volume of target receiving dose greater than 95 percent of prescribed dose as a measure for target coverage, and rectal volume receiving dose greater than 99 percent of prescribed dose as a measure of rectal toxicity.

The results of the presented study show that for analyzed target volume definition methods bony anatomy matching is more appropriate for prostate treatment with carbon ions and provides higher treatment plan robustness than the soft tissue registration method. The soft tissue registration seems to be less adequate for treatment with particles because of larger anatomy variations in the beam path that may have an impact on dose homogeneity. In case of bony anatomy registration method motion induced density variations in the beam path seem to be clinically negligible. The extension of the clinical target volume by isotropic five millimeter safety margin provide better treatment plan robustness than the other analyzed target volume definition methods. However, it is expected that further investigation on patient specific, anisotropic safety margins definition may lead to an improvement in dose delivery. It is important to mention that in the presented study such aspects as patient positioning or beam application uncertainties have not been taken into account in robustness analysis. The presented treatment planning study is a part of the project developing methods for prostate treatment at Heidelberg Ion Beam Therapy Centre, Germany.

Fig. 1 The treatment plan optimized on the target volume defined as CTV plus 5 mm safety margin (left) and dose recalculation on the pre-treatment MVCT from 9th day of treatment (right). The shifts of the dose distribution induced by anatomical changes are visible on the recalculated image. Color description for segmented regions: Blue – Bladder, Red – Clinical Target Volume plus 5 mm safety margin, Brown – Rectum.

Bibliography: “Dosimetric Comparison of Image Guidance by Megavoltage Computed Tomography versus Bone Alignment for Prostate Cancer Radiotherapy” Jörn Kalz et al., 2008; “Respiratory motion management in particle therapy” E. Rietzel, Ch. Bert, 2010; “Treatment planning for heavy-ion radiotherapy: physical beam model and dose optimization” M. Krämer et al., 2000.

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A 200 TIME-OF-FLIGHT PIXEL IMAGING ASIC, TDCPIX

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The development of a 200 ps time-of-flight pixel imaging ASIC operating in single hit detection mode is presented. The pixel chip, TDCpix, which is currently under design, will feature 1800 square pixels of 300 á 300 µm² arranged in a matrix of 45 rows á 40 columns. In the primary target application, the Gigatracker detector in the CERN based experiment NA62, the ASIC is connected to a silicon pixel sensor, where it will time stamp the arrival time of particles with a timing resolution of better than 200 ps rms and a detection efficiency above 99% for a hit rate of 200 MHz. The read-out architecture of the TDCpix is entirely driven by the input signals. Each pixel hit is read out independently without the need of an external trigger signal. All pixels in the matrix share the maximum hit data bandwidth of 200 MHz. The front-end electronics is optimized for input charges between 1 and 10 fC. The arrival time measurement is based on a continuously running time stamping counter with a bin size of 100 ps. In order to achieve an arrival time resolution of better than 200 ps the front-end electronics contains a time-over-threshold discriminator, which allows the positive and negative signal crossings to be measured. The pulse width of the time-over-threshold signal is a measure of the input signal amplitude and allows compensating for the arrival time measurement error or time walk due to the finite slew rate of the amplified input signal. The data read-out for a pixel hit contains the address of the pixel and two time tags from the time-over-threshold discriminator allowing the time walk compensation to be performed off-line. A demonstrator ASIC has been produced and successfully tested. It contains one 45 pixel column with the full front-end and time tagging chain and a simplified read-out scheme. Extensive tests using electrical charge injection, radioactive sources, infrared laser pulses and a charged particle beam were conducted. The electrical noise on the amplifier without and with the sensor connected was 130 and 180 electrons respectively. The time tagging resolution was 70 ps for the laser pulse sent directly into the center of the pixel and 175 ps for the charged particle beam. The TDCpix ASIC opens possibilities to imaging applications where precise time tagging and high read-out rates are required. We would like to present the development of the TDCpix as well as the achieved results from the demonstrator ASIC.

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DOSE AND LET PAINTING WITH CHARGED PARTICLES

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Particle beams show a changing linear energy transfer (LET) when they travel through matter, being highest at the very end of their track. Particularly, particles heavier than protons, such as carbon ions may show peak LET values of up to several hundred keV/µm in

monoenergetic regime, however, the maximum dose-average LET encountered is somewhat diluted due to scattering, energy straggling, and the addition of low-LET secondary particles originating from inelastic nuclear reactions.

This feature can be exploited to not only optimize for the dose but also for the LET, as a high LET decreases the radioresistivity (oxygen enhancement ratio, OER) of hypoxic tumors. However, spread out Bragg peaks with a homogeneous dose distribution in the target volume show a very inhomogeneous LET distribution due to the weighting of the single pristine peaks. As a consequence, the high-LET areas are at the edges of the target volume, with the risk to harm near-by organs at risk. Furthermore, the mean LET decreases for larger target volumes. By optimizing the configuration of treatment fields, the LET distribution can be moved into the target volume or into smaller sub-volumes to enable LET boosts to hypoxic areas within the tumor, thus offering the possibility of further increasing the therapeutic window.

