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53 patients (78%) received concomitant chemoradiation (Group A) and 15 patients (22%) sequentially (Group B). The mean dose administered was 60 Gy, 2 Gy per fraction, 5 fractions per week. All patients received daily treatment with glutamine; 10 gr. each 8 hours, from five days before starting radiotherapy treatment to fifteen days after it was completed. All patients were visited in weekly based schedule during radiotherapy treatment, and monthly up to tree months after its completion. The oesophagitis was assessed by using the RTOG scale. In DVH, V50 was used as a best parameter to predict acute oesophagitis,

Results: From November 2007 to August 2010, 68 lung cancer patients (57 men and 11 women) were included. 23 patients (34%) were affected of limited small cell carcinoma and 45 patients (66%) of non small cell carcinoma. 53 patients (78%) received concomitant chemoradiation (Group A) and 15 patients (22%) sequentially (Group B). The mean dose administered was 60 Gy, 2 Gy per fraction, 5 fractions per week. All patients received daily treatment with glutamine; 10 gr. each 8 hours, from five days before starting radiotherapy treatment to fifteen days after it was completed. All patients were visited in weekly based schedule during radiotherapy treatment, and monthly up to tree months after its completion. The oesophagitis was assessed by using the RTOG scale. In DVH, V50 was used as a best parameter to predict acute oesophagitis.

Conclusions: The results of our study show a clear benefit in using glutamine for prevention of acute oesophagitis in lung cancer patients treated with chemoradiotherapy (diminishing their intensity) comparing with those of historical series without use of glutamine. They are comparable to those obtained in similar studies where glutamine was used. V50 > 30% is a good predictor parameter of developing oesophagitis.

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BRACHIAL PLEXUS - CONTOURING AND DOSE-VOLUME ASSESSMENT IN BREAST CANCER LOCOREGIONAL RADIOTHERAPY

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Purpose: Brachial plexopathy is a known issue following axillary radiotherapy (RT) in locally advanced breast cancer (LABC). We attempted to adapt RTOG guidelines on brachial plexus (BP) contouring (head and neck cancer) to breast cancer patients receiving post-mastectomy locoregional radiotherapy (LRRT), to determine (a) feasibility of identifying BP in the treatment position for breast cancer, and (b) RT dose received by BP with respect to the planned dose.

Materials: Planning CT sets (non-contrast) of 10 LABC patients who had completed LRRT including posterior axillary boost were retrieved. Treatment consisted of chest wall irradiation (50 Gy in 25 fractions, 6-10 MeV electrons, 80-100% isodose), and supraclavicular and axillary RT with an anterior photon field (6 MV, 40 Gy in 20 fractions) and a posterior axillary field (6 MV, 10 Gy in 5 fractions). Anatomy & radiology texts, RTOG & ASTRO contouring CMEs were consulted for identification of BP. Vertebral bodies C5-T1, anterior and middle scalene muscles were contoured and used as guide to identify probable location of BP.

Results: 10 LABC patients (right 4, left 6) with median age 47 years (range 40-65 years) received LRRT, to a dose equivalent of 50 Gy in 25 fractions. Mean ipsilateral BP volume was 13.8 cc (range 12.1-16.1 cc). Medians of maximum and mean BP doses were 54.65 Gy (range 53.64-56.61 Gy) and 36.62 Gy (range 31.61-44.27 Gy), respectively. The mean global dose maximum of the respective plans was 58.93 Gy (range 57.19-60.75 Gy). Mean BP volume receiving >50 Gy was 27.81% (median 22.01%, range 13.01%-51.80%).

Conclusions: BP contouring in LABC LRRT is feasible, with some uncertainty in regions of altered anatomy (C5-6, shoulder). The maximum BP doses always exceeded prescribed dose of 50 Gy, and although lower than tolerance dose (60 Gy) should be evaluated to reduce adverse events.

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COMBINATION THERAPY APPROACH TO MITIGATING LUNG EFFECTS: TOO MUCH OR TOO LITTLE?

