Abstracts

Presentation Number: CT-05

International Multicenter Randomized Study On Thoracic Radiotherapy (TRT) In Extensive Stage Small Cell Lung Cancer (ES-SCLC): Patterns Of Disease Recurrence.

B. J. Slotman¹, C. Faivre-Finn², H. van Tinteren³, J. Praag⁴, J. Knegjens⁵, S. el Sharouni⁶, M. Hatton⁷, A. Keijser⁸, S. Seran¹, ¹VU University Medical Center, Amsterdam, Netherlands, ²The Christie NHS Foundation Trust, Manchester, United Kingdom, ³Netherlands Cancer Institute, Amsterdam, Netherlands, ⁴Erasmus MC, Rotterdam, Netherlands, ⁵The Netherlands Cancer Institute, Amsterdam, Netherlands, ⁶UMC Utrecht, Utrecht, Netherlands, ⁷Weston Park Hospital, Sheffield, United Kingdom, ⁸IKNL, Amsterdam, Netherlands

Purpose/Objective(s): Prophylactic cranial irradiation (PCI) reduces the risk of brain metastases, and it improves survival in ES-SCLC patients who respond to chemotherapy. Since most patients have residual intrathoracic disease after chemotherapy, we performed a randomized trial evaluating the role of TRT in addition to PCI. In this analysis, we report on the recurrence patterns. Analysis of survival and toxicity having been submitted to ASCO 2014.

Materials/Methods: Patients with confirmed ES-SCLC who responded to 4-6 cycles of platinum-etoposide were randomized to TRT (30 Gy/10fx) or no TRT. All received PCI. The primary study endpoint was overall survival. Analysis was based on intent to treat.

Results: 498 patients were enrolled (249 per arm); 3 patients withdrew informed consent leaving 247 (TRT) and 248 patients (control arm). Median follow-up was 24 months. The rate of intrathoracic recurrence as first site of relapse was 41.7% in TRT arm vs. 77.8%, in the control arm (p<0.001); this was 20.6% and 48.0 % respectively (p<0.001) for intrathoracic recurrence as the only site of first relapse. Progression elsewhere, with or without progression in thorax and/or brain as first site of relapse, occurred in 59.5% in the TRT arm, compared to 38.3% in the control arm (P<0.001) with no significant difference in the risk of brain metastases as first site of relapse (8.5% vs. 4.0%; p=0.06). Progression-free survival was longer in the TRT-arm (HR=0.73, CI 0.61-0.87; p=0.001). There was no significant difference in overall survival in the first year. At 2 years, overall survival was 13% (CI 9-19) in the TRT arm and 3% (CI 2-8%) in the control arm (P=0.004).

Conclusions: TRT improves progression free survival, results in fewer intrathoracic recurrences and improves 2 years overall survival. TRT should be offered to all ES-SCLC patients with a response to initial chemotherapy. The higher rate of progression outside thorax and brain in the TRT arm warrants studies on consolidative radiotherapy to other sites of distant disease.

Patterns of recurrence (simultaneous: recurrences occurring <30days at different sites)

<table>
<thead>
<tr>
<th>First site of progression</th>
<th>TRT (n=247)</th>
<th>no TRT (n=248)</th>
<th>All sites of progression</th>
<th>TRT (n=247)</th>
<th>no TRT (n=248)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>213 (86.2%)</td>
<td>223 (89.9%)</td>
<td>Total</td>
<td>213 (86.2%)</td>
<td>223 (89.9%)</td>
</tr>
<tr>
<td>Thorax</td>
<td>51 (20.6%)</td>
<td>119 (48.0%)</td>
<td>Thorax</td>
<td>49 (19.8%)</td>
<td>114 (46.0%)</td>
</tr>
<tr>
<td>Brain</td>
<td>11 (4.5%)</td>
<td>8 (3.2%)</td>
<td>Brain</td>
<td>10 (4.0%)</td>
<td>6 (2.4%)</td>
</tr>
<tr>
<td>Other sites</td>
<td>96 (38.9%)</td>
<td>21 (8.5%)</td>
<td>Other sites</td>
<td>90 (36.4%)</td>
<td>19 (7.7%)</td>
</tr>
<tr>
<td>Thorax + Brain</td>
<td>4 (1.6%)</td>
<td>1 (0.4%)</td>
<td>Thorax + Brain</td>
<td>5 (2.0%)</td>
<td>3 (1.2%)</td>
</tr>
<tr>
<td>Thorax + Other sites</td>
<td>45 (18.2%)</td>
<td>73 (29.4%)</td>
<td>Thorax + Other sites</td>
<td>50 (20.2%)</td>
<td>77 (31.0%)</td>
</tr>
<tr>
<td>Brain + Other sites</td>
<td>3 (1.2%)</td>
<td>1 (0.4%)</td>
<td>Brain + Other sites</td>
<td>5 (2.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Thorax + Brain + Other sites</td>
<td>3 (1.2%)</td>
<td>0 (0.0%)</td>
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<td>4 (1.6%)</td>
<td>4 (1.6%)</td>
</tr>
</tbody>
</table>

