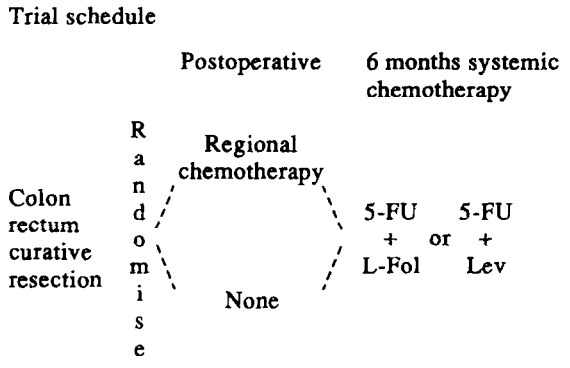

Figure 1. Schedule of EORTC trial Gl 40911. Rectum: radiation should be administered either before surgery, or, if not, decision for postoperative radiotherapy should be made prior to randomisation. 5-FU, 5-fluorouracil. L-Fol, levo-folinic acid; Lev, levamisole (see protocol for exact drug dosages).

30%, 2000 patients need to be randomised. The hope is that this will become the largest trial ever conducted in Europe on this subject. Oncologists in Europe can only compete with US investigators by conducting large-scale international studies with original rationale, and not with small regional or even national studies that merely try to reproduce American data.

Therefore, the EORTC trial with its original design should be strongly supported, and European investigators can more effectively contribute to progress in the adjuvant treatment of colorectal cancer by entering their patients in this study.

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Adjuvant Treatment of Colon Cancer

I. Taylor

WILS AND COLLEAGUES (pp. 578–579) make a plea for large trials to determine the efficacy of adjuvant treatment in colon cancer—and who could possibly disagree. There is no shortage of small or moderate sized trials and these have appeared at regular intervals since the early 1960s. However, controversy still exists. Even though meta-analyses and overviews demonstrate a probable benefit for certain regimes, the degree of magnitude is likely to be modest at best. Single large trials are still required and the results of on-going ones awaited with great interest. To demonstrate a moderate (10%) improvement in survival will require randomisation of several thousand patients whereas most available studies have included only a few hundred patients, and

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are unlikely to demonstrate benefit with any significant degree of confidence. This dilemma has been recognised in recent years, and has resulted in the setting up of large multicentre trials. The UK AXIS (Adjuvant X-ray and Infusion Study) is an example of one such trial designed to determine the efficacy of intraportal chemotherapy (with or without radiotherapy for rectal cancer). The data monitoring committee for this trial has recently reviewed data from the first 2200 patients and recommends continuation.

Undoubtedly, the recent trials of systemic chemotherapy using 5-fluorouracil (5FU) and levamisole or 5FU and leucovorin are providing exciting data. These regimes require 6–12 months of treatment and are commenced approximately 6 weeks postoperatively. Important questions remain relating to the optimum dose, the best combination and the minimum length of treatment likely to provide survival benefit. In order to answer them, there is a need for even more prospective randomised trials.

There is also evidence to suggest that adjuvant chemotherapy should be commenced in the early postoperative period (even intra-operatively) to achieve optimum responses. The patient may indeed be at greatest risk of developing micro-metastases during the peri-operative period and high-dose chemotherapy at this stage may be of relevance. The protocol described by Wils and colleagues, and organised in collaboration with the EORTC is designed to address two questions. The first relates to the role of early locally directed peri-operative treatment and the second to the optimum regime of subsequent systemic chemotherapy. Early regional chemotherapy can be delivered either by portal vein infusion or by intra-peritoneal chemotherapy. It is feasible that this study could be combined with the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) AXIS trial with appropriate patients undergoing a second randomisation to determine which systemic chemotherapy regimen (either 5FU and leucovorin or 5FU and levamisole) should be given. Collaboration of this type would undoubtedly increase patient accrual and enable important questions to be answered quickly.

The physical barrier between the U.K. and continental Europe has now been breached, and surely the time has arrived for clinical researchers to collaborate on a pan-European scale. If this could be achieved, then one of the main inhibiting factors in randomised trials, the inordinate length of time required to accrue large numbers of patients, could be overcome. It is opportune for the EORTC and the UKCCCR to join forces in trials relating to colorectal cancer.

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Papers

Serum p53 Auto-antibodies: Incidence in Familial Breast Cancer

J.A. Green, B. Mudenda, J. Jenkins, S.J. Leinster, M. Tarunina, B. Green and L. Robertson

Inactivation of the p53 gene, which codes for a tumour suppressor protein, is known to occur in the majority of human malignancies. An ELISA technique has been developed which has detected auto-antibodies to p53 in the serum of 25.6% of 176 women with breast cancer, considerably higher than previously reported with an immunoblotting technique. The incidence of auto-antibodies in those cases with a family history of breast cancer was 9.1%, compared to 29.4% in those with no family history ($P=0.029$). In women without clinical breast cancer, 4 out of 36 (11.1%) of those with a positive family history were seropositive, compared to 1 out of 73 control women. Auto-antibodies were more frequently seen in the serum of breast cancer patients whose biopsies demonstrated overexpression of p53 protein. We conclude that auto-antibodies to p53 may have a role in the molecular characterisation of familial breast cancer.
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INTRODUCTION

THE PRODUCT of the p53 gene is a nuclear protein which has an important role in regulation of the growth of both normal and malignant cells, and may act as a stop or checkpoint in the late G_1 phase of the cell cycle [1]. Transfection of mutant p53 into immortalised primary human bronchial epithelial cells results in increased tumorigenicity [2], while the insertion of the non-mutated p53 gene into human cancer cell lines has been shown to cause both suppression of growth and reversal of the malignant phenotype [3]. Mutation in the p53 gene is one of a number of related genetic changes in the development of malignancy in a wide range of human tumour types, and may result in the