fibrosis, 3−4 = severe fibrosis). The development of severe fibrosis is dramatically higher in the combined control groups (N = 14) compared to the group of animals treated with TNF-a siRNA for 22 or more days (P = 0.00003). Interestingly, mice dosed with chitosan/siRNA only until day 10 developed fibrosis. We hypothesized that prevention of radiation-induced fibrosis is linked to the duration of administration and therefore a successful therapy against RIF is only given if chitosan/siRNA nanoparticles have been administered until say 22 or longer.
Conclusion: This study describes a novel strategy to prevent radiation-induced fibrosis by targeting TNF-a knockdown in systemic macrophages.

2005 ORAL

Die hard? Radiation sensitivity of cancer stem cells from established human cell lines

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Background: Cancer stem cells (CSC) are postulated to mediate tumour radiaton resistance and late relapse. Recently developed technologies to isolate cells expressing specific surface markers of CSC allow to study the radiobiological properties with functional assays in cell lines where CSC where CSC were postulated to represent a subpopuolation. We aimed to identify CSC in a panel of eight cell lines from different organs and test their radiobiological differences.
Materials and Methods: Cell lines were stained with specific CSC antibodies and sorted into CSC populations with FACS or magnetic beads. Sorted and unsorted populations were analyzed for γH2AX foci and radiosensitivity. CSC phenotype was confirmed with anchorage indepent growth test and activated Notch1 immunoblotting. All in vitro experiments were performed in both chemically defined low growth factor containing media and serum containing media. Xenograft tumours were treated with fractioned radiation to test selection for CSC and tumourigenicity was tested in SCID mice.
Results: CSC specific surface markers were detected in all of the tested cell lines in good agreement with evidence from primary tumours of the tested tumour types. The CSC fractions of the breast cancer cell line MDA-MB-231, and pancreatic cancer cell lines Panc-1 and PSN-1 all had less residual γ-H2AX foci compared to the unsorted cell lines pointing to radiation resistance of CSC. However, only MDA-MB-231 CSC and none of the other cell lines CSC had increased postradiation clonogenic survival compared to unsorted cells. Enhanced anchorage independent growth in MDA-MB-231 but not in PSN-1 and over expression of activated Notch1 confirmed the CSC phenotype of MDA-MB-231 and PSN-1 subpopulations. Notch1 expression was also enhanced in PSN-1 and Panc-1. The expression of surface markers in MDA-MB-231 was shifted to a CSC-type pattern after fractionated radiation und xenograft tumourigenicity was enhanced in MDA-MB231 but not in PSN-1 CSC subpopulations.
Conclusions: Although we reliably identified subpopulations expressing previously described organ type specific CSC surface markers in cell lines we could not confirm the radioresistant phenotype in this model in general. This is critical to consider in exploring models essential for assessing the biological advantage of CSC.

2006 ORAL

Local tumour control after simultaneous fractionated irradiation and EGFR-blockade by monoclonal antibodies (Cetuximab) versus tyrosine kinase inhibitors (Erlotinib) in different head and neck squamous cell carcinoma (HNSCC) models

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Background: A wide variability of response to EGFR inhibition and radiotherapy has been observed between different tumours but also between different classes of drugs. Here, potential mechanisms of this heterogeneity are evaluated.
Material and Methods: The effect of radiotherapy alone (30 fractions/6 weeks) or with simultaneous EGFR inhibition by the antibody cetuximab versus the TK inhibitor erlotinib is compared in different HNSCC xenograft models. Endpoint is permanent local tumour control, measured tumour control dose 50% (TCD50) for the irradiation arms and tumour growth delay for the drugs alone. Immunohistochemical (IHC)/immunoflourescence (IF) techniques are used for proliferation/micromilieu, western blots for expression/phosphorylation of receptors/downstream molecules.
Results: Preliminary data on the first tumour models, UT-SCC-5 (ELISA: EGFR-low) and SAS (EGFR-moderate), both expressing no mutations of the EGFR-TK binding domain or of KRAS, are available. TCD50 values are listed below. In UT-SCC-5, local tumour control was not different after irradiation alone or combination with erlotinib or cetuximab. Tumour growth delay was not influenced by the drugs alone, but slightly prolonged after combined treatment in some irradiation dose groups. In SAS tumours, cetuximab significantly improved local tumour control, whereas erlotinib tends to impair local control. IHC/IF evaluations and western blot data after 6 treatment days are currently available for UT-SCC-5. Briefly, a slight reduction of S-phase after combined irradiation and Erlotinib was observed, but no effect in the other groups or on Ki67 (proliferation) and Pimonadizole (hypoxia). Total EGFR and ErbB2 decreased in both Cetuximab arms, Erlotinib in both arms decreased phosphorylation of ErbB2 and, when given alone, decreased MAPK phosphorylation.
Conclusion: Local control of UT-SCC-5 tumours after fractionated irradiation was not improved by simultaneous cetuximab or erlotinib treatment, whereas in SAS tumours cetuximab significantly improved local control and Erlotinib tended to impair local control. Western blot and IHC/IF data of both tumour models are underway and will be presented.

	TCD50 (Gy) [95% C.I.], p-values vs. irradiation alone		
	Irradiation alone	irradiation + cetuximab	irradiation + Erlotinib
UT-SCC-5	111.9 [97; 128]	119.5 [101.2; 159.1], n.s.	103.4 [93; 117], n.s.
SAS	110.6 [98; 126]	76.3 [63; 89], p = 0.001	129.7 [112; 160], p = 0.06

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2007 ORAL

First report on the patient database of the identification of the genetic pathways involved in patients overreacting to radiotherapy: GENEPI-II

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Background: For radiotherapy, a dose-response relationship has been found, implying that higher doses also lead to higher tumor control rates. This is hampered by normal tissue toxicity. However, as the incidence of severe, late irreversible tissue damage could not exceed 5%, the 5% most radiosensitive patients thus determine the prescribed radiation doses. Identifying the most radiosensitive group would therefore have huge clinical implications.
Methods: A tissue bank containing skin fibroblasts, whole blood, lymphocytes, plasma and lymphoblastoid cell lines from clinically radiation hypersensitive patients was established from patients in Europe and Canada. A control group of patients, namely those who do *not* exhibit abnormal reactions to radiotherapy is already available from the GENEPI I study. Overreacting individuals (CTCAE3.0 severe acute side effects grade **2 or more** occurring at very low radiation doses where these side effects are unexpected or grade **3−4** lasting more than 4 weeks after the end of radiotherapy and/or requiring surgical intervention at any time; severe late side effects grade **3−4** occurring or persisting more than 90 days after the end of radiotherapy) excluding known hypersensitivity syndromes, had to exhibit severe acute **or** late side effects after radiotherapy **without** concurrent chemotherapy, biologicals, targeted drugs or radio-protectors at doses from which these side effects are reported to occur in less than 1/500 patients. 3D radiation dose distribution should be known and dosimetry checks are included.
Results: At present, 33 patients have been identified: 10 males and 23 females. Patient groups include breast (15), prostate (5), cervix (4), head and neck (3), lymphoma (3), endometrium (1), lung (1) cancer and medulloblastoma (1). The mean age was 56.6±15.2 years (S.D.) (range 3−78). The radiation dose was 49.3±17.6 Gy (15−90). The mean time to develop severe side effects after radiotherapy was 675±40.3 days (0–2705). 8/33 (28.6%) experienced severe acute side effects, the other 25 patients late damage. Severe side effects included acute skin

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

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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

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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

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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

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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