29. Anderson N, Lokich JJ. Cancer chemotherapy and infusional scheduling. *Oncology* 1994, **8**, 99–116.
30. De Gramont A, Krulik M, Cady J, *et al.* High dose folinic acid and 5-fluorouracil bolus and continuous infusion in advanced colorectal cancer. *Eur J Cancer Clin Oncol* 1988, **24**, 1499–1503.
31. de Gramont A, Bosset J-F, Milan C, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997, **15**, 808–815.
32. Anonymous. Portal vein chemotherapy for colorectal cancer: a meta-analysis of 4000 patients in 10 studies. *J Natl Cancer Inst* 1997, **89**, 497–505.
33. Piedbois P, Buyse M, Gray R, *et al.* Portal vein infusion is an effective adjuvant treatment for patients with colorectal cancer. *Proc ASCO* 1995; **14**, Abstract 444.
34. Scheithauer W, Marczell A, Depisch D, *et al.* Combined intravenous and intraperitoneal chemotherapy with 5-fluorouracil (5FU) and leucovorin versus 5-FU and levamisole for adjuvant therapy of resected colon carcinoma. *Proc ASCO* 1996, **14**, Abstract 507.
35. Moertel CG, Fleming TR, Macdonald JS, *et al.* Intergroup study of fluorouracil plus levamisole as adjuvant therapy for stage II/ Dukes' B2 colon cancer. *J Clin Oncol* 1995, **13**(12), 2936–2943.
36. Mamounas EP, Rockette H, Jones J, *et al.* Comparative efficacy of adjuvant chemotherapy in patients with Dukes'B vs Dukes' C colon cancer: results from four NSABP adjuvant studies (C-01, C-02, C-03, C-04). *Proc ASCO* 1996, **14**, Abstract 461.
37. Wolmark N, Fisher B, Rockette H, *et al.* Postoperative adjuvant chemotherapy for BCG for colon cancer: results from NSABP protocol C-01. *J Natl Cancer Inst* 1988, **80**, 30–36.
38. Riethmuller G, Holz E, Schlimok G, *et al.* Monoclonal antibody (Mab) adjuvant therapy of Dukes C colorectal carcinoma: 7-year update of a prospective randomized trial. *Proc ASCO* 1996, **14**, Abstract 1385.
39. Peters GJ, van der Wilt CL, van Groeningen CJ, *et al.* Thymidylate synthase inhibition after administration of fluorouracil with or without leucovorin in colon cancer patients: implications for treatment with fluorouracil. *J Clin Oncol* 1994, **12**(10), 2035–2042.
40. Johnston PG, Fisher ER, Rockette HE, *et al.* The role of thymidylate synthase expression in prognosis and outcome of adjuvant chemotherapy in patients with rectal cancer. *J Clin Oncol* 1994, **12**(12), 2640–2647.
41. Zhao-Shi Zeng, Sarkis AS, Zuo-Feng Zhang, *et al.* p53 nuclear overexpression: an independent predictor of survival in lymph node-positive colorectal cancer patients. *J Clin Oncol* 1994, **12**(10), 2043–2050.

PII: S0959-8049(98)00252-4

Contra:

P. Rougier

Hôpital Ambriose Paré, Department of Gastro-entérology, 9, ave Charles de Gaulle, 92100 Boulogne cedex, France

COLORECTAL CANCER is estimated to rank third in incidence in men in Europe, it is the second most frequent cancer in women and approximately 60 000 people will die from colorectal adenocarcinomas among the 150 000 new cases which will be diagnosed this year. Adjuvant treatment aims at increasing life expectancy, especially of people at high risk of recurrence after resection of colon carcinoma Astler-Coller stage B2 and C [1], or UICC stage II and III [2]. After more than 30 years of efforts, the results of recently published large randomised trials have given important indications on what adjuvant treatment to administer and whom it will benefit. However, there is no single standard treatment, but many efficient protocols, and clinicians and patients have to choose which will be the more appropriate in each case.

