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Original Article

Palliative Lung Radiotherapy: Higher Dose Leads to Improved Survival?

T.S. Lewis [*], J.A. Kennedy [*], G.J. Price [*†], T. Mee [*‡], D.K. Woolf [*‡], N.A. Bayman [*], C. Chan [*], J.H. Coote [*], C. Faivre-Finn [*‡], M.A. Harris [*], A.M. Hudson [*‡], L.S. Pemberton [*], A. Salem [*‡], H.Y. Sheikh [*], H.B. Mistry [‡§], D.C.P. Cobben [*‡]

[*] *Department of Radiotherapy Related Research, The Christie NHS Foundation Trust, Manchester, UK*
[†] *Manchester Academic Health Science Centre, University of Manchester, Manchester, UK*
[‡] *Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK*
[§] *Division of Pharmacy and Optometry, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK*

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Abstract

Aims: Choosing the optimal palliative lung radiotherapy regimen is challenging. Guidance from The Royal College of Radiologists recommends treatment stratification based on performance status, but evidence suggests that higher radiotherapy doses may be associated with survival benefits. The aim of this study was to investigate the effects of fractionation regimen and additional factors on the survival of palliative lung cancer radiotherapy patients.
Materials and methods: A retrospective univariable ($n = 925$) and multivariable ($n = 422$) survival analysis of the prognostic significance of baseline patient characteristics and treatment prescription was carried out on patients with non-small cell and small cell lung cancer treated with palliative lung radiotherapy. The covariates investigated included: gender, age, performance status, histology, comorbidities, stage, tumour location, tumour side, smoking status, pack year history, primary radiotherapy technique and fractionation scheme. The overall mortality rate at 30 and 90 days of treatment was calculated.
Results: Univariable analysis revealed that performance status ($P < 0.001$), fractionation scheme ($P < 0.001$), comorbidities ($P = 0.02$), small cell histology ($P = 0.02$), 'lifelong never' smoking status ($P = 0.01$) and gender ($P = 0.06$) were associated with survival. Upon multivariable analysis, only better performance status ($P = 0.01$) and increased dose/fractionation regimens of up to 30 Gy/10 fractions ($P < 0.001$) were associated with increased survival. Eighty-five (9.2%) and 316 patients (34%) died within 30 and 90 days of treatment, respectively.
Conclusion: In this retrospective single-centre analysis of palliative lung radiotherapy, increased total dose (up to and including 30 Gy/10 fractions) was associated with better survival regardless of performance status.

Key words: Lung cancer; outcomes research; palliative care; radiotherapy

Introduction

Lung cancer is the malignancy with the highest incidence worldwide and the leading cause of cancer death [1]. In the UK, lung cancer accounts for 13% of new cancer cases and 22% of cancer deaths. Eighty-five per cent of lung cancer cases are non-small cell lung cancer (NSCLC), with most of the remainder being small cell lung cancer (SCLC) (13%). One-year survival in England and Wales ranges from 82% for patients with stage I NSCLC to 16% for patients with stage IV NSCLC [2]. At presentation, 57% of patients are not candidates for curative therapy due to tumour volume, presence of metastases, patient fitness and/or comorbidities [3]. An increasing number of patients are receiving immunotherapy (sometimes in combination with chemotherapy) or tyrosine kinase inhibitors, which have been shown to improve survival [4,5]. Across hospitals in England in the

Author for correspondence: D.C.P. Cobben, Department of Radiotherapy Related Research, Dept 58, Floor 2a, Room 21-2-19, The Christie NHS Trust, Wilmslow Road, Manchester, M20 4BX, UK. Tel: +44 161-446-3622.
E-mail address: david.cobben@christie.nhs.uk (D.C.P. Cobben).

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2017–2018 financial year, 58% of all radiotherapy courses for lung cancer had palliative intent [6].

The primary treatment of patients with advanced lung cancer is systemic therapy (including chemotherapy, immunotherapy and targeted agents). However, palliative radiotherapy still has a role for those who are unresponsive to systemic therapy, those who relapse and those who have contraindications to, or are not fit for, systemic therapy [7]. Palliative radiotherapy is also often used to manage local symptoms [8,9]. These symptoms are often linked to local tumour effects, such as haemoptysis, chest pain, dyspnoea, cough, dysphagia and superior vena cava compression [10]. Palliative radiotherapy is intended to alleviate the aforementioned symptoms and improve quality of life. In a 2008 systematic review of palliative radiotherapy for lung cancer, improvement in total symptom score was reported in 65.4–77.1% of patients depending on the dose of radiotherapy administered [11].

The dose-fractionation schedule is selected when palliative radiotherapy is recommended to a patient. A balance between successful palliation of the symptoms, fitness of the patient, toxicity and convenience is sought in collaboration with the patient [10]. Toxicities of palliative radiotherapy may include: fatigue, dysphagia, odynophagia, dyspnoea, cough, skin erythema and, rarely, radiation myelopathy [10].

