studies are not informative about risks from childhood exposure to ^{131}I. In contrast, very large increases in the incidence of childhood thyroid cancer have occurred following the Chernobyl accident. Data from the Ukraine, Belarus, and Russia suggest that the risks from childhood ^{131}I exposure are high and may not differ substantially from those associated with external radiation. To date, findings from studies of environmental radiation exposure are inconsistent. Additional data from studies of populations exposed to radiation from nuclear weapons testing and production in the former Soviet Union will become available in the near future. These data should help clarify the role of radionuclides in the etiology of thyroid cancer.

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Thyroid Carcinoma After Chernobyl

D. Williams. *University of Cambridge, Strangeways Research Laboratory, Cambridge, UK*

4 years after the world's worst nuclear accident at Chernobyl an excess of thyroid cancer cases was noted among children who had been exposed to fallout from the disaster. That increase has continued and new cases are still being seen in those who were children at the time of the accident. It is now 15 years since the accident, and so far approaching 2000 cases of thyroid cancer have occurred in the affected area, which involves most of Belarus, the northern part of Ukraine and a small part of the Russian Federation. Collaborative research to study these cases is ongoing, the results so far show that the diagnoses of thyroid cancer are substantiated, with many of the early cases showing marked local invasion. The increase is almost exclusively in papillary carcinoma, so far very few follicular or medullary carcinomas have occurred, there are no reliable reports of increases in non thyroid malignancies, although these cannot yet be entirely excluded. The increase is very largely in those who were children at the time of the accident, with a very marked association of age with sensitivity. The findings after Chernobyl differ greatly from those after the atomic bomb explosion. In Japan the exposure was very largely to whole body radiation from gamma rays and neutrons. After Chernobyl the exposure was to isotopes in fallout, and apart from the inert gas xenon, the largest components were radioactive isotopes of iodine (including Tellurium 132 which decays to Iodine 132).

Exposure to isotopes of iodine gives the thyroid over a 1000 times the average dose to the rest of the body, explaining the specificity for thyroid cancer. Radiation is particularly effective in inducing double strand breaks in DNA, and papillary carcinoma is linked to rearrangement in the ret oncogene, providing an explanation for the specificity for papillary carcinoma, although follicular carcinoma may still show a rise in incidence with a longer latent period than papillary carcinoma. The particular sensitivity of children can be linked to a combination of a higher thyroid dose and the biology of thyroid growth, which falls to a very low level in adult life. The post Chernobyl thyroid carcinomas form the largest group of human tumours of one type, due to a known cause on a known date; to facilitate study of the changes that lead to radiation induced carcinogenesis an international tumour bank has been created. Currently this holds extracted nucleic acids from several hundred tumours and these are now available for study by approved projects. Chernobyl was a major disaster for the population exposed, and for the economies of the countries involved, particularly Belarus. Few of the patients with thyroid cancer have died from the disease, but help is still needed in the affected areas, and continuing study of the occurrence of thyroid cancer and surveillance for other possible effects remains essential.

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Prognostic factors, treatment and follow-up of patients with papillary (PTC) and follicular (FTC) thyroid carcinoma

Martin Schlumberger. *Institut Gustave Roussy, Villejuif, France*

Prognostic factors for PTC and FTC include age at initial treatment, tumor burden (tumor size, extrathyoid extension, lymph node metastases, distant metastases) and tumor histotype.

More than 85% of PTC and FTC patients belong to a low risk group, with specific mortality rates below 2% at 25 y and can be individualized at the time of initial treatment by using the TNM or MACIS scoring systems.

Initial treatment includes surgery (near-total thyroidectomy and in case of PTC central neck dissection). A lobectomy may be sufficient for unifocal micro-PTC and for small minimally invasive FTC. Post-operative radioiodine ablation is performed selectively, i.e. only in high risk patients. Then, levothyroxine treatment is given to all patients with PTC and FTC with the aim to decrease serum TSH to low level.

The search for persistent or recurrent disease is based on neck ultrasonography, serum thyroglobulin (Tg) determination and total body scanning with radioiodine (131I). TSH stimulation can be obtained either by withdrawing levothyroxine therapy for 4 weeks or by intra-muscular injections of recombinant human TSH.

Neck recurrences are treated with 131I and surgery, typically using an intra-operative probe. Lung metastases are treated with 131I in case of uptake; and bone metastases are treated by surgery when feasible, followed by radioiodine and external radiotherapy; embolisation and cement injections may also be useful. Bio- and chemotherapy are not effective and should be given only to patients with progressive disease in the frame of controlled trials.

