Retrospective Analysis of Factors Influencing Rate of Recurrence in Non-Small Cell Carcinoma Patients After Curative Surgery.

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Abbreviations used in the text

• **ADC**	Adenocarcinoma
• **ALK**	Anaplastic lymphoma kinase
• **ATS**	American thoracic society
• **AJCC**	American joint committee on cancer
• **BTOG**	British Thoracic Oncology Group
• **CI**	Confidence interval
• **COPD**	Chronic obstructive pulmonary disease
• **CT**	Computed tomography
• **CTC**	Circulating tumour cells
• **CtDNA**	Circulating tumour DNA
• **DOB**	Date of birth
• **DODx**	Date of diagnosis
• **DOSx**	Date of surgery
• **EBUS**	Endobronchial Ultrasound
• **EGFR**	Epidermal growth factor receptor
• **ENH**	East and North Hertfordshire
• **ERS**	European respiratory society
• **H_0**	Null Hypothesis
• **H_1**	Hypothesis
• **IHC**	Immunohistochemistry
• **IASLC**	International association for the study of lung cancer
• **KRAS**	Kirsten rat sarcoma virus
• **LN**	Lymph node
• **LC**	Lung cancer
• **LCINS**	Lung cancer in never smokers
• **LUL**	Left upper lobe
• **LLL**	Left lower lobe
• **M**	Metastasis
• **MDT**	Multi-disciplinary team
• **N**	Nodal status

• **NET**	Neuroendocrine tumour
• **NHS**	National Health Service
• **NOS**	Not otherwise specify
• **NSCLC**	Non-Small Cell Lung Cancer
• **OR**	Odds ratio
• **PET**	Positron emission tomography
• **PORT**	Postoperative radiotherapy
• **PRS**	Post recurrence survival
• **R0**	Resection margin clear
• **R 1-2**	Resection margin positive
• **RDP**	Researcher development Programme
• **RUL**	Right upper lobe
• **RML**	Right middle lobe
• **RLL**	Right lower lobe
• **RT**	Radiotherapy
• **SCC**	Squamous cell carcinoma
• **SCLC**	Small cell lung cancer
• **SD**	Standard deviation
• **SE**	Service evaluation
• **SEER**	The surveillance, epidemiology and end result program
• **SES**	Socio-economic status
• **SLND**	Systemic lymph node dissection
• **SPSS**	Statistical package for social sciences
• **T**	Tumour status
• **TOR**	Type of recurrence
• **UH**	University of Hertfordshire
• **UICC**	Union of International Cancer Control
• **VATS**	Video- assisted thoracoscopic surgery
• **VPI**	Visceral pleural invasion
• **WHO**	World health organization

ABSTRACT

Introduction: Surgical management of NSCLC in its early stage offers the highest long-term chances of survival, either on its own or as a part of multimodality treatment. However, the possibility of cancer recurrence in the future is a real concern and it increases significantly as the disease advances. Till date, there was no comprehensive study to find out the factors influencing the recurrence.

Aims: Our aim was to measure the rate of recurrence in lung cancer patients who had curative intent surgery and try to determine any factors that may influence recurrence and survival in patients after lung cancer surgery.

Methods: Observational study to investigate the rate and the factors influencing recurrence after lung cancer surgery. 252 patients with lung cancer at East and North Hertfordshire (ENH) NHS Trust who had curative intent surgery between 2010-19 were reviewed. Demographics, co-morbidities, pathological parameters, surgical figures, recurrence, and survival data were collected.

Results: The overall recurrence rate noted in the examined cohort was 24.6% (62 patients), with more than half of the cancer recurrences taking place at local and locoregional sites, representing 13.1% (33 patients). Furthermore, 11.51% of the cases (29 patients) were recognized as having distant metastasis. In the univariate analysis of exposure variables, a significant relation was found between tumour location and cancer recurrence, with a p-value of 0.03. Additionally, a correlation between residual tumour status and cancer recurrence was also detected, with a p-value of 0.02. However, no association was noted between the surgical approach and cancer recurrence, indicated by a p-value of 0.06. The multivariate analyses gave only slightly better contributions toward the understanding of the risk of recurrence. Tumour stage and resection margin status were found to be the most important predictors; stage III tumour and positive residual margin, where applicable, were most predictive of recurrence (p - value < 0.01). The surgical approach exhibited a somewhat elevated but statistically insignificant recurrence risk with open thoracotomy compared to VATS, although it approached significance at $p \approx 0.05$. In the analysis of continuous variables, age did

not indicate any potential association with recurrence. However, when assessed by group, patients aged 75 and older presented a slightly increased recurrence risk, although this difference was not statistically significant at the margin with a p-value of 0.1.

Discussion: Interestingly, more than fifty percent of recurrences within our cohort presented at local sites when juxtaposed with distant metastasis. The probability of recurrence escalates concomitantly with progressive tumour staging and the presence of positive residual tumour margins. Both univariate and comprehensive multivariate analyses have indicated that tumour stage III and the status of resection margin adequacy act as significant predictors, with p-values of 0.001 and 0.002, respectively. An elevated incidence of recurrence was noted among patients who underwent open thoracotomy as opposed to those who were subjected to VATS. Nevertheless, the significance of this association was deemed non-specific (p-value of 0.06) in the context of univariate analysis, although it approached significance at $p \approx 0.05$ in the realm of multivariate analysis. Moreover, the anatomical localization of the tumour demonstrated a significant correlation with recurrence in univariate analysis with a p-value of 0.03, although it exhibited low accuracy in multivariate analysis.

Conclusions: The recurrence rate in patients treated for NSCLC identified in our study is in line with published data. Both univariate and multivariate analysis highlighted the role of tumour staging and extension of tumour resection as the factors determining recurrence. Surgical approach and age were marginally significant secondary predictors whose strength and effect depended on the research context, so they should be interpreted cautiously. Furthermore, the anatomical location of tumour was significantly correlate with recurrence on univariate analysis, although it showed low accuracy on multivariate analysis.

Overview of the Thesis

Most of the chapters in this thesis consist of self-analysed observations. Each chapter includes an introduction, methods, results, discussion and conclusion. Consequently, the introductory and methodology chapters (Chapters 1 and 2) provide only a brief overview of the background and design of the study, which are then expanded upon in the subsequent individual chapters.

The thesis begins with an abstract that summarises the entire project.

Chapter 1 offers a brief description of lung cancer incidence, pathological classification, diagnosis, tumour nodal metastases staging systems, treatment, prognosis, and recurrence statistics. It includes a review of the literature and introduces the original basic concepts of the study, which are further elaborated in the following chapters. Additionally, the research question along with the aims and objectives of the study are outlined at the end of this chapter.

Chapter 2 summarises the study methods, detailing the research design, selection criteria, and study population. The latter part of the chapter focuses on data collection and statistical analysis, with ethical considerations for the study discussed at the end.

In Chapter 3, we analysed the impact of patient variables on cancer recurrence. The patient variables considered included demographic factors such as age and sex, smoking history, and pre-existing medical conditions that encompassed previous cancer history, as well as other respiratory, cardiovascular diseases, and diabetes.

In Chapter 4, the analysis focused on how tumour variables affect cancer recurrence. The tumour variables considered in this study included tumour histology, the anatomical location of the tumour, tumour staging, status of visceral pleural invasion, and the margin of residual tumour.

In Chapter 5, the analysis shifted to the impact of surgical and treatment variables on cancer recurrence. The variables examined included the optimal surgical approach, the type of operation performed, and the systemic nodal dissection employed, along with any postoperative or adjuvant therapy provided.

Chapter 6 presents the overall cancer recurrence rates within the cohort, and multivariate analysis conducted to identify the relationship between individual variables and cancer recurrence. The

rates of recurrence and the details of the multivariate analysis are discussed in Chapter 7, which also addresses the limitations of the study at the end.

The final chapter, Chapter 8, provides a brief summary that highlights the main conclusions of this thesis and reviews potential future directions for research.

1 Background to the study

1.1 Introduction

This chapter seeks to furnish a thorough examination of various pivotal elements associated with lung cancer, with a particular emphasis on non-small cell lung carcinoma (NSCLC) within the context of the United Kingdom.

To commence, it will investigate the incidence of lung cancer, accentuating the prevalence rates and demographic determinants that influence its manifestation within the UK. Subsequently, the chapter will engage in a detailed discussion regarding the classification of lung cancer, specifically highlighting the differentiation between non-small cell lung carcinoma and small cell lung carcinoma. The chapter will then scrutinize the diagnostic methodologies employed in the identification of lung cancer, elaborating on the various techniques utilized to ascertain and validate the disease. Following the diagnostic analysis, attention will be directed towards tumour staging and the prevalent management strategies, as well as prognostic outcomes for NSCLC within the United Kingdom. Moreover, it will address the statistical data concerning the recurrence of NSCLC subsequent to complete surgical resection in recent years. In addition, the chapter will articulate the research question and explore the aims and objectives pertinent to this study.

1.2 Incidence of lung cancer in the UK

In the United Kingdom, lung cancer ranks as 3rd most common type of cancer, accounting for 13% of all new cases (2016-2018), with an estimated 48,500 new cases annually, or more than 130 cases each day **[1]**.

The incidence rate of lung cancer per 100,000 individuals was recorded at 81.5 for males and 66.1 for females per 100,000 population in England during the year 2021 (Cancer Research UK, 2022). A notable declining trend was observed in the rate of newly diagnosed cases specifically among males across the years under review. People of age 75 and above account for more than 44% of all new lung cancer cases diagnosed every year in the UK (Cancer Research UK, 2022). The rate of incidence is lower in the Asians, Blacks, and people of mixed or multiple racial backgrounds when compared to the White ethnic group in England (2013–2017) **[1]**.

While lung cancer in men is starting to decline in the Europe, lung cancer in women is continuing to climb and has surpassed breast cancer in several nations **[2]**.

Lung carcinoma arises due to a gradual build-up of genetic alterations that transform normal bronchial epithelial cells into neoplastic entities. However, unlike numerous other neoplasms, the primary environmental factor responsible for inducing genetic harm is unequivocally established: tobacco smoke **[3]**. The genetic changes most frequently associated with lung cancer due to tobacco use occur in the genes EGFR, KRAS, and TP53 **[3]**.

1.3 Lung cancer histological classification

Primary lung cancer is divided into two basic types: **1.** Non-Small Cell Lung Cancer (NSCLC), and **2.** Small Cell Lung Cancer (SCLC) **[3]**.

NSCLC comprises of 80 to 85%, making it the most prevalent type of lung cancer. Non-small-cell carcinoma can manifest as squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma **[4]**. In the 2015 Classification of lung tumours as outlined by the World Health Organization, which integrated pertinent genetic and immunohistochemical (IHC) characteristics of various tumour subgroups **[5]**.

Significant changes in the approach to adenocarcinoma, as outlined in the 2011 IASLC/ATS/ERS Classification of lung adenocarcinoma **[6]**, were incorporated into the 2015 and 2021 WHO classifications **[7]**. Squamous cell carcinoma (SCC) tumours are presently categorized into keratinizing, non-keratinizing, and basaloid subtypes. Additionally, lymphoepithelial carcinoma is included within the SCC classification. SCLC belongs to the category of neuroendocrine carcinomas, which falls under the classification of neuroendocrine neoplasms affecting the lungs. Rare tumours such as pleomorphic carcinoma, which includes giant cell and spindle cell carcinoma, pulmonary blastoma, and carcinosarcoma, are the member of the sarcomatoid carcinoma group. It is explicitly mentioned that diagnoses of large cell and adenosquamous carcinoma should not be made from small biopsy and cytology samples; instead, not-otherwise-specified NSCLC should be used in these situations **[7]**. Figure 1 illustrates the classification of this summary.

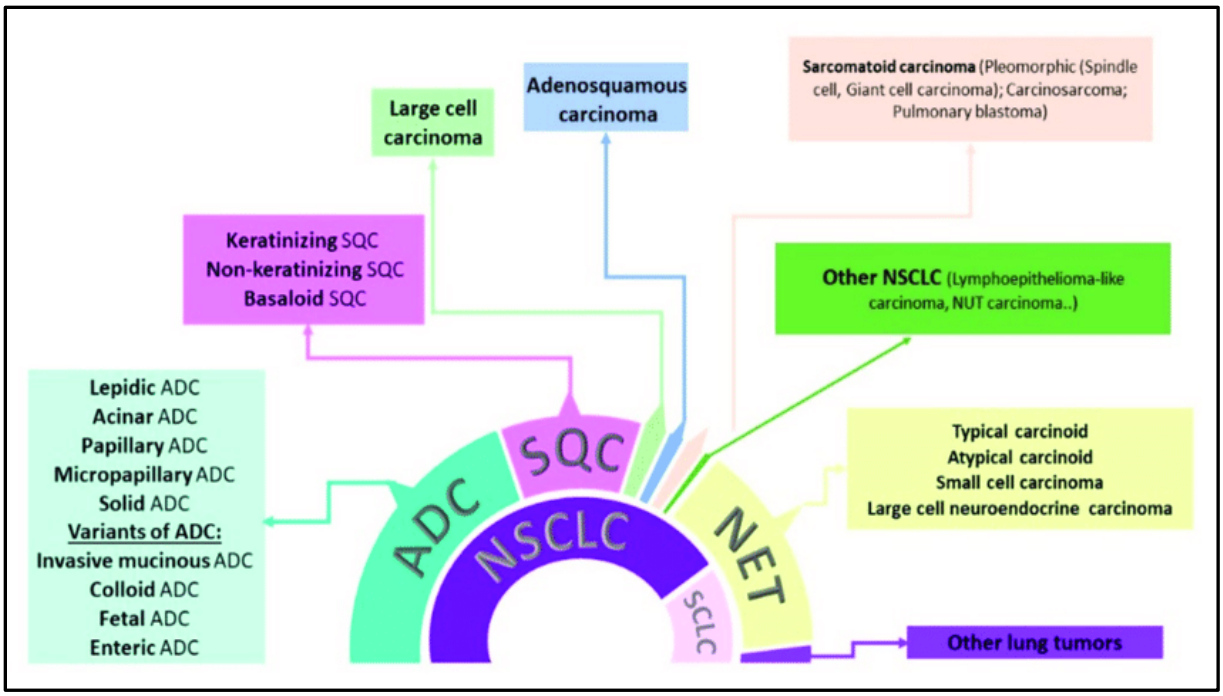

Figure 1: Lung tumour classification using resection specimens. The conventional division of lung tumours into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) is represented by the inner circle. The WHO 2021 classification of lung tumours is shown by the outer circle, where SCLC is included in the neuroendocrine tumour category alongside other forms of lung cancer. NETs are neuroendocrine tumours; ADCs are adenocarcinomas; SQCs are squamous cell carcinomas. [8]

1.4 Diagnosis

Diagnosis and staging of lung cancer are imperative in the strategic planning of treatment. The methodologies for clinical staging, encompassing anatomic and metabolic imaging, endoscopic examinations, and minimally invasive surgical interventions, should be executed in a stepwise manner and with incrementally invasive measures **[9]**.

A chest X-ray and CT chest and abdomen scan are typically used for the initial assessment of patients who are susceptible to lung cancer **[10]**. The accurate identification of specific histological subtypes requires tissue samples obtained by a variety of techniques, including bronchoscopy, trans-bronchial needle aspiration, trans-thoracic needle aspiration and core biopsy **[11]**.

It is also important to note that, in addition to tumour tissues, liquid biopsy has just recently emerged as a useful source of material for diagnostic purpose, not only for lung cancer, but many other types of cancer. Technological progress and the accumulation of new knowledge have led to a situation in which it is essential to collect substantial quantities of samples through minimally invasive techniques for the comprehensive analysis of a growing array of unique biomarkers. This issue is that we frequently require new tissue sources because conventionally obtained cytological samples are insufficient for thorough molecular analysis. Liquid biopsy is defined as a non-solid biological material/tissue sample, in theory. Any material derived from tumours that circulates in the blood or any other bodily fluid is known as a liquid biopsy. Circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) are the blood components most often researched or utilized in the diagnosis of non-small cell lung cancer (NSCLC). Exosomes contains proteins and RNAs released by the tumour in the surrounding environment, which can have important diagnostic, prognostic and therapeutic applications **[12, 13]**.

1.5 Tumour Staging

Lung cancer is classified utilizing TNM international staging, a system established by the Union for International Cancer Control (UICC) and the eighth edition of the American joint committee on cancer (AJCC) is constantly being updated **[14]**.

The TNM staging system (*Table 1*) attempts to describe the neoplasm physically: **T** describes the neoplasm's physical characteristics; **N** denotes the presence and location of lymph node (LN) metastases; and **M** denotes presence or absence of distant metastases **[15]**. TNM stages I through IV are categorized into condensed phases that serve as a framework for therapy **[14]**.

Table 1: TNM Staging of Lung Cancer [15].

T	N	M
Tis - Carcinoma *in situ*	**N0:** No regional lymph node metastasis	**Mx -** It is impossible to assess distant metastases.

Tx - Cytology is positive.	**N1:** Ipsilateral peri-bronchial, ipsilateral hilar involvement	**M0:** no distant metastases.
T1a: ≤ 2cm in diameter	**N2:** Ipsilateral mediastinal, subcarinal involvement	**M1a:** Separated tumour nodule/s in the contralateral lung: pleural nodule tumour or malignant pleural effusion/ pericardial effusion.
T1b: > 2cm - 3cm in diameter.	**N3:** Contralateral mediastinal or hilar, scalene or suprascapular	**M1b:** Distant metastasis.
T2a: > 3cm but < 5cm (or tumour with any other T2 descriptor - main bronchus, > 2cm from carina, invades visceral pleura, partial atelectasis - but < 5cm).	**N4:** Contralateral mediastinal or hilar, scalene or suprascapular	
T2b: > 5cm but < 7cm **T3:** >7cm or spread into chest wall, mediastinal pleura, pericardium, diaphragm, main bronchus 2cm from carina, total atelectasis, phrenic nerve, multiple nodules in same lobe		

T4: Invasion of the mediastinum, heart, great vessels, carina, oesophagus, vertebrae, and trachea; nodules in more than one lobe of the same lung**.**		

The resulting TNM stage is then used to determine a unified stage. This unified stage as depicted in Figure 2, Figure 3, and Figure 4 is widely recognized by the lay people, with Stage I indicating the early phase of cancer and Stage IV denoting the most advanced stage, often indicating the presence of metastatic disease **[16].**

In the context of resected tumours, the process of pathological staging, involving the methodical examination of the resected specimens, serves as the most robust prognostic factor and plays a crucial role in informing subsequent therapeutic interventions **[9]**.

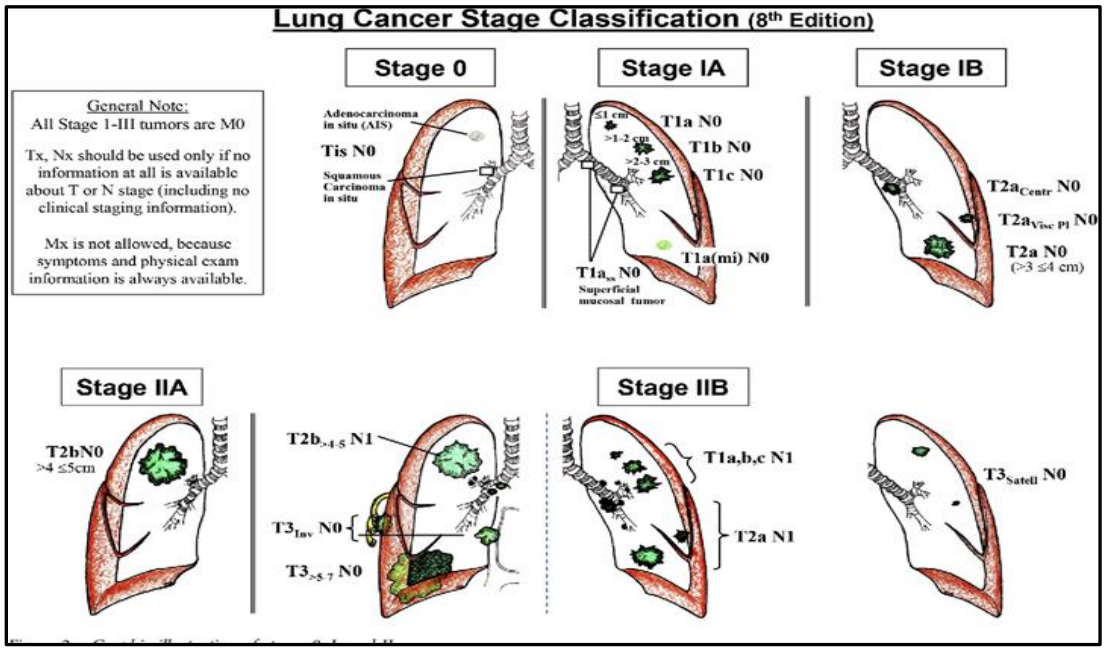

Figure 2: Graphic illustration of Stage 0 (Tis N0), Stage IA (T1a-c N0 M0), Stage IB (T2a N0 M0), Stage IIA (T2b N0 M0) and Stage IIB (T1a-c N1 M0, T2a-b N0 M0 and T3 N0M0) [16].

General Note: as illustrated in Figure 2

1. All stage I to III tumours are M0.
2. Tx Nx should be used only if no information at all available about T or N stage (including no clinical staging information).
3. Mx is not allowed, because symptoms and physical examination is always available

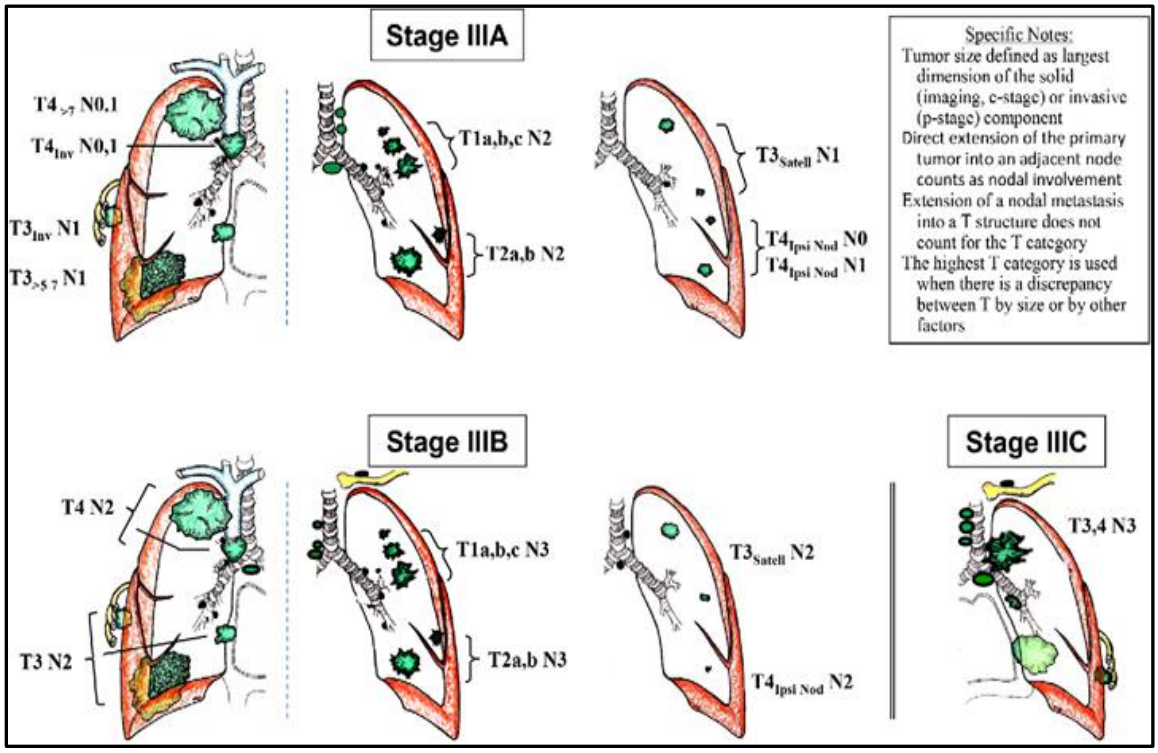

Figure 3: Graphic illustration of stage IIIA (T1a-c N2 M0, T2a-b N2 M0, T3 N1 M0, T4 N0 M0 and T4 N1 M0), Stage IIIB (T1a-c N3 M0, T2a-b N3 M0, T3 N2 M0 and T4 N2 M0) and Stage IIIC (T3 N3 M0 and T4 N3 M0). [16].

Specific notes: as illustrated in Figure 3

1. Tumour size defined as largest dimension of the solid (imaging, c-stage) or invasive (p-stage) component.
2. Direct extension of the primary tumour into an adjacent node counts as nodal involvement.
3. Extension of the nodal metastasis into a T structure does not count for the T category.
4. The highest T category is used when there is a discrepancy between T by size or other factors

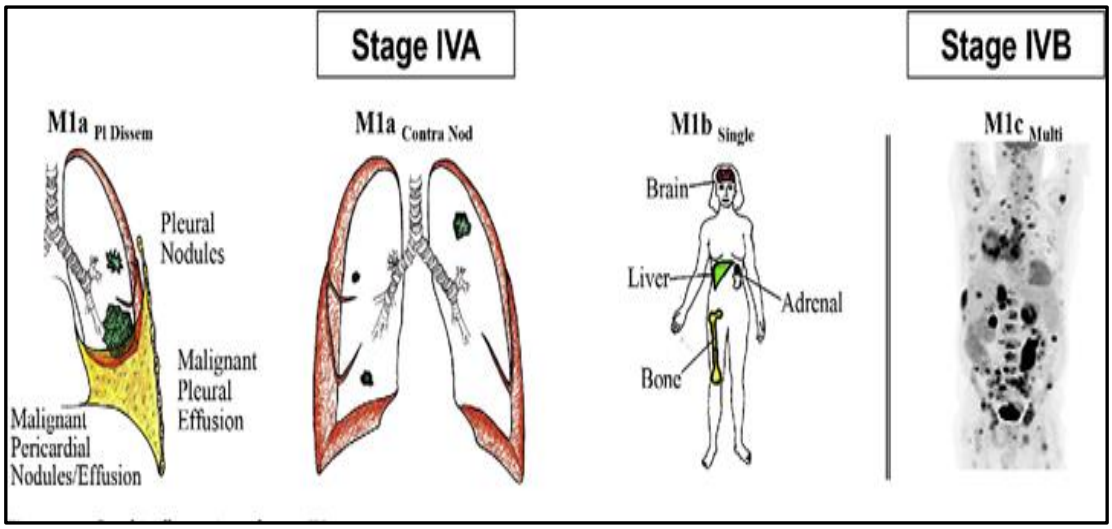

Figure 4: Graphic illustration of Stage IV (Any T Any N M1). M1 is further divided into M1a, M1b (single organ outside chest) and M1c (multiple metastases i.e. one or more organs) [16].

