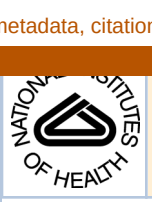



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# Predicting Radiation Pneumonitis after Chemoradiotherapy for Lung Cancer: An International Individual Patient Data Meta-analysis

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## Abstract

**Background—**Radiation pneumonitis is a dose-limiting toxicity for patients undergoing concurrent chemoradiation therapy (CCRT) for non-small cell lung cancer (NSCLC). We performed an individual patient data meta-analysis to determine factors predictive of clinically significant pneumonitis.

**Methods—**After a systematic review of the literature, data was obtained on 836 patients who underwent CCRT in Europe, North America and Asia. Patients were randomly divided into training and validation sets (2/3 vs. 1/3 of patients). Factors predictive of symptomatic pneumonitis (grade ≥ 2 by one of several scoring systems) or fatal pneumonitis were evaluated using logistic regression. Recursive partitioning analysis (RPA) was used to define risk groups.



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Conflict of Interest Statement

Dr. Palma was the recipient of the 2009 Canadian Association of Radiation Oncologists' Elekta Research Fellowship. Dr. Senan has received research funding from Sanofi-Aventis, speaking honoraria from Varian Medical Systems Inc, has a departmental master research agreement with Varian Medical Systems Inc,, and is a member of the trial management group for the phase III PROCLAIM study, which is sponsored by Eli Lilly.

**Results—**The median radiotherapy dose was 60 Gy, and median follow-up was 2.3 years. Most patients received concurrent cisplatin/etoposide (38%) or carboplatin/paclitaxel (26%). The overall rate of symptomatic pneumonitis was 29.8% (n=249), with fatal pneumonitis in 1.9% (n=16). In the training set, factors predictive of symptomatic pneumonitis were lung volume receiving ≥20 Gy ($V_{20}$) [OR:1.03 per 1% increase, p=0.008], and carboplatin/paclitaxel chemotherapy [OR:3.33, p<0.001], with a trend for age [OR: 1.24 per decade, p=0.09]; the model remained predictive in the validation set with good discrimination in both datasets (c-statistic>0.65). On RPA, the highest risk of pneumonitis (>50%) was in patients >65 years of age receiving carboplatin/paclitaxel. Predictors of fatal pneumonitis were daily dose >2 Gy, $V_{20}$, and lower-lobe tumor location.

**Conclusions—**Several treatment-related risk factors predict the development of symptomatic pneumonitis, and elderly patients who undergo CCRT with carboplatin-paclitaxel chemotherapy are at highest risk. Fatal pneumonitis, although uncommon, is related to dosimetric factors and tumor location.

### Keywords

Non-small cell lung cancer; radiotherapy; chemotherapy; pneumonitis

## INTRODUCTION

Concurrent chemoradiotherapy (CCRT) is the standard of care in patients presenting with a locally advanced non-small cell lung cancer (NSCLC), as the role of surgery in patients with documented mediastinal nodal disease remains controversial (1). Compared to sequential chemotherapy and radiation therapy, CCRT results in improved survival outcomes, at the cost of increased acute toxicity (1). Currently, a number of different radiation schedules and chemotherapy combinations are in clinical use for CCRT.

Symptomatic radiation pneumonitis is a clinically important toxicity, occurring in 15–40% of patients receiving CCRT for NSCLC (2). The risk of pneumonitis limits the radiotherapy dose that can be safely delivered and the size of the volumes treated. Radiation pneumonitis can limit quality of life, and uncommonly result in oxygen dependence or death (2).

Several studies have identified relationships between baseline patient- or dose-related factors and rates of radiation pneumonitis (2), but predictive models have not been widely implemented for several reasons: many earlier studies included heterogeneous groups of patients not necessarily applicable to modern NSCLC treatment (i.e. patients treated without chemotherapy, with older radiotherapy techniques, or for non-lung malignancies); correlations between baseline variables and pneumonitis outcomes are generally weak; and results are rarely validated in separate datasets (2, 3). As a result, the ability of a physician to predict the risk of clinically significant pneumonitis for any particular patient is limited.

