, 30 mg/m^2 d15, every 4 weeks ×6) (D. Nitti).
(b) FEMTX similar to FAMTX except for epirubicin 70 mg/m^2 replacing DOX (J. Wils).
(c) 5-FU/CDDP (5-FU 800 mg/m^2 ci, d1–5, CDDP 100 mg/m^2 d1 or 2 (Ph. Rougier).
(d) PELF (CDDP, epirubicin, 5-FU, FA) (F. Di Costanzo).

One study investigates the role of intraperitoneal chemotherapy (mytomycin C, MMC, 50 mg bound to activated charcoal suspension) in radically resected gastric cancers stage T3 or T4 (H. Rosen).

The concept of neoadjuvant therapy is appealing and is being evaluated in two trials.

(a) FLP in T3 or T4 Nx M0 tumours (FA 500 mg/m^2 i.v., 2 h infusion, 5-FU 2.0 g/m^2 24 h ci weekly × 5, CDDP 50 mg/m^2 i.v. 1 h infusion d1,15,29, repeated on day 50 for 3 cycles) (U. Fink, H.J. Wilke).
(b) FAMTX in cancers of any stage for four courses (I. Songun).

One study is investigating ECF (epirubicin 50 mg/m^2, CDDP 60 mg/m^2 every 3 weeks, 5-FU 200 mg/m^2 daily) given 3 cycles before and 3 cycles after surgery (D. Cunningham, W. Allum).

Local recurrence is a major site of failure even after curative surgery. The role of radiotherapy in that occurrence has not been adequately investigated. One trial is exploring that approach with intra-operative radiotherapy (15 Gy) and postoperative external beam radiation (40–44 Gy) versus surgery alone (F. Guillemin).

Advanced disease. 'Second-generation' regimens have been developed in advanced gastric cancer [12]. Established active treatments in gastric cancer include FAMTX [6], 5-FU/CDDP [13], ELF [14], EAP [15], ECF [16]. Currently running phase III trials in advanced gastric cancer are comparing:

(a) FEMTX to FEMTX plus neupogen (J. Wils);
(b) FAMTX to PELF (CDDP, epidoxorubicin, FA and 5-FU) (G. Cocconi);
(c) weekly × 6 high-dose 5-FU 3.0 g/m^2 every 50 days, versus weekly × 6 high-dose 5-FU 2.6 g/m^2 and FA 250 mg/m^2 every 50 days, versus weekly × 6 high-dose 5-FU 2.0 g/m^2, FA 250 mg/m^2, CDDP 50 mg/m^2 (day 1,15,29) every 50 days, versus FAMTX (H.J. Wilke, J. Wils).

Four phase II trials are investigating various schedules including intensive weekly chemotherapy.

(a) 5-FU, (500 mg/m^2 bolus i.v.), epidoxorubicin (35 mg/m^2), CDDP (40 mg/m^2), FA (250 mg/m^2), glutathione (1500 mg/m^2) and G-CSF (5 μg/kg) (S. Cascinu).
(b) Weekly high-dose 5-FU (3 g/m^2 c.i. over 48 h) (A. Cervantes-Ruiperez).
(c) Docetaxel 85 mg/m^2 and CDDP 75 mg/m^2 (A. Roth).
(d) FLP (FA 100 mg/m^2, 5-FU 350 mg/m^2 bolus d 1–5, CDDP 100 mg/m^2 d1 or 2), versus FP (5-FU 800 mg/m^2 c.i. d1–5, CDDP 100 mg/m^2 d1 or 2) (M. Ychou).

Gastric lymphoma

Three trials are investigating the treatment of low-grade gastric lymphomas, two as a phase II anti-helicobacter therapy alone (A. Ruskone-Fourmestreaux, J. Raemaekers) one as a phase III comparing anti-helicobacter therapy to chlorambucil (R. Souhami). One is also investigating, in lymphoma of any stage, treatments adjusted to the level of malignancy (A. Ruskone-Fourmestreaux).

