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SURGICAL DEBATE

Surgical excision alone is adequate treatment for primary colorectal cancer

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This debate examines the arguments for and against the proposal that surgical excision alone is adequate treatment for primary colorectal cancer. The arguments in favour are that the results from curative surgery are excellent and that despite many trials of adjuvant chemotherapy, radiotherapy and immunotherapy, the proposed benefits remain unproven. Recent improvements in surgical technique, particularly for dissection of rectal tumours, have shown the way towards further improvement using surgery alone, and it is clear from a national survey that technical factors related to individual surgeons play a large part in determining recurrence rates. With optimum primary treatment, surgical excision alone is indeed adequate therapy. The arguments against this motion are that although a considerable number of patients do survive with surgery, the 5-year survival rate is poor when there is extensive local invasion or lymphatic metastases. Surgery starts therapy by reducing the tumour load, but other modalities are required to destroy the cells which might subsequently develop into metastases. Trial results with adjuvant therapy are encouraging, although many contain too few patients. We cannot be content with the results of treatment of Dukes' Stage B and C tumours; more trials are needed to determine the best treatment for these patients.

This debate is concerned with the management of patients with localised colorectal cancer, in other words those patients who are suitable for 'curative' surgical excision. The management of patients who do not undergo curative excision is beyond the scope of this debate. The overall 5-year survival rate after curative resection is about 50%, with wide variation between Dukes' A tumours (>90%) and Dukes' C tumours (30%). It will clearly be difficult to improve on the excellent results with surgery alone with Dukes' A tumours, but unfortunately this represents only a small percentage of patients. Even with mass screening programmes, there is still a large proportion of patients who fall in the less favourable categories of Dukes' B and C. Is surgery sufficient therapy for these patients, or should some form of adjuvant treatment be given?

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The case for the motion

The case for the motion can be summarised as follows. Surgical excision gives good results in the management of colorectal cancer. Survival rates in this disease are considerably greater than for almost all other tumours of the gastrointestinal system. Despite many attempts to demonstrate improvement in the outcome with adjuvant therapy using chemotherapeutic agents, radiotherapy or immune stimulants, there has been no conclusive evidence that these have affected the prognosis. Technical factors appear to be important in the surgery of colorectal cancer, as shown by the wide variation of survival rates between different surgeons contributing to the Large Bowel Cancer Project. Careful surgical technique can therefore achieve very good results, which renders the use of unpleasant adjuvant therapies unnecessary.

Surgical excision has been the treatment of primary colorectal cancer for over 50 years. Overall survival of approximately 50% is regularly achieved. This compares well with surgery for other gastrointestinal malignancies (oesophagus, stomach, pancreas) in which the 5-year

survival after curative excision is about 20% or less. Throughout this period there have been improvements in operative mortality and changes in emphasis in surgical technique, but the basic principle of surgical excision of the tumour and draining lymph nodes remains unchallenged. The 5-year survival after excision of Dukes' A tumour is >90%, with Dukes' B this is still about 60%, and only with Dukes' C tumour does the survival rate fall to 30%.

Many trials have been conducted into the possible benefits to be gained by the addition to surgery of adjuvant radiotherapy, chemotherapy or immunotherapy. These have been inconclusive.

Buyse *et al. (1)* performed a meta-analysis of all trials in the English language press to December 1986. There were 27 randomised trials of adjuvant therapy (excluding liver perfusion) in which crude mortality and 5-year survival were reviewed. In radiotherapy trials, 1542 patients were included but no significant benefit was demonstrated. Sixteen trials compared the results of adjuvant chemotherapy using various regimens with untreated controls, and although chemotherapy showed a small benefit, this failed to reach statistical significance. In a small subgroup of studies using 5-fluorouracil (5FU) for more than 1 year the benefit just reaches significance, but this must be accepted with caution. It is reasonable to assume that there is a tendency to favour publication of positive results so that published trials may be biased towards a greater treatment effect.

In a further review in 1989, Mayer *et al. (2)* looked at six randomised trials of combined chemotherapy for colonic carcinoma. All treatment groups included 5FU and CCNU, with or without vincristine and an immunostimulant. These were compared prospectively with controls, immunotherapy or 5FU alone. Five of these trials, including 2450 patients, demonstrated no advantage *(3–7)*. The sixth trial *(8)* showed a marginally significant advantage in favour of both chemotherapy and immunotherapy alone against controls. However, in this trial, the advantage in the immunotherapy group was due entirely to fewer coincidental cardiovascular deaths. In the combined chemotherapy group, the 5-year survival was 67%, compared with 59% in the control group. The complications of chemotherapy were considerable. Only 66% of patients completed the whole course and there was a 1% incidence of both leukaemia and myelodysplastic syndrome, presumably due to the use of CCNU.

