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Prof. dr hab. n. med. Krzysztof Składowski

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FaDu-derived radiochemotherapy-resistant clonal cell lines as an experimental model system in exosome research: preliminary study

A. Abramowicz[1], I. Tinhofer-Keilholz[2], P. Widlak[1], M. Pietrowska[1]
[1] Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland
[2] Department of Radiooncology and Radiotherapy, Charite University Hospital, Berlin, Germany

Introduction/Rationale
Exosomes are small nanovesicles secreted into extracellular milieu by fusion of late endosomes with plasma membrane. They can be found in various body fluids like blood, urea, cerebrospinal fluid or saliva. However their function is still intensively studied, their impact on intercellular communication and immune response modulation is increasingly studied making them a promising object for biomarkers investigation as well as for disease development and therapy response comprehension. Indeed, variable sensitivity of cancer cells within a tumor to treatment is commonly observed and the cause of this phenomenon is certainly multi-faceted and as desirable as elusive.
Here in our study we examined FaDu cells diverse in terms of sensitivity to radiation and cisplatin treatment as an experimental model for investigation of a potential role of exosomes in response to genotoxic agents by characteristics of proteome components of their cargo.

Materials and Methods
The four clonal cell lines (C78, C5, C46 and C54) derived from human HNCC cell line FaDu (ATCC HTB-43), established in the late sixties from a punch biopsy of an hypopharyngeal tumor, were characterized according to their radiochemosensitivity. The clonogenic assay was performed using doses of 2, 4, 6 and 8 Gy of ionizing radiation and doses of 10, 100, 500, 1000 ng/mL of cisplatin. Cell viability and proliferation ability were assessed using crystal violet assays. For immnodetection of stress-induced proteins like p53 the Western blot analysis was performed. Exosomes were isolated using ultrafiltration method and purified by size-exclusion chromatography with Sepharose 2B. They were evaluated by Western blot and electron microscopy techniques.

Results
Our studies indicate that the selected clonal cell lines varied in their sensitivity to genotoxic agents. The C78 clonal cell line was clearly resistant to both ionizing radiation and cisplatin. The low doses of treatment (2 Gy or 10 ng/mL of cisplatin) had no significant influence on clonal ability of this cell line, whereas for other more sensitive cell lines: C54, C46, a two-fold decrease in the number of colonies was observed. In case of cisplatin dose of 100 ng/mL completely inhibited the growth of C54 and C46 cells while about one fifth of C78 and C5 cells was still able to create colonies. Moreover, sensitivity of individual clones was correlated with p53 status: resistant cells express p53 protein at the same level as in FaDu wild type cell line, whereas p53 was not detected for sensitive clones. Western blot analysis and electron microscopy confirmed the presence of exosomes in samples derived from the examined cell lines.

Conclusions/Novel Aspects
Based on the presented results we conclude that the FaDu-derived radiochemotherapy-resistant clonal cell lines have a great potential in proteomic studies of exosomes secreted by cells of varying sensitivity to genotoxic agents.

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Implantable Cardioverters-Defibrillators and Cardiac Resynchronization Therapy – Defibrillator Devices in the Setting of Helical Tomotherapy: An in vitro Study

S. Blamek[1], M.Tajstra[2], E. Gadula-Gacek[2], D. Gabryś[1], B. Niewiadomska[3], A. Bekman[3], Ł. Dolla[4], M. Gąsior[2], P. Marczyński[5]

[1] Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Silesian Center for Heart Diseases, 3rd Department of Cardiology, Zabrze, Poland,
[3] Department of Medical Physics, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland,
[4] Department of Radiotherapy and Brachytherapy Planning, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[5] Independent Cooperator, Kraków, Poland

Introduction/Rationale
The aim of the study was to test the susceptibility of modern implantable cardioverters-defibrillators (ICDs) and cardiac resynchronization therapy-defibrillator devices s to scattered ionizing radiation and electromagnetic interference during conventionally fractionated radiotherapy delivered with a helical tomotherapy (HT) device operating with a 6 MV accelerator.

Materials and Methods
A set of 24 cardiac implantable electronic devices (CIEDs) from three manufacturers was tested. The devices were programmed in the same way as it is done in clinical conditions. The CIEDs were placed on an anthropomorphic phantom in both subclavian areas and scanned with computed tomography. A standard plan for prostate cancer treatment was prepared. The phantom with CIEDs was irradiated with daily fractions of 2 Gy and after each fraction the devices were interrogated to search for potential malfunctions or operation parameter changes. A total dose of 78 Gy was delivered to the target volume (44 Gy pelvic lymph nodes and 34 Gy boost to the prostate). Four CIEDs were tested simultaneously, consequently, six radiotherapy courses were needed to complete the study. The capacitor charge test was performed after each fraction in 16 devices offering this function and full interrogation report was recorded for analysis. Dosimetric measurements with thermoluminescent dosimeters were performed to verify the dose delivered to the CIEDs.

Results
In two devices software errors were detected. In one, the left ventricle (LV) pulse amplitude originally set to 4.5 changed spontaneously either to 4.375 V or to 4.625 V several times and returned to the predefined value after 66 Gy. A partial reset of the device memory with patient data loss and inadequate detection of ventricular fibrillation (VF) without defibrillation after delivery of 42 Gy was observed in another device, from a different vendor. After next 7 fractions the same device detected a nonexisting VF again and delivered an inappropriate shock. According to the TLD measurements, the mean maximum doses did not exceed 15 cGy for the whole course of radiotherapy.

Conclusions/Novel Aspects
The operation of at least some models of modern CIEDs can be negatively affected by the helical tomotherapy machine. Further studies are needed to elucidate the exact source of interference as the energy of photons and doses accumulated in the CIEDs were within limits considered safe according to the current knowledge.

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^{1}H NMR based metabolomic in monitoring of the head and neck cancer treatment toxicity

Ł. Boguszewicz[1], A. Hajduk[2], A. Skorupa[1], M Ciszek[1], J. Mrochem-Kwarciak[3], K. Składowski[2], M. Sokół[1]

[1] Department of Medical Physics, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] 1st Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[3] Analytics and Clinical Biochemistry Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland

Introduction/Rationale
Sequential and concurrent radiotherapy and chemotherapy, a standard organ preservation treatment for head and neck squamous cell carcinomas (HNSCC), results in temporary or permanent toxicity considered as changes in normal tissues and/or involved regions. Furthermore, anticancer treatment affects composition and concentrations of metabolites in body fluids. In case of HNSCC the acute radiation sequelae (ARS) was studied only at the genomic, proteomic and lipidomic levels. We aimed to identify and investigate molecular processes of treatment toxicity in HNSCC patients using high resolution ^{1}H NMR and NMR-based metabolomics of blood serum.

Materials and Methods
45 HNSCC patients were treated with radiotherapy/chemoradiotherapy (RT/CHRT). Severity of ARS was monitored throughout and after the treatment until the resolution of all the ARS symptoms. The patients were divided into two classes (of high and low ARS) on the basis of the highest individual ARS value observed during the treatment. Blood samples were collected within a week after RT/CHRT completion. ^{1}H NMR spectra of serum samples were acquired on a 400.13MHz spectrometer at 310K and analyzed using principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA). Additional statistical analyses (Mann-Whittney test, Pearson correlation) were performed on quantified metabolites.

Results
The metabolic features characteristic for high ARS are the increased signals of N-acetyl-glycoprotein (NAG) – the NMR marker of inflammation, and acetate – a product of beta-

oxidation of adipose tissue fatty acids. The high ARS group showed also the decreased signals of metabolites involved in energy metabolism: branched chain amino acids (BCAAs), alanine, creatinine, carnitine and glucose as well as decreased choline containing compounds reflecting disturbed membrane metabolism. Furthermore, we observed the positive correlations between C-reactive protein (CRP) and N-acetyl-glycoprotein as well as acetate and a percentage weight loss during the treatment. CRP was also negatively correlated with alanine and BCAAs. NAG was found to be positively correlated with C-reactive protein (CRP), while alanine and BCAAs showed negative correlation with CRP. We also observed a positive correlation between acetate and a percentage-weight-loss during the treatment.

Conclusions/Novel Aspects
^{1}H NMR is an efficient tool for detection of RT/CHRT toxicity markers in human serum. The results indicate at least three concomitant processes related to high treatment toxicity (high ARS): inflammation, altered energy metabolism and disturbed membrane metabolism. The combination of clinical and molecular approaches could deliver comprehensive information on treatment response, allowing monitoring and/or prediction of tolerance/toxicity of therapy as well as its outcome. Such approach gives a step forward into personalized therapy.

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[1] Department of Medical Physics, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] 1st Radiation and Clinical Oncology Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[3] Analytics and Clinical Biochemistry Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland

Introduction/Rationale
Head and neck cancer involves different squamous cell carcinomas located in larynx, pharynx, oral cavity, and tongue, which play crucial roles in respiratory, nutritional, social and communicative functions. Treatment-induced toxicity in these organs often leads to a considerable impairment and seriously affects the patient's quality of life. Moreover, despite recent advances in treatment modalities, the overall survival and quality of life of patients with HNSCC have not improved significantly over the past decades, especially for patients with advanced stages. In recent years more attention is given to personalized medicine, which is considered to lead to significant improvement in disease control. This study presents our first approach to predict the treatment outcome in HNSSC patients.

Materials and Methods
30 HNSCC patients treated with radiotherapy/chemoradiotherapy (RT/CHRT) were included into the study. Blood samples were collected several days before and within a week after RT/CHRT completion. All patients were followed up regularly in terms of loco-regional and distant recurrences for at least 3 years. ^{1}H NMR diffusion edited spectra of serum samples were acquired on a 400.13MHz spectrometer at 310K and analyzed using principal component analysis (PCA). Additional statistical analyses were performed on quantified signals arising from lipids at 0.9 and 1.3 ppm.

Results
The PCA method clearly separated patients with treatment failure or disease recurrence confirmed within 6 months after the treatment completion (ETF – early treatment failure). Statistical and visual analysis showed that in patients with ETF lipid signals at 0.9 and 1.3 ppm does not statistically change after the treatment while in patients without ETF lipid signals are significantly lower after the treatment when compared to pretreatment values.

Conclusions/Novel Aspects
Monitoring of serum lipid signals via ^{1}H NMR may be potentially successful in "real time detection" of patients with potential early treatment failure. More frequent monitoring of serum lipids, e.g. weekly, may give better understanding to lipid metabolism during anticancer treatment. It may be also possible to modify treatment scheme for selected patients in order to improve treatment outcome. Such approach gives a step forward into personalized therapy.
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Dose distribution deformation based on deformable registration

Iwona Brąclik[1], Wojciech Osewski[2], Krzysztof Ślosarek[1]

[1] Radiotherapy Planning Department
[2] Radiotherapy Department; Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, PL

Introduction/Rationale
Deformable image registration (DIR) is interesting technique for multi-modality image fusion, anatomic image segmentation, four-dimensional dose accumulation and lung ventilation imaging. It is playing important role in image guided radiotherapy and adaptive radiotherapy. DIR is a method of aligning different images: CT to MR, PET to CT or CT to CT.

Materials and Methods
Last year in our institution Velocity system was used for re-irradiation patients with recurrence malignancy disease. DIR

was performed for 50 patients with recurrence disease. Among all there was16 head and neck region, 16 thorax region, 10 pelvis region, 7 abdomen region and 1 brain site. That group contained both patients with radical intent and palliative treatment. Dose distribution transferred to the new volume, through standard rigid registration, was compared with deformed dose distribution based on DIR. Dose distributions in the tumor volumes and organs at risk were analyzed.

Results
Aligned images: CT, MR and PET were compared, combined or analyzed. Re-irradiation in the same region is very often in oncology patients, especially in head and neck region and lungs. Re-irradiation to high curative doses is very difficult because of nearness of organs at risk such as: spinal cord, mandible. DIR might be useful tool to assess the dose distribution delivered to the tumor volume and organs at risk. Directly comparison of dose distribution between first cycle of radiotherapy and second one with tumor recurrence is very difficult, due to difference between two CT volumes. Usage of DIR reduce the difference between two CT volumes and gives a possibility to deform dose distribution from first radiotherapy cycle to the new CT volume. This operation gives high accuracy information about already delivered dose.

Conclusions/Novel Aspects
The DIR is very useful method to analyze dose distribution in re-irradiation of recurrence cancer tumors in regions with many life worth organs (e.g. head and neck or lung). That method allows to deliver higher dose to tumor volume and to save organs at risk.

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Influence of Low Iodine-131 Doses on Susceptibility to Ionizing Radiation and Biomarkers of Health Risk

Antonina Cebulska-Wasilewska[1,3], Mateusz Krzysiek[2], Grażyna Krajewska[1], Artur Stępień[3], Artur Stępień[3,], Paweł Krajewski[1]

[1] Central Laboratory for Radiological Protection, Konwaliowa 7, Warsaw, Poland,
[2] Institute of Nuclear Physics, Polish Academy of Sciences, Krakow, Poland,
[3] Central Center for Radiation Emergency, 5thMilitary Hospital & Public Polyclinic, Krakow, Poland

An emerge of the ^{131}I in the ambient air might be a one of the first sign of misfortune. Despite the fact that precautions are clearly established, nuclear power plants accident or any radioactive threat might happen. Iodine in human body is preferentially concentrating in the thyroid, thus ^{131}I is frequently used in nuclear medicine to diagnose or cure it. We have reported earlier strong variability in biomarkers of health risk[1] detected in lymphocytes of patients after diagnostic as and now we report cellular responses to high X-rays challenging dose as well as DNA repair capacity, observed in whole blood samples collected from 41 subjects exposed to diagnostic ^{131}I dose, and 30 persons unexposed. Aim of this study was to find out how results of the DNA repair competence with SCGE assay and sister chromatid exchanges (SCE), that were applied to study an association between biological end points on molecular and cellular levels. On average, lymphocytes of ^{131}I diagnosed subgroup expressed statistically significant increase in repair efficiency of DNA damage induced by challenging dose, when compared to average from respective unexposed control group. That increase was followed by strong and significant decrease in percentage of HFC. The increase in repair efficiency have also corresponded to significant decrease in MN frequency, that had been reported before[1]. However, molecular (DNA) and cellular responses (SCE, HFC and MN) of cells from persons exposed to low (diagnostic) I-131, were still characterized by high variability between individual responses. Presented here results show that variability between individual responses of the DNA and cellular responses (SCE, and HFC) are dependent on gender and cancer predisposition in immediate families. When investigated groups are stratified according to polymorphism in XRCC genes, results of investigated biomarkers which are associated with various DNA repair mechanisms, reveal significant dependence on polymorphism in XRCC13 (241) and XRCC1(399) genes. Although, still observed inter-individual variability in biomarkers levels suggests necessity of enlarging polymorphism's study, though, model of short-term battery is proposed, applicable for triage and prediction of health risk from IR.

References:
[1] Cebulska-Wasilewska A. et al.(2011) J. of Kor. Radiat. Ind., Vol. 5, No 4. ISNN 1976-2402

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10-years of CBS and IORT (INTRABEAM) combined with postoperative EXRT for early breast cancer: incidence and kinetics of local recurrence (LR) and distant metastases (DM)

A. Celejewska, J. Wydmański, A Tukiendorf

Radiotherapy Department, Cancer Center and Institute of Oncology, Gliwice, Poland
Department of Epidemiology, Cancer Center and Institute of Oncology, Gliwice, Poland

Aim of the study
To evaluate efficacy and tolerance of the IORT + EXRT (+\-chemotherapy) for T1-T2 breast cancer with a special focus on incidence and kinetics of LR and DM during 5-yr and 10-yr follow-up.

Material and methods
Series of 215 patients (T1-T2) treated in 2003-2006 are subdivided into two groups: low risk (A) with 109 cases and intermediate risk (B) with 106 cases. Median age was 54 yrs (27-77 yrs). IORT was delivered during CBS using

low energy (20-50 kV) radiation beam with RBE=1,7 by spherical applicators (2-5 cm.) adjusted to the site after tumor removal. Biological dose for a/b=4 was BED=12,8 $_{izoGy2.0.}$ External fractionated irradiation (EXRT) was delivered using high energy photons (6-20 MV) by Linac with 3-D IMRT technique. BED for EXRT was 50 $_{izoGy2.0.}$ In the group (A) only IORT + EXRT were given , and in the group (B) EXRT was combined with chemotherapy either during CHT or thereafter. Time interval between IORT and EXRT ranged from $\leq$ 60 days to even more than 150 days.

Results
Overall 5-yr LR free survival was 96.3% and 94.4% for 10-yr follow-up. DM free survival was respectively 95.2% and 89.9%, and DFS 92.0% and 84.8%. There were 12 (5,5%) LR and 21 (9,7%) DM recorded during 10-yr follow-up. However, respective accumulated incidence of the LR and DM show by so-called "biophasic", but not countinous curves. From there curves has been calculated that 35% of the LR and 65% of the DM occured between 5-10 yrs. Analysis of time interval between IORT and EXRT shows that begining of the EXRT delayed by more than 60 days result higher incidence of the LR and DM by 2-5 folds. Similar trend was noted when EXRT was delayed after chemotherapy compared with EXRT delivered during postoperative chemiotherapy.

Conclusions
IORT combined with EXRT is effective and tolerable for early breast cancer but 5-yr follow-up is too short to record all LR and DM, and at least 10-yr follow-up is recommended. EXRT delayed by more 60 days after IORT should be avoided otherwise incidence of the LR and DM significantly increases. Similar trend was noted when EXRT was delayed and delivered after chemotherapy in group (B), in contrary EXRT with CHT decreses incidence of both failure types.