The combination of 5-fluorouracil (5-FU) and levamisole was the first efficient adjuvant chemotherapy for colon cancer Dukes' stage C curatively resected (Table 1). In 1990, Moertel and colleagues reported a very significant benefit for Dukes' C patients receiving a 1 year combination of weekly 5-FU and biweekly oral levamisole [5]. After that publication, this combination was considered as the standard adjuvant treatment for colon cancer [7], but many physicians, especially in Europe, were not convinced for many reasons:

- The combination of 5-FU and oral levamisole is no more active than 5-FU alone in metastatic patients, but is more toxic;
- There is no clear explanation for the mechanism of action of 5-FU and oral levamisole;
- Oral levamisole has no antitumour activity in randomised trials [6, 8];
- There was no 5-FU alone arm in the INT 0035 trial and it is possible that the positive results reported by Moertel and colleagues were to the 5-FU efficacy alone and, if the previous adjuvant trials using 5-FU alone were individually not effective, this was in part related to the small number of patients included. A meta-analysis has demonstrated that there was a significant benefit when all these trials using 5-FU were analysed together [9].
- More active combinations of 5-FU were known at this time, especially with leucovorin or methotrexate in metastatic patients [10, 11];
- The survival rate of the control group was abnormally low (around 40% at 5 years) and the quality of the 'radical' surgery has been questioned by many surgeons thinking that a better quality of surgical excision very significantly increase the control group survival rate and decrease the need for adjuvant chemotherapy; presently there is an ongoing trial in The Netherlands which aims to reproduce the INT 0035 trial results.

Because, since 1984 the combination of 5-FU and leucovorin has been known to be effective in metastatic colorectal

Table 1. *Trials on adjuvant chemotherapy in colon cancer stage B2 and C (Astler-Coller) using the 5-fluorouracil (5-FU) + levamisole (LEV) combination*

Study [ref.]	Treatment	No. of patients	Disease free survival at 5 years (%)	Overall survival at 5 years (%)	*P*-value
Windle and colleagues [3]	Control	45	NR	55	0.046
	5-FU (oral)	42	NR	45	
	5-FU + LEV	44	NR	68	
NCCTG (Dukes' B and C) [4]	Control	135	45	55	< 0.05
	LEV	130	59	60	
	5-FU + LEV	136	59	62 (for Dukes' C)	
Intergroup B2 [5]	Control	159	77	91	NS
	5-FU + LEV	159	84	85	
Intergroup C [5, 6]	Control	315	47	55	
	LEV	310	53	64	0.006
	5-FU + LEV	304	66	71	

NR, not recorded; NS, not significant.

cancer, this combination has been used as adjuvant treatment for colon cancer stage B2 and C. Four trials have been reported and all demonstrated a significant survival benefit, but only three had an untreated control group (Table 1). The largest [12] was a pooled trial from the Canadian NCI, an Italian group (GIVIO) and a French group (FFCD) which included 1,526 patients who were randomised between a control group (no additional treatment) and a group receiving six cycles of a monthly schedule of 5-FU (400 mg/m^2/day for 5 days) and leucovorin (200 mg/m^2/day); after a median follow-up of 37 months there was a significant increase in disease free survival (71% at 3 years versus 62%; $P = 0.0001$) [12]. The second was conducted by the Mayo Clinic–NCCTG and has been prematurely closed, after inclusion of 317 patients, due to the results published with the 5-FU–levamisole combination. However, with a median follow-up of 42 months there was a significant increase in disease free survival at 3 years (77% versus 64%; $P = 0.0001$) and a borderline increase in overall survival (75% versus 71%; $P = 0.04$) [13]. The third has been reported by an Italian group [14], and the fourth is the NSAPB trial C03 which reported the superiority of the 5-FU–leucovorin combination (weekly schedule) over the MOF protocol for stage B2 and C cancers; in this trial, 1,081 patients were randomised, the disease free survival at 3 years was 73% versus 64% ($P = 0.0004$) and the overall survival was 84% versus 77% ($P = 0.003$) [15] (Table 2). These results are concordant and clearly demonstrate the efficacy of the 5-FU–leucovorin combination. This combination has some advantages over the 5-FU–levamisol combination, with a good tolerance, better compliance and treatment duration of only 6 months and explains why many physicians adopted it as adjuvant treatment for resected colon cancers even before the results of comparative trials comparing 5-FU–levamisole with 5-FU–ac folinic acid.

