ADVERSE RESPIRATORY OUTCOMES FOLLOWING CONVENTIONAL LONG-COURSE RADIOTHERAPY FOR NON-SMALL-CELL LUNG CANCER IN PATIENTS WITH PRE-EXISTING PULMONARY FIBROSIS – A COMPARATIVE RETROSPECTIVE STUDY

RUNNING TITLE: ADVERSE OUTCOMES POST-RADIATION IN PATIENTS WITH PULMONARY FIBROSIS

AUTHORS:

Dr Clare Bajraszewski MBBS (Hons), BMedSc)[1]

Associate Professor Renee Manser (MBBS, MSc, PhD, FRACP)[2, 3, 4]

Dr James Chu (MBBS (Hons))[1*]

Dr R. Ashley Cox (BMBS, FRCR)[1†]

Dr Phillip Tran (MBBS, FRANZCR)[1]

Miss Mary Duffy (RSCN, RGN, RSM, Grad Dip Oncology And Palliative Care Nursing)[5]

Associate Professor Louis Irving (MBBS, FRACP)[2, 3, 4]

Dr Alan Herschtal (PhD, BE (Hons), BSc)[6§]

Associate Professor Shankar Siva PhD, MBBS, FRANZCR)[1,7]

Professor David Ball (MBBS, MD, FRANZCR)[1,7]

1- Division of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

2- Department of Respiratory and Sleep Medicine, Royal Melbourne Hospital, Grattan Street, Parkville VIC, 3050

3- Department of Haematology and Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

4- Department of Medicine (Royal Melbourne Hospital), University of Melbourne, Victoria, Australia

5- Department of Nursing, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

6- Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

7- Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia

Present addresses: * Alfred Health, Melbourne, Victoria, Australia

†Royal United Hospital, Bath, United Kingdom

§ Novotech, Melbourne, Victoria, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/1754-9485.13041

DR. CLARE BAJRASZEWSKI (Orcid ID : 0000-0003-4944-5513)
DR. DAVID BALL (Orcid ID : 0000-0002-0491-6919)

Article type : Radiation Oncology Original Article

Abstract

Introduction

There is some evidence to suggest that patients with underlying pulmonary fibrosis (PF) have increased risk of adverse respiratory and survival outcomes, when treated with conventional, long-course radiotherapy (RT) for non-small-cell lung cancer (NSCLC). We performed a retrospective analysis to determine the size of these risks.

Methods

Data from 21 patients with PF (cases) were retrospectively analysed for respiratory toxicity and mortality outcomes, and compared with patients without PF (non-cases). Age and mean lung dose were included as covariates in regression analyses. The additional predictive value of other patient, disease and treatment characteristics on radiation pneumonitis (RP) risk and severity was explored.

Results

There was a numerical (though not statistically significant) increase in grade ≥2 RP among PF cases (OR 2.74, p=0.074). Cases were significantly more likely to discontinue radical treatment early (OR 6.10, p=0.015). There was a significant association between increased RP severity and underlying PF (p=0.039), with RP strongly implicated in the death in 3 of 21 cases (14.3%) compared to 1 non-case (1.2%). Cases experienced increased grade ≥2 respiratory toxicity otherwise (OR 4.35, p=0.020), and poorer median overall survival (0.6 versus 1.7 years, p<0.001). Two cases, and no non-cases, died during the proposed RT period. None of the analysed patient, disease or treatment factors, was a significant additional predictor of RP risk/ severity.

Conclusion
Patients with PF are at increased risk of treatment discontinuation, respiratory morbidity and mortality, and poor survival following conventional RT for NSCLC. Caution should be exercised when offering high-dose RT to these patients.

KEYWORDS: non-small cell lung cancer, pulmonary fibrosis, radiation therapy, radiation pneumonitis, respiratory toxicity

Introduction

Radiation pneumonitis (RP), or pulmonary inflammation due to radiotherapy (RT), can cause significant morbidity and occasionally mortality following thoracic RT. RP generally occurs six weeks to six months post RT and may cause asymptomatic radiological changes, or symptomatic cough, fever and dyspnoea. The risk of clinically significant RP following radical dose RT for lung cancer is estimated at 13-37%[1].

Several studies have assessed risk factors for RP, though sometimes with inconsistent findings [2]. Postulated patient-related factors include older age [3–5], female gender [6], poor pre-treatment performance status [7], elevated pre-treatment CRP [8], low pre-treatment IL-8, radiation-induced TGF-beta elevation [9], and smoking [10]. Postulated treatment-related contributors include mean lung dose (MLD) [3,11,12], increased fraction size [13,14], various V10-V50 parameters [3,11,12,15], and chemotherapy [14].
Findings around the impact of underlying lung function have varied. Reduced pulmonary function was found to increase RP risk by Robnett [6], Monson [7], and Inoue [8] but not Wang [4]. Choi [16] found that those with FEV1 < 50% predicted, usually experienced a small improvement or only a minor decline in pulmonary function post RT.

There has been some evidence of an association particularly between underlying pulmonary fibrosis (PF) and RP, which is the subject of this study. Due to cases of patients with PF who have developed severe and sometimes fatal pulmonary complications, radiation oncologists are frequently reluctant to treat such patients radically.

Pre-treatment interstitial changes on imaging have been identified as a risk factor for RP post conventional thoracic RT for lung and other cancers [10,17–19] - including fatal RP [20]. Conversely, Yamada did not find radiologic fibrosis to elevate RP risk[21]. Ueki [22], Bahig [23], and Yoshitake [24] have demonstrated increased RP risk with interstitial lung disease (ILD) following stereotactic body radiotherapy (SBRT).

The current study aimed to further elucidate the risk of adverse outcomes for patients with PF, specifically in the context of radical long-course, conventional RT (henceforth referred to as 'conventional RT', to distinguish from SBRT) for NSCLC. We wished to compare, between patients with and without PF, the risks of RP and other respiratory toxicity; early cessation of radical treatment; and longer-term survival. Importantly, based on risk factors for RP identified in existing studies, we wished to account for the potential confounders of age and MLD by including these as covariates in regression analyses.