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Purpose: Easily distributed countermeasures are urgently required for use following a mass radiological or nuclear event. However, survivors of the acute radiation syndrome that results from whole body exposure have been shown to be susceptible to late morbidities that could occur as part of a multi-organ dysfunction syndrome. Therefore, the late effects seen in such organs as the lung in the context of total body irradiation (TBI) are of considerable concern. Although the clinical progression to lung late effects (pneumonitis and fibrosis) is well recognized, the complex nature of the pathways leading to their development, which includes cellular, molecular and temporal components, has led to our group's contention that no single agent or strategy is likely to be an effective measure against these potentially lethal endpoints. We have developed a system to assess combinations of agents for countermeasure use; importantly, such mitigating strategies also may be beneficial in the clinical context.

Materials: Using a systematic experimental system to test agents, involving an appropriate "2-strain" murine model with a TBI + lung irradiation schedule (5+10 Gy), we have assessed therapies that include a broad-based anti-inflammatory agent (simvastatin) administered in combination with a number of complementary agents, including G31P (a high affinity antagonist of CXCL8), captopril (an ACE inhibitor), and EUK-207 (an SOD-catalase mimetic); all agents were assessed using combinations of acute and chronic administration regimens.

Results: Both captopril and EUK-270 alone have demonstrated considerable efficacy at reducing lethality due to pulmonary late effects, whether administered acutely or chronically, through differential mechanisms that appear to be associated with reduction in cytokine expression and the resultant decrease in infiltrating inflammatory cells. In addition, these beneficial results were further enhanced when the drugs were given in combination with simvastatin, although there is a differential strain effect. However, when the radiation dose to the lung was increased by 1 Gy, there was an unexpected toxicity, apparent as a sensitization and early acute death.

Conclusions: Two agents have been identified as potential mitigators of lung late effects and are undergoing further analysis. However a surprising reduction in lethality was seen following a small increase in lung dose, suggesting that systemic injury due to TBI may affect the pharmacology of combination therapies, possibly through alterations in immune response and drug metabolism. These findings may have profound implications on the treatment of victims following a likely accident or terrorism event and potential mechanisms are currently being pursued.Supported by U19 AI-091036-1 and RC1 AI081244-01

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DOSE-EFFECT RELATIONS FOR PREDICTING ACUTE ESOPHAGITIS AFTER IMRT CONCURRENT CHEMORADIOTHERAPY OF NON SMALL CELL LUNG CANCER BASED ON DOSE-SURFACE DISTRIBUTIONS

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Purpose: Predicting acute esophagitis (AE) in NSCLC patients receiving IMRT is challenging. Currently, only dosimetric parameters (e.g. *V70, V50, V35*) derived from conformal treatments are applied in the clinic to limit or predict AE. There is, however, a lack of consensus on the most predictive parameter. In this study, we aim to analyze the IMRT dose distribution received on the esophagus surface, and relate these to AE.

Materials: A group of 31 consecutive patients treated in the Antoni van Leeuwenhoek Hospital with AE Grade 0 to 3 (CTCv.3.0) was selected for this study. Twenty patients scored as Grade 0-2 were categorized as non-toxic (NT), while 11 patients with Grade 3 were categorized as toxic (T). All patients underwent daily concurrent chemoradiotherapy using IMRT with 66Gy in 24 fractions. The dosimetric parameter used in treatment planning to avoid AE was $V35 \leq 65\%$. The delineated esophagus from the planning CT and the delivered dose were available for each patient, allowing a 2D esophagus surface dose map (ESDM) to be computed (Fig. 1a). To analyze the dose distribution on the esophagus surface, two hypotheses were tested. H1: The dose delivered to a specific location of the esophagus is associated with AE. H2: The local dose distribution, independent of the esophagus anatomy, is associated with AE. To test H1, ESDMs of all patients were mapped on an identical esophagus grid. To test H2, ESDMs of all patients were mapped according to the location of the voxel with the highest dose, accounting for translation along and rotation around the length of the esophagus (Fig. 1b). After the inter-patient dose mapping, a voxel-by-voxel based t-test, followed by a permutation based multiple comparisons test, were conducted to test the dose distribution differences between NT and T patients for both hypotheses. Finally, the region that received a significantly higher dose for NT than T could be highlighted according to the two-sided significance level of $p \leq 0.05$.