The preliminary results of trials comparing 5-FU–levamisole with 5-FU–ac folinic acid were reported at the ASCO meeting in May 1996 and are more or less in favour of the superiority of the 5-FU–leucovorin combination and of the marginal role of levamisole (Table 3).

Besides the interest of systemic chemotherapies, efficacy of locoregional chemotherapy was emphasised, especially intraportal chemotherapy because: (i) during the initial stages of metastasis most of the malignant cells go through the liver and reach other sites in the body via the portal circulation; (ii) the liver is the most frequent site of distant metastases which are supplied by portal vein blood flow at the onset of their development. This concept was developed by Taylor and colleagues [19]. The portal route has been widely used and four [19–22] of the seven randomised trials [19–26] tested intraportal postoperative chemotherapy which reported a significant survival benefit, and a recent meta-analysis is in favour of a small but significant decrease in the relative mortality rate of 13% after administration of intraportal chemotherapy [28].

Table 2. *Trials on adjuvant chemotherapy in colon cancer stage B2 and C (Astler-Coller) using the 5-fluorouracil (5-FU) + folinic acid combination*

Study [ref.]	No. of patients	Regimen	Disease free survival at 3 years (%)	*P* value	Overall survival at 3 years (%)	*P* value
IMPACT (GIVIO + NCIC + FFCD) [12]	1,526	Observation	71	< 0.0001	83	0.027
		5-FU + folinic acid (monthly)	62		78	
NCCTG [13]	317	Observation	77	< 0.0001	75	0.04
		5-FU + folinic acid (monthly)	64		71	
Italian [14]	239	Observation	74*	< 0.005	79*	0.004
		5-FU + folinic acid (monthly)	59		65	
NSAPB C 03 [15]	1,081	MOF	73	< 0.0004	84	0.003
		5-FU + folinic acid (weekly)	64		77	

*At 5 years. Negative results of the largest trial ever reported using portal vein infusion on 12 randomised patients [27] MOF, lomustine, vincristine, 5-FU.

Table 3. Trials on adjuvant chemotherapy in colon cancer stage B2 and C (Astler-Coller) comparing the 5-fluorouracil (5-FU) + levamisole (LEV) combination with the 5-FU + folinic acid combination with or without LEV

Study [ref.]	No. of patients	Protocol	Disease free survival (%)	*P* value	Overall survival (%)	*P* value
INT 0089 B_2-C [16]	3,759	(1) 5-FU + LEV/12 months (2) 5-FU + folinic acid (weekly)/8 months (3) 5-FU + folinic acid (monthly)/6 months (4) 5-FU + folinic acid (monthly) + LEV/6 months		(1) versus (2) NS (2) versus (3) NS (3) versus (4) NS		(1) versus (2) NS (2) versus (3) NS (3) versus (4) NS
NCCTG-NCIC B_2-C [17]	915	5-FU + LEV/6 months 5-FU + folinic acid (monthly)/6 months 5-FU + folinic acid (monthly)/12 months 5-FU + folinic acid (monthly) + LEV/12 months	64 66 69 70	NS	63 66 72 75	0.03
NSAPB C-04 B_2-C [18]	2,151	5-FU + LEV/12 months 5-FU-folinic acid (weekly)/12 months 5-FU + folinic acid + LEV (weekly)/12 months	60 64 64	0.06 NS	69 74 72	0.05 NS

NS, not significant.

Adjuvant intraperitoneal chemotherapy with 5-FU has been much less studied. Its use seems logical as it can potentially act on microscopic peritoneal tumour deposits and results in a high 5-FU level in the portal blood flow [29], which may also act on liver micrometastases. Only a small randomised study testing that hypothesis has been reported in patients at high risk of recurrence, it was unable to demonstrate an increase in overall survival, but demonstrated a decrease in the rate of peritoneal carcinomatosis [30]. Its feasibility is now established and a randomised multicentric trial has been conducted. This trial compares a control group of patients receiving no treatment after surgical excision of their colon cancer with a group receiving a 6-day course of intraperitoneal 5-FU initiated 3–4 days after surgery (after passing gas). More than 200 patients have been entered and the feasibility of that approach demonstrated. However, no data have yet been published on survival [31]. At this point in time, there is no demonstration of a survival advantage with adjuvant intraperitoneal chemotherapy. Nevertheless, this early locoregional treatment is attractive and warrants further studies testing its utility combined with systemic adjuvant treatment [32].