Hepatocarcinoma

Hepatocarcinomas are insensitive to any therapy: chemotherapy, immunotherapy, radiation [17]. Despite some evidence of a benefit in survival when using chemoembolisation or alcoholisation for limited tumours, the available data do not show any benefit in survival as compared to the patients receiving no treatment [18]. The presence of androgen and oestrogen receptors, predominantly in the malignant liver cells, makes hormonotherapy appealing. Anti-androgen therapy does not improve survival [19]. Anti-oestrogen therapy trials disclosed contradictory results [20, 21].

Trying to generate definitive data, the EORTC-GITCCG is launching a trial of anti-oestrogen therapy with 20 mg tamoxifen versus placebo for patients at any stage and after any treatment modality (H. Bleiberg).

Biliary tract cancer

The outcome of biliary tract cancer is dismal. There is no recognised effective treatment. The EORTC–GITCCG is starting a randomised phase II of 5-FU 3 g/m^2 c.i. over 24 h weekly × 6 every 50 days versus FA 250 mg/m^2, 2 h i.v. infusion followed by 5-FU 2.0 g/m^2 c.i. over 24 h weekly × 6 and CDDP 50 mg/m^2, 1 h i.v. infusion d1,15,29 every 50 days (E. Van Cutsem, M. Ducreux).

Endocrine tumours

Presently, the Rotterdam Cancer Centre is running a study comparing the efficacy of Sandostatin, Intron-A and the combination of both (J.G.M. Klijn).

Pancreatic cancer

Pancreatic cancer is one of the most aggressive cancers with very few cases being resectable and most advanced tumours being unresponsive to chemo- and radiotherapy. One surgical question is being investigated in a trial comparing standard to pyloris preserving surgery (D.C.M. Meijder).

Adjuvant. An adjuvant study is comparing:

(a) split-course radiotherapy (40 Gy) with 5-FU as a radiosensitiser (500 mg/m^2 d1–3 of each radiotherapy course) with
(b) systemic chemotherapy (FA 20 mg/m^2 i.v. bolus before 5-FU 475 mg/m^2 i.v. bolus d1–5 every 4 weeks for 6 months) with
(c) radiotherapy followed by chemotherapy (i.e. combining the two previous arms) with
(d) a group of patients receiving no adjuvant treatment (J. Neoptolemos).

Advanced. Reviews of chemotherapy treatments of metastatic pancreatic cancer showed that chemotherapy has no clinically meaningful activity [22, 23]. Nevertheless, two recent studies that compared chemotherapy with best supportive care showed a significant benefit for chemotherapy [24, 25]. For locally advanced disease, the combination of chemotherapy and radiotherapy probably offers the best palliation and should be further investigated [26].

The new camptothecin derivative, CPT-11, is poorly active [27], while docetaxel seems more promising [28].

More recently, based on an enlarged definition of the clinical benefit, gemcitabine has been proposed as a standard treatment in the U.S.A. [29]. Despite these results, it is generally considered in Europe that, for the time being, treatment of advanced pancreatic cancer should remain within the scope of formal clinical trials.

Presently, three randomised phase II trials are exploring various combinations.

(a) 5-FU (1000 mg/m^2 d 1–4 ci), CDDP (100 mg/m^2 d1), with or without interferon alpha 2b (3MU/d1–5 every 4 weeks (T. Kok).
(b) 5-FU bolus (500 mg/m^2 d1–5 every 4 weeks) versus 5-FU continuous infusion (1000 mg/m^2 d1–5) (Ph. Rougier).
(c) FLP (FA 100 mg/m^2, 5-FU 350 mg/m^2 bolus d1–5, CDDP 100 mg/m^2 d1 or 2) versus FP (5-FU 800 mg/m^2 c.i. d1–5, CDDP 100 mg/m^2 d1 or 2) (M. Ychou).

