Journal of Radiotherapy in Practice

cambridge.org/jrp

Original Article

Cite this article: Weiss E, Ricco A, Mukhopadhyay N, Rezai Gharai L, Deng X, Jan N, and Guy C. (2023) Predictors of high-grade radiation pneumonitis following radiochemotherapy for locally advanced non-small cell lung cancer: analysis of clinical, radiographic and radiotherapy-related factors. *Journal of Radiotherapy in Practice*. **22**(e70), 1–7. doi: 10.1017/S1460396923000043

Received: 14 July 2022
Revised: 3 November 2022
Accepted: 9 November 2022

Key words:
lung cancer; overall survival; radiation pneumonitis; radiochemotherapy; volumetric modulated arc therapy

Author for correspondence:
Dr Elisabeth Weiss, Department of Radiation Oncology, Virginia Commonwealth University Health, 401 College Street, PO Box 980058, Richmond, VA 23298, USA. Tel: +1 804 828 7232. E-mail: elisabeth.weiss@vcuhealth.org

Predictors of high-grade radiation pneumonitis following radiochemotherapy for locally advanced non-small cell lung cancer: analysis of clinical, radiographic and radiotherapy-related factors

Elisabeth Weiss[1], Anthony Ricco[1], Nitai Mukhopadhyay[2], Leila Rezai Gharai[3], Xiaoyan Deng[2], Nuzhat Jan[1] and Christopher Guy[1]

[1]Department of Radiation Oncology; [2]Department of Biostatistics and [3]Department of Radiology, Virginia Commonwealth University Health, Richmond, VA, USA

Abstract

Purpose: In this study, the relation between radiation pneumonitis (RP) and a wide spectrum of clinical, radiographic and treatment-related factors was investigated. As scoring of low-grade RP can be subjective, RP grade ≥3 (RP ≥ G3) was chosen as a more objective and clinically significant endpoint for this study.

Methods and Materials: 105 consecutive patients with locally advanced non-small cell lung cancer underwent conventionally fractionated radio-(chemo-)therapy to a median dose of 64 Gy. A retrospective analysis of 25 clinical (gender, race, pulmonary function, diabetes, statin use, smoking history), radiographic (emphysema, interstitial lung disease) and radiotherapy dose- and technique-related factors was performed to identify predictors of RP ≥ G3. Following testing of all variables for statistical association with RP using univariate analysis (UVA), a forward selection algorithm was implemented for building a multivariate predictive model (MVA) with limited sample size.

Results: Median follow-up of surviving patients was 33 months (9–132 months). RP ≥ G3 was diagnosed in 10/105 (9·5%) patients. Median survival was 28·5 months. On UVA, predictors for RP ≥ G3 were diabetes, lower lobe location, planning target volume, volumetric modulated arc therapy (VMAT), lung V5 Gy (%), lung Vspared5 Gy (mL), lung V20 Gy (%) and heart V5 Gy (% and mL). On MVA, VMAT was the only significant predictor for RP ≥ G3 ($p = 0{\cdot}042$). Lung V5 Gy and lung V20 Gy were borderline significant for RP ≥ G3. Patients with RP ≥ 3 had a median survival of 10 months compared to 29·5 months with RP < G3 ($p = 0{\cdot}02$).

Conclusions: In this study, VMAT was the only factor that was significantly correlated with RP ≥ G3. Avoiding RP ≥ G3 is important as a toxicity per se and as a risk factor for poor survival. To reduce RP, caution needs to be taken to reduce low-dose lung volumes in addition to other well-established dose constraints.

Introduction

Radiation pneumonitis (RP) is one of the clinically most common toxicities of radiation therapy for lung cancer. Symptomatic RP has been reported in about 20% of patients with locally advanced non-small cell lung cancer (NSCLC).[1,2] For example, RP was noticed in 20/71 (28%) NSCLC patients treated with concurrent radiochemotherapy using three-dimensional conformal radiotherapy (3DCRT).[3] In another study evaluating 576 NSCLC patients treated with 3DCRT or intensity-modulated radiotherapy (IMRT) with or without chemotherapy, 117/576 (20%) patients developed symptomatic RP.[4] Many factors have been investigated for their association with RP risk. In the QUANTEC report, mean lung dose (MLD) and the per cent lung volume receiving ≥20 Gy (lung V20 Gy) have been established as reproducible dosimetrical predictors.[2] In a multivariate analysis evaluating clinical and treatment-related factors, V20 Gy was the strongest predictor of RP.[3] The 6-month cumulative incidence of RP ≥ G2 was 14% in patients with V20 ≤ 25 and 63% in patients with V20 ≥ 26%.[3] Other clinical and tumour characteristics, including age, gender, pulmonary function, smoking status, chemotherapy, tumour size and location, have also commonly been linked to RP risk, but findings were less consistent.[1] The report by Jin et al. on 576 irradiated NSCLC patients identified smoking status as the only significant predictor for RP in addition to lung dose.[4] Never smokers had a RP risk of 37% compared to 14% for current smokers and 23% for former smokers. In this study, neither age, nor sex, performance status, the application or type of chemotherapy nor

pulmonary function were related to RP development.[4] In contrast, the study by Robnett et al. reported on 147 patients treated with definitive radiochemotherapy.[5] Performance status was identified as the strongest predictor of RP with a 16 versus 2% risk of severe RP for performance status 1 versus 0.[5] In this study, sex (higher risk for women) and lung function (higher risk for forced expiratory volume in 1 second (FEV1) <2l) were also significantly associated with RP risk. Review reports on the RP risk have summarised the findings for different parameters.[1,2] While the importance of different parameters can vary between studies, dosimetrical findings have been more consistent and led to commonly accepted recommendations for radiation treatment planning.[2]

