reactions, acute diarrhea, extreme skin fibrosis, myelitis, fistula, plexopathy, pneumonitis, strictures, cerebellar ataxia, skin edema and chronic diarrhea.
Conclusions: The establishment of an international tissue bank of the rare group of patients with extreme hypersensitivity to radiotherapy was proven to be feasible and should enable in-depth molecular studies.

Poster discussion presentations (Wed, 23 Sep, 11:15−12:15)

Radiotherapy

2008 POSTER DISCUSSION

Second malignancies in high dose volumes of first tumor radiotherapy

D. Bartkowiak[1], B. Welte[2], P. Suhr[1], D. Bottke[1], W. Dörr[3], K.R. Trott[4], T. Wiegel[1]. *[1]University of Ulm, Department of Radiotherapy and Radiation Oncology, Ulm, Germany; [2]RADIO-LOG, Strahlentherapie, Neu-Ulm, Germany; [3]University of Technology Dresden, Department of Radiotherapy and Radiation Oncology – Radiobiology Laboratory, Dresden, Germany; [4]University College London, UCL Cancer Centre, London, United Kingdom*

Purpose: To characterise second tumors that developed in or near the high dose volume of a previous radiotherapy, with regard to their frequency, entities, latency and dose dependence.
Patients: 9944/15449 tumor patients of the radiation oncology department in Ulm, who were treated between 1981 and 2003, survived at least one year after radiotherapy. One hundred of these patients developed second tumors in or near the irradiated volume of this first therapy but with a different histopathological type, suggesting an independent carcinogenesis.
Results: Major primary entities were breast cancer (27%), lymphoma (24%) and pelvic gynecologic tumors (17%). Main second tumors were carcinomas of the upper (18%) and lower (12%) gastrointestinal tract, head and neck tumors (10%), lymphoma (10%), breast cancer (9%), sarcoma (9%) and lung cancer (8%). Overall second tumor latency was 7.4 (1−42) years in median. Short latencies were observed in second colorectal cancer (3.5 years) and leukemia (4.3 years), while for second sarcoma the delay was 11.7 and for second breast cancer even 17.1 years. The relatively frequent second tumors of the upper gastrointestinal tract were associated with median radiation doses of 24 Gy. In contrast, second colorectal cancer and sarcoma developed after median doses of 50 Gy.
Conclusions: Between 1 and 42 years after first tumor radiotherapy, 1% of the patients developed second tumors in or near the irradiated site, i.e. after median to high radiation doses. Follow-up after first radiotherapy clearly must be extended beyond the usual 5 years to identify potentially radiation induced second malignancies. For an estimate of the risk and dose response relationship, a case-case and a case-control study will be performed as part of the EC-funded ALLEGRO study on early and late health risks from radiation therapy.

2009 POSTER DISCUSSION

Prevalence of erectile dysfunction in men with prostate cancer (PCa) prior to definitive radiotherapy: a prospective assessment

A. Gruen[1], J. Korde[1], F. Geiger[2], B. Kimmig[1], R. Galalae[1]. *[1]University Hospital Kiel, Radiation Oncology, Kiel, Germany; [2]University Hospital Kiel, Paediatrics, Kiel, Germany*

Background: To measure and assess the prevalence of erectile dysfunction (ED) in patients with localized prostate cancer, who are candidates for radical curative radiation treatment.
Materials/Methods: Starting November 2007, 62 patients with higher risk prostate cancer were prospectivelly assessed using the validated instrument International Index of Erectile Function-5 (IIEF-5) to evaluate the pretherapeutic erectile function status prior to planned definitive radiation therapy. Median initial PSA was 13.45 ng/ml, median Gleason score was 7, and median clinical T category was T2c. Patients were grouped for analysis in five groups: I (IIEF-5 score 22−25, no ED), II (score 17−21, minimal ED), III (score 12−16, mild to intermediate ED), IV (score 8−11, moderately severe ED), and V (score 5−7, severe ED).
Results: Median age at assessment was 69.6 years. From the analyzed 62 patients 34 (55%) showed a severe ED (group V), 3 pts. (5%) a moderately severe ED, 10 pts. (16%) a mild to intermediate ED, 9 pts. (15%) a minimal ED, and only 6 pts. (10%) no evidence of ED (10%). The cumulative evidence for severe and moderately severe ED was 60%.
Conclusions: Evaluation of erectile dysfunction with the International Index of Erectile Function-5 was feasible and not time-consuming. However, the prevalence of erectile dysfunction prior to radiotherapy was quite pronounced, which questions the value of post therapeutic ED status assessment without knowledge and comparison with base levels.

