
Article:
Fornacon-Wood, I., Banfill, K., Ahmad, S. et al. (22 more authors) (2023) Impact of the COVID-19 pandemic on outcomes for patients with lung cancer receiving curative-intent radiotherapy in the UK. Clinical Oncology, 35 (10). e593-e600. ISSN 0936-6555

https://doi.org/10.1016/j.clon.2023.07.005

Abstract

Background

Previous work found that during the first wave of the COVID-19 pandemic, 34% of patients with lung cancer treated with curative-intent radiotherapy (RT) in the UK had a change to their centre's usual standard of care treatment (Banfill 2021). We present the impact of these changes on patient outcomes.

Material/methods

The COVID-RT Lung database was a prospective multicentre UK cohort study including patients with stage I-III lung cancer referred for and/or treated with radical RT between April and October 2020. Data was collected on patient demographics, RT and systemic treatments, toxicity, relapse, and death. Multivariable cox and logistic regression were used to assess the impact of having a change to RT on survival, distant relapse and ≥ grade 3 acute toxicity. The impact of omitting chemotherapy on survival and relapse was assessed using multivariable cox regression.

Results

Patient and follow-up forms were available for 1280 patients. 765 (59.8%) were aged over 70 and 603 (47.1%) were female. Patients with stage I-II NSCLC who had a change to their RT had no significant increase in distant relapse ($p=0.859$) or death ($p=0.884$), however did have increased odds of ≥ grade 3 acute toxicity ($p=0.0348$). Patients with stage III NSCLC who had a change to their RT had no significant increase in distant relapse ($p=0.216$) or death ($p=0.064$), however did have increased odds of ≥ grade 3 acute toxicity ($p<0.001$). Patients with stage III NSCLC who had their chemotherapy omitted had no significant increase in distant relapse ($p=0.0827$) or death ($p=0.0661$).

Conclusion

This study suggests changes to RT and chemotherapy made in response to the COVID-19 pandemic did not significantly affect distant relapse or survival. Changes to RT, namely increased hypofractionation, led to increased odds of ≥ grade 3 acute toxicity. This data is important as hypofractionated treatments can help to reduce hospital attendances in the context of potential future emergency situations.

Key words: COVID-19; lung cancer; radiotherapy; reduced fractionation; hypofractionation; chemotherapy

Introduction

The COVID-19 pandemic put an unprecedented demand on NHS services which in turn affected cancer treatments, including radiotherapy [3,4]. The effects of the COVID-19 pandemic on outcomes for patients with cancer is of increasing concern. It is known that patients with cancer have higher rates of severe disease and death with COVID-19 compared to the general population [5], however evidence is still lacking on the indirect impact of COVID-19 on cancer treatments.

Radiotherapy plays a key role in the treatment of lung cancer, with 25-50% of patients receiving radiotherapy at some point during their cancer journey [6]. Radiotherapy alone or in combination with chemotherapy and/or immunotherapy is an important treatment modality in the curative-intent setting. These patients are particularly vulnerable due to the immunosuppressive nature of treatments and multiple comorbidities [7]. Therefore, guidelines were rapidly produced at the start of the pandemic with the aim to reduce hospital visits without compromising treatment benefit by using reduced-fractionation regimens for patients receiving curative-intent radiotherapy [2].

COVID-RT lung was a UK data collection initiative that aimed to assess the impact of the COVID-19 pandemic in patients with stage I-III lung cancer receiving curative-intent radiotherapy [1]. Previous analysis reported that 34% of patients had a change to their centre's usual standard of care treatment [1]. 17.5% of patients had a different radiotherapy dose and/or fractionation, generally with an increased use of hypofractionated regimens as was recommended by UK guidelines [2]. In patients with stage III disease considered for chemotherapy, 10.7% of patients had this treatment modality omitted, and 6.7% had a reduced chemotherapy dose. We present in this paper the impact of these changes to treatment on patient outcomes.

