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Purpose: Large changes in bladder shape and size during a course of radiotherapy (RT) make adaptive RT (ART) appealing in treatment of muscle invasive bladder cancer. We are running a two-center clinical trial of ART for bladder cancer where the primary aim of the trial is to reduce gastro-intestinal morbidity due to sparing of the bowel and the rectum We here report on initial clinical experience and outcome of this trial.
Materials/methods: The present study reports preliminary results on the first nine bladder cancer patients included in the ART trial. All patients received 60 Gy in 30 fractions to the bladder; in four patients the pelvic lymph nodes received 48 Gy simultaneously. Patients were set-up by use of cone-beam CT (CBCT) guidance and treatment was delivered by volumetric modulated arc therapy (VMAT). In our ART strategy, the first five fractions were delivered using large non-adaptive margins - the bladder contours from the CBCTs acquired prior to the first four fractions were used to create a library of three plans corresponding to a small, medium and large size bladder. DVHs for organs at risk were calculated by summation of the selected plans calculated on the planning CT and compared to our previous standard non-adaptive RT plans involving population-based margins.
Results: The frequency of which the small and medium size plans were selected was equal, whereas the large size plan was used on less than 27% of the (total of 225) plan selection fractions. The median rectal volume receiving 50 Gy or more was 5% [0-41%], compared to 17% [0-62%] if the patients had been treated with standard, non-adaptive RT. For the bowel cavity, the median volume receiving more than 45 Gy was 269 cm^3 [83-486 cm^3], compared to 337 cm^3 [126-553 cm^3] if not treated with adaptation. No grade 3-4 gastro-intestinal morbidity was observed.

Conclusion: Daily adaptive plan selection in RT of bladder cancer results in a considerable normal tissue sparing, and is expected to reduce the risk of gastro-intestinal morbidity.

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ENTERVISION WP4. Biological Dosimetric Phantom. Proof of Concept Preliminary results

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

Keywords: Ion beam therapy, radiobiology, dosimetry

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Realistic on-the-fly dose calculation for low energy X-rays Intra-Operative Radiation Therapy

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Purpose: The aim of this work was to develop a new algorithm to compute dose from a mobile accelerator of low energy X-rays Intra-Operative Radiation Therapy (XIORT) (ex: INTRABEAM®, Carl Zeiss) in heterogeneous conditions, such as a patient 3D volume, within 2-3 seconds. XIORT needs accurate and fast dose calculation. In this work a hybrid Monte Carlo tool is developed which takes into account all the components of the XIORT X-rays up to 50 keV and predicts in a satisfactory way the dose delivered to the patient. The tool is being included in Radiance® from GMV [1], a powerful Treatment Planning System for IORT.
Materials and methods: A few analytical algorithms exist which only consider the primary x-ray beam [2]. A hybrid Monte Carlo code which takes into account the photoelectric and the Compton effects for X-rays up to 50 keV, was developed to compute dose in 3D-CT volumes. Full Monte Carlo simulations have been generated with penEasy to validate our tool in homogeneous and heterogeneous conditions [3]. For the spherical applicators (from 0.75 cm to 2.5 cm radius) and the needle, a genetic algorithm was employed to determine the energy spectra which reproduce the measured dose distribution in water. Once the energy spectrum is obtained, it is implemented in the hybrid Monte Carlo algorithm. The absorbed dose distributions were then simulated in water and heterogeneous media both with penEasy and the hybrid Monte Carlo algorithm for the spherical applicators and the needle.
Results: The energy spectra for all the spherical applicators and the needle are similar to energy spectra from other Monte Carlo studies and measurements [4]. Dose distributions computed by the fast hybrid Monte Carlo tool are in a good agreement with penEasy full simulations in water and heterogeneous media. The algorithm gives also a good prediction of the measured dose distribution in water, and comparison to measured data in heterogeneous phantoms is being carried out. Computation time is below 5 seconds in a single core of a modern PC.
Conclusions: The hybrid Monte Carlo algorithm is a fast and robust tool to compute dose distributions in a patient geometry. It is being implemented in the Intra-Operative Radiation Therapy Treatment Planning System Radiance® from GMV, and can be used for any XIORT system.

Keywords: Intraoperative radiotherapy, Monte Carlo simulations, dose calculation

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The SMAC-mimetic Debio 1143 efficiently enhanced radiotherapy in head and neck squamous cell carcinoma models

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The small molecule Debio 1143 (D1143) is an orally-active, SMAC-mimetic designed to promote apoptosis in tumor cells by blocking the activity of inhibitor of apoptosis proteins (IAPs). This study aimed to test the efficacy of D1143 as a single agent or in combination with radiotherapy (RT) in head and neck squamous cell carcinoma (HNSCC) models.
The effect of D1143 was assessed by the colony forming assay on a panel of HNSCC cell lines. Tumor cells were incubated at various concentrations of D1143 and treated with increasing doses of radiation. The number of surviving colonies was then recorded and compared to an untreated group. In parallel, various treatment sequences were tested, (before, during or post-irradiation) to determine the effect of D1143 on primary apoptosis (early, pre-mitotic apoptosis) and secondary apoptosis (late, post-mitotic reproductive cell death). The in vivo radiosensitizing effect of oral treatment with D1143 was further evaluated in nude mice bearing HNSCC tumor xenografts.
D1143 alone selectively inhibited colony formation of several cell lines. In addition, combination experiments found D1143 to be highly effective in enhancing cell death induced by RT. A synergistic effect of D1143 was observed in the majority of the tested cell lines treated by RT. Interestingly, the radiosensitizing effect of D1143 was preeminent when cells were co-incubated with D1143 24 hours after irradiation, showing that D1143 efficiently impacts late apoptosis due to mitotic catastrophe and/or other cell death events that arise after irradiation.
In mice bearing HNSCC radio-resistant tumors, D1143 given orally in combination with RT delayed the tumor growth for more than 40 days when compared to RT.
These results show that D1143 exhibits activity as a single agent and can potentiate the effects of radiotherapy in HNSCC models indicating that D1143 has a promising therapeutic potential for the treatment of HNSCC.