Acknowledgement: This study was supported by grants from the Dutch Cancer Society (CKTO) and Cancer Research UK and supported by the Dutch Lung Cancer Research Group and The Christie NHS Foundation Trust Clinical Trials Unit.
A Gene Expression Platform to Predict Benefit from Adjuvant External Beam Radiation in Resected Non-Small Cell Lung Cancer

B. Creelan, S. A. Eschrich, W. J. Fulp, J. F. Torres-Roca, H. Lee Moffitt Cancer Center, Tampa, FL

Purpose/Objective(s): Currently, no genomic decision-making tool exists for adjuvant radiation after resection of non-small cell lung cancer (NSCLC). Our objective was to retrospectively determine if our previously published 10-gene panel, called radiosensitivity index (RSI), would classify patients into radioresistant (RSI−poor) or radiosensitive (RSI−good) using disease-free survival (DFS).

Materials/Methods: Inclusion criteria: pathologic stage III NSCLC at time of resection, negative margins, at a single institution between 2000 and 2012. For radiation group (RT), at least 45 Gy of external beam radiation was required. An identical stage group (control) did not receive radiation. Gene expression profiling was done on primary lung tumor mRNA. DFS was defined as time-to-recurrence or death. Predefined cut-point was lowest quartile of calculated RSI. Two-sided log-rank and Cox regression were used. Similar inclusion criteria were then applied to two extramural datasets (E1; E2).

Results: Of 154 screened, 95 were eligible (53 RT and 42 control). Demographics: median age 67 yrs, 54% female, 96% white, and 91% current/former smokers. Operations consisted of 56% lobectomy, 26% pneumonectomy, and 18% segmentectomy/wedge. Adjuvant doublet consisted of 48% taxane, 32% gemcitabine, or 20% other. Mean RT dose 54.8 Gy, median follow-up 3.5 yrs. Histology: 64% adenocar, 25% squamous, 10% large-cell. Mean tumor volume 58 cm³, 77% pN2, 58% had angiolymphatic invasion and 51% were poorly-differentiated. Mean preoperative PET SUV max was 9.5. No imbalance in clinical factors were observed between RSI−good vs. RSI−poor.

On univariate analysis, for RT group, median DFS for RSI−good vs RSI−poor was 5.8 yrs vs. 1.4 yrs, HR 4.2 (95% CI 1.9 - 9.5), p = 0.02. 5-year DFS was 63% vs 22%, p = 0.01. No significant difference was observed for the chemo-only control group, with median DFS for RSI−good vs. RSI−poor: 2.3 vs 2.7 yrs, HR 0.7 (95% CI 0.3 - 1.6), p = 0.98. A test for interaction confirmed that the effect was restricted to the RT group and not the control, with p = 0.04. On multivariate analysis, for the RT group, the RSI remained an independent predictive variable with HR 3.8 (95% CI 1.6 - 9.2), p = 0.003.

For E1, 486 screened, 74 eligible. median DFS for RSI−good vs. RSI−poor in RT group was 2.0 yrs vs 0.8 yrs, HR 2.2 (95% CI 1.0 - 4.8), p = 0.05. For E2, 139 screened, 26 eligible, median DFS for RT group 12.1 vs. 0.7 yrs, HR 3.6 (0.6 - 10.1), p = 0.18. No association trend was identified in either control group. By random effects model, the predictive effect of RSI was consistent across all three RT groups, with summary HR 1.6 (95%CI 1.3 - 2.1), Q = 1.33.

Conclusions: RSI appears to be predictive for benefit from adjuvant radiation. Additional independent prospective validation is required.

Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer

R. D. Timmerman¹, C. Hu², J. Michalski³, W. Straube³, J. Galvin⁴, D. Johnstone⁵, J. Bradley³, R. Barriger⁶, A. Bezjak⁷, G. M. Videtic⁸, L. Nedzi¹, M. Werner-Wasik⁹, Y. Chen⁹, R. U. Komaki¹⁰, H. Choy¹,¹ University of Texas Southwestern Medical School, Dallas, TX, ²American College of Radiology, Philadelphia, PA, ³Washington University Medical Center, St. Louis, MO, ⁴Thomas Jefferson Hospital, Philadelphia, PA, ⁵Medical College of Wisconsin, Milwaukee, WI, ⁶Indiana University Medical Center, Indianapolis, IN, ⁷Princess Margaret Hospital, Toronto, ON, ⁸Cleveland Clinic, Cleveland, OH, ⁹University of Rochester Medical Center, Rochester, NY, ¹⁰M.D. Anderson Cancer Center, Houston, TX

Purpose/Objective(s): Patients with early stage but medically inoperable lung cancer historically had poor primary tumor control and high mortality with conventional radiotherapy. SBRT appeared to improve outcomes, as suggested by the initial published results of RTOG 0236. Herein, we update those results with longer follow-up.

Materials/Methods: The study was a Phase 2 North American multicenter study of patients aged 18 years or older with biopsy-proven peripheral T1-T2N0M0 non-small cell tumors (measuring ≤5 cm in diameter) and medical conditions precluding surgical treatment. The prescription dose was 18 Gy per fraction X 3 fractions (54 Gy total) with entire treatment lasting between 1½ and 2 weeks. The study opened May 26, 2004, and closed October 13, 2006; data were analyzed through October 15, 2013. The primary end point was 2-year actuarial primary tumor control; secondary end points were disease-free survival (ie, primary tumor, involved lobe, regional, and disseminated recurrence), treatment-related toxicity, and overall survival.

Results: A total of 59 patients accrued, of which 55 were evaluable (44 patients with T1 tumors and 11 patients with T2 tumors) with a median follow-up of 4.0 years (7.2 years for surviving patients). Four patients had an in-field/marginal (primary) tumor failure (range, 1.8-4.8 years after SBRT); the estimated 5-year primary tumor failure rate was 7%. Nine additional patients had recurrence within the involved lobe (range 0.1-5.9 years after SBRT); the 5-year primary tumor and involved lobe (local) failure rate was 20%. Seven patients experienced regional failure (range, 2.8-5.2 years after SBRT); the 5-year local-regional failure rate was 38%. Fifteen patients experienced disseminated recurrence; the 5-year disseminated failure rate was 31%. The rates for disease free and overall survival at 5 years were 26% and 40%, respectively. The median overall survival was 4 years. Protocol treatment-related grade 3 and 4 adverse events were reported in 15 patients and in 2 patients, respectively, modestly more than was described in the previous 3-year report. No grade 5 adverse events were reported.

Conclusions: Patients with inoperable non-small cell lung cancer treated with SBRT had a survival rate of 40% at 5 years. While tumor control rates remain high compared to conventional fractionation results, late failures were observed particularly in the involved (untreated) residual lobe. However, an excess of late-appearing toxicity was not observed.

Residual Post-Treatment FDG Avidity in Regional Lymph Nodes Impacts Local-Regional Control in Patients Receiving Definitive Chemoradiation for Non-Small Cell Lung Cancer: A Secondary Analysis of ACRIN 6668/RTOG 0235

S. Markovina¹, F. Duan², B. J. Snyder³, B. A. Siegel⁴, M. Machtay⁴, J. D. Bradley⁵, ¹Washington University, St. Louis, MO, ²Brown University, Providence, RI, ³Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, ⁴University Hospitals Case Medical Center, Cleveland, OH, ⁵Washington University School of Medicine, St. Louis, MO

Purpose/Objective(s): The primary objective of ACRIN 6668/RTOG 0235 demonstrated that peak standardized uptake value (SUV\textsubscript{peak}) on post-treatment [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET) correlates with survival in locally advanced non-small cell lung cancer (NSCLC). The purpose of this secondary analysis was to determine how metabolic response of the regional lymph nodes (RLNs) compares to that of the primary tumor, and if SUV parameters of RLNs correlate with outcomes in patients accrued to this trial.