Specific Note: as illustrated in Figure 4

1. M1a is divided into:

- *M1a- Pleural: cancer present in pleural and pericardial nodules*
- *M1a- Contralateral: Cancer presents in separate tumour nodule in opposite lobe of lung*
- *M1a- Effusion: fluid around lung or heart that contains cancer cells, i.e. malignant pleural effusion and malignant pericardial effusion.*

1.6 Treatment and Prognosis

Since the development of minimally invasive surgery, video-assisted thoracoscopic surgery (VATS) is now the most commonly used procedure, and VATS lobectomy has become a standard surgical procedure for stage I NSCLC **[17,18]**. In terms of surgical outcomes, VATS lobectomy has a number of advantages over open thoracotomy including less postoperative pain, shorter hospital stays, fewer complications and earlier functional recovery **[17,18]**.

Stage I and stage II patients have 5-year survival rates of nearly 75% and 55%, respectively **[19]**. Individuals with stage IIIA and stage IIIB prior to surgery are less likely to be cured by surgery alone, but they may be considered operable in the case of a trial of combining surgery with adjuvant treatment. Stage IV tumours and stage IIIC tumours with node involvement should generally be regarded as inoperable **[19]**.

Patients in Stage I-II and rare cases of Stage III, where the tumour is deemed operable, frequently undergo surgical intervention aimed at achieving a radical excision. The resection margin clearance is R0, not means radical occurrence of an incomplete (R1-2) excision ranges from 2% to 17% and is linked to a reduced overall survival and increased risk of recurrence in comparison to an R0 excision **[4, 20, 21, 22]**.

The presence of visceral pleural invasion (VPI) was a major predictable risk for patterns of recurrence following resection, including pleural seeding and bilateral lung metastases in patients with NSCLC, especially adenocarcinoma **[23]**.

The remaining cancer cells persisting in situ following a non-radical surgical removal offer justification for additional therapeutic interventions in the form of adjuvant Chemotherapy, Adjuvant radiation and sequential or concurrent chemo-radiotherapy. Nevertheless, there is a scarcity of data regarding the most effective supplementary treatment strategy **[20, 24, 25]**.

1.7 Recurrence statistics

Surgical management of early-stage lung cancer offers the highest long-term chances of survival, either on its own or as a part of multimodality treatment.

Recurrence of the disease is as real concern and approximately 20% of all NSCLC patients experience relapse after complete removal of the tumour **[26,27]** and this significantly increases depending on the stage of lung cancer **[26]**. There are evidence of prognostic factors influencing the recurrence such as type of tumour **[27]**, tumour stage **[27,28,29]** surgical technique **[27]** neo/ adjuvant therapy **[30]**. Thus, postoperative NSCLC recurrence has been linked to a poor prognosis.

To achieve enhanced patient selection accuracy and ensure a complete cure, it is imperative to engage in thorough research and analysis to comprehend the variables that impact cancer recurrence post-surgery.

1.8 Research Question

What are the factors influencing rate of cancer recurrence in NSCLC patients after curative surgery?

Hypothesis, H_1: there is an association between cancer recurrence and Patient factors (age, sex, smoking, co-morbidities), Pathological factors (tumour histology, tumour stage and angiolymphatic invasion), surgical factors (the optimization of surgical margin in relation to tumour size, resection extent and surgical technique) and adjuvant therapy (adjuvant chemotherapy, combined or sequential chemo-radiation and radiotherapy), against the alternative, H_0: there is no association between cancer recurrence and patient factors, pathological factors, surgical factors and adjuvant therapy.

1.8.1 Research Aims

- Ascertain rate of recurrence in NSCLC patient treated with curative surgery.
- Identify factors influencing the rate of recurrence in lung cancer patients after curative surgery.

1.8.2 Research Objectives

- To determine the rate of recurrence following lung cancer surgery in our local population
- To identify factors that predict recurrence in patients with resected NSCLC, specifically:

- To determine how patient variables such as age, gender, smoking and comorbidities (diabetes, respiratory problem, cardiovascular problem, previous cancer) influence lung cancer recurrence.
- To evaluate the association of operation performed (wedge resection vs. lobectomy vs. pneumonectomy), surgical approach (VATS vs. open), surgical margin, lymph node sampled/ dissection with rate of recurrence.
- To assess the relationship between tumour variables – tumour histology, tumour location, tumour staging, visceral pleural invasion, residual tumour staging - and rate of recurrence.
- To compare the rates of local and distant metastasis.

2 Methodology

2.1 Research Design and Selection Criteria

This study employs an observational cohort design aimed at identifying the variables that could potentially impact the recurrence rate subsequent to surgical treatment for lung cancer.

A total of 338 patients were reviewed who had been diagnosed with lung cancer at East and North Hertfordshire (ENH) NHS Trust and had undergone curative surgery at Papworth or Harefield Hospital during the period of 2010 to 2019 and clinical information was extracted from documents such as clinical letters, radiology reports, multidisciplinary team (MDT) outcomes, surgical documentation, radiology and pathology reports as well as the yearly surveillance radiology scans up to 5 years post treatment or curative intent surgery.

The inclusion criteria (Table 2) were composed of the subsequent aspects: (1) diagnosed with NSCLC and all subtypes (Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) (2) had curative intent surgery or surgery within a multimodality treatment approach and (3) received either long term surveillance or adjuvant therapy post-surgery.

Table 2: Selection Criteria.

Inclusion Criteria	Exclusion Criteria
1. Diagnosis: NSCLC (adenocarcinoma, squamous cell carcinoma and large cell carcinoma)	1. Diagnosis: other cancers (small cell carcinoma, mesothelioma, carcinoid tumours, thymoma, hamartomas)
2. Underwent curative intent surgery or had surgery as a part of multimodality treatment.	2. Stage 4 NSCLC or NSCLC patients who did not have curative intent surgery.
3. Long term surveillance follow-up or post operative adjuvant therapy.	3. Neither long term surveillance follow-up nor post operative adjuvant therapy

Among these patients, 86 individuals who were diagnosed with small cell carcinoma, mesothelioma, thymoma, carcinoids, or advanced NSCLC who did not undergo curative surgery were excluded (Table 2) from the study cohort.

2.2 Study Population

The studied population (Figure 5, Figure 6) consisted of 252 consecutive patients, with 114 (45.24%) being females and 138 (54.76%) males, having a mean age of 69.62 ± 8.35 years and an age range of 43-91 years. These patients were diagnosed with NSCLC, including 163 adenocarcinomas, 72 squamous cell carcinomas, 12 with mixed histology, and 5 large cell carcinomas, at the East and North Hertfordshire NHS Trust. They underwent curative surgery at Papworth Hospital or Harefield Hospital between 2010 and 2019. The surgeries involved 200 lobectomies, 13 pneumonectomies, and 37 wedge resections, with most including extensive mediastinal lymph node dissection. Among these cases, 64 individuals received adjuvant chemotherapy, 11 patients received sequential or concurrent chemo-radiation, and 7 patients underwent adjuvant radiotherapy. The remaining 170 patients either did not require adjuvant therapy or chose not to undergo it.

All participants in the study underwent a comprehensive surveillance regimen extending up to five years, which included annual radiological imaging for the purpose of identifying recurrences. The mean for the follow up time for detection of recurrence within the cohort population was calculated to be 868.69 ± 763.81 days.

Furthermore, Among these 252 patients, 62 experienced cancer recurrence, with 33 patients that showed recurrence at local sites and 29 patients with distant recurrence.

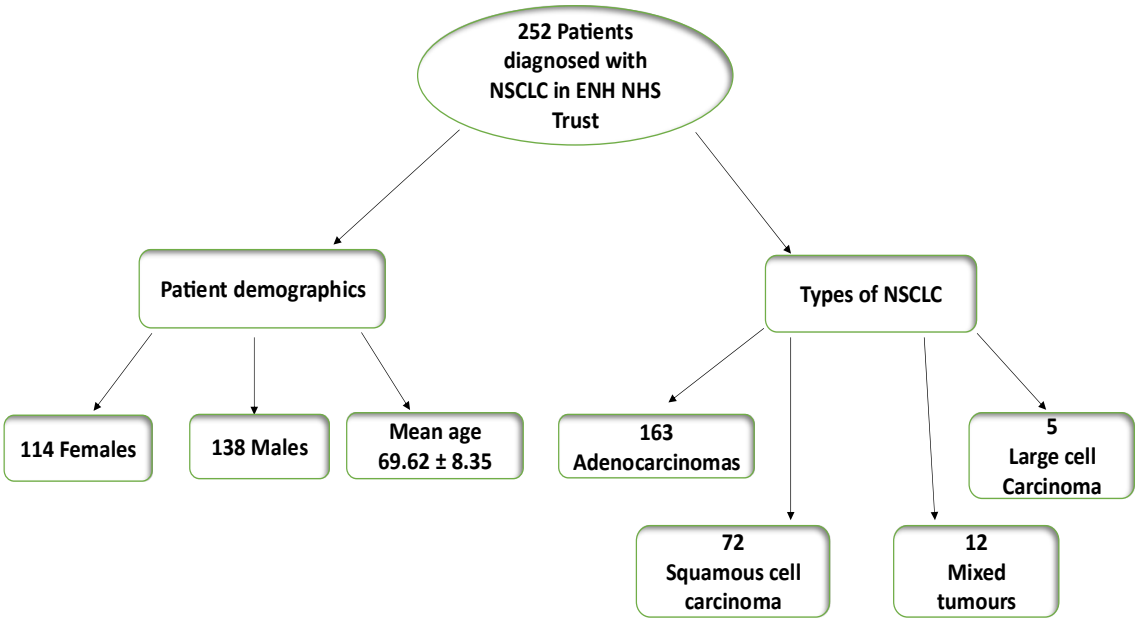

Figure 5: Flow chart of distribution of patients for study population.

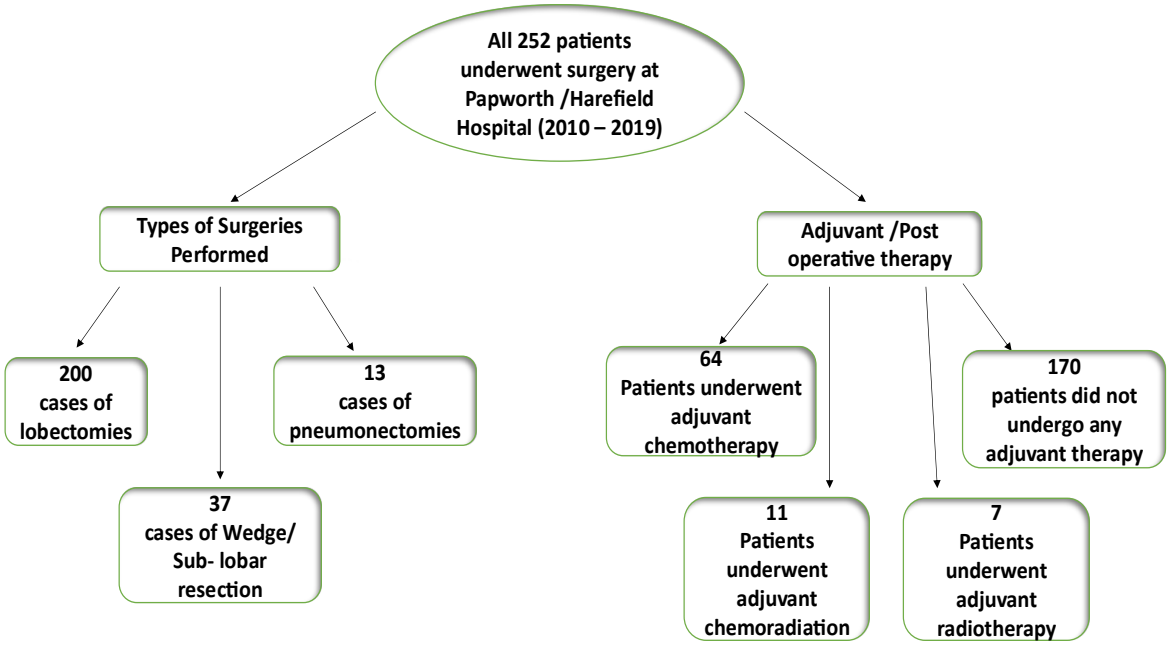

Figure 6: Flow chart of distribution of patients for study population.

3.3 Data Collection

The demographic characteristics of the patient (including age, gender, smoking history, presence of comorbidities (diabetes, respiratory problems and cardiovascular diseases), and history of previous cancers), tumour characteristics (such as, tumour type and tumour staging), specifics of the treatment administered (including year of diagnosis, date of surgery, type of surgery performed, surgical approach, extent of nodal dissection, visceral pleural invasion status and resection margin), as well as information on adjuvant therapy (chemotherapy, combined or sequential chemo-radiation and radiotherapy) and post-treatment follow-up or surveillance up to 5 years with yearly radiological scans (including details on recurrence and survival outcomes) were obtained from the National Lung Cancer Database. The dataset was constructed and further segregated as shown in Table 3 to conduct a more complex analysis of variables.

Table 3: Overview of each Variable within the dataset.

Variables	Description
DOB	Date of birth of patient [dd/mm/yyyy]
Sex	Sex of patient [M male; F female]
Age	Age of patient at the time of diagnosis [Age = DODx – DOB]
Smoking	History of smoking [0 non-smoker; 1 Smoker]
Diabetes	History of Diabetes [0 Non diabetic; 1 Diabetic]
Respiratory problems	History of Respiratory Problems [0 No; 1 Yes]
Cardiovascular problems	History of Cardiovascular problems [0 No; 1 Yes]
Previous Cancers	History of previously diagnosed cancers [0 No; 1 Yes]
DODx	Date of diagnosis of patient [dd/mm/yyyy]

Type of tumour	Type of NSCLC tumour [0 Mixed histology; 1 Adenocarcinoma; 2 Squamous cell carcinoma; 3 Large cell carcinoma]
Tumour location	Location of primary tumour [1 RUL; 2 RML; 3 RLL; 4 LUL; 5 LLL, 6 Right lung NOS; 7 Left lung NOS; 8 Both Lungs NOS]
Tumour staging	TNM staging of tumour used to derive a unified stage of tumour [1 Stage 1, 2 Stage 2, 3 Stage 3, 4 Stage 4]
DOSx	Date of curative surgery [dd/mm/yyyy]
Type of Surgery	Operation performed on patient [1 wedge resection; 2 Lobectomy; 3 Pneumonectomy]
Nodal dissection	Patient underwent Lymph-node dissection or nodal sampling [0 Incomplete/ Sampling; 1 Complete dissection]
Surgical approach	Open Thoracotomy or VATS [0 open; 1 VATS]
Pleural invasion	Visceral Pleural invasion status [0 No; 1 Tumour invades beyond pleura]
Resection margin	Resection margin [0 Negative for residual tumour; 1 Positive for residual tumour
Post-surgery Treatment	Adjuvant therapy after surgery [0 None; 1 Adjuvant Chemotherapy; 2 Chemo-radiotherapy; 3 Radiotherapy]
Date of Recurrence	Date of tumour recurrence after curative surgery [dd/mm/yyyy]
Type of Recurrence	Local or distant recurrence [0 no recurrence; 1 local; 2 distant]
Date of Death	Date of patient demise [dd/mm/yyyy]

3.4 Statistical Analysis

Descriptive statistics were recorded as absolute and relative frequencies, mean ± standard deviation, range as well as prevalence of cancer recurrence. Additionally, we performed chi-squared test for recurrence (outcome) and recurrence predictors (exposure) of interest to explore any association between them. chi-squared test was performed only for categorical exposures. For continuous exposures (age and tumour stage), we performed t-test instead of chi-squared test.

Additionally, multivariate analysis using logistic regression was also carried out to determine other independent predictors of the hazard of cancer coming back while other factors are controlled for. The analyses were done in R software version 4.3.3 and SPSS to enhance the reliability and exhaustiveness of the assessment on the identified dataset.

3.5 Ethical Considerations

We used a retrospective study design. Patients did not undergo any novel interventions. Analysis was performed using anonymised data. Approval for this study was granted by the ENH Trust as a service evaluation (reference number: SE2024018). Hence, approval from UH Health, Science, Engineering and Technology Ethics Committee with Delegated Authority (ECDA) committee were deemed unnecessary.

3 The Impact of the patient variables on cancer recurrence.

3.1 Introduction

Despite the advancements in oncology, lung cancer remains the major contributor to mortality from malignant neoplasms **[31,32]**. The condition is often associated with elderly individuals and individuals who have been smoking for a prolonged time, resulting in a considerable number of patients with coexisting health conditions **[33]**.

The occurrence of lung cancer is documented to be correlated with age. The majority of patients present with advanced-stage illness upon initial diagnosis. The occurrence of primary lung cancer was predominantly identified in elderly populations in the past **[34]**. Nevertheless, the association between survival rate and the age at which the disease is diagnosed is a topic of debate. Currently, there is limited research investigating the connection between age and the clinical and pathological features of individuals diagnosed with NSCLC. Elderly patients demonstrate increased mortality rates when compared to younger individuals across a variety of solid cancer types, regardless of the specific clinical features of the primary neoplasm. This trend is observed even in patients diagnosed with advanced or metastatic NSCLC **[35]**.

Gender, conversely, has been proposed as an independent prognostic factor that influences the outlook of patients who have undergone treatment for NSCLC. Several retrospective analyses have documented enhanced survival rates among female patients who have undergone NSCLC resection in comparison to their male counterparts with similar TNM staging **[36, 37, 38, 39, 40, 41]**. Research has documented that the recurrence patterns exhibited comparable characteristics in both male and female subjects, and the gender of the patient did not correlate with an elevated risk of recurrence **[27, 42]**

Recognized as a well-established environmental risk factor for NSCLC, cigarette smoking plays a crucial part in the advancement of lung carcinogenesis. Research studies indicate that individuals who smoke are at a greater risk of developing NSCLC and experience a poorer prognosis compared to non-smokers **[43, 44, 45]**. There exists empirical evidence suggesting that individuals who persist in smoking after a diagnosis of early-stage lung carcinoma exhibit an elevated risk of

recurrence, the emergence of a second primary neoplasm, or overall mortality in comparison to those who cease smoking at that juncture **[46,47]**.

Throughout the historical timeline, therapeutic determinations in the domain of oncology have predominantly emphasized parameters such as the disease's stage and the individual's performance status (PS). Nonetheless, the importance of additional factors such as the prevalence of comorbidities and their impact on treatment outcomes has largely been overlooked. Among elderly individuals with cancer, these coexisting conditions tend to escalate with advancing age, potentially impacting survival rates and exacerbating the likelihood of treatment-related complications **[48]**.

We aim to evaluate the patient-related variables that encompass demographic factors such as age and sex, a history of smoking, as well as pre-existing medical conditions including diabetes mellitus, respiratory ailments, cardiovascular diseases, and prior cancer history, and their influence on the recurrence of cancer in patients with n NSCLC following curative resection.

3.2 Methods

252 patients, who had been diagnosed with non-small cell lung carcinoma at the ENH NHS Trust and had undergone surgery with curative intent surgery between 2010 to 2019, were systematically reviewed for the purposes of this retrospective analysis, and relevant data was collected.

The patient-related variables consisted of demographic factors such as age and sex, a documented history of tobacco use, in addition to pre-existing medical conditions including diabetes mellitus, respiratory disorders, cardiovascular diseases, and previously identified malignancies.

As elaborated in Chapter 2, the age at the point of diagnosis was calculated by deducting the date of birth from the date of diagnosis. The smoking status was stratified into non-smokers and individuals with a history of smoking, which comprises both current smokers and those who have quit smoking. The history of diabetes, respiratory conditions, cardiovascular diseases, and previously diagnosed cancers were regarded as comorbidities or pre-existing health issues among the subjects of this study.

Descriptive statistics were recorded for the patient- related variables. Consistent with the methodology outlined in Chapter 2, we conducted chi-squared tests and t-tests to investigate the associations between recurrence and patient related variables.

3.3 Results

3.3.a. Age

The average age was determined to be 69.62 years, with a standard deviation of 8.35 years, and ages ranged from 43 to 91 years. The average age of patients who experienced a recurrence of lung cancer was 68.53 years ± 8.76076, whereas the average age of those who did not experience recurrence was 69.97 years ± 8.21282.

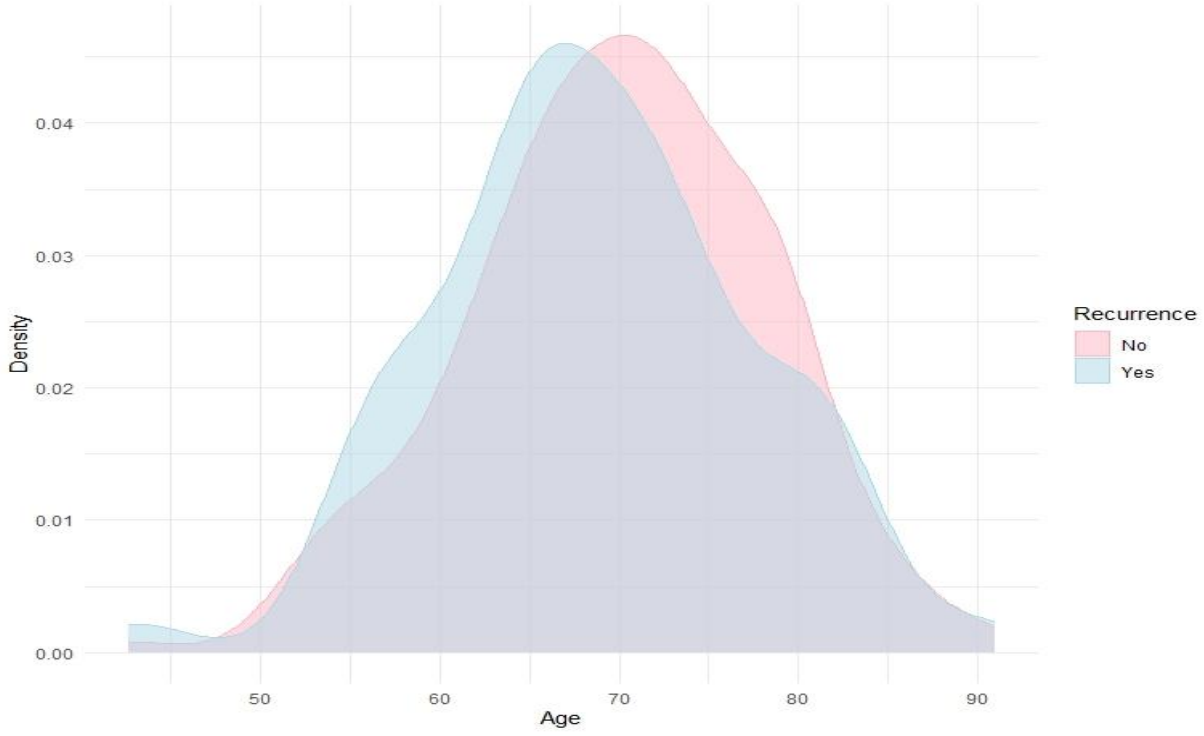

Figure 7: Patient age at cancer diagnosis stratified by recurrence status. The age of patients at the time of diagnosis (ranging from 50 – 90 years old) is plotted on the X-axis while the recurrence probability density at a given age is plotted on the Y-axis. Pink curve (No): density of ages where recurrence did not occur. Blue curve (Yes): density of ages where recurrence occurred.

The graph in Figure 7 shows a bimodal distribution for both recurrence and non-recurrence cases. This suggests that there are two predominant age groups within the population where the probabilities of recurrence and non-recurrence peak. For non-recurrence cases, the primary peak appears to be centred around the mid-60s, with a secondary peak around the mid-70s. This indicates that there is a higher probability of individuals not experiencing a recurrence in these age ranges. Conversely, for recurrence cases, the primary peak appears to be centred around the mid-70s, with a secondary peak around the mid-60s. This suggests that individuals in this population are more likely to experience a recurrence as they get older, especially in the 70-80 age range. The overlapping nature of the two curves, especially in the mid-60s to mid-70s age range, suggests that age alone is not a definitive predictor of recurrence status, and other factors likely play a role. However, this graph provides valuable insights into the age-related patterns of recurrence probability within the population.