Recently, the Quantitative Analysis of Normal Tissue Effects in Clinic (QUANTEC) project reviewed more than 70 published articles to provide normal-tissue dose constraints for radiation-induced lung injury (4). Due to inconsistent relationships between patient- and treatment-related factors and pneumonitis risk, QUANTEC recommended the pooling of individual patient data from many institutions to undertake meta-analyses in an effort to overcome some of the limitations of previous studies. Consequently, we undertook a collaborative project entitled “Systematic analysis of toxicity after radical irradiation: pneumonitis and esophagitis” (STRIPE) to combine patient-level data from several institutions worldwide. The goal of this first component of the STRIPE project was to develop and validate a predictive model for radiation pneumonitis in patients receiving modern CCRT for the treatment of locally-advanced NSCLC.

## METHODS

A systematic review was conducted to identify articles published in MEDLINE between 1993 and August 2010 reporting on dosimetric predictors of radiation pneumonitis after CCRT for non-small cell lung cancer. Reference lists from candidate articles were hand-searched for additional articles, and international experts were individually contacted to identify additional published or unpublished datasets. Authors were then contacted and invited to submit datasets with individual patient data, whether published or unpublished. The search strategy and results are shown in Online Appendix 1. Institutional Research Ethics Board approval was obtained.

Patients were included in the analysis if they were treated with concurrent chemoradiotherapy for NSCLC with radical intent. Patients who did not receive full-doses of radiation due to the development of toxicity *during* treatment remained included. Two-dimensional radiotherapy was not allowed; radiotherapy had to be delivered as three-dimensional conformal radiation therapy or intensity modulated radiation therapy. Patients who received either induction (or neoadjuvant, prior to CCRT) or adjuvant (after CCRT) chemotherapy were permitted. Patients were excluded from the analysis if the histology was small-cell lung cancer, if they had stage IV disease, or if they underwent surgical resection. Patients were staged according to the American Joint Committee on Cancer (AJCC) sixth edition.

The primary endpoint of this study was symptomatic radiation pneumonitis, defined as: Grade 2 or higher as per the Common Terminology Criteria for Adverse Events [CTC-AE] version 3.0 (i.e. symptomatic), and/or requiring steroids. In individual datasets, the scoring systems used including CTC-AE versions 2 and 3, the Radiation Therapy and Oncology Group (RTOG) scale, the Southwest Oncology Group scale, and two in-house scales. In each of these scoring systems, any patient scored as having Grade ≥2 pneumonitis equivalent was scored as meeting the primary endpoint in this current study. The timing of pneumonitis was not widely available; therefore actuarial rates were not reported.

The volume of lung considered as the organ at risk (OAR) was defined as the total lung volume minus the gross tumor volume [i.e. total lung – GTV]. For patients whose $V_{20}$ data was only available using the definition of lung OAR as total lung minus planning target volume [i.e. total lung – PTV], the corresponding "total lung – GTV" values were calculated by imputation based on a linear relationship between the two definitions, which was found to be a good fit with r=0.988. The resulting equation for V20 was: V20(lung-GTV) =3.02528 + 1.00823*V20(lung-PTV); indicating that a patient with a V20 of 30% using the lung-PTV definition would have a V20 of 33.3% using the lung-GTV definition; a similar imputation was done for mean lung dose (MLD). Six patients had only data with the lung OAR defined as the total lung volume minus clinical target volume [i.e. total lung – CTV], and these patients were excluded as there was insufficient data for imputation. Performance status was scored by different institutions using either the Eastern Cooperative Oncology Group (ECOG) scale or the Karnofsky Performance Scale (KPS). In order to combine these into a single variable, patients were classified patients as having "Good performance status" (ECOG 0–1 or KPS 70–100) or "Poor performance status" (ECOG >1 or KPS <70).

