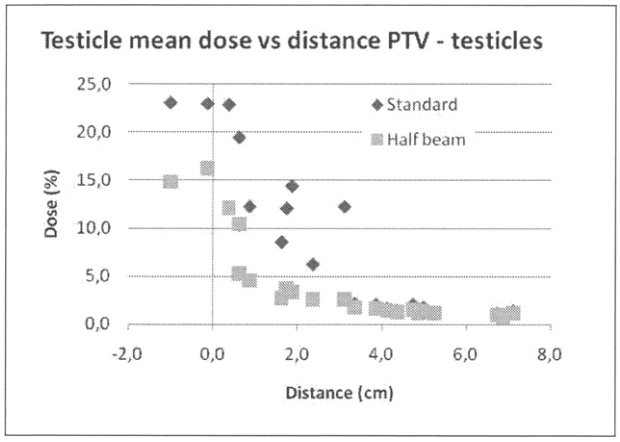
Lung and heart collaborate in early radiation-induced cardiac diastolic function impairment

Ghobadi, G.; van der Veen, S.; Wopken, K.; de Boer, R.; de Jong, J.; Brandenburq, S.; Lanqendijk, H.; Coppes, R.; van Luijk, P.

DOI:
10.1016/S0167-8140(11)71803-5

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.

89 poster

HIGH AND LOW LET RADIATION MAY DIFFERENTIALLY INDUCE PULMONARY TOXICITY SIGNALS

M. Niemantsverdriet[1], M. J. van Goethem[2], R. Bron[3], W. Hogewerf[3], S. Brandenburg[4], H. Langendijk[1], P. van Luijk[1], R. Coppes[5]
[1] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Department of Radiation Oncology, Groningen, Netherlands
[2] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Groningen, Netherlands
[3] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Department of Cell Biology, Groningen, Netherlands
[4] KERNFYSISCH VERSNELLER INSTITUUT, Groningen, Netherlands
[5] UNIVERSITY OF GRONINGEN, Department of Radiation Oncology, Groningen, Netherlands

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.

90 poster

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

C. Dickie[1], A. Griffin[2], M. Sharpe[3], P. Chung[4], C. Catton[4], J. Wunder[2], P. Ferguson[2], B. O'Sullivan[4]
[1] PRINCESS MARGARET HOSPITAL, Radiation Therapy, Toronto, Canada
[2] PRINCESS MARGARET HOSPITAL, Orthopaedic Department, Toronto, Canada
[3] PRINCESS MARGARET HOSPITAL, Radiation Physics, Toronto, Canada
[4] PRINCESS MARGARET HOSPITAL, Radiation Oncology, Toronto, Canada

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.

91 poster

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

G. Ghobadi[1], S. van der Veen[1], K. Wopken[1], R. de Boer[2], J. de Jong[3], S. Brandenburg[4], H. Langendijk[5], R. Coppes[1], P. van Luijk[5]
[1] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Radiation Stress Cell Biology and Stem Cell Biology, Groningen, Netherlands
[2] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Cardiology Department, Groningen, Netherlands
[3] UNIVERSITY MEDICAL CENTER GRONINGEN, Department of Nuclear Medicine and Molecular Imaging, Groningen, Netherlands
[4] KERNFYSISCH VERSNELLER INSTITUUT, Groningen, Netherlands
[5] UNIVERSITY MEDICAL CENTER GRONINGEN / UNIVERSITY OF GRONINGEN, Radiation Oncology, Groningen, Netherlands

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.

Results: Heart irradiation increased LV end-diastolic pressure (66%) and relaxation time (22%) 8 weeks after irradiation, indicating cardiac functional changes particularly in LV diastolic function. The structural analysis of irradiated heart subsequently revealed pronounced cardiac perivascular fibrosis. Co-irradiation of the lungs additionally reduced LV volume parameters decreasing the cardiac output significantly. Interestingly, even irradiation of the lungs alone also increased LV relaxation time (25%) and cardiac output. However, no cardiac perivascular fibrosis was seen. Since also right ventricle hypertrophy and pulmonary hypertension is observed after lung irradiation, LV diastolic functional changes is likely due to a decreased amount of blood received by LV from the irradiated lungs.
Conclusions: Heart and lung irradiation independently impair LV diastolic performance, explaining enhanced pulmonary toxicity early after co-irradiation of the heart. This implies a tight interaction between lungs and heart in thoracic irradiation. Knowledge on heart-lung interaction provides critical information for treatment optimization in thoracic irradiation by development of more accurate predictive models and intervention strategies.

