**Comparative Effectiveness of Aggressive Locoregional Therapy in Metastatic Lung Cancer: Associations Between High-Dose Thoracic Radiation Therapy and/or Chemoradiation Therapy and Survival in a Large Population-Based Cohort**

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**Purpose/Objective(s):** Palliative thoracic radiation therapy (RT) plays an integral role in the treatment of patients with metastatic non-small cell lung cancer (NSCLC). Randomized trials have suggested that slightly higher dose RT regimens improve overall survival (OS), but data are limited on the benefit of more significant dose-escalation. The evidence supporting concurrent chemoradiation (CRT) in stage IV lung cancer is also scant, and similar to RT dose intensification, aggressive locoregional therapy may theoretically lead to either improved OS or higher treatment-related morbidity or mortality. We aimed to determine the comparative effectiveness of RT dose-escalation and CRT in a population-based cohort with stage IV NSCLC.

**Materials/Methods:** The cohort consisted of 27 063 patients in the National Cancer Database with stage IV NSCLC treated with thoracic RT between 20-55 Gray (Gy) in 2004-2011. High versus intermediate versus low-dose (HD vs ID vs LD, respectively) RT was defined as biologically effective dose (BED 10) above 50 Gy, between 35-50 Gy, and below 35 Gy, respectively. Landmark analysis requiring a minimum of 6 months OS and propensity-score matching were each performed in sensitivity studies to further adjust for confounding. Among patients who received any chemotherapy (CT), a separate analysis was performed to examine the impact of CRT on OS.

**Results:** The median follow-up was 3.9 and 18 months for the entire cohort and surviving patients, respectively. The 5 most common treatment schemes were 30/10 (Gy/fraction, 23% of entire cohort), 35/14 (8%), 37.5/ 15 (7%), 40/20 (3%), and 50/20 (3%). There were 10%, 62%, and 27% in the LD, ID, and HD groups, respectively. Median OS following LD, ID, and HD RT were 1.3, 3.8 and 5.8 months, respectively (P < .001). On MVA the hazard ratios (HR) for HD and IR RT were 0.37 and 0.51, respectively, compared to LD RT (P < .0001). There were no OS differences among the various dose regimens in the HD cohort. On landmark analysis for patients surviving at least 6 months, the OS advantage of HD (HR = 0.74 vs LD, P < .0001) but not ID RT (HR = 0.94, P = 0.25) was preserved. Propensity score matching resulted in a final cohort of 3 765 patients, with 33% each in the three groups; the superior HR for ID and HD were maintained (0.41 and 0.57 for HD and ID RT, respectively, vs. LD, P < .0001). Among those who received any CT (59% of total), the median OS for patients treated with CRT (19% of total) was 5.3 vs 5.6 months (P = .667). On MVA, the HR for CRT was 1.01 (P = .46).

**Conclusion:** The delivery of higher-dose RT, but not concurrent chemotherapy, was associated with a significant improvement of OS. This population-based study supports higher dose palliative regimens and motivates prospective study of escalation beyond 35 Gy; however, CRT does not appear to provide additional survival benefit in this compromised population.