Further studies are required to identify those factors which contribute to high local recurrence rates and are amenable to treatment.

312
PRE- AND POSTOPERATIVE RADIOTHERAPY IN THE PREVENTION OF LOCAL REGIONAL RECURRENCE OF RECTAL CANCER

B. Glimelius
Department of Oncology, University of Uppsala, Akademiska sjukhuset S-751 85 Uppsala, Sweden

In patients with rectal carcinoma, pre- and postoperative radiotherapy has been used in addition to surgery in order to decrease the local recurrence rates and possibly improve survival. The conclusions that can be reached after results achieved in 18 randomized trials including more than 7000 patients are that using preoperative radiotherapy, a clear dose-response relationship is present. At comparable doses, preoperative radiotherapy is more efficient than postoperative in reducing local failures. This has also been confirmed in the only trial comparing preoperative with postoperative radiotherapy. In order to reach similar efficacy, 15 Gy higher dose is required postoperatively. Neither approach alone has had any significant influence on survival in individual trials, although it is likely that a survival benefit will be seen after moderate dose preoperative radiotherapy. Toxicity profiles, both acute and late also favour a preoperative approach, although inappropriate techniques will result in unacceptably high toxicity levels. Further research should focus on timing the most optimal chemotherapy in addition to preoperative radiotherapy.

313
COMBINED RADIO-CHEMOTHERAPY AS ADJUVANT TREATMENT OF RECTAL CANCER. RATIONAL RESULTS AND POSSIBLE FUTURE DIRECTIONS

J.F. Bosset, J.C. Horiot, J.J. Pavy, G. Mantion, E.P. Pelissier
Dept Radiotherapy, CHU Minjoz, 25030 Besancon, France

After curative surgery, the prognosis and the patterns of failure of colon and rectal cancers are quite different. The overall 5 year survivals are respectively 55% and 45% with a median time to the diagnosis of recurrence of 18 and 13 months. Liver and peritoneal metastases account for 60% of the recurrences of colon cancer whereas local failures (LF) represent about 10%. On the contrary, LF, liver and lung metastases are equally distributed and account each for 30% of rectal cancer failures. These figures explain why adjuvant treatment should be adapted to the site of the primary. The aims of adjuvant treatment in rectal cancer are both survival and local control, keeping acute and late toxicity to an acceptable level.

The postoperative approach permits to select patients on the basis of the pathological findings. None of the four randomised published trials demonstrated that a 50 Gy postoperative dose is able to decrease significantly the LF rate in Dukes B and C patients. Increasing the dose seems inappropriate for multicentric trials and will certainly conduct to an increased acute and late toxicity.

Combined postoperative radiotherapy and chemotherapy produced a benefit in some studies at the expense of a high rate of acute toxicity and treatment interruption in about 20–30% of the patients. Moreover, the treatments induced unacceptable high rate of late toxicity after sphincter sparing procedures.

On the other hand, moderate dose, in the 25–35 Gy range, preoperative irradiation significantly reduced LF in four large randomised trials totalling more than 3000 patients. This reduction in LF had the same magnitude for all Dukes' stages (50 to 65%). Furthermore in the latest report of the Stockholm 2 trial, a definite increase in overall survival was observed in patients treated by preoperative irradiation.

The comparison of the therapeutic ratio issued from the post or preoperative adjuvant therapeutic approach, definitely favours the preoperative irradiation.

The next step is to evaluate in selected patients (T3–T4 resectable stages), the optimal integration of chemotherapy with preoperative irradiation and whether post operative chemotherapy should be added. These two questions are addressed in the current EORTC 22921 protocol. Beside the main goal of this trial, increase in overall survival, the evaluation of sphincter function and quality of life have also been selected as a new end point in this trial.

314
NO ABSTRACT

315
PREDICTION OF RADIOSENSITIVITY: MOLECULAR AND CELLULAR ASSAYS

A.C. Begg
Division of Experimental Therapy, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Accurate prediction of response to conventional radiotherapy can guide the radiation oncologist to modify treatment for individual patients, or patient groups, to increase the chance of cure and limit morbidity. One of the most important parameters affecting radiotherapy outcome is intrinsic radiosensitivity. This presentation will assess the molecular and cellular assays available at present and those being developed. Molecular assays can be divided into those measuring some aspect of DNA damage and those measuring the presence, mutation or expression of genes suspected to be involved in radiosensitivity. The performance of some assays has been tested by comparing results with cell killing. Almost none of them has yet been tested in clinical trials of radiotherapy for predictive potential. Mixed results have been obtained with DSB induction and repair, some finding a good correlation with cell kill, but with many exceptions. Much progress has recently been made in discovering critical genes in DSB repair (e.g. ku70, ku80, scid). In addition, several oncogenes and supressor genes have been associated with radiosensitivity changes. However, the complexity of the cell's response to radiation hinders the choice of genes to screen for radiosensitivity prediction, although there is now clear hope for the future. The most trusted cellular assay is that of colony formation after *in vitro* radiation. Reports of positive correlations with radiotherapy outcome exist, although more studies and more rapid assays are needed. Alternatives are those for chromosome damage, apoptosis induction and cell cycle blocks. Results of their predictive potential can be expected in the next few years.

316
APOPTOSIS: RELEVANCE TO RADIOTHERAPY

W.G. McKenna, R.J. Muschel
Departments of Radiation Oncology, Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, PA 19104, U.S.A.

Apoptosis is a central part of normal development. Under some circumstances, however, apoptosis can also be seen in response to a number of abnormal stimuli which include hormonal or growth factor manipulations, aberrant gene expression, particularly of oncogenes or anti-oncogenes, and in response to a number of toxic agents including chemotherapeutic drugs and X-rays. It is for these latter reasons that apoptosis has generated great interest among oncologists and cancer biologists both because of the potential insights it may yield into carcinogenesis and in the hope of generating new strategies for cancer treatment. Control of apoptosis, like carcinogenesis, seems to be linked to some of the genes which also regulate cell cycle progression. Thus, the Rb, p53 and myc oncogenes which in the normal cell are involved in cell cycle regulation also are involved in the control of apoptosis. There is some evidence that the radiosensitivity of cells may be related to their rate of spontaneous apoptosis or to the extent of induction of apoptosis by X-rays. Our group has focussed on the relationship of cell cycle perturbations by radiation to the induction of apoptosis by X-rays. These studies suggest several new areas for the development of new therapeutic strategies which will be discussed.

317
THE IMPACT OF DNA REPAIR IN RADIOTHERAPY

T.J. McMillan
Radiotherapy Research Unit, Institute of Cancer Research, Sutton, Surrey SM2 5NG, U.K.

DNA repair has an impact on radiotherapy at two levels. 1: The prolongation of treatment, either by fractionation or decreasing dose-rate allows a greater time for repair during the treatment period resulting in a reduced cytotoxicity in both tumour and normal tissues. 2: DNA repair is an important determinant of variation in cellular sensitivity. Thus variation in normal tissue damage and tumour response may be determined to a significant degree by DNA repair capacity. There have been significant advances recently in the understanding of the mechanisms and genetics of DNA repair in mammalian cells. This includes the identification of the xrcc5 gene as being part of a DNA dependent protein kinase and its association with V(D)J recombination. Such progress