Several factors have recently found increasing interest for their potential association with RP. For example, emphysema and interstitial lung disease (ILD), particularly idiopathic lung fibrosis, were identified as strong predictors for RP following stereotactic lung radiotherapy with RP ≥ G3 observed in 32% (9/28) ILD patients.[6] The significance of these conditions in the setting of conventionally fractionated radiotherapy is less well known.[7]

An association of RP with metabolic diseases and their treatment, such as diabetes or statin use for hyperlipidaemia, has rarely been reported.[8,9] The pathophysiologic mechanism of diabetes mellitus causing inflammation and endothelial dysfunction is presumed to exacerbate the inflammatory effects of radiotherapy on lung tissue and thereby increase RP risk.[8] A higher RP incidence with diabetes mellitus was only recently endorsed in clinical investigations.[8] Statins were found to have an anti-inflammatory effect in lung tissue in animal studies.[9] The effect of statins on a reduced RP risk in humans requires further evaluation.

Also, cardiac radiation dose at various levels, including mean heart dose (MHD) and heart V5 Gy–V40 Gy, is currently at the centre of investigations for its effect on overall survival.[10,11] A connection between cardiac dose and RP has been suggested but is less clear.[12,13] The magnitude of irradiated heart volumes may be important for the manifestation of RP.

Similarly, lung volumes vary considerably between patients. An earlier study investigated the impact of lung volumes spared from defined dose levels on the development of RP and observed a higher incidence of RP in patients with smaller spared lung volumes.[14] In addition, the assessment of low-dose lung volumes such as lung V5 Gy on RP risk has been controversial. Lung V5 Gy was not significantly related to RP in a large randomised study.[10] Other observations found detrimental lung toxicity in patients with large low-dose lung volumes.[13,15] Further evaluation of these findings appears warranted and thus gives rise to this study.

An increasing number of investigations into RP have been including analyses of larger numbers of clinical and demographic factors to weigh the importance of factors from different categories against each other.[13,15–17] Given the wide spectrum of factors that might affect the RP risk, in this study we investigated a large number of parameters (clinical and radiographic characteristics, tumour features, radiation dose and technique parameters) that are either well-established or have rarely been analysed. Some factors analysed in our study were only recently found to be of interest with respect to RP development, but have not been investigated so far, such as heart volume and absolute volumes for different heart dose levels. In addition to determining risk factors for RP ≥ G3, we planned to also investigate the influence of RP ≥ G3 on overall survival in our patient cohort. A detrimental effect of RP on overall survival was observed in only few previous studies.[18–20]

Materials/Methods

Patient characteristics

All consecutive patients with locally advanced NSCLC who underwent conventionally fractionated radiotherapy and concomitant chemotherapy (no immunotherapy) at our institution between 2009 and beginning of 2018 were included in this analysis. Patients were staged with chest CT, FDG-18 PET-CT, and MRI or CT of the brain had pathologically confirmed diagnosis of NSCLC and underwent pulmonary function testing. Follow-up visits were performed every 3 months for the first 2 years and every 6 months for next 3 years followed by annual visits. All visits included a CT chest and additional diagnostic tests as clinically indicated. Tumour control, acute and long-term treatment-related side effects were assessed during weekly under-treatment visits and on follow-up visits.

Treatment planning

For treatment planning, patients underwent a 4D CT (Brilliance Big Bore™, Philips Medical Systems, Andover, MA) using 3 mm slice thickness, 512 × 512 axial resolution and images sorted in 10 breathing phase bins. Depending on the available image management software at the time, tumour delineation was performed using an internal gross tumour volume (iGTV) that was created based on GTV propagation or based on a reconstructed maximum intensity projection image using commercial software (MIM Maestro™, MIM, Cleveland, OH). Patients with >1·0 cm respiratory tumour motion underwent three repeated moderate inspiration breath hold CT scans with active breathing control (ABC™, Elekta, Stockholm, Sweden) from which an iGTV was generated. For both scenarios, iGTV to clinical target volume (CTV) expansions were 0·6–0·8 cm. Planning target volumes (PTVs) were created through CTV expansion by 0·5 cm. Treatment planning included heterogeneity correction (Pinnacle™, Philips Radiation Oncology Systems, Fitchburg, WI or Eclipse™, Varian, Palo Alto, CA). Plans were optimised to achieve 95% PTV coverage by the prescription dose. Normal tissue dose constraints were unchanged over the years and included the following parameters: spinal cord Dmax ≤ 45 Gy, brachial plexus Dmax ≤ 66 Gy, MLD ≤ 20 Gy, lungs V20 Gy ≤ 30%, lungs V30 Gy ≤ 20%, mean oesophagus dose ≤ 34 Gy, oesophagus V60 Gy ≤ 17%, oesophagus Dmax ≤ 105% of prescription dose, heart V60 Gy ≤ 30%, heart V45 Gy ≤ 60%, MHD ≤ 35 Gy. Treatment was performed typically with 6 MV photon beams with image guidance including daily planar imaging and weekly cone beam computed tomography. Treatment-specific characteristics are listed in Table 1.

