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Early Stage NSCLC (ES-NSCLC) with Gross Endobronchial Disease (GED) Predicts for Worse Overall Survival (OS) after Treatment with 5-Fraction Stereotactic Body Radiation Therapy (SBRT)

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Purpose/Objective(s): SBRT is an effective treatment for ES-NSCLC. Central tumors however pose a therapeutic challenge due to proximity to critical organs such as central airways. Five fraction approaches have been advocated to limit treatment induced toxicity. In this report, we evaluate the dosimetric parameters of central airways and identify GED as a predictor of poor overall survival in a diverse cohort of patients.

Materials/Methods: Medically inoperable ES-NSCLC patients were treated with robotic SBRT per institutional protocol. The majority (n=41) underwent bronchoscopy for mediastinal staging, biopsy, fiducial placement and identification of GED. Proximal bronchial tree (PBT) was contoured based on the RTOG atlas, and included trachea (T), mainstem bronchus (MB) and secondary bronchi (SB). Dosimetry for PBT and each of the three subvolumes was analyzed. An additional structure, eval-PBT, was created as the subtraction of GTV from PBT.

Results: From December 2010 to December 2015, 50 patients with biopsy proven ES-NSCLC (stage I-III; stage II – 19) with median age of 75 were treated (50 Gy in 5 fractions). At median follow up of 36 months, OS did not differ between peripheral (n=39) and central tumors (n=11) (54% vs 46%; p=0.41). Local control for peripheral tumors was significantly better than central tumors (94% vs 60%; p=0.018). Of 41 patients who underwent bronchoscopy, five central tumors were found to have GED involving the RUL (n=2), RLL (n=1), LUL (n=1) and LLL (n=1). LC and OS for tumors with GED was 66% and 20%. Cox regression analysis identified GED as a predictor of OS (HR: 4.216, p=0.009). Three patients with GED likely experienced grade 5 bronchial strictures. Median Dmax to PBT was 62.3 Gy (33.7-68) in central tumors. This represented the Dmax to SB. Median Dmax to MB were 12.1 Gy (1.3-37.1) and 30.8 Gy (15.2-68) in central tumors. This represented the Dmax to SB, however remained relatively poor for central tumors. Furthermore, it is likely that high Dmax delivered to PBT resulted in Grade 5 toxicity for central tumors with GED. Future ES-NSCLC SBRT trials should require pretreatment bronchoscopy for central tumors to confirm these preliminary findings and to hone PBT dosimetric constraints.


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Occult Hilar and Mediastinal Nodal Disease for Clinical Early Stage, Node-Negative Non-small Cell Lung Cancer Staged with PET-CT

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Purpose/Objective(s): The aim of this study was to identify clinicopathologic factors that predict for occult hilar and mediastinal adenopathy in patients diagnosed with clinical stage I/II, node-negative non-small cell lung cancer (NSCLC) staged with PET-CT, with the goal to identify a subset of patients who may require additional work-up to identify nodal metastases prior to definitive treatment.

Materials/Methods: Of 5754 patients with lung cancer treated at a single institution between 2008 – 2016 identified from a cancer registry, 143 were included who had NSCLC, staged with PET-CT as clinically node negative, and underwent surgical resection of the primary along with nodal sampling. Patients were excluded if PET-CT read was unavailable, preoperative invasive nodal evaluation was performed, and if they had metastatic disease or prior cancer history. Patients were grouped as pathologically node negative (N=103) or pathologically node positive (N=40). Cox proportional hazards model was used for univariate and multivariate analysis, with all factors significant at p<0.1 included in the multivariate analysis. A propensity score analysis was performed on patients matched 1:1 for age, tumor diameter, tumor location, max SUV of primary and histology.

Results: For the entire cohort of 143 patients, the median age was 65 (34-83), and 60 (42%) were never-smokers. Adenocarcinoma and squamous histology were found in 61.5% and 33.6% of patients, respectively. One-hundred fourteen (78%) had a peripheral tumor, with median diameter of 2.5 cm (0.9-8.2 cm). Fifty-six (39%), 26% and 27% were staged as clinical T1a, T1b and T2a, respectively. Thirty-two (22%) and 6% were diagnosed with pathological N1 and N2 disease, respectively. Thirty-seven (26%) had LSVSI and 22% had visceral-pleural invasion (VPI). On univariate analysis, higher clinical tumor stage (p=0.01), tumor size (p=0.02), central tumor location (p=0.03), higher pathological tumor stage (p=0.008), presence of LSVSI (p<0.0001) and VPI (p=0.02) significantly correlated with occult nodal metastases. On multivariate analysis, higher pathological T stage (p=0.0015) and LSVSI (p<0.0001) correlated with occult nodal metastases. Thirty-nine pairs were analyzed after matching for age, tumor diameter, tumor location, max SUV of primary and histology. Clinical tumor stage (p=0.04) and LSVSI (p<0.0001) correlated with occult nodal metastases on multivariate analysis.

