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Original Article

Influence of tumour laterality on patient survival in non-small cell lung cancer after radiotherapy

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ABSTRACT

Background: Lung cancer survival after radiotherapy remains poor and greater knowledge of normal tissue risk factors is needed to further optimise treatments. In this work, we investigate tumour laterality in a large cohort of patients treated with curative-intent radiotherapy, including the effect of dose on the right and left lungs.

Methods: 1101 NSCLC patients were included in the analysis, treated with 55 Gy in 20 fractions. Tumour laterality was determined by comparing the centre of mass of the tumour volume with the centre of mass of the lung. Right and left lungs were segmented from the whole lung contour and the mean dose to each volume calculated. Laterality and mean lung doses were included in multi-variable cox-regression survival models.

Results: 1026 patients were eligible for inclusion; 579 right-sided and 447 left-sided tumours were identified. All tumour and patient characteristics were balanced with laterality. The multi-variable models were controlled for known clinical factors: tumour volume ($p < 0.001$), age ($p < 0.001$), performance status ($p < 0.05$) and nodal stage ($p < 0.01$). Multi-variable analysis showed laterality to be highly significant ($p < 0.01$) with right-sided tumours showing worse overall survival than left-sided tumours (15 versus 18 months). The right lung mean dose was found to be significant ($p = 0.03$) for overall survival but the left lung mean dose was not ($p = 0.78$).

Conclusion: Our study showed that right-sided lung tumours show worse overall survival for NSCLC treated with curative-intent radiotherapy. Results suggest that the effect of laterality is through a difference in dose–response for individual lungs, with the larger, right lung, having the greater impact on survival.
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Survival in non-small cell lung cancer (NSCLC) remains poor; in the UK less than 10% of patients survive at five years. This is despite recent advances in radiotherapy technology that have enabled a larger proportion of locally advanced patients to be treated with curative intent, while maintaining the dose received by normal tissues within acceptable safety limits [1,2].

To fully realise the potential for improved survival, the risk of normal tissue toxicities needs to be minimised. However, there remains uncertainty in the safety tolerances that should be applied to organs at risk. There has been much recent interest in the effect of radiation dose to the heart for NSCLC patients and the impact on adverse cardiac events and survival [3–5]. Research is currently ongoing to investigate the effect of radiation on cardiac substructures. By contrast, safety tolerances for the normal lung tissue have not recently been revisited and are generally believed to be better understood. Normal lung safety tolerances are primarily based on a pooled analysis, undertaken in 1998, of 540 NSCLC patients showing that mean lung dose is predictive of radiation induced pneumonitis [6]. Additionally, a study by Graham showed the importance of the volume of lungs receiving 20 Gy as also being predictive of radiation induced pneumonitis [7].

One characteristic of the tumour that is likely to drive the mean lung dose is position and in particular, laterality. Importantly, lungs are asymmetric with the right lung being larger than the left. Tumour laterality drives the spatial distribution of the planned dose and therefore the mean lung dose received by the patient. Recent work has investigated the tumour location for patients treated with stereotactic ablative radiotherapy (SABR). Shaverdian et al. [8] reported that lower lobe tumours were associated with worse relapse free survival. Interestingly, the authors discuss the variation in ventilation and perfusion across the lungs, with the lower lobes being overperfused, potentially fuelling a more

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aggressive disease. However, these were small, stage one, NSCLC tumours and they did not discuss any potential impact of the tumour position on the dose to normal tissues.

An epidemiology study looked at the effect of tumour laterality on 5 paired organs, including the lung in >97,000 lung cancer patients [9]. They showed that left-sided tumours had better survival, although this finding was not statistically significant. This study did not selectively look at patients treated with radiotherapy for curative intent, and therefore it did not include any analysis of the dose to normal tissues or account for tumour volume.

In this paper, we investigate the impact of tumour laterality and its influence on lung mean dose and overall survival. In particular, we will include the mean dose to the right and left lung volumes in the analysis individually.

