symptomatic pseudo-progression after SRT of brain metastases needs to be considered as a serious radiation induced toxicity. Reduction of the high dose volume of normal brain tissue may prevent this toxicity.

**OC-0056**

**FLAME: Influence of dose escalation to 95Gy for prostate cancer on urethra-related toxicity and QOL**


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**Purpose or Objective:** Following EBRT for prostate cancer, patients can develop aggravation of urinary symptoms mostly due to urethral dose. With dose-escalated EBRT it is suggested that genitourinary toxicity increases with increasing dose. In the experimental arm of the FLAME-trial (284 patients) a dose of 77Gy to the entire prostate gland in 35 fractions was administered, with an integrated boost up to 95Gy to the macroscopic lesions. No dose constraints for the urethra were set during the trial. The objective of this study is to evaluate urethral dose parameters, urethra-related toxicity and prostate-specific QoL scores for patients treated with and without dose-escalated EBRT.

**Material and Methods:** Between 2009 and 2015, 571 intermediate and high risk prostate cancer patients were enrolled in the FLAME trial, a phase 3, single blind, multi-center randomized controlled trial (NCT01168479). The control arm (287 patients) received a dose of 77Gy to the entire prostate gland in 35 fractions. The experimental arm (284 patients) received the same dose, but with an integrated boost up to 95Gy to the multi-parametric MRI-based intraprostatic lesion. For this study, the urethra was delineated retrospectively on T2 weighted MRI, using a circle shape with a diameter of 3 mm, to obtain dose parameters. These dose parameters, the Genitourinary Toxicity scores (CTCAE v3.0) and the urinary symptoms scale of the EORTC QLQ-PR25, were compared for both treatment arms. The physician in attendance scored toxicity at baseline, weekly during treatment, 4 weeks after treatment and every 6 months up to 10 years. QoL was filled out 1 week before treatment and the next questionnaires were sent to the patient every 6 months up to 10 years. Mean differences between groups at 1 year of follow up were calculated using an independent samples t-test (dosimetry and QoL), Chi-square test or Fisher’s exact test (toxicity). Statistical significance was considered P<0.01.

**Results:** Results after analysis of 100 patients (50 patients in each treatment arm) with a median follow-up of 22 months show for the control arm an average Dmean (mean dose to the urethra) of 77.3 + 0.5 Gy (range 75.9-78.0 Gy), with an average Dmax (maximum dose to the urethra) of 79.6 ± 0.8 Gy (range 78.0-81.3). In the experimental arm, average Dmean was 82.0 ± 2.8 Gy (range 77.4-89.0 Gy) and average Dmax was 89.7 ± 0.6 Gy (range 80.7-97.7 Gy). For both Dmean and Dmax the difference between treatment arms was significant (p<0.000). Grade 3 GU toxicity did not occur, grade 2 GU toxicity occurred in a subset of patients, although no significant difference was found between both treatment arms for the separate GU items (table 1). Urinary symptoms-related QoL was not significantly different across treatment arms.

**Table 1. Incidence of GU toxicity at 1 year after radiation treatment.**

<table>
<thead>
<tr>
<th>Time of follow up</th>
<th>Treatment group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77Gy</td>
<td>95Gy</td>
</tr>
<tr>
<td>Urinary frequency/urgency</td>
<td>15 (30%)</td>
<td>14 (29%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Bladder spasms</td>
<td>0 (0%)</td>
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<td>Incontinence, urinary</td>
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<td>Hemorrhage</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Dysuria</td>
<td>5 (10%)</td>
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**Conclusion:** Results showed a significant difference in urethral dose, but no significant differences in toxicity or quality of life when comparing both treatment arms of the FLAME trial.

**OC-0057**

**Cardiotoxicity and cardiac substructure dosimetry in dose-escalated lung radiotherapy**

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**Purpose or Objective:** Radiotherapy of lung cancer delivers quite high doses of radiation to the heart. We explored associations between overall survival (OS) and radiation dose to heart and its substructures and electrocardiographic (ECG) changes.

