Conclusion: We demonstrate that neural stem cells in the ventricle-hippocampal region are highly radiosensitive and that apoptosis of the stem cells could be an initial step of radiation injury. Ionizing radiation accelerates differentiation of stem cells into oligodendrocyte lineage leading to myelin synthesis disorder. These evidences pave the way for the understandings of a mechanism of radiation-induced leukoencephalopathy.

757 POSTER

Intraluminal application of potential radioprotectors in an animal model of localized hypofractionated small bowel irradiation

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Purpose: The risk of normal intestinal toxicity is a major dosis-limiting factor during radiation therapy for abdominal and pelvic malignancies. Investigations have been directed toward increasing normal tissue tolerance by using radioprotectors, however, intraveneous administration of potential radioprotectors, i.e. amifostine, has produced limiting nausea and vomiting. The presented animal model was developed for intraluminal application of potential radiation biology modifiers and localized fractionated small bowel irradiation.

Methods: Fourty two male Sprague-Dawley rats were orchiectomized and a 5 cm segment of small bowel was sutured to the inside of the scrotum to form an artificial "scrotal hernia". In addition, a proximal Bishop-Koop ileostomy was fashioned for intraluminal drug application; small intestine was re-anastomosized end-to-side using 6-0 absorbable interrupted sutures. After 4 weeks postoperative recovery small intestine in the scrotal hernia was sham-irradiated or exposed locally to hypofractionated orthovoltage radiation of daily 5 x 5 Gy or 5 x 7,5 Gy. In treatment groups 10 min. before irradiation 50 mg Ethyol (Amifostine) dissolved in 9M buffer was administered intraluminally. Specimens of sham-irradiated or irradiated intestines were procured at 2 weeks after the end of irradiation and assessed for morphologic changes by semiquantitative histopathology and for extracellular matrix-associated pan-TGFbeta by immunohistochemistry. In addition, the enteric nerve system (ENS) was assessed using electron microscopy.

Results: Surgery and anaesthesia related mortality rates were 5% and 2%, respectively. Irradiated animals exhibited characteristic dose-dependent intestinal mucosal denudation, inflammation, subserosal thickening, differences between the irradiated groups were significant (p=0.02). Amifostine-treated animals in the 7.5 Gy group showed a slight but not significant reduced intestinal injury at 2 weeks than irradiated animals treated with buffer. Using electron microscopy irradiated specimens exhibited characteristic alterations of the ENS.

Conclusion: This animal model allows the application of fractionated small bowel irradiation in combination with local testing of potential radioprotectors locally. Amifostine and other locally acting radioprotectors should undergo further testing, particular as modifiers of chronic intestinal radiation toxicity.

758 POSTER

Chromosomal damage and survival of keratinocytes and fibroblasts after irradiation with 200 kV and 25 kV X-rays

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Purpose: A relative biological effectiveness (RBE) of 1 is generally accepted for soft X-rays (25-30 kV), which are applied in diagnostic radiology (mammography). However, it has been shown, that soft X-rays can be more effective in cell killing and chromosomal damage. The present study was initiated to define biological effects of low-energy X-rays in vitro.

Methods: Experiments were performed with 25 kV X-rays and 200 kV reference X-rays on neonatal human keratinocytes (HEKn), human fibroblasts (HFIB) and NIH/3T3 mouse fibroblasts. Cell survival was studied with graded doses in a clonogenic assay, chromosomal damage in a micronucleus (MN) assay.

Results: The surviving fraction at 2 Gy for keratinocytes was 46±5% after 200 kV and 33±11% after 25 kV X-rays. Linear-quadratic cell survival analysis yielded a=0.31±0.03 Gy-1 and b=0.048±0.011 Gy-2 for 200 kV and a=0.40±0.10 Gy-1 and b=0.048±0.054 Gy-2 for 25 kV. For 3T3 fibroblasts SF2 of 53±3% after 200 kV and 61±18% after 25 kV were observed. Values of a=0.24±0.02 Gy-1 and b=0.022±0.002 Gy-2 for 200 kV and a=0.10±0.05 Gy-1 and b=0.070±0.010 Gy-2 for 25 kV X-rays were derived. The induction of binucleated (BN) cells in the MN assay was highly dependent on the cell line studied, but independent on radiation quality. Compared to the effect of conventional, 200 kV X-rays, 25 kV X-rays resulted in an increased number of chromosomal damages expressed as either the percentage of BN cells with micronuclei (%BNC + MN) or the number of micronuclei per BN cell (MN/BNC).

Conclusion: Cell survival after 25 kV and 200 kV X-irradiation was similar, although for 3T3 fibroblasts, a reduction in survival at higher doses was observed after 25 kV X-rays. Induction of micronuclei after irradiation with 25 kV X-rays was significantly higher than with 200 kV, resulting in a RBE value of about 1.2. This indicates a higher potential of the soft X-rays for the induction of genetic damage.

