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BIOLOGIC BASIS FOR HYPER- AND ACCELERATED FRACTIONATION. Withers, H.R. Radiation Oncology and JCCC, UCLA, Los Angeles, CA 90024-1714, USA.

There are 2 quite distinct ways of improving the therapeutic differential with fractionated dose radiotherapy: a) reduced dose per fraction (hyperfractionation), and b) reduced overall treatment duration, that is, increased dose intensity (accelerated treatment).

Hyperfractionation exploits both the greater repair capacity of the slowly-responding normal tissues and the self-sensitizing effect of division cycle related variations in radiosensitivity which occur in proliferative tissues (tumors), but negligibly in non-proliferative normal tissues. An advantage has been established in nonrandomized and randomized studies.

Increased dose intensity reduces the previously-underestimated effect of accelerated growth of tumor clonogens which begins during a standard course of radiotherapy. Even though the visible tumor mass is shrinking, an effect of rapid accelerated growth has become obvious in many nonrandomized studies.

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**PRESENT STATUS AND UPDATED RESULTS OF THE TRIALS ON HYPERFRACTIONATION (HF) AND/OR ACCELERATED FRACTIONATION (AF).**

J.C. Horiot on behalf of the EORTC cooperative group of Radiotherapy.

From 1978 to March 1993, 2047 patients (pts) were entered in clinical studies on various schemes of HF and AF compared to classical fractionation (CF). This presentation is limited to 2 randomized trials in head and neck cancers with a total of 807 pts. Protocol 22791 compared CF (70 Gy/35-40 fr/7-8 wks, using 2 fr.x1.15 Gy/day) in T2-T3, No-N1 < 3 cm in oropharyngeal carcinoma. 356 pts were entered from 1980 to 1987. Locoregional control (LRC) was significantly higher (p=0.01 logrank) after HF compared with CF. At 5 years, 56% of pts are LRC free in the HF arm as compared to 38% in the CF arm. The treatment regimen was an independent significant prognostic factor for LRC (p=0.007 logrank). This improvement of LRC was responsible for a trend to an improved survival (p=0.07 logrank). There was no difference in late normal tissue damage between the 2 treatment modalities. In protocol 22851, a short first course (28.8 Gy/18 fr/8 days) allows normal tissue repopulation during an early rest period (between day 9 and day 20) before resuming the second course in 4-5 wks with a cumulated total dose of 72 Gy/45 fr. From 1985 to March 1993, 451 pts were entered, the control arm being CF. Cell kinetics evaluation is part of the study. The most striking result is that the pts with fast growing tumors (short pre-treatment Tpot) treated with CF had the worst local control. Conversely, pts with Tpot <4.5 days receiving AF had the same outcome than pts with Tpot > 4.5 days receiving CF. These interim results seem to confirm the radiobiological predictions.

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CONTINUOUS, HYPERFRACTIONATED, ACCELERATED RADIOTHERAPY (CHART)

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CHART was introduced in January 1985 to overcome tumour cell repopulation and so to increase the rate of cure by completing all radiotherapy in 12 days. A second objective was to reduce the incidence of late morbidity by using a small dose per fraction. By April 1993 a total of 468 patients, mainly with head and neck, bronchial and oesophageal carcinoma, had been treated at Mount Vernon. The results achieved in the pilot group were compared with those in comparable cases given conventional treatment. CHART appeared to achieve favourable tumour responses combined with a lowered incidence of late radiation change. Randomised controlled trials initiated by the Medical Research Council, the Cancer Research Campaign and the Department of Health began to accrue patients in April 1990. By April 1993, 13 European centres had entered 653 cases to the head and neck study and 358 to one in bronchial carcinoma. Entry to these studies is planned to be concluded in March 1994.

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CLINICAL EXPERIENCES IN MULTI-INSTITUTIONAL TRIALS-RTOG

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Since 1977, the Radiation Therapy Oncology Group (RTOG) has been engaged in clinical trials of altered fractionation radiotherapy. Disease sites studied included the lung, head and neck, brain, bladder, cervix, melanoma, pelvis, liver and brain metastases.

Results of Phase I-II studies of hyperfractionation (HF) clearly demonstrated that total doses higher than those used in conventional fractionation (CF) can be achieved with acceptable acute toxicity and no significant increase of late toxicity. Comparisons with previous RTOG studies using CF suggested a benefit in overall survival with HF in the lung. A clear dose-response relationship was evident in lung with 69.6 Gy superior to lower doses with HF and 60 Gy with CF. In malignant glioma, best survival was seen in patients receiving 72 Gy; survival decreased with increase of dose >72 Gy. In head and neck cancer, 2-year local-regional control was 25% for the assigned dose of 67.2 Gy compared to 43-45% for an assigned dose of 72-81.6 Gy (P=0.01). Interfraction interval < 4.5 hrs was associated with higher incidence of grade 4+ toxicity. In advanced cervical cancer, there were less late effects with HF than historical CF.

The results of these phase I-II studies led to a number of phase III trials. In the lung, two phase III trials were completed recently. One compared HF to CF + chemotherapy in NSCLC; the other compared chemotherapy (CT) + CF to CT + accelerated fractionation (AF) in limited SCLC. Other phase III trials in progress are comparing CF to HF and/or AF in malignant glioma, head and neck cancer and brain metastases. Results of these phase III trials should establish whether altered fractionation is better than CF for the different disease sites.