The choice of radiotherapy dose and fractionation scheme in the palliative setting is challenging because there is conflicting evidence regarding the optimal fractionation scheme in order to achieve palliation of symptoms and possibly improve survival. A 2015 meta-analysis found that when the patients were stratified by performance status no significant difference was found in 1-year overall survival [10]. More recently, two studies reported that higher fractionation schemes were associated with increased survival [12,13]. Fractionation schemes utilised varied from 10 Gy/one fraction up to doses more typically associated with the curative intent setting, such as 60 Gy/30 fractions [10]. Current Royal College of Radiologists (RCR) and American Society for Radiation Oncology (ASTRO) guidance suggest the use of palliative regimens with doses up to 39 Gy/13 fractions and 42 Gy/14 fractions, respectively, for patients with NSCLC [14,15]. Longer fractionation schemes can inconvenience patients with multiple hospital visits towards the end of their lives and also have healthcare resource implications.

The time taken for palliative radiotherapy to reach effect has been shown to occur at 5–7 weeks, with palliation occurring 2 weeks earlier in the 16 Gy/two fraction arm compared with the 30 Gy/three fraction arm [16]. Peak palliation occurs at 8–9 weeks. Frank *et al.* [17] defined radiotherapy as futile if the patient dies less than 30 days after treatment, as the patient has not yet benefitted fully from the treatment but has still been exposed to the risks of radiotherapy-related acute toxicity [17]. This issue has been debated at RCR forums and a consensus agreed that there should be a target of under 20% of patients that die within 30 days of palliative radiotherapy [18]. Patients with an acute presentation of symptoms, such as superior vena cava obstruction, often also have a short life expectancy and are incorporated into this figure.

There are predictive factors that have been investigated to guide the treatment decisions and give prognostic information in the context of palliative radiotherapy. From the literature, the following factors have been found to be significantly correlated with survival during multivariable analysis: T and N status, extrathoracic disease status, lactate dehydrogenase levels, completion of planned treatment, leukocyte count and C-reactive protein levels [10,12,13,17,19,20]. These factors have not been consistently examined through the literature and when included they are not always reproducibly significant and as such they are not incorporated in commonly used guidelines [14,15,21].

The aim of our study was to retrospectively analyse predictive factors for survival in palliative radiotherapy in lung cancer.

Materials and Methods

Cohort Selection

Patients treated for lung tumours with palliative radiotherapy between 1 January 2013 and 8 May 2018 were identified from the UK Computer-Aided Theragnostics (ukCAT) database. The ukCAT database contains the anonymised electronic patient records from a single large cancer centre and was established to model clinical outcomes. Consent is on an opt-out basis (REC reference 17/NW/0060). For this study, consent for patient data access was granted by the ukCAT database management committee (reference: 2017–008). Data from this study were part of a clinical audit (reference: SE18/2221). All research was carried out in accordance with the Declaration of Helsinki. Further details are given in the Supplementary Material.

Detailed patient and tumour characteristics are collected prospectively at the time of the first appointment in our institution. All patients included within the analysis had confirmed histology consistent with lung cancer (see Figure 1). The data specification included the following items: treatment intent and lung or mediastinal cancer. Local guidance recommends the following fractionation schemes: 30 Gy/10 fractions, 20 Gy/five fractions or 10 Gy/one fraction. Therefore, 30 Gy/10 fractions was the highest fractionation scheme included in this study.

Patients were staged with the IASLC seventh edition for TNM staging [22]. The comorbidity score was an overall score calculated with the Adult Comorbidity Evaluation 27 tool [23].

Primary Technique for Radiotherapy Delivery

The primary techniques for radiotherapy delivery were grouped into four larger groups that were deemed to be sufficiently similar. Parallel pair, two field or tangent pair ($n = 890$); single field ($n = 28$); three or more fields ($n = 5$); and all the intensity-modulated radiotherapy techniques

were grouped together ($n = 2$). Brachytherapy was excluded.

Statistical Analysis

A combined NSCLC and SCLC patient cohort ($n = 925$) and NSCLC-only patient cohort ($n = 664$) were analysed.

Overall survival was measured from the date of the first fraction. Patients who had not died by 8 May 2018 were considered to be right-censored and were excluded from the analysis. The percentages of patients who died within 30 and 90 days of receiving radiotherapy were calculated.

A univariable and multivariable survival analysis was conducted using the Cox proportional hazards model. The multivariable model was built using a complete case (no missing variable data) analysis ($n = 422$). *P*-values and hazard ratios with 95% confidence intervals were reported. Survival curves were plotted using the Kaplan–Meier method and differences between survival curves were assessed using the Log-rank test. A SCLC patient cohort was not analysed separately, as the number of complete cases was deemed to be insufficient ($n = 95$).

Due to there being a low number of patients with performance status 0 and 4, performance status was grouped as follows: good (0–1), mid (2) and poor (3–4), for the survival analysis. Due to there being a low number of patients treated with 8 Gy/one fraction, they were grouped with the patients treated with 10 Gy/one fraction for the survival analysis. The software used for statistical analysis was R® Version 3.5.1.