Methods and materials

COVID-RT Lung is a prospective, multicentre UK cohort study. Data was prospectively collected on all patients with stage I-III lung cancer referred for and/or treated with curative-intent radiotherapy (biologically equivalent dose >50 Gy) between April and October 2020. The data collection procedure has been described previously [1]. For this analysis, the following baseline clinical information was extracted from the COVID-RT Lung database on the 25/07/2022: age at the time of treatment; gender; histology; stage; baseline Eastern Cooperative Oncology Group (ECOG) Performance Status (PS); radiotherapy dose and fractionation; dates of radiotherapy; chemotherapy delivery; and immunotherapy delivery. Data was also collected on whether patients had a change to their centre's standard of care treatment pre-COVID-19, radiotherapy treatment, or chemotherapy treatment. The specific changes made to radiotherapy and chemotherapy treatment were not recorded. A reduction in systemic treatment was defined as a reduced number of planned cycles and/or a reduced dose for any single cycle. Follow-up data was collected 12 months after the end of treatment, or earlier for acute toxicity or if the patient died. Follow-up data was collected on: distant and loco-regional relapse within a year post radiotherapy, death, ≥ grade 3 treatment related acute toxicity (toxicity within 3 months of the end of radiotherapy) and late toxicity (toxicity from 3 months after the end of radiotherapy) according to CTCAE v5.0 (oesophageal, pulmonary and cardiac toxicity, infection and chest pain).

Baseline characteristics were summarised as counts and percentages, and medians with the lower and upper quartiles. Age was dichotomised at 70 years in line with the UK Government's shielding advice. Dose per fraction was grouped into < 2 Gy/fraction, 2 Gy/fraction, >2-2.9Gy/fraction, 3-5.9 Gy/fraction and ≥ 6 Gy/fraction. These groupings were chosen to highlight different fractionation regimens; 2 Gy/fraction represents conventional fractionation, and above that moderate to ultra-hypofractionation. Patients with a radiological diagnosis of cancer were assumed to have NSCLC. Hazard ratios (HR) and 95% confidence intervals were estimated to describe the hazard of death, and distant and loco-regional relapse for patients who had a change to their radiotherapy dose and/or fractionation, in response to the COIVD-19 pandemic, using multivariable cox regression. Regressions were adjusted for age, gender, PS, whether the patient received chemotherapy, and radiation dose per fraction. Adjusted odds ratios (aOR) and 95% confidence were estimated to describe the risk of developing ≥ grade 3 acute toxicity for patients who had a change to their radiotherapy dose and/or fractionation, in response to the COVID-19 pandemic, using multivariable logistic regression, adjusting for age, gender, PS, whether the patient received chemotherapy, and radiation dose per fraction. HRs and 95% confidence intervals were estimated to describe the hazard of death and distant relapse for patients who had their chemotherapy omitted using multivariable cox regression, adjusting for age, gender, PS, whether the patient had a change to their radiotherapy dose/and or fractionation, and radiation dose per fraction. Multivariable analysis was not performed for the SCLC data, or late toxicity, due to insufficient sample size in these

cohorts. Multivariable logistic regression was used to determine whether patients who had a change to their chemotherapy regimen in response to the COVID-19 pandemic were also more likely to have a change to their radiotherapy dose and/or fractionation, adjusting for age and PS. Mean dose per fraction was compared between groups using the t-test. Patients who had their radiotherapy delivered in < 15 fractions were removed from the stage III NSCLC and SCLC analyses, as they are palliative or Stereotactic Ablative Body Radiotherapy (SABR) regimens.

All statistical analyses were performed in R 4.0.0[8] with package *survival* v3.1-12.[9]

Results

Completed patient and follow-up forms were available in the COVID-RT Lung database for 1280 patients (out of 1717) treated between April and October 2020. Median follow-up was 213 days (119, 376). Baseline characteristics split by change to local standard of care treatment are presented in Table 1. 765 (59.8%) were aged over 70 and 603 (47.1%) were female. 259 (33.9%) patients aged over 70 had a change to their treatment and 116 (25.3%) patients with a PS of 2-3 had a change to their treatment.

Changes to local standard of care treatment have been presented previously [1]. To briefly summarise, the main change to treatment for patients with stage I-II disease was a change to radiotherapy dose and/or fractionation (16.1%), followed by radiotherapy being given instead of surgery (9.5%) [1]. For patients with stage III disease, the main change was a change to radiotherapy dose and/or fractionation (19.5%), followed by having their chemotherapy omitted (10.7%), or receiving a reduced chemotherapy dose (6.8%) [1].

Table 1 Baseline characteristics.