Analysis

Based on a comprehensive database that was created from electronic medical charts and radiation therapy documentation, a retrospective IRB-approved analysis was performed to identify predictors of RP ≥ G3 including 25 clinical (gender, race, diffusing capacity for carbon monoxide—DLCO, diabetes type II, statin use, smoking history), radiographic (emphysema, ILD on pre-treatment CT) and radiotherapy dose- and technique-related factors. The latter comprised PTV, tumour location, treatment technique, lung volume (mL), MLD (Gy), lung V5 Gy (%), lung Vspared5 Gy (mL), lung V20 Gy (%), lung Vspared20 Gy (mL), heart volume (mL), MHD (Gy), heart V5 Gy/30 Gy/60 Gy (each in % and mL). Factors selected for analysis were chosen according

https://doi.org/10.1017/S1460396923000043 Published online by Cambridge University Press

Table 1. Treatment and radiation plan characteristics

Characteristic	All patients, $n = 105$ (100%) Count (%) or median (1st–3rd IQR)
PTV size, mL	431 (280–584)
Radiotherapy dose, Gy	64·0 (60·0–66·0)
Concurrent chemotherapy	75 (71)
Carboplatin/paclitaxel	61 (58)
Carboplatin/pemetrexed	12 (11)
Cisplatinum/etoposide	2 (2)
Chemotherapy cycles per patient	2 cyc in 5 (5%); 4 cyc in 19 (18%)
	5 cyc in 3 (3%); 6 cyc in 43 (41%)
	7 cyc in 5 (5%)
Technique	
3DCRT	38 (36%)
IMRT	53 (51%)
VMAT	14 (13%)
Lung volume, mL	3444 (2802–4399)
Mean lung dose, Gy	16·3 (13·9–17·8)
Lung V5 Gy, %	60 (49–71)
Lung spared of 5 Gy, mL	1345 (864–1863)
Lung V20 Gy, %	28 (22–30)
Lung spared of 20 Gy, mL	2562 (2082–3290)
Heart volume, mL	633 (527–765)
Mean heart dose, Gy	12·4 (6·9–24·8)
Heart V5 Gy, %	56 (24–84)
Heart V5 Gy, mL	335 (164–508)
Heart V30 Gy, %	16 (7–34)
Heart V30 Gy, mL	103 (39–196)
Heart V60 Gy, %	2 (0–5)
Heart V60 Gy, mL	10 (0–28)

All lung doses are for Lungs-CTV.
3DCRT: three-dimensional conformal radiotherapy; cyc: cycles; IMRT: intensity-modulated radiotherapy; IQR: interquartile range; PTV: planning target volume; VMAT: volumetric modulated arc therapy.

to previously identified associations with RP risk or were newly investigated such as heart doses in ml and heart volume. For this analysis, all diagnostic pre-treatment images were analysed by a thoracic radiologist for the presence of ILD according to Fleischner Society criteria.[21] In addition, the extent of emphysema involvement of the lung was quantified based on visual assessment of percentage lung involvement. For this analysis, emphysema affecting ≤25% of the lung volume was compared to >25% involvement.

RP was graded according to Common Terminology Criteria for Adverse Events v5. Scoring of low-grade RP can be subjective; RP ≥ G3 was therefore chosen as a more clearly defined and clinically significant endpoint for this study based on severity of symptoms and the need for steroid treatment and oxygen supplement. Survival data were obtained from the patients' medical records and the local cancer centre tumour registry.

Statistics

Statistical analysis was performed to identify the predictive power of clinical and dosimetrical parameters towards RP. Initially, individual variables were checked using univariate logistic regression (UVA) to find marginal associations. Primary model building for association with RP ≥ G3 on this limited-size cohort set was performed using a stepwise forward logistic regression algorithm (multivariate predictive model (MVA)). Entry threshold for predictive variables was set at 10%. Many of the predictors demonstrated collinearity, especially the dosimetric factors. The multivariate forward selection method was expected to eliminate such predictors in the course of variable selection. Overall survival times were computed using Kaplan–Meier method. All analyses were performed in SAS 9.4. To demonstrate the predictive value of individual variables that showed borderline significance in MVA, receiver operating characteristic curves were created to assess accuracy of prediction. Analysis of differences between treatment techniques was performed with unpaired two-tailed *t*-tests.