Colorectal cancer

Colorectal cancer is extremely frequent, accounting for approximately 150 000 new cases per year in Europe. Approximately two-thirds of the patients will die from advanced disease.

Adjuvant. Surgery is the only chance for cure and considerable efforts have been made to improve the benefit of surgery with adjuvant chemotherapy. Three regimens have disclosed an advantage in survival, one with 5-FU and levamisole, two with 5-FU and leucovorin [30, 31].

Attempts to improve these results are many. Sixteen trials have been launched in various European countries. The expected number of patients for each trial varies from 400 to 4000. Overall, 10 concepts are being investigated by using 19 schedules of chemotherapy (Table 1).

(a) Six trials are comparing chemotherapy to control (B. Cedermark, B. Glimelius, R. Jakesz, A. Jakobsen, K.M. Tveit, J. Bury, S. Simnett).
(b) Three trials are comparing modulated 5-FU with 5-FU alone (R. Herrmann, J. Bury, D. Cunningham).
(c) Five trials are comparing various modalities of 5-FU modulation (R. Jakesz, Ph. Rougier, D. Kerr, B. Cedermark, B. Glimelius, A. Sobrero).
(d) One trial is comparing intraportal 5-FU with intraportal plus systemic chemotherapy (R. Herrmann) and two are comparing intraportal plus systemic with systemic chemotherapy alone (B. Nordlinger, Ph. Rougier, G. Zeitoun).
(e) One trial is comparing high- versus low-dose FA before 5-FU (D. Kerr).
(f) One trial is investigating immunotherapy (J. Wilkinson).
(g) One trial is investigating intraportal chemotherapy (R. Labianca).

Table 1. Treatment concepts investigated in adjuvant colorectal cancer

	Concepts	Co-ordinator
(a)	Chemotherapy versus control	
	FU/FA versus surgery alone	Cedermark, Glimelius, Jakesz
	FU/LEV versus surgery alone	Jakobsen, Tveit
	FU/FA/LEV versus surgery alone	Cedermark
	FU IP versus surgery alone	Bury, Simnett
(b)	FU modulation versus FU alone	
	FU/LEV versus FU	Herrmann
	FU/FA versus FU	Bury, Cunningham
(c)	FU/LEV versus FU other modulation	
	FU/LEV versus FU/LEV/IFN	Jakesz
	FU/LEV versus FU/LEV/FA	Jakesz
	FU/LEV versus FU/LEV/FA/IFN	Jakesz
	FU/LEV versus FU/FA	Nordlinger, Rougier, Plukker
(d)	FU/FA versus FU other modulation	
	FU/FA versus FU/FA/LEV	Kerr, Cedermark
(e)	FU multiple modulation versus other multiple modulation	
	FU/LEV/FA versus FU/LEV/MTX	Sobrero
(f)	FU intraportal versus systemic	
	FU IP versus FU	Herrmann
	FU IP versus FU/LEV	Herrmann
	FU IP vs FU/FA	Labianca
(g)	FU systemic versus FU intraportal + FU systemic	
	FU/FA versus FU IP + FU/FA	Nordlinger, Rougier, Labianca
	FU/LEV versus FU IP + FU/LEV	Nordlinger, Rougier
	FU/FA/LEV versus FU IP + FU/FA/LEV	Zeitoun
(h)	High-dose FA versus low-dose FA	
	FA 200 mg/m^2 versus FA 20 mg/m^2	Kerr
(i)	Immunotherapy	
	FU/FA versus Panorex	Wilkinson
	FU/FA versus FU/FA + Panorex	Wilkinson

FU, 5-fluorouracil; FA, folinic acid; LEV, levamisole; IP, intraportal; IFN, interferon; MTX, methotrexate.