Mayer *et al. (2)* also reviewed radiotherapy and combined chemotherapy for rectal carcinoma. In five trials of adjuvant radiotherapy, three showed a decrease in locoregional recurrence *(9–11)* and two showed no difference *(12–13)* compared with randomised controls. However, recurrence was not confirmed histologically and there was no overall survival benefit. Two trials *(4,14)* combining chemotherapy and radiotherapy demonstrated a 15% improved disease-free survival, but numbers were too small to be statistically significant and overall survival was not altered. The NSABP trial *(11)* compared postoperative chemotherapy (FUra (5FU), semustine (CCNU), vincristine) against radiotherapy or control (untreated). This demonstrated a significant benefit in disease-free survival ($P=0.006$) and overall survival ($P=0.05$) in the chemotherapy arm. However, this advantage was only seen in males, particularly those under 65 years of age, and such subgroup analysis is inherently retrospective and may be unjustified.

Adjuvant immunotherapy has been included in many trials but has proved disappointing, presumably because the antigenicity of colorectal cancer is not sufficiently different from normal colon. Recently, the use of levamisole has stimulated further interest. A randomised trial of levamisole against controls failed to show any effect *(15)*. Windle *et al. (16)* prospectively compared 5FU and 5FU with levamisole against a control group. Overall survival was 68% in the 5FU/levamisole group compared with 56% in the control group. However, the patients who received 5FU alone fared somewhat worse with a survival of 48%.

Moertel *et al. (17)* have recently used 5FU and levamisole as adjuvant treatment for Dukes' B2 and C colorectal carcinoma. They showed a significantly reduced death rate in Dukes' C lesions. However, there may have been more locally advanced lesions in the control arm and median follow-up is only 3-years. Also, as Hobbs has pointed out *(18)*, it seems reasonable to assume that adjuvant immunotherapy is most likely to be successful in patients with minimal tumour who are no longer having cytoreductive treatment. The use of non-specific immunomodulators such as levamisole with 5FU may therefore be illogical.

Factors related to individual surgeons appear to be a major determinant not only of operative mortality but also of 5-year survival *(19)*. Presumably these factors include attention to the detail of surgical excision, gentle handling of the tumour, and use of cytotoxic irrigation of the bowel ends or the abdominal cavity *(20)*. The importance of technical factors, particularly in dissection of the mesorectum, has been emphasised by Heald *(21)*, who has demonstrated a low recurrence rate after complete excision of the mesorectum, outside the plane of lymphatic drainage. Thus, it seems more appropriate to aim to improve the results of surgical excision to equal those achieved in the best hands, rather than to search for additional, perhaps harmful, adjuvant therapies.

The side-effects and complications of adjuvant therapy are frequently dismissed in published reports. Nevertheless, radiotherapy for rectal carcinoma and adjuvant chemotherapy both have unpleasant side-effects and some complications. Side-effects of radiotherapy include tenesmus and diarrhoea, and those of chemotherapy include stomatitis, diarrhoea, nausea and hair loss. The complications include radiation enteritis, bone marrow suppression, opportunistic infections and blood dyscrasias. The incidence of these side-effects and complications varies with the regimen used, but the experience of many surgeons is that they are sufficient to outweigh the supposed benefit of the adjuvant therapy in many patients.

In conclusion, surgery offers adequate therapy for many patients with colorectal cancer, and adjuvant

radiotherapy or chemotherapy have not been proved to offer any additional benefit. These treatments do have side-effects, and our efforts to improve results could best be concentrated on those areas of surgical technique which can prevent dissemination during surgery and local recurrence afterwards.

The case against the motion

The case against this motion rests on the following arguments. The 5-year survival of patients with locally invasive tumour or with local metastases (Dukes' B and C) leaves room for considerable improvement. It is conceded that surgery is the major component of therapy, but this should be seen as only the start of treatment, which should then be continued with adjuvant therapy designed to remove cells dispersed before and during the surgical operation. Although the results of many trials are inconclusive, this appears to depend more on the lack of sufficient patient numbers rather than inadequate treatment regimens. The recent publication of definite survival advantages with various forms of postoperative therapy in large studies confirms this impression. We cannot be content with the results obtained in the treatment of Dukes' B and Dukes' C tumours. Further large-scale studies are underway and it is anticipated that these will confirm the benefit of adjuvant therapy.