759 POSTER

Tumor interstitial fluid pressure in patients: possible correlation with tumor size

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Purpose: Interstitial fluid pressure (IFP) is determined by the volume of free interstitial fluid and the distensibility of the interstitium. Normal tissues have low vascular permeability and an extensive lymphatic network, and therefore contain only small quantities of interstitial fluid at low pressure. IFP in normal tissues is between -5 and +5 mmHg. Malignant tumors are very permeable and lack functional lymphatics, which allows free fluid to accumulate in the interstitium, producing a high tumor interstitial fluid pressure (TIFP). A high TIFP may be associated with hypoxia and poor prognosis in radiotherapy. TIFP may increase with tumor size. In this study, we evaluated whether TIFP is correlated with tumor size.

Materials and Methods: From August 1998 to December 2000, we measured TIFP using a modified wick-in-needle technique in 33 biopsy-proven uterine cervical cancer patients and 33 primary or metastatic head and neck cancer patients in whom the tumor was accessible by direct inspection and palpation and was sufficiently thick (>1 cm) to permit accurate needle placement. Blood pressure was checked before TIFP measurement. Tumor size was measured by clinical and radiological methods.

Results: In cervical cancer, the mean TIFP was 29.1 mmHg and had no significant relationship with tumor size (p = 0.59). In head and neck cancer, the mean TIFP was 26.5 mmHg and was significantly related to tumor size (p = 0.03).

Conclusion: The mean TIFP was elevated at 29.1 mmHg in cervical cancer and 26.5 mmHg in head and neck cancer. TIFP was significantly related to tumor size in head and neck cancer.

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760 POSTER

Influence of percutaneous radiotherapy on skin microcirculation

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Purpose: Acute and chronic skin reactions represent serious side effects in radiotherapy (RT). Both are accompanied by histologically proven changes of capillary vessels. The aim of this investigation was to show evidence for these changes under in-vivo-conditions.

Methods: Morphologic modifications of the nutritive skin capillaries have been investigated by means of the capillary microscopy in eight irradiated patients with different malignant tumours. Treatment has been delivered by linear accelerator with 6 or 15 MV photons. Measurements were performed before, during, at the end of treatment and twice in follow up. An investigation of the deeper plexus of thermal regulation of the skin took place with the laser doppler flowmetry (LDF). Investigation areas were the irradiated field and un-irradiated skin (controls). Acute and chronic skin reactions were scored by RTOG/EORTC toxicity criteria respectively LENT/SOMA tables.

Results: An edema formation was shown in all patients during RT leading to reduced skin transparency. Therefore capillary density could be

determined only in five of these patients, who had a reduction of the capillary density in the irradiated field at the end and 3 months after RT. A dilatation of the skin capillaries we saw in all patients already early in time during the RT (usually after 10,0 Gy). Micro bleedings/micro thromboses occurred in 5 resp. 6 cases. In agreement with published data we found a rise of the LDF quotient (irradiated/unirradiated skin) under radiotherapy in 7 of 8 patients, only in one case it was missing.

Conclusion: Already very early during radiotherapy pronounced modifications in the capillary morphology can be found: capillary dilatations. The reduction of the capillary density follows later. Microhemorrhagia and capillary thrombosis, associated with edema formation, can be interpreted as damage of the capillary endothelium leading to increased permeability. Damage of this vessel compartment is crucial for nutrition of the skin. It is accompanied by an increase in blood flow in the thermal regulation plexus, possibly as a sign of increased inflammatory blood circulation caused by opening of functional arterial- venous shunts.

Radiotherapy techniques

761 POSTER

Expression of epidermal growth factor receptor (EGFR) and proliferation markers during fractionated radiotherapy in fadu human squamous cell carcinoma xenografts

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Purpose: Rapid repopulation of clonogenic tumor cells is the major cause for the time factor in FaDu human squamous cell carcinoma (hSCC) during fractionated radiotherapy (RT). In this tumor, acceleration of repopulation ocurs after three weeks of treatment. Because EGFR blockade is a promising therapeutic concept to inhibit proliferation, we examined the expression of EGFR during fractionated radiotherapy in the human SCC FaDu.

Methods: FaDu xenografts grown in nude mice were irradiated with 12 to 18 fractions fractions of 3 Gy under clamp hypoxia. The fractions were given daily or every second day up to 36 days. Tumors were excised one or two days after the end of RT and routinely processed for immunohistochemistry. For the estimation of proliferation, BrdU was injected 1 hour prior to tumor dissection. EGFR, BrdU, and Ki67 were immunostained on paraffin sections. The results were compared to the radiobiological data.