Methods

1101 advanced (stage 3–4) NSCLC patients, treated radically with 55 Gy in 20 fractions, were included in the analysis (patients treated between 2010 and 2013). Institutional approval had been gained to analyse the data of these patients (research ethics committee reference: 17/NW/0060). No further discrimination was made based on patient or disease characteristics, and detailed information on patients' co-morbidities was only available for a proportion of the full cohort. Radiotherapy planning information was collected from the treatment planning system archive (Philips Pinnacle treatment planning system, vr9.0-9.8). All patients had planning CT, planned dose distributions and radiotherapy planning contours available. All patients were scanned and treated with free breathing. Contours included a whole lung contour and either a gross tumour volume (GTV) or motion-adapted GTV (mGTV).

As individual lung contours were not available in the treatment plans for these patients the combined lung contour was used to automatically segment the right and left lung volumes. The combined lung contour was first split into individual, isolated, volumes. The two largest volumes were kept as the right and left lungs. This step removed any small volumes from the analysis, which may result from the auto-thresholding of the lung in the treatment planning system incorrectly including air in other organs. Ideally, these should have been removed at the planning stage but did remain for some patients. The larger volume was assigned to be the right lung while the smaller was assigned to be the left lung, corresponding to the anatomical volume differences. Labels were confirmed by comparing the centre of mass (COM) coordinate of the labelled right and left lungs against the COM of the combined lung contour, i.e. patient's post-surgery or with lung collapse may be mislabelled by this approach. Additionally, lung volumes were checked to ensure they remained inside clinically acceptable values. The average total lung capacity is approximately 5.2 L (standard deviation 0.7 L) for females and 7.0 L (standard deviation 1.0 L) for males [10]. Therefore, a threshold of <8 L was set across the study population. Any larger volumes would indicate that the segmentation was incorrect and the patient was removed from further analysis. These volumes were used to calculate the mean dose received by the right and left lung for every patient (after subtraction of the overlapping GTV/mGTV).

Tumour laterality was calculated by determining whether the COM of the GTV/mGTV was placed to the right or left of the centre of the combined lungs. This allowed patients to be classified automatically as having right-sided or left-sided tumours. Additional patient and tumour characteristics were collected for comparison between groups. Importantly, tumour volume (total of primary and nodal disease) was collected for all patients as volume is a known predictor for survival but will also influence the spatial distribution of dose delivered to any anatomical region, including the lungs.

Patient and tumour characteristics were investigated between the right and left-sided tumour groups to ensure that all parameters were well balanced and no bias was present. To investigate any correlation between mean dose to the contralateral and ipsilateral lungs scatter plots were created. A Pearson correlation was calculated for right and left-sided tumours for the mean dose delivered to each lung.

A cox-regression uni-variable analysis investigated individual parameters (patient and tumour) significantly associated with patient survival. These parameters were also included in cox-regression multi-variable survival models. Hazard ratios were calculated for all variables with 95% confidence intervals. A multi-variable model was constructed to investigate the effect of laterality alone before a second model included the mean dose on the right and left lung volumes and included the mean dose to the heart. As not all patients had heart contours available, we used ADMIRE vr2.0 to propagate heart contours from a set of atlas patients, validation is included in supplementary materials (S4). This allowed possible interactions between tumour laterality, mean dose to left and right lungs and mean heart dose to be investigated in a multi-variable model.

Two further exploratory analysis were undertaken. First, as the dose–response to the heart, or cardiac sub-structures is still unclear, we explored the effect of mean dose to the left and right lung volumes alone in a multi-variable model. Second, a sub-set analysis was performed where patients had histology available. Histology can drive tumour location, squamous cell carcinoma (SCC) tends to arise centrally while adenocarcinomas tend to arise in the periphery of the lungs. This allowed us to explore whether spatial location of the dose may be driving any laterality effect. Differences in tumour volume and individual lung mean dose were explored for SCC and adenocarcinomas. Additionally, separate multi-variable models were created for SCC and adenocarcinomas to investigate the influence of laterality in each histological subtype.

Finally, Kaplan–Meier's curves were plotted comparing right and left-sided tumours. A Log-rank test was performed to show any significance in overall survival, with mean survival times calculated. All statistical analysis was performed using R, vr3.3.2.

Results

From the 1101 patients identified for this analysis, 75 patients were excluded because of incorrect lung segmentation with volumes outside the defined acceptable clinical range of 8 L. Incorrect segmentations resulted in volumes much greater than an accepted clinical range, with calculated lung volumes greater than 50 L. For the 1026 patients that remained in the analysis, the median right lung volume was found as 1.9 L (1st and 3rd quartiles:1.6 L and 2.4 L) and the left lung median volume as 1.6 L (1.3 L, 2.1 L). Patient demographics are included in Table 1.