Results

Patient Characteristics

In total, 925 patients with NSCLC and SCLC remained in the cohort for analysis after filtering the originally extracted patient data. Figure 1 shows how the initial patient data downloaded from the electronic patient records system was refined in order to provide a more complete and comparable dataset. Any outlying data were checked manually. There were 816 events within the cohort; 109 patients were censored. The median overall survival was 129 days (95% confidence interval 120–138).

Table 1 summarises the main patient, tumour and treatment characteristics. The gender distribution of the patients was 55:45 male to female. The most common performance status was 2 (35%). In total, 545 of 925 (76%) patients had stage IV disease; 261 of 925 (28%) patients were treated for SCLC and 664 of 925 (72%) patients were treated for NSCLC. Of the patients with NSCLC, most (97%) had either squamous cell carcinoma or adenocarcinoma. As expected, the patients with a high performance status had a high comorbidity score.

The most frequently used fractionation scheme was 30 Gy/10 fractions, with 551/925 (60%) patients being prescribed this regimen.

Death Within 30 and 90 Days of Treatment

Eighty-five patients (9%) in the combined NSCLC and SCLC cohort died within 30 days of treatment. Three hundred and sixteen patients (34%) of the combined NSCLC and SCLC cohort died within 90 days of treatment. Seventy-two patients (11%) with NSCLC died within 30 days of treatment. Two hundred and forty-five patients (37%) with NSCLC died within 90 days of treatment.

Univariable Survival Analysis

The univariable analysis, see Table 2, highlighted six covariates: performance status, fractionation scheme, comorbidities, small cell histology, gender and 'lifelong never' smoking status that were associated with patient survival.

Univariable Subset Survival Analysis

When the patients were subdivided into good, mid and poor performance status the fractionation scheme was still found to be a predictor of patient survival. The 30 Gy/10 fractions scheme showed a clear survival advantage in each performance status subset (see Figure 2). This correlation of increased survival with increased fractionation persisted when SCLC patients were removed from the dataset for patients with good, mid and poor performance status (see Tables 2 and 3).

Multivariable Survival Analysis

The multivariable analysis highlighted that only fractionation scheme and performance status were predictors of patient survival (see Table 2).

The lack of interaction between fractionation scheme and performance status via Kaplan–Meier survival plots discussed above was further assessed in a multivariable analysis including only these two variables ($n = 925$). No interaction was found (interaction hazard ratio = 0.97, confidence interval = 0.85–1.10, $P = 0.60$) and both performance status and fractionation scheme retained independent effects on overall survival (performance status hazard ratio = 1.20; confidence interval = 1.07–1.35; $P = 0.002$ and fractionation scheme hazard ratio = 1.70; confidence interval = 1.42–2.02; $P < 0.001$).

Discussion

In this single-centre retrospective analysis of palliative lung radiotherapy, performance status and fractionation scheme were the only covariates shown to have a significant correlation with patient survival on multivariable analysis. Performance status was correlated with overall survival in a predictable manner: those with a good performance status out-survived those with a mid performance status, who out-survived those with a poor performance status.

In this cohort, when examining both NSCLC and SCLC together, every increase in fractionation regimen through