Results: EGFR immunosignal was predominantly confined to the cell membrane of tumor cells with some cytoplasmic staining. The membrane staining score was significantly increased during the second part of the fractionated RT, when acceleration of repopulation was observed in functional assays. The BrdU and Ki67 labelling indices were not significantly different, whereas the proportion of BrdU positive versus BrdU negative tumor cells in the viable tumor area was increased.

Conclusion: Upregulation of EGFR might contribute to acceleration of repopulation in FaDu hSCC after three weeks of fractionated radiotherapy. EGFR blockade in combination with radiotherapy might be a useful approach to counterbalance the time factor in tumors overexpressing EGFR.

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762 POSTER

Basic treatment equivalent (BTE) - a better measure of linear accelerator workload

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Purpose: 1. To develop a better measure of linear accelerator throughput that considers complexity. 2. To prospectively test the model in departments of radiation oncology in Australia, New Zealand, U.K. and Canada.

Methods: Treatment durations of linear accelerator treatments were collected prospectively. Patient-, tumour- and treatment technique-related factors were collected and assessed for significant variables that impact upon treatment duration using multivariate analysis. The significant variables were then weighted and included into a model of linear accelerator Basic Treatment Equivalent (BTE) using the generalised estimating equation with exchangeable correlation structure.

Results: Treatment times were collected on 7929 patient episodes, on 2424 patients in 26 departments of radiation oncology in Australia and New Zealand. Significant factors for treatment duration were number of fields, number of shields, number of junctions, patient performance status, first fraction of treatment, beam type and whether an anaesthetic was required. A treatment BTE can be calculated by BTE= F(0.42 + 0.18B1 + 0.57B2 + 0.12J + 0.13N + 0.11S + 0.05W + 0.15P + 0.2E + 0.66A) where F=1.5 for the first fraction and 1 for all subsequent fractions and B1 = photon beam, B2 = mixed photon/electron, J = junction, N = number of fields, S = number of shields, W = number of wedges, P = number of port films or electronic portal imaging exposures, E = 1 if performance status is ECOG > 2 (otherwise E=0), A = 1 if use of sedation or anaesthesia required (otherwise A=0) and BTE = predicted treatment time in minutes/10.This allows the calculation of a relative weight for each radiotherapy technique in comparison to a simple treatment of a parallel pair of fields that took 10 minutes.

The BTE model has now been tested prospectively in several U.K and Canadian departments and shown to be a more accurate assessment of linear accelerator throughput compared with fields or patients per hour. Some of these results will be presented.

Conclusion: BTE is a better measure of linear accelerate throughput compared with number of patients or fields per hour as the model also considers variations in technique complexity. This model has proven useful to predict treatment durations for more efficient bookings and also to compare departments that have dissimilar casemix.

763 POSTER

The effect of treatment techniques on the volume of small bowel in the pelvic radiotherapy fields

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Aim: The dose of radiation and volume of radiotherapy field are two important factors that contribute to the acute and late gastrointestinal side effects of pelvic radiotherapy. In general the effectiveness of several treatment techniques in displacing small bowel out of radiation field is reported. This study reports the results of the relationship between the different treatment techniques and amount of small bowel in the field.

Materials and Method: The volume of small bowel in the pelvic box radiotherapy fields of 6 patients were evaluated. The study included 5 patients with cancer of the endometrium and 1 patient with bladder cancer. Barium sulfate was diluted 50% by adding water and this mixture was administered 1–2 hours before simulation. Pelvic small bowel volumes were compared using several treatment positions including, prone with bladder distention (pos. 1), prone with bladder distention and with anterior abdominal wall compression (pos. 2), and supine without bladder distention (pos. 3). Patients were instructed to drink fluids prior to simulation and not to void until its end for pos. 1 and 2. Small bowel volumes were determined by dividing the area of opacification in the AP and lateral views into 1 cm segments and summing the products of the segment lengths in the two projections.

Results: The minimum and maximum volumes of small bowel in the pelvic radiotherapy field were 38 and 959 cm^3, 0 and 894 cm^3, 268 and 1132 cm^3 for the positions 1, 2, and 3, respectively. The mean volumes of small bowel in the field were 384.2 ± 126.2 cm^3, 301.3 ± 177.3 cm^3, and 652.8 ± 150.6 cm^3 for the positions 1, 2, and 3 respectively. It was found that pos. 2 was significantly better than the other two positions in terms of displacing small bowel out of the radiotherapy field ($p < 0.05$).

Conclusion: It's reported that certain maneuvers can minimize the small bowel volume in the pelvic radiotherapy fields and reduce the risk of small bowel injury. The current study appears to confirm that oral contrast is a useful adjunct in treatment planning to localize dose limiting small intestines. This study also demonstrates that small intestines can be displaced out of the radiation field by using bladder distention and compression device in the prone position.

764 POSTER

Assessment of organ motion using gated radiotherapy tools

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Purpose: Recent advances aimed at decreasing toxicity related to internal organ motion include respiratory-gated radiotherapy. The accuracy of such