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Triphasic [^{18}F]-Fluorodeoxyglucose CT-PET in the differential diagnosys of lung nodules and mediastinal lymph nodes: initial results

Andrea d'Amico[1], Olgierd Chrabański[1], Izabela Gorczewska[1], Marcin Zieliński[2]
[1] MSC Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Department of Thoracic Surgery, Pulmonary Hospital, Zakopane, Poland

Introduction/Rationale
CT-PET with [^{18}F]-Fluorodeoxyglucose (FDG) is a well established method for characterization of solitary lung nodules (SPN) and staging/restaging patients with non-small cell lung cancer (NSCLC). However, several non neoplastic processes can lead to an aspecific FDG uptake, thereby decreasing the specificity of the examination. Basing on the assumption that neoplastic and inflammatory processes should have different FDG accumulation kinetics, biphasic acquisition was suggested in order to better define the nature of lesions showing FDG uptake ("Dual-point PET"). Recentely, a more complex model was proposed to distinguish malignancy from inflammation by a triphasic FDG CT-PET acquisition, with scan after 60, 90 and 120 minutes. The values of Maximum standardized uptake values (SUVmax) calculated for every lesion and their slopes were showed to be more effective in differential diagnosys.

Materials and Methods
All patients with SPN diagnosis at Zakopane Pulmonary hospital were prospectively sent to Gliwice PET laboratory and underwent triphasic PET scan from march 2016. Patients with previous history of malignancy were excluded. A whole-body FDG-PET was carried out 60' after FDG injection, with successive thoracic acquisition at 90' and 120'.

Results
Twenty-six patients with SPN were prospectively enrolled and had triphasic CT-PET. Only patients for whom histopatological specimens were obtained after thoracotomy were succesively taken into account. Ten patients with overall 19 lesions (both SPN and mediastinal FDG uptake sites) were enclosed for further statistical analysis.
SUVmax values with SUVmean, metabolic tumor volume and total lesion glicolysis were obtained for every lesion. Differences between SUVmax at 60, 90 and 120 min were calculated (ΔSUV90-60, ΔSUV120-90 and ΔSUV120-60). A strong positive correlation was found between ΔSUV120-90 and presence of malignancy, whereas significative correlation between malignancy and ΔSUV120-60. No signicative correlation between presence of cancer and ΔSUV90-60.

Conclusions/Novel Aspects
The three-point evaluation of FDG kinetic in a small group of patients suspected for lung malignancy may add valuable information to predict the presence of intrathoracic malignancy. If validated in a large patients dataset, triphasic PET could influence the radiotherapy planning of NSCLC patients by characterization of mediastinal FDG uptakes suspected for cancer spread.

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Evaluation of the 18-FDG-PET/CT in radiotherapy planning for unresectable or inoperable gastric cancer patients

K. Dębiec[1], I. Gorczewska[2], P. Leszczyńska[3], K. Gorczewski[2], W. Leszczyński[3], M. Kalemba[4], J. Wydmański[5]

[1] Radiotherapy and Chemotherapy I Clinic, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[2] Department of PET diagnostics, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[3] Department of Radiotherapy Planning, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[4] Department of Nuclear Medicine and Endocrine Oncology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[5] Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Introduction/Rationale
The aim of this study is evaluation the usefulness of the 18-FDG-PET/CT examination in gross tumour volume (GTV) delineation for unresectable or inoperable gastric cancer patients. The research includes a comparison of differences in visibility of the tumour volume between PET examination and then CT alone. Additionally the MTV region which corresponds to defined in CT study infiltration was estimated.

Materials and Methods
Retrospectively, 29 examinations of 18-FDG-PET/CT for radical gastric cancer patient's radiotherapy planning were analysed. Since 5 patients (1 due to excess of blood glucose levels, 1 due to false-negative PET and 3 patients because of 18-FDG-PET/CT discovered distant metastases) were excluded from the study, in further analysis the 24 cases were evaluated (17 unrespectable and 7 inoperable). Non-contrast total-body spiral CT scans were obtained first, followed immediately by FDG-PET imaging. The CT and PET scans were automatically registered (both in a therapeutic position). Analysis involved measurements of metabolic tumour volumes (MTVs) on PET/CT workstations. To obtain MTVs there were used different threshold values: SUV absolute value of 2.5%, 10%, 20%, 30%, 40%, 50%, 60% and 70% of SUVmax, and liver uptake-based. Moreover the GTVs were defined in radiotherapy planning system (Eclipse 13.10....). First the GTVs based on the CT scans alone were created and next on the PET dataset, blinded to CT. The PET based volumes (manually delineated GTV_{PET} and semi-automatically obtained MTVs) were correlated with the referenced $GTV_{CT.}$ The volumes of GTV_{CT} and GTV_{PET} were quantitatively compared with an index of conformity (CI), which is the ratio of the intersection of two GTVs to their union.

Results
The mean CI was 0.52 (range, 0.12-0.82), and in 13 patients (54%) GTV_{PET} was larger than $GTV_{CT.}$ Moreover, cranio-caudal diameter of GTV_{PET} in 16 cases (64%) was larger than GTV_{CT} . Manual PET delineation (GTV_{PET}) reached the best correlation with CT-based tumour volume (Pearson correlation = 0.55, $p<0.0001$). Among the analyzed MTVs statistically significant correlation with GTV_{PET} revealed for MTV_{10} ($r = 0,63$; $p = 0,0014$); MTV_{liv} ($r = 0,60$; $p = 0,0021$), $MTV_{2,5}$ ($r = 0,54$; $p = 0,0063$); MTV_{20} ($r = 0,44$; $p = 0,0344$); MTV_{30} ($r = 0,44$; $p = 0,0373$).

Conclusions/Novel Aspects
The incorporation of 18-FDG-PET/CT studies may improve the gastric cancer's radiotherapy planning. The 18-FGD-PET examination is a source of biological information about the tumour, which does not provide the CT alone. The manual delineation method of 18-FDG-PET lesions shows better correlation with tumour defined by CT, than semi-automatic method which applies a threshold based on a percentage of SUVmax within the tumour. The autosegmentation of the tumour volume in gastric cancer radiotherapy should be based on lower levels of the SUVmax cut-off. The obtained MTV must be precisely verified by a physician who preparing a treatment.

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Nanocarriers of doxorubicin via thermally induced aggregation of its polymeric conjugates

A. Dworak, D. Lipowska, R. Szweda, D. Szweda, J. Suwiński, B. Trzebicka

Centre of Polymer and Carbon Materials, Polish Academy of Science, Zabrze, Poland

Carriers with the active species connected in different way are frequently used to improve the efficiency of treatment and to overcome or lower the undesired side effects caused by therapeutics. The development of carriers is frequently considered to constitute a focal points of research, aimed at the control of release and targeted delivery of active species. Amongst the studied carriers those based upon synthetic polymers play an important role due to actual or expected advantages.
Here we outline a novel approach to carriers using thermoresponsiveness of synthetic polymers as the key to its self-organization into particles of desired size, containing covalently bound active species. The particles can be stabilized and in certain conditions disintegrated with simultaneous release of the drug.
Here doxorubicin was chosen as a payload on nanocarriers. Nanoparticles were formed by thermal co-aggregation of thermoresponsive chains with part of azide groups linked with DOX and respective polymeric partner with alkynes what allowed for their crosslinking in Huisgen reaction proceeding in water under mild conditions. Degradation and simultaneous DOX release takes place by breaking of carbamate bonds in the nanocarrier. There are reasons to expect that the outlined approach, using thermoresponsiveness and water-based coupling reactions, is of fairly broad scope and opens a route to a new class of carriers.

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Cardiac toxicity after breast cancer patients treatment

D. Gabrys[1], A. Piela[2], A. Walaszczyk[3], R. Kulik[4], A. Namysl-Kaletka[1], I. Wzietek[1], K. Trela-Janus[1], S. Blamek[1]

[1] Radiotherapy Department
[2] Oncological and Reconstructive Surgery Department
[3] Center for Translational Research and Molecular Biology
[4] Radiotherapy and Brachytherapy Planning Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland

Radiation and anthracyclines are known to induce cardiac damage. Despite the use of 3D planning the heart is still irradiated with non-negligible doses, therefore this problem needs further investigation. We perform an analysis of cardiac function in the left sided breast cancer survivors. Patients were treated with surgery alone (S), additional radiation (RT), additional anthracycline based chemotherapy (A) or both (RA).
A total of 140 patients were subjected to cardiological evaluation more than 8 years after primary treatment. We performed ECG and ECHO (in a part of patients we also had an ECG and ECHO performed before surgery), blood tests, chest X-ray. We also collected additional relevant information on patients (history, comorbidities, current treatment, etc.). Distribution of patients was as follows 50% RA arm, 18% S, 8% RT, 24% A. The mean time from the beginning of the treatment to examination was 12.2 years (8-15.9) in S, 11.7 (8-16.9) in A, 10.7 (8-15.3) in RT, 10.1 (8.1-14.5) in RA. The majority of patients were treated with amputation (74%), the remaining with BCT. In chemotherapy arms 47% were treated with FAC, 31% with CAF, 19% with AC, and 3% with TE. Hormonal treatment was given to 64% of patients, in the majority of them it was Tamoxifen-based. Radiotherapy dose varied between 50 and 70 Gy.
There was no significant difference in ejection fraction (EF) between the groups: median 56 (47-65) in S, 50 (25-65) in A, 55 (47-62) in RT and 54 (35-67) in RA. Other evaluated parameters like size of the right and left ventricle, left atrium, thickness of septum and posterior wall also did not differ between groups. In the whole group in 21% of patients we observed chronic cardiac insufficiency. In 58% of patients there were other cardiovascular disorders as hypertension, hypercholesterolemia, atherosclerosis, arrhythmias, and valvular disorders. Only in one patient treated with radiation and chemotherapy we found impaired heart function without other additional causes.
In the current series no unequivocal association between treatment regimen and long-term cardiac dysfunction could be found. Further studies in a wellbalanced patient population are needed to elucidate the impact of contemporary anthracycline-based systemic treatment and modern irradiation techniques on cardiac outcome. The research received funding from National Science Center Poland under grant no. N N 402 6856401685640

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Machine log file analysis as a part of treatment Quality Assurance with proton scanning beams

J. Gajewski[1], M. Bednarczyk[2], K. Skowrońska[1], L. Stolarczyk[1], T. Kajdrowicz[1], P. Olko[1]

[1] Institute of Nuclear Physics, Kraków, Poland
[2] University of Strasbourg, Strasbourg, France

Modern cancer treatment methods use high energetic ions to irradiate the treatment volume while spearing the surrounding healthy tissue. Advanced modalities employ a narrow pencil ion beams of different energies and sizes to scan the volume point by point while being deflected by set of scanning magnets. A treatment plan prepared by a Treatment Planning System (TPS) implies specified beam positions, number of Monitor Units (MU) and energies for each spot. During irradiation single pencil beam parameters, such as: position, current or energy are controlled every 250 ìs by Proton Therapy System (PTS), in particular by Scanning Controller (SC) equipped with Plane-Parallel Ionisation Chambers (PPIC) and Multi-Wire Proportional Chambers (MWPC). Information about measured quantities is stored in log files and allows to verify quality of the treatment after irradiation by comparison with the treatment plan.
Dedicated software for log importing and analysis has been prepared in Matlab R2016a environment. Selected data, such as: information about position of the beam at a defined distance from the isocenter or amount of charge generated by the beam in PPICs and MWPCs, may be analysed. Prepared software recalculates position of the beam to isocentre plane and using data about site configuration, also stored in log files, recalculates charge to MU considering several correction factors (e.g. temperature and pressure factor (K_{PT}), PPIC position dependent gain and chamber charge-MU calibration). Moreover software allows to compare all the calculated data with the treatment plan and displays the results in a graphical form. After log importing it is possible to generate a corresponding treatment plan based on beam positions and weights measured by PTS during treatment. TPS can then recalculate new dose distribution and compare it to the original one. Alternatively the comparison may be performed for two 3D dose distributions in an external software, using e.g. gamma index analysis.
An example brain tumour treatment plan was irradiated in gantry-1 room at Bronowice Cyclotron Centre (CCB) and log files were analysed. It has been verified that all spots were delivered within 1 mm distance from the planned position, which meets the acceptance criterion. The delivered MU/spot are consistent with the planned within 5%. Gamma index test comparing planned and delivered layers showed above 98% of pixels passing the criteria (2 mm and 2%) of the test, whereas the biggest differences were observed in distal region.
Log file analysis performed after treatment is a promising tool for verification of treatment quality with proton pencil beam scanning technique. Ultimately, along with TPS it allows to calculate 3D dose distribution, compare it with the original plan and point out regions under- or over-irradiated.

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Somatostatin receptor scintigraphic imagining and clinical decision making in advanced esthesioneuroblastoma

M. Gawkowska[1], Ewa Chmielik[1], A. de Amico[1], W. Bal[1], E. Nowicka[1], B. Bobek-Bilewicz[1], R.Tarnawski[1]
Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Management of advanced esthesioneuroblastoma is challenging mainly due to the rarity of the entity. There are no well establish standard of treatment. Addition of radiotherapy to maximal safe resection is commonly accepted. The role of chemotherapy is controversial although is recommended in advanced stages. Esthesioneuroblastoma express receptor for somastatin enabling scintigraphy imagining with radioactive somatosatin analogies. The aim of the study is to describe our experience in application of receptor scintigraphic imagining (PET/CT with Ga-68 Dotatate) in decision making for management based on the two cases of patients with advanced ENB.

Materials and Methods and Results
The first patients is a 39 year old male referred in 2012 to MCCIO with recurrent and metastasizes to lymph nodes neck. ENB was diagnosed 5 years earlier. He had underwent 3 local surgery and two lymphadenectomy since 2008.
At presentation PET/CT with Ga-68 Dotatate showed large local and the neck's lymph nodes region of pathological activities. FDG PET/CT showed trace of pathological activities in the neck's lymph nodes.
The patient was treated exclusively by radiotherapy. The SIB technique was applied: the postoperative bed plus surrounding nasal sinuses were treated to the total dose 54 Gy (df 1,8 Gy) plus simultaneous boost 0,2 Gy to metastatic cervical lymph to the total dose of 60 Gy. Ga-68 Dotatate PET/CT scans was performed 4 times after treatment and for the first thirty months gradual decline in pathological activities was observed. Since then the pathological activities have been fluctuating, with tendency to increase in retropharyngeal node, but still fulfilling the criteria for stable disease.
The second case concerns 56 years old women referred in 2012 to MCCIO due to recurrent ENB. Earlier In the same year the patient underwent subtotal resection of tumor situated in the base of a skull . Eight months after surgery local recurrence was visualized on MRI examination and ENB was confirmed. The PET/CT with Ga-68 Dotatate showed only scarcely pathological activities in the peripherals of the tumor. The PET/CT with F-18 FDG showed strong homogenous pathological activities in the visualized tumor. The patients received neoadjuvant chemotherapy , after 2 courses - the MRI showed partial remission of the mass. After completion of chemotherapy radiotherapy was started. Forty five Gy in 25 fraction was delivered to the residual tumor. Three months after radiotherapy complete metabolic response was observed in Dotatate and PDG PET scans. Six months after treatment assuming that the maximal shrinkage of the tumor was obtained, a boost with radiosurgery to the residual mass to a total dose of 16 Gy at 88 % isodose was given in two fraction. 21 months after the first presentation in MCCIO , the patient was diagnosed with metastases to the tibia . One fraction of radiotherapy enabled complete disappearance of pain. At the same time PET/CT with Ga-68 Dotatate and F-18 FDG show no active uptake in the region occupied earlier by tumor.
One year later dissemination to cauda equine was identified. Palliative radiotherapy was applied (30 Gy in 10 fraction). Rapid relive in symptoms was reported.
On the last follow up visit 36 months after the first presentation in MCCIO, the patients is well, except blindness.

Conclusions
Our assumption is that imagining by receptor scanning is probably the best way to clinically assessed the degree of differentiation of ENB and to predict a response to chemotherapy.
Supposing that, similar to childhood neuroblastoma, low expression of somatostain receptors correlate with more aggressive course of disease we propose that chemotherapy should be consider in patients with sparse uptake on PET/CT with somatostain analogies and with strong activities on 18-FDG PET. On the opposite side there are tumors with limited pathological uptake on FDG PET but with high uptake on PET/CT with somatostain analogies. In that cases radiotherapy as the sole modality of treatment (or with surgery) should be a reasonable option.

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The efficacy and safety of stereotactic radiation therapy in patients with multiple intracranial meningiomas – a case report

Hanna Grzbiela[1], Małgorzata Stąpór-Fudzińska[2], Rafał Tarnawski[1]
[1] III Radiotherapy and Chemotherapy Clinic
[2] Radiotherapy Planning Department Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Gliwice, Poland

Introduction/Rationale
Radiation therapy in patients with multiple meningiomas requires an extremely precise target definition and dose delivery, making the stereotactic techniques a useful tool in treatment of multiple intracranial lesions.

Case presentation
We present the case of a 61-year-old man diagnosed with meningioma of the left frontal lobe in 2011. He underwent neurosurgery with total tumor excision (pathology was atypical meningioma WHO 2) and radiotherapy (54 Gy in 27 fractions to the tumor bed), but one year after the completion of treatment he began to complain about diplopia and left upper eyelid ptosis. The MRI revealed a recurrent tumor and the patient received stereotactic radiotherapy (14 Gy in a single fraction). Some months later the MRI showed a stable parasagittal mass, but two new lesions were found – one in the sella turcica region and the other adjacent to the greater wing of the right sphenoid bone. The patient underwent transsphenoidal biopsy (pathology was transitional partial atypical meningioma WHO grade 2), but was not qualified for neurosurgery due to high risk of

bleeding. Instead, he received stereotactic radiotherapy with CyberKnife™ to the parasellar lesion (18 Gy in 3 fractions). The MRI scan performed three months later revealed stable parasagittal and parasellar lesions, but considerable progression of the tumor adjoining the sphenoid bone. CyberKnife™ stereotactic radiotherapy was used to irradiate the progressing tumor – the patient received 22 Gy in 4 fractions.