	No change to treatment (N=860)	**Change to treatment (N=420)**	**All patients (N=1280)**
Age in years, n (%)			
< 70	351 (40.8)	161 (38.3)	512 (40.0)
≥ 70	506 (58.8)	259 (61.7)	765 (59.8)
Missing	3 (0.3)	0	3 (0.2)
Gender, n (%)			
Female	422 (49.1)	181 (43.1)	603 (47.1)
Male	437 (50.8)	239 (56.9)	676 (52.8)
Missing	1 (0.1)	0	1 (0.1)
PS, n (%)			
0	100 (11.6)	65 (15.5)	165 (12.9)
1	416 (48.4)	239 (56.9)	655 (51.2)
2-3	342 (39.8)	116 (27.6)	458 (35.8)
Missing	2 (0.2)	0	2 (0.2)
Histology, n (%)			
NSCLC	508 (59.1)	276 (65.7)	784 (61.3)
SCLC	62 (7.3)	54 (12.9)	116 (9.1)
Radiological diagnosis	289 (33.6)	215 (51.2)	379 (29.6)
Missing	1 (0.1)	0	1 (0.1)
Stage, n (%)			
I	395 (45.9)	147 (35.0)	542 (42.3)
II	135 (15.7)	56 (13.3)	191 (14.9)
III	327 (38.0)	215 (51.2)	542 (42.3)
Missing	3 (0.3)	2 (0.5)	5 (0.4)
Mean dose per fraction in Gy/fraction (SD)	6.92 (10.29)	7.25 (14.42)	7.03 (11.80)
Dose per fraction grouped			
< 2 Gy/fraction	36 (4.2)	1 (0.2)	37 (2.9)
2 Gy/fraction	37 (4.3)	9 (2.1)	46 (3.6)
>2-2.9 Gy/fraction	371 (43.1)	210 (50.0)	581 (45.4)
3-5.9 Gy/fraction	48 (5.6)	67 (16.0)	115 (9.0)
≥ 6 Gy/fraction	358 (41.6)	128 (30.5)	486 (38.0)
Missing	10 (1.2)	5 (1.2)	15 (1.2)

Abbreviations: Gy, gray; NSCLC, non-small cell lung cancer; PS, performance status; RT, radiotherapy; SCLC, small-cell lung cancer; SD, standard deviation.

Changes to radiotherapy dose and/or fractionation

Stage I-II NSCLC

106 (15.0%) patients with stage I-II NSCLC had a change to their radiotherapy dose and/or fractionation. Table 2 presents toxicity and outcomes data for these patients. Rates of distant and loco-regional relapse and death were similar between stage I-II NSCLC patients who had a change to their radiotherapy and those who did not (6.6% vs 8.7%, 11.3% vs 11.7% and 11.3% vs 13.0%). For patients who had a change to their radiotherapy, 5 (4.7%) had ≥ grade 3 acute toxicity and 1 (0.9%) had ≥ grade 3 late toxicity. For patients who did not have a change to their radiotherapy, 13 (2.2%) had ≥ grade 3 acute toxicity and 8 (1.3%) had ≥ grade 3 late toxicity.

Multivariable analysis showed that patients with stage I-II NSCLC who had a change to their radiotherapy dose and/or fractionation had no significant increased hazard of distant relapse (HR=1.09 (0.412, 2.90), p=0.859), loco-regional relapse (HR=1.25 (0.609, 2.58), p=0.541), or death (HR=0.951 (0.480, 1.88), p=0.884). These patients did, however, have increased odds of developing ≥ grade 3 acute toxicity (aOR=3.46 (1.01, 10.6), p=0.0348) in this dataset. The full multivariable results can be found in Supplementary Tables 1-2. Patients with stage I-II NSCLC who had a change to their radiotherapy dose and/or fractionation received a higher dose per fraction (mean 12.1 vs 9.22, p<0.001) compared to patients who had no change.

Table 2 Toxicity and disease status for patients with stage I-II NSCLC split by whether they had a change to their radiotherapy dose and/or fractionation or not.