Results

Population

One hundred and five patients with complete follow-up and clinical/radiographic data were included in this study. The patient cohort included inoperable American Joint Committee on Cancer stage IIB and III NSCLC; two-stage IV patients with solitary oligometastases outside the chest treated with curative approach were included as well. All except three had a positive smoking history or were current smokers. Patient-specific characteristics are listed in Table 2.

Treatment characteristics

Patients were treated with daily conventionally fractionated radiotherapy to a median dose of 64·0 Gy with 1·8/2·0 Gy single fraction dose. Initially, 3DCRT was used in 38 (36%) patients using typically four or five static fields. Later, treatment technique was changed to IMRT delivered in 54 (51%) patients using step-and-shoot technique with five to seven fields. More recently, VMAT was employed in 14 (13%) patients using typically two to four arcs. See Table 1 for relevant radiotherapy-related parameters.

RP

RP ≥ G3 was diagnosed in 10/105 (9·5%) patients (seven RP G3, one RP G4, two RP G5). On UVA, predictors for RP ≥ G3 were diabetes, tumour location in the upper lobe, PTV, VMAT, lung V5 Gy (%), lung Vspared5 Gy (mL), lung V20 Gy (%), heart V5 Gy (% and mL). On MVA, VMAT was the only significant predictor for RP ≥ G3 ($p = 0{\cdot}042$), see Table 3. Lung V5 Gy (%, $p = 0{\cdot}073$) and lung V20 Gy (%, $p = 0{\cdot}08$) were borderline significant for predicting RP ≥ G3 but showed high prediction accuracy with AUC values of 0·86 and 0·84, respectively (Figure 1).

Overall survival

Median follow-up of surviving patients was 33 months (9–132). The 3-year OS rate was 43·4%, and median survival was 28·5 months. Patients with RP ≥ 3 had a median survival of 10·0 months compared to 29·5 months with RP < 3 or no RP ($p = 0{\cdot}02$). Corresponding 2-year OS rates were 26·7 and 56·9% (Figure 2).

https://doi.org/10.1017/S1460396923000043 Published online by Cambridge University Press

Table 2. Baseline patient demographics and disease characteristics (n = 105)

Characteristic	Count (%) or median (1st–3rd IQR)
Age, years	61 (54–66)
Gender	
Male	65 (62)
Female	40 (38)
Race	
White	63 (60)
Black or African American	42 (40)
Karnofsky index ≥70%	95 (90)
Smoking pack years	40 (30–55)
FEV1% predicted ($n = 92$)	72 (56–86)
DLCO% uncorrected ($n = 90$)	59 (44–70)
Diabetes type II	11 (10)
Statin use	28 (27)
Interstitial lung disease	15 (14)
Emphysema >25% of lung	54 (51)
Tumour location upper lobe	64 (61)
Histology	
Adenocarcinoma	50 (33)
Squamous cell carcinoma	46 (44)
Other	9 (9)
AJCC stage	
IIB	14 (13)
IIIA-C	89 (85)
IV (oligometastatic)	2 (2)

DLCO: diffusion capacity for carbon monoxide; FEV1: forced expiratory volume in 1 second; IQR: interquartile range.

Table 3. Results of UVA and MVA for RP ≥ G3

	UVA	MVA
Covariate	OR (95% CI) *p*-value	
Diabetes type II	4·661 (1·005, 21·613) $p = 0·049$	
Tumour location upper lobe	0·239 (0·058, 0·984) $p = 0·048$	
PTV size, mL	1·002 (1·000, 1·004) $p = 0·04$	
Technique 3DCRT + IMRT versus VMAT	0·105 (0·025, 0·432) $p = 0·002$	0·149 (0·024, 0·933) $p = 0·042$
Lung $V_{5\ Gy}$, %	1·130 (1·058, 1·206) $p = 0·0003$	1·074 (0·993, 1·162) $p = 0·073$
Lung Vspared5 Gy, mL	0·997 (0·996, 0·999) $p = 0·002$	
Lung $V_{20\ Gy}$, %	1·447 (1·158, 1·807) $p = 0·001$	1·282 (0·971, 1·693) $p = 0·08$
Heart $V_{5\ Gy}$, mL	1·005 (1·002, 1·009) $p = 0·003$	
Heart $V_{5\ Gy}$, %	1·038 (1·008, 1·069) $p = 0·012$	

Cursive text indicates borderline significance.
95% CI: 95% confidence interval; 3DCRT: three-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; MVA: multivariate analysis; OR: odds ratio; PTV: planning target volume; UVA: univariate analysis; VMAT: volumetric modulated arc therapy.

Discussion

High-grade RP remains the most detrimental side effect of radiotherapy to the chest. In our cohort, RP ≥ G3 was observed in approximately 10%, similar to RP rates reported in other publications.[12,15] Univariate logistic regression confirmed several established risk factors, such as tumour location, PTV size and lung V20 Gy (%).