2010 POSTER DISCUSSION

Prospective evaluation of lung radiation acute toxicity in non small cell lung cancer (NSCLC): impact of the timing

S. Dussart[1], M.A. Mahé[2], V. Servois[3], D. Arpin[4], S. Helfre[5], B. Prevost[6], C. Carrie[7], L. Claude[7]. *[1]Centre Léon Bérard, Biostatistics Unit, Lyon, France; [2]Centre René Gauducheau, Radiation Oncology, Nantes, France; [3]Institut Curie, Radiology, Paris, France; [4]Hôpital de la Croix Rousse, Pneumology, Lyon, France; [5]Institut Curie, Radiation Oncology, Paris, France; [6]Centre Oscar Lambret, Radiation Oncology, Lille, France; [7]Centre Léon Bérard, Radiation Oncology, Lyon, France*

Background: the incidence and severity of acute radiation pneumonitis (ARP) after conformal radiation therapy (RT) for NSCLC remain controversial. The literature is incomplete, while different classifications are often used and timing of evaluation are heterogeneous. A prospective complete evaluation of ARP is proposed through a French multicentric study (preliminary results of the ongoing Gating 2006 randomized protocol).
Material and Methods: 65 pts, median age 63 y. [44−79], good performans status, sex ratio 6.2 were evaluated for ARP. All of them had proven non- metastatic NSCLC, treated either with curative RT in post operative situation (32%) or as exclusive treatment (68%). They had clinical, functional evaluation, thoracic computed tomography (CT) and FDG PET-scan before RT (or before surgery if appropriate). Median dose of RT was 66 Gy [40−70], 2 Gy/fr., 5 days a week. ARP evaluation included clinical, functional and CT evaluations 6−8 and 12 weeks after the end of RT. All the CT evaluations were reviewed by a panel of experts and ARP was scored according to the RTOG (acute) classification. ARP was considered as moderate in case of clinical symptoms (grades 1−3), CT abnormalities (gr. 3) without needs of specific treatment (gr 1−2). ARP was considered as severe in case of severe clinical symptoms ($\geqslant$gr. 3), CT abnormalities (gr. 3) and needs of corticoids or oxygen at least in the management (gr. $\geqslant$3).
Results: At 6−8 weeks, 10 pts (15%) had moderate ARP and 4 (6%) others had developed severe ARP.
At 12 weeks, 19 pts (29%) had moderate ARP and 3 others (5%) had developed severe ARP. 14 pts (22%) had no sign of ARP at the first evaluation but had ARP at 12 weeks. In contrast, 6 pts (9%) had ARP at 6−8 weeks (1 severe ARP among them) while at 12 weeks, they had no sign of ARP left.
The only significant predictive factor for severe ARP was the normal lung volume irradiated over 5 Gy (V5). Neither clinical factor (age, sex, smoking status, histology), treatment (surgery, concomitant chemo/corticoids), baseline functional parameters (FEV1, diffusion parameters), nor other RT parameters (photon energy, number of fields, . . .) were associated with ARP.
Conclusions: ARP is generally underestimated due to the lack of prospective complete evaluation. After conformal modern RT, the incidence of severe complications requiring treatment reaches about 5%, while moderate ARP without need of treatment is seen in about 30%. The timing of ARP evaluation is highly critical and should not happen too early, while more than one third of the patients develop ARP after 6−8 w. after the end of RT.

2011 POSTER DISCUSSION

Temporal lobe damage following active scanning proton radiation therapy for skull base tumors

B. Pehlivan[1], C. Ares[1], O. Stadelmann[1], A. Lomax[1], E.B. Hug[1]. *[1]Paul Scherrer Institut, Center for Proton Radiation Therapy, Villigen, Switzerland*

Background: In several reports on particle therapy, temporal lobe (TL) changes constitute the most frequent normal tissue damage after high dose skull base irradiation. For critical normal tissues with defined OAR tolerance threshold doses, toxicities have been successfully minimized. In contrast a TL threshold has not been established yet. Our aim was to perform a dose-volume correlation with clinical outcomes in patients treated for skull base tumors with high dose proton radiotherapy.
Material and Methods: Between October 1998 and November 2005, 62 patients with chordomas and chondrosarcomas of the skull base have been treated at Paul Scherrer Institute (PSI) with proton radiation therapy using the spot scanning technique. Median total dose for chordomas was 73.5 Gy (RBE) (range, 67–74 Gy (RBE)) and 68.4 Gy (RBE) (range 63−74 Gy (RBE)) for chondrosarcomas. Radiotherapy was delivered at 1.8 – 2 Gy (RBE) dose per fraction. Toxicity was assessed according to the Common Terminology Criteria (CTCAE v.3.0). Volumes for both TLs and brain parenchyma were defined retrospectively on planning CTs. Dose volume histogram analysis was performed evaluating the dose that 3 cc