	Change to RT (N=106)	**No change to RT (N=600)**
Acute toxicity ≥ grade 3	5 (4.7)	13 (2.2)
Missing	6 (5.7)	34 (5.7)
Oesophageal	1 (0.9)	4 (0.7)
Pulmonary	2 (1.9)	4 (0.7)
Cardiac	0	2 (0.3)
Infection	2 (1.9)	2 (0.3)
Chest pain	0	0
Other	0	1 (0.2)
Late toxicity ≥ grade 3	1 (0.9)	8 (1.3)
Missing	22 (20.8)	121 (20.2)
Oesophageal	0	1 (0.2)
Pulmonary	0	2 (0.3)
Cardiac	0	0
Infection	1 (0.9)	3 (0.5)
Chest pain	0	2 (0.3)
Other	0	0
Disease status		
Distant relapse	7 (6.6)	52 (8.7)
Loco-regional relapse	12 (11.3)	70 (11.7)
No evidence recurrence	79 (74.5)	416 (69.3)

Death	12 (11.3)	78 (13.0)

Abbreviations: RT, radiotherapy.

Supplementary Table 3 presents ≥ grade 3 acute and late toxicity for patients with stage I-II NSCLC who received 5 fraction SABR versus 3 fraction SABR. Rates of ≥ grade 3 acute (2.3% vs 3.5%) and late toxicity (1.5% vs 2.1%) were similar between patients who received 5 fraction SABR versus 3 fraction SABR. Overall toxicity rates were low. There were no cases of ≥ grade 3 chest wall pain for patients who received 3 or 5 fraction SABR in this data.

Stage III NSCLC

77 (18.1%) patients with stage III NSCLC had a change to their radiotherapy dose and/or fractionation. Table 3 presents toxicity and outcomes data for these patients. Patients who had a change to their radiotherapy had lower rates of distant (10.4% vs 21.3%) and loco-regional (7.8% vs 21.6%) relapse, but death rates were similar (23.4% vs 25.9%). A higher proportion of patients who had a change to their radiotherapy had ≥ grade 3 acute and late toxicity compared to patients who did not have a change to their radiotherapy (acute toxicity 19.5% vs 9.2%, late toxicity 5.2% vs 1.7%). For patients who had a change to their radiotherapy, the majority of ≥ grade 3 acute (80.0%) and late (75.0%) toxicity was seen in patients who received concurrent chemotherapy; however, for patients who did not have a change to their radiotherapy, the majority of ≥ grade 3 acute (46.9%) and late (66.7%) toxicity was seen in patients who had no chemotherapy, although numbers are low (Supplementary Table 4).

Multivariable analysis revealed that patients with stage III NSCLC who had a change to their radiotherapy dose and/or fractionation had no significant increased hazard of distant relapse (HR=1.71 (0.731, 4.00), p=0.216), loco-regional relapse (HR=0.880 (0.316, 2.45), p=0.806), or death (HR=2.89 (0.940, 8.89), p=0.064). They did however, have increased odds of developing ≥ grade 3 acute toxicity (aOR=4.78 (2.11, 10.7), p<0.001) in this dataset. The full multivariable results can be found in Supplementary Tables 5-6. Patients with stage III NSCLC who had a change to their radiotherapy dose and/or fractionation received a higher dose per fraction (mean 3.01 vs 2.65, p<0.001) compared to patients who had no change to their radiotherapy dose and/or fractionation.

Table 3 Toxicity and disease status for patients with stage III NSCLC split by whether they had a change to their radiotherapy dose and/or fractionation or not.

	Change to RT (N=77)	**No change to RT (N=348)**
Acute toxicity ≥ grade 3	15 (19.5)	32 (9.2)
Missing	11 (14.3)	7 (2.0)
Oesophageal	5 (6.5)	15 (4.3)
Pulmonary	6 (7.8)	7 (2.0)
Cardiac	0	0
Infection	2 (2.6)	4 (1.1)
Chest pain	0	1 (0.3)
Other	1 (1.3)	5 (1.4)
Late toxicity ≥ grade 3	4 (5.2)	6 (1.7)
Missing	22 (28.6)	63 (18.1)
Oesophageal	3 (3.9)	1 (0.3)

Pulmonary	1 (1.3)	4 (1.1)
Cardiac	0	0
Infection	0	0
Chest pain	0	0
Other	0	1 (0.3)
Disease status		
Distant relapse	8 (10.4)	74 (21.3)
Loco-regional relapse	6 (7.8)	75 (21.6)
No evidence recurrence	46 (59.7)	188 (54.0)
Death	18 (23.4)	90 (25.9)

Abbreviations: RT, radiotherapy.

