properties are dynamic in nature. Therapeutic agents inhibiting tumor cell reprogramming may have the potential to increase the effectiveness of radiotherapy. Moreover, monitoring of CSC-related biomarker before and during the course of radiotherapy may be able to predict therapy response and clinical outcome.

Proffered Papers: Clinical 3: Lung

OC-0135
Can we select stage I NSCLC patients at high risk for early death prior to SBRT treatment?
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Purpose or Objective: This study analyzed whether short-term death of patients with peripheral stage I NSCLC can be predicted reliably to select a sub-group of patients, which will not have a benefit from SBRT and which can be referred to wait and see.

Material and Methods: 802 patients with early stage NSCLC treated with SBRT in 5 institutes for whom information on overall survival within the first six months after treatment was available were included in this analysis. The probability of dying within six months after treatment was modeled by multivariate logistic regression; this interval was chosen because death of early stage NSCLC is a rare event within six months after diagnosis. Model fitting was performed using the LASSO method which simultaneously serves to select models that are most closely related to the outcome. The performance of the model that would be achieved on an independent dataset was estimated using double 10-fold cross-validation (CV). Because with CV the estimation of test performance depends somewhat on the splitting of the data sets, double 10-fold CV was repeated 100 times, resulting in 1000 models from which the variance in the performance measure could be obtained. The variables age, gender, ECOG status, operability, FEV1 and Charlson comorbidity index (CCI) where considered for model building.

Results: Using different variable combinations for model building resulted in different sample sizes and model performances (Table 1). Common among all models was the identification of the CCI as the most frequently selected and thus most important variable predicting six-months death, with increasing values predicting higher probability of death. Gender was consistently the second-most frequently selected variable. Regressing on the individual components of the CCI with the LASSO method showed that presence of a second solid tumor was the most important predictor, followed by various forms of heart disease (Figure 1). Replacing the CCI by these individual components in model building confirmed the strong relation between the presence of a second tumor and early death, but led to a worse model performance than with the full CCI (Table 1). Overall the accuracy of all models predicting six-months death was poor with maximum AUC=0.62.

Conclusion: General patient characteristics together with comorbidity data, especially the history of a previous malignancy, can predict early death, however, prediction accuracy is insufficient to select patients to wait and see instead of offering SBRT as a curative treatment.

OC-0136
Primary Study Endpoint Analysis of NRG Oncology/RTOG 0813 Trial of SBRT for centrally located NSCLC
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Figure 1: Results of variable selection by the LASSO method when using the individual components of the CCI for predicting death within six months after treatment. 10-fold CV was repeated 1000 times, resulting in a total of 1000 individual models. Shown is the frequency with which a variable was selected into a model.

Table 1: Results of the model fitting procedure applied to three sub-samples of the data. MI: Myocardial infarct; PVD: Peripheral vascular disease; CVD: Cardiovascular disease.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Age, Gender, ECOG (Operability, FEV1, CCI)</th>
<th>Age, Gender, CCI</th>
<th>Age, Gender, MI, PVD, CVD, CCI (second tumor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>802</td>
<td>802</td>
<td>802</td>
</tr>
<tr>
<td>Number of events</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>AUC</td>
<td>0.51±0.092</td>
<td>0.50±0.092</td>
<td>0.50±0.092</td>
</tr>
<tr>
<td>Accuracy (%)</td>
<td>0.82±0.01</td>
<td>0.82±0.01</td>
<td>0.82±0.01</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>0.74±0.01</td>
<td>0.74±0.01</td>
<td>0.74±0.01</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>0.55±0.01</td>
<td>0.55±0.01</td>
<td>0.55±0.01</td>
</tr>
</tbody>
</table>

Purpose or Objective: NRG/RTOG 0813 is a phase I/II study designed to determine the maximal tolerated dose (MTD) and efficacy of SBRT for NSCLC with centrally located tumors. We hereby report the primary endpoint of the phase I portion of the study.

Material and Methods: Medically inoperable pts with biopsy proven, PET staged T1-2 (<5cm)N0M0 NSCLC and centrally located tumors (within or touching the zone of the proximal bronchial tree or adjacent to mediastinal or pericardial pleura) were successively accrued onto a dose-escalating 5 fraction SBRT schedule ranging from 10-12 Gy/fraction delivered over 1.5-2 weeks. Dose-limiting toxicity (DLT) was defined as any grade 3 or worse toxicity (per CTCAE v.4) occurring within first year, possibly, probably, or definitely related to treatment from a pre-specified list of cardiac, esophageal, respiratory or neurological toxicities. Any potential DLT within the initial year post-SBRT could have led to dose reduction for subsequent patients accrued, using TITE-CRM (time-to-event continual reassessment method) statistical design. MTD was defined as SBRT dose associated with a 20% probability of DLT.

Results: 120 pts were accrued Feb 2009 to Sept 2013 from 43 participating centers. Numbers (n) accrued into each cohort, n eligible for analysis (20 pts were excluded as they did not receive protocol treatment (12) or were ineligible (8)), and n evaluable for DLT analyses (11 not evaluable, 10 of whom died in the first year without a DLT) are shown in the table. Pts were elderly (median age 72), slightly more females (57%), majority had performance status 0-1 (84%). Most cancers were T1 (65%) and squamous cell (45%). Median follow up was 26.6 months. There were 5 events that met the definition of DLTs; Table details the protocol pre-specified DLTs and the worst treatment-related AEs (ie occurring at any time). MTD is 12.0 Gy/fr; Bayesian-based probability of DLT on this arm was 7.2% (95% CI 2.8 -14.4%). The grade 5 AEs occurred at a mean 13 mo post-SBRT (range 5.5-14mo).

Conclusion: The rates of toxicity pre-specified as DLT were relatively low. The highest dose level allowed by the protocol was reached, and associated with 7.2% rate of DLT. This phase I/II trial of SBRT provides data to inform patients of the potential toxicities with a 5 fraction SBRT schedule for centrally located NSCLC, but data on efficacy are still awaited.