Table 2 shows the tumour position results and dose received to the segmented right and left lungs in each group. 579 tumours were right-sided lung tumours and 447 left-sided lung tumours; therefore 30% more right-sided tumours were found. No significant differences were found between any patient or tumour characteristics between the right and left-sided tumour groups (Supplementary material, S1). The median tumour volumes (primary + nodal disease) were 38.0 cm^3 (1st and 3rd quartiles: 14.1 cm^3, 74.30 cm^3) for right-sided tumours and 35.8 cm^3 (15.3 cm^3, 72.6 cm^3) for left-sided tumours. A Welch two sample t-test performed comparing right and left lung tumour volume showed no significant difference ($p = 0.86$).

Table 1
Patient demographics from the 1026 patients selected for analysis. Not all patients had complete sets of records available; the 'Total in group' column shows the number of data points available for each variable.

	Female	470	(100%)
Age (median)		73 (38–94)	1026 (100%)
Tumour size (cm^3) (median)		35.8	1026 (100%)
Smoking history	Current	143	325
	Ex-smoker	177	(32%)
	Life-long non smoker	5	
Co-morbidity score (ACE27)	0	42	347
	1	108	(34%)
	2	122	
	3	75	
T Stage	T1	147	934
	T2	407	(91%)
	T3	217	
	T4	163	
N stage	N0	507	938
	N1	131	(91%)
	N2	240	
	N3	60	
Performance Status	0	127	910
	1	412	(89%)
	2	313	
	3	58	
Induction chemotherapy	Yes	250	1026
	No	776	(100%)

Lung mean doses are listed in Table 2, shown for the combined lung volume and for the right and left lungs and their contralateral counterparts individually. Across all patients the mean dose was 12.3 Gy for the combined lung volume, with the right lung receiving a mean dose of 12.9 Gy and left lung a mean dose of 12.0 Gy. The following correlations between dose to contralateral and ipsilateral lungs were performed:

Correlation for ipsilateral lungs for right/left tumours: The mean lung doses of ipsilateral lungs were 19.3 Gy and 20.4 Gy for right and left-sided lung tumours, respectively. A Welch two sample t-test showed a significance difference in the dose received, $p = 0.03$, with left-sided lung tumours showing greater ipsilateral lung dose.

Correlation for contralateral lungs for right/left tumours: The mean lung dose of the contralateral lungs were 6.2 Gy and 6.4 Gy for right and left-sided tumours, respectively. The t-test showed there was no statistical significance between these groups, $p = 0.3$.

Correlation between ipsilateral and contralateral lungs for right/left tumours: Fig. 1 plots the correlation between the contralateral and ipsilateral mean lung doses for right-sided and left-sided tumours. Right-sided lung tumours displayed a moderate correlation, Pearson's correlation coefficient of 0.57. For left sides tumours the Pearson correlation was 0.36, Fig. 1.

Survival analysis

Tumour laterality and mean right and left lung doses were included in a uni-variable cox-regression, Table 3. The uni-variable analysis showed laterality is highly significant, survival being worse in patients with right-sided tumours ($p = 0.01$), hazard ratio (HR) 1.21 (1.05–1.41 95% CI). The right lung mean dose was highly significant ($p < 0.001$), HR 1.03 (1.02–1.03), analysed as a continuous variable. However, the left lung mean dose showed no significance in the uni-variable survival analysis ($p = 0.41$). Additionally, mean dose to the heart was significant on uni-variable analysis, ($p < 0.001$), HR 1.02 (1.02–1.03), analysed as a continuous variable. Other variables tested showed agreement with the published literature with gender, tumour size, T-stage (categorical), N-stage (categorical) and performance status (categorical) showing significance in the uni-variable analysis.