Results: In H1, no significant region was found to be associated with AE. This result implies that there is no evidence that the esophagus has a non-homogeneous radiosensitivity. This finding needs to be further analyzed with clinical or biological evidence. In H2, a significant region was found to be associated with AE (Fig. 1c). This result suggests that AE is associated with local dose distribution, especially the length and circumference of the high dose region on the esophagus. The locations of the significant regions suggest that especially the dose to the entire esophagus circumference is related to AE.

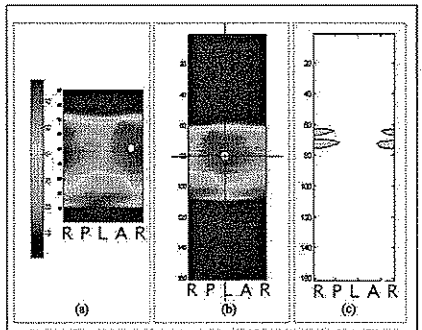

Figure 1: Inter-patient dose mapping and the significant dose region in the H2 test. (a) A 2D ESDM example of one patient. The x-axis corresponds to right (R), posterior (P), left (L), anterior (A) and right (R) of the esophagus. (b) Example of mapping the ESDM in H2 test. The highest dose voxel (white point) is mapped to the center of the new dose map. (c) The region ($P<0.05$) that received significantly higher dose for patients with complications.

Conclusions: The dose that is given to a specific esophagus location is *not* associated with AE, while the shape of the local dose distribution is associated with AE. The region that gives significantly higher dose to T patients suggests that dose-length-circumference parameters may be predictive for AE in high dose IMRT and concurrent chemotherapy.

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EARLY PROCTOSCOPY PREDICTS LATE RECTAL TOXICITY IN PROSTATE CANCER TREATED WITH RADIOTHERAPY

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Purpose: To predict short term (one year) mucosal complications with grade and incidence of clinical late rectal toxicity.

Materials: Patients with prostate adenocarcinoma treated with curative or adjuvant RT underwent endoscopy one year after the end of RT. Mucosal changes were classified by Vienna Rectoscopy Score (VRS). Late toxicity data were analyzed according to the Kaplan-Meier method. Comparison between prognosis groups was performed by log rank analysis.

Results: After a median follow-up of 45 months (range 18-99), the 3-year incidence of grade > 1 and > 2 rectal EORTC/RTOG late toxicity was 34% and 24% respectively. The occurrence of grade >2 rectal toxicity was higher in patients presenting grade > 2 (32% vs 15 %, p=0.02) or > 3 telangiectasia (47% vs 17%, p=<0.01) and an overall VRS score > 2 (31% vs 16 %, p=0.04)or >3 (48% vs 17%, p=0.01) at one year proctoscopy. Patients presenting grade > 2 congested mucosa had an higher incidence of grade > 1 rectal toxicity (77% vs 47% p=0.01).

Conclusions: Early proctoscopy (1 year) can predict late rectal toxicity and therefore can be used as surrogate end-point for late rectal toxicity in studies aimed at reducing this frequent complication

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EFFECT OF ACETYLSALICYLIC ACID (ASA) AS A RADIOPROTECTOR

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Purpose: Post-ionizing radiation cell injury occurs by means of oxidative/nitrosive stress mediators. Protection of normal tissues from radiation injury might increase the therapeutic ratio. It is demonstrated that acetylsalicylic acid (ASA), a member of the non-steroidal anti-inflammatory group, can inhibit the release of prostaglandins that play a role in many forms of tissue damages and that it might prevent tissue/cell damages in various diseases, with its similar antioxidant properties. With clinical/preclinical studies, it is shown that ASA might reduce oxidative injury and genocytotoxicity and that it has a place in protection from cancer.

