Materials and Methods: There were 365 evaluable patients with at least one year of follow-up for the development of rectal bleeding. Rectal bleeding was assessed using the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scoring schema. There were 74 patients with Grade 2 or more late rectal bleeding. For all patients, DNA was genotyped using Affymetrix Genome-Wide Human SNP Array 6.0. A quality control test was performed with SNP missing rate > 5%, minor allele frequency (MAF) < 5%, and Hardy-Weinberg equilibrium (p < 10E-5). As a result, 613,496 SNPs remained. For the analysis, we split the patients into two groups: a group of patients with Grade 0 or 1 late rectal bleeding and the other group of patients with Grade 2 or more.

To predict late rectal bleeding toxicity, we designed a machine learning-based multi-SNP model. Our model mainly consists of two steps: in the first step, principal component analysis (PCA) is used to filter out irrelevant SNPs and in the second step L1-penalized regression (LASSO) is used to remove redundant SNPs and to build a sparse regression model. In particular, normal tissue complication probability (NTCP), which was calculated using logistic regression with a few principal components derived from the first step, was used as a response variable in the second step. For unbiased assessment of the predicted model, the dataset was split into two groups: training dataset (2/3 of samples) and validation dataset (1/3 of samples). In the model design, only the training dataset was used with 10-fold cross validation. After 50 iterations of the proposed method, SNPs were ranked based on the frequency that each SNP was used in the LASSO models. In a manner of forward feature selection, the validation dataset was tested with the LASSO models that were constructed using the training dataset. The area under the receiver operating characteristic (ROC) curve (AUC) was used as a performance metric.

Results: Using the training data, univariate analysis was performed using Chi-square test. With a threshold of p=0.001, 749 SNPs remained. These SNPs were fed into our model. The cross-validation with the training dataset resulted in AUC=0.85 (standard deviation: 0.02) and the best final model with the validation dataset resulted in AUC=0.68 (p=0.004) with 360 SNPs as shown in Fig. 1.

Conclusions: A novel machine learning method demonstrated a large number of SNPs contribute to clinical radiosensitivity for the radiation-induced late rectal bleeding. However, evaluation on other datasets is necessary to validate our model.

Purpose/Objective: Single-nucleotide polymorphisms (SNPs) in the ataxia telangiectasia mutated (ATM) gene have been associated with clinical radiation pneumonitis, but those findings have not been correlated with the pulmonary function impairment. Therefore, we investigated the association between SNPs in the ATM gene and the risk of diffuse capacity of the lung for carbon monoxide (DLCO) change in patients with non-small-cell lung cancer (NSCLC) treated with radiation therapy (RT).

Materials and Methods: From November 1998 through June 2009, 448 consecutive patients with inoperable or unrespectable primary NSCLC underwent definitive (≥60 Gy) radio(chemo)therapy; exclusion criteria were patients with a history of thoracic surgery, RT, or lung cancer or those who did not have undergone pulmonary function test before and after RT within one year. Ultimately, 100 patients met the selection criteria for this study. We genotyped two SNPs of the ATM gene (rs189037 and rs228590), and assessed correlation with DLCO impairment using logistic regression analysis.

Results: The dataset consisted of 58 men and 42 women, with a median age of 64 years (range, 38-83 years). Of all these patients, 86 were whites and 82% had stage III/IV diseases according to the 6th edition of the AJCC stage grouping criteria. The median mean lung dose was 17.5 Gy (range, 4.7-29.5 Gy). Median DLCO change within one year after RT was 0.81 (range 0.22-1.79). Early DLCO change (3-6 months after RT) had the same range but the median value was 0.77. The genotype distribution of all studied SNPs was: rs189037, 29% AA, 49% AG, 22% GG; and rs228590, 33% CC, 49% CT, 19% TT. Univariate and multivariate analyses showed that the AA genotype of ATM rs189037 was associated with significantly higher DLCO impairment after definitive radiation than the GG/AG genotypes (univariate beta regression coefficient -0.12; 95% confidence interval [CI], -0.24--0.008; P = 0.037; multivariate beta regression coefficient -0.10; 95% CI, -0.20--0.005; P = 0.04). However, similar results were not observed for rs228590 (univariate beta regression coefficient -0.10; 95% CI, -0.25--0.12; P = 0.096).

Conclusions: The AA genotype of ATM rs189037 was associated with higher risk of lung injury, compared with the GG/AG genotypes in patients with NSCLC treated with radio(chemo)therapy. This response marker may be used for guiding therapy intensity in an individual patient, which would further the goal of individualized therapy.
physiological methods and validated questionnaires. Ten single nucleotide polymorphisms (SNPs) have previously been suggested to be predictive of late radiation induced toxicity by GWAS studies or candidate gene studies. The objective of this study was to test the ten SNPs in this unique cohort. The strength of the reportings as well as the clinical data available served as the rationale for using our rather small cohort as a validation cohort.

