Ann R Coll Surg Engl 1995; 77: 81–84

REVIEW

Adjuvant chemotherapy for colorectal cancer

Z Rayter MS FRCS
Senior Registrar in Surgery

J L Mansi MD MRCP
Consultant Medical Oncologist

R J Leicester OBE FRCS
Consultant Surgeon

Departments of Surgery and Medical Oncology, St George's Hospital, London

Key words: Colorectal cancer; Adjuvant chemotherapy

Colorectal cancer is the second most common cancer in the Western world, and yet the survival after potentially curative excisional surgery has improved little over the last half century. Newer tumour prognostic markers are not superior to conventional Dukes' staging and there are currently no markers which predict response to chemotherapy. Adjuvant chemotherapy has had a chequered past, but recently a number of important prospective studies have demonstrated its proven benefit in patients with Dukes' stage C colorectal cancer. However, several issues still require clarification. (1) Do immunomodulators such as levamisole have a significant role in adjuvant chemotherapy? (2) Which patients derive most benefit from adjuvant chemotherapy? (3) Do prognostic markers have a role in predicting these patients? Approximately 30% of patients with Dukes' stage B cancers die of metastatic disease and the role of adjuvant chemotherapy in patients with these tumours seems worth exploring. Only a large randomised trial can give answers to these important questions. Such a trial would also encourage the widespread introduction of standard methods of surgical and pathological assessment.

Colorectal cancer is the second most common cancer in the Western world. Approximately 24 000 people in England and Wales develop this disease annually, and over half (17 223 in 1990) will die from it *(1)*. Despite advances in anaesthesia and surgical technology, the outlook has barely changed over the last half century and it is only recently that some slight improvement in survival has been made (R Doll, 7th King's Fund Forum, 1990). One of the reasons for the poor prognosis is the relatively late stage of presentation of the disease in many patients so that, in some series, only 56% of patients undergo a 'curative' resection; this figure has changed little over the last two decades *(2)*. Curative resection rates are considerably higher in specialist centres and may reach 75% of the total patient group referred, a figure which probably reflects a selected group of patients. Of patients undergoing curative resection, approximately half will die from recurrent, mostly metastatic, disease *(1)*. The stage of presentation of colorectal cancer among the general population is unlikely to change in the forseeable future unless a national screening programme is implemented. Although screening an at-risk population has been shown to shift the distribution of cancers to a more favourable stage, there is as yet no evidence that this leads to a lower mortality from colorectal cancer. Population screening studies currently nearing completion will answer this question in the near future *(3)*.

Factors which predispose to local recurrence have recently been reviewed *(1)*, and are patient, surgeon and tumour related. Patient factors such as age, sex and emergency operation probably have only a marginal influence on local recurrence or disease-free survival. The operating surgeon, however, has been clearly shown to influence local recurrence; this may be due to different perspectives as to what constitutes a curative resection, as well as completeness of excision.

Pathological factors related to the tumour are probably the most important factors influencing survival. Dukes' staging remains the most accurate predictor of outcome *(4)*. The crude 5-year survival figures vary somewhat, but

Correspondence to: Mr Zenon Rayter, Department of Surgery, Level 3, St James' Wing, St George's Hospital, Blackshaw Road, London SW17 0QT

are of the order of 90% for Dukes' stage A, 70% for Dukes' stage B, 60% for Dukes' stage C1, and 26% for Dukes' stage C2 *(4)*. A more refined histopathological staging by Jass *et al. (5)* has demonstrated an ability to increase the proportion of patients in whom outcome can be confidently predicted from 21% to 47%. This pathological staging system again emphasised the importance of lymph node metastasis as a prognostic marker and also demonstrated that the type of infiltrating margin of the tumour, the degree of lymphocytic infiltration and the extent of direct spread were also independent prognostic factors for colorectal cancer.

Other prognostic factors reported by pathologists are degree of differentiation of the tumour, the presence of vascular invasion, the presence of signet cells, and the production of mucin. A recent, albeit small study suggested that production of the MUC1 mucin is significantly higher in tumours which have metastasised *(6)*.

Much effort has been expended in the search for better prognostic markers with variable success. The prognostic significance of the DNA content of tumour cells as measured by flow cytometry is still unclear. Even in those studies in which the DNA content had prognostic significance, its predictive power was still less than that of Dukes' staging. The protein product of the tumour-suppressor oncogene p53 has been implicated in a variety of tumours. In colorectal cancer an increased level of the mutated p53 protein expressed by the tumour is associated with poor survival and correlates significantly with allelic loss on the short arm of chromosome 17, the most common chromosomal alteration observed *(7)*. The initial promise of argyrophil nucleolar organiser regions as prognostic markers in skin and lymphoid tumours has not been maintained for colorectal cancer *(8)*. It remains to be seen whether markers of response (or lack of response) to chemotherapeutic agents will be discovered, such as has been described for breast cancer *(9)*.