Materials: The rats were applied with whole-body irradiation (6 Gy, single dose) using Cobalt-60. Glutathione (GSH), malondialdehyde (MDA), myeloperoxidase (MPO) and nitric oxide (NO) levels, indicators of oxidative/nitrosive stress likely to occur in the lung tissue of rats, were measured. The radioprotective effects of ASA and how these effects differed from that of amifostine (WR-2721) were compared. Control (C; n=6), Radiation (R; received irradiation; n=5), Radiation+ASAG (R+ASAG; received irradiation and 25 mg/kg/dayx5 ASA by gavage; n=5), Radiation+ASAIP (R+ASAIP; received irradiation and 25 mg/kg ASA by i.p.; n=5) and Radiation+Amifostine (R+WR-2721; received irradiation and 200 mg/kg WR-2721 i.p.; n=5) rat groups were formed/used. Some 72 hours after irradiation, the MDA, GSH, MPO and NO levels in the homogenate prepared from the lungs of the groups were measured. All data were statistically evaluated. At the endpoint of the study, light microscopic findings of lung tissues were histopathologically assessed.

Results: When the levels of MPO were compared, radiation significantly increased the level of MPO. In both ASA groups, MPO had values close to the control group. WR-2721 application was not found to be significantly different from C or R group. There was no significant difference in other markers between the groups. With respect to the levels of MDA, it was observed that both ASA applications tended to reduce the levels of MDA. Histopathologically, a radioprotective effect was observed with ASA and WR-2721, which was more evident in the ASAG group.

Conclusions: ASA is an agent that has not been used as a radioprotector in the clinic yet and it is worth supporting with more advanced studies.

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EFFECT OF ACETYLSALICYLIC ACID ON RADIATION-INDUCED GENO/CYTOTOXICITY IN RAT BONE MARROW

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Purpose: The aim of our study was to evaluate the potential radioprotective effects ofacetylsalicylic acid (ASA)against geno/cytotoxicity and to compare its effectwith that of WR-2721 (amifostine). ASA, a member of the non-steroidal anti-inflammatory group, can reduce oxidative injury in various diseases.

Materials: The rats were applied with whole-body irradiation (6 Gy, single dose) using Cobalt-60. Control (C; n=5), Radiation (R; received irradiation; n=5), Radiation+ASAG (R+ASAG; received irradiation and 25 mg/kg/dayx5 ASA by gavage; n=5), Radiation+ASAIP (R+ASAIP; received irradiation and 25 mg/kg ASA by i.p.; n=5) and Radiation+Amifostine (R+WR-2721; received irradiation and 200 mg/kg WR-2721 i.p.; n=5) rat groups were used. The study was terminated 72-h after irradiation. Femurs of each rat were bilaterally harvested. Contents of bone marrow were utilized for the geno/cytotoxicity tests by separating the same amount of the specimens. The effect of WR-2721, as a representative of clinically used radioprotector, was compared with that of ASA, using the the cytogenetic tests, the chromosomal aberration (CA) and the micronucleus (MN) test systems, in the rat's femoral bone marrow cells. We also investigated the cytotoxicity tests, the mitotic index (Mi), and the ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs).The rats were applied with whole-body irradiation (6 Gy, single dose) using Cobalt-60. Control (C; n=5), Radiation (R; re-

ceived irradiation; n=5), Radiation+ASAG (R+ASAG; received irradiation and 25 mg/kg/dayx5 ASA by gavage; n=5), Radiation+ASAIP (R+ASAIP; received irradiation and 25 mg/kg ASA by i.p.; n=5) and Radiation+Amifostine (R+WR-2721; received irradiation and 200 mg/kg WR-2721 i.p.; n=5) rat groups were used. The study was terminated 72-h after irradiation. Femurs of each rat were bilaterally harvested. Contents of bone marrow were utilized for the geno/cytotoxicity tests by separating the same amount of the specimens. The effect of WR-2721, as a representative of clinically used radioprotector, was compared with that of ASA, using the the cytogenetic tests, the chromosomal aberration (CA) and the micronucleus (MN) test systems, in the rat's femoral bone marrow cells. We also investigated the cytotoxicity tests, the mitotic index (MI), and the ratio of polychromatic erythrocytes (PCEs) to normochromatic erythrocytes (NCEs).