Materials and Methods: The patients in this cohort have received EBRT 70-78 Gy for prostate cancer with curative intent. Functional toxicity endpoints have been examined by sigmoidoscopy, manometry, endoanal ultrasonography and impedance planimetry in an earlier study. Objective endpoints include the Vienna Rectoscopy Score (VRS), cross sectional area (CSA) of rectum at distension, maximum resting pressure (MRP) and maximum squeezing pressure (MSP) of anal sphincters. The subjective measure RT-Anorectal dysfunction score (RT-ARD) was obtained from the questionnaires. Biological material from the patients in this cohort is available from an established research biobank. The SNPs were investigated in DNA from fibroblasts with TaqMan SNP assays. Statistical analyses was carried out with Stata13.

Results: Spearman’s rank correlation. All SNPs in the cohort were in Hardy-Weinberg equilibrium. Preliminary results showed no statistically significant correlations between the risk-allele average and toxicity end points tested. Spearman’s rank correlations p (rho) were as follows: VRS \( \rho = 0.17 \) p = 0.33, MRP \( \rho = -0.08 \) p = 0.64, MSP \( \rho = 0.02 \) p = 0.91, CSA \( \rho = 0.03 \) p = 0.88, RT-ARD \( \rho = -0.26 \) p = 0.13.

Conclusions: Preliminary results indicate no correlation between risk-allele average and late radiation toxicity end points tested. The cohort will be expanded with 234 patients having received the same treatment and with the same questionnaire data on morbidity.

OC-0085
Mitochondrial DNA variation as a biomarker for the development of radiation-induced lung toxicity

Purpose/Objective: Radiation-induced lung toxicity (RILT) varies significantly between patients at similar doses to the lung and can seriously affect the quality of life. The identification of prognostic biomarkers for radiation-induced toxicity is crucial for personalized RT: to select patients for proton therapy or dose escalation. We hypothesized variation in the mitochondrial genome (mtDNA) is a biomarker for RILT, since mitochondria and RT have several processes in common, among which reactive oxygen species (ROS) production.

Materials and Methods: Blood DNA was isolated from 372 (training set, Maastricht) and 68 (test set, Ghent) lung cancer patients. After exclusion of patients that had surgery, had other tumors within 5 years prior to lung cancer, received a palliative dose or for which baseline dyspnea score was unknown, 277 and 53 patients were remaining for the training and test set respectively. Baseline dyspnea (at the start of RT) and maximal dyspnea 3-6 months after RT were scored according to the CTCAE version 3.0 criteria. The endpoint of analysis was dyspnea grade>=2 after RT. Additionally, DNA was obtained from fibroblasts of 21 breast cancer patients for which the toxicity grade after radiotherapy was known (LEN7/SOMA criteria). mtDNA was resequenced using mitochhips and homoplasmic deviations from the revised Cambridge reference sequence were recorded. Variants were classified into 7 functional categories based on their theoretical effect on OXPHOS function.

Results: Using the 7 functional categories as input features, logistic regression analysis corrected for baseline dyspnea score resulted in an AUC of 0.78 for the training set, which was significantly better than the current international gold standard Mean Lung Dose (AUC 0.57; p < 0.001). The AUC for the test set was 0.66 but the power of the validation was limited due to the small sample size. Validation in a second external test set is ongoing. Additionally, using mtDNA variation data we were able to classify breast cancer patients in the correct toxicity group with 80% accuracy.

Conclusions: Our data showed that mtDNA variation is a valuable biomarker for RILT. Furthermore, we have preliminary data in breast cancer patients that the predictive effect of mtDNA might be applicable to radiation toxicity in general.

Proffered Papers: Brachytherapy 2: Prostate HDR

OC-0086
Dosimetric inter- and intra-observer contouring and registration variability for prostate brachytherapy
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Purpose/Objective: (1) To quantify the geometric and dosimetric variability of prostate contouring on US for low-dose-rate brachytherapy. (2) To assess the dosimetric variability of registrations of T1-weighted MRI with C-arm cone beam CT (CBCT) and the currently performed US-CBCT registrations.

Materials and Methods: VariSeed studies of eleven patients previously treated with low-dose-rate brachytherapy at our institute were enrolled in a multi-observer study. Six observers performed three sessions of prostate contouring on US and registrations of US- and MRI-CBCT.

Prostate contours were sampled at 10 degree increments of the polar and azimuthal angles from the center of mass. The