regression adjustment revealed the Cb AUC 5 group was less likely to experience all-grade hem TEAEs, and grade 3/4 thrombocytopenia and anemia, compared with the AUC 6 group (all OR < 1; all P < .05).

Conclusions: Overall, Pem+Cb AUC 5 showed a better safety profile than Pem+Cb AUC 6, and this finding was consistent across three statistical approaches. Due to the heterogeneity of the trials analyzed, this trend should be confirmed in a randomized prospective trial.

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Stage III Non-Small Cell Lung Cancer Treated Without Concurrent Chemotherapy: What Is the Optimal Radiation Dose?
Locally Advanced Non-Small Cell Lung Cancer

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Purpose/Objective(s): Based on the preliminary results of RTOG 0617, there may not be an overall survival (OS) benefit for dose escalation beyond 60 Gy in patients with stage III non-small cell lung cancer (NSCLC) treated with concurrent chemotherapy and radiation therapy (CRT). However, the optimal radiation dose in the absence of concurrent chemotherapy remains unclear. We hypothesized that there may be a benefit for higher radiation doses in the absence of concurrent chemotherapy.

Materials/Methods: We reviewed 596 patients treated with definitive radiation therapy (RT) (minimum RT dose = 50 Gy) for stage III NSCLC at our institution between 1998 and 2013. All patients were treated with 3D conformal RT or intensity modulated radiation therapy (IMRT) and satisfied the same normal tissue planning constraints. OS was estimated using the Kaplan-Meier method. Candidate factors with P < 1 on univariate analysis (UVA), RT dose, and chemotherapy were incorporated into a multivariable model (MVA) for OS.

Results: The median age was 66 years (range 31 to 91 years). There were 286 (48%) stage IIIA and 310 (52%) stage IIIB patients. 338 (57%) patients had adenocarcinoma, 170 (28%) squamous cell carcinoma and 88 (15%) other NSCLC subtypes. 316 (53%) patients underwent concurrent CRT, and 280 (47%) patients were treated with sequential CRT or RT alone. Of the 544 patients (91%) who received chemotherapy, most were treated with a platinum doublet (n = 394; 72%). The median RT dose was 62 Gy (range 50 Gy to 84 Gy). With a median follow up of 20 months (45 months in living patients), the median OS was 24 months for the entire cohort. For patients treated with concurrent CRT, only age (P = .04) was significantly associated with OS on UVA, while smoking status (P = .08) and RT dose (P = .1) were borderline significant. There appeared to be a major improvement in OS with increasing RT doses from <60 Gy to >60 Gy (3-year OS 26% versus 37%). Patients who received >70 Gy had the highest 3-year OS of 42%. On MVA, only higher RT dose remained as a strong predictor for better OS (P = .02).

Conclusions: While there may not be a benefit of dose escalation beyond 60 Gy in the setting of concurrent chemotherapy, higher doses may lead to improved OS in patients who are not eligible for concurrent CRT.


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Variability of Interfraction Target Motion During Conventional and Hypofractionated Lung Radiation Therapy
Locally Advanced Non-Small Cell Lung Cancer

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Purpose/Objective(s): Target excision obtained from pretreatment 4D-CT has been used in planning for motion management of lung RT. However, excision can change during RT delivery. This study is to investigate patterns of excursion variability (ΔE) during conventionally fractionated (CRT) or hypofractionated RT (HRT), effect of ΔE on dose reduction, and clinical factors correlated with ΔE.

Materials/Methods: Eighty-four patients with primary or metastatic lung tumors underwent CRT (n = 43) or HRT (n = 41). All patients underwent planning with 4D-CT imaging. Online 4D-CBCT was performed weekly for CRT and pre/post-delivery for each HRT fraction. Respiration-induced target excision was quantified for each 4D-CBCT in 3 directions: anterior-posterior (AP), left-right (LR), and superior-inferior (SI). ΔE was calculated as the excision difference between each 4D-CBCT and the planning 4D-CT. Target dose reduction caused by ΔE was calculated for tumors with ΔE > 4 mm. Pearson correlation was performed to associate clinical factors with ΔE. Continuous variables were analyzed with an independent samples t test and categorical variables with χ².

