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

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

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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.

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

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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.

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NO ABSTRACT

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PREDICTION OF RADIOSENSITIVITY: MOLECULAR AND CELLULAR ASSAYS

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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.

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APOPTOSIS: RELEVANCE TO RADIOTHERAPY

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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.

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THE IMPACT OF DNA REPAIR IN RADIOTHERAPY

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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

holds out promise for the prediction of radiosensitivity of normal and tumour cells and for the rational modification of the radiation response.

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THE EFFECT OF RADIATION ON CELL CYCLE PROGRESSION AND ITS RELATION WITH RADIOSENSITIVITY

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Ionizing radiation can block cell cycle progression of mammalian cells in G2, at the restriction point (in G1) or during initiation of DNA synthesis (G1/S). These checkpoints are thought to facilitate the repair of lesions that would otherwise result in chromosome mutations and possible aberrant cell growth or cell death. Abnormalities in the pathways of checkpoint control in yeast and higher eukaryots have been found to affect the sensitivity to DNA damaging agents.

In mammalian cells cyclins and cyclin dependent kinases are key proteins in the mechanisms of cell cycle control. Radiation can decrease the expression of cyclin B or prevent dephosphorylation of the cdc2 kinase and thereby inactivate the MPF complex and arrest cells at the G2/M border. In addition radiation can induce p53 expression and subsequent induction of p21 which will inhibit cyclin D and E/CDK complexes and arrest cells in G1. Analogies of these mechanisms have been found in yeast where the relevance of checkpoints is now investigated.

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STRATEGIES TO OFFSET TUMOR CLONOGEN PROLIFERATION

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Tumor clonogen repopulation is considered a major obstacle of curing certain cancers with radiotherapy. Strategies to overcome this phenomenon include shortening of radiotherapy and administration of drugs that inhibit cellular proliferation. The former is achieved with concomitant boost technique in which the coned-down boost is delivered as second daily irradiations *during* rather than *following* the wide-field treatment. A 72% local-regional control rate was achieved in >150 patients treated for T2-3 oropharyngeal cancers.

We developed a strategy for more advanced tumors in which cisplatin and 5-FU were given during the boost phase of radiation. This tactic restricts the intensified treatment to gross disease and limits the volume of normal tissues exposed to the combined therapy, thereby allowing for delivery of greater doses of cytotoxic drugs. A phase I study showed that 10 mg/m^2/day of cisplatin and 400 mg/m^2/day of 5-FU were tolerated. Updated results and details of dose-limiting toxicity will be presented. Based on this experience, a combination of fludarabine (F-ara-A) and radiation was designed. F-ara-ATP competes with dATP for taking up by elongating DNA strands and upon incorporation acts as an effective chain terminator. Therefore, it would potentiate radiation effects not only by suppressing cell proliferation but also by inhibiting repair of radiation-induced DNA lesions. A phase I study will begin soon.

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PREDICTIVE ASSAYS: A USEFUL TOOL?

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In recent years, numerous studies have been performed to evaluate whether the tumor response to radiotherapy (RT) in clinic might be predicted by biological parameters, known to be associated with radioresistance of experimental tumors. In that aim, assays have been developed to analyse tumor hypoxia, cell kinetics, intrinsic radiosensitivity, repair or proliferating genes, apoptosis... So far, promising results have been obtained in cervical carcinoma treated by RT, showing that PO_2 measurements, intrinsic radiosensitivity (SF2), and the % of apoptosic cells were predictive of tumor outcome. Some studies have also evaluated the predictive value of the potential doubling time and labeling index, especially in head/neck carcinoma treated with conventional RT. Promising results have also been reported in this field. However, these assays will prove to be useful in clinical practice, if it is possible to achieve strong statistical significance in multivariate analysis, obtained in large series of patients and taking into account known predictive factors such as tumor size and nodal status. It should also be pointed out that many factors are likely to be involved in the radioresistance of human tumors, and a multiple approach to predictive assays will be required in the future trials.

