(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.