In vivo dose response studies for laser driven particle beams

M. Oppelt1, M. Baumann2, E. Beyreuther3, K. Brüchner4, L. Karsch5, M. Krause6, L. Laschinsky1, L. Lessmann3, M. Schürer1, J. Pawelke1

1OncoRay - National Center for Radiation Research in Oncology, Laser-Radiooncology, Dresden, Germany
2OncoRay - National Center for Radiation Research in Oncology, Experimental Radiotherapy and Radiobiology of Tumors, Dresden, Germany
3Helmholtz-Zentrum Dresden-Rossendorf, Radiation Physics, Dresden, Germany

Purpose/Objective: The development of proton and ion acceleration by ultra high intensity lasers for cancer therapy promises the realization of compact and economic particle accelerators that can be integrated in already existing clinics. For translational research toward the clinical application the radiobiological consequences of laser accelerated and therewith ultra-short pulsed particle beams with high pulse dose have to be investigated. After extensive in vitro dose response studies with laser driven electron and proton beams, in vivo experiments have been performed within the joint research project 'onCOOPtics' as next translational step.

Materials and Methods: A mouse tumor model suitable for currently available low energy laser protons was developed, tested and successfully used. The already in vitro established laser based irradiation technology was further developed for the animal model in terms of beam transport, beam monitoring, dose delivery and dosimetry allowing to apply a prescribed dose to each tumor and to determine the absolute dose received. For precise and reproducible positioning at the irradiation site a system for mouse fixation, tumor positioning and position verification was implemented as described in [Schürer et al 2012]. Experiments were carried out at the 30 Terawatt Jena Titanium:Sapphire (JeTi) laser system. Laser pulses of 28 fs down to 40 fs in duration were focused in a hydrogen gas jet at laser intensities of energies to up to a few 10 MeV. In vivo tumor irradiation was realized for murine sarcoma KHT and human squamous cell carcinoma FaDu. Dose sup to 14 Gy were applied at mean dose rates of 1-2 Gy/min and irradiation induced tumor growth delay was investigated. Comparison irradiations were performed at a conventional therapy LINAC with the same setup for irradiation and absolute dose determination.

Results: The reliability and stability of all implemented setup components and methods were proven by numerous irradiations over a period of several months. Dose response curves of tumor growth delay were generated for direct comparison of ultra short pulsed laser accelerated and conventional continuous electron beam. The ongoing data evaluation by now shows no significant difference in RBE for laser driven electrons.

Conclusions: The successful establishment of all technical requirements for and the world wide first performance of systematic animal studies with laser accelerated electrons mark an important step towards the clinical application of laser accelerated particle beams. The realization of in vivo studies with laser driven proton beams is now feasible.

The authors thank for the contribution of the Jeti accelerator crew at Friedrich-Schiller-University Jena, Ralf Bergmann (HZDR) and for the support by the German Ministry of Education and Research (BMBF) grant no. 03Z1N511.

Reference: Schürer et al; Irradiation system for pre-clinical studies with laser accelerated electrons; Biomed Tech 2012; 57(Suppl. 1).

OC-0171
LET dependent response of the rat cervical spinal cord after carbon ion irradiation

M. Saage1, P. Peschke2, P. Huber2, J.P. Debus3, C.P. Karger1
1Heidelberg University Hospital, Radiation Oncology, Heidelberg, Germany
2DKFZ (German Cancer Research Center), Clinical Cooperation Unit Molecular Radiooncology, Heidelberg, Germany
3DKFZ (German Cancer Research Center), Medical Physics in Radiation Oncology, Heidelberg, Germany

Purpose/Objective: For treatment planning with carbon ions, the local effect model (LEA) is used to predict the relative biological effectiveness (RBE) in normal and tumor tissue. Uncertainties in the predicted RBEs translate into uncertainty of the prescribed dose, which can lead to severe side effects. Therefore, the RBE-models have to be validated using experimental data. In a previous study in rat [1], the RBE for late reactions of the cervical spinal cord after irradiation with carbon ions was measured in the entrance region and at the center of a 10 mm spread-out-Bragg-peak (SOBP). A significant dependence of the RBE and the fractionation parameter α/β on LET was found. Based on this study, we systematically extend this database to several intermediate LET-values.