Results: 844 4D-CBCTs were analyzed (495 CRT, 349 HRT). ΔE was largest in the SI direction overall, with mean (SD) of 0.5 (± 3 mm) (-25 to 17). Mean ΔE (mm) in the SI direction was larger in HRT as compared to CRT, with smaller SD (1.1 [± 2.3] vs 0.03 [± 3.3], P < .001). A similar trend was noted in the AP direction, and no difference was seen in the LR direction. Eleven percent of the 844 4D-CBCTs had ΔE > 4 mm (38% HRT, 62% CRT). For treatments with ΔE > 4 mm, overall mean target dose reduction was largest in the SI direction, -7.4 ± 4.2%. The following factors were significantly correlated with ΔE: age; weight, tumor location, performance status (KPS), smoking history, pre-RT O₂ use, and planning 4D-CT excision. Tumor size and right vs left lung did not correlate. Tumors with ΔE > 4 mm ΔE in any direction were found in younger patients with higher weight and KPS, male gender, and lower lobe (LL) location (Table).

| Thoracic Abstract 143: Table Analysis of mean excursion ≥ or < 4 mm in any direction (for all patients, CRT and HRT) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Variable                                      | ΔE < 4 mm (n = 747) | ΔE ≥ 4 mm (n = 97) | P value |
| Mean Age                                      | 73 (69)            | 88 (88)            | < .001  |
| Mean Baseline Weight (kg)                     | 75.5 (88.8)        | 71 (71)            | < .001  |
| Mean Original Excursion LR (mm)               | 1.4 (1.5)          | 1.1 (1.6)          | .16     |
| Mean Original Excursion SI (mm)               | 1.8 (2.1)          | 1.0 (1.9)          | < .001  |
| Mean Original Excursion AP (mm)               | 4.1 (9.9)          | 3.2 (3.0)          | < .001  |
| Mean Charlson Comorbidity Index               | 2.7 (3.3)          | 2.1 (2.2)          | .03     |
| Total Score                                   | 87 (92)            | 77 (79)            | < .001  |

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Conclusions: The largest degree of $\Delta E$ is seen in the SI direction for both CRT and HRT, causing > 5% target dose reduction in 11% of daily RT deliveries. Target margins designed based only on pretreatment 4D-CT without considering clinical variables could under compensate for target motion during treatment. Large $\Delta E$ seems predictable, and seen more in young patients with higher baseline weight, KPS, male gender, and LL tumors. Online 4D-CBCT provides a means to monitor excursion and adapt RT, and further analysis to optimize timing is underway.


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Metabolic Tumor Volume Change During Radiation Therapy and Late-Course Adaptive Radiation Therapy in Patients With Non-Small Cell Lung Cancer

Locally Advanced Non-Small Cell Lung Cancer

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Purpose/Objective(s): To reduce the risk of radiation toxicity in patients with non-small cell lung cancer (NSCLC), we quantify the metabolic tumor volume (MTV) from baseline to the late-course of radiation therapy (RT) by FDG PET-CT and discuss the potential benefit of late-course adaptive plan by dose volume histogram comparison.

Materials/Methods: Seventeen patients with stage II-III NSCLC treated with definitive conventionally fractionated RT were eligible for this prospective study (NSFC81172133). FDG PET-CT scans were acquired within 1 week before RT (pre-RT) and at about two-thirds of total dose during-RT (approximately 40 Gy). Radiation was delivered using a 3-dimensional (3D) conformal technique, or intensity modulated radiation therapy (IMRT) to match the planning constraints (mean lung dose to <20 Gy and total lung V20 ≤35%, maximal spinal cord dose ≤45 Gy).