Methods

Patient selection

Patients with PF (cases) and without PF (non-cases) were sourced from the database of patients having commenced radical RT for lung cancer at Peter MacCallum Cancer Centre (PMCC), between 1st January 2000 and 23rd December 2012.

Inclusion criteria included a confirmed histological diagnosis of NSCLC and commencement between these dates of radical conventional RT, with or without chemotherapy (based on 'intention-to-treat'). To screen for appropriate patients, those on the database were coded according to whether their radiation prescription was typical of NSCLC or small-cell lung cancer (SCLC), and radical or palliative intent. Those with non-standard prescriptions had histology and treatment intent confirmed manually from their history.

Exclusion criteria included: SBRT; SCLC/ non-lung histology; lack of histologic diagnosis (or significant uncertainty); palliative intent treatment; prior lung RT (or documented overlap with previous RT for non-lung cancers); non-lung/mediastinum treatment site; brachytherapy boost; and treatment at an associated private facility.

To identify 'potentially relevant' patients who might have PF, a search of the database, in combination with PMCC's electronic notes and diagnostic imaging systems, was performed. Search terms included: fibrosis; pneumonitis; idiopathic pulmonary; interstitial lung; cryptogenic fibrosing alveolitis/ CFA; usual interstitial pneumonitis/ UIP; rheumatoid; SLE; lupus; connective tissue disease/disorder; scleroderma; dermatomyositis; polymyositis; vasculitis; Sjogren; amiodarone; gold; sulfasalazine; sarcoid; methotrexate; honeycomb; traction bronchiectasis; ground glass; reticular opacity.

Manual review of the electronic clinical record for each 'potentially relevant' patient was performed. We identified 'cases' with pre-treatment PF based on documented past history, imaging reports with suggestive changes, histopathology and lung function tests. Patients without evidence to support PF, and who did not otherwise meet exclusion criteria, were deemed valid 'non-cases'. Non-case subjects were sourced from this group, plus the remaining patients in the database coded as having received radical RT for NSCLC. A random number generation technique was used to yield a 4:1 ratio of non-cases to cases, and manual file review undertaken to confirm eligibility. Where a patient was deemed ineligible due to one or more of the listed exclusion criteria, they were excluded and the next randomly identified non-case selected.

Where PF status was uncertain on initial file review, a respiratory physician (RM) undertook additional evaluation of the history, available imaging and other investigations to confirm their status; where there was still insufficient information to confidently establish PF status, the patient was excluded as both a case and a non-case (but descriptive and outcome data still collected).

Patient status was followed to April 4, 2018. For selected patients, information was collected corresponding to baseline characteristics, documented RP and other toxicity and mortality outcomes, from PMCC and third party records. Toxicities were graded as per the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [25] with grade 2 designating at least moderate symptoms, limiting instrumental activities of daily living (ADL) and requiring medical intervention. Grade 3 designates severe symptoms, requiring oxygen and limiting self care ADL; grade 4 indicates life-threatening respiratory compromise requiring urgent intervention; and grade 5 indicates fatality.

The highest-grade toxicity identified within the relevant timeframe for each patient was used for analysis. Where there was no mention of a particular toxicity in a follow up letter, grade was presumed 0-1 (where toxicity was significant enough to require medical intervention, it is presumed highly likely to have been documented).

The project received ethical approval via the PMCC Ethics Committee (HREC 13/139).

Objectives

Our primary objective was to compare the risk of development of grade ≥2 RP between PF cases and non-cases, within 6 months of completion of conventional RT for NSCLC. Our hypothesis was that patients with a pre-treatment diagnosis of PF were more likely to develop significant RP.

The secondary objectives were:
- To compare the grade of RP between cases and non-cases.
- To compare the risk of development of other grade ≥2 respiratory toxicity within 6 months post RT, including dyspnoea/cough not formally diagnosed as RP; respiratory infection; and accelerated pulmonary fibrosis. The highest toxicity available for each patient was included in analysis. Where multiple concurrent respiratory factors were felt to have led to fatality, each was graded as 5.
- To characterise overall survival (OS) for all patients, and to compare OS between cases and non-cases.
- To compare outcomes during the RT treatment course between groups (development of significant respiratory issues during the RT course; early termination of RT; and death during the proposed RT period).

As an exploratory objective, subject to the availability of sufficient data, we aimed to explore any additional RP risk conferred by various patient, disease, and treatment-related characteristics. Patient characteristics included age; gender; performance status; family history of PF; smoking status; potential risk factors for PF (inorganic/organic exposures; underlying sarcoidosis or connective tissue disease; potentially causative drug exposures such as amiodarone); cardiac and pulmonary comorbidities; and baseline pulmonary function.

Disease characteristics included histology; stage (AJCC 7th edition) [26]; tumour location; history of significant weight loss (≥5% from baseline – where no baseline was documented, an 'average' weight of 85kg and 70kg was assumed for males and females respectively) [27].

Treatment characteristics included the use and schedule of chemotherapy; lung surgery before/ after RT; total RT dose; fractionation; MLD, V5, V20, V30 and V40.

Statistical methods

Standard statistical methods (logistic regression, ordinal logistic regression, Fisher's exact test, and Kaplan-Meier product limit method) were used, carried out using the base package of the R language for statistical computing and commonly used add-on packages.

Ordinal logistic regression was used for ordinal valued output variables for analyses where the number of levels in the output variable was >2. For the model testing association between RP grade and PF diagnosis, Grades 0-1 RP collectively were regarded as 'low' toxicity, grade 2 as 'intermediate' and grade ≥3 as 'high' toxicity. The odds ratio for ordinal logistic regression is the ratio of the odds of a Pre-Treatment PF Diagnosis of 'Yes' between any two adjacent levels of RP Grade i.e. either intermediate versus low, or high versus intermediate, assumed to have the same odds ratio.

