FACTORS SURROUNDING TREATMENT DECISIONS IN NON-SMALL CELL LUNG CANCER

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Abstract

Introduction

Despite good outcomes from both thoracic surgery and radical radiotherapy, more than 1 in 5 people who appear eligible for curative treatment of lung cancer do not receive any treatment at all. Spotlight data from the National Lung Cancer Audit (NLCA) found 15% of people chose not to receive treatment, rather than for medical reasons. The reasons behind this are unclear and are likely influenced by regional differences as well as personal patient beliefs, which are difficult to capture using quantitative data.

In addition, this research took place during the COVID-19 pandemic when social and healthcare restrictions were in place and diagnoses of lung cancer fell. Times of high healthcare demand are likely to exacerbate any pre-existing disparities in care. It is therefore important to identify any people who were disproportionately disadvantaged by the pandemic, to attempt to mitigate for these in the future.

Objectives

This thesis aims to examine some of the factors which contribute to decision-making for people with non-small cell lung cancer. It also aims to identify any groups who were disadvantaged by the COVID-19 pandemic.

Methods

This thesis utilised mixed-methods to investigate several factors surrounding decision making in the treatment of early-stage lung cancer. A narrative review was undertaken to define the meaning of cure in non-small cell lung cancer (NSCLC). Using retrospective Lung Cancer Clinical Outcomes data from 2017-18 collated by the NLCA, 90-day mortality stratified by age and performance status (PS) were calculated and compared to outcomes from the same dataset in 2004-12. Tables were produced with the intention of being used to enhance communication. Medical records were obtained for people with early-stage lung cancer and analysed using multivariable logistic

regression to identify independent predictors of treatment with curative intent. Semi-structured interviews of people with lung cancer and healthcare workers were conducted and analysed using the Framework approach to identify perceived barriers to curative intent treatment in the East Midlands.

The Rapid Cancer Registration Dataset (RCRD) collated during 2019 and 2020 was used to examine the impact of the early stages of COVID-19 restrictions on lung cancer treatment and survival. 2020 data were divided according to COVID-19 restrictions at the time of diagnosis and compared with baseline data from 2019. Multivariable logistic regression and testing for interactions were used to examine likelihood of receiving curative intent and systemic anti-cancer treatment (SACT). Survival analyses using Cox regression and Kaplan Meier curves were performed.

Results

Outcomes following thoracic surgery for lung cancer have continued to improve with an overall 90-day mortality of 3.1% compared with 5.9% in 2004-12. The majority of procedures were performed via VATS which conferred a survival advantage in this retrospective study.

12% of people with PS 0-2, stage I-II lung cancer in the East Midlands did not receive active treatment. 17% of these people chose not to receive treatment; two-thirds did not receive treatment due to comorbidities or inadequate lung function. Adjusted odds for receiving surgery were significantly reduced by: age ≥80 (OR=0.31; 95% CI 021-0.44), PS=1 (OR=0.2; 95% CI 0.14-0.29), FEV1 50-79% (OR=0.53; 95% CI 0.38-0.75) and TLCO 50-79% (OR=0.24; 95% CI 0.1-0.56). Diagnosis hospital, sex and deprivation did not significantly alter ORs. Older age and PS=2 decreased the likelihood of receiving radical radiotherapy, but this did not persist with adjustment for lung function (OR 0.88, 95% CI 0.4-193; and OR 0.5, 95% CI 0.16-1.6, respectively). Diagnosing hospital did significantly reduce the likelihood of receiving radical radiotherapy for 2 out of 4 trusts included in analysis.

People with potentially curative NSCLC (n=6) and lung cancer clinicians (n=15) underwent semi-structured interviews. 3 themes were identified: emotional treatment barriers; practical barriers; facilitators. Clinicians focused on practical barriers like hospital location and transport, with facilitators often already established to minimise these. In contrast, patients' greatest barriers were emotional, particularly fear of an operation and potential side-effects, especially in those with previous cancer experience.

Overall curative intent treatment of NSCLC during the early-stages of the pandemic was well sustained with a fall in line with a drop in diagnoses, however SACT prescriptions fell from 63% in 2019 to 57% during the 1st National Lockdown (p=0.006). The composition of treatment also altered, with comparatively more people receiving radical radiotherapy in place of surgery, and increased use of combined chemo-immunotherapy as use of cytotoxic chemotherapy alone fell. No particular patient groups were especially disadvantaged. Survival fell from the 1st National Lockdown onwards and worsened as 2020 progressed.

Discussion

This work examined some of the factors surrounding decision making in curative intent treatment for NSCLC in the UK. It provided reassuring evidence that real-world short-term post-operative survival continues to improve. These findings however may not always be clearly communicated as fear of surgery and preconceived treatment beliefs are common emotional barriers to treatment. However, fewer people in this research chose not to receive treatment than in previous analyses, which is reassuring. During COVID-19, good efforts at continuing treatment were made however longstanding disparities in treatment continue to exist. Future work to develop a personalised risk communication tool may be useful in shared decision making and dispelling myths around treatment.

Acknowledgements

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COVID Statement

This PhD was undertaken beginning in the summer of 2020. Owing to the COVID-19 pandemic which began earlier that year, research plans were adjusted, with both positive and negative consequences.

The most significant impact was on the DECLINE study, which was intended to form the bulk of this research. As a result of changes in the ethics process in order to prioritise COVID-19 research, the national ethics application could not be submitted until Summer 2021. In addition, NHS trust ethics and availability could only be processed once this had been completed. Relevant trusts had differing availability, with several trusts not being able to complete ethical approval for many months due to poor staffing and prioritising of other studies. As a result, the time available to complete the research was significantly shortened.

In addition, as a mixed methods study including interviews of both patients and health care professionals, some people were reticent about additional contact with health care workers, and particularly of researchers attending their homes to conduct the interview, meaning several interviews were conducted over the telephone, potentially missing important non-verbal cues. For health care workers, the somewhat novel use of video calls was beneficial and provided easier co-ordination of interview scheduling.

A significant positive however, was the additional opportunity to study the impact of the first wave of COVID-19 on lung cancer treatment and outcomes in England. This provided a unique chance to research discrepancies in delivery of lung cancer care during a time of high healthcare demand.

Publications Arising from this Thesis

What is the Definition of Cure in Non-small Cell Lung Cancer?

Morgan H, Ellis L, O'Dowd EL, Murray RL, Hubbard R, Baldwin DR. Oncol Ther. 2021 Dec;9(2):365-371. doi: 10.1007/s40487-021-00163-3.

Ninety-day mortality following lung cancer surgery: outcomes from the English national clinical outcomes audit.

Morgan H, Baldwin D, Hubbard R, Navani N, West D, O'Dowd E. *Thorax* 2022; 77(7):724-726. doi: 10.1136/thoraxjnl-2021-218308.

Epidemiology of Lung Cancer and Risk Factors.

Burzić A., Morgan H., Baldwin D. (2022). In: Baptiste, J.V., Schwartzstein, R.M., Thomson, C.C. (eds) Lung Cancer Screening. Springer, Cham. https://doi.org/10.1007/978-3-031-10662-0_1

Important parameters for cost-effective implementation of lung cancer screening.

Morgan H and Baldwin D. Br J Radiol. 2023 Apr 1;96(1145):20220489. doi: 10.1259/bjr.20220489.

The Impact of COVID-19 on Lung Cancer Incidence in England: Analysis of the National Lung Cancer Audit 2019 and 2020 Rapid Cancer Registration Datasets.

Gysling S, Morgan H, Ifesemen OS, West D, Conibear J, Navani N, O'Dowd EL, Baldwin DR, Humes D, Hubbard R. Chest. 2023 Jun;163(6):1599-1607. doi: 10.1016/j.chest.2023.01.008.

Impact of the SARS-CoV-2 pandemic on lung cancer survival in England: an analysis of the rapid cancer registration dataset.

Morgan H, Gysling S, Navani N, Baldwin D, Hubbard R, O'Dowd E. Thorax. 2023 Dec 15;79(1):83-85. doi: 10.1136/thorax-2022-219593.

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List of Abbreviations

6MWT	6-minute walk tests
AGP	Aerosol generating procedure
ALK	Anaplastic lymphoma kinase
ASR	Age standardised incidence rates
BED	Biologically Effective Dose
BTS	British Thoracic Society
CDF	Cancer drugs fund
CHART	Continuous hyperfractionated accelerated radiotherapy
CI	95% confidence intervals
COSD	Cancer Outcomes and Services Dataset
CPEX	Cardiopulmonary exercise testing
CT	Computed tomography
DBH	Derby and Burton Hospitals
DFS	Disease free survival
DGH	District general hospital
EBUS	Endobronchial ultrasound
EGFR	epidermal growth factor
ERS	European Respiratory Society
FEV1	Forced expiratory volume in 1 second
FEV1%	Percentage predicted FEV1
FVC	Forced vital capacity
FVC%	Percentage predicted FVC
GP	General Practice
HCP	Healthcare practitioner
HQIP	Healthcare Quality Improvement Partnership
IASLC	International Association for the Study of Lung Cancer
IMD	Index of multiple deprivation
IQR	Inter-quartile range
KMH	King's Mill Hospital
LCCO	Lung cancer clinical outcomes
MDT	Multi-disciplinary team
NCRAS	National Cancer Registration and Analysis Service
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NLCA	National Lung Cancer Audit
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
NUH	Nottingham University Hospitals
OR	Odds ratio
PD1	Programmed Death 1
PD-L1	Programmed Death Ligand 1

PFS	Progression free survival
PFT	Pulmonary function tests
PS	Performance status
RCP	Royal College of Physicians
RCR	Royal College of Radiologists
RCRD	Rapid Cancer Registration Dataset
ROS1	c-ROS oncogene 1
SABR	Stereotactic ablative radiotherapy
SACT	Systemic anti-cancer therapy
SCC	Squamous cell lung cancer
SCLC	Small cell lung cancer
SEER	Surveillance, Epidemiology, and End Results
SES	Socioeconomic status
TB	Tuberculosis
TKIs	Tyrosine kinase inhibitors
TLCO	Transfer capacity of the lungs for carbon monoxide
TLCO%	Percentage predicted TLCO
TLHC	Targeted lung health checks
TNM	Tumour Node Metastases
UK	United Kingdom
UKLCC	United Kingdom Lung Cancer Coalition
ULH	United Lincolnshire Hospitals
USA	United States of America
VATS	Video assisted thoracic surgery
VIOLET	VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer

Chapter 1. Introduction

This chapter reviews up-to-date epidemiology of lung cancer in the UK, as well as current treatments. It also provides an overview of changes in lung cancer care that occurred during the COVID-19 pandemic. Finally, it sets out the overall aims for this thesis and provides an overview of each chapter.

1.1 Epidemiology

Lung cancer is the second commonest cause of cancer worldwide, having only been exceeded by female breast cancer in recent years.(1) In 2020 there were 2.21 million new diagnoses of lung cancer globally, representing 11.4% of all cancer diagnoses. Although there has been a recent decline in overall incidence worldwide, lung cancer rates show significant geographic diversity and gender disparities. As nearly 80% of lung cancer is attributable to cigarette smoking, the observed trends primarily reflect the maturity of the tobacco epidemic worldwide.(2, 3)

1.1.1 Incidence and mortality

Worldwide

There is significant geographical variation in lung cancer incidence rates, with high-income countries demonstrating a three to four-times higher incidence than low-income.(1, 4) The global incidence in men is around double that of women, although this difference again varies by region.

Polynesia, Micronesia and Eastern Asia had the highest incidence rates in 2020 at 34.4 to 37.3 age standardised (ASR) incidence per 100,000 population. In contrast, incidence in Western, Middle and Eastern Africa is low at 2.2 to 3.5 ASR per 100,000.(4) These figures are likely to change in the future as around 80% of tobacco users live in low- and middle-income countries, suggesting these regions will see an increase in incidence in the future.(5)

Owing to the high fatality of lung cancer, mortality rates closely follow incidence. In 2020, lung cancer is estimated to have caused 18.0% of total cancer deaths for males and females combined worldwide and is the leading cause of cancer related death.(1) Age-standardised mortality rates in high-income countries are nearly double that of the lowest-income (31.6 vs 13.7 per 100,000 in males).(1) Following the pattern of incidence, male lung cancer mortality has been steadily declining since 2000, whereas it has been

increasing in women. This is with exception of the United States of America (USA), where mortality has also been decreasing in women.(6)

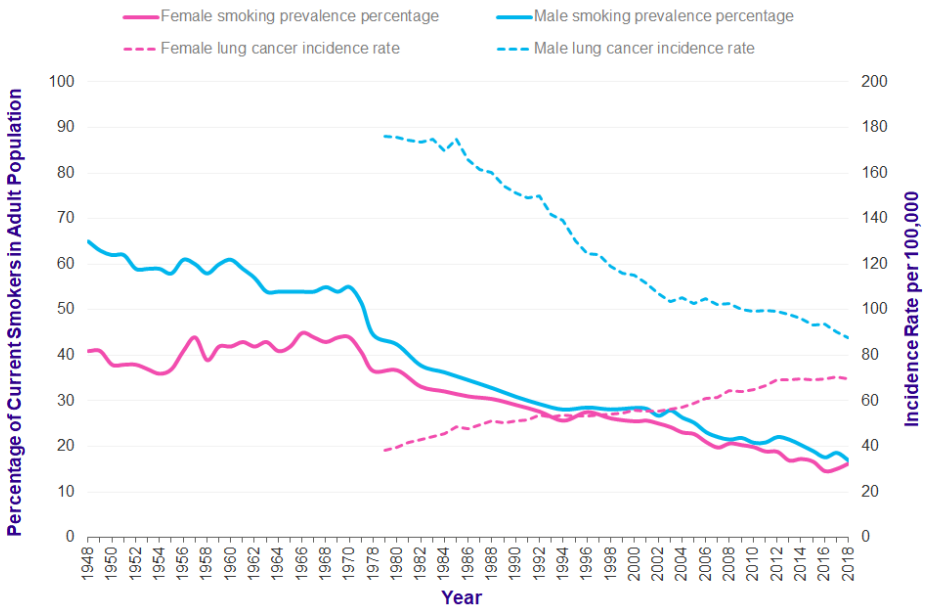


Figure 1-1 Smoking prevalence and age standardised incidence rates for lung cancer in Great Britain, 1948-2018; (With permissions from Cancer Research UK (5))

United Kingdom

In the United Kingdom (UK) incidence has been decreasing since the 1970s, however in recent years this has started to plateau, with a 1% increase over the last decade. For males, rates have continued to decrease by around a third in this time. In females however, the incidence continues to increase by nearly the same amount, with a third more cases annually in 2017 compared with 1993 (Figure 1-1).(7) In the west, smoking rates in men have declined since the 1950s. After a lag, we observed a drop in lung cancer incidence since the 1970s. As the peak in smoking occurred later in women, so did the peak in incidence.(2)

1.1.2 Risk factors

1.1.2.1 Smoking

The link between lung cancer and smoking is well established, with the first evidence being published in the 1950s.(8) In Europe, an estimated 87% of lung cancers in males are caused by cigarette smoking versus 70% in females

(9). The differing trends in smoking worldwide also at least partially explains the variation in lung cancer rates between countries.(1)

Socioeconomic status (SES) also significantly contributes to variation in smoking rates within countries. People of lower SES are more likely to smoke. In the USA, people living in poverty smoke for nearly twice as many years as people with a high income (10). In the UK, 27% of the lowest SES smoke, compared with 8% of the highest SES group.(11) This correlates with higher rates of lung cancer in the most deprived. Rates are 174% higher for women in the most socially deprived quintile compared with the least, and 168% higher for men.(7)

Smoking cessation substantially reduces the risk of death from lung cancer, with greater effects being seen in those who stop at a younger age. Stopping smoking before middle age reduces the risk of lung cancer by more than 90%.(2) Studies have shown that European countries with higher tobacco control efforts have reduced smoking prevalence and improved lung cancer mortality rates. It is predicted that the improved implementation of tobacco control policies could potentially prevent 1.65 million cases over a 20-year period across Europe.(12)

Through passive smoking, non-smokers can be exposed to carcinogens and other substances in cigarette smoke. Meta-analyses have concluded around a 25% increased risk of lung cancer in never smokers exposed to significant levels of second-hand smoke.(13, 14)

E-cigarettes and vaping have increased in use over the last few years. A heating coil is used to vaporise fluid containing nicotine and flavourings from a replaceable cartridge. The use of vaping varies, with some people using them as a method of smoking cessation, some people using them alongside cigarettes, and others who were previous never smokers. 40% of people aged 18-24 who vape were previously never smokers.(15) Vaping liquids contain a variety of substances, including both known and suspected carcinogens.

Currently, long term data are lacking regarding risk of lung cancer from e-cigarettes.

1.1.2.2 Other risk factors

Whilst smoking in the biggest risk factor for developing lung cancer, up to 25% of cases worldwide occur in people who have never smoked.(16) 3-5% of lung cancer cases worldwide have been attributed to air pollution, with more than half of these in China and other East Asian countries.(17) Lower SES countries tend to have higher levels of air pollution, which is at least partly attributable to the burning of biomass fuel in these countries.(17) Particulate matter in air pollution is a Group 1 carcinogen.(18)

Radon may be accountable for up to 10% of lung cancer cases, and is the most significant risk factor in never smokers.(19) Whilst the highest concentrations of radon occur in areas of work underground (particularly uranium mines), air pollution with radon occurs in all settings.(20) Smoking increases the risks conferred even by high radon exposure, from less than 1% in never smokers to 16% for smokers. (21, 22)

Asbestos causes the vast majority of cases of malignant mesothelioma, and is also thought to cause 5-10% of lung cancer cases worldwide.(23) Asbestos exposure also shows a synergistic effect with tobacco smoking, rather than additive. Whilst asbestos exposure increases lung cancer risk by 5-fold, cigarette smoking continues to exceed this, increasing risk by around 10-fold. In a smoker, the cumulative risk of lung cancer following asbestos exposure is increased 50-fold.(23, 24)

Chronic inflammation secondary to infections has been implicated in the formation of lung cancer. Of note, pulmonary tuberculosis (TB) has been shown to increase lung cancer risk. Whilst the worldwide incidence of TB is decreasing by approximately 2% a year, it continues to represent a significant burden of disease.(19, 23) HIV infection also increases the risk of lung cancer. It is the most common non-AIDS defining malignancy in HIV positive individuals.(23)

Whilst environmental exposures are very important in the development of lung cancer, genetic factors also play a role. 1st degree family members are estimated to have a 2-3.5 times increased risk of developing lung cancer, although it should be noted that risk is increased by 1.75 times for spouses, suggesting that a portion of this risk is due to shared environmental exposures.(25) The association is strongest in those who are younger at presentation, with the highest risk in those aged less than 50 years.(26, 27)

1.2 Classification of Lung Cancer

1.2.1 Histology

Lung cancer is divided into two main histological sub-types: non-small cell lung cancer (NSCLC) which makes up around 85% of tumours, and small cell lung cancer (SCLC), around 15%. NSCLC is further divided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma.(28) Historically, squamous cell carcinoma was the most common histological subtype, but since the 1990s the incidence of adenocarcinoma has been increasing, and is now the commonest type in North America, Europe and Japan. These changes are thought to be due to changes in the type of cigarettes smoked (e.g., filtered, low tar) as well as genetic predisposition.(29, 30)

SCLC is generally considered a more aggressive tumour due to its propensity to metastasize early.(31) Nearly 70% of SCLC has spread to distal sites at presentation.(32) Owing to the different disease processes and therefore treatment and outcomes of NSCLC and SCLC, this thesis mainly focuses on NSCLC, with inclusion of SCLC mentioned where appropriate.

1.2.2 Staging

Lung cancer is staged according to the size and spread of disease at diagnosis. This is done using the Tumour, Node, Metastasis (TNM) system, with guidance produced by the International Association for the Study of Lung Cancer (IASLC).(33) The 8th edition of TNM staging has been in use since 2018

and is summarised in Table 1-1.(34) The TNM stage is commonly converted to a number stage, which is often used in treatment guidelines (Table 1-2).

Table 1-1 TNM staging of lung cancer, 8th edition(33, 34)

<table>
<tr><td colspan="6">Tumour</td></tr>
<tr><td colspan="3">T1</td><td colspan="2">T2</td><td rowspan="2">T3</td><td rowspan="2">T4</td></tr>
<tr><td>T1a</td><td>T1b</td><td>T1c</td><td>T2a</td><td>T2b</td></tr>
<tr><td>≤1cm</td><td>>1cm ≤2cm</td><td>>2cm ≤3cm</td><td>>3cm ≤4cm</td><td>>4cm ≤5cm</td><td>>5cm≤7cm</td><td>>7cm</td></tr>
<tr><td colspan="3"></td><td colspan="2">Involvement of main bronchus without carina</td><td>Invasion of chest wall, pericardium, phrenic nerve</td><td>Invasion of mediastinum, diaphragm, spine</td></tr>
<tr><td colspan="3"></td><td colspan="2">Invasion visceral pleura</td><td>Nodules in same lobe</td><td>Nodules in different lobe of ipsilateral lung</td></tr>
<tr><td colspan="3"></td><td colspan="2">Post-obstructive pneumonitis extending to hilum</td><td></td><td></td></tr>
<tr><td colspan="6">Node</td></tr>
<tr><td colspan="3">N0</td><td colspan="2">N1</td><td>N2</td><td>N3</td></tr>
<tr><td colspan="3">No nodal spread</td><td colspan="2">Ipsilateral peribronchial, hilar and/or intrapulmonary nodes</td><td>Ipsilateral mediastinal and/or subcarinal nodes</td><td>Contralateral and/or scalene or supraclavicular nodes</td></tr>
<tr><td colspan="6">Metastasis</td></tr>
<tr><td colspan="3">M0</td><td colspan="2">M1a</td><td>M1b</td><td>M1c</td></tr>
<tr><td colspan="3">No distant metastases</td><td colspan="2">Intrathoracic metastasis</td><td>Single extra-thoracic metastasis</td><td>Multiple extra-thoracic metastases</td></tr>
</table>

For SCLC, disease is also staged using TNM 8th edition, having previously been staged as limited or extensive. Limited-stage disease is confined to the thorax, and extensive-stage has spread outside of the thorax.(35)

Table 1-2 Relationship of TNM and numbered staging of lung cancer

	T1	T2a	T2b	T3	T4
N0	IA	IB	IIA	IIB	IIIA
N1	IIB			IIIA	
N2	IIIA			IIIB	
N3	IIIB			IIIC	
M1a	IVA				
M1b	IVA				
M1c	IVB				

Lung cancer tends to present at the more advanced stages, which is one reason for its high fatality. In the UK, the majority of people present with stage IIIB-IV disease (Figure 1-2).(36) Advanced-stage NSCLC has a worse survival with 3% 5-year survival at stage IV compared to 57% at stage I.(37)

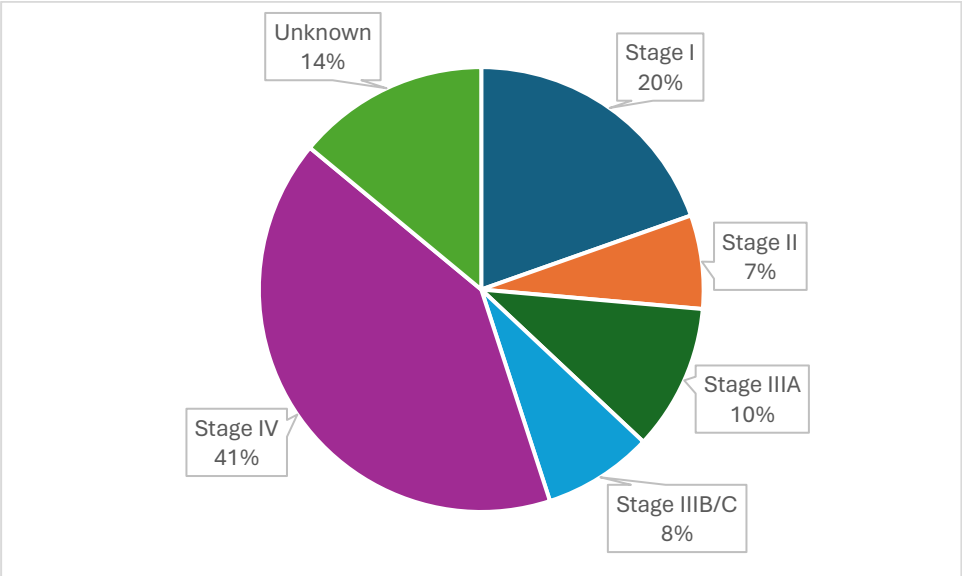


Figure 1-2 Stage at diagnosis of lung cancer in England in 2021(36)

1.3 Treatment

Treatment of lung cancer is broadly determined by the stage of disease and patient fitness, as well as histological subtype. For people with early-stage NSCLC the goal of treatment is curative. Stage IIIA disease can also be treated with curative intent, however this requires multi-modality treatment. For people with advanced stage disease, treatment intention is disease control

rather than cure. In this case systemic anti-cancer treatment (SACT) is used to minimise symptoms and prolong life. SCLC is treated with combination chemo-radiotherapy even in limited stage disease, although some patients with very early stage disease (T1aN0M0) may be offered surgical resection, as part of a multidisciplinary team discussion. For all of these treatments performance status (PS) is an important prognostic indicator, with people usually being considered fit enough for treatment with a PS 0-2 as with worse fitness the risks of treatment outweigh the benefits.(38) The World Health Organisation (WHO) PS classification is summarised in Table 1-3.(39)

Table 1-3 WHO PS classification(39)

PS 0	Able to carry out all normal activity without restriction
PS 1	Restricted in strenuous activity but ambulatory and able to carry out light work
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
PS 3	Symptomatic and in a chair or in bed for greater than 50% of the day but not bedridden
PS 4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair.

1.3.1 Treatment with Curative Intent

1.3.1.1 Surgery

For people with early-stage disease who are physically fit, surgical resection is the gold-standard of treatment. To be resected, each case must be both resectable and operable. Resectability refers to the size and location of the tumour, and whether the whole cancer can be safely resected. Operability refers to whether the person is able to undergo treatment and takes into account PS, comorbidities and other tumour factors.(40)

In the UK, guidance advises assessment of pulmonary and cardiovascular fitness prior to surgery. All people should have full pulmonary function testing (PFT) with measurement of FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity) and TLCO (transfer capacity of the lungs for carbon monoxide) and must have sufficient lung function to both survive the operation and not have unacceptable levels of breathlessness following resection. This is usually considered a predicted post-operative FEV1 and

TLCO of 40% or more. People also routinely have an echocardiogram to assess cardiac function.(41, 42) In cases where people have borderline fitness, additional testing in the form of 6-minute walk tests (6MWT) or shuttle walk testing, as well as cardiopulmonary exercise testing (CPEX) may be completed.(41, 42)

Lobectomy is the gold standard of treatment for early-stage NSCLC.(35, 42) Here, the cancer containing lobe of the lung is removed entirely, alongside systematic nodal dissection, which should be performed in all people undergoing surgical resection of lung cancer.(42, 43) Where the tumour cannot be completely resected in one lobe, pneumonectomy – or the removal of a whole lung – may be required.(43) Pneumonectomy is associated with increased short- and long-term morbidity and mortality compared with lobectomy.(44, 45) Where tumours are small and peripheral, sublobar resection through either a wedge or segmental resection are sometimes used. These are lung preserving techniques and are therefore useful in people with limited pulmonary reserve.(42) Sublobar resections have historically been found to result in increased local recurrence, however a more recent study has concluded no difference in disease free survival (DFS).(46, 47)

For people with tumours ≥4cm or nodal involvement, post-operative adjuvant systemic therapy is recommended.(42) This has traditionally been through platinum based chemotherapy, which offers a small 4% increase in survival at 5 years.(48) More recently, other SACT has been recommended in the UK.(49) Adjuvant treatment with osimertinib in people with epidermal growth factor (EGFR) positive mutations offers improved DFS at 24 months.(50) Immunotherapy using pembrolizumab has also been shown to improve DFS, but is not yet recommended in the UK.(51)

1.3.1.2 Radical Radiotherapy

For people who are not suitable for surgery or choose not to receive it, radical radiotherapy offers an alternative treatment with curative intent.(35) Lung toxicity is the greatest limiting factor for delivering radiotherapy, and is more common in people with pre-existing lung disease.(42) There are however, no

predetermined lower limits of lung function to deliver radiotherapy, and management should be considered on a case-by-case basis.(52)

For peripheral lesions radiotherapy can often be delivered in the form of stereotactic ablative radiotherapy (SABR) which delivers high radiation in a small number of radiotherapy sessions or fractions. If a tumour is located centrally, it may be amenable to SABR but it should not be used for ultracentral tumours due to the high toxicity rates.(52, 53)

An alternative to SABR is conventionally fractionated radiotherapy, or lower doses of radiotherapy delivered in more fractions.(35) Continuous hyperfractionated accelerated radiotherapy (CHART) delivers radiotherapy in many small fractions with multiple radiotherapy sessions in one day.(54)

Retrospective, observational studies concluded SABR had more than double the risk of death compared with surgical resection.(55, 56) However, a large number of people who receive radiotherapy will be less fit than their surgical counterparts, with competing causes of death. Randomised control trials to compare the two treatments have been repeatedly limited due to slow accrual, but recent meta-analysis has concluded no difference in long-term survival amongst those who are fit.(57)

1.3.2 Treatment in Advanced Stage Disease

For people with advanced stage disease, systemic treatment is required as the cancer has spread outside of the thorax. In NSCLC in the UK, three types of SACT are used, depending on the exact histology of the cancer: targeted treatments, immunotherapy, and traditional chemotherapy.(35) NSCLC with mutations in various oncogenic drivers including EGFR, anaplastic lymphoma kinase (ALK) and c-ROS oncogene 1 (ROS1) are susceptible to treatment with tyrosine kinase inhibitors (TKIs) targeting different mutation profiles.(58) Treatment with appropriate targeted therapies extends progression free survival (PFS) compared with traditional chemotherapy.(59) For people without mutations, immunotherapy targeting Programmed Death 1 (PD1) and Programmed Death Ligand 1 (PD-L1) is recommended as it offers a survival

advantage compared with chemotherapy alone.(35, 51, 60-62) Where PD-L1 expression is ≥50%, single agent immunotherapy is used.(63, 64) If PD-L1 expression is <50%, combination therapy of platinum-doublet chemotherapy and immunotherapy is recommended.

Radiotherapy is used in advanced stage cancer to palliate symptoms such as pain or endobronchial obstruction.(35, 52)

1.3.3 Small cell lung cancer

The proportion of lung cancer which is small cell has been falling, making up 7% of cancers in England in 2021.(36) Due to the aggressive nature of SCLC and the propensity to spread early, the majority of these are diagnosed as extensive stage disease.(65) People with limited-stage disease are treated with combination platinum chemotherapy with concurrent twice-daily thoracic radiotherapy, if tolerated.(35) Twice-daily radiotherapy offers a survival advantage over once-daily and should be used where the patient is fit enough.(66)

In extensive-stage SCLC, combination chemo-immunotherapy in the form of atezolizumab plus combination platinum chemotherapy has been shown to extend progression free survival from 4.3 to 5.2 months, and overall survival by 2 months, from 10.3 to 12.3 months.(67) In people who respond to systemic treatment, thoracic radiotherapy is considered.(35)

People with both limited and extensive stage SCLC should be offered prophylactic cranial irradiation if their disease does not progress or responds to first-line treatment, respectively.(35) Cranial irradiation reduces the incidence of symptomatic brain metastases as well as prolonging progression-free and median overall survival.(68)

1.3.4 Supportive care

1.3.4.1 Smoking Cessation

All people diagnosed with lung cancer who are current smokers should be offered smoking cessation therapy.(35) Stopping smoking at the time of

diagnosis confers a survival benefit and is associated with decreased post-operative complications, improved response to chemotherapy, and decreased incidence of secondary cancers.(69, 70)

1.3.4.2 Best Supportive Care

All people with advanced stage disease, and those with early-stage disease who are not fit enough for treatment, should be referred for supportive care alongside or in the absence of other treatments.(35) Palliative care focusing on symptom control rather than anti-cancer treatment improves quality of life and mood, as well as extending median overall survival by three months in untreated metastatic NSCLC.(71)

1.4 Variation in Lung Cancer Outcomes

1.4.1 International Variation

For nearly 30 years, EUROCARE have compared cancer survival between European countries. In their most recent publications using data from 1999-2007, the UK had the worst 5-year lung cancer survival at 9%, compared with 13% for the European mean.(72, 73) The UK also lags behind when compared with similar income countries as demonstrated in SURVMARK-2, completed by the International Cancer Benchmarking Partnership (ICBP). In 2010-14, 5-year lung cancer survival was 14.7% in the UK compared with the greatest survival of 21.7% in Canada.(74) Whilst these difference are partly explained by differences in cancer registry data, stage specific survival was significantly lower in the UK for both early-stage and advanced-stage NSCLC.(75) Survival has improved in recent years, however again, not to the same extent as in other countries. From 1995 to 2014, UK 5-year survival improved by 4.8%, with the greatest improvement of 9.2% in Denmark.(74)

1.4.2 Variation within the UK

There is also variation in treatment rates and outcomes within the UK, which may partially explain the international variation. 84% of UK healthcare practitioners felt that regional inequalities in lung cancer care impacted survival rates.(76) Treatment rates vary for all modalities, including surgery,

radical radiotherapy and chemotherapy.(77) The reasons for this are multifactorial, with higher rates of cancer, lower treatment rates, and worse survival amongst those people who are most deprived. (78-80) National policy likely also plays a part, with only 26 out of 62 radiotherapy centres in England commissioned to deliver SABR in 2019. (81) Geographical differences also exist, with people being more likely to receive surgery if they are first seen at a surgical, rather than referral, centre.(82) Previous work has shown a rural urban divide, with people living in urban areas having worse outcomes, although these differences disappear when taking SES into account.(83)

1.4.3 Strategies for Improving Outcomes

As a result of these regional disparities, and the poor outcomes when compared internationally, the UK has made efforts to improve lung cancer outcomes. The United Kingdom Lung Cancer Coalition (UKLCC) was formed in 2005 with the ambition to double five-year survival in 10 years. Principles were established in their 2015 report '25 by 25' with the aim of improving five-year survival to 25% by 2025, with an update released following the COVID-19 pandemic.(76, 84) This was further asserted by the NHS Long Term Plan of 2019, which included the key targets of increased the number of people diagnosed at an early-stage, and reducing nationwide variation and inequalities.(85)

One of the strategies employed to increase early-stage diagnosis and therefore curative intent treatment was through low-dose computed tomography (CT) screening. Surgical resection rates of over 65% have been shown in most screening trials and pilots, with a reduction in mortality observed in two large randomised trials.(86-89) As a result of these positive findings, Targeted Lung Health Checks (TLHC) were established at pilot sites throughout the UK.(90) At baseline, the overall detection rate in these areas was 2.1%, with 66% stage I disease and 83% surgical resection rate.(86) On the strength of these outcomes, and evidence of cost effectiveness, the UK National Screening Committee recommended targeted screening for people aged 55-74 at high risk of lung cancer in June 2022.(91, 92) TLHC are being rolled out into

additional areas of England. Moving forwards, it will be essential to ensure the people at highest risk access screening, as they are traditionally the least likely to engage.(93)

Other recommendations include widening access to SABR, prioritising checking of biomarkers for use in targeted therapies, and running frequent public awareness campaigns. A key target is to improve rates of curative intent treatment in people with stage I-II disease, PS 0-2 to 85%.(84) Identifying the reasons some people are not offered treatment will be essential to improving this measure.

1.5 The COVID-19 Pandemic

This research took place from 2020 to 2023, coinciding with the initial and most significant stage of the COVID-19 pandemic. The pandemic had an unprecedented impact on healthcare and society both in the United Kingdom (UK) and across the world. To manage the high numbers of inpatients with SARS-CoV-2, the National Health Service (NHS) was redirected towards acute care, and the risk of overwhelming the system was publicized to the general public. In addition, people were advised to 'Stay at Home', particularly if they had potentially infective symptoms like a cough.(94)

1.5.1 The Impact on Healthcare Services

31 million fewer general practice (GP) appointments were made between April 2020 and March 2021 compared with the previous 12 months.(95) Hospital admissions in England fell by 34.2%, with an even greater reduction in cancer and scheduled respiratory admissions.(96) Combined with the overlap of respiratory symptoms between lung cancer and COVID-19, this culminated in a 26% reduction in lung cancer incidence rate in England during the first National Lockdown of 2020, compared with the same time period in 2019.(97) In addition to a fall in diagnoses, PS 0-1 fell from 52% to 47% and curative intent treatment fell from 81% to 73% of eligible patients.(98)

This highlights the unmet needs during the initial stages of the pandemic, but it is unclear whether the population was uniformly affected. During periods of

increased strain on healthcare services, the most vulnerable populations are more likely to be affected.(99) Within the UK, lockdown measures have exacerbated long-standing healthcare inequity, with females, older people, ethnic minorities and people from more deprived backgrounds being disproportionately impacted.(100) Investigating how lockdown restrictions impacted lung cancer treatments and outcomes is essential to planning future healthcare provision during both normal working and potential future public health emergencies.(101) By identifying those people who were disproportionately disadvantaged from receiving lung cancer treatment during 2020, we may be able to identify those people who are most vulnerable at other times.

1.5.2 Changes in Lung Cancer Guidance

Changes in guidance for the diagnosis and management of lung cancer were made during the pandemic in order to minimize the risk to patients, clinicians, and to redistribute healthcare resources to manage emergent needs. Guidelines varied internationally and evolved over the course of the pandemic, as more information about the novel SARS-CoV-2 virus became available.(102-105) For cancers specifically, the National Institute for Health and Care Excellence (NICE) recommended prioritising treatment for conditions with a high chance of cure, which excludes the majority of lung cancer diagnoses.(106)

1.5.2.1 Diagnosis

UK guidance focused on minimising risk of exposure of both patients and healthcare practitioners whilst maintaining an effective cancer pathway.(107) Diagnostic tests including bronchoscopy and PFTs were limited due to both a redistribution of clinical staff, and minimising high risk procedures, particularly aerosol generating procedures (AGPs).(108) Where spirometry was adequate, full PFTs could be avoided.(109)

Bronchoscopic services including endobronchial ultrasound (EBUS) were continued but with advice to avoid in people with a low risk of cancer where

appropriate, and taking into consideration the individual risk of mediastinal disease and probability of lung cancer, patients may be referred directly to treatment.(109, 110) In cases where the Herder score indicated a high lung cancer probability, treatment could be commenced without pathological confirmation.