The multi-variable cox-regression analysis including tumour laterality alone showed that patients with right-sided tumours have significantly worse survival ($p < 0.01$), HR 1.26 (1.08–1.48). Tumour volume was also found to be highly significant ($p < 0.001$) as was age, ($p < 0.001$), N-stage ($p < 0.01$) and performance status ($p < 0.05$). Mean dose to the heart was also significant ($p = 0.2$), HR 1.02 (1.00–1.03). Right and left mean lung doses, with mean dose to the heart, were included in a second multi-variable model. In this analysis, the left lung mean dose, right lung mean

Table 2
Patient numbers for right and left-sided tumours are included with median tumour volumes and mean doses (across all patients) for the whole lung volume and individual right and left lung volumes. No significant differences were found between these groups except for the ipsilateral lungs, where left sided tumours delivered a significantly higher mean dose to the left lung compared to the right sided tumours ($p = 0.03$).

	Number patients	Median tumour volume (cm^3)	Both lung mean dose (Gy)	Right lung mean dose (Gy)	Left lung mean dose (Gy)
Both Lungs	1026	35.8	12.3	13.6	12.1
Right lung	579	38.0	12.9	19.3	6.2
Left lung	447	35.8	12.0	6.4	20.4

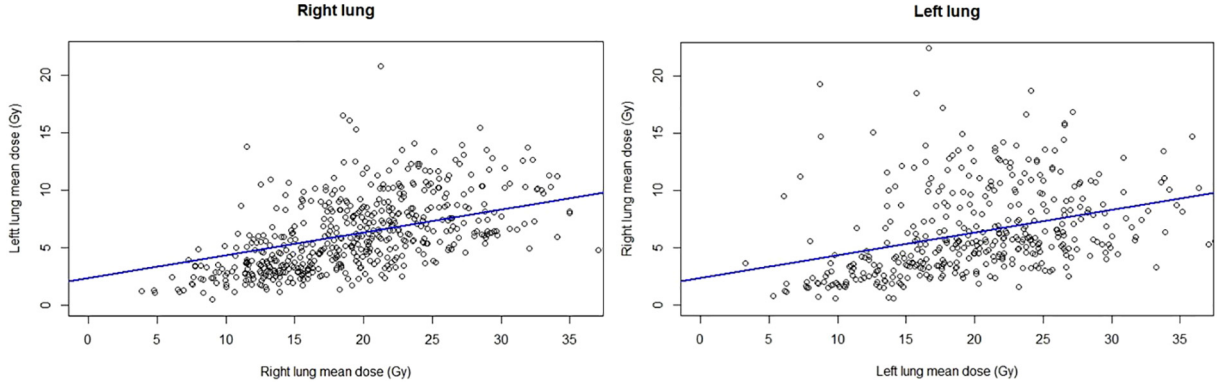

Fig. 1. Scatter plots showing the correlation between mean lung dose for the ipsilateral and contralateral lungs for right-sided and left-sided tumours. Right-sided lung tumours showed a moderate correlation of 0.57 whereas left-sided tumours showed no significant correlation, 0.36.

Table 3
Uni-variable and multi-variable survival analysis. The first multi-variable model explores patient and tumour characteristics with laterality alone. The second includes the mean doses for the right and left lungs and mean dose to the heart. The hazard ratio with 95% confidence intervals are included, categorical or continuous variables are indicated in the table.

