OAR	SD,cm				Mean SD, cm			
	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 1	Pat. 2	Pat. 3	Pat. 4
Rectum	0.34	0.48	0.46	0.37	-0.06	-0.06	-0.06	-0.04
Sigmoid	1.39	0.96	0.72	0.66	0.44	0.22	0.18	0.17
Anus	0.81	0.99	0.54	0.68	-0.07	-0.13	-0.09	-0.09
Femoral heads	1.66	1.49	1.45	1.47	-0.44	-0.4	-0.41	0.43
Penile bulb	0.43	0.33	0.27	0.39	-0.02	-0.04	-0.03	-0.11

A SD of 0.5-1 cm was measured for the anus with the largest discrepancies for its proximal part. A good correlation between delineations was observed for the rectum with a SD of 0.3-0.5 cm with the largest discrepancy for its distal part. The sigmoid had a SD of 0.6-1.4 cm between observers with the largest discrepanties for its distal part. A SD of 1.4-1.7 cm was observed between delineation of the femoral heads with largest discrepanties for their distal parts. A small SD of 0.3-0.4 cm was obtained for the penile bulb.
Conclusions: Given SD < 0.5 cm for the rectum and penile bulb, the suggested guidelines were easy to follow and found sufficient in delineation of these OARs. Larger SD in delineation of the anus, sigmoid and femoral heads appeared to result from incomplete guidelines for those OARs. Stricter guidelines with better definition of OAR anatomical borders-particuly the proximal borders of the anus and distal borders of sigmoid and femoral heads- are needed.

PROFFERED PAPERS: PREVENT 3: CARDIAC TOXICITY

OC-0258
Dosimetric modeling of cardiac toxicity in patients with esophageal cancer receiving radiotherapy
A. Konski[1], M. Snyder[1], P. Phiip[2], A. Shields[2], W. Scott[3], E. McSpadden[1], J. Myers[4]
[1]Wayne State University, Radiation Oncology Department, Detroit, USA
[2]Wayne State University, Medical Oncology Department, Detroit, USA
[3]Fox Chase Cancer Center, Surgical Oncology Department, Philadelphia, USA
[4]Fox Chase Cancer Center, Radiation Oncology Department, Philadelphia, USA

Purpose/Objective: New treatments are being introduced in the treatment of locally advanced esophageal cancer. Some, such as trastuzumab, can potentially increase cardiotoxicity. The purpose of this study was to model cardiac toxicity using an empirical normal tissue complication probability (NTCP) model in patients with esophageal cancer treated in part with radiotherapy.
Materials and Methods: Cardiactoxicity as measured by Common Toxicity Criteria Adverse Events (CTCAE) v3.0 and Radiation Therapy Oncology Group (RTOG) toxicity grading scale was identified by retrospective chart review. The probability of cardiac toxicity as a function of absorbed dose in a partial volume was modeled by the method of Lyman, by converting the dose volume histograms into an equivalent fractional volume receiving the maximum dose in the DVH, using the effective volume method of Kutcher and Burman. The parameters in this model (D50, slope *m*and volume exponent *n*) were determined by maximum likelihood estimation. Doses prescribed in fractional doses other than 1.8 Gy were converted to equivalent dose in 1.8 Gy fractions assuming an α/β ratio of 1.4 Gy, determined from this data set by intercomparing combinations of total dose and dose per fraction giving similar levels of toxicity.
Results: From 6/02 to 4/12, 150 patients (113 male and 37 female) with locally advanced esophageal cancer undergoing pre-operative or definitive CRT at 2 NCI Comprehensive Cancer Centers form the basis of this analysis. The mean radiotherapy dose was 4912 (range:3000-5940) cGy. Chemotherapy was at the discretion of the treating medical oncologist. Thirty-four (23%) developed a cardiac toxicity with 10 being symptomatic (≥ grade 3 toxicity). The mean time to any toxicity was 8 (range:1-29) months. Cardiac toxicity types were Pericardial effusion-27; Heart failure- 2, Atrial Fibrillation-1, Cardiomegaly-1, Ischemia-1, MI-1, Sick sinus syndrome-1. The maximum likelihood fit of the Lyman model parameters to patients with cardiac symptoms were n = 0.4 m= 0.34, TD50=54.2 Gy for men and TD50=41.8 Gy for women, p=0.027.
Conclusions: These results are comparable to earlier reports. What is not known, however, is the use of a single toxicity endpoint rather than combined endpoints. The pathophysiologic etiology of pericardial effusion most likely is not the same as heart failure, one being an effect on the pericardium while the other an effect on the cardiac myocytes. Further work is needed to clarify the dose resulting in toxicity to each cardiac structure necessary to result in cardiactoxicity and why we see a difference between men and women.