The benefit of a combination of systemic and locoregional (portal or intraperitoneal) chemotherapy is presently unknown. Only a few of the ongoing randomised trials conducted have the aim of determining the respective value of locoregional and systemic treatment which perhaps acts on different subsets of tumour cells (Table 4). Two are particularly geared to offer a reply to such questions: (i) a large Italian intergroup trial (GOIRC + ACOI) is comparing in a three-arm study: intraportal chemotherapy during 7 postoperative days versus systemic 5-FU potentiated by L folinic acid for 6 months versus a combination of these two treatments; (ii) a large randomised trial (EORTC 40911; FFCD 9204) initiated by the EORTC Gastro Intestinal Tract Group and the FFCD (Fondation Française de Cancérologie Digestive), which, after stratification of stage B_2 and C adenocarcinoma on the location (colon versus rectum), aim to compare a group receiving a combination of postoperative locoregional treatment (intraportal or intraperitoneal) and systemic treatment for 6 months versus a group receiving systemic treatment alone. In this trial a second parallel randomisation will allow the comparison of two different systemic treatments: 5-FU + levamisole (control arm) versus a combination of 5-FU + L folinic acid (investigational arm). Presently there are 1,850 patients entered, this trial is now closed to entry. This trial will be analysed, by a two-by-two analysis method, to establish the value of locoregional treatment associated with a systemic treatment compared with a systemic treatment alone. For the systemic treatment, the value of 5-FU combined with L folinic acid compared with the conventional 5-FU + levamisole combination will be established.

Non-specific immunotherapy has been used for many years without any clear evidence of efficacy. Bacille Calmette-Guérin (BCG) and its methanol extractil residue (MER) have been used alone as immunostimulants or combined with chemotherapy, and they have failed to increase overall survival. Interferon-gamma [33] or polyadenylic–polyuridylic acid [34] have even demonstrated a deleterious effect on survival!

Better results have been reported with the use of specific immunotherapy: monoclonal antibody (17-1A; Panorex^R),

Table 4. Current adjuvant trials in colon carcinomas

Study	Stage	Regimen
ECOG 5283	B_2	Observation Autologous vaccine
MAOP 5186A	C	5-FU continuous i.v. + LEV 5-FU bolus i.v. + LEV
ECOG 1290	C	5-FU + LEV Autologous vaccine
AXIS (U.K.)		Observation Intraportal 5-FU + heparin
EORTC 40 911 FFCD 9204	B_2-C	Locoregional 5-FU + 5-FU i.v. + LEV and Locoregional 5-FU + 5-FU i.v. + L folinic acid 5-FU i.v. + LEV 5-FU i.v. + L folinic acid
Italian Intergroup		5-FU + L folinic acid i.v. Intraportal 5-FU 5-FU + L folinic acid i.v. + intraportal 5-FU

ECOG, Eastern Cooperative Oncology Group; FFCD, Fondation Française de Cancérologie Digestive; MAOP, Mid Atlantic Oncologic Program; AXIS, adjuvant x-ray and 5-FU infusion study; EORTC, European Organization for Research and Treatment of Cancer; 5-FU, 5-fluorouracil; i.v., intravenous; LEV, levamisole.

administered five times in the postoperative period gave, in a small randomised trial, a significant reduction of the relative risk of death of approximately 30% compared with untreated controls [35] and this approach has challenged the 5-FU–levamisole adjuvant treatment and is presently tested against adjuvant chemotherapy. Tumour vaccines have been tested, using autologous tumour for adjuvant treatment of colorectal cancer. Hoover and colleagues reported [36] and updated [37] a randomised controlled trial using an autologous tumour mixed with BCG. This vaccine was administered weekly for 3 consecutive weeks beginning on week 4–5 after surgery, and included 80 patients with a median follow-up of 68 months. A 75% reduction in the risk of recurrence was noted in the treated group compared with the control group ($P = 0.016$). Because of the low number of patients included, no conclusion can be drawn regarding overall survival, but the ECOG is currently conducting two randomised studies using autologous vaccines, on the basis of these encouraging results.