1.5.2.2 Curative Treatment

Thoracic surgical capacity was limited by both reduced theatre space and ventilator requirements. In addition, concerns over the high mortality of COVID-19 in people with lung cancer resulted in efforts to minimise nosocomial infection.(111) Because of this, thoracic surgery was recommended to prioritise people at highest risk of stage progression (stage IIB/IIIA). In people with small tumours <2cm, SABR was recommended in preference if surgical capacity was reduced.(109) Where possible, hypofractionation of SABR was encouraged, to minimise trips to hospital.(112)

1.5.2.3 SACT Treatment

As mentioned, treatment of advanced stage NSCLC was not a priority for continuation, as advanced stage NSCLC is not a considered a curable disease.(106) In NSCLC specifically, the potential risks of immunosuppression were minimised through recommending single agent immunotherapy over combined chemo-immunotherapy, which had been initially introduced as first line treatment in 2019.(113, 114)

1.5.3 COVID-19 Lockdowns

Government guidance on restrictions varied throughout 2020 depending on COVID-19 activity at the time.(94) A timeline of key events is included in Table 1-4.

Table 1-4 Key dates for COVID-19 restrictions in 2020 in England.(69)

COVID-19 Key Dates in 2019-20
31/12/2019 - first cases of viral pneumonia reported in Wuhan
30/01/20 - first case of SARS-CoV-2 in UK
26/03/20 - UK first National Lockdown 10/05/20 - Plan for lifting lockdown announced
15/06/20 - Non-essential shops re-open 04/07/20 - 1st local lockdown
14/10/20 - 3-tier system introduced 05/11/20 - 2nd National Lockdown 02/12/20 - 2nd National Lockdown ends 21/12/20 - Tier 4 restrictions introduced

1.6 Thesis rationale

This thesis examines factors surrounding curative intent treatment of NSCLC. It will explore the meaning of 'cure' in the context of lung cancer, provide an analysis of contemporary outcomes from thoracic surgery, examine the reasons some people choose not to receive treatment with curative intent, and finally explore changes in lung cancer treatment and survival during the COVID-19 pandemic.

1.6.1 Thesis Objectives

Specific objectives for these research projects:

1. To explore the meaning of 'cure' in NSCLC, and examine how this varies between patients, clinicians, and policymakers.
2. To produce up-to-date short-term mortality figures following surgery for early-stage NSCLC.
3. To identify physiological or demographic factors which decrease the likelihood of receiving surgery or radical radiotherapy in people with early-stage, good PS lung cancer across the East Midlands.

4. To explore perceived barriers to treatment with surgery and radical radiotherapy from people who have chosen not to receive treatment, and from health care providers.
5. To examine how lung cancer treatment and survival changed during the COVID-19 pandemic in England, for both treatments with curative intent, and non-curative treatment in the form of SACT.
6. To identify factors associated with variation in treatments and outcomes for those diagnosed with lung cancer during the COVID-19 pandemic.

1.6.2 Overview of Chapters

Chapter 1: Introduction and Thesis Overview

This chapter provides an overview of the current literature regarding early-stage NSCLC and treatments which are used with curative intent. It also provides an overview of other chapters, and where they sit in the thesis overall.

Chapter 2: Defining Cure in the Context of Non-Small Cell Lung Cancer

This chapter investigates the various ways 'cure' can be defined in the context of NSCLC. Through narrative review it explores the meaning of 'cure' to different stakeholder groups including statisticians, policymakers, and people with lung cancer.

Chapter 3: Thoracic Surgery for Lung Cancer: Contemporary outcomes from the English National Clinical Outcomes Audit

This chapter examines short-term mortality following curative intent lung cancer surgery in England. It includes an analysis of the lung cancer clinical outcomes (LCCO) dataset produced as part of the National Lung Cancer Audit (NLCA). It provides a continuation of work previously published by O'Dowd et al., 2016 by updating 90-day mortality figures in view of advances in surgical practice.(115)

Chapter 4: DECLINE: What Patient Factors are Associated with Not Receiving Treatment in Early-Stage Lung Cancer?

This chapter aims to identify patient features which impacted the likelihood of receiving curative intent treatment for people with early-stage, good PS lung cancer across the East Midlands. This was completed through review of medical records for people diagnosed with lung cancer from four NHS hospital trusts and generation and subsequent analysis of a patient database. Examined factors include demographics, physiological health data such as lung function and echocardiography, and details of their lung cancer diagnosis.

Chapter 5: DECLINE: Perceived Barriers to Curative Treatment for People with Early-stage Lung Cancer – Semi-Structured Interviews of Patients and Health Care Professionals

This chapter investigates the reasons some people choose not to receive potentially curative lung cancer treatment. It includes a qualitative study through thematic analysis of semi-structured interviews of both health care professionals, and people who have refused either surgery or radical radiotherapy.

Chapter 6: The Impact of the COVID-19 Pandemic on the Curative Treatment of NSCLC in England: An Analysis of the Rapid Cancer Registration Dataset

The COVID-19 pandemic provided a unique opportunity to examine the changes in treatment and survival of people with newly diagnosed lung cancer during a period of high pressure on the health service. At these times, the most vulnerable people are more likely to be the most disadvantaged, therefore analysis of outcomes during this time was felt to be highly relevant to this thesis.(99)

This first COVID-19 chapter examines changes which occurred in the use of surgery and radical radiotherapy in people with early-stage lung cancer between 2019 and 2020. This is done through a detailed analysis of the rapid

cancer registration database (RCRD) produced by NLCA during the COVID-19 pandemic. It aims to identify any demographic factors which affected the likelihood of receiving curative intent treatment.

Chapter 7: The Impact of the COVID-19 Pandemic on the use of SACT in NSCLC in England: An Analysis of the Rapid Cancer Registration Dataset

This second COVID-19 chapter also includes analysis of the RCRD. This chapter describes changes in the use of SACT in people with advanced stage lung cancer during the 2020 COVID-19 pandemic, including both treatment rates and differing prescriptions. It aims to identify overarching changes in practice and identify demographic features which decreased the likelihood of receiving SACT during 2020.

Chapter 8: The Impact of the COVID-19 Pandemic on Lung Cancer Survival in England: An Analysis of the Rapid Cancer Registration Dataset

This final COVID-19 chapter also includes analysis of the RCRD. It examines the differences in survival for people diagnosed with lung cancer in 2020 compared with 2019. It aims to identify any groups of people who were particularly disadvantaged during the pandemic, as demonstrated by worsened survival.

Chapter 9: Summary of Thesis and Future Research

A summary of the thesis chapters and description of ideas for ongoing research which have arisen as a result of this work.

1.7 Chapter Summary

- Lung cancer is the second commonest cancer worldwide and the leading cause of cancer related death.
- Poor outcomes from lung cancer are partly attributable to diagnosis at a late stage, with good survival following treatment with surgery or radical radiotherapy in early-stage disease.

- Lung cancer survival in the UK is lagging behind similar income countries, with recent improvements negatively impacted by the COVID-19 pandemic.
- The pandemic brought with it the possibility of exacerbating already present disparities in cancer care.
- This thesis will examine some of the factors which impact curative intent treatment of NSCLC in the UK.

Part of the introduction was published in the book 'Lung Cancer Screening' by *Springer* in 2022.

Chapter 2. What is the Definition of Cured in Non-small Cell Lung Cancer?

Through narrative review, this chapter examines the different definitions of 'cure' in the context of lung cancer. It highlights the importance of defining and discussing treatment intent with people with cancer in the clinical setting.

2.1 Background

People with cancer and their relatives often want to know if their disease can be cured, by which they may mean to continue a life free from cancer. However, defining 'cure' is not as easy as it might first seem and has generated a great deal of discussion and debate. A common definition of cure in cancer is difficult to give, because the public, patients, clinicians and policymakers use word to refer to different concepts.(116) The first attempt to define 'cure' was in 1963, and referred to a group of disease-free survivors of Hodgdkin's lymphoma whose annual mortality had equaled that of the general population.(117) More recently, a collaboration of medical doctors, epidemiologists, patients and patient advocates produced the Siracusa charter to provide guidance on using the term 'cured' in clinical settings. They defined 'cured' cancer as 'complete clinical remission of a cancer, regardless of the presence or absence of late sequelae of treatments.'(118) Progress in diagnosis and treatments has resulted in many cancers now being considered curable.

2.1.1 Survival in Non-small Cell Lung Cancer

Lung cancer is the most common cause of cancer related death worldwide, with over 1.8 million annual deaths, double that of the next most common, colorectal cancer.(1) Surgery and radical radiotherapy are referred to as treatment with curative intent, but oncologists and other clinicians are often reticent to use the word cure with cancer patients, due to the possibility of late recurrence.(119)

Evidence of cancer outcomes is usually published in terms of one, five, or ten-year survival, rather than the proportion cured. This serves the dual purpose of being easier for patents to understand – it provides a tangible description of their likely outcomes – and also better assessing variations in survival times. The English Office for National Statistics shows that lung cancer has the lowest 10-year survival of all the commonest cancers in England at 9.5% for all patients.(37) Predicted survival in lung cancer is closely related to stage at

presentation (Figure 2-1). One of the reasons for the poor prognosis of lung cancer is that the majority of patients present with advanced stage disease where our treatment aim changes to one of disease control, rather than cure.(36)

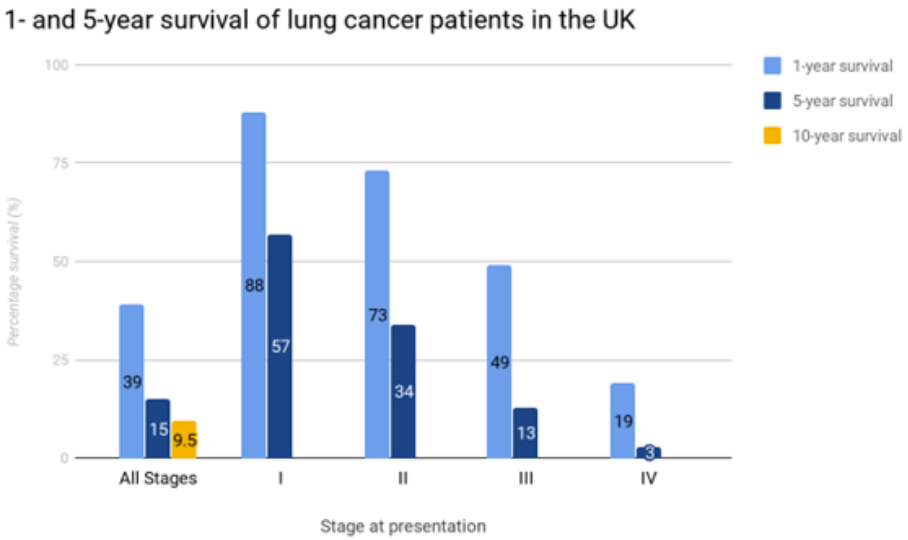


Figure 2-1 One and five-year survival for NSCLC in the UK(7)

People with stage I/II disease and acceptable fitness are treated with curative intent, through either surgery or radical radiotherapy. Five-year survival following surgical resection is reported at 40-70%.(120, 121) Retrospective studies found a five-year survival following radical radiotherapy of 12%, although this figure will be impacted by including those people who were less fit and considered inoperable.(122) More recent data has suggested that long-term outcomes for surgery and SABR in stage I disease are similar.(123)

Estimates of disease recurrence are similar following both radical radiotherapy and surgical resection, with recurrence rates of 20-30% within 5 years of treatment.(124-126) The majority of patients recur in the first 12-24 months, with recurrence rates being calculated at 6-10% per person year for the first 3-4 years, then dropping to 1-2% over the following 2 years.(55, 126) Following recurrence, 5-year survival is 15%.(125, 126)

Prolonged survival is often used as a surrogate for cure, however this is not always appropriate. The concept of cure in cancer is complex and is

considered differently according to personal or professional perspectives. Epidemiologists consider statistical cure, when the mortality rate of the cancer population returns to that of the general population.(127) Clinicians may be more focused on personal cure where they consider the likelihood of each individual patient surviving their cancer in the long term.(128) In contrast, patients and the public may be more interested in their quality of life both during and following treatment, and have a different, personalised approach to what cure means to them. This is termed 'psychological cure'. These different definitions risk miscommunication between clinicians and people with cancer, possibly resulting in misaligned treatment aims.(118)

2.1.2 Aims

This chapter seeks to clarify the concept of cure by exploring the various definitions and show how these apply to NSCLC.

2.2 Methods

A comprehensive overview of the literature was generated through a narrative review. Relevant articles were identified by searching PubMED, OVID and EMBASE databases. Search terms used are included in Table 2-1, as text words and medical subject headings where appropriate. Relevant articles were identified through screening of titles and abstracts. In addition, reference lists of relevant articles were manually searched.

Table 2-1 Search terms used

Lung	Lung Pulmon* Bronch* Respiratory
Cancer	Cancer* Carcino* Neoplas* Malignan*
Cure	Cure* Curative Statistical cure Personal cure
Non-small cell	Non-small cell NSCLC Adenocarcinoma Squamous cell
Survival	Surviv* Outcome*
Radical radiotherapy	Radical radiotherapy SABR Stereotactic ablative radiotherapy CHART Continuous hyperfractionated accelerated radiotherapy
Surgery	Surgical Surger* Resect*

2.3 Discussion

2.3.1 Statistical Cure

Statistical cure is used in epidemiology and public health to consider the outcome of the whole population of cancer patients. It is useful to policymakers to standardise care across different settings, such as follow-up time.(116, 125) It occurs when the mortality rate of cancer patients returns to the baseline level of the general age matched population. In other words, if no more cancer patients in a cohort die or relapse from their disease, the risk of death is equal to that of disease-free controls, and statistical cure has been reached.(126)

Cure models are used to separate fatal cases from those with the same mortality as the general population.(129) If relative survival is plotted on a survival curve, as patients either die or relapse, they are removed, reaching a time point after which no more patients relapse or die from their cancer or its treatments. At that point, the curve will remain flat. The time point from diagnosis when this occurs is called the cure point, or time to cure.(125, 126) The proportion of patients still alive is the cure fraction.(116) Figure 2-2 illustrates these points. A number of statistical techniques can be applied in models to establish the factors that are important in determining cure for each particular disease.(130)

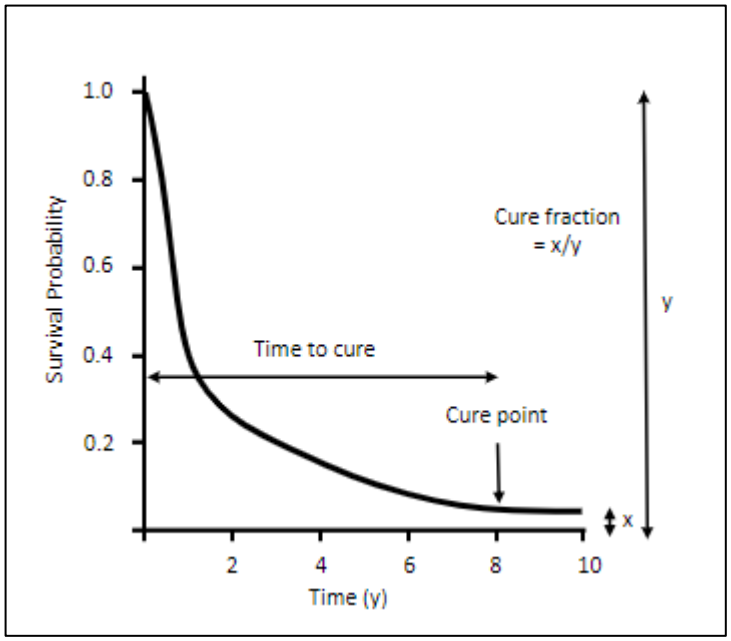


Figure 2-2 - Schematic Survival Curve of Relative Survival to Illustrate the Concept of Statistical Cure (130)

In some instances, the relative survival curve may not appear to flatten, implying that either the disease is incurable, or insufficient time has passed for statistical cure to be achieved. Breast cancer patients, for example, can relapse decades after their initial treatment. In these cases, 5 or even 10-year survival, are inadequate surrogates for statistical cure.(126)

Colorectal cancer is the third most common cause of cancer and curative treatments are well established, which has allowed examination of statistical cure. As survival of colorectal cancer has improved, many patients will now

die from causes other than the cancer, most commonly heart disease. Ninety percent of people with stage I colorectal cancer diagnosed at age 70 will not die of their cancer within 10 years but instead are more likely to die from other causes; they have been cured.(128) For colorectal cancer, the time to statistical cure has been estimated to vary from 7-11 years, based on age, gender and stage of malignancy at diagnosis.(116)

For NSCLC, statistical cure is less well established. Attempts have been made to estimate both the cure fraction and time to cure, however the low overall survival has made the calculation challenging. Seven papers have utilised a variety of mixed cure models, survival curves and conditional relative survival to calculate this, as summarized in Table 2-2. The time to reach a conditional relative survival of >90% or >95% of the general population is often used as a surrogate for time to cure. A review paper estimated to vary between 6-11%, with a time to cure of 9 to more than 10 years, where it could be calculated.(116) A study using the Surveillance, Epidemiology and End Results (SEER) database in America calculated a much higher cure fraction of 17%, with time to statistical cure of nine years from diagnosis.(125) Estimates using the EUROCARE-5 cancer registries, found the cure fraction for lung cancer varied from 6-10% across Europe.(131) Earlier work demonstrated a four-fold variation in cure based on age at presentation, with 16.2% of 15-44 year olds being cured, compared with 3.5% of 75-99 year olds.(129)

Table 2-2 Summary of research of cure fraction and time to care for lung cancer

**range as results stratified by sex and age at diagnosis; ^ results stratified by country; ~results stratified by sex and year of diagnosis*

Paper	**Population**	**Age**	**Years collected**	**Number of cases**	**Method**	**Cure fraction**	**Time to cure**
Yu et al., 2012(128)	New South Wales, Australia	15-89	1972-2006	23027	Conditional relative survival >90%	-	>10 years
Janssen-Heijnen et al., 2010(132)	9 European countries	15-74	1985-2004	5053	Conditional relative survival >90%	-	>10 years
Cvancarova et al., 2013(133)	Norway	-	1963-2007	-	Relative survival curves	10.2%	-
Dal Maso et al., 2014(134)	Italy	15-74	1985-2005	85053	Mixed cure models; conditional relative survival >95%	6-30%*	6-10 years*
Tai et al., 2005(125)	Connecticut and Detroit, USA (SEER)	<60	1973-1992	24408	Kaplan-Meier for cancer-specific survival rates	17%	9 years
Francisci et al., 2009(129)	18 European countries (EUROCARE-4)	15-99	1988-1999	-	Parametric survival models	4.1-10.3%^	-
Dal Maso et al., 2020(131)	17 European countries (EUROCARE-5)	15-74	1990-2007	946582	Mixed cure models; conditional relative survival >95%	5-10%~	5-9 years~

Whilst the majority of NSCLC does recur in the first five years following treatment, these data suggest that the commonly used 5-year survival would be insufficient as a surrogate for statistical cure, and therefore not appropriate as an end point for follow-up.(125) Of people with NSCLC who are disease free at 5-years, 9-10.6% will have a recurrence in the subsequent 5-years.(135, 136) Due to the difficulty differentiating between a locoregional recurrence, and a new primary NSCLC, this may be an over estimation, but does support the notion that 5-year survival cannot be used as an accurate surrogate for statistical cure.

2.3.2 Personal Cure

Whilst the epidemiological approach is a useful way in which to understand how statistical cure from lung cancer relates to overall mortality in a population, statistical cure does not readily translate to what an individual patient can expect for the future. This is instead considered by personal cure, which is the time at which an individual cancer patient has no detectable cancer cells, and their life expectancy is no longer shortened by their malignancy.(118) The issue is that, personal cure is influenced by both statistical cure and individual factors such as disease stage, fitness and co-morbidities. Thus, average survival figures taking these factors into account have to be used in communicating with patients.

In reality, if detailed information is required by a patient or carer, survival at 1-year and 5-years, and how this is influenced by prognostic markers such as PS and stage of cancer, is likely to be easier for patients to understand, and provide a more personalised prognosis. Patients will often want to discuss how different modalities of curative-intent treatment influence this. When talking to people with lung cancer, we must clearly explain our treatment goals to the individual and define precisely what we mean when we use the word ‘cure’. In some cases it is maybe better to avoid discussion of cure and instead refer to the chance of long-term survival.(137)

2.3.3 Psychological Cure

Psychological cure is a term applied to describe a person's perception of their cancer as no longer being a threat to their life, regardless of the actual status of their disease.(119) Patients' opinions on this vary with some cancer patients finding the concept of cure reassuring, and others feeling the risk of their cancer will always be there, and cure is therefore an inappropriate word. In the case of slowly progressive or indolent cancers, they may never be cancer free, but are still more likely to die of another cause.(138) Patients also highlight the importance of quality of life, rather than simply survival time.(139) Some patients refer to a psychological cure, where they acknowledge that there is still a continued risk of a cancer returning, but they feel the treatment they have had is effective enough to prevent the cancer impacting their mortality, so they are able to continue their lives, considering themselves no longer a cancer patient.(119)

In 1985, Dr Mullan, an American physician, published an article describing his experiences as a cancer patient, and 'the goal of cure'.(140) He described three phases of cancer survivorship: diagnosis and treatment; extended survival and remission; and finally permanent survival or cure. Since then, advances in treatment mean many patients now live with metastatic cancer, who would not have done previously. This change has resulted in an alternative possible outcome of prolonged 'extended survival', rather than cure, and affects how many patients feel about their cancer journey.(119)

2.3.4 Communication with Patients and Carers

Whilst there are clear statistical definitions of cure from cancer, these are difficult to translate into a personalised estimate because of the many variables that may influence whether a patient achieves cure. In addition, numerical literacy is essential for interpreting probability and making informed healthcare decisions.(141) 30% of lay people in a healthcare setting struggled to understand and apply percentages, which limits their use in explaining possible outcomes.(142) There is also inconsistency in how often healthcare professionals attempt to discuss possible cure and what this

means. Only 70% of cancer surgeons ever explained the definition of cure to their patients, with only 40% consistently discussing the possibility of cure preoperatively.(143) The majority of oncologists are hesitant to use the term 'cured' with their patients, and report less than half of cancer patients actually ask if they have been cured.(118, 119)

These limitations in communication are reflected in people's understanding of the goals of their treatment. Surveys have found that shortly after their diagnosis, less than half of newly diagnosed lung cancer patients know the goal of their treatment, and only 39% were satisfied with the discussion of this.(144) Nearly 70% of patients with metastatic lung cancer believed they would be cured by systemic chemotherapy and over half of patients with stage IV lung cancer who received surgical treatment similarly felt they would be cured.(145) An alternative approach to this discussion may be of benefit. Looking at alternative methods of communicating outcomes, most people preferred visual communication of probabilities, with the greatest understanding when possible results were personalised to their case.(146)

Alternative language is sometimes used by both patients and oncologists when discussing long term outcomes. 'Cancer survivor' is sometimes preferred to 'cured'. It has a wide definition, from someone who has been diagnosed with cancer and has started treatment, to being alive five years following diagnosis, regardless of the state of the disease, to a patient who has undergone personal cure, with no chance of their cancer returning.(147) It is important therefore that clinicians try to be as clear as possible on each occasion they communicate. If used, the terms survival and cure should be explained in a way that can be understood by the patient and their family or carers.

2.4 Chapter Summary

- Cure has several different definitions, relevant to different people:
    - Statistical cure refers to the time point at which mortality for a person with cancer returns to that of the general population.

    - Personal cure refers to the point at which an individual has no cancer cells in their body.
    - Psychological cure is the point at which a person with cancer considers themselves no longer at risk.
- Exploring goals of treatment and the concept of cure is commonly not done well with people with lung cancer.
- Cure of NSCLC is sometimes possible, but should be carefully explained to people with lung cancer to ensure clinicians, patients and relatives clearly understand the meaning of the term and treatment intentions.

This chapter was published in part in an article in the journal *Oncology and Therapy* in August 2021.(148)

Chapter 3. Thoracic Surgery for Lung Cancer: Contemporary outcomes from the English National Clinical Outcomes Audit

This chapter compares survival in the first 90-days following thoracic surgery for lung cancer from 2017-18 with results from 2004-12. It provides easy read tables which could be used as a communication aid in the lung cancer process.

3.1 Introduction

3.1.1 Background

Prior to any treatment, accurately assessing and communicating treatment risks is essential. Thoracic surgical resection is the gold standard treatment in Stage I-IIIA NSCLC.(42) Pre-operatively, British guidance recommends use of the Thoracoscore prediction tool to produce an individualized risk score(42). This is a logistic regression model which uses nine variables to predict in-hospital mortality following thoracic surgery.(149) Variables include:

- Age
- Sex
- American Society of Anesthesiologists classification
- Performance status (PS)
- Dyspnoea score
- Priority of surgery (urgent or elective)
- Surgery: pneumonectomy or lobar resection
- Diagnosis: benign or malignant
- Comorbidity score.

A logit model is then applied to calculate an overall score which predicts in-hospital death. Other mortality prediction tools use a similar selection of demographic features.

Owing to changes in surgical techniques and population differences, prediction scores are at risk of 'calibration drift' and over-estimating mortality as time progresses.(150, 151) On validation in a contemporary UK population, the Thoracoscore was found to be inaccurate and over-estimated mortality in high risk patients.(152) Four other mortality prediction scores showed the same errors, with just one (the Modified Eurolung) achieving acceptable levels of calibration in the studied population.

One reason for inaccurate results from these calculators is change in surgical technique. Minimally-invasive surgery in the form of video-assisted thoracic

surgery (VATS) made up less than 10% of lobectomies for lung cancer in the UK in 2008-09.(153) By 2016, VATS was used in more than 50% of cases.(154) Observational data consistently shows a small in-hospital mortality benefit for VATS compared with thoracotomy or open lobectomy.(153) Traditionally, open surgery has been used in tumours which are locally invasive.(155) These more advanced stage surgeries may confer a higher risk due to more extensive disease and there is some debate about the potential benefits of minimally invasive surgery in these cases.(155, 156)

In addition to potential inaccuracies of mortality prediction scores, the majority calculate either in-hospital or 30-day mortality. Mortality tends to double from 30 to 90-days post-operatively, with 90-day being both more relevant to the individual, and now considered the standard measure of surgical outcomes.(157-159) When extrapolated from 30-day to 90-day mortality, the Thoracoscore and other risk prediciton models were inaccurate and underestimated mortality.(152) 90-day mortality prediction scores have been developed. This research group used national UK audit data to produce a 90-day score in 2011. This benefited from using UK wide surgical outcome data through NLCA. Whilst it performed as well as other scoring systems, it failed to meet required levels of accuracy on external validation.(38, 115) A different UK group has developed the RESPECT-90 score using data from two tertiary UK centers. This has shown good internal calibration but is yet to be externally validated.(160)

Whilst this is promising, all multivariable prediction models are at risk of the same ‘calibration drift’ and will therefore become more inaccurate as time and techniques progress. For this reason, this research group produced easy to read summary tables of 90-day mortality as an alternative assessment of risk (Figure 3-1).(115) These utilised all lung cancer surgical outcomes from 2004 to 2012 from across the UK, and were stratified by age and PS, the two most signifcant predictors of surgical outcome.(38)

Summary table for 90 day mortality for those undergoing lobectomy (a) and pneumonectomy (b). The 95% confidence intervals are presented in brackets below the risk%, with the total number in each group underneath.

(a) 90 day mortality following lobectomy.

Age (years)	Performance status		
	0	1	2
<70	2% (1–2%) 2534	3% (2–4%) 1467	7% (3–10%) 222
70–80	4% (3–6%) 1361	6% (5–7%) 1420	8% (5–12%) 219
>80	6% (3–9%) 263	7% (5–10%) 377	17% (8–25%) 72

(b) 90 day mortality following pneumonectomy.

Age (years)	Performance status		
	0	1	2
<70	7% (5–10%) 436	12% (8–16%) 289	–
70–80	18% (12–25%) 143	12% (7–18%) 154	–

Figure 3-1 Original tables produced by O'Dowd et al., 2016(115)

For the same reasons that prediction scores become inaccurate over time, these tables also require updating with contemporary data to remain accurate. I therefore reproduced these tables using contemporary UK data.

3.1.2 Aims of this Chapter

1. To produce updated mortality tables following lung cancer surgery, stratified by age and PS at diagnosis, which may be utilised in the consenting process.
2. To compare short-term post-operative mortality from recent data with previous results.
3. To compare mortality between different surgical access – VATS versus open surgery.

3.2 Methods

3.2.1 Dataset

The dataset was extracted from the LCCO audit, produced by the NLCA. The NLCA was established in 2004 to assess the care of people with lung cancer(161). It is commissioned by the Healthcare Quality Improvement Partnership (HQIP), and from 2014-2022 was managed by the Royal College of Physicians (RCP). Data relating to diagnosis, treatment and survival for patients diagnosed with lung cancer in England, Wales, Jersey and Guernsey is prospectively collected by hospital trusts. A subset of this information is submitted to the Cancer Outcomes and Services Dataset (COSD), part of the National Cancer Registration and Analysis Service (NCRAS). The LCCO publication is produced in partnership with the Society for Cardiothoracic Surgeons (SCTS) and reports on surgical activity and outcomes for people with lung cancer. It includes data from 27 surgical units in England. Since 2016, the NLCA case ascertainment has been 100% for English trusts (162).

Data were extracted for all people treated with surgery for lung cancer in England in 2017 and 2018. Variables included demographic details: patient age, sex, PS, Charlson co-morbidity score and predicted FEV1 percentage, vital status and date of death; cancer information: post-operative staging, tumour morphology; operation information: surgeon and NHS trust, procedure type, surgical access, date of procedure and date of discharge.

3.2.2 Inclusion Criteria

Data were included for adults with potentially curative NSCLC treated with thoracic surgery between 1st January 2017 and 31st December 2018. In order to exclude people receiving palliative procedures, inclusion criteria were:

- Age ≥ 18
- Stage IA, IB, IIA, IIB, IIIA
- PS 0, 1, 2

Patients with any of these variables missing were excluded.

3.2.3 Statistical analysis

Data analysis was completed using STATA/SE 17.0 (StataCorp LLC, Texas). Patients were grouped by procedure type (sublobar resection, lobectomy and pneumonectomy) and surgical access. Owing to low numbers of robotic surgeries, surgical access was grouped into minimally accessible surgery (VATS and robotics, from now referred to as 'VATS') or open (includes open and converted operations). Mortality was calculated for both stage I-IIB and I-IIIA. There was minimal change in 90-day mortality therefore stage IIIA patients were included. Results were stratified by age category and PS. These variables have previously been found to have the most influence on post-operative mortality.(38) Age was grouped into three categories (<70, 70-80 and >80) according to previous work by O'Dowd to allow direct comparison.(115) On subgroup analysis, where groups would have included fewer than 50 patients, age was instead grouped as <70 years and ≥70 to maintain accuracy. 90-day post-operative mortality with 95% confidence intervals (CI) were calculated for each subgroup. When comparing VATS and open techniques, outcomes were stratified by stage of disease instead of PS, to account for the more extensive surgical procedures required for stage IIIA compared with stage I disease.

3.3 Results

3.3.1 Inclusion and exclusion criteria

13578 people with NSCLC were included in the LCCO dataset between 1st January 2017 and 31st December 2018. Following exclusion as per Figure 3-2, 10546 people were included in the final dataset.

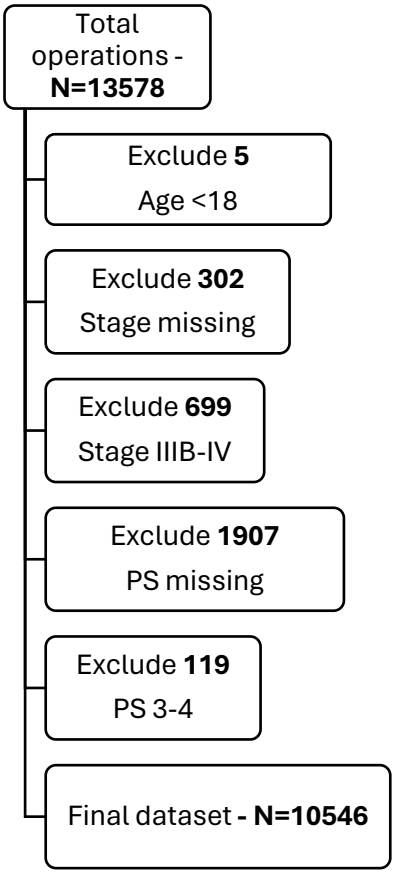


Figure 3-2 - Inclusion and exclusion criteria for analysis of post-operative surgical mortality

3.3.2 Demographics

Demographics are summarized in Table 3-1 and are as expected for this cohort. The median age was 70 (interquartile range (IQR) 64-76). Most had a PS of 0 (46%) or 1 (46%) with just 8% having a PS of 2. Median FEV1 was 84% predicted (IQR 69-99%), although 42% of values were missing. 63% of the group had a Charlson co-morbidity score of 0-1.

The greatest number of procedures were for stage IA disease (41%). Only 15% were for stage IIIA disease. Adenocarcinoma was the most common tumour type at 61%. Lobectomy or bi-lobectomy formed the majority (77%) of operations. 59% of lobectomies were completed via VATS. 60% of all procedures were completed via VATS.

Table 3-1 Demographics of study population.

			Number	Percentage
Total			10546	
Sex	Male		4940	*47%*
Age	Median (IQR)		70	*(64-76)*
PS		0	4838	*46%*
		1	4827	*46%*
		2	881	*8%*
FEV1%	Median (IQR)		84%	*(69%-99%)*
Tumour type	Adenocarcinoma		6478	*61%*
	Squamous cell		2879	*27%*
	Carcinoid		645	*6%*
	Other		544	*5%*
Stage	IA		4295	*41%*
	IB		2267	*22%*
	IIA		1062	*10%*
	IIB		1368	*13%*
	IIIA		1553	*15%*
Procedure	Pneumonectomy		352	*3%*
	Lobectomy		8156	*77%*
	Sublobar resection		1949	*18%*
Access	Open		3510	*35%*
	Converted to open		561	*6%*
	VATS		5822	*58%*
	Robotic		162	*2%*

3.3.3 Mortality Tables

90-day mortality for the whole group was 3.1% (95% CI 2.8-3.5%). This was highest following pneumonectomy at 8% (95% CI 6-11%). For lobectomy it was 2.99% (95% CI 2.6-3.4%) and lowest for sublobar resections at 2.67% (95% CI 2.0-3.4%).

Owing to low numbers, it was not possible to stratify mortality following pneumonectomy. For lobectomies, 90-day mortality increased as both PS and age increased (Table 3-2).

Table 3-2 90-day mortality following lobectomy or sublobar resection for lung cancer, stratified by PS and age.

90-day Mortality 95% CI *Total in group (died)*		**Lobectomy**			**Sublobar resection**		
Performance Status		**0**	**1**	**2**	**0**	**1**	**2**
Age	<70	**1%** 1-2% *2155 (25)*	**3%** 2-4% *1476 (39)*	**6%** 4-10% *236 (14)*	**2%** 1-4% *355 (6)*	**3%** 1-6% *310 (10)*	**3%** 2-10% *72 (2)*
	70-80	**3%** 2-4% *1509 (42)*	**4%** 4-5% *1814 (79)*	**4%** 3-7% *312 (14)*	**1%** 1-3% *344 (5)*	**3%** 1-5% *518 (16)*	**3%** 2-8% *108 (3)*
	>80	**6%** 3-10% *214 (12)*	**4%** 3-7% *357 (15)*	**5%** 2-12% *83 (4)*	**0** 0 *64 (0)*	**6%** 2-12% *144 (9)*	**3%** 3-18% *34 (1)*

People who had a sublobar resection were less fit, with 39% PS 0 compared with 48% of those who received lobectomy (p<0.0001). They were also older, with 38% age <70 compared with 47% for those received lobectomies (p<0.0001) (Table 3-3). There was no difference in overall 90-day mortality between sublobar resections and lobectomies (2.99% vs 2.67% respectively; *p=0.447).* When stratified by age and PS, mortality again increased with age and PS, as expected. Generally, mortality in each subgroup was improved compared with lobectomy, with the exception of age <70 and PS 0, and age >80 and PS 1, where it was worse with sublobar resections. This may be hampered by low numbers.

Table 3-3 Comparison of demographics between people who received lobectomy and sublobar resection

		Lobectomy	Sublobar	
Total		8,156	1,949	
Stage	**I**	4,883	1,603	*p<0.001*
		60%	82%	
	II	2,065	191	
		25%	10%	
	IIIA	1,208	155	
		15%	8%	
PS	**0**	3,878	763	*p<0.0001*
		48%	39%	
	1	3,647	972	
		45%	50%	
	2	631	214	
		8%	11%	
Age	**<50**	257	47	*p<0.0001*
		3%	2%	
	50-59	959	152	
		12%	8%	
	60-69	2,651	538	
		33%	28%	
	60-69	3,412	916	
		42%	47%	
	80-89	877	296	
		11%	15%	

3.3.4 Comparison with 2004-12

On comparison with data from 2004-12 (supplied via private correspondence), demographics were largely similar. PS was missing in 13% of cases 2004-12 but were excluded from this dataset. The current dataset had more people with stage IA disease (41% vs 29% in 2004-12). Other stages were similar, with an additional 8% missing stage data in 2004-12, where missing data were excluded from the current data. FEV1 and Charlson co-morbidity index were similar in both datasets.

Results were compared with outcomes from 2004-12 (Table 3-4). Mortality significantly improved in three subgroups: age <70 and PS 0; age 70-80 and PS 1; age >80 and PS 2.