We will present LET distributions of regular treatment plans as well as plans that have LET boosts assigned to specific regions that could be hypoxic areas, either changing the distribution of the pristine peaks or using optimized, multi-modal treatment plans with different particle species, with the aim to "paint" the dose as well as the high-LET target volume into the treatment plan and do inverse planning of the optimal field and particle selection.

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ADAPTING BIOLOGICAL FEEDBACK IN RADIOTHERAPY

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One of the limitations of conventional radiotherapy is that the response to treatment, both for tumors and normal tissues, is not determined until therapy has been completed. If the tumor and normal tissue response could be evaluated during radiotherapy, treatment may be adapted based on the individual patient's response. This may maximize the probability of controlling the tumor and minimize the likelihood of damaging normal tissues. A prerequisite for adaptation of radiotherapy based on changes in tumor biology and normal tissue function during treatment is that these changes can be quantified. This requires a feedback system with reproducible spatial and temporal data. Such information may be derived from medical imaging in the form of positron emission tomography (PET), single photon emission tomography (SPECT), and magnetic resonance imaging (MRI). For tumor tissue, relevant resistance factors are typically hypoxia, proliferation and metabolism, and imaging surrogates such as FDG-PET, FLT-PET, FMISO-PET and magnetic resonance spectroscopy (MRS) have been proposed. Normal tissues may potentially be monitored by e.g. dynamic contrast enhanced MRI (tissue perfusion in general), ^{99m}Tc-MAA-SPECT (lung perfusion), fMRI (brain function) and FDG-PET (brain and lung metabolism). The frequency and timing of imaging during treatment may impact on the effectiveness of biologically adapted radiotherapy. Also, soft tissue

deformations may be relevant, and deformable image registration algorithms is expected to play a role in adaptive strategies. In this overview, imaging studies and proposed adaptive strategies will be presented.

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THERANOSTICS OF FOLATE RECEPTOR POSITIVE CANCER USING TERBIUM-RADIOLABELED FOLATE CONJUGATES

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Background: Compared to other lanthanides, terbium (Tb) comprises clinically attractive radionuclides such as ¹⁵²Tb and ¹⁵⁵Tb with suitable decay properties for PET and SPECT and ¹⁴⁹Tb and ¹⁶¹Tb suitable for targeted radionuclide therapy based on alpha- or beta-emitting radiation. To evaluate these four radioisotopes we employed the folic acid/folate receptor (FR) targeting strategy which has been thoroughly investigated over years by our group. The folate receptor (FR) is frequently overexpressed on a variety of tumor types but highly restricted in normal tissues and organs. Hence, using the vitamin folic acid as a targeting agent for imaging and therapy of FR-positive cancer diseases is a highly attractive concept.

Methods: A DOTA-folate conjugate was radiolabeled with all four Tb-radioisotopes under standard conditions in acetate buffer (¹⁶¹Tb) or in a solution of alpha-hydroxybutyrate (¹⁵²Tb, ¹⁵⁵Tb, ¹⁴⁹Tb). Cell uptake was studied in FR-positive KB tumor cells. Biodistribution studies were performed over seven days using ¹⁶¹Tb-DOTA-folate. PET and SPECT scans were acquired of KB tumor bearing mice 24 h after injection of 2.5 MBq ¹⁵²Tb-, 5.5 MBq ¹⁵⁵Tb- and 11 MBq ¹⁶¹Tb-radiolabeled DOTA-folate respectively. The folate radiocjugates radiolabeled with ¹⁴⁹Tb (~ 2.5 MBq) or ¹⁶¹Tb (~ 11 MBq) were investigated with regard to their therapeutic anticancer efficacy in KB tumor bearing mice.

Results: The tissue distribution of the ¹⁶¹Tb-DOTA-folate resulted in a high tumor uptake (~ 20 % ID/g, 24 h p.i.) which was retained over time. PET/CT and SPECT/CT studies allowed excellent tumor visualization even 24 h after injection of the ¹⁵²Tb-, ¹⁵⁵Tb- and ¹⁶¹Tb-radiolabeled folate tracer, see Fig. 1. Targeted radionuclide therapy studies performed with ¹⁴⁹Tb- and ¹⁶¹Tb-DOTA-folate revealed a significant inhibition of tumor growth and a prolonged survival (> 1.7-fold and > 2-fold) of treated mice compared to untreated controls.

Figure 1: PET/CT image of a KB tumor-bearing mouse 24 h after injection of ¹⁵²Tb-DOTA-folate (A) and SPECT/CT images of KB tumor-bearing mice 24 h after injection of ¹⁵⁵Tb-DOTA-folate (B) and ¹⁶¹Tb-DOTA-folate (C). (tu = KB tumor xenograft, ki = kidney).