SURVIVAL RATES AND PREDICTORS OF MORTALITY IN LUNG CANCER:

A MULTI-CENTRE STUDY

IN KERALA

Dr Nisha K Jose

PhD THESIS

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SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL

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SURVIVAL RATES AND PREDICTORS OF MORTALITY IN LUNG CANCER: A MULTI-CENTRE STUDY IN KERALA

A THESIS SUBMITTED BY

DR NISHA K JOSE

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DOCTOR OF PHILOSOPHY

2025

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr Nisha K Jose, hereby certify that I had personally carried out the work depicted in the thesis entitled, "**Survival rates and predictors of mortality in lung cancer: a multi-centre study in Kerala.**"

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Signature

Nisha

Dr Nisha K Jose

Date: 17/06/2025

CERTIFICATE BY THE RESEARCH GUIDE

Name of the Guide: Dr Jeemon Panniyammakal

Division/Department: Associate Professor, AMCHSS, SCTIMST

This is to certify that **Dr Nisha K Jose,** department of **Health Sciences, Achutha Menon Centre for Health Sciences Studies** of this institute has fulfilled the requirements prescribed for the Ph.D. degree of the Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum.

The thesis entitled, **Survival rates and predictors of mortality in lung cancer: a multi-centre study in Kerala**" was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Signature 18/6/25

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Dr Jeemon Panniyammakal

Date

APPROVAL OF THE THESIS

The thesis entitled

"Survival rates and predictors of mortality in lung cancer: a multi-centric study in Kerala."

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(Name & Signature of thesis examiner)

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LIST OF ABBREVIATIONS

Sl No	Abbreviation	Full Form
1	NCDs	Non-Communicable Diseases
2	WHO	World Health Organization
3	ICD	International Classification of Diseases
4	COPD	Chronic Obstructive Pulmonary Diseases
5	CD	Communicable Diseases
6	DALYs	Disability Adjusted Life Years
7	LMICs	Low Middle-Income countries
8	CVD	Cardio Vascular Diseases
9	AAR	Age-Adjusted rate
10	SCLC	Small Cell lung Cancer
11	NSCLC	Non- Small Cell lung Cancer
12	SCC	Squamous Cell Carcinoma
13	ETS	Environmental Tobacco Smoke
14	NCRP	National Cancer Registry Program
15	AIS	Adenocarcinoma Insitu
16	MIA	Minimally Invasive Adenocarcinoma
17	OR	Odds Ratio
18	CI	Confidence Interval
19	CP	Chlorophenols
20	PA	Phenoxyacetic Acid
21	SMR	Standardized Mortality Rate
22	PM	Particulate Matter
23	PAHs	Polycyclic Aromatic Hydrocarbons
24	IARC	International Agency for Research on Cancer

25	EPA	Environmental Protection Agency
26	RR	Relative Risk
27	HPV	Human Papilloma Virus
28	EBV	Epstein-Barr Virus
29	DNA	Deoxyribonucleic acid
30	IHC	Immuno Histo Chemistry
31	LCC	Large Cell Carcinoma
32	TNM	Tumour Node Metastasis
33	AJCC	American Joint Committee on Cancer
34	CT	Computed Tomography
35	MRI	Magnetic Resonance Imaging
36	PET	Positron Emission Tomography
37	CTCs	Circulating Tumour Cells
38	ECOG	Eastern Cooperative Oncology Group
39	OS	Overall Survival
40	ICMR	Indian Council of Medical Research
41	KM	Kaplan Meir
42	CoxPH	Cox Proportional Hazard Model

Survival rates and predictors of mortality in lung cancer: a multi-centre study in Kerala

SYNOPSIS

by

Dr. Nisha K Jose

for PhD Degree

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

Introduction:

Non-communicable diseases (NCDs), including cancer, are responsible for 74% of all deaths worldwide. In recent years, there has been a surge in the incidence and mortality rates of NCDs globally. Cancers are a major contributor to the disease burden, and projections forecast that the global burden of cancer will continue to grow for at least the next two decades. Lung cancer is a worldwide health problem and is now reported as the most frequently diagnosed cancer. Globally, lung cancer was not only the most diagnosed cancer but also the leading cause of cancer-related deaths. In India, lung cancer accounts for 5.9% of all cancers and 8.1% of all cancer-related deaths.

The differences in reported cancer-related mortality rates are due to the differences in cancer care between high-income countries and low-middle-income countries. According to a global study conducted in 67 countries, the 5-year survival rate remains poor (9%) in India as opposed to Europe (20%), Japan (33%) and the United States of America (19%). Available data from India indicates that 90% of lung cancer cases are diagnosed at an advanced stage of the disease, which reduces overall survival.

Justification-Rationale:

In India, survival analysis studies are scarce as it requires long-term follow-up and a good database. Among cancers, lung cancer contributes to the highest mortality rate in India. Therefore, we conducted the present study to understand the survival rates and factors associated with lung cancer mortality in India.

