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# Radiation Oncology Strategies for Patients with Poor Pulmonary Function in Non-small Cell Lung Carcinoma

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## Abstract

Lung cancer is the leading cause of cancer deaths worldwide. Recently, there is an emerging interest on lung cancer screening which can increase the incidence of lung cancer among the population in the coming. There was 20% reduction in mortality from lung cancer in the National Lung Screening Trial (NLST) with the use of low-dose computed tomography. NLST criteria included people between ages 55-74 years, ≥30 pack-years of smoking or <15 years since cession of smoking. Patients with early stage disease and young age, good performance status and pulmonary function tests are treated with curative intent including either surgery or combined treatment modalities, concurrent chemo-radiation therapy. Treatment of choice for medically inoperable group of patients is definitive radiation therapy (RT). Patients with poor pulmonary function (PF) are considered a contraindication to definitive RT. We discuss the role of RT and importance of dose escalation to achieve improved local control rates among patients with different stages of non-small cell lung carcinoma (NSCLC) with poor PF. Till date, there are no clinical practice guidelines or randomized prospective phase III studies to treat this subset of high-risk patients with RT dose escalation using advanced RT techniques like intensity modulation radiation therapy, volumetric modulated arc therapy (IMRT, VMAT). Also, there is limited evidence on the use of newer chemotherapy regimens with advanced RT techniques for NSCLC patients with poor PF except for retrospective data or phase I/II studies. Different tools to estimate and measure radiation pneumonitis (RP) along with the review of the published data on RP was done. Impact of newer RT techniques along with adaptive RT using mid-course PET scans for RT planning using photons and protons are also addressed.

**Keywords:** Radiation pneumonitis; NSCLC; High-risk patients; Pulmonary function tests; SBRT; LA-NSCLC

## Role of Radiation Therapy (RT) and RT Dose Escalation on Outcomes for Non-small Cell Lung Carcinoma (NSCLC)

Several published series from North America, Europe and Asia demonstrated that stereotactic body radiation therapy for early stage NSCLC (stages I-II) treated to biologically equivalent doses (BED) of ≥100 Gy [1-3] have shown improvement in local control rates, 90-98%. The local recurrence rates noted with conventional radiation therapy doses (60-66 Gy) ranged 6.4-70% (median of 40%) among the pooled data from 18 published series treated between 1988-2000 for stage I inoperable NSCLC patients [4]. Locally advanced operable patients with Stage IIIA NSCLC (98% N2 disease) treated with dose escalation RT to a dose of 61.2 Gy resulted in higher mediastinal nodal clearance (MNC) rates in RTOG 0229 study [5]. The MNC was 63% and the 2-year progression free survival (PFS) was 33 months for patients with MNC compared with only 14 months in those patients who did not achieve MNC, which also translated into improvement in the 2 year overall survival (OS) rates, 67% versus 54%. There was diversity in the outcomes about the benefit of dose escalation in inoperable locally advanced NSCLC treated with definitive RT. In a phase I study from University of Michigan by Kong, an RT dose of >74 Gy resulted in improvement in overall survival [6]. With each 1 Gy increment of RT dose, the 5-year local control improved by 1.25% and the risk of death decreased by 3%. In a Radiation therapy oncology group (RTOG) group analysis of 1390 patients, RT dose escalation was associated with improvement in loco-regional control rates [7]. A recent RTOG 0617 showed worse outcomes with poor OS in the 74 Gy arm compared with 60 Gy arm [8]. Median overall survival was 28.7 versus 19.5 months and the 18-month overall survival rate was 67% versus 54%, $p<0.001$, for the 60 and 74 Gy arms, respectively. Additionally, concurrent chemo-radiation therapy was proven to be superior to sequential CRT in the meta-analysis [9] by Auperin with an absolute benefit in overall survival (OS) at 2, 3, and 5 years of 5.3%, 5.7% and 4.5%. There was increase in incidence of grade 3-4 esophageal toxicity in concurrent CRT patients of 18% versus 4% in the sequential group, but there was no difference in the incidence of grade 3-4 pulmonary toxicities.