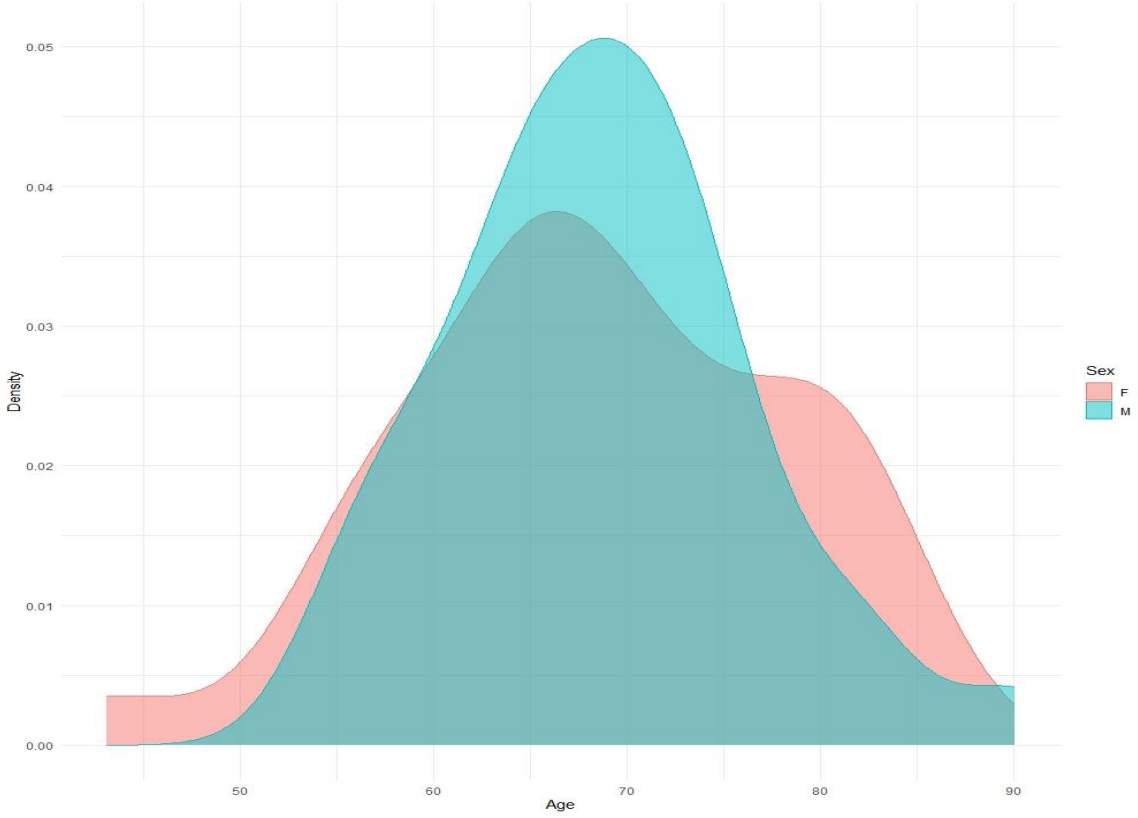

Figure 8: Density curve of sex-stratified age of patients showing recurrence. The age ranging from 50 to 90 years old is plotted on the X-axis while recurrence probability density of a particular age value is plotted on the Y-axis. Pink curve (F): density distribution for females and blue curve (M): density distribution for males.

The mean age for females who experienced cancer recurrence was recorded as 68.28 ± 9.87 years. The mean age for males who experienced recurrence was 68.74 ± 7.84 years. The graph in Figure 8 illustrates the density distribution of age across different sexes that shows a clear bimodal distribution for females, with two distinct peaks. This suggests that there are two predominant age groups within the population represented in the data. For females, the primary peak appears to be centred around the mid-60s, with a secondary peak around the mid-70s. This indicates that there is a higher probability of females being in these age ranges compared to others. For males, the primary peak appears to be centred around the early-70s, with a secondary peak around the early 60s. This suggests that males in this population tend to be slightly older on average compared to females. The overlapping nature of the two curves, especially in the mid-60s to mid-70s age range, suggests that there is a significant degree of overlap in the age distributions between the sexes. However, the distinct peaks and the slight shift in the primary peaks indicate that there are some underlying differences in the age patterns between females and males.

3.3.b. Sex

Our research cohort comprised of 114 [45.24%] females and 138 [54.76%] males. 24.56% of female within the sample experienced cancer recurrence. 24.64% of males within the sample experienced cancer recurrence. The prevalence of cancer recurrence among males are slightly higher than the females but almost indistinguishable.

Mean time to recurrence among males was 852.15 days (SD 679.37) ranging from 55 days to 3235 days. Mean time to recurrence among females was 889.69 days (SD 872.88) ranging from 151 days to 3583 days.

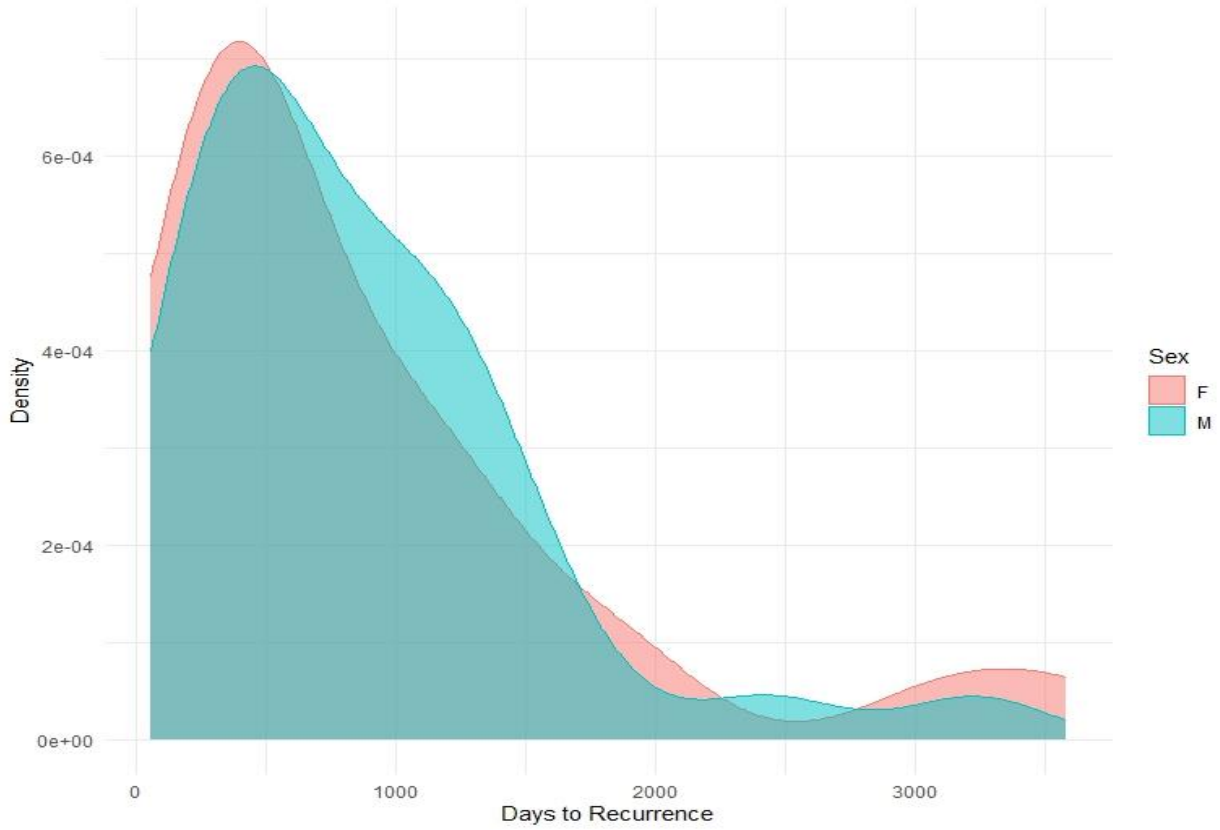

Figure 9: Sex-stratified density curve. Days to recurrence ranging from 0 to around 3,000 days is plotted on the X-axis while the recurrence density is plotted on the Y-axis. Pink curve: density distribution for females, while the blue curve: density distribution for males.

The graph in *Figure 9* depicts that the density distribution of time to recurrence (in days) for NSCLC, broken down by sex (female and male), shows a clear bimodal distribution for both females and males, with two distinct peaks. This suggests that there are two predominant time frames within the population where the probabilities of recurrence are highest. For females, the primary peak appears to be centred around 500-600 days, with a secondary peak around 3,000 – 3400 days. This indicates that there is a higher probability of females experiencing a recurrence in these time frames, while for males, the peak appears to be centred around 800-900 days. This suggests that males in this population tend to experience recurrence at slightly longer time frames compared to females. The overlapping nature or fluctuating baseline of the curves, especially in the 2,500-3,000-day range, suggests that sex alone is not a definitive predictor of time to recurrence, and other factors likely play a role. However, this graph provides valuable insights into the sex-related patterns of recurrence probability within the population.

3.3.c. Smoking History

Among the 252 patients included in our study, 189 (93.1%) were documented as ever smokers that comprised of current smokers who persisted in the behaviour following their diagnosis and former smokers who had discontinued smoking either prior to or after the diagnosis of NSCLC, while 14 cases (6.90%) were accounted for nonsmoker. 49 patients had no recorded documentation of smoking history and was hence accounted under missing values.

The prevalence of cancer recurrence among smokers and non-smokers within the cohort population showed 28.57% of non-smokers within the sample experienced cancer recurrence, while 21.69% of ever smokers within the sample experienced cancer recurrence as illustrated in Figure 10.

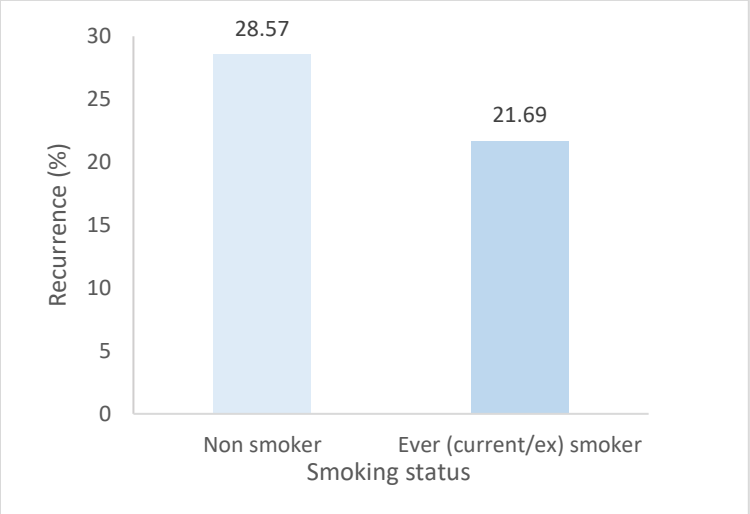

Figure 10: Prevalence of cancer recurrence in Smokers and non-Smokers. The smoking status of the patient is plotted on the X-axis while the prevalence of recurrence (%) is plotted on the Y-axis. Light blue column (non-smoker): patients who never smoked or smoked very little, while the blue column (ever smoker): patient who are current and ex-smokers.

3.3.d. Pre-existing health problems

The pre-existing health conditions such as respiratory ailments, cardiovascular disorders, diabetes, and a prior history of cancer can potentially influence survival rates and aggravating the probability

of treatment-associated complications in patients with NSCLC. In our cohort sample, comorbidities were organized into classifications such as diabetes, respiratory diseases, cardiovascular diseases, and previous cancer. Table 4 shows the distribution of patients with pre-existing health problems within the study population.

Table 4: Incidence of pre-existing health problems within the cohort population.

Pre-existing health problems		Number of patients		Total number of patients documented
		Frequency	(%)	
Diabetes	Yes	27	13.5	200
	No	173	86.5	
Respiratory diseases	Yes	98	49.49	198
	No	100	50.51	
Cardiovascular diseases	Yes	86	43.43	198
	No	112	56.57	
Previous Cancer	Yes	54	21.43	252

The clustered bar graph in Figure 11 shows prevalence of recurrence among patients with pre-existing health problems. 14.8% of diabetic patients experienced cancer recurrence, while 24.28% experienced recurrence among non-diabetic individuals. Among patients with pre-existing respiratory disease, 21.43% experienced cancer recurrence, in contrast to 25% among those

without a history of respiratory comorbidities. Similarly, 17.44% of patients with pre-existing cardiovascular disease experienced cancer recurrence, while 27.68% of patients without a cardiovascular disease history experienced cancer recurrence. Moreover, 27.78% of patients with a previous cancer history experienced cancer recurrence, compared to 23.74% of patients without a prior cancer history.

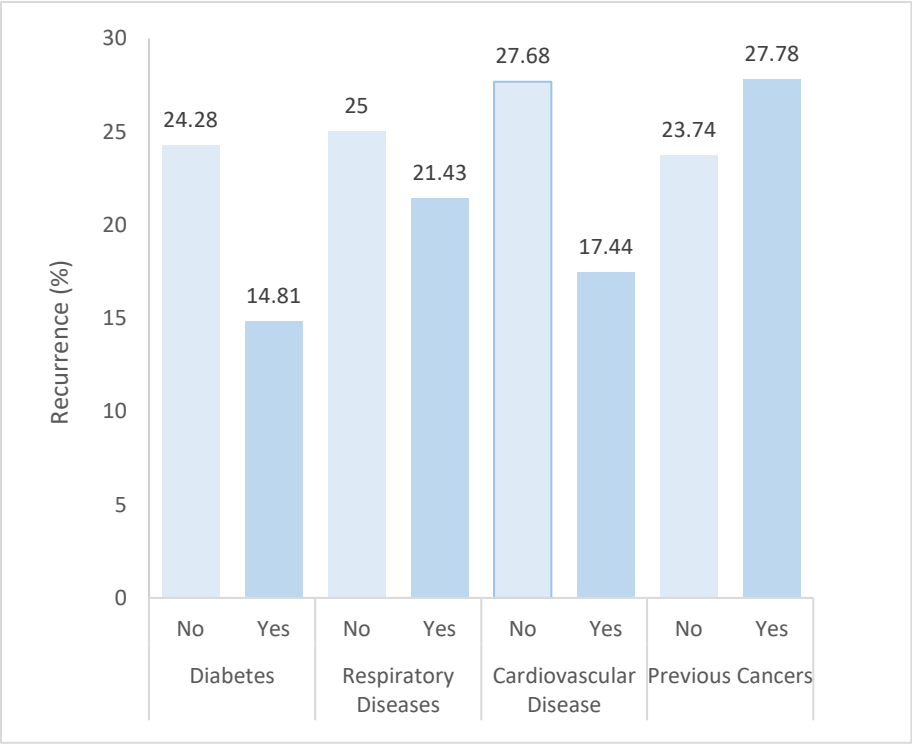

Figure 11: Pre-existing Health problems stratified prevalence of cancer recurrence. The type and status of pre-existing health problems (patients with and without diabetes, respiratory disease, cardiovascular disease and previous cancer) is plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis. Light blue columns (No): patients with no pre-existing health problems, while blue columns (Yes): patients with history of pre-existing health problems.

3.3.e. Statistical analysis

From the data collected, we have then performed statistical analyses to identify potential factors that might contribute to lung cancer recurrence. In the univariate analysis conducted with the t-

test, the results indicate that there is no significant relationship between cancer recurrence and the age of the patient, as recorded by a p-value of 0.2584 (Figure 7).

Similarly, the univariate analysis utilizing the chi-squared test, as illustrated in Table 5 indicates that there is no statistically significant relationship between cancer recurrence and the patient's sex, indicated by a p-value exceeding 0.05. Additionally, the analysis shows no significant correlation (p-value > 0.05) between cancer recurrence and smoking habits. Moreover, there is insufficient evidence to suggest an association (p-value >0.05) between cancer recurrence and pre-existing health conditions such as diabetes, respiratory diseases, cardiovascular diseases, and a prior history of cancer.

Table 5: Univariate Analysis to explore association between patient variables and cancer recurrence using Chi-squared test.

Variables	Chi-squared stats	P-value
Sex	6.40E-31	1
Smoking	0.069924	0.7914
Diabetes	0.70696	0.4005
Respiratory diseases	0.18205	0.6696
Cardiovascular disease	2.3131	0.1283
Previous Cancer	0.18734	0.6651

3.4 Discussion

The mean age of patients at the time of diagnosis and curative surgery within our cohort study was observed as 69.62 years with standard deviation of 8.35, which is similar to published data **[27]**.

In individuals who underwent curative intent surgery, there was a notable correlation between advanced age and reduced overall survival and recurrence, as indicated by Wang C. et al **[49]**. The influence of age on predicting outcomes stands out as an autonomous variable, with younger individuals demonstrating a more favourable prognosis with decreased risk of recurrence, according to research by Chen T. et al **[35]**. Tas et al **[50]** established that advanced age serves as a significant negative prognostic indicator. Furthermore, they identified that this could be due to numerous concurrent health conditions and present signs of frailty. In the studied cohort, the older group was significantly larger than the younger one. Despite, the mean age being almost indistinguishable between the patients who had recurrence and who did not have recurrence, it was apparent that the current research elucidated that participants within the examined demographic exhibited an increased propensity for experiencing recurrences as they progress in age, especially among the subgroup of individuals aged 70 to 80 years. This finding aligns with several published data **[49,50]**. Consequently, the data indicate a reduced probability of recurrence in younger age groups, similar to what proposed by Chen T. et al **[35]**.

The evolution of lung cancer from primarily afflicting men to affecting individuals regardless of gender represents the change in smoking habits following the Second World War **[42]**. In 2002, Kellar et al **[42]** reported a similarity in the recurrence patterns between male and female patients. Similarly, even though the mean age for the recurrence of cancer was equivalent between male and female subjects with the studied cohort, it remains evident that males within this demographic exhibit a marginally elevated average age in comparison to females.

The time to recurrence in our cohort demonstrates a similar trend across both male and female. More specifically, the average time to recurrence from the date of surgery was documented at 852 days for males, with a standard deviation of 679 and 889 days for females, with a standard deviation of 872. This suggests that females in this population tend to experience recurrence at slightly longer time frames compared to males.

Despite significant advancements in tobacco control, the prevalence of cigarette smoking continues to pose a substantial risk for the development of lung cancer **[51]**. Fink-Neuboeck, N. et al **[52]** reported that in the majority of instances, second primary lung cancer is perceived as being caused by tobacco use, following the development of the initial tumour. Recent studies indicates that lung cancer in never smokers (LCINS) exhibits distinct epidemiological, clinic-pathological,

and molecular features when compared to lung cancer in individuals with a history of smoking **[53,54,55,56]**. Notably, LCINS is more prevalent among women, individuals of East Asian ancestry, and younger populations, with adenocarcinoma being the predominant histological subtype **[53, 54, 55, 56, 57]**. The process of lung carcinogenesis is intricate and involves multiple stages characterized by irreversible genetic alterations that disrupt cellular functions such as proliferation and differentiation, ultimately leading to invasion and metastasis **[58]**. Mutations in specific "driver genes" can facilitate uncontrolled cell growth, and certain driver gene mutations are more commonly observed in LCINS. Specifically, mutations in epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma virus (KRAS), as well as rearrangements in anaplastic lymphoma kinase (ALK) represent the three primary recurrent oncogenic changes identified in LCINS tumours, with EGFR mutations being the most prevalent **[59]**.

It has been revealed through this investigation that over 90% of the individuals involved in the research were either active smoker, had ceased smoking prior to or subsequent to their diagnosis of lung cancer. This correlates well with the generally recognized epidemiological features of lung cancer patients, among which 10% of the cases did not smoke, whereas 90% of them were related to smoking factors. While tobacco smoking plays a massive role in lung cancer, other environmental and genetic factors may also contribute to its onset in non-smokers. Interestingly, the prevalence of cancer recurrence was 8% higher in individuals who had never smoked compared to ever smokers. This could be the fact that adenocarcinoma is the most frequently observed histological subtype associated with LCINS and the mutually exclusive occurrence of certain mutations (mutations in EGFR, KRAS, as well as rearrangements in ALK) provides compelling evidence for distinct genetic pathways to cancer in ever-smokers versus never-smokers **[53,54,55,56,57,58,59]**.

Patients with cancer who also have comorbid conditions experience poorer outcomes compared to patients without any comorbidities **[60]**.

Approximately half of the patients exhibited pre-existing chronic respiratory conditions. This could be potentially attributed to the predominance of individuals within this group with an extensive background of tobacco consumption. Numerous studies have illustrated the considerable impact of chronic pulmonary disease and impaired lung function on complications

and mortality among postoperative patients **[61, 62, 63]**. Kim et al **[61]** demonstrated that the impact of COPD on the incidence of postoperative complications is rather modest during the initial phases of the disease, but escalates as spirometric parameters worsen, resulting in the lack of statistically notable variances within the cohort under investigation. The influence of chronic pulmonary disease on cancer recurrence is indeed a subject of ongoing debate. In our study, we found that the incidence of cancer recurrence was not affected by the pre-existing respiratory disease.

43% of individuals presented with cardiovascular disease, including conditions like hypertension, arrhythmias, coronary artery disease, and valvular heart disease. This could possibly be linked to the fact that the average age at diagnosis exceeded 69 years. Elderly individuals presenting with a medical background of chronic illnesses, notably hypertension, and particularly those with cardiac arrhythmias, are at a heightened susceptibility to experiencing complications following surgical procedures as indicated by Lembicz M. et al **[64]**.

It is particularly noteworthy that a limited number of patients exhibited a history of diabetes within the studied cohort, and this condition did not present a significant impact on the recurrence of cancer.
Interestingly, although did not reach significant statistically, our population with co-morbidities shown less recurrence rate than no comorbidities.

Studies indicate patients diagnosed with non-small cell lung cancer (NSCLC) who underwent surgical intervention exhibited notably improved survival rates if they had a previous history of hormone-dependent cancers compared to those with non-hormone-dependent cancers **[65,66,67,68]**. The most prevalent malignancies preceding NSCLC included breast, prostate, and colon cancers **[69]**. A study by Milano et al. utilizing the SEER database analysed 3,529 female patients with NSCLC who had previously been treated for breast cancer. The findings indicated that patients with localized stage II NSCLC experienced a significantly longer overall survival (OS) compared to those with regional and distant stages, with respective OS durations of 5.1 years, 1.9 years, and 4.6 months **[66]**. Similarly, research by Ko et al. revealed that individuals with a history of breast and thyroid cancers had significantly extended OS compared to those with gastrointestinal and genitourinary malignancies **[67]**. Furthermore, Pages et al. reported that NSCLC patients with prior breast and uterine cancers had the highest OS, followed by those with

skin, kidney, colon, rectum, prostate, and bladder cancers **[68]**. On the other hand, Massard et al. conducted an investigation into NSCLC patients with various extra thoracic malignancies, categorizing these prior cancers into tobacco-related, hormone-independent, and miscellaneous types; however, no significant differences in survival were observed among these categories **[70]**. Nakao, K. et al. demonstrated that individuals with a history of cancer exhibit lower survival rates compared to those without such a history, a factor that must be considered when evaluating the feasibility of curative surgical interventions **[71]**. Numerous studies in the current literature examine the influence of prior cancer history on overall survival rates in patients diagnosed with NSCLC. However, the effect of a history of previous cancer on the recurrence dynamics following surgical intervention remains ambiguous. In the studied cohort, we found that patients with a history of previous cancer diagnosis showed a higher incidence of cancer recurrence in comparison to those without a history of previous cancer, although it did not reach statistically significant level.

Overall, the univariate analysis, conducted via the chi-squared test and t-test, did not reveal a statistically significant correlation (p-value >0.05) between cancer recurrence and patient variables like age, sex, smoking habits and pre-existing health problems.

3.5 Conclusion

The role of age as a prognostic factor influencing recurrence is indeed a topic of debate. However, other factors such as tumour characteristics, treatment modalities, and overall health also play significant roles, making it a complex issue.

In the present study, we found no significant gender differences in cancer recurrence and patterns of metastasis. The absence of a measurable gender-specific effect is consistent with existing literature.

Smoking is one of the most recognized risk factors for the development of non-small cell lung cancer (NSCLC), which aligns with our study showing that the majority of patients diagnosed with NSCLC had a prolonged history of smoking. Interestingly, the prevalence of cancer recurrence among smokers was found to be lower than among non-smokers. This phenomenon may be

ascribed to the extensive corpus of research indicating that adenocarcinoma constitutes the predominant histological subtype associated with LCINS, while the distinct presentation of particular genetic mutations (mutations in EGFR, KRAS, as well as rearrangements in ALK) provides compelling evidence for the presence of divergent molecular pathways to oncogenesis in individuals with a smoking history compared to those devoid of such history**.**

There is limited data in the literature regarding the burden of comorbidities influencing NSCLC recurrence, with most studies focusing on the effects of comorbidities on postoperative complications, treatment outcomes, and overall survival. In our study, we found that the majority of patients had coexisting health problems, likely due to the fact that most patients were above 65 years of age at the time of diagnosis. However, compared to patients without comorbidities, individuals with conditions such as diabetes, chronic respiratory disease, or cardiovascular disease were found to have a lower prevalence of cancer recurrence, although statistically not significant.

Interestingly, the current investigation recorded that patient with a history of previous cancer had a higher prevalence of recurrence compared to those without a cancer history, although statistically not significant. There was a paucity of published literature addressing the implications of prior cancer history. The majority of scholarly literature primarily focuses on comprehensive survival rates; however, the impact of previous cancer history on the patterns of recurrence continues to be unclear.

Nonetheless, the univariate analysis, executed through the chi-squared test and the t-test, failed to establish a statistically significant association between cancer recurrence and patient variables such as age, sex, smoking habits and pre-existing health conditions.