Age and MLD were considered as confounding variables and included as covariates in regression analyses.

Results

2213 patients were coded as having received radical RT for lung cancer. 1382 patients were flagged as 'potentially relevant' in the keyword search. Of these patients, 21 were deemed valid PF cases; 8 were deemed 'equivocal' and excluded from analysis as both cases and non-cases.

Valid non-cases were selected from a total of 1370 patients: 454 patients presumed to have had radical conventional RT for NSCLC based on histology coding and

fractionation; and 916 patients flagged as 'potentially relevant' in the keyword search, but deemed to be valid non-cases after file review.

Using random number generation and file review to confirm eligibility, 84 eligible non-cases were identified. (3 of the randomly selected patients' PF status were deemed 'equivocal', bringing the total of 'equivocal' patients to 11.) Figure 1 details the patient selection process.

Note that one case and one non-case had no clinical information obtainable after treatment. The case died less than 2 weeks post RT with the cause not documented, and the status of the non-case was unknown beyond 5 days post RT. These patients' toxicity was designated as grade 0 in the absence of further information. For patients whose respiratory status was not known to a full 6 months post RT or who died prior to that timepoint, their maximum recorded toxicity grade was used for analysis. Of patients known to have survived more than 6 months after RT, 6 non-cases did not have their respiratory status known to a full 6 months post RT– the status of 3 was known to more than 5 months, and the others' to between 5 weeks and 4.5 months.

Tables 1-3 show the baseline patient, disease and treatment characteristics. There was a numerically higher median MLD in the non-case group but this did not reach statistical significance (p=0.09).

Risk of RP

10 of 21 PF patients experienced grade ≥2 RP in the 6 months post treatment, compared to 19 of 84 non-PF patients and 3 of 11 'equivocal' patients.

Using a logistic regression model, the rate of grade ≥2 RP was compared between cases and non-cases. MLD and age were considered as confounding variables and controlled for as covariates. The 11 patients where PF status was 'equivocal' were removed from this comparison, as were 19 non-cases and 1 case where MLD was missing. There was a numerically increased rate (though not statistically significant) of grade ≥2 RP among cases (OR 2.74, p=0.074, 95% CI 0.91-8.41).

Severity of RP

Using an ordinal logistic regression model controlling for MLD and age, the severity of RP was compared between groups (the 'equivocal' PF patients and those with missing MLD were again removed from the comparison). There was a statistically significant association between severity of RP and a diagnosis of PF according to the above-defined odds ratio (OR 3.23, p=0.039, 95% CI 1.06-9.90).

RP was strongly implicated in patient death (grade 5) in 3 of 21 cases compared to 1 of 84 non-cases (table 4). Where there were multiple concurrent significant respiratory contributors to fatality, each was graded as 5.

Respiratory toxicity other than RP

Significantly more cases (18 of 21) compared to non-cases (46 of 84) had other grade ≥2 respiratory toxicity within 6 months of treatment (OR 4.35, 95% CI 1.24-20.75, p=0.020).

Overall Survival

Figure 2 characterises the overall survival for all patients, and Figure 3 compares survival between cases and non-cases. Non-cases had significantly better survival than cases (p<0.001), with a median survival of 1.7 years (95% CI 1.2-2.5) compared to 0.6 years (95% CI 0.1-1.0). At one year, 68% of non-cases had survived compared to 33% of cases; 44% compared to 10%, at 2 years; and 29% compared to just 5%, at 5 years.

Adverse Events During RT

Using Fisher's exact test, there was no significant difference in grade ≥2 respiratory issues during RT, between cases and non-cases. These occurred in 11 of 21 cases and 31 of 84 non-cases (OR 1.87, p=0.22, 95% CI 0.64-5.54). However, cases more frequently discontinued proposed radical treatment: 5 of 21 cases and 4 of 84 non-cases ceased RT prematurely (OR 6.10, 95% CI 1.17-34.35, p=0.015).

Two cases, and none of the non-cases, died during the proposed RT period. One patient died from a contralateral pneumonitis, felt either infective or inflammatory. The other patient's death was multifactorial, with renal/ cardiac failure,

gastrointestinal bleeding and contralateral aspiration pneumonia. Neither was graded with significant RP given the timing and contralateral nature.

Other Factors Contributing to RP

To address the exploratory objective, logistic and ordinal logistic regression models were developed, assessing the contribution of the described patient/ disease/ treatment factors to RP risk and severity. Age, MLD and PF diagnosis were included as covariates. Predictors were omitted when the data was insufficient for modelling. None of these factors was found to be a significant predictor of grade ≥2 RP risk or RP severity.

Discussion

Our results confirm that patients with PF exhibit demonstrably poorer toxicity and survival in the setting of conventional RT for NSCLC. A strength of our study is the direct comparison between PF cases and non-cases, for a range of toxicity and mortality outcomes both during and after the RT course.

Cases included both patients who had a documented pre-treatment diagnosis of PF; those where underlying PF was identified on pre-RT workup, or during/ after RT; and some only identified retrospectively for the purposes of this study. In clinical practice, these patients also come to the attention of radiation oncologists in a variety of circumstances.

While the numerical increase in grade ≥2 RP did not reach accepted levels of statistical significance (potentially limited by small numbers), there was a statistically significant association between PF status and RP severity. A proportionally higher number of patients had the concerning grade ≥3 RP (5 of 21 cases, 23.8%, compared with 5 of 84 non-cases, 6.0%) – resulting in hospitalisation, threat to life or indeed death. RP was strongly implicated in the deaths of 3 cases (14.3%) compared to 1 non-case (1.2%). PF patients were also more likely to experience other grade ≥2 respiratory issues post RT. We postulate multiple mechanisms. Immunologically, patients with PF exhibit upregulation of pro-inflammatory cytokines, which may result in increased susceptibility to RP. Clinically, they have reduced baseline respiratory reserve and may tolerate RP poorly. Radiation-induced lung toxicity in these patients

may be a continuum from pneumonitis to related worsening out-of-field PF. Further worsening respiratory reserve renders patients at higher risk of respiratory deterioration/ death, causes frequently being multifactorial. The primary cause can be difficult to differentiate retrospectively with overlapping clinical and radiological features. The three PF patients with grade 5 RP had significant issues with in-field RP, with/ without related worsening out-of-field fibrosis, requiring long-term oxygen and ongoing steroids. In two of the three the acute presentation ultimately resulting in death was also related to superimposed infection; but certainly RP with/without worsening fibrosis, with poor respiratory reserve, was a core factor.