Materials/Methods: Patients included in the analysis had locally advanced NSCLC, were treated with concurrent chemoradiation therapy using RT doses of ≥60 Gy, and had identifiable FDG-avid RLNs, distinct from primary tumor, on pre-treatment FDG-PET. Core lab SUV measurements performed at ACRIN headquarters were used for this secondary analysis. Event time was calculated from the date of the post-treatment FDG-PET scan 12-16 weeks after completion of radiotherapy. Local-regional failure was reported by the treating institution and was defined as failure within the treated RT volume (including primary tumor site or RLNs). Distributional comparisons were conducted using the Wilcoxon signed-rank test. The association with outcomes was assessed using Kaplan-Meier curves (log rank test) and univariate Cox proportional hazards modeling.

Results: 176 patients had uptake in both the primary tumor and RLNs on the pre-treatment FDG-PET scan; 139 of these patients (79%) also had post-treatment FDG-PET with SUV data. Pre-treatment, both SUV\textsubscript{peak} and SUV\textsubscript{max} were greater for the lung primary than for RLNs (p<0.0001 for both). Post-treatment, SUV for the lung primary was not significantly different from RLN, for either SUV\textsubscript{peak} (3.10 ± 2.42 vs. 2.84 ± 2.03, respectively; p=0.18) or SUV\textsubscript{max} (3.75 ± 3.06 vs. 3.47 ± 2.53, respectively; p=0.32). Neither continuous nor categorical post-treatment SUV of RLNs was associated with overall survival. However, the continuous post-treatment SUV\textsubscript{peak} and SUV\textsubscript{max} of RLNs were associated with inferior local-regional control (p < 0.01 for both).

Conclusions: Residual post-treatment FDG avidity is similar between the primary tumor and RLNs. Residual high metabolic activity in the RLNs is associated with worse local-regional control. Based on these data, future trials evaluating the utility of an RT boost should consider inclusion of both the primary tumor and FDG-avid RLNs in the boost volume to maximize local-regional control.

Acknowledgment: This ACRIN (now ECOG-ACRIN)/RTOG project has been funded at least in part with Federal funds from the Department of Health and Human Services under Grant Number CA80098.

Author Disclosure: S. Markovina: None. F. Duan: None. B.J. Snyder: None. B.A. Siegel: None. M. Machtay: None. J.D. Bradley: None.
Definitive Hyperfractionated Accelerated (AHF) Radiochemotherapy (CRT) vs. Neoadjuvant AHF-CRT and Surgery (S) for Patients (pts) with operable Stage IIIA(N2)/selected IIIB Non-Small-Cell Lung Cancer (NSCLC) following Induction Chemotherapy (IND-C): Results from a Multicenter Phase III Study

M. Stuschke¹, C. Pöttgen¹, T. Gauler¹, G. Friedel², S. Veit², V. Heinrich³, S. Welter⁴, W. Spengler³, H. Schmidberger⁵, D. Lütke-Brintrup¹, N. Lehmann¹, K. Jöckel¹, M. Schuler¹, G. Stamatis⁴, W. Eberhardt¹,
¹University Hospital Essen, Essen, Germany, ²Robert-Bosch-Krankenhaus Klinik Schillerhöhe, Gerlingen, Germany, ³University Hospital Tübingen, Tübingen, Germany, ⁴Ruhrlandklinik, Essen, Germany, ⁵University Hospital Mainz, Mainz, Germany

Purpose/Objective(s): Definitive CRT or neoadjuvant CRT+S were compared in this randomized trial. To optimize loco-regional control, AHF and concurrent chemotherapy were used. All N2/N3 patients had pathological proof of nodal involvement. PET/CT was recommended. The alternative hypothesis H1 underlying this trial was a 5 year survival of 25% in the definitive AHF-CRT and 40% in the neoadjuvant AHF-CRT+S arm.

Materials/Methods: Pts with pathologically proven operable IIIA(N2) / selected IIIB NSCLC received IND-C (3 cycles Cisplatin/Paclitaxel) and neoadjuvant AHF-CRT to 45 Gy(1.5Gy bid/ concurrent Cisplatin/Vinorelbine). Pts were reevaluated in last week of CRT and discussed in the multidisciplinary board. Operable pts were then randomized either to definitive CRT (arm A) or surgery (arm B). Pts in arm A received a risk-adapted boost to 65/71 Gy at 2 Gy per fraction without break and concurrent Cisplatin/Vinorelbine. Mean lung dose was held below 18 Gy.