The case of Dukes' B patients is controversial. In the intergroups trial using the 5-FU–levamisole as well as the 5-FU–folinic acid combination, the results are negative in terms of overall survival, except for the NSABP which reported an equivalent benefit for Dukes' B and C carcinomas [38]. This lack of efficacy is probably due to the fact that this stage mixed patients with very different risk of recurrence. However, when poor prognostic factors are present [39], for instance for a young patient operated upon for an occlusive or perforated colon cancer, it seems acceptable to treat him with an adjuvant and well tolerated chemotherapy due to his high risk of recurrence.

CONCLUSION

We can conclude that there is no standard adjuvant chemotherapy, but many effective adjuvant treatments and only recommendations according to specific situations can be made:

1. Administration of an adjuvant chemotherapy is mandatory for Dukes' C colon cancer using an active protocol: 5-FU–levamisole for 5-FU–folinic acid. The choice of the most efficient, the less toxic and the less costly protocol is logical.
2. In the future, immunotherapy has to be incorporated into protocols as do the most efficient chemotherapy protocols like LV5FU2 [40], protracted intravenous perfusion of 5-FU [41] or weekly high-dose 5-FU [42].
3. New effective drugs which are now available (Tomudex, UFT, CPT11, oxaliplatin, capecitabine, etc.) have to be tested alone or in combination with 5-FU. However, it is important to keep in mind that most of the patients are cured by surgical excision and, thus, the toxicity of the new protocols has to be very low in the adjuvant setting.
4. Participation in large prospective randomised trials is the best way to contribute to the improvement of therapeutic possibilities.
5. Dukes' B2 patients with high risk of recurrence factors should be characterised and included in prospective trials.
6. Better characterisation of patients using molecular biology thymidylate synthase (TS) expression, *P53* mutation) [43, 44] would allow better selection for adjuvant peri-operative treatment.