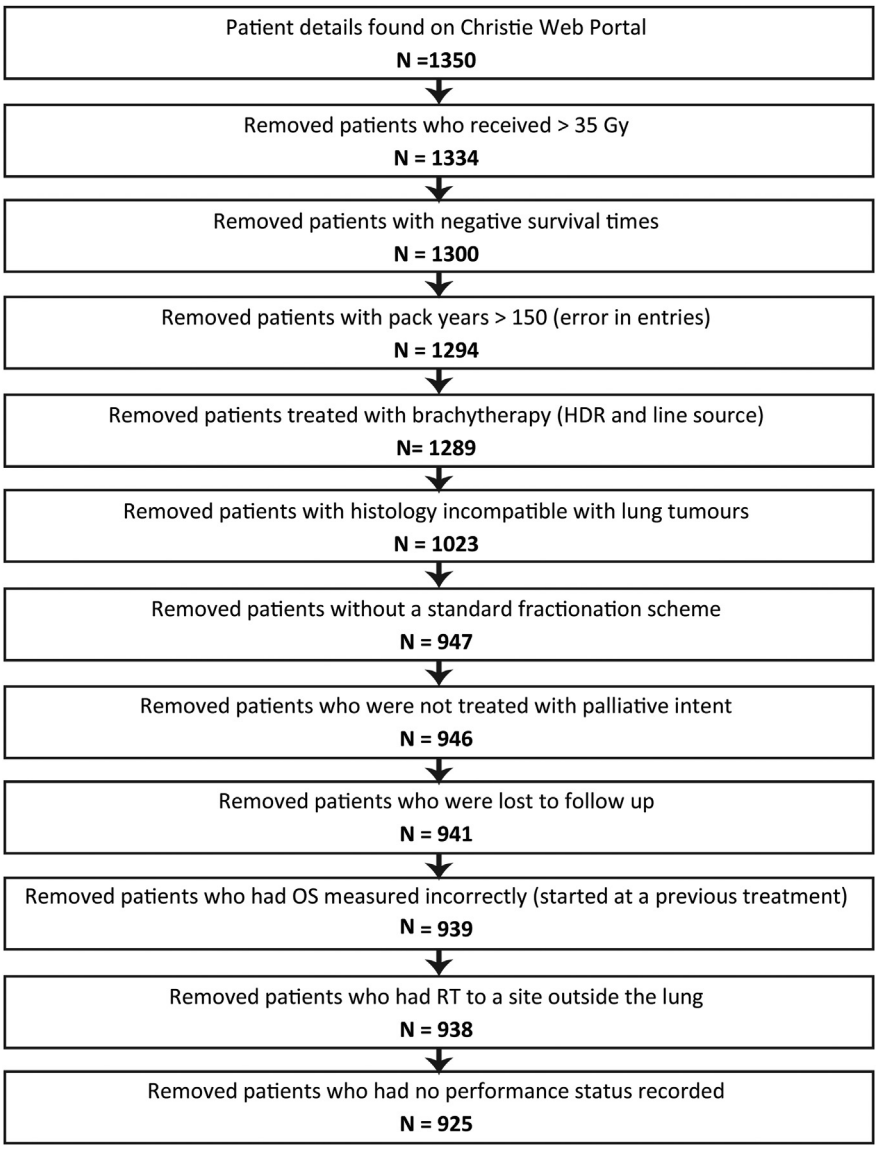

Fig 1. A flowchart to show the selection of the dataset utilised.

all performance status strata resulted in an increased median overall survival. The difference in median overall survival between receiving 10 Gy/one fraction and 30 Gy/10 fractions in patients with a good, mid and poor performance status was 126, 80.5 and 77 days, respectively. The cohort of NSCLC patients was also examined in isolation to ensure that there was not a confounding effect from the SCLC patients. The results were similar, with every increase in fractionation regimen through all performance status strata resulting in an increased median overall survival. It should be noted that to date all published prospective studies comparing different palliative thoracic radiotherapy fractionation schemes have been carried out in the NSCLC setting.

Performance Status

The finding that performance status is significantly correlated with survival is in concordance with other survival analyses [12,15,17]. There has been less clarity as to the optimal fractionation scheme in order to increase survival in palliative lung radiotherapy.

Radiotherapy Fractionation and Overall Survival

Janssen *et al.* [13] reported in a retrospective analysis of 125 patients that increasing equivalent dose in 2 Gy fractions (EQD2) led to significantly better survival outcomes. These patients had stage III and IV lung cancer, including both NSCLC and SCLC. EQD2 of 31–40, 41–46 and 47–52 Gy led to 6-month overall survival of 30, 38 and 57%, respectively, and 1-year overall survival of 11, 26 and 36%, respectively [13]. On multivariable analysis, EQD2 was significant, although the confidence intervals were wide (n = 125, relative risk = 1.43, confidence interval = 1.06–1.94, P = 0.018) [13]. The doses of radiotherapy were higher compared with those used in this study. It should be noted that 29% of the patients could

Table 1
Baseline patient characteristics of this large cancer centre's cohort

Covariate	Number of patients (% proportion of patients with data present)
Gender	
Male	510 (55%)
Female	415 (45%)
Age	
Range	36–93
Interquartile range	14
Mean	69
ECOG performance status	
0	65 (7%)
1	315 (34%)
2	325 (35%)
3	213 (23%)
4	7 (1%)
Good (0+1)	*380 (41%)*
Mid (2)	*325 (35%)*
Poor (3+4)	*220 (24%)*
Histology	
Small cell lung cancer	261 (28%)
Non-small cell lung cancer	664 (72%)
Non-small cell lung cancer subgroups	
Adenocarcinoma	323 (35%)
Adenosquamous cell carcinoma	7 (1%)
Large cell carcinoma	14 (1%)
Squamous cell carcinoma	320 (35%)
Comorbidities	
0	221 (28%)
1	257 (33%)
2	202 (26%)
3	96 (12%)
N/A	149
TNM stage	
2a	9 (1%)
2b	11 (2%)
3a	61 (8%)
3b	95 (13%)
4	545 (76%)
N/A	204
Tumour location	
Lung, upper lobe	533 (65%)
Lung, middle lobe	60 (7%)
Lung, lower lobe	230 (28%)
Lung, not otherwise specified (N/A)	102
Tumour side	
Left	301 (40%)
Right	462 (60%)
N/A	162
Smoking	
Lifelong never	27 (3%)
Light former	7 (1%)
Ex-smoker	457 (60%)
Current smoker	272 (36%)
N/A	159
Pack years	
Range	0–150
Interquartile range	20
Mean	42
N/A	234
Fractionation scheme	
8 Gy/1 fraction	10 (1%)
10 Gy/1 fraction	97 (10%)
20 Gy/5 fractions	267 (29%)
30 Gy/10 fractions	551 (60%)
8 Gy + 10 Gy/1 fraction	*107 (12%)*
Primary radiotherapy technique	
Intensity-modulated radiotherapy	2 (0%)
Parallel pair and two field	890 (96%)
Single field	28 (3%)
Three+ field	5 (1%)

not complete their full fractionation course due to acute toxicity [13].

