Purpose or Objective: To compare radiation dosimetry of various cardiac structures and other thoracic tissue, such as lung fields and non-treated breast, associated with breast irradiation (left versus right-sided) in supine versus prone treatment positions.

Material and Methods: Twenty-four post-lumpectomy patients (8 left-sided, 16 right-sided) underwent non-contrast 2mm slice thickness radiotherapy (RT) planning CT scans in the supine and prone positions. Optimized tangential breast RT plans were generated. In all cases, prescribed RT dose was 50Gy in 2Gy daily fractions. Twenty specific structures (whole heart, atria and ventricles, major vessels, cardiac valves, epicardial coronary arteries including left anterior descending (LAD), ipsilateral/contralateral lung and non-treated breast) were contoured on each CT dataset based on a published reference atlas. Maximum, minimum, mean doses and volume (cm³) were compared for all structures in both supine and prone positions. Whole heart V5, V25 and V30 as well as lung V20 were evaluated. The independent two-sample t-test was used to determine the impact of treatment laterality and the paired t-test for the treatment positioning on RT dosimetry respectively, with p<0.05 considered significant.

Results: Left compared to right-sided breast irradiation significantly increased maximum (p<0.001) and mean (p<0.001) whole heart dose, as well as doses to individual cardiac structures, in both prone and supine positions. Prone versus supine positioning significantly increased maximum whole heart dose 25.8Gy versus 19.2Gy (p<0.001) and mean LAD artery 8.4Gy vs. 5.0Gy respectively (p<0.03). Whole heart V5 (3.9 vs. 2.5%), V25 (1.4 vs. 0.8%), and V30 (1.1 vs. 0.7%), did not differ significantly between prone and supine positions. Table 1 illustrates comparisons of other individual cardiac structures. As anticipated, maximum dose (48.5 vs. 50.3Gy), mean dose (3.3 vs. 6.5Gy) and V20 (5.3% vs. 11.5%) to the ipsilateral lung (p<0.001 for all comparisons) were reduced when patients were treated in the prone versus supine position.

Conclusion: A statistically higher radiation dose was seen to the whole heart and various cardiac structures, including atria, ventricles and LAD artery, for left compared to right-sided breast cancer patients. Furthermore, prone positioning increased maximum whole heart and LAD artery doses, despite its known benefit in reducing dose-volume effects to lung tissue. This is one of few studies to assess differential radiation doses to individual cardiac structures.

Poster: Clinical track: Lung

PO-0678
Do blood-biomarkers enhance clinical models for NSCLC patients treated with radical radiotherapy? S. Carvalho1, E.G.C. Troost2, J. Bons3, P. Menheere1, P. Lambin1, C. Oberti1
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Purpose or Objective: A prognostic model for non-small cell lung cancer (NSCLC) patients with validated clinical variables [gender, World Health Organization performance status, forced expiratory volume in 1 second, number of positive lymph node stations, and total gross tumor volume], and blood-biomarkers related to hypoxia [osteonentin (OPN) and carbonic anhydrase IX (CA-IX)], inflammation [interleukin-6 (IL-6), IL-8, and C-reactive protein (CRP)], and tumor load [carcinoembryonic antigen (CEA), and cytokeratin fragment Cyfra 21-1 (Cyfra 21-1)] was developed and validated. Finally, the model was extended with alpha-2-macroglobulin (α2M), serum interleukin-2 receptor (sIL2R), toll-like receptor 4 (TLR4), and vascular endothelial growth factor (VEGF).

Material and Methods: The model was developed and validated on respectively 182 and 181 inoperable stage I-IIIB NSCLC patients treated radically with (chemo)radiotherapy. It included the mentioned clinical features, and blood-biomarkers were selected by least absolute shrinkage and selection operator (LASSO). Discrimination was reported by means of internal 10-fold cross-validated (CV) and external concordance index (c-index).

Results: The inclusion of OPN and Cyfra 21-1 (hazard ratios of 3.3 and 1.7) in this clinical model significantly increased the c-index from 0.66 to 0.70 (10-fold CV = 0.64 and 0.67). The calibration slope of the prognostic index in the validation cohort was 0.66 (p<0.01), therefore requiring re-calibration. Further extension of the model by selecting from the 4 additional blood biomarkers yielded a c-index of 0.67 (10-fold CV = 0.66), TLR4 was left unincorporated, and resulted in a better fitting model (likelihood ratio test: p=0.01; Table 1). Hypoxia is known to be present in NSCLC adversely affecting disease progression and response to radiation treatment. Likewise, tumor load is often associated with disease development and prognosis. The value of hypoxia and tumor load associated markers OPN and Cyfra 21-1 was confirmed in this study. Extension of the model included α2M, sIL2R, and VEGF, with higher concentrations of these new markers being associated with a worse prognosis. α2M, a previously identified candidate predictor for radiation pneumonitis was found to be a prognostic factor in NSCLC. IL-2 was already identified as an independent prognostic marker in patients with advanced NSCLC. The correlation of IL-2 with shorter survival was confirmed in these cohorts and may be of relevance for patients receiving IL-2 immunotherapy. Finally, VEGF, the angiogenesis factor found in a variety of solid tumors including NSCLC, was found to be of added value in the extended model.
Table 1 - Multivariable Cox PH regression of the clinical variables and blood-biomarkers fitted on the validation dataset, after a feature selection made by LASSO, by including the offset of the re-calibrated linear predictor and allowing for a selection among the new blood-biomarkers. Performance of the model expressed in terms of internal Harrell’s c-index, corrected for optimism by a 10-fold CV (between brackets).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Hazard Ratio</th>
<th>95% CI HR</th>
<th>p-value</th>
<th>c-index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibrated PI</td>
<td>2.4</td>
<td>1.7–3.5</td>
<td>&lt;0.01</td>
<td></td>
</tr>
<tr>
<td>dDM</td>
<td>0.4</td>
<td>1.3–0.5</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>dIL2R</td>
<td>0.3</td>
<td>1.1–1.9</td>
<td>&lt;0.01</td>
<td>(0.66)</td>
</tr>
<tr>
<td>VEGF</td>
<td>1.4</td>
<td>0.9–2.4</td>
<td>0.3</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: In conclusion, we improved and validated a clinical model with inclusion of hypoxia and tumor-load related blood-biomarkers. New immunological markers were associated with overall survival. Currently we are aiming to extend these models to include imaging information (Radiomics).