Results: The outcomes have shown that the MI of bone marrow cells was significantly decreased after irradiation in R, R+ASAIP and R+WR-2721 rats in comparison to the C rats ($p = 0.018$, $p = 0.001$ and $p = 0.004$, respectively). On the other hand, no statistically significant difference was found between the C rats and R+ASAG rats. In addition to the results obtained by irradiation alone ($p = 0.0001$), the averages of R+ASAG, R+ASAIP and R+WR-2721 groups showed lower PCE/NCE ratios when compared to C ($p = 0.002$, $p = 0.0001$ and $p = 0.005$, respectively). Group R showed lower PCE/NCE ratios when compared to R+ASAG, R+ASAIP and R+WR-2721 groups ($p = 0.0001$).There was no significant difference in other tests between the groups.With respect to the averages of CA, it was observed that both ASA and WR-2721 applications tended to reduce the average of CA.

Conclusions: The results indicate the potential beneficial effects of ASA against RT-induced geno/cytotoxicity in rat bone marrow, which is a similar effect that may be comparable to that observed for WR-2721. In spite of WR-2721, ASA has not been used clinically for this purpose yet; further experimental studies are needed to prove this result and to rule out potential protection of tumor cells and to exploit the clinical advantage of ASA.

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FACTORS ASSOCIATED WITH PITUITARY FUNCTION AFTER GAMMA KNIFE RADIOSURGERY (GKS) OF PITUITARY ADENOMAS

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Purpose: GKS is one of the treatment options for pituitary adenoma when neurosurgical and pharmacological treatment have failed. The authors undertook a retrospective analysis of the incidence and time course of pituitary insufficiency following GKS. The aim is to define clinical and healthy-tissue dosimetric factors predicting the development of hypopituitarism in order to optimize the GKS procedure.

Materials: Between 2001 and 2008, 367 patients (PTs) with a diagnosis of pituitary adenoma were treated; diagnosis was of non functioning pituitary adenoma (NFPA) in 193 PTs and secreting pituitary adenoma (SPA) in 174 PTs. In this study we considered only 130 PTs who had a follow up of at least 6 months. Diagnosis was of NFPA in 68 PTs and SPA in 62 PTsPTs had an endocrinological follow-up range of 6-103 months (mos) after GKS. Hypopituitarism was defined as a new pituitary deficit in (at least) one of the three hormonal axes (hypogonadism, hypotiroidism and hypoadrenalism). Before GKS, 62 PTs had no prior pituitary deficit for all hormonal axes and 94 PTs had no prior pituitary deficit for hypotiroidism and hypoadrenalism axes. Median marginal dose was 15 Gy for NFPA and 25 Gy for SPA at 50% reference isodose. No PT had undergone any radiation therapy prior to GKS and all of them had at least one transpheroidal surgical treatment. For all 130 PTs tumor, pituitary stalk and pituitary gland were outlined using magnetic resonance images on the Leksell Gamma Plan; the goal of dose planning was to provide complete tumour coverage while minimizing the radiation dose to the normal pituitary gland and optical pathways; many dose-volume (DVH) data were used during statistical analysis.The predictive value of the considered variables was tested by univariate and multivariate logistic analyses. Regarding the DVH parameters, best cutt-off values discriminating between PTs with/without toxicity were assessed by receiving-operator curve (ROC) analyses.