Nieder *et al.* [12] found that lower dose/fractionation regimens (17 Gy/two fractions and 20–24 Gy/five to six fractions) were significantly associated with lower overall survival on multivariable analysis when compared with regimens with an EQD2 of 45Gy. Unlike our study, when Nieder *et al.* [12] carried out a subset analysis and excluded those with performance status 3–4 this survival advantage was no longer significant.

More recently, Nieder *et al.* [19] compared the following palliative fractionation regimens of 17 Gy/two fractions versus 30 Gy/10 fractions versus regimens with an EQD2 of 34–50 Gy for those aged 80 years and over. They found a median overall survival difference of 2.4, 2.6 and 11.8 months, respectively, with significant differences in survival for doses $\leq$30 Gy and doses $>$30 Gy. This could be an analysis of a subset of the patients of those included in the previously mentioned study, although this is not explicitly mentioned (the cohort is selected from the same hospital and the time period) [12,19].

In the 2015 Cochrane analysis, a meta-analysis incorporating 14 trials, the authors were unable to obtain enough original individual patient data in order to conduct a time-to-event analysis [16,24–26]. Therefore, the authors were only able to perform a meta-analysis of 1-year overall survival. This meta-analysis of 1-year overall survival for all patients regardless of performance status showed that receiving more fractions and a higher dose was favourable for survival, depending on which model was used (fixed effects versus random effects model) [10]. Due to large heterogeneity in the data for good performance status patients, the authors did not present these data in a summary statistic [10]. Although the data for poor performance status patients showed low heterogeneity and no 1-year overall survival advantage in using a more fractionated regimen, the evidence was rated as moderate [10]. In addition, Frank *et al.* [17] investigated 159 patients with NSCLC and

Table 2
Univariable and multivariable survival analysis

		Univariable survival analysis NSCLC + SCLC cohort		Multivariable analysis NSCLC + SCLC cohort $N = 422$, $E = 367$		Multivariable analysis NSCLC-only cohort $N = 327$, $E = 284$	
Covariat	*N* (*E*)	Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)	*P*-value	Hazard ratio (95% confidence interval)	*P*-value
Sex							
Female (reference)	925 (816)	1		1		1	
versus male		1.14 (0.99–1.31)	0.06	1.03 (0.83–1.27)	0.82	0.95 (0.74–1.22)	0.67
Age	925 (816)	1.00 (1.00–1.01)	0.35	1.00 (0.99–1.01)	0.85	0.99 (0.98–1.01)	0.48
Performance status							
Good (0–1) versus mid (2) versus poor (3–4)	925 (816)	1.32 (1.21–1.45)	<0.001	1.22 (1.05–1.42)	0.01	1.25 (1.05–1.49)	0.01
Histology							
Adenocarcinoma (reference)	925 (816)	1		1		1	
versus adenosquamous		1.25 (0.59–2.65)	0.56	1.51 (0.55–4.17)	0.42	1.54 (0.56–4.26)	0.41
versus large cell		0.68 (0.36–1.28)	0.24	0.91 (0.42–2.01)	0.82	0.84 (0.38–1.87)	0.67
versus squamous cell		1.00 (0.85–1.18)	0.98	1.06 (0.83–1.36)	0.62	1.08 (0.84–1.39)	0.56
versus small cell		0.80 (0.68–0.96)	0.02	0.76 (0.56–1.01)	0.06	NA	NA
Comorbidities							
0 versus 1 versus 2 versus 3	776 (673)	1.09 (1.02–1.18)	0.02	1.06 (0.94–1.18)	0.34	1.08 (0.94–1.23)	0.27
Combined TNM stage							
IV (reference)	721 (642)	1		1		1	
versus III		0.89 (0.74–1.08)	0.23	0.98 (0.75–1.28)	0.87	1.05 (0.76–1.43)	0.78
versus I+II		1.03 (0.63–1.67)	0.92	0.74 (0.38–1.44)	0.38	0.70 (0.33–1.49)	0.36
Tumour location							
Lower lobe (reference)	823 (720)	1		1		1	
versus middle lobe		0.87 (0.64–1.17)	0.35	1.83 (0.79–4.23)	0.16	1.37 (0.49–3.79)	0.55
versus upper lobe		0.93 (0.80–1.11)	0.46	0.90 (0.71–1.14)	0.36	0.87 (0.67–1.14)	0.32
Tumour side							
Left (reference)	763 (669)	1		1		1	
versus right		0.99 (0.85–1.15)	0.88	1.04 (0.83–1.29)	0.75	0.98 (0.76–1.25)	0.85
Smoking status							
Current smoker (reference)	766 (663)	1		1		1	
versus light former		0.88 (0.36–2.14)	0.78	0.42 (0.13–1.39)	0.16	0.43 (0.13–1.43)	0.17
versus ex-smoker		0.92 (0.78–1.08)	0.31	0.95 (0.75–1.21)	0.69	0.98 (0.74–1.29)	0.88
versus lifelong never		0.57 (0.37–0.89)	0.01	NA*	NA*	NA*	NA*
Pack years	691 (598)	1.00 (1.00–1.01)	0.4	1.00 (0.99–1.00)	0.59	1.00 (0.99–1.00)	0.30
Fractionation scheme							
30 Gy/10F versus 20 Gy/5 F versus 8 + 10 Gy/1F	925 (816)	1.73 (1.56–1.91)	<0.001	1.48 (1.23–1.77)	<0.001	1.54 (1.25–1.89)	<0.001
Primary radiotherapy technique							
IMRT (reference)	925 (816)	1				1	
versus parallel pair and two field		2.03 (0.29–14.41)	0.48	2.03 (0.28–14.86)	0.49	2.30 (0.31–17.05)	0.42
versus single field		2.13 (0.29–15.74)	0.46	2.03 (0.25–16.50)	0.51	2.23 (0.27–18.30)	0.46
versus 3+ field		1.64 (0.19–14.06)	0.65	1.54 (0.16–15.15)	0.71	1.83 (0.18–18.15)	0.61

