– **At PET3**: Both SUVmax and MTV decreased DFS ($p = 0.003$ and $p = 0.004$ respectively) in HNC. For cervix cancer, only MTV was correlated with DFS.

Conclusion: 18F-FDG PET at 40 Gy seems to be a prognostic factor of DFS in HNC and cervix cancer, potentially being used to intensify treatment for bad responders.

2001 ORAL

Nanoscale Radiotherapy − NBTXR3 Hafnium Oxide Nanoparticles as Promising Cancer Therapy

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Background: There is considerable interest in approaches that could improve the therapeutic window of radiotherapy, which represents a crucial modality of treatment in oncology. We present the rationale for designing NBTXR3 nanoparticles activated by radiotherapy and validate the concept. We performed the Monte Carlo calculations for the first time based on the "local model" simulation that showed a dose enhancement of radiation to tumour cells of approximately nine-fold. NBTXR3 was shown to deposit high energy when the ionizing radiation source is "on" and to have chemically inert behavior in cellular and subcellular systems demonstrated by very good systemic tolerance, thus decreasing potential health hazards.

Material and Methods: We used conventional methods, implemented in different ways, to explore interactions of high Z matter and ionizing radiation with biological systems. In addition, microtomography was performed to explore the nanoparticle volume occupancy inside the tumour and its persistence overtime in mouse tumour models. The antitumour activity of NBTXR3 and tolerance were evaluated in Ewing tumour (A673) and fibrosarcoma (HT1080) using high energy source.

Results and Conclusion: We created and developed NBTXR3 nanoparticles with a crystalline hafnium oxide core which provide high electron density structure and inert behavior in biological media. NBTXR3 nanoparticles' characteristics, size, charge and shape, allow for efficient interaction with biological entities, cell membrane binding and cellular uptake. The nanoparticles were shown to form clusters at the subcellular level in tumour models. Of most importance, we show NBTXR3 intratumour bioavailability with dispersion of nanoparticles in the three dimensions and persistence within the tumour structure, supporting the use of NBTXR3 as effective antitumour therapeutic agent. Antitumour activity of NBTXR3 showed marked advantage in terms of survival, tumour specific growth delay and local control in A673 and HT1080 human tumour models. Changing radiotherapy benefit-risk ratio is challenging. These data are supportive for the first clinical development of hafnium oxide nanoparticles, with an on/off mode of action through successive fractions of radiation therapy using current equipment available in hospitals.

2002 ORAL

4D List Mode PET/CT in Free Breathing Stereotactic Radiotherapy

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Background: Target movement is still a major problem in high precision radiotherapy like stereotactic body radiotherapy (SBRT). Techniques like gating or tracking can solve this problem but often require invasive intervention or prolonged application time, 4 D CT pictured only few breathing phases, which could be a problem especially for patients with poor lung function.

4D list mode-capable PET/CT allows valid detection of target motion and reduction of planning target volume (PTV) up to 35% compared to planning based on CT in maximal inspiration and exspiration.

The aim of this study was evaluation of this new method particularly with regard to feasibility, local tumour control rate, and toxicity.

Material and Methods: 140 patients with 167 lesions were enrolled. They suffered from primary or secondary thoracal or abdominal cancer. Planning procedure included free breathing contrast enhanced PET/CT with list mode-based reconstruction. For liver lesions, accuracy was improved by additional MRI with different contrast enhanced phases. Planning target volume (PTV) contained gross tumour volume (GTV), 2 mm set-up margin and safety margins based on list mode detected motion. All patients underwent SBRT with prescribed radiation dose to the 65% enclosing isodose. Normally, 3 x 12.5 Gy were delivered. Tumours close to lung hilus, stomach, or small bowel received 7.0 Gy in 5 fractions. All patients received prophylactic antiemetic medication one hour before starting SBRT. In case of radiotherapy close to the stomach, patients got proton pump inhibitors for three months starting with first SBRT.