OC-0259
Radiotherapy/chemotherapy-related cardiovascular disease in breast cancer patients: a population-based study
N.B. Boekel[1], M. Schaapveld[1], J.A. Gietema[2], O. Visser[3], B.M.P. Aleman[4], F.E. van Leeuwen[1]
[1]The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Epidemiology, Amsterdam, The Netherlands
[2]University Medical Center Groningen, Medical Oncology, Groningen, The Netherlands
[3]Comprehensive Cancer Center, Research, Amsterdam, The Netherlands
[4]The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Radiation Oncology, Amsterdam, The Netherlands

Purpose/Objective: Several studies have shown that breast cancer treatment may increase the risk of cardiovascular disease after ten or more years. However, most reports are based on older treatment regimens. It is not known whether more contemporary radiation techniques are associated with excess cardiovascular disease. In addition, it is not clear whether current chemotherapeutic regimens, especially regimens containing anthracyclines, increase the risk of cardiovascular disease in breast cancer survivors.
The aim of this study is to assess the effect of radiotherapy and chemotherapy for breast cancer on cardiovascular morbidity and mortality.
Materials and Methods: We have constructed a large population-based cohort of patients diagnosed with invasive breast cancer between 1989 and 2004 (n=93,630). Information on patient characteristics, primary and secondary malignancies, and basic treatment information (e.g. type of surgery, radiotherapy yes/no, chemotherapy yes/no) were provided by the Netherlands Cancer Registry. Detailed treatment information was collected through electronic files from radiotherapy institutes, trials, and regional studies. Date and cause of death were acquired through linkage with the Central Bureau for Genealogy and Statistics Netherlands, respectively, until January 2010. Data on cardiovascular morbidity were acquired through linkage with two registries: the Hospital Discharge Registry (LMR) and the Cardiac Interventions Registry (BHN).
Results: Of the initial 93,630 patients, 69,123 survived at least five years after breast cancer diagnosis. The median follow-up of five-year survivors was 9.7 years (range 5-21 years).
We distinguished four mutually exclusive treatment categories: surgery only (33%), radiotherapy with or without surgery (46%), radiotherapy and chemotherapy with or without surgery (15%), and chemotherapy with or without surgery (6%). 52% of the patients treated with radiotherapy were irradiated for left-sided breast cancer. Due to the anatomical position of the heart, the radiation-dose to the heart is higher during left-sided radiotherapy than during right-sided radiotherapy.
At the PREVENT meeting, results will be presented on the evaluation of mortality rates in comparison with the general population. Secondly, we will present comparisons of cardiovascular mortality rates and incidence of different cardiovascular diseases between the above stated treatment categories, and more specifically by type of chemotherapeutic, radiation field, and laterality.
Conclusions: Based on our results, conclusions will be drawn with respect to the effects of modern radiotherapy regimens and specific chemotherapeutics for breast cancer.

OC-0260
Effects of a tocotrienol-enriched formulation in a rat model of local heart irradiation
M. Boerma[1], V. Sridharan[1], P. Tripathi[1], S. Sharma[2], E.G. Moros[3], N. Aykin-Burns[1], M. Hauer-Jensen[1]
[1]University of Arkansas for Medical Sciences, Pharmaceutical Sciences, Little Rock, USA
[2]University of Arkansas for Medical Sciences, Radiation Oncology, Little Rock, USA
[3]Moffitt Cancer Center and Research Insitute, Radiation Oncology, Little Rock, USA