Less often reported factors were also significant on UVA. Patients with diabetes mellitus were found to have a higher RP risk which agrees with few other reports.[8,22] Kong et al. reported that the diagnosis of diabetes mellitus, HbA1c>6·15% and fasting glucose levels >121 mg/dL were all associated with increasing RP ≥ G3 by a factor>2 on MVA.[8] Diabetes mellitus, particularly if poorly controlled, warrants further confirmation as a risk factor for RP.

In addition, UVA indicated that the absolute lung Vspared5 Gy was significantly related to RP ≥ G3. Biere et al. also observed the importance of sparing uninvolved lung volumes.[14] They reported that patients with smaller lung volumes spared (often female patients with smaller lungs) had a higher risk of RP. Total lung volumes in our cohort varied by a factor of five. Based on these observations, there might therefore be a minimum lung volume that should not receive any radiation dose to prevent high-grade RP. Patients with larger lung volumes might have a smaller RP risk because larger parts of their lungs can be spared from any radiation.

In our cohort, heart V5 Gy (% and mL) was associated with RP ≥ G3 on UVA. So far, little information is available on the relation between radiation dose to the heart and RP. Shepherd et al. observed that heart V16 Gy was related to RP ≥ G2 in postoperative radiotherapy for lung cancer,[13] whereas Huang et al. found heart $V_{65\ Gy}$ associated with RP.[12] While synergistic effects between lung and heart response to radiation have been discussed, higher lung doses are often found with lower lobe tumour locations leading also to higher heart doses because of the proximity of lung tumours to the heart. On the contrary, Wijsman et al. using IMRT and VMAT did not observe a correlation between incidental heart dose and RP risk, potentially because of the ability to selectively spare heart with modern conformal radiotherapy techniques.[23] Heart volumes in our study varied by a factor of more than four indicating that there might be large variations in the absolute heart volumes receiving certain dose levels. Further investigation into the importance of cardiac DVH parameters in addition to the relevance of functional subvolumes of the heart appears warranted.

On MVA, both lung V5 Gy and V20 Gy were borderline significant with high AUC values >0·8. While lung V20 Gy is one of the accepted standard volume thresholds for RP, lung V5Gy has been more controversial.[2] Several reports indicated that low-dose lung volumes, such as V5Gy or V10Gy, are associated with an increased RP risk.[13,24–26] Contrary to a large randomised trial that did not identify lung V5Gy as a predictor of RP, a recent large prospective

https://doi.org/10.1017/S1460396923000043 Published online by Cambridge University Press

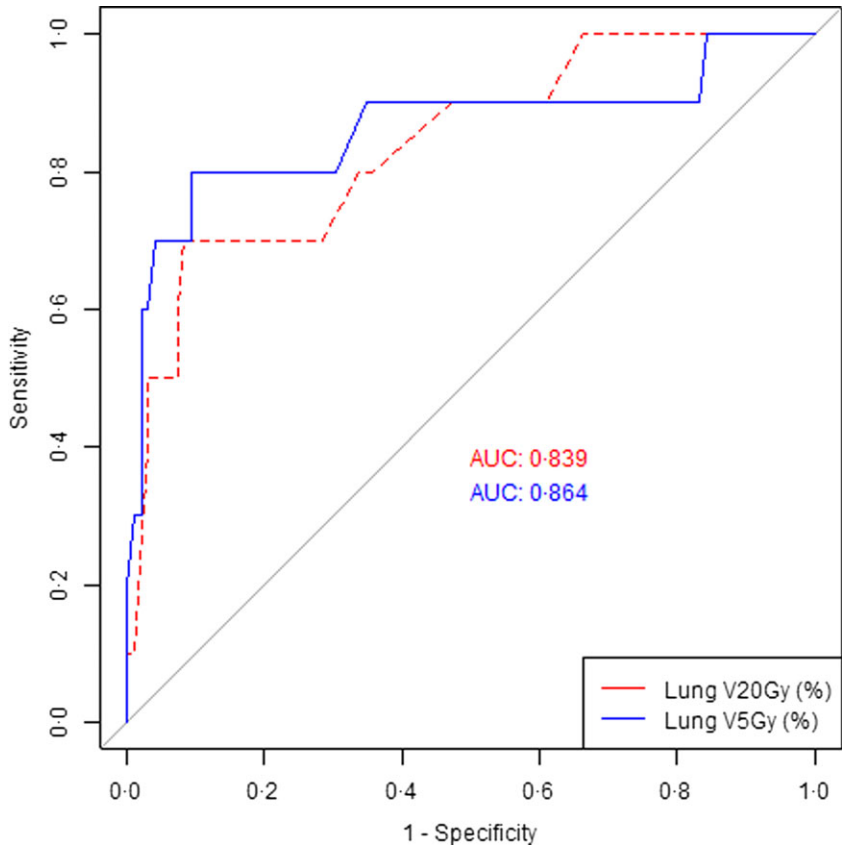

Figure 1. Receiver operating characteristic (ROC) analysis for RP ≥ G3. Lung V5 Gy and lung V20 Gy were borderline significantly associated with RP ≥ G3. Both parameters show high prediction accuracy.