Advanced. Advanced colorectal cancer has long been considered poorly sensitive to chemotherapy. Actually, 5-FU was the only active agent available, generally given intravenously as a bolus. The response rate probably does not exceed 15% [32]. Biochemical modulation of 5-FU, mainly with the use of folinic acid and methotrexate, produced higher response rates and a median survival time that, in major studies, appeared to be around 1 year [33, 34]. Prolonged infusion time over 24 or 48 h or indefinitely also seemed to improve response rates with potential benefit on survival [35–37]. Finally, the chronomodulation of 5-FU seems to be superior to continuous, flat administration [38].

Despite this obvious progress, the prognosis of the patients with advanced colorectal cancer remains dismal. However, new agents, 'Tomudex' [39], CPT-11 [40] and oxaliplatin [41] are available in some countries. These may lead the way to improvements in this area.

This and the high occurrence of advanced colorectal cancer may explain the large number of studies running in Europe. 18 trials are exploring 12 concepts (Table 2).

(a) One trial is comparing early treatment, at an asymptomatic stage, to late treatment when the patient has symptoms (A.M. Sargeant).

(b) Three trials are comparing continuous infusion to bolus 5-FU (E. Aranda Aguilar, H.J. Schmoll, C.H. Köhne, H.J. Weh, A. Sobrero, R. Labianca).

(c) Two trials are investigating 5-FU modulation (F. Di Costanzo, M. Borner) among which one is still comparing 5-FU bolus with and without low-dose FA (M. Borner).

(d) One trial is giving 3 different doses of 5-FU (400, 500, 600 mg/m^2) combined with FA (B. Glimelius).

(e) Three trials are comparing different schedules of 5-FU continuous infusion (H.J. Schmoll, C.H. Köhne, D. Cunningham, T. Maughan).

(f) One trial is comparing constant 5-FU infusion with or without pharmacokinetic adjustment (E. Gamelin).

(g) One trial is comparing no further treatment to prolonged chemotherapy, in patients whose disease has not progressed during the first 12 weeks of chemotherapy (T. Maughan).

Table 2. Treatment concepts investigated in advanced colorectal cancer

	Concepts	Co-ordinator
(a)	Immediate versus delayed treatment	
	FU b/FA immediate versus FU b/FA delayed	Sargeant
(b)	FU continuous infusion versus FU bolus	
	FU ci (48) versus FU b	Aranda Aguilar
	FU ci (24) FA versus FU b	Schmoll, Köhne, Weh
	FU b/MTX versus FU b/MTX alternated with FU ci/FA	Sobrero, Labianca
(c)	Modulation of 5-FU	
	FU b versus 5-FU b/LD FA	Borner
	FU b/FA/hydroxyurea versus various schedules	Di Costanzo
(d)	Dose of 5-FU	
	FU b/FA 400 versus 500 versus 600 mg/m^2	Glimelius, Jacobsen
(e)	Comparison of different schedules of 5-FU continuous infusion	
	FU ci (24) versus FU ci (24) + FA	Schmoll, Köhne
	FU PVI versus FUPVI + MMC	Cunningham
	FU PVI versus FU b, ci (48)	Maughan
(f)	Duration of treatment	
	3 months versus > 3 months	Maughan
(g)	Pharmacokinetic adjustment	
	FU ci (8)/FA weekly versus same + pharmacokinetic adjustment	Gamelin
(h)	Combination 5-FU/oxalipatin	
	FU b ci, (48)/FA versus FU b, ci (48)/FA/oxaliplatin	de Gramont
(i)	UFT versus FU	
	UFT + LD FA versus FU b/FA	Chazard
(j)	5-FU continuous infusion versus Tomudex	
	FU PVI versus Tomudex	Maughan
	FU b, ci (48) versus Tomudex	Maughan
(k)	Hepatic arterial	
	FU/FA HA versus FU/FA iv	Lorenz, Kerr
	FU/FA HA versus FUDR HA	Lorenz
	FUDR HA versus FU/FA iv	Pancera, Lorenz
(l)	Second-line therapy	
	CPT-11 versus best supportive care	Cunningham
	CPT-11 versus FU b or ci or PVI	Rougier
	2nd line FU b, ci/FA + oxaliplatin	de Gramont
(m)	Phase I combination with new agents	
	CPT-11 alternating with FU b/FA	Van Cutsem

FU, 5-fluorouracil; FA, folinic acid; b, bolus; ci, continuous infusion; (), hours infusion; MTX, methotrexate; LD, low dose; PVI, protracted venous infusion; MMC, mitomycin C; UFT, uracil/ftorafur.