Purpose/Objective: Radiation-induced heart disease (RIHD) is a long-term side effect of radiotherapy of intrathoracic and chest wall tumors when radiation fields encompass all or part of the heart. Tocotrienols are forms of vitamin E with potent radioprotective properties. This study investigates the effects of pre-treatment and

post-treatment with tocotrienols in a rat model of local heart irradiation.
Materials and Methods: Male Sprague-Dawley rats received localized image-guided X-ray irradiation of the heart with a single dose of 21 Gy. Groups of animals received a tocotrienol-enriched oral formulation 24 hours before irradiation, or in combination with pentoxifylline (PTX) starting 3 months after irradiation. At 6 months after irradiation, cardiac function and tissue structure were measured with echocardiography and histopathology. At time points from 6 hours to 9 months after irradiation, left ventricular molecular changes were examined with real-time PCR and Western-Blots. In addition, mitochondria were isolated from left ventricular tissue samples to examine mitochondrial membrane potential, mitochondrial transition pore activity, and respiration.
Results: Local heart irradiation caused long term changes in cardiac function and structure, coinciding with changes in the expression of mediators of the epidermal growth factor receptor (EGFR) pathway, and changes in mitochondrial membrane properties and respiration. Pretreatment of rats with tocotrienols prevented these effects of radiation. Unexpectedly, the late treatment with PTX caused bradycardia and arrhythmia in irradiated animals. This adverse event was not prevented when tocotrienols were added to the PTX treatment. On the other hand, addition of tocotrienols reduced cardiac numbers of macrophages and mast cells and enhanced left ventricular gene expression of the EGFR mediator neuregulin-1.
Conclusions: These studies suggest that tocotrienols may be potent protectors against cardiac radiation toxicity. Further studies should address the effects of tocotrienols when administered after irradiation, alone or in combination with other potential mitigators.

OC-0261
ACE-inhibition reduces acute cardiac damage to ameliorate radiation-induced lung dysfunction
S.J. van der Veen[1], G. Ghobadi[1], R.A. de Boer[2], H. Faber[1], G.W. Bosman[1], S. Brandenburg[3], J.A. Langendijk[4], P. van Luijk[4], R.P. Coppes[1]
[1]University of Groningen/University Medical Center Groningen, Cell Biology and Radiation Oncology, Groningen, The Netherlands
[2]University of Groningen/University Medical Center Groningen, Cardiology, Groningen, The Netherlands
[3]University of Groningen/University Medical Center Groningen, Kernfysisch Versneller Instituut, Groningen, The Netherlands
[4]University of Groningen/University Medical Center Groningen, Radiation Oncology, Groningen, The Netherlands

Purpose/Objective: The radiation dose that can be delivered to thoracic tumors is limited by the risk of radiation-induced lung toxicity (RILT). ACE-inhibition has been shown to ameliorate RILT in rats although the exact mechanism is not elucidated (1). Recently, we found that pulmonary vascular remodeling plays an important role in the development of RILT in rats resulting in pulmonary hypertension, right ventricle hypertrophy and eventually to cardio-pulmonary dysfunction (2). We hypothesized that the protective effect of ACE-inhibition might be due to reduced vascular remodeling and pulmonary hypertension. Therefore, in this study we investigated if ACE-inhibition ameliorates early radiation-induced cardio-pulmonary dysfunction by protection of pulmonary vascular remodeling.
Materials and Methods: To elucidate the exact protective mechanism of ACE-inhibition on early radiation-induced cardio-pulmonary function loss rats' lungs, heart or heart and lung were irradiated to 20 Gy using high-precision proton beams. Captopril was administered in the drinking water immediately after irradiation. Cardio-pulmonary performance was assessed in the irradiated rats (± captopril) using biweekly breathing rate measurements. At 8 weeks post-irradiation, when early radiation-induced cardio-pulmonary dysfunction peaks (2), left- and right-sided cardiac hemodynamics were measured, CT scans and histopathology were analyzed.
Results: At 8 weeks post-irradiation breathing rate measurements showed that captopril significantly improved the rats' cardiac/ pulmonary function, but only in the rats where the heart was included in the radiation field. Consistently, CT scans showed improvement of pulmonary density/structure by captopril only in the heart-irradiated groups.
This protective effect could not be explained by protection of the pulmonary vasculature or pulmonary artery pressure changes, which were equally damaged with or without captopril. Interestingly, besides decreasing the presence of pleural and pericardial effusion, left ventricle hemodynamic measurements showed better cardiac function parameters in the captopril treated rats. Next to that, captopril treatment reduced perivascular fibrosis in the irradiated hearts.
Conclusions: Captopril ameliorates early radiation-induced cardio-pulmonary dysfunction by reducing acute heart damage and consequentially reduces excess RILT caused by inclusion of the heart in the irradiation field (3). ACE-inhibition may be a promising strategy to reduce early cardio-pulmonary complications induced by radiotherapy to the thoracic area in patients receiving a dose to the heart.

