T-regulator cells or myeloid-derived suppressor cells, and overexpression of certain ligands (e.g., programmed death ligand-1 [PDL-1]) that inhibit the host's existing antitumor immunity. The latter effect is thought to take place by the cancer cells' overexpressing ligands that can bind inhibitory co-receptors expressed by T lymphocytes (also known as "immune checkpoints"). Recent advances in melanoma research have led to the development of immunotherapies that have substantial antitumor effects in other types of cancer as well, including lymphoma, renal cell carcinoma, and non-small lung cancer (NSCLC). These advances have been paradigm-shifting for several reasons. For example, the observed immune response patterns have led to marked deep tumor regression that often outlasted the period of study. Such responses are unprecedented for disease that has been refractory to other types of treatment. Second, these new forms of immunotherapy have shown activity in tumors traditionally viewed as unresponsive to immune therapies, raising hopes that any type of cancer might be "targetable" by immunotherapies if the right agent can be found. This antitumor activity has been most impressive in NSCLC, particularly among patients with unresectable disease treated with primary radiation therapy, a modality known to stimulate antigen production. It is conceivable that treatment such as this acts as a type of "in situ vaccine" to prime the immune response. Nascent preclinical and early clinical findings have supported this possibility, suggesting that radiation, through its immune-stimulating properties, may eventually be useful as a form of systemic therapy in addition to a means of local tumor control.

123

Prompt Gamma-ray Timing experiment during different modalities of proton beam delivery

T. Kormoll[1] , A. Duplicy[2], W. Enghardt[1], C. Golnik[1], R. Loeschner[2], J. Petzoldt[1], T. Werner[1] and G. Pausch[1]
[1] OncoRay – National Center for Radiation Research in Oncology, Dresden, Germany
[2] IBA Proton Therapy, Ottignies-Louvain-la-Neuve, Belgium

Purpose: Prompt Gamma-ray Timing (PGT) is a method for range verification in hadron therapy which requires only minor or no interference with clinical routine due to a very low hardware footprint. The principal feasibility of the method for range verification has already been shown in theoretical considerations [1] and in proof-of-pricipal experiments [2]. Further considerations of the clinical feasibility show that a high-throughput data acquisition system is crucial [3]. In this work, PGT measurements during phantom irradiation with clinical beam currents – both during pencil beam scanning (PBS) and passive beam formation (double scattering, DS) are presented.
Materials and Methods: By exploiting the time structure of the beam on the nanosecond scale, it is possible to measure the duration of the emission of secondary photons. This duration is linked with the transit time of the projectiles in the target. Longer transit times reflect a larger range. Since no direct start signal is available, a classical time-of-flight measurement against the accelerator RF is used. Experiments were conducted at the University Proton Therapy Dresden (UPTD) center where an IBA Cyclone 230 isochronous cyclotron is installed with a fixed RF frequency of 106 MHz. For actual clinical application, it is required that the bunch width and phase remain constant or are monitored. The shown data do not incorporate any kind of bunch timing correction and the conditions are assumed to be constant.
As a photon detector, a $CeBr_3$ crystal in the extends of ø2"×1" coupled to a PMT is used. It is either read out with a CAEN DT5730 waveform digitizer or with a Target Systemelektronik U100 dedicated system which is also a sampling ADC based readout module. Online pulse processing algorithms are applied in both cases to achieve a high throughput rate. The ADCs were synchronized to the RF.
Experiments during DS were conducted parasitically during the workflow training with an anthropomorphic phantom. For the PBS measurements dedicated beam time could be scheduled at the therapeutic treatment room. A rectangular dose distribution was impinged on a homogeneous PMMA target. In DS mode, a lead shielding was placed between the detector and the nozzle in order to reduce background radiation which originates from the nozzle.
Results: In both cases, it was possible to identify the individual phases of beam delivery. In DS mode, the periodic modulation at 600 Hz which is synchronized with the beam formation equipment can be seen. In PBS, single layers and single spots can be recognized (figure 1). After data selection, the beam microstructure is revealed in PBS as well as in DS mode although it is considerably less clear in the DS case.
Conclusions: The experimental techniques which are required for a clinical implementation of PGT are being evaluated under clinical beam conditions. The beam delivery mode has major impact on the data quality.