IMRT, intensity-modulated radiotherapy; *N*, number of patients; *E*, number of events.
* There were no lifelong never smokers when performing a complete case analysis.

compared 30 Gy/10 fractions, 25 Gy/five fractions, 15 Gy/three fractions and 10 Gy/one fraction, finding no statistically significant correlation between overall survival and radiotherapy regimen.

It is difficult to directly compare this study with others finding a positive correlation between increased fractionation and overall survival, as the fractionation schemes utilised in each study are variable with a large range in EQD2. The maximum palliative lung fractionation scheme used in this cohort was 30 Gy/10 fractions (EQD2 32.5), whereas Nieder *et al.* [12] and Janssen *et al.* [13] reported much higher doses used, with maximum radiotherapy doses of EQD2 45 and 47–52 Gy, respectively.

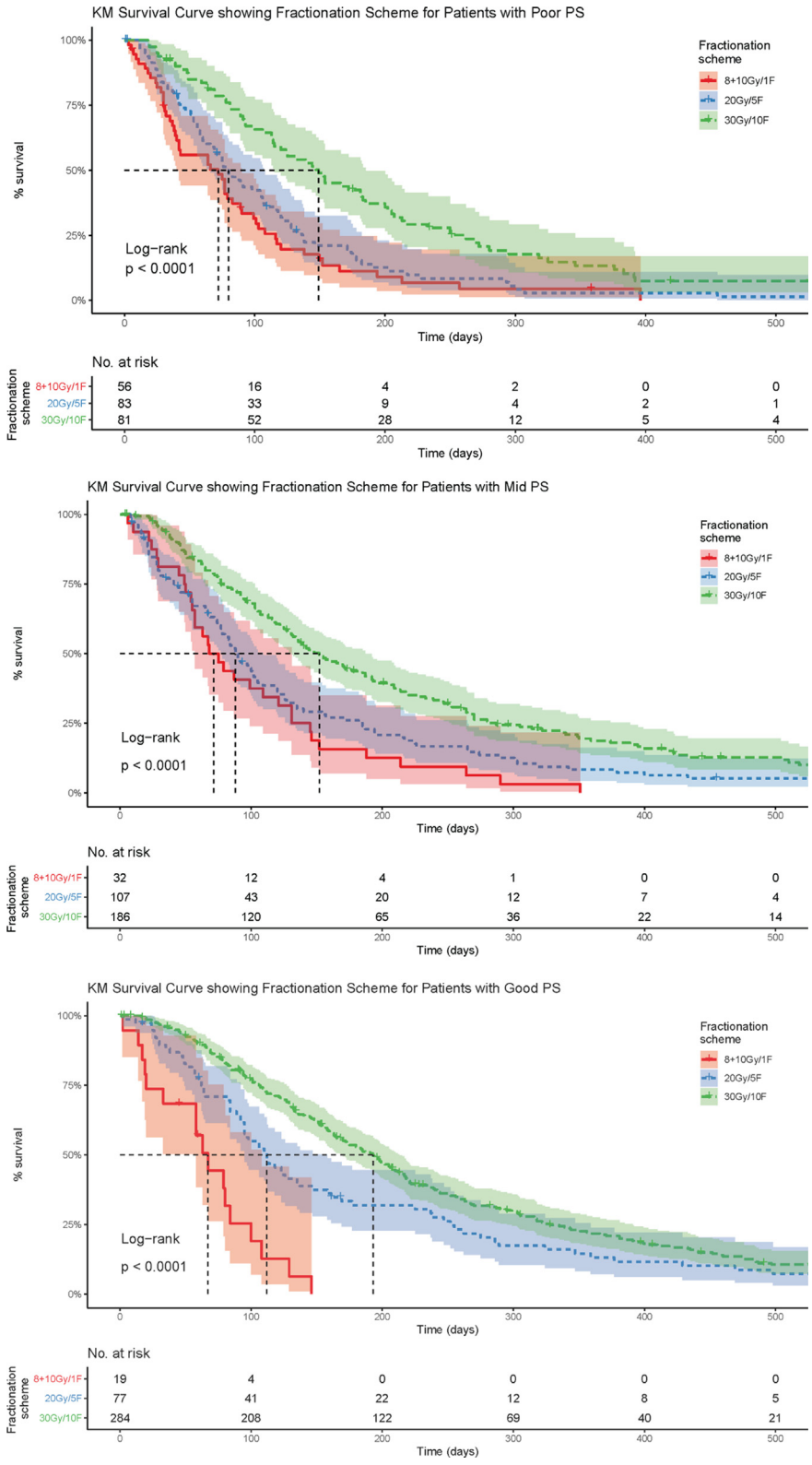

Fig 2. Univariable subset analysis Kaplan–Meier survival curves examining varying fractionation schemes and the correlating overall survival when all patients were divided by performance status strata in the combined non-small cell lung cancer/small cell lung cancer patient cohort.

Table 3
Univariable subset survival analysis results examining varying fractionation schemes and the correlating overall survival when all patients were divided by performance status strata in both the combined non-small cell lung cancer/small cell lung cancer (NSCLC/SCLC) patient cohort and the NSCLC patient-only cohort

	Fractionation scheme 8 + 10 Gy/1 fraction	Fractionation scheme 20 Gy/5 fractions	Fractionation scheme 30 Gy/10 fractions
Good performance status (0–1) Combined NSCLC and SCLC cohorts	Median overall survival 67 days (n = 19, 95% confidence interval 58–108)	Median overall survival 112 days (n = 77, 95% confidence interval 95–158)	Median overall survival 193 days (n = 284, 95% confidence interval 170–213)
Mid performance status (2) Combined NSCLC and SCLC cohorts	Median overall survival 71.5 days (n = 32, 95% confidence interval 57–131)	Median overall survival 88 days (n = 107, 95% confidence interval 78–109)	Median overall survival 152 days (n = 186, 95% confidence interval 131–187)
Poor performance status (3–4) Combined NSCLC and SCLC cohorts	Median overall survival 72 days (n = 56, 95% confidence interval 40–90)	Median overall survival 80 days (n = 83, 95% confidence interval 66–107)	Median overall survival 149 days (n = 81, 95% confidence interval 115–185)
Good performance status (0–1) NSCLC cohort only	Median overall survival 67 days (n = 17, 95% confidence interval 58–129)	Median overall survival 106 days (n = 57, 95% confidence interval 92–137)	Median overall survival 185 days (n = 189, 95% confidence interval 162–207)
Mid performance status (2) NSCLC cohort only	Median overall survival 67 days (n = 29, 95% confidence interval 55–131)	Median overall survival 84 days (n = 88, 95% confidence interval 67–102)	Median overall survival 139 days (n = 130, 95% confidence interval 118–187)