	Uni-variable		Multi-variable		Multi-variable (All)	
	HR (95% CI)	p	HR (95% CI)	P	HR (95% CI)	P
Tumour volume (log) (continuous)	1.35 (1.27–1.45)	<0.001	1.27 (1.17–1.39)	<0.001	1.28 (1.17–1.41)	<0.001
Laterality (right vs. Left)	1.21 (1.05–1.41)	0.01	**1.26 (1.08–1.48)**	**0.004**	–	–
Left lung mean dose (continuous)	1.00 (0.99–1.01)	0.41	–	–	**1.00 (0.99–1.00)**	**0.22**
Right lung mean dose (continuous)	1.03 (1.02–1.03)	<0.001	–	–	**1.01 (1.00–1.03)**	**0.33**
Age (continuous)	1.01 (1.01–1.02)	0.002	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Gender (Male vs. female)	1.20 (1.04–1.39)	0.01	1.17 (1.0.00–1.37)	0.06	1.16 (0.00–1.34)	0.07
T-Stage						
(T1 reference)	**T2** 1.37 (1.05–1.68)	0.02	1.02 (0.79–1.33)	0.85	1.02 (0.79–1.32)	0.88
	T3 1.65 (1.27–2.13)	<0.001	1.07 (0.80–1.43)	0.66	1.07 (0.80–1.43)	0.63
	T4 1.78 (1.36–2.33)	<0.001	1.12 (0.83–1.53)	0.46	1.12 (0.82–1.52)	0.47
N-stage						
(N0 reference)	**N1** 0.98 (0.78–1.24)	0.86	0.86 (0.68–1.10)	0.24	0.86 (0.68–1.11)	0.25
	N2 1.58 (1.32–1.88)	<0.001	1.32 (1.08–1.62)	<0.01	1.33 (1.08–1.64)	<0.01
	N3 1.42 (1.05–1.92)	0.02	1.62 (1.18–2.22)	<0.01	1.61 (1.17–2.22)	<0.01
Performance status						
(PS 0 reference)	**1** 1.29 (1.03–1.63)	0.03	1.26 (0.98–1.62)	0.06	1.27 (0.99–1.63)	0.06
	2 1.35 (1.07–1.72)	0.01	1.51 (1.17–1.96)	<0.01	1.51 (1.17–1.96)	<0.01
	3 1.79 (1.27–2.53)	<0.001	1.54 (1.06–2.23)	0.02	1.54 (1.06–2.23)	0.02
Mean heart dose (continuous)	**1.02 (1.02–1.03)**	**<0.001**	**1.02 (1.00–1.03)**	**0.02**	**1.01 (1.00–1.03)**	**0.07**

Results in bold highlight the impact of laterality in both multi-variable models.

dose and heart mean dose were not significant ($p = 0.22$, 0.33, 0.07 respectively). Tumour volume remained highly significant ($p < 0.001$), as did age, N-stage and performance status. These results suggest an interaction between dose between the lung volumes and the heart.

The equivalent multi-variable models excluding the mean dose to the heart are included in the supplementary material (S2). In this analysis, dose to the right lung is significant ($p = 0.03$) but not the mean dose to the left lung ($p = 0.78$).

Additionally, a sub-set analysis with patients grouped by tumour histology is included in the supplementary material (S3). 522 patients had confirmed tumour histology, 325 adenocarcinoma and 197 SCC. Tumour volumes were significantly different with SCC larger, median volume 56.0 cm^3 versus 14.1 cm^3 for adenocarcinoma ($p < 0.001$). Larger tumour volumes result in significantly larger doses for each lung volume for SCC: right lung mean dose 17.4 Gy versus 9.3 Gy ($p < 0.001$), left lung mean dose 14.1 Gy versus 8.4 Gy ($p < 0.001$). However, despite these larger tumour volumes and mean lung dose for SCC, Table S2 shows that laterality remains significant, in the multi-variable analysis, only for adenocarcinoma. Right versus left tumours HR 1.44 (1.03–2.01, $p = 0.03$), where in SCC it is not significant ($p = 0.16$).

Finally, a Kaplan–Meier survival curve was plotted with patients grouped on tumour laterality, Fig. 2. Right-sided lung tumours do significantly worse than left-sided lung tumours (Log-rank $p = 0.006$). The median survival time was 15 months for right-sided tumours and 18 months for left-sided tumours.

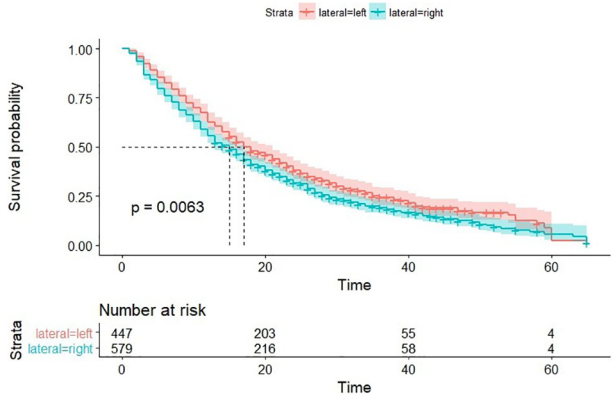

Fig. 2. Kaplan–Meier's survival curves categorised by tumour laterality with numbers at risk included. These curves show the uni-variable Kaplan–Meier as all other clinical variables are well balanced with laterality. Right-sided tumours show a significantly worse survival than left sided tumours (log-rank $p = 0.006$).