For the endpoint of symptomatic pneumonitis, patients were randomly divided into a training set (two-thirds of patients) and a validation set (one-third of patients) using a random number generator, without stratification. In the training set, logistic regression was used to determine factors predictive of pneumonitis. Any variables associated with the development of pneumonitis on univariable analysis (with a cutoff alpha of 0.10) with data available for at least two-thirds of patients were considered for entry into a stepwise

multivariable model with entry and removal allowed at the 10% level of significance. Data was required on two-thirds of patients since patients with missing data are excluded from multivariable logistic modeling. The performance of the multivariable model was then evaluated using the validation set.

A recursive partitioning analysis (RPA) was then constructed in the training set to stratify patients into risk groups. This RPA is independent of the multivariable analysis described above. The classification method of recursive partitioning was used, with a minimum number of observations per node of 20 before a split was considered, and a default number of minimum observations of 7 in a terminal node. This RPA stratification was then re-tested on the validation set. RPA was done independently of the multivariable analysis. RPA cutoffs were rounded to increase clinical utility.

For the endpoint of fatal pneumonitis, there were insufficient numbers of events to allow for modeling with a training and validation set, and therefore the dataset was analyzed as a whole. For this endpoint, logistic regression was used for continuous variables and Fisher's exact test used for categorical variables.

Survival estimates were calculated using the Kaplan-Meier method, and median follow-up was calculated using the reverse Kaplan-Meier estimate. All statistical tests were two-sided with a $p \leq 0.05$ indicative of statistical significance, done using SAS 9.2 (Cary, North Carolina, USA) or R 2.13 (Vienna, Austria).

## RESULTS

Data was available on 836 patients from 12 different sources (Table 1), all previously reported in whole or in part, including 10 manuscripts (3, 5–13) and 2 abstracts (14, 15), some of which provided updated datasets. The final composite dataset included patients treated at centers in Europe (n=297, 36%), North America (n=286, 34%) and Asia (n=253, 30%). Baseline clinical characteristics are shown in Table 2. The median total dose delivered was 60 Gy, most often in fractionated doses of 2 Gy per day (73%), 1.8 Gy per day (13%) or 1.2 Gy twice daily (8%). Median follow-up was 2.3 years. There were 415 deaths in the cohort during the follow-up period, with a median overall survival (OS) of 1.7 years, 2-year OS of 44% and 5-year OS of 22%. The overall rate of symptomatic pneumonitis was 29.8% (n=249).

Most patients received concurrent cisplatin/etoposide (38%) or carboplatin/paclitaxel (26%). 'Other' chemotherapy regimens included: cisplatin doublets (24%) [with docetaxel (11%), vinorelbine (7%), gemcitabine (2%) or other drugs (4%)], carboplatin doublets (5%), or gemcitabine (6%). Elderly patients (age >65) were more likely to receive 'other' types of chemotherapy (delivered to 43% of elderly patients vs. 32% of younger patients; p=0.02), corresponding to less use of cisplatin-etoposide in elderly patients (32% vs. 42%, respectively), with similar rates of use of carboplatin-paclitaxel (25% vs. 26%, respectively).

Results from the univariable analysis and multivariable analysis on the training dataset (n=557) are shown in Table 3. On multivariable analysis, factors predictive of development of radiation pneumonitis were $V_{20}$ [odds ratio (OR) 1.03 per 1% increase in $V_{20}$, p=0.008], chemotherapy regimen [OR for carboplatin/paclitaxel 3.33, relative to cisplatin-etoposide; p<0.001], and with a trend toward significance for advanced age [OR per 10-yr increase 1.24, 95% CI 0.97–1.59, p=0.09]. The c-statistic for this model was 0.66, indicating good discrimination.

Assessment of the model on the validation set (n=279) is shown in Table 4, with very similar results as in the training set: chemotherapy and $V_{20}$ significantly predicted

pneumonitis risk (both p<0.001) with a trend toward significance for age (p=0.089), with similar ORs as in the training set, and the c-statistic of 0.69 confirmed good discrimination. The risk of pneumonitis based on cutoffs of $V_{20}$ for the whole cohort combined is shown in Table 5.