Poor performance status (3–4) NSCLC cohort only	Median overall survival 64 days (n = 42, 95% confidence interval 38–103)	Median overall survival 75 days (n = 58, 95% confidence interval 56–108)	Median overall survival 139 days (n = 54, 95% confidence interval 100–185)

There were several potential biases in our study that need to be explored. This was a retrospective, single-centre study. The conclusions that can be drawn are therefore limited due to both known and unknown confounding factors. It is likely that the patients receiving a larger number of fractions are also the patients receiving systemic treatment. It would have been beneficial to include previous systemic therapies (chemotherapy, tyrosine kinase inhibitors and immunotherapies) and previous radiotherapy in our analysis, as these treatments could have a major impact on survival. It is likely that patients with SCLC would have only received higher fractionation schemes if they had shown a good response to systemic therapies, as recommended in RCR guidance (see Table 4). This could have been a confounding factor, as these patients showing a good response to systemic therapy would probably go on to have longer survival. Unfortunately, due to some patients receiving systemic treatment at multiple hospitals and a lack of integrated databases there was not sufficient access to information on these previous treatments. Improvements in electronic registration and database integration mean that in future analysis we expect to take the role of systemic treatments in palliative lung radiotherapy into account.

It would have also been interesting to see if mutation status (such as epidermal growth factor receptor and anaplastic lyphoma kinase rearrangement) was correlated to survival, but unfortunately these data were unavailable. There was a large proportion of missing data in several of the covariates examined (see Supplementary Material) and this reduced the power of the multivariable analysis. It would be informative to carry out regular audits on which data are not being fully recorded and why.

Treatment field size was another important prognostic indicator that would have been valuable to include, as tumour volume is known to be a factor associated with poorer survival, but this was also unavailable [27]. There was little variance in the radiotherapy technique, with the vast majority of patients treated with parallel pair/two field (96%). Therefore, a meaningful comparison of radiotherapy technique effect on overall survival did not take place. Granton *et al.* [28] have recently reported a decreased incidence of dysphagia following oesophageal-sparing intensity-modulated radiotherapy as opposed to parallel pair beams. If this technique becomes standard of care, it would be worthwhile investigating its effect on overall survival, toxicity and patient-reported symptoms.

Performance status has been shown in this study to be a prognostic indicator of overall survival and is used in multiple guidelines to determine treatment. Yet, performance status is not entirely objective, with the clinician's judgement playing a large role in determining the patient's score.