Results
One months after the irradiation of the parasellar tumor, the patient reported a much better sharpness of vision and also regression of other symptoms, including ptosis of the left upper eyelid. After the last course of radiation therapy, within the next year no further tumor progression was observed. The patient did not report any neurological or other symptoms, which could be associated with the toxicity of radiation therapy.

Conclusions/Novel Aspects
In patients with multiple intracranial meningiomas, stereotactic radiation therapy can be considered as a safe and effective method of treatment.

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Consolidation treatment with somatoatatin analogues after radiopeptide therapy

D. Handkiewicz-Junak[1], A. Syguła[1], J. Szczasny[2], T. Olczyk[1], K. Hasse-Lazar[1], B. Jurecka-Lubieniecka1, A. Ledwon[1], A. Kotecka[1], B. Jarzab[1]

[1] Nuclear Medicine and Endocrine Cancer Department
[2] Radiology Department; MSC Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland

Introduction/Rationale
Although neuroendocrine tumours (NET) constitute a very heterogeneous group, most of them express somatostatin receptors that enable treatment with somatostatin analogues, that proved to be effective both as bio- or radiopeptide therapy. However, little is now about sequencing this two treatment modalities. The aim of our prospective study was to evaluate results of radiolabeled somatostatin analogues (PRRT) with or without „cold" somatostatin analogues (SA) as consolidation treatment.

Materials and Methods
Patient with well differentiated NET treated with PRRT (4 to 5 cycles repeated every 6 do 12 weeks) were eligible for the study. Carcinoid syndrome or second primary malignancy were exclusion criteria. After the last cycle of PRRT response to radiopeptide treatment was evaluated with scintigraphic, radiological and biochemical examination. Thereafter patients were randomly assigned either to treatment with Sandostatin LAR 20 mg (SAA-group) or observation group (OBS-group). Randomisation was 2:1. Initiation of next line of therapy was left to discretion of treating physician. Patients were followed-up at 4-12 months intervals with radiological examinations (CT or MRI) and receptor scintigraphy. Median time to progression was measured from the start of PRRT treatment till the day of disease progression confirmed in radiological or scintigraphic examination (diagnosis of new foci of pathological radiotracer uptake).

Results
One hundred twenty five patients were included into the study. Eighty one patients were randomly assigned to somatostatin analogues and 44 to observation group. The median follow-up the calculated from the start of PRRT was 62 months for the whole group of patients. During that time 52 (42%) progressed, 36 and 16 respectively in the SSA- and OBS-group ($p<0,05$). The median time to progression in the whole group of patients was 49 months and there was no difference in time to progression between SSA- and OBS-group.

Conclusions/Novel Aspects
Although biotherapy with somatostatin receptor proved to be effective to prolong DFS in patients with inoperable NET our preliminary results suggest that consolidation treatment with SA did not improve results of PRRT.

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Commissioning of the new ocular proton radiotherapy facility at the CCB IFJ PAN

T. Horwacik, B. Michalec, L. Grzanka, E. Durlak, E. Ogrodowicz, T. Nowak, M. Ptaszkiewicz, L. Malinowski, A. Rogóż-Duda, Ł. Góra, T. Kajdrowicz, J. Swakoń, P. Olko

The Henryk Niewodniczański Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland

Introduction/Rationale
A new cyclotron-based (C-230, IBA, Belgium) ocular proton radiotherapy facility has been commissioned at the Cyclotron Centre Bronowice in the Institute of Nuclear Physics of the Polish Academy of Sciences (CCB IFJ PAN). The new eye beam-line was designed and constructed at CCB IFJ PAN basing on experience gained over 5 years of clinical operation of the 60 MeV proton beam eye-line using in-house developed AIC-144 cyclotron. Advantages of the new eye therapy facility are increased proton range, stable beam delivery and improved robotic chair (BFI, France) for patient positioning. The patient's position verification system (PPVS) incorporates two orthogonal X-ray tubes (VMS Inc.) and two retractable flat-panel detectors (Hamamatsu). The Eclipse Ocular Proton Planning (EOPP, VMS Inc.) is used for treatment planning.

Materials and Methods
Each component of the new installation underwent detailed acceptance procedures including vendor and user-specific tests. Within requirements, acceptance procedures were specified to meet national health and CE certification regulations. To configure the EOPP TPS several proton beam parameters were determined based on percentage depth dose and lateral profile measurement in water. A survey was conducted to obtain a geometric model of the facility, including location of PPVS components and of axial and lateral beam forming devices. Preparation of quality assurance procedures concerning dosimetry was an important element of the facility's commissioning process. An intensive on-site, hands-on training programme was conducted for technical and medical personnel, followed by mock-up treatment runs involving anthropomorphic and eyeball phantoms.

Results
The commissioning tests included:
- survey to obtain geometrical model of the installation;
- verification of proton beam's, Patient Positioning System's (PPS) and Patient Position Verification System's (PPVS) geometry alignment;
- assessment of dose delivery precision;
- determination of dose versus monitor units dependence;
- dosimetry of proton beam in reference conditions (measured in water according to IAEA TRS 398 protocol);
- effectiveness of safety installations;
- evaluation of proton beam parameters stability over the working day;
- preparation of dosimetric and quality assurance procedures;
- gathering beam data for treatment planning system configuration;
- hands-on training for technical and medical personnel;
- mock-up treatment runs including production of specific beam forming elements (patient collimator and range modulator wheel).

Conclusions/Novel Aspects
The new installation for treatment of ocular tumors has been successfully commissioned at the CCB IFJ PAN and started clinical operations. This facility replaced the AIC-144 cyclotron-based ocular installation. By September 2016 proton radiotherapy was performed on 25 patients.

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Fast Monte Carlo simulation on GPU platform for particle therapy

Xun Jia

Monte Carlo (MC) simulation is widely regarded as the most accurate particle transport simulation method in radiation therapy. It plays a critical role in a variety of problems ranging from dose calculation for treatment planning to prediction of secondary particle distributions for treatment verification. Yet the long computation time posts a significant challenge hindering its applications in research and routine clinic. To overcome this challenge, we have performed extensive studies to develop high-performance MC simulation tools on graphics processing unit (GPU), a computational platform originally designed to solve computer graphics problems. Employing the high parallel-processing power of a GPU card and GPU-friendly parallelization implementations, we have achieved typically over 100 times speed up compared to conventional CPU-based MC simulations. For proton or carbon ion simulations, it takes 10∼100 seconds to transport 10 million particles on one GPU card. This presentation will first give an overview of the GPU-MC project at UT Southwestern medical center. It will then focus on the development of two packages for particle therapy: goPMC for proton therapy and goCMC for carbon ion therapy. A few applications of these packages in different clinical and research problems will be presented. Finally, I will present our recent studies on the extension of our MC tools to handle simulations at a microscopic level for microdosimetry and DNA damage calculations.

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Half-body irradiation as palliative treatment of patients with multiple painful bone metastases with application tomotherapy

Bozena Jochymek, Krzysztof Szczepanik, Leszek Miszczyk

Background
Hemibody irradiation is commonly performer treatment in cases of widespred paintfull skeletal metastases. HBI can be delivered as single fraction using 2D planning with large fields or 3D planning with tomotherapy. Among the downsides of clasic HBI are non- conformalty of beam-application with the inability to individallly spare organs at risk and its acute and late toxicity. With the development and clinical use of highly conformal radiation technologies such as Helical Tomotherapy we can spare organs at risk. This method offers advantages over the standard LINAC-based approach for beter control over and improvement of dose -distribution on target-structures and OARS. MV_CT-based guidance provides image-adapted beam-delivery after correction for patient movement and set-up errors. Patient were immobilised in supine position using customised thermoplastic mask. For contouring Varian Eclipse. PTV consist of bone metastasis with proper margins.

Aims
Evaluation of the acute toxity of single-fraction HBI and an assessment of its tolerance, evaluation of analgesic uptake, pain intensity and quality of life after HBI and comparison traditional and tomotherapy methods.

Material and Methods
23 patients were irradiated. The patients were examined on the day of irradiation and 2 and 4 weeks later. The intake of analgesic, pain level (from 0 to 10), and the quality of life(EORTC QLQ-C30) were evaluated. While blood cell and platelet counts were checked and diarrhea, skin toxicity, emesis intensity, and nausea were evaluated. Performance status improvement and weigh lost were assessed.

Results
Over the course of one month, the incidence of patients using analgesic and strong opioids decreased, the mean pain level decreased. Quality of life was improved.
No major hematologic, pulmonary or skin toxicity was noted. Most frequent symptoms were diarrhoea and vomites.

Conclusion
Presented form of hemibody irradiation is an effective treatment modality, giving an increase of life quality without significant radiation morbidity. Single- dose HBI is a safe treatment, causing a low percentage of low-level, acceptable adverse radiation sequels.

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Collaborative network for particle therapy centers in Italy, Poland, Austria, Czech Republic and Sweden (IPACS) on harmonization of modern proton therapy

Thomas Björk-Eriksson[1,2], Maurizio Amichetti[10], Anna Bäck[2,3], Joanna Bartoszewska[8], Andrzej Chmiel[8], Marzena Cygan-Bakoniak[5], Eleonora Góra[4], Joanna Góra[6], Magnus Gustafsson[2,3], Eugen Hug[6], Tomasz Kajdrowicz[5], Kamil Kisielewicz[4], Jirí Kubeš[7], Tomasz Kuszewski[9], Krzysztof Lis[9], Krzysztof Małecki[8], Ulrike Mock[6], Håkan Nyström[2], Paweł Olko[5], Adam Płoszaj[8], Zuzana Poulova[7], Marta Ptaszkiewicz[5], Beata Sas-Korczyńska[4], Katarzyna Skowrońska[5], Tomasz Skóra[4], Rafał Stando[9], Markus Stock[6], Marco Schwarz[10], Maret Sooaru[3], Rafał Tarnawski[5], Vladimír Vondrácek[7]

[1] Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden
[2] The Skandion Clinic, Uppsala, Sweden
[3] Department of Therapeutic Radiation Physics, Sahlgrenska University Hospital, Gothenburg, Sweden
[4] Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Cracow Branch, Krakow, Poland
[5] Cyclotron Centre Bronowice, the Henryk Niewodniczański Institute of Nuclear Physics, Polish Academy of Sciences, Krakow, Poland
[6] EBG MedAustron GmbH, Wiener Neustadt, Austria
[7] Proton Therapy Center, Prague, Czech Republic
[8] University Children's Hospital, Krakow, Poland
[9] Holycross Cancer Center, Kielce, Poland
[10] Agenzia Provinciale per la ProtonTerapia, Trento, Italy

Introduction/Rationale
Large clinical trials (ClTr) demonstrating superiority of protons compared to photons are sparse. Introduction of such new radiation therapy techniques requires huge effort and needs guidance. To partly overcome these problems a proton therapy (PT) network was formed. This initiative mainly attracted physicians and medical physicists from Italy, Poland, Austria, Czech Republic and Sweden forming the IPACS-group, Fig 1. The aim is to harmonize introduction of PT and create a solid platform for ClTr in order to increase the evidence for PT.

Materials and Methods
A first face-to-face meeting (f-t-f-) was held in Krakow in October 2014 and was followed by biannual f-t-f- and monthly online meetings. As a first step target and organ-at-risk delineations from five patients with malignancies in the head- and neck region were used for treatment planning (TP), see Fig 2. All centers created TPs based on the common agreed TP-protocol and ICRU report 78. TPs from all centers were compared and discussed.

Results
TPs from the IPACS centers are under comparative analysis. Even though TPs were designed according to the same TP-protocol some systematic differences were discovered. These were often due to different interpretations of the protocol originating from differences in local clinical practice and were reduced after discussions, Fig 3.

Conclusions/Novel Aspects
Discussions on TP-variables helped creating optimized and homogenized TPs. The IPACS group has become a forum for support and help in the introduction of PT. Collaboration like the IPACS group will not only enlarge the number of patients included in ClTr but also assure the quality of the TPs with increased patient safety.

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Using 3D dosimetry in radiotherapy: DosLab-Poland experience

M. Kozicki[1], K. Kwiatos[1], M. Jaszczak[2], P.Maras[3], S. Kadłubowski[4], E. Sąsiadek[1], M. Dudek[2]

[1] Department of Man-Made Fibres, Lodz University of Technology, Poland
[2] Institute of Materials Science and Engineering, Lodz University of Technology, Poland
[3] Medical Physics Department, Copernicus Hospital, Poland
[4] Institute of Applied Radiation Chemistry, Lodz University of Technology, Poland

Introduction/Rationale
The irradiation techniques that have been implemented in radiotherapy demand for corresponding and reliable dosimetry allowing for precise, high resolution measurements of radiation dose distribution in three dimensions. For this reason the 3D dosimetry studies have been initiated in1980s. Presently, several research groups make efforts to elaborate 3D dosimetry routines using a few 3D dosimeters: i) polymer gels, ii) dye gels, iii) dye plastics, iv) Fricke gels and v) radio-fluorogenic (RFG) gels. Currently, the DosLab-Poland group has been focused on 3D polymer gel dosimetry and 3D dye gel dosimetry. This announcement is to present the 3D dosimetry idea in general and to show recent achievements in modification of VIP 3D gel dosimeter that can be used in conjunction with magnetic resonance imaging (MRI) or computed tomography (CT), and a new dye gel 3D dosimeter to be used with optical computed tomography (OCT).

Materials and Methods
VIP 3D radiotherapy polymer gel dosimeter has been modified by alteration of its composition. Two components: N-vinylpyrrolidone (NVP) and N,N'-methylenebisacrylamide (MBA), have been examined in various concentrations in a co-solvent solution. The new gel (called VIC) samples have been irradiated with Clinac 2300 CDS, Varian, USA, and measured with NMR (0.47 T) relaxometer in order to derive R_2 ($1/T_2$) versus absorbed dose calibration relations and for further discussion of the geląs main characteristics. Some samples have also been analysed with CT towards elaboration of CT data processing. Another 3D gel dosimeter has been prepared from scratch by using a solution of a copolymer of polyethylene and polypropylene, and 2,3,5-triphenyltetrazolium chloride (TTC). The gel samples have been irradiated with a technical linear accelerator emitting electrons, ELU-6e (Elektronika, Russia) and measured spectrophotometrically (UV-Vis, Jasco, Japan) in order to discuss their dose response.

Results
The main characteristics of new VIC polymer gel dosimeter have been obtained following NMR measurements: i) a broad linearity in dose response; the gel saturates for doses of over 50 Gy, ii) its dose sensitivity has been much boosted in comparison with the VIP gel, iii) the gel is stable from 20 h till 6 days after irradiation, iv) the gel keeps a 3D dose distribution unchanged within the time period mentioned. This gel can be measured with CT; however it requires appropriate measurement protocol and data processing including filtering. The new dye 3D gel dosimeter responds to doses of a high range – no saturation was seen for doses 2-500 Gy. Also, we observed a great linearity within such the high dose range.

Conclusions/Novel Aspects
The VIC and the new dye gel 3D dosimeters show promise for 3D radiotherapy dosimetry. These gels can be applied for e.g. verification of 3D dose distributions obtained with other dosimetric techniques.

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Multikinase inhibitors (MKIs) in patients with radioiodine (RAI) refractory thyroid cancer (TC) – the evaluation of treatment tolerance on the basis of 10-year experience

J. Krajewska[1], A. Kukulska[1], T. Olczyk[1], E. Paliczka-Cieślik[1], D. Handkiewicz-Junak[1], A. Kropińska[1], T. Gawlik[1], B. Michalik[1], E. Gubała[1], B. Jarząb[1]

[1] Nuclear Medicine and Endocrine Oncology Department, M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice Poland

Introduction/Rationale
Thyroid cancer is characterized by a good radiosensitivity, therefore RAI treatment constitute the first line approach in disseminated TC. Unfortunately, about 30 % of patients show RAI refractoriness. MKIs are a new therapeutic option for these patients, resulting mainly in prolongation of the time to disease progression, what was demonstrated for some drugs in different phase III studies. However, recently MKI-related toxicity and its potential impact on the quality of life have been discussed. Therefore, a retrospective analysis of the frequency and severity of MKI-related side effects in patients treated due to advanced TC was carried out. Only VEGFR inhibitors were considered. The comparison of the efficacy of different drugs was not the purpose of this study.

Materials and Methods
The study group involved 71 TC patients: 39 with medullary TC and 32 with RAI-refractory differentiated TC. Twenty four of patents received lenvatinib, 20-vandetanib, 16-sorafenib, 9-cabozantinib, 4-motesanib nd 3-axitinib. In five subjects 2 lines of treatment were administered. All side effects were classified according to the *Common Terminology Criteria for Adverse Events (CTCAE)*, version 4.0. So far 55 treatment courses were summarized. Median treatment duration was 21.3 months (range 0.7-100.0 months).