## What are the Concerns to Treat High Risk Patients with RT?

Poor pulmonary function (PF) is considered a contra-indication to definitive radiation therapy with a challenge on the feasibility of radiation as a treatment option for these patients. The important challenge in these patients is the ability to complete the planned course of treatment without any treatment breaks or delays, particularly in the past when older radiation methods were used. Use of modern RT techniques using multiple beams helps to limit the dose to the surrounding normal tissue compared with the typical postage stamp fields but needs expertise in the use and delivery of these newer RT methods. It is also important to integrate these newer methods along with emerging newer chemotherapy molecules as there only limited

safety data available till date. Impact of RT on early and late radiation induced lung toxicity (RILT) among high-risk patents needs to be studied in phase III studies utilizing the validated standard tools to estimate radiation pneumonitis (RP). Most commonly used tools used in the past to measure RP were RTOG late effects in normal tissue-subjective objective management analysis for late lung injury (LENT-SOMA) [10] and the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 (NCI CTCAE 4.0). Recently, the most clinically meaningful endpoint for RP was established by the quantitative analysis of normal tissue effects in the clinic (QUANTEC), [11].

## Risk Factors for Radiation Pneumonitis

Known patient related factors [12-14] contributing to high risk for RP are age, gender, Karnofsky's performance score (KPS), smoking status, presence of co-morbidities [13,14]. Females are knows to have more RILT. Association of socio-demographic factors with RP was studied in 1450 patients treated in 9 RTOG studies [13] by Movsas et al. On multivariate analysis, factors predictive of ≥grade 3 RILT were lower lobe primaries, married/live-in relationship, presence of family/friends with cancer, the interaction of high KPS with female sex. Other treatment related factors contributing to RP were addition of chemotherapy (sequential versus concurrent), radiation dose-volume parameters like MLD (mean lung dose), V20 (volume of lung receiving 20 Gy), NTCP (normal tissue complication probability) of the lung tissue. Plasma levels of TGF-β (transforming growth factor beta) and IL's (interleukins) levels are studied in pre-clinical and clinical studies [14] correlating with RILT. It was hypothesized that vascular endothelial cells which are known important targets of radiotherapy may be involved in the pathogenesis of RP. Variations in the levels of circulating endothelial progenitor cells (EPCs) and TGF-β1 during radiation therapy in patients with NSCLC and the correlation with RP was studied in a prospective study. Early variations (at weeks 2 and 4 of RT) of EPCs and TGF-β1 were significantly associated with the risk of RP (P<0.01), [15].

