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Purpose/Objective: The deaths due to radiation pneumonitis and fibrosis seen in the lethally-irradiated victims of the Tokai-mura incident form part of the characteristic spectrum of outcomes seen in late responding tissues that make up the radiation-induced multi-organ dysfunction syndrome (RI-MODS). Additionally, we have identified an increased sensitivity in previously irradiated animals to otherwise survivable insults experienced in the months to years post-injury, with a differential response between those animals irradiated as adults versus neonates; we believe that this precipitated susceptibility may be mechanistically similar to overt RI-MODS. These observations have led us to incorporate multiple organs/endpoints, delayed insult and age into a screening system for testing potential mitigation agents for use in both accidental and therapeutic scenarios.
Materials and Methods: Our group has developed an integrated preclinical testing system that, although individually focused on separate organs of interest, nonetheless, is integrated through common radiation delivery systems, drug delivery protocols and assessment tools. Murine models investigating the delayed radiation response in lung, the central nervous system, erythropoietic bone marrow, skin and immune systems have been developed and verified. Mitigating agents are delivered no earlier than 3 days post-radiation and models are followed for up to 18 months prior to sacrifice.
Results: A number of agents now have undergone preliminary testing using our model, including agents targeted at free radicals, inflammation, as well as specific signaling molecules. Early results indicate the utility of this system in identifying potential efficacy in individual organs or tissues, as well as, importantly, possible areas of clinical concern. Both the model and critical drug data will be presented.
Conclusions: There is a significant need for the development of agents targeted at delayed radiation-induced effects in the context of whole body irradiation. We have introduced a preclinical testing system that provides a broad test-bed for screening potential mitigation candidates. Importantly, its focus on several critical organs allows for multiple endpoints to be assessed, thereby allowing for broad spectrum mitigation strategies to be developed, whilst allowing for the identification of possible areas of toxicity that may adversely affect and/or limit wide-scale treatment protocols. Furthermore, through this system, we have identified sensitivity to secondary, delayed insults (e.g. trauma, infection), particularly in special populations, such as children, suggesting that multiple treatment strategies may need to be developed dependent on age at time of irradiation.
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PO-0899

Monitoring of subclinical pulmonary inflammation during adjuvant breast cancer treatment

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Purpose/Objective: Adjuvant treatment of breast cancer is commonly associated with the development of pulmonary injury and inflammation. The aim of the study was to investigate changes in serum levels of surfactant protein-D (SP-D), a potential specific marker of lung disease, during postoperative breast cancer therapy incorporating irradiation combined with administration of trastuzumab or hormone therapy.
Materials and Methods: A total of 38 patients with primary breast cancer, aged between 30 and 76 years (median = 51.5 years), were monitored throughout a three-month period starting prior to the initiation of radiation therapy (RT) and until two months after the completion of RT. Serum levels of SP-D were serially determined at four predefined time-points in all patients and 31 healthy controls, using enzyme linked immunosorbent assay. All assays were performed in duplicates.
Results: No disease progression was observed after clinical examination, radiological imaging and quantitative assessment of cancer markers CEA and CA 15-3. Pre-radiotherapy levels of SP-D were significantly higher in breast cancer patients compared to healthy controls (p=0.0240). Serum SP-D expression exhibited a gradual increase during adjuvant therapy (p=0.0032). More specifically, a significant increase in SP-D levels was observed in patients treated with a combination of radiotherapy and trastuzumab (p=0.0310). SP-D levels exhibited a significantly lower rate of change in patients under treatment with irradiation and hormone therapy (p=0.0428).
Conclusions: SP-D is abundantly produced by pulmonary alveolar type II and Clara cells, thus its corresponding circulating levels can effectively reflect alterations in the alveolar compartments and epithelium. In the absence of clinical and imaging evidence of acute therapy-induced complications, our observations of the rate of change of serum SP-D expression indicate that the combined administration of RT and trastuzumab in breast cancer patients is likely to be associated with the development of subclinical pulmonary inflammation. On the contrary, treatment with radiation and hormone therapy appears to exert a protective effect against pulmonary toxicity.