(D3), 2 cc (D2), 1 cc (D1) and 0.5 cc (D0.5) of these three critical structures received, and correlated with TL late adverse events. Equivalent uniform dose (EUD) analysis over all TLs as function of 'a' parameter for Grade 0, Grade 1 and Grade 3 events was performed.
Results: After mean follow-up time of 38 months (range, 14–92 months), 2 patients experienced Grade 3 TL toxicity. In addition to high grade toxicity, asymptomatic circumscribed white matter changes in the TL (Grade 1 leukoencephalopathy) were observed in 5 patients. A trend for correlation between Grade 1 and 3 toxicities and higher doses delivered to 3, 2, 1, and 0.5 cc was found. Due to the limited number of events, a statistical significant dose-volume threshold was not established. There was a strong trend for Grade 1 and 3 events to occur when the EUD (a = 20) was $\geqslant$60 Gy. This would imply a dependence on small areas of dose at and above this dose.
Conclusions: Tolerance of TL and brain parenchyma to fractionated radiotherapy appears to be a steep function of tissue volume included in high dose regions. We have not found a statistical significant threshold dose-volume value due to the reduced number of events, but a trend between the volume of tissue receiving higher doses and the clinical outcome was evident. This finding supports the concept to establish an OAR maximally permissible dose for TL parenchyma.

2012 POSTER DISCUSSION

Single nucleotide polymorphisms in the gene for vascular endothelial growth factor and radiation induced late toxicity

T. Langsenlehner[1], R. Partl[1], G. Tauber[1], A. Gerger[2], G. Hofmann[2], W. Renner[3], K.S. Kapp[1], U. Langsenlehner[4]. *[1]Medical University of Graz, Department of Therapeutic Radiology and Oncology, Graz, Austria; [2]Medical University of Graz, Division of Oncology, Graz, Austria; [3]Medical University of Graz, Clinical Institute of Medical and Laboratory Diagnostics, Graz, Austria; [4]Steiermaerkische Gebietskrankenkasse, Internal Outpatient Department, Graz, Austria*

Background: Aim of the present investigation was to investigate the influence of single nucleotide polymorphisms (SNPs) in the vascular endothelial growth factor (VEGF) gene on late side effects in prostate cancer patients treated with radiation therapy.
Materials and Methods: We analyzed the association between 7 SNPs in the VEGF gene (−2578C>A, −2489C>T, −1498T>C, −634G>C, −7C>T, 936C>T, 1612G>A) and late side effects after external beam radiotherapy in 99 prostate cancer patients from the Austrian PROCAGENE study. The study was done according to the Austrian Gene Technology Act and has been approved by the local Ethical Committee. Written informed consent was obtained from all participating subjects. All subjects were Caucasian. Genotypes were determined by a 5'-nuclease assay (TaqMan™).
Patients were generally treated with high energy photons (18 MV) in a three-field technique using an anterior and two lateral fields to the prostate and seminal vesicles. All fields were treated daily, 5 days/week. The total dose prescribed to the 95% isodose value at the International Commission on Radiation Units and Measurement point ranged from 66 – 70.4 Gy delivered in 1.8–2 Gy per fraction. Three-dimensional treatment planning was performed in all patients.
Statistic analysis was done using SPSS 11.0 for Windows. Numeric values were analyzed by Student's t-test and rank sum test, proportions of groups were compared by *chi2*-test. Threshold for significance was $P < 0.05$. Late genitourinary and gastrointestinal toxicity was graded according to standard Radiation Therapy Oncology Group (RTOG) criteria.
Results: After a median follow-up time of 28 months 10% of patients experienced $\geqslant$Grade 2 late rectal and/or genitourinary side effects. Late toxicity $\geqslant$2 was significantly more frequent among carriers of the VEGF −634 G>C polymorphism (16.7%) than among non-carriers (2.2%, $p = 0.020$). Genotype distribution of the other polymorphisms did not show a significant association with late toxicity.
Conclusion: The present results suggest that SNPs in the VEGF gene might influence the development of severe late side effects after radiotherapy. Our findings support the hypothesis that genetic polymorphisms in major regulators of normal tissue response may be predictive of clinically meaningful adverse radiation effects. Additional investigations of SNPs influencing angiogenic and inflammatory pathways and radiation induced late toxicity are indicated by the present results.