The outcome for Dukes' stage C1 tumours is only slightly worse than that for Dukes' stage B tumours with 5-year survival rates of 60% and 70% respectively *(4)*. This may be due to haematogenous spread, although it could be that micrometastatic spread to regional lymph nodes has already occurred but is not detected by routine histopathological techniques. Using monoclonal antibodies to cytokeratins it has recently been demonstrated that micrometastases were present in normal lymph nodes on routine haematoxylin and eosin staining, and this was positively correlated with vascular invasion *(10)*. The majority of patients who develop metastatic disease develop secondaries in the liver, mostly within the first 2 years after resection of the primary tumour. Liver metastases that become clinically evident within 6 to 24 months after resection were probably already present at the time of operation. However, because tumour cells have been shown to be shed into the portal circulation at the time of surgery *(11)*, it is possible that some patients who develop liver metastases 24 months or more after curative surgery do not have these metastases at the time of their original presentation. Most cells shed into the venous circulation are rapidly destroyed, but some survive to form micrometastases, which are initially supplied by the portal vein *(12)* until the micrometastases develop into hepatic tumour deposits, which are then principally supplied by the hepatic artery. It is therefore logical to suggest that the portal system is the route by which high concentrations of cytotoxics should be delivered in an attempt to prevent the establishment of liver metastases.

The study of Taylor *et al. (13)* was the first prospective randomised trial to test this form of adjuvant chemotherapy, and compared surgery alone in 127 patients with infusion of 5-fluorouracil (5-FU) and heparin into the portal vein at the time of surgery and for 7 days after surgery in 117 patients. Patients in the adjuvant perfusion arm of the study appeared to benefit with a 5-year survival of approximately 70% compared with approximately 45% for the surgery only patients. Subset analysis, with its inherent methodological problems, showed that the benefit in survival was limited to patients with Dukes' B colon cancer, and was not seen in patients with rectal cancer or Dukes' stage C disease. Interestingly, the difference in the survival curves did not become apparent until after 2 years' follow-up. Several other large trials reported by different centres have been inconclusive. In the largest trial reported to date, from the NSABP C-02 study of portal 5-FU infusion *(14)*, there was some advantage in disease-free survival in the active treatment group at 4 years (74% *vs* 64%; $P=0.02$), and potentially some overall survival advantage (81% *vs* 73%; $P=0.07$). There was no reduction in liver metastasis as the first site of tumour recurrence, and the authors concluded that the survival advantage probably accrued from the systemic rather than the regional effects of the chemotherapy. More recently, the results of a study by Fielding *et al. (15)* comparing portal vein infusion of 5-FU and heparin with intraportal heparin after surgery have shown that there was a significant survival advantage of approximately 16% in patients with Dukes' stage C tumours receiving 5-FU plus heparin. The current AXIS trial, which aims to recruit 4000 patients randomised to receive intraportal 5-FU or surgery alone should be large enough to produce a definitive answer as to the benefits of intraportal chemotherapy.

The role of adjuvant systemic chemotherapy has had a chequered history. Many early trials were not randomised and used a variety of cytotoxic agents, either singly or in various combinations, leading to difficulties in comparison and showing little overall survival benefit. However, a meta-analysis of all trials published up to 1986 has shed some light on to the situation *(16)*. In all the trials which employed 5-FU for at least 1 year, the overall reduction in the odds ratio of death was 0.83 (95% confidence interval 0.70–0.98%; $P=0.03$) and the absolute 5-year survival benefit was 3.4% (95% confidence interval −8.0% to 1.2%). All other combinations of drugs failed to show any significant benefit. A more recent study to combination chemotherapy (5-FU, vincristine, and MeCCNU) reported from the NSABP C-03 study