Keywords: SMAC-mimetic, radiosensitization, IAP inhibitor

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Radiosensitizing effect of a RasGAP derived peptide on cell survival in human cancer cells in vitro and in vivo

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In this study we used TAT-RasGAP$_{317-326}$, an engineered peptide derived from RasGAP and we studied its radiosensitizing properties i*n vitro* on cell survival and proliferation of several human cancer cells and *in vivo* on tumor growth of xenograft tumors in mice.
Clonogenic assays with 4 human cancer cells (PANC-1, HCT116 p53$^{+/+}$, HCT116 p53$^{-/-}$, and HeLa) and a non tumorigenic cell line (HaCaT) were performed. Cells were exposed to 0, 1, 2 and 4 Gy with or without 20 µM TAT-RasGAP$_{317-326}$.
TAT-RasGAP$_{317-326}$ radiosensitizing effect was also tested in tumor xenograft mouse model. During 10 days, mice bearing subcutaneous HCT116 (WT or p53 mutant) tumors received every day 1.65 mg/kg TAT-RasGAP$_{317-326}$ i.p. injected and were locally irradiated with 3 Gy.
At all the tested radiation doses TAT-RasGAP$_{317-326}$ showed a significant supra-additive radiosensitizing effect on all the tested tumor cell lines. By combining radiation and TAT-RasGAP$_{317-326}$ the cell surviving fraction at 2 Gy was decreased by a factor ranging from 2.1 to 3.8-fold. Without radiation TAT-RasGAP$_{317-326}$ had no effect on cell survival and proliferation. Furthermore, TAT-RasGAP$_{317-326}$ showed no sensitizing effect on the non tumorigenic cell line exposed to radiation.
In vivo, TAT-RasGAP$_{317-326}$ also induced a significantly radiosensitizing effect as shown by a significant higher reduction in tumor volume as much as by a significant tumor growth delay. Combination of TAT-RasGAP$_{317-326}$ and radiotherapy allowed to delay the tumor volume growth by 10 days in HCT116 p53$^{+/+}$ tumors and by 34 days HCT116 p53$^{-/-}$ tumors compared to the group of mice that received only radiotherapy. Like *in vitro* TAT-RasGAP$_{317-326}$ had no effect on tumor volume if not combined with radiotherapy.
Results showed that TAT-RasGAP$_{317-326}$ has a radiosensitizing effect on *in vivo* and *in vitro* cancer cells without any notable effect on healthy tissues. Therefore TAT-RasGAP$_{317-326}$ should be considered as a novel and attractive radiosensitizer compound.

Keywords: RasGAP, peptide, radiosensitizer

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NOTCH and radiotherapy: does it matter?

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Purpose: Patients with advanced NSCLC have 5 year survival rates of less than 15 %. The NOTCH pathway plays an important role during lung development and physiology and is often deregulated in NSCLC. Notch inhibitors are being widely tested in clinical trials however information on the efficacy of Notch inhibition in combination treatments remains understudied. Here we investigated the prognostic and predictive impact of NOTCH signaling in human NSCLC in preclinical mouse models and in vitro in human and murine (KRAS/P53 GEMM) NSCLC cell lines.
Material & Methods: The expression of Notch receptors, ligands and target genes was investigated in 90 patients with early stage NSCLC and correlated with disease-free survival. Human and murine NSCLC with overexpression or attenuation of the Notch pathway were used in vitro and to generate xenograft tumors to investigate the role of Notch signaling in tumor progression and response to radiation therapy. The role of Notch signaling in hypoxia tolerance, radio-sensitivity and chemo-sensitivity was assessed in vitro and in vivo. Tumor perfusion, hypoxia and proliferation were analyzed in xenograft tumors and correlated to NOTCH signaling activity.
Results: Patients with high NOTCH activity in tumors showed significantly worse disease-free survival. Ectopic NOTCH1 activation did not affect the proliferation or intrinsic radio-sensitivity of NSCLC cells in vitro. In contrast, tumors with blocked NOTCH activity grew slower than wild type tumors while tumors with high NOTCH1 activity grew significantly faster were more hypoxic and radio-resistant. Results will be presented on the possible mechanisms by which NOTCH signaling contribute to radiation and chemo-resistance.
Conclusions: We conclude that NOTCH signaling plays an important role in NSCLC growth and response to therapy. Further knowledge into the mechanism of therapy resistance may provide improved intervention schedules/combinations if NOTCH inhibitors are applied in combination with standard of care treatment.

Keywords: notch, radiotherapy, hypoxia