Results
MKI treatment was withdrawn due to its poor tolerance in 8 patients (14.5%) whereas 29 (52.7%) required dose reduction. Among the most common adverse effects were hypertension (73%), skin reactions (70.3%), diarrhea (54.1%), weight loss (54.1%) and stomatitis (43.2%). The majority of side effects fulfilled G1 (mild) and G2 (moderate) criteria except of hypertension mainly classified as G3 (the necessity of the administration of at least 2 antihypertensive drugs). Weight loss, skin reactions and diarrhea were the most common reason of dose reduction. Weight loss led to drug withdrawal in 2 subjects, myocardial infarction in 2 other patients, whereas in remaining 4 patients: lymphopenia (1), QTc prolongation (1), tracheo-esophageal fistula (1) and purulent meningitis (1).

Conclusions/Novel Aspects
MKIs represent relatively safe and well-tolerated treatment option in TC patients. Adverse effects, mainly mild and moderate are rarely related to the necessity of drug withdrawal. Dose reductions and concomitant medications diminished the severity of side effects and improved treatment tolerability.

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The efficacy of radical radiotherapy for patients with primarily diagnosed prostae cancer with metastases to regional lymph nodes

T. Krzysztofiak, W. Majewski

Zakład Brachyterapii Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie Oddział w Gliwicach
Zakład Radioterapii Centrum Onkologii – Instytut im. Marii Skłodowskiej-Curie Oddział w Gliwicach

Introduction/Rationale
The treatment of patients with prostate cancer metastatic to regional lymph nodes is a matter of debate. Usually, the palliative approach such as hormonal treatment is applied. However, in a selected patients with regional nodal metastases a radical treatment may be also considered. In this study we've analyzed 22 patients with high risk prostate cancer and regional lymph node involvement treated with radial radiotherapy + hormonal treatment (HT) between 2008-2014.

Materials and Methods
Retrospective analysis of 22 patients diagnosed with prostate cancer and regional lymph nodes involvement

(N+) treated with radical radiotherapy was performed. Men had diagnosed high risk prostate cancer. The mean highest pre-treatment PSA level was 79 ng/ml and varied between 7.1ng/ml and 241ng/ml. The median age was 65years (SD +/- 8years). The lymph nodes involvement was determined by radiological imaging (CT, MR, PET scan). All patients received neoadjuvant hormonotherapy for at least 2 months (mean time - 7 months). A total of 20 patients continued HT for 2-3 years. All patients underwent conventional radiotherapy (20 with dynamic techniques, 2 with conformal radiotherapy). The total radiation dose to the prostate ranged from 75.6 to 78Gy, the total radiation dose to elective pelvic lymph nodes varied between from 44 to 50 Gy and a boost dose to the involved lymph nodes ranged from 60 to 75,6Gy. All patients had IGRT using 2D-2D kV verification, 13 patients were verified using gold markers, the rest with pelvic bones alignment. Median follow-up after RT was 40 months.

Results
The treatment was well tolerated-all patients completed radiotherapy without delays. The 3-year and prognosed 5-year biochemical Control Rate (bCR) in a studied group was 78% and 65%, respectively. The 3-years and 5-years prognosed Overall Survival rate was 88% and 73%. We observed 5 failures (3 nodal progressions – outside a boost region, 1 bone metastases, 1 biochemical relapse). Two nodal progressions were accompanied by bone metastases. No relapse in a nodal boost region was observed. No dose – effect relationship was observed neither for bCR (p=0,81) nor OS (P=0.76). Among the analyzed factors like: age, Gleason score, maximum PSA level, time of hormonotherapy, only tumor stage (T stage) was associated with biochemical control rate.

Conclusions/Novel Aspects
The results showed very good outcome for node positive, high risk prostate cancer patients treated with ADT and radical radiotherapy. No dose – effect relationship suggest that metastatic pelvic lymph nodes may not require such dose escalation as primary tumor. Although this analysis is retrospective, it also raises the need for prospective, randomized trials.

23 Linac–based stereotactic radiotherapy as a salvage treatment in patients with Cushing's disease. Is there a chance for achieving hormonal control?

Dorota Księżniak-Baran[1], Magdalena Stankiewicz[1], Kornelia Hasse-Lazar[2], Sławomir Blamek[1]

[1] Radiotherapy Department, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Branch Gliwice
[2] Department of Nuclear Medicine and Endocrine Oncology, Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Branch Gliwice

Introduction/Rationale
The purpose of our study was to evaluate efficacy and safety of stereotactic radiotherapy in patients suffering from Cushing's disease (CD), performed with the use of linear accelerator.

Materials and Methods
Twelve patients with Cushing's disease (9 women, 3 men) were included into the study. All patients were symptomatic. The mean and median age at the time of radiosurgery was 38 and 37.5 years, respectively (range 21-72). Before SRS, all patients had at least two neurosurgical procedures. Anterior pituitary insufficiency was diagnosed in 2 (15%) cases. Diabetes insipidus occurred in one (8%) case. Mean and median applied doses were 12 Gy (range 5-22Gy). The treatment was applied in 1-2 fractions (1 fraction in 11 patients, 2 fractions in one patient).

Results
After SRS treatment, complete hormonal evaluation was performed in 9 (75%) cases. The median follow-up was 3.9 years (range: 1.6 – 10), two patients were lost from follow-up after radiosurgery. Hormonal response was defined as a normalization or more than 50% reduction in serum ACTH or serum cortisol or urine cortisol levels. In 3 cases hormonal response was diagnosed. In the non-responding patients another scheme of the pharmacological treatment or qualification for surgery (adrenalectomy or neurosurgical procedure) were advised. In two cases another course of radiotherapy was conducted (in first case systematic depletion of the ACTH levels was observed, in the second, still no apparent response was seen). There was one case of new hormonal deficits found (11%). Radiological stabilization of the adenoma was seen in 7 patients (78%). In one case (11%) regression and in one progression was diagnosed (patient received neurosurgical treatment with consequent fractionated radiotherapy). Two-, five-, and ten-year local control was 100%, 86%, and 86%, respectively. There were no new visual deficits after SRS observed in our investigation

Conclusions/Novel Aspects
Stereotactic radiosurgery provides satisfactory radiological control in patients suffering from Cushing's disease. Long term hormonal control requires more aggressive treatment.

24 Radiochemotherapy with protons

Jirí Kubeš, PTC Prague, Czech rep.

Introduction
Pencil beam scanning technology opened possibility to use proton for many new indications which could not be irradiated with passive modes. Examples of these indications are head and neck cancer, anal cancer, pancreatic cancer and lung cancer.

Material and methods
Head and neck cancer: 27 patients with head and neck cancer were treated with radical or postoperative radiotherapy to the primary tumor and the bilateral neck lymph node areas using full IMPT between August 2013 and June 2015. 10 patients (37 %) suffer from paranasal sinu-

ses cancer, 7 (26 %) had tonsillar cancer and 10 (37 %) had nasopharyngeal cancer. The radiotherapy (70-78 GyE/35-39 fractions) was combined with concomitant chemotherapy in all cases (weekly cis-platinum, 40 mg/m^2, 4-6 applications). Dosimetric data, acute toxicity and short term results were evaluated. Preliminary data for other diagnosis will be discussed

Results
All patients finished radiotherapy without interruptions. Median of follow up time is 18 months. Dosimetric parameters are excellent (Table 1). Acute toxicity gr. 3 (RTOG) was observed for skin (25.93 %), mucositis (14.81 %) and pharynx and esophagus (11.11 %). Late toxicity with maximum gr. 2: skin and xerostomia (each one 7.4 %) and a temporary tracheostomy was needed in one case. Disease progression was observed in 3 (11%) cases, no patient had in field progression, 1 have marginal relapse, 1 leptomeningeal dissemination and one distant metastasis. 2 patients died from cancer.

Conclusion
Proton chemoradiotherapy of head neck cancers with bilateral neck irradiation is feasible, with excellent dosimetric parameters, low rate of acute and late toxicity. Short term results look promising. Preliminary data for anal cancerlooks also promising, as well as for lung tumors and pancreatic cancer,

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Physical Aspect of Total Marrow Irradiation (TMI)

P. Leszczyńska[1], M. Radwan[1], W. Leszczyński[1], Ł. Dolla[1], K. Ślosarek[1], L. Miszczyk[2]

[1] Department of Radiotherapy Planning, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland

[2] Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Centre and Institute of Oncology, Gliwice Branch, Poland

Introduction
The aim of this study is to present a radiotherapy planning technique for total marrow irradiation (TMI).This is an advanced technique of bone marrow cells irradiation for patients undergoing steam-cell transplant for a wide variety of hematological malignancies especially multiple myeloma. TMI provide irradiation of the bone marrow cells with simultaneous dose sparing of normal tissues. The most important organs at risk during whole bones irradiation are: lungs, lens, brain, kidneys, liver, intestines, heart, bladder and oral cavity.

Description of Method
Patient preparation. Patient is immobilized with utilization of special block set and thermoplastic masks for the head and neck, chest, abdomen and pelvis regions. Additionally the arms and legs are fixed.
CT imaging. For CT scanning the head first supine whole body protocol is used with 5mm slice thickness. Patient is imaging from the top of the head to the end of the legs. Subsequently for radiotherapy planning the CT sequence is duplicated and flipped.
Contouring. Whole body bones are contoured excluding hand, mandible, ethomid and craniofacial bones. Additionally 5mm margin is added to long bones of the extremities to minimize the movement impact.
TMI irradiation protocol. The total radiation dose is 12Gy in 3 fractions, within 3 consecutive days. Alternatively boost for lesions visible in PET are irradiated. Total dose for boost is 24Gy in 6 fractions (dose per fraction – 4Gy).
Dose prescription. 85% of target volume receives at least 99% of prescribed dose (12Gy).
Dose constrains for organs at risk (tab.).
Irradiation techniques. For each patients two plans are prepared. Basic plan is calculated at TomoTherapy system. In case of breakdown or problem with machine the alternative plan is prepared at Linac VMAT technique. The length of the irradiated target is limited (approx.120 cm for VMAT and approx.160 cm for HD-TT). Therefore total marrow irradiation has to be split into two parts: first the upper segment form the top of the head to the middle of the femur with head first supine orientation and second lower segment from the middle of the femur to the end of the feet with legs first supine orientation.
Dosimetric verification. VMAT treatment plans are verified by using EPID dosimetry system, Arc Check or Map Check arrays. Every singe arc is measured separately. Relative dose measurements for Tomotherapy treatment plans based on Octavius array. The absolute dose is verified with utilization of the Cheese Phantom.
Treatment setup verification. Tomotherapy treatment utilize the MVCT verification for head region and for the pelvis region. The mean shifts value is calculated and applied during treatment.
For VMAT treatment plans the patient setup verification using kV images for every isocenter and for every treatment fraction. Longitudinal shifts are constant values from the treatment plan. Vertical and lateral values are set regarding to kV images.

Conclusions/Novel Aspects
Total marrow irradiation allows to irradiate the whole body bones with simultaneous dose reduction in normal tissues. This technique minimizes the effects of radiation and reduces treatment toxicity.

Organ	Mean dose [Gy]	Median dose [Gy]
Brain	7,6	7,5
Lens	3,0	3,0
Oral cavity	5,5	5,0
Lungs	8,0	8,0
Heart	7,7	7,0
Liver	8,0	7,3
Kidneys	6,5	5,7
Intestines	7,7	7,0
Bladder	6,7	5,8

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Biomarkers for individualisation of radiochemotherapy in HNSCC – the German DKTK experience

Annett Linge[1,2,3,4], Fabian Lohaus[1,2,3,4], Michael Baumann[1,2,3,4,5], Mechthild Krause[1,2,3,4,5]

[1] German Cancer Research Center (DKFZ), Heidelberg and German Cancer Consortium (DKTK), partner site Dresden, Germany
[2] OncoRay – National Center for Radiation Research in Oncology (NCRO), Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany
[3] Department of Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany;
[4] National Center for Tumor Diseases (NCT), partner site Dresden, Germany
[5] Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology, Germany

Patients with locally advanced head and neck squamous cell carcinomas (HNSCC) are currently receiving a standard therapy, which is mainly based on their TNM status and their operability. However, despite the same tumour entity and comparable clinical parameters, patients are responding differently to the treatment. With the standard treatment, patients with very radiosensitive tumours are currently being over-treated and suffer from side effects whereas patients with radioresistant tumours may benefit from an escalated therapy regime. Therefore, a multicentre retrospective/prospective study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) has been set up to explore potential biomarkers which may predict response to radiotherapy. Most promising biomarkers will then be further validated in a prospective study, which is currently recruiting patients. Within both studies, biomaterial is being centrally processed for biomarker analyses at all partner sites. Imaging data and treatment plans are also being evaluated. To date, we showed that patients with HPV positive oropharyngeal tumours have a superior loco-regional control (LRC) after postoperative radiochemotherapy and may benefit from a de-escalated therapy regime whereas patients with cancer stem cell marker expressing, hypoxic tumours have a poor LRC. For patients with locally advanced HNSCC, who received primary radiochemotherapy, we showed that the tumour volume is also an important parameter, which has to be considered for individual treatment adaption. Further biomarker analyses are currently going on at all DKTK-ROG partner sites (based on their individual experience), which will be followed by an integrative analysis of all data to stratify patients for individual patient treatment using de-escalated or escalated therapy regimes.

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Radiochemotherapy induced phenotypical changes in peripheral blood mononuclear cells of colorectal cancer patients

Katalin Lumniczky[1], Noémi E. Bogdándi[1], Piroska Virág[2], Zsolt Fekete[2], Ioana Brie[2], Ottilia Barbos[2], Éva Fodor-Fischer[2], Géza Sáfrány[1]

[1] National Public Health Centre – National Research Directorate for Radiobiology and Radiohygiene, Budapest, Hungary
[2] "I. Chiricuta" Institute of Oncology, Cluj, Romania

Introduction
Tumour growth is very often associated with a progressively developing systemic immune suppression. Various cell types are responsible for this immune suppression, among which regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) play a particularly important role. Radiotherapy can influence these cells and thus radiotherapy-induced changes in the pool and function of these cells might represent prognostic markers of therapy-response. Our main objective was to identify immunological markers which might have a prognostic value for radiotherapy-response.

Methods
The rate and phenotype of Tregs and MDSCs was studied in the peripheral blood mononuclear cells of colorectal cancer patients before and after radiochemotherapy.

Results
The rate of MDSCs was moderately increased in tumour patients, which further increased after therapy. However, these changes were present only in patients responding poor to radiochemotherapy. The moderate increase of the Treg fraction within the CD4+ population indicated the relative radioresistance of this cell type. CTLA4-expressing Treg cells were significantly elevated in those patients, which responded poor to therapy.

Conclusion
Both the rate of MDSCs and certain Treg activation markers might serve as prognostic markers as well as predictive markers of therapy response. Furthermore, follow-up of therapy induced changes on Treg CTLA-4 levels might identify those patient categories which would mostly benefit from an anti-CTLA4 immunotherapy.
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Alanine-based QA protocol for dose assessment in ocular melanoma proton radiotherapy

Gabriela Mierzwińska[1], Barbara Michalec[1], Bartłomiej Sadowski[1], Michael P.R. Waligórski[1,2]

[1] The Henryk Niewodniczański Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland
[2] Centre Of Oncology, Maria Skłodowska-Curie Memorial Institute, Krakow Branch, Poland

Introduction/Rationale
The aim of our study was to introduce and test an in vivo dosimetry method for a 60 MeV passively scattered proton beam from the AIC-144 cyclotron at the Institute of Nuclear Physics in Krakow, used for ocular melanoma radiotherapy in years 2011-2016. Several properties make alanine a suitable detector for clinical dosimetry of a proton beam. It is known for its tissue–equivalence, linear response after doses in range 1–100Gy (clinical range), relative efficiency close to unity for protons over the therapeutic range of energies, and a stable in time concentration of the radiation-generated free radicals, which can be easily measured via Electron Paramagnetic Resonance (EPR) spectroscopy.

Materials and Methods
We exposed commercially available alanine detectors placed at a fixed location outside the beam line - on the back side of the final beam collimator, over 49 therapy sessions. We discovered that the dose recorded by alanine detectors for the same dose at the reference point (13.64 Gy) strongly depends on the facility geometry and the used set of beam forming elements- range shifter and range modulator. The analysis of collected data resulted with best-fitting of three analytical functions relating the alanine dose readout with water equivalent total thicknesses of beam–forming elements on the optical bench.

Results
Using these functions which covered the whole range of individual patient setups used clinically, it was possible to back–calculate the individual doses received by patients at the reference point from doses recorded with the alanine detectors. Basing on these results, we developed a protocol which is consistent with the Quality Assurance dosimetry system applied in routine patient exposures. This protocol was then tested in clinical conditions for 4 patients, with respect both to fraction and to total doses. A retrospective analysis of these patient exposures, covering all sources of uncertainties showed that the overall uncertainty of back–calculating from alanine dosimetry the total dose received at the reference point was within 16.1 %.

Conclusions/Novel Aspects
The overall uncertainty of developed system may be then used to resolve legal issues which define a radiotherapy class A accident as delivery of patient dose outside the range 75–125% of total planned dose. After further improvement in terms of decreasing uncertainty of the developed system, it would also be able to resolve a class B accident, which is delivery of total patient dose within 75–90% or 110–125% of the planned dose.

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CyberKnife (CK) radioablation for prostate cancer patients – early results of 400 patients treatment

Leszek Miszczyk[1], Agnieszka Namysł-Kaletka[1], Aleksandra Napieralska[1], Grzegorz Woźniak[1], Małgorzata Stąpór-Fudzińska[2], Grzegorz Głowacki[1], Andrzej Tukiendorf[3]

[1] Radiotherapy Department
[2] Treatment Planning Department
[3] Department of Epidemiology, M. Sklodowska-Curie memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Purpose
The toxicity and effectiveness evaluation of prostate cancer patients (PCP) radioablation.