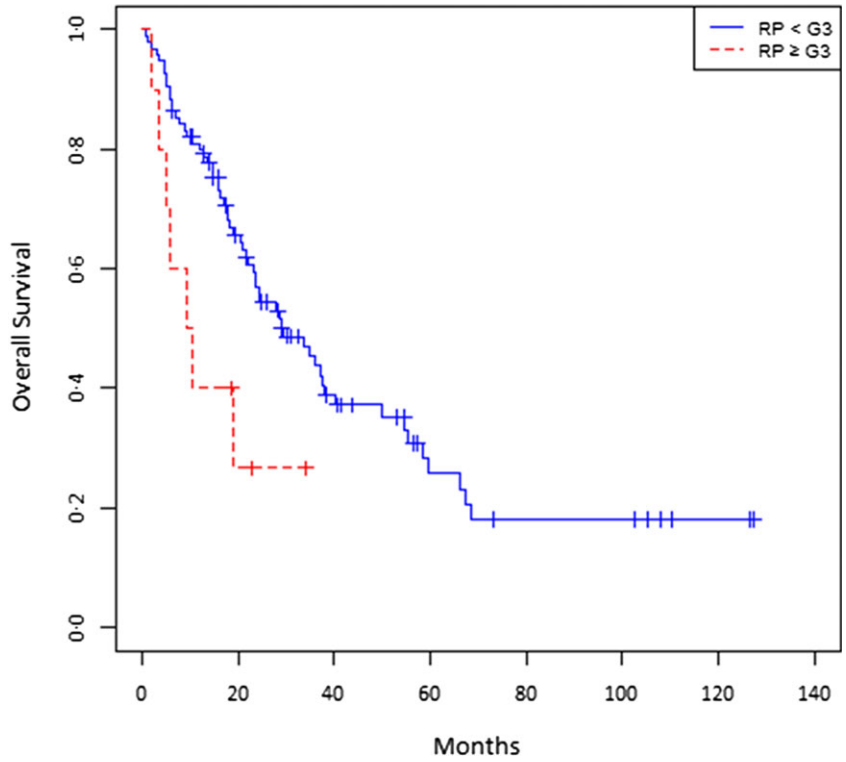

Figure 2. Overall survival depending on radiation pneumonitis grade. Patients with RP ≥ G3 had significantly worse survival compared to patients with lower grade or no RP, $p = 0{\cdot}02$.

study with >1300 patients confirmed the importance of lung V5 Gy.[10] Both lung V5 Gy and V20 Gy were significantly associated with RP ≥ G2, whereas for RP ≥ G3 MLD and V20 Gy were found significant.[15] Similarly, in a recent analysis of IMRT-treated NSCLC patients, low and intermediate lung dose levels were associated with RP ≥ G2, but MLD, V20 Gy and particularly V30 Gy were identified as the strongest predictors of RP compared to clinical and low-dose factors.[27] In the absence of lung V5 Gy dose

https://doi.org/10.1017/S1460396923000043 Published online by Cambridge University Press

constraints in current NCCN guidelines, keeping lung V5 Gy volumes lower than 60 to 75% has been shown to reduce RP risk.[15,24]

The only significant predictor of RP ≥ G3 on MVA in our cohort was VMAT. Over the last two decades, complex treatment techniques have evolved which have enabled superior target dose conformality while reducing dose to critical normal tissues resulting in improved tumour control, survival and lower treatment-related toxicity.[10,28,29] VMAT has been used for stereotactic lung cancer treatments for several years but is also increasingly used for locally advanced lung cancer radiotherapy. Using one or more arcs, VMAT achieves highly conformal dose distributions at the target, which can be at the expense of large volumes receiving low doses if unconstrained. In a planning study, Jiang et al. compared IMRT with single and partial arc VMAT without using low lung dose constraints.[30] Higher lung V5 Gy/10 Gy and lower lung V20 Gy/30 Gy doses were observed for both single and partial arcs compared to IMRT for total and contralateral lung. In a clinical analysis, Wijsmans et al. found lower lung V5 Gy with VMAT compared to IMRT without using low lung dose constraints.[31] Although lung V5 Gy was lower with VMAT in this study, interestingly grade 4 and 5 toxicities were only observed in the VMAT group. In addition, the number of patients with late RP ≥ G3 nearly doubled in the VMAT group. Other reports also did not find increased low doses to the lungs or increased toxicity with VMAT either with (lung V5 Gy < 65% and V10 Gy < 45%)[32] or without using explicit low lung dose constraints.[33] In our cohort, RP ≥ 3 occurred only after IMRT (four G3, one G4) and VMAT treatments (three G3, two G5). No particular low-dose lung constraints were used in our study resulting in a higher likelihood for large low-dose volumes with IMRT and even more so with VMAT.