As to outcomes during treatment, the rate of grade ≥2 respiratory issues during RT was not significantly different between groups. However, PF patients significantly more frequently did not complete prescribed radical treatment. Both deaths during the proposed RT period occurred in PF patients, with respiratory issues being causative or contributory.

The finding of increased RP risk and severity is in line with anecdotal clinical experience, and most of the existing literature. A small number of previous studies have correlated pre-treatment interstitial changes on imaging and RP. Makimoto [17] evaluated patients who received high dose conventional RT for both SCLC and NSCLC, and found interstitial changes on chest X-ray (CXR) and / or computed tomography (CT) were a risk factor for RP outside the treatment field. Ozawa [19] evaluated a population treated with conventional RT both curatively and palliatively for lung cancer (both SCLC and NSCLC, with treatment to lung, mediastinum and other areas including the thoracic spine), and found CT-detected interstitial changes to predict RP extending outside of the treated field. Patients with pre-treatment interstitial changes on CT were found to have an increased risk of significant RP by Sanuki [18] (in patients with primary lung cancer and thymic tumours), and Li [10] (in SCLC patients).

In terms of survival, in Ohe's study [20] of patients receiving chemotherapy and conventional RT for lung cancer, found PF changes on pre-treatment CXR to significantly correlate with treatment related death (from RP), with 2 of 8 patients with PF dying. Pre-existing PF changes were not related to death from chemotherapy. We found that PF patients, as expected, had worse overall survival compared to non-cases and this may relate both to respiratory toxicity and the natural history of PF.

There have been some contrasting findings in the existing literature. Fibrotic changes on CT were not found to increase RP risk by Yamada [21] in the setting of conventional RT for both SCLC and NSCLC – noting that patients with fibrotic change on CXR did not receive RT. Exclusion of the more severe end of the disease spectrum may have biased their findings away from significance. SBRT studies have also demonstrated an increase in significant RP[22–24] and mortality[23,28] in patients with ILD, though it is difficult to draw comparisons with the conventional RT setting given the differing biology of radiation response.

It was postulated that for PF patients, additional patient/ disease/ treatment factors may further increase RP risk. Our study did not clearly identify additional predictive factors, which may have been limited by patient numbers and a number of missing descriptive data.

Limitations of this retrospective study include the small patient cohort due to the relative rarity of PF, which may have influenced statistical outcomes. As retrospective, information was limited to what was available in the clinical record and obtainable from third parties. Symptoms were graded retrospectively and may have multifactorial aetiology, with malignancy and other cardiorespiratory pathologies potentially confounding assessment. Where there was insufficient information to designate a patient as a valid case or non-case, they were excluded as 'equivocal'; this is a potential limitation as it distinguishes the study cohort from the general population of NSCLC patients receiving radiation. Finally, the lung volume for DVH purposes was defined variably by treating clinicians (with variable exclusion of the gross tumour, clinical target volume, or planning target volume).

Conclusion:

Our results demonstrate that patients with underlying PF must be carefully selected for treatment with conventional RT for NSCLC. They are at risk of a host of adverse treatment-related outcomes, particularly respiratory, with multiple competing risks to survival. It is crucial that patients undertake fully informed consent regarding the risks of RT, including a real risk of treatment-related death. Alternatives such as systemic therapy alone can be considered, however may also come with risks.

PF is a relatively rare entity where our understanding is currently incomplete. It would be beneficial for large prospective databases to incorporate data on the presence of subclinical or clinical PF; and to study additional predictive patient, disease, and

treatment factors in a wider-scale, prospective fashion. This would help further quantify risk for the individual patient, and may allow adjustment of treatment regimens to modulate risk.

Acknowledgements:
We thank Morgan Hunter (Peter Mac) for statistical input, and Dr Manish Jain (MIA) for helping facilitate imaging access.

REFERENCES

1. Rodrigues G, Lock M, D'Souza D, Yu E, Van Dyk J. Prediction of radiation pneumonitis by dose-volume histogram parameters in lung cancer - a systematic review. Radiother Oncol. 2004;71(2):127–38.
2. Kong FM (Spring), Wang S. Non-dosimetric risk factors for radiation-induced lung toxicity. Semin Radiat Oncol. 2015;25(2):100–9.
3. Claude L, Pérol D, Ginestet C, Falchero L, Arpin D, Vincent M, et al. A prospective study on radiation pneumonitis following conformal radiation therapy in non-small-cell lung cancer: Clinical and dosimetric factors analysis. Radiother Oncol. 2004;71(2):175–81.
4. Wang J, Cao J, Yuan S, Ji W, Arenberg D, Dai J, et al. Poor baseline pulmonary function may not increase the risk of radiation-induced lung toxicity. Int J Radiat Oncol Biol Phys. 2013;85(3):798–804.
5. Palma D, Senan S, Tsujino K, Barriger R, Rengan R, Moreno M, 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):444–50.
6. Robnett TJ, Machtay M, Vines EF, Mckenna MG, Algazy KM, Gillies Mckenna W. Factors predicting severe radiation pneumonitis in patients receiving definitive chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys. 2000;48(1):89–94.
7. Monson J, Stark J, Reilly J, Sugarbaker D, Strauss G, Swanson S, Decamp M, Mentzer S BE. Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. Cancer. 1998;82(5):842–50.
8. 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):649–55.
9. Wang S, Campbell J, Stenmark MH, Zhao J, Stanton P, Matuszak MM, et al. Plasma levels of IL-8 and TGF-β1 predict radiation-induced lung toxicity in

non-small cell lung cancer: a validation study. Int J Radiat Oncol Biol Phys. 2017;98(3):615–21.

10. Li F, Zhou Z, Wu A, Cai Y, Wu H, Chen M, et al. Preexisting radiological interstitial lung abnormalities are a risk factor for severe radiation pneumonitis in patients with small-cell lung cancer after thoracic radiation therapy. Radiat Oncol. 2018;13(1):1–9.
11. Hernando ML, Marks LB, Bentel GC, Zhou S-M, Hollis D, Das SK, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys. 2001;51(3):650–9.
12. Fay M, Tan A, Fisher R, Mac Manus M, Wirth A, Ball D. Dose-volume histogram analysis as predictor of radiation pneumonitis in primary lung cancer patients treated with radiotherapy. Int J Radiat Oncol Biol Phys. 2005;61(5):1355–63.
13. Roach M, Gandara DR, Yuo H-S, Swift PS, Kroll S, Shrieve DC, et al. Radiation pneumonitis following combined modality therapy for lung cancer: analysis of prognostic factors. J Clin Oncol. 1995;13(10):2606–12.
14. Segawa Y, Takigawa N, Kataoka M, Takata I, Fujimoto N, Ueoka H. Risk factors for development of radiation pneumonitis following radiation therapy with or without chemotherapy for lung cancer. Int J Radiat Oncol Biol Phys. 1997;39(1):91–8.
15. Boonyawan K, Gomez DR, Komaki R, Xu Y, Nantavithya C, Allen PK, et al. Clinical and dosimetric factors predicting grade ≥2 radiation pneumonitis after postoperative radiotherapy for patients with non-small cell lung carcinoma. Int J Radiat Oncol Biol Phys. 2018;101(4):919–26.
16. Choi N, Kanarek D. Toxicity of thoracic radiotherapy on pulmonary function in lung cancer. Lung Cancer. 1994;10(Supplement 1):S219–30.
17. Makimoto T, Tsuchiya S, Hayakawa K, Saitoh R, Mori M. Risk factors for severe radiation pneumonitis in lung cancer. Jpn J Clin Oncol. 1999;29(4):192–7.
18. Sanuki N, Ono A, Komatsu E, Kamei N, Akamine S, Yamazaki T, et al. Association of computed tomography-detected pulmonary interstitial changes with severe radiation pneumonitis for patients treated with thoracic radiotherapy. J Radiat Res. 2012;53(1):110–6.
19. Ozawa Y, Abe T, Omae M, Matsui T, Kato M, Hasegawa H, et al. Impact of preexisting interstitial lung disease on acute, extensive radiation pneumonitis: Retrospective analysis of patients with lung cancer. PLoS One. 2015;10(10).
20. Ohe Y, Yamamoto S, Suzuki K, Hojo F, Kakinuma R, Matsumoto T, et al. Risk

factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. Eur J Cancer. 2001;37(1):54–63.

21. Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. Eur J Cancer. 1998;34(1):71–5.
22. Ueki N, Matsuo Y, Togashi Y, Kubo T, Shibuya K, Iizuka Y, et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. J Thorac Oncol. 2015;10(1):116–25.
23. Bahig H, Filion E, Vu T, Chalaoui J, Lambert L, Roberge D, et al. Severe radiation pneumonitis after lung stereotactic ablative radiation therapy in patients with interstitial lung disease. Pr Radiat Oncol. 2016;6(5):367–74.
24. Yoshitake T, Shioyama S, Asai K, Nakamura K, Sasaki T, Ohga S, et al. Impact of interstitial changes on radiation pneumonitis after stereotactic body radiation therapy for lung cancer. Anticancer Res. 2015;35(9):4909–14.
25. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017.
26. Edge SB, Fritz AG, Byrd DR, Greene FL, Trotti A, Compton CC. AJCC Cancer Staging Manual, 7th edition. Springer. 2010;
27. Australian Bureau of Statistics. Australian Health Survey: First Results, 2011-12. 2012.
28. Chen H, Senan S, Nossent EJ, Boldt RG, Warner A, Palma DA, et al. Treatment-related toxicity in patients with early-stage non-small cell lung cancer and coexisting interstitial lung disease: a systematic review. Int J Radiat Oncol Biol Phys. 2017;98(3):622–31.

Figure Legends

Figure 1. *Flow diagram detailing the selection method for cases with PF, and non-cases without PF.*

Figure 2. *Kaplan-Meier curve of Overall Survival for all patients.*

Figure 3. *Kaplan-Meier curves of Overall Survival by Pre-Treatment PF Diagnosis.*

Tables

Table 1. *Patient characteristics. Where ECOG performance status was documented as a range, it was upgraded to the higher number.*
Abbreviations: ECOG = European Cooperative Oncology Group; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; DLCO = diffusion capacity of the lungs for carbon monoxide.