4 The Impact of tumour variables on cancer recurrence.

4.1 Introduction

In spite of the notable progresses achieved in both diagnostic methodologies and therapeutic interventions, lung cancer continues to be the foremost contributor to mortality associated with cancer on a global scale **[31,32,72]**. NSCLC constitutes roughly 85% of all lung neoplasms, with ADC and SCC representing the two predominant histological classifications **[3,73,74]**. In contrast, adenosquamous carcinoma and large cell carcinomas exhibit a low incidence; however, they demonstrate a pronounced propensity for invasion and a dismal prognosis **[75, 76].**

To date, numerous investigations have elucidated the prognostic implications of the novel classification system in forecasting mortality and recurrence, predominantly concerning lung adenocarcinoma. However, a limited number of studies have been identified that specifically address squamous cell carcinoma, adenosquamous carcinoma, large cell carcinomas or other subtypes of lung malignancies **[49,77,78,79]**. Among this constrained volume of studies, a notably smaller segment evaluated the prognostic implications of this classification in relation to recurrence behaviour and post-recurrence survival (PRS) in NSCLC, especially in the realm of SCC **[49, 80, 81, 82, 83, 84].**

A variety of modern revisions in the management strategies for individuals diagnosed with NSCLC have led healthcare professionals to consider the histological subtypes while making clinical decisions. Epidemiological data indicate that the prevalence of ADC among individuals with NSCLC has persistently escalated, particularly within the non-smoking female demographic, and it is considered that ADC possesses an intrinsic molecular mechanism that is inherently different from that of SCC. **[85,86,87].** Moreover, although the therapeutic effectiveness of molecular targeted therapies in patients diagnosed with ADC possessing mutations in the epidermal growth EGFR gene or the ALK gene has been extensively documented, such mutations are rarely detected in individuals with SCC **[88,89,90].** Taking into account these variables, a comprehensive examination of the prognostic disparities correlated with the histological classification of NSCLC is increasingly essential.

A multitude of pulmonary neoplasms frequently manifest in particular anatomical regions and exhibit a heightened propensity for metastasizing to favoured sites. Empirical research has

illustrated that the location of the primary tumour holds significant relevance to prognosis and risk recurrence, particularly in the context of resectable NSCLC **[91, 92]**.

Lung carcinoma can further be classified into central and peripheral subtypes based on the location of the primary tumour. The location of the tumour (central versus peripheral) has been identified as a prognostic indicator pertinent to the clinical outcomes associated with lung carcinoma. Nevertheless, the influence of the anatomical positioning of tumours on the dynamics of recurrence continues to be unclear. According to the majority of prior research, neoplasms infiltrating segmental or proximal bronchi have been categorized as central-type tumours; conversely, neoplasms arising in subsegmental or more distal bronchi have been classified as peripheral-type tumours **[93,94]**. Nonetheless, discrepancies in definitions concerning tumour localization persist across various studies.

ADC has traditionally been understood to predominantly manifest in peripheral lung tissues; however, it is also observed in centrally situated lung regions **[95]**. While the majority of SCC is typically found in the main or lobar bronchus, there has been a notable increase in the documentation of peripheral SCC in recent years **[96,97,98,99,100,101,102,103,104,105]**. Furthermore, pulmonary large-cell neuroendocrine carcinoma can similarly be categorized into central and peripheral types based on the tumour's anatomical location.

Recent investigations in the fields of radiology, oncology, and surgical data have demonstrated that the primary anatomical location serves as a critical influence in metastatic lung neoplasms. The identification of such factors is essential for guiding clinical therapeutic interventions. A plethora of studies has demonstrated that peripheral pulmonary neoplasms are associated with a more favourable prognosis, relevant to both squamous cell carcinoma (SCC) and adenocarcinoma (ADC); however, the correlation with recurrence remains a subject of ongoing debate. **[106, 107, 108].**

The TNM classification system presently employed for the categorization of NSCLC was initially introduced in 1940s by Pierre Denoix **[109]** and was formalized by UICC in the 1950s, subsequently undergoing adaptations by the AJCC Staging in 1970s. This staging framework has since undergone additional modifications every 6-8 years and, more recently, in 2016 **[110]**, but the principals remain the same. Lung cancer staging constitutes the systematic evaluation of the extent of the primary neoplasm alongside the dissemination of the neoplastic process within the

organism. The TNM staging framework informs clinical decision-making, delivers prognostic insights and determines suitability for participation in clinical trials, while also facilitating international comparisons **[111,112]**. There exist two principal classifications of staging for NSCLC **[113]**: 1. Clinical staging, 'cTNM' and 2. Pathological staging, 'pTNM'.

Clinical staging is predicated upon thorough history-taking and comprehensive physical examination, in conjunction with laboratory, radiological, and bronchoscopic findings prior to the recommendation of primary therapeutic interventions **[113]**. Pathologic staging is contingent upon both gross and microscopic evaluations of the tumour, as well as additional tissue submitted for analysis. This classification is typically determined based on the entirety of the resection specimen; however, it may also be designated from a biopsy specimen provided that the tissue is sufficient to assess the highest pT category **[114]**. Advancements in the staging process informed by imaging results have facilitated a more precise correlation between clinical staging and the surgical-pathological stage, thereby enhancing the accuracy of prognostic predictions **[115]**. Several past studies have recorded that tumour stage remains the most important prognostic factor in predicting recurrence rates and overall survival **[27,28,29,113, 114, 115,116]**.

Conversely, the pleural invasion by lung tumour was identified as early as 1958 by Brewer **[117]** and associates as a determinant of unfavourable prognosis in lung carcinoma. In addition to the infiltration of the thoracic wall or mediastinal pleura, VPI emerged in the mid-1970s as a distinct entity within the TNM classification, which has remained invariant to this day **[109]**: it elevates the T classification from T1 to T2, whereby a neoplasm of any dimension that invades the visceral pleura is designated as T2 **[112,118]**. Nevertheless, the 7th edition of the TNM lung cancer staging system **[118]** excluded VPI from the tumour size cohort analysis due to a lack of sufficient data and inconsistent pathological methodologies. Currently, there is a lack of additional information regarding the staging characteristics of excised lung cancers that exhibit VPI. Recent research indicates that VPI may not be a poor prognostic indicator for tumours smaller than 3 cm, particularly those under 2 cm in patients with stage I NSCLC **[119,120,121,122,123,124]**. Research with poor outcomes indicated that tumours smaller than 3 cm, particularly those under 2 cm, with VPI should not be reclassified as T2a. These findings contradicted earlier studies that had shown VPI significantly worsened survival rates and increased recurrence risk **[125,126,127,128,129,130,131,132,133]**.

The foundation for defining complete resection was established by the UICC residual tumour classification, which assesses tumour presence or absence in three crucial areas post-treatment: the primary site, lymph nodes, and distant sites **[134,135,136,137]**. The classification's clinical significance stems from its ability to indicate treatment efficacy and guide clinicians in determining the need for additional therapy.

In contrast to complete resection (R0), incomplete resection, which includes microscopic remnants (R1) and gross residual tumour (R2), was significantly associated with a less favourable outcome and increased chances of recurrence **[4,20,21,22,138]**. Nonetheless, a more pressing issue is that numerous patients, even those diagnosed with early-stage NSCLC, have encountered local recurrence subsequent to what is referred to as R0 resection. These findings imply that the UICC R-staging system may not accurately reflect the proportion of patients who have undergone incomplete resection. This prompted surgical professionals to advocate for enhanced delineations of complete resection that integrated quality benchmarks for tumour excision and lymph node classification **[139,140, 141]**.

In the year 2001, the Complete Resection Subcommittee was commissioned by the Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (IASLC) to acknowledge the existence of resections that did not entirely meet the criteria for complete resection, despite the absence of any residual disease, and thus introduced the terminology uncertain resection, subsequently designated as R(un). It is significant to note that this categorization designated cases exhibiting a positive PLC examination result as R(un), in contrast to R1. Furthermore, cases demonstrating extracapsular extension (ECE) of neoplastic tissue in nodes that were excised separately, or those located at the margin of the principal lung specimen, were classified as R1, as opposed to R0 **[118, 137]**.

In this study, we mainly aim to provide an insight about the impact of tumour variables like tumour histology, location of tumour, tumour staging, VPI and residual tumour status – on cancer recurrence.

4.2 Methods

252 patients, who had been diagnosed with non-small cell lung carcinoma at the ENH NHS Trust and had undergone surgery with curative intent surgery between 2010 to 2019, were systematically reviewed for the purposes of this retrospective analysis, and relevant data was meticulously collected.

The tumour-related variables consisted of tumour histology, location of tumour, tumour staging, VPI and residual tumour status.

As detailed in Chapter 2, type of tumour has been classified into several subtypes including adenocarcinoma, squamous cell carcinoma, large cell lung carcinoma, and mixed histology, which encompasses adenosquamous carcinomas and sarcomatoid variants such as pleomorphic carcinoma of the lung, including spindle cell carcinoma.

The anatomical site of the primary neoplasm has been classified into several categories: right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), left lower lobe (LLL), with the designation of right lung not otherwise specified (NOS) incorporating right paratracheal, right hilar, and bilateral involvement, alongside left lung NOS which includes left paratracheal, left hilar, and bilateral participation, as well as both lungs NOS representing synchronous tumours.

Tumour staging has been delineated into Stage I, which comprises stage 1A and 1B; Stage II, which consists of stage 2A and 2B; and Stage III, which encompasses stage 3A, 3B, and 3C.

VPI has been classified as PL0 and PL1-3, while the residual tumour status has been identified as R0 and R1-2.

Descriptive statistics were recorded for the tumour related variables. Consistent with the methodology outlined in Chapter 2, we conducted chi-squared tests and t-tests to investigate the associations between recurrence and tumour related variables.

4.3 Results

4.3.a. Tumour Histology

A majority of 163 (64.68%) patients were diagnosed with adenocarcinoma, whereas squamous cell carcinoma was identified in 72 (28.57%) individuals. Additionally, 12 (4.75%) cases showed mixed histology, with 5 (1.98%) cases identified as large cell carcinoma.

In our cohort population as shown in Figure 12, 8.33% of patients with NSCLC mixed histology experienced cancer recurrence. 26.38% of patients with adenocarcinoma experienced cancer recurrence. 25% of patients with squamous cell carcinoma experienced cancer recurrence. 0% of patients with large cell carcinoma experienced cancer recurrence.

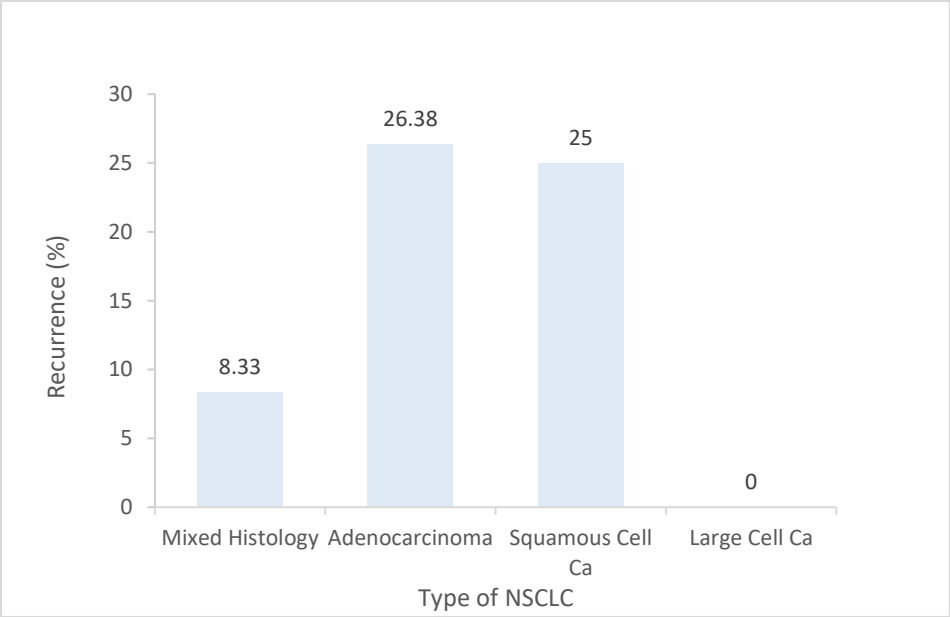

Figure 12: Type of NSCLC tumour stratified prevalence of cancer recurrence. The type of tumour (histology) is plotted on the X-axis while the prevalence of cancer recurrence within each type of tumour (%) is plotted on the Y- axis.

In the examined cohort, within the patients ascertained to have adenocarcinoma, 98 individuals were classified as stage I, 34 as stage II, and 19 as stage III; 12 patients diagnosed with ADC had no recorded documentation of tumour staging and was hence accounted under missing values. Conversely, among the patients diagnosed with squamous cell carcinoma, 43 were categorized as

stage I, 19 as stage II, and 8 as stage III; only 2 patients diagnosed with SCC had no recorded documentation of tumour staging and was hence accounted under missing values.

The prevalence of recurrence for adenocarcinoma and squamous cell carcinoma in relation to the tumour stage is depicted in *Figure 13*. 22.44% of cases of stage I adenocarcinoma experienced cancer recurrence, whereas 23.25% of stage I squamous cell carcinoma cases experienced recurrence. Among stage II adenocarcinoma patients, 38.23% experienced recurrence, while 26.31% of individuals with stage II squamous cell carcinoma encountered a recurrence of cancer. 36.84% of those diagnosed with stage III adenocarcinoma experienced cancer recurrence, in stark contrast to a significant 75% of stage III squamous cell carcinoma patients who experienced recurrence of lung cancer.

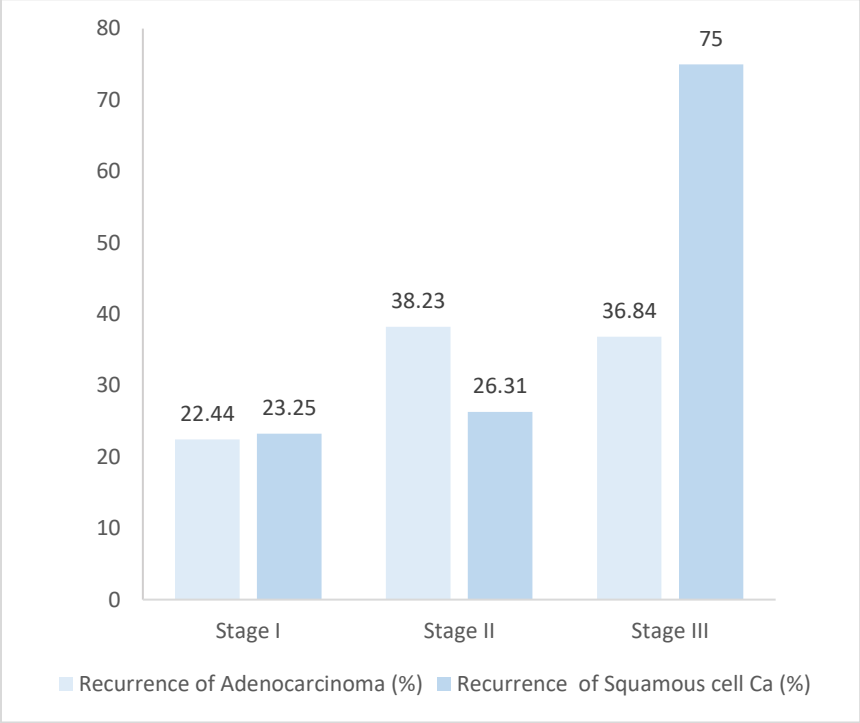

Figure 13: Tumour stage stratified adenocarcinoma and squamous cell carcinoma recurrence. The stages of tumour are plotted on the X-axis while the prevalence of cancer recurrence within adenocarcinoma and squamous cell carcinoma (%) is plotted on the Y-axis. Legend indicates that the light blue columns represent the recurrence of adenocarcinoma in different stages and the blue columns represents recurrence in squamous cell carcinoma in different stages.

4.3.b. Tumour Location

A total of 77 patients, accounting for 30.68% of the entire cohort, were found to have tumours situated in the right upper lobe (RUL). Additionally, 56 patients (22.31%) presented with tumours in the left upper lobe (LUL), while 47 patients (18.73%) had tumours in the right lower lobe (RLL). Tumours located in the left lower lobe (LLL) were identified in 36 patients (14.34%), and 19 individuals (7.57%) had tumours in the right lung, not otherwise specified (NOS). In contrast, only 8 patients (3.19%) had tumours in the right middle lobe (RML), 5 patients (1.99%) had tumours in the left lung NOS, and a mere 3 patients (1.20%) exhibited early synchronous tumours affecting both lungs and had both tumours removed simultaneously. Patients with synchronous tumours were discussed at MDT to determine the final stage of either two synchronous stage one primary tumours or stage 4. Final MDT outcome were recorded and analysed as per MDT outcome accordingly.

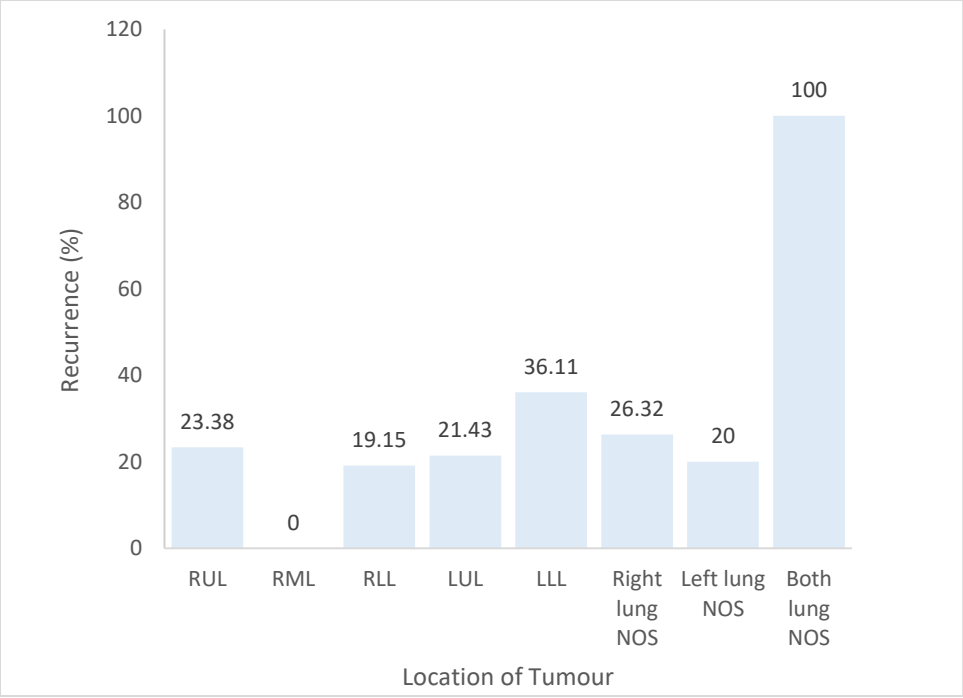

Figure 14: Tumour location stratified prevalence of lung cancer recurrence. The location of tumour is plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis.

A total of 23.38% of patients with tumours situated in RUL experienced a recurrence of cancer. In contrast, 21.43% of patients with tumours in LUL experienced similar outcomes, while 19.15% of those with RLL tumours experienced recurrence. Notably, 36.11% of patients with tumours located in LLL experienced cancer recurrence. Furthermore, 26.32% of patients with tumour classified as right lung not otherwise specified (NOS) experienced recurrence, and 20% of those with left lung NOS tumours experienced recurrence of the disease. Alarmingly, 100% of patients with synchronous tumours affecting both lungs experienced cancer recurrence. It is important to note that patients with tumours in RML did not report any recurrence. The prevalence of cancer recurrence based on tumour location within the cohort is illustrated in *Figure 14*.

To improve the understanding of how tumour location affects cancer recurrence, patients were systematically reclassified into two distinct categories based on the anatomical position of their tumours: those with tumours located in the upper lobes of the lungs and those with tumours situated in the lower lobes. Upon analysis, it was found that a notable 26.51% of patients whose tumours were located in the lower lobes experienced a recurrence of cancer versus 21.28% in the upper lobes.

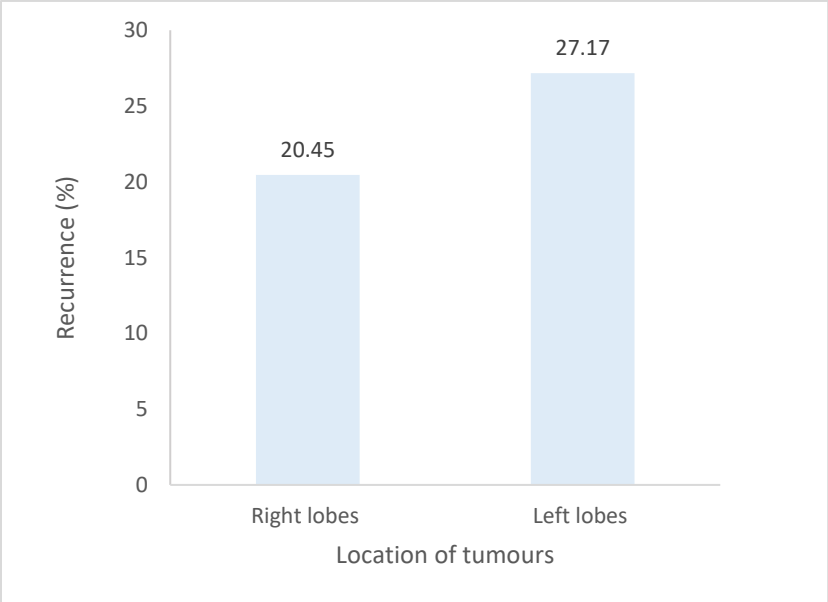

Figure 15: Tumour location (right lobes vs left lobes) stratified prevalence of lung cancer recurrence. The location of tumour is plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis.

Furthermore, patients were methodically categorized into right and left lobes based on the anatomical placement of their tumours. It was observed that a significant 27.17% of patients with tumours situated in the left lobes experienced a recurrence of cancer versus 20.45% in the right lobes. The data suggests that patients with left lobe tumours may require closer monitoring and potentially more aggressive treatment strategies to mitigate the risk of recurrence. The distribution of cancer recurrence in relation to tumour location—specifically comparing the right lobes to the left lobes—within the studied cohort is depicted in *Figure 15*.

Additionally, patients were categorized into two distinct groups based on the anatomical location of their tumours: central tumours, which are located near the trachea or bronchus, and peripheral tumours, which are situated in the peripheral lobes. The analysis of the data revealed a noteworthy finding: a significant 33.33% of individuals diagnosed with central tumours experienced a recurrence of cancer. In contrast, the recurrence rate for patients with peripheral tumours was found to be relatively lower, recorded at 23.21% (*Figure 16*).

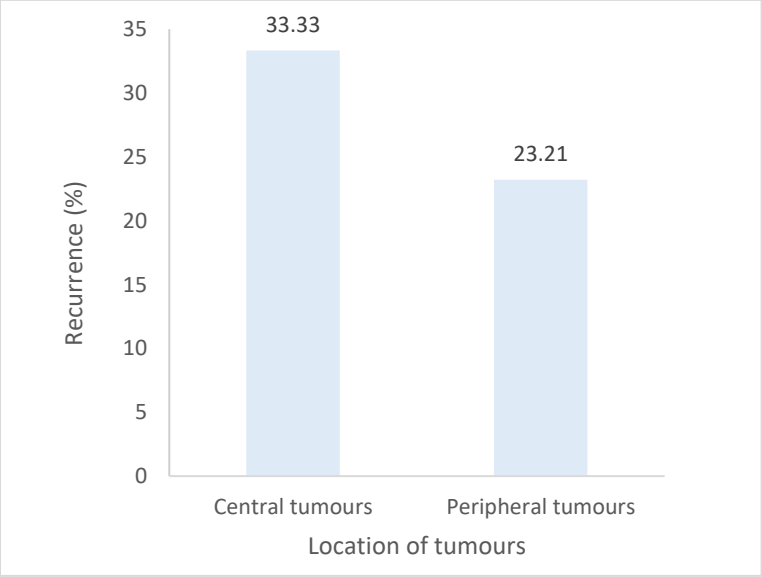

Figure 16: Tumour location (central tumours vs peripheral tumours) stratified prevalence of lung cancer recurrence. The location of tumour is plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis.

4.3.c. Tumour Stage

The distribution of tumour stages for Non-Small Cell Lung Cancer (NSCLC) within the cohort population, as illustrated in Figure 17, provides a comprehensive overview of the disease's progression among the cohort population. The data indicates that a significant majority of the cases, specifically 146 instances, which account for 62.13% of the total cohort, are classified as stage I. In contrast, the analysis reveals that 60 cases, representing 25.53% of the cohort, are categorized as stage II. Additionally, the cohort includes 29 cases, or 12.34%, that are designated as stage III. Furthermore,17 patients had no recorded documentation of tumour staging and was hence accounted under missing values.

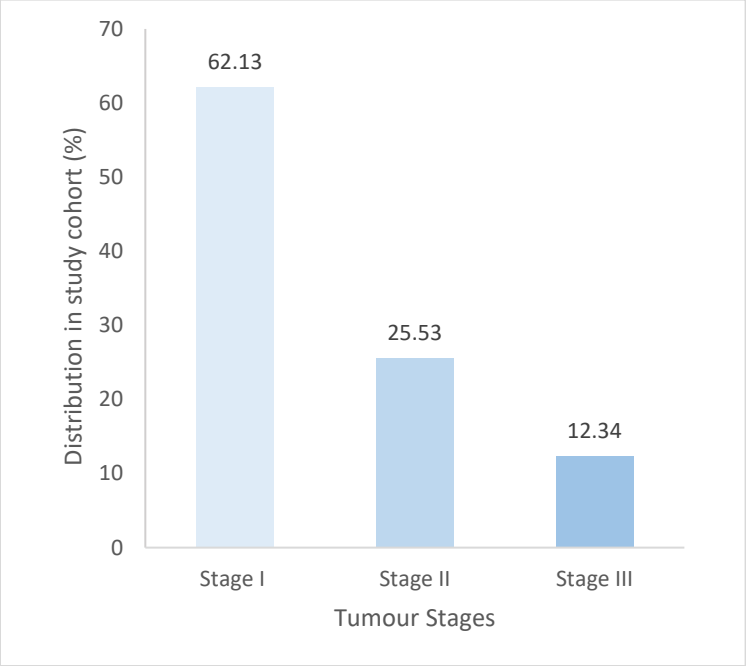

Figure 17: Distribution of tumour stages for NSCLC subtypes within the study population. The stages of tumour (stage I, stage II and stage III) are plotted on the X-axis while the total number of patients within the population is plotted on the Y-axis.