92 poster

MANAGEMENT OF ORAL MUCOSITIS UNDER RADIATION THERAPY

I. Wildfang[1], B. Tschechne[2], D. Schröder[3], H. Niebuhr[2], P. Panagiotou[4], S. Luft[2], S. Fanaei[2], V. Hoffmeister[2], R. Musch[5]
[1] GEMEINSCHAFTSPRAXIS FÜR STRAHLENTHERAPIE UND RADIOONKOLOGIE/KLINIKUM HANNOVER SILOAH, Hannover, Germany
[2] PRAXIS TSCHECHNE/ LUFT/ JORDAN, Lehrte, Germany
[3] PRAXIS SCHRÖDER, Hannover, Germany
[4] GEMEINSCHAFTSPRAXIS DR. MED. HADDADIN & PANAGIOTOU, Garbsen, Germany
[5] ONKOLOGISCHE PRAXISGEMEINSCHAFT SÜD, Berlin-Tempelhof, Germany

Purpose: Our experience with the radioimmunochemotherapy of head & neck patients showed that nearly all patients display strong mucositic adverse reactions (grade 3/4) additional to other side effects. It represents a major therapeutic challenge as the often under-diagnosed side-effect increases incidents of local & systemic infections, decreases quality of life, and in severe cases therefore leads to a therapy interruption or even discontinuation.According to the recommendation of international guidelines we established a preventive oral regimen as part of our routine supportive care. We used MuGard®as an muco-adhesive oral rinse which forms a protective coating.
Materials: The investigated patient collective was an unselected group of diverse head & neck tumorstages, health status and comorbidities. Nearly all Patients were treated with cetuximab and cisplatin in addition to radiotherapy. 47 patients received the oral gel as a mouth rinsing solution additionally to an antimycotics / panthenol solution either prophylactically or as a treatment option after beginning mucositis.
Results: Under this treatment we observed 47 patients. 18 Patients had received prior surgery. Patients treated prophylactically (32) exhibited mostly only mild cases of oropharyngeal mucositis. In 4 patients we observed a grade III mucositis and in 2 patients a grade IV mucositis. Of the 15 patients treated after mucositis onset 11 showed an improvement, 2 were stable and in 2 patients mucositis worsened to a grade III mucositis. There were no specific side effects of the oral gel observed and all patients were mostly compliant. In 1 case therapy had to be interrupted because of a severe mucositis.
Conclusions: A treatment of head & neck cancer patients receiving MuGard®additionally to antimycotics / panthenol seems to effectively reduce most commonly observed mucositis and leads to an improved patient compliance and increases their QoL. Rates of infections and pain symptoms decrease significantly. It is probably even more important that the patients can eat & drink regularly and thus can cope with their treatment more easy compared to patients only receiving standard treatment. Especially a prophylactic treatment of patients receiving radiotherapy seems to be advised.

93 poster

MEAN ESOPHAGEAL RADIATION DOSE IS PREDICTIVE FOR GRADE OF ACUTE ESOPHAGITIS IN LUNG CANCER PATIENTS TREATED WITH CONCURRENT 3D CONFORMAL RADIOTHERAPY AND CHEMOTHERAPY

A. Ozgen[1], M. Hayran[2], Y. Güney[1], P. Kara[1], B. Kucukplakci[1]
[1] ANKARA ONCOLOGY HOSPITAL, Department of Radiation Oncology, Ankara, Turkey
[2] HACETTEPE UNIVERSITY FACULTY OF MEDICINE, Preventive Oncology, Ankara, Turkey

Purpose: To define the predictive factors for acute esophagitis (AET) in lung cancer patients treated with concurrent chemotherapy (CCT) and three-dimensional conformal radiotherapy (3D-CRT) in our institution.
Materials: The data of 72 patients treated with concurrent 3D conformal radiotherapy and chemotherapy at our institution for lung cancer patients between 2008-2010 were prospectively evaluated. Acute esophagitis was graded according to the Radiation Therapy Oncology Group criteria. The mean dose of radiotherapy to lung cancer patients was 61.02 ± 2.41. Cisplatin was used agent for CCT. Total radiotherapy dose (TD), mean dose of esophagus, total volume of esophagus, percentage of esophagus volume treated were analyzed according to esophagitis grades.
Results: Rate of acute esophageal toxicity was 59.7 % (43/72) and of grade ≥1 was 33.3 % (24/72). The mean esophageal dose was associated with an increased risk of esophageal toxicity (Jonckheere-Terpstra test, p<0.001). However, the total dose and the volume of the esophagus irradiated were not associated with an increased risk of esophageal toxicity (Kruskal Wallis test, p=0.35 and p=0.85, respectively). The mean radiation dose received was found to be highly correlated with the duration of Grade 2 esophagitis (Spearman test, r=0.82, p<0.001). The mean dose ≥28Gy showed statistical significance with respect to the AET Grade 2 or worse (Receiver operating characteristic curve analysis, 95% CI, 0.929-1.014).
Conclusions: The mean esophageal dose was significantly associated with a risk of any Grade esophageal toxicity in patients with lung cancer treated with concurrent 3D conformal radiotherapy and chemotherapy.