Objectives:

The research objectives are: (1). To assess the survival rates and median survival time among lung cancer patients in Kerala, India, by establishing a lung cancer registry with

two-year follow-up at six participating institutions and (2). To identify the predictors of mortality outcomes among lung cancer patients in Kerala

Methods:

We set up a hospital-based cancer registry in Kerala. We selected hospitals from three zones of Kerala– north, central, and south. A total of six tertiary care hospitals participated in the registry. Patients of pathologically proven primary lung cancer (ICD-11 code C 33 and C 36) were recruited. Patients diagnosed with lung cancer from January 2017 to December 2019 were included in the registry. All patients were followed up for two years from the date of diagnosis. Patients with thoracic metastatic lung disease from a non-pulmonary primary cancer were excluded.

We obtained institutional ethical clearances from all six sites, including the institute ethics committee of Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCT/IEC/1658 /DECEMBER-2020). The study was registered in the clinical trial registry of India (CTRI/2021/ 02/031/031299). Data regarding socio-demographic characteristics, presenting complaints, performance status at diagnosis using the Eastern Cooperative Oncology Group scale (ECOG), date and mode of diagnosis, investigations, past medical history, treatment modalities, and treatment outcome were retrieved from the patient chart using a predesigned structured proforma. The patient/caregiver was contacted telephonically to assess the vital status during data collection. They were contacted every six months until two years after diagnosis if the primary outcome of interest (all-cause mortality) had not occurred at any contact.

The data were entered into an Excel spreadsheet and analyzed using Stata 13. Data on continuous measurements were presented as mean and standard deviation. The categorical variables were presented in numbers (%). We employed Kaplan-Meier survival curves and

log-rank tests to depict the survival probability according to categorical variables. The Cox proportional hazard model was employed to determine the all-cause mortality predictors.

Results:

A total of 761 patients with primary lung cancer diagnosed from 2017 to 2019 were included in the study. The proportion of study participants who lost to follow-up was 6.8%. The mean age of the study population was 65.1±10.2 years. More than one-third (37.8%) of the study population belonged to the age group of 65-74 years, followed by 32.5% in the age group of 55-64 years. Most of the participants (81.1%) included in the study were males, with a male-to-female ratio of 4.28:1. One-third of the participants (33.9%) belonged to the 'normal weight' category based on body mass index (BMI). Further, 15.5% and 9.8% belonged to the underweight and overweight BMI categories, respectively. ECOG performance scoring was one, two, three, and four in 40.9%, 41.1%, 17.7%, and 0.3% of participants, respectively.

Smoking history data were unavailable for 10.9% (83) of the study population. In total, more than half of males (55.0%) and 1 (0.1%) female participants reported ever smoking status in their lifetime. Additionally, one-third (33.8%) of participants never smoked in their lifetime.

In our study, 61.5% of the participants were presented with a tumour located in the right lung. The upper lobe of the lung was involved in 53.9% of the participants. The most common pathological type was adenocarcinoma (56.4%), and it was the most common type of lung cancer among males and females. Squamous cell carcinoma was identified in a quarter of the participants (25.8%). Additionally, small cell carcinoma was identified in 7.4% of the participants. Large cell carcinoma was the least common (1.2%) and was only present in males. Metastasis was reported predominantly in bone (38%), brain (27.0%), adrenal gland (20.2%), and liver (10.9%).

The median survival of the study population was 8.6 months (IQR-2.9-21.6). Cumulative mortality rates at the end of six months, one year, and two years were 39.9%, 57.8%, and 70.2%, respectively. The overall mortality rate was 6.38 (CI-3.03-12.97) per 100 person months.

In the bivariate analysis, sex, consumption of alcohol, smoking history, number of symptoms, BMI, number of metastatic sites, vessel invasion, pleural involvement, lymph node status, ECOG performance score, tumour size, histological type, and TNM staging were associated with time to all-cause mortality. The mortality risk was 30% higher in males than females (HR=1.3, 95% CI 1.06-1.64). Compared to the Nx type, the N2 type and N3 type had eight times (HR=7.9, 95% CI 3.51-17.8) and 14 times (HR=14.3, 95% CI 2.89-71) higher mortality, respectively. Undifferentiated carcinomas had a 1.3 times higher mortality risk (HR=1.3, 95% CI 1-1.78) compared to adenocarcinoma. Mortality risk was more than two times in participants with pleural invasion (HR=2.49, 95% CI 1.93-2.70) compared to participants without pleural invasion and vessel involvement (HR=2.3, 95% CI 1.93-2.70) compared to those participants without vessel involvement. Consumption of alcohol was associated (HR=1.49, 95% CI 1.2-1.74) with a 50% higher risk of mortality compