radiation dose from the $^{10}B(n,\alpha)^{7}Li$ reaction, 2) the intermediate-LET proton dose released from the $^{14}N(n,p)^{14}C$ reaction in tissue, 3) the intermediate-LET protons released from the $^{1}H(n,n')p$ reaction in tissue, and 4) the low-LET *photon dose* mainly from the $^{1}H(n,\gamma)$ reaction in tissue, but in part also from minor photon contamination in the neutron beam.

Conventionally, the biologically effective "photon radiotherapy equivalent" dose has been derived from multiplying each dose component by a constant relative biological effectiveness (RBE) factor, or in the case of the boron dose, the compound biological effectiveness (CBE) factor. The estimations for the RBE and the CBE are obtained from cell culture studies and irradiation with photons, BNCT beam alone, and the beam in the presence of the boron compound [5]. The RBE and CBE factors are applied as fixed, although they depend on the cumulative irradiation time and the dose rate, and, ideally, they should be derived for each irradiation component individually. Furthermore, the radiation dose components have synergistic effects. The conventional fixed RBE-based dose calculation in BNCT tends to lead to unrealistically high estimated tumor doses, which may not be reflected in clinical outcomes and may not be comparable with photon irradiation data.

Recently, an alternative method for calculating the effective dose was proposed [6]. The photon-isoeffective dose calculation formalism takes into account the dose rate and the cumulative dose per fraction in a modified linear-quadratic model, and it also considers the synergistic interactions between different radiation components. The isoeffective dose calculation formalism predicted the response of melanoma lesions to BNCT better than the fixed RBE approach.

In this study the tumor doses calculated with the RBE model and using the photon-isoeffective formalism are correlated with the clinical responses of the patients treated with BNCT in Finland. For glioma patients, the doses are compared with the overall survival time, whereas for patients with head-and-neck cancer, tumor responses are evaluated. The BNCT dose response rates are compared with those obtained with conventional radiotherapy and responses reported in similar patient groups.

Keywords: BNCT, neutron, dosimetry, glioma, head and neck cancer

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**Human Sphingolipid Biomarkers of Single Dose Radiotherapy: A Clinical trial**

R. Kolesnick
Sloan-Kettering Institute
NYC, NY USA

Single dose radiotherapy (SDRT), facilitated by image guidance and intensity modulation technologies that improve precision in tumor targeting to reduce risk of normal tissue toxicity, has revolutionized cancer treatment with local control rates ≥90%, even in tumors resistant to conventional fractionation. While classic radiobiology focuses on response of tumor cells rather than non-tumor microenvironmental cells, initial pre-clinical studies in our lab found disruption of tumor vasculature obligate for SDRT cure. This endothelial cell dysfunction results from activation of acid sphingomyelinase (ASMase), converting sphingomyelin to the second messenger ceramide in endothelial plasma membranes, events inhibitable by VEGF-121 or VEGF-165. Conversely, precisely timed delivery of anti-angiogenic agents, such as anti-VEGFR2 Ab DC101 (Imclone), de-represses ASMase activity, synergistically increasing SDRT-induced ceramide elevation, enhancing endothelial dysfunction. That ceramide is critical for anti-angiogenic radiosensitization is evidenced by □n□-ceramide Ab inhibition of DC101-enhanced endothelial damage and radiosensitization. These results translate *in vivo*, as anti-VEGFR2 DC101 or anti-VEGF G6-31 (Genentech) synergistically increase SDRT-induced endothelial injury in numerous solid tumor types, only if delivery timed to maximally enhance ASMase signaling. In contrast, tumors in *asmase*$^{-/-}$ mice, which provide damage-resistant vasculature, are radioresistant and unaffected by either anti-angiogenic agent. This presentation will review fundamentals of this "New Biology" and present unpublished data that define mechanism of coupling of ceramide-driven endothelial dysfunction to DNA repair in tumor cells.

