ENTERVISION biological dosimetric phantom. Proof of concept and results

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Development of clinical treatment protocols for radiation therapy is dependent on the availability of information on the biological efficacy of radiation doses. In order to gain robust data, multiple cell irradiation experiments must be performed at different dose points, using a range of cell lines. Therefore, it is important to be able to verify the biological effects of complex dose distributions in homeomorphic phantoms, alongside
measurements of physical dose. One of the ENTERVISION projects focuses on the development of a biological dosimetric phantom. Firstly, the phantom and desired set-ups were evaluated then its suitability for radiobiology studies were accessed during a set of cell irradiations. Status: The phantom was irradiated mimicking the patients' pathway starting with the CT scan, followed by treatment planning and being irradiated. For the irradiation, an uniform dose distribution was delivered with a proton beam and the process was repeated using a carbon ion beam. The dose was measured from pinpoint ionisation chambers readings and the uniformity was assessed with radiochromic films. The experimental results were compared with the TPS and Monte Carlo calculations. Using MC simulations it was also investigated how the simulation of a more detailed geometry would affect the obtained results. From the radiobiology studies the cell survival by analyzing its proliferation was studied. Results: The calculated mean deviation was below 2% for both beams used. This brings the result within the acceptance threshold as desired by CNAO QA procedures. Conclusion: The experimental results obtained showed good agreement with both TPS and Monte Carlo simulations. And the radiobiological results showed the possibility of multi-variable analysis (LET and Dose) that is available to be done with the ENTERVISION Phantom.

Keywords: LET, RBE, Radiobiology,

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Evaluation of Patients Dose in PET Studies from CT Contrast Agents

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Introduction: The increased availability of PET-CT devices in addition to the interchange of people and technology between nuclear medicine and radiology explains the increased use of CT techniques like enhanced contrast CT in nuclear medicine. The benefits of the use of contrast agents, especially in terms of the increased accuracy, for enhancing different image modalities are understood and well discussed in the literature. On the other hand, in terms of evaluating the different side effects from the use of these contrast agents only the visible and short-term reactions have been discussed. In respect to studying for a possible increase in dose exposure from the interaction of the radiopharmaceutical radiation with the contrast agent in a contrast enhanced PET-CT study and its effect in the patient radiation exposure is yet to be investigated.
Materials and Methods: This study is aimed to investigate the dose deposition differences with respect to the nuclear medicine isotope radiation interaction with the high density and atomic number of the contrast agent due to increased absorption and scatter of the internal radiation in the patients' tissue. This has been performed with the use of Monte Carlo simulations of 10 patient studies where contrast agent had been used.
Results: Preliminary results show an increase in the dose deposition in the regions enhanced by contrast and its surroundings.
Conclusion: Further quantification of this increased dose deposition in different organs at risk and its estimated effect will be presented.

Keywords: PET-CT, Nuclear Medicine, Patient dose

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Proton radiotherapy at PTC Czech in Prague

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Purpose: In the last two decades, particle therapy is slowly spreading from complementary programs of research institutions to dedicated healthcare facilities. Together with this evolution, particle therapy is refocusing from passive modes to the active pencil beam scanning mode (PBS). Higher degree of freedom, in sense of treatment conformity in PBS, is followed by more extensive demands in patient geometry determination. PTC Czech in Prague launched in December 2012 in PBS and it is the only mode of proton beam delivery currently used for patient treatment. The use of PBS technique raised new challenges such as plan robustness during the treatment course and mitigation of breathing motion influence on PBS treatment field delivery. The purpose of this poster is to demonstrate some of motion management studies conducted in the course of preparation for lung/breast lesions treatment.
Materials and Methods: A study with "MartiXX phantom" simulating breathing movement was conducted in order to examine the use of the repainting technique combined with respiratory gating. The goal was to evaluate the benefit of this combination for dose distribution delivery robustness against prolonged treatment time in the case of repainting itself. In another study, four Hodgkin's lymphoma patients, where respiratory gating system (Dyn'R) was applied, were examined. The inter-fractional movement of diaphragm on their setup X-ray images was evaluated. For the evaluation a script for edge detection using ITKsnap library was created. The error of this method was 1 mm.
Results: The evaluation of the "MartiXX phantom" experiment demonstrated significant mitigation of breathing motion when respiratory gating was applied. In this case, the treatment time was increased by 98 %. The use of gating combined with 5 times repainting demonstrated only mild improvement in movement mitigation compared to gating only case at cost of 233 % time increase. The degree of the dose distribution delivery improvement was evaluated through gamma analysis of dose planes acquired with MartiXX detector for dynamic and static case.
The evaluation of the diaphragm movement showed for 3 patients the difference trespassing the 5 mm threshold in 2-3 setups out of 7-11 of total, while in the case of the fourth patient all deviations were beneath 4 mm.
Conclusions: The selected studies for this poster suggest a strong benefit of respiratory gating. Additional mitigation technique like repainting might improve the outcome of dose delivery, but at a high treatment time cost. Nevertheless, the choice of the mitigation strategy should be always verified with a PET-QA in order to adopt the strategy if needed. Further, the evaluation of diaphragm position reproducibility gives some encouraging results although there are some papers [6] claiming low correlation of tumor lesion and diaphragm position.