Results: After GKS, 8 PTs (12.9%) showed a new pituitary deficit at least one of three hormonal axes at a median of 51 mos and 6 PTs (6.3%) developed a new pituitary deficit at least in one of two hormonal axes with a median of 46 mos. The results of the univariate analyses showed that a few clinical and many dosimetric parameters were associated with a higher rate of new pituitary deficits. According to the ROC curve analysis, the best predicting DVH cutt-off of the mean dose to the stalk and to the residual normal pituitary gland is > 7.3 Gy (for all three axes) and > 17.1 Gy respectively. Preliminary results of multivariate analysis confirmed the significant correlation between the mean dose to the stalk and to the pituitary and the rate of new pituitary toxicities.

Conclusions: The analysis showed a dose-dependence incidence of new hormonal deficits after pituitary adenoma GKS; the risk of hypopituitarism could be reduced using the outlined dose-volume predictors.

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GEMCITABINE PRE-TREATMENT DOES NOT INCREASE RADIATION INDUCED LUNG TOXICITY AFTER RAT LUNG IRRADIATION

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Purpose: Concurrent chemoradiotherapy has been generally accepted as the current standard in the management of locally advanced non small-cell lung carcinoma (NSCLC). Gemcitabine may be of particular interest for this combined modality approach, as this agent has been recognised as a potent tumour cell radiosensitizer. However, the effect of gemcitabine on the development of radiation-induced pneumonitis, the main complication after chest irradiation, is unknown. The aim of the study was to investigate whether gemcitabine pre-treatment affects the development of radiation induced lung toxicity (RILT) in rats.

Materials: Male Wistar rats were accurately irradiated with 150 MeV protons to involve 100% lung volume (9.4-13.8 Gy), or laterally located lung tissue involving 50% of the total lung volume (15-22 Gy). Rats received either 150 mg/kg gemcitabine 24 hours prior to irradiation or sham pre-treatment. RILT was assessed in vivo by means of bi-weekly lung function analysis and assessment of structural changes in lung tissue by means of CT-scan at week 8. Secondly, lung tissue was obtained bi-weekly to perform histological analysis. Since tissue cytokine expression seems to reflect the inflammatory tissue response, quantitative PCR was performed at week 8. Relative mRNA expression of TGF- TNF-α, IL-1 and IL-6 was analyzed. A dose of 13 Gy and 20 Gy were used for QPCR and histological analysis for 100% and 50% lateral irradiation, respectively.

Results: After 100% lung irradiation, gemcitabine pre-treatment did not affect the development of RILT on all end-points investigated. Surprisingly, gemcitabine reduced the development of radiation pneumonitis after 50% lateral lung irradiation, with respect to lung function and CT-based density changes. This coincided with a significant lower expression of IL-6. Gemcitabine did not significantly affect the level of parenchymal or vascular inflammation.

Conclusions: Gemcitabine pre-treatment does not increase the development of RILT after rat lung irradiation. Gemcitabine based concurrent chemoradiotherapy schedules may result in higher local control rates without increasing radiation-induced lung toxicity, but this remains to be determined in the clinical setting.

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HALF BEAM TECHNIQUE REDUCES DOSE TO TESTICLES IN IRRADIATION OF RECTAL CANCER

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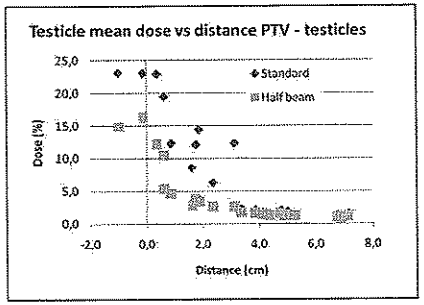
Purpose: The testicles may receive a considerable dose, primarily due to scattered radiation, when male patients are undergoing irradiation of rectal cancer. The testicular dose is of concern as it may lead to permanent reduction in serum testosterone and reduced fertility. Reduced testosterone is associated with decreased sexual function with diminished libido, depressed mood, and osteoporosis. The aim of the study was to investigate whether a half beam technique would result in reduced testicular dose.