**Material and Methods:** We analysed data from 79 patients in IDEAL CRT, a phase I/II trial of isotoxic radiotherapy (RT) dose escalation trial, sponsored by University College London (C13530/A10424). Mean and maximum prescribed doses were 69 and 75.6Gy calculated as 2Gy fractionation equivalents (EQD2, α/β=10Gy). Whole heart, left ventricle (LV), right ventricle (RV), right atrium (RA), left atrium (LA) and AV node (AVN) were outlined on RT planning scans and differential dose volume histograms (DVHs) extracted, converting physical DVHs to EQD2s (α/β=3). Patient-to-patient DVH variability was represented using a small number of Varimax-rotated principal components (PCs) explaining 95% of total variance. ECGs were analysed at baseline, 6 and 12 months (mo) after treatment, and changes in heart rate (HR) recorded, with patients dichotomised according to presence or absence of ‘any ECG rhythm change’ (conduction abnormalities or ischaemia). OS was modelled using Cox regression from the start of treatment. Univariate analysis (UVA) and multivariate analysis (MVA) of clinical factors included ‘any rhythm ECG change’ at 6 and 12 months, change in HR at 6 or 12 months, planning target volume (PTV), and prescribed dose (PD). MVA of whole heart dosimetric factors included all 7 Heart PCs, PTV, and PD. MVA of heart substructures included heart substructure PCs with p < 0.2 on UVA having similar dosimetric distributions to significant Heart PCs, PTV and PD.

**Results:** Results after analysis of 100 patients (50 patients in each treatment arm) with a median follow-up of 22 months show for the control arm an average Dmean (mean dose to the urethra) of 77.3 + 0.5 Gy (range 75.9-78.0 Gy), with an average Dmax (maximum dose to the urethra) of 79.6 ± 0.8 Gy (range 78.0-81.3). In the experimental arm, average Dmean was 82.0 ± 2.8 Gy (range 77.4-89.0 Gy) and average Dmax was 89.7 ± 0.6 Gy (range 80.7-97.7 Gy). For both Dmean and Dmax the difference between treatment arms was significant (p<0.001). Grade 3 GU toxicity did not occur, grade 2 GU toxicity occurred in a subset of patients, although no significant difference was found between both treatment arms for the separate GU items (table 1). Urinary symptoms-related QoL was not significantly different across treatment arms.

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Results: ECGs at baseline and 6 mo were available for 54 patients, and at baseline and 12 mo for 49 patients. At 6 mo and 12 mo, 10 and 6 patients had ischemic changes and 12 and 15 patients had conduction abnormalities (AF or sinus tachycardia). Median PTV was 403.4cm3 (Range 138.7-1262.1). Larger PTV and ‘any ECG rhythm change’ at 6 mo were associated with worse OS (HR = 1.005, 95% CI: 1 - 1.01 p 0.04; HR = 7.9843, 95% CI: 1.293 - 47.583 p 0.03 respectively) on MVA. Increasing values of Heart PC2, Heart PC3 and Heart PC7 (characterizing heart volume (vol) receiving 10-30Gy plus 70-80Gy, 65-75Gy and 1-5Gy respectively) were associated with worse OS (HR = 0.844, 95% CI: 0.715 - 0.995 p 0.05). Mean heart dose (MHD) was 24.9Gy (Range 5.9-48.3Gy). LA vol receiving 65-75Gy and 70-80Gy with the 65-75Gy localising to LA. Median PTV was 403.4cm3 (Range 138.7-1262.1). Larger PTV and ‘any ECG rhythm change’ at 6 mo were associated with worse OS (HR = 1.005, 95% CI: 1 - 1.01 p 0.04; HR = 7.9843, 95% CI: 1.293 - 47.583 p 0.03 respectively) on MVA. Increasing values of Heart PC2, Heart PC3 and Heart PC7 (characterizing heart volume (vol) receiving 10-30Gy plus 70-80Gy, 65-75Gy and 1-5Gy respectively) were associated with worse OS (HR = 0.844, 95% CI: 0.715 - 0.995 p 0.05). Mean heart dose (MHD) was 24.9Gy (Range 5.9-48.3Gy). LA vol receiving 65-75Gy was associated with worse OS on MVA (HR = 1.129, 95% CI: 1.033 - 1.235 p <0.01).