PO-0679
Comparison of toxicity and outcome in stage III NSCLC patients treated with IMRT or VMAT
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Purpose or Objective: Intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) are widely used in the treatment of advanced stage non-small cell lung cancer (NSCLC). These techniques deliver conformal dose distributions at the cost of increased target dose heterogeneity (particularly IMRT) and larger volumes of surrounding healthy tissues receiving low doses (particularly VMAT). We evaluated whether these dosimetric differences between IMRT and VMAT are of influence on treatment toxicity and outcome.

Material and Methods: We retrospectively assessed a cohort of 189 consecutive patients with stage III NSCLC having undergone radical (chemo-)radiotherapy using IMRT (until 2011) or VMAT (starting in 2011). Most patients (n=182) received 66 Gy in 33 (once-daily) fractions to the primary tumour and involved hilar/mediastinal lymph nodes based on FDG-PET/CT. Concurrent chemoradiation (CCR; n=112) consisted of 2 courses of etoposide cisplatinum, whereas sequential treatment (n=56) consisted of 3 courses of gemcitabine cisplatinum. Acute and late toxicity were assessed using the RTOG radiation morbidity scoring criteria for esophageal and pulmonary toxicity. Follow-up visits were planned every 3 months (first 2 years), biannually thereafter. Median overall survival (OS) was calculated using Kaplan-Meier survival analysis. Differences between the groups receiving IMRT and VMAT were statistically tested using the Mann-Whitney-U or Chi-square test, where appropriate.

Results: Gender, age, performance score, clinical (tumour and nodal) stage and radiation dose did not significantly differ between the IMRT (n=93) and VMAT (n=96) groups. Patients undergoing IMRT, however, received less concurrent chemotherapy compared to patients treated with VMAT (n=51 vs n=71; p= 0.007). Incidences of grade2 and ≥3 acute esophageal toxicity (AET) were significantly lower for IMRT compared to VMAT (28 vs 57 patients, p<0.001; and 6 vs 17 patients, p=0.025, respectively). Maximum grade acute and late pulmonary toxicity did not differ between groups (p=0.57 and p=0.14, respectively). Grade ≥3 late esophageal toxicity was scored in 1 and 3 patients after IMRT and VMAT, respectively. Median follow-up for the patients alive was 32 months (range 2.4-82.1 months). Median OS was 23.9 months (95% CI 19.6-28.1), without a significant difference between the groups (23.9 and 24.9 months for IMRT and VMAT, respectively; p=0.70).

Conclusion: Patients treated with VMAT showed significantly higher incidence of Grade ≥2 and ≥3 AET, which may be due to a higher percentage of patients receiving CCR in the VMAT-group. Median OS did not differ between groups. Currently the target volumes and dosimetric data are evaluated for differences between the groups, for we hypothesized that VMAT enables treatment of larger tumour volumes, leading to increased AET.

PO-0680
Predictive models of the extent and CT appearance of radiation induced lung injury for NSCLC
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Purpose or Objective: The purpose of the present study was to investigate the extent and appearance of early radiologic injury in the lung after radiotherapy (RT) for non-small cell lung cancer (NSCLC). Furthermore, the ability of planned mean lung dose to predict the risk of a radiologic response was explored.

Material and Methods: Eligible follow-up computed tomography (CT) scans acquired within 6 months after commencement of radiotherapy were retrospectively evaluated for radiologic injuries in a cohort of 213 NSCLC patients treated to 60 or 66 Gy in 2 Gy fractions at a single institution from 2007 to 2013. Radiologic injuries were divided in two categories based on CT appearance. Category 1 represented ground-glass opacity (GGO) and interstitial changes. Both are characterized by moderately increased densities in the lung parenchyma, but where GGO appears diffuse, amorphous, and with poorly defined vessel structures, interstitial changes are identified by more pronounced vessels and borders. Category 2 indicated patchy or confluent consolidation in the lung. The volume fraction of injured lung corresponding to either category was estimated in each scan. To investigate the relationship between the volume fraction of injured lung and mean lung dose, a logistic regression analysis was performed. Four different cut-points were chosen to define radiologic injury response. These were volume fractions of injured lung larger than 5%, 10%, 15% or 20%. Both individual and combined categories were investigated.

Results: Radiologic injuries of category 1 and 2 were found in follow-up scans for 81% and 42% of the patients, respectively. The mean volume fraction of injured lung was 6.5% (range 0-95%) and 1.7% (range 0-22%) for category 1 and 2, respectively, and 8.2% (range 0-95%) when the categories were combined. The logistic normal tissue complication probability (NTCP) models are shown in the figure for the combined categories of lung appearance. The risk of radiologic response was found to be significantly associated with mean lung dose. The mean lung dose resulting in 50% risk of radiologic response (DS0) increased from 17 to 29 Gy as the cut-point used for dichotomization increased from 5 to 20% of volume fraction of affected lung (see table). A logistic relationship between radiologic response and mean lung dose was also found for the individual categories of lung.