In our study, high-grade RP was significantly associated with decreased 2-year survival by a factor of 2·13. A three-fold increase in median survival was observed in patients without high-grade RP. RP as a risk factor for overall survival was observed in few studies previously.[18–20] Inoue et al. observed significantly worse survival in lung cancer patients developing severe RP compared to no or mild RP following delivery of definitive radiotherapy.[19] Beukema et al. observed that oesophagus cancer patients treated with 3D CRT had significantly worse survival if they developed RP.[18] Following VMAT, Shen et al. observed that RP in NSCLC patients was significantly related to overall survival (HR 1·39).[20] Only one patient developed RP G5 making the effect of RP-related death as a factor for worse survival less likely. It might not be the development of RP itself, but other risk factors associated with developing RP that influence survival rates.[18] This observation might also apply to our patients, where VMAT patients who were found to have higher RP ≥ G3 risk had larger PTV, an indicator for worse outcome.

Our study has several limitations including small cohort size. We included only patients who had complete datasets and a minimum follow-up of 9 months for surviving patients to allow for observation of RP development including assessment of RP resolution after respective treatment. To avoid underreporting of toxicities and consistent grading of toxicities, patients followed in outside institutions were excluded. High-grade RP (RP ≥ G3) was selected as the endpoint of this study to allow more reliable classification compared to lower-grade toxicity. Also, low rates of high-grade RP result in low statistical power. As a consequence, the authors selected $p < 0{\cdot}1$ as a statistically significant cut-off in this study as it is often the case in similar clinical studies. A large variety of parameters were included in this risk factor analysis. While several dose-volume parameters are likely correlated, univariate logistic regression was employed to determine the significance of each factor individually prior to multivariate analysis. An imbalance in RP events is inherent to a cohort with limited sample size. Despite low toxicity rates and small sample size, various standard RP-related risk factors (PTV size, lung V20 Gy) were identified as significant on UVA validating our approach. This study did not investigate chemotherapy, a well-known risk factor for RP, as chemotherapy agents did not change over time.

The analysis confirmed several well-established and less often reported risk factors for high-grade RP. Further investigations into low-dose lung volumes, lung volumes spared radiation dose and VMAT are warranted given this study's findings are observed in a relatively small cohort.

Conclusions

In this study, VMAT was the only factor that was significantly correlated with RP ≥ G3. Lung V5 Gy and lung V20 Gy were reliable predictors of RP ≥ G3 with AUC values >0·8. Overall survival was significantly worse in patients who experienced RP ≥ G3. Avoiding RP ≥ G3 is therefore important not only as a toxicity per se but also as a risk factor for poor survival. When using VMAT, caution needs to be taken to reduce low-dose lung volumes in addition to other well-established dose constraints.

Acknowledgements. None.

Financial Support. Biostatistical analysis of this work was supported in part by the Massey Cancer Center institutional grant through the National Institutes of Health (grant number P30CA016059).

Conflicts of Interest. The authors declare none.

Ethical Standards. This retrospective study was approved by the local ethics committee.

References

1. Giuranno L, Ient J, De Ruysscher D, Vooijs M A. Radiation-induced lung injury (RILI). Front Oncol 2019; 6 (9): 877.
2. Marks L B, Bentzen S M, Deasy J O et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010; 76 (suppl 3), 70–76.
3. Tsujino K, Hirota S, Endo M et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2003; 55: 110–115.
4. Jin H, Tucker S L, Liu H H et al. Dose-volume thresholds and smoking status for the risk of treatment-related pneumonitis in inoperable non-small cell lung cancer treated with definitive radiotherapy. Radiother Oncol 2009; 91: 427–432.
5. Robnett T J, Machtay M, Vines E F, Mckenna M G, Algazy K M, Mckenna W G. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2000; 48: 89–94.
6. Bahig H, Filion E, Vu T et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pract Radiat Oncol 2016; 6 (5): 367–374.
7. Lee Y H, Kim Y S, Lee S N et al. Interstitial lung change in pre-radiation therapy computed tomography is a risk factor for severe radiation pneumonitis. Cancer Res Treat 2015; 47 (4): 676–686.
8. Kong M, Lim Y J, Kim Y et al. Diabetes mellitus is a predictive factor for radiation pneumonitis after thoracic radiotherapy in patients with lung cancer. Cancer Manag Res 2019; 11: 7103–7110.
9. Williams J P, Hernady E, Johnston C J et al. Effect of administration of lovastatin on the development of late pulmonary effects after whole-lung irradiation in a murine model. Radiat Res 2004; 161: 560–567.

https://doi.org/10.1017/S1460396923000043 Published online by Cambridge University Press

