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Experimental study of Radiation induced DNA damage by internal Auger electron cascade compared to external -rays

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and, if needed, a new plan was re-optimized adaptively. Set up was verified with gated orthogonal X rays and non-gated cone beam CT in treatment room. Threshold for gate-on signal was initially set at 10% pressure signal dynamic and qualitatively adjusted in an asymmetric way according to results of plan recalculation in 30% expiration and inspiration. Gating signal was fed to the accelerator to enable beam delivery. Each slice was re-scanned 5 times to smear out possible interplay effects. Acute and early toxicity was scored according to CTCAE 4.0 scale.

Results: GTV and diaphragm excursion between end expiration and adjacent 30% phases was reduced to less than 5 mm. GTV (D95%) and critical OAR (D1%) DVH in 30% inspiration and expiration phases showed on average minimal (less than 3%) differences as compared to planning end expiration plan. Toxicity was minimal with no G3 event; 15% acute G2 and 10% G2 toxicity at 3 months was observed.
Median follow up was rather short (3 months) nevertheless in 23 patients the dose limiting OAR was either stomach or small bowel or esophagus, therefore early toxicity data are informative.

Conclusion: Active scanning with carbon ion beams for the treatment of moving target using abdominal compression, 4D simulation, robust planning gating and rescanning is feasible and safe. Longer follow up is needed to evaluate oncological outcome

Keywords: organ motion, active scanning

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Carbon ion radiotherapy: do we understand each other?
How to compare differentt RBE-weighted dose systems in the clinical setting.
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In carbon ion radiotherapy (CIRT), mainly two calculation models are adopted to define relative biological effectiveness (RBE)-weighted doses (D_{RBE}): the Japanese Kanai model and the Local Effect Model (LEM). Taken the Japanese longest-term clinical data as a reference, the use of a different RBE model, with no correction for the Gy (RBE) scale, leads to deviations in target absorbed dose (D_{abs}) with a potentially significant impact on tumor control probability.
In this study we validate a conversion method linking the two D_{RBE} systems, confirming D_{RBE} prescription dose values adopted in our LEM-based protocols.
The NIRS beamline was simulated with a Monte Carlo (MC) code, according to design information about elements position, size and composition. Validation went through comparison between simulated and measured pristine and Spread Out Bragg Peaks, ridge filter based, in water. CT scan, structure set, plan and dose files of 10 treatment fields delivered at NIRS were exported in DICOM format, for prostate (3.6 Gy (RBE)$_{NIRS}$ per 16 fractions), Head & Neck (4 Gy (RBE)$_{NIRS}$ per 16 fractions) and pancreas (4.6 Gy (RBE)$_{NIRS}$ per 12 fractions) patients. Patient specific passive system geometries (range shifter, MLC, compensator, collimator) were implemented, for each field, to simulate delivered D_{abs} distributions. The MC code was then interfaced with LEM to calculate D_{RBE} resulting from the application of a different RBE model to NIRS physical dose. MC and TPS calculated D_{abs} and D_{RBE} were compared in terms of dose profiles and target median dose. Patient CT and structure sets were also imported in a LEM-based commercial TPS where plans were optimized prescribing the non-converted and converted D_{RBE} values, respectively.
The agreement between MC and measured depth dose profiles in water, in terms of particle range, peak to plateau ratio and spread out profile shape, demonstrated beamline model accuracy. Patient dose distributions were correctly reproduced by MC in the target region, with an overall target median dose difference < 2%. MC median D_{RBE} resulted 16% higher than NIRS reference, for the lower prostate dose

level, 10% for head and neck and 4.5% for pancreas, in agreement with respective LEM-based prescription doses, adopted in our protocols. Deviations are expected to be close to zero around a prescription D_{RBE} = 5 Gy (RBE). Aside from unavoidable differences in dose profile shape, severe target under-dosage was shown in LEM-based optimized plans, when uncorrected D_{RBE} were prescribed.
The delivery of a voxel by voxel iso-effective plan, if different RBE models are employed, is not feasible; it is however possible to minimize differences in dose deposited in the target. Dose prescription is a clinical task which ultimately depends only on the radiation oncologist clinical decision; in this study we made an attempt to avoid systematic errors which could potentially compromise tumor control.

Keywords: Relative Biological Effectiveness, carbon ion radiotherapy, Local Effect Model

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Experimental study of Radiation induced DNA damage by internal Auger electron cascade compared to external γ-rays
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Purpose: The aim of this study is to compare the radiation induced DNA damage done by internal Auger-electron cascades with external exposures of sparsely ionizing radiation such as γ-rays.
Background: Auger emitters decay by internal conversion (IC) or electron capture (EC) producing a number of Auger cascade electrons. These electrons are so low in energy that their range in tissue is in the order of nm-μm. This means that if the decay happens nearby the DNA, the Auger cascade electrons can produce a cluster of complex DNA damage. These clusters of DNA damage are much harder to repair and are therefore believed to be much more harmful to the cell than dispersed DNA damage, which are primarily produced by low LET radiation. Due to their short tissue range and the severe DNA damage produced, Auger emitters may be able to kill only the target cell while sparing non-targeted cells. This makes them a potential tool for radionuclide therapy(1,2,3,4).
Material/Methods: In order to compare the radiation effects by the Auger emitter to that of external γ-rays we need to be able to estimate the dose delivered. As Auger cascade electrons have a very short range the precise spatial distribution of the decays is of high importance.
We are currently working with two Auger emitters, Cs-131 and La-135. First experiments have been performed using HeLa cells, which were incubated with either Cs-131 or La-

135 for internal exposure. Theses ions seem to be taken up by the cells. However more knowledge about the bio-kinetics of these auger emitters is needed to estimate the dose rates and the dose distribution in the cell. As the cells take up the Auger emitter, the dose rate by the internal Auger decays are continuously changing as a function of cellular accumulation and half-life of the isotope.