Statistic / Level	Pre-Treatment PF Diagnosis			
	No (n = 84)	**Yes (n = 21)**	**Equivocal (n = 11)**	**Overall (n = 116)**
Age at Treatment Start (years)				
Median [range]	70 [35 - 88]	76 [46 - 86]	73 [54 - 87]	71.5 [35 - 88]
Gender				
Female	31 (37%)	3 (14%)	0	34 (29%)
Male	53 (63%)	18 (86%)	11 (100%)	82 (71%)
ECOG Performance Status				
0	15 (18%)	5 (24%)	2 (18%)	22 (19%)
1	37 (44%)	10 (48%)	6 (55%)	53 (46%)
2	19 (23%)	3 (14%)	2 (18%)	24 (21%)
3	7 (8%)	2 (10%)	0	9 (8%)
Unknown	6 (7%)	1 (5%)	1 (9%)	8 (7%)
Smoking History				
Current	11 (13%)	2 (10%)	1 (9%)	14 (12%)
Former	67 (80%)	18 (86%)	7 (64%)	92 (79%)
Never	6 (7%)	1 (5%)	1 (9%)	8 (7%)
Unknown	0	0	2 (18%)	2 (2%)
Respiratory comorbidities other than PF				
No	33 (39%)	7 (33%)	4 (36%)	44 (38%)
Yes	51 (61%)	14 (67%)	7 (64%)	72 (62%)
Cardiac comorbidities				
No	59 (70%)	9 (43%)	7 (64%)	75 (65%)
Yes	25 (30%)	12 (57%)	4 (36%)	41 (35%)
Sarcoidosis, Connective Tissue Disease				
No	81 (96%)	17 (81%)	10 (91%)	108 (93%)
Yes	3 (4%)	4 (19%)	1 (9%)	8 (7%)
Relevant Drug Exposure				
No	81 (96%)	16 (76%)	10 (91%)	107 (92%)

Yes	3 (4%)	5 (24%)	1 (9%)	9 (8%)
Exposure Other Than Smoking				
Yes	2 (2%)	7 (33%)	2 (18%)	11 (9%)
Possible	3 (4%)	1 (5%)	1 (9%)	5 (4%)
No	2 (2%)	0	0	2 (2%)
Unknown	77 (92%)	13 (62%)	8 (73%)	98 (84%)
Pre-Treatment FEV_1 (L)				
Median [range]	1.72 [0.64 - 4.66]	1.97 [1.12 - 2.98]	2.23 [1.15 - 2.91]	1.79 [0.64 - 4.66]
Unknown	33	3	6	42
Pre-Treatment FVC (L)				
Median [range]	2.82 [1.33 - 6.24]	2.73 [1.94 - 4.22]	3.45 [2.46 - 4.27]	2.86 [1.33 - 6.24]
Unknown	34	3	6	43
Pre-Treatment DLCO (mL/mmHg/min)				
Median [range]	14.4 [5.17 - 35]	12.22 [4 - 22.9]	13.5 [11.3 - 25.5]	13.6 [4 - 35]
Unknown	35	5	7	47
History of Significant Weight Loss				
No	54 (64%)	12 (57%)	6 (55%)	72 (62%)
Yes	24 (29%)	8 (38%)	4 (36%)	36 (31%)
Unknown	6 (7%)	1 (5%)	1 (9%)	8 (7%)

Table 2. *Disease characteristics.*

Statistic	Pre-Treatment PF Diagnosis			
	No (n = 84)	**Yes (n = 21)**	**Equivocal (n = 11)**	**Overall (n = 116)**
Histology				
Adenocarcinoma	30 (36%)	5 (24%)	3 (27%)	38 (33%)
Squamous	32 (38%)	8 (38%)	5 (45%)	45 (39%)
NSCLC, not otherwise specified	16 (19%)	5 (24%)	1 (9%)	22 (19%)
Large cell	3 (4%)	3 (14%)	2 (18%)	8 (7%)
Other	3 (4%)	0	0	3 (3%)
Stage at Diagnosis				
I	15 (18%)	6 (29%)	3 (27%)	24 (21%)
II	13 (15%)	4 (19%)	0	17 (15%)

III	48 (57%)	11 (52%)	7 (64%)	66 (57%)
IV	7 (8%)	0	0	7 (6%)
Unknown	1 (1%)	0	1 (9%)	2 (2%)
Site				
Hilum	5 (6%)	0	1 (9%)	6 (5%)
Lower lobe	16 (19%)	6 (29%)	3 (27%)	25 (22%)
Middle lobe	4 (5%)	0	0	4 (3%)
Upper lobe	53 (63%)	15 (71%)	6 (55%)	74 (64%)
Mediastinum	1 (1%)	0	0	1 (1%)
Other	5 (6%)	0	1 (9%)	6 (5%)

Table 3. *Treatment characteristics.*

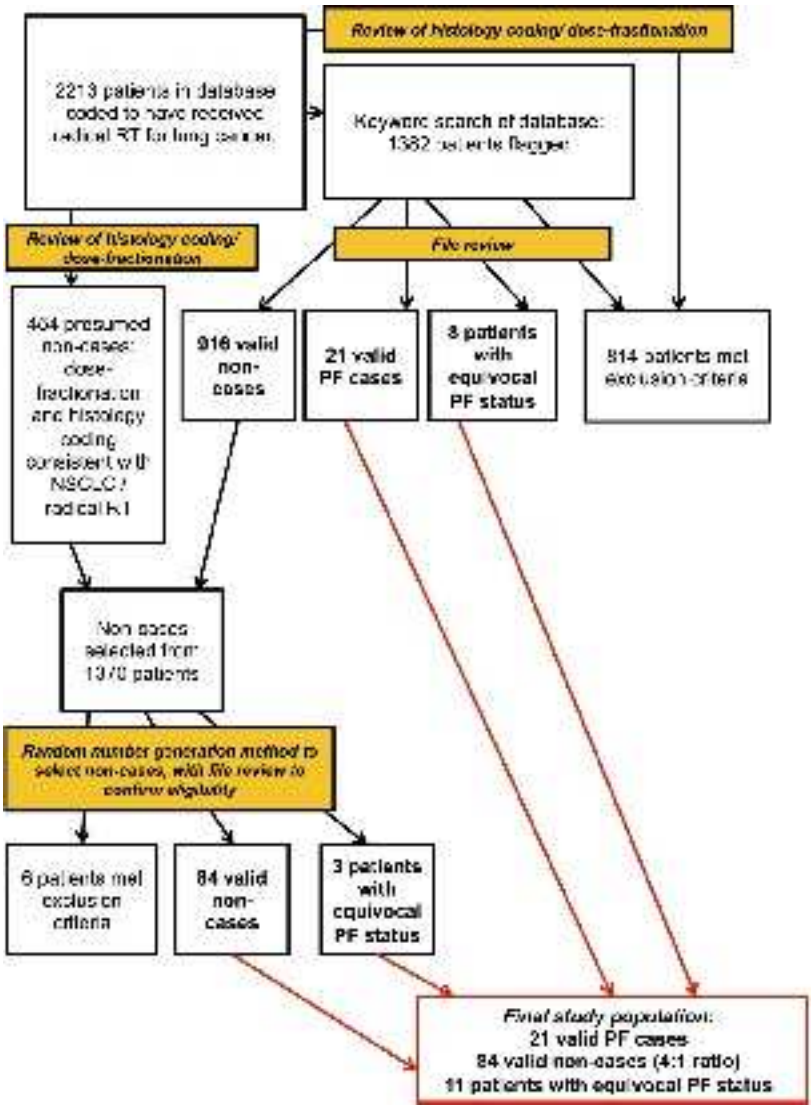
Abbreviation: Gy = Gray.