Clinical history, laboratory findings, early and late toxicity scores, PET/CT, and MRI in cases of liver lesions were gathered at the 6-week follow-up visit and then at 3-month, 6-month, 9-month, and 12-month follow-ups.

Results: All lesions were visible in PET and movement was detected by list mode PET/CT in all cases. The patients tolerated planning procedure and SBRT very well. No early or late toxicity $\geqslant$ grade 2 (CTCAE v.3.0) was reported.

1/167 lesions showed an in field relapse, local control is 98.5% (2 to 23 months observation time, mean 7.9).

Conclusion: Good tumour control rate and low toxicity demonstrate excellent applicability of 4D list mode-based target delineation in free breathing high precision radiotherapy.

2003 ORAL

Perfusion and Permeability Study in High Grade Glioma Patients: Implications on Outcome and Importance of Steroids Uptake Before Radiotherapy

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Background: High grade gliomas (HGG) represent the most frequent group of primary malignant brain neoplasm. Conventional imaging evaluation is not a direct measurement of tumour aggressiveness. Evaluation of microvascular characteristics as Perfusion and Permeability could be more appropriate.

Material and Methods: At Institut Gustave Roussy, since January 2008 and up to December 2010, all patients diagnosed with HGG and residual disease 1 week before Radiotherapy (RT) were evaluated with perfusion and permeability magnetic resonance imaging, and treated either to Stupp protocol (60 Gy in 30 fractions plus concomitant temozolomide (TMZ) 75 mg/m^2, then adjuvant TMZ, 150–200 mg/m^2) for grade IV or RT alone in grade III gliomas (with TMZ after failure). Disease free survival (DFS) was estimated using the Kaplan–Meier method; comparison between groups was performed using the log-rank test. Multivariate analysis was performed by Cox model. Chi-square tests were used to analyze the relationship between variables of interest.

Results: Median follow up was of 15 months and 79 patients were studied. Median age was 60 years (range: 17−82), there were 15 grade III and 64 grade IV gliomas (81%). A total of 49 patients was under steroids (64%) just before RT. There were 42 patients with tumours presenting detectable permeability (53%) and median relative cerebral blood volume estimate (r-CBV) was 4 (range: 1.7 to 8.3). Median DFS was 9 months. There was no difference between the high perfusion (r-CBV > 4) and the low perfusion group (r-CBV $\leqslant$ 4) with a HR of 0.78. Patients with detectable permeability had a worse DFS when compared to "no permeability" group (respectively 22% vs. 38% at 1 yr, with a HR of 1.32), but without statistical significance ($p = 0.3$). There was no correlation between permeability and perfusion ($p = 0.85$). Patients under steroids had a worst DFS ($p = 0.04$) and this item was not correlated to bulk of residual tumour. Multivariate analysis confirmed this result ($p = 0.03$).

Conclusions: Patients under steroids before RT presented a worse prognosis. In our series, no correlation was shown between perfusion and permeability in HGG with residual disease, and higher values of rCBV had no impact on outcome. High permeability could be still interesting to study in the future as a possible independent prognostic marker, even if no definitive assumption could be made because of the limited number of patients studied.

2004 ORAL

Rosiglitazone(RGZ) Attenuates Pulmonary Fibrosis and Radiation-induced Intestinal Damage