Material and Methods
400 PCP (213 low risk [LR] and 187 intermediate risk [IR] (including T_{2c}) treated with CyberKnife using the fd 7.25 Gy to the TD 36.25 Gy. At the treatment start 60.3% of patients used ADT and this percentage gradually decreased to 0% 38 months later. The median of FU was 15.0 months.

Results
9 patients (2.25%) failed (5 in LR and 4 in IR group) - 4 had local relapses and 5 locoregional nodal dissemination. None of the patients had G3/4 late adverse effects (EORTC/RTOG). The maximal frequency of G2 late effects was 1.2% for GI (gastro-intestinal) (26 months after treatment) and 2.5% for GU (genito-urinary) (32 months after treatment). 0.3% of G3 GI and 0.5% of G3 GU acute reactions, one month after radioablation and on the treatment completion day, were noted respectively. 1.6% of patients had G2 GI acute adverse effects (1 month after SABR) and 6% G2 GU (CK completion day). The PSA median declined 1.5 ng/ml during the first month and 0.6 ng/ml during the next three months after treatment.

Conclusions
The obtained results allow to conclude that CK based radioablation of LR and IR PCP is a safe, well tolerated and effective treatment modality.
Additionally, the inclusion of T_{2c} patients in the IR group and the low percentage of IR patient failures permit us to assume that a such treatment modality could be performed even for more advanced cases.

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Osteopontin (OPN) as an instant, predictive biomarker of tumor hypoxia and distant dissemination of HNSCC in patients treated by radiation and chemotherapy

J. Mrochem-Kwarciak[1], T. Rutkowski[2], A. Wygoda[2], R. Deja[1], Ł. Boguszewicz[3], P. Widłak[4], K. Składowski[2]

[1] Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Analytics and Clinical Biochemistry Department, Gliwice, Poland
[2] Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, I Radiation and Clinical Oncology Department, Gliwice, Poland
[3] Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Department of Medical Physics, Gliwice, Poland
[4] Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology Gliwice Branch, Center for Translational Research and Molecular Biology of Cancer, Gliwice, Ploland

Introduction/Rationale
Plasma OPN to be a putative marker of tumor hypoxia in patients with head and neck squamous cell carcinomas (HNSCC). Additionally, OPN has been recognized as important in the processes of tumorigenicity and metastasis. The aim of the study was to assess clinical utility of OPN as the biomarkers of treatment outcome of radiotherapy (RT) or radiochemotherapy (CHRT) in HNSCC.

Materials and Methods
Between 01/2009 and 08/2013 251 patients in the mean age of 59 years with squamous cell carcinoma of oropharynx (39%), hypopharynx (13%), larynx (44%) or oral cavity (4%) were treated with RT alone (48%) or combined with chemotherapy (52%). The median duration of symptoms prior the treatment was 33 months (range: 1 – 70). The stage of disease was determined due to a TNM scale. There were 15 (6%), 112 (45%), 74 (29%), and 50 (20%) patients with T1, T2, T3 and T4 tumor stage, respectively, and 99 (40%), 26 (10%), 105 (42%), and 21 (8%) patients with N0, N1, N2 and N3 nodal stage of disease, respectively (no patients with distant metastases were included). OPN was indicated in plasma before treatment and immediately after treatment completion. In statistic overview of the results STATISTICA 9.1 (StatSoft) program was used. While interpreting the results median value was used. U Mann-Whitney test was used for analysis of correlation between protein concentration and the stage of the disease. Multivariate Cox analysis of factors related to OS was carried on. Log-rank test was used to compare OPN as categorized value acc. to median respectively.

Results
Pretreatment OPN levels were higher in patients with advanced T stage compared with early stage ($p=0.024$). There was no correlation between N stage and OPN ($p=0.58$). Median plasma levels of OPN measured before (67.9 ng/ml) and after (97.8 ng/ml) treatment differed ($p=0.0001$).
OPN levels before treatment were significantly related to overall survival (OS) ratio in both, univariate ($p=0.019$) and multivariate analysis (0.001).
Posttreatment OPN levels (97.8 ng/ml) were also associated with survival time in univariate analysis ($p=0.04$). Additionally, OPN after treatment was significantly higher in patients with distant metastasis ($p=0.015$).

Conclusions/Novel Aspects
High levels of OPN before therapy have been associated with advanced stage and adverse prognosis. OPN after therapy may play important role in the process of tumor development and metastasis. OPN concentrations increase during treatment may reflect acute mucosal reaction after radiotherapy.
Pretreatment OPN is an independent prognostic determinant of survival.

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Craniospinal irradiation – experience of Radiotherapy Department in Gliwice

Napieralska A.[1], Radwan M.[2], Brąclik I.[2], Blamek S.[1]

[1] Radiotherapy Department, Maria Skłodowska-Curie Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Radiotherapy and Brachytherapy Planning Department, Maria Skłodowska-Curie Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland

Introduction/Rationale
To assess standard method of craniospinal irradiation (CSI): static-junctions image guided (SJIG) with additional emphasis on actual, everyday treatment delivery implementation, treatment results and pattern of progression.

Materials and Methods
Retrospective analysis of CSI treatment plans of 40 patients, aged 4-43 (27 male and 13 female) with diagnosis of brain tumor (histopathologically: 22 medulloblastoma, 10 ependymoma, 5 germinoma, 2 PNET (primitive neuroectodermal tumor) and 1 anaplastic oligodendroglioma). CSI with total dose (TD) of median 36Gy (range 24 to 36Gy) and boost to the tumor bed of 9 to 28.8 Gy (median 18Gy). All patients had been treated with one treatment plan with static junctions between fields. To assure correct delivery of the treatment the couch was always moved in longitudinal axis by a constant value derived from prepared treatment plans, and all other shifts were corrected according to the results of every day imaging on the treatment machine during each fraction. All plans were reviewed by the authors with regard to actual treatment couch movement between each single field of every fraction during all days of the treatment. Differences between planned and treated distances between isocenters positions were used to create second (treated) plans.
Planned (P) and treated (T) parameters as D_{70}, D_{75}, D_{80}, D_{85}, D_{90}, D_{95}, D_{98}, D_2, D_{min}, D_{max}, $mean_{TD}$, $median_{TD}$, homogeneity index - HI(RTOG) and D_{max}/D_{min} were assessed and compared.

Results
Parameters for all the patients for all the treatment plans were: median D_{70}(P/T) -0.023% (SD±1.969), median D_{80} (P/T) -0.026% (SD±2.010), median D_{90}(P/T) 0.000% (SD±3.371), median D_{95}(P/T) -0.001% (SD±4.465), median D_{98}(P/T) -0.056% (SD±5.811), median D_2(P/T) -0.102% (SD±6.523). Median D_{min}(P/T)-0.125%(SD±7.890), median D_{max}(P/T) 0.037% (±6.313). Median$_{TD}$(P/T) 0.000% (SD±1.774), mean$_{TD}$(P/T) -0.010% (SD±1.827). HI(P) range: 1.077-1.812 (median 1.216), HI(T) range:1.081-1.869 (median 1.246). D_{max}/D_{min}(P) range: 1.125-2.098 (median 1.340, mean 1.405), D_{max}/D_{min}(T) range: 1.125-2.826 (median 1.423, mean 1.512). During follow-up of median time of 58 months 10 patients died. Tumor relapse was observed in 16 patients – in 13 cases in brain, in 1 in brain and in spine, in 1 patient in spine and in 1 multiple bone metastases occurred. Among those 16 patients, 8 died due to progression of the disease. Plans of all the patients with disease progression were assessed and compared with diagnostic imaging with regard to underdosage in recurrence area. Patients with spine relapse had plans with HI of 1.234 (P), 1.245 (T) and 1.154 (P), 1.193 (T), respectively. Spine metastases were observed in areas which were covered with homogenous dose during the treatment according to both - planned and treated plans. No neurologic complications caused by CSI irradiation were observed and all patients completed treatment as planned.

Conclusions/Novel Aspects
SJIG is safe treatment method and provides very good long-term outcome. Treatment planning is simple and less time consuming than the junction-shift techniques with excellent reproduction of the planned dose distribution during actual treatment delivery.

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Measurement of dose in the environment of Cardiovascular Implantable Electronic Devices (CIEDs) for prostate cancer patients treated by Tomotherapy

Beata Niewiadomska[1], Adam Bekman[1], Aleksandra Woźnica[1], Łukasz Dolla[2], Sławomir Blamek[3]

[1] Department of Medical Physics, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Department of Radiotherapy and Brachytherapy Planning, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[3] Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland

Introduction/Rationale
CIEDs response to therapeutic radiation is generally unpredictable. Typically, CIEDs are located at the periphery of the treatment field(s). Peripheral dose is made up of contributions from leakage radiation, collimator head scatter, and internal scatter (patient, phantom). The contributions of each of these components vary based on the distance from the field edge and the treatment technique. The aim of this work was to estimate the out-of-field dose in area of modern cardiac implantable electronic devices (CIEDs) placed far from the treatment field (about 32 cm) in tomotherapy (prostate cancer case) by means of thermoluminescence dosimetry (TLD). Thermoluminescence detectors due to their small dimensions, very good sensitivity, well known dose and energy response are widely used in verification of dose outside the treatment region.

Materials and Methods
The dose around CIEDs was measured with thermoluminescence detectors TLD LiF:Mg, Ti (MTS-N, IFJ Kraków) in solid disc form, manual reader (Harshaw 3500, Ohio) and oven (PTW, Freiburg). The TLDs were calibrated with a 6 MV photon beam on a Varian 23Ex Clinac accelerator in a PMMA phantom (field size 15x15cm, SSD=100cm). Detectors were placed at a depth of 5cm PMMA. In order to evaluate the dose from scatter radiation and to account for the patient anatomy an anthropomorphic phantom was used. CIEDs were located in the subclavian area of the phantom and covered with bolus material. Under out of field dose were tested 24 new generation Implantable Cardioverters-Defibrillators (ICD) and Cardiac Resynchronization Therapy – Defibrillator (CRT-D) Devices. A set of four devices was irradiated simultaneously using a tomotherapy plan for a patient with prostate cancer. A total dose of 78 Gy was delivered to the target volume (44 Gy pelvic lymph nodes-phase I and 34 Gy boost-phase II) with 39 daily fractions of 2 Gy with 6 MV photons. Eight TLDs were located on each CIED (two on the anterior surface, two on the posterior surface and one on each side surfaces (top, bottom and both lateral)). The scheme of signal acquisition included few fractions due to improve the signal-noise ratio. TLD measurements were compared with values calculated by the treatment planning system (TPS).

Results
The average measured dose d_{mean} of first phase (22 fraction*2Gy) was d_{mean} = 8.5 cGy (SD 1.3) and the dose varied between 5.6-12.15 cGy. During second phase (17 fraction*2Gy) we obtained d_{mean} = 3.39 cGy (SD 0.3), and the dose range was 2.92-4.04 cGy. To comparison, TPS calculate d_{mean} = 2.21 cGy, and d_{mean} = 0.00 cGy for first and second phase of irradiation, respectively.

Conclusions/Novel Aspects
All measured doses are on average less than 0.2% of the prescribed dose. Measurement accuracy and sensitivity of MTS-N (LiF:Mg, Ti) are sufficient to determine the out of field dose. Due to the large distance from target volume we measured primarily the contribution of photons coming from collimators and through accelerator head. Obtained d_{mean} is a good representation for environment of each CIED. TPS calculations underestimate radiation dose delivered to CIEDs.

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The feasibility of reirradiation using intensity-modulated radiation in selected patients with recurrent gliomas.

Nowicka E., Gawkowska M., Bal W., Jarząb M., Grzbiela H., Bobek-Billewicz B., Tarnawski R.
MSC Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Background
Brain gliomas often recur after initial treatment and for high grade tumours recurrences are inevitable. While there is no standard treatment for recurrent gliomas, reirradiation is an option, especially for patients who are not candidates for surgery. The aim of this study is to determine the feasibility and early results following reirradiation in selected patients with recurrent gliomas.

Methods
Between 2011 and 2016, 22 adult patients with recurrent gliomas were reirradiated with IMRT at the time of tumor recurrence or progression. There were 8 women (36%) and 14 men (64%). The primary histological diagnosis included: low grade gliomas: astrocytoma fibrillare in 11 pts, astrocytoma diffusum in 2 pts, oligostrocytoma in 3 pts , high grade gliomas in 6 pts: oligostrocytoma anaplasticum in 2 pts, GBM WHO IV in 3 pts and ganglioglioma WHO III in 1 pt. Median age at primary diagnosis was 31,8y (range, 18,3-70,1).The median time between primary radiotherapy and reirradiation for the whole group was 72,1 mo (range, 10,3 -178,6mo) and for LGG was 86,7mo (range, 10,3-178 mo) and for HGG 37,9 (range, 15,9-108mo). Primary radiotherapy was performed with 3DCRT in 11 pts and IMRT in 11 pts. Mean dose was 57Gy/g (range, 50-60 Gy/g). Tumor recurrence was confirmed in gadolinium-enhanced magnetic resonance imaging (MRI) in all patients. 12 pts were reoperated and one re-biopsied and the microscopic diagnosis was established by pathology examination. In eight pts HGG was confirmed. All tumours recurred in filed. In all but one pts IMRT technique of reirradiation was used. Mean dose for reirradiation was 38,6Gy/g (range, 16-45Gy/g). In 7 pts the stereotactic boost to recurrent tumour was used with mean dose of 13,7Gy (12-18 Gy) of in two-three fractions. In 13 pts chemotherapy was administered with temozolamid concurrently (11 pts) or PCV/ CCNU after radiotherapy.

Results
Median follow-up time from primary diagnosis was 107 mo (range, 22-203 mo) and 7,2 months (range, 0-54 months) from reirradiation. Median time to recurrence was 68,3 mo (range, 6,4-170 mo), for LGG- 81,9 mo (range, 64-170 mo) and HGG 34,9 mo (range13,6-102). All but one patient completed the planned course of radiotherapy. The response was assessed in MRI three months after completion of radiotherapy: 12 (50%) patients achieved complete or partial response. Stable disease (SD) was observed in 8 patients. Two patients progressed. Median survival for LGG and HGG were: 107 mo (range, 39- 203mo) 78,9 mo (range, 22-133) respectively. Median survival after reirradiation for whole group of pts was 7,2 months (range, 0,1-54,1 mo). Median PFS was 4,8 mo (range, 0,1-49,4). There were no difference in PFS and OS according to PS at reirradiation, gender, age, and primary histology.

Conclusions
Reirradiation is one of the treatment options for recurrent gliomas and IMRT can be a feasible treatment modality for recurrent brain tumours and it may provide benefit in disease control.

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Unusual presentation of dissemination via cerebrospinal fluid in malignant gliomas-the Centre of Oncology Institute Gliwice experience

Nowicka E., Gawkowska M., Bal W., Jarząb M., Grzbiela H., Bobek-Billewicz B., Tarnawski R.
MSC Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

High grade gliomas recurrences are inevitable. Local recurrences (central and in-field) are found to be the main recurrence pattern but there are incidence of rare presentation of dissemination via cerebrospinal fluid. Symptomatic spinal metastases occur rarely. Autopsy series suggest that approximately 25% of patients with intracranial GBM have evidence of spinal subarachnoid seeding, although the exact incidence is not known as examination of the spine is not routinely performed. The aim of this study is to present unusual form of recurrent pattern of malignant gliomas in patients treated in 3rd Radiothearapy and Chemotherapy Department, Institute of Oncology, Gliwice. Between 2011 and 2016 there were 8 adult patients: one woman and seven men, diagnosed and treated with brain gliomas spinal dissemination. Median age at diagnosis was 25,1 y (range,19,8-48,6). All patients were primarily operated. The histologic diagnosis were: Astrocytoma diffusum-2 pt, Ganglioglioma III- 1 pt, Glioblastoma multiforme -5 pts. All tumours were supratentorial. Postoperative treatment was administered according to guidelines: radio-chemotherapy in 6 pts, postoperative radiotherapy in 1pt and close follow up in 1 pt. In all but one pts tumour subsequently recurred in field. Tumour recurrence was confirmed in gadolinium-enhanced magnetic resonance imaging (MRI) and in 2pts with primary LGG, the signs of radiologic anaplastic transformation was shown. Radiotherapy and/or chemotherapy with temozolamid was administered on first recurrence. The craniospinal dissemination showed up as second independent relapse in four pts or coexisting with local progression in remaining. Median time from diagnosis to dissemination was 17,8 mo (range, 6,6-62,2mo). In all patients the clinical symptoms suggesting dissemination via cerebrospinal fluid occurred. The diagnosis was confirmed in craniospinal MRI. The MRI showed infiltration in spinal canal. One patient was operated due to rapid clinical progression of spinal compression symptoms. Patients were offered palliative therapy: local radiotherapy in 2 patient, radiotherapy to spinal axis with temozolamid chemotherapy in 2 pts, sequential chemotherapy EP and radiotherapy in 1 pts and sole chemotherapy in one pts. Median dose for spinal irradiation was 20Gy/g (range, 18-39Gy) with dose per fraction 1,8Gy/g (range, 1,5-

4,0Gy). Five patients died irrespective of therapy. Three patients are alive. Median survival from the date of dissemination is 3,6 mo (range, 0,5-12,7). We discuss the unusual aspects of malignt gliomas spinal dissemination, although rare but they should be considered in the differential diagnosis of clinical symptoms. The prognosis of leptomeningeal dissemination of recurrent malignant gliomas is poor with a mean survival time of two to four months. Radiotherapy and chemotherapy result in minimal palliative efficacy, without increased survival.