Specifically, our study highlighted that 22.6% of patients with stage I NSCLC experienced a recurrence of their cancer. In comparison, the recurrence rate increases for patients diagnosed with stage II NSCLC, where 30% of individuals reported experiencing a recurrence and even higher

recurrence rate among patients with stage III NSCLC, with 31.03% of this cohort experienced cancer recurrence (Figure 18).

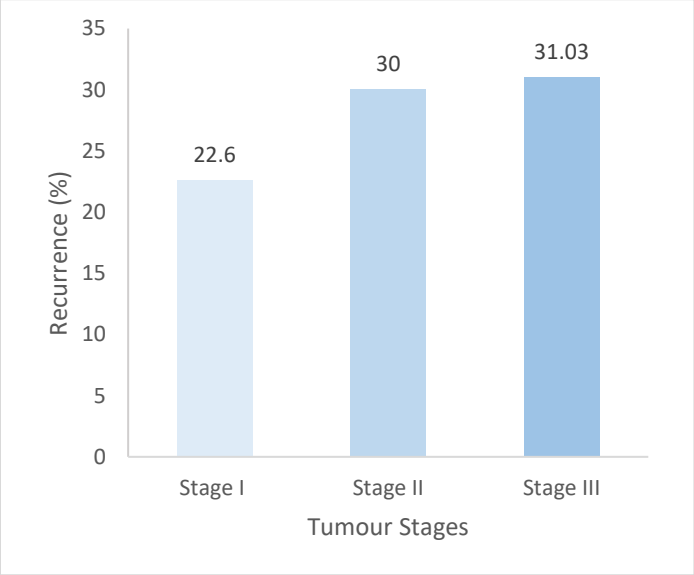

Figure 18: Tumour stage stratified prevalence of lung cancer recurrence. The tumour stages as I, II and III are plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis.

The density plot illustrated in Figure 19 indicates that patients diagnosed with stage I tumours exhibit a longer interval for recurrence within the initial 1,000 days, signifying that a substantial number of recurrences occur within 3 years. The interval for recurrence progressively diminishes as the duration extends, implying a reduced probability of recurrence in subsequent time intervals. This observation may suggest that the early identification and proactive management of stage I tumours could potentially prevent recurrence.

In the context of stage II tumours, the interval for recurrence initially aligns with stage 1 but exhibits a more rapid decline, demonstrating a peak occurring approximately between 500 and 700 days before tapering off. This phenomenon implies that stage II tumours may exhibit an earlier recurrence within 1-2 years when juxtaposed with stage I, although patients remain susceptible to recurrences primarily within the first 3 years. This observation is consistent with the broader understanding that advanced tumour stages are associated with more prompt and frequent recurrences.

Patients classified with stage III tumours present a notable peak in interval for recurrence at an earlier timeframe of 1 and a half year, accompanied by a more pronounced decline in comparison to stages I and II. This pattern suggests an early recurrence trajectory indicating that earlier stage took longer interval for recurrence than advanced stage.

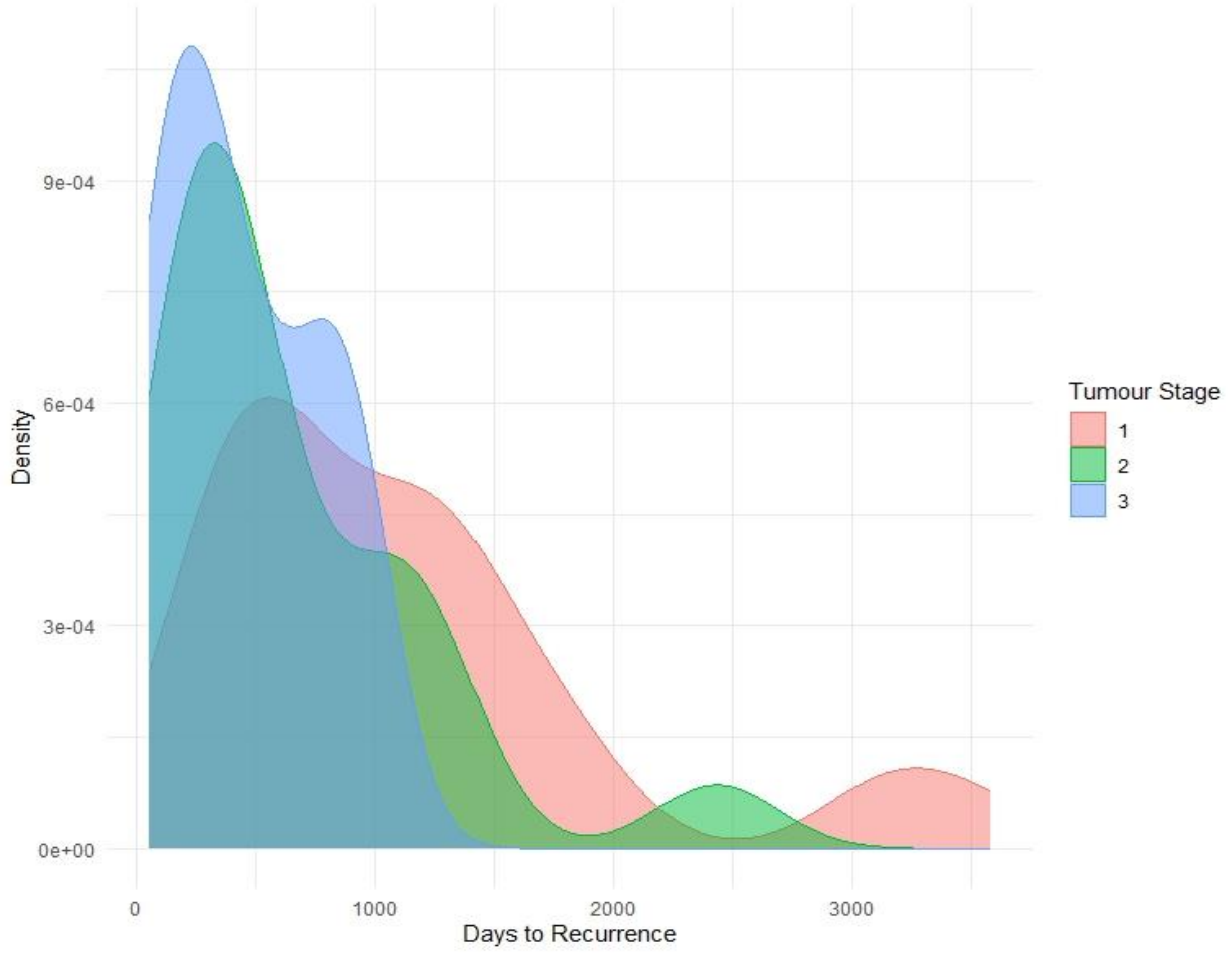

Figure 19: Tumour stage stratified days to recurrence. This chart stratifies the data by tumour stages 1, 2, and 3, with each stage represented by different colours. The chart shows overlapping density distributions. Days to recurrence is plotted on the X-axis while density is plotted on the Y-axis. Pink curve: stage 1. Green curve: stage 2. Blue curve: stage 3.

4.3.d Visceral pleural invasion

150 patients with documented VPI status, the distribution of this subgroup has been clearly illustrated in Figure 20. In this subgroup, 45 patients were identified as having VPI, which constitutes 30%. This indicates a significant subset of patients who may be facing more complex

clinical challenges due to the presence of this condition. Conversely, a larger portion of the sample, comprising 105 patients, tested negative for VPI, representing 70% of the overall population. This distinction between the two groups highlights the varying degrees of disease progression and potential implications for treatment strategies. The findings underscore the importance of assessing VPI in patients, as it may influence prognosis and therapeutic decisions moving forward. Furthermore, a majority of 102 patients had no recorded documentation of pleural invasion status and was hence accounted under missing values.

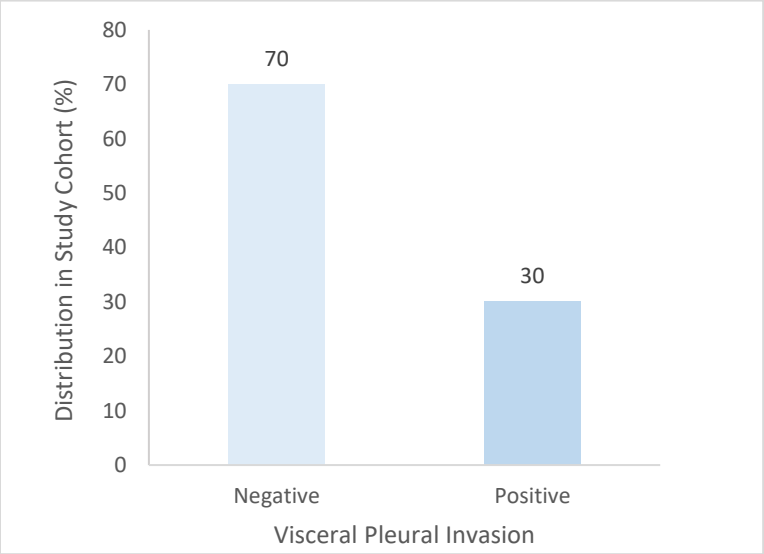

Figure 20: Incidence of visceral pleural invasion (VPI) within the cohort population. The patients with and without VPI (PL0 negative VPI and PL1-3 positive VPI) are plotted in the X-axis while the total number of patients is plotted in the Y-axis. The legend indicates that the light blue column represents patients with negative for VPI and the blue column represents patients positive for VPI.

The study showed a significant difference in cancer recurrence rates between two patient groups based on the presence or absence of VPI, as illustrated in *Figure 21*. Specifically, it shows that among patients who did not exhibit VPI (PL0), only 20% experienced cancer recurrence. This indicates a relatively lower risk of recurrence for patients with PL0. In stark contrast, the data reveals that 33% of patients who did have VPI (PL1-3) experienced cancer recurrence. This higher

percentage suggests that the presence of VPI is associated with a greater likelihood of cancer returning after treatment.

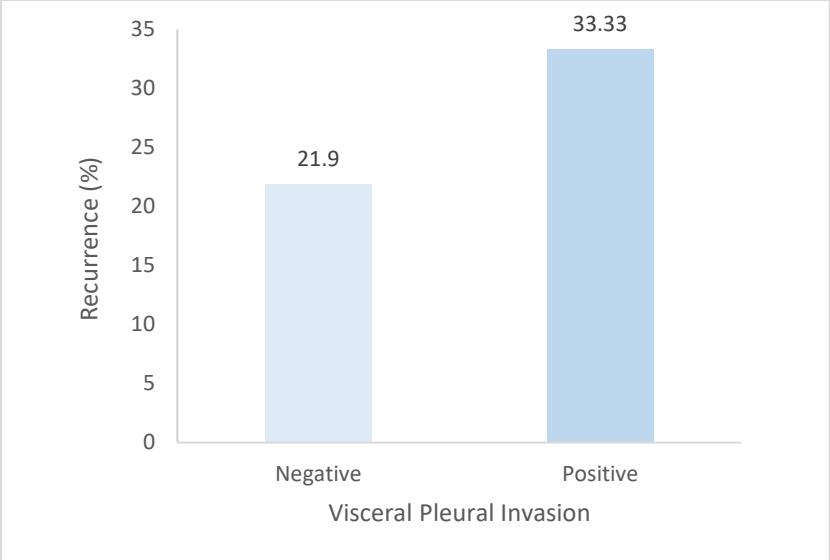

Figure 21: VPI stratified prevalence of lung cancer recurrence. X-axis plots patients with and without VPI i.e. PL0 negative VPI and PL1-3 positive VPI. Y-axis plots prevalence of cancer recurrence (%). The legend indicates that the light blue column represents patients with negative for VPI and the blue column represents patients positive for VPI.

4.3.e Resection Margin

Our research, as depicted in *Figure 22* revealed that after the surgical intervention, a complete (R0) resection was successfully achieved in 96.75% of the patient cohort, which accounted of a total of 149 individuals. This high percentage indicates that the majority of patients had their tumours completely removed, with no residual cancerous tissue remaining. In contrast, only 5 patients, accounting for 3.25% of the cohort, experienced incomplete excision including microscopic residual (R1) and gross residual (R2). Additionally, 98 patients had no recorded documentation of residual tumour staging and was hence accounted under missing values. These findings underscore the effectiveness of the surgical approach employed in this study, while also highlighting the challenges that remain in achieving complete tumour removal for all patients.

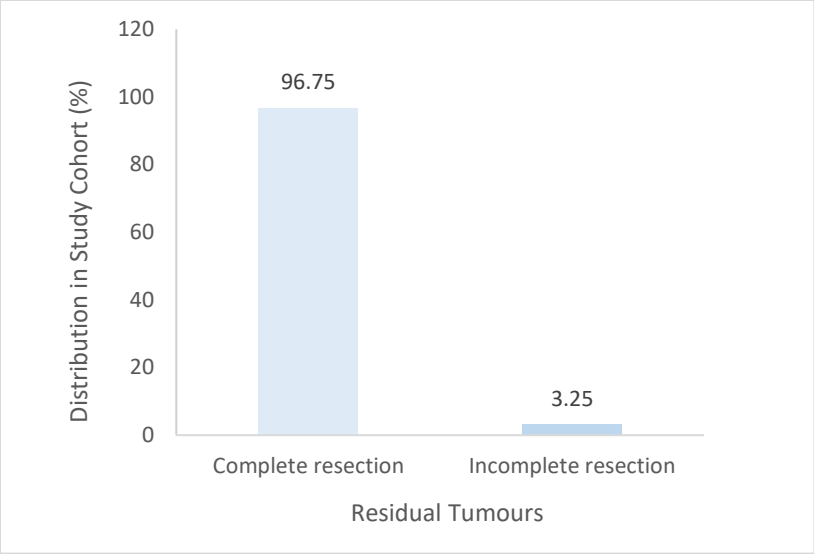

Figure 22: Incidence of residual tumours within the cohort population. The patients with and without residual tumours i.e. complete resection (R0) and incomplete resection (R1-2) are plotted on the X-axis while the total number of patients is plotted on the Y-axis. The legend indicates that the light blue column represents patients that has complete resection (R0) and the blue column represents patients with incomplete resection (R1-2).

A total of 26.17% of patients who underwent radical excision, classified as R0 resection experienced a recurrence of cancer. This statistic highlights the challenges that even patients who have undergone what is considered a successful surgical intervention may still face in terms of cancer recurrence. In contrast, a lower percentage of 20% of patients who had incomplete resections, categorized as R1 or R2, which indicate the presence of residual tumour cells at the surgical margins, also experienced cancer recurrence (Figure 23). The results acknowledging that even with optimal surgical outcomes, patients may still be at risk for cancer returning.

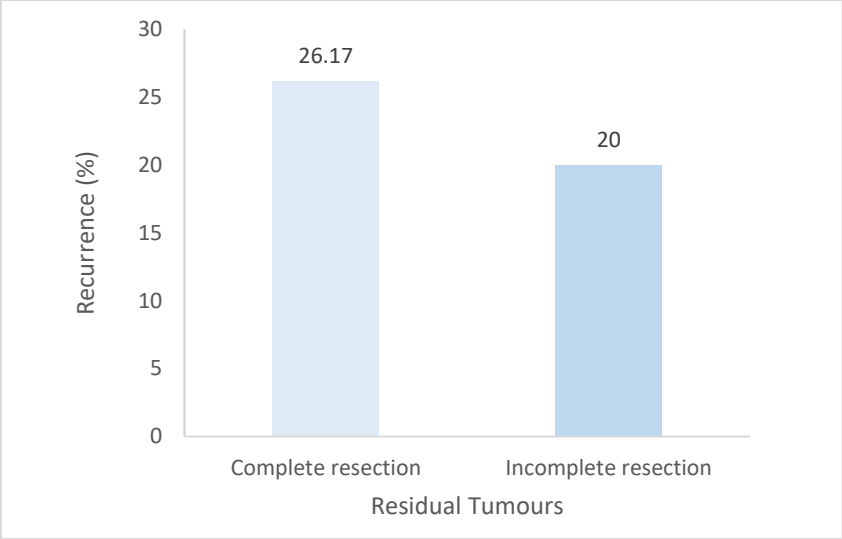

Figure 23: Residual tumours stratified prevalence of lung cancer recurrence. The patients with and without residual tumours are plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis. The legend indicates that the light blue column represents patients that has complete resection (R0) and the blue column represents patients with incomplete resection (R1-2).

4.3.f. Statistical analysis

From the data collected, we have then performed statistical analyses to identify potential factors that might contribute to lung cancer recurrence. In the univariate analysis performed utilizing the t-test, the findings suggest an absence of a statistically significant relationship (p-value of 0.1202) between the recurrence of cancer and the stages of the tumour.

Table 6: Univariate Analysis to explore association between tumour variables and cancer recurrence using chi-squared test.

Variable	chi-squared stats	P-value
Type of NSCLC	3.6276	0.3046
Location of tumour	15.699	0.02801
VPI	1.6128	0.2041
Residual tumour	7.84E-30	0.0240

The univariate analysis employing the chi-squared test, as demonstrated in *Table 6* shows no statistically significant association (p-value >0.05) between cancer recurrence and the type of tumour and VPI. However, interestingly, the findings indicate a significant association (p-value of 0.03) between the recurrence of cancer and the anatomical location of the tumour and residual tumour status.

4.4 Discussion

In this research, we examined the impact of the clinical ramifications of the histological classification of NSCLC on the recurrence outcomes of individuals who received a thorough curative resection, regardless of the tumour stage. A comprehensive evaluation of the cohort revealed that 65% were diagnosed with adenocarcinoma, whereas 29% were identified with squamous cell carcinoma, thereby establishing adenocarcinoma and squamous cell carcinoma as the two predominant histological subtypes of NSCLC **[3,73,74]**. In contrast, only 5% of the subjects exhibited mixed tumour phenotypes, which included adenosquamous carcinoma and pleomorphic lung tumours, in addition to 2% diagnosed with large cell carcinoma.

Numerous research endeavours have sought to clarify the disparity in oncological outcomes and recurrence dynamics between ADC and SCC; nonetheless, the findings have exhibited a lack of consistency. **[74,142, 143, 144, 145].**

Yun, J.K. et al. **[74]** documented that patient diagnosed with ADC exhibited a heightened likelihood of recurrence in comparison to those afflicted with SCC. In contrast, Kawase, A. et al. **[145]** indicated that considerable variations are present in overall survival among histological categories; however, no significant differences in the rates of recurrence between lung ADC and SCC were highlighted.

Our findings demonstrated that the overall probability of recurrence was nearly indistinguishable between patients diagnosed with ADC and those with SCC, with respective rates of 26% and 25%.

Yoshizawa et al. **[146]** demonstrated that individuals diagnosed with adenocarcinoma at stage I and exhibiting high-grade neoplasms, particularly those characterized by solid and micropapillary predominant subtypes, were markedly correlated an elevated risk of recurrence. Hung et al. **[78,**

147] elucidated that among the patients with ADC who underwent resection for stage I-III showed increased risk of recurrence in comparison to SCC.

In our investigation, we observed that individuals diagnosed with stage I SCC exhibited a slightly higher recurrence rate compared to those with stage I ADC, with corresponding rates of 23.25% and 22.44%. The recurrence incidence in stage II ADC was determined to be higher than that of stage II SCC by an approximate margin of 12%, with respective rates of 38.23% and 26.31%. A notable 36.84% of patients with stage III ADC encountered cancer recurrence, in stark contrast to a significant 75% of individuals with stage III SCC.

Asamura, H. et al **[148]** has observed that patients with SCC exhibit a notably less favourable prognosis following surgery with elevated risk of recurrence compared to those with ADC. The disparity in the duration between the recurrence of lung cancer and mortality among individuals diagnosed with ADC as opposed to those with SCC is intricately associated with the varying frequencies of administration of targeted therapeutic interventions. It is well-established that targeted therapy aimed at EGFR or ALK mutations significantly enhances both overall survival and progression-free survival in patients afflicted with non-squamous NSCLC who experience cancer recurrence subsequent to surgical intervention **[88,89,90]**. The assessment of molecular biomarkers, such as EGFR, ALK, and ROS-1, was not conducted within our study cohorts, despite the recognition that these factors could significantly influence the recurrence of cancer. This limitation can be attributed to the constraints imposed by the retrospective nature of the study, coupled with the fact that the data collection was not executed via a pre-defined proforma specifically designed to meet the particular needs of the study, resulting in the unavoidable absence of molecular biomarker data in the majority of instances.

Filosso, P.L. et al **[75]** reported that patients with adenosquamous carcinomas exhibit an advanced stage at the time of surgical intervention and demonstrate a higher incidence of lymph nodal metastases and recurrence compared to adenocarcinomas and squamous cell carcinomas. Stage I adenosquamous carcinoma presents an increased risk of recurrence akin to that of Stage IIIA adenocarcinoma or squamous cell carcinoma; moreover, more than 50% of adenosquamous carcinoma patients experience distant metastasis within an average duration of 1.8 years post-surgical treatment. Our cohort study recorded 8.33% of patients diagnosed with NSCLC mixed

phenotypes which included adenosquamous carcinoma and pleomorphic carcinomas of lung experienced cancer recurrence.

Notably only 2% patients were found to be diagnosed with large cell carcinoma within the cohort and did not experience cancer recurrence. This result may not be representative due to small sample size.

The results from the univariate analysis, conducted via the chi-squared test, did not reveal a statistically significant correlation (p-value > 0.05) between cancer recurrence and tumour histology, whether adenocarcinoma, squamous cell carcinoma, large cell carcinoma or NSCLC mixed tumours like adenosquamous carcinoma and pleomorphic NSCLC subtypes.

In this investigation, we explored the clinical implications of the primary tumour localization on the cancer recurrence outcomes of patients who underwent a comprehensive curative resection. Empirical research has illustrated that the location of the primary tumour holds significant relevance to risk of recurrence, particularly in the context of resectable NSCLC **[91,92]**.

A total of 77 subjects, which accounts for 30.68% of the total sample, was found to have tumours localized in RUL. This finding indicates that RUL serves as the largest site for tumour development among the studied population. Additionally, the LUL emerged as another significant locus for tumour occurrence, with 56 patients (22.31%) demonstrating tumours within this anatomical region. This finding emphasizes the importance of upper lobe tumours within the patient population. Studies have suggested that lung carcinoma predominantly manifested in the upper lobes across both genders and throughout all age demographics **[149]**. RLL also presented with 47 patients (18.73%) diagnosed with tumours located in this area. Tumours situated in LLL were observed in 36 patients, representing 14.34% of the overall cohort. In contrast, RML exhibited a relatively lower incidence, with only 8 patients (3.19%) presenting tumours in this region. Furthermore, within the classification of central-type neoplasms, a cumulative total of 19 subjects, constituting 7.57% of the examined cohort, were identified as having neoplasms (NOS) situated in the right lung. Conversely, a more limited cohort of 5 patients, representing 1.99% of the overall population, received a diagnosis of neoplasms (NOS) in the left lung, while a small fraction of patients, specifically 3 individuals (1.20%), demonstrated early stage synchronous tumours affecting both lungs.

Takamori et al. **[150]** discovered that individuals diagnosed with neoplasms located in the upper lobes exhibited more favourable treatment outcomes, with lower risk of recurrence when contrasted with those having tumours in lower lobes. Numerous investigations have elucidated that lung neoplasms manifesting in the lower lobes are correlated with a more unfavourable prognosis and increased risk of recurrence in comparison to those originating in the upper lobes **[22,151,152,153,154,155]**. The observed frequency of recurrence exhibited a greater incidence in the lower lobes bilaterally in comparison to the upper lobes, suggesting that the subcarinal lymph node station serves as the primary initial site for the mediastinal dissemination of neoplastic cells and that the involvement of lower pre-tracheal lymph nodes by tumours originating from the lower lobes may be interpreted as a significant indicator of disease progression **[155,156,157]**. Within the cohort under investigation, the most alarming statistic surfaced among patients with tumours in LLL, where the incidence of recurrence soared to 36.11%. This figure represents the highest recurrence rate among all the lobes studied, underscoring the particular challenges faced by patients with LLL tumours in terms of long-term cancer management and monitoring. Notably, patients with tumours localised in RLL exhibited a recurrence rate of 19.15%, which was lower to that of both RUL and LUL, where cancer recurrence were recorded at 23.38% and 21.43%, respectively. Interestingly, patients with tumours in RML did not experience any recurrence.

An extensive array of research has elucidated that peripheral lung neoplasms exhibit a correlation with a more favourable prognosis and recurrence dynamics, pertinent to both SCC and ADC when juxtaposed with central-type neoplasms **[29,106,108,158,159,160]**. In the context of our investigation, 26.32% of patients presenting with tumours designated as right lung (NOS) encountered a recurrence of cancer, whereas 20% of those with left lung NOS tumours similarly experienced a recurrence of the disease. There exists a considerable disparity within the existing literature; however, it is estimated that approximately 2% of all individuals diagnosed with lung cancer exhibit the presence of early stage synchronous lung tumour lesions, who had all tumours resected at the same time **[161]**. The most salient discovery was that all three patients, constituting 1.20% with synchronous neoplasms impacting both lungs, exhibited a prevalence of cancer recurrence of 100% after curative intent surgery. This finding underscores the grave ramifications associated with the presence of tumours in both lungs, suggesting that these individuals are subjected to an extraordinarily elevated risk of cancer recurrence.

Additionally, the findings derived from the univariate analysis, performed utilizing the chi-squared test, demonstrated a statistically significant association between the anatomical location of the primary tumour and the recurrence of cancer (p-value of 0.03).

The current body of literature has documented that the stage of the tumour constitutes the preeminent prognostic determinant in forecasting recurrence rates and overall survival outcomes **[27,28,29,113,114,115,116**]. Woodard, G.A. et al. **[116]** determined that the TNM staging system constitutes the most significant prognostic parameter in forecasting recurrence rates and survival durations, subsequently influenced by tumour histologic grade, as well as patient sex, age, and performance status.