Ultimately, new agents are upcoming:

(a) Oxaliplatin combined with bolus and continuous infusion of 5-FU/FA is being compared with the same schedule of 5-FU/FA alone as first-line treatment or is given as second-line treatment in patients progressing after 5-FU (A. de Gramont).
(b) Uracil/ftorafur with FA is being compared with standard 5-FU bolus with low-dose FA (M. Chazard).
(c) 'Tomudex' is being compared with protracted or continuous 5-FU infusion (T. Maughan).
(d) CPT-11 is being investigated as second-line treatment after failure of an adequate regimen of 5-FU versus best supportive care (D. Cunningham) or another choice of 5-FU therapy (Ph. Rougier) or in phase I alternating CPT-11 and 5-FU/FA bolus (E. Van Cutsem).

Radiotherapy. Radiotherapy has not been much investigated in colon cancer. One trial is investigating whether the addition of radiation therapy improves overall survival and/or local disease-free interval in patients with completely resected, histologically proven adenocarcinoma of the colon T4-N0 and T3-4, N1-2)(A.M. Sargeant).

In contrast, radiotherapy is considered by many as a standard treatment for rectal cancer. Pre-operative radiotherapy has been able to halve the rate of local recurrence. Although postoperative radiotherapy alone did not show similar benefit, a definite impact on the local recurrence rate and survival was shown when combined with chemotherapy. However, immediate and late small bowel toxicity is high [42].

It has been argued that, in previous trials of radiotherapy, surgery was suboptimal. Therefore, a new trial has been launched investigating the role of radiotherapy before standardised total mesorectal surgery (G.J. Liefers, L. Pahlman, C. van de Velde). The role of pre-operative radiotherapy combined with or without chemotherapy is being investigated by the EORTC Radiotherapy (J.F. Bosset) and Nordic Colorectal Cancer Study Group (K.M. Tveit, B. Glimelius, N. Wilking), which is also investigating the role of intra-operative radiotherapy.

The best way of delivering 5-FU is being investigated in a three-arm study comparing: bolus 5-FU versus protracted venous infusion (PVI) of 5-FU given before and after pelvic radiotherapy versus bolus 5-FU/FA/Lev given before and after pelvic radiotherapy (D. Johnston).

Adjuvant treatment after metastases resection. In colorectal cancer, liver and/or lung metastases can sometimes be resected. The 5-year survival is approximately 25% [43]. Would 'adjuvant' chemotherapy improve survival? This question is being examined in a large intergroup trial comparing 5-FU/FA after liver or lung metastases resection with no immediate further treatment (H. Bleiberg, D. Nitti, A. Fields, B. Langer, R. Labianca, S. Marsoni, F. Lazorthes, G.J. Poston). Intra-arterial 5-FU/FA is also under investigation (M. Lorenz).

Intra-arterial treatment. Unresectable liver metastases have been treated by intra-arterial chemotherapy. Although this approach is successful in experienced centres, it has never been shown to be superior to systemic treatment [44]. Moreover, the morbidity of the procedure might be unacceptable in comparison with the most recently developed systemic treatments. Nevertheless, the rationale for using local treatment is appealing and deserves further research within the frame of clinical trials.