328 (77.2%) patients with stage III NSCLC received 55 Gy in 20 fractions. Of which, 169 (51.5%) had radiotherapy alone, 79 (24.1%) received concurrent chemotherapy and 80 (24.4%) sequential chemotherapy. 30 (7.1%) patients with stage III NSCLC received 60-66 Gy in 30-33 fractions. Of which, 24 (80.0%) received concurrent radiotherapy, 5 (16.7%) received sequential radiotherapy and 1 (3.3%) had radiotherapy alone.

17 (21.5%) patients with stage III NSCLC who received 55 Gy in 20 fractions with concurrent chemotherapy had ≥ grade 3 acute toxicity, 7 (8.9%) of which were pulmonary and 5 (6.3%) oesophageal. 4 (5.1%) patients had ≥ grade 3 late toxicity. 5 (20.8%) patients with stage III NSCLC who received 60-66 Gy in 30-33 fractions with concurrent chemotherapy had ≥ grade 3 acute toxicity, 1 (20.0%) pulmonary, 1 (20.0%) oesophageal and 2 (40.0%) infection. 4 (16.7%) patients had ≥ grade 3 late toxicity.

SCLC

34 (31.2%) patients with SCLC had a change to their radiotherapy dose and/or fractionation. Supplementary Table 7 presents toxicity and outcomes data for these patients. Patients who had a change to their radiotherapy had higher rates of distant relapse (35.3% vs 26.7%), loco-regional relapse (20.6% vs 14.7%), and death (35.3% vs 26.7%). 2 (5.9%) patients who had a change to their radiotherapy had ≥ grade 3 acute toxicity and 2 (5.9%) had ≥ grade 3 late toxicity. For patients who did not have a change to their radiotherapy, 9 (12.0%) had ≥ grade 3 acute toxicity and none had ≥ grade 3 late toxicity. There was no significant difference in dose per fraction between patients with SCLC who had a change to their radiotherapy dose and/or fractionation and those who had no change to their radiotherapy dose and/or fractionation (mean 10.4 vs 5.86, p=0.537).

Changes to chemotherapy regimen

Stage III NSCLC

261 (61.4%) patients with stage III NSCLC were considered for chemotherapy as part of their management plan. However, 48 (18.0%) had their chemotherapy omitted and 35 (13.4%) had their chemotherapy dose and/or number of planned cycles reduced (Table 4). Patients who had their chemotherapy omitted had a higher rate of distant relapse compared to those who had no change (31.2% vs 14.6%), and a higher rate of death (35.4% vs 20.2%). 56 (21.5%) patients with stage III NSCLC who were considered for chemotherapy had consolidation immunotherapy. Of the patients with stage III NSCLC who had a change to their chemotherapy regimen, 12 (14.5%) also had a change to their RT dose and/or fractionation. Patients who had a change to their chemotherapy regimen were significantly less likely to have a change to their radiotherapy dose and/or fractionation (aOR=0.479 (0.222, 0.963), p=0.0470).

Multivariable analysis demonstrated no significant increase in distant relapse (HR=1.85 (0.923, 3.71), p=0.0827), loco-regional relapse (HR=1.03 (0.468, 2.27), p=0.940) or death (HR=1.80 (0.961, 3.40) P=0.0661) for patients who had their chemotherapy omitted, suggesting the higher rates of distant relapse and death in this group were not significantly associated with having their chemotherapy omitted. The full multivariable results can be found in Supplementary Table 8.

Table 4 Disease status for patients with stage III NSCLC split by whether they had their chemotherapy omitted, reduced, or received standard of care chemotherapy i.e. no change to chemotherapy regimen.

	Chemotherapy omitted (N=48)	**Chemotherapy dose/number of cycles reduced (N=35)**	**No change to chemotherapy (N=178)**
Diseased status			
Distant relapse	15 (31.2)	5 (14.3)	26 (14.6)
Loco-regional relapse	10 (20.8)	2 (5.7)	28 (15.7)
No evidence recurrence	24 (50.0)	23 (65.7)	98 (55.1)
Death	17 (35.4)	5 (14.3)	36 (20.2)