Results of the STRIPE recursive partitioning analysis are shown in Figure 1. Based on chemotherapy regimen, age>65, $V_{20}$, and MLD, patients can be divided into a high-risk group (patients >65 years of age receiving carboplatin-paclitaxel); two intermediate-risk groups; and two low-risk groups. The differences in pneumonitis rates between these groups was statistically significant (p<0.001). Application of the categories formed by the RPA to the validation set was consistent with those by the training data set. There was a strong correlation ($r^2$=0.902) between the pneumonitis rates in the training and validation sets in each of the risk categories, and the differences in pneumonitis rates between the risk groups remained statistically significant.

Fatal pneumonitis occurred in sixteen patients (1.9%), an insufficient number to allow for detailed modeling with a training and validation set, or construction of a RPA model, and therefore the dataset was analyzed as a whole. Total daily dose greater than 2 Gy (7% if >2 Gy vs. 1.5% if ≤ 2Gy; p=0.01), $V_{20}$ (OR 1.09 per 1% increase, p=0.044), and tumor location (1% for upper lobe, 0% for middle lobe, and 5% for lower lobe, p=0.007) were found to be associated with fatal pneumonitis.

## DISCUSSION

The onset of radiation pneumonitis after radical CCRT for NSCLC is associated with significant morbidity and occasionally mortality. To our knowledge, this is the largest study evaluating predictors of radiation pneumonitis following CCRT for lung cancer; it is one of very few studies employing separate training and validation datasets; and importantly it identifies several treatment-related variables that can be used to optimize the therapeutic ratio in patients undergoing CCRT. A key finding is the suggestion that age, dosimetric parameters, and choice of chemotherapy regimen can allow for significant stratification of radiation pneumonitis risk. Although fatal pneumonitis isuncommon, it was associated with large daily doses, high $V_{20}$ values, and lower-lobe tumors. As a result, efforts to minimize $V_{20}$ and fraction size are warranted in the setting of concurrent CCRT.

The findings of this study are congruent with the existing literature regarding pneumonitis risk, and extend those findings in several important ways. Increasing age and delivery of concurrent taxane-based chemotherapy have been separately identified as risk factors for radiation pneumonitis (4, 16, 17). Taxanes are potent radiosensitizers when given concurrently with radiotherapy (16, 17). A recent study of a cohort of lung cancer patients predominantly treated with carboplatin-paclitaxel CCRT found that both chemotherapy use and age were associated with large increases in pneumonitis risk: the incidence of pneumonitis in patients receiving chemotherapy was 63% (vs. 16% in patients not receiving chemotherapy) with a trend toward increased risk in patients receiving carboplatin-paclitaxel specifically. Pneumonitis occurred in 77% of patients aged 61–70, with lower rates in patients of different ages (16). These data support the finding that the choice of chemotherapy regimen plays an important role in pneumonitis risk, particularly in the elderly.

Several chemotherapy regimens are available for concurrent CCRT, and the choice of chemotherapy regimen is the subject of some controversy. Several platinum-based chemotherapy regimens have demonstrated encouraging clinical outcomes (1). In the context of palliative chemotherapy, a meta-analysis has demonstrated that cisplatin is a more

active first-line treatment against NSCLC than carboplatin: cisplatin achieves superior response rates, and in some subgroups improved survival (18).. The carboplatin-paclitaxel CCRT combination has been compared in a 3-arm randomized non-inferiority study against irinotecan-carboplatin and mitomycin-vindesine-cisplatin, with the latter considered the "standard" arm (19). All three arms received 60 Gy of radiation, but the "standard" arm incorporated split-course radiotherapy. Although survival outcomes were similar in all 3 arms, the non-inferiority endpoint was not met. Grade 3 or higher pneumonitis rates were not statistically different between the arms, whereas rates of grade 2 pneumonitis, or rates in elderly patients, were not reported. The National Comprehensive Cancer Network (NCCN) clinical practice guidelines recommend cisplatin-etoposide as the chemotherapy of choice for CCRT, with carboplatin-paclitaxel reserved for patients unable to tolerate full-dose cisplatin (1)., Although efficacy is of primary importance in choosing a chemotherapy regimen, avoidance of toxicity should also be a consideration.