2013 POSTER DISCUSSION

Single nucleotide polymorphisms at 241 codon of XRCC3 gene is associated with acute skin reactions after radiotherapy for breast cancer

M. Mangoni[1], G. Gorini[2], F. Carozzi[3], L. Livi[1], F. Paiar[1], S. Bisanzi[3], C. Sani[3], E. Barletta[4], A. Seniori Costantini[2], G. Biti[5]. *[1]University of Florence, Radiotherapy Unit Clinical Physiopathology Department, Firenze, Italy; [2]ISPO Cancer Prevention and Research Institute, Occupational and Environmental Epidemiology Unit, Firenze, Italy; [3]ISPO Cancer Prevention and Research Institute, Analytical and Biomolecular Cytology Unit, Firenze, Italy; [4]Department of Experimental Pathology and Oncology, University of Florence, Firenze, Italy; [5]Radiotherapy Unit Clinical Physiopathology Department, University of Florence, Firenze, Italy*

Background: Single nucleotide polymorphisms (SNPs) in genes related to the biological response to radiation damage may affect normal tissue radiosensitivity. The purpose of this study was to evaluate if certain SNPs located in DNA repair and damage response genes are correlated with the occurrence of acute side effects during radiotherapy for breast cancer.
Material and Methods: 87 breast cancer patients receiving radiation therapy after a breast-conserving surgery were recruited in a prospective epidemiologic study. SNPs in XRCC1 (codon 399 and 194), XRCC3 (codon 241), XPD (codon 312 and 751), GSTM1 and GSTT1 genes were analyzed.
The development of acute skin reactions associated with SNPs was modelled using Cox proportional hazards, accounting for biologically effective dose (BED).
Results: Overall, 8 patients developed severe acute toxicity. We found a significant association with variant XRCC3 (Thr241Met) genotype and moist desquamation or interruption of radiotherapy due to toxicity; none of the XRCC1, XPD and GST polymorphisms evaluated conferred an increased risk of acute skin radiation-induced reactions.
Conclusions: Our results suggest that XRCC3 (Thr241Met) is associated with increased risk of acute skin reactions after radiotherapy. More SNPs and critical SNPs association are under evaluation.

2014 POSTER DISCUSSION

Treatment regimen determines whether a HIF-1 inhibitor enhances or inhibits the effect of radiation therapy

H. Harada[1], S. Itasaka[1], K. Shibuya[1], M. Hiraoka[1]. *[1]Kyoto University Graduate School of Medicine, Department of Radiation Oncology and Image-Applied Therapy, Kyoto, Japan*

Background: Hypoxia-inducible factor 1 (HIF-1) has been reported to promote tumour radioresistance; therefore, it is recognized as an excellent target during radiation therapy. However, the inhibition of HIF-1 in unsuitable timing can suppress rather than enhance the effect of radiation therapy because its anti-angiogenic effect increases the radioresistant hypoxic fraction. In the present study, we analyzed changes of HIF-1 activity after treatment with radiation and/or a HIF-1 inhibitor, YC-1, and optimized their combination.
Materials and Methods: We constructed a novel reporter gene, *5HRE-ODD-luc*, which expresses a luciferase bioluminescence under the regulation of HIF-1-dependent 5HRE promoter. We established a stable transfectant of HeLa cell with the reporter gene, and subcutaneously transplanted the cells to immunodeficient mice. We performed a series of optical imaging experiments and monitored the changes of HIF-1 activity in the tumour xenograft.
Results: Hypoxic tumour cells were reoxygenated 6 h postirradiation, leading to von Hippel-Lindau (VHL)-dependent proteolysis of HIF-1a and a resultant decrease in HIF-1 activity. The activity then increased as HIF-1a accumulated in the reoxygenated regions 24 h postirradiation. Meanwhile, YC-1 temporarily but significantly suppressed HIF-1 activity, leading to a decrease in microvessel density and an increase in tumour hypoxia. On treatment with YC-1 and then radiation, the YC-1-mediated increase in tumor hypoxia suppressed the effect of radiation therapy; while on treatment in the reverse order, YC-1 suppressed the postirradiation upregulation of HIF-1 activity and consequently delayed tumor growth.
Conclusions: These results indicate that treatment regimen determines whether a HIF-1 inhibitor enhances or inhibits the therapeutic effect of radiation and suppression of the postirradiation upregulation of HIF-1 activity is important for the best therapeutic benefit.