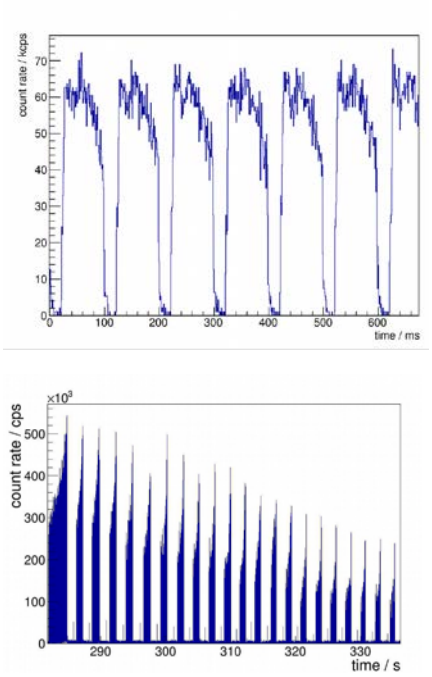

Figure 1: Count rate over time during DS (left) and PBS (right), recorded at 2 Gy/min at different distances.

Keywords: Prompt Gamma-ray Timing, Range Verification, Hadron Therapy

References:
[1] C. Golnik et al. "Range assessment in particle therapy based on prompt γ-ray timing measurements." Physics in Medicine and Biology 59 (2014): 5399.
[2] F. Hueso-González et al. "First test of the prompt gamma ray timing method with heterogeneous targets at a clinical proton therapy facility." Physics in Medicine and Biology 60 (2015): 6247.
[3] G. Pausch et al. "Scintillator-Based High-Throughput Fast Timing Spectroscopy for Real-Time Range Verification in Particle Therapy", SCINT Proceedings, 2015.
[4] T. Kormoll et al. "Prompt Gamma Timing Range Verification for Scattered Proton Beams", ANIMMA Conference Record, 2015.

124

Proton Beams for Physics Experiments at OncoRay

S. Helmbrecht[1], F. Fiedler[1], M. Meyer[1], P. Kaever[1] and T. Kormoll[2]

[1]Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany
[2]OncoRay – National Center for Radiation Research in Oncology, Dresden, Germany

Purpose: At the OncoRay center in Dresden at proton therapy facility is in operation. The first patient was treated in December 2014. The system is driven by an IBA (IBA Proton Therapy, Louvain-la-Neuve, Belgium) Cyclone 230 isochronous cyclotron with a maximum proton energy of 230 MeV. Patients are treated in one room equipped with a 360° rotating gantry. Besides patient treatment a strong focus is on research. A dedicated experimental room is part of the facility. In the current state of expansion this room is equipped with a fixed beam line. Beam energies between 70 and 230 MeV and currents up to about 120 nA at 230 MeV can be provided.
Materials and Methods: An in house developed control system (figure 1) allows for a parallel operation of the treatment and the experimental beamline. Absolute priority for the treatment room is ensured by the control software.
The beam current is controlled by a dedicated hardware directly. Continuous wave beams as well as pulsed beams with repetition rates up to 333 Hz with variable duty cycles are available. The beam is monitored by means of a segmented ionization chamber. The beam can be activated manually, for a defined time or until a certain charge has been reached at the beam exit. A direct continuance after a beam switch to the treatment room is possible.
Results: The proton therapy system itself is operated by an IBA team, that ensures excellent beam stability and availability. Since only one treatment room is present, experiments can be performed conveniently during the day shifts. Requests from the treatment room cause interruptions of 1-2 min duration in intervals of about 20 min.
Conclusions: In summary, the OncoRay center is equipped with an experimental beamline that combines the reliability and beam quality of a commercial clinical proton therapy system with the flexibility of an in house developed control system whose design parameters are governed by the needs of physical and translational research.

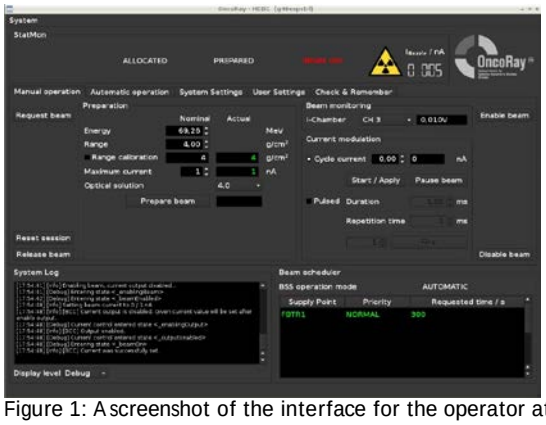

Figure 1: A screenshot of the interface for the operator at the control room for the experimental area.