Statistic / Level	**Pre-Treatment PF Diagnosis**			
	No (n = 84)	**Yes (n = 21)**	**Equivocal (n = 11)**	**Overall (n = 116)**
Surgery within 6 months of RT				
Yes (planned surgery post neoadjuvant RT)	1 (1%)	0	0	1 (1%)
Yes (salvage surgery for residual or recurrent disease)	2 (2%)	0	0	2 (2%)
No surgery	81 (96%)	21 (100%)	11 (100%)	113 (97%)
Mean Lung Dose (Gy)				
Median [range]	14.9 [4 - 23.5]	10.8 [3.4 - 20.29]	10.38 [6.65 - 15.56]	13.8 [3.4 - 23.5]
Unknown	19	1	3	23
Total Radiation Dose Prescribed (Gy)				
< 50	1 (1%)	0	0	1 (1%)
50-59	10 (12%)	3 (14%)	1 (9%)	14 (12%)
≥ 60	73 (87%)	18 (86%)	10 (91%)	101 (87%)
Total Radiation Dose Received (Gy)				
< 50	4 (5%)	3 (14%)	1 (9%)	8 (7%)
50-59	11 (13%)	5 (24%)	1 (9%)	17 (15%)
≥ 60	69 (82%)	13 (62%)	9 (82%)	91 (78%)

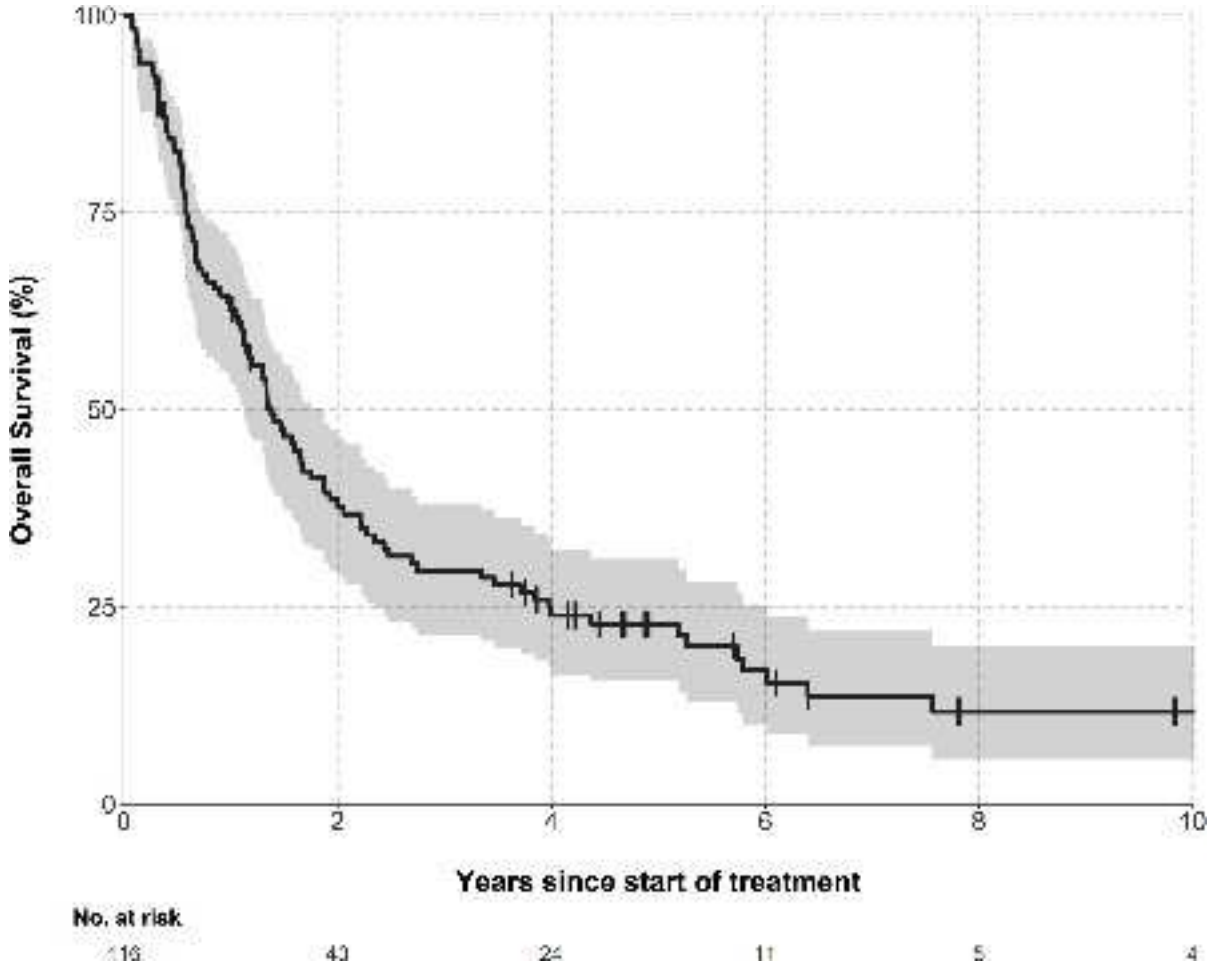
Fractionation				
Standard	81 (96%)	20 (95%)	10 (91%)	111 (96%)
Hypo-fractionated	3 (4%)	1 (5%)	1 (9%)	5 (4%)
Chemo/RT Sequence				
No chemotherapy	24 (29%)	10 (48%)	4 (36%)	38 (33%)
Concurrent chemotherapy	54 (64%)	10 (48%)	7 (64%)	71 (61%)
Sequential chemotherapy and RT	0	1 (5%)	0	1 (1%)
Both concurrent and sequential	6 (7%)	0	0	6 (5%)