(a) Intra-arterial 5-FU/FA (FA 200 mg/m^2, 5-FU c.i. 1000 mg/m^2) d1-5 is being compared with intra-arterial FUDR (0.2 mg/kg) d1–14 every 28 days and with intravenous 5-FU/FA (FA 200 mg/m^2, 5-FU c.i. 800 mg/m^2) days 1–5 every 28 days (M. Lorenz).
(b) Intra-arterial administration of FUDR/dexamethasone is being compared with 5-FU/FA i.v. bolus and with the administration of both modalities (G. Pancera).
(c) Intravenous bolus and continuous 5-FU/FA (FA 200 mg/m^2 d1–2; 5-FU bolus 400 mg/m^2 d1–2, 5-FU c.i. 600 mg/m^2 d1–2, every two weeks) is being compared with the same schedule given by the hepatic arterial route (D. Kerr).

Anal cancer

Recent studies have shown that prolonged radiotherapy combined with 5-FU and MMC can improve colostomy-free survival time and overall survival [45]. An attempt to improve these results by combining split-course radiotherapy with PVI 5-FU delivered during the two radiotherapy sequences and MMC given before each radiotherapy course is currently being investigated (J.F. Bosset, F. Roelofsen).

DISCUSSION

Clinical research in the field of the gastrointestinal cancers is expanding rapidly. Progress has been modest with only little gain in survival for patients with advanced disease. Besides cisplatin, practically no new active agent has been identified in GIT cancer for the last 40 years. However, since the early 1990s, agents with demonstrated activity are manifold: topoisomerase I inhibitors, CPT-11 and topotecan; another platinum derivative, oxaliplatin; thymidylate synthase inhibitors such as 'Tomudex'; taxoids such as paclitaxel and docetaxel and other agents such as vinorelbine or gemcitabine. The development of the new technologies already shows that other new compounds targeting other mechanisms of tumour growth and/or tumour invasiveness are upcoming and will soon expand to the field of clinical research. The precise place of these agents in our armamentarium remains to be settled and this will require rapidly accruing trials with large numbers of patients.

In parallel with the emergence of new active agents, most European countries have started organising clinical research on a national basis. The present list of trials underlines the magnitude of the interest expressed for GIT cancers among European physicians. We have identified in 14 countries, 43 co-operative groups organising 84 multicentric clinical trials (Appendices 1 and 2). Four pharmaceutical companies are also involved in major projects in gastrointestinal cancers. Obviously, many questions are raised at the same time. Too many studies have a low accrual rate of which a significant proportion will not be able to reach the required number of patients. In colorectal cancers, for example, a total of 43 trials exploring 22 concepts are currently open for patients' registration (Tables 1 and 2). Each question by itself appears to be important but it would certainly be more effective to have less concepts investigated at the same time and more patients per study. It may be asked whether some investigators would not have modified their choice if they had known about each other?

Establishing the Gastrointestinal Tract Cancer Liaison Office will help to keep investigators informed of what is being done in their field in Europe. It will promote and

facilitate interactions between researchers and stimulate intergroup studies. Under the auspices of the EORTC, the GITCLO organises biennial meetings where investigators exchange their opinions and may discuss their data. One may hope that the national co-operative groups will take advantage of that new accessibility to what's going on in their field of interest to define more accurately priorities and to design studies in a way that will allow further pooling of the results. This has already been performed for two adjuvant studies in gastric cancer (FAMTX and FEMTX versus control) and in the adjuvant treatment after resection of liver or lung metastases of colorectal origin for which biostatisticians and data centres have already foreseen the basis for a common analysis.

As a result of the GITCLO activities, an attempt has been made to initiate a first Pan European Intergroup Trial for adjuvant treatment of colon cancer [46]. This study allows the co-operative groups to compare standard adjuvant treatment (bolus 5-FU and folinic acid) versus a potentially more active schedule (infusional 5-FU) or a simpler way of delivering treatment (Tomudex) (J. Wils).

We hope that our undertaking will be successful and that the present attempt to clarify the situation of clinical research in the field of cancers of the digestive system in Europe will speed up therapeutic progress in the best interest of the patients.

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