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Background: Rosiglitazone (RGZ) is a peroxisome proliferator activated receptor (PPAR) gamma agonist with anti-inflammatory, anti-fibrotic

and antineoplastic properties. The aim of this study was to evaluate radioprotective effect of RGZ on a murine model of late pulmonary damage and of acute intestinal damage.
Materials and Methods: *Lung fibrosis*: C57BL/6 mice were treated with the radiomimetic agent bleomycin 40 mg/kg every 2 days for 5 administrations, with or without RGZ(5 mg/kg/day) started 24h before bleomycin treatment. To obtain an independent qualitative and quantitative measure for lung fibrosis we used high resolution CT, performed twice a week during the entire observation period. Hounsfield Units (HU) of section slides from the upper and lower lung region were determined. On day 31 mice were sacrificed and lungs collected for histopathological analysis.
Acute intestinal damage: mice underwent 12 Gy total body irradiation (TBI) with or without RGZ(5 mg/kg/day) started 24h before TBI. Mice were sacrificed 24 or 72h after TBI and ileum and colon segments were collected for histopathological analysis.
Results: *Lung fibrosis:*starting from 10th day of bleomycin treatment, mice showed typical CT features of lung fibrosis including irregular septal thickening, and patchy peripheral reticular abnormalities with intralobular linear opacities, Accordingly HU lung density was dramatically increased. RGZ markedly attenuated the radiological signs of fibrosis and strongly inhibited HU lung density increase (60% inhibition at the end of the observation period). Histological analysis revealed that in bleomycin-treated mice fibrosis involved 50−55% of pulmonary parenchyma and caused an alteration of the alveolar structures in 10% of parenchyma, while in RGZ-treated mice fibrosis involved only 20−25% of pulmonary parenchyma without alterations of the alveolar structures.
Acute intestinal damage: 24h after 12 Gy TBI intestinal mucosa showed villi shortening, mucosal thickness and crypt necrotic changes; chorion showed oedema and inflammatory infiltrate. RGZ showed an histological improvement of tissue structure, with villi and crypts normalization and oedema reduction.
Conclusions: These results demonstrate that RGZ displays a protective effect on pulmonary fibrosis and radiation-induced intestinal toxicity in mice, and although further investigations are necessary, it could be proposed as radioprotective agent.

2005 ORAL

Dose per Pulse Is a Relevant Factor That Impacts Radiation Response on Two Glioblastoma Cancer Cell Lines

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Background: The question to what extent delivery time or dose rate impact tumour cell survival has a long history in radiation therapy. While there is increasing evidence in the recent literature that extended delivery time might impact cancer cell survival, we are short of studies investigating the potential effect of modified dose rate on cancer cells, mostly due to technical challenges.
Material and Methods: To perform our experiments, we used the TrueBeam STx linear accelerator (Varian Medical Systems, Palo Alto, CA, USA), which allows generating a pulsed photon beam of the nominal energy of 10 MV with the flattening filter in place (X10) as well as flattening filter-free, referred to as X10 and X10 FFF, respectively. Removing of the flattening filter leads to a decrease of the beam's mean energy and to an increase of dose delivered per pulse (DPP) of radiation. To validate the radiobiological effect of these two beams on cancer cells, we treated two glioblastoma cell lines, T98G and U87-MG, with either 5 or 10 Gy single dosage using different dose rates (with flattening filter: 20 and 400 MU/min; without flattening filter: 400 and 2400 MU/min) and tested their potential effect on cancer cell survival with the colony formation assay. To better understand the molecular mechanism we performed microarray chip analysis.
Results: In our experimental setting dose delivered per pulse seemed to be a crucial factor that influences cancer cell survival. Comparing the effect on cancer cells of the radiation with 400 MU/min using X10 to 400 MU/min using X10 FFF, the X10 FFF beam was more efficient in reducing cancer cell survival than the X10. Throughout this treatment, delivery time was kept the same while dose per pulse was significantly higher in the treatment using X10 FFF. This effect became more relevant the higher the single dose. In addition, treatment with X10 FFF comparing 400 MU/min to 2400 MU/min did not show any significant difference. In this experiment, delivery time was significantly faster using 2400 MU/min, while the dose per pulse was kept the same.
Conclusions: The results presented here show that dose per pulse might become a crucial factor which influences cancer cell survival. Understanding the mechanisms by which dose rate and dose per pulse influence cancer cell survival might lead to new approaches for the therapy of treatment-resistant tumours and is currently a topic of investigation in our laboratory.