The findings of this study must be considered in the context of its strengths and limitations. The large sample size that incorporates data from several institutions worldwide improves statistical power and the generalizability of the results, and the results have been validated in a separate dataset. However, several important limitations must be borne in mind. Adequate data was not available on some variables of interest, such as smoking status, co-morbidities, pulmonary function, and timing of radiation pneumonitis symptoms, and some data required imputation, which may have added a degree of imprecision. Some factors were not routinely captured at most institutions, including baseline patient factors (e.g. pulmonary function), biological factors (e.g. transforming growth factor beta levels), or more detailed dosimetric factors (e.g. normal tissue complication probabilities), which have been previously suggested as a predictors of pneumonitis risk (2). Individual-level chemotherapy dosing was generally not available. There may also be differences between patients treated at different institutions that have not been captured, including differences in genetic risks of pneumonitis, treatment factors, or follow-up practices. Some of these unmeasured factors could have influenced the final results. These findings described may not be generalizable to patients with baseline characteristics or treatment parameters that differ from the population included herein, such as the patients aged>75, who are a minority of the patients included. These limitations underscore the importance of developing multi-institutional databases that can be populated prospectively, to allow for the construction of more detailed prediction models. Despite these limitations, the data presented here showing strata of risk based on $V_{20}$, MLD, and other clinical factors will allow clinicians to better predict and modify risk in patients undergoing CCRT.

The overall rates of radiation pneumonitis reported herein are in keeping with previously published CCRT studies, usually ranging between 15–40% for similar patient populations (2). One study of radiation dose escalation in combination with carboplatin-paclitaxel (RTOG 0117) reported a maximum tolerated dose of 74 Gy in 37 fractions in patients with a $V_{20} \leq 30\%$; at this dose level 33% of patients developed grade 2 or higher pulmonary toxicity. At a higher dose level (75.25 Gy in 35 fractions), 6/8 patients developed pulmonary toxicity, illustrating the dose-limiting effects of radiation pneumonitis (20). However, comparisons of pneumonitis rates across studies are limited by heterogeneity in patient populations, treatment, and outcome scoring.

Several previous studies have reported correlations between radiation dosimetric parameters and pneumonitis. $V_{20}$ and MLD are frequently correlated with pneumonitis and are most commonly used in clinical practice, yet other variables have been shown to be predictive, including volume of lung receiving ≥5 Gy (V5), ≥13 Gy (V13), ≥25 Gy ($V_{25}$) and ≥30 Gy ($V_{30}$) (2). However, dosimetric variables tend to be very collinear (i.e. increasing $V_{20}$ tends to lead to an increase in the other parameters), and therefore differences in predictive value

among different dosimetric variables may be small. The relative merit of decreasing one dosimetric variable (e.g. lowering the $V_{20}$) at the expense of another (e.g. raising the $V_5$) is unknown.

In conclusion, this study suggests that in patients undergoing concurrent chemoradiation therapy for NSCLC, pneumonitis risk is associated with the type of chemotherapy regimen, dosimetric parameters, and patient age. Fatal pneumonitis is uncommon, but is associated with large doses per fraction, large $V_{20}$, and lower-lobe tumors. Further research is needed to evaluate methods to mitigate pneumonitis risk in patients undergoing curative-intent CCRT.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Summary

Radiation pneumonitis is a dose-limiting toxicity for patients undergoing concurrent chemoradiation therapy (CCRT) for non-small cell lung cancer. This individual-patient data meta-analysis demonstrated that several treatment-related risk factors predict the development of symptomatic pneumonitis, and elderly patients who undergo CCRT with carboplatin-paclitaxel chemotherapy are at highest risk. Fatal pneumonitis was uncommon, but related to dosimetric factors and tumor location.