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Prophylactic surgery in patients with multiple endocrine neoplasia type 2a

S. Wells[1], J. Moley[2], M. Skinner[1], M. DeBenedetti[2]. [1] *Duke University, Surgery, Durham, USA;* [2] *Washington University, Surgery, St. Louis, USA*

Patients with the type 2 Multiple Endocrine Neoplasia(MEN)syndromes, MEN 2a, MEN 2b and Familial Medullary Thyroid Carcinoma(FMTC)inherit dominant/negative mutations in the RET protooncogene. The diseases have distinguishing phenotypes,which are characterized by medullary thyroid carcinoma,(MEN 2a, MEN 2b and FMTC)pheochromocytomas(MEN 2a and MEN 2b), hyperparathyroidism (MEN2a) and a generalized neural hypertrophy (MEN 2b). Virtually all patients with these syndromes express medullary thyroid carcinoma (MTC), which is the most common cause of death.

However, the time of onset and the biological agressiveness of the MTC vary, being earlier and more rapid in patients with MEN 2b but later and more indolent in patients with FMTC. The MTC cells secret calcitonin (CT), which is an excellent tumor marker. With direct DNA analysis for mutations in the RET protooncogene it became possible to detect members of MEN 2a, MEN 2b or FMTC kindreds who had inherited a mutated alleal. We advised total thyroidectomy in family members who had distinctive RET mutations. The operation was a total thryoidectomy with removal of lymph nodes in the central zone of the neck. Stimulated plasma CT levels were determined before and immediately after surgery, and at yearly intervals thereafter. Since 1970 we have accrued 83 families (1186 patients) with MEN 2a,38 families (57 patients) with MEN 2b and 9 families (147 patients) with FMTC. We have performed thyroidectomies on 83 patients based on genetic testing. Postoperative evaluation ranges from one month to eight years (mean 4.6 years). Preoperative stimulated plasma CT levels were in the normal range in 30 (36%) patients and in 75 (90%) patients stimulated plasma CT levels were in the normal range, postoperatively. On histologic evaluation of thyroidectomy specimens in 5(6%) patients had no evidence of a C-Cell disorder and in 16 (19%) patients only C-Cell hyperplasia was present. In MEN 2a, MEN 2b or FMTC direct DNA analysis for mutations in the RET protooncogene is the method of choice for identifying kindred members who have inherited a mutated alleal. Measurement of stimulated plasma CT levels in the postoperative period is an excellent method of determining the success of the surgery and for evaluating recurrent and persistent disease. In this setting total thyroidectomy appears to be curative in patients with early disease and represents a model of preventative oncology.

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Low dose hyper-radiosensitivity

M.C. Joiner[1], S.C. Short[2], B. Marples[1], M.I. Saunders[2]. [1] *Gray Cancer Institute, Northwood, United Kingdom;* [2] *Mount Vernon Hospital, Northwood, United Kingdom*

Purpose: To review the phenomena of low-dose hyper-radiosensitivity (HRS) and increased radioresistance (IRR) and explore the possible impact of HRS on clinical radiotherapy. Materials and Methods: Clonogenic survival of cell populations has been determined accurately by automated microscopy or FACS. Experiments have been carried out on more than 45 cell lines, altering the size, timing and dose rate of one or more radiation exposures. The effect of HRS has also been determined in mouse normal-tissue models and in human tumour xenografts. Measurements of basal-cell density have been made in skin biopsies exposed to successive small radiation doses from patients undergoing radiotherapy. Results: HRS has been demonstrated in more than 78% of the cell lines tested. It also occurs in some tumours and normal tissues in vivo. It produces increased cell kill per unit dose at doses below one gray which is more apparent in more radioresistant cell lines compared with both sensitive cell lines and

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

J. Bourhis, E. Deutsch. *Institut Gustave Roussy Villejuif, France*

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

Jens Overgaard. *Danish Cancer Society, Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus C, Denmark*

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

M. Martin[1], P. Reisdorf[1], M.-C. Vozenin-Brotons[2], J.-L. Lefaix[3], S. Delanian[4]. [1] *Service de Génomique Fonctionnelle, CEA, Cedex Evry, France;* [2] *METSI, IPSN, Villejuif, France;* [3] *LRT, CEA, Bruyères le Châtel, France;* [4] *Service de Radiothérapie, Hop St Louis, APHP, Paris, France*

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

M. Lorenz. *The German Cooperative on Liver Metastasis, Germany*

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

J. Fielding[1], S. Weeden[2]. [1] *CRC Institute for Cancer Studies, Department of Surgery, Birmingham, United Kingdom;* [2] *Cancer Division, MRC Clinical Trials Unit, London, United Kingdom*

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).