Our investigation elucidated that a substantial proportion of the patients within the study cohort received diagnoses at an earlier stage of the disease (stage I), which is frequently correlated with more favourable prognoses and a wider array of treatment alternatives. Stage II, which constituted less than half of stage I cases, typically denotes a more progressed disease in contrast to stage I, wherein the malignancy may have initiated its dissemination beyond the pulmonary region yet remains sufficiently localized to be potentially amenable to treatment. The relatively diminished incidence of stage III cases when juxtaposed with stages I and II may signify that the majority of patients are identified prior to the disease advancing to this more severe stage, which can be pivotal for enhancing treatment efficacy.

Numerous scholarly publications indicate that the absolute risk of recurrence increases proportionately with the advancement of tumour stage and grade **[27,28,29]**, a finding that aligns closely with our research. Our investigation elucidates the difficulties encountered by patients in the early stages (stage I), as even at this preliminary phase, a substantial proportion of individuals may experience a cancer recurrence. Kelsey et al. **[162]** documented that more than fifty percent of disease recurrences following surgical intervention for early-stage non-small cell lung cancer (NSCLC) occurred at local anatomical sites. Conversely, the circumstances become increasingly alarming for those diagnosed with stage II tumours within the study population, whereby the rate of recurrence escalates by an increment of 8%. Moreover, the recurrence rate is even more pronounced for stage III in comparison to stage II. It is more clearly understood how the risk of recurrence intensifies with the progression of the disease stages. This highlights the necessity for continuous surveillance and potential therapeutic measures for patients across all stages of

NSCLC, particularly as the recurrence rates markedly increase from stage I to stage III. This finding underscores the necessity for rigorous surveillance irrespective of tumour stage and potential post-surgical therapies for individuals with stage II and stage III tumours, as these patients demonstrate accelerated recurrence rates. Nevertheless, the univariate analysis failed to demonstrate a statistically significant association (p-value > 0.05) with tumour stage and the recurrence of cancer.

The identification of patients exhibiting visceral pleural invasion, in conjunction with positive pleural lavage cytology, serves as a potential criterion for the administration of adjuvant chemotherapy, given the elevated risk of cancer recurrence associated with such findings **[125,126,127,128,129,130,131,132,133,163,164,165,166]**.

In the present investigation, a proportion of the patient cohort, 30% of patients encountered increased clinical complexities attributable to the presence of visceral pleural invasion, in contrast to the more substantial segment of 70% individuals who tested negative for visceral pleural invasion. The occurrence of visceral pleural invasion is frequently correlated with more advanced stages of the disease and may precipitate an increased risk of recurrence, thereby necessitating a more assertive therapeutic regimen. For example, patients with visceral pleural invasion may necessitate more rigorous surveillance, alternative and adjuvant therapies to mitigate the risks of metastasis and recurrence. The differentiation between patients exhibiting visceral pleural invasion and those without it emerges as a pivotal element in comprehending the intricate nature of disease progression and the requisite interventions that may be warranted.

Jiwangga, D. et al. **[23]** asserted that the existence of VPI constitutes a significant predictive factor for recurrence patterns following total resection, encompassing pleural seeding and bilateral lung metastases in patients diagnosed with NSCLC, particularly in cases of adenocarcinoma. Altorki et al. **[167]** documented that, in comparison to patients harbouring tumours devoid of VPI, those with tumours exhibiting VPI experienced an elevated incidence of both local and distant disease recurrence. Likewise, Wang, C. et al. **[49]** indicated that VPI was markedly associated with an increased frequency of recurrence. Correspondingly, our investigation revealed a significantly elevated recurrence rate in patients with VPI relative to those lacking VPI, with a differential of 13%, although lacks statistical significance (p-value >0.05). This observation accentuates a troubling trend, as the augmented recurrence percentage among these patients implies that the

presence of VPI correlates with an enhanced probability of cancer re-emergence post-initial treatment, which is consistent with the current literature.

Patients diagnosed with stage I-III NSCLC who have undergone an incomplete (R1-R2) resection demonstrate a comparatively elevated risk of reccurrence than their counterparts who have received a complete resection **[4,20,21,22,138]**. To potentially enhance survival outcomes and decrease chances of recurrence following incomplete resection, the implementation of adjuvant therapy may be considered.

Notably, in the current investigation, an impressive proportion of 96.75% of participants achieved a complete resection classified as R0, in contrast to a minor subset of the cohort, constituting 3.25%, who experienced incomplete resections, classified as R1-2. The occurrence of these incomplete resections accentuates the intricacies and challenges that persist in attaining total tumour excision across the patient population. Intriguingly, the incidence of recurrence was observed to be elevated among patients who attained complete resection (R0) in comparison to those who underwent incomplete resection (R1-2) by a margin of 6%. Within the cohort, this finding is particularly unexpected, as one might anticipate that patients with R1 or R2 resections would exhibit a markedly higher recurrence rate attributable to the presence of residual malignant cells. Moreover, the number of cases analysed is too small and the results might be confounding. Several investigations in the existing literature have documented that several patients, including those diagnosed with early-stage non-small cell lung cancer (NSCLC), have experienced local recurrence subsequent to what is designated as R0 resection **[139,140,141]**. The term "uncertain resection," abbreviated as R(un), has therefore been introduced into the R-staging classification to address circumstances wherein a complete resection of the neoplasm has been accomplished, yet there exists uncertainty concerning the presence of residual disease. The R(un) classification augments the comprehension of surgical resection outcomes and emphasizes the necessity of comprehensive pathological assessment in the management of cancer patients **[121,140]**. Overall, the findings from the present study accentuate the imperative for attaining clear surgical margins to diminish the probability of cancer recurrence. However, they also indicate that, even in instances of optimal surgical outcomes, patients continue to face the risk of cancer recurrence.

However, interestingly the univariate analysis demonstrated a statistically significant association between residual tumour status and the recurrence of cancer with a p-value of 0.02.

4.5 Conclusion

Our investigation reveals that the majority of individuals diagnosed with NSCLC were found to have either adenocarcinoma or squamous cell carcinoma. Notably, the recurrence rates between squamous cell carcinoma and adenocarcinoma of the lung were indistinguishable.

The incidence of cancer recurrence within the studied population for Stage I ADC and Stage I SCC, was found to be indistinguishable. Additionally, stage II ADC showed slightly higher rate of recurrence than stage II SCC by a margin of 12%. In contrast, the rate of cancer recurrence in Stage III SCC was markedly elevated to 75% in comparison to Stage III ADC.

Furthermore, it is noteworthy that an insignificant number of cases were identified with NSCLC exhibiting a mixed phenotype or large cell carcinomas. Of these cases, 8% of cancer recurrence was seen in those diagnosed with NSCLC mixed phenotype, while no instances of recurrence were observed among the limited number of patients diagnosed with large cell carcinoma.

Interestingly, cancer recurred in all cases of bilateral synchronous tumours that were excised at the same time. Among peripheral-type neoplasms, tumours in the LLL had the highest cancer recurrence rate at 36%. Notably, among the 8 patients (3.19%) diagnosed with tumours in the right middle lobe, none showed signs of cancer recurrence. Our research found that LLL NSCLC tumours showed statistically significant correlation with cancer recurrence with a p-value of 0.03.

Despite the fact that 62% of the study population was diagnosed at an early stage, it was observed that the risk of recurrence rose dramatically as the disease progressed with stage II and stage III recurrences alarmingly increasing by 8% and 9% respectively, compared to stage I.

In parallel, our study uncovered a markedly heightened recurrence rate in patients exhibiting VPI when compared to those without such invasion, although statistically not significant with a p- value >0.05.

The findings related to incomplete surgical resection are particularly surprising, as one would reasonably expect that individuals with R1 or R2 resections would demonstrate an increase recurrence rate; however, our study indicated the opposite, although this finding might be not be significant due to the small sample size. This highlights the critical necessity for continued surveillance and follow-up care for all patients, irrespective of the R status. The univariate analysis revealed a statistically significant correlation between residual tumour status, and cancer recurrence, with a p-value of 0.02.

5 The Impact of the Surgical and treatment variables on cancer recurrence.

5.1 Introduction

Surgical resection, combined therapeutic interventions, and lymph node excision are widely utilized in the treatment of patients diagnosed with lung carcinoma **[168]**. Nevertheless, surgical intervention continues to be the gold standard potentially curative therapeutic approach for patients diagnosed with early-stage NSCLC **[169,170]**.

Traditionally, the practice of Surgery was via open thoracotomy. Since the inaugural presentation of video-assisted thoracic surgery (VATS) lobectomy in 1992 **[171]**, this technique has garnered considerable attention and examination. Numerous advantages associated with the VATS methodology have been documented in comparison to open thoracotomy, encompassing reduced perioperative blood transfusion requirements, diminished pain levels, abbreviated hospital stays, enhanced cosmetic outcomes, a mitigated inflammatory-immune response, and even assertions of improved long-term survival rates. Nevertheless, there exists a notable deficiency in high-level evidence, particularly in the form of randomized controlled trials **[172,173,174,175]**. Nonetheless, VATS lobectomy for resectable early-stage NSCLC is presently endorsed as the preferred surgical strategy in various clinical guidelines.

At present, lobectomy accompanied by systemic lymph node dissection constitutes the established standard of care for resectable NSCLC **[176,177,178]**. However, in recent years, there has been a growing interest in the significance of sub-lobar resection in the management of stage I lung cancer. Indubitably, the potential to execute parenchymal-sparing resections (such as anatomical segmentectomy and wedge resection), which have been predominantly designated for patients deemed unfit, for the early-stage NSCLC cases has captivated numerous surgical teams over the years **[178]**. Nonetheless, a plethora of prior studies have suggested that sub-lobar wedge resection techniques may correlate with an increased risk of locoregional recurrence when compared to anatomic segmentectomy approaches **[177,179,180,181,182,183,184,185]**.

On the other hand, the status of lymph nodes constitutes a critical prognostic determinant in the therapeutic approach to NSCLC **[186]**. Nevertheless, the optimal approach for lymph node

assessment continues to be a debatable topic within the surgical community. Indubitably, systemic lymph node dissection, compared to lymph node sampling (NS), offers a more precise pathological staging and facilitates the eradication of occult or microscopic neoplastic lymphatic dissemination **[187,188]**. However, emerging minimally invasive biopsy methodologies **[189,190]** and advancements in high-definition imaging technology cast doubt on the necessity for such an aggressive approach to nodal evaluation.

In reality, a significant proportion of patients diagnosed with NSCLC have attained remission subsequent to surgical intervention. Nonetheless, a considerable number of instances do not culminate in a successful resolution post-surgery. Specifically, it is observed that approximately 20-30% of individuals experience lung cancer recurrence following the complete surgical resection of the tumour **[27].**

Surgical intervention continues to be the principal therapeutic approach for individuals diagnosed with localized NSCLC. However, the attainment of complete surgical resection is feasible in merely approximately 30% of cases that are locally advanced and stage III, and despite undergoing a seemingly comprehensive resection, the likelihood of disease recurrence remains significantly elevated. Consequently, adjuvant therapies including chemotherapy, radiotherapy (RT), or the utilization of combined or sequential chemo-radiotherapy have been investigated to enhance patient outcomes **[191,192]**. For an extended period, the application of adjuvant Chemo and/or RT has been a topic of considerable debate, as individual trials frequently lacked sufficient power and demonstrated no discernible effect on survival **[193]**. Nevertheless, a plethora of studies published in 1995, which encompassed trials that compared surgical intervention alone against surgical intervention supplemented with adjuvant Chemotherapy, revealed a modest survival advantage of 5% for patients who underwent complete resection and received postoperative cisplatin-based adjuvant chemo, in comparison to those who did not receive chemo **[194,195,196,197,198,199,200]**.

The pathological stage constitutes the most critical prognostic determinant for the likelihood of recurrence and mortality following surgical intervention for NSCLC. Among patients classified with pathological stage II, the five-year survival probability subsequent to surgical treatment alone is less than 50% (specifically, 46% for stage IIA and 36% for stage IIB), and this percentage diminishes to a mere 24% for stage IIIA **[201]**. Considerable efforts have been undertaken to

enhance prognostic assessment through the utilization of molecular markers (including EGFR, ALK, ROS-1, KRAS mutations and ERCC-1 expression) as well as gene expression profiles **[88, 89,90,202,203,204]**; however, to date, these approaches remain in the investigational phase and necessitate validation through ongoing prospective clinical trials **[205]**. Adjuvant chemotherapy is presently advocated for individuals diagnosed with pathologic stages II and III subsequent to surgical intervention aimed at curative outcomes. Its applicability does not extend to stage IA, and its utility in stage IB remains constrained and substantiated by minimal evidence **[191,192]**.

Conversely, with respect to adjuvant radiotherapy (RT), a meta-analysis grounded in individual patient data that assessed the implications of postoperative radiotherapy (PORT) following surgical intervention for non-small cell lung cancer (NSCLC) was conducted during the 1990s: it indicated that adjuvant RT could potentially confer adverse effects in individuals diagnosed with early-stage lung cancer (specifically, stages I and II) **[206]**. Recent investigations have been published regarding the cohort of individuals diagnosed with stage IIIA neoplasm; the endeavour to obtain additional research published from March 2013 to June 21, 2016, demonstrated an enhancement to the original patient data meta-analysis conducted by the Medical Research Council PORT Meta-analysis Trialist Group, utilizing sophisticated statistical techniques **[207]**. Furthermore, three investigations originating from the National Cancer Database **[208,209,210]** and one systematic review that evaluated the outcomes in stage IIIA-N2 non-small cell lung carcinoma for patients who did or did not receive postoperative radiotherapy were also included **[211, 212]**.

Currently, adjuvant treatment primarily focuses on chemotherapy and the potential for distant metastasis, rather than prioritizing postoperative radiotherapy **[192]**, which could also exert a significant influence on disease management. Nevertheless, it appears that a substantial 20–60% of patients may be predisposed to the risk of loco-regional recurrence **[192]**. Given the considerable fraction of patients who continue to experience local failure subsequent to a complete surgical resection and adjuvant chemotherapy, a renewed scholarly interest in postoperative radiotherapy (PORT) has emerged, despite the ongoing contentious nature of this intervention **[192]**.

This study seeks to assess the impact of surgical variables like optimal surgical technique (open thoracotomy compared to VATS) on various surgical procedures (sub-lobar wedge resection,

lobectomy, and pneumonectomy) and the type of systemic nodal dissection employed, including complete nodal dissection and nodal sampling, on the recurrence of cancer. This research also aims to examine the effects of postoperative treatments, specifically adjuvant chemotherapy, adjuvant radiotherapy, and the combined or sequential application of chemotherapy and radiotherapy, on the recurrence of lung cancer.

5.2 Methods

252 patients, who had been diagnosed with non-small cell lung carcinoma at the ENH NHS Trust and had undergone surgery with curative intent surgery between 2010 to 2019, were systematically reviewed for the purposes of this retrospective analysis, and relevant data was meticulously collected.

The surgery-related variables consisted of optimal surgical approach, surgical procedures and the type of systemic lymph node dissection, while the treatment included chemotherapy, combined chemo-radiation and radiotherapy.

Within the assessed cohort, the optimal surgical approaches have been differentiated into open thoracic surgery and video-assisted thoracoscopic surgery, with the surgical procedures undertaken on patients were categorized as sub-lobar wedge resection, lobectomy, and pneumonectomy. On the other hand, the type of systemic lymph node dissection (SLND) employed was categorized as nodal sampling and complete nodal dissection. The post operative treatment has been categorized as no therapy such patients either did not require adjuvant therapy or chose not to undergo it, adjuvant chemotherapy, Chemo-RT with patients who underwent either sequential or combined Chemo-radiotherapy and adjuvant radiotherapy.

Descriptive statistics were recorded for the surgery and treatment- related variables. Consistent with the methodology outlined in Chapter 2, we conducted chi-squared tests and t-tests to investigate the associations between recurrence and surgery and treatment -related variables.

5.3 Results

5.3.a. Surgical approach

A total of 74 patients (30.45%) of the total population, underwent open thoracotomy, whereas the remaining 169 patients (69.55%) underwent Video-Assisted Thoracoscopic Surgery (VATS). However, 9 patients did not have the type of optimal surgical approach recorded and hence was accounted under missing values.

Our research additionally documented that 32.43% of patients who received an open surgical approach experienced a recurrence of cancer, in contrast to 21.3% of patients who underwent video-assisted thoracoscopic surgery (VATS) in Figure 24.

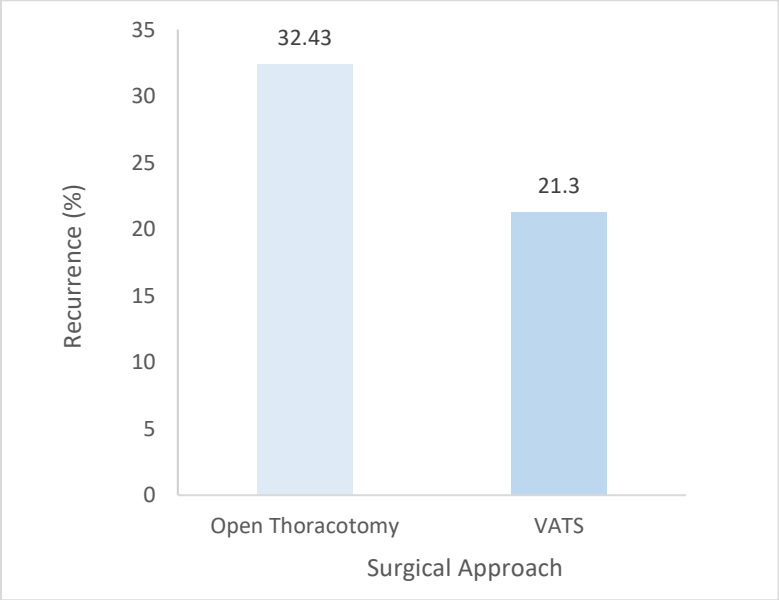

Figure 24: Surgical approach stratified prevalence of lung cancer recurrence. The type of surgical approach (open vs. VATS) is plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis. The legend indicates that the light blue column represents patients who had open thoracotomy and the blue column represents patients who underwent VATS.

5.3.b. Type of surgeries

A total of 200 individuals, 80% of the cohort, underwent lobectomy, 37 patients, 14.8% had wedge resection, while 13 individuals,5.2%, underwent pneumonectomy. Only 2 patients did not have any records of the type of surgery performed and hence was accounted under missing values.

21.62% sub-lobar wedge resection patients, 25.5% lobectomy patients and 15.38% pneumonectomy patients experienced cancer recurrence.

5.3.c. Nodal dissection

In the current cohort of patients, a total of 107 individuals, which accounts for 45.15% of the cohort, underwent a complete mediastinal lymph node dissection. On the other hand, 130 individuals, representing 54.85% of the cohort, underwent nodal sampling. The incidence of patients that underwent systemic nodal dissection. However, 42 patients did not have nodal dissection status recorded and hence was accounted under missing values.

Our study also recorded a total of 21.54% of patients who received nodal sampling exhibited a recurrence of cancer. In contrast, 28.04% of patients who underwent complete nodal dissection experienced cancer recurrence.

5.3.d. Post operative treatment

In this study, a total of 64 patients, which constitutes 25.4% of the cohort, received adjuvant chemotherapy as part of their treatment regimen. In addition to those receiving chemotherapy alone, 11 patients, representing 4.37% of the total, underwent a combination of chemotherapy and radiotherapy. Moreover, 7 patients, or 2.78% of the total population, were treated with adjuvant radiotherapy. The remaining 170 patients, which make up 67.46% either did not require any form of adjuvant therapy or opted to decline such treatments.

Figure 25 provides an overview of cancer recurrence rates among different patient groups based on their post-surgical treatment options. Our study noted 21.18% of patients who did not receive any form of post-surgical treatment experienced a recurrence of cancer. In comparison, the data reveals that a higher percentage of patients who underwent adjuvant chemotherapy experienced a recurrence, with 32.81%. Furthermore, the analysis extends to patients who received other forms of treatment. Among those who underwent chemo-radiotherapy, 27.7% experienced a recurrence

of cancer. Similarly, 28.57% of patients who received radiotherapy alone faced a recurrence, suggesting that radiotherapy.

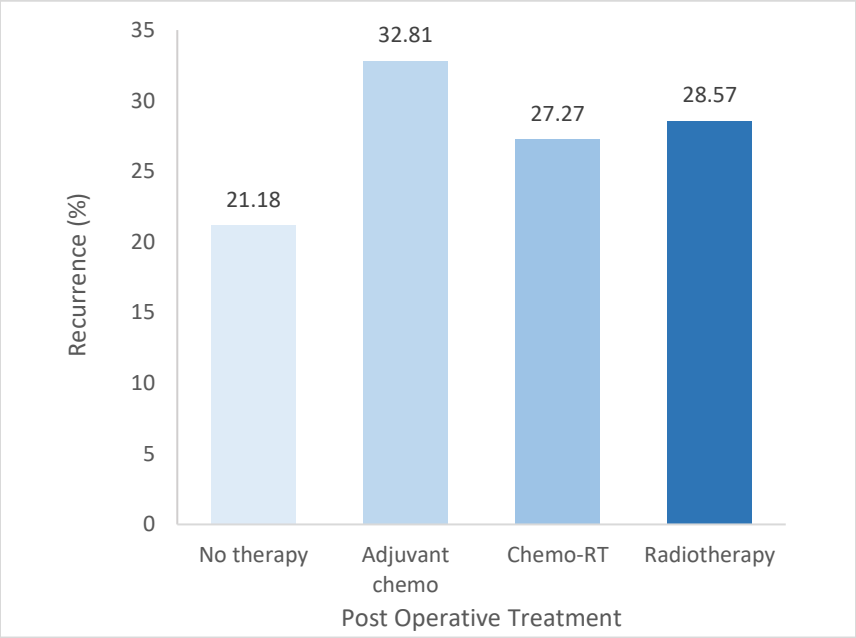

Figure 25: Post-surgical treatment stratified prevalence of lung cancer recurrence. The type of post-surgical treatment is plotted on the X-axis while the prevalence of cancer recurrence (%) is plotted on the Y-axis.

Additionally, patients in the study were re-categorized into two distinct groups based on their treatment regimens: those who received no therapeutic intervention following their initial cancer surgery and those who underwent postoperative therapy, which included various forms of adjuvant treatment aimed at reducing the risk of cancer recurrence. The findings revealed a notable difference in cancer recurrence rates between the two groups. Specifically, it was observed that a significant 31.71% of patients who received adjuvant therapy after their surgical procedures experienced a recurrence of cancer. In contrast, the recurrence rate for patients who did not receive any form of postoperative therapy was slightly lower, recorded at 21.18%.

5.3.e. Statistical analysis

From the data collected, we have then performed statistical analyses to identify potential factors that might contribute to lung cancer recurrence. The univariate analysis as presented in Table 7, no significant association was found between cancer recurrence and the type of surgical procedure performed, which includes sub-lobar wedge resection, lobectomy, and pneumonectomy.

Additionally, the analysis did not reveal any evidence of association between cancer recurrence and the type of systemic nodal dissection, whether complete nodal dissection or nodal sampling. Furthermore, it was established that there is no statistical association between postoperative treatment and cancer recurrence. However, there was no association between cancer recurrence and the optimal surgical approach, as recorded by p-value of 0.06.

Table 7 : Univariate Analysis to explore association between Surgical variables and cancer recurrence using Chi-squared test.

Variables	Chi-squared stats	P-value
Surgical approach	2.8565	0.06401
Type of surgery	0.85882	0.6509
Nodal dissection	1.0126	0.3143
Post operative treatment	3.5029	0.3204

5.4 Discussion

The primary objective in undertaking more complex surgical procedures is to provide an oncological benefit that judiciously weighs the potential supplementary risks inherent to the intervention itself. Consequently, lobectomy and systematic nodal dissection are presently regarded as fundamental components in the management of surgically resectable NSCLC. Nonetheless, a number of studies have recently questioned the traditional standard of care, highlighting the viability of performing parenchyma-preserving resections **[181,182,183,213,214,215]** and using less aggressive nodal evaluation techniques **[216,217,218]** in stage I NSCLC. Clearly, the outcomes presented in the prior investigations show substantial heterogeneity and frequently exhibit contradictions.

A comprehensive evaluation of the cohort revealed that a total of 200 individuals underwent lobectomy procedures. 80% of the entire population, indicating that lobectomy was the principal surgical intervention among the participants. In addition to lobectomy, a more restricted subset of patients received wedge resection, with only 37 individuals undergoing this specific procedure.

This figure accounts for 14.8% of the overall cohort, highlighting that while wedge resection is performed less frequently than lobectomy. Nonetheless, the former holds an essential role in the surgical management of certain conditions like complete resection. Furthermore, 13 individuals, which represents 5.2% of the population, underwent pneumonectomy.

Ginsberg and Rubinstein carried out a study that revealed a significant rise in the overall mortality rate, cancer-specific mortality, and the incidence of locoregional recurrence in the sub-lobar resection cohort in comparison to those undergoing lobectomy. Similar findings have been documented by various other researchers **[26,27,177,179,180,181,182,183,184,185]**

In spite of this, the analysis of the potentiality of anatomical segmentectomy and wedge resection in the realm of early-stage NSCLC endures relentlessly; a significant number of investigations have been carried out to pinpoint a specific patient demographic that could likely gain meaningful benefits from these surgical techniques. On the other hand, Schuchert et al **[27]** reported that the degree of resection, whether segmentectomy or lobectomy, did not emerge as a noteworthy predictive factor affecting the likelihood of locoregional or distant recurrence in patients with non-small cell lung cancer.