## SBRT for High-Risk Stage I NSCLC: Impact on Outcomes and RT Pneumonitis

Poor baseline PFT alone should not be considered an exclusion criterion to treat early stage NSCLC with SBRT. Primary analysis of the RTOG 0236 data showed the 3-year primary tumor control of 98% in 59 medically inoperable T1-T2N0M0 peripheral NSCLC patients treated with SBRT to 18 Gy in 3 fractions to a total dose of 54 Gy [2]. A secondary analysis [16] was done among 55/59 patients with the evaluation of pulmonary function changes after SBRT. A baseline PFT's and the change in PFT's at 6 weeks, every 3 months for 2 years was analyzed to see the difference in the pattern of symptomatic radiation lung toxicities. The NCI CTCAE v3.0 was used for grading adverse vents along with modified RTOG SBRT pulmonary toxicity scale. Baseline FEV1 <40% predicted (forced expiratory volume in 1 second) was noted in 35% of patients, severely reduced DLCO (diffusion capacity of lung for carbon monoxide) in 40%, severe cerebro-vascular disease in 44%, and 69% with more than one condition. A change of atleast 15% in PF was considered significant for RP. At 2 years of follow-up, mean percentage predicted FEV1 (mean: 60.8% at base line and 51% at 2 years) and DLCO (mean: 60.7% @ baseline versus 46.6% at 2 years) declines were 5.8% and 6.3% and ≥70% of patients had no decline in PFT results. Majority of patients had grade 0 or 1 PFT changes at 2 years with no significant change in oxygen saturation. Logistic regression analysis performed showed baseline PF tests were not predictive of pulmonary toxicity following SBRT. There was no relationship between RT pneumonitis and normal lung tissue doses, V5, V10, V20 (volume of lung receiving 5, 10, 20 Gy levels) and MLD (mean lung dose). There was no difference in overall survival (OS) noted among patients with % predicted FEV1 above and below the mean value (60.7%), p=0.27. Medically inoperable patients with poor baseline PF had a trend for better OS, with a median survival of 48 months versus 32 months for patients with normal baseline PF along with cardiac, other co-morbid conditions. A pooled data from 5 international institutions [17] was analyzed for clinical outcomes and PF changes among 411 patients with early stage NSCLC. Median FEV1 was 1.4 L (65% predicted), median DLCO was 11.7 mL/min/mmHg (53% predicted). Two year OS was 64% for all patients and grade 2 pneumonitis was noted in 6%. MLD predicted for grade 2 RP was 6.9 Gy (p=0.01). There was no correlation between pre-treatment PFT and more than grade 2 pneumonitis. Correlation with the RT dosimetric parameters and PF changes were evaluated by the same authors in 191 patients with early stage NSCLC (T1-3N0M0) [18]. Median tumor size was 2.4 cm (maximum of 8.5 cm, and the median RT dose was 54 Gy delivered in 3 fractions. MLD was 5.6 Gy. Outcomes were measured using Lyman's NTCP (normal tissue complication probability) model. The PTV doses were converted to biologically effective doses and lung doses to 2 Gy equivalent doses before correlation analyses. Loss of FEV1 >10% within 6 months was noted among 27% (median change -1.4%) while a DLCO drop of >10% was noted in 41% of patients (median change -7.6%). There was no statistically significant correlation noted with relative early and late PFT changes and RT parameters like V5-V45, MLD apart from GTVmax dimension (gross tumor volume) and PTV mean dose (planning target volume).

Phase I-II studies on RT dose escalation done for LA-NSCLC utilized different scoring systems [19] to document radiation pneumonitis like, RTOG, SWOG (south west oncology group), NCI-CTC (National Cancer Institute-Common Toxicity Criteria) and CALGB (Cancer And Leukemia Group B). The reported incidence of grade 2 RP varied 11-21% and grade 3 RP was 16-31%. Predictors of radiation pneumonitis and fibrosis [20] were evaluated in a dose escalation study by Kong et al in 109 patients with medically inoperable and LA-NSCLC patients treated to a maximum RT dose of 103 Gy. Eighty four patients were treated to >69 Gy (77%). Grade 2 or 3 RP was noted in 14.6% and grade 2 or 3 fibrosis noted in 13.8%. On multivariate analysis (MVA), lung-dosimetric parameters were associated significantly (p<0.001) with RP, like MLD, V20 and the NTCP of the lung. A pooled analysis of data from University of Michigan and China in 260 patients with stage I-III NSCLC patients treated between years 2001-2009 with 3 dimensional conformal radiotherapy techniques (3D CRT). The incidence of RP in patients with poor pulmonary function [21] was estimated with an assessment of baseline pulmonary function tests, FEV1 (forced expiratory volume in 1 second), diffusion capacity of lung for carbon monoxide (DLCO), forced vital capacity (FVC) along with the DVH parameter, mean lung dose (MLD). The primary end point was symptomatic RILT (SRILT), including ≥grade 2 RP and fibrosis. COPD was noted in 28% of patients and 91% patients had stage III disease. Median age was 65 years. MLD was 15 Gy and the optimal cutoff points for FEV1, DLCO and FVC were 65.1%, 65.8% and 72.1%. MLD for SRILT was 16.4 Gy but 14.8 Gy for non-SRILT patients (p=0.004). At an MLD cutoff of 17.4 Gy, the RILT was 17.6% for patients with low MLD and 38.7% for high MLD (p=0.001). On multivariate analysis (MVA), MLD and age (65 years) were associated with SRILT. They created a MLD- based

model to predict the SRILT using age, MLD and FEV1 and categorized the RP into low-risk, moderate-risk and high-risk groups. This model showed slight improvement in predicting the SRILT.