Materials and Methods: Experiments were performed at the experimental beam line at the Heidelberg Heavy Ion Beam Therapy Center (HIT). The cervical spinal cord of female Sprague-Dawley rats

Conclusions: IMRT results in less V5 exposure than VMAT planning of breast patients. High V5 lung values clearly increase pneumonitis risk. More research on low dose exposure is needed to create guidelines for dose constraints. Systematic comparison of IMRT to VMAT can optimize future planning in breast cancer patients.

OC-0170
In vivo dose response studies for laser driven particle beams

M. Oppelt1, M. Baumann2, E. Beyreuther3, K. Brüchner4, L. Karsch5, M. Krause6, L. Laschinsky1, L. Lessmann3, M. Schürer1, J. Pawelke1

1OncoRay - National Center for Radiation Research in Oncology, Laser-Radiooncology, Dresden, Germany
2OncoRay - National Center for Radiation Research in Oncology, Experimental Radiotherapy and Radiobiology of Tumors, Dresden, Germany
3Helmholtz-Zentrum Dresden-Rossendorf, Radiation Physics, Dresden, Germany
was irradiated at six different depths of a 6 cm SOBP using a field size of 10 x 15 mm² including the segments C1-C6. The corresponding linear energy transfer (LET)-values ranged between 16 and 99 keV/µm. Irradiations were performed with single and split doses using a series of increasing dose levels. Endpoint of the study was the occurrence of forelimb paresis grade II within 300 days. Rats with paresis grade II were sacrificed, the cervical spinal cord was taken out and processed for histological examinations.

Results: Preliminary analysis of the data shows that with increasing LET the RBE-values for single and split doses increase. In general, the TD50 (dose at 50 % effect probability) values decrease with increasing LET. Compared to the historical data [2] the TD50-values in the plateau region are comparable within experimental uncertainties. With increasing LET the fractionation ratio (TD50 of 2 vs. 1 fraction) decreases suggesting an increasing $a/b$-ratio.

The latency time decreases with increasing LET. It is significantly shorter for peak irradiation than for plateau irradiation. Latency times for peak irradiations were found to be dose dependent while no dose dependence was observed for plateau irradiations.

Conclusions: On the basis of this preliminary analysis the LET effect is clearly visible, meaning that high LET irradiations are more effective than low LET irradiations. With these studies we extent the database on experimental tolerance doses and RBE-values of the rat cervical spinal cord. The data allow to study and assess accuracy and limitations of RBE-models by comparing measured and calculated RBE-values. Further experiments with six fractions will be performed, which will allow a more robust determination of a/b-ratio as a function of LET. To elucidate the mechanisms of the radiation damage, an additional MRI and histology-based longitudinal study is ongoing.

References

PROFFERED PAPERS: GEC-ESTRO 3: PROSTATE

OC-0172
Urethral stricture after high dose rate brachytherapy for prostate cancer
T. Lo
1Lahey Clinic, Radiation Oncology, Burlington, USA

Purpose/Objective: Urethral stricture is one of the known complications in the treatment for prostate cancer, regardless of the particular therapeutic modality. We reviewed our experience in patients treated with high dose rate (HDR) brachytherapy for prostate cancer, identifying incidence, timing, and outcomes in those who developed urethral stricture after the procedure. We also attempted to seek a solution in treatment technique and planning to prevent such occurrence.

Materials and Methods: Since 1997, 448 patients had undergone HDR brachytherapy for clinically localized prostate cancer in our institution. Over 95% of our patients had intermediate or high risk tumor and practically all patients received neo-adjuvant hormone therapy. The HDR protocol typically called for 3 treatment sessions with one overnight stay. A single radioactive iridium-192 source was used with a nominal activity of 370 GBq. The prescribed dose of 6 Gy per session covered at least 95% of the prostate volume (PTV). All patients received supplementary external beam radiation therapy following completion of the brachytherapy procedure, and external beam dose ranged from 45 Gy to 50.4 Gy (median 50 Gy) using conventional fractionation schemes. For the past two years, the brachytherapy regimen was changed to a single fraction of 13 Gy, thus all patients could be treated on an outpatient basis. All urethral strictures were diagnosed cystoscopically. Patient demographics, operative, and postoperative data were reviewed.