1. Astler VB, Coller FA. The prognostic significance of direct extension of carcinoma of the colon and rectum. *Ann Surg* 1954, **139**, 846–851.
2. International Union Against Cancer. *TNM Classification of Malignant Tumours*. New York, Wiley-Liss, 1997, 67–69.
3. Windle R, Bell PRF, Shaw D. Five year results of a randomized trial of adjuvant 5-fluorouracil and levamisole in colorectal cancer. *Br J Surg* 1987, **74**, 569–572.
4. Laurie J, Moertel CG, Fleming T, *et al.* Surgical adjuvant therapy of large bowel carcinoma: an evaluation of levamisole and combination of levamisole and fluorouracil. *J Clin Oncol* 1989, **7**, 1447–1456.
5. 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.
6. Moertel CG, Fleming T, MacDonald JS, *et al.* Fluorouracil plus levamisole as effective adjuvant therapy after resection of stage III colon carcinoma. A final report. *Ann Intern Med* 1995, **122**, 321–326.
7. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990, **264**, 14440–1450.
8. Arnaud JP, Buyse M, Nordlinger B, *et al.* Adjuvant therapy of poor prognostic colon cancer with levamisole: result of an EORTC double-blind randomized clinical trial. *Br J Surg* 1989, **76**, 284–289.
9. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer. Why we still don't know. *JAMA* 1988, **259**, 3571–3578.
10. 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.
11. Advanced Colorectal Cancer Meta Analysis Project. Meta-analysis of randomised trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. *J Clin Oncol* 1994, 12, 960–969.
12. IMPACT Investigators. Efficacy of adjuvant fluorouracil and folinic acid in colon cancer. *Lancet* 1995, **106**, 939–944.
13. O'Connell M, Mailliard J, MacDonald J, *et al.* 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.
14. Francini G, Petrioli R, Lorensini L, *et al.* Folinic acid and 5-fluorouracil as adjuvant treatment chemotherapy in colon cancer. *Gastroenterology* 1994, **106**, 899–906.
15. Wolmark N, Rockette N, 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.
16. Haller DG, Catalano PJ, MacDonald JS, Mayer RJ. Eastern Cooperative Oncology Group (ECOG), Southwest Oncology Group (SWOG), Cancer and Acute Leukemia Group B (CALGB). Fluorouracil (FU), leucovorin (LV) and levamisole (LEV) adjuvant therapy for colon cancer. Preliminary results of INT-0089. *Proc Am Soc Clin Oncol* 1996, **15**, 211.
17. O'Connel MJ, Laurie JA, Shepherd L, *et al.* A prospective evaluation of chemotherapy duration and regimen as surgical adjuvant treatment for high-risk colon cancer: a collaborative trial of the North Central Cancer Treatment Group and the National Cancer Institute of Canada trials group. *Proc Am Soc Clin Oncol* 1996, **15**, 209.
18. Wolmark N, Rockette H, Mamounas EP, *et al.* The relative efficacy of 5-FU + leucovorin (FU–LV), 5-FU + levamisole (FU–LEV), and 5-FU + leucovorin + levamisole (FU–LV–LEV) in patients with Dukes' B and C carcinoma of the colon: first report of NSABP C-04. *Proc Am Soc Clin Oncol* 1996, **15**, 205.
19. 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.
20. 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.
21. 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.
22. Gray BN, de Zwart J, Fisher R, *et al.* The Australian and New Zealand trial of adjuvant chemotherapy in colon cancer. In Salmon SE, ed. *Adjuvant Therapy of Cancer V*. Philadelphia, Grüne & Stratton, 1987, 537–546.
23. Wereldsma JCJ, Bruggink EDM, Meijer WS, Roukema JA, Van Putten WLJ. Adjuvant portal liver infusion in colorectal cancer with 5-fluorouracil/heparin versus urokinase versus control. *Cancer* 1990, **65**, 425–432.
24. Metzger U, Mermillod B, Aeberhard P, *et al.* Intraportal chemotherapy in colorectal carcinoma as an adjuvant modality. *World J Surg* 1987, **11**, 452–458.
25. 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.
26. Fielding LP, Hittinger R, Grace RH, Fry JS. Randomised controlled trial of adjuvant chemotherapy by portal vein perfusion after curative resection for colorectal adenocarcinoma. *Lancet* 1992, **340**, 502–506.
27. Rougier Ph, Shamoud T, Nitti D, *et al.* Adjuvant portal-vein infusion of fluorouracil and heparin in colorectal cancer: a randomised trial. *Lancet* 1998, **351**, 1677–1681.
28. Piedbois P, Buyse M, Gray R, *et al.* Portal vein infusion is an effective adjuvant treatment for patients with colorectal cancer. *Proc Am Soc Clin Oncol* 1995, **14**, 192.
29. Speyer JM, Sugarbaker PH, Collins JM, Dedrick RL, Klecker RW, Myers CE. Portal levels and hepatic clearance of 5-fluorouracil after intra-peritoneal administration in humans. *Cancer Res* 1981, **41**, 1916–1922.