94 poster

PHASE II STUDY TO EVALUATE IF SELECTIVE TARGETING BY PREOPERATIVE INTENSITY MODULATED RADIATION THERAPY CAN REDUCE WOUND COMPLICATIONS IN LOWER LIMB SOFT TISSUE SARCOMA

B. O'Sullivan[1], C. Dickie[2], G. Anthony[3], A. Parent[2], P. Chung[1], C. Catton[1], J. Wunder[3], M. Sharpe[4], R. Bell[3], P. Ferguson[3]
[1] PRINCESS MARGARET HOSPITAL, Radiation Oncology, Toronto, Canada
[2] PRINCESS MARGARET HOSPITAL, Radiation Therapy, Toronto, Canada
[3] PRINCESS MARGARET HOSPITAL, Surgical Oncology, Toronto, Canada
[4] PRINCESS MARGARET HOSPITAL, Radiation Physics, Toronto, Canada

Purpose: To determine if preoperative intensity modulated radiotherapy (IMRT) can minimize the dose to superficial tissues used for wound closure at the time of resection and halve the risk of wound complications (WC) from the 43% rate in our previous Phase III trial (SR2) of pre- vs post-op RT in lower extremity soft tissue sarcoma (LE-STS) to 21%.
Materials: Seventy patients were enrolled from July 2005 to June 2009; 59 were evaluable for the primary endpoint of WC. Females and males were equally represented; mean age was 55 years (range 26 - 86). Median tumour size was 9.5 cm with 44% (n=26) >10cm. Almost all were deep to fascia (98%) and very few low grade (2%). Malignant fibrous histiocytoma (35.6%) and myxoid liposarcoma (32.2%) were the most common histologies. The surgical team delineated the area of skin, subcutaneous tissues, and fascia that would later be undermined and raised as surgical flaps (SF) to close the wound. This was performed on the RT planning work station to provide an organ at risk for IMRT optimization and dose avoidance. Prior to surgery, the IMRT dose distribution was mapped back onto the patient's skin using an optical localization system to guide the placement of incisions to the lower dose skin region. MORFEUS, a biomechanical model-based deformable registration algorithm, was used to quantify elements of the surgical flaps that included individual length, volume, variable thickness across length and width, and the proportion overlap by the PTV.
Results: There were 18 WC (30.5%), 6 requiring secondary operations This was not statistically significantly different from the LE-STS preop RT arm of SR2 (p=0.2, Fisher's exact). However primary wound closure was more frequent than SR2 trial (55/59, 93.2% vs 50/70, 71.4%; p=0.002), and the number of secondary operations for WC was reduced (6/18, 33% vs. 13/30, 43%). Also, the MORFEUS algorithm showed a significantly higher proportion of the SF receiving the prescribed dose in the complication group (p=0.003) which remained significant on multivariate analysis. There were 3 local recurrences (5 %, none near the SF) and 15 (25%) distant metastases (mean follow-up 33.4 months).
Conclusions: The 30.5% incidence of WC is lower than the 43% risk seen in the SR2 trial, but does not reach the baseline level of 21%. The SF sparing capabilities of preop IMRT lowered the need for tissue transfer following tumor resection and reduces the risk of WC and subsequent secondary operations for LE-STS. The observation that WC is reduced when the SF is proportionally excluded from the PTV may provide a dose estimate below which WC can be minimized.
Author Disclosure Information: B. O'Sullivan, None **C.I. Dickie**, None **A. Griffin**, None **A. Parent**, None **P. Chung**, None **C. Catton**, None **J. Wunder**, None **M. Sharpe**, None **R. Bell**, None,**P. Ferguson**, None