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Dose distribution reconstruction for gated VMAT technique

W. Osewski[1], L. Dolla[2], R. Kulik[2], K. Slosarek[2,3]

[1] Radiotherapy Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[2] Radiotherapy Planning Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[3] Electroradiology Institute, Humanitas University in Sosnowiec, Poland

Introduction/Rationale
The aim of this work was to present new additional method for dose distribution verification for dynamic treatment techniques. In our institution VMAT technique is used for radiosurgery. High dose per fractions requires high precision. Small sizes of treatment fields in radiosurgery causes difficulties in dose distribution verification using standard methods. For gated VMAT technique radiation delivery is not continuous because of patient breathing control system usage. Beam interruptions can influence on dose distribution. There was a need to solve this problem. That's why new method of dose distribution reconstruction based on information from Trajectory Log Files (TLF) was developed. This method allows us to verify how real dose distribution looks like in the patient.

Materials and Methods
All measurements were performed on TrueBeam accelerators with 120HD Millenium collimator and gating system. Energy of XFFF-6MV without flattening filter was used. Maximum dose rate was 14 Gy/min. For dose distribution calculation Eclipse version 13.6 and AAA algorithm was used. ArcChek phantom was used to verify calculated dose distribution. For additional dose distribution verification homemade DDcon software was used. DDcon was designed to perform dose distribution reconstruction based on TrueBeam TLFs. Those files are generated for every single field or arc during therapy and they contain information about actual accelerator parameters such as actual MLC leaves position, gantry angle, collimator angle, delivered MU's and many more. Using those files and RTPlan dicom file, exported form Eclipse TPS, DDcon software generates new RTPlan dicom file were planned leaves positon, gantry angles and MU values are changed to actual one from TLFs. After that new RTPlan file is imported back to TPS and the dose is recalculated using the same algorithm as it was done during treatment plan preparation. Dose reconstruction for gated VMAT technique will be presented on the example of a patient with lung tumour were total planned dose was 30 Gy delivered in three 10 Gy fractions.

Results
Verification treatment plan was calculated on ArcCheck phantom volume. All plan geometry reminded unchanged. After measurement the measured dose distribution was compared with calculated one using gamma index (3%, 2 mm) and it was less than one in 97.4% of analyzed dose distribution area. Using collected TLFs the reconstruction was performed for QA plan and for all treatment fractions. Differences between calculated dose distribution and reconstructed for QA plan were very small (gamma index(3%,2mm) was 100%). Summed reconstructed dose distribution for all fractions was compared with: calculated dose distribution where gamma index(3%,2mm) was 100% and with measured dose distribution where gamma index (3%,2mm) was 97.7%.

Conclusions/Novel Aspects
Presented method is consistent with phantom measurements but in some cases it is more sensitive and precise. When standard methods fails then presented dose distribution reconstruction method is very helpful to decide if the prepared treatment plan will be delivered properly. Additionally Calculation of reconstructed dose distribution on good quality CBCT gives us full information about real dose distribution in the patient.

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Virtual versus conventional radiotherapy simulation: a single institution experience report

Maciej J. Pelak[1], Kinga Dębiec[2]

[1] Prof. Kornel Gibiński Memorial University Clinical Center of Silesian Medical University of Katowice, Department of Radiotherapy, Katowice, Poland
[2] Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, I Radiation and Clinical Oncology Department, Gliwice, Poland

Introduction/Rationale
The aim of virtual simulation in radiotherapy is the same as for conventional: to correctly allocate the beam isocenter on the patient physically. The rationales for virtual simulation include: lower device and staff cost as well as sparing patient effort and treatment planning time. Few centers are equipped with both modalities, thus not many institutions are able to report their experience. In the present paper we analyze virtual simulation in terms of its reliability compared to the conventional simulation and its practical impact on the patient workflow.

Materials and Methods
130 prostate cancer patients irradiated for prostate cancer with definite intent in Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch were randomly selected for evaluation. 65 have undergone virtual simulation procedure and for another 65 conventional simulation modality was used. Age, irradiation modality (single and 2-stage) as well as IGRT setup (prostatic fiducials and skeletal DRR) were distributed equally across the patient groups. Compared were the mean patient couch shifts as measured by daily IGRT verification procedure in X (left – right), Y (cranial-caudal) and Z (anterior-posterior) axis. Separately analyzed were the first shifts recorded. Also recorded were the treatment planning time for both groups and the patient residence location. All comparisons were done by Mann-Whitney U test.

Results
For X and Y axis there were no significant differences in either mean shifts (X: 0,23 cm vs 0,23 cm for virtual and conventional simulation, respectively; p= 0,42; Y: 0,68 cm vs 0,69 cm; p= 0,92) or their standard deviations (X: 0,15 cm vs 0,15 cm; p= 0,47; Y: 0,5 cm vs 0,47 cm; p=0,31). Interestingly, significant differences were observed for Z axis: between both the means and standard deviations (0,3 cm vs 0,21 cm; p= 0,007 and 0,22 cm vs 0,18 cm; p= 0,006, respectively). The difference was significant for mean first Z axis shifts as well (0,36 cm vs 0,26 cm; p= 0,049), which was not the case for other two axis (X: 0,24 cm vs 0,19 cm; p= 0,33; Y: 0,77 cm vs 0,71 cm; p= 0,85). The use of virtual simulation has significantly shortened the median treatment planning time (15 vs 19 days; p= 0,002.). Virtual simulation procedure also spared the patients a median travel of 77,4 km (range: 2 – 490 km). Out of the patients who underwent the virtual simulation, in 6 cases re-setting the isocenter using either a linac IGRT device or the conventional simulator was necessary.

Conclusions/Novel Aspects
Virtual simulation reduces staff and patient effort while delivering reliability comparable to that of conventional simulation. Attention must be paid by treatment planning team to correctly allocate the isocenter especially in anterior-posterior axis in order to avoid inaccuracy that would have to be compensated later by linac staff.

37 Dosimetric verification of treatment planning system in proton spot scanning pencil beam radiotherapy

A. Pedracka[1], L. Stolarczyk[1], M. Liszka[1], W. Komenda[1], B. Sadowski[1], K. Skowronska[1], P. Olko[1]
[1] Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland

Introduction/Rationale
Pencil beam spot scanning (PBS) system in Cyclotron Center Bronowice IFJ PAN (CCB) consist of a delivery system (IBA Proteus C-235), an oncology information system (ARIA®), and a treatment planning system TPS (Eclipse v13.6). To improve the accuracy of calculated dose distributions beam model containing a table named depth dose normalization correction factor (DDNCF) was created. DDNCF table contains factors, which scale number of MU for each plan depending on its range and modulation. Dosimetric verification of beam model with DDCNF table introduced to TPS was an important part of commissioning.

Materials and Methods
To perform verification of beam model with DDNCF table plans of simple geometry were prepared. Homogeneous cubes with different ranges (from 5 cm to 27 cm) and modulations (between 2 cm - 27 cm) were used. Tests were conducted for different field sizes (from 3cm x 3cm, to 10cm x 10cm) and gantry positions (0, 15, 25, 335, 345 deg). Plans were prepared with and without the use of range shifter. Assigned dose for each of them was 2 Gy. Measurements were performed in gantry treatment room in water phantom BluePhantom2 (IBA Dosimetry) with Markus ionization chamber PTW23343 and PTW Unidos Webline electrometer according to TRS-398 protocol. The relative difference (RD) between doses prescribed by TPS Dprescribe and measured Dmeasure was calculated with the formula: RD = [(Dmeasure / Dprescribe) - 1] · 100%.

Results
Before using the beam model with DDNCF table relative differences between doses measured Dmeasure and prescribed Dprescribe were in interval from -5% to 3%. The biggest relative differences were determined for plans with ranges above 25 cm and plans with range shifter. After applying the beam model with DDNCF table values of relative difference RD for all plans are in an assumed interval +/- 1.5%.

Conclusions/Novel Aspects
Beam model with DDNCF table is able to calculate dose with the accuracy better than 1.5% for all clinically used ranges and modulations.

38 Molecular profiling of tumor-derived exosomes in plasma of cancer patients

M. Pietrowska[1], S. Funk[2], M. Gawin[1], Ł. Marczak[3], P. Widłak[1], T. Whiteside[2]
[1] Center for Translational Research and Molecular Biology of Cancer, Maria Sklodowska - Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland
[2] University of Pittsburgh Cancer Institute, Pittsburgh PA, USA
[3] Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznań, Poland

Introduction/Rationale
Tumor-derived exosomes (TEX) present in body fluids of cancer patients are thought to be responsible for delivering suppressive signals to immune cells, interfere with anti-tumor immunity and thus have impact on response to therapy or even outcome. We propose that the unique molecular and proteomic profiles of TEX in cancer patients' plasma, which are similar if not identical to the

profiles of cancer cells from which TEX originate, can serve as an equivalent of a "liquid biopsy." If so, then they would allow for serial, real-time, non-invasive monitoring of tumor presence, progression/regression during a therapy and predicting outcome for cancer patients.

Materials and Methods
The methods for exosome isolation from plasma were described in a recently published report [1]. Proteins derived from exosomes were subjected to qualitative and quantitative analysis using mass spectrometry (LC-MS analysis with MS/MS-based identification). Proteins were consecutively digested with two enzymes: endoproteinase Lys-C and trypsin. Exosomal proteins enzymatically fragmented were fractionated using SAX homemade tip-columns, and peptides were separated chromatographically using nanoLC system equipped with C18 column, analyzed and identified by tandem mass spectrometry (MS/MS).

Results
We have preliminary data for immunocapture of CSPG4+ MTEX (melanoma derived exosomes) from plasma of melanoma patients. Having first performed titrations to determine the optimal ratio of exosomes vs. biotinylated CSPG4-specific mAb 225.28, we established that 7ìg of mAb 225.28-coated beads was optimal for capture of $2.1X10^9$ exosomes present in combined fractions #3 and #4 (pre-capture) separated by mini-SEC from 1 mL of patients' plasma. In this experiment, captured MTEX represented 33% of recovered exosomes. Western blot analysis showed that captured MTEX were enriched in VLA-4 and TYRP, while these markers were not or barely detected in non-captured exosomes or in the bulk exosome fraction. Our preliminary mass spectrometry data obtained with proteins from (1) pre-capture (MeP input), (2) captured (MeP cap) and non-captured (MeP uncap) melanoma exosomes indicated that we could discriminate between these exosome preparations. The immunocaptured MTEX (2) contained 55 proteins that were not shared with the other two fractions.

Conclusions/Novel Aspects
Quantitative analysis could be implemented to monitor the presence and concentration of exosomal proteins in TEX that are relevant to melanoma and its progression, and to incorporate these proteins as components of the targeted assay.

[1] Hong C.S., Funk S., Muller L., Boyiadzis M., Whiteside T.L. Isolation of biologically active and morphologically intact exosomes from plasma of patients with cancer. *J Extracell Vesicles* 2016, *5*,29289.

39 Radiation-induced injury of the exocrine pancreas after chemoradiotherapy for gastric cancer

P. Polanowski[1], Jerzy Wydmanski[2], A. Tukiendorf[3] B. Masłyk[4]

[1] I Radiation and Clinical Oncology Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[2] Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[3] Department of Epidemiology, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland
[4] Department of Analytics and Clinical Biochemistry, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Poland

Introduction
Knowledge of development of the radiation-induced injury of healthy organs and tissues has important clinical aspect. There is a lack of data on the pancreas in current protocols with regard to organ at risk. Treatment fields applied during the radiotherapy of gastric cancer comprise almost the whole pancreas. The aim of this study was to analyze radiation - induced injury of the exocrine pancreas after radiochemotherapy of gastric cancer.

Material
127 patients with locally advanced gastric cancer were analyzed. Patients have acceded to participation in randomized clinical trial comparing tolerance and efficacy preoperative and postoperative radiochemotherapy.

Methods
The exocrine pancreatic function was assessed on the grounds of á-amylase and lipase levels in blood serum. Pancreatic enzymes were assayed before, during and after treatment. The treatment regimen was made up of preoperative or postoperative radiochemotherapy conducted to total dose of 45 Gy in 25 fractions, with 5 fractions per week for 5 weeks. The scheme of concurrent chemotherapy was based on 5-fluorouracil.

Results
α-amylase and lipase deficiency were found in 19,7% and 48,2% of patients, respectively. Age and pretreatment levels of pancreatic enzymes were statistically significant factors of radiation - induced injury of the exocrine pancreas. The risk of decline of α-amylase concentration is inferior in younger patients (<65 years) in comparison with elder patients. The probability of hipoamylasemia was lower than 0,2 for patients with pretreatment α-amylase level above 50U/L. The same probability of hipolipasemia was with pretreatment lipase level above 55U/L. Exocrine pancreatic function return to norm in 39% patients with hipolipasemia and 31% patients with hipoamylasemia. Recovery of exocrine pancreatic function was the most marked within 500 days. Mean dose in whole volume of pancreas was in range 32-48 Gy.

Conclusions
Patients treated with radiochemotherapy due to gastric cancer have increased risk of exocrine pancreatic insufficiency. The pancreas should be incorporated into organs at risk. The assay of lipase level in blood serum should be a standard procedure in order to diagnose exocrine pancreatic insufficiency. Injury of the pancreas was reversible.

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Ionizing radiation affects profile of serum metabolites: increased level of 3-hydroxybutyric acid in serum of cancer patients treated with radiotherapy

M. Ros-Mazurczyk[1], A. Wojakowska[1], L. Marczak[2], K. Polanski[3], M. Pietrowska[1], K. Jelonek[1], I. Dominczyk[1], A. Hajduk[1], T. Rutkowski[1], K. Skladowski[1], P. Widlak[1]

[1] Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland
[2] Polish Academy of Science, Institute of Bioorganic Chemistry, Poznan, Poland
[3] University of Warvick, Coventry, Great Britain

Introduction/Rationale
Radiotherapy causes molecular changes observed at the level of body fluids, which are potential biomarker candidates for assessment of radiation exposure. We analyzed radiotherapy-induced changes in profile of small metabolites detected in sera of head and neck squamous cell cancer (HNSCC) patients using the GC/MS approach.

Materials and Methods
Twenty patients with HNSCC were enrolled into this study. Patients were treated with radical radiotherapy alone, using continuous accelerated irradiation scheme. Blood samples were collected from each patient in two points of time: pre-treatment (A) and post-treatment (B). Metabolite extracts were analyzed using GC/MS technique.

Results
There were 22 compounds, including carboxylic acids, sugars, amines and amino acids, which levels significantly differed between pre-treatment and post-treatment samples. Among metabolites upregulated by radiotherapy was 3-hydroxy-butyric acid, which level increased about 3-fold in post-treatment samples.

Conclusions/Novel Aspects
Compounds affected by irradiation were associated with several metabolic pathways, including catecholamine biosynthesis and amino acid metabolism.

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Feasibility study of patient plan verification method for scanning proton beam at the IFJ in Krakow, Poland

M. Liszka[1], M. Rydygier[1], B. Sadowski[1], A. Pędracka[1], W. Komenda[1], L. Stolarczyk[1], P. Olko[1]

[1] Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland

Introduction/Rationale
At the Institute of Nuclear Physics Polish Academy of Science (IFJ PAN) two gantry (rotating arm) facilities have been installed. Each of them is equipped with a scanning beam nozzle, which will find application mainly in radiotherapy of central nervous system tumours located next to critical organs as well as in paediatric patients treatment. Providing a proper dose distribution during radiotherapy is essential for successful patient treatment. For this reason the feasibility and accuracy of dosimetric verification of treatment plan has been investigated.

Materials and Methods
Verification of the plan is performed for the selected gantry angle and it includes two steps performed separately for each field:

- Dose measurements at 5 points. Each point is selected in a region of the smallest possible gradient of the dose distribution. Measurements are preformed using Markus ionization chamber positioned in water phantom (IBA-Dosimetry, Blue Phantom), orthogonally to the beam direction and the gantry angle is set to 0 degree.
- Gamma index calculation of the dose spatial distribution for planes exported from treatment planning system (TPS) and planes measured using MatriXX PT (IBA-Dosimetry) device. This comparison is performed for 5 planes (different depths) of each field. MatriXX PT is positioned in water phantom (IBA-Dosimetry, DigiPhant), orthogonally to the beam direction and the gantry angle is set to 270 degree.

The study were performed for 10 head and neck clinical cases.Total doses of 2 CGE of each verification plan were delivered in 2-4 fields. Used medical data are the basis for treatment plan comparison performed by collaborative network of particle therapy centres in Italy, Poland, Austria, Czech Republic and Sweden (IPACS-group).

Results
Field specific dosimetry shows that treatments can be delivered accurately and precisely, agreement between measured and planned dose is better than ±3?% (received values were between -2.83% and 2.76%). Good correlation and quantitative agreement within 90% of gamma index (3mm/3%) were found between the measured and planned spatial dose distribution. Received results of gamma index were between 90.91% and 100% with mean value of 95.88 (±2.95)%.

Conclusions/Novel Aspects
This study demonstrates the feasibility of precise spatial dosimetry for treatment verification. It also indicates some technological and methodological improvements needed for clinical application.

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How can protontherapy improve radiation oncology?