Table 4
Palliative radiotherapy guidelines from The Royal College of Radiologists (RCR) and American Society for Radiation Oncology (ASTRO)

RCR guidance [14]	
Good performance* NSCLC patients	20 Gy/5 fractions over 1 week or 30 Gy/10 fractions over 2 weeks or 36 Gy/12 fractions over 2.5 weeks or 39 Gy/13 fractions over 2.5 weeks
Poor performance status* NSCLC patients	17 Gy/2 fractions over 8 days or 10 Gy/1 fraction
Metastatic SCLC patients†	30 Gy/10 fractions
ASTRO guidance [15]	
Performances status 0–2, stage III NSCLC and life expectancy of >3 months patients	30 Gy/10 fractions to 42 Gy/14 fractions + concurrent chemotherapy
Good performance status* NSCLC patients	30 Gy/10 fractions or more
Poor performance status* NSCLC patients	20 Gy/5 fractions or 17 Gy/2 fractions or 10 Gy/1 fraction

NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.
* Good and poor performance status undefined.
† Patients who respond well to primary chemotherapy but who have persistent intrathoracic disease/symptoms.

Discrepancies between clinician- and patient-reported performance status have been documented and been shown to be associated with poorer survival [29]. As performance status determines treatment regimen and is sometimes an entry criteria to clinical trials, the treating clinician may be assigning performance status to fit the treatment rather than vice versa [30].

Previous studies have established that fractionation does not have a bearing on symptom control but can increase acute toxicity [10]. Unfortunately, in this cohort it was not possible to carry out an analysis on symptomatic improvement or toxicity due to its retrospective nature. The question remains: does a higher fractionation scheme not only lead to a longer overall survival, but also to a better quality of life?

RCR and ASTRO palliative lung radiotherapy fractionation guidance is summarised in Table 4. Neither ASTRO nor RCR guidance defines good, mid or poor performance status [14,15]. This makes it difficult to determine if clinicians are following the guidance explicitly. In the 2015 Cochrane review on palliative lung radiotherapy, good performance status was defined as a score of 0–1 and poor as 2–4 [10]. Other studies have classified a score of 0–1 as good, 2 as moderate and 3–4 as poor [31]. A number of patients in this study were prescribed an alternative dose of radiotherapy than that recommended by the RCR or ASTRO. According to RCR guidance, in this cohort, only 17 patients (2.6%) with a good performance status were undertreated (with 8 Gy/one fraction or 10 Gy/one fraction) and 110 patients (16.6%) with a poor performance status were over-treated (with 20 Gy/five fractions or 30 Gy/10 fractions). According to ASTRO guidance, 74 patients (11.1%) with a good performance status were undertreated as they were given <30 Gy/10 fractions and 54 patients (8.1%) with a poor performance status were over-treated as they were given >20 Gy/five fractions. Moderate performance status patients are not defined within either guidance.

Nine per cent of patients within this large centre's cohort died within 30 days of receiving palliative radiotherapy. This is consistent with other published data, including Spencer *et al.* [32,33], who examined the 30-day mortality of 3628 patients who received palliative lung radiotherapy, resulting in a 30-day mortality rate of 14%. It is also within the RCR forum suggested limit of 20% [18].

Future

Although this study has limitations, it adds to the justification for the need of a prospective multicentred randomised controlled trial to examine the effects of varying fractionation schemes and radiotherapy techniques on survival in today's era of modern systemic therapies. This future study should include both doctor- and patient-reported outcomes. The TOURIST (Thoracic Umbrella Radiotherapy Study in Stage IV) trial, a UK-based trial, is currently under development and is aiming to answer these questions (Woolf D, Lee C, Shah R, Ahmed M, Fraser I, Billingham L *et al.*, unpublished data).

An area of unmet need are studies evaluating dose/fractionation regimens in the SCLC setting. To our knowledge there is only one prospective trial, currently recruiting, that is looking into a dose–effect relationship in patients with extensive stage SCLC. This trial compares 30 Gy/10 fractions versus 45 Gy/15 fractions in patients who have shown a response to standard of care chemotherapy (Clinicaltrials.gov identifier: NCT02675088).

The data coming from ongoing and future studies should be used to create decision tools to help patients with lung cancer considered for palliative treatment to balance survival gain and quality of life.

Conclusions

In this retrospective, single-centre analysis of palliative lung radiotherapy, although limited by a lack of data on systemic anticancer treatments, toxicity and quality of life, we found that increased fractionation regimens (up to and

including 30 Gy/10 fractions) were associated with better survival regardless of performance status.

Conflict of interest

C. Faivre-Finn has declared research grants from AstraZeneca, MSD and Elekta and sits on the advisory boards of AstraZeneca and Pfizer. D. Woolf has declared travel grants, consultancy and speaker fees from AstraZeneca and travel grants from Roche. G. Price acknowledges the support of Cancer Research UK via funding to the Cancer Research Manchester Centre (C147/A18083) and (C147/A25254).

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2020.05.003.

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