(1) Ghosh et al. Int J Radiat Oncol Biol Phys 2009
(2) Ghobadi et al. Thorax 2011
(3) van Luijk et al. Cancer Res 2005

PROFFERED PAPERS: GEC-ESTRO 5: HIGHLIGHTS: BEST OF BRACHYTHERAPY 2013

OC-0262
High dose rate (HDR) brachytherapy treatment verification using an electronic portal imaging device (EPID)
R.L. Smith[1], M.L. Taylor[1], A. Haworth[2], L.N. McDermott[1], J.L. Millar[3], R.D. Franich[1]
[1]RMIT University, School of Applied Sciences and Health Innovations Research Institute, Victoria, Australia
[2]Peter MacCallum Cancer Centre, Physical Sciences, Victoria, Australia
[3]The Alfred Hospital, William Buckland Radiotherapy Centre, Victoria, Australia

Purpose/Objective: This study describes a new treatment verification system, based on electronic portal imaging device (EPID) images, for HDR brachytherapy. The phantom study incorporates verification of both source position and dose as the brachytherapy treatment plan is delivered, identifying the potential for real time identification of incorrect dose to patients.
Materials and Methods: An a-Si EPID (IAS11-19, Varian Medical Systems,Palo Alto, CA, USA) was used for all measurements. Response characteristics of the EPID were determined for use with an Ir-192 HDR brachytherapy source, including linearity, reproducibility, variation in exposure time, image acquisition time,photon energy dependence and source position determination in three dimensions.A treatment plan was delivered to the phantom and for each dwell position in the delivered plan, planar EPID dose distributions were compared with the TPS calculated at the same plane.
Results: Analysis of the EPID images containing the source response distribution, yielded the location of the source to better than ± 1mm for coordinates parallel to the plane of the EPID at source-to-detector distances up to 200mm. The source distance from the EPID surface could be determined to within ± 1.5 mm. The comparison of TPS and measured dose at a plane 100mm from the brachytherapy source agreed to within ± 2% for a 100 x 100 mm region of the EPID plane centered at the source (x,y)coordinates, and agreed to within ± 7% across the entire EPID panel (300x400mm). Delivery of an erroneous treatment plan with missing or incorrectly located dwell positions was easily identifiable with this system.
Conclusions: This is the first system, to our knowledge, providing a check of both source position and dwell time during dose delivery. The EPID images are sensitive enough to reveal clinically relevant source position and dwell time errors. We have established a proof-of-principle that an EPID can be used for treatment verification in HDR brachytherapy.

OC-0263
HDR brachytherapy dosimetric predictors of biochemical control of prostate cancer
P. Hoskin[1], A. Rojas[1], P. Ostler[1], R. Hughes[1], L. Bryant[1], G. Lowe[1]
[1]Mount Vernon Hospital, Cancer Centre, Northwood Middlesex, United Kingdom

Purpose/Objective: To correlate the dose-volume parameters D_{90} (Gy) and V_{100} (%) (i.e. minimum dose to 90% of the prostate volume and volume that received 100% of the prescribed iso-dose, respectively) with biochemical control in patients with advanced prostate cancer treated with external beam radiotherapy (EBRT) followed by a boost of high-dose rate brachytherapy (HDR-BT).
Materials and Methods: 108 patients, participating in a randomised trial of EBRT± HDR-BT, received EBRT to 35.75 Gy in 13 fractions followed by HDR-BT of 2 x 8.5 Gy. Kaplan-Meier freedom-from-biochemical relapse (FFbR) rates were obtained by stratifying the data by those whose D_{90} and V_{100} were at or above and below the first (Q1), second (Q2) and third (Q3) quartile. Differences between groups were compared using the log-rank test. Univariate and multivariate hazard ratios for D_{90} and V_{100} and other co-variates (prostate specific antigen (PSA), androgen deprivation therapy (ADT)) were obtained using Cox's proportional hazard model.