M. Schwarz

Protontherapy Department, Trento Hospital, Trento, Italy
TIFPA-INFN, Trento, Italy

Protontherapy(PT) is increasingly available over Europe and it is expected that by 2020 about 50 treatment rooms will be available in our Continent. The number of patients treated with protons, albeit small, will be noticeable in the bigger arena of radiation oncology as a whole. It realistic to expect that PT will bring the following advantages to our field

1) Access to better dose distributions. This is the main driver for PT, and the challenge is on how to facilitate a transition from classical PT indications (e.g. base of skull lesions) to new disease sites (e.g. liver, lung), where PT can have a significant edge with respect to state of the art photon therapy (XRT).
2) Improve the management of geometrical uncertainties during planning. The planning target volume (PTV) was a suitable tool for photon radiotherapy of the 90's, but it is inadequate for modern days PT and XRT. The need for protons to generate robust distributions is likely to favor some significant changes in this respect.
3) Improve the knowledge on dose tolerances for healthy tissues. PT does allow to shape dose distributions much better than XRT, in particular at medium to low dose levels. This will help us better understand the mechanics of dose effect relations that are often simplistically described as 'serial' or 'parallel'.
4) Show how to design and deliver RT services for large populations. In current XRT most if not everything happens at the department level. The cost and complexity of PT requires a multidepartment approach, which is a challenge for the current organizational and cultural standards, but which may turn out as a new way to work for radiation oncology as a whole.

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Application of high field MR micro-imaging in polymer gel dosimetry – preliminary results

A. Skorupa[1], M. Kozicki[2,3], P. Maras[4], M. Ciszek[1], Ł. Boguszewicz[1], M. Sokół[1]

[1] Department of Medical Physics, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland
[2] Department of Man-Made Fibres, Lodz University of Technology, Lodz, Poland
[3] GeVero Co. Poland
[4] Medical Physics Departament, Copernicus Memorial Hospital, Lodz, Poland

Introduction/Rationale

The continuing progress in radiotherapy treatment planning and delivery methods enables employment of smaller and smaller therapy field sizes (< 2 cm diameter). However, dosimetric characterization of these fields is difficult with use of conventional methods (ionization chambers, thermoluminescent detectors). Polymer gel dosimetry may become an important technique for determination of 3D dose distributions within these small fields. To date, clinical 1.5 T or 3 T MRI scanners have been frequently used for conversion of the spin-spin relaxation rate (R2 = 1/T2) maps to the absorbed dose maps in the polymer gel phantoms. Application of higher magnetic field strengths enables acquisition of images with higher resolution. The purpose of this work was to evaluate the R2-dose relation and quality of the images (signal to noise ratio and uniformity) obtained using 9.4 T MR micro-imaging system.

Materials and Methods

The calibration tubes containing VIPARnd (VIP) gels (12 cm long, 3 cm diameter) were irradiated to the prescribed doses ranging from 0 (control sample) to 35 Gy using medical linear accelerator. MRI experiments were performed on a 9.4 T Bruker scanner equipped with a Micro2.5 gradient system of 1T/m and a transmit/receive birdcage radio frequency coil with an inner diameter of 30 mm. The gels were scanned using a multi-echo sequence (repetition time/echo spacing/number of echoes = 6000 ms/10 ms/64, in-plane resolution: 0.1 x 0.1 mm, slice thickness: 1 mm, number of averages: 4). R2 images were obtained by mono-exponential fitting of signal intensities as a function of echo time in Paravision software. The mean R2 values from the regions of interest located in the center of the tubes were used to obtain the R2-dose calibration relation. Additionally, the influence of varying echo spacing, number of echoes and in-plane image resolution on R2-dose relation was also examined.

Results

The obtained R2-dose relation was as follows: R2 [s^{-1}] = 0.098 x D [Gy] + 5.405 (R^2=0.999). Variation of echo spacing, number of echoes and in-plane resolution affected mainly the intercept in this relation. The obtained preliminary results revealed marked non-uniformity of the R2 maps obtained from homogenously irradiated tubes (increased R2 for pixels located near the coil edge in comparison to the values in the center). However, the observed non-uniformities can be reduced using correction factors measured from a set of tubes filled with a homogeneous gelatin gel characterized by R2 range typically encountered in polymer gel dosimetry. Determination of these factors is planned as a next experimental step in this work.

Conclusions/Novel Aspects

Application of high field MR micro-imaging coupled to development of appropriate image post-processing methods may facilitate dosimetric verification of small radiation fields in modern radiotherapy.

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Application of wedges in the eye line treatment facility in the IFJ CCB Kraków

U. Sowa, T. Nowak, T. Horwacik, T. Kajdrowicz

The Henryk Niewodniczański Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland

Introduction/Rationale

In ocular proton radiotherapy, physical wedges may be applied to spare critical tissue like optic disc or macula. In lot of cases the wedges may be applied to reduce the high dose volume. Adding a wedge in the beam line may automatically change some of the field properties, such as the range and the modulation, in the region where the wedge is working. Additionally the use of wedge cause also broadening the lateral penumbra on the wedged side, what cause necessity of the collimator extension.

Materials and Methods

The measurements were performed in the water phantom in the spread out Bragg peak (SOBP) using rectifying diode. The diode water equivalent thickness was determined by comparing the depth profiles measurements carried out using diode detector and Markus chamber. Four PMMA wedges, with approximate angle values 15 deg, 30 deg, 45 deg, 60 deg (expressed as physical wedge angles) were tested. The wedges were attached to open field, 20 mm diameter collimator, 64 mm upstream from the isocenter. Lateral and depth measurements were performed to quantify the difference in the dose distribution in the radiation field with and without the wedges. The wedge angles were evaluated during depth dose measurements of proton beam in the wedged side, in the beam axis and four another locations from beam axis (2mm, 4,5mm 7mm, 9mm from axis). The measurements of lateral profiles were performed in various depths from 5 mm WET to 30 mm WET, at 5 mm intervals.

Results

The depth dose measurements (SOBP) at four various locations from the beam axis shows the broadening of distal fall-off and range decrease of proton beam on the wedged side. Based on this data we were calculated the wedge angles, expressed in water equivalent thickness. The measurements of the lateral profiles at different depths enabled us to determine the depth at which the effect of the wedges were observed as decrease of field size on the 95% dose level. To reduce this effect, the collimator must be extended to the outline equal to the situation without the wedge with the therapeutic value on the 95% level. The shape of lateral profile shows some dose increase within the field along a relatively narrow volume beneath the thin edge of the wedge, as a result of small-angle proton scatter.

Conclusions/Novel Aspects

Based on collected data the beam model implemented in Eclipse Ocular Proton Planning (EOPP) system written by Varian Medical Systems will verify what enable us to use the wedge clinically.

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Commissioning of spot scanning proton therapy system in Cyclotron Center Bronowice

L. Stolarczyk[1], J. Gajewski[1], M. Kłodowska[1], W. Komenda[1], D. Krzempek[1], J. Kunst[1], N. Mojżeszek[1], M. Liszka[1], A. Pędracka[1], M. Rydygier[1], B. Sadowski[1], U. Sowa[1], P. Olko[1]

[1] Cyclotron Center Bronowice, Institute of Nuclear Physics PAN, Kraków, Poland

Introduction/Rationale

Dosimetric commissioning of 360^0 gantry with dedicated spot scanning nozzle (IBA) with treatment planning system Eclipse ver.13.6 (Varian Medical Systems, Palo Alto, CA) requires not only extensive measurements and simulations of spot in-air profiles and depth dose distributions, but also consideration for example of angular dependence of spots and shape of low-dose tails. The final part is verification of dose model from TPS against measurements of absolute dose and dose distributions.

Materials and Methods

Spot profiles in air were measured with IBA-Dosimetry scintillation detector (Lynx ®) and TL detectors (MCP-N). Angular dependence of spot shape was checked every 20^0. Depth dose distributions were obtained with Monte Carlo simulations and normalized to the entrance dose (at 2 cm depth in water) measured with Markus type ionization chamber (PTW). Time stability of measured depth dose profiles and spot profiles was checked. TPS was verified by regular measurements of simple geometry plans including plans of nonsymmetrical shapes performed with cylindrical and plane-parallel ionization chambers. For end to end tests anthropomorphic head phantom, TL detectors and radiochromic films were used.

Results

Dose model commissioned in TPS for spot scanning beam is based on double Gaussian fluence distribution and scaled with range and modulation dependence factors (from 0.953 to 1.030) to ensure proper dose calculations. Final checks performed in water phantom showed agreement between calculated and measured dose better than 2%. For dummy patients range and dose distributions were verified in anthropomorphic phantoms. The agreement of range calculated in TPS and measured in a phantom is better than 1.5 mm.

Conclusions/Novel Aspects

Spot scanning proton therapy system in Cyclotron Center Bronowice is ready for clinical operation.

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Immunotherapy and the abscopal effect of radiotherapy

Rafał Suwiński

M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch

Recent developments in immunotherapy for various types of malignancies are commonly considered as one of the major breakthroughs in oncology. While immunotherapy is currently used mostly in treatment for advanced metastatic disease there is a rapidly growing interest in attempts to combine it with other treatment modalities including radiation therapy. The presentation focuses over the phenomenon of the abscopal effect of radiotherapy both when used alone or when combined with immunotherapy. The literature was searched to find reports on abscopal responses to radiotherapy defined as the responses of malignant tumors attributable to immune system activation beyond the irradiated volumes. The search indicates that, by far, most of the abscopal responses were observed when CTLA-4 inhibitors were combined with radiotherapy in treatment for metastatic melanoma. The frequency of such responses is relatively high (25-50%) suggesting its clinical utility. Some preclinical data that show the abscopal responses in combined therapy with PD-1/PDL-1 inhibitors and radiotherapy are also discussed. In accordance with the other authors we hypothesize that tumor rejection due to immunological responses might be considered as the sixth "R" of radiotherapy (repopulation, repair, redistribution, reoxygenation, radiosensitivity, rejection). Certainly, recent clinical and preclinical data suggest that combining immunotherapy and radiotherapy may create new fascinating treatment regimes in various malignancies. During the presentation same examples of on-going research in this field will be discussed.

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Detection of the GoldAnchor™ markers implanted in the liver by the CyberKnife system during the real-time image-guided robotic radiotherapy of patients with liver metastases

Krzysztof Szczepanik[1], Małgorzata Stąpór-Fudzińska[2], Dawid Bodusz[1], Bożena Jochymek[1], Ewa Telka[1], Leszek Miszczyk[1]

[1] Department of Radiotherapy, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch

[2] Department of Radiotherapy and Brachytherapy Planning, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch

Introduction/Rationale

The use of fiducial markers allows the precise location of the tumor and thus, the dose escalation without increasing the risk of side effects. The aim of this study was to compare the detection of markers implanted amounts in the liver and the quantity makers by the CyberKnife system located on the therapeutic machine.

Materials and Methods

The analysis was based on the results of irradiation of 55 patients (31 women, 24 men) diagnosed with metastasis cancer to the liver. All patients were treated between January 2012 and August 2016 in the Department of Radiotherapy, Cancer Center – MSC Institute in Gliwice. Total implanted 165 gold markers. All markers were detected on X-ray images by the panel and they were determined as active treatment. 261 images were used to retrospective analysis.

Results

In 15 patients (27.3%) who were implanted gold markers, the system detected all markers in each fraction. In 36 patients (65.5%), the system detected the same number of markers in all fractions. In 10 patients (18.2%), while one of the three fractions of treatment, the system detected one marker less compared to the other two fractions. In 77.2%, 9.8%, 10.4% and 2.6% of cases the CyberKnife system detected: 2, 1, 3 and 4 markers. In 27 patients (49.0%) the system detects at least three markers. There was a case where the system is not detected a single marker.

Conclusions

The analysis showed that the detection of gold markers in different fractions of radiotherapy in the same patient appears to be repeatable. Therefore, gold markers seem to be an effective tool for the precise location of the position of the irradiated volume during the treatment.

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Interplay of NF-κB- and p53-dependent signaling pathways in cellular response to ionizing radiation

K. Szoltysek[1], P. Janus[1], A. Walaszczyk[1], T. Stokowy[2], P. Widlak[1]

[1] MSC Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland

[2] Department of Clinical Science, University of Bergen, Bergen, Norway

Introduction/Rationale

Exposure of mammalian cells to damaging factors, such as ionizing radiation (IR), induce a variety of cell signaling pathways, including pathways regulated by NF-kB and p53 transcription factors. Under stress conditions p53 induces cell cycle arrest and/or cell death while the influence of NF-κB activation on the cell fate is more complex, but rather cytoprotective. Here we aimed to identify (candidate) genes co-regulated by both transcription factors in response to IR.

Materials and Methods

U2-OS cells, existed in three cellular variants: wild type cells and cells with downregulated RelA subunit or p53 protein (siRNA approach), were used as an experimental model. All cellular variants were irradiated with different

doses of IR (4Gy and 10Gy) or treated with pro-inflammatory stimulation (TNFα cytokine) to determine 'general' and 'specific' patterns of response to different types of cellular stress. Functional genomics analyses were performed to determine global gene expression profile (RNA-seq approach) and genomic NF-κB and p53 binding sites (ChIP-seq or ChIP-q-PCR approach) in response to certain type of treatment.

Results
Strong activation of both NF-κB and p53 pathways was observed in response to IR. Both transcription factors were recruited to promoter regions of selected target genes (e.g. *IL8*, *CDKN1A*) and their expression level was increased. Performed global gene expression analysis revealed that both, IR and pro-inflammatory stimulation affects a number of genes in wild type cells. Majority of those genes are downregulated in cells lacking RelA (NF-κB subunit) or p53 protein, especially in cells exposed to IR. Moreover, RelA-mediated influence on observed genes involved in response to genotoxic stress is dependent on a dose of radiation.

Conclusions/Novel Aspects
We concluded that IR activates both: NF-κB and p53 transcription factors. Transcriptional regulation of cellular response to stress is determined by the type of stimulating factor and the level of induced DNA damage.
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49 Radiosurgery: planning, verification and realization of gated VMAT technique

Krzysztof Ślosarek

Radiotherapy Planning Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice, Poland

Introduction/Rationale
Radiosurgery requires very precise delivering of high fraction doses. This means that, it is necessary to develop procedures and treatment techniques that will ensure realization of this goal.

Materials and Methods
Imaging studies dedicated for treatment plan preparation were done on the CT scanner (Siemens AS) equipped with the respiratory gating system (RPM - Varian MS). Dose distribution calculations were performed in the ECLIPSE planning system v13.6 (AcurosXB algorithm) with 4D option. Beams XFFF-6MV or XFFF-10 MV, dose rate 14 or 24 Gy/min were used. Verification of dose distribution was checked with ArcCheck matrix (Sun Nuclear). TrueBeam (Varian MS) accelerators with OBI system were used for irradiation. This technique will be presented on the example of patient who was treated several times (thorax, adrenals and lungs), in period of six months. Volumes and dose distributions were deformed with Velocity software (Varian MS).
Results
Calculated dose distribution achieve therapeutic goals. Dosimetric verification confirm good agreement between planed and real dose distribution (gamma index 3% and 3 mm in 95%). Dose distribution deformation based on deformable image registration allows to sum doses for different volumes. OBI system allows to set up patient position with precision of 1 mm.

Conclusions/Novel Aspects
Respiratory gated VMAT technique is a procedure that requires a major commitment of physicians, physicists and dosimetrists. FFF beams (high dose rate) usage reduces time of therapeutic session what influence on treatment precision.

50 Identification of serum proteins associated with the risk of metastasis of breast cancer patients

A. Walaszczyk[1], M. Pietrowska[1], A. Wojakowska[1], A. Abramowicz[1], P. Rodziewicz[2], J. Polańska[3], K. Behrendt[1], E. Nowicka[1], R. Tarnawski[1], P. Widłak[1]

[1] MSC Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Institute of Bioorganic Chemistry, Polish Academy of Science, Poznan, Poland
[3] Silesian University of Technology, Gliwice, Poland

Introduction/Rationale
Breast cancer is the second most common malignant disease in women, and one of the leading causes of cancer-related death worldwide. The major factor that contributes to breast cancer mortality is the presence of distant metastasis. Because of lack of reliable prognostic markers, currently about 80% of patients with early diagnosed breast cancer receive an adjuvant therapy. Hence, knowledge of biomarkers associated with risk of disease progression might be helpful in planning of an optimal therapy, and protecting of large group of patients from toxicity of unnecessary treatment.

Materials and Methods
We selected a group of 15 patients who suffered from cancer relapse and metastasis during 5-year follow-up, and 45 patients who benefited from successful treatment. Blood samples were collected before the start of the therapy, after the surgical resection of tumors and one year after the end of therapy. For the identification of multi-peptide signatures in blood serum samples MALDI ToF/ToF mass spectrometry was exploited. To identify components of serum proteome we used 2D-PAGE and LC-MS/MS approach.

Results
We have identified 42 proteins whose abundances were significantly different between pre- and post-treatment samples in either group of patients. The largest group of proteins, generally upregulated in post-treatment samples, consisted of factors associated with inflammation, acute phase response and complement activation.

Conclusions/Novel Aspects
Serum proteome might be a source of knowledge about the presence of certain factors reflecting e.g. spread of cancer cells. Specific patterns of serum proteome observed before and after treatment could be used not only for monitoring of response to a therapy but also for prognosis of a long-term outcome.

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51 Inflammation related to acute radiation toxicity is the major factor affecting molecular changes observed in blood of cancer patients treated with radiotherapy

P. Widlak[1], M. Pietrowska[1], K. Jelonek[1], M. Roś[1], A. Wojakowska[1], J. Polanska[1], E. Chawińska[1], I. Domińczyk, T. Rutkowski, W. Majewski, L. Miszczyk, K. Składowski

[1] Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland
[2] Silesian University of Technology, Gliwice, Poland

Introduction
Ionizing radiation effects the proteome and metabolome of irradiated cells and tissues, yet data concerning changes induced during radiotherapy (RT) in human blood are fragmentary and inconclusive. We hypothesized that the type and intensity of acute radiation toxicity is the primary factor affecting molecular changes observed in blood of patients subjected to a partial body irradiation during cancer treatment. RT-induced changes in serum proteome and lipidome were compared in two groups of cancer patients, where similar treatment plans were employed regarding the doses and irradiated volumes, yet different radiation toxicities were observed.