SCLC

104 (95.4 %) patients with SCLC were considered for chemotherapy as part of their management plan. However, 7 (6.7%) had their chemotherapy omitted and 14 (13.5%) had their chemotherapy dose and/or number of planned cycles reduced (Supplementary Table 9). Patients who had their chemotherapy omitted or reduced had higher rates of distant relapse compared to those who had no change (42.9% vs 50.0% vs 26.5%), and loco-regional relapse (57.1% vs 21.4% vs 10.8%). Rates of death were similar between patients who had their chemotherapy reduced vs no change (35.7% vs 28.9%), and 1 (14.3%) patient who had their chemotherapy omitted died

Of the patients with SCLC who had a change to their chemotherapy regimen, 10 (47.6%) also had a change to their RT dose and/or fractionation. Patients who had a change to their chemotherapy regimen were not significantly more or less likely to have a change to their radiotherapy dose and/or fractionation (aOR=2.35 (0.851, 6.51), p=0.0965).

Discussion

The initial analysis of the COVID-RT Lung data found a third of patients had their treatment changed, from what they would usually have received, due to the COVID-19 pandemic. The most common change was receiving a different radiotherapy dose and/or fractionation to the centre's usual standard of care, typically increased use of hypofractionated radiotherapy [1]. This increased used of hypofractionated radiotherapy during the COVID-19 pandemic is in line with UK recommendations to reduce hospital attendances [2]. The key findings in this analysis are that there was no significant impact on distant/loco-regional relapse or mortality for patients with NSCLC who had a change to their radiotherapy dose and/or fractionation, and there was a small increase in ≥ grade 3 acute toxicity. Furthermore, for patients with stage III NSCLC who were considered for chemotherapy, omitting or reducing chemotherapy dose and/or number of cycles did not lead to a significant impact on distant/loco-regional relapse or mortality.

The effect of hypofractionated radiotherapy on outcomes is an important consideration, particularly as it has the advantage of fewer hospital visits and reduced overall treatment times. Although we did not have information on the specific radiotherapy regimen changes that took place in this study, patients who had a change to their radiotherapy received a higher dose per fraction, indicating increased use of hypofractionation. A randomised phase III trial with 96 patients with stage II-III NSCLC not fit for concurrent chemotherapy compared 60 Gy in 15 fractions over 3 weeks (hypofractionated arm) to 60 Gy in 30 fractions over 6 weeks (conventional arm), reporting no significant difference in 1-year survival (37.7% in the hypofractionated arm vs 44.6% in the conventional arm), local and distant relapse, and ≥ grade 3 toxicity, although there was a higher rate of grade 2 toxicity in the hypofractionated group [10]. The trial was stopped early due to futility. A retrospective analysis of 111 patients with NSCLC compared node-negative patients (a surrogate for patients not eligible for SABR) to node-positive patients (a surrogate for those unfit for chemo-radiotherapy) who received 60 Gy in 15 fractions at one institution [11]. The study found acceptable 1-year survival rates (86.5% node-negative versus 69.1% node-positive), local control and ≥ grade 3 toxicity. The study is limited by selection bias, as patients were treated with 60 Gy in 15 fractions when conventional radiotherapy or SABR was not appropriate. A retrospective population-based study in the UK, however, reported significantly worse survival for patients with stage I-III NSCLC treated with 55 Gy in 20 fractions compared to 60-66 Gy in 30-33 fractions (25 months v 28 months, $p = 0.02$) [12]. This study was retrospective in nature, and did not distinguish between patients who received concurrent and sequential chemotherapy. The survival differential may therefore be caused by selection bias rather than the hypofractionated regimen, as patients in the UK often receive 55 Gy in 20 fractions following induction chemotherapy or if they are not fit enough for chemotherapy.

Patients with NSCLC who had a change to their radiotherapy dose and/or fractionation had increased odds of developing ≥ grade 3 acute toxicity. This is to be expected due to the higher dose per fraction used in hypofractionated radiotherapy. The rate of COVID-19 infection in the COVID-RT Lung study was low (33 (2.1%) patients) [1]. Outcomes for patients with cancer who are infected with COVID-19 are worse [5], so our results suggest the changes to treatment put in place to reduce COVID-19 exposure were effective and may have prevented vulnerable deaths due to COVID-19, at the expense of a small increase in acute toxicity. Data on long-term toxicity was not collected. For patients with stage III NSCLC who had a change to their radiotherapy, the majority of toxicity was seen in patients who received concurrent chemotherapy; however for patients who did not have a change to their radiotherapy, the majority of toxicity was seen in patients who had no chemotherapy. There was a higher rate of patients with PS 2-3 in the no change to treatment group, which may explain this difference in toxicity, however it is important to note that numbers for this analysis were low.