Table 3-4 Mortality at 90 days following lobectomy, comparing 2017-18 and 2004-12

90 day Mortality % (95% CI) Total in group		Performance Status					
		0		1		2	
		2017-18	*2004-12*	2017-18	*2004-12*	2017-18	*2004-12*
Age	**<70**	**1%** (1-2%) 2155	***2%*** *(1-2%) 2534*	**3%** (2-4%) 1476	***3%*** *(2-4%) 1467*	**6%** (4-10%) 236	***7%*** *(3-10%) 222*
		p=0.006		*p=1*		*p=0.674*	
	70-80	**3%** (2-4%) 1509	***4%*** *(3-6%) 1361*	**4%** (4-5%) 1814	***6%*** *(5-7%) 1420*	**4%** (3-7%) 312	***8%*** *(5-12%) 219*
		p=0.156		*p=0.011*		*p=0.056*	
	>80	**6%** (3-10%) 214	***6%*** *(3-9%) 263*	**4%** (3-7%) 357	***7%*** *(5-10%) 377*	**5%** (2-12%) 83	***17%*** *(8-25%) 72*
		p=0.997		*p=0.084*		*p=0.022*	

3.3.5 Surgical access

As stage increased, procedures were more likely to be open, with 57% of stage IIIA operations completed as open procedures, compared with 25% of stage I (Table 3-5). The conversion rate from VATS to open however, remained static at 5-6% for all stages.

Table 3-5 Surgical access and conversion rates for lung cancer surgery, stratified by stage at operation

Stage	**Surgical Access**		
	Open	**Open (converted from VATS)**	**VATS**
	Percentage (n)		
I	25% (1544)	5.47% (342)	68% (4245)
II	48% (1126)	5.25% (122)	45% (1043)
IIIA	57% (840)	6.1% (90)	36% (533)

90-day mortality for open lobectomy was almost double that of VATS at 3.97% (CI 3.34-4.7%) compared with 2.32% (CI 1.92-2.8%). This increased mortality was present at all stages except for stage I in patients aged <70

years where mortality was the same (Table 3-6). Differences in mortality were of lower magnitude in <70 years.

Table 3-6 90-day mortality for both open and VATS lobectomy, stratified using age and stage at time of operation

Percentage (95% CI) *Total in group (died)*		**Age**			
		<70		**≥70**	
		VATS	**Open**	**VATS**	**Open**
Stage	**I**	**1.4%** 0.9-2.1% *1461 (20)*	**1.4%** 0.8-2.6% *710 (10)*	**2.3%** 1.7-3.1% *1721*	**3.5%** 2.4-5% *750 (26)*
	II	**2.5%** 1.3-4.5% *406 (10)*	**3.8%** 2.5-5.9% *521 (20)*	**3.8%** 2.4-5.8% *531 (20)*	**6.6%** 4.7-9% *519 (34)*
	IIIA	**2.4%** 1.0-5.6% *210 (5)*	**2.8%** 1.5-5.2% *354 (10)*	**5%** 2.8-8.6% *241 (12)*	**7.8%** 5.3-11% *348 (27)*

3.4 Discussion

For people with lung cancer, postoperative mortality continues to improve with an overall 90-day mortality of 3.1%. Most procedures were performed via minimally invasive VATS, which in this retrospective study conferred a survival advantage at 90-days post-operatively of 2.32% versus 3.97% for open procedures.

3.4.1 Comparison with other studies

These results were compared directly with mortality tables using the same data source (NLCA) from 2004-12 as per O'Dowd et al., 2016. These show peri-operative mortality has improved, with 90-day mortality in the most recent series nearly half that of 2004-12 at 3.1% vs 5.9%.(115) 90-day post-operative mortality in America between 2004-13 was 5.7%.(159) More recently, analysis from two tertiary UK hospitals reported 90-day mortality of 3.1% for all lung resections, matching results here.(152) It should be noted however that both of these earlier studies included higher risk or missing data when compared to this study. O'Dowd included stage I-IIIA as here, but PS included an additional 1% of PS>=3 and 13% missing PS.(115) The American

study included 12.9% of people with stage IIIA-C disease and 4.3% with stage IV. PS was not provided.(159) These higher risk people may have worsened mortality in the earlier studies, however this is likely not enough to account for the whole difference.

This is evidenced by the stratified results here; compared with 2004-12 mortality tended to have improved or remained static for all groups from the earlier NLCA datasets, with significant reductions in mortality for both the lowest risk (PS 0, age <70) and highest risk groups (PS 2, age >80).(115) In England, there was a 20% increase in lung cancer operations between 2014 and 2018.(163) This increase includes higher risk people with more people of PS 2, age >80 in this study over 2 years compared with the number in the same group over eight years in the study by O'Dowd et al., 2016. The improvement in overall 90-day mortality is therefore not just due to the difference in demographics.

Sublobar resections are typically reserved for people with peripheral tumours where pulmonary function is poor.(42, 164) This means that recipients are potentially higher risk but have a lower risk procedure. Retrospective observational studies from both China and America found no difference in short-term post-operative mortality between sublobar and lobar resections.(165, 166) Similarly, randomized trials from both Japan and America have found no difference in mortality between sublobar and lobar resections at 30 and 90-days.(167, 168) Concerns had been raised that sublobar resections may increase the risk of future local recurrence compared with anatomical resections in the form of lobectomy, which could negate any possible survival benefits from more limited resections. Whilst these trials demonstrated increased local recurrence in the sublobar groups at 5-years, they both found total recurrence were similar. This corresponded with equal overall and disease-free survival at 5-years, suggesting people are not disadvantaged by having less extensive sublobar resections.(47, 168)

Since 2016 the majority of lung cancer operations in the UK have been VATS.(154) Our results suggest a short-term mortality benefit from minimally

invasive surgery which persists in stage IIIA disease where resection would be more extensive. This may be affected by the retrospective nature of this study, as open procedures may have been required in more complex cases. Our results closely follow other observational data from the UK which persistently shows a small in-hospital survival benefit from VATS.(153) A randomized trial from China found no difference in short-term mortality between VATS and open surgeries in people with stage I and II disease.(169) The UK based VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer (VIOLET) trial randomized people to VATS or open surgery for stage IIIA NSCLC. This did not find any difference in in-hospital or 1-year mortality. Importantly 1-year disease recurrence was also no different between treatments.(170) VATS also decreased morbidity with a shorter length of hospital stay, decreased adverse events and improved pain control, suggesting minimally invasive approaches should be used where possible.

3.4.2 Strengths and limitations

Through using NLCA data I have been able to present outcomes which reflect current practice in the whole of England. The benefit of this is these tables are easily reproducible as surgical techniques and patient selection differ and can therefore be repeated with future data to remain contemporaneous. Generally, group sizes were large enough after stratification to provide useful estimates, however group sizes for people aged >80 are smaller resulting in wide confidence intervals.

Despite this, it is important to note that as a retrospective observational study, the results may be biased through patient selection. This is particularly true for open versus minimally invasive procedures, where an open technique may have been used for more complex cases which had an innately higher mortality risk. I did not account for other variables, such as lung function and comorbidities. These are likely to be worse in people with increased PS and may have acted as confounders. However, I did not seek to produce another mortality prediction tool, rather an easily usable point of reference.

Another potential source of bias is the exclusion of data with missing age, stage and PS variables. Again, this was done as the purpose of the research was to report on current outcomes rather than generate a prediction score, however does risk missing relevant cases. It was not possible to ascertain from the data available if data were missing at random or not. If data were, for example, more frequently missing from underperforming or busy centres, there is the possibility of underreporting mortality.

Finally, robotic technique was combined with VATS. This was a practical choice owing to low patient numbers in the robotic group. Short-term outcomes are non-inferior or improved with robotic procedures, however they are operator dependent.(171, 172) Oncological outcomes are yet to be prospectively compared, but retrospective data suggests non-inferior disease-free survival.(172) As only 162 people had robotic surgery, combining these surgical techniques is unlikely to have significantly altered results.

3.4.3 Clinical relevance and Conclusions

As surgical mortality risk calculators consistently underperform in lung cancer, I sought to provide an alternative method of individualizing and communicating risk to people in the pre-operative consenting period. By stratifying real world outcomes using the strongest predictors of mortality, I hope these tables may offer a compromise between general outcomes and personalised, calculated predictions. They are particularly relevant as thoracic surgery for lung cancer is increasing, with more people of higher risk profiles undergoing surgery.(36, 163) Risk calculators particularly overestimate mortality in high risk groups, which may inappropriately deter people from surgery.(152)

Updating these tables in future as surgical techniques and populations change will be essential to maintaining their relevance and accuracy. Between 2004-12 and 2017-18 significant improvements in short-term survival are demonstrated. To maintain relevance of these tables they should be reproduced at periodic intervals, ensuring people are provided accurate

information during treatment decision-making. This interval should be determined by changes in surgical techniques, such as increased use of robotic surgery, as well as changes in the population and frequency of surgery. Here, 5-years between studies was a sufficient interval to demonstrate this improvement.

It should be noted that these values were calculated for all-comers to thoracic surgery for lung cancer. Lung cancer screening is now recommended in the UK which will potentially result in a fitter population with lower risk undergoing lung cancer resection.(92) This should be taken into account when reproducing tables, with the possibility of requiring separate values for these populations.These tables demonstrate just one aspect of risk, which is individualized to each person's journey. Four parameters of risk specific to thoracic surgery have been described: morbidity and mortality, breathlessness and quality of life, pain, and cancer recurrence.(173) These other areas should also be addressed as part of shared decision-making.

3.5 Chapter Summary

- Compared with 2004-12, in 2017-18 there was a decrease in 90-day mortality for people with lung cancer undergoing surgery with curative intent.
- Peri-operative mortality from VATS is approximately half that of open procedures, and should be used where clinically appropriate.
- The included tables should be used to enhance communication during shared decision making.

This work was published in Thorax in July 2022.(174)

Chapter 4. DECLINE: What Patient Factors are Associated with Not Receiving Treatment in Early-Stage Lung Cancer?

The DECLINE study was a mixed methods research project which was undertaken to examine the reasons some people with early-stage non-small cell lung cancer (NSCLC) do not undergo potentially curative treatment. It was formed of two arms: a quantitative arm described here in Chapter 4, and a qualitative arm described in Chapter 5.

This chapter utilises a locally generated database to examine demographic and physiological factors which impact the likelihood of receiving curative intent treatment in good fitness, early-stage lung cancer in the East Midlands.

4.1 Introduction

4.1.1 Background

In stage I-II NSCLC, treatment with curative intent markedly improves survival for people who are fit (performance status (PS) 0-2). Without treatment prognosis is poor, with median survival of less than a year, even for people with stage I disease.(175) Surgical resection is the standard of care in those deemed operable, with radical radiotherapy an alternative for those who are less fit, or decline surgery.(42) Despite the survival advantages, in the UK, nearly 1 in 5 people who appear eligible for curative intent treatment do not receive any treatment at all.(98) This varies significantly in England, with evidence that people seen in surgical centres are more likely to receive surgical resection.(79)

I sought to identify the risk factors and reasons for people not receiving treatment across a cancer alliance through detailed medical records review of those people who, according to Trust-level cancer centre data, would be eligible for treatment with curative intent.

4.1.2 Aims

1. To calculate the percentage of people who received curative intent treatment for lung cancer across the East Midlands Cancer Alliance.
2. To identify features which affect the likelihood of receiving treatments, stratified by hospital trust first seen.
3. To quantify the reasons why people did not receive surgical treatment.

4.2 Methods

4.2.1 Hospital Trusts

Four hospital trusts were included in this research. Nottingham University Hospitals (NUH) is a tertiary respiratory centre and thoracic surgery centre which provides care for 2.5 million people across Nottingham.(176) Royal Derby Hospital is a large district general hospital (DGH) which is part of University Hospitals of Derby and Burton NHS Foundation Trust.(177) Only Royal Derby hospital was included in analysis, as other hospitals in the trust

refer to a different surgical centre. It covers a mixed urban and rural population. United Lincolnshire Hospitals (ULH) include 3 DGHs: Lincoln County, Boston and Grantham hospitals.(178) This is a largely rural trust. Finally, King's Mill Hospital (KMH) is another DGH which covers a rural and previously industrial population.(179)

NUH delivers all thoracic surgery for the other trusts, with surgeons visiting the other hospitals for outpatient clinics and attending multi-disciplinary team (MDT) meetings either virtually or remotely. Some radical radiotherapy was delivered in each hospital however between 2016 and 2019 stereotactic ablative radiotherapy (SABR) was delivered only at NUH, with Derby beginning delivery in 2023.

4.2.2 Ethics Approval

The study received ethical approval through NHS REC (No 21/WM/0263), CAG approval (No 21/CAG/0169). It was sponsored by the University of Nottingham and received ethical approval from each participating NHS Trust. The study was funded by a grant from the Roy Castle Lung Cancer Foundation. Relevant documents are included in Appendix A.

4.2.3 Selection Criteria and Database Generation

All adults diagnosed with lung cancer between 1st January 2016 and 31st December 2019 were extracted from local cancer registry data recorded by each trust. These years were selected to avoid the COVID-19 pandemic which may have altered practice. Data were pseudonymised prior to transfer outside of the trust.

People with stage I-II disease and PS 0-2 were selected for inclusion in the final database. Stage was coded using 8th edition International Association for the Study of Lung Cancer (IASLC). Data were excluded if these variables were missing. Attempts were made to identify any eligible people that were excluded due to missing data through review of scans and clinical letters, but this was not always possible due to time and resource constraints.

The selected data were re-identified locally in each trust. The researcher (HM) visited each trust and completed a thorough review of medical notes for each person included in the final dataset. This involved reviewing letters and test results relevant to the diagnosis from digital or paper Medical Notes. Physiological values including pulmonary function tests (PFTs), echocardiogram results and exercise testing (shuttle walk tests, 6-minute walk test (6MWT), cardiopulmonary exercise testing (CPEX)) were extracted where available. Index of Multiple Deprivation (IMD) was calculated using postcodes and divided into 5 quintiles, with 1 being the least deprived and 5 the most. First treatment received was recorded to avoid treatment of recurrence or metastasis, which are not relevant in this analysis. However, where people receive combined therapy, only the first element of that treatment is captured. Palliative radiotherapy and advanced supportive care were considered as 'no active treatment'. Where the person did not receive treatment with surgery, relevant clinical letters were reviewed to identify the reason for this. Reasons for not receiving treatment were only taken directly from the medical letters: Patient choice; Lung function; Co-morbidities; Unresectable; Small cell cancer; or Medical trial. Where no reason was stated by the diagnosing or treating clinicians, this was recorded as 'no reason' rather than inferring from other data (e.g. physiological values such as lung function).

As surgery and radical radiotherapy, as well as some diagnostic testing, is performed at NUH for all patients, some people may be included in more than one trust extraction. Dates of birth were cross referenced to identify possible duplications and confirmed with 2 additional identifiers prior to exclusion.

The final dataset included: age, sex, stage, PS, hospital trust first seen, first treatment received, percentage predicted FEV1 (FEV1%), percentage predicted FVC (FVC%), percentage predicted TLCO (TLCO%), ejection fraction, and 6MWT.

4.2.4 Statistical analysis

Age was divided into 10-year bands. FEV1% and TLCO% were categorised using European Respiratory Society (ERS) and British Thoracic Society (BTS)lung cancer thoracic surgery guidelines:<30%; 30-49%; 50-79%; ≥80%.(41, 42) Left ventricle ejection fraction (LVEF) was categorised using European Society of Cardiology and American College of Cardiology guidelines: normal - ≥50; mild left ventricular systolic dysfunction (LVSD) – 40-49; moderate LVSD – 30-39; severe LVSD - <30.(180, 181) Treatment was categorised as: surgery, radiotherapy, SACT and no active treatment. Treatment with curative intent was considered as surgery or radiotherapy.

Demographics and physiological values were compared between treatment modalities. Median and inter-quartile range (IQR) were calculated for continuous data, and percentages for categorical. Significance was calculated using surgery as the reference group; continuous data were compared using the Wilcoxon rank-sum test and categorical using chi-squared. It should be noted that for comparisons of SACT and no treatment in the LVSD category results may be invalid due to low numbers.

Odds of receiving surgery were initially calculated using univariate logistic regression for individual patient factors. Known potential confounders of age, stage, sex and PS were included in the first multivariate model (adjusted odds ratio – aOR1). Subsequently lung function (TLCO and FEV1) was controlled for in addition (aOR2) due to significance as univariate analysis. Models were separately generated and calculated for the odds of receiving surgery, and then odds of receiving radiotherapy in those people who did not receive surgical treatment.

4.3 Results

4.3.1 Inclusion Criteria

8605 people were diagnosed with lung cancer across the 4 included trusts between 2016 and 2019. Following inclusion criteria, 1183 people were included in the final dataset (Figure 4-1).

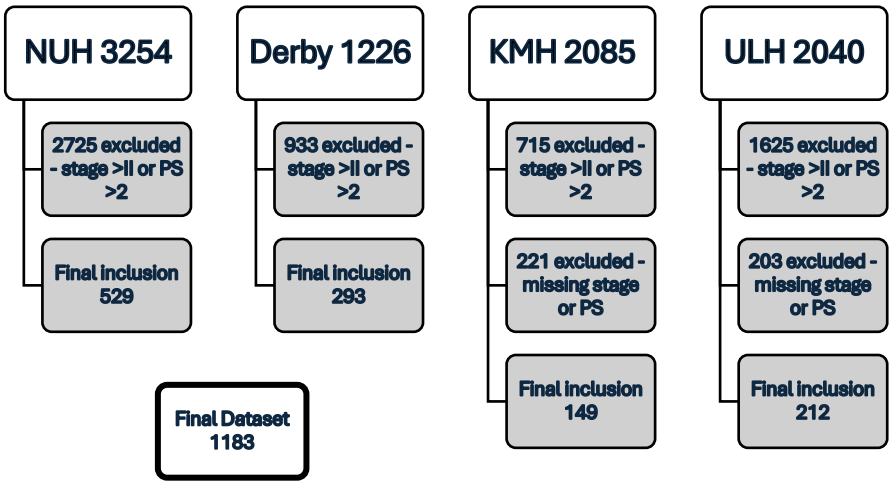


Figure 4-1 Numbers included in final dataset per hospital trust, following inclusion criteria

4.3.2 Demographics

65% of people had treatment with surgery (Table 4-1). 59% of people who did not have surgery received radiotherapy, equating to 86% of eligible people receiving treatment with curative intent. 12% of people did not receive any active treatment.

Median age was 73 (IQR 67-79) with 50% male participants. People who received surgery were younger (median age 71) than those who received radiotherapy (76 years; $p<0.0001$) or no active treatment (79.5 years; $p<0.0001$) (Table 4-1).

People who received radiotherapy or SACT as first-line treatment were less likely to have a PS of 0 compared with those who received surgery (13% and 21% vs 55% respectively; $p<0.0001$ for both). Similarly, only 7% of people who received no active treatment had PS 0, with 42% PS 2.

There were more people who received radiotherapy than received surgery in the most deprived group, (30% vs 19%; p=0.001). It should be noted however that there was a large amount (25%) of missing data in this category.

*Table 4-1 Demographics of the cohort, divided according to treatment received. SACT - Systemic anti-cancer therapy. *p<0.0001 compared with Surgery. ^p=0.001 compared with Surgery*

		Total	Surgery	Radiotherapy	SACT	None
Total		**1183**	771	244	28	140
Age	Median	**73**	71	76*	73	79.5*
	IQR	**67-79**	65-76	71-82	64-82	73-86
Sex	Male	**595**	376	132	19	68
		50%	49%	54%	68%	49%
	Female	**588**	395	112	9	72
		50%	51%	46%	32%	51%
Stage	I	**784**	525	169*	8	82
		66%	68%	69%	29%	59%
	II	**399**	246	75	20	58
		34%	32%	31%	71%	41%
PS	0	**472**	423	33*	6*	10*
		40%	55%	14%	21%	7%
	1	**521**	310	145	15	51
		44%	40%	59%	54%	36%
	2	**190**	38	66	7	79
		16%	20%	35%	4%	42%
IMD (1 least deprived)	1	**147**	106	21	2	18
		12%	14%	9%	75	13%
	2	**143**	105	29	0	9
		12%	14%	12%	0%	6%
	3	**161**	105	34	2	20
		14%	14%	14%	7%	14%
	4	**195**	121	46	6	22
		16%	16%	19%	21%	16%
	5	**243**	145	72^	6	20
		21%	19%	30%	21%	14%
	Missing	**294**	189	42	12	51
		25%	25%	17%	43%	36%

Treatment also differed by hospital trust. Both Derby and ULH treated fewer people with radiotherapy than NUH. 14% of those people diagnosed in Derby received radiotherapy, 10% in ULH, compared with 27% in NUH (p<0.0001 for both) (Figure 4-2). The percentage of people treated with surgery was similar

at all 4 trusts. Overall, a greater proportion did not receive active treatment in Derby (17%) and ULH (19%) compared with NUH (7%) (p<0.0001 for both).

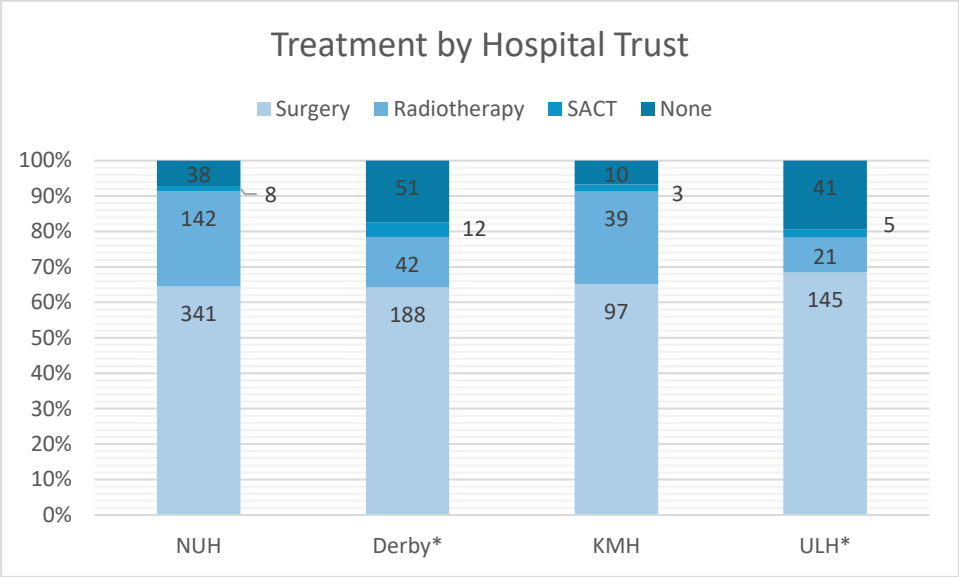


*Figure 4-2 Number of people who received treatment for early-stage lung cancer with PS ⍰2, according to trust of first diagnosis. *p<0.0001 compared with NUH*

Physiologically, people who were treated with radiotherapy had worse lung function than those who received surgery (median TLCO% - 47% vs 68%; p<0.0001) (Table 4-2). Those who did not receive treatment had a median TLCO% again lower than for those receiving surgery (42% vs 68%; p<0.0001). Lung function was worse in those who had radiotherapy instead of surgery because of 'Inadequate lung function' (see Section 4.3.3) than those who had radiotherapy for other reasons, such as patient choice, other comorbidities or unresectable disease (median TLCO: 39% vs 57%; p<0.0001). This was also true for those who did not have any active treatment (TLCO 33% vs 53%; p<0.0001).

Few people had exercise testing, with just 3 people across the whole dataset who had CPEX. More people had shuttle walk tests or 6MWT completed, often as part of pre-operative anaesthetic assessment after the decision for surgery had been made. The results of these were frequently missing from the medical records. The majority of reported 6MWT were from Derby (44/45). People who did not receive active treatment walked a shorter distance than those who received surgery (184 vs 379 metres; p=0.004).

There was no difference in distance walked between those who received radical radiotherapy and surgery (316 vs 379 metres; p=0.15).

*Table 4-2 Physiological measures of lung function and echo results, divided by treatment received. FEV1% - percent predeicted forced expiratory volume in 1 second; FVC% percent predicted forced vital capactiy; TLCO% - percent predicted transfer capacity of the lung for carbin monoxide; LVSD – Left ventricle systolic dysfunction. For significance tests, numbers compared with Surgery. *p<0.0001 ~p<0.001 ^p<0.01*

		Total	Surgery	Radiotherapy	SACT	None
Total		**1183**	771	244	28	140
FEV1%	**Median**	**81%**	86%	67%*	57%~	66%*
	IQR	**63-97%**	71-99%	49-85%	44-94%	45-90%
	Missing	**86**	39	17	2	28
		7%	5%	7%	7%	20%
FVC%	**Median**	**99%**	102%	89%*	84%^	90%*
	IQR	**85-112%**	89-115%	77-106%	73.5-105.5%	75-106%
	Missing	**155**	73	35	8	39
		13%	9%	14%	29%	28%
TLCO%	**Median**	**62%**	68%	47%*	53.5%^	42%*
	IQR	**49-76%**	56-81%	37-60%	47.5-61%	31-54%
	Missing	**474**	277	95	16	86
		40%	36%	39%	57%	61%
LVSD	**Normal**	**493**	359	88*	6	40*
		42%	47%	36%	21%	29%
	Mild	**52**	32	17	1	2
		4%	4%	7%	4%	1%
	Medium	**29**	13	9	0	7
		2%	2%	4%	0%	5%
	Severe	**17**	3	11	0	3
		1%	0.39%	5%	0%	2%
	Missing	**592**	364	119	21	88
		50%	47%	49%	75%	63%

4.3.3 Reasons for Treatment

The most common reason to receive radiotherapy in preference to surgery was inadequate lung function, with all other co-morbidities combined (frequently other malignancy, cardiovascular disease, dementia) contributing a similar number (Table 4-3). In total, 73% of people who received radiotherapy had a medical reason for this recorded. The reasons people did not receive any active treatment were similar, with only 24 people in 4 years choosing not to receive treatment across the whole region, which equates to 2% of the dataset or 17% of those who didn't receive treatment. There was no difference in frequency of reasons between hospital trusts.

Table 4-3 Reasons not to receive surgery

	Radiotherapy		SACT		No Active Treatment	
Total	**244**	**100%**	**28**	**100%**	**140**	**100%**
Patient choice	44	18%	1	4%	24	17%
Lung function	90	37%	7	25%	45	32%
Co-morbidities	81	33%	2	7%	51	36%
Unresectable	2	1%	4	14%	3	2%
Small cell	1	0%	7	25%	2	1%
Trial	3	1%	0	0%	0	0%
No reason recorded	23	9%	7	25%	15	11%

4.3.4 Odds of Receiving Treatment

Surgery

Lung function had the greatest impact on the likelihood of surgery, particularly TLCO (Table 4-4). People with FEV1 50-79% were nearly half as likely to receive surgery as those with FEV1 ≥80% (aOR1 0.53; 95% CI 0.38-0.75) although this became non-significant when also adjusting for TLCO (aOR2 0.72; 95% CI 0.45-1.14). People with moderately reduced TLCO (50-79%) were around a quarter as likely to receive surgery as those with normal lung function, regardless of FEV1 (aOR2 0.27; 95% CI 0.12-0.63).

Other significant factors were age and PS. The oldest people (age ≥80) consistently had decreased odds of receiving surgery compared with those aged 70-80, even when corrected for lung function (aOR2 0.41; 95% CI 0.24-0.70). PS of 1 or 2 decreased the likelihood of surgery even after lung function

was taken into account, with people with PS 1 being a quarter as likely to receive surgery (aOR2 0.25; 95% CI 0.15-0.43).

Worsening cardiovascular function, as measured by LVEF, decreased the odds of receiving surgery for people with medium and severe LVSD. After adjusting for lung function, only severe LVSD continued to significantly reduce the likelihood (aOR2 0.07; 95% CI 0.01-0.4). Missing LVEF data also decreased the odds, however this is likely artefactual as people who were never planned for surgery for reasons other than cardiac function may have never had echocardiography testing.

Location did not affect the likelihood of receiving surgery, with no difference between hospital trusts or with deprivation index.

Radiotherapy

For those people who did not receive surgery, lung function did not impact the likelihood of receiving radical radiotherapy (TLCO 50-79; aOR2 0.93, 95% CI 0.15-5.83) although it did modify other exposure variables (Table 4-5). Age ≥80 nearly halved the chance of radiotherapy compared with age 70-80, however this again became non-significant once lung function was considered (aOR2 0.88; 95 CI 0.4-1.93). PS 1 did not impact the odds of receiving radical radiotherapy, regardless of lung function (aOR2 1.54; 95% CI 0.52-14.57). The least fit people with a PS of 2 were a third as likely to have radical radiotherapy, however this was again dependent on lung function, with the aOR becoming non-significant when adjusted for lung function (aOR1 0.33, 95% CI 0.16-0.69; aOR2 0.5, 95% CI 0.16-1.6)., did not alter the likelihood of receiving radiotherapy.

The likelihood of receiving radical radiotherapy did differ between trusts, with both Derby and ULH having approximately a 1 in 5 chance of receiving radical radiotherapy, a difference which persisted after adjusting for lung function. The very least deprived people (IMD 1) also had reduced odds of receiving radiotherapy, a difference which was only apparent after adjusting for lung function (aOR2 0.23; 0.06-0.89).

Table 4-4 OR for receiving surgery. OR - unadjusted; aOR1 - adjusted for age, sex, PS and stage; aOR2 - adjusted for age, sex, PS, stage TLCO% and FEV1%

Surgery		OR	95% CI	aOR1	95% CI	aOR2	95% CI
		n=1183		*n=1183*		*n=699*	
	<60	2.77	*1.58-4.86*	2.1	*1.11-3.98*	0.87	*0.37-2.02*
Age	**60-69**	1.61	*1.16-2.22*	1.43	*0.99-2.07*	1.57	*0.91-2.71*
	70-79	1	-	1	-	1	-
	≥80	0.26	*0.19-0.36*	0.31	*0.21-0.44*	0.41	*0.24-0.70*
		n=1183		*n=1183*		*n=699*	
Sex	**Male**	1	-		-		-
	Female	1.19	*0.94-1.51*	1.02	*0.76-1.36*	1.27	*0.83-1.95*
		n=1183		*n=1183*		*n=699*	
PS	**0**	1	-		-		-
	1	0.17	*0.12-0.24*	0.2	*0.14-0.29*	0.25	*0.15-0.43*
	2	0.03	*0.02-0.05*	0.04	*0.02-0.06*	0.08	*0.04-0.17*
		n=1183		*n=1183*		*n=699*	
Stage	**I**	1	-		-		-
	II	0.79	*0.62-1.02*	0.81	*0.60-1.11*	0.72	*0.46-1.12*
		n=1183		*n=1183*		*n=699*	
	NUH	1		1	-		-
Hospital	**Derby**	0.99	*0.73-1.33*	1.26	*0.88-1.80*	1.1	*0.64-1.89*
	KMH	1.03	*0.70-1.51*	1.28	*0.81-2.03*	1.58	*0.74-3.39*
	ULH	1.19	*0.85-1.68*	1.73	*1.10-2.72*	1.36	*0.74-2.50*
		n=1094		*n=1094*		*n=699*	
	<30	.	.	.	.	.	.
FEV1 %	**30-49**	0.1	*0.64-0.16*	0.12	*0.07-0.20*	0.32	*0.16-0.63*
	50-79	0.49	*0.37-0.65*	0.53	*0.38-0.75*	0.72	*0.45-1.14*
	≥80	1	-	1	-	1	-
		n=709		*n=709*		*n=699*	
	<30	0	*0.00-0.02*	0	*0.00-0.03*	0.01	*0.00-0.07*
TLCO %	**30-49**	0.03	*0.01-0.07*	0.04	*0.02-0.09*	0.05	*0.02-0.13*
	50-79	0.19	*0.08-0.41*	0.24	*0.10-0.56*	0.27	*0.12-0.63*
	≥80	1	-	1	-	1	-
		n=1183		*n=1183*		*n=699*	
	Normal	1	-	1	-	1	-
LVSD	**Mild**	0.6	*0.33-1.08*	0.9	*0.43-1.85*	1.6	*0.60-4.23*
	Medium	0.3	*0.14-0.65*	0.15	*0.06-0.40*	0.31	*0.09-1.02*
	Severe	0.08	*0.02-0.28*	0.03	*0.01-0.13*	0.07	*0.01-0.40*
	Missing	0.6	*0.46-0.77*	0.41	*0.30-0.57*	0.45	*0.28-0.73*

		n=873		*n=873*		*n=538*	
IMD (1 least deprived)	**1**	1.75	*1.12-2.72*	1.7	*0.98-2.96*	1.21	*0.57-2.57*
	2	1.87	*1.19-2.93*	1.71	*0.99-2.95*	1.38	*0.65-2.96*
	3	1.27	*0.84-1.92*	1.21	*0.74-2.01*	1.24	*0.59-2.58*
	4	1.11	*0.75-1.63*	1.23	*0.77-1.98*	1.18	*0.58-2.38*
	5	1	-	1	-	1	-

Table 4-5 OR for receiving radiotherapy in people who did not receive surgery. OR - unadjusted; aOR1 - adjusted for age, sex, PS and stage; aOR2 - adjusted for age, sex, PS, stage TLCO% and FEV1%

Radical Radiotherapy		OR	95% CI	aOR 1	95% CI	aOR2	95% CI
		n=403		*n=403*		*n=210*	
Age	**<60**	0.45	*0.16-1.26*	0.39	*0.13-1.15*	0.51	*0.14-1.94*
	60-69	1.41	*0.77-2.59*	1.37	*0.7-2.7*	2.36	*0.88-6.32*
	70-79	1	-	1	-	1	-
	≥80	0.6	*0.39-0.94*	0.56	*0.35-0.9*	0.88	*0.4-1.93*
		n=403		*n=403*		*n=210*	
Sex	**Male**	1	-	1	-	1	-
	Female	0.95	*0.34-1.41*	0.86	*0.56-1.32*	1.2	*0.61-2.35*
		n=403		*n=403*		*n=210*	
PS	**0**	1	-		-		-
	1	1.07	*0.55-2.07*	1.01	*0.49-2.07*	1.54	*0.52-4.57*
	2	0.37	*0.19-0.73*	0.33	*0.16-0.69*	0.5	*0.16-1.6*
		n=403		*n=403*		*n=210*	
Stage	**I**	1	-		-		-
	II	0.51	*0.34-0.77*	0.48	*0.31-0.75*	0.44	*0.22-0.87*
		n=403		*n=403*		*n=210*	
	NUH	1		1	-		-
Hospital	**Derby**	0.22	*0.13-0.36*	0.2	*0.11-0.35*	0.2	*0.08-0.49*
	KMH	0.97	*0.48-1.98*	1.33	*0.62-2.84*	0.85	*0.2-16.7*
	ULH	0.15	*0.08-0.27*	0.19	*0.09-0.38*	0.16	*0.06-0.42*
		n=363		*n=363*		*n=210*	
	<30	0.45	*0.17-1.14*	0.46	*0.16-1.26*	0.58	*0.11-3.07*
FEV1 %	**30-49**	1.01	*0.56-1.80*	1.21	*0.63-2.33*	1.05	*0.42-2.67*
	50-79	1.07	*0.65-1.77*	1.15	*0.68-1.95*	1	*0.46-2.18*
	≥80	1	-	1	-	1	-
		n=214		*n=214*		*n=210*	
	<30	0.51	*0.08-3.14*	0.42	*0.06-2.86*	0.35	*0.05-2.75*
TLCO %	**30-49**	0.84	*0.15-4.55*	0.71	*0.12-4.15*	0.54	0.09-3.37
	50-79	1.2	*0.22-6.65*	1.04	*0.17-6.18*	0.93	0.15-5.83
	≥80	1	-	1	-	1	-
		n=403		*n=403*		*n=210*	
	Normal	2.96	*0.83-10.63*	3.41	*0.91-12.82*	2.48	*0.43-14.25*
LVSD	**Mild**	0.67	*0.24-1.92*	0.61	*0.19-1.9*	0.93	*0.18-4.79*
	Medium	1.92	*0.51-7.21*	1.41	*0.33-5.95*	.	.
	Severe	0.57	*0.37-0.89*	0.56	*0.34-0.91*	0.89	*0.42-1.89*

	Missing	0.6	*0.46-0.77*	0.41	*0.30-0.57*	0.45	*0.28-0.73*
IMD (1 least deprived)		*n=298*		*n=298*		*n=161*	
	1	0.38	*0.18-0.81*	0.48	*0.2-1.13*	0.23	*0.06-0.89*
	2	1.16	*0.49-2.78*	1.36	*0.51-3.64*	0.66	*0.14-3.13*
	3	0.56	*0.28-1.12*	0.59	*0.27-1.28*	0.29	*0.08-1.07*
	4	0.59	*0.31-1.14*	0.8	*0.39-1.64*	0.34	*0.1-1.16*
	5	1	-	1	-	1	-

4.3.5 Survival

Overall 1-year survival for the cohort was 86% (95% CI 84-88%). Surgery was associated with improved 5-year survival (Figure 4-3). The median survival for surgery was not reached, and for radiotherapy was 30 months. Median survival was 16 months for those who did not receive any active treatment, with 57% 1-year survival.

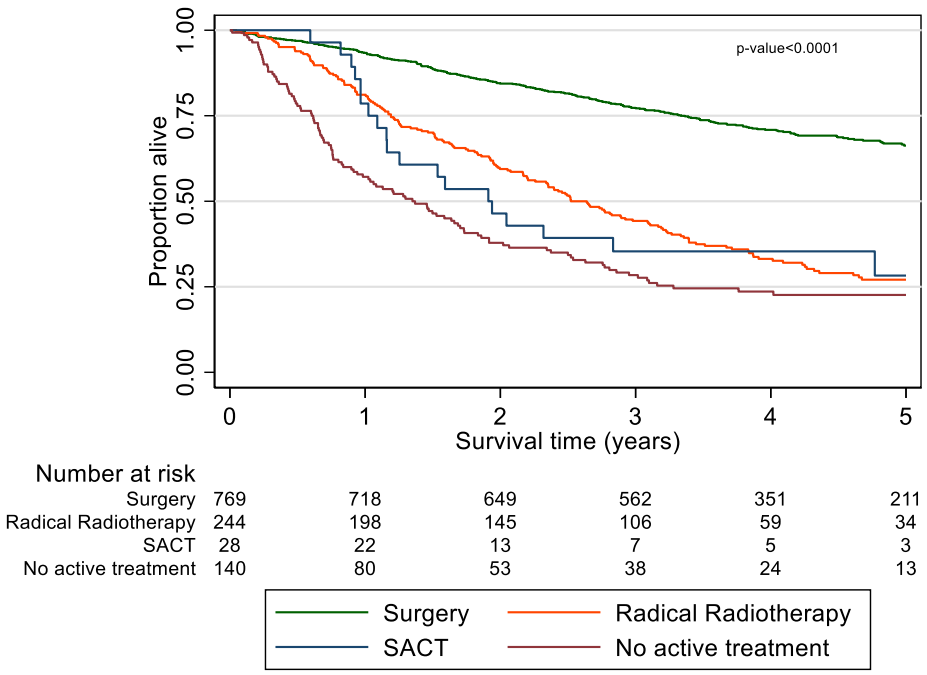


Figure 4-3 Kaplan-Meier showing unadjusted survival following treatment

4.4 Discussion

4.4.1 Key findings

86% of people with lung cancer in the East Midlands who appear eligible for treatment with curative intent received potentially curative treatment either through surgery or radical radiotherapy. 12% did not receive any active treatment. The odds of people receiving surgery was the same for all included

trusts, but lower for people receiving radiotherapy at ULH and Derby. Patient choice was the reason not to have active treatment in 17% of cases, which equates to 24 people from 4 trusts over 4 years.