Keywords: Motion management

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Targeting NOTCH pathway in Glioblastoma

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Glioblastoma multiforme (GBM) is the most common malignant brain tumor in adults. The current standard of care includes surgery followed by radiotherapy (RT) and chemotherapy with temozolomide (TMZ). Treatment often fails due to the radiation and TMZ resistance of a small percentage of cells with stem cell-like behavior (CSC). The Notch signaling pathway is expressed and active in human glioblastoma and Notch inhibitors attenuate tumor growth *in vivo* in xenograft models. Here I will discuss the results of studies investigating combination treatments of RT Temozolomide and NOTCH inhibitors in an orthotopic model of Glioblastoma. Small Animal image guided preciscion Radiotherapy (SmART) treatment planning and delivery was used to achieve highly accurate dose prescriptions and treatment monitoring. Studies will be presented that investigate the role for NOTCH signaling in treatment response in different 2D and 3D culture systems.

Keywords: notch, glioblastoma, stem cell, radiotherapy, temozolomide, image guided radiotherapy, bioluminescence, resistance

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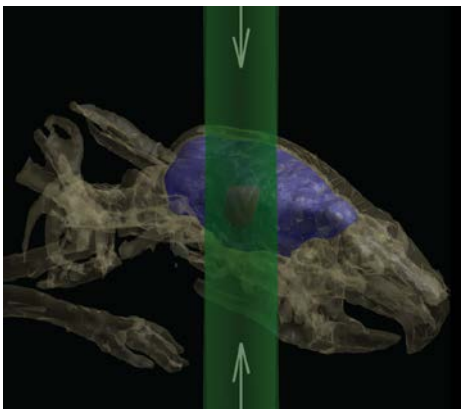

Figure Legend: SmART image-guided treatment plan for orthotopic GBM model. PTV (red), normal brain (blue) and parallel irradiation beams (green)

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Stroma mediated wound healing signals and cell response to radiation

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Stroma mediated wound healing signals induced by radiotherapy have been well characterized in normal tissue response and fibrosis. They are complex and involve the crosstalk between the various cellular type of the tissue including fibroblasts, endothelial, immune, epithelial cells as well as soluble paracrine factors including growth factors and proteases. In addition, recent studies suggest that these wound healing signals may share similarities with the ones produced by tumor's microenvironment. Therefore, their modulation may impact both normal tissue and tumor response to radiation therapy.
This lecture will illustrate the two important aspects of stroma mediated wound healing signals in normal tissue and tumour response to radiotherapy.
In a recent study (1), we investigated the role of macrophages in radiation-induced lung fibrosis, profiled alveolar (AM) and interstitial macrophages (IM) and show that both macrophage subtypes are playing specific and opposite role in fibrogenesis. Acute depletion of AM post-irradiation was shown and associated with cytokine secretion. This acute depletion was followed by a repopulation mediated via the recruitment and proliferation of monocytes/macrophages from the bone marrow. Interestingly, the newly recruited Alveolar macropahages exhibited hybrid polarization (M1/M2), associated with the up-regulation of both Th1 and Th2 cytokines. At delayed times points post-irradiation, interstitial macrophages were M2 polarized and simultaneously, a down-regulation of Th1 cytokines and up-regulation of Th2 cytokines was observed in irradiated lungs. The specific depletion of hybrid AM enhanced the severity of fibrosis whereas anti-fibrotic treatment based upon pravastatin administration decreased M2-IM levels. We also found that M2-IM were able to activate fibroblast into myofibroblasts when co-cultured.
In another study (2), we assessed the crosstalk between primary lung fibroblast and carcinoma cells (TC-1) in response to radiotherapy. We found that fibroblasts were not able to modulate intrinsic radiosensitivity of TC-1 but produce diffusible factors able to modify tumor cell fate. More specifically, RhoB deficient fibroblasts stimulated TC-1 migration through MMPs production whereas WT fibroblasts produce TGF-□.In addition RhoB deficiency stimulated pro-inflammatory signals (IL-6) that would impact on immune recruitment and favor antitumor immune response. In addition, co-irradiation of fibroblasts and TC-1 abrogated the pro-migratory phenotype by repression of TGF-ß and MMP secretion. This last result suggests that conversely to, the current view; irradiated stroma would not enhance