30. Sugarbaker PH, Gianola FG, Speyer JC, Wesley R, Barofsky I, Meyers CE. Prospective, randomized trial of intravenous versus intra-peritoneal fluorouracil in patients with advanced primary colon or rectal cancer. *Surgery* 1985, **98**, 414–421.
31. Nordlinger B, Bouteloup PY, Favre JP, *et al.* Early post-operative intraperitoneal chemotherapy is feasible and well tolerated in colon cancer. A prospective randomized study. *J Cancer Res Clin Oncol* 1990, **116**, 686.
32. Brodsky JT, Cohen AM. Peritoneal seeding following potentially curative resection of colonic carcinoma: implications for adjuvant therapy. *Dis Colon Rectum* 1991, **34**, 723–727.
33. O'Connell MJ, Wiesenfeld M, Wieand HS, *et al.* Interferon-gamma (IFN-γ) as postoperative surgical adjuvant therapy for colon cancer: significant immune stimulation without evidence of therapeutic benefit. *Proc Am Soc Clin Oncol* 1992, **11**, 167.
34. Lacour J, Laplanche A, Malafosse M, *et al.* Polyadenylic–polyuridylic acid (AU) as an adjuvant in resectable colorectal carcinoma: a 6 1/2 year follow-up analysis of a multicentric double blind randomized trial. *Eur J Surg Oncol* 1992, **18**, 599–604.
35. Riethmuller G, Schneider-Gadicke E, Schlimok G, *et al.* Randomised trial of monoclonal antibody for adjuvant therapy of resected Dukes' C colorectal carcinoma. *Lancet* 1994, **343**, 1177–1183.
36. Hoover HC, Surdyk MG, Dangel RB, Peters LC, Hanna MG. Prospectively randomized trial of adjuvant active-specific immunotherapy for human colorectal cancer. *Cancer* 1985, **55**, 1236–1243.
37. Hoover HC, Brandhorst JS, Peters LC, *et al.* Adjuvant active specific immunotherapy for human colorectal cancer: a 6.5-year median follow-up of a phase III prospectively randomized trial. *J Clin Oncol* 1993, **11**, 390–399.
38. Mamounas EP, Rockette H, Jones J, *et al.* Comparative efficacy of adjuvant chemotherapy in patients with Dukes' B and C colon cancer: results from four NSABP adjuvant studies (C-01, C-02, C-03, C-04). *Proc Am Soc Clin Oncol* 1996, **15**, 205.
39. Moertel CG, Loprinzi CL, Witzig TE, *et al.* The dilemma of stage B2 colon cancer. Is adjuvant therapy justified? A Mayo Clinic/North Central Cancer Treatment study. *Proc Am Soc Clin Oncol* 1990, **9**, 108 (abstract).
40. Gamont A, Bosset JF, Milan C, *et al.* A prospective randomized trial comparing 5FU bolus with low dose folinic acid (FUFOLld) and 5FU bolus plus continuous infusion with high dose folinic acid (LV5FU2) for advanced colorectal cancer. *Proc Am Soc Clin Oncol* 1995, **14**, 194.
41. Lokich J, Ahlgren JD, Gullo JJ, Phillips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. *J Clin Oncol* 1989, **7**, 425–432.
42. Kohne CH, Hecker H, Schoffski P, Wilke H, Schubert U, Schmoll HJ. Weekly high dose infusional (CI) 5-FU plus folinic acid (FA) has a major impact on survival in patients with advanced colorectal cancer. Results of a multivariate analysis using RECPAM. *Proc Am Soc Clin Oncol* 1996, **15**, 201.
43. Laurent-Puig P, Olschwang S, Delattre O, *et al.* Survival and acquired genetic alterations in colorectal cancer. *Gastroenterology* 1992, **102**, 1136–1141.
44. Lenz HJ, Danenberg KD, Johnson P, *et al.* p53 status and thymidylate synthase (TS) expression are associated and predict for recurrence in patients with stage II colon cancer (CC). *Proc Am Soc Clin Oncol* 1996, **15**, 215.

PII: S0959-8049(98)00253-6

Arbiter:

H.J. Schmoll

Department of Internal Medicine, Division of Haematology and Oncology, Martin Luther University Halle, Ernst-Grube Strasse 40, 06120 Halle, Germany

In Europe at least 60 000 patients with resectable colon cancer die every year from their disease. Soon after the development of 5-fluorouracil (5-FU) and from the beginning of the early 1950s, clinical trials have been performed to improve the cure rate of these patients by the use of adjuvant chemotherapy. A recent meta-analysis analysed the results of 12 079 patients treated within 29 prospective randomised trials reported from 1953 to 1993 with 5-FU-based adjuvant chemotherapy. Despite the large heterogeneity in terms of patient selection, prognostic factors, as well as schedule and dose of chemotherapy, a small but significant survival benefit was detected with an odds ratio of 0.81 (95% confidence interval (CI) 0.69–0.94), which implies an increase of 5% in survival with chemotherapy [1]. The more recent studies performed according to proper methodology and active chemotherapy (either 5-FU plus levamisol or 5-FU plus folinic acid) have unanimously proven that adjuvant chemotherapy is effective and increases the 5-year survival rate by 10–15%.