Uptake curves are therefore produced by incubating HeLa cells with Auger-electron emitters for various amounts of time and with different levels of radioactivity to calculate the changing dose rate and accumulated dose. These conditions will be mimicked as closely as possible with external γ-rays, by moving the cells closer to the source (Cs-137). DNA damage will be assessed by flow cytometry measurements (MUSE) of phosphorylated histone H2AX (γ-H2AX) and/or the clonogenic cell survival assay.

Keywords: Auger, RBE, Internal Radiotherapy

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Towards analytic dose calculation for MR guided particle beam therapy

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Purpose: The importance of MRI steadily increases in radiation oncology not only as multimodality imaging device but also as an implemented online imaging technology. Imaging using MRI shows advantages compared to CT or CBCT offering superior soft tissue contrast without additional dose. Also in particle beam therapy integrated MR guided treatment units have great potential. A complete understanding of the particle beam characteristics in the presence of magnetic fields is required. So far, studies in this area are limited.

Material and Methods: Protons (60-250MeV) and carbon ions (120-400MeV/u) in the clinically required energy range impinging on a phantom of 35x35x50cm³ size were simulated using the MC framework GATE 7. Homogeneous magnetic fields of 0.35T, 1T and 3T perpendicular to the initial beam axis were applied. The beam deflection, shape, and the energy spectrum at the Bragg peak area was analyzed. A numerical algorithm was developed for deflection curve generation solving the relativistic equations of motion taking into account the Lorentz force and particle energy loss. Additionally, dose variations on material boundaries induced by magnetic fields were investigated for 250MeV protons.

Results: Transverse deflections up to 99mm were observed for 250MeV protons at 3T. Deflections for lower field strengths (e.g. future hybrid open-MRI proton delivery systems) yielded 12mm for 0.35T and 34mm for 1T. A change in the dose distribution at the Bragg-peak region was observed for protons. Energy spectrum analysis showed an asymmetric lateral energy distribution. The different particle ranges resulted in a tilted dose distribution, see Fig.1.The numerical algorithm successfully modeled the deflection curve, with a maximum deviation of 1.8% and calculation

times of less than 5ms. For a 250MeV proton beam passing in a 3T field through multiple slabs (water-air-water), only a 4% local dose increase at the first boundary was observed in single voxels due to the electron return effect, more than a factor 10 lower compared to a photon beam [1].
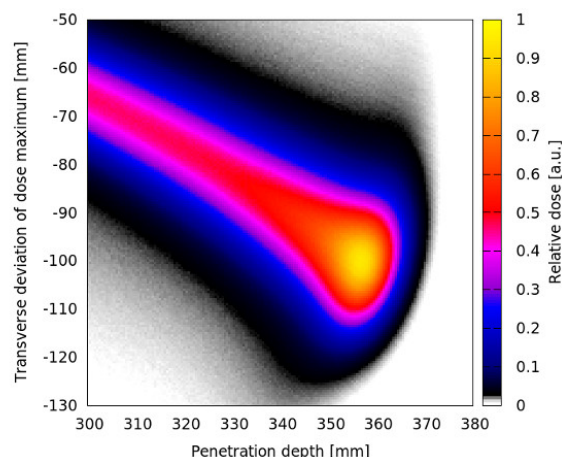

Fig1: Deformed 2D dose distribution at the Bragg peak area for a 250MeV proton beam in a 3T field

Conclusion: Beam deflections in magnetic fields could be described by a numerical algorithm. The observed change in dose distribution in the Bragg-peak region has to be taken into account in future dose calculations. However, local dose changes due to boundary effects seem to be negligible for clinical applications. Current work in progress deals with the inclusion of magnetic field effects in a dose calculation algorithm for particles.

Keywords: particle therapy, Monte Carlo, Magnetic Resonance Imaging

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The Biology of Single Dose Radiotherapy

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The mechanism of tumor cure by ionizing radiation is regarded tumor cell autonomous, effected by misrepair of radiation-induced DNA double strand breaks (DSBs), to a large extent *via* the function of error prone non-homologous end joining (NHEJ). This model prevails at the low dose range, with cure depending on tumor phenotypic propensity for NHEJ misrepair, and requires repeated exposures for tumor ablation. Here we report high (>10Gy) single dose radiotherapy (SDRT) employs an alternative dual target model, inducing in addition to DSBs also an early wave of acid sphingomyelinase (ASMase)-mediated microcirculatory ischemia/reperfusion (I/R) injury. Reactive oxygen species (ROS) induced therein in parenchymal tumor cells disrupt activation of homology-directed repair (HDR), leading to catastrophic reprograming of DSB repair. We show Ku- and 53BP1-mediated NHEJ are not affected, although MDC1/53BP1 resolution is delayed, while engagement of the HDR mediator cluster in DSB repair is aborted, promoting a divergent DSB repair pathway, generation of massive chromosomal alteration and reproductive tumor clonogen demise. Scavenging of ROS with the SOD-mimetic tempol reversed the loss-of-function HDR and tumor cell lethality, aborting tumor cure by SDRT. We define I/R-mediated loss-of-function HDR as the detrimental SDRT damage response,