PO-0900

Patient-reported urinary incontinence after EBRT for prostate cancer and its relation to dose

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Purpose/Objective: To provide a dose-volume response analysis of patient-reported urinary incontinence after external beam radiation therapy (EBRT) for prostate cancer.
Materials and Methods: The study population consisted of 302 long-term prostate-cancer survivors who had been treated with pelvic radiation therapy to a total dose of 70 Gy at 2 Gy per fraction at the Sahlgrenska University Hospital in Sweden during 1993 – 2006 and 332 non-irradiated control men from the Swedish Population Registry matched for age and residency. We used reactivated treatment data and delineated the entire urinary bladder following its outer contour to be able to export and analyse bladder dose-volume histograms. Patient-reported outcomes (PROs) were taken from a study-specific, validated, postal questionnaire including information on demographics, disease, treatment, quality of life and physical health including urinary symptoms [1]. Urinary incontinence was defined as 'urinary leakage, more than a few drops, weekly or more often during the last six months'(cf. LENT-SOMA Grade 1-2 toxicity for bladder/urethra). We used Logistic regression to investigate a possible causal relationship between dose and the studied outcome. Dose-volume response modelling was performed using the Logistic function with mean absorbed and fractionation-corrected dose ($EQD_{2,3}$using the Linear-quadratic model with an α/β=3).Model was fitted to data using the maximum likelihood method with parameter confidence intervals (CIs) calculated with profile likelihood estimation. Using a grid-search, the dose parameter where probability of outcome is 50% (D_{50})was considered in increments of 0.1 Gy; the curve steepness parameter where probability of outcome is 50% (γ_{50}) was considered in increments of 0.01.
[1] Alsadius D., Radiother Oncol., 2011 Dec; 101(3):495-501.
Results: The median follow-up for survivors was 7 years (range, 1 to 14 years). Among the survivors, 15% reported incontinence versus 7% of the controls (prevalence ratio: 2.1, 95% CI: 1.3-3.4). Both absorbed and fractionation-corrected mean dose were significant predictors for the outcome (P=0.008 and P=0.011,respectively). The mean dose model including the control background symptom rate of 7% resulted in D_{50}-values of 94.1 Gy for absorbed dose and 99.4 Gy_3 for fractionation-corrected dose (68% CI: 81.5-123.3 and 83.5-139.0, respectively). Corresponding γ_{50}-values were 1.14 and 1.02 (68% CI: 0.87-1.47 and 0.79-1.31, respectively).

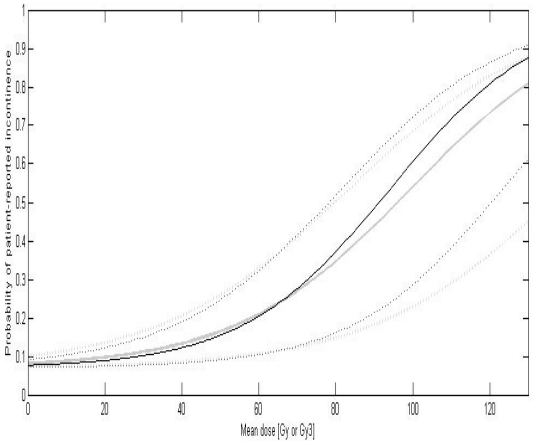

Figure: The excess risk of patient-reported urinary incontinence according to the mean dose model based on absorbed dose (solid black) and fractionation-corrected dose into equivalent 2-Gy fractions using the Linear-quadratic model with α/b=3 for late effects (solid grey). Dotted lines indicate 68% confidence intervals.

Conclusions: Efforts to maintain the mean absorbed urinary bladder dose below 29 Gy (mean fractionation-corrected dose of 22 Gy_3) in prostate-cancer treatments with EBRT may keep the prevalence of patient-reported urinary incontinence below 10%. Both dose representations provide similar results for the clinically relevant range of dose values.

PO-0901

Modeling RBE for spinal cord after carbon ion radiotherapy: comparison with experimental and clinical Data

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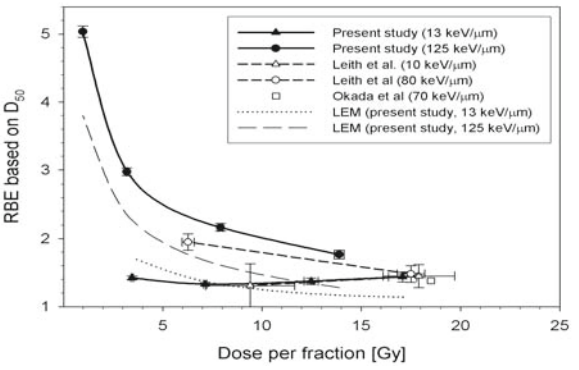
Purpose/Objective: In carbon ion radiotherapy, the increased relative biological effectiveness (RBE) has to be modeled to arrive at the biologically effective dose. In this study, the RBE of carbon ions was measured in the spinal cord and the results were compared to predictions of the local effect model (LEM) as well as to clinical data on normal tissue reactions.