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**Targeted Treatment for the Non- Small Cell Lung Cancer**

R. Komaki
Department of Radiation Oncology
University of Texas MD Anderson Cancer Center
rkomaki@mdanderson.org

Lung cancer is the leading cause of cancer-related death in the United States and throughout the world. Although overall mortality rates from lung cancer in the United States have dropped from 85% two decades ago to 70% in 2015, tumor control and survival outcomes after standard therapy are still poor.

Early detection involving the use of low-dose spiral computed tomography (CT) among former or current smokers led to a 20% reduction in the rate of lung-cancer death in these individuals. Early stage lung cancer can be cured in some patients by stereotactic body radiation therapy SBRT). Advancement of sophisticated radiation treatment equipment and understanding physics of utilization of the equipment for SBRT rapidly became clinical application for the primary lung or hepatic lesions as well as or other metastatic lesions. Because of high dose per fraction, technical aspects and quality assurance to deliver the radiation to the tumor precisely and avoid high dose of radiation to the critical surrounding normal tissue are critical issues for SBRT.

To understand tumor motion and control tumor motion have been major challenge for mainly lung lesions. To visualize hepatic lesion or other metastatic lesions e.g pancreas or soft tissue can be difficult without contrast enhancement or fiducial markers. The most challenging part of SBRT in addition to controlling tumor motion is lesions to be treated by this technique close to the critical organs e.g. blood vessels, brachial plexus, esophagus, major air way etc.

Technologic advancements of imaging and radiotherapy to conform the gross target volume(GTV) with tighter margins but adequate clinical targeted volume (CTV) and planning tumor volume (PTV) considering daily set up variations which are supposed to minimize the dose to nearby normal tissues. Thus the technical advancement such as intensity modulated radiotherapy (IMRT) compared to 2 or 3 dimensional radiotherapy improved outcomes among patients with locally advanced lung cancer, as has the addition of concurrent chemotherapy to radiation therapy. Further improvements are expected from the use of charged particle therapy with protons or other particles; randomized comparisons of proton therapy vs. intensity-modulated photon radiation therapy for lung cancer are underway in the United States.

Approximately 50% of Non-Small Cell Lung Cancer patients have Adenocarcinoma Histology.

Among the patients with Adenocarcinoma of Lung, 50% of them have genetic mutation. If they have ALK, EGFR, K-Ras or B-Raf mutation, we can target the mutated genes.

For many years, immunomodulation or immunotherapy as a means of cancer therapy has been studied. Cancer cells are well known to have the ability to bypass immune surveillance through a variety of different mechanisms, including reduced expression of tumor antigens, downregulation of major histocompatibility complex (MHC) class I and II molecules for tumor antigen presentation, secretion of immunosuppressive cytokines such as tumor growth factor-beta (TGF-ß), recruitment or induction of immunosuppressive cells such as

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.

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**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.

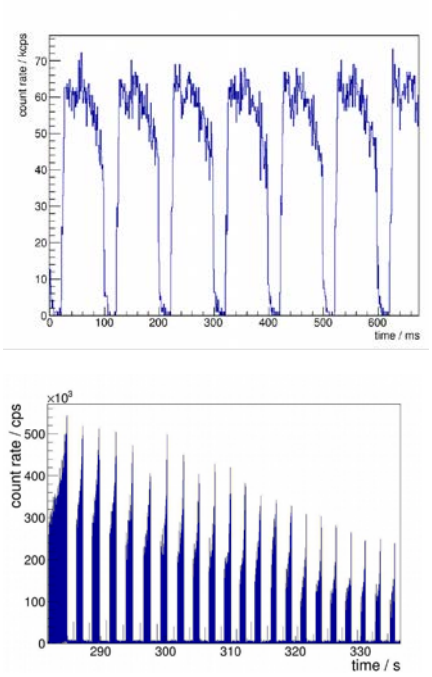


Figure 1: Count rate over time during DS (left) and PBS (right), recorded at 2 Gy/min at different distances.

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

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**Proton Beams for Physics Experiments at OncoRay**

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