10. Chun S G, Hu C, Choy H et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017; 35 (1): 56–62.
11. Thor M, Deasy J O, Hu C et al. Modeling the impact of cardiopulmonary irradiation on overall survival in NRG oncology trial RTOG 0617. Clin Cancer Res 2020; 26 (17): 4643–4650.
12. Huang E X, Hope A J, Lindsay P E et al. Heart irradiation as a risk factor for radiation pneumonitis. Acta Oncol 2011; 50 (1): 51–60.
13. Shepherd A F, Iocolano M, Leeman J et al. Clinical and dosimetric predictors of radiation pneumonitis in patients with non-small cell lung cancer undergoing postoperative radiation therapy. Pract Radiat Oncol 2021; 11 (1): e52–e62.
14. Briere T M, Krafft S, Liao Z, Martel M K. Lung size and the risk of radiation pneumonitis. Int J Radiat Oncol Biol Phys 2016; 94 (2): 377–384.
15. McFarlane M R, Hochstedler K A, Laucis A M et al. Predictors of pneumonitis after conventionally fractionated radiotherapy for locally advanced lung cancer. Int J Radiat Oncol Biol Phys 2021; 111 (5): 1176–1185.
16. Dang J, Li G, Zang S, Zhang S, Yao L. Risk and predictors for early radiation pneumonitis in patients with stage III non-small cell lung cancer treated with concurrent or sequential chemoradiotherapy. Radiat Oncol 2014; 9: 172.
17. Palma D A, Senan S, Tsujino K et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys 2013; 85 (2): 444–450.
18. Beukema J C, Kawaguchi Y, Sijtsema N M et al. Can we safely reduce the radiation dose to the heart while compromising the dose to the lungs in oesophageal cancer patients? Radiother Oncol 2020; 149: 222–227.
19. Inoue A, Kunitoh H, Sekine I, Sumi M, Tokuuye K, Saijo N. Radiation pneumonitis in lung cancer patients: a retrospective study of risk factors and the long-term prognosis. Int J Radiat Oncol Biol Phys 2001; 49 (3): 649–655.
20. Shen L, Liu C, Jin J et al. Association of lung and heart dose with survival in patients with non-small cell lung cancer underwent volumetric modulated arc therapy. Cancer Manag Res 2019; 11: 6091–6098.
21. Lynch D A, Sverzellati N, Travis W D et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner society white paper. Lancet Respir Med 2018; 6 (2): 138–153.
22. Kalman N S, Hugo G D, Mahon R N, Deng X, Mukhopadhyay N D, Weiss E. Diabetes mellitus and radiation induced lung injury after thoracic stereotactic body radiotherapy. Radiother Oncol 2018; 129 (2): 270–276.
23. Wijsman R, Dankers F J W M, Troost E G C et al. Inclusion of incidental radiation dose to the cardiac atria and ventricles does not improve the prediction of radiation pneumonitis in advanced-stage non-small cell lung cancer patients treated with intensity modulated radiation therapy. Int J Radiat Oncol Biol Phys 2017; 99 (2): 434–441.
24. Khalil A A, Hoffmann L, Moeller D S, Farr K P, Knap M M. New dose constraint reduces radiation-induced fatal pneumonitis in locally advanced non-small cell lung cancer patients treated with intensity-modulated radiotherapy. Acta Oncol 2015; 54 (9): 1343–1349.
25. Shi A, Zhu G, Wu H, Yu R, Li F, Xu B. Analysis of clinical and dosimetric factors associated with severe acute radiation pneumonitis in patients with locally advanced non-small cell lung cancer treated with concurrent chemotherapy and intensity-modulated radiotherapy. Radiat Oncol 2010; 5: 35.
26. Song C H, Pyo H, Moon S H, Kim T H, Kim D W, Cho K H. Treatment-related pneumonitis and acute esophagitis in non-small-cell lung cancer patients treated with chemotherapy and helical tomotherapy. Int J Radiat Oncol Biol Phys 2010; 78 (3): 651–658.
27. Meng Y, Luo W, Wang W et al. Intermediate dose-volume parameters, not low-dose bath, is superior to predict radiation pneumonitis for lung cancer treated with intensity-modulated radiotherapy. Front Oncol 2020; 10: 584756.
28. Liao Z X, Komaki R R, Thames H D Jr et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010; 76 (3): 775–781.
29. Jegadeesh N, Liu Y, Gillespie T et al. Evaluating Intensity-modulated radiation therapy in locally advanced non-small-cell lung cancer: results from the national cancer data base. Clin Lung Cancer 2016; 17: 398–405.
30. Jiang X, Li T, Liu Y et al. Planning analysis for locally advanced lung cancer: dosimetric and efficiency comparisons between intensity-modulated radiotherapy (IMRT), single-arc/partial-arc volumetric modulated arc therapy (SA/PA-VMAT). Radiat Oncol 2011; 6: 140.
31. Wijsman R, Dankers F, Troost E G C et al. Comparison of toxicity and outcome in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy using IMRT or VMAT. Radiother Oncol 2017; 122 (2): 295–299.
32. Bourbonne V, Delafoy A, Lucia F, Quéré G, Pradier O, Schick U. Toxicity after volumetric modulated arc therapy for lung cancer: a monocentric retrospective study. Transl Lung Cancer Res 2021; 10 (1): 156–166.
33. Bertelsen A, Hansen O, Brink C. Does VMAT for treatment of NSCLC patients increase the risk of pneumonitis compared to IMRT? A planning study. Acta Oncol 2012; 51 (6): 752–758.

https://doi.org/10.1017/S1460396923000043 Published online by Cambridge University Press