Keywords: Cyclotron, hadron therapy, radiation research

125
Nanoparticle Enhanced MRI-Guided Radiation Therapy: Final proof of concept before phase I trial.

S. Kotb[1], F. lux[1], Claire-Rodriguez-Lafrasse[2], O. Tillement[1], L. Sancey[1].
[1] Institut Lumière Matière, UMR5306, Université Claude Bernard Lyon1-CNRS, 69622 Villeurbanne Cedex, France.
[2] Laboratoire de Radiobiologie Cellularie et Moléculaire, EMR3738, Faculté de Médecine Lyon-Sud, Université Lyon 1, Oullins, France.

Purpose: Radiation therapy is currently prescribed to more than 60 % of cancer patients[1]. However, effective treatment is often limited by tumor visualization and collateral damage of healthy tissues. One possibility to overcome this problem, besides using a local approach such as stereotactic radiosurgery, is combining radiation with nanoparticles containing high-Z elements which are known to boost locally the efficacy of radiation exposure during cancer therapy. In this context, we developed gadolinium-based nanoparticles named AGuIX (Activation-Guided Irradiation by X-ray) for MRI-guided radiotherapy.
Material and methods: (AGuIX) nanoparticles were obtained as previously described[2]. We performed *in vitro* radiosensitization clonogenic assay with 220kVp X-ray at doses ranging from 0 to 6 Gy on B16F10 mouse melanoma cell line, in addition to cell uptake characterization using TEM and confocal microscopy. *In vivo*, B16F10 mouse melanoma cells were orthotopically grafted into mouse brains to mimic human melanoma brain metastases. After intravenous injection of 10 μmol of (AGuIX) into mice bearing B16F10, MR and intravital two photon microscopy imaging were performed to determine the maximum tumor uptake, and tumor vs. healthy tissue ratio before radiation therapy. Similar to the clinical workflow, an image guided cone-beam CT (CBCT) was performed prior to irradiation exposure to calculate the delivered dose during whole brain radiotherapy (WBRT) to the brain, the metastases and other organs at risk.
Results: Radiosensitization shows a significant effect ($P<0.05$) when the (AGuIX) are combined with 220 kVp X-rays exposure *in vitro*. The percentage enhancement factor at 2 Gy (%EF 2 Gy) was 60 % compared with that for radiation alone, with a significant increase in DNA double strand breaks ($P<0.01$). *In vivo* the (AGuIX) nanoparticles accumulate passively in brain tumors; such phenomenon has previously been reported in brain-tumor bearing animals[3]. After radiation exposure, the increase in life spans (ILS) compared to control group was 8.3% for the animals that were only irradiated and increased to 25% with pre-injection of (AGuIX) nanoparticles; such increase corresponds to 15.4% compared to irradiated animals ($P=0.0025$). Histological observation of the brains indicated the presence of large metastases for the control and irradiated only group compared to the group treated by the combination of irradiation with nanoparticles[4,5].
Conclusion: (AGuIX) nanoparticles are not only potential radiosensitizing agent, but it also acts as positive contrast agent for MRI, which allows accurate delineation of the tumor region instead of using conventional CT. Regulatory toxicity investigations demonstrated the absence of any side effects, even at repeated injections. A clinical trial phase I on patients with multiple brain metastases will be launched in France winter 2016.

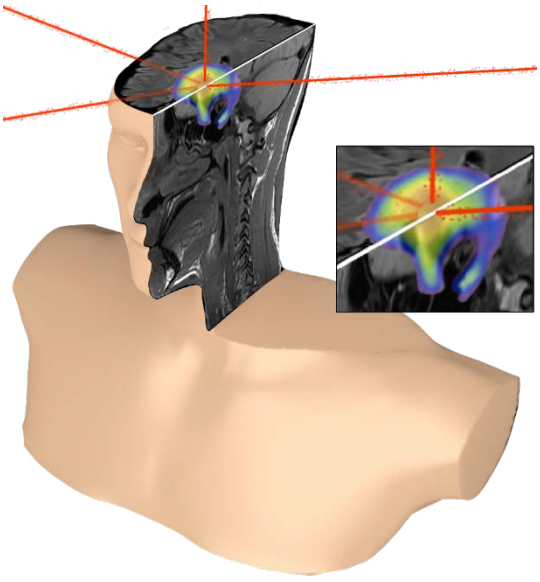
Fig. 1. Guided and enhanced radiotherapy with (AGuIX) nanoparticles.