Conclusion: Tumor stage (AJCC 7th edition T1b and higher) and LSVSI predict for occult hilar and mediastinal nodal metastases in patients diagnosed with node negative NSCLC on PET-CT. This data suggests that it is important to identify a pre-surgical correlate with LSVSI. These patients should undergo additional nodal evaluation prior to definitive therapy as they may be upstaged, with vast prognostic and treatment implications.


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Local Consolidative Radiation Prolongs Disease Control of Patients with Oligometastatic NSCLC Harboring EGFR Activating Mutation Treated with First-Line EGFR-TKIs

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Purpose/Objective(s): Most NSCLC patients(pts.) with sensitizing EGFR mutations (L858R, Exon 19 deletion) have an impressive initial response, but most of the patients develop acquired resistance of TKI therapy after 9-14 months. More effective strategies to prevent resistance emergence are needed. For oligometastatic NSCLC patients with sensitive EGFR mutations, the role of local consolidative radiotherapy(LCR) remains debatable.

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The purpose of this study was to investigate the efficacy of LCR in oligometastatic NSCLC pts.

**Materials/Methods:** The records of pts. with initial stage IV NSCLC harboring EGFR mutation with oligometastasis in our Hospital were reviewed. Eligible pts. were treated with first-line EGFR-TKIs or EGFR-TKIs plus LCR (before progression). LCR regimens consist of stereotactic radiosurgery for all the brain oligometastasis and conventional fractional radiotherapy for extracranial metastasis. Overall survival (OS) and progression-free survival (PFS) were estimated by Kaplan-Meier curves.

**Results:** From January 2013 to December 2016, a total of 98 pts. were enrolled, while 49 pts. received first-line EGFR-TKIs plus LCR (LCR group) and 49 pts. received first-line EGFR-TKIs only (non-LCR group).

- The baseline characteristics were well balanced between the two groups.
- In the LCR group (n = 49), the median PFS was 10 months; in the non-LCR group (n = 49), the median OS was also longer in the LCR group (35 vs. 29 months, p = .043).
- Among 98 pts., 64 have undergone brain oligometastases; the median PFS and OS were 17 months and 31 months, respectively, in the LCR group (n = 35) compared to 10 months and 24 months, respectively, in the non-LCR group (n = 29, p = .035; p = .019).
- For pts. with extracranial metastasis (n = 34), the median PFS was 18 months vs. 10 months, favoring the first-line LCR group (n = 14; p = .034); median OS was 43 months in the LCR group vs. 34 months in the non-LCR group (p = .338).

**Conclusion:** Our retrospective data suggest that first-line TKIs plus LCR is a promising therapeutic strategy that led to remarkable PFS improvement and survival benefits for pts. with oligometastatic EGFR-mutant NSCLC, particularly for pts. with brain oligometastasis. Hence, it should be considered as an important medical treatment during clinical management.


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**Radiation Therapy for Locally Advanced Lung Cancer: Which Cases Require Adaptive Planning?**

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**Purpose/Objectives:** The advantages of highly conformal radiation treatments may be negated if patient anatomy changes. Here we characterize the reasons for re-simulation and adaptive re-planning.

**Materials/Methods:** We conducted a chart-review of patients with locally advanced lung cancer treated with chemo-radiation. Inclusion criteria included: dose of at least 50 Gray (Gy), standard fractionation, treated between 1/2016-12/2018. Both small cell and non-small cell lung histologies were included, definitive and neoadjuvant. Exclusion criteria were SBRT, and adjuvant indications. We included patients that underwent re-simulation and adaptive re-planning during the course of treatment, performed at the discretion of the treating physician based upon carina / tumor miss-match on CBCT or if anatomical changes were observed on the CBCT or unsatisfactory simulation technique. Primary tumor (pGTV) and lymph nodes were contoured according to co-registered FDG PET/CT, without elective node irradiation and CBCT was used for IGRT. Reasons for re-planning for classified as:

1. Change in pGTV volume (> 20% compared with first scan)
2. Other major anatomical changes
3. Change of simulation technique (use of breath hold)

Dosimetric parameters of lung V20, mean lung dose (MLD) and volume of heart receiving 40 Gy (heart V40) were compared between first and second plan, after normalizing the prescription dose to 60 Gy. Statistical tests used: paired t test, Wilcoxon test.

