High and low let radiation may differentially induce pulmonary toxicity signals

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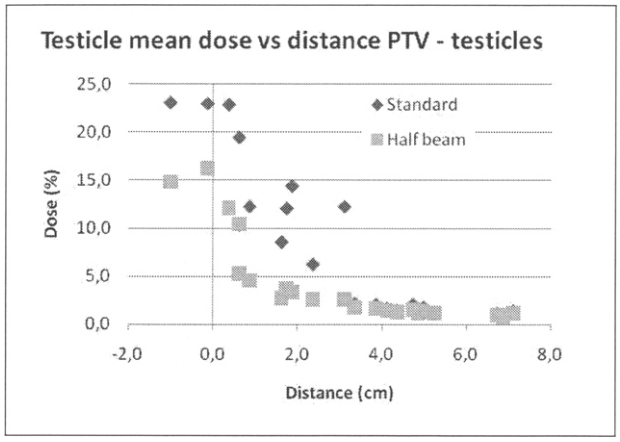
was in average 104.1% for both plans.



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: Prelimminary 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 (prelimminary RBEearly=16.8/13.5=1.25). However, for late pulmonary function loss the difference was much smaller (prelimminary 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.