Materials and Methods
Sixty patients with head and neck cancer (HNC) and 60 patients with prostate cancer (PC) received definitive intensity-modulated RT. Blood samples were collected before RT, just after and one month after the end of RT. Endogenous serum peptidome and a fraction of serum phospholipids were profiled in individual samples by MALDI-ToF mass spectrometry. Moreover, serum proteins were identified and quantified using the shotgun LC-MS/MS approach. Statistical significance of differences between consecutive samples was assessed. Processes associated with the quantified proteins and their functional interaction were predicted using gene ontology tools.

Results
RT significantly affected the mass profiles of endogenous peptidome and lipidome. The majority of changes observed during the treatment were reversed during the follow-up, yet several changes could still be detected one month after the completion of RT. It is noteworthy that the extent of changes observed in serum of HNC patients was generally higher than in PC patients, even though the doses and volumes of irradiated tissues were comparable in both groups. Similarly, there were much more identified proteins that changed their abundance in serum of HNC patients compared to PC patients, which corresponded to differences in acute radiation toxicity noted between both groups. RT-upregulated proteins were associated with acute phase, inflammatory response and complement activation, while RT-downregulated proteins represented apolipoproteins and blood coagulation factors.

Conclusions
RT-induced changes observed at the level of serum proteome and lipidome reflected the most general response of patient's body to radiation, including inflammation and acute phase response. We concluded that the type of acute radiation toxicity associated with specific features of irradiated tissue was the primary factor determining molecular response detected at the level of blood, while the volume of normal tissue irradiated with low-to-medium doses had only secondary effect.

52 High-dose-rate brachytherapy for recurrent prostate cancer – effective tool for the individualised treatment

P. Wojcieszek[1], M. Szlag[2], A. Cholewka[2], S. Kellas-Ślęczka[1], B. Białas[1], A. Andrejczuk[1], M. Fijałkowski[1]

[1] Brachytherapy Department, MSC Memorial Cancer Center and Institute of Oncology, Gliwice
[2] Radiotherapy Planning Department, MSC Memorial Cancer Center and Institute of Oncology, Gliwice

Introduction/Rationale
High-dose-rate brachytherapy (HDR BT) accompanied by real-time imaging is one of the most precise tools for the individualized prostate cancer treatment. Interstitial technique and/or optimization potential allow to deliver conformal irradiation with extraordinary accuracy. It also let provide radioablative doses per fraction (>7Gy) and thus short overall treatment time. The aim is to present HDR BT capacity of treatment individualization in the locally recurrent prostate cancer.

Materials and Methods
Eighty three men with prostate cancer local relapse were treated with HDR BT (3x10Gy/28 days) in MSC Cancer Center Gliwice. Early and late toxicity were evaluated with CTCAE 4.0. Biochemical relapse was set due to Phoenix criteria (PSA nadir +2 ng/ml). Overall and biochemical-free survival were estimated with Kaplan-Meier method.

Results
Median follow-up after salvage HDR was 41 months. The 5-year OS was 86%. The 5-year biochemical disease-free survival was 67%. One patient (1%) suffered from grade 3 acute genitourinary toxicity, 11 patients (13%) developed grade 3 late genitourinary toxicity. Mild gastrointestinal adverse events were reported in 5 patients (6%).

Conclusions/Novel Aspects
Salvage HDR BT provides highly individualized treatment for local recurrence of the prostate cancer. It is efficient especially for the patients after primary radiotherapy failure. Even though high dose of radiotherapy is delivered in the target volumes, HDR BT makes further dose escalation possible. Future research should explore reduction of interstitial implantation and dose decrease to avoid unnecessary adverse events.

53 Thyroid function after postoperative radiation therapy in patients with breast cancer

Edyta Wolny-Rokicka MD,PhD[1,2], Andrzej Tukiendorf PhD Associate Professor[3], Jerzy Wydmański MD, PhD Associate Professor of Radiation Oncology[4], Danuta Roszkowska MSc[5], Bogusław Staniul MD,PhD[6]

[1] Department of Radiotherapy, Regional Clinical Hospital in Zielona Gora, Zielona Gora, Poland
[2] University of Zielona Gora, Faculty of Medicine and Health Sciences, Zielona Gora, Poland
[3] Department of Epidemiology and Silesia Cancer Registry, Center of Oncology – Maria Sklodowska-Curie Memorial Institute, Branch in Gliwice, Gliwice, Poland
[4] Department of Radiotherapy, Center of Oncology – Maria Sklodowska-Curie Memorial Institute, Branch in Gliwice, Poland
[5] Department of Physics, Regional Clinical Hospital in Zielona Gora, Zielona Gora, Poland
[6] Department of Surgery, Regional Hospital in Sulechow, Sulechow, Poland

Introduction
The aim of this study was to assess thyroid function in the breast cancer patients, who were exposed to the therapeutic external beam radiation, to assess possible progressive changes in thyroid function and to established relationship between the incidence of primary hypothyroidism, the time required to become hypothyroid and dose of (RT), factors such as: chemotherapy, hormonotherapy and immunotherapy compared with index of serum thyroidstimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3).

Materials and Methods
70 female undergoing 3D conformal and IMRT radiation therapy for breast cancers were enrolled in a non-randomized prospective study between April 2012 and May 2015. The patients after mastectomy were irradiated to a scar of the chest wall and the ipsilateral supraclavicular and the axillary areas (group 2). Patients after BCT (group 1) were irradiated to the breast and/ or with lymph nodes depends on stages of disease. The total doses were: 50 to 70 Gy in 5 to 7 weeks. The median follow-up term was 24 months (range, 1–40 months). The thyroid function was evaluated by measuring TSH, fT4, and fT3 levels. The minimum, maximum and mean thyroid dose for the thyroid gland doses for 20 Gy (VS20) were calculated for all patients.

Results
The statistically significant results were obtained for the group 2. After two years since the end of RT the chance of the event increased to 6%. There was no effect of age and treatment.

Conclusions
Routine thyroid function monitoring in breast cancer patients after radiotherapy should be consider.

54 The comparison and estimate of the prognostic value of lipids profiles in 2 groups of patients with prostate cancer in depends on advancement

Edyta Idalia Wolny-Rokicka MD,PhD[1], Jerzy Wydmański MD, PhD Assoc. Professor of Radiation Oncology[2], Andrzej Tukiendorf PhD Assoc. Professor[3]

[1] Lubuski Center of Oncology, Radiotherapy Department, Clinical Hospital in Zielona Góra, Zielona Góra, Poland
[2] Department of Radiotherapy, Center of Oncology – Maria Sklodowska-Curie Memorial Institute, Branch in Gliwice, Poland
[3] Department of Epidemiology and Silesia Cancer Registry, Center of Oncology – Maria Skłodowska-Curie Memorial Institute, Branch in Gliwice, Poland

Introduction
Lipid profile and prostate cancer have controversial relationship and is still questionable if they could be a prediction in risk of cancer. To study change and assessment significance of plasma lipid profiles patients with prostate cancer (PCa) we compared locally advanced patients who were exposed to the therapeutic external beam radiation and prostate cancer patients with metastases to the bones.

Materials and Methods
In 103 histopathologically diagnosed cases (71 locally advanced and 32 palliative patients) were taken to analyze blood samples total cholesterol (CHL), triglycerides (TG),high density lipoprotein cholesterol (HDL) and low density lipoproteins cholesterol (LDL) for comparison. Patients were grouped according stages and assessed involved of statins factor in both groups

Results
We noticed negative effect of time of observation on LDL/HDL ratio with an approximate increase of 0.0025 with each day in palliative patients. It was elevated statistically significant ($p=0.04$). In contrast HDL/CHL ratio was decreased ($p=0.02$) what was observed in locally advanced group. A values of TG/HDL ratio was not statistically significant in both group.

Conclusions
As the survival of cancer patients are increasing, control of lipid profile is gaining importance.

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Correlating parameters platelet counts (PLT) and mean platelet volume (MPV) with tumor and possibility finding his threshold of size

Edyta Wolny-Rokicka MD,PhD[1,2], Jerzy Wydmański MD,PhD Assoc.Professor of Radiation Oncology[3], Andrzej Tukiendorf PhD Assoc. Professor[4], Piotr Mróz PhD[5], Agnieszka Namysł-Kaletka MD,PhD[3], Katarzyna Gramacka Lab Msc[6], Jakub Lipiński MSc[7]

[1] Radiotherapy Department, Regional Clinical Hospital in Zielona Gora, Zielona Gora, Poland
[2] University of Zielona Gora, Faculty of Medicine and Health Sciences, Zielona Gora, Poland
[3] Department of Radiotherapy, Center of Oncology – Maria Sklodowska-Curie Memorial Institute, Branch in Gliwice, Poland
[4] Department of Epidemiology and Silesia Cancer Registry, Center of Oncology – Maria Sklodowska-Curie Memorial Institute, Branch in Gliwice, Poland
[5] University of Zielona Gora, Faculty of Computer Science, Electrical Engineering and Automation, Institute of Metrology, Electronics and Computer Science, Zielona Gora, Poland
[6] Laboratory, Regional Clinical Hospital in Zielona Gora, Zielona Gora, Poland
[7] University of Zielona Gora, Faculty of Computer Science, Electrical Engineering and Automation, Zielona Gora, Poland

Introduction
The mechanisms of platelet action in capacity cancer progression have been supposed, exact pathophysiological mechanisms and up to this time not been completely elaborated. The correlation between PLT, MPV and many other cancer types has been investigated previously, but the correlation between PLT and MPV and tumor of volume has not yet been studied. The present study aims to detect the association between tumor of volume of lung cancer, platelet counts (PLT) and mean platelet volume (MPV).

Materials and Methods
We retrospectively reviewed the medical records of 99 cases who had undergone surgical staging procedures between January 2009 and December 2010. 66 patients were undergoing radical operating treatment and 33 patients had only biopsies - as an inoperable cases. In group was: 81% male and 19% female. According histopatology profile: non-small cell carcinoma and adenocarcinoma both 23 %, Squamous - 36%, Small cell carcinoma -11%, Carcinoid - 6%. Survival was recorded from the time of surgery procedure to death or last observation. The last follow-up date was July 31 2016. We measured volume of tumor using information from histopathology protocol and using model for ellipsoid ($V=4/3\pi$ r(abc)). Pretreatment PLT and MPV were evaluated. The tumor of volume was defined and assessed the impact of parameter tumor into value of PLT and MPV. The venous blood samples was drawn from peripheral blood before surgery and evaluated by measuring the complete blood count (CBC) with a hematology analyzer (Abbott CD3700,CD RUBY, USA). The reference value in our hospital for this parameters are: PLT - normal 0,27 - 4,2 $x10^3/mm^3$, MPV: 7-11 fl.

Results
Median survival time after surgery was 20 months and 7 for patients after biopsies. Patients with normal PLT levels have longer survival time (median: 11 months) vs thrombocytosis group (9,5) but it was not significant (p=0,6). Following both the PLT and MPV, a break-point that is equal approximately to 18.5 cm3 (3.3 cm of the diameter) stands for a segmented relationships between tumor volume and analyzed blood indicators.

Conclusions
As regards the final inference it is required to refer to supplemented statistical findings to precise medical practice. After a overstepping of break-point of tumor volume a inflammatory processes are started and they are associated with poor prognosis. MPV may be a valuable biomarker for the diagnosis and follow up of various types of cancer.

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The efficacy of palliative radiotherapy for patients with lung cancer: the quality of life (QoL) analysis

Malgorzata Wyduba[1], Wojciech Majewski[2]

[1] Department of Anesthesiology and Intensive Therapy, MSC Memorial Cancer Center and Institute of Oncology, Gliwice Branch
[2] Radiotherapy Department, MSC Memorial Cancer Center and Institute of Oncology, Gliwice Branch

Aim
To evaluate the efficacy of palliative radiotherapy in patients with lung cancer, based on a prospective assessment of Quality of Life (QoL).

Materials and Methods
The study group consist of 54 patients with lung cancer treated with palliative radiotherapy in 2014-2015. The mean patients age was 64 years (46-81 years). There were 18 women (33%) and 36 men (67%). Thirty eight patients (70%) were in a good general condition (ZUBROD 0-1), whereas the rest in poor general condition: 12 (22%) ZUBROD-2 and 4 patients (8%) ZUBROD-3. Stage IIIA was diagnosed in 6 patients (11%), Stage IIIB in 8 (15%) and stage IV in 40 patients (74%). Radiotherapy was performed with 6 or 20 MV photons. Simple 2D radiotherapy with two opposed AP-PA fields was used in 48 patients (83%), whereas the rest was treated with 3DCRT using 3- or 4- field technique. The radiation schemes were as follows: 20 Gy with 4 Gy per fraction- 29 patients (54%), 20-30 Gy with 2 Gy per fraction- 16 patients (30%), 30 Gy with 3 Gy per fraction- 7 patients (13%) and 2 patients did not completed the planned RT (10 Gy in 2 Gy per fraction).
The prospective study based on QLQC30, RSCL and Pain questionnaires filled by each patient before, at the completion of radiotherapy and 3-4 months post-treatment. In this study the evaluation of changes of pain intensity (NRS scale 0-10), general QoL (scored 0-100) and dyspnea was performed. With NRS scale- the higher point

means more pronounced pain. With general QoL scale the higher point means better QoL. The intensity of dyspnea is scored on a 4-point scale (never, sometimes, often, very often), with higher score meaning more pronounced symptom. The comparison was performed with non-parametric Wilcoxon test.

Results
The median intensity of pain before treatment was 4 points. At the completion of radiotherapy it was 6 points. At the last measurement 3-4 months post-treatment it was 3 points. The differences with respect to the pre-treatment value were significant (p=0.0002 and p=0.007).
The median general QoL was scored 67 points before treatment. At the completion of radiotherapy it was 33 points, at the last measurement 3-4 months post-treatment it was 73 points. Only the difference between pre-treatment and post-treatment value was significant (p=0.000 and p=0.13).
The median dyspnea score before radiotherapy was 2 points. At the completion of radiotherapy it was 3 points, at the last measurement 3-4 months post-treatment it was 2 points. The difference between pre-treatment and post-treatment value was significant, and there was a trend to improvement between pre-treatment and 3-4 month post-treatment value (p=0.0002 and p=0.06).

Conclusions/Novel Aspects
At the completion of palliative radiotherapy in lung cancer patients a deterioration of general status and increase in existing symptoms may be expected. At longer follow-up the symptoms improve and general status remains stable as compared to the pre-treatment status. Patients with expected survival of at least 3-4 months seem to benefit from palliative radiotherapy.

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Assessment of radiotherapy effects in treatment of anaplastic thyroid carcinoma

Z. Wygoda, D. Handkiewicz-Junak, J. Krajewska, B. Jarząb

Institute of Oncology – MSC Cancer Center, Branch Gliwice
Dept. of Nuclear Medicine and Endocrine Oncology

Introduction/Rationale
Anaplastic thyroid carcinoma is one of the most aggressive human malignant neoplasms with significant and rapid disease progression. The problems with possibility of surgical resection are due to involvement of neck soft tissues and blood vessels and massive lymph node metastases of the neck and mediastinum during initial diagnostic of thyroid tumor with suspicion to anaplastic cancer. Difficulty in breathing is consequence of early trachea involvement, neoplasm spreading to soft tissues and skin manifests itself in skin ulcerations. The main aim in this disease stage is to ensure permeability of the respiratory tract with tracheostomy, however, this surgical intervention is often difficult or sometimes impossible because of neoplasm spreading along the trachea to bifurcation. Locoregional radiotherapy as a palliative treatment in this stage of disease is recommended as a treatment giving the maximal comfort for patient in terminal period of anaplastic thyroid carcinoma.

Materials and methods
The group of 47 patients with inoperable anaplastic thyroid carcinoma was assessed: 35 women aged 52-76 years old (median 67) and 12 men aged 44-72 years old (median 63). Neoplasm disease was stated by thin needle biopsy in all patients. Time from first symptoms of disease as thyroid tumor or lymph nodes enlargement to first medical assessment was 1-5 months (median 2,5). All patients presented inoperable neoplasm disease during first examination in Institute of Oncology. Neck lymph node metastases were stated in 41 patients, mediastinal lymph node metastases were stated in 18 patients, distant metastases were observed 14 patients.
Palliative radiotherapy of thyroid mass and involvement regional lymph nodes was performed in all patients. Tracheostomy was performed in all patients before radiotherapy: in 38 patients as a planned surgery, in 9 patients as a urgent surgical intervention due to significant trachea narrowing and difficulty in breathing. Non-coplanar conformal technique od radiotherapy was used in 31 patients, the technique of two opposite fields was used in 16 patients with significant tumor enlargement or massive lymph node metastases. All patients were irradiated with 6 MV X-ray with total dose 16-30 Gy (fraction dose 2-4 Gy).

Results
All patients are died in 4-8 months form the first symptoms of disease (thyroid tumor or lymph node metastases) and in 3-5 months after diagnostic procedures. The survival time from radiotherapy was 1-3 months. Symptoms as neck pain, difficulty in breathing or dysphagia were reduced temporarily in 31 patients, however in other 16 patients radiotherapy effect was non-satisfactory. Rapid progression of disease was usually observed after radiotherapy

Conclusions/Novel Aspects
Radiotherapy in inoperable, advanced anaplastic thyroid carcinoma is only palliative treatment but can give the possibility of temporarily significant reduction of pain and other symptoms connected with neck involvement by cancer mass in 2/3 patients.