Discussion

This work shows that tumour location in patients undergoing radiotherapy plays an important role in overall survival. Patients with left-sided lung cancer tumours do significantly better than those with right-sided tumours with median survival times of 18 and 15 months respectively (Log-rank $p = 0.006$). In multi-variable survival analysis, patients with right-sided tumours have worse survival, confirming the significant impact of laterality (HR 1.26, $p < 0.01$). It could be concluded that laterality drives survival, however our analysis indicates that laterality may be acting as a surrogate for mean dose to the individual lung volumes. Including the mean dose to the right and the left lungs into the multi-variable model showed that the right lung mean dose was significantly associated with patient survival ($p = 0.03$). However, left lung mean dose was not significantly associated with survival. This was also seen in the uni-variable survival analysis where right lung mean dose was significant ($p < 0.001$) but the left lung mean dose was not significant. However, Table 3 includes mean dose to the heart, when this is included into the multi-variable model none of the mean doses to the left, right or heart volumes shows significance. This indicates that the difference in survival with laterality may be acting through a complex interaction between a differential dose–response of the lung volumes and an interaction with the heart. However, without clearer guidance on the heart dose sensitivity and relevant individual sub-structures we are reluctant to draw any strong conclusions from this analysis.

It is worth discussing briefly the method used to classify tumour laterality. Tumour laterality was not available in the electronic records for these patients, therefore an automatic

classification system was implemented to enable the large cohort analysis. In this paper we used the clinician contoured tumour volume to calculate its COM and compare it against the COM of the lungs. This allowed tumours to be labelled right or left-sided. In our institution clinicians delineate the entire target volume under the one contour, i.e. primary disease and any nodal involvement. Therefore, it would be possible for patients with small tumours and extensive nodal involvement, crossing the mid-line, to be mis-classified. We performed a manual inspection of the N3 patients (60) where there was the highest change of extensive mediastinal lymph node involvement and found that none was mis-labelled. Therefore, we are confident that this will not be a common occurrence in the larger cohort of patients and will not influence the results.

Anatomically, there is a difference in lung volumes, with the right lung larger than the left (the right lung has three lobes whereas the left has two lobes). The right lung is approximately 20% larger than the left and we found approximately 30% more right-sided lung cancer tumours. However, it was found that tumour characteristics and patient demographics were not significantly different between right and left-sided tumours (S1). Additionally, approximately two-thirds of the heart volume is situated in the left hemi-thorax. This asymmetry in the anatomy will drive the selection of beam angles in creating the plan. (Plans in this study were approximately 2/3 3D-conformal and 1/3 intensity modulated radiation therapy, no difference in patient characteristics and results was found between delivery techniques.) For left-sided tumours, the heart position may act to protect the right lung from excess radiation dose. This may explain the difference in the scatter plots in Fig. 1, where, for left-sided tumours we see no significant correlation with the dose to the right lung, whereas for the right-sided tumours, there is a moderate correlation with the contralateral (left-sided) dose.

The previously published epidemiology study of >97,000 lung cancer patients by Roychoudhuri et al. [9] showed, for lung cancer, patients treated with radiotherapy as part of their treatment, the difference between 5-year survival for patients with right-sided and left-sided tumours was 6.08% and 6.14% for males and 5.26% and 5.50% for females, respectively. However, these differences were not found to be significant in their analysis. The work investigated the impact of laterality across 5 major paired-organs after any treatment for cancer, not just radiotherapy, and did not investigate any effect from the radiation dose received by normal tissues. Interestingly, a study performed on NSCLC patients treated with pneumonectomy found that surgical resection of the right lung resulted in worse early and late survival than resection of the left lung [11]. A further aspect of tumour location that may drive survival is the lobe where the tumour is situated. A recent meta-analysis by Lee et al investigated the published literature and concluded that there was no significant difference in survival for patients treated with radiotherapy based on lobe location [12]. This disagrees with the conclusion from the paper by Shaverdian et al [8] which reported lower lobe tumours have worse survival in stage 1 patients. However, neither study analysed dose to normal tissue as presented in this paper.