The most frequent reason to receive either radiotherapy or no active treatment was inadequate lung function or other comorbidities. Lung function, particularly TLCO, had the greatest impact on the likelihood of receiving surgery, although older age and PS >0 both also decreased the odds. Following adjustment for lung function, age and PS did not affect the chance of radiotherapy.

Median lung function, regardless of treatment group, exceeded the recommended threshold for thoracic surgery in national guidelines. However, where the reason not to have surgery was recorded as 'Inadequate lung function', median TLCO was comparatively lower and did fall below treatment thresholds.

4.4.2 Previous Work in the Literature

The results reported here are broadly similar to those of the NLCA from the same time period. Between 2017-19 81% of people with stage I-II, PS 0-2 NSCLC across England received treatment with curative intent, with national variation of 72-93% in 2019.(98, 182, 183) The 86% treated here are slightly higher than the reported results for East Midlands from this time period, which varied from 80-82%.(184) This difference may be accounted for through missing data, which will be discussed in 4.4.3.

Spotlight audits into curative intent treatments were conducted by the NLCA in 2015 and 2017-18. Initially, 46% of people who were not treated with surgery had radical radiotherapy, which increased to 62% in the later audit and is similar to the 59% found here.(185, 186) 46% received best supportive care in 2015, decreasing to 25% in 2017-18 compared with the 35% found here.

These spotlight audits attempted to investigate the reasons people did not receive surgery but were limited by 75% missing data in this field. In 2017-18

comorbidities (including respiratory disease) accounted for 11% of people who did not have surgery.(185, 186) Here, with more complete data, non-respiratory comorbidities were the reason for no active treatment in 32% of people, with a further 36% attributable to inadequate lung function. Comorbidities have been found to decrease surgical rates in multiple studies and were the reason for no surgery in 29% of cases in an American study.(187-189)

Unsurprisingly, increasing age also decreases the likelihood of surgery, a finding which persists after adjustment for PS and comorbidities.(186, 187, 189-191) Here, I found that age ≥80 decreases the likelihood of surgery to less than half that of 70-80 year olds even after adjusting for lung function. This does not hold true however for receiving radiotherapy, where the difference in age resolves once adjusted for lung function.

The impact of patient preference on surgical decision making is variable in the literature. The NLCA 2015 spotlight audit found 31% of people chose not to have treatment, which decreased to 15% in 2017-18.(186, 192) American data from 1988-2002 found 1.5% of stage I-II NSCLC refused recommended surgery, although this was extracted directly from the SEER database and may have not captured all refusals.(189) An Australian study published in 2010 reported 50% of treatment refusal in lung cancer was due to personal choice, although this study had 85% locally advanced or metastatic disease and included non-curative intent treatments.(188) 10% of people with early-stage disease surveyed in an American 2010 study refused surgery.(187) Establishing reasons for this decision is difficult from quantitative data and is better explored through qualitative research. Socioeconomic status may be important as suggested by decreased surgery rates shown in people who are unmarried and socially isolated.(189-191) Decreased education and lack of insurance, particularly in American settings, are also associated with reduced cancer surgeries, and worse outcomes.(187, 190, 193) This may be confounded however by poor general health often experienced by more deprived individuals.

4.4.3 Strengths and weaknesses

Selection of data for inclusion in this study was limited by missing stage and PS in provided datasets from local trusts. Time limitations prevented further notes review of those people missing inclusion criteria data and therefore some relevant cases are likely to have been missed. Given the dramatic variation in missing data between trusts, this may have biased the results. It should be noted that the datasets were generated from local hospital NCRAS submission data, suggesting national data collection may be similarly flawed, unless subsequent data pulls are requested.

Utilising a deep dive medical notes review facilitated excellent clarity of the reasons people did not receive treatment, with just 10% having no reason recorded (Table 4-3) and no missing data, compared with 75% in the NLCA spotlight audit.(185) Data collection was however limited by the completeness of the medical records, with physiological data being particularly difficult to collect. In many cases pre-operative exercise testing in the form of shuttle walk testing or 6MWT were reportedly conducted by anaesthesia, however usually no record of these results was available. Additionally, both exercise testing and echocardiograms were often only conducted in the pre-operative phase, and therefore were frequently not done for people receiving radiotherapy or no treatment.

Finally, the first treatment given was recorded as 'treatment received'. This was to avoid treatment of local or regional recurrence. However, particularly with SACT and radiotherapy, this risks people who received combined chemoradiotherapy being coded as one or the other.

4.4.4 Clinical Relevance and Conclusions

Surgical resection is the gold standard of treatment for people with early-stage NSCLC, however in high-risk individuals radical radiotherapy is recommended as an alternative.(42) Radiotherapy may be offered to people at high risk of post-operative dyspnoea, or who are surgically unfit due to other comorbidities, or following patient preference. Currently, there is no

lower limit on lung function requirements for radiotherapy, with cases instead being considered on an individual basis.(52) I note that median TLCO for all groups was above the 40% threshold for surgery in current guidelines.(41, 42) Where the treatment reason in medical records was recorded as 'Inadequate lung function' however, this did fall to below the required level. ERS recommends FEV1% and TLCO% >80% requires no further pre-operative testing.(41) Predicted post-operative FEV1 and TLCO of 30% has been suggested by ERS and 40% by BTS as a cut-off for high risk indviduals.(41, 42) These values do not neccesarily correlate with acceptable levels of post-operative dyspnoea which may be better represented by functional tests.(42) In this cohort, exercise testing was very rarely used. In people with borderline or low lung function, performing functional tests of lung function such as 6MWT would have provided additional data which may have reassured clinicians and increased offers of treatment.

Retrospective comparison of survival between surgery and radiotherapy has been limited owing to increased comorbidities in the radiotherapy population. Whilst early survival was similar, long-term survival was significantly shorter in SABR, with more than double the risk of death.(55, 56) Further analyses suggests cancer specific survival however is similar, with the increased deaths following radiotherapy due to competing causes.(194) Prospective trials of radiotherapy versus surgery in medically fit people have been limited by low accrual, however have concluded no difference in long-term survival.(57, 123)

Radiotherapy-induced lung toxicity occurs in 20-35% of people treated for lung cancer and risks lifelong dyspnoea.(195, 196) This risk is further increased by respiratory comorbidities which are common in the lung cancer population, particularly amongst those who are deemed medically inoperable. In people with lung fibrosis, the risk of radiation induced toxicity rises to as high as 71%, with 33% treatment related mortality.(197) These risks however should be balanced against the risks of no treatment, as radiotherapy may be the only available alternative treatment to people who

have medically inoperable lung cancer. People with stage I lung cancer who received no treatment have a median survival of just 7.6-16 months, with 4-10% 5-year survival, depending on comorbid status.(175, 198)

Possible ways of improving surgery numbers are through modifying treatment approaches to minimise risk, or through improving patient fitness. Prehabilitation introduces interventions prior to treatment with the aim of improving a person's functional status, thereby improving their tolerance of treatment and decreasing morbidity.(199, 200) Most commonly multimodality therapy is used, which includes physical activity, psychological support, nutritional input and smoking cessation.(200, 201) For people who have been offered surgical treatment for lung cancer, these programmes have been shown to improve functional status, particularly exercise capacity as measured by 6MWT, as well as decreased post-operative length of stay and complications.(201-204) They are non-inferior, and may even exceed outcomes from traditional enhanced recovery pathways, and have been successfully implemented within NHS trusts.(201, 204, 205)

There is less evidence regarding prehabilitation to improve status from inoperable to operable. Only a small number of studies have compared pre- and post-intervention lung function, with meta-analysis finding a small increase in FVC, of less than 3% predicted.(203) Prehabilitation has also been shown to improve aerobic capacity on CPEX, but did not change ventilatory efficiency which is a useful predictor of complications following lung resection.(206, 207) Despite these limitations, a Welsh group utilised prehabilitation in people who were considered unfit for surgical resection of lung cancer. Following intervention, 87% of high-risk people with TLCO<50% were fit for curative intent treatment, and 59% were considered fit for surgery, compared with 21% prior to prehabilitation. Prehabilitation also improved PS, dyspnoea scores and frailty. Ultimately, 55% of high-risk people underwent surgery. Compared with the low-risk group with TLCO>80%, 1-year mortality was higher in the high-risk group at 29% compared with 8%.(202)

Surgical techniques including parenchymal sparing surgery may be used to try and preserve lung function in higher risk patients.(41, 42) Sublobar resections include segmentectomy and wedge resections, and remove a smaller portion of lung than the traditional gold standard of lobectomy. Currently, 20% of resections for lung cancer in the UK are sublobar.(163) In small, stage IA, peripheral tumours, 2 large randomised controlled trials confirmed no difference in 5-year disease free survival between sublobar and lobar resections.(47, 168) Lung function as measured by FEV1 was non-clinically significantly improved by 2-3% at 6-12 months post-operatively, so benefit in post-operative dyspnoea however may be limited. In addition, these techniques are restricted by the stage and position of the tumour so are not applicable to all cases.

Our findings show that there may be some people who have lung function above that required for surgery. Given the dismal outcomes without treatment, MDTs should endeavour to highlight cases where people with early-stage disease do not receive treatment, with the aim of identifying individual barriers and possible alternative routes of treatment. Implementing prehabilitation services should be a priority, with future research focus into optimising medically inoperable patients.

4.5 Chapter Summary

- 12% of people with PS 0-2, stage I-II lung cancer in the East Midlands did not receive active treatment.
- 17% of these people chose not to receive treatment; two-thirds did not receive treatment due to comorbidities or inadequate lung function.
- Reduced TLCO had the greatest impact on likelihood of receiving surgery.
- Older people and people with PS>0 were less likely to receive surgery or radiotherapy, however for radiotherapy this was dependent on lung function.

- For the 4 trusts in the region, there was no difference in the odds of receiving surgery, but radiotherapy was less likely in 2 trusts.
    - These regional differences could be due to personal reasons which would not be captured by quantitative data.

Chapter 5. DECLINE: Perceived Barriers to Curative Treatment for People with Early-stage Lung Cancer – Semi-Structured Interviews of Patients and Health Care Professionals

This chapter forms the qualitative arm of the DECLINE study. Through semi-structured interviews of people with early-stage lung cancer and clinicians working in lung cancer, it examines some of the barriers and facilitators to treatments experienced by people across the East Midlands.

5.1 Introduction

5.1.1 Background and Rationale

As demonstrated in Chapter 4, 17% of people in the East Midlands who did not receive treatment with curative intent for early-stage lung cancer, chose not to receive treatment but the reasons for this are not clear. Treatment rates do vary between NHS Trusts, suggesting there may be regional differences which contribute to treatment decisions.(98) People who are more deprived are also less likely to receive surgical treatment, suggesting there are individual differences between patients.(208) The reasons for this are not immediately clear and may be contributed to by both patient factors such as preference and ability for travel, or the practice of local clinicians.

Previous work concluded that for those people who do receive treatment, trust in their surgeon and a good relationship with their medical team is essential in opting to have treatment.(209-211) It is unclear whether the same beliefs hold true and influence a person deciding not to receive treatment, or whether there are additional barriers to care – either practical or emotional. Healthcare practitioners (HCPs) may experience healthcare system barriers which influence their referrals for curative treatment. By identifying and then addressing any reversible barriers experienced by either patients or HCPs, we would be able to provide more equitable care for all.

5.1.2 Aims

1. Describe barriers to treatment with curative intent for people with early-stage lung cancer and good PS across the East Midlands, as perceived by both patients and HCPs.
2. Describe facilitators to treatment for the same groups.

5.2 Methods

5.2.1 Study Design

A pragmatic mixed methods study was conducted to investigate the reasons some people do not receive curative intent treatment for their early-stage NSCLC. The quantitative component has been discussed in Chapter 4;

conclusions from quantitative and qualitative components of the study will be collated at the end of this chapter. A pragmatic paradigm is suitable for exploring this area as it considers the practical consequences of a person's beliefs and actions. It considers that people have a diverse experience of lived reality which impacts their decisions and world view.(212) This is directly applicable to the research question which explores how people's prior experiences have impacted their recent treatment decisions, with the ultimate aim of identifying practical action plans which target commonly raised issues. Using a mixed methods study allows us to consider the question from different perspectives. The quantitative arm provides relevant detail on the scale of treatment refusal in the East Midlands, whilst qualitative semi-structured interviews allow consideration of people's actual behaviour, and the lived experiences which influence this.(213, 214)

Opinions on lung cancer treatment decisions were gathered through semi-structured interviews of both patient participants and HCPs. Semi-structured interviews were used to maximise depth of information gathered whilst ensuring consistency between interviews. Semi-structured interviews allow the researcher to fully explore a participant's opinions if they introduce a new theme, whilst also prompting the researcher with questions to allow consistency between interviews and keeping questions on topic.(215, 216)

Two participant groups are used in this study: patients and HCPs. This allowed consideration of the topic from two different relevant viewpoints, to ensure barriers that arise both within healthcare, and from a patient's perspective were fully captured. Different interview guides were used for the two participant groups (Appendix A) to ensure relevance of questions. These were informed by review of the relevant literature and developed in collaboration with experienced qualitative researchers supervising this research. Interview guides were reviewed after the first few interviews to ensure clarity and suitability of questions, with minor adjustments made where needed.

5.2.2 Inclusion Criteria

Participants were recruited through lung cancer MDTs for the four hospital trusts which refer to Nottingham University Hospitals for thoracic surgery:

- Nottingham University Hospitals (NUH)
- United Lincolnshire Hospitals (ULH)
- Derby and Burton Hospitals (DBH)
- King's Mill Hospital (KMH).

The clinical lung cancer lead for each trust disseminated information about the study to all relevant members of the MDT. This included information on identifying potential patient participants as well as an invitation to participate as an HCP participant.

Inclusion criteria for patient participants were:

- Diagnosis of stage I-IIIa NSCLC in the last 3 months;
- PS 0-2;
- Offered either radical radiotherapy or surgery, but patient chose not to receive this treatment, or patient refused further investigations with likely stage I-IIIa disease;
- Excluded if unable to speak English language.

Inclusion criteria for HCPs were:

- Consultant or fully qualified nurse specialist.
- Working in a relevant clinical speciality:
    - Respiratory physician working in lung cancer;
    - Thoracic surgeon;
    - Clinical oncologist;
    - Lung cancer specialist nurse.

The study opened on different dates for each trust when capacity and capability approval was granted at each site, between August 2022 and January 2023. Recruitment ended on 30th June 2023 for all sites.

5.2.3 Recruitment and Data Collection

HCPs were recruited through emailing the lung cancer lead for each trust who disseminated an invitation email to all relevant team members, which included a Participant Information Leaflet (Appendix A). After the first round of interviews, purposeful sampling was used by emailing specific trusts and specialities to ensure full breadth of sampling. Potential participants contacted the research team via email, where a time for interview was arranged. This could be over video call or in person. A consent form (Appendix A) was sent ahead of time, with any additional questions answered over email or just prior to interview.

Patient participants were identified by local HCPs, with details of inclusion criteria included as part of the initial email invitation. In order to maximise recruitment, follow-up emails were sent reminding HCP of the study, and MDT lists were reviewed by local clinicians to identify any potential participants which may have been missed. Any potential participants were first approached by a member of their usual clinical team and provided with basic information about the study. Those who were interested were consented for sharing their contact information and basic information regarding their diagnosis with the research team. The researchers contacted them via telephone over the next 24-48 hours and provided more information, answered any questions, and arranged an interview if they were happy to participate. The patient information leaflet was either provided by their clinical team, or posted to the patient in advance of the interview. At least 48 hours passed between providing study information and conducting the interview. Interviews were conducted over the telephone or in-person, with consent taken at the time of the interview, or via return post in the case of telephone interviews.

Participant numbers are difficult to determine *a priori* in qualitative research as recruitment should continue until themes are saturated.(217, 218) The study began with the intention of recruiting around 20 patient participants, and 20 HCPs, however intended to stop recruitment when thematic

saturation had been reached. Saturation of themes was reached for HCPs and recruitment halted, however patient recruitment was challenging and therefore recruitment continued for the maximal time available for the study.

5.2.4 Analysis

All interviews were recorded using an encrypted device and transcribed using secure digital transcription software provided by the University of Nottingham. Transcripts were checked for accuracy and anonymised during which stage the researcher familiarised themselves with the content. Data were analysed using NVivo 14 (Lumivero, LLC) to collect and organise quotes. Thematic analysis was undertaken using the Framework method.(219, 220) Open coding of an initial subset of transcripts was used to generate preliminary topics which were then rationalised into themes and subthemes. These were used to develop thematic matrices, encouraging transparency by linking verbatim quotes with subthemes.(221) Subsequent transcripts underwent indexing and mapping onto existing Frameworks, with emerging themes added as they were identified. Validity was ensured through investigator triangulation, with coding and themes being discussed with the research group throughout the analysis period.(222) Following initial generation of themes a subset of transcripts from both participant groups were double-coded by researcher MB to ensure accuracy and reproducibility of findings.(221, 223) HCP and patient groups were separately analysed with matrices being independently generated for each group.

Finalised matrices were reviewed and data interpreted. Through comparisons between participants, analysis moved from a semantic to a latent approach, with assumptions being made about the underlying subtext of the data in the context of participants' wider experience, as well as considering how subthemes interact. Final comparisons of each subtheme were made between participant groups.(219)

5.2.5 Reflexivity Statement

The main researcher (HM) conducted all the interviews and initial coding and Framework generation. HM has experience working clinically with people with lung cancer as a respiratory physician and therefore risked incorporating their previous experience in the analysis of the data. Prior to commencing the research, HM's assumptions included that distance travelled would be a significant reason for some people to not receive treatment, particularly for those from the more rural referring hospitals. In addition, older age was expected to contribute to people not wishing to receive treatment.

Several strategies were implemented to avoid personal bias and assumptions on the subject matter. Throughout, HM collaborated frequently with other members of the research team. Notably, prior to commencing interviews, topics for the interview guides were discussed with the whole research team, with final scripts checked and agreed with EOD, RM and MB, who have significant qualitative experience. Bracketing was used to separate preconceptions from the analysis process, using the method of memo writing to keep notes throughout both data collection and analysis.(224, 225). During analysis, double-coding was employed to ensure reliability and reproducibility.(223) Researcher MB independently analysed and coded a subset of transcripts from both patient and HCP participants. Triangulation was used to increase validity with discussion of codes and emerging themes with the wider research team.(222)

Two of the supervisors for this study (EOD and DB) work as lung cancer clinicians in one of the included Trusts. In order to avoid bias or coercion, they did identify potential patients for the study but did not approach them for recruitment and were not included as HCP participants.

5.2.6 Ethics Approval

Ethics approval was as part of the wider DECLINE project and is described in section 4.2.2.

5.3 Results

5.3.1 Recruitment

15 HCPs were interviewed after which thematic saturation was reached with a reasonable distribution of participants from across all four trusts and all specialities, therefore recruitment was halted before the intended 20 HCPs were recruited (Table 5-1). In total 57 potential participants were invited to participate via email, of whom an additional 4 expressed interest but were unable to co-ordinate a time for the interview.

Table 5-1 Health Care Professional Participants for interview

Identifier	Hospital Trust	Specialty
HCP01 -	NUH x 8	Nurse Specialist x 6
HCP15	DBH x 2	Clinical Oncologist x 3
	KMH x 3	Respiratory Physician x 4
	ULH x 2	Thoracic Surgeon x 2

Patient recruitment was more challenging, with few patients identified who met inclusion criteria. As Chapter 4 demonstrated, most people who reached stage and PS inclusion criteria but did not receive treatment were deemed unfit for treatment by their clinical team, rather than refusing potential treatment. In total 6 patients were interviewed from across three trusts: no patients were recruited from ULH. An additional 6 patients were approached by the clinical teams who eventually chose not to participate in the study. 1 was recently bereaved, 1 had cognitive impairment, 1 did not want his medical information to be shared outside the medical team, and 3 simply did not want to participate in research. Of the 6 patients, 3 underwent some kind of treatment (Table 5-2). All patients were interviewed between diagnosis and before starting treatment. During the course of the interviews, it was identified that 3 participants were considered unfit for surgical treatment due to their lung function (P01, P04, P05), with 1 of these also not suitable for radiotherapy (P01). Whilst these patients did not completely fulfil inclusion

criteria, their transcripts were analysed and included as they did provide useful contributions to the topic.

Table 5-2 Patient participants for interview

Demographic	Number
Age	Median 71; Range 59-91
Sex	Male – 3 Female - 3
Ethnicity	Caucasian - 6
Stage	Stage I – 4 Stage II - 2
PS	PS 0 – 3 PS 1 – 2 PS 2 -1
Treatment	None – 3 SABR – 2 Chemorad - 1
Hospital Trust	NUH – 4 KMH -1 DBH - 1

5.3.2 Themes and sub-themes

Three broad themes were identified: Emotional Barriers to Treatment; Practical Barriers to Treatment; and Treatment Facilitators. These were further classified into sub-themes, which are summarised in Table 5-3.

Table 5-3 Themes and Sub-themes

Themes	Sub-themes
Emotional Barriers to Treatment	Fear of treatment
	Previous experience of cancer
	Futility of treatment
	Absence of symptoms
	Denial of cancer risk

Practical Barriers to Treatment	Transport and accessibility of hospitals
	Working and caring responsibilities
	Financial pressures
	Healthcare system pressures
	Poor communication within consultations
Treatment Facilitators	Family and social support
	Charity and support groups
	Good relationships with HCPs
	Written information

5.3.2.1 Emotional Barriers to Treatment

Fear of treatment

All patient participants demonstrated emotional barriers to treatment, with these being the key reasons most people eventually decided not to have treatment, rather than because of practical barriers which are discussed below. Fear was particularly prevalent, with people describing both fear of an operation and potential side-effects or complications as reasons not to have treatment. One patient felt the explanation of what surgery entailed was 'something like a house of horrors. It frightened me to death' (P02). Most HCPs also recognised the thought of 'chest being cracked open and tubes everywhere' (HCP02) as a frequent reason people opted not to have surgery. Generally, patients were less afraid of radiotherapy, a belief which several HCPs also noted. Nurses, surgeons and respiratory physicians all felt some people chose radiotherapy because 'It's not invasive'. (HCP14). Patients agreed with this, with participant P02 (quoted above) opting for chemo-radiotherapy instead of surgery. The other common fear was of side effects, particularly worsening breathlessness. One patient perceived this risk reduced with radiotherapy in place of surgery, feeling it was 'the less of all the evils' (P04) but another felt 'The radiotherapy was the same… could make me breathing worse' (P03) and that neither treatment was worth the risk of

worsened breathlessness. Symptom burden also impacted the likelihood of accepting additional risks from treatment. Several HCPs felt that 'they're not willing to take the risk of chemotherapy or radiotherapy that's then going to make them potentially poorly when they don't feel unwell' (HCP05). Patients reflected that staying well was important, and they 'Don't want to spend the time left in and out of hospital' (P06).

Previous experience of cancer

This fear was particularly exacerbated by previous negative experience of cancer treatments – either personally or in a family member. Often, the experience was not of the proposed treatment, and in fact may be a completely different cancer. All of the patient participants had some kind of previous negative experience although this varied in clinical relevance to their case. One lady had recent experience of a friend: 'He's had lung cancer, he's had the surgery and six months down the line he's still struggling. I don't want that' (P03); whereas another recognised that his father who had complications of throat cancer treatment 'was playing on my mind… even though mine was in a different place' (P02). HCPs tended to report previous experience as the most common emotional barrier to treatment. Often clinical advances meant that patients' prior experience did not reflect the current risk profiles of treatments, but patients may not be receptive to this. Several were frustrated that they 'couldn't get [a patient] round to the fact that things… have moved on and improved and the side effects are not as severe' (HCP01) and that with some prior knowledge, 'treatment option is discarded from the very first meeting' (HCP09).

Futility of treatment

Several patient participants felt treatment was futile due to their comorbid status or age, with emphysema particularly mentioned as being life-limiting, compared to their malignancy. The oldest participant reported 'I'm 91, nearly 92; if I had been 71 it would have been different. I would have it' (P06). Two patients recognised they were more likely to die from their comorbid

emphysema than their lung cancer: ‘with having emphysema. Which is going to kill me? And at the moment it's emphysema and that's why I went for keep an eye on it’ (P01). HCPs generally interpreted comorbidities as practical barriers to treatment, with both age and respiratory comorbidities increasing operative risk, rather than making the treatment itself futile as people are more likely to die from conditions other than their cancer. Only one HCP – a clinical oncologist – reflected on competing causes of death and felt that clinicians were not generally very good at balancing prognoses: ‘I'm not sure that we're necessarily that good at talking to patients about what their prognosis is from their severe COPD. And that can be quite a stumbling block when you're trying to explore with someone with a particular treatment of their small localised lung cancer is the right thing to do or not’ (HCP10).

Denial of cancer risk

A less commonly reported emotional barrier was patients not accepting the full risk of their cancer. HCPs felt this was often linked to their agitation at the time of diagnosis, and people can be ‘so overwrought by everything that you know they just don't see. They don't hear’ (HCP01). Another HCP reflected this was ‘normally the people who are completely blindsided when you see them in clinic. And maybe some of that is denial’ (HCP08). Generally, interviewed patients agreed. The patient participants all understood their diagnosis, however had commonly not explored the prognosis of an untreated cancer. One lady felt: ‘I don't want to know how long, what the prognosis is’ (P03). Preparing people for their diagnosis and treatment options early on in the patient journey was felt to reduce this risk and is discussed in Facilitators in 5.3.2.3.

5.3.2.2 Practical Barriers to Treatment

Most HCPs focussed on practical barriers to treatment, such as transport and carer responsibilities as being the commonest reasons people chose not to receive treatment. In contrast, whilst practical barriers were widely reported by patients, they were usually surmountable with assistance from family,

health care workers, and charities, with patients ultimately refusing treatment because of emotional barriers described above.

Transport and accessibility of hospitals

Transport and accessibility of hospital appointments was recognised as a barrier to attendance by both study groups. HCPs focussed on transport between hospitals being a greater issue, however patients reported challenges even attending local hospitals. Both surgeons and nurses who worked in peripheral hospitals had experience of people making treatment decisions based on the distance to hospital, with 'one patient who refused an operation because it was not done closer to his home' (HCP07) and 'we have quite a few people that don't want to travel to Nottingham and choose radiotherapy [over surgery] just because of that' (HCP14). In contrast, a physician working in Lincoln – which covers the areas furthest from Nottingham's surgical centre – experienced that people preferred to travel greater distances if it expedited appointments: 'Do you want to come to the surgeon's Lincoln Clinic or would you like to go as soon as possible? And they always say as soon as possible. So although that's not true, a few don't, but generally, they just want to be seen' (HCP08). An oncologist agreed with this, and could not recall any patients refusing treatment because of transport, a fact they attributed to the availability of hospital transport if needed: 'I've not had patients say to me I don't want to do the radiotherapy purely because of the travel… We're lucky that we get medical transport sorted for us very readily by our radiotherapy department' (HCP04). In contrast, patients discussed the difficulties they faced even attending local hospitals, although all participants had been able to overcome these obstacles and had never missed appointments. Transport options varied between participants with one lady using public transport: 'I just go for it and walk down the bottom of the road across the road and I caught my bus within 5 minutes' (P04), but most used cars, either driving themselves, by family, or a private taxi: 'No problems [getting there], I've got a car' (P03). Ultimately, several patients used hospital transport as a failsafe for attending appointments, with one

acknowledging that without it ‘I wouldn't be able to get there’ (P02). Private transport presented the additional challenge of parking, which ‘is very hard to get. You have to go a long time before your appointment!’ (P03) When on site accessibility was an issue, with long distances between car parks and clinics: ‘then if you get in the car park where the blue badges are, it’s still a walk’ (P01), and the layout of the hospital site making distances even longer: ‘There's like a concrete path which they say is inaccessible because they've got two things blocking off so you can't use that concrete. Which to me is absolutely crazy because I can't see any reason for it’ (P04).

Financial pressures

Whilst problems with transport were surmountable by the patient participants, use of taxis and private cars did create additional financial pressures. Oncologists and nurses particularly agreed with this, with a nurse recognising ‘Then it's parking - like every single hospital - which really puts them off. Then it's cost of parking that they mention’ (HCP14). The alternative of private taxis are also expensive, a fact which has been exacerbated during the pandemic, as ‘We've been really discouraging patients to use the public transport if they're on chemo, if they had radiotherapy, but then it's so expensive when they try to get taxi everyday’ (HCP03). Patients agreed with this, with one man who was reliant on taxis planning on seeking additional financial aid: ’All the money for all the taxis, I’ll talk to Macmillan and see what they say’ (P05).

Working and caring responsibilities

Some HCPs felt people who are more deprived seemed to be disproportionately affected by the financial impact. One nurse had experience of ‘some unfortunately on the zero-hour contracts… will lose their job’ (C11). All patient participants except one were not in paid employment, and he was not worried about job retention: ‘I knew once everything was fine, they’d have me back’ (P02), meaning he did not experience additional financial

pressures through loss of earnings. With the exception of cost of transport, finances were not described as a barrier by any patients.

In addition to paid employment, carer roles were frequently mentioned by HCPs as a reason for refusing treatment, with all specialities having experience of this. They reported patients being concerned about who would provide care for their relative in their absence: ‘they don't want to risk becoming poorly because then it would leave their spouse to be sort of institutionalized’ (HCP02). This caused feelings of frustration for some HCP as they felt refusing treatment would have a greater long term impact on their ability to provide care: ‘it's a debate between can you take two or three days to have potentially curative surgery or can, or will you not have the surgery for those two or three days and then die earlier and therefore not be able to care for the family member’ (HCP06). None of the patient participants were carers. One lady did express similar concerns over not being able to complete her own activities of daily living though, preferring not to be reliant on others: ‘Key-hole surgery, they said it was gonna be weeks before I could hoover, shop, do anything. I've got to be careful not to lift anything... Friends have said they'll come and do the cleaning it and use hoover and everything, but preferred to do it myself’ (P03).

Healthcare system pressures

HCPs frequently mentioned various ways increased pressure on healthcare services were impacting their practice. Several team members described their patient load as ‘we're just full. And we're ever growing’ (HCP14). This increasing number of patients has contributed to increased waiting times in some trusts: ‘as a lot of places have we got a bit of a delay with the two week waits at the minute’ (HCP11). Delays in the cancer pathway were not linked to refusal of treatment directly by any HCP or patients but they did impact the relationship between clinicians and patients. Patients largely did not share the same concerns about outpatient waiting times although one lady had refused to attend as an emergency because ‘you're likely to have something like 11-12 hours waiting. So I just said I just can't do that’ (P04).

HCPs reflected that nurses often had the closest relationship with patients, both because of continuity and the perception they have more time. Nurses intended to ‘see them from pre-diagnosis all the way through until they are discharged or die’ (HCP12) allowing a closer relationship so patients ‘know us as nurse specialists, we're not just another face that pitches up when they get a diagnosis’ (HCP01). Several doctors however reported ‘continuity is ideal but can't always happen’ (HCP09), a situation repeated by several patients: ‘it doesn't help when you go to the surgeries and you get a different doctor every time’ (P04). One nurse acknowledged this resulted in patients perceiving nurses as less busy and often sharing pertinent information with her rather than the doctors: ‘it’s not that they don’t want to say it to you just that they are very conscious that doctors are very busy and I’ve got time to talk to this nurse’ (HCP01).

The patients all reported good relationships with their medical team, especially the nurses who had ‘been brilliant’ (P02). They also found continuity contributed to this and one explained: ‘it does help having same person every time because you know what you going through’ (P02). This positive relationship continued beyond diagnosis even in those who had no treatment. One respiratory physician felt that patients ‘worry that we'll be peed off or annoyed if they've taken up clinic… and they then decide not to have anything’ (HCP05). This concern was also voiced by a patient who ‘was surprised that I've got another appointment when I refused [surgery]’ (P03), which resulted in her feeling supported.

Poor communication within consultations

Patients sometimes found poor communication impacted their understanding of their diagnosis which may impact decision making when it came to treatment. Sometimes the language itself was confusing for patients: ‘they said a nodule, but I didn't know what they meant by a nodule. I didn't cause I'm not that way inclined’ (P01). Many HCP tried to avoid medical jargon as ‘plain English is what most of the patients want us to use’ (HCP01). Choice of words was linked to continuity by one doctor who thought varying vocabulary

could increase potential confusion: ‘it's just that simple thing where a patient can go home confused because last week the doctor called it a lesion, but now you're calling it a tumour or a mass’ (HCP09). Two patients both mentioned difficulty in understanding the HCP because of accents: ‘Some of them were foreigners and it took me two or three attempts to understand them, if you know what I mean’ (P02). Non-English-speaking patients rather than accents were mentioned as a barrier to communication by some HCPs with particular concern over using family members as translators because of the risk of not accurately providing information which would subsequently impact treatment decisions: ‘they used to use a family member to translate… the family members still not told them that got cancer’ (HCP11).

5.3.2.3 Treatment Facilitators

Charity and financial support

The majority of facilitators to treatment tackled practical barriers with several having been touched on above in 5.3.2.2. Specialist nurses and charities were essential to co-ordinating transport and providing financial support, with their benefits recognised by both HCPs and patients: ‘There's the Macmillan beyond diagnosis service that we can refer to. So they can help with sort of practical things, shopping, finance, financial advice and things like that’ (HCP12). This enabled patients to attend appointments by helping with transport: ‘I go past Macmillan and I was thinking of going in there… All the money for all the taxis’ (P05). Without hospital transport for appointments, one patient reflected ‘I wouldn’t have been able to get there’ (P02).

Family and social support

Where people had good social support through family and friends, they experienced both practical and emotional benefits. Family provided transport and assistance in accessing services, a benefit described by both HCP and patients. Several patients relied on family members to attend hospital appointments: ‘my sister takes me’ (P01). HCP also experienced this, feeling that generally patients trusted family and friends to rally and help with

transport: ‘They’re gonna find somebody, you know, I’ll find a neighbour, I’ll find someone will take me in… So sometimes they have to pull their family and like a bit of a rota’ (HCP11).

As well as the practical benefits, participants who attended clinic with family members found this aided their understanding of their diagnosis, as their family often retained information more easily: ‘My sister comes with me. She can remember the big words and the little words, I can only remember the little-uns’ (P01). HCPs agreed that people who attended hospital appointments with a family member tended to be better informed and ready to make treatment decisions: ‘the older the patient gets, the more they rely on that support and help to go through the information to make that final decision’ (HCP15). One participant continued to take emotional support from their friends after they had been bereaved, feeling they had a responsibility to ‘live on for them’ (P05).

All but one patient felt their relatives supported their treatment decisions and did not feel pressured by them, although one did feel guilty that she was letting her sons down by not opting to have treatment. Even though she felt her sons were ‘happy to go along with what I want’ she also described ‘worry that I’m being selfish’ by opting not to have treatment (P06). HCPs all concurred that having family present in a consultation tended to motivate a patient towards having treatment: ‘it would be more likely they'd encourage them to have the treatment rather than not’ (HCP02).

Finally, patients relied on their relatives for emotional support, gaining benefits from their presence and being able to reflect on their diagnosis: ’Just the fact that [my daughter] was there, we were able to talk it over’ (P04).

Good relationships with HCPs

A good relationship between patients and HCPs was reported by the majority of participants – both patients and HCP. Whilst this was not highlighted by any patients as impacting their decision to have treatment, they did link

understanding with good communication, and many HCPs felt to this was beneficial to the decision-making process.

Several HCPs – surgeons and respiratory physicians – aimed to give patients confidence in their medical team, to encourage them towards treatment: ‘I think that if I can draw up really nicely and really well, the patients are more reassured that I have a smooth artistic hand and therefore more confident in my surgical techniques’ (HCP06). Patients did not specifically mention trust in HCPs as contributing to their decision making.

As mentioned previously, medical jargon was often not understood by patients and HCPs sought to avoid this by using plain language and continuity of care and terms where possible: ‘I try to always make sure that it's been clear whether we're looking at a curative approach or whether we're looking at managing it and controlling it’ (HCP13). Patients also found this helpful to aid their understanding, with all patients being happy to ask questions, and one explaining that asking doctors to ‘Come down a peg or two, please. They come down and explain a little bit longer’ (P01). Nearly all HCPs highlighted that they used specific terms like cancer, cure and control to ensure that patients had a clear understanding of both their diagnosis and the goals of treatment, allowing them to make informed decisions about their care: ‘I just want to make sure that you've got the right information to make those decisions’ (HCP03). Several respiratory physicians explained they found introducing this terminology early on in the patient journey gave people time to consider their diagnosis between appointments, priming them to be ready to discuss treatment options as soon as possible: ‘Often it will shatter their world the first time you meet them, you tell them they’ve got cancer and you don't think you can cure it… when they come back a week later with their biopsy results, they've often had time to sort of compute that and come to terms with it... So I think getting in early, although not pleasant for the patient, sometimes it's helpful in terms of their pathway’ (HCP05).

Written Information

Written information in the form of charity produced patient information leaflets were used by HCPs to provide additional information and avoid patients forgetting the essentials: ‘Obviously we give it to them verbally, but they get so much information… getting a bit too much information overload. So then they get the copy of the information sheets’ (HCP10). Whilst HCPs felt these would be beneficial to a patient’s understanding, aiding them to make informed treatment decisions, all patient participants admitted they hadn’t read much of it as they found the volume overwhelming: ‘I'm still reading some of that, not all of it… And a lot of it isn’t for me… I can't read all this. I'm not that quick’ (P01). One did reflect that having written information was useful as she did find all the information retention difficult: ‘I find it a lot more helpful because the stage I am at the moment and I find that my mind is getting awfully cluttered sometimes’ (P04).