Materials: A treatment planning study was performed using CT-scans from 22 male rectal cancer patients. All patients had been treated with a 3-field technique (PA and wedged lateral fields, isocentre in the middle of the PTV) to a total dose of 46-50 Gy and had the entire testicles visible in the images. Half beam technique was planned by locating the isocentre as caudal in the target volume as possible. Treatment plans were normalized to 100% ITV mean dose. The left and right testicles were delineated. Mean and maximum testicular dose was compared for the two plan alternatives.

Results: The mean dose to the testicles was in average reduced from 3.8 Gy (range 0.5 10.6 Gy) for the standard technique, to 1.9 Gy (0.4 7.5 Gy) for the half beam technique, for a prescribed dose of 46 Gy to ITV. The average maximum dose was reduced from 8.9 Gy (range 0.9 20.3 Gy) to 5.0 Gy (0.6 17.6 Gy). The dose reduction was present for both supine and prone treatment positions; the testicle mean dose was reduced from 4.1 Gy to 2.1 Gy (supine), and from 3.3 Gy to 1.7 Gy (prone). The advantage of using the half beam technique diminishes with increasing distance from PTV to testicles, with no effect for distances ≥ 3.4 cm (figure). The minimum ITV dose for the standard and half beam technique was in average 93.2% and 92.1% of the prescribed dose respectively. The global maximum point dose was in average 104.1% for both plans.



Conclusions: Half beam technique significantly reduced the testicular dose of rectal cancer irradiation as an average mean dose reduction of 48% was achieved. This reduction may in particular be of clinical relevance for young patients. The technique is simple to use and could be an alternative or supplement to other methods for reducing testicular dose.

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HIGH AND LOW LET RADIATION MAY DIFFERENTIALLY INDUCE PULMONARY TOXICITY SIGNALS

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Purpose: Pulmonary toxicity hinders the treatment of cancer in the thoracic area with curative doses of radiation. Induction of radiation-induced early pulmonary inflammation is caused primarily by cell death whereas induction of late fibrosis results of a cascade of radiation-induced events acting in concert with cell death. High LET (linear energy transfer) radiation is aimed at efficiently killing tumour cells while minimizing dose to normal tissues to prevent toxicity. Although it is well established that in culture cell death is induced more prominently by high than by low LET radiation, it is largely unknown if the induction of other biological processes contributing to normal tissue toxicity is enhanced similarly and if a potential difference has an impact on manifestation of normal tissue toxicity.

Materials: To investigate potential differences in induction of early (inflammation/pneumonitis) and late (fibrosis) pulmonary toxicity we irradiated rat lungs with high and low LET radiation and monitored pulmonary function loss by measuring breathing-rate. To investigate the cellular mechanisms potentially differentially regulated by high and low LET radiation we irradiated a cell line with different doses of high and low LET radiation, performed a cell-survival assay and isolated protein and RNA. P53 phosphorylation at specific serine residues was monitored and the possible impact of the phosphorylation sites on cell-death was assayed by transfection of p53 expression plasmids mutated for the same phosphorylation sites. Expression of late normal tissue toxicity (fibrosis) marker PAI-1 was monitored by QPCR.

Results: Preliminmary data indicate that the tolerance dose of the rat lung for early loss of pulmonary function to high LET irradiated rat lungs is much lower (13.5 vs. 16.8 Gy) than the tolerance for low LET radiation (preliminmary RBEearly=16.8/13.5=1.25). However, for late pulmonary function loss the difference was much smaller (preliminmary RBElate=1.06), indicating that some of the cellular processes inducing pulmonary toxicity are differentially regulated. With High LET radiation cell-survival was lower than at the same physical dose of low LET radiation. P53 phosphorylation at serine 315 was similar for high and low LET radiation whereas phosphorylation of p53 serine 37, required for cell-death was relatively much higher for high LET radiation than for low LET radiation. Induction of p53 regulated late tissue toxicity (fibrosis) marker PAI-1 was very similar at the same physical dose.