2006 ORAL

Novel Technology of Laser Driven Proton Beams for a Potential Application in Cancer Therapy: in Vitro Dose Response Studies

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Background: The development of the new technology of proton and ion acceleration by ultra-high intensity lasers for cancer therapy is the goal of the German joint research project "onCOOPtics". The laser based acceleration promises compact and economic therapy facilities that are suitable for already existing clinics. In contrast to conventional particle acceleration the laser based method results in beams of very short pulses with ultra-high pulse dose and correspondingly peak dose rate. Within the project multidisciplinary issues like development and optimization of high-intensity laser systems, efficient proton acceleration schemes and proton beam transport are handled. Moreover, the physical and real-time dosimetric characterization as well as the investigation of radiobiological consequences of laser accelerated beams are essential. These imply translational investigations starting from *in vitro* cell irradiation.
Material and Methods: Systematic *in vitro* cell experiments were performed at the 150 terawatt laser facility DRACO at HZDR. Proton pulses up to 20 MeV were accelerated, whereas the broad proton spectrum was downward limited to 6 MeV using an energy-filter-system. An in-house developed integrated dosimetry and cell irradiation system (IDOCIS) was tested and calibrated allowing precise dosimetry as well as the exact positioning of each cell sample. Cell survival and residual DNA double strand breaks were determined after irradiation of the tumour cell line SKX in a dose range from 0.5 Gy to 4.3 Gy. Additionally, reference irradiation were performed with continuous proton beam at a conventional Tandem accelerator and with a 200 kVp X-ray tube.
Results: A stable and reproducible laser driven proton beam was achieved for experiments over weeks including real-time dose and energy spectrum monitoring as well as precise absolute dosimetry. The comparison of the radiobiological effectiveness of conventional and laser accelerated proton beams show no significant difference for *in vitro* cell irradiation.
Conclusions: These first systematic *in vitro* cell response studies with precise dosimetry of laser driven protons represent an important step toward the development of laser accelerated particles for radiotherapeutic application. Further experiments with other human cell lines and *in vivo* studies are under way.
The work was supported by the BMBF, grant no. 03ZIK445.

Poster Presentations (Mon, 26 Sep, 09:30−12:00) **Radiobiology/Radiation Physics/Radiotherapy**

2007 POSTER

Study on Liver Cancer Target Volume Variations Between 4D-CT and 3D-CT Associated With Active Breathing Control Device

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Background: The study aimed to observe and analyze the variations of liver cancer GTV between 4D-CT and 3D-CT associated with active breathing control device (ABC).
Methods: 13 cases with primary liver cancer were selected and underwent CT simulation and localization. Each case underwent 4D-CT scanning first, with ABC device working on to monitor and analyzes the breath wave. Afterwards, 3D-CT scanning were underwent, respectively when patient breathing freely, at the end of inspiration and expiration. GTVs were contoured, according the same criterion by one radiologist and one radiation oncologist jointly, respectively on 6 CT series: CT0 series (4D-CT end-exhale), CT50 series (4D-CT end-inhale), 4D-CT MIP series, 3D-CT free breathing CT series, 3D-CT end-exhale series, and 3D-CT end-inhale series, which were named GTV4D-0, GTV4D-50, GTVMIP, GTVFB, GTVEE, GTVEI. Afterwards, GTV4D-M were obtained by merging GTV4D-0 and GTV4D-50, meanwhile GTV3D-M were obtained by merging GTVEE and GTVEI. The volume of all GTVs were measured and analyzed using SPSS software. Paired Wilcoxson test was applied.
Results: There was no significant difference between GTVEI and GTVEE ($P = 0.325$), as well as GTVEI and GTV4D-0 ($P = 0.125$), GTVEE and GTV4D-50 ($P = 0.325$), GTV4D-0 and GTV4D-50 ($P = 0.125$), GTV4D-M