normal tissues. We have demonstrated enhanced cell kill using courses of 0.4-0.5 Gy two or three times per day compared with single daily doses of 1.2-1.5 Gy in vitro. We term such successive low-dose treatment "ultrafractionation". Optimal HRS "resensitisation" can be achieved with interfraction intervals greater than 4 hours. Conclusions: Our data suggest the use of very low doses per fraction in ultrafractionation may offer a real therapeutic gain over conventional treatment in some tumours with higher than average SF2, by exploiting low-dose hypersensitivity.

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The role of apoptosis in radiation response

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Cell death after exposure to ionizing radiation generally occurs either through unrepaired DNA damage and subsequent chromosome breaks associated with mitotic death or through induction of "Programmed cell death" (apoptosis). Radio-induced apoptosis is an active process requiring endonuclease activation and is regulated by numerous genes and pathways, which are frequently impaired in cancer cells. Some genes are pro-apoptotic (ex: p53) and others anti-apoptotic (bcl2). There are no specific aspects regarding the genetic regulation of apoptosis after ionizing radiation, as compared to apoptosis induced by other agents. In tumor cells, the proportion of cells which enter into apoptosis after irradiation is variable according to the cell type and the degree of genetic alterations. For example p53 may or may not have an impact on radiation-induced apoptosis, depending on the alterations of other regulatory genes. Since many apoptosis pathways are frequently disrupted in cancer cells (p53 mutation, Fas/Fas Ligand abnormalities etc...), targeting apoptosis to restore cell death after ionizing radiation is hence very appealing. Many examples have been studied successfully and some of them will be presented at the meeting.

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Hypoxia and its modification

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It is a common feature that solid tumors outgrow their vasculature and that the tumor cells thereby become hypoxic due to diffusion-limited access to oxygen (so-called chronic hypoxia). In addition, fluctuations in tumor blood flow due to temporary closure of blood vessels may create acute (transient) hypoxia. The occurrence of tumor hypoxia has been widely established by measurements of oxygenation status and has shown to be a common feature in solid tumors.

The presence of hypoxia in viable tumor cells creates a problem since such cells are resistant to cancer therapy, especially radiotherapy, as the full effect of ionizing radiation demands the presence of oxygen. In addition, recent research has demonstrated that hypoxia turns on genes that tend to make tumors more aggressive and increase their metastatic behavior. Hypoxia is not related to factors such as tumor size, grade, etc. But it represents an independent feature of poor prognosis. This also includes the indicators of indirect hypoxia – such as low hemoglobin values, which, among other indicators, have been found to be associated with poor outcome to radiotherapy.

As a consequence of these findings, several strategies have been used to overcome hypoxia in an attempt to improve the therapeutic outcome. Hypoxic modification of radiotherapy has been intensively studied in clinical trials over the last 30 years. The use of normobaric and hyperbaric oxygen, hypoxic cell radiosensitizers (drugs that mimic the effect of oxygen), and increase of hemoglobin concentration (by blood transfusion or EPO) are among the methods studied. Some benefit of hypoxic modification has been found in squamous cell carcinomas (especially head and neck) and, although the overall improvement in local control and consequential survival is of moderate magnitude, meta-analysis has clearly demonstrated that significant improvement can be achieved. Better identification of patients who may need hypoxic modification is needed in order to employ a more aggressive therapeutic strategy, but such methods are not yet available.

The presentation will provide an overview of the trials performed so far and an indication of optimal strategies for future studies of hypoxic modification, especially in attempts to improve the outcome of radiotherapy in certain tumor types.

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TGF-b1 and radiation-induced fibrosis: a key regulation step and a specific therapeutic target

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Fibrosis is a frequent sequel of cancer treatment in normal human tissues. The main cellular component of the fibrotic tissue is the myofibroblast, an activated type of fibroblast which deposits the scar tissue. We will present data on the role played by TGF-b1 in fibrosis of the skin induced by radiotherapy. The effects of TGF-b1 on myofibroblasts will be addressed, as well as the activity in these cells of the Smad proteins, which transduce the signal of TGF-b1 from its receptor to its nuclear targets. Recent data concerning the treatment of established radiation fibrosis will be also presented, as well as the possible mechanisms involved in fibrosis regression. These results show that the TGF-b1 pathway may constitute a specific target for antifibrotic agents such as antioxidants, and that the down regulation of TGF-b1 activity results in desactivation of fibrosis myofibroblasts.

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Relevance of regional chemotherapy in colorectal liver metastases

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Metastatic progression of colorectal cancer occurs in up to 70% isolated in the liver. After diagnosis less than 10% of liver metastases are suitable for surgery. Systemic chemotherapy was found to be ineffective in the treatment of unresectable hepatic metastases. For this reason, intraarterial chemotherapy was introduced as treatment alternative to the systemic chemotherapy. Long-term intraarterial chemotherapy regimens with FUdR (floxuridine) in patients with colorectal liver metastases, using implantable pumps and ports, resulted in improved response rates, which was confirmed by several randomized trials. However, an improvement in median survival has not yet been demonstrated after regional chemotherapy of hepatic metastases. Since the intraarterial therapy with FUdR had been reported to result in a high rate of local toxicity, 5-FU (5-Fluorouracil) was introduced into regional chemotherapy of the liver. A randomized trial demonstrated superiority of intraarterial 5-FU versus intraarterial FUdR therapy, but no benefit versus systemic treatment. The median time to progression among 168 patients treated with HAI 5-FU/LV, iv 5-FU/LV, and HAI FUdR was 18.7 months, 17.6 months, and 12.7 months, respectively. A nearly two fold increase in time to progression as well as a survival benefit was reported only among those patients with an intrahepatic tumour burden of <25% who were treated with 5-FU/LV via HAI. These negative results were once more confirmed by a recent study using HAI 48 h-continuous infusion. Apparently, the benefit of intraarterial chemotherapy remains questionable. Regional chemotherapy cannot be considered as standard treatment and should not be conducted outside controlled clinical trials.

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Patient survival after D1 and D2 resections for gastric cancer: long-term results of MRC randomized surgical trial

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In this prospective trial D1 resection (removal of regional perigastric nodes) was compared with D2 resection (extended lymphadenectomy to include level 1 and 2 regional nodes). Central randomization followed a staging laparotomy.

Out of 737 patients with histologically proven gastric adenocarcinoma registered, 337 patients were ineligible by staging laparotomy because of advanced disease and 400 were randomized. The 5-year survival rates were 35% for D1 resection and 33% for D2 resection (difference -2%, 95% CI = -12%-8%). There was no difference in the overall 5-year survival between the two arms (HR = 1.10, 95% CI 0.87-1.39, where HR > 1 implies a survival benefit to D1 surgery). Survival based on death from gastric cancer as the event was similar in the D1 and D2 groups (HR = 1.05, 95% CI 0.79-1.39) as was recurrence-free survival (HR = 1.03, 95% CI 0.82-1.29).