The many thousands of people who die annually of colorectal cancer demonstrate that surgical excision alone is inadequate treatment for the primary disease *(22)*. Despite the technical improvements of recent years, and the recognition of the importance of such factors as excision of the mesorectum, early detection and the surgeon's expertise, we appear to be stuck stubbornly with a 50% 5-year survival for operable disease *(23)*. Prognostic indicators such as Dukes' staging and tumour grade remain incomplete predictors of survival. Despite attempts at more radical cure, for example by partial hepatectomy in selected cases, we appear to be reaching the limits of what can be achieved by surgery alone.

Surgery is the mainstay of primary therapy. The goals of adjuvant therapy are the prevention of dissemination at the time of surgery and the control or eradication of distant disease. These should be achieved with minimal effect on normal tissues, minimal morbidity and optimum ease of administration. Adjuvant treatments after primary 'curative' surgery should be judged in terms of improved long-term survival rather than disease-free intervals. Properly planned and administered trials are required for this.

Cytotoxic drug schedules are empirical, as our knowledge of their *in vivo* modes of action on tumour cells is incomplete *(24,25)*. The rate of cell proliferation, and hence the chemosensitivity, is believed to be maximum when tumours are small, thus the therapeutic gain may be greater at the time of surgery than when the disease is advanced or recurrent.

Systemic 5-fluorouracil has been the most widely used single-agent therapy in colorectal cancer. Its overall success in producing improved survival has been disappointing, and must be set against its side-effects, particularly stomatitis *(26)*. However, an extensive meta-analysis of published randomised trials *(1)* in which 5FU was used either alone or in conjunction with other therapy has suggested a 5-year survival benefit of up to 5.7%. The optimum route, scheduling, duration of treatment and timing of administration of 5FU are uncertain. Other agents, such as mitomycin C or the nitrosoureas, are less successful than 5FU when used alone, and are more difficult to use safely.

Multiple-agent schedules aim to take advantage of theoretical and actual synergies between drugs. Higgins *(27)* reported a 10% 5-year survival advantage in patients with colorectal tumours treated with long-term 5FU and methyl-CCNU.

Stimulation of the immune system with BCG adjuvant therapy may produce a small survival advantage in patients with operable Dukes' B/C tumours *(28)*.

Combination of 5FU with an immune stimulant may improve these results. In a trial involving 1296 patients, Moertel *et al. (17)* reported that the combination of 5FU and oral levamisole reduced by 41% the risk of recurrence in patients who had undergone 'curative' surgery for Dukes' C colon cancer. It is too early to assess the benefit in Stage B patients. It is premature to accept that this regimen should be recommended routinely on the basis of this single study, particularly as treatment-related morbidity is considerable. Nevertheless, these encouraging results show that outcome can be improved after 'curative' surgery.

Radiotherapy is unsuitable treatment for colonic tumours. Effective radiotherapy for rectal carcinoma must be designed to minimise damage to normal tissues, particularly small bowel. Treatment outcome is judged on either prevention of local recurrence or on survival. The wide range of pre- and postoperative regimens testifies to the unsatisfactory overall results of treatment. The timing in relation to surgery, technical expertise, type of radiation, route (external or intracavity), fields, fractionation, total dosage, patient selection and manoeuvres to reduce side-effects all affect the results. The biological complexity of radiotherapy is often not fully appreciated. For example, some regimens may actually increase tumour cell proliferation as a result of complex processes of repair, redistribution and repopulation *(25,28)*. The inadequacies of conventional radiotherapy may stem more from a lack of understanding of tumour cell kinetics than from innate radioresistance in colorectal carcinomas. Recent developments may help to improve individual treatment schedules *(28,29)*.

The theoretical advantages of preoperative treatment in reducing dissemination must be set against the ensuing delay of the operation and the additional morbidity associated with irradiated tissue, as well as the possible inadequacy of the regimen. Trials such as the US Veterens Administration Surgical Adjuvant Trial *(27)* which used 20 Gy in 10 fractions over 14 days before

surgery have found a 5-year survival benefit of up to 13% with radiotherapy. Meta-analysis of nine trials of preoperative radiotherapy suggested a possible survival benefit of up to 9% (*30*).

The place of postoperative radiotherapy also remains controversial. Anecdotal evidence indicates that some tumours are curable by radiotherapy. However, three randomised trials showed no benefit of 40–50 Gy treatment given postoperatively (*17*). A trend to survival benefit and reduced local recurrence for patients with Dukes' C rectal tumours must be set against serious morbidity, which may affect 10% of treated patients. Meta-analysis of four trials of postoperative radiotherapy suggested a possible survival benefit of up to 11% (*30*).