Results: Overall survival rate of the entire cohort of our patients was 98.6%, with a mean follow-up of 55 months. Two patients died from metastasis and 2 other patients died from unrelated causes. Twenty-two patients (5%) have developed urethral strictures to-date. The median time between radiation therapy and the diagnosis of urethral stricture was 4 years (range 1-8 years) with nearly all strictures located in the bulbomembranous urethra. At last follow-up, 2 of the 22 patients had a patent urethra. The remaining 20 patients did not have a stable patent urethra. Nine (41%) of these patients required a urethral dilation schedule, and 3 patients (14%) needed either suprapubic tube or urethral catheter drainage. Five patients (23%) required multiple endoscopic procedures or dilations, while 3 patients (14%) required dilation at last follow-up.

Conclusions: Risk of urethral stricture from HDR brachytherapy for clinically localized prostate cancer appears real. Although incidence of radiation induced urethral stricture remains relatively low, it could result in significant morbidity for the patients. With improved catheter placement technique and meticulous treatment planning accomplishing ‘donut’ dosimetry presently, we could expect reduced incidence of this complication after HDR brachytherapy for prostate cancer.

OC-0173
Determination of a dose constraint for the minimization of urinary morbidity after brachytherapy of the prostate
M. Steggerda1, T. Witteveen1, F. van den Boom1, L. Moonen1
1The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Radiation Oncology, Amsterdam, The Netherlands

Purpose/Objective: Inverse treatment planning requires constraints for adequate dose coverage of the prostate and limitation of the dose to the organs at risk. The purpose of this study was to investigate if there is a relation between the dose to the different sub-segments of the lower urinary tract and enhanced lower urinary tract symptoms (LUTS) after low dose rate brachytherapy with 1-125 seeds, and if there is, to determine a dose constraint for treatment planning purposes.

Materials and Methods:

This study involved 225 patients treated for prostate cancer with 1-125 seeds with a prescribed dose of +4 Gy. The patients filled in an International Prostate Symptom Score (IPSS) questionnaire before (baseline) and 1 week, 6 weeks and 3 months after the implantation of the seeds. These post-implant scores cover the time period when LUTS levels are expected to be maximal. On post-implant fuses CT-TRUS images the prostate, the urethra, the bladder wall, the bladder neck and the external sphincter were delineated (see figure) and cumulative dose volume histograms (CDVHs) were determined. The bladder neck was defined by the urethral orifice connecting the bladder and the prostatic urethra plus a 5 mm margin in all directions. The external sphincter was defined by that part of the urethra that connects the prostatic and the membranous trajectory plus a 5 mm margin in all directions. The endpoint was the mean IPSS during the first 3 months after the treatment. For binary analysis the patients were stratified in a group with enhanced LUTS (mean post-implant IPSS ≥12 and mean increase over baseline IPSS ≥5, or catheter dependency) and a group with non-enhanced LUTS.

Results: Multivariat linear regression analysis revealed that the dose to 0.5 cm³ of the bladder neck $D_{0.5cc-blne}$ (p=0.002), the prostate volume prior to treatment $V_{pr}$ (p=0.005) and the baseline IPSS (p=0.001) were independently correlated with the mean IPSS. When high is defined as ≥175 Gy and ≥2 cm³ for $D_{0.5cc-blne}$ and $V_{pr}$, respectively, and low as ≤ than these values, 68% of the patients with a high $D_{0.5cc-blne}$ and a high $V_{pr}$ suffered from enhanced LUTS, against 31%, 36% and 23% for the combinations high-low, low-high and low-low of these parameters, respectively (p=0.0001). Conclusions: Prostate volume and dose to the bladder neck are correlated with post-implant IPSS. A combination of a large prostate and a high dose to the bladder neck is highly predictive for enhanced early LUTS. To minimize the incidence of enhanced LUTS, $D_{0.5cc-blne}$ should be constrained to a maximum value of 175 Gy during the treatment planning process.