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HYPERFRACTIONATED (HF) AND ACCELERATED (AF) RADIOTHERAPY (RT) IN HEAD AND NECK CANCERS: FACTS FROM TRIALS, IMPACT ON STANDARD PRACTICE

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From 1978 to 1995, 2165 patients (pts) were entered in trials of HF or AF RT. Two randomized trials in head and neck cancers accrued 867 pts: Protocol 22791 (356 pts, 1980–87) compared CF (70 Gy/35–40 fr/7–8 wks) to HF (80.5 Gy/70 fr/7 wks) in T2–T3, N0–N1 oropharyngeal carcinoma. Locoregional control (LRC) was higher ($P = 0.01$) in HF versus CF. At 5 years, 56% of the pts are LRC free with HF versus 38% with CF. There was no difference in late normal tissue damage between the two treatment modalites. Protocol 22851 (511 pts, 1985–95) compared AF (72 Gy/5) fr/5 wks) to CF (70 Gy/35 fr/7 wks) in T2 T3 T4 head and neck cancers (hypopharynx excluded). Acute and late toxicity were increased in the AF arm. A better local control ($P = 0.01$) and progression free survival ($P = 0.004$) were achieved in the AF arm. These two trials show evidence of the major improvement brought by schemes based upon new radiological concepts. At 5 years, a 61% LRC is observed with AF versus 47% with AF. The progression free survival data suggest that the improvement in LRC contributed to a decrease in distant metastases in the AF arm.

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CHART—THE IMPLICATIONS OF EARLY RESULTS OF THE RANDOMISED CONTROLLED TRIALS

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Randomised controlled trials of CHART compared to conventional radiotherapy in non-small cell carcinoma of the bronchus and squamous cell carcinoma of the head and neck commenced in April of 1990 and entry was completed in March of 1995 when 563 and 918 patients respectively had been entered. Patients were entered by 13 centres at Bristol, Cardiff, Clatterbridge, Dresden, Glasgow, Jonkoping, Leeds, Mount Vernon, Nottingham, Portsmouth, The Royal Marsden, Sheffield and Umea. In both studies the CHART arm received a total of 54 Gy intersection dose (ID) in 36 fractions over 12 consecutive days treating 8.00 am, 2.00 pm and 8.00 pm inclusive of Saturdays and Sundays.

In carcinoma of the bronchus the patients in the conventional arm received 60 Gy ID in 6 weeks and in the head and neck arm 66 Gy ID in $6\frac{1}{2}$ weeks all in 2 Gy fractions. For the first 3 years a quality of life assessment was carried out together with a health technology survey which costed both conventional and CHART radiotherapy. A quality assurance programme ensured a high standard of care at each centre.

A Data Monitoring Committee chaired by Professor R.L. Souhami supervised the two studies. Tumour control, survival and morbidity data will be available in June of 1995.

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RISK ASSESSMENT AND RISK MANAGEMENT IN FAMILIAL PREDISPOSITION TO BREAST CANCER

M. Baum

Risk factors for breast cancer are usually expressed as relative rates, but is essential in counselling women that the relative risks are translated into absolute values in order for women to plan their lives appropriately and in the cost benefit analysis of the various preventive regimes that might be considered. Thus at one extreme there might be a 30 year old woman whose mother developed breast cancer at around the menopause and has a late first pregnancy whose relative risk might be considered 2.5 which in absolute terms might translate into a 5% hazard for developing breast cancer before the age of 50. At the other extreme would be a woman of a similar age where genetic linkage studies suggest there is a dominant gene inherited through the germ line with an 80% penetrance. She would have a 40% chance of developing breast cancer before the age of 60 and thus about a 1 in 5 chance of dying of the disease. In the first instance with appropriate counselling the woman in question might choose to live with the risk whereas at the other extreme the woman might rationally accept the offer of prophylactic mastectomy. Of course