indicated that patients given chemotherapy experienced a significantly improved disease-free survival ($P=0.02$) and overall survival ($P=0.05$) compared with surgery only controls *(17)*. However, the definitive study which has really focused attention on adjuvant chemotherapy was that published by Moertel *et al.* in 1990 *(18)*. This intergroup study randomised 1296 patients with colorectal cancer; 325 with Dukes' stage B2 disease (extension of tumour into pericolic/perirectal fat) and 971 with Dukes' stage C disease. The patients with Dukes' stage B2 disease were randomised to surgery alone or surgery with 5-FU and levamisole for 1 year. The 971 patients with Dukes' stage C disease were randomised to either surgery alone, surgery plus levamisole or surgery plus levamisole and 5-FU. This study demonstrated a highly significant reduced risk of cancer recurrence of 41% and a reduction in mortality of 33% in patients with Dukes' stage C carcinoma compared with the surgery alone or surgery/levamisole group after a median follow-up of 3 years. There was also a trend for increased survival in patients with Dukes' stage B2 disease, although this did not achieve conventional levels of statistical significance. On the basis of these results, the National Cancer Institute (NCI) in the United States suggested that 5-FU/levamisole should be standard adjuvant treatment for all patients who had undergone curative resection for Dukes' stage C colorectal cancer. The latest update on this study now seems to justify the NCI's enthusiasm for this regimen and was presented at the American Society of Clinical Oncology (ASCO) in 1992 *(19)*. At a median follow-up of 5 years with an estimated 99.1% of expected recurrences and 85% of expected cancer deaths recorded, there have been 141 (45%) cancer deaths in the surgery alone group of 315 patients, compared with 100 (33%) cancer deaths in the 304 patients randomised to 5-FU and levamisole, maintaining the previously demonstrated 33% reduction in the cancer death rate ($P<0.004$). This study has been criticised for not having one arm of the trial containing adjuvant chemotherapy with 5-FU alone, and therefore does not answer questions raised about the immunomodulatory activity, if any, of levamisole. It is interesting to note that the only Dukes' stage B cancers considered to be tumours with a poor prognosis were those with extramural spread; other potential poor prognostic factors were not analysed. The results of five additional randomised trials presented at the 1993 ASCO meeting showed an improvement in relapse-free survival and/or overall survival with 5-FU and folinic acid in Dukes' stage B and C colon cancer. The NSABP study (C-03) showed a significant survival benefit for 5-FU and folinic acid given for 48 weeks when compared with MOF (5-FU, semustine and vincristine) *(20)*. A further intergroup trial, with a no chemotherapy control arm was prematurely closed in 1989 because of the results of the 5-FU and levamisole trial, which showed a 13% reduction in the relapse rate after 6 months of 5-FU and folinic acid *(21)*. Similar results were obtained from an overview of three trials, two from Italy and one from Canada *(22)*. These results suggest a proven place for adjuvant chemotherapy in Dukes' stage C patients who have undergone a potentially curative resection for colorectal cancer, although this requires further corroboration. In addition, the specific pathological criteria for adjuvant treatment need to be more clearly defined, especially in relation to Dukes' B stage tumours. There has been no prospective randomised study comparing 5-FU with 5-FU/-levamisole.

The UK Co-ordinating Committee on Cancer Research (UKCCCR) survey of treatment patterns for colorectal cancer by clinicians (66% of whom were surgeons) reported that 60% of the 600 respondents who used adjuvant chemotherapy were treating young patients who had undergone curative resection of Dukes' stage C tumours. The chemotherapy regimens used were 5-FU/folinic acid (41%), 5-FU/levamisole (35%) and 5-FU alone (24%). The majority of respondents (88%) would be willing to enter patients into a national trial of adjuvant systemic chemotherapy. The UKCCCR has set up a national trial (QUASAR) to assess the value of high-dose *versus* low-dose folinic acid in combination with 5-FU and the value of adding levamisole to 5-FU. A no treatment arm has also been included. Currently the majority of patients with Dukes' B cancer do not receive adjuvant chemotherapy. A similar situation for node-negative breast cancer also exists in the United Kingdom, although studies have demonstrated a significantly prolonged disease-free survival in poor prognosis node-negative breast cancer given adjuvant chemotherapy *(23,24)*.

It is obvious that for a significant benefit of adjuvant chemotherapy for selected patients with Dukes' B stage cancer to be demonstrated, a large number of patients will be required because few disease-related events will occur. Despite this, a prospective randomised trial of adjuvant chemotherapy should be performed as this would provide a large database which would prove useful for analysing which, if any, tumour-related prognostic factors influence response to treatment. It would also encourage the introduction of standard surgical and pathological reporting. Such a trial, comparing 5-FU/levamisole with 5-FU alone is easy to administer on an outpatient basis and is associated with minimal toxicity. Conversely, regimens employing folinic acid/5-FU can be associated with marked toxicity and require much closer supervision to detect and avoid life-threatening toxicity such as neutropenic sepsis or dehydration and renal failure secondary to diarrhoea. More has been learned recently about the putative immunostimulatory actions of levamisole *(25)*. The possibility of an interaction with histocompatibility antigens and NK cell activity is likely *(26)*. New trials of adjuvant chemotherapy incorporating levamisole should contain studies into its mechanism of action, and this would also answer the question as to whether levamisole has a synergistic effect on the action of 5-FU *in vivo*. The evidence of the benefit of adjuvant chemotherapy for Dukes' stage C colorectal cancer is now substantial. It is time that adjuvant chemotherapy in patients with Dukes' stage B colorectal cancer also be adequately evaluated.

References

1 Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, the mechanisms, management and adjuvant therapy. *Br J Surg* 1994; **81**: 7–19.