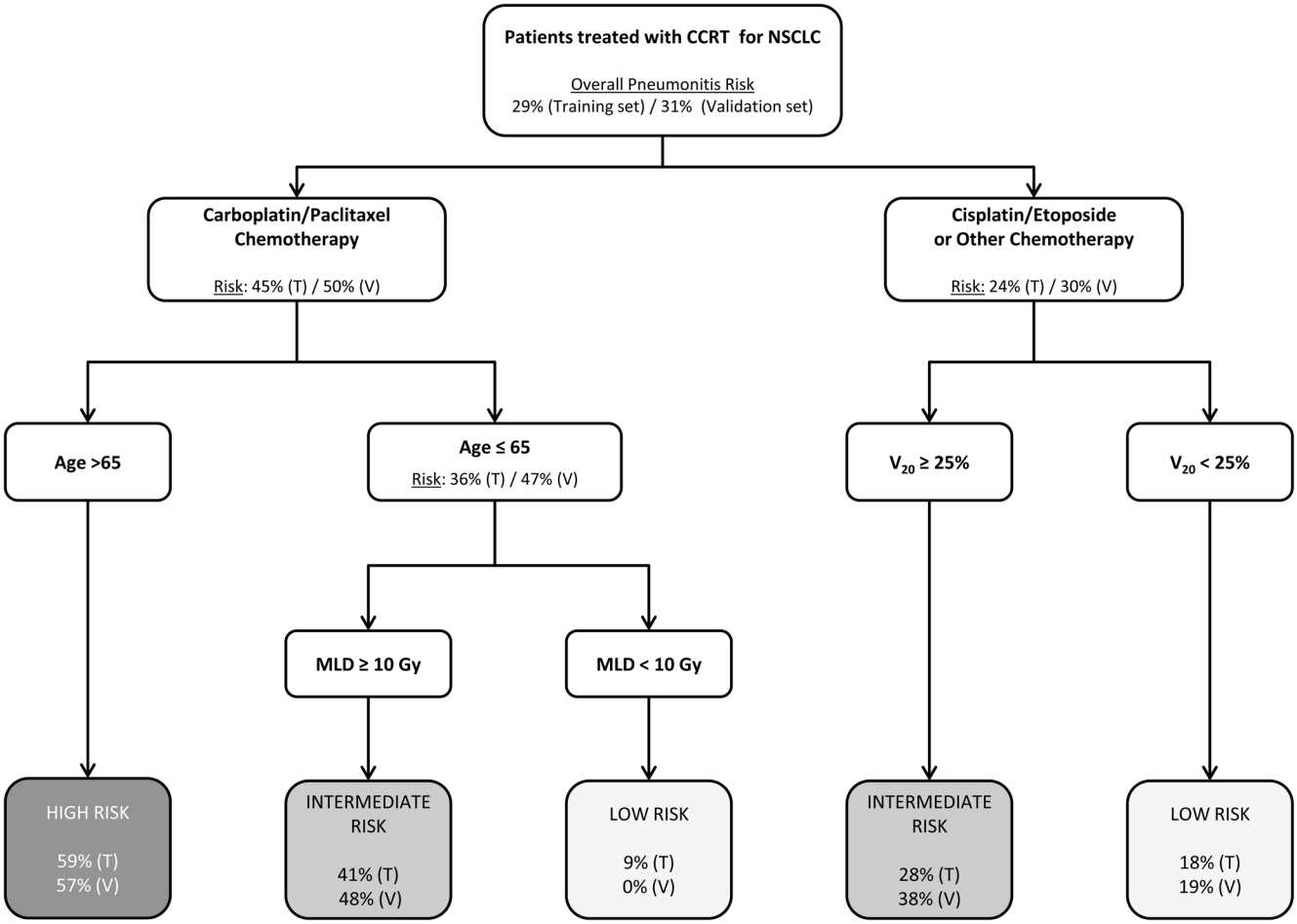


**Figure 1.**

Recursive partitioning analysis of radiation pneumonitis risk in patients undergoing concurrent chemoradiation therapy (CCRT) for non-small cell lung cancer (NSCLC). Patients were randomly divided into a training set (T) and validation set (V). MLD: mean lung dose; $V_{20}$: volume of lung receiving ≥ 20 Gy.