5.4 Discussion

5.4.1 Key Findings

Similar barriers to curative intent treatment in early-stage lung cancer were reported by both patients and HCPs, however there was variation between groups. HCPs tended to place more emphasis on practical barriers, with lots of effort placed on minimising these. The patients in this cohort however primarily reported emotional barriers as the reason not to receive treatment, particularly fear of surgery and its complications, as well as preconceived treatment ideas based on previous negative experiences of cancer treatments. Generally, people were keen for treatments available to them, which was recognised by most patients and all the HCPs.

5.4.2 Previously in the Literature

The reasons why people choose not to receive treatment has not been extensively studied in the lung cancer population, especially in those people with potentially curative disease. More work has been done regarding decision making around SACT, as well as screening and diagnosis, both of which share some aspects with this population but also important

differences. The population of interest in this study have been diagnosed and therefore have overcome initial barriers to presentation. They also have potentially curative disease, meaning they are balancing a very different set of potential benefits compared to people with advanced disease, where treatment is for disease control.

Person-centred care, or shared decision-making, is aimed for as the standard of care in medical practice. Lung cancer clinicians are more likely to accept a person's choice not to have treatment where their prognosis is limited, and more likely to question the decision or feel it is irrational where people have potentially curative disease.(226, 227) They were also more likely to take patient preference into account when patients were older or less fit, and where treatment recommendations were more complex.(227) This suggests a flexible relationship with decision-making roles, where some patients are given more accountability than others. Patients themselves often experience a dichotomy of wanting to make autonomous decisions, whilst expecting to be guided towards one particular option by their doctors.(228) This study concurred, with participants expressing surprise that their doctor would not express a treatment preference.

Sufficient time and information are essentials for informed consent, a concept which is central to person-centred care.(210, 229) Insufficient time in appointments limits a person's understanding of their diagnosis, and is identified as an issue throughout the lung cancer journey, worldwide.(210, 229) Medical jargon and unclear language is commonly described as a barrier to understanding.(230, 231) This is closely linked to trust in HCP and a positive doctor-patient relationship, which facilitates both diagnosis and treatment.(229, 232-234) The UK has a particular issue with people believing their potential lung cancer symptoms are not severe enough to warrant taking up limited NHS resources, with doctor-patient relationships complicated by discontinuity within a stretched NHS.(235) This is compounded by the stigma of believing they do not deserve care due to cigarette smoking and believing their disease to be self-inflicted.(230, 234, 235) People are more likely to

contact a nurse than a doctor, as they feel their time is less valuable, an idea also found in this study.(236)

Other practical barriers include transport, financial issues, and carer responsibilities.(230, 233, 237) Financial concerns vary worldwide due to the differences in payment for healthcare and health insurance availability, a particular issue in North America.(230, 238, 239) Difficulty with transport could be increased with increasing distance to the hospital, which may contribute to the lower treatment rates reported for people first diagnosed at non-surgical centres.(79, 82) People in rural areas (with presumed further distance from hospital) are less likely to receive surgery, however these are largely attributed to deprivation rather than location.(83, 240) In our study, transport itself was less of a problem compared with parking at the hospital. The cost of parking is a particular issue in UK NHS hospitals, and was frequently mentioned by both HCP and patient participants in this study. Previous work reported similar findings in a lung cancer screening population in the UK.(241)

As found here, presence of family in an appointment tends to be beneficial to reaching treatment decisions.(210, 229, 231) This may be because a second person presents a second opportunity to understand medical information but may also simply be a sign of the benefits of social support, such as help with transport and activities of daily living.(242) Those who are socially isolated tend to be less likely to receive treatment. People with dependents were more likely to engage with lung cancer care and it is established that unmarried people are less likely to receive treatment.(235, 243)

Emotional barriers tended to be the reasons people in this study did not receive treatment. Previous work has found that people with close friends or family who have previously been treated for cancer were more likely to believe that cancer treatment was worse than the cancer itself, and more likely to refuse treatment.(227, 244) Fatalistic beliefs and nihilism are particular barriers to lung cancer diagnosis, and whilst were not a particular concern for our patient participants with potentially curative disease, were

identified by HCP as being exacerbated by outdated previous experience.(234, 235, 241)

All of these issues – both emotional and practical barriers – are exaggerated in those people who are more socially deprived.(230, 233, 245, 246) The reasons for this are complex, and include greater vulnerability and fewer resources, as well as lower health literacy and understanding.(247) Given that lung cancer has a higher incidence in more deprived people, minimising their barriers to care should be a priority. Improving cancer education and awareness in these groups, as well as establishing support networks, are possible targets for reducing health inequalities in these groups.(230, 235, 247)

5.4.3 Strengths and Weaknesses

The main weakness of this study is the low numbers of patient participants, as well as the uneven distribution across the region, with no patient participants from ULH. People who are more deprived are less likely to engage in research.(248) This has obvious impacts on lung cancer research, with low patient accrual in many qualitative studies.(229, 235) Whilst this study did not include formal measures of deprivation of participants, this may be one of the factors which influenced low patient recruitment from DGHs, particularly ULH. In addition, here I was recruiting people who had the stress of a recent diagnosis, as well as choosing not to receive some aspects of medical care, making them less likely to participate. Finally, the recent COVID-19 pandemic delayed receipt of ethics and opening of the study, meaning there was a shorter recruitment window than intended. With low numbers there is an increased risk of bias as well as missing key themes. For example, work and financial pressures were more frequently mentioned by HCPs than patient participants, which may be as a result of failing to recruit people who were still in work and unable to give up additional time to participate in research.

Whilst participants were not equally distributed across the region, and were all Caucasian, they do show a good distribution of sex, age and PS, as well as

including people who opted for no treatment as well as choosing alternative treatment to surgery. Recruitment of HCP was adequate, as I reached saturation of themes and achieved representation from all specialities and hospital Trusts.

Despite low numbers, I did identify multiple themes of barriers to care, which may impact future clinical practice. This study is unique in addressing barriers amongst people who have potentially curative lung cancer; previous work has focussed on screening or included people with non-curative disease. By including both patients and HCPs I established barriers working within the healthcare system, and those personal to patients.

5.4.4 Clinical Findings and Conclusions

Generally, HCPs perceived major barriers to treatment as practical, whereas patients tended to report emotional barriers to care. Efforts have been made to minimise practical barriers, with support from charities and lung cancer nurses.

In terms of outstanding practical barriers to care, the availability and cost of parking and transportation was a frequent complaint, particularly amongst those with limited mobility. Where possible, providing hospital transport or free parking close to the required hospital department would be greatly beneficial to many people.

Less focus has been placed on reducing emotional barriers, although the importance of communication skills and social support was identified by HCPs. People who are socially isolated and with previous negative experiences of cancer care are at higher risk of refusing treatment. Identifying these people at an early stage in their cancer journey may allow HCPs time to explore and placate some of their fears. Identifying people at risk of treatment refusal based on emotional barriers such as fear during the early, diagnostic period, of their cancer journey would be essential to facilitate intervention. Possible interventions should be explored with the at-risk population. Focus groups could be used to explore options. Due to the time

sensitive nature of cancer treatment, and the biases introduced by conducting research with people who have undergone or refused treatment, a possible cohort would be the lung cancer screening population. The developed intervention could then be implemented in people who have been diagnosed with early-stage lung cancer, with pre- and post-intervention surveys to establish their effectiveness. Due to the low overall numbers of treatment refusal, aiming for a measurable change in treatment uptake would be unfeasible, and qualitative data would be more representative. Possible interventions include personalised risk profiles of each treatment option for each patient, or peer-to-peer support with someone who had undergone the same treatment regime.

5.5 Chapter Summary

- Previous negative cancer experiences and fear of treatments are common reasons people chose not to receive curative intent lung cancer treatment.
- Clinicians tend to place more focus on practical rather than emotional barriers, with the inverse true for patients.
    - Car parking and site accessibility acted as a possible barrier for some people.
- Efforts have been made to address practical barriers to care. Future efforts focusing on overcome emotional barriers such as preconceptions about treatments may help more people access treatment.

5.6 Conclusions from the DECLINE study

The studies described in Chapters 4 and 5 were conducted in combination as a mixed methods study entitled ‘DECLINE’. The aims of this were to explore the reasons people in the East Midlands may not receive potentially curative treatment for their early-stage NSCLC and to identify any potentially reversible barriers to treatment.

In the majority of cases, people did not receive treatment because of comorbidities or inadequate lung function, with people choosing not to have treatment in only 17% of cases. It should be noted however, that median lung function met national guidance for surgery in both those who received radiotherapy and no active treatment.

This frequency of treatment refusal was echoed in interviews, with HCPs reporting most patients were keen for any treatments offered to them. Patients commonly refused treatment because of fear of surgery, radiotherapy, and their associated risks, an emotion which was compounded by previous negative experience of cancer treatment. Practical barriers to treatment such as transport to appointments were commonly identified by HCPs but were less of an issue for patients, often due to identified facilitators such as hospital transport or supportive relatives.

In future, efforts to provide emotional support to treatment sceptic patients may encourage more to have potentially curative treatment of their cancer. In addition, it may be beneficial to discuss people who are considered borderline fit for treatment in a high-risk MDT, to maximise treatments offered to all those who are eligible.

Chapter 6. The Impact of the SARS-CoV-2 Pandemic on Curative Intent Treatment of Non-Small Cell Lung Cancer in England: An Analysis of the Rapid Cancer Registration Dataset

This chapter utilises the Rapid Cancer Registration Dataset to explore the changes which occurred in curative intent lung cancer treatment during the COVID-19 pandemic, and examine whether some people with early-stage lung cancer were comparatively disadvantaged.

6.1 Introduction

6.1.1 Background

During periods of increased strain on healthcare services, such as those seen during COVID-19 lockdowns, the most vulnerable populations are more likely to be affected.(99) Within the UK, lockdown measures exacerbated long-standing healthcare inequity, with females, older people, ethnic minorities and people from more deprived backgrounds being disproportionately impacted.(100) Investigating how lockdown restrictions impacted lung cancer treatments and outcomes is essential to planning future healthcare provision during both normal working and potential future public health emergencies.(101) By identifying any groups of people who were disproportionately disadvantaged from receiving lung cancer treatment during 2020, I hoped to identify those people who are most vulnerable.

The aims therefore, of this and the subsequent two chapters, are to describe how lung cancer treatments and survival changed in England in relation to national lockdown policy, and to identify any patient groups who were disproportionately affected. These results will help inform future policy in healthcare, to prioritise equitable care.

6.1.2 Changes in Guidance

During the pandemic, guidelines were adjusted to minimise potential risks of infection to patients and healthcare workers, as well as focusing clinical work towards the acute setting. Key adjustments in early-stage NSCLC included minimising bronchoscopy services with direct referral to treatment in high probability cases, and recommendation of SABR in preference to surgery where tumours were <2cm.(109, 110)

6.1.3 Aims

1. Describe the changes in radical treatment of NSCLC during COVID-19 restrictions of 2020 in England.

2. Describe changes in the lung cancer pathway from diagnosis to radical treatment during this time.
3. Identify any demographic features which increased risk of disrupting lung cancer treatment.

6.2 Methods

6.2.1 Rapid Cancer Registration Dataset

The RCRD differs from the usual NLCA data. The NLCA is usually reported using data from the NCRAS which is processed and collated from several national datasets.(249) The NLCA is considered to capture 100% of lung cancer cases presenting to secondary care.(250)

The COVID-19 pandemic drastically delayed the collation of this 'gold standard' dataset, and therefore the RCRD was extracted for 2019 and 2020 to allow timely observation of the impact of the pandemic on cancer services. Compared to the usual NLCA dataset, the RCRD was collated from fewer data sources, with death certificate only diagnoses not included, and will not match National Statistics data published in due course. As it is rapidly collated with reduced cross-checking, it is also more likely to include inaccuracies.(251)

The RCRD for 2019 was compared with quality assured data from 2018. In the assumption that the number of lung cancer cases in 2018 and 2019 were the same, 4300 people were missing from the 2019 RCRD.(98, 249) The majority of these were advanced stage or death certificate only diagnoses. It may therefore be assumed that the numbers reported for 2019 and 2020 are an underestimate of true cases in both years. To allow comparison with like-for-like data, I have compared the RCRD from 2020 with 2019, which was extracted in the same way.

For the purposes of these analyses, extracted data were: sex; age at diagnosis; WHO PS at diagnosis; comorbidity using Charlson index; index of multiple deprivation (IMD 1-5); stage at diagnosis according to TNM (Tumour

Nodal Metastases) 8th edition; tumour morphology; date of diagnosis; date of death; censor date; diagnosis trust; treatments including: SACT prescription, radiotherapy prescription, surgical procedures, and initial date of treatment. Age was divided into 3 categories: <65, 65-80, >80. Tumour type was divided according to histology into three categories: NSCLC not otherwise specified (NOS); adenocarcinoma; SCC. Time to treatment was measured from the diagnosis date to the first prescription of each respective treatment.

Final censor date was 7th October 2021, therefore any people diagnosed on or after 8th October 2020 will have had less than 1 year follow-up, with those diagnosed at the end of December 2020 only having data for the 9 months following diagnosis. The latest recorded date for surgery was 12th January 2021, radiotherapy 25th February 2021, and SACT 26th April 2021.

64462 people were included in the complete dataset for both 2019 and 2020 combined. Relevant demographics will be included for each population included in the separate analyses.

6.2.2 Analysis

6.2.2.1 Inclusion Criteria

Inclusion criteria were:

1. Aged 18 or over;
2. Diagnosed with NSCLC;
3. Between 1st January 2019 and 31st October 2020;
4. Stage I-IIIA at diagnosis.

6.2.2.2 Time Periods

The last recorded date of surgery was 12th January 2021 and radiotherapy was 25th February 2021. By restricting to diagnoses on or before 31st October I allowed around 10 weeks for surgical treatment. Where surgery predated diagnosis, diagnosis date was replaced with surgery date.

Data were divided into four time periods according to date of diagnosis, using key dates from lockdown guidance to determine groups (Table 1-4):

- 2019
- Pre-pandemic: January 1st – 25th March 2020
- 1st National Lockdown: 26th March - 10th May 2020
- Local Lockdowns: 11th May – 31st October 2020.

6.2.2.3 Classification of Radiotherapy

Radiotherapy prescriptions were quantified using consensus statements from the Royal College of Radiologists (RCR)(52). Prescriptions were considered as first-line treatment where the start date was within 90 days of diagnosis, and treatment was targeted to a lung primary with or without local nodes. They were classified using number of fractions and dosage in Gray into three categories: SABR, other radical intent radiotherapy, palliative (Table 6-1). Where prescriptions did not meet the defined criteria, Biologically Effective Dose (BED) was calculated, with prescriptions of BED >=100 classified as radical intent treatment, and <100 classified as palliative.(52, 252)

Table 6-1 Classification of radiotherapy prescriptions(52)

Type of Radiotherapy	Gray	Fractions
SABR	30-34	1
	48/54	3
	45-50	4
	45/50/55/60	5
	60	8
Other radical intent radiotherapy	40/50-60	15
	55	20
	45/50	25
	45/60	30
	66	33
	54	36
	>=55	20-33
Palliative	10	1
	17	2
	20	5
	30	10
	36	12
	39	13

6.2.2.4 Thoracic Surgery

Thoracic surgery was considered potentially curative in cases of pneumonectomy, wedge or sleeve resections and lobectomies or bi-lobectomies.

6.2.2.5 Analysis

Radical treatments were considered SABR, other radiotherapy with radical intent, or curative surgery.

Simple descriptive measures were used to compare demographics between time periods. Statistical significance was compared between the 1st National Lockdown and 2019. Continuous measures were compared using median and Wilcoxon log rank, and categorical using chi squared.

Trust size was divided into quartiles based on the number of lung cancer diagnoses annually by each trust in 2019: small trusts 2-197; medium 199-309; large 314-444; very large 461-733. This was to allow comparison between large and small trusts which may have been impacted differently by COVID.

The percentage of people who received each treatment was calculated for each time period. To allow comparison of actual numbers, treatments were also counted according to month of diagnosis as the time periods were uneven. Time to treatment was calculated from diagnosis date to date of first treatment in days.

Logistic regression was used to calculate odds ratios (OR) for treatment with surgery, radical radiotherapy and any curative intent treatment. Univariable analysis was first completed for each time period compared with 2019. Possible confounders of age, PS, sex, comorbidities, IMD, trust size and ethnicity were then adjusted for in turn, with those variables which showed an association (change in 10% of OR) included in the final analysis. The final multivariate analysis included age, sex, PS and comorbidities.

6.3 Results

6.3.1 Inclusion and Exclusion

Following the inclusion criteria detailed above, 21506 people were included in the analysis (Figure 6-1).

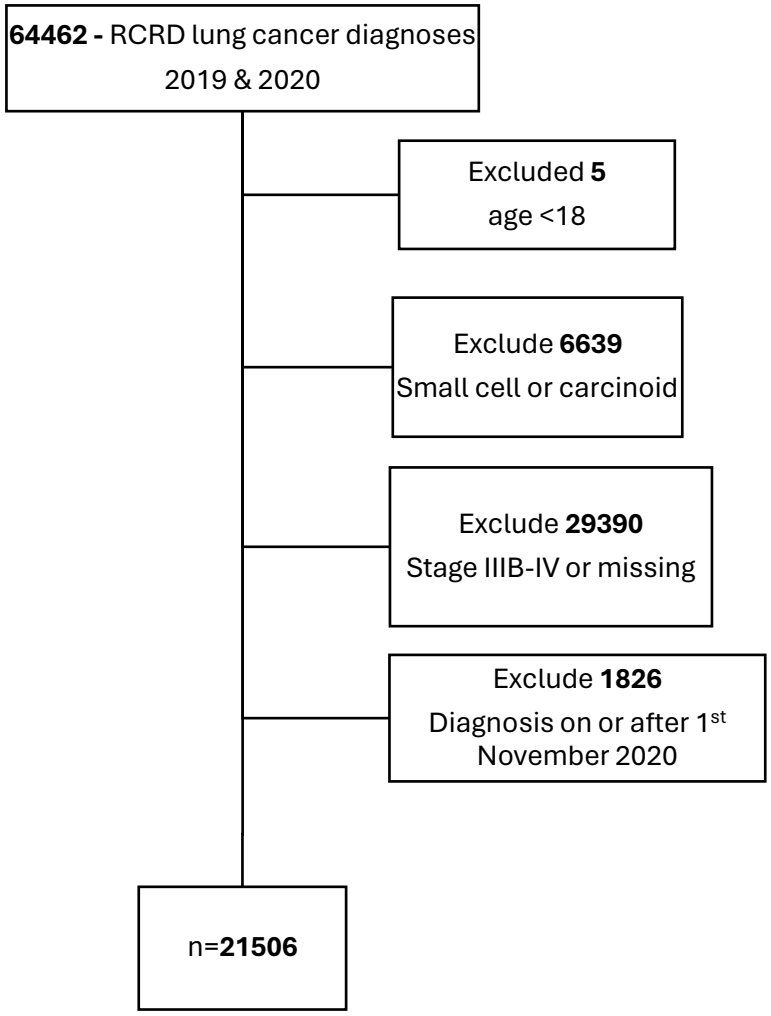


Figure 6-1 Inclusion and exclusion criteria for radical therapy analysis

6.3.2 Demographics

Demographics were largely as expected for the cohort (Table 6-2). There were no differences in demographics between the 1st National Lockdown and 2019. As the year progressed PS worsened, with 70% of people having PS 0-2 at diagnosis compared with 77% in 2019.

Table 6-2 Demographics of people diagnosed with stage I-IIIA NSCLC in England during 2019 and 2020. P-value compares 1st National Lockdown with 2019.

		2019	Pre-Pandemic	1st National Lockdown	Local Lockdown	*P-value*
Total	TOTAL	12,329	3,099	1,100	4,978	
Sex	Male	6,169	1,490	518	2,478	*0.061*
		50%	*48%*	*47%*	*50%*	
	Female	6,160	1,609	582	2,500	
		50%	*52%*	*53%*	*50%*	
Age	Median	74	73	73	75	*0.001*
	IQR	*67-80*	*67-80*	*66-79*	*68-71*	*1*
Stage	I	6,189	1,655	557	2,712	*0.500*
		50%	*53%*	*51%*	*54%*	
	II	2,558	626	240	903	
		21%	*20%*	*22%*	*18%*	
	IIIA	3,582	818	303	1,363	
		29%	*26%*	*28%*	*27%*	
PS	PS 0-2	9,487	2,344	817	3,485	*0.132*
		77%	*76%*	*74%*	*70%*	
	PS 0	3,224	787	289	1,088	*0.299*
		26%	*25%*	*26%*	*22%*	
	PS 1	4,300	1,037	352	1,543	
		35%	*33%*	*32%*	*31%*	
	PS 2	1,963	520	176	854	
		16%	*17%*	*16%*	*17%*	
	PS 3	1,498	400	145	761	
		24%	*24%*	*26%*	*28%*	
	PS 4	286	81	32	159	
		2%	*3%*	*3%*	*3%*	
	Missing	1,058	274	106	573	
		9%	*9%*	*10%*	*12%*	
Charlson	0	7,073	1,791	643	2,750	*0.326*
		57%	*58%*	*58%*	*55%*	
	1	2,015	521	194	919	
		16%	*17%*	*18%*	*18%*	
	2-3	2,261	564	185	893	
		18%	*18%*	*17%*	*18%*	
	4+	980	223	78	416	
		8%	*7%*	*7%*	*8%*	
Trust Size	Small	2,898	748	245	1,285	*0.004*
(Number	*(2-197)*	*24%*	*24%*	*22%*	*26%*	

of diagnoses in 2019)	Medium *(199-309)*	2,888	755	270	1,202	
		23%	*24%*	*25%*	*24%*	
	Large *(314-444)*	3,087	838	320	1,299	
		25%	*27%*	*29%*	*26%*	
	Very large *(461-733)*	3,456	758	265	1,192	
		28%	*24%*	*24%*	*24%*	
Ethnicity	White	11,246	2,786	989	4,459	*0.012*
		91%	*90%*	*90%*	*90%*	
	Black	146	32	12	63	
		1%	*1%*	*1%*	*1%*	
	Asian	182	58	16	75	
		1%	*2%*	*1%*	*2%*	
	Other	205	54	10	69	
		2%	*2%*	*1%*	*1%*	
	Missing	550	169	73	312	
		4%	*5%*	*7%*	*6%*	
IMD (1 least deprived)	1	1,714	397	123	741	*0.053*
		14%	*13%*	*11%*	*15%*	
	2	2,254	598	187	936	
		18%	*19%*	*17%*	*19%*	
	3	2,446	574	233	969	
		20%	*19%*	*21%*	*19%*	
	4	2,711	693	246	1,074	
		22%	*22%*	*22%*	*22%*	
	5	3,204	837	311	1,258	
		26%	*27%*	*28%*	*25%*	

6.3.3 Treatments

6.3.3.1 Stage I-II; PS 0-2

I note a fall from 58% to 51% of people who received surgery Pre-Pandemic when restrictions were yet to be introduced. This is likely due to people being diagnosed in this time period, but treatment occurring in subsequent weeks (i.e. during the 1st National Lockdown).

The percentage of people who received radical treatment of any kind during the 1st National Lockdown was unchanged compared with 2019 at 77% vs 76% (p=0.59) for people with stage I-II, PS 0-2 (Table 6-3). Whilst the total

percentage remained static, the composition changed with a decrease in surgery (58% to 51%; p=0.001) and compensatory increase in radical radiotherapy (18% to 26%; p<0.0001).

*Table 6-3 Percentage of people with NSCLC who received radical treatment during 2019 and 2020; *p-value compares 1st National Lockdown with 2019*

		2019	**Pre-Pandemic**	**1st National Lockdown**	**Local Lockdown**	***P-value***
Stage I-II; PS 0-2	Radical treatment	76%	72%	77%	73%	*0.590*
	Radio-therapy	18%	21%	26%	20%	*<0.0001*
	Surgery	58%	51%	51%	52%	*0.002*
Stage IIIA; PS 0-2	Radio-therapy	20%	29%	26%	23%	*0.103*
	Surgery	28%	22%	27%	24%	*0.625*
	SACT	54%	43%	49%	44%	*0.157*
Stage IIIA; PS 0-2	Radio-therapy & SACT	25%	35%	27%	26%	*0.739*
	Surgery & SACT	32%	22%	40%	29%	*0.086*

Whilst percentage of people treated radically remained steady, actual numbers treated dropped from April 2020 onwards (Figure 6-2). This was predominantly through a reduction in surgery with radiotherapy, particularly SABR, remaining roughly steady. Numbers of people receiving surgery began to increase again in June 2020, but had not reached pre-pandemic levels by October 2020.

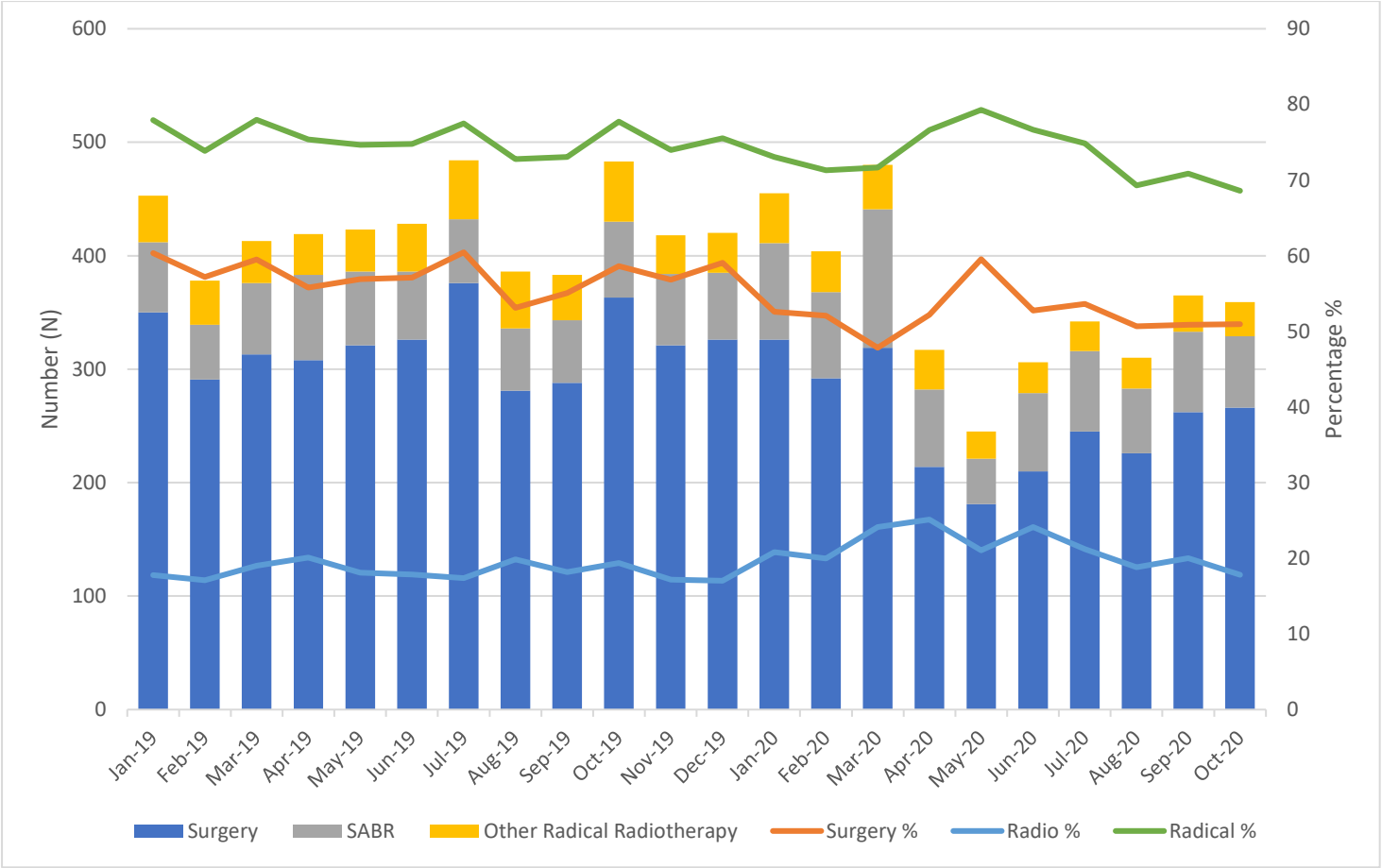


Figure 6-2 Numbers and percentage of people with Stage I-II PS 0-2 treated radically during 2019 and 2020

6.3.3.2 Stage IIIA

Stage IIIA NSCLC is treated with a range of multi-modality treatments including SACT and for this reason was considered separately.

Percentages of people receiving treatment did not change from 2019 to 1st National Lockdown (Table 6-3). There was however a decrease in SACT and surgery use during the Pre-Pandemic, combined with an increase in radiotherapy.

Considering the treatment of stage IIIA by month, again, overall treatment numbers decreased from April 2020 onwards. Radical radiotherapy was used increasingly in the Pre-Pandemic period, with treatment numbers exceeding those of surgery for those diagnosed in February and March 2020, and remaining equal from June until October 2020.

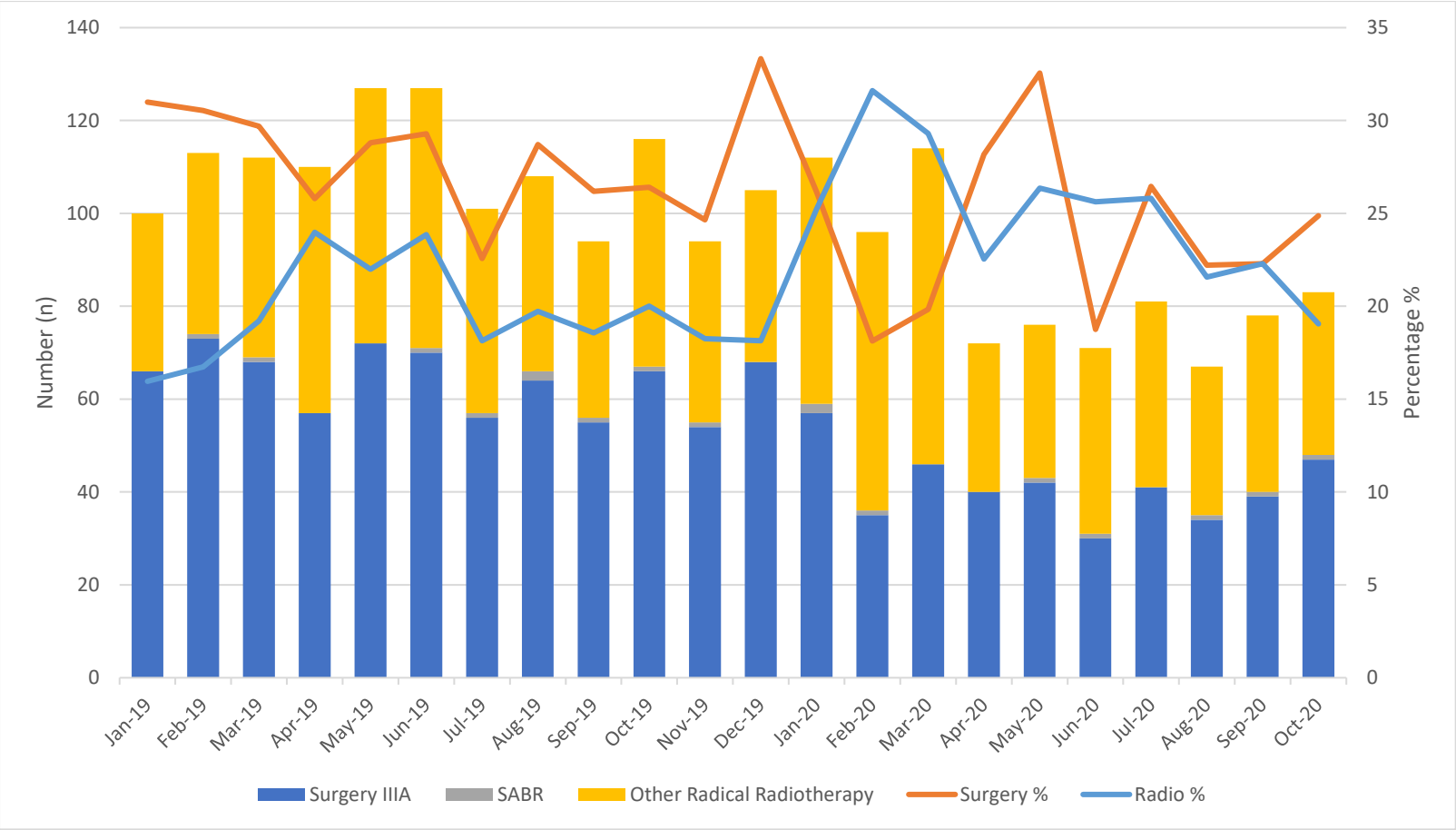


Figure 6-3 Numbers (left y axis) and percentage (right y axis) of people with stage IIIA PS 0-2 NSCLC who received radical treatment during 2019 and 2020.

