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