## Table 1

Sources of individual patient data

| Institution | Number of Patients |
|---|---|
| Hyogo Medical Center, Japan | 190 |
| Indiana University School of Medicine, Indianapolis, USA | 98 |
| VU University Medical Center, Amsterdam, Netherlands | 84 |
| Pulmonart Multicenter Study | 68 |
| University of Pennsylvania, Philadelphia, USA | 68 |
| University of Navarra, Pamplona, Spain | 67 |
| Washington University School of Medicine, St. Louis, USA | 64 |
| National Cancer Center, Goyang, Korea | 63 |
| Campus Bio-Medico University, Rome, Italy | 51 |
| Duke University, Durham, USA | 33 |
| Karolinska University Hospital, Stockholm, Sweden | 27 |
| London Regional Cancer Program, London, Canada | 23 |
| **Total** | **836** |

## Table 2

Baseline clinical characteristics.

| Variable | N with data available | Median (Range) or number (%) |
|---|---|---|
| **Age** | 836 | 63 (26–86) |
| **Sex** | 836 | |
| Male | | 603 (72%) |
| Female | | 233 (28%) |
| **Good Performance Status** * | 396 | 382 (96%) |
| **Smoking History** | 511 | 462 (55%) |
| **Histology** | 525 | |
| Adenocarcinoma | | 155 (30%) |
| Large Cell | | 58 (11%) |
| Squamous | | 212 (40%) |
| NSCLC NOS | | 100 (19%) |
| **Tumor Lobe Location** | 487 | |
| Upper | | 327 (67%) |
| Middle | | 25 (5%) |
| Lower | | 135 (28%) |
| **Tumor stage** | 836 | |
| TX | | 36 (4%) |
| T1 | | 90 (11%) |
| T2 | | 245 (29%) |
| T3 | | 196 (23%) |
| T4 | | 269 (32%) |
| **Nodal Stage** | 836 | |
| NX | | 26 (3%) |
| N0 | | 48 (6%) |
| N1 | | 38 (5%) |
| N2 | | 488 (58%) |
| N3 | | 236 (28%) |
| **Stage Grouping** | 836 | |
| IB | | 1 (0.1%) |
| II | | 11 (1.3%) |
| III | | 824 (98.6%) |
| **Neoadjuvant Chemotherapy** | 531 | 296 (56%) |
| **Concurrent Chemotherapy** | 836 | 836 (100%) |
| **Concurrent Chemotherapy Agents** | 633 | |
| Cisplatin-Etoposide | | 243 (38%) |
| Carboplatin-Paclitaxel | | 164 (26%) |

| Variable | N with data available | Median (Range) or number (%) |
|---|---|---|
| Other** | | 226 (36%) |
| **Adjuvant Chemotherapy** | 498 | 116 (23%) |
| **Prescribed Radiation Dose (Gy)** | 834 | 60 (36–84) |
| **Dose Per Fraction (Gy)** | 796 | 2 (1.2–2.15) |
| **Lung volume receiving ≥5 Gy (%)** | 404 | 38 (14–100) |
| **Lung volume receiving ≥20 Gy (%)** | 819 | 30 (7–78) |
| **Mean Lung Dose (Gy)** | 759 | 17 (2–47) |

IQR: interquartile range; NSCLC: non-small cell lung cancer; NOS: not otherwise specified

*defined as Eastern Cooperative Oncology Group Performance Status of 0–1 or Karnofsky performance status of ≥70.