6.3.4 Odds Ratios

The overall odds of receiving radical treatment of any type during the 1st National Lockdown was unchanged compared with 2019 (OR 0.96*; 95% CI 0.82-1.11*) (Table 6-4). When considered by separate therapies, the odds of receiving surgery were reduced during all time periods of 2020, with a compensatory increase in the odds of receiving radical radiotherapy. This was most pronounced during the 1st National Lockdown, where the OR for receiving radiotherapy was 1.62 *(95% CI 1.27-2.07)* and 0.69 for receiving surgery *(95% CI 0.0.59-0.80).*

Table 6-4 Univariable and multivariable analysis for receiving radical treatment during 2019 and 2020. Adjusted for age, sex, PS, stage and co-morbidities

		2019	Pre-Pandemic	1st National Lockdown	Local Lockdowns
All radical therapy	Univariable OR	1	0.93	0.97	0.83
	95% CI	-	*0.86-1.01*	*0.85-1.09*	*0.85-1.09*
	Multivariable OR	1	**0.89**	**0.96**	**0.90**
	95% CI	-	***0.81-0.98***	***0.82-1.11***	***0.83-0.97***
Radical radio-therapy	Univariable OR	1	1.27	1.70	1.69
	95% CI	-	*1.1-1.47*	*1.34-2.16*	*1.48-1.94*
	Multivariable OR	1	**1.24**	**1.62**	**1.63**
	95% CI	-	***1.06-1.44***	***1.27-2.07***	***1.42-1.87***
Surgery	Univariable OR	1	0.81	0.80	0.78
	95% CI	-	*0.75-0.88*	*0.70-0.91*	*0.73-0.83*
	Multivariable OR	1	**0.72**	**0.69**	**0.80**
	95% CI	-	***0.66-0.80***	***0.59-0.80***	***0.74-0.87***

Table 6-5 Univariable and multivariable analysis for receiving any radical treatment during 1st National Lockdown compared with 2019, stratified by demographics. Adjusted for age, sex, PS, stage and co-morbidities. P-value for interaction between variable and COVID-19 time period

All Curative Treatments		Uni-variable	95% CI	Multi-variable	95% CI	P-value
TOTAL	**-**	0.97	0.85-1.09	**0.96**	0.82-1.11	
Sex	Male	0.89	0.74-1.06	**0.87**	0.71-1.08	*0.0109*
	Female	1.04	0.87-1.24	**1.05**	0.85-1.30	
Charlson	0	1.1	0.92-1.30	**1.10**	0.89-1.35	*0.0006*
	1	0.72	0.54-0.97	**0.60**	0.43-0.85	
	2-3	0.71	0.52-0.96	**0.89**	0.62-1.28	
	4+	1.3	0.82-2.08	**1.30**	0.74-2.26	
PS	0	1.28	0.92-1.80	**1.19**	0.84-1.69	*<0.0001*
	1	1.09	0.86-1.39	**0.99**	0.77-1.26	
	2	1.06	0.78-1.44	**1.05**	0.76-1.46	
	3	0.47	0.23-0.97	**0.44**	0.21-0.93	
	4	.	-	**.**	-	
	Missing	0.72	0.49-1.08	**0.77**	0.50-1.20	
Age	<65	0.92	0.69-1.24	**1.01**	0.73-1.40	*0.0003*
	65-80	1	0.85-1.19	**1.04**	0.85-1.27	
	>80	0.75	0.56-0.99	**0.74**	0.53-1.03	
IMD (1 least deprived)	1	0.95	0.65-1.38	**0.84**	0.54-1.31	*0.4644*
	2	0.85	0.63-1.15	**0.80**	0.56-1.14	
	3	1.21	0.92-1.60	**1.22**	0.87-1.70	
	4	1.22	0.94-1.59	**1.24**	0.90-1.71	
	5	0.76	0.60-0.96	**0.77**	0.58-1.02	
Trust size	Small	0.95	0.73-1.24	**0.92**	0.66-1.27	*<0.0001*
	Med	0.89	0.70-1.15	**0.90**	0.66-1.21	
	Large	0.98	0.78-1.24	**1.09**	0.82-1.44	
	V large	1.09	0.84-1.41	**0.98**	0.72-1.34	
Stage	I	0.92	0.77-1.11	**0.86**	0.69-1.07	*<0.0001*
	II	0.98	0.75-1.29	**1.01**	0.73-1.40	
	IIIA	0.97	0.76-1.24	**1.09**	0.83-1.44	

Table 6-6 Univariable and multivariable analysis for receiving radiotherapy during 1st National Lockdown compared with 2019, stratified by demographics. Adjusted for age, sex, PS, stage and co-morbidities. P-value for interaction between variable and COVID-19 time period

Radio-therapy		Uni-variable	95% CI	Multi-variable	95% CI	*p-value*
TOTAL	**-**	1.7	1.34-2.16	**1.62**	1.27-2.07	
Sex	Male	1.6	1.15-2.22	**1.54**	1.09-2.16	*0.6443*
	Female	1.82	1.29-2.55	**1.72**	1.21-2.45	
Charlson	0	2.31	1.65-3.23	**2.16**	1.53-3.04	*0.3443*
	1	1.18	0.70-1.97	**1.08**	0.63-1.85	
	2-3	1.21	0.70-2.10	**1.34**	0.75-2.39	
	4+	1.16	0.52-2.61	**1.17**	0.50-2.72	
PS	0	1.77	1.06-2.93	**1.73**	1.04-2.89	*0.5997*
	1	2.39	1.62-3.53	**2.21**	1.49-3.30	
	2	1.02	0.65-1.61	**1.09**	0.67-1.78	
	3	0.53	0.20-1.37	**0.46**	0.16-1.32	
	4	.	-	**.**		
	Missing	11.03	1.44-84.67	**13.32**	1.68-105.51	
Age	<65	1.21	0.75-1.95	**1.19**	0.13-1.93	*0.0011*
	65-80	2.15	1.55-2.96	**2.00**	1.43-2.78	
	>80	1.43	0.83-2.48	**1.30**	0.73-2.31	
IMD (1 least deprived)	1	1.38	0.69-2.77	**1.46**	0.71-3.03	*0.6455*
	2	1.19	0.61-2.32	**1.20**	0.60-2.38	
	3	2.31	1.35-3.96	**2.24**	1.29-3.90	
	4	1.86	1.15-3.00	**1.74**	1.05-2.86	
	5	1.61	1.05-2.48	**1.47**	0.94-2.30	
Trust size	Small	1.36	0.80-2.30	**1.36**	0.79-2.35	*<0.0001*
	Med	1.33	0.83-2.12	**1.25**	0.77-2.08	
	Large	2.02	1.29-3.17	**2.18**	1.37-3.47	
	V large	2.27	1.39-3.70	**1.96**	1.18-3.24	
Stage	I	1.7	1.16-2.50	**1.73**	1.17-2.54	*0.0161*
	II	2.19	1.19-4.04	**2.27**	1.22-4.23	
	IIIA	1.42	0.97-2.08	**1.41**	0.95-2.07	

Table 6-7 Univariable and multivariable analysis for receiving surgery during 1st National Lockdown compared with 2019, stratified by demographics. Adjusted for age, sex, PS, stage and co-morbidities. P-value for interaction between variable and COVID-19 time period

Surgery		Uni-variable	95% CI	Multi-variable	95% CI	*p value*
TOTAL	**-**	0.8	0.70-0.91	**0.69**	0.59-0.80	
Sex	Male	0.72	0.60-0.88	**0.62**	0.50-0.78	*0.0168*
	Female	0.86	0.72-1.02	**0.76**	0.61-0.93	
Charlson	0	0.89	0.76-1.05	**0.76**	0.62-0.92	*0.0797*
	1	0.56	0.41-0.78	**0.44**	0.30-0.63	
	2-3	0.58	0.41-0.82	**0.67**	0.44-1.01	
	4+			**0.97**	0.50-1.90	
PS	0	1.03	0.79-1.34	**0.92**	0.69-1.22	*0.0311*
	1	0.67	0.53-0.84	**0.56**	0.44-0.71	
	2	0.84	0.54-1.29	**0.79**	0.51-1.24	
	3	0.39	0.05-2.92	**0.37**	0.05-2.80	
	4	.	-	**.**	-	
	Missing	0.61	0.41-0.92	**0.6**	0.38-0.96	
Age	<65	0.8	0.61-1.05	**0.54**	0.61-1.15	*0.0459*
	65-80	0.8	0.68-0.94	**0.72**	0.59-0.87	
	>80	0.43	0.27-0.69	**0.39**	0.24-0.64	
IMD (1 least deprived)	1	0.84	0.58-1.22	**0.68**	0.43-1.06	*0.3932*
	2	0.94	0.69-1.27	**0.88**	0.61-1.27	
	3	0.81	0.62-1.07	**0.70**	0.50-0.97	
	4	0.93	0.71-1.21	**0.77**	0.55-1.07	
	5	0.62	0.48-0.81	**0.55**	0.41-0.75	
Trust size	Small	0.9	0.69-1.17	**0.79**	0.56-1.10	*<0.0001*
	Med	0.77	0.59-1.00	**0.69**	0.51-0.95	
	Large	0.75	0.59-0.96	**0.71**	0.53-0.95	
	V large	0.8	0.61-1.03	**0.59**	0.44-0.80	
Stage	I	0.7	0.59-0.84	**0.56**	0.46-0.69	*0.0922*
	II	0.94	0.72-1.22	**0.88**	0.64-1.23	
	IIIA	0.81	0.61-1.0	**0.86**	0.62-1.18	

When considering individual patient groups, there were no demographic features which significantly altered the adjusted OR for receiving curative therapy on either type (Table 6-5). When considering the two treatments separately, some groups did have differing odds (Tables 6-6 and 6-7). People with stage I disease had lower odds of receiving surgery (OR 0.56; 95% CI 0.46-0.69) during 1st National Lockdown than in 2019. There was no difference in OR for people diagnosed with stage II disease (OR 0.88; 95% CI 0.64-1.23). The oldest group (aged over 80) were also less likely to receive surgery than they were in 2019 (OR 0.39; 95% CI 0.24-0.64). People diagnosed at larger trusts had increased odds of receiving radical radiotherapy, whereas those at the smallest trust had no difference in OR compared with 2019 (very large – OR 1.96; 95% CI 1.18-3.24; small – OR 1.36; 95% CI 0.79-2.35).

6.3.5 Time to Treatment

The median time from diagnosis to treatment was consistently shorter for surgery than radical radiotherapy at 22-29 days compared with 42-49 days. This may be an artefact of diagnosis date in surgical patients occurring on or post-surgery in cases where people did not have a pre-operative biopsy. The percentage of people whose diagnosis date occurred post-operatively increased towards the end of 2020; 23% in 2019, 24% Pre-Pandemic, 22% during 1st National Lockdown, and 29% during Local Lockdowns.

Time to treatment was shorter for both treatments during all times of 2020 and shortest during 1st National Lockdown. Compared with 2019, surgery occurred on average 5 days earlier (24 vs 29 days; $p<0.0001$) and radical radiotherapy 7 days earlier (42 vs 49 days; $p<0.0001$).

6.3.5.1 Biopsy and method of diagnosis

The percentage of people treated with radical radiotherapy who were diagnosed using cytology or histopathology, significantly decreased from 2019 to the 1st National Lockdown (46% to 33%; $p=0.009$) (Table 6-8) suggesting fewer people were biopsied prior to treatment during the pandemic. This is

also true for people treated with surgery (93% to 89%; p=0.002) although this will include intra-operative histopathology samples.

Table 6-8 Diagnosis method during 2019 and 2020. P-value compares 1st National Lockdown with 2019.

		2019	Pre-COVID	1st National Lockdown	Local Lockdowns	*P-value*
Radio-therapy	Clinical Diagnosis	52%	50%	64%	64%	*0.009*
	Histo-pathology	46%	49%	33%	34%	
	Unknown	2%	1%	3%	3%	
Surgery	Clinical Diagnosis	5%	6%	8%	7%	*0.002*
	Histo-pathology	93%	92%	89%	89%	
	Unknown	2%	2%	2%	4%	

6.4 Discussion

6.4.1 Key Findings

Radical treatment of NSCLC was well maintained during lockdowns in 2020. Whilst overall treatment numbers fell, this was due to the lower numbers of people being diagnosed with early-stage lung cancer, with the percentage of fit people treated well maintained. The composition of treatment did change however, with people being more likely to receive radical radiotherapy, and less likely to receive surgery, compared with 2019.

Whilst no patient groups were particularly disadvantaged from receiving radical treatment, people with stage I disease were less likely to receive surgery whilst the odds were maintained for people with stage II disease. In addition, the oldest patients were less likely to receive surgery. This suggests there may have been risk averse behaviour amongst clinicians, with those people who either may not benefit, or more likely to be harmed, not receiving surgical therapy. People diagnosed in the largest trusts were more likely to receive radical radiotherapy, whilst in the smaller trusts the odds were unchanged compared with 2019.

In addition, the cancer pathway was altered in 2020, with shorter time to treatment during lockdowns. Fewer people treated with radical radiotherapy

were diagnosed using histopathology, suggesting fewer biopsies were conducted during the pandemic.

Whilst generally treatments were maintained for those diagnosed with early-stage disease, it should be noted that actual numbers treated fell as fewer people were diagnosed at an early-stage who were fit enough for treatment.(97) Therefore, regardless of the efforts made, a large number of people who in previous years would have received curative intent treatment did not, either never presenting and dying before diagnosis, or presenting with more advanced disease or unfit for treatment.

6.4.2 Previous Work in the Literature

To our knowledge, this is the first study looking at radical treatment for all people diagnosed with early-stage lung cancer on a national level during the pandemic. Most studies to date have been small, single centre retrospective observational studies, and all only looked at either surgery or radiotherapy, rather than treatments in combination. Owing to the international variation in COVID-19 cases and restrictions, there is also variation in treatment rates. A national analysis from Poland showed a relative 32% reduction in lung cancer surgeries during their largest COVID-19 wave.(253) A French nationwide study of discharges following lung cancer surgery showed a much smaller reduction (12,227 operations to 11,634).(254) In contrast, single centre Chinese, American, Japanese and Spanish studies, all showed no change in surgical treatment rates.(255-258) A state-wide retrospective study from Illinois, America, actually showed a relative 26.4% increase in lung cancer surgeries during 2020, whilst other cancer surgeries for colorectal and breast, decreased.(259)

In the case of radical radiotherapy, one single centre retrospective German study found significantly increased number of SABR patients per month during 2020 than prior to COVID-19.(260) Initial results of a multicentre UK prospective study (COVID-RT Lung) found 34% of curative-intent radiotherapy

prescriptions were altered from the pre-COVID standard of care, with 9.5% of stage I-II patients receiving radical radiotherapy instead of surgery.(261)

In the literature, there is also variation in time to treatment, although it should be noted that definitions varied, with some studies including time to diagnosis, and others measuring time from diagnosis to treatment. Generally, time to surgery was increased (257, 262) or unchanged.(256, 263) Where reported, nearly all studies found a longer time to diagnosis, or delayed presentation to healthcare.(262, 264) In contrast, a national study from the Netherlands found time to diagnosis was significantly shorter during the pandemic, which they attributed to the decreased number of patients presenting.(265) In the United States, guidance recommended delaying surgical treatment of nodules <2cm for 3 months to allow reduction of COVID-19 cases.(103) Balancing the high mortality from COVID-19 infection in people with lung cancer against the risk of worse survival from delayed resection is key.(266, 267) Modelling suggests delaying treatment would improve 5-year overall survival during times with high COVID-19 infection rates, but be detrimental if community infection rates were low.(268)

In this study, time to treatment from diagnosis decreased for both treatment with surgery and radical radiotherapy, by 5 and 7 days respectively ($p<0.0001$; $p<0.0001$), although time to diagnosis was not measured. The reasons for this are likely multi-factorial as fewer people were diagnosed during this period meaning waiting lists may have been shorter. In addition, the lung cancer pathway was streamlined with emphasis on reducing the exposure risks of patients and staff to COVID. This included avoiding full PFTs where spirometry was adequate, and treating without pathological confirmation where the lung cancer probability was high, based on the Herder score.(109) On validation in a UK cohort, the Herder model demonstrated good accuracy (AUC 0.924).(269) This study confirmed that fewer people had histopathological diagnosis prior to radiotherapy during National Lockdown, with similar results from prospective UK data, where 12% of radical radiotherapy patients had variation in their diagnostic pathway, most commonly no biopsy before

treatment.(261) Evidence suggests this does not affect SABR treatment outcomes, with the same overall survival in people with or without pathology.(270, 271)

6.4.3 Strengths and Weaknesses

To our knowledge, this is the first study looking at national changes in treatment patterns for lung cancer during the COVID pandemic, with previous work looking at one trust or region. Given the scarcity of evidence at the beginning of the pandemic, guidance varied between countries. There was also variation in infection rates and restrictions both internationally and within the UK, making national research divided by COVID restrictions essential.

A potential bias of this research is the exclusion missing stage data from the analysis. This accounted for 5581 people, less than 9% of the original dataset. Analyses were not conducted to establish whether these data were missing completely at random or if they were more frequently missing from certain groups. For example, trusts which experienced particularly high cases of COVID or trusts where services were struggling to maintain cancer services, may have subsequently uploaded incomplete cancer registry data. In this case, these results would potentially under-report the true impact of COVID.

Unfortunately, the dataset does not provide data on when people first presented to cancer services, therefore I cannot compare the overall pathway length, instead comparing time from diagnosis to treatment. I am therefore unable to comment on whether people delayed presentation to services or longer time to diagnosis, both of which were found to be prolonged in other studies.(262, 264)

By dividing the data according to lockdown time periods, I have been able to demonstrate how national lockdown policy impacted treatment. However, these time periods do vary in length, and therefore have different patient numbers in each group. To compensate for this, I also presented treatment numbers by month. I was also limited by the final entry date for treatments,

particularly surgery. This prevented analysis of November and December 2020, which coincided with a second peak in COVID cases and further national lockdowns and should be reviewed when similar follow-up data is available.

6.4.4 Clinical Relevance and Conclusions

Surgery is currently the standard of care for management of early-stage NSCLC, with SABR recommended in inoperable cases or as patient choice.(35) Retrospective data suggests superior survival from surgery, however these results are biased through inclusion of those people not fit enough for surgery.(272) Small but randomised control trials suggest a 3-year survival of 91-95% following SABR, which is similar to thoracic surgery outcomes.(123, 124) Moving forwards, examining outcomes of those people who received radiotherapy but would have been considered 'operable' prior to the pandemic would be of interest.

The relative increase in radical radiotherapy reported here may impact long term outcomes for those people who would be considered 'operable' outside of the pandemic. COVID-RT-Lung concluded that in the UK, male patients, age over 70 and stage III disease all predicted a change to radiotherapy treatment from the standard of care.(261) Generally in the UK, more healthcare disruption during COVID-19 was reported amongst females, more deprived, older people and ethnic minorities.(100) It is reassuring that this study did not identify any particular groups within early-stage NSCLC who had unmet needs exacerbated by the pandemic.

Whilst no demographic groups were identified here as being particularly disadvantaged to receiving radical treatment, large trusts had increased odds of prescribing radiotherapy. This may be due to the varied impact of COVID between trusts, or uneven distribution of radiotherapy services even before the pandemic. In 2019 58% of NHS radiotherapy centres delivered lung SABR.(273) This was expanded during 2020, with the aim of a full rollout by April 2021.(274) More recent data on distribution is not available but the UK Lung Cancer Coalition identified key targets for improving lung cancer care,

particularly equity of access to SABR and surgery.(84) In order to achieve national targets of 25% 5-year survival by 2025, radical therapy needs to be accessible by all.

6.5 Chapter Summary and Key Points

- This chapter examined how radical treatment of early-stage NSCLC was impacted by social restrictions of the COVID-19 pandemic in 2020.
- Radical radiotherapy use increased where thoracic surgery declined.
- No patient groups were particularly disadvantaged, but radical radiotherapy was affected by trust size, with increased availability in larger trusts.

Chapter 7. The Impact of the SARS-CoV-2 Pandemic on the use of Systemic Anti-Cancer Therapy of Non-Small Cell Lung Cancer in England: An Analysis of the Rapid Cancer Registration Dataset

Using the RCRD, the chapter examines the impact COVID-19 had on SACT use as well as exploring whether any people were disadvantaged by the pandemic to a greater extent than others.

7.1 Introduction

7.1.1 Background

The beginning of the COVID-19 pandemic and national restrictions implemented in 2020 impacted how people presented to lung cancer services. In addition to fewer diagnoses overall, a slight stage shift was observed, with a 1% increase in stage IV diagnoses to 44% in 2020 compared with 2019.(98) This stage shift potentially resulted in more people being suitable for treatment with SACT. However, the accompanying 5% reduction in PS 0-1 to 47% may have restricted people suitable for treatment.(98)

Alongside the policy changes which affected diagnosis, UK national guidance on the treatment of cancers changed to reflect the potential risks of immunosuppression. NICE recommended prioritising SACT for conditions with a high chance of cure.(275) Treatment for advanced stage NSCLC focuses on disease control rather than cure, meaning these people would not be prioritised if healthcare restrictions were required. However, as SACT offers a survival advantage and reduced symptom burden, it should be used to improve quality and quantity of life. As previously described in Chapter 6, it is important to identify whether any particular groups of people with advanced stage NSCLC were disproportionately disadvantaged, as this has implications for future healthcare provision and planning.

Finally, with the recent advent of novel SACT for NSCLC in the form of targeted and immunotherapies, there have been frequent changes in guidance over the last decade. Given the initial limited evidence and uncertainty of pandemic duration and impact, guidelines during 2020 were frequently updated, providing the opportunity to examine how efficiently guideline changes are implemented in clinical practice.

7.1.2 Change in SACT Guidance

In the case of NSCLC, specific guidance was released including recommending single agent immunotherapy over combined chemo-immunotherapy (Table 7-1). In addition, SACT guidance was significantly changed during 2019 with

combined chemo-immunotherapy being introduced via the Cancer Drugs Fund (CDF) in May and October for non-squamous NSCLC and November 2019 for SCC, regardless of PD-L1 status.(276-278)

Table 7-1 Adjustments to SACT guidelines for NSCLC during the COVID-19 pandemic

Guidelines for SACT
2019
Non-squamous 6 **Targeted treatments** for EGFR and ALK positive(279-285) Squamous or non-squamous Single agent **immunotherapy** Pembrolizumab for PD-L1≥50%(63) Combined **chemo-immunotherapy** PD-L1<50% (added in January, June and September 2019)(276-278) Platinum doublet **chemotherapy** alone(286)
'Pre-Pandemic' - 1st January 2020 - 25th March 2020
22/01/20 - Osimertinib approved for untreated EGFR positive non-squamous(287)
'1st National Lockdown' - 26th March 2020 - 10th May 2020
26/03/20 - Prioritise chemotherapy for treatment with curative intent - Choose single agent immunotherapy over combined chemo-immunotherapy - Single agent Pembrolizumab use extended to PD-L1<50%(114) - Single agent Atezolizumab approved for use in PD-L1<50%(107) - Dabrafenib plus tametinib for BRAF positive metastatic disease(114) - GCSF recommended for most myelosuppressive regimes
'Local Lockdowns' - 11th May 2020 - 7th October 2020
12/08/20 - Entrectinib for ROS-1 positive non-squmaous(288)
'Late 2020' - 08th October 2020 – 31st December 2020
No changes made

7.1.3 Aims

1. To describe changes in SACT use for NSCLC in England during the COVID-19 restrictions of 2020.
2. Identify any demographic groups who were disproportionately disadvantaged from receiving SACT.

7.2 Methods

7.2.1 Rapid Cancer Registration Dataset

The RCRD is described in detail in Chapter 6.2.1. It is key to note that the RCRD for 2019 failed to capture 4300 diagnoses compared with traditional NLCA methods of data collection.(289) A similar number is presumed to be missing from 2020 data. The majority of these were advanced stage or death certificate only diagnoses, which is relevant to the cohort included in this analysis.

Extracted data are as described in 6.2.1. As previously, censor date and therefore duration of follow-up varied, however the latest date of entry for SACT data was 26th April 2021, therefore all treatments analysed must have occurred before this time. The final censor date was 7th October 2021, meaning people diagnosed on or after 8th October 2020 do not have a full year of follow-up.

7.2.2 Analysis

7.2.2.1 Inclusion Criteria

Inclusion criteria were:

1. Aged 18 or over;
2. Diagnosed with NSCLC;
3. Between 1st January 2019 and 31st October 2020;
4. Stage IIIB-IVB at diagnosis.

Exclusion criteria were:

1. Death or treatment date precedes diagnosis date.

7.2.2.2 Time Periods

People were divided according to COVID-19 restrictions at the time of diagnosis, as detailed in Table 1-4. People diagnosed on or after 8th October 2020 were considered separately owing to the shorter follow-up time of less than 1 year.

7.2.2.3 Statistical Methods

Data were analysed using STATA/SE 17.0 (StataCorp LLC, Texas). Patients were categorised using PS, grouped into 0-1 and 2-4, with PS 0-1 being considered eligible for treatment. SACT prescriptions were compared to national guidance for first-line treatment of NSCLC provided by NICE during 2019 and 2020. Prescriptions were categorised into four categories: targeted treatments, single agent immunotherapy, combined chemo-immunotherapy, and platinum doublet chemotherapy alone. SACT drugs not recommended by NICE for first-line treatment of advanced NSCLC were classified as 'other SACT'.

Demographics were compared across time periods. For tests of statistical significance, 2019 was used as reference group and compared to the 1st National Lockdown. Percentages of eligible patients (PS 0-1) prescribed each type of SACT were calculated for each time period. Logistic regression was used to calculate odds ratios (OR) for receiving SACT of any type during each time period, using 2019 as the reference group. As described in section 6.2.2.5, univariable analysis was first conducted. Possible confounders were sequentially adjusted for in the multivariable models with changes in 10% of OR being considered significant. The final model was adjusted for age, sex, PS and comorbidities. For the period of the 1st National Lockdown, unadjusted and adjusted OR were calculated for stratified exposure variables and tested for interactions: sex, age, PS, IMD, comorbidities, trust size and lung cancer morphology.

Patient factors were compared between prescriptions of chemotherapy alone and in combination with immunotherapy for the final period of 2020. This period was selected as it was the most recent and contemporaneous guidance was closest to current practice.

7.3 Results

7.3.1 Inclusion and Exclusion Criteria

The initial RCRD dataset included 64462 people diagnosed with any type of lung cancer between 1st January 2019 and 31st December 2020. Following exclusions as described in Figure 7-1, a total of 29296 individuals were included in the final dataset for analysis.

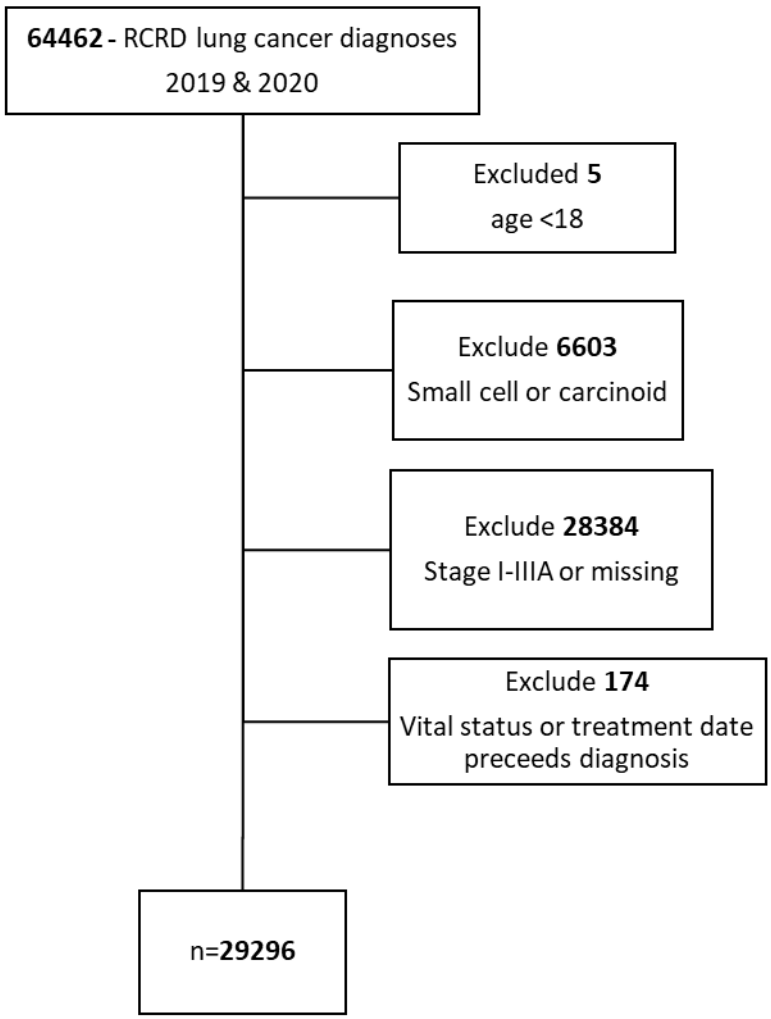


Figure 7-1 Inclusion and exclusion criteria

7.3.2 Demographics

Demographics were broadly similar between all time periods, and representative of the usual cohort, with a median age of 73 throughout and slight male predominance (range from 54%-57%) (Table 7-2). Both PS and stage at diagnosis varied between time periods. More people were diagnosed

at the most advanced stage IV-B, both during and after the 1st National Lockdown, making up 42-43% of diagnoses compared with 39% in 2019. In addition, people tended to be less fit, with PS 0-1 falling from 46% to 40% by the end of 2020. Cancer morphology was more frequently NOS during 1st National Lockdown at 53% compared with 44% in 2019 ($p<0.0001$). Finally, distribution of trust size varied throughout 2020. Relatively fewer people were diagnosed at the largest trusts during lockdown, with more in the smallest trusts.

Table 7-2 Demographics divided by COVID-19 restrictions at time of diagnosis. P-value compares 1st National Lockdown with 2019

	2019	**Pre-Pandemic**	**1st National Lockdown**	**Local Lockdown**	**Late 2020**	***P-value***
TOTAL	14,912	3,500	1,460	6,125	3,299	
	100%	*100%*	*100%*	*100%*	*100%*	
Sex						*0.127*
Male	8,126	1,959	826	3,286	1,778	
	54%	*56%*	*57%*	*54%*	*54%*	
Female	6,786	1,540	634	2,837	1,521	
	46%	*44%*	*43%*	*46%*	*46%*	
Missing	0	1	0	2	0	
		0.03%		*0.03%*		
Age						*0.1056*
Median	73	73	73	73	73	
IQR	*65-80*	*65-79*	*65-79*	*65-80*	*66-80*	
Stage						*0.037*
IIIB	1,705	421	136	606	327	
	11%	*12%*	*9%*	*10%*	*10%*	
IIIC	912	203	84	308	201	
	6%	*6%*	*6%*	*5%*	*6%*	
IV	12,295	2,876	1,240	5,211	2,771	
	82%	*82%*	*85%*	*85%*	*84%*	
PS						*0.099*
PS 0	2,393	614	206	777	438	
	16%	*18%*	*14%*	*13%*	*13%*	
PS 1	4,401	1,015	435	1,696	884	
	30%	*29%*	*30%*	*28%*	*27%*	
PS 2	2,521	588	264	1,087	525	
	17%	*17%*	*18%*	*18%*	*16%*	
PS 3	3,210	740	335	1,395	733	
	22%	*21%*	*23%*	*23%*	*22%*	
PS 4	1,213	277	98	562	250	
	8%	*8%*	*7%*	*9%*	*8%*	
Missing PS	1,174	266	122	608	469	
	8%	*8%*	*8%*	*10%*	*14%*	
Morphology						*<0.0001*
Adeno-carcinoma	5,786	1,328	517	2,223	1,211	
	39%	*38%*	*35%*	*36%*	*37%*	
SCC	2,547	602	173	844	469	
	17%	*17%*	*12%*	*14%*	*14%*	

NSCLC	6,579	1,570	770	3,058	1,619	
NOS	*44%*	*45%*	*53%*	*50%*	*49%*	
Charlson Index						*0.376*
0	10,688	2,478	1,054	4,394	2,424	
	72%	*71%*	*72%*	*72%*	*73%*	
1	1,732	467	161	742	378	
	12%	*13%*	*11%*	*12%*	*11%*	
2-3	1,810	391	166	718	358	
	12%	*11%*	*11%*	*12%*	*11%*	
4+	682	164	79	271	139	
	5%	*5%*	*5%*	*4%*	*4%*	
Ethnicity						*0.261*
White	13,138	3,057	1,269	5,317	2,814	
	88%	*87%*	*87%*	*87%*	*87%*	
Black or	198	46	21	63	44	
mixed	*1%*	*1%*	*1%*	*1%*	*1%*	
Asian or	246	57	18	88	51	
mixed	*2%*	*2%*	*1%*	*1%*	*2%*	
Other	291	69	27	112	41	
	2%	*2%*	*2%*	*2%*	*1%*	
Missing	979	239	115	501	294	
	7%	*7%*	*8%*	*8%*	*9%*	
IMD						*0.646*
1 (Least	2,168	516	232	850	504	
deprived)	*15%*	*15%*	*16%*	*14%*	*15%*	
2	2,779	660	278	1,188	601	
	19%	*19%*	*19%*	*19%*	*18%*	
3	2,963	742	286	1,191	657	
	20%	*21%*	*20%*	*19%*	*20%*	
4	3,237	708	304	1,349	720	
	22%	*20%*	*21%*	*22%*	*22%*	
5 (Most	3,765	874	360	1,547	817	
deprived)	*25%*	*25%*	*25%*	*25%*	*25%*	
Trust Size (Number of diagnoses in 2019)						***<0.0001***
Small	3,789	1,017	469	1,805	949	
(2-197)	26%	29%	32%	30%	29%	
Medium	3,669	923	349	1,585	845	
(199-309)	26%	27%	24%	26%	26%	
Large	3,672	790	361	1,475	836	
(314-444)	26%	23%	25%	24%	26%	
Very large	3,182	748	266	1,199	649	
(461-733)	22%	22%	18%	20%	20%	

7.3.3 Overall SACT Prescriptions

The percentage of people with PS 0-1 prescribed SACT of any type was lower for each time period of 2020, compared with 2019 (Table 7-3). Prescriptions during the Pre-Pandemic period reduced to 58% from 63% in 2019 which is likely due to people being grouped by diagnosis date, and therefore a portion of these people being diagnosed in the Pre-Pandemic period but commencing treatment after the beginning of the pandemic in the UK. During the 1st National Lockdown 57% of eligible people were prescribed SACT of any type, a significant decrease from 2019 ($p=0.006$). There was national variation, with prescriptions ranging between cancer alliances from 49%-76% in 2019 to 41-72% during Lockdown. The lowest percentage of prescriptions was seen during the final three months of 2020, at 54% of people with PS 0-1 ($p<0.0001$, compared with 2019).

The median time from diagnosis to SACT prescription was largely unchanged from 2019 to the 1st National Lockdown at 35 days in 2019 (IQR 26-51 days) compared with 34 days (IQR 23-49 days) ($p=0.0706$). Throughout 2020, median time to treatment ranged from 34 to 37 days, being longest in the Pre-Pandemic period.

Table 7-3 Number and percentage of people prescribed SACT during 2019 and 2020 divided by COVID-19 restrictions at time of diagnosis

	2019			**Pre-Pandemic**			**1st National Lockdown**			**Local Lockdowns**			**Late 2020**		
	N (total)	**N (PS 0-1)**	**% PS 0-1**	**N (total)**	**N (PS 0-1)**	**% PS 0-1**	**N (total)**	**N (PS 0-1)**	**% PS 0-1**	**N (total)**	**N (PS 0-1)**	**% PS 0-1**	**N (total)**	**N (PS 0-1)**	**% PS 0-1**
Total numbers diagnosed	**14912**	**6794**	**-**	**3500**	**1629**	**-**	**1460**	**641**	**-**	**6125**	**2473**	**-**	**3299**	**1322**	**-**
Total SACT	5,335	4,267	63%	1,166	942	58%	467	367	57%	1,898	1,453	59%	987	720	54%
Chemo	2,048	1,588	23%	338	268	16%	131	108	17%	567	424	17%	304	220	17%
Chemo-io	851	738	11%	255	227	14%	96	78	12%	389	321	13%	240	187	14%
Immuno	1,093	886	13%	249	201	12%	123	90	14%	448	335	14%	211	145	11%
Targeted	649	511	8%	189	141	9%	61	46	7%	275	204	8%	162	120	9%
Other	694	544	8%	135	105	6%	56	45	7%	219	169	7%	70	48	4%

Table 7-4 OR for being prescribed SACT divided by COVID-19 restrictions at time of diagnosis. Adjusted for age, sex, comorbidities and PS

	2019	Pre-Pandemic	1st National Lockdown	Local Lockdowns	Late 2020
Unadjusted OR	**1**	0.90	0.84	0.81	0.77
95% CI	**-**	*0.83-0.97*	*0.75-0.95*	*0.76-0.86*	*0.71-0.83*
Adjusted OR	**1**	**0.80**	**0.82**	**0.85**	**0.76**
95% CI	**-**	***0.72-0.88***	***0.74-0.94***	***0.79-0.92***	***0.69-0.84***

A small but significant decrease in odds of receiving SACT of any type was observed for all time periods throughout 2020 (Table 7-4). This includes the Pre-Pandemic period (OR 0.80; 95% CI 0.72-0.88). The OR were lowest during Late 2020 (OR 0.76; 95% CI 0.69-0.84).

7.3.4 Odds Ratios by Demographic Features

On stratifying OR to receive SACT during 1st National Lockdown by demographic features, older people were less likely to receive SACT during 1st National Lockdown than in 2019, with an adjusted OR=0.58 (95% CI 0.36-0.92) in over 80-year-olds, and OR=1.04 (95% CI 0.81-1.34) for people aged less than 65, however this interaction was not significant (p=0.5287) (Table 7-5). There was a significant interaction between COVID-19 period and trust size (p<0.0001), however 95% CI for each trust size approached or included 1 indicating there was no difference in SACT prescription when stratified by size of trust. No other demographic groups were identified who were comparatively disadvantaged during National Lockdown.

Table 7-5 OR for being prescribed SACT during the 1st National Lockdown compared with 2019 for exposure variables. Adjusted for age, sex, co-morbidities and PS. P-value for interaction between diagnosis period and key variable.

	Exposure	Uni-variable	95% CI	Multi-variable	95% CI	P-value
TOTAL	**2019**	**1**	**-**	**1**	**-**	
	Lockdown	0.84	*0.75-0.95*	**0.82**	0.74-0.94	
Sex	Male	0.85	0.73-1.00	**0.84**	0.70-1.01	*0.5287*
	Female	0.83	0.70-0.99	**0.80**	0.65-0.98	
Comorbid-ity	0	0.79	0.69-0.90	**0.81**	0.69-0.95	*0.2646*
	1	1.14	0.81-1.61	**1.00**	0.66-1.50	
	2-3	0.95	0.65-1.39	**0.71**	0.45-1.12	
	4+	1.00	0.48-2.07	**0.79**	0.33-1.87	
PS	0	0.90	0.65-1.23	**0.93**	0.67-1.29	*0.5637*
	1	0.77	0.63-0.94	**0.76**	0.62-0.94	
	2	0.84	0.62-1.15	**0.79**	0.57-1.09	
	3	0.81	0.42-1.55	**0.69**	0.36-1.35	
	4	.	.	**.**	.	
	Missing	1.00	0.66-1.50	**1.1**	0.70-1.72	
Age	<65	0.88	0.71-1.10	**1.04**	0.81-1.34	*0.8771*
	65-80	0.79	0.67-0.92	**0.77**	0.64-0.92	
	>80	0.66	0.43-1.01	**0.58**	0.36-0.92	
IMD (1 least deprived)	1	0.65	0.49-0.87	**0.6**	0.42-0.84	*0.2384*
	2	0.95	0.73-1.23	**0.9**	0.66-1.23	
	3	0.72	0.55-0.94	**0.72**	0.52-0.99	
	4	0.95	0.75-1.22	**0.99**	0.73-1.34	
	5	0.92	0.72-1.16	**0.87**	0.65-1.16	
Trust size	Small	0.87	0.70-1.08	**0.78**	0.60-1.01	*<0.0001*
	Med	0.84	0.67-1.06	**0.83**	0.63-1.09	
	Large	0.86	0.69-1.08	**0.94**	0.72-1.23	
	V large	0.82	0.63-1.08	**0.71**	0.51-0.99	
Stage	IIIB	0.80	0.56-1.14	**0.74**	0.48-1.15	*0.9055*
	IIIC	0.86	0.55-1.35	**0.85**	0.48-1.50	
	IV	0.86	0.76-0.98	**0.83**	0.71-0.96	

7.3.5 Trends in Specific SACT Types

The pattern of prescriptions varied throughout both years (Table 7-3 and Figure 7-2). Prior to COVID, from January 2019 to February 2020, prescriptions of chemotherapy alone decreased steadily. In contrast

prescriptions of combined chemo-immunotherapy increased gradually over the same time period. This corresponds with changes in guidance of first-line treatment, with combined chemo-immunotherapy being introduced during 2019 (Table 7-1). Prescriptions of targeted therapies and single agent immunotherapy remained roughly steady over this time.

During the 1st National Lockdown, prescription numbers fell from March to May 2020 for all SACT types. However, because of the lower total number of diagnoses during this time, percentage of people prescribed treatments actually rose in April (Figure 7-2). This is particularly true for single agent immunotherapy, with the highest percentage of people being prescribed this occurring in April 2020. Whilst numbers of chemo-immunotherapy decreased during this same time, the magnitude was less than for other treatments.

In the period following the 1st Lockdown, prescription numbers recovered for all therapies. Immunotherapy alone and targeted therapies remained roughly static with numbers prior to the pandemic. Although chemo-immunotherapy use increased, it did not match the trajectory seen prior to the pandemic. Chemotherapy alone also did not quite follow the decline previously seen.