Most patients with stage III NSCLC received the moderately hypofractionated regimen of 55 Gy in 20 fractions in this study, compared with the conventional radiotherapy regimen of 60-66 Gy in 30-33 fractions (77.2% vs 7.1%). Rates of ≥ grade 3 acute toxicity were similar between both regimens for patients who also received concurrent chemotherapy. A randomised phase II trial including 130 patients with stage III NSCLC and PS 0-1 receiving either concurrent or sequential chemotherapy with standard 55 Gy in 20 fractions over 4 weeks (SOCCAR) reported that 32% of patients who had concurrent chemotherapy had ≥ grade 3 acute toxicity [13]. Our study reported a lower rate of ≥ grade 3 acute toxicity (21.5%), which may relate to the use of more advanced radiotherapy techniques, such as IMRT and VMAT, being used since the completion of SOCCAR recruitment in 2010.

This analysis found that patients with stage III NSCLC who had their chemotherapy omitted did not have a significant increase in risk of distant/loco-regional relapse or death in the multivariable analysis. This is an important observation given that one study found chemotherapy attendances had declined by 41.5% in the first wave of the pandemic [14]. There was, however, a higher rate of distant relapse and death in the chemotherapy omitted group compared to standard of care. This suggests there is a baseline difference between patients who had their chemotherapy omitted and those who did not, which was taken into account in the multivariable analysis by adjusting for potential confounders. However, the confidence interval for both distant relapse and death is close to 1, suggesting there may be a small effect of omitting chemotherapy that could not be detected with the sample size available in COVID-RT Lung. Unfortunately, a limitation of this study is that we could not collect more data as this is a unique dataset from a fixed time period. The risk of death due to COVID-19 is less now as many vulnerable patients with lung cancer are vaccinated and there are more effective treatments for patients hospitalised with COVID-19 [15]. Therefore, given the evidence that chemotherapy given in addition to radiotherapy improves survival in patients with stage III NSCLC [16], chemotherapy should no longer be omitted due to COVID-19 risk.

The results from this study are encouraging since the National Lung Cancer Audit found decreased 1-year survival for patients with lung cancer from 2019 to 2020, reversing the improvement in survival seen previously [17]. Our analysis did not find an increased risk of death for patients who had a change to radiotherapy or chemotherapy treatments between April and October 2020; however, our data only included patients who were treated with curative intent. Previous analysis found that patients who had a change to treatment were more likely to be elderly (≥ 70 years) [1], which is in line with the UK Government's shielding advice. This is important to consider when interpreting the mortality results from this analysis.

This study is subject to limitations, namely the retrospective nature of the study and the sample size. Due to the unique circumstance of data collection, more data could not be collected during the time period encapsulating the first wave of the COVID-19 pandemic, from April to October 2020. Unfortunately, 437 follow-up forms were not filled out and therefore these patients could not be included in the outcomes analysis. Despite this, our study provides valuable information to inform treatments for patients with lung cancer in such exceptional circumstances.

In conclusion, this study showed that changes made to radiotherapy and chemotherapy treatments during the COVID-19 pandemic did not significantly impact distant/loco-regional relapse or survival. Patients who had a change to their radiotherapy treatment, namely increased hypofractionation, had increased odds of ≥ grade 3 acute toxicity. This data is important as it can inform practice in the context of potential future emergency situations requiring a need to reduce hospital attendances. Furthermore, hypofractionated treatments are a more convenient and cheaper alternative to conventional fractionation regimens without significant compromise on tumour control or mortality.

References

[1] Banfill K, Croxford W, Fornacon-Wood I, Wicks K, Ahmad S, Britten A, et al. Changes in the Management of Patients having Radical Radiotherapy for Lung Cancer during the First Wave of the COVID-19 Pandemic in the UK. Clin Oncol 2022;34:19–27. https://doi.org/10.1016/j.clon.2021.10.009.