Conclusion: We found evidence of a possible association between lower OS in IDEAL-CRT patients and high PTV, ischaemic or conduction change on ECG at 6 mo, and relatively high heart volume receiving doses <5Gy, 10-30Gy, 65-75Gy and 70-80Gy with the 65-75Gy localising to LA. Further prospective studies are required to improve understanding of cardiac irradiation in NSCLC.

OC-0058
Coronary calcifications in breast cancer patients and association with cardiovascular risk factors
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Purpose or Objective: Breast cancer patients with cardiovascular risk factors are at increased risk of radiation- and chemotherapy- induced cardiovascular complications. Presence of coronary artery calcifications (CAC) is a major independent risk factor for cardiovascular disease (CVD). This study investigates the prevalence of CAC in breast cancer patients on radiotherapy (RT) planning CT scans, and its association with cardiovascular risk factors.

Material and Methods: This study was conducted within the Utrecht cohort for Multiple Breast cancer interVention studies and Long-term evAuation (UMBRELLA), and includes 561 breast cancer patients undergoing planning CT scans at the UMC Utrecht between October 2013-March 2015. CAC was automatically scored using a validated algorithm that identifies CAC with a supervised pattern and threshold of 130 Hounsfield Units. Patients were categorized according to CAC (Agatston) scores: 0, 1-10, 11-100, 101-400, >400.

Cardiovascular risk factors (diabetes, smoking status, hypercholesterolemia, hypertension, history of CVD) were collected for 36 patients with intermediate to high CVD risk (scores>100), and for a random selection of patients with fair to moderate CVD risk (1< scores<100, n=36) and low CVD risk (without CAC, i.e. scores of 0, n=36). Demographic, disease characteristics, and presence of cardiovascular risk factors were compared between groups using Chi-square analysis and Kruskal-Wallis test for categorical and continuous data respectively.

Results: Median age of the cohort was 58 years (range: 26-85). There were 427 (76%) patients without CAC, 50 (9%) with scores between 1-10, 43 (7%) with scores between 11-100, and 36 (7%) patients with scores >100. Patients with scores >100 had significantly more often diabetes than those without CAC (28% vs. 3%, p<0.001). Patients with scores >100 had more often three to four CVD risk factors compared to patients with scores between 1-100 or without CAC: 30%, 5%, 0% respectively, p<0.002. Ten (28%) patients with scores >100 did not have any other CVD risk factor.

Conclusion: CAC is present in one in four breast cancer patients. In one third of patients with CAC scores >100, no other CVD risk factors were present, and these patients would not have been identified as high risk using standard CVD risk factors. Since CAC can be automatically detected without additional cost or radiation exposure in breast cancer patients undergoing RT, it represents a simple and useful way to detect those requiring additional cardio protective measures.

OC-0059
A radiation dose-response relationship for risk of heart failure in survivors of Hodgkin lymphoma
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Purpose or Objective: Cardiovascular diseases are increasingly recognized as late effects of Hodgkin lymphoma (HL) treatment. Radiation therapy is known to contribute to the risk of heart failure (HF), but a dose-response relationship has yet not been well described. The purpose of this study was to identify risk factors for HF, and to quantify effects of radiation dose to the heart, chemotherapy, and other cardiovascular risk factors.

Material and Methods: We conducted a nested case-control study in a cohort of 2,617 5-year HL survivors, treated between 1965-1995. Cases were patients who developed HF (scores>100), and for a random selection of patients with fair to moderate CVD risk (1< scores<100, n=36) and low CVD risk (without CAC, i.e. scores of 0, n=36). Demographic, disease characteristics, and presence of cardiovascular risk factors were compared between groups using Chi-square analysis and Kruskal-Wallis test for categorical and continuous data respectively.