The combination of low-dose preoperative radiotherapy with 40–50 Gy postoperative treatment is designed to reduce the risk of tumour dissemination at surgery, while minimising tissue damage preoperatively. Although there may be theoretical advantages to a combined chemotherapy/radiotherapy regimen, the combination of 5FU and radiotherapy (*10,31*) is not well tolerated by patients, and may even reduce survival. Such regimens cannot presently be recommended (*32*).

An alternative approach is to concentrate chemotherapy where metastases are most likely, in the portal circulation and abdominal cavity. Taylor *et al.* (*33*) have shown some advantage to patients with Dukes' B colon tumours using 5FU for hepatic perfusion by the intraportal route starting at operation and continuing postoperatively. They reported overall deaths reduced by 50%, with 26 of 111 treated and 54 of 133 untreated controls dying in their randomised study (*33*). Five subsequent studies, mostly reported as abstracts, and reviewed elsewhere (*30*), have included 1263 patients. Mortality was reduced by 23% (95% CI = 13%) in the treatment groups. Overall, intraportal 5FU reduces mortality by 33% (Table I). A large trial (*30*) has recently been started in an effort to confirm the merits of this treatment.

A recent review examined the theoretical basis of intraperitoneal adjuvant chemotherapy (*34*). The penetration of systemically administered cytotoxic agents into the peritoneal cavity is low, and it is likely that malignant cells shed into the peritoneal cavity during operation are the source of local recurrence. Unfortunately, the only clinical study of intraperitoneal 5FU in colon cancer (*35*) failed to show any advantage in terms of survival against a control group given intravenous 5FU. There was a reduction in intraperitoneal recurrences in the treated group, so it seems that this form of therapy may merit further investigation.

Table I. Results of meta-analysis of trials of adjuvant therapy for colorectal cancer. From the AXIS Trial handbook (reference 30).

Mode of therapy (number of trials)	*Reduction in mortality (%) (95% confidence limits)*
Prolonged single agent CTX (12)	10 (7)
Prolonged multiple agent CTX (7)	14 (7)
All CTX (19)	12 (5)
Preoperative RT (9)	9 (7)
Postoperative RT (4)	14 (11)
All RT (13)	11 (6)
Portal vein infusion (6)	33 (11)

CTX: chemotherapy; RT: radiotherapy

Future developments in molecular biology, the use of monoclonal antibodies for targeted immunotherapy and diagnosis, and improvements in analytical technology may ultimately provide some additional benefit for the patient. The variety of adjuvant techniques currently in use, or being assessed for their effectiveness is further evidence that surgical therapy alone is considered by many investigators to be inadequate primary treatment for localised colorectal cancer.

Although the present status of adjuvant therapy is perhaps unsatisfactory, it is clear that many patients could be helped by some form of adjuvant therapy in addition to primary 'curative' surgery. Recent US NIH consensus advice suggests that TNM stage 1 disease (Dukes' A) does not require any adjuvant therapy, and that stage II (Dukes' B) disease should be treated only in the context of clinical trials. Levamisole and 5FU are recommended for stage III colon cancer, if the patient is not to be enrolled into an alternative controlled trial. A recent editorial recommended that adjuvant therapy after surgery for rectal cancer (Stage II/III) is appropriate with postoperative 5FU and methyl-CCNU and radiotherapy at 45–55 Gy to the pelvis (*36*).

Meta-analysis of published trials (*1,30*) has suggested that a small survival benefit does exist for all types of adjuvant therapy, but the optimum protocols are not known (Table I). However, a small survival benefit of adjuvant treatment will help large numbers of patients with such a common disease.

Chairman's comments

We can all agree that surgical results after excision of Dukes' A colorectal carcinoma can hardly be improved. The management of Dukes' B and C tumours requires some consideration. Clearly, there is room for improvement in the reported survival rates. The question at issue is not really whether surgery is adequate therapy for these patients (for many of them it clearly is not), but whether there is any adjuvant therapy that can confer benefit in terms of survival, without incurring unacceptable side-effects. There is now a growing body of evidence, outlined above, that there may be a small percentage improvement in survival with some relatively innocuous adjuvant therapies. Side-effects are reduced, and efficacy improved when these therapies are directed to the sites of likely recurrence. For this reason the current AXIS trial (*30*) is to be welcomed and should be supported by all surgeons who would like to see an improvement in the results of surgical therapy for colorectal cancer. By the recruitment of a sufficiently large number of patients in conditions approximating closely

to routine practice, this trial should be able to tell us whether regional chemotherapy and local radiotherapy have any role in the management of colorectal cancer.

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