Materials and Methods: The cranial part of the spinal cord of rats was irradiated with 1, 2, 6 or 18 fractions (Fx) of photons or carbon ions, respectively [1]. Carbon ion irradiations were performed in the plateau region (13 keV/mm) or in the middle of a 1 cm spread-out Bragg peak (SOBP, 125 keV/mm). Biological endpoint was the onset of paresis grade II within 10 months after irradiation. Dose response curves were measured and RBEs were calculated based on D_{50} (dose at 50% complication probability). In addition α/ß-values were determined.

Results: The RBE-values were 1.44±0.08, 1.37±0.05, 1.33±0.02 and 1.42±0.02 for the plateau- and 1.77±0.06, 2.17±0.06, 2.97±0.05, and 5.04±0.08 for the peak-irradiations (1, 2, 6, and 18 Fx, respectively). The respective predictions by the clinically applied local effect model (LEM I) were 1.14, 1.19, 1.37, and 1.72 for the plateau- and 1.28, 1.61, 2.35, and 3.80 for the peak irradiations, respectively. The α/ß-values were 2.8±0.4 Gy for photons, 2.1±0.4 Gy for the plateau and 37.0±5.3 Gy for the peak-irradiations, respectively.



Conclusions: Carbon ion irradiations of the spinal cord are significantly more effective in the Bragg-peak than in the plateau region. A significant fractionation effect was found only for the plateau. The clinically applied LEM-version correctly describes the main features although it generally underestimated the RBE in the Bragg-peak by about 25% (fig. 1). In contrast, a retrospective clinical study determined the biologically equivalent tolerance dose for 5% probability of MRI-detected temporal lobe reactions (D_5) to be 68.8±3.3 GyE [2]. This value complies well with clinical experience from photon therapy and hence, there is no indication for a significant underestimation of the RBE in patients. Meanwhile, improved versions of the LEM (LEM II-IV) are available [3,4], which show good agreement with the measured RBE-values for the peak region. To clarify the relation between experimental, clinical and calculated RBEs, the clinical data have to be reanalyzed using LEM IV. Further work is ongoing to systematically determine RBE and α/ß-values at several positions in an extended SOBP corresponding to different LET-values.

1. Karger CP et al. IJROBP 2006;66:1488–1497
2. Schlampp I et al. IJROBP 2010 IJROBP 2011;80:815-823,
3. Elsässer T et al. IJROBP 2008;71, 866–872
4. Elsässer T et al. IJROBP 2010;78, 1177–1183

PO-0902

Effect of post radiation therapy chronic otitis media on dose parameters associated with sensory neural hearing loss

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Purpose/Objective: Post radiation therapy (RT) chronic otitis media (COM) has been implicated with incidence of sensory neural hearing loss (SNHL) in head & neck cancer (HNCa) patients. The goal of this study is to examine the association and evaluate the effect of post-RT COM on the dose parameters associated with post-RT SNHL in head and neck cancer (HNCa) patients receiving RT ± chemotherapy (chemo) using logistic modeling.

Materials and Methods: Radiation oncology and otolaryngology records of 395 HNCa patients who received RT±Chemo were retrospectively reviewed to code incidence of post-RT COM and SNHL using air & bone conduction thresholds for high frequency hearing at 4 kHz. The criteria for SNHL was 10 dB increase in hearing threshold with respect to baseline evaluation. Median follow up was 5.7 Years (range: 0.5-30 years). Mean doses received by the middle ear and cochlea were estimated by treatment plan evaluation and used for analysis. A Fisher's exact test used to determine association between post-RT COM and SNHL. A logistic function was used to describe the dose response for incidence of SNHL for patients treated with RT only and those with Chemo+RT. In each group the model was fitted first to all patients (including those with post RT COM) treated with the specific modality (RT only or RT+Chemo) and then to the subset of the patients treated with that modality who did not have occurrence of post-RT COM. Maximum likelihood method was used to optimize the fit.

Results: Post-RT COM was observed in 31.5% patients. Fisher's exact test indicated that post-RT COM was significant in the incidence of SNHL ($p < 0.001$). The estimated TD_5 & TD_{10} for RT Only group were 34.3 Gy, 41.9 Gy when all the patients were included and those for subset of patients without post-RT COM were 37.1 Gy, 44.7 Gy. Those for Chemo+RT group were 29.8 Gy, 37.4 Gy when all patients included and those for subset of patients without post-RT COM were 38.1 Gy,