**Results:** Out of 248 lung cancer patients, 48 cases underwent re-planning (19%). Male were 79%; histology: SCLC 9/48 (19%) and NSCLC 39/48 (81%). Stage 3a-3b in 92%. Mean radiation dose was 59.8 Gy (SD 3.4); planning technique VMAT 29/48 (60.4%), hybrid 8/48 (16.7%), and 3D-conformal 11/48 (23%). Tumor location was central in 26/48 (54%). Timing of re-planning was 1st third; 2nd third; final third in 23%, 46% and 31% respectively.

1. Changes in pGTV were observed in 41/48 (85%) of pts. pGTV decreased in volume in 36/41 (88%) of pts., mean decrease was -140.6 ml (range -7.7–475 ml). pGTV volume enlarged in 5/41(12%), mean increase: 56.8 ml (range 7-144 ml).
2. Other anatomical changes were observed in 18/48 (37%), including: pleural fluid accumulation, new atelectasis, resolution of atelectasis and absorption of pneumothorax.
3. Change in simulation technique was needed in 9/48 (18.7%) including breath hold or continuous positive airway pressure (CPAP) to expand the normal lung.

Comparing the dosimetric variables between first and second plan: lung V20: 27.1Gy (SD 7.4) vs. 25.6Gy (SD 7) p = 0.07, MLD 15.7Gy (SD 4) vs. 14.7Gy (SD 3.4) p = 0.005, heart V40 was 10.9cc (SD 13.0) vs. 6.5cc (SD 9.5) p = 0.004.

**Conclusion:** Adaptive re-planning was performed in 19% of LA lung pts. who were monitored with daily IGRT-CBCT. In most cases tumor volume decreased or centrally located tumor caused distal atelectasis that resolved. These anatomical changes could potentially lead to increased toxicity and geographical miss, which can be corrected by adaptive re-planning.

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**Patients with ypN2 Non-Small Cell Lung Cancer after Neoadjuvant Chemotherapy Followed By Surgery Can Benefit from Postoperative Radiotherapy- a Retrospective Study of Surveillance, Epidemiology, and End Results Database**

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**Purpose/Objective(s):** Neoadjuvant chemotherapy followed by surgery (NCS) is a common therapy pattern of resectable non-small cell lung cancer (NSCLC). However, for patients with ypN2 disease after aforementioned treatment, there is no evidence that postoperative radiotherapy (PORT) should be adopted or not. Our study is to evaluate the effect of PORT on survival of patients with ypN2 NSCLC after NCS from Surveillance, Epidemiology, and End Results (SEER) database.

**Materials/Methods:** We filtered data from SEER database by the inclusion criteria of patients with NSCLC diagnosed at 2004-2015, treated with NCS, and with ypN2 disease (2004-2009 AJCC 6th, 2010-2015 AJCC 7th). We excluded patients with unclear basic information (such as sex, histology or cause of death), multiple primary malignant tumor and M1 disease. All data were analyzed using statistical analysis software and propensity-score matched analysis was used to match the base-line characteristics between PORT group and non-PORt group. Kaplan-Meier method was used to estimate overall survival (OS) and cancer specific survival (CSS). Univariable and multivariable Cox proportional hazards models were adopted to estimate hazard ratios (HR) of predictors of survival.

**Results:** From 331 patients receiving NCS, 215 meeting the criteria were included in the final analysis. There were 112 patients (52.1%) with PORT. The baseline characteristics of majority were as follows: age≤65 (55.3%), white (82.3%), female (54.4%), grade 3-4 (63.3%), adenocarcinoma (60.0%), tumor size of 3-5 cm (38.6%), lobectomy (80.0%) and positive lymph nodes≥4 (51.2%). There were 200 patients remained after the prosperity score matching between the PORT group and the non-PORT.