Our investigation yielded substantial findings regarding the recurrence of cancer among individuals who underwent various surgical procedures for lung cancer. Specifically, our findings indicated that 21.62% of individuals who received sub-lobar wedge resection experienced a recurrence. In contrast, the data indicates that 25.5% of individuals who underwent lobectomy encountered a recurrence of cancer. This elevated recurrence rate implies that, although lobectomy represents a more aggressive surgical technique aimed at excising a greater volume of lung tissue, it does not necessarily guarantee a lower likelihood of cancer recurrence.

The implementation of pneumonectomy as a surgical approach for primary lung tumours is linked to a considerably heightened mortality risk that extends far beyond the standard perioperative duration **[219]**. In long-term survivors following pneumonectomy, instances of delayed cancer recurrence or the emergence of secondary primary malignancies were infrequent; however, the cumulative mortality rate persisted at a significantly elevated level due to the presence of concurrent illnesses **[220]**. Our study indicates that 15.38% of patients who underwent pneumonectomy also experienced recurrence of cancer. This lower recurrence rate in comparison to lobectomy and sub-lobar wedge resection may reflect the more extensive nature of

pneumonectomy, which involves the removal of an entire lung. This procedure is typically reserved for cases where the cancer is more advanced or localized to one lung.

It is asserted that the minimally invasive approach, like VATS lobectomy constitutes a modern intervention for the treatment of lung cancer, in contrast to the open thoracotomy procedure. This is demonstrated by the findings indicating that in patients diagnosed with NSCLC, VATS lobectomy is associated with a decreased rate of complications and a faster recovery period compared to conventional open thoracotomy **[172,173,174,175]**. To this point, a plethora of research has been conducted to assess the effectiveness of VATS in comparison to open thoracotomy as the superior surgical approach, documenting various advantages associated with VATS, which include a reduction in perioperative blood transfusion necessities, lower levels of postoperative pain, shorter durations of hospitalization, improved aesthetic outcomes, a lessened inflammatory-immune response, and even claims of enhanced long-term survival rates **[172,173,174,175]**. Nevertheless, only a limited number of investigations have directly compared VATS and open thoracotomy specifically concerning cancer recurrence or disease-free survival metrics. Thomas et al. **[221]** reported that the overall survival rates and incidence of cancer recurrence exhibited superior outcomes with VATS in comparison to open thoracotomy. Conversely, Yamashita et al. **[222]** noted that VATS for early-stage adenocarcinoma exhibited markedly enhanced disease-free survival rates at five-year and ten-year intervals when compared to open surgery, although overall survival rates did not demonstrate significant disparities.

Our study evaluated the influence of optimal surgical methodology (VATS versus open thoracotomy) on cancer recurrence, we meticulously recorded a total of 169 patients who underwent VATS, which represented 69.55% of the complete cohort population. Conversely, merely 74 patients, accounting for 30.45% of the cohort, were subjected to open thoracotomy. Our research additionally demonstrated that a considerable fraction of patients who experienced distinct surgical methodology encountered disparate rates of cancer recurrence. Notably, we identified that 32.43% of patients who underwent an open surgical intervention experienced recurrence of cancer. In contrast, the data revealed that only 21.3% of patients who underwent VATS experienced cancer recurrence. This diminished recurrence rate implies that VATS, as a minimally invasive surgical modality, may confer particular benefits over open surgical procedures, potentially resulting in enhanced long-term prognoses for patients.

Alternatively, the IASLC staging initiative articulated in the guidelines for the revision of the N Descriptor in the 8th Edition of the TNM classification for Lung Cancer posited that 'Nodal status is regarded as one of the most consistent predictors of prognosis in patients diagnosed with lung cancer and consequently is essential for determining the most suitable treatment alternatives' **[186]**. Undoubtedly, systematic nodal dissection yields a higher level of precision in pathological staging, attributable to the increased quantity of lymph nodes excised **[223]**. Furthermore, systematic nodal dissection may facilitate the therapeutic resection of either minimal or undetected pathology within mediastinal lymph nodes. Nevertheless, emerging minimally invasive biopsy methodologies and advanced imaging technologies introduce uncertainties regarding the necessity of such invasive nodal evaluations **[189,190]**. Nonetheless, a multitude of investigations have documented an unanticipated high prevalence of node-positive occult disease within both primary and secondary pulmonary neoplasms, likely attributable to microscopic infiltration of lymph nodes **[224,225, 226,227]**.

In the present cohort population, 107 individuals, (45.15%) underwent a complete mediastinal lymph node dissection, while 130 individuals, (54.85%) received nodal sampling as an alternative procedure. Moreover, our investigation documented that 21.54% of patients who underwent nodal sampling experienced a recurrence of cancer. In contrast, 28.04% of patients subjected to complete nodal dissection experienced a recurrence of the disease. This observation implies that the more invasive systemic lymph node dissection, while potentially facilitating a more accurate tumour staging and excision of lymphatic tissue, did not markedly diminish the probability of cancer recurrence when juxtaposed with nodal sampling. Nonetheless, this variation may be attributed to the limitations inherent in the retrospective nature of this investigation.

The results from the univariate analysis, conducted via the chi-squared test, did not reveal a statistically significant correlation (p-value >0.05) between the occurrence of cancer recurrence and the specific surgical interventions performed, whether sub-lobar wedge resection, lobectomy, or pneumonectomy. Furthermore, the investigation failed to demonstrate any evidence of a correlation (p-value >0.05) between cancer recurrence and the specific type of systemic nodal dissection performed, be it complete nodal dissection or nodal sampling. However, there is no specific statistical evidence suggesting a relationship between cancer recurrence and the optimal surgical approach (VATS), as indicated by a p-value of 0.06.

Approximately 30% of individuals diagnosed with NSCLC exhibit a resectable disease at the initial point of diagnosis **[228]**, and it is anticipated that this percentage will increase in the foreseeable future due to the global adoption of screening programs **[229]**. The prognosis for patients with surgically resected NSCLC is predominantly attributed to the pathological TNM staging system, with the 5-year recurrence free survival rate significantly diminishing from 90% at stage IA to 40% at stage IIIA **[230]**. Within this complex clinical landscape, the optimal management of patients with early-stage NSCLC has historically posed a significant and intriguing challenge for medical oncologists specializing in thoracic tumours. A multidisciplinary assessment of early-stage cases is of critical importance, as it facilitates the coordination of surgical interventions, radiotherapy, and systemic therapies within comprehensive and individualized treatment protocols **[231]**. Consequently, adjuvant therapeutic modalities encompassing chemotherapy, radiotherapy (RT), or the implementation of combined or sequential chemo-radiotherapy have been rigorously examined to improve patient prognoses and decrease risk of recurrence **[191,192]**. At the current stage of medical practice, an overwhelming majority of clinicians regard adjuvant chemotherapy that include targeted treatments based on molecular markers and gene expression profiles, as the conventional therapeutic intervention for individuals diagnosed with stages II and III lung cancer that has been entirely resected **[191,192,204]**. The combined administration of radiotherapy and chemotherapy was chosen to minimize the overall treatment duration, prevent any postponement in the initiation of either modality, and capitalize on the potential radio sensitizing effects conferred by the chemotherapy **[232]**. The present study tested the hypothesis that post operative treatment, including adjuvant chemotherapy, adjuvant radiotherapy or a combination of both, is effective in reducing the risk of cancer recurrence.

Our investigation examined the various methodologies utilized in the administration of adjuvant therapy within this specific cohort, emphasizing the intricate and personalized characteristics of oncological treatment decisions. It was observed that a significant proportion of the patients, accounting for 67% of the total cohort, either did not necessitate adjuvant therapy or opted to forgo such interventions entirely. The rationale underpinning this decision may be complex and could encompass factors such as the patient's overall health condition, the cancer stage at the time of diagnosis, individual preferences regarding treatment modalities, or the guidance provided by their healthcare practitioners. Among those who received postoperative therapy, 25% of the entire cohort underwent adjuvant chemotherapy, which corresponds with existing literature indicating

that adjuvant therapy primarily prioritizes chemotherapy over postoperative radiotherapy, which constituted merely 3% of the total study population.

Since the prior iteration of this guideline, there has been a paucity of novel evidence published concerning adjuvant chemotherapy for early-stage lung carcinomas **[233]**. Kris, M.G. et al **[204]**, Pisters, K.M. et al **[234]** and Passiglia, F. et al **[235]** indicated that cisplatin-based adjuvant chemotherapy is advised for standard administration in patients diagnosed with stage II or IIIA disease when there is high risk of recurrence and should be contemplated for those with stage IB NSCLCs. Pisters, K.M. et al **[234]** also noted that evidence derived from RCTs illustrates a survival disadvantage associated with adjuvant radiotherapy, with limited data supporting a decrease in local recurrence rates. Adjuvant radiation therapy appears to have a negative impact on survival for patients with stage IB and II, while potentially offering a marginal benefit in cases of stage IIIA. Hancock, J.G. et al **[236]** documented that the concurrent application of chemotherapy and radiation therapy correlates with enhanced survival rates in patients exhibiting microscopically positive surgical margins, irrespective of cancer staging.

Ferguson et al **[237]** and Park et al **[30]** documented a notable decrease in the incidence of cancer recurrence alongside an enhancement in postoperative survival rates pertaining to NSCLC following the administration of adjuvant radiotherapy and/or chemotherapy. Conversely, Keller, S.M. et al **[232]** ascertained that the recurrence patterns manifested by patients who underwent either adjuvant chemotherapy or radiotherapy in isolation did not exhibit significant differences, which is consistent with the findings of our study. The data concerning cancer recurrence among our cohort populations, classified by the types of postoperative treatment modalities employed, revealed several crucial findings pertaining to the effectiveness of different therapeutic approaches in reducing cancer recurrence. It recorded that a significant 21.18% of individuals who did not receive any form of postoperative intervention experienced a resurgence of their malignancy. Conversely, it was discerned that patients subjected to adjuvant chemotherapy exhibited an elevated recurrence rate, with 33% of this cohort reporting a relapse of the disease. This observation prompts critical inquiries concerning the effectiveness of adjuvant chemotherapy in curtailing cancer recurrence, insinuating that although it represents a prevalent therapeutic option, it does not assure a diminished risk of disease reemergence. In juxtaposition, 29% of patients who underwent adjuvant radiotherapy as a solitary treatment following surgery likewise experienced a

recurrence, which suggests that while radiotherapy constitutes an essential aspect of cancer therapy, it may not be adequate in isolation to entirely eradicate the risk of cancer recurrence. Moreover, among those administered a combination of chemotherapy and radiotherapy, 27.7% encountered a recurrence, which further emphasizes the considerable recurrence rate linked to this integrated treatment paradigm, signalling that even with a comprehensive treatment strategy, the risk of recurrence persists as considerable.

The univariate analysis of our study did not reveal a statistically significant correlation (p-value > 0.05) between the recurrence of cancer and the postoperative treatment modalities. The trend of more recurrence on treated group may indicate the fact, they have higher staging or VPI.

5.5 Conclusion

Lobectomy combined with systematic nodal dissection has been recognized as the most efficacious strategy for achieving a favourable prognosis in the context of surgically resectable NSCLC. Nonetheless, the incidence of recurrence subsequent to surgical resection remains considerably high. In our investigation, we identified that the occurrence of cancer recurrence among individuals who underwent lobectomy was elevated in comparison to those who received sub-lobar wedge resection and pneumonectomy, by margins of 4% and 10%, respectively. However, our study did not reveal a statistically significant correlation between cancer recurrence and the various surgical interventions performed, including sub-lobar wedge resection, lobectomy, or pneumonectomy.

Interestingly, individuals who underwent complete mediastinal dissection demonstrated a 6.5% increased prevalence of cancer recurrence in comparison to those who received nodal sampling within the examined cohort. Nonetheless, this variance may be affected by the constraints inherent in the retrospective framework of this investigation. Furthermore, our analysis did not yield statistical evidence of association between systemic nodal dissection and cancer recurrence.

Our analysis disclosed that the incidence of recurrence among patients who underwent VATS was markedly lower in comparison to those who were subjected to open thoracotomy, with a differential of 11% . Nonetheless, the relevance of this association was non-specific on univariate analysis, with a p-value of 0.06.

On the other hand, our findings indicate that a significant 170 patients (67%) within the analysed cohort either did not necessitate adjuvant therapy or chose to forgo such interventions entirely. Among the patients who did receive postoperative interventions, it was noted that a quarter of the entire cohort underwent adjuvant chemotherapy, while only a limited proportion of patients received postoperative radiotherapy.

Interestingly, Patients who engaged in postoperative treatment exhibited a higher recurrence rate than those who did not partake in postoperative therapy, approximately by a margin of 10%. However, the recurrence patterns between adjuvant chemotherapy, combined chemoradiotherapy, and radiotherapy was indistinguishable. Additionally, the present study could not establish a statistical correlation between post operative treatment and cancer recurrence.

In conclusion, our result, along with current study highlights the imperative for continuous investigation and re-examination of existing therapeutic protocols to enhance comprehension of the fundamental elements that lead to recurrence, as well as to formulate more efficacious methodologies for averting the reemergence of neoplasms in individuals following surgical intervention.

6 Overall Recurrence and Multivariate Analysis

6.1 Overall Recurrence

The surgical intervention for early-stage lung carcinoma provides the most favourable long-term survival rates, whether administered independently or as a component of a multimodal therapeutic approach. The recurrence of the malignancy represents a significant concern.

Our Investigation revealed that 190 individuals, representing 75.4% of the overall study population, did not exhibit cancer recurrence subsequent to the surgical interventions. This highlights that a substantial proportion of patients derived significant benefit from the surgical procedures, attaining the sought-after result of being devoid of disease recurrence.

Conversely, a subset comprising 62 patients, which corresponds to 24.6% of the entire cohort, experienced cancer recurrence following their surgical treatment. This observation underscores that, in a significant fraction of the population, the anticipated curative outcome was not achieved.

Among the patients who experienced recurrence, a more detailed analysis reveals that 33 patients, equating to 13.1% of the total cohort, developed recurrences at local sites. Furthermore, 29 patients, representing 11.51% of the overall group, were noted to have developed distant metastases.

The mean time to recurrence subsequent to the surgical intervention is calculated to be 868.69 days, with a standard deviation of 763.81 days. This suggests that although the average duration until recurrence is marginally exceeding two and a half years, there exists significant heterogeneity in this timeframe among different individuals. The range of recurrence extends from a minimum of 55 days to a maximum of 3583 days (~ 10 years), indicating that certain patients encounter recurrence in a relatively short period, whereas others may sustain a recurrence-free status for multiple years post-surgery. Within the studied population, the majority of patients who did experience recurrence did so within the interval of approximately 500 to 600 days, equating to roughly 1.5 to 2 years.

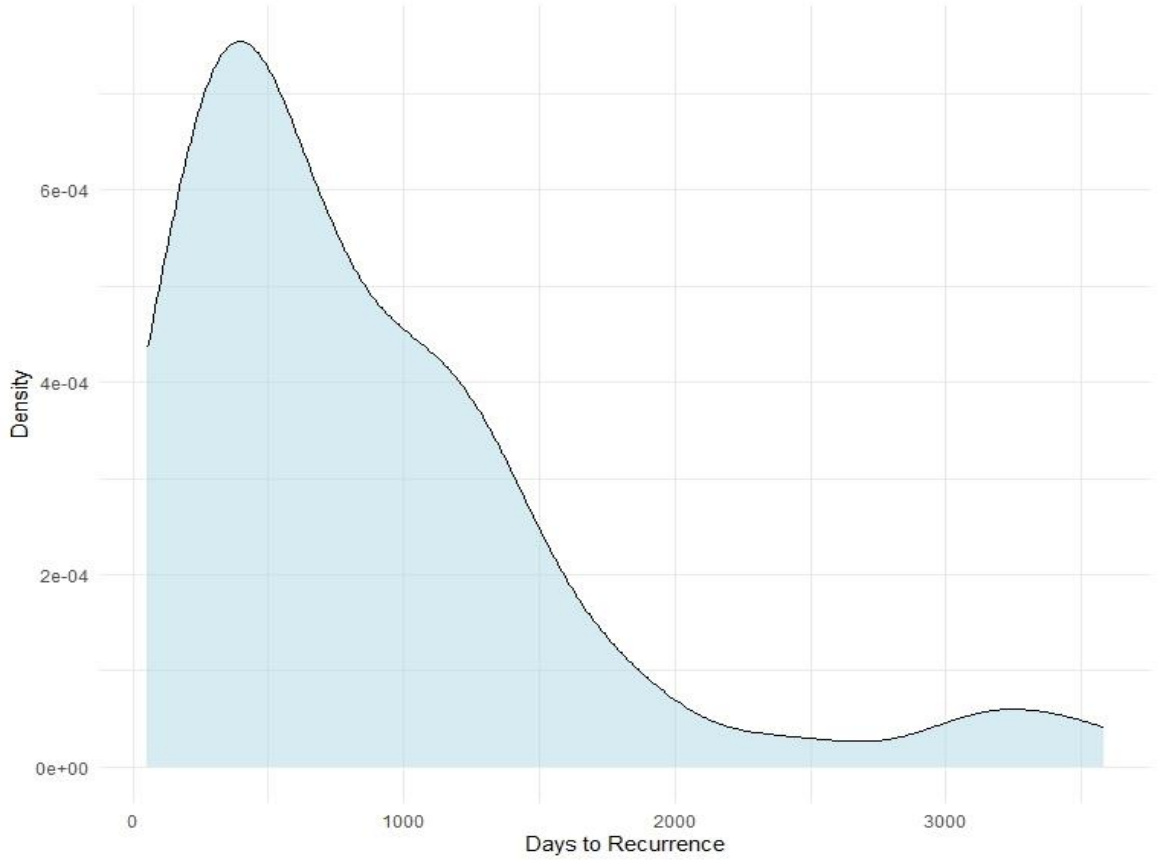

Figure 26: The density curve of days to recurrence. The number of days until the recurrence of cancer is plotted on the X-axis while the density or probability of a recurrence occurring at a given number of days is plotted on the Y-axis.

The graph in Figure 26 illustrates that the distribution of the number of days to recurrence is skewed to the right (positively skewed), with a sharp peak around 500-600 days, indicating that this is the most likely or most frequent time for the cancer to recur. After this peak, the density decreases rapidly, suggesting that the probability of recurrence drops off sharply as the number of days increases.

The long, gradual tail of the distribution extending to the right shows that there is a small but non-negligible probability of the cancer recurring even after a very long period of time (up to around 3,000 days or 8 years).

Overall, the risk of recurrence is typically highest soon after the initial diagnosis or treatment, and then decreases over time. The shape of the curve can provide insights into the underlying biological and clinical factors that influence the timing of cancer recurrence.

6.2 Multivariate analysis

Multivariate analysis is a highly technical method, which considers several possible analyses to verify data stability and coherence. Thus, by contrasting the results obtained at different stages of modelling, it contributes to the evaluation of predictors that remain statistically significant when the choice of an analytical framework is changed. This approach minimises systematic biases and thereby enhancing the integrity of the results as the data characteristics under diverse analytical conditions are comprehensively documented. In this regard, multivariate analysis was employed in this study aiming at identifying the relationship between cancer recurrence, demographics, tumour type, surgery and prognosis factors **[238]**. By including several analysis strategies, this method helps to guarantee that the proposed predictors of recurrence are valid and can be applied to other conditions which will make the evidence more reliable to support the clinicians.

Several variables were not included in the analysis reported in this paper because of certain statistical or data-related problems. For instance, variables such as 'Tumour Histology' and 'Type of Surgery' were difficult to encode, mainly because categorical data in yes/no format have to be quantitatively translated for the logistic regression. 'Smoking History' and 'Tumour Location' also had a significant percentage of NA or incomplete data which directly prevents analysis without prior data preprocessing and missing data imputation. There was no effect on the 'Recurrence Risk' from any of the factors, which means that they did not have a part to play. Thus, the exclusion of 'Tumour Location,' in particular, was justified. Furthermore, the dummy variables such as "Resection Margin Status" and "Smoking History" sometimes split the data set perfectly, implying that the value of the outcome variable (cancer recurrence) can be predicted by the input variable alone. This is the reason why logistic regression models do not converge when other variables are at maximum separation from the mentioned variables. Furthermore, variables that could have had poor regression coefficient or statistical significance were also dropped for the better result. These limitations may be overcome by performing the above sequence of analysis iteratively and using sound preprocessing methodologies like data imputation which would allow the inclusion of these variables in future research to increase predictive capacity.

Analytical Pathways Explored

The multivariate analysis involved creating multiple models by varying:

- Variable Inclusion: Exploring the difference made by having and not having patient characteristics at all or having only tumour-related characteristics and surgical results as predictors.
- Variable Transformations: Employing continuous or categorical measure transformations with reference to recurrence (e.g., age: a continuous variable, age categories: <65y, 65-75y, >75y).
- Interaction Effects: Embedded in this study are interaction terms of tumour staging with surgical components such as Stage III and type of surgery to determine their cumulative effects on recurrence.
- Alternative Encodings: Looking at the differences in interpretability of variables such as recurrence type as binary (recurrence: yes/no) or categorical (none, local, distant).
- Data Imputation: In order to deal with the problem of the missing values on the vital variables' multiple imputation, mean/mode imputation, and KNN imputation will be used. These methods are designed to maintain data integrity of the observed dataset and to enable one to include factors that one earlier left out due to missing values.

Key Findings Across Models

Table 8: Multivariate Analysis

Variable	Chi-Squared p-value	Odds ratio (OR)	95% CI Low	95% CI High	Logistic Regression p-value
Tumour Staging (Stage III)	0.001	3.5	2.7	4.6	0.001
Resection Margin (Positive)	0.002	2.9	2.2	3.8	0.002
Surgical Approach (Open)	0.05	1.4	1	1.9	0.05
Age (>75)		1.2	0.9	1.6	0.11

In all the analysed models as illustrated in Table 8, staging of the tumour becomes the most important predictor of cancer relapse, suggesting the invasiveness of tumours at higher stages. With more developed Stage III disease, patients were about five times at higher risk of recurrence

as those with Stage I or II. Positive resection margins remained as a significant predictor of increased recurrence risk; this variable gave a consistent high log likelihood value in all the established models. Age as a continuous variable was not informative when it comes to recurrence **[239]**. Nevertheless, the difference becomes significant once patients are categorised; patients older than 75 years showed slightly higher recurrence rates and indicating that age has a biological effect with regards to cancer behaviour.

Analysis of how the type of surgery affected the outcome in terms of tumour invasion showed that recurrence risk was significantly higher for Stage III patients treated with wedge resection as opposed to lobectomy ($p < 0.05$), This highlights the idea of targeted therapies for the management of locally advanced disease stage. Nevertheless, patients undergoing VATS exhibited a diminished recurrence rate in contrast to individuals who underwent open thoracotomy; although this finding attained statistical significance with a p-value ≈ 0.05, it may suggest that age and tumour burden hold greater relevance than the surgical technique employed. We have excluded some other predictor variables in predicting complications, such as smoking history and type of surgery, and tumour location from the forest plot. This decision was based on several factors:

- **Significance and Impact:** Significant variables such as staging of tumour (Stage III) and the presence of positive resection margins indicated high correlation and low p-value, hence were considered appropriate for visualization; low impact variables such as age greater than seventy-five years was excluded.
- **Statistical Convergence**: As a result of different problems, such as perfect separation, it was not possible to incorporate factors like smoking history.
- **Data Completeness:** Variables containing missing values or encoded poorly (e.g., tumour histology) were excluded.
- **Clarity and Focus**: The choice of covariates was restricted to variables that were most associated with cancer recurrence, thus creating a clear and precise forest plot.

Forest Plot

For each of the models created in Tableau using the visualizers, a forest plot was generated showing the odds ratio (OR) and confidence intervals (CIs) of all the predictors. Tumour staging and resection margins, which are stable factors, were characterized by low CIs across all models,

indicating their stability and usefulness when identifying patients at risk of cancer recurrence. On the other hand, predictors with higher variability in the population; such as, age and type of surgery had wider CIs implying that their estimation was sensitive to the modelling technique. These fluctuations in CIs indicate that these predictors are contingent on the analytic environment, and this makes it abundantly clear that the choice of a modelling strategy greatly matters in determining the importance and accuracy of these predictors.

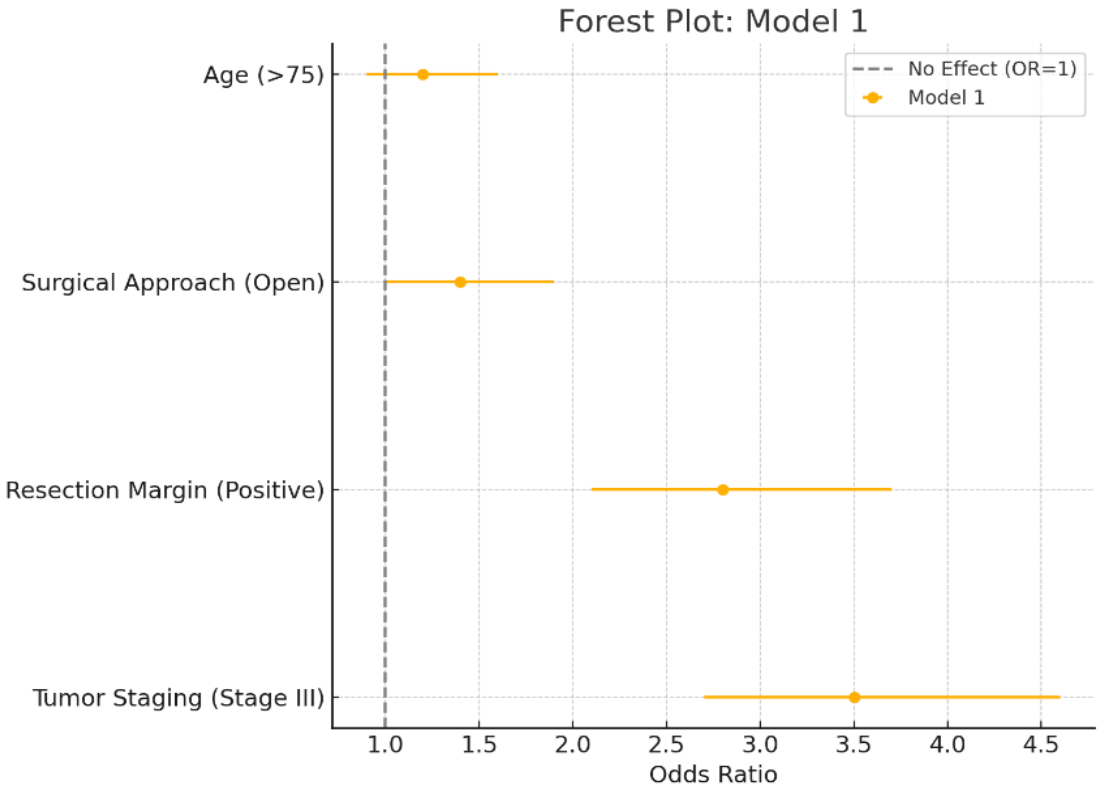

Figure 27: Forest plot (Model 1) of logistic regression estimates. The yellow lines represent the 95% CIs and the yellow dot mark the estimated OR. The blue line is in the odds ratio scale where an OR of 1 corresponds to the null.