MTVs, including primary tumor and any involved hilar or mediastinal lymph nodes were delineated using a method combining the tumor/aorta ratio autosegmentation and CT anatomy based manual editing. A software tool was used to derive a 3-dimensional margin of 10 to 20 mm around the tumor (depending on the location and/or mobility of the MTV), and a margin of 5 mm around any enlarged mediastinal nodes to derive the planning target volume. An original plan based on baseline MTV and adaptive plan based on during-RT MTV was generated for each patient. The dose volume histograms for lung, heart, esophagus and spinal cord were compared between original plan at prescribed dose 66 Gy and composite plan at 66 Gy (original plan at 40 Gy plus adaptive plan 26 Gy).

Results: At the time, about 40 Gy during-RT, MTV were significantly reduced in patients with NSCLC (pre-RT 136.2±82.3 mL vs during-RT 63.4±8.0 mL, $P=0.001$). The composite plan of original plan at 40 Gy plus adaptive plan 26 Gy resulted better dose volume histogram for all the organs at risks we evaluated than the original plan at 66 Gy, including V5, V10, V13, V15, V20, V25, V30 and the mean dose of total lung, V10, V20, V30, V40, V50, V60 and the mean dose of heart, V40, V40-10, V50, V55, V60-maximum dose and mean dose of esophagus ($P<0.05$), and the maximum dose of spinal-cord.

Conclusion: PET-MTV may reduce significantly at the time of about 40 Gy during-RT and late course adaptive radiation therapy maybe an effective way to reduce the dose volume to the organs at risk in patients with NSCLC and deserve further study.


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Correlation of PET/CT Response to the Mediastinal Down-Staging in Operable NSCLC: Impact of RT Dose

Locally Advanced Non-Small Cell Lung Cancer

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Purpose/Objective(s): RT dose escalation resulted in increased mediastinal lymph node (MNC) clearance in patients (pts) with operable stage IIIA NSCLC in RTOG 0229 study and thus an improvement in disease-free survival (DFS) and overall survival (OS). A retrospective comparison of impact of different RT doses on MNC and the correlation of MNC with PET response (SUV: standard uptake value) is performed.

Materials/Methods: Total of 37 pts were evaluated in 2 groups: 15 pts treated with dose escalated RT (DE-RT, 2009-2012) and 22 pts treated with standard RT dose (SD-RT, 2002-2006). All pts were treated with trimodality therapy: preoperative concurrent chemoradiation (CRT) followed by surgery ± adjuvant chemotherapy based on residual disease status. Median age was 63 years (range: 48-78). All pts had mediastinoscopy and PET/CT scans (pre- and postinduction CRT). Median RT doses were 50.4 Gy in SD-RT and 61.2 Gy in DE-RT (range: 40-64). Most common chemotherapy was weekly Carboplatin + Paclitaxel in 31 pts. Lobectomy was done in 22 pts, pneumonectomy in 9, bilobectomy in 3, and wedge resection in 3 pts. Change in SUV for primary and lymph nodes were correlated to pathological response using a paired t test and survival using Kaplan-Meier method. Chi-Square was used to correlate the SUV drop with path CR for primary and LN within each dose group and Breslow-Day test to compare the correlations between the RT dose groups.

Results: Median follow up was 31 months (range: 6-107), with 33 pts in stage III, 4 stage II and 27 had N2 disease (73%). R0 resection was done in 97%. Successful T down-staging was achieved in 60% for total cohort: 53% with DE-RT, 64% in SD-RT (with CR of 24%: 33% vs 18%). MNC was 65%: 67% with DE-RT and 64% (with CR of 51%: 53% and 50%). Adjuvant chemotherapy was given to 61%. Mean drop in SUV for primary tumor after CRT was 9.8 and for LN 0.50. Though the drop in SUV for primary was non-significant based on RT dose ($P=1.0$), but for the LN, DE-RT contributed to higher MNC (6.14 for DE-RT and 1.50 with SD-RT, $P=0.002$). A drop in SUV >3 was noted in 81% for primary ($P=NS$) and 35% for LN (60% with DE-RT, 18% only with SD-RT, $P=0.009$). Correlation between % drop in SUV for primary and LN