2 Gordon NLM, Dawson AA, Bennett BB, Innes G, Eremin O, Jones PF. Outcome in colorectal adenocarcinoma: two seven year studies. *Br Med J* 1993; **307**: 707–10.

3 Rayter Z, Leicester RJ. Colorectal cancer screening and surveillance. In: Allen-Mersh T, ed. *Bailey and Love's Textbook of Surgical Oncology*. London: Chapman and Hall, (in press).

4 Goligher JC. Treatment of carcinoma of the colon. *Surgery of the Anus Rectum and Colon*. 5th Edition. London: Baillière Tindall, 1984: 549.

5 Jass JR, Love SB, Northover JMA. A new prognostic classification in rectal cancer. *Lancet* 1987; **1**: 1303–6.

6 Nakamori S, Ota DM, Cleary KR, Shirotani K, Irimura T. MUC1 mucin expression as a marker of progression and metastasis of human colorectal carcinoma. *Gastroenterology* 1994; **106**: 353–61.

7 Remvikos Y, Tominaga O, Hammel P *et al.* Increased p53 protein content of colorectal tumours correlates with poor survival. *Br J Cancer* 1992; **66**: 758–64.

8 Rayter Z, Surtees P, Tildsley G, Corbishley C. The prognostic value of argyrophil nucleolar organiser regions (AgNORs) in colorectal cancer. *Eur J Surg Oncol* 1992; **18**: 37–40.

9 Rayter Z. Steroid receptors in breast cancer. *Br J Surg* 1991; **78**: 528–35.

10 Greenson JK, Isenhart CE, Rice R, Mojzisik C, Houchens D, Martin EW Jr. Identification of occult micrometastases in pericolic lymph nodes of Dukes' B colorectal cancer patients using monoclonal antibodies against cytokeratin and CC49. *Cancer* 1994; **73**: 563–8.

11 Fisher ER, Turnbull RB. The cytologic demonstration and significance of tumour cells in the mesenteric venous blood in patients with colorectal carcinoma. *Surg Gynecol Obstet* 1955; **100**: 100–6.

12 Archer SG, Gray BN. Vascularisation of small liver metastases. *Br J Surg* 1989; **76**: 545–8.

13 Taylor I, Machin D, Mullee M, Trotter G, Cooke T, West C. A randomised controlled trial of adjuvant portal vein cytotoxic perfusion in colorectal cancer. *Br J Surg* 1985; **72**: 359–63.

14 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 protocol C-02. *J Clin Oncol* 1990; **8**: 1466–75.

15 Fielding PL, 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**: 502–6.

16 Buyse M, Zelenuich-Jacqotte A, Chalmers TC. Adjuvant therapy of colorectal cancer. Why we still don't know. *JAMA* 1988; **259**: 3571–8.

17 Wolmark N, Rockette H, Fisher B *et al.* The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from the national surgical adjuvant breast and bowel project protocol C-03. *J Clin Oncol* 1993; **11**: 1879–87.

18 Moertel CG, Fleming TR, MacDonald JS *et al.* Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. *N Engl J Med* 1990; **322**: 352–8.

19 Moertel CG, Fleming T, MacDonald JS, Haller D, Laurie J. The Intergroup study of fluorouracil (5-FU) plus levamisole and levamisole alone as adjuvant therapy for stage C colon cancer. *Proc Am Soc Clin Oncol* 1992; **11**: 161.

20 Wolmark N, Rockette H, Fisher B *et al.* Leucovorin-modulated-5-FU (LV-FU) as adjuvant therapy for primary colon cancer: NSABP C-03. *Proc Am Soc Clin Oncol* 1993; **12**: 197.

21 O'Connell M, Mailliard J, MacDonald J, Haller D, Mayer R, Wieand H. An intergroup trial of intensive course 5-FU and low-dose leucovorin as surgical adjuvant therapy for high risk colon cancer. *Proc Am Soc Clin Oncol* 1993; **12**: 190.

22 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 (RCT's). *Proc Soc Am Clin Oncol* 1993; **12**: 191.

23 Fisher B, Redmond C, Dimitrov NV *et al.* A randomised clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen receptor-negative tumours. *N Engl J Med* 1989; **320**: 473–8.

24 Mansour EG, Gray R, Shatila AH *et al.* Efficacy of adjuvant chemotherapy in high-risk node-negative breast cancer: an intergroup study. *N Engl J Med* 1989; **320**: 485–90.

25 De Brabander M, De Cree J, Vandebroek J, Verhaegen H, Janssen PAJ. Levamisole in the treatment of cancer: anything new? *Anticancer Res* 1992; **12**: 177–88.

26 Goodrich KH, Alvarez X, Holcombe RF. Effect of levamisole on major histocompatibility complex class I expression in colorectal and breast carcinoma cell lines. *Cancer* 1993; **72**: 224–30.

Received 13 July 1994