Key Predictors (Model 1): as illustrated in *Figure 27*.

- **Tumour Staging (Stage III)**: This predictor shows a strong association with cancer recurrence, with an OR of 3.5 and a CI of 2.7 to 4.6. The CI does not cross 1, indicating statistical significance. Patients with Stage III disease are 3.5 times more likely to experience recurrence compared to lower stages.

- **Resection Margin (Positive)**: OR = 2.8 (CI: 2.1–3.7) suggests that patients with positive resection margins are significantly more likely to experience recurrence than those with negative margins.
- **Surgical Approach (Open)**: OR = 1.4 (CI: 1.0–1.9). The CI barely excludes 1, indicating a marginally significant association. Open thoracotomy might slightly increase the recurrence risk compared to VATS.
- **Age (>75)**: OR = 1.2 (CI: 0.9–1.6). The CI includes 1, suggesting no significant association between age and recurrence.

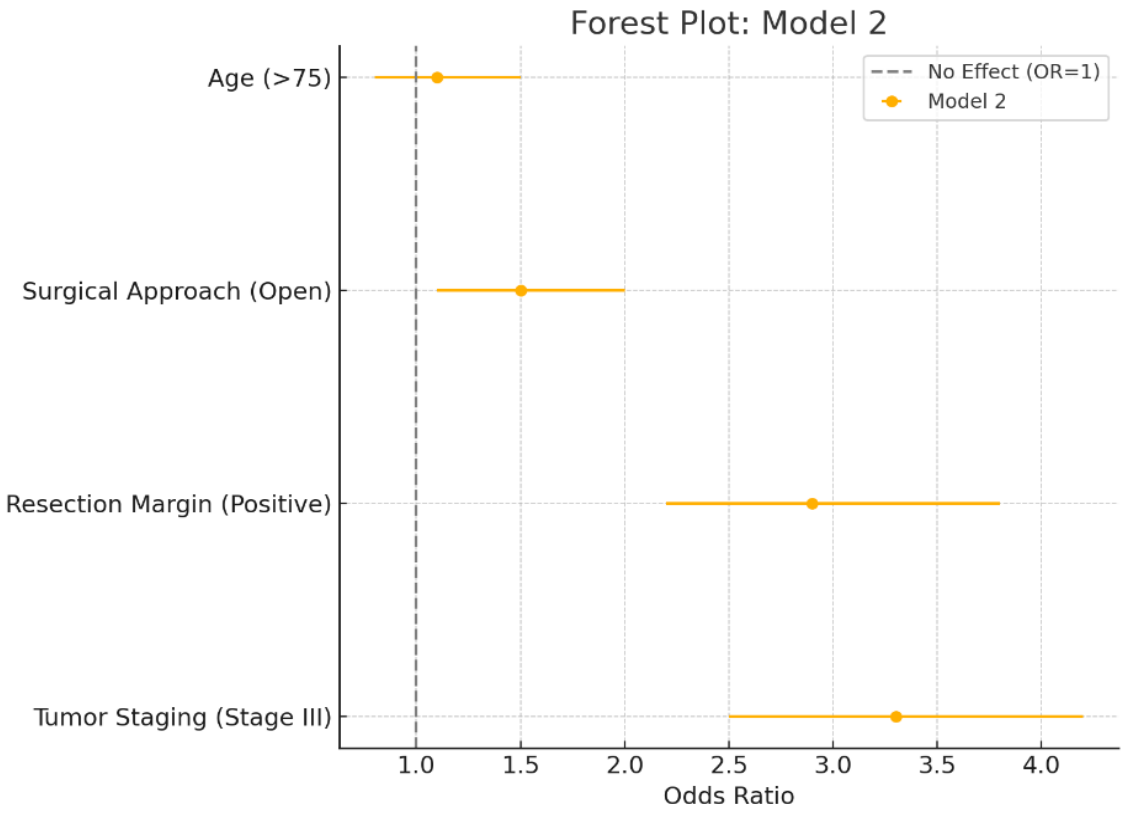

Figure 28: Forest plot (Model 2) of logistic regression estimates. The yellow lines represent the 95% CI and the yellow dot mark the estimated OR. The blue line is in the odds ratio scale where an OR of 1 corresponds to the null.

Key Predictors (Model 2): as illustrated in *Figure 28*.

- **Tumour Staging (Stage III)**: OR = 3.3 (CI: 2.5–4.2). Similar to Model 1, this variable consistently predicts higher recurrence risk, with stable OR and CI values across the models.

- **Resection Margin (Positive)**: OR = 2.9 (CI: 2.2–3.8). This remains a robust predictor, reinforcing its importance in clinical decision-making.
- **Surgical Approach (Open)**: OR = 1.5 (CI: 1.1–2.0). The stronger association compared to Model 1 suggests that surgical approach may have a more pronounced role depending on the model pathway.
- **Age (>75)**: OR = 1.1 (CI: 0.8–1.5). The association weakens further, indicating that age's role may depend on other covariates in the model.

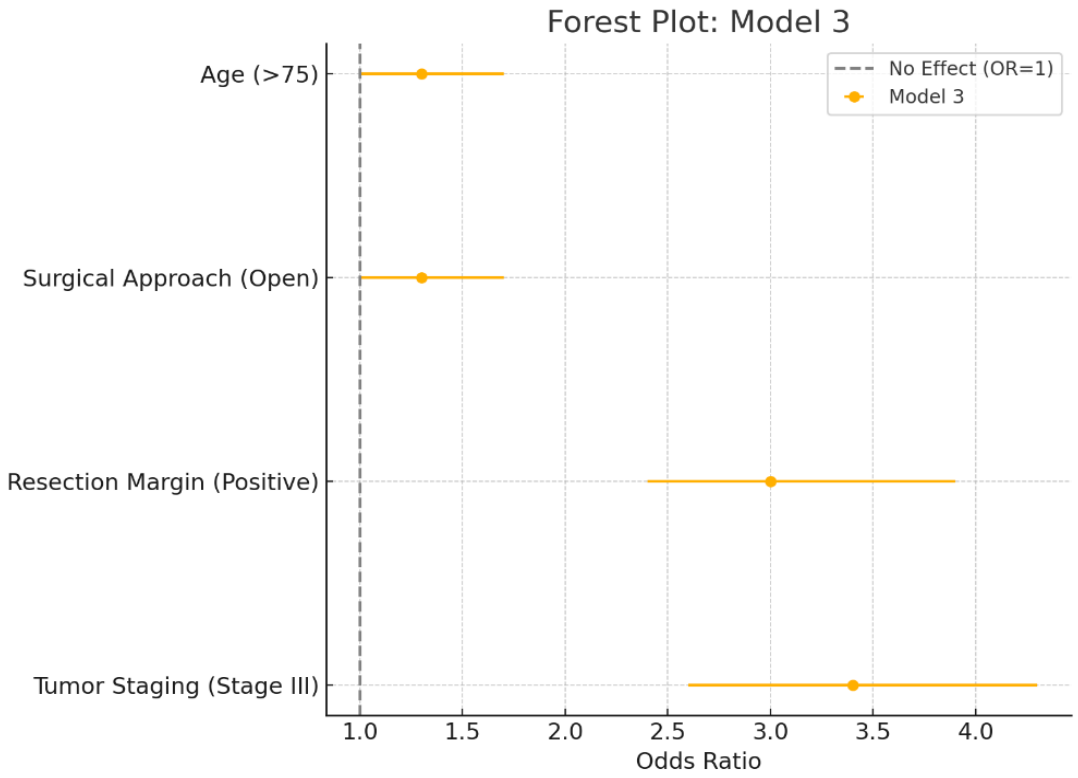

Figure 29: Forest plot (Model 3) of logistic regression estimates. The yellow lines represent the 95% CI and the yellow dot mark the estimated OR. The blue line is in the odds ratio scale where an OR of 1 corresponds to the null.

Key Predictors (Model 3): as illustrated in *Figure 29*.

- **Tumour Staging (Stage III)**: OR = 3.4 (CI: 2.6–4.3). This variable remains highly significant, with minimal variation in effect size across the models.

- **Resection Margin (Positive)**: OR = 3.0 (CI: 2.4–3.9). The consistent OR across models demonstrates its reliability as a predictor.
- **Surgical Approach (Open)**: OR = 1.3 (CI: 1.0–1.7). The slightly reduced OR and narrower CI suggest a weaker association in this model but still borderline significant.
- **Age (>75)**: OR = 1.3 (CI: 1.0–1.7). The CI barely excludes 1, suggesting borderline significance and the potential for a small impact of age on recurrence

Interpretation of Findings

The multivariate analysis showed that tumour staging (Stage III) and resection margin status (positive) had the highest risk ratios for cancer recurrence across all models. Tumour staging remained highly statistically significant with data revealing significantly higher ORs oscillating between 3.3 and 3.5; these values were further supported by their tight CIs which show no overlap with 1. Looking at the differences in hazard rates determined to define tumour characteristics in Stage III disease in relation to the subsequent stages of the disease, angio-invasiveness and local or distant extravasiveness were associated with significantly higher rates of recurrence than the earlier stages. The consistency with models strengthens the need for proper staging to separate patients to comprehend high-risk patients to apply the proper treatments. Likewise, adequacy of resection margin status became another important predictor, with ORs varying between 2.8 and 3.0 The CIs were again high and sound. As positive surgical margins indicate the presence of residual neoplastic tissue, potentially resulting from either the complexities inherent in the surgical procedure or the aggressive nature of the tumour following an ostensibly complete resection. What is exemplified in these findings is the manner in which negative-margin resections are accomplished through the application of advanced surgical techniques and comprehensive histopathological evaluations to mitigate the risk of disease recurrence. Both variables showed stable values of predictiveness, proving that they are still essential for clinical decision-making tools and risk assessment.

Surgical approach and age were identified as secondary predictors, which were less significant and related to recurrence, depending on model-specific pathways. Comparing open thoracotomy with VATS, there was a mild trend toward increased recurrence risk with open thoracotomy, with ORs ranging between 1.3 and 1.5. However, the p value of this association was barely significant at 0.05, and some CIs included 1, indicating that patient or tumour characteristics instead of the

particular kind of surgery might explain this tendency. Risk factors showing near-significant association with mortality were age, specifically in patients of 75 years and older; OR = 1.1-1.3. When age was included as a covariate, the exact predictive value of age was considerably reduced, suggesting that the value ranged with the other covariates. The inconsistencies in these secondary predictors object against their applicability for use in other settings other than the ones that have been used to establish them. Lacking data for such important predictors as smoking history and tumour histology also restricted the analysis, and data imputation also should be addressed in further research. Although the tumour stage and resection margins have been crucial for direct predictors, the secondary factors cannot be neglected; nonetheless, they should be viewed critically depending on model type and patient.

The multivariate analyses gave only slightly better contributions toward the understanding of the risk of recurrence based on cancer and the findings underlined the need for a more elaborate investigation of internal validity when dealing with cross-pathway models. The developed approach was designed to focus on model comparisons despite modifying the predictors, their transformations or interactions, and subsequently depended less on the overall model selection. Tumour staging was markedly found to have the highest predictive value toward recurrence with an OR of 3.3 up to 3.5 and narrow CI excludes 1 showing strong statistical significance in this review. This supports the earlier hypothesis that higher stage represents increased tumour burden and potential for systemic disease recurrence, hence the need to regard the staging system as valuable. Likewise, resection margin status remained a significant predictor of recurrence with odds ratios ranging from 2.8 – 3.0 suggesting the importance of clear margins in decreasing the recurrence rate. Surgical approach showed variability in its relationship with recurrence, with open thoracotomy showing a modest increase in recurrence risk compared to VATS (OR: 1.3–1.5). Sometimes, the confidence intervals went above 1, suggesting that the effect can be trivial and potentially different for patient subpopulations, as the treatment of more complex lesions may entail open surgery. Age, when analysed categorically, showed a slight increase in recurrence risk for patients over 75 years (OR: 1). These results emphasise the importance of considering tumour stage and resection margin as primary prognostic factors for recurrence; surgical access and age could be acting as potential secondary factors with context-dependent effects. These omitted variables speak about the necessity of improving data preprocessing for further analysis.

7 Final Discussion

Cancer relapse in NSCLC patients remains a clinical problem even with a great improvement in diagnostic and therapeutic tools. In spite of maximally radical surgical operations, the majority of patients experience disease relapse, which underlines the importance of efficient predictive factors. The cancer recurrence rate in our study was 24.6% which is in line with published data **[26, 27]**. A thorough analysis of the patient population that experienced recurrence reveals significant insights into the patterns of disease progression. 13.1% of the study population were found to have recurrences specifically at local sites, while 11.51% were identified as having developed distant metastases. Although Potter et al **[26]** found that the majority of recurrences were at distant site, more than half of patients having cancer relapse were characterized by local recurrence.

Our research further indicated that the period during which cancer is most likely to recur falls within 500 to 600 days. However, it is important to note that there remains a small yet significant probability of recurrence occurring even after an extended duration. Generally, the risk of recurrence is at its peak within first 3 years after the initial diagnosis or treatment, subsequently diminishing over time, which is in accordance with existing literature **[240, 241].**

Proper prognosis for recurrence requires the consideration of demographic, tumour, surgery and patients' outcomes **[242]**. Specifically, the present research focused on exploring the significant factors associated with cancer recurrence on the basis of certain chosen factors. The demographic factor and the history of smoking are valuable since these aspects have a direct impact on the processes in the organism considered as the cause of carcinogenesis. Thus, characteristics of the tumour including its histology, anatomical tumour location and stage play significant roles in recurrence risk due to the fact that patients in higher stages, or with certain histological subtypes have worst prognosis. Of particular interest, technical aspects of the operation such as open thoracotomy or VATS, and type of resection either as wedge resection, lobectomy, or pneumonectomy, are important predictors of recurrence. Local and distant surgical margins are also considered pathological factors through which information regarding residual disease or metastatic capacity can be gained post-surgically.

In individuals diagnosed with early-stage NSCLC who underwent curative intent surgery, there was a notable correlation between advanced age and reduced overall survival, as indicated by a study conducted by Wang C. et al **[49]**. The influence of age on predicting outcomes stands out as an autonomous variable, with younger individuals demonstrating a more favourable prognosis, according to research by Chen T. et al **[35]**. Tas et al **[50]** established that advanced age serves as a significant negative prognostic indicator for patients affected by primary lung cancer. Furthermore, they identified potential reasons for this phenomenon, emphasizing how elderly patients frequently exhibit numerous concurrent health conditions and present signs of frailty. In our study, the older group was significantly larger than the younger one. Despite, the fact that the mean age was almost indistinguishable between patients who had cancer recurrence and those without, the current research elucidated that participants within the examined demographic exhibited an increased propensity for experiencing recurrences as they progress in age. This finding aligns with several published data **[49,50]**. In univariate analysis, when age as continuous variables were analysed, age was not indicative of any tendency toward recurrence. However, when analysed by group, patients aged 75 and older had a slightly higher recurrence risk. Although univariate analysis did not reveal any evidence of a correlation between age and cancer recurrence, a categorical analysis conducted through multivariate methods indicated a slight elevation in recurrence risk for patients aged over 75 years (OR 1). However, this analysis demonstrated a non-specific correlation with cancer recurrence, as evidenced by a p-value of 0.11.

Empirical research has illustrated that the location of the primary tumour holds significant relevance to prognosis, particularly in the context of resectable NSCLC **[91,92]**. Research has indicated that lung cancer primarily appears in the upper lobes in both male and female patients, particularly among individuals of African American and Caucasian backgrounds, spanning various age groups **[149]**. This finding aligns with our study, which highlighted the significance of upper lobe tumours in our patient cohort, where most individuals were documented as having tumours in the RUL and LUL. Numerous investigations have elucidated that lung neoplasms manifesting in the lower lobes are correlated with a more unfavourable prognosis and cancer recurrence in comparison to those originating in the upper lobes **[22,151,152,153,154,155]**. In the observed cohort, a particularly concerning statistic emerged among patients with tumours located in the LLL, where the rate of recurrence escalated to 36.11%. Furthermore, it is noteworthy that cancer reappeared in every instance of bilateral synchronous tumours. Additionally, the results from the

univariate analysis revealed a statistically significant correlation between the anatomical positioning of the primary tumour and the recurrence of cancer (p-value of 0.03). However, a multivariate analysis that adjusted for tumour location and missing data taken into account revealed a limited capacity to detect cancer recurrence. The precision, recall, and F1-score for recurrence all had zero values, indicating that the method was less successful in predicting recurrence and had low accuracy. The calculated Area Under the Receiver Operating Characteristic Curve (ROC AUC) of 0.394 also commend poor performance of the model. This could be due to the class imbalance problem and the fact that for understanding the relation between predictors, non-linear relationships must be handled. Possible improvement for the future concerns the classes distribution, better optimization of features, and reduction of overfitting.

The literature indicates that the probability of cancer recurrence escalates with the progression of tumour staging, a finding that is congruent with our research, as it delineates the increasing risk of recurrence in tandem with disease stage advancement **[27,28,29]**, a finding that aligns closely with our research. Our study recorded that the recurrence rate is even more pronounced for stage III in comparison to stage I and stage II. This demonstrated the advanced nature of stage III tumours, wherein the malignancy has generally disseminated beyond the pulmonary system and may involve adjacent lymph nodes or other anatomical structures, thereby complicating therapeutic interventions and heightening the probability of recurrence. While the univariate analysis conducted taking all three stages into account did not reveal a statistically significant relationship between tumour stages and cancer recurrence, when stage III patients were analysed categorically a statistical significance was recorded. A comprehensive multivariate analysis indicated that tumour staging was highly significant and demonstrated notably elevated odds ratios ranging from 3.3 to 3.5, supported by narrow confidence intervals that did not include 1. An examination of hazard rates related to tumour characteristics in stage III disease, compared to subsequent stages, showed that angio-invasiveness and local or distant extravasation were linked to significantly higher recurrence rates than those observed in earlier stages. The consistency observed across models underscores the importance of accurate staging to identify high-risk patients, thereby facilitating the application of appropriate treatment strategies. The presence of a stage III tumour was identified as the most significant predictor of recurrence, with a p-value of less than 0.001 that

supports the earlier hypothesis that higher stage represents increased tumour burden and potential for systemic disease recurrence, hence the need to regard the staging system as valuable.

A multitude of investigations within the existing academic corpus suggest that the categorization of residual tumour holds significant prognostic value. Patients diagnosed with stage I-III NSCLC who have undergone an incomplete (R1-R2) resection demonstrate a comparatively poorer prognosis than their counterparts who have received a complete resection (R0) **[4,20,21,22,138]**. This observation within the cohort is particularly surprising, as one would typically expect that patients undergoing R1 or R2 resections would demonstrate a significantly elevated recurrence rate due to the presence of remaining malignant cells. However, the study revealed that patients who underwent R0 resection had a slightly higher recurrence rate, highlighting the complex nature of cancer treatment and the possibility of residual microscopic disease that may not be detectable during the surgical procedure. Numerous studies in the current literature have indicated that several patients, including those with early-stage NSCLC, have experienced local recurrence following what is classified as R0 resection. Univariate analysis as well as a comprehensive multivariate analysis identified the adequacy of resection margin status as a significant predictor (p value 0.002), with OR ranging from 2.8 to 3.0. The CIs were robust and reliable. Similar to LVI, positive margins indicate the presence of residual disease, which may result from either surgical challenges or the aggressive nature of the tumour following what appeared to be a complete excision. This suggests the importance of clear margins in decreasing the recurrence rate.

The current body of literature offers limited understanding of the most effective surgical technique—VATS versus open thoracotomy—in relation to the recurrence of NSCLC. Research efforts have predominantly focused on the advantages of VATS over open thoracotomy, especially concerning overall survival outcomes. Our findings revealed that the recurrence rate among patients who underwent VATS was significantly lower than that of those who had open thoracotomy, with a difference of 11%. However, no association was observed in univariate analysis between cancer recurrence and the chosen surgical method, as evidenced by a p-value of 0.06. When comparing open thoracotomy to VATS, there was a slight inclination towards a higher recurrence risk associated with open thoracotomy, with OR ranging from 1.3 to 1.5. Nevertheless, the significance of this association was marginal, with a p-value ≈ 0.05, and some CI included the value of 1. The relationship between surgical approach and recurrence exhibited variability,

implying that the effect may be minimal and potentially vary among different patient subgroups, particularly as the management of more complex lesions may necessitate open surgical intervention.

A univariate analysis was also performed to confirm the results of the multivariate analysis and to investigate each predictor separately. Both analyses highlight the importance of tumour staging and the thoroughness of tumour resection as critical determinants of recurrence. While the surgical approach and patient age emerged as marginally significant secondary predictors, their influence and relevance are context-dependent, warranting careful interpretation. These results emphasize the necessity for meticulous preoperative planning and surgical precision. Furthermore, they indicate the importance of tailoring treatment strategies to individual patients, or at a minimum, to specific groups based on the assessed recurrence risks associated with tumour characteristics.

7.1 Limitations

Our study is inherently limited by its retrospective design and small sample size. The study relied on accuracy of written records entered into an NHS clinical database, which was not collected for research purposes. Since the data was not gathered using a pre-designed proforma tailored to the specific requirements of the study, some data were inevitably missing in most cases. Additionally, certain variables that could potentially impact the outcome of cancer recurrence such as molecular biomarkers may not have been recorded at all.

8 Conclusion

The current study was a step towards providing valuable insight into the prognostic factors such as demography, comorbidities and smoking status, tumour factors (histology and tumour staging), surgical factors (surgical approach, operation performed, visceral pleural invasion and resection margin) and adjuvant therapy influencing post-surgical recurrence in NSCLC patients, which could be beneficial in formulating strategies to reduce recurrence.

In this cohort study, it was observed that the recurrence rate among NSCLC patients who underwent surgery with curative intent aligns closely with already published studies. Generally, the risk of recurrence is at its peak within 2 years after the initial diagnosis or treatment, subsequently diminishing over time**.**

Furthermore, the study under consideration shows that tumour staging and resection margin status are the leading indicators, where stage III and R1-2 margins exhibit the most prominent effects. Although tumour location was marginally significant, age and other potential predictors demonstrated less consistent or non-significant impacts in the surgical approach. From the logistic regression analysis, it was observed difficulty in constructing a model that accurately predicts recurrence based on class imbalance and model constraints. However, the presented model showed a rather high recall for non-recurrence and unsatisfactory accuracy of recurrence prediction. These results indicate that in future cases it is imperative to work at improving the sensitivity of model parameters, balancing the subclass distributions, as well as examining non-linear relations in order to achieve higher predictive precision.

8.1 Future directions

Future studies may delve deeper into the phenomena of cancer recurrence and overall survival disparities among post-surgery NSCLC patients in comparison to individuals subjected to cyberknife intervention as a control cohort. This endeavour has the potential to enhance comprehension of prognostic determinants and offer valuable insights for the development of therapeutic approaches.

Will be very valuable to follow up, this group with survival analysis, to explore whether recurrence is the main risk factor for mortality and also to find out those two unfavourable outcomes share the same risk factors.

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Publications

1. Retrospective analysis of rate of recurrence in non-small cell lung cancer (NSCLC) patients treated with curative surgery.
   Jayeeta Dutta, Yadee Myint, Alison MacMillan, Thida Win.
   British Thoracic Oncology Group Conference Belfast 2024.

2. Influence of smoking status on cancer recurrence following curative intent surgery in lung cancer.
   Jayeeta Dutta, Mayurun Selvan Danilo Faccenda, Alison MacMillan, Thida Win.
   British Thoracic Oncology Group Conference Belfast 2025.

3. The influence of age on post-surgical lung cancer recurrence.
   Jayeeta Dutta, Mayurun Selvan, Danilo Faccenda, Alison MacMillan, Thida Win.
   British Thoracic Oncology Group Conference Belfast 2025.

4. Sex influence on post -surgical lung cancer recurrence.
   Jayeeta Dutta, Mayurun Selvan, Danilo Faccenda, Alison MacMillan, Thida Win.
   British Thoracic Oncology Group Conference Belfast 2025.

5. Recurrence pattern of post-surgical resection in lung cancer patient with curative intent.
   Jayeeta Dutta, Mayurun Selvan, Danilo Faccenda, Alison MacMillan, Thida Win.
   British Thoracic Oncology Group Conference Belfast 2025.

6. A comparison of Lung Cancer outcome of two surgical referral centres from single district Hospital.
   Amy Clark, Jayeeta Dutta, Mayurun Selvan, Alison MacMillan, Thida Win.
   British Thoracic Oncology Group Conference Belfast 2025.