Conclusions: Part of the cellular response is not analogous for high and low LET radiation; the difference may eventually result in a different manifestation of normal tissue toxicity in the lungs. In thoracic tumor treatment using high LET radiation, the probability of developing late toxicity may be lower than previously anticipated.

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IMRT, DESIGNED WITH EVIDENCE-BASED BONE AVOIDANCE OBJECTIVES, REDUCES THE RISK OF BONE FRACTURE IN THE MANAGEMENT OF EXTREMITY SOFT TISSUE SARCOMA

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Purpose: To evaluate the potential for IMRT, designed with evidence-based bone avoidance objectives, to reduce the risk of radiation induced fracture in the combined modality local treatment of extremity soft tissue sarcoma (E-STS).

Materials: Our prospectively collected sarcoma database was searched to determine the number of E-STS patients treated with IMRT and limb sparing surgery from July 2005 to November 2009, and for those who subsequently developed a radiation induced fracture. E-STS IMRT approved plans (n = 141, 110 lower extremity and 31 upper extremity) were identified that employed bone avoidance objectives established from our previous study of fracture risk in E-STS [1]. The IMRT planning goal was to reduce the mean dose to bone <37 Gy and the maximum dose anywhere along the length of bone <59 Gy with target coverage prioritized. Preoperative (pre-op) IMRT was used in 122 patients, and 16 were treated postoperatively (post-op), all with 2 Gy per fraction schedules. Three patients were re-irradiated for recurrent disease using a hyperfractionated regime of 44 Gy delivered twice daily 6 hours apart over 4 weeks. Mean and max bone dose as well as mean CTV dose were evaluated to ensure compliance with bone avoidance objectives and target coverage guidelines. Mean follow up was 28 months from the time of surgery.

Results: For pre-op IMRT overall: the mean dose to bone, max bone dose and CTV mean dose were 26.9 + 9.9 Gy, 50.7 + 4 Gy and 51.1 + 1 Gy respectively. For post-op IMRT: the mean bone dose, max bone dose, and CTV mean dose were 31.7 + 18 Gy, 55.4 + 13 Gy and 64.5 + 2 Gy respectively. Target coverage criteria were satisfied in all cases. Bone avoidance objectives were achieved in 99% of pre-op and 75% of post-op plans. Two patients experienced a bone fracture. The first had recurrent disease following previous RT at the same site and received a further 44 Gy using the hyperfractionated twice daily regime. The other patient received pre-op RT and experienced a fracture following a traumatic recreational event unrelated to radiotherapy.

Conclusions: The risk of fracture appears lower than our previously reported incidence of 2 10%. The preferential use of pre-op IMRT underpins attention to reduction in adverse RT morbidities associated with larger treatment volumes and higher doses typically used in the postoperative setting. The additional bone avoidance objectives are both practical and beneficial, although we recommend longer follow up to establish their long term utility. Bone sparing IMRT should be especially considered for re-irradiation settings.

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LUNG AND HEART COLLABORATE IN EARLY RADIATION-INDUCED CARDIAC DIASTOLIC FUNCTION IMPAIRMENT

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Purpose: For many thoracic tumors treated with radiotherapy, escalation of the radiation dose to the tumor is expected to result in increased local control. However, the dose that can be administered safely is limited by the tolerance dose of the lung for the development of early radiation pneumonitis (RP). Besides irradiated volume, we demonstrated that dose to the heart is an additional risk factor for the development of RP. To test the hypothesis that this increased risk results from the damage to the heart, cardiac performance was evaluated early after lung and/or heart irradiation.

Materials: Rat's heart and/or 50% of lungs were irradiated with 20 Gy using high-precision proton irradiation. To assess cardiac performance early after irradiation, cardiac hemodynamics, including left ventricle (LV) pressure and volume was evaluated 8 weeks post-irradiation. Cardiac pressure changes were assessed by means of left-sided cardiac catheterization. ECG-gated FDG-PET-scans were used to measure volume changes. Cardiac structural changes were subsequently assessed using histology evaluation of the heart tissue.