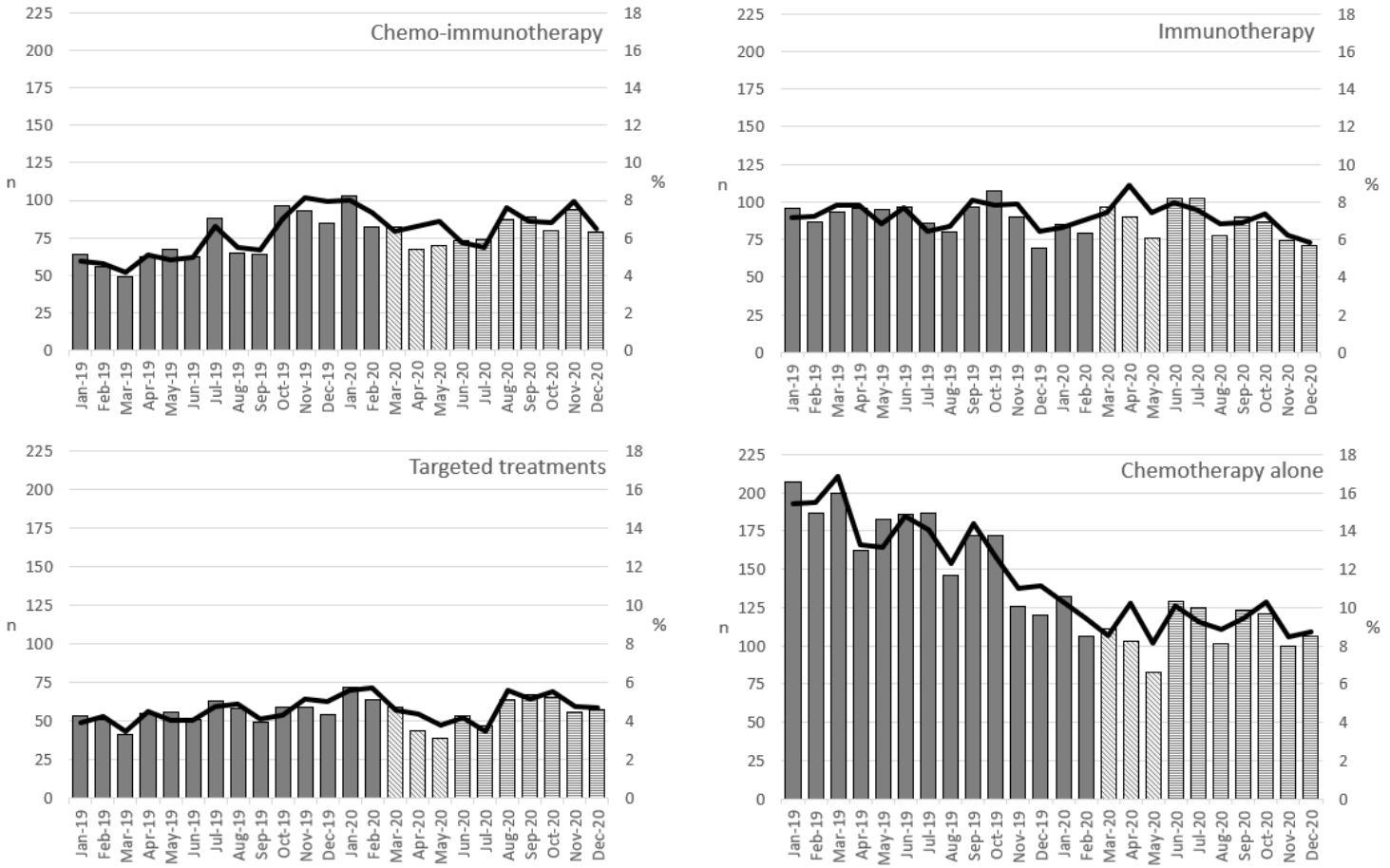


Figure 7-2 Graphs showing number (bars, left y-axis) and percentage of prescriptions (line, right y-axis) for different SACT during 2019 and 2020

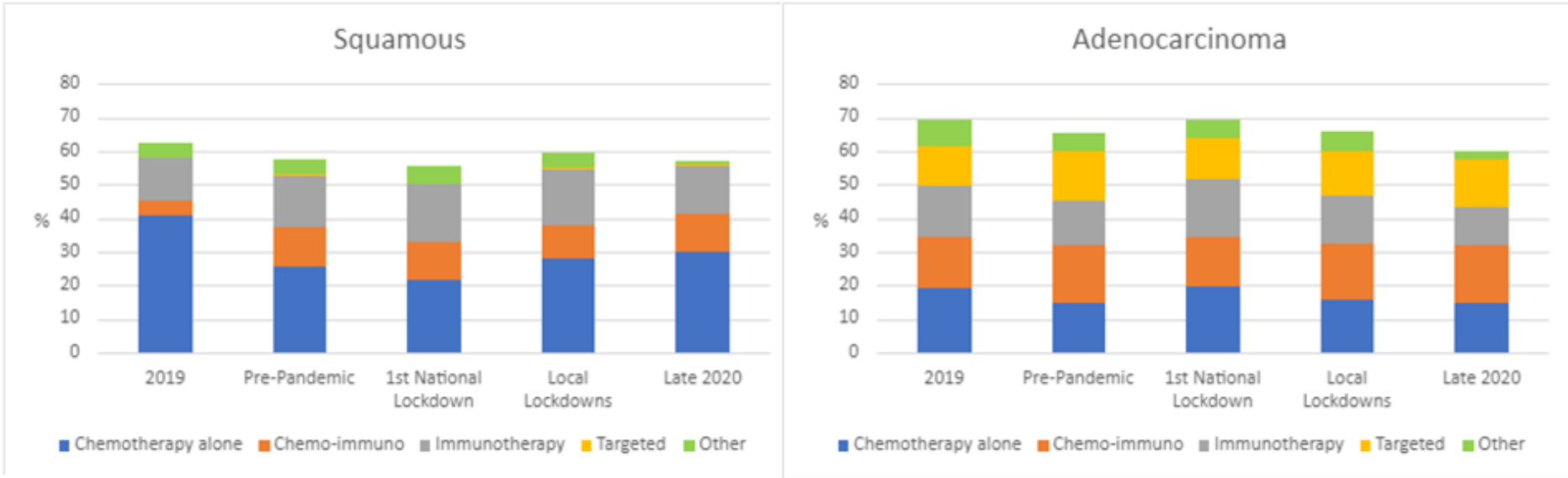


Figure 7-3 Percentage of people with PS 0-1 prescribed different SACT divided by NSCLC morphology

7.3.6 Variation by NSCLC Morphology

SACT prescription varied between different NSCLC morphologies throughout both 2019 and 2020 (Figure 7-3). Following introduction of combined chemo-immunotherapy for both SCC and non-squamous NSCLC (adenocarcinoma) regardless of PD-L1 status in 2019, prescriptions of chemotherapy alone fell, with chemo-immunotherapy use increasing. However, use of combined chemo-immunotherapy in SCC was less frequent than in adenocarcinoma. During Late 2020, 15% of people with adenocarcinoma PS 0-1 were prescribed chemotherapy alone, and 17% chemo-immunotherapy. For people with SCC, this was 30% vs 12%.

7.4 Discussion

7.4.1 Key Findings

Throughout 2020 there was a small but significant decrease in SACT prescriptions compared with 2019, with the lowest treatment percentages seen during the final 3 months of 2020. The composition of treatments also varied, with a dramatic fall in chemotherapy alone over 2019 which coincides with the introduction of combined chemo-immunotherapy and upward trend of this treatment. During the 1st National Lockdown, all SACT types decreased from baseline, except for single agent immunotherapy which remained roughly steady. Recovery of SACT prescriptions did occur over the summer of 2020, however had not reached baseline levels by the end of the year. People aged over 80 had decreased odds of receiving SACT during the 1st National Lockdown, however no other groups were disproportionately disadvantaged.

Guidelines in NSCLC seem to be rapidly implemented, with these changes in prescriptions closely mirroring change in guidance both before and during the pandemic. This does however vary by cancer morphology. People with SCC more frequently received chemotherapy alone than people with adenocarcinoma, despite combined chemo-immunotherapy being licenced in both groups for the same population and conferring a survival advantage.(60-62, 278)

7.4.2 Previous Work in the Literature

To our knowledge this is the first study describing in detail the use of SACT in NSCLC during the pandemic however similar trends were observed nationally for other types of cancer. In England, total new SACT prescriptions for all cancers were at their lowest during April 2020, at 64% of the number in the same month of 2019. Over the remaining months of 2020, treatment returned towards normal, with 96% of the expected prescriptions in September 2020 for all cancers combined.(290) Scotland observed similar reductions for all cancers, with 28.7% decrease in March 2020. For lung cancer specifically, SACT appointment attendance decreased by 13.2%.(291) In Ontario, Canada, there was a 3.5% reduction in attendance to SACT appointments for all cancers over 2020. Similarly to this study, this varied by month, with the greatest reduction of 14.3% in May 2020.(292) Reductions in SACT seem to have been greatly impacted by the local severity of the pandemic, with no change in overall SACT use in Australia, where COVID-19 infection rates were low.(293)

As observed here, prescriptions varied by SACT type. National prescriptions of cytotoxic SACT in particular have been slow to increase, not reaching the numbers of 2019 by September 2021.(290) More detailed assessment showed 52% of people prescribed SACT for colorectal cancer at a tertiary UK centre had altered treatment during the pandemic, with 8% receiving a different chemotherapy regime to usual care. Changes to SACT were less likely the further from 1st National Lockdown treatment ocurred. As here, a change in treatment was more likely in older people.(294)

7.4.3 Strengths and Weaknesses

Utilising the RCRD for this work has allowed analysis of how the pandemic affected the whole of England, rather than just one hospital or trust. These findings are therefore more representative of actual practice, particularly during local lockdowns, where the pandemic will have disproportionately affected different areas of the country. In addition, the large number of patients allowed more detailed analysis of events. By dividing the timescale

according to COVID restrictions, I aimed to quantify proportional effects on how guidance and practice interacted as opposed to absolute treatment numbers. Understanding how healthcare providers react to changes in guidance, particularly during a time pressured situation such as the COVID era, is essential to identifying ongoing barriers to treatment.

It is however acknowledged that the RCRD has some inconsistencies. When compared with quality assured data from 2018, an estimated 4300 people were missing from the 2019 dataset, the majority of whom had advanced disease at presentation.(289) However, as the data used here for 2020 and 2019 have been prepared in the same way, the relative changes between years should remain accurate. Overall figures however may be an overestimate of treatment rates, due to missing data.

As described in section 6.4.3, missing stage data were excluded from this analysis which may have introduced bias.

As these data only included those patients diagnosed in 2019 and 2020, treatment numbers may be inaccurate for those people diagnosed in the latter months of 2020 who could reasonably have been prescribed therapy in 2021, leading to falsely low results. However, as the median time to treatment was 34-35 days, and the final date for collection of SACT data was 26th April 2021, this is unlikely to have significantly contributed to the observed decrease in prescriptions. Clinical practice is likely to have been affected by further COVID-19 waves and the 2nd national lockdown of December 2020.

7.4.4 Clinical Relevance

At the beginning of the pandemic, healthcare providers expressed concerns about immunosuppression and SARS-CoV-2 infection, which have subsequently been shown to be unfounded.(266, 295) Chemotherapy prescription was associated with lower all-cause mortality in people with solid organ malignancies who caught SARS-CoV-2. Immunotherapy was also protective, whilst targeted (or biological) therapies did not affect outcomes.

In lung cancer specifically, SACT of any type of radiotherapy in the last 4 weeks did not affect overall survival following COVID infection.(296) Survival in people with NSCLC prescribed pembrolizumab alone or in combination with chemotherapy was unchanged during 2020 compared with the preceding year.(297) Given these findings, and a return towards pre-pandemic SACT guidance, persisting changes in clinical practice suggests there may be a national move towards more targeted and personalised therapies. During 2021, biologic and immunotherapy prescriptions quickly returned to pre-pandemic levels, whilst cytotoxic therapies have not.(290) Increased experience using newer and more targeted therapies gained by clinicians during the height of the pandemic may have contributed to confidence in prescribing and persisting changes in practice.

These results suggest that within lung cancer care, guidance is quickly adopted by oncologists, which is essential as novel therapies become increasingly available. Despite this, it should be noted that a significant number of people with lung cancer continue to be prescribed chemotherapy alone, even as we return to normal ways of working and combined therapies are recommended as first-line NICE guidance. In NSCLC, immunotherapy monotherapy confers a survival advantage in people with a PD-L1 ≥50%, and when used in combination is more effective than platinum chemotherapy alone regardless of PD-L1 status.(60-62) Despite these benefits, 30% of fit people with SCC received chemotherapy alone during the final three months of 2020. Those who received combined chemo-immunotherapy were both younger and fitter, suggesting people with better physiological reserve may be given combined therapy. At the time, combined chemo-immunotherapy for SCC was only available through the CDF, which may have contributed to the difference between SCC and adenocarcinoma. As of February 2022 this is no longer the case.(278) Differences in the chemotherapy backbone of combined therapy may have also contibuted to these findings, with SCC requiring a more myelosupressive regime than adenocarcinoma. Given the survival benefits from immunotherapy in combination or as a single agent,

further consideration of factors which impact the likelihood of receiving combined chemo-immunotherapy versus chemotherapy alone may be beneficial.

This work identified that the only group who were less likely to receive SACT during National Lockdown were people aged >80, although this interaction was non-significant. This is reassuring and suggests that the efforts of the NHS were effective at continuing to deliver high quality care. Previous work has shown that there is both a higher incidence and worse survival in people with lung cancer who are more deprived.(83) Furthermore, people with NSCLC who are more deprived are less likely to receive chemotherapy.(208) There is also geographical variation in chemotherapy treatment rates across the UK, ranging from 22% to 35%, which is associated with a reduction in 6 month survival.(77) The reasons for this are not completely clear and may be linked to other health factors not adequately captured by demographics. Current smokers are more likely to be part of the most deprived groups.(298) As a result they have a higher incidence of comorbidities and worse health outcomes which may then contribute to lower SACT rates.(299) Whilst it is positive that these health inequalities do not appear to have been exacerbated during lockdown from these data, continuing to practice inclusive healthcare is essential.

7.5 Chapter Summary and Key Points

- This chapter examined how prescriptions of SACT for advanced stage NSCLC varied during the pandemic in England.
- Prescriptions declined overall, with older people being less likely to receive SACT during National Lockdown than in 2019.
- Chemotherapy alone was used less frequently, with increased use of combined chemo-immunotherapy.
- National guidance tended to be closely followed, although prescriptions of combined chemo-immunotherapy varied by cancer morphology with fewer people with SCC prescribed combined therapy compared to adenocarcinoma.

This work was presented as an oral presentation at the British Thoracic Oncology Group (BTOG) conference 2022.(300)

Chapter 8. The Impact of the SARS-CoV-2 Pandemic on Lung Cancer Survival in England: An Analysis of the Rapid Cancer Registration Dataset

As the final portion of this thesis examining the impact of COVID-19 on lung cancer in England, this chapter considers the survival up to 1-year following diagnosis for people diagnosed during the initial stages of the pandemic.

8.1 Introduction

8.1.1 Background

As discussed in Chapters 6 and 7, fewer people were diagnosed with lung cancer during 2020, with the lowest incidence rates during the 1st National Lockdown.(97) Treatment of NSCLC was likely to be affected, with a relative increase of radical radiotherapy compared to surgery in early-stage disease, and overall decreased use of SACT in advanced disease, with a relative increase in immunotherapy monotherapy.

At the beginning of the pandemic, modelling of different possible social restrictions in England estimated a 6.0-7.7% increase in lung cancer deaths at 1-year as a result of the pandemic.(301) The true impact of the pandemic on lung cancer deaths is however unclear. As a rapidly fatal condition without treatment, delays in diagnosis and alterations in treatment are likely to have worsened survival. Again, identifying whether any groups of people were disproportionately affected by restrictions is key to planning both service recovery from the pandemic, and advanced planning in case of future natural disasters.

8.1.2 Aims

1. Calculate survival up to 1 year following diagnosis with lung cancer during COVID-19 restrictions in 2020 in England.
2. Compare risk of dying both early and later in the patient journey across the same time period.

8.2 Methods

8.2.1 Dataset and Inclusion Criteria

The RCRD as described in Chapter 6.2.1 was used for analysis. It is important to note that compared with the traditional NLCA dataset, the RCRD did not include death certificate only diagnoses, which will falsely improve survival figures compared with previous NLCA results.(289)

All people aged 18 or older diagnosed with lung cancer (ICD-10 C34) between 1st January 2019 and 31st December 2020 were included. Data were collected until death or censor date (7th October 2020). Those people with missing censor date, or where censoring occurred before diagnosis date, were excluded. Stata/SE 17.0 (StataCorpLLC) was used for analysis.

8.2.2 Time Periods

Data were divided into 5 groups according to social restrictions at the time of diagnosis. These are described in Chapter 6.2.2.2.

8.2.3 Analysis

Simple descriptive characteristics were calculated for each time period using percentages for categorical variables, and median and IQR range for continuous data. Significance was calculated using chi-squared tests for categorical data and Wilcoxon Ranked Sum for continuous data.

Percentage survival was calculated at set time points from diagnosis: 90 days, 6 months, 9 months and 1-year (excluding 'Late 2020'). Survival was stratified by lung cancer type - small cell lung cancer (SCLC) and NSCLC – and stage at diagnosis. Kaplan-Meier curves were produced for 1-year survival and logistic regression to calculate significance. Hazard Ratios (HR) were calculated for risk of death at 9 months or 1-year, as applicable, using cox regression. Proportional hazards assumptions were not met, therefore HR were calculated for 0-90 days from diagnosis, and 91-270 or 365 days. Univariate cox regression was first completed for each time period. Possible confounding variables of sex, age, PS, stage, comorbidities were sequentially added to the multivariate models with a change of 10% being considered significant. The final model included sex, age, PS, stage and Charlson comorbidity index.

8.3 Results

8.3.1 Inclusion Criteria

A total of 66462 people were diagnosed with lung cancer and included in the RCRD for 2019 and 2020. Following exclusions as detailed in Figure 8-1, 63808 people were included in the final analysis.

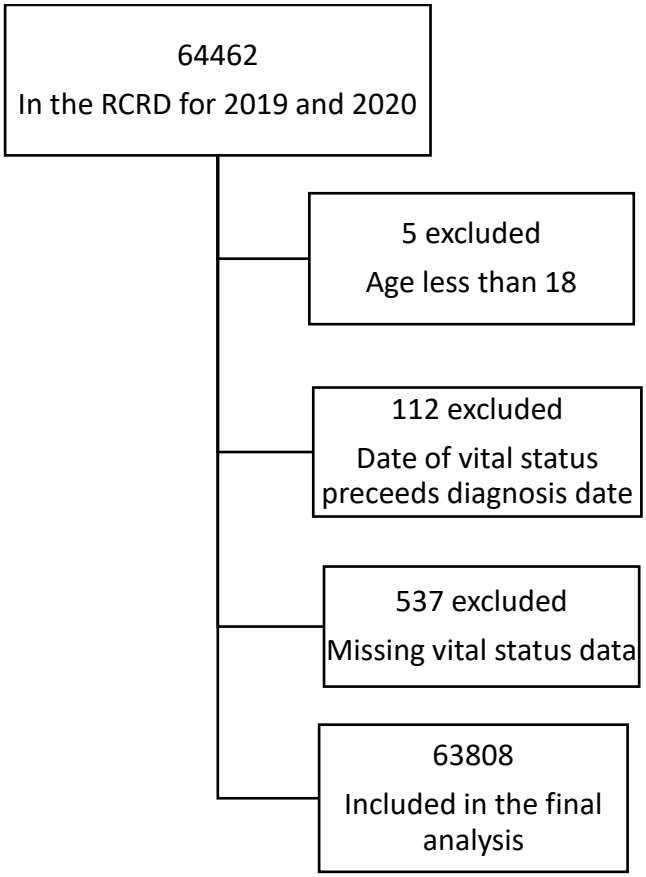


Figure 8-1 Inclusion and exclusion criteria for dataset

8.3.2 Demographics

Demographics were largely similar for all time periods and representative of the usual cohort (Table 8-1). During 2020, fewer people had a PS of 0-1 at diagnosis, with the lowest proportion occurring during Local Lockdowns at 46%, compared with 52% in 2019 ($p<0.0001$). PS data were more frequently missing as 2020 progressed, with 17% missing data from October to December 2020, compared with 10% in 2019 ($p<0.0001$). As 2020 progressed stage at diagnosis was also more frequently missing, with 13% missing stage

data during October to December 2020 compared with 7% in 2019 ($p<0.0001$).

Table 8-1 Demographics for people diagnosed with lung cancer during 2019 and 2020, divided by period of COVID-19 lockdowns. PS – performance status; NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer

		2019	Pre-Pandemic	1st National Lockdown	Local Lockdowns	Late 2020
Total	TOTAL	33,033	7,916	3,063	12,452	7,344
Sex	Male	17,155	4,089	1,599	6,443	3,691
		52%	52%	52%	52%	50%
	Female	15,878	3,826	1,464	6,009	3,653
		48%	48%	48%	48%	50%
	Missing	0	1	0	0	0
		0%	0%	0%	0%	0%
Age	Median	73	73	72	73	74
	IQR	66-80	66-79	65-79	66-80	66-80
Stage	I	6,550	1,723	608	2,360	1,491
		20%	22%	20%	19%	20%
	II	2,669	652	251	785	462
		8%	8%	8%	6%	6%
	III	7,080	1,636	587	2,302	1,393
		21%	21%	19%	18%	19%
	IV	14,281	3,282	1,377	5,776	3,067
		43%	41%	45%	46%	42%
	Missing	2,453	623	240	1,229	931
		7%	8%	8%	10%	13%
PS	PS 0	6,666	1,624	584	2,057	1,293
		20%	21%	19%	17%	18%
	PS 1	10,436	2,414	939	3,581	2,071
		32%	31%	31%	29%	28%
	PS 2	5,459	1,318	498	2,204	1,176
		17%	17%	16%	18%	16%
	PS 3	5,401	1,313	538	2,276	1,240
		16%	17%	18%	18%	17%
	PS 4	1,682	389	148	744	340
		5%	5%	5%	6%	5%
	Missing	3,389	858	356	1,590	1,224
		10%	11%	12%	13%	17%

Lung cancer type	Carcinoid	611	138	52	178	104
		2%	2%	2%	1%	1%
	NSCLC	29,426	7,139	2,801	11,207	6,641
		89%	90%	91%	90%	90%
	SCLC	2,996	639	210	1,067	599
		9%	8%	7%	9%	8%
Charlson Co-morbidity	0	21,548	5,136	2,033	8,120	4,873
		65%	65%	66%	65%	66%
	1	4,568	1,159	436	1,850	1,056
		14%	15%	14%	15%	14%
	2-3	4,958	1,158	403	1,753	1,007
		15%	15%	13%	14%	14%
	4+	1,959	463	191	729	408
		6%	6%	6%	6%	6%

8.3.3 Percentage survival

Patterns of survival were the same for the whole dataset and NSCLC alone, which is as expected as NSCLC formed the vast majority of diagnoses. For both groups there was no difference in survival between 2019 and the Pre-Pandemic period of 2020 (Table 8-2). As 2020 progressed survival worsened, with the worst survival for those diagnosed in Late 2020. This decrease began from the 1st National Lockdown and was apparent within the first 90 days of diagnosis (90-day survival 69% vs 72% in 2019).

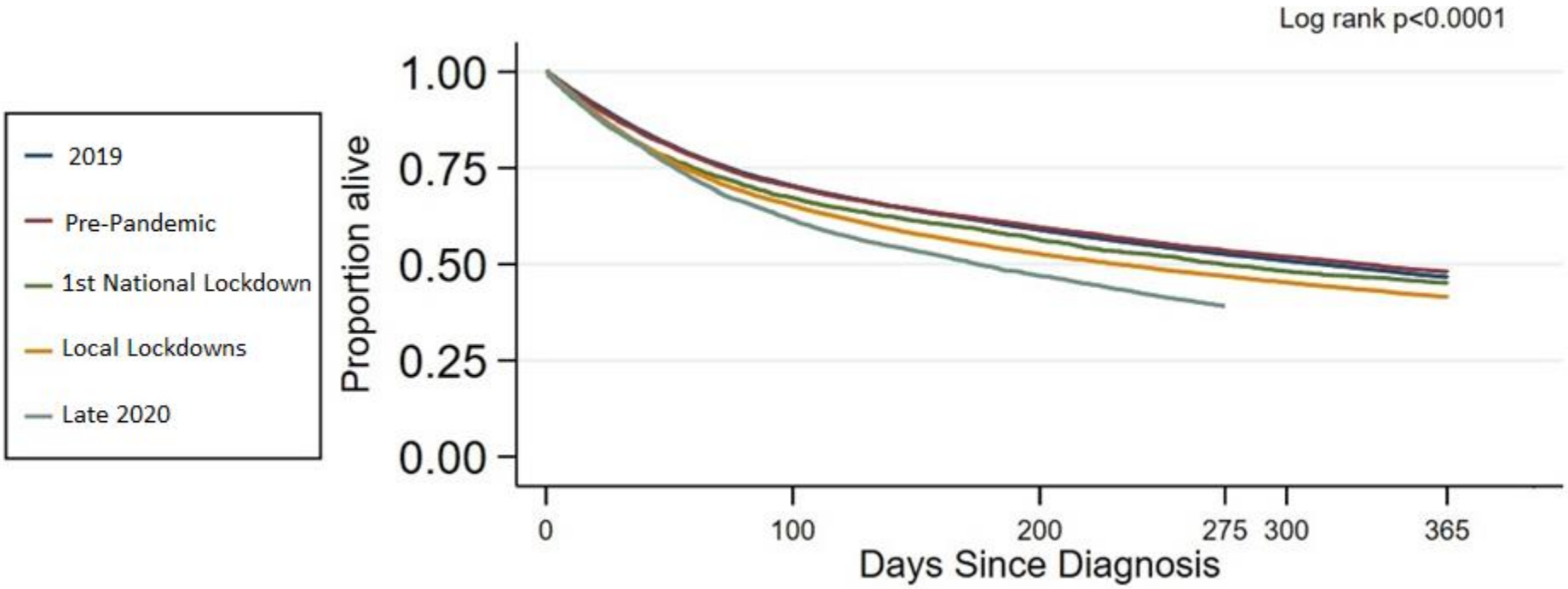
For those with SCLC, survival in 2020 was largely similar until the final three months of 2020 (Table 8-2). During Late 2020, there was a 13% difference in 9-month survival compared with 2019 (29% vs 42%). This difference again began within 90-days of diagnosis.

Table 8-2 Unadjusted percentage survival at 90 days, 6 months, 9 months and 1 year following diagnosis with lung cancer for 2019 and 2020. NSCLC – non-small cell lung cancer; SCLC – small cell lung cancer

	Survival	2019	Pre-Pandemic	1st National Lockdown	Local Lockdowns	Late 2020
	Total n	33,033	7,916	3,063	12,452	7,344
TOTAL	**90 Days**	72%	71%	69%	67%	64%
	6 months	61%	61%	58%	55%	49%
	9 months	53%	54%	50%	47%	40%
	1 year	47%	48%	45%	41%	.
NSCLC	**90 Days**	72%	72%	68%	66%	64%
	6 months	61%	62%	58%	54%	49%
	9 months	53%	55%	50%	47%	40%
	1 year	48%	49%	45%	42%	.
SCLC	**90 Days**	69%	65%	72%	67%	60%
	6 months	56%	53%	60%	53%	46%
	9 months	42%	39%	43%	40%	29%
	1 year	29%	29%	35%	30%	.

8.3.3.1 Kaplan-Meier curves

The Kaplan-Meier Survival Curves (Figure 8-2) demonstrate an early separation in survival, with survival from the 1st National Lockdown onwards being worse from around 30 days after diagnosis. This difference persisted throughout 2020, with those diagnosed during Late 2020 having continued worsened survival as time progressed.



Number at risk:	0	100	200	300	400
2019	33033	23221	19430	16747	14689
Pre-Pandemic	7916	5528	4686	4081	3604
1st National Lockdown	3063	2053	1718	1467	1330
Local Lockdowns	12452	8014	6445	5538	3591
Late 2020	7344	3315	2500	1758	0

Figure 8-2 Unadjusted Kaplan-Meier graph for people diagnosed with lung cancer in England in 2019 and 2020, divided by COVID restrictions at time of diagnosis; 8/10/20 onwards is excluded due to censor date and subsequent lack of data p <0.0001

8.3.3.2 Percentage Survival by Stage

Table 8-3 Percentage survival at 9-months following diagnosis with lung cancer for 2019 and 2020.

		2019	Pre-Pandemic	1st National Lockdown	Local Lockdowns	Late 2020
Un-adjusted	Stage I/II	86%	87%	86%	84%	79%
	Stage IIIA	65%	65%	66%	60%	50%
	Stage IIIB-IV	32%	32%	29%	28%	20%
	Miss-ing	55%	53%	42%	49%	40%
Adjusted for PS 0-1	Stage I/II	89%	90%	90%	89%	85%
	Stage IIIA	71%	73%	73%	70%	62%
	Stage IIIB-IV	43%	42%	41%	39%	30%
	Miss-ing	58%	60%	52%	54%	45%

To account for any stage shift that occurred during 2020, 9-month percentage survival was stratified by stage at diagnosis (Table 8-3). Unadjusted survival is initially maintained for stage I/II and IIIA until Local Lockdowns, at which point it decreases, with the greatest reduction seen for those diagnosed in Late 2020. For stage IIIB-IV and missing stage data, the difference begins earlier in the 1st National Lockdown. After adjusting for PS 0-1, the survival disadvantage is somewhat improved for stage I/II and IIIA with a smaller difference which only occurs in Late 2020. The observed worsened survival however persists for those with advanced or missing stage data, particularly during Late 2020.

8.3.4 Hazard Ratios

Proportional hazards assumptions were not met, HR were therefore separately calculated for death within 0-90 days of diagnosis and 91-270 or 91-365 days as applicable.

Risk of death within 90-days of diagnosis was greater for all time periods in 2020 compared to 2019, including the Pre-Pandemic period (Table 8-4). The risk of early death was highest for those diagnosed in Late 2020 at 1.26 (95% CI 1.20-1.32).

This excess risk of death normalised 91-365 days from diagnosis for those diagnosed Pre-Pandemic and during the 1st National Lockdown (HR 0.95; 95% CI 0.91-1.00 and HR 1.00; 95% CI 0.93-1.08 respectively). As 2020 progressed however, the risk again increased. Overall, the greatest excess risk of death occurred during Late 2020, 91-270 days after diagnosis (HR 1.51; 95% CI 1.42-1.60).

*Table 8-4 Hazard ratios (HR) for risk of death following diagnosis of lung cancer, compared with 2019. Calculated using Cox regression and adjusted for age, sex, comorbidities, performance status and stage at diagnosis. *indicates HR for 91-270 days due to shorter follow-up.*

Death within:	Time Period	2019	Pre-Pandemic	1st National Lockdown	Local Lockdown	Late 2020
0-90 days	Unadjusted HR	1	1.02	1.16	1.23	1.35
	95% CI	-	*0.97-1.07*	*1.08-1.24*	*1.18-1.27*	*1.29-1.41*
	Adjusted HR	1	1.08	1.16	1.11	1.26
	95% CI	-	*1.03-1.13*	*1.08-1.24*	*1.07-1.15*	*1.20-1.32*
91-365 days*	Unadjusted HR	1	0.91	0.97	1.12	1.55*
	95% CI	-	*0.87-0.96*	*0.90-1.05*	*1.07-1.16*	*1.46-1.65**
	Adjusted HR	1	0.95	1.00	1.06	1.51*
	95% CI	-	*0.91-1.00*	*0.93-1.08*	*1.02-1.10*	*1.42-1.60**

8.4 Discussion

8.4.1 Summary of findings

Survival following lung cancer diagnosis was worse throughout 2020 and deteriorated as the year progressed. The difference in survival was apparent for all stages, however the difference was greatest for people with more advanced disease at diagnosis. Even after adjusting for PS and stage, the risk of dying was greater within the first 90-days of diagnosis throughout 2020, both during and outside of lockdown periods. The increased risk of death persisted after 90-days for those diagnosed from May 2020 onwards suggesting changes early in the diagnostic journey have long term impacts on survival.

8.4.2 Strengths and limitations

As mentioned previously, the RCRD dataset for 2019 missed 4300 diagnoses, the majority of which were death certificate or advanced stage, and should

also be assumed to be missing from 2020 as the data was collected in the same way.(289) After accounting for missing registry data, the NLCA estimated a fall in 1-year lung cancer survival from 40.7% in 2019 to 39% during 2020.(302) This means that all survival estimates presented here are likely to be overestimates of the true results and are incomparable to previous years. This is particularly relevant to SCLC, where the reported survival is the same (Table 8-2) but 481 fewer people were diagnosed in 2020. It is likely these missing people died before diagnosis, meaning survival for the 2020 periods are overestimated and therefore the difference not demonstrated here.

As a retrospective observational study I was able to present accurate results of outcomes during the initial stages of the pandemic. Missing data were minimal, with less than 1% of the original dataset excluded due to missing vital status data suggesting these results are accurate to the data available. By grouping data according to COVID restrictions at the time of diagnosis, I sought to establish the relationship between healthcare restrictions and short-term outcomes. Owing to the October 2021 censor date I was unable to calculate 1-year survival from October 2020 onwards. However by calculating 9-month survival and drawing Kaplan-Meier curves I was able to demonstrate a decline in survival as the year progressed.

8.4.3 Previous work

These results demonstrate how measures taken to control the SARS-CoV-2 pandemic impacted lung cancer survival, from as early as the 1st National Lockdown. Between March and May 2020, when restrictions were most stringent, the risk of dying was greatest in the first 90-days following diagnosis, returning to baseline between 91-365 days, suggesting that differences early in the patient journey are important for long term outcomes, a feature which has been previously reported.(303)

The excess risk of early death continued throughout 2020 and was worst for those diagnosed after October 2020. A detailed analysis of the RCRD revealed

a stage shift towards more stage IV diagnoses and fewer PS 0-1 in the period following 1st National Lockdown.(97) Stage and PS are important prognostic indicators in lung cancer, as well as determining treatment intent and eligibility, respectively.(7, 304) The demonstrated worsening survival could be explained by a delay in presentation and subsequently worsening fitness as the year progressed. These results show a persistent increase in HR for death even taking PS and stage into account, suggesting there are additional factors not adequately captured by audit data. Ongoing lockdowns throughout the year may have also impacted this.

The worsened survival reported here is in line with, and even exceeds, those from modelling estimates. These suggested that diagnostic delays caused by pathway changes could result in a 3.5-4.5% in lung cancer deaths at 1 year.(301) Here I observed a 6% absolute decrease in 1-year survival between May and October 2020, and 13% decrease in 9-month survival between October and December. In Ontario, Canada, 1-year survival for lung cancer was slightly higher during the pandemic period.(305) Similarly, 6-month overall survival was unchanged in the Greater Paris area.(306) Given the baseline variation in lung cancer survival between countries, as well as variation in COVID-19 policy and impact on healthcare services, it is unsurprising there is variation between countries.

The observed decrease in survival here is likely multi-factorial. I have described in Chapters 6 and 7 the changes in treatment of lung cancer 2020. The greater impact observed in advanced stage disease compared with early stage may be influenced by the shorter prognosis of this group without treatment and decreased use of systemic anti-cancer therapy during 2020 as discussed in Chapter 7.(98, 290) In addition, the cancer pathway varied. Delays in treatment also worsen survival in lung cancer.(307) Whilst time to both curative intent treatment and SACT was not extended during the pandemic, an extended pre-diagnosis period is not captured by data here and may have contributed to this. Referrals via the 2 week wait and GP pathways decreased, with a compensatory increase in emergency presentations.(97)

People diagnosed via emergency pathways have worse outcomes.(308) This is likely due to delayed presentation and worsened fitness meaning people are not eligible for treatment.

8.4.4 Clinical Relevance and Conclusions

People who were diagnosed with lung cancer in 2020 were more likely to die in the year following diagnosis than those in 2019 even after adjustment for stage and PS, with those diagnosed in the final quarter of 2020 having the worst survival. It is likely the observed reduction in survival is multifactorial, being influenced both by delayed presentation and subsequent diagnosis, poorer PS, and decreased treatment eligibility.

Improving cancer outcomes is highly politically relevant, with the NHS Cancer Plan aiming to diagnose 75% of all cancers at an early-stage, with lung cancer being a key tenant.(309) The UKLCC are aiming for 25% 5-year survival by 2025.(84) Prior to the pandemic, gains had been made, with the UKLCC highlighting the need to recover and improve on these. Modelling suggests the pandemic related reductions in survival will persist for at least the next 5-years.(301) Healthcare restrictions in Canada are predicted to cause 3082 excess lung cancer deaths, an increase of 1.1%, with the peak in additional deaths in 2022.(305) Australian data suggests 6 months of healthcare disruption during the pandemic would result in additional cancer deaths between 2020-44.(310) The UKLCC has highlighted healthcare policy recommendations to try and avoid these outcomes.(84) Modelling in the Canadian study found that increasing cancer capacity by ≥10% should avoid most of the excess deaths, suggesting the impact of the pandemic can be mitigated.(305)

Timely diagnosis is key to improving outcomes. A randomised control trial examining patient pathways in the UK found shortening the diagnostic pathway from 30 to 15 days improved median survival from 312 to 503 days.(311) Whilst treatment was not delayed during the pandemic in England, time to diagnosis was not measured, and this does not take into account the

pre-diagnosis period before presentation to medical services. Presentations of cough to primary care during the pandemic had one of the largest reductions of a range of cancer indicator symptoms.(312) This may have been because of the overlap of symptoms with COVID-19.(313) People with potential cancer symptoms also avoided attending their GP because of worries about wasting healthcare professional's time and placing extra strain on the NHS.(236) Public awareness is therefore essential to improving timely diagnoses. The Be Clear on Cancer campaign doubled two week wait referrals for lung cancer in England and significantly increased lung cancer diagnoses.(314) Public awareness may also result in a stage shift, with 8.8% more people being diagnosed at stage I/II following a local campaign in Leeds.(315) Key components of a public awareness campaign post-COVID have been identified: validation, endorsement, motivation and action. These were utilised to run a 'Do-it-yourself' themed campaign in Manchester during November and December 2020 which coincided with an increase in lung cancer referrals.(316)

Lung cancer screening is another essential facet of increasing early-stage diagnosis. In a meta-analysis, lung cancer specific mortality was reduced by 16%, and all-cause mortality reduced by 6.7% in the American National Lung Screening Trial.(89, 317) The UK National Screening Committee has recommended lung cancer screening in 2022, with Targeted Lung Health Checks already rolled out in high risk areas of England.(91, 318) These were paused during the pandemic. The UKLCC and NHS Cancer Services Recovery Plan prioritised resumption of these services with further sites being rolled out subsequently.(84, 309)

These results show a reduction in survival over the short-term, with outcomes worsening as 2020 progressed. The true magnitude of the pandemic may not be seen for several years and is not fully reflected in 1-year survival, particularly amongst those people with early-stage disease who had alterations to their treatment as described in Chapter 6. As lockdowns and healthcare pressures continued into 2021, it would be beneficial to establish

survival patterns in this period. Moving forwards, a focus on awareness campaigns and prompt access to diagnostic pathways is essential to return to the pre-pandemic trajectory of improving lung cancer survival.