**see text for details.

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## Table 3

Univariable and multivariable analysis of factors predictive of symptomatic radiation pneumonitis in the training dataset (n=557).

| Factor | Univariable Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| **Age (per 10-yr increase)** | 1.26 | 1.03–1.54 | .027 | 1.24 | 0.97–1.59 | 0.090 |
| **Chemotherapy Regimen** | | | <0.001 | | | <0.001 |
| Cisplatin-etoposide | 1 | -Reference- | | 1 | -Reference- | |
| Carboplatin-paclitaxel | 2.78 | 1.65–4.68 | | 3.33 | 1.89–5.87 | |
| Other | 1.17 | 0.69–1.96 | | 1.38 | 0.78–2.41 | |
| **Volume of lung receiving ≥20 Gy ($V_{20}$)** | 1.02 | 1.00–1.04 | .028 | 1.03 | 1.01–1.05 | 0.008 |
| **Mean lung dose** | 1.03 | 1.00–1.05 | .068 | | | NS |
| **Male sex** | 1.01 | 0.67–1.53 | .948 | | | |
| **Smoker** | 0.39 | 0.19–0.80 | .010 | | | |
| **Histology** | | | .783 | | | |
| Adenocarcinoma | 0.74 | 0.41–1.32 | | | | |
| Large cell | 1.04 | 0.47–2.31 | | | | |
| NSCLC NOS | 1.26 | 0.50–3.21 | | | | |
| Squamous | 1 | -Reference- | | | | |
| **T Stage** | | | .562 | | | |
| 1 | 1.11 | 0.60–2.07 | | | | |
| 2 | 0.78 | 0.48–1.26 | | | | |
| 3 | 1.09 | 0.67–1.77 | | | | |
| 4 | 1 | -Reference- | | | | |
| **N Stage** | | | .308 | | | |
| 0 | 0.45 | 0.17–1.14 | | | | |
| 1 | 0.63 | 0.25–1.56 | | | | |
| 2 | 0.93 | 0.62–1.40 | | | | |
| 3 | 1 | -Reference- | | | | |
| **Tumor location (lobe)** | | | .746 | | | |
| Lower | 0.96 | 0.56–1.65 | | | | |

| Factor | Univariable Analysis | | | Multivariable Analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p-value | OR | 95% CI | p-value |
| Middle | 1.52 | 0.49–4.72 | | | | |
| Upper | 1 | -Reference- | | | | |
| **Neoadjuvant Chemotherapy** | 1.49 | 0.92–2.41 | .106 | | | |
| **Adjuvant Chemotherapy** | 0.87 | 0.49–1.55 | .642 | | | |
| **Total radiation dose** | 1.00 | 0.97–1.03 | .963 | | | |
| **Dose per fraction** | 0.87 | 0.39–1.95 | .740 | | | |
| **Volume of lung receiving ≥5 Gy (V5)** | 0.99 | 0.98–1.01 | .202 | | | |

OR: odds ratio; CI: confidence interval; NSCLC: non-small cell lung cancer; NOS: not otherwise specified.

## Table 4

Multivariable analysis of factors predictive of symptomatics radiation pneumonitis in the validation dataset (n=279).

| Factor | Multivariable Analysis | | |
|---|---|---|---|
| | OR | 95% CI | p-value |
| **Age (per 10 yr increase)** | 1.38 | 0.95–2.01 | .089 |
| **Chemotherapy Regimen** | | | <0.001 |
| Cisplatin- Etoposide | 1 | -Reference- | |
| Carboplatin- paclitaxel | 5.52 | 2.25–13.55 | |
| Other | 3.39 | 1.50–7.68 | |
| **Volume of lung receiving ≥20 Gy(V20)** | 1.07 | 1.03–1.11 | <.001 |

OR: odds ratio; CI: confidence interval.

## Table 5

Risk of radiation pneumonitis based on $V_{20}$ (volume of lung receiving 20 Gy or more) in the whole cohort of patients (training and validation set combined).

| Lung volume receiving ≥20 Gy | Symptomatic pneumonitis (% of patients) | Fatal pneumonitis (% of patients) |
|---|---|---|
| <20% | 18.4% | 0.0% |
| 20–29.99% | 30.3% | 1.0% |
| 30–39.99% | 32.6% | 2.9% |
| ≥40% | 35.9% | 3.5% |