Table 4. *RP severity by grade*

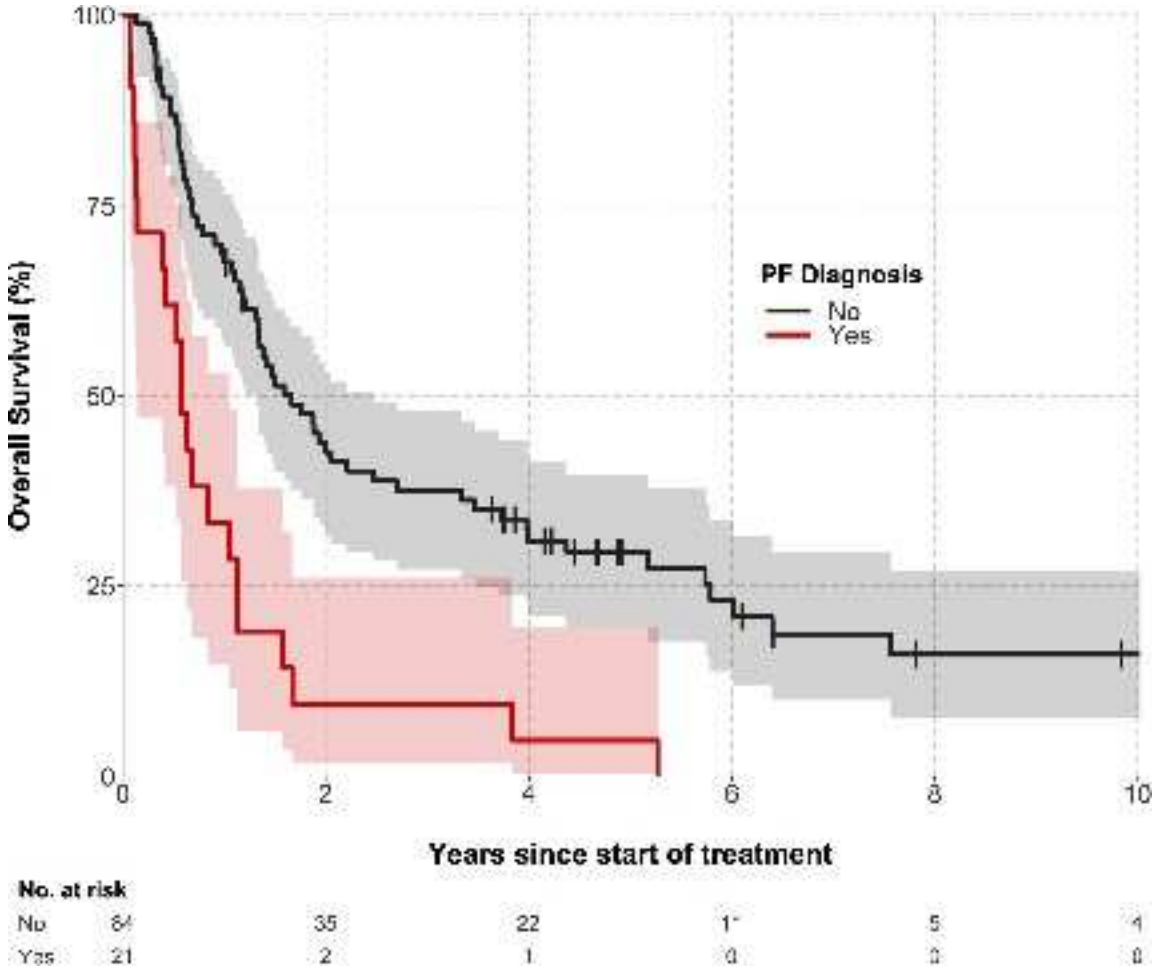
Radiation Pneumonitis Grade	**Pre-Treatment PF Diagnosis**			
	No	**Yes**	**Unknown**	**Sum**
0-1	65	11	8	84
2	14	5	2	21
3	3	1	1	5
4	1	1	0	2
5	1	3	0	4
Sum	84	21	11	116



ara_13041_f1.jpg



ara_13041_f2.tiff



ara_13041_f3.tiff

Author/s:
Bajraszewski, C;Manser, R;Chu, J;Cox, RA;Tran, P;Duffy, M;Irving, L;Herschtal, A;Siva, S;Ball, D

Title:
Adverse respiratory outcomes following conventional long-course radiotherapy for non-small-cell lung cancer in patients with pre-existing pulmonary fibrosis: A comparative retrospective study

Date:
2020-05-09

Citation:
Bajraszewski, C., Manser, R., Chu, J., Cox, R. A., Tran, P., Duffy, M., Irving, L., Herschtal, A., Siva, S. & Ball, D. (2020). Adverse respiratory outcomes following conventional long-course radiotherapy for non-small-cell lung cancer in patients with pre-existing pulmonary fibrosis: A comparative retrospective study. JOURNAL OF MEDICAL IMAGING AND RADIATION ONCOLOGY, 64 (4), pp.546-555. https://doi.org/10.1111/1754-9485.13041.