8.5 Chapter summary

- Lung cancer survival was worse throughout all time periods in 2020 and deteriorated as the year progressed.
- The risk of dying increased within the first 90-days of diagnosis and persisted to 1-year.
- These findings exceed modelling estimates produced at the start of the pandemic.
- This may be partially explained by a stage-shift towards stage IV disease and worsened PS at presentation, caused by delayed presentation and diagnosis.

8.6 Conclusions from COVID-19 Research

I examined the impact of the early stages of the COVID-19 pandemic on the treatment and short-term survival of people with lung cancer across England, with the particular aim of identifying any groups of people who may have been disproportionately disadvantaged. Overall, treatment of the eligible population was well maintained in both early-stage and advanced-stage disease. There was an observed shift however in treatment modalities, with an increased use of radical radiotherapy in preference to surgery for potentially curative disease, and decreased use of chemotherapy alone in advanced-stage disease. Both changes were in line with contemporary treatment recommendations. Future research looking at long-term recurrence and survival of these groups may be of interest, with the impact particularly on people with early-stage disease potentially not being seen for many years.

It should be noted however, that whilst the percentage of those treated were well maintained, absolute treatment numbers fell in line with a substantial decrease in diagnoses. During the 1st National Lockdown there was a 26%

reduction in incidence of lung cancer in England, without over-recovery as the year progressed.(97) This reduction was seen equally across all ages, comorbidities and levels of deprivation. Given the rapid mortality of untreated lung cancer, those people who did not present in 2020 may never be diagnosed, dying before presentation and diagnosis. For people who would have ordinarily presented with early-stage disease, there may be a rebound effect of increased advanced stage diagnoses in future years.

In the event of future pandemics or other catastrophes, focus must be placed on sustaining the diagnosis of people with lung cancer, as it is not possible to treat those people who never present to services and untreated lung cancer is rapidly fatal. As no specific groups were identified who were disproportionately disadvantaged, interventions should be population wide.

8.6.1 Summary of Chapters 6, 7 and 8

- The COVID-19 pandemic had significant impacts on the presentation, diagnosis, treatment and survival of people with lung cancer in England.
- Overall curative intent treatment of people with good PS, early-stage disease was well maintained, but there was a shift from surgery to radical radiotherapy.
- Treatment with SACT for people with advanced stage disease fell, with cytotoxic chemotherapy being affected to a greater degree than immunotherapy alone, which remained roughly steady.
- Both 90-day and 1-year survival fell during 2020.
- All of these effects were more prominent towards the end of 2020.

This work was published in the journal *Thorax* in November 2023.(319)

Chapter 9. Conclusions and Future Research

This chapter considers the important conclusions from this thesis and makes some suggestions for future research.

9.1 Conclusions

This thesis has examined some of the factors surrounding treatment with curative intent for NSCLC in the UK. It has considered contemporary outcomes from surgical treatment and examined some of the barriers to treatment in the East Midlands. In addition, it explored treatment changes during the COVID-19 pandemic, and particularly sought to identify any people who were disproportionately disadvantaged. Key findings are summarised below.

9.1.1 Short-term Mortality Following Thoracic Surgery for Lung Cancer

90-day post-operative mortality was calculated for people who underwent thoracic surgery for lung cancer. Fewer people underwent pneumonectomies and more surgery was completed as VATS. 90-day mortality continues to improve, falling by nearly half from 5.9% in 2004-12 to 3.1% in this research.(115) More people from the highest risk categories underwent surgical treatment, with improved mortality in this subgroup. Results were presented in tables stratified by age and PS with the aim of using them as communication aids during the consenting process.

9.1.2 DECLINE: Perceived Barriers to Curative Treatment for People with Early-stage Lung Cancer

A mixed methods study was undertaken to examine the reasons some people did not undergo treatment with curative intent in the East Midlands. Quantitative work showed that most people did not undergo surgical treatment or radical radiotherapy because of co-morbidities or inadequate lung function, rather than because of patient choice. Poor lung function, older age and PS >0 all decreased the odds of receiving surgery. Inadequate lung function also decreased the odds of receiving radiotherapy, but age and PS did not significantly impact this, following adjustment for lung function. The likelihood of receiving surgery did not differ between different NHS trusts, but people presenting to Lincolnshire or Derbyshire were less likely to receive radiotherapy.

Semi-structured interviews of people who chose not to receive surgery and HCPs working in lung cancer were undertaken. This qualitative work concluded that people chose not to have surgery for emotional reasons, particularly fear of treatment and preconceptions about what treatment would entail. HCPs tended to primarily consider more practical barriers to treatment, such as travel and work and carer responsibilities. Consequently, facilitators to treatment tended to also focus on practical barriers, although patients reflected the benefit of a good relationship with their medical team. Moving forwards, focussing on people's concerns and fears early in the patient journey may help to improve treatment uptake amongst people who are unsure about receiving treatment.

9.1.3 The Impact of the COVID-19 Pandemic on Lung Cancer Care in England

This research took place during the COVID-19 pandemic. Lung cancer referrals and diagnoses fell during the early phase of the pandemic. To establish if any groups of people with lung cancer were disproportionately disadvantaged by lockdowns, treatment and survival of people with lung cancer were compared from 2020 to 2019. Fewer people overall underwent treatment with curative intent during the 1st National Lockdown, although the percentage of those treated remained roughly stable. People were more likely to receive treatment with radical radiotherapy and less likely to have surgery when compared with 2019.

Treatment of advanced stage cancer also varied compared with 2019. People were more likely to receive single agent immunotherapy and less likely to receive chemotherapy alone, which reflected the change in guidance introduced at the start of the pandemic.

1-year survival also worsened, with changes seen as early as the first 90-days following diagnosis. Survival worsened as 2020 progressed, with those diagnosed in the final months of 2020 having the worst overall survival. This

was likely due to a combination of factors including decreased diagnoses and the described changes in treatment.

For all of these studies, no groups were disproportionately disadvantaged, which is reassuring, however overall treatments and survival fell during the early stages of the pandemic. These results will influence planning as we enter the recovery stages of the pandemic.

9.2 Future Research

9.2.1 Surgical Mortality

Mortality prediction tools are innately flawed as they are likely to become outdated as surgical techniques and populations change from the data used to generate a tool.(151) Accurately predicting outcomes from treatment however and communicating this clearly to people is an essential part of the decision making and consenting process.

The tables produced here are intended to be used as a communication aid pre-operatively. It will be essential to continue to update them as treatment changes. For example, robotic assisted thoracic surgery is being used more frequently and is likely to affect immediate post-operative survival. More people who are high risk are being operated on, which will also affect overall outcomes. These results should therefore be reproduced in several years to reflect this change in practice.

In order to optimise the utility of these figures as a communication aid, further work could be undertaken to present them in the most easily understood way. Numerical literacy is important for interpreting probability and making informed healthcare decisions.(141) Only 70% of lay people understand percentages which may limit their use when discussing risk. However verbal descriptors of risk (e.g. ‘negligible’ or ‘high risk’) are also limited in their use as they are interpreted differently both between clinicians and patients.(142) Looking at alternative methods of communicating risk, most people preferred visual communication of probabilities, with the greatest understanding when possible outcomes were personalised to their

case.(146) Work to produce a lung cancer specific, personalised communication tool to communicate post-operative risk would be beneficial. This also links to the next steps of DECLINE, described below.

9.2.2 DECLINE: Perceived Barriers to Treatment of Lung Cancer

In this research, people who chose not to undergo surgical treatment generally did so because of fear, which particularly affected those with previous negative experiences of cancer treatment and led to inaccurate preconceptions of the realities of treatment. In order to combat these, developing a personalised risk communication tool for surgery or radical radiotherapy would be useful in dispelling myths. The first stage in developing this tool could be focus group qualitative research with people with lung cancer to establish what methods of communication they would find useful, for example pictorial representations, electronic or paper based. Any developed tools could then be trialed in a pilot setting to establish if they improve comprehension of risk pre-operatively.

This research confirmed the likelihood of receiving radiotherapy varied between trusts in the East Midlands. This may be because of a discrepancy in oncology availability at these sites. An organisational audit of members of the MDT, clinicians' allocated sessions for lung cancer care, and availability of required infrastructure such as radiotherapy machines may help inform the reasons these trusts had disparities in treatment delivery.

The other possible research project arising from DECLINE would be to extend the study to people with advanced-stage disease. 39% of people with good PS do not undergo systemic treatment.(36) Whilst these people are not suitable for curative intent treatment, they would still benefit from prolonged survival by receiving SACT. Performing semi-structured interviews with people who chose not to undergo SACT would be useful in establishing the reasons they did not receive treatment. As a different population with different risks and benefits, they are likely to have different reasons from the group interviewed here.

9.2.3 The Impact of COVID-19 on Lung Cancer Care

The research produced here included data from 2019 and 2020. Given the significant second wave and associated lockdowns seen at the end of 2020 and into the beginning of 2021, extending these analyses with data from 2021 and survival data from 2022 would be beneficial. This would also include the initial recovery phase of the pandemic which would provide useful information on whether any patient groups were excluded from recovery efforts.

The true extent of presentation at a more advanced stage and the treatment changes made during the pandemic may not be seen for many years. This is particularly true for those people treated with radical radiotherapy in place of surgery. Looking forwards, examination of recurrence rates and survival analysis over 5-years would provide useful real-world evidence towards confirming if radiotherapy has worse outcomes than surgery.

Finally, within NSCLC, adherence to recommended treatments varied between histology subtypes. Fewer people with squamous cell cancer received first line treatment with combined chemo-immunotherapy than people with adenocarcinoma. The reasons for this were not apparent from this retrospective data. It may be possible to identify patient factors that decrease the likelihood of guideline driven therapy in squamous cell disease through analysis of linked data from the Cancer Outcomes and Services Dataset and SACT Dataset.

9.3 Conclusions

This thesis has examined some of the factors surrounding potential barriers to curative intent treatment in NSCLC. Context was provided by first defining the meaning of ‘cure’ in lung cancer. The qualitative work provided unique insight into the opinions of people who have chosen not to receive treatment, although this work was limited by low patient numbers and may not have captured all the issues faced by people across the East Midlands. In addition, the research into treatments during COVID-19 provided reassuring evidence

that vulnerable groups were not disproportional disadvantaged during the initial phases of the pandemic.

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Appendices

Appendix A: Documents associated with the DECLINE study

HRA Approval

Dr Manpreet Bains
Associate Professor in Qualitative and Mixed methods research
University of Nottingham
C118 Clinical Sciences Building Nottingham City Hospital Nottingham
NG5 1PBN/A

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

10 June 2022 Dear

Dr Bains

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**DECLINE: Decisions against curative treatment for lung cancer in eligible patients**
IRAS project ID:	**302336**
Protocol number:	**21065**
REC reference:	**21/WM/0263**
Sponsor	**University of Nottingham**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?

HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?

Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **302336**. Please quote this on all correspondence. Yours

sincerely,

Barbara Cuddon Approvals

Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Angela Shone*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of materials calling attention of potential participants to the research [advertisement poster DECLINE]	2	22 November 2021
Cover Letter		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Public and employer's liability]		25 October 2021
HRA Schedule of Events [HRA Assessed Version]	1.0	09 November 2021
IRAS Application Form [IRAS_Form_26102021]		26 October 2021
Letter from sponsor [Sponsor letter UoN]	1	25 October 2021
Organisation Information Document [Delegation log]	1	19 October 2021
Organisation Information Document [OID DECLINE]	3	10 November 2021
Other [Protocol DECLINE - TRACKED CHANGES]	1.1	07 December 2021
Other [Patient interview guide]	1.0	07 December 2021
Other [Clinician interview guide]	1.0	07 December 2021
Other [REC responses]	1	07 December 2021
Participant consent form [consent form DECLINE]	1.1	07 December 2021
Participant consent form [Digital consent form DECLINE]	1.1	07 December 2021
Participant information sheet (PIS) [PIS patient DECLINE]	1.1	07 December 2021
Participant information sheet (PIS) [PIS clinician DECLINE]	1.1	07 December 2021
Research protocol or project proposal [Protocol DECLINE]	1.1	07 December 2021
Summary CV for Chief Investigator (CI) [Manpreet Bains CV]		
Summary CV for student [Helen Morgan CV]		
Summary CV for supervisor (student research) [Emma O'Dowd summary CV]		
Summary of any applicable exclusions to sponsor insurance (non- NHS sponsors only) [ADDITIONAL INDEMNITY - PROFESSIONAL]	1	22 July 2021

IRAS project ID	302336

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
All sites will perform the same research activities therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No study funding will be provided to sites as per the Organisation Information Document	It is expected that a Chief Investigator would be appointed at study sites	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtaina Letter of Access based on standard DBS checks and occupational health clearance.

CAG Approval

Health Research Authority

2 Redman Place

Stratford
London
E20 1JQ

Tel: 020 7104 8100

Email: cag@hra.nhs.uk

09 June 2022

Dr Manpreet Bains
University of Nottingham
C118 Clinical Sciences Building
Nottingham City Hospital
Nottingham
NG5 1PB

Dear Dr Bains,

Application title:	**DECLINE: Decisions against curative treatment for lung cancer in eligible patients**
CAG reference:	**21/CAG/0169**
IRAS project ID:	**302336**
REC reference:	**21/WM/0263**

Thank you for submitting a **research** application under Regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 ('section 251 support') to process confidential patient information without consent.

Supported applications allow the controller(s) of the relevant data sources, if they wish, to provide specified information to the applicant for the purposes of the relevant activity without being in breach of the common law duty of confidence. Support provides a lawful basis to allow the information to be processed by the relevant parties for the specified purposes without incurring a breach of the common law duty of confidence only. Applicants must ensure the activity remains fully compliant with all other relevant legislation.

The role of the Confidentiality Advisory Group (CAG) is to review applications submitted under these Regulations and to provide advice to the Health Research Authority on whether application activity should be supported, and if so, any relevant conditions. This application was considered at the CAG meeting held on 02 December 2021.

This outcome should be read in conjunction with the provisional support letter dated 16 December 2021.

Health Research Authority decision

The Health Research Authority, having considered the advice from the Confidentiality Advisory Group as set out below, has determined the following:

The application to allow;

- a researcher (who is not considered part of the direct care team) to view confidential patient information of approximately 5000 patients at participating Trusts in order to modify full dates and pseudonymise the dataset for analysis,

- and also for a researcher (who is not considered part of the direct care team) to view confidential patient information of approximately 150 patients from this dataset at participating Trusts, in order to undertake a review of clinical notes relating to the lung cancer diagnosis, in order to extract information about why treatment was not received. No confidential patient information will be recorded as part of this review,

is fully supported, subject to compliance with the standard conditions of support.

Please note that the legal basis to allow access to the specified confidential patient information without consent is now in effect.

NUH Capacity and Capability

Template Version No: 1.6

Authorisation When Using This Organisation Information Document as An Agreement

(when used as an Agreement, the Participating NHS Organisation is a "Party" to the Agreement and the Sponsor is a "Party" to the Agreement – collectively the "Parties").

Authorisation on behalf of Participating NHS / HSC Organisation It is not intended that this confirmation requires wet-ink signatures, or a passing of hard copies between the Sponsor and participating NHS / HSC organisation. Instead, Sponsors are expected to accept confirmation by email from an individual empowered by the Participating NHS / HSC Organisation to agree to the commencement of research (including any budgetary responsibility, where the study involves the transfer of funds).	
^ Authorised on behalf of Participating NHS / HSC Organisation by:	
Name	Maria Koufali
Job Title	Managing Director of Research & Innovation
Organisation Name	Nottingham University Hospitals NHS Trust
Date	27 June 2022

DBH Capacity and Capability

Template Version No: 1.6

Authorisation When Using This Organisation Information Document as An Agreement

(when used as an Agreement, the Participating NHS Organisation is a "Party" to the Agreement and the Sponsor is a "Party" to the Agreement – collectively the "Parties").

Authorisation on behalf of Participating NHS / HSC Organisation It is not intended that this confirmation requires wet-ink signatures, or a passing of hard copies between the Sponsor and participating NHS / HSC organisation. Instead, Sponsors are expected to accept confirmation by email from an individual empowered by the Participating NHS / HSC Organisation to agree to the commencement of research (including any budgetary responsibility, where the study involves the transfer of funds).	
^ Authorised on behalf of Participating NHS / HSC Organisation by:	
Name	Dr Teresa M Grieve
Job Title	Assistant Director of R&D
Organisation Name	University Hospitals of Derby and Burton NHS Foundation Trust
Date	28 November 2022

KMH Capacity and Capability

Template Version No: 1.6

Authorisation When Using This Organisation Information Document as An Agreement

(when used as an Agreement, the Participating NHS Organisation is a "Party" to the Agreement and the Sponsor is a "Party" to the Agreement – collectively the "Parties").

Authorisation on behalf of Participating NHS / HSC Organisation It is not intended that this confirmation requires wet-ink signatures, or a passing of hard copies between the Sponsor and participating NHS / HSC organisation. Instead, Sponsors are expected to accept confirmation by email from an individual empowered by the Participating NHS / HSC Organisation to agree to the commencement of research (including any budgetary responsibility, where the study involves the transfer of funds).	
^ Authorised on behalf of Participating NHS / HSC Organisation by:	
Name	Elizabeth Gemmill
Job Title	Director of Research
Organisation Name	Sherwood Forest Hospitals
Date	05 July 2022

ULH Capacity and Capability

Contact: Research & Innovation T: 01522 512512 ext 582923

Email: R&I@ULH.nhs.uk

Lincoln County Hospital

Greetwell Road

Lincoln LN2 5QY

Dr Kate Scheele
Respiratory Medicine

United Lincolnshire Hospitals NHS Trust Lincoln County Hospital

Greetwell Road Lincoln

Date: 23rd August 2022 IRAS
Ref: 302336

Dear Dr Scheele

Re: IRAS No: 302336 - DECLINE v1.0

I am pleased to confirm that with effect from the date of this letter, the above study has Trust Research & Innovation authorisation to commence at United Lincolnshire Hospitals NHS Trust. The research must be conducted in line with the Protocol and fulfil any contractual obligations agreed. If you identify any issues during the course of your research that are likely to affect these obligations you must contact the R&I Office as soon as possible.

In order for the United Lincolnshire Hospitals NHS Trust to comply with targets set by the Department of Health through the 'Plan for Growth', there is an expectation that the first participant will be recruited within 70 days of receipt of a Valid Application. **It is essential that you notify the ULHT Research Team as soon as you have recruited your first participant to the study, and ensure that the date is recorded on the EDGE Database by your local EDGE User.**

If we have not heard from you within the specified time period we will contact you not only to collect the data, but also to record any issues that may have arisen to prevent you from achieving this target. It is essential that you get in touch with us if there is likely to be a problem in achieving this target so that we can discuss potential solutions. The Trust is contractually obliged to meet the 70 day target and if an adequate reason acceptable to the NIHR has not been submitted to explain the issues preventing the recruitment of your first participant, the Trust will be financially penalised. In addition, we are required to publish the Title, REC Reference number, local target recruitment and actual recruitment as well as 70 days data for this study on a quarterly basis on the ULHT public accessed website.

Undertaking research in the NHS comes with a range of regulatory responsibilities. Please ensure that you and your research team are familiar with, and understand the roles and responsibilities both collectively and individually.

It is important that you familiarise yourself with the Standard Operating Procedures, Policies and all other relevant documents which can be located by visiting https://www.ulh.nhs.uk/about/training-and-research/research-and-development.

The R&I Office is keen to support and facilitate research where ever possible. If you have any questions regarding this or other research you wish to undertake in the Trust, please contact this office.

On behalf of the Trust, I wish you every success with the

study. Yours sincerely

Hannah Finch

Head of Research & Innovation

Cc.

Dr Manpreet Bains, Chief Investigator, University of Nottingham Dr Helen Morgan, Co-Investigator, University of Nottingham

Ms Angela Shone, Sponsor Contact, R&I, Jubilee Campus, Nottingham
Isobel Thomas, LCRF Manager

Angela Dillon, Edge Administrator

This Trust actively supports clinical research Help us, help you by getting involved!

Information sheets for participants

Patient Participant Information Sheet

(Final version 1.1: 07/12/21)

Title: Decisions around care in lung cancer

IRAS project ID: 302336

Sponsor Reference: 20165

Chief investigator: Dr Manpreet Bains

Co-investigators: Dr Helen Morgan, Dr Emma O'Dowd, Professor Rachael Murray, Professor Richard Hubbard, Professor David Baldwin

Invitation paragraph

Before you decide to take part in this study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Take time to decide whether or not you wish to take part.

Purpose of the study

Recent data has shown that one fifth of people eligible for curative treatment of their lung cancer, don't receive that treatment. We know that in a third of these cases, it is patient choice to refuse surgery, but we don't know the reasons why. The aim of this study is to understand the barriers experienced by both patients and clinicians when treating lung cancer patients. We hope this information can be used to improve local services in the future.

This is an educational study and is being conducted as part of a PhD.

Why have I been invited?

You are being asked to take part because you have a recent diagnosis of lung cancer.

Do I have to take part?

Participation is entirely voluntary. If you decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw from the study at any time without giving a reason. Whether you take part or not will not change the treatment you receive or your legal rights.

What will happen to me if I take part? What do I have to do?

If you agree to take part, we will contact you to arrange a time and place to meet for an informal interview. Our researchers will travel to a place which is convenient for you. This could be your home. The interview could also take place over the telephone or video call, if COVID restrictions are in place. The researcher will ask to talk about what experiences you have had with your lung cancer care so far. We will ask about what is important to you and what your thoughts are regarding treatment for your lung cancer, and any reasons you would or wouldn't have treatment. The interview is expected to take around 45 minutes. The interview will be recorded so that the researcher can remember everything clearly. The recording will be sent to a university approved external company to write out everything that is said; your information will be kept confidential throughout this process.

Are there possible disadvantages in taking part?

Taking part will not affect your treatment in any way. Sometimes it can be upsetting discussing your cancer diagnosis. The researchers are trained in communication skills and will support you if this happens. The interview can be stopped at any time if you want it to or if you are too distressed to continue. The researchers are able to direct you to support after the interview in the form of your cancer nurse or helplines.

What are the possible benefits of taking part?

This study will help us to build an understanding of how people with lung cancer feel about possible treatments. It will help us to understand what barriers stop local people from having treatment for their lung cancer. In the future this may be used to make changes to local lung cancer services so they are more easily accessed by everyone who needs them.

You will also be given a £10 shopping voucher to thank you for your time.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting PALS for your hospital. (Nottingham 0800 183 0204; Lincoln 01522 707071; Derby 01332 785756; Mansfield 01623 672222)

Will my taking part in this project be kept confidential? How will my information be used?

We will need to use information you give us for this research project.

This information will include your name, age, sex and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Once the interviews have been transcribed, all personal details will be removed. Quotes used in publications will not identify you in any way. The files will be kept on a password protected computer in the University of Nottingham. The transcripts will be kept securely in a locked filing cabinet in the University of Nottingham.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept **strictly confidential**, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access

to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- our leaflet is available from https://www.nottingham.ac.uk/utilities/privacy.aspx
- by asking one of the research team
- by sending an email to helen.morgan@nottingham.ac.uk, or
- by ringing us on 0115 748 4098 ext 31378

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All other data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer

scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

What will happen if I don't want to carry on with the study?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

To safeguard your rights, we will use the minimum personally-identifiable information possible in any record keeping.

What will happen to the results of the research project?

We expect to present findings from the research at conferences and in academic journals. Any quotes will be anonymised, and you will not be identifiable from any of the published research.

We will happily provide you with a summary of the results from this study, but please be aware it may take a while after your participations for all results to be analysed. Please contact the researchers below if you are interested.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting FMHS-ResearchEthics@nottingham.ac.uk

Who is organising and funding the research?

The research is being organised by the University of Nottingham. It is funded by the Roy Castle Lung Cancer Foundation.

Ethical review of the study

The research has been approved by the xxxxxxxxxx NHS Research Ethics Committee.

Who can I contact for more information?

Dr Helen Morgan

Clinical research fellow; Faculty of Medicine & Health Sciences; Clinical Sciences Building, City Hospital Campus, NG5 1PB; 0115 748 4098 ext 31378; **helen.morgan@nottingham.ac.uk**

Dr Emma O'Dowd

Consultant respiratory physician; Department of respiratory medicine; Nottingham City Hospital, NG5 1PB; 0115 96911; **emma.o'dowd@nottinghm.ac.uk**

Dr Manpreet Bains

Chief Investigator, Associate Professor in Qualitative and Mixed-Methods Health Research; University of Nottingham; 0115 823 1360; **manpreet.bains@nottingham.ac.uk**

Clinician Participant Information Sheet

(Final version 1.0: 19/10/21)

Title: Perceived barriers to curative treatment for patients with early stage lung cancer

Short title: Lung cancer treatment refusal

IRAS project ID: 302336

Sponsor Reference: 20165

Chief investigator: Dr Manpreet Bains

Co-investigators: Dr Helen Morgan, Dr Emma O'Dowd, Professor Rachael Murray, Professor Richard Hubbard, Professor David Baldwin

Invitation paragraph

Before you decide to take part in this study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Take time to decide whether or not you wish to take part.

Purpose of the study

Recent data has shown that one fifth of people eligible for curative treatment of their lung cancer, don't receive that treatment. We know that in a third of these cases, it is patient choice to refuse surgery, but we don't know the reasons why. The aim of this study is to understand the barriers experienced by both patients and clinicians when treating lung cancer patients. We hope this information can be used to improve local services in the future.

Why have I been invited?

You are being asked to take part because you are involved in the diagnosis or treatment of lung cancer patients, and work within the East Midlands Cancer Alliance.

Do I have to take part?

Participation is entirely voluntary. If you decide to take part, you will be given this information sheet to keep and you will be asked to sign a consent form. You can withdraw from the study at any time without giving a reason. This would not affect your legal rights.

What will happen to me if I take part? What do I have to do?

If you agree to take part, we will contact you to arrange a time and place to meet for an informal interview. Our researchers will travel to a place which is convenient for you, which could be your place of work or another public place. The interview could also take place over the telephone or online, if COVID restrictions are in place. The interview will be audio recorded so that the researcher can remember everything clearly. The interview is expected to take around 45 minutes. After the interview, the recordings will be transferred to a professional transcription service, to write down what was said. The company are approved by the University of Nottingham and an agreement is in place to keep all information confidential.

Are there possible disadvantages in taking part?

There are no disadvantages to taking part. None of your answers will be discussed with any of your colleagues or employer, and will be kept confidential by the research team.

What are the possible benefits of taking part?

This study will help us to build an understanding of how we treat lung cancer locally, and what barriers there are to accessing services for patients. In the future this will be used to make changes to local lung cancer services so they are more easily accessed by everyone who needs them.

Will my taking part in this project be kept confidential? How will my information be used?

<u>We will need to use information you give us for this research project.</u>

This information will include your name, age, sex and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Once the interviews have been transcribed, all personal details will be removed. Quotes used in publications will not identify you in any way. The files will be kept on a password protected computer in the University of Nottingham. The transcripts will be kept securely in a locked filing cabinet in the University of Nottingham.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

We will follow ethical and legal practice and all information about you will be handled in confidence.

If you join the study, we will use information collected from you during the course of the research. This information will be kept strictly confidential, stored in a secure and locked office, and on a password protected database at the University of Nottingham. Under UK Data Protection laws the University is the Data Controller (legally responsible for the data security) and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights we will use the minimum personally – identifiable information possible.

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/

- our leaflet is available from https://www.nottingham.ac.uk/utilities/privacy.aspx
- by asking one of the research team
- by sending an email to helen.morgan@nottingham.ac.uk, or
- by ringing us on 0115 748 4098 ext 31378

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant and we will do our best to meet this duty.

All other data will be kept securely for 7 years. After this time your data will be disposed of securely. During this time all precautions will be taken by all those involved to maintain your confidentiality, only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's and our funders' policies we may share our research data with researchers in other Universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified) but if we need to share identifiable information we will seek your consent for this and ensure it is secure. You will be made aware then if the data is to be shared with countries whose data protection laws differ to those of the UK and how we will protect your confidentiality.

What will happen if I don't want to carry on with the study?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have. We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

To safeguard your rights, we will use the minimum personally-identifiable information possible in any record keeping.

What will happen to the results of the research project?

We expect to present findings from the research at conferences and in academic journals. Any quotes will be anonymised, and you will not be identifiable from any of the published research.

We will happily provide you with a summary of the results from this study, but please be aware it may take a while after your participations for all results to be analysed. Please contact the researchers below if you are interested.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet. If you remain unhappy and wish to complain formally, you can do this by contacting FMHS-ResearchEthics@nottingham.ac.uk

Who is organising and funding the research?

The research is being organised by the University of Nottingham. It is funded by the Roy Castle Lung Cancer Foundation.

Ethical review of the study

The research has been approved by the xxxxxxxxxx NHS Research Ethics Committee.

Who can I contact for more information?

Dr Helen Morgan

Clinical research fellow; Faculty of Medicine & Health Sciences; Clinical Sciences Building, City Hospital Campus, NG5 1PB; 0115 748 4098 ext 31378; **helen.morgan@nottingham.ac.uk**

Dr Emma O'Dowd

Consultant respiratory physician; Department of respiratory medicine; Nottingham City Hospital, NG5 1PB; 0115 96911; **emma.o'dowd@nottinghm.ac.uk**

Dr Manpreet Bains

Chief Investigator, Associate Professor in Qualitative and Mixed-Methods Health Research; University of Nottingham; 0115 823 1360; **manpreet.bains@nottingham.ac.uk**

Perceived barriers to curative treatment for patients with early stage lung cancer

Patient Participant Interview Guide – v1.0 - 07/12/2021

Short title: DECLINE

Patient Facing Title: Decisions around care in lung cancer

Study Sponsor: The University of Nottingham

IRAS Project ID: 302336

Sponsor Reference: 21065

Introduction

Thank them for coming and taking part
Anything you say will be confidential to the research team. If you change your mind in the future you can withdraw from the study at any time. Contact details are on the information sheet.
Interview will be recorded
Collect signed copy of consent form
The purpose of the interview is to understand what factors affect people with lung cancer who are making decisions about treatment
Any other questions?

Opening

To start with, I'd like to talk about your recent diagnosis of lung cancer, and what's happened so far.

Can you tell me about how you were diagnosed?

How did you feel being told you had cancer?

Do you remember what was discussed following this?

e.g. Further tests, Treatment options

Treatment related

Can you tell me about any treatment that was discussed?

Who with? (healthcare professionals)

How did you feel about this? Could it have been handled better?

What treatment options did you talk about?

Were you given more than one option?

What did you think about the offer? Are you pleased with the options you were given?

Have you discussed the treatment options with anyone? (prompt: family, friends, charity/helplines, online research)

What treatment (if any) will you be having?

What is the goal of treatment? (prompt: to cure the cancer, to live longer, to make you feel better)

Why did you decide to have/not have treatment?

How do you feel about your decision now?

Communication

How did you find the appointment with the hospital doctors?

Were the doctors easy to talk to?

Who was most helpful?

Did you understand everything they told you? (If not, what did you do about it?)

Did you have a chance to ask questions?

Did you feel comfortable asking questions?

If you had a question, who would you feel most comfortable asking? (eg doctor, nurse, GP)

Did anyone come to your appointments with you?

Who was this person?

Were they included in the discussion?

What role did they have in helping you make a decision about treatment?

Who do you feel made the decisions about your treatment?

Roles of doctors/nurses/patient/relatives

Practicalities

I'd like to talk about the practicalities of attending hospital appointments.

How do you get to (your local) hospital?

Surgery/radiotherapy would be in Nottingham; how would you get there?

Does anyone come to hospital visits with you?

How would they get to Nottingham if you were in hospital?

Do you currently work / care for someone / volunteer?

How has your cancer affected that?

Were these things you considered when you were making decisions about your treatment?

Is there anything else which makes getting to and from the hospital difficult?

Previous experience

Sometimes people have previous experience with cancer or similar health problems which can impact their opinions.

Do you know anyone else who'd had lung cancer?

If no, any other type of cancer?

If yes, expand: what was their relationship to you?

What was their experience like?

Closing

Is there anything else that you thought about regarding the treatment for your cancer?

Has this conversation made you think about things differently?

If you have any further questions about your cancer or your treatment then you can get in touch with your lung cancer nurse specialist.
Do they have any questions for me?
Thank them for their time.

Perceived barriers to curative treatment for patients with early stage lung cancer

Clinician Participant Interview Guide – v1.0 - 07/12/2021

Short title: DECLINE

Patient Facing Title: Decisions around care in lung cancer

Study Sponsor: The University of Nottingham

IRAS Project ID: 302336

Sponsor Reference: 21065

Introduction

Thank them for giving up their time and taking part

Anything you say will be confidential to the research team. If you change your mind in the future you can withdraw from the study at any time. Contact details are on the information sheet.

Interview will be recorded

Collect signed copy of consent form

The purpose of the interview is to understand what role doctors and nurses have in treatment decisions for people with lung cancer

Any other questions?

Opening

To start with, we'll talk about your role as a healthcare professional, and the roles of other members of the MDT.

What is your role in lung cancer services?

How long have you been in this role?

On average, how many patients do you see a week with lung cancer?

Are they usually new or follow-up appointments?

How long do you get for each?

Is your contact mainly face-to-face, over the phone, in-patients or outpatients?

Decision making roles

In your experience, who should be involved in treatment decisions in lung cancer patients?

What is the role of the patient in making decisions about their treatment?

How do you think their family and friends contribute to this?

What is your role in decision making?

And the roles for other members of the MDT:

i.e. Surgeon / Oncologist / Respiratory physician / Lung cancer nurse

What do you think is the best balance between doctors, nurses etc and the patient and relatives? (Prompt: mostly patient, mostly doctor, shared equally)

In your experience, do you usually strike the right balance?

How do you think this could be improved?

Treatment discussions

Next we're going to discuss communication within consultations.

Before recommending treatment options, what factors do you take into account?

When discussing treatment options, what information do you give the patient? (Prompt: just information about treatment you offer, or the other treatments available.)

To what extent do you discuss treatment goals with your lung cancer patients?

Do you always discuss this, or just when the patient asks?

Do you always discuss prognosis with patients?

(Prompt: Do you give them all the information, or a trimmed down version?)

To what extent are all patients given the same information?

What factors would influence you to change what information you give them?

Communication

What approaches have you found make communication easier?

Do you tend to do this regularly? (If not, why not?)

Do you use any communication aids when talking to patients?

What are these? (written, graphs, website recommendations etc)

How often do you use them?

Why do you use them?

Do you find them helpful? Do you think patients find them helpful?

Refusal

Finally, some people with lung cancer refuse treatments that are offered to them.

What would you do if a patient decided not to have treatment for their lung cancer?

In your experience, why do people refuse lung cancer treatment?

How do you think they feel later on about their decision?

How often do you refer people with lung cancer for a second opinion?

Is this just when the patient asks, or do you suggest it?

Do they have any questions for me?

Thank them for their time.

Consent Form for DECLINE

CONSENT FORM

(Final v1.1: 07/12/2021)

Title of Study: Decisions around care in lung cancer

IRAS Project ID: 302336

Sponsor Ref: 21065

Name of Researcher: _____

Name of Participant: _____

1. I confirm that I have read and understand the patient information sheet version number XXX dated XXX for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis.
3. I understand that relevant sections of my data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these

individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential.

4. I understand that the interview will be recorded and that anonymous direct quotes from the interview may be used in the study reports. I will not be identified and my personal details will remain confidential.

5. I agree to the possibility of anonymised data generated by this study being used in future research, which may include countries outside the UK.

6. I agree to take part in the above study.

_____ _____

Name of Participant **Date** **Signature**

_____ _____ _____

Name of Person taking consent Date Signature

Advertisement Poster for DECLINE

DECISIONS AROUND CARE IN LUNG CANCER

Researchers from the University of Nottingham
and funded by the Roy Castle Foundation
are collecting information looking at why some people with lung cancer don't receive treatment.

They will be reviewing some identifiable information for people diagnosed with lung cancer between **January 2016 and December 2019**.

For a small number of people we will read their medical records relevant to their lung cancer diagnosis.

All of the information will be anonymised so that it is not identifiable before it leaves the hospital, and no individuals will be identifiable from the final research.

This research will be completed between January and September 2022.

The research team have support from The Health Research Authority, on advice from the Confidentiality Advisory Group, under section 251 of the NHS Act 2006.

If you were diagnosed between January 2016 and December 2019, and don't want to be included, please contact Helen Morgan at:

helen.morgan@nottingham.ac.uk

Tel No 0115 748 4098 ext 31378

ROY CASTLE LUNG CANCER FOUNDATION

For more information on the study, please use the QR code to access the Roy Castle website.

University of Nottingham
UK | CHINA | MALAYSIA

Appendix B: Oral and Poster Presentations

Oral Presentations

Use of systemic anti-cancer treatments in advanced stage non-small cell lung cancer during the SARS-CoV-2 pandemic in England and Wales: an analysis of the Rapid Cancer Registration Dataset

Morgan H., Gysling S., Hubbard R., Conibear, J., Navani, N., Baldwin, D., O'Dowd E.

British Thoracic Oncology Group Conference; January 2022

*1st Place Abstract Prize

Poster Presentations

90-Day mortality following lung cancer surgery: contemporary outcomes from the English National Clinical Outcomes Audit

Morgan H., Baldwin D., Hubbard R., Navani N., West D., O'Dowd E.

British Thoracic Oncology Group Conference; January 2022

The Impact of the SARS-CoV-2 Pandemic on Lung Cancer Survival in England: An Analysis of the Rapid Cancer Registration Dataset

Morgan H., Gysling S., Baldwin, D., Hubbard R., O'Dowd E.

East Midlands Thoracic Society Conference, November 2022

*1st Place Poster Prize

Perceived barriers to curative treatment for patients with early-stage lung cancer: a mixed methods study

Morgan H., Hubbard B., Baldwin R., Murray, R., Bains, M., O'Dowd E.

British Thoracic Oncology Group Conference; April 2023

‘Something like a house of horrors’: a mixed methods study examining the reasons for refusal of potentially curative treatment in early-stage lung cancer

Morgan H., Hubbard B., Baldwin R., Murray, R., Bains, M., O’Dowd E.

*1st Place Poster Prize

‘Something like a house of horrors’: a mixed methods study examining the reasons for refusal of potentially curative treatment in early-stage lung cancer

Morgan H., Hubbard B., Baldwin R., Murray, R., Bains, M., O’Dowd E.

British Thoracic Society Conference; November 2023