Laterality studies for other patient groups have focused on breast cancer, where it is found that left-sided tumours are associated with worse normal tissue toxicities and survival [13], opposite to our analysis. Here, this difference is attributed to cardiac toxicity, where left-sided tumours result in a higher dose to the heart and in particular the left coronary artery. We performed a secondary analysis to include the mean dose to the heart (S2). This analysis showed that laterality still remained significant with right-sided tumours doing worse ($p < 0.01$). Dose to the heart was also significant in this analysis ($p = 0.02$).

Additionally, breast cancer patients are generally younger and healthier than NSCLC patients, with less co-morbidities, than the NSCLC patient population. Lifestyle plays an important role in NSCLC with the majority of patients being ex or current smokers. Indeed, a limitation of our analysis is lack of data on the actual cause of death of these patients; due to treatment related toxicities, tumour progression or recurrence or other cause. Additionally, we do not have accurate information on patient co-morbidities for this retrospective cohort. The majority of lung cancer patients smoke and therefore, have associated chronic cardiac and respiratory illnesses. Approximately a third of the patients in this analysis (n = 347) had an ACE27 co-morbidity score recorded. Therefore, we could not control for this variable in the full analysis. However, we did analyse this sub-set in a uni-variable analysis and found no statistical significance for patient survival. The ACE27 scale is based on all co-morbidities and more detailed information on specific patient co-morbidities is required. These observations highlight the need for prospective studies, where there is a focus on capturing detailed co-morbidities for every patient. This will allow more robust future analysis to answer these questions.

Tumour histology can be used as a surrogate for tumour position; adenocarcinoma tends to be located peripherally in the lung while SCC tends to arise in the central airways. The small histology subset analysis (S3) can therefore, be interpreted as central versus peripheral disease. Here, despite the larger tumour volumes and therefore mean lung doses for SCC, laterality was not significantly associated with survival. This may be because more central disease results in a more uniform spread of radiation across both lung volumes. In patients with adenocarcinoma histology, and therefore generally more peripheral disease, radiotherapy treatments can be optimised to better spare the contra-lateral lung volume. For adenocarcinoma, laterality was significantly associated with survival, right-sided tumours resulting in higher mortality, HR 1.44, $p = 0.03$.

Considering the tumour histology sub-set analysis as central versus peripheral disease is interesting in the context of recent work performed with murine models [14] and now being translated to NSCLC patients [15]. This work investigates the interaction of radiation effects between the lungs and the heart. For patients receiving greater than 15 Gy mean dose to the whole lung volume they noted elevated pulmonary hypertension in measurements taken 6 and 12 weeks post radiotherapy. As the right lung is larger, this may also cause an asymmetric effect with excess dose to the right lung having a greater impact on survival. Results from the murine models suggest the elevated pulmonary hypertension arises from damage to the micro-vasculature, with the greatest effect seen in the periphery of the lungs. This is interesting as laterality seems to be a greater effect for the adenocarcinoma disease where the dose is focused more on the periphery. This hypothesis needs further validation in prospective studies.

The patients in our institution are treated with free breathing. It would be interesting to test this result in further populations of lung cancer patients treated with other breathing management strategies to investigate if this has an influence. Furthermore, it is commonly accepted that the lung displays a parallel structure. Therefore, wherever excess dose in the lung was incident it would have the same impact on survival. Our results suggest otherwise, with excess dose to the right lung showing a greater effect. One hypothesis that should be considered is that the lung may display an aspect of seriality, where excess dose can also affect the lung function further along the organ's structure. As the right lung is larger, this may account for the observed greater impact on patient survival. This hypothesis should be tested in animal models or in future imaging studies investigating the impact of radiation dose on lung function.

Further analysis is clearly required to understand this apparent differential dose–response between the lung volumes. Methods to quantify the spatial dose distributions versus patient survival may, ultimately, allow a dose–response map of the lungs to be created. This will be the focus of further research where such a map could feed directly into the plan optimisation for every patient.

In conclusion, our analysis indicates the effect of laterality is through a difference in the dose–response for individual lungs. These results show that the excess dose to the right lung has a greater impact on overall patient survival and therefore suggest that individual dose constraints should be considered for each lung volume.

The authors declare no potential conflicts of interest.

Statistical analysis was performed by Dr Alan McWilliam with discussion with Prof Marcel van Herk

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.04.022.

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