Results: With 161 randomized from 300 planned pts(1/2004-8/2012), the trial was closed after second planned interim analysis for slow accrual + futility. 246 pts (70 F/176 M; stages, 75 T1-3 N2 / 80 T4 N0-1/ 91 T4 N2 or T1-3N3; histology, 95 SCC / 107 ADC / 44 other) were enrolled from 5 centers. 5-y overall survival of all 246 enrolled pts was 34% and was 42% for the 161 randomized pts. Overall survival of the randomized pts was not different between arms (p>0.25, log-rank test) and was significantly higher than the expected value of 25% at 5 years in arm A. Median follow-up was 78 mo. Progression-free survival at 3 and 5 years was 35 (25-46)% at both time points in arm A, and 40 (29-50)% and 32 (22-43)% in arm B (p=0.71, log-rank test).

Freedom from isolated loco-regional recurrence as the first site of relapse (ffLR) was analyzed after central review of follow-up imaging and clinical data from the highest recruiting center covering 71% of all patients. Actuarial ffLR at 5 years were similar in both arms. Treatment-related mortality was 2.5% in patients from arm A and 6.2% in arm B.

Conclusions: Progression free survival was encouraging with both treatment arms. Intensified definitive AHF-CRT following IND-C can result in high ffLR in pts with operable stage IIIA(N2)/selected IIIB NSCLC.

Acknowledgment: Deutsche Krebshilfe: No 70-3070-Eb


Higher Doses to Smaller Volumes Explains Higher Proton Therapy Radiation Pneumonitis Rates Found

N. Pham¹, R. Castillo¹, R. Castillo², B. Hobbs², T. Guerrero², ¹UTMDA, Houston, TX, ²MDACC, Houston, TX

Purpose/Objective(s): To determine if higher irradiated lung dose rather than irradiated lung volume or mean lung dose (MLD) is more critical for induction of radiation pneumonitis (RP) symptoms.
Materials/Methods: We retrospectively analyzed the clinical and dosimetric data from 275 esophageal cancer cases treated with thoracic radiotherapy using IMRT, proton, or 3D-CRT. RP symptoms were evaluated using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4). For each patient, the percentage lung volume irradiated, mean irradiated lung dose (MILD), mean lung dose (MLD), lung dose regions (low dose volume, ≤10 Gy or CGE, V_{low}; moderate-dose volume, >10-40 Gy or CGE, V_{mod}; and high dose volume >40 Gy or CGE, V_{high}), as well as V5 to V50 were determined. The effects of MILV, MILD, MLD, lung dose regions, percentage lung volume irradiated, dosimetric parameters, patient and treatment characteristics, or metabolic radiation dose response (PMRR) with pulmonary toxicity were studied using logistic regression.

Results: Proton therapy irradiated less lung volume (> 0.1 Gy or CGE) than IMRT (3.711 L in IMRT, 1.261 L in proton and 3.058 L in 3D-CRT) but the mean irradiated lung dose is higher in the proton versus IMRT group (12.04 Gy in IMRT, 17.21 CGE in proton and 11.70 Gy in 3D-CRT), despite the lower MLD received by the proton group (11.26 Gy in IMRT, 6.09 CGE in proton and 10.62 Gy in 3D-CRT). We found the rate of symptomatic radiation pneumonitis is 2 times higher for proton than IMRT (25% in proton, 13.6% in IMRT, and 27.8% in 3DCRT). The PMRR was significantly different between the three modalities (0.15 in proton, 0.10 in IMRT, and 0.10 in 3DCRT, p = 0.044 Kruskal-Wallis test).

Conclusions: Despite smaller irradiated lung volumes, subjects treated with proton therapy (v. IMRT) were two times more likely to develop symptomatic RP. The higher mean irradiated lung dose resulting in a more intense local response is the likely culprit.

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Presentation Number: 51

Time Will Tell: Is 60 Gy in 3 Fractions the Optimal SBRT Schedule for Stage I Non-Small Cell Lung Cancer?

K. Stephens, N. M. Woody, C. A. Reddy, A. Magnelli, T. Zhaung, T. Djemil, G. M. M. Videtic, Cleveland Clinic, Cleveland, OH

Purpose/Objective(s): Four years into our lung stereotactic body radiotherapy (SBRT) experience, analysis suggested no differences in local failure (LF) by dose/fractionation schedule for patients with medically inoperable stage I non-small cell lung cancer (NSCLC). Now with 10 years of experience we seek to re-confirm this association.