An International data meta-analysis [22] on 836 patients with LA-NSCLC treated with concurrent chemo-radiation therapy evaluated the clinically significant predictors of RP. Additionally, recursive partitioning analysis (RPA) was used to define the risk groups. Overall rate of symptomatic RP was 29.8%, with fatal pneumonitis of 1.9%. The median RT dose was 60 Gy. Type of chemotherapy regimen (Carboplatin/Paclitaxel based) and V20 were significant for symptomatic RP on MVA with a trend for age. On RPA, the highest risk of RP (>50%) was seen in patients greater than 65 years of age receiving Carboplatin/Paclitaxel. Predictors of fatal pneumonitis were daily RT dose >2 Gy, V20 and lower lobe tumor location.

## RT Strategies to Reduce the Risk of RP and Improve Clinical Outcomes?

Several radioprotective agents were used in the past to reduce the risk of radiation injury to the lung and found to be not beneficial in preventing RP. Amifostine was tried in three phase III studies [23-25] but has not shown any advantage. Technological advances like improved patient immobilization, quantifying respiratory motion using 4D CT simulation to generate the internal target volume (ITV), image guidance tools like daily CBCT will all help in reducing the expansions around the GTV and CTV, thus reducing the size of PTV will help to minimize the risk for RP and also enhance radiation delivery to tumors. Adaptive radiation therapy using mid-course PET (positron emission tomography) scan for radiation therapy planning is being incorporated into the upcoming and ongoing clinical trials to achieve RT dose escalation and reduce the risk of RP. A phase II RTOG 0515 study [26] by Bradley et al compared the GTV volumes with or without PET/CT fusion for RT planning for 52 NSCLC patients treated with definitive RT (≥60 Gy). The GTV was statistically significantly smaller for PET/CT derived plans (98.7 versus. 86.2 mL; $p<0.0001$) compared with CT alone based planning and the MLD was smaller for PET/CT based plans (19 versus. 17.8 Gy; $p=0.06$). There was no difference in the number of involved lymph nodes or mean esophageal doses. Only one patient developed elective nodal failure. Changes in PET scan during treatment and the drop in SUV (standardized uptake value) was correlated with clinical outcomes [27] in a phase I study by FM Kong from university of Michigan. RTOG 1106/ACCRIN 6697 study [28] is currently recruiting patients to treat with RT dose escalation with the use of mid-course PET scan at 40-46 Gy level in patients with inoperable, LA-NSCLC. The primary end point is to determine if the dose can be escalated using mid-course PET/CT scan to improve the local-regional, progression-free survival at 2 years. Preliminary data using proton therapy with dose escalation on reducing the incidence of radiation pneumonitis is promising. A phase II study done by Chang from MD Anderson cancer center for 44 LA-NSCLC patients treated with dose escalation RT [29] (74 Gy, radiobiologically equivalent, along with concurrent weekly Carboplatin and Paclitaxel) with proton therapy utilizing PET/CT for adaptive RT planning. One of 44 patients developed grade 3 radiation pneumonitis. Comparison of adaptive and non-adaptive RT planning done with the use of mid-course PET/CT scan showed an improvement in sparing the esophagus and the dose to spinal cord was less. There was no difference in the incidence of grade 3 radiation pneumonitis among the two groups of patients [29,30]. But there are no studies done so far to evaluate the benefit of dose-escalation using proton therapy for the high-risk patients.

## Conclusions

Radiation therapy is an important part of treatment for both early and locally advanced NSCLC. Use of modern techniques with image guidance helps to reduce the volume of normal tissues being in the RT fields and thus minimize the risk of symptomatic radiation related lung toxicities even in high-risk patients. Type of chemotherapy regimen has shown an impact on RP and it is important to sequence the treatment pattern for high-risk patients. Multidisciplinary team care involving radiation oncology, medical oncology and pulmonology teams, and a close monitoring for RT pneumonitis among these patients helps to evaluate RP early and thus reduce the chances of grade 4 or 5 morbidities or mortality even in high-risk patients.

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