[2] Faivre-Finn C, Fenwick JD, Franks KN, Harrow S, Hatton MQF, Hiley C, et al. Reduced Fractionation in Lung Cancer Patients Treated with Curative-intent Radiotherapy during the COVID-19 Pandemic. Clin Oncol 2020;32:481–9. https://doi.org/10.1016/j.clon.2020.05.001.

[3] Richards M, Anderson M, Carter P, Ebert BL, Mossialos E. The impact of the COVID-19 pandemic on cancer care. Nat Cancer 2020;1:565–7. https://doi.org/10.1038/s43018-020-0074-y.

[4] Spencer K, Jones CM, Girdler R, Roe C, Sharpe M, Lawton S, et al. The impact of the COVID-19 pandemic on radiotherapy services in England, UK: a population-based study. Lancet Oncol 2021;22:309–20. https://doi.org/10.1016/S1470-2045(20)30743-9.

[5] Venkatesulu BP, Chandrasekar VT, Girdhar P, Advani P, Sharma A, Elumalai T, et al. A Systematic Review and Meta-Analysis of Cancer Patients Affected by a Novel Coronavirus. JNCI Cancer Spectr 2021;5:1–11. https://doi.org/10.1093/jncics/pkaa102.

[6] National Cancer Registration & Analysis Service and Cancer Research UK. “Chemotherapy, Radiotherapy and Tumour Resections in England: 2013-2014” workbook. London: NCRAS; 2017.

[7] Passaro A, Bestvina C, Velez Velez M, Garassino MC, Garon E, Peters S. Severity of COVID-19 in patients with lung cancer: evidence and challenges. J Immunother Cancer 2021;9:2266. https://doi.org/10.1136/JITC-2020-002266.

[8] R Core Team. R: A Language and Environment for Statistical Computing 2020.

[9] Therneau TM. A Package for Survival Analysis in R. R package version 3.1-12 2020. https://cran.r-project.org/package=survival.

[10] Iyengar P, Zhang-Velten E, Court L, Westover K, Yan Y, Lin MH, et al. Accelerated Hypofractionated Image-Guided vs Conventional Radiotherapy for Patients with Stage II/III Non-Small Cell Lung Cancer and Poor Performance Status: A Randomized Clinical Trial. JAMA Oncol 2021;7:1497. https://doi.org/10.1001/jamaoncol.2021.3186.

[11] Zeng KL, Poon I, Ung Y, Tsao M, Zhang L, Cumal A, et al. Accelerated Hypofractionated Radiotherapy for Centrally Located Lung Tumours Not Suitable for Stereotactic Body Radiotherapy or Chemoradiotherapy. Clin Oncol 2023;35:e173–81. https://doi.org/10.1016/j.clon.2022.11.013.

[12] Brada M, Forbes H, Ashley S, Fenwick J. Improving Outcomes in NSCLC: Optimum Dose Fractionation in Radical Radiotherapy Matters. J Thorac Oncol 2022;17:532–43. https://doi.org/10.1016/j.jtho.2022.01.006.

[13] Maguire J, Khan I, McMenemin R, O’Rourke N, McNee S, Kelly V, et al. SOCCAR: A randomised phase II trial comparing sequential versus concurrent chemotherapy and radical hypofractionated radiotherapy in patients with inoperable stage III Non-Small Cell Lung Cancer and good performance status. Eur J Cancer 2014;50:2939–49. https://doi.org/10.1016/j.ejca.2014.07.009.

[14] Lai AG, Pasea L, Banerjee A, Hall G, Denaxas S, Chang WH, et al. Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: Near real-time data on cancer care, cancer deaths and a population-based

cohort study. BMJ Open 2020;10. https://doi.org/10.1136/bmjopen-2020-043828.

[15] NICE. COVID-19 rapid guideline: Managing COVID-19. 2023.

[16] Pignon JP, Stewart LA. Randomized trials of radiotherapy alone versus combined chemotherapy and radiotherapy in Stages IIIa and IIIb nonsmall cell lung cancer: A meta-analysis. Cancer 1996;77:2413–4. https://doi.org/10.1002/(SICI)1097-0142(19960601)77:11<2413::AID-CNCR34>3.0.CO;2-Y.

[17] Conibear J, Nossiter J, Foster C, West D, Cromwell D, Navani N. The National Lung Cancer Audit: The Impact of COVID-19. Clin Oncol 2022;34:701–7. https://doi.org/10.1016/j.clon.2022.09.002.