Materials/Methods: Using 12/31/2013 as the last follow up date for this analysis we reviewed an IRB approved registry of patients treated with definitive intent lung SBRT for stage I NSCLC between 10/2003 and 12/2012. Patients were treated on a Novalis/BrainLAB system with motion controlled by abdominal compression or breath-hold and image guidance during delivery by Exactrac. Patient, tumor and treatment factors were analyzed for correlation with LF using Cox proportional hazards.

Results: 600 patients were identified for analysis: Median age 74 (37-97 years), Charlson score 3 (0-12), pre-SBRT hemoglobin (HGB) 12.8 (8.2-17.8), FEV1 1.34L, and DLCO 53%. 53% were male, 21% active smokers, and 94% medically inoperable (61% pulmonary, 20% cardio-vascular, 6% refused, 4% age/KPS, 10% other). Median tumor size was 2.2 cm (mean 2.6, range 0.7-10 cm), PET SUV 7.49 (1-59), 75% were peripheral per RTOG 0236 definition, and 78% had biopsy proven disease (22% radiographic). SBRT dose was at physician discretion using a risk adapted and trial based approach: 351 patients (59%) received 48-50 Gy in 4-5 fx, 131 (22%) 60 Gy/3 fx, 88 (15%) 30-34 Gy/1 fx, and 30 (5%) 60 Gy/8 fx or 50 Gy/10fx. At last follow-up 53% of patients had died, and median overall survival was 31.9 months. Crude rates of local, lobar, regional, distant and any failure were 9, 4, 12, 25, and 34% respectively. Univariate correlates with LF were analyzed for correlation with LF using Cox proportional hazards.

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**Conclusions:** 1) Given the association of 60 Gy in 3 fractions with reduced LF we recommend further study of the ideal dose/fractionation regimen in stage I NSCLC, preferably in a randomized trial. 2) Maximum PET SUV (non-modifiable) and pre-SBRT HGB (modifiable) were also correlated with LF.


**Presentation Number:** 58

**Sbrt for Lung Metastases: A Pooled Analysis of 651 Patients and 868 Lesions of the German Working Group Stereotactic Radiotherapy**


1 University Hospital, Heidelberg, Germany, 2 University Hospital, Freiburg, Germany, 3 University Hospital, Zurich, Switzerland, 4 University Hospital, Mannheim, Germany, 5 University Clinic, Luebeck, Germany, 6 Klinikum rechts der Isar, TU Muenchen, Munich, Germany, 7 University of Muenster, Muenster, Germany, 8 University Hospital, Magdeburg, Germany, 9 University of Munich, Munich, Germany, 10 MH, Hannover, Germany, 11 University Hospital, Frankfurt, Germany, 12 Hospital Augsburg, Augsburg, Germany, 13 University Hospital, Dresden, Germany, 14 Radiation Oncology, Paderborn, Germany, 15 University Hospital, Jena, Germany, 16 University Hospital, Hamburg, Germany, 17 University Hospital, Marburg, Germany, 18 University Hospital, Wuerzburg, Germany

**Purpose/Objective(s):** SBRT for early stage NSCLC has been characterized in many studies and pooled analyses resulting in clear recommendations regarding patient selection, planning, delivery, dose and quality assurance. This report of the German working group stereotactic radiotherapy pools SBRT patient data of German centers and aims to describe local control, overall survival and toxicity for the subgroups of different primary tumors.

**Materials/Methods:** All radiotherapy departments in Germany were contacted and invited to participate in this study. 651 patients with 868 lung metastases treated with SBRT were included in this database. Biggest subgroups were NSCLC (n=223), colorectal cancer (n=196), renal cell cancer (n=58) and breast cancer (n=54). 264 were treated as single fraction radiosurgery, 313 in a three fraction approach, 291 lesions with different fractionation.

**Results:** The PTV encompassing isodose ranged from 33.5 Gy BED to 177 Gy BED. For the entire patient cohort a local control rate after 1 year of 90.8% was achieved. 5.9% of the patients experienced grade 3 toxicities. Pneumonitis grade 1 was found in 14.9%, grade 2 in 4.6% and grade 3 in 0.8%. One patient with grade 5 toxicity was reported. Kaplan Meier estimations of local control and overall survival are currently in preparation. In addition multivariate analysis are planned in order to identify the relevant factors for therapy success depending on primary tumor histology.

**Conclusions:** Despite a very heterogeneous practice throughout Germany excellent results regarding local control and toxicity could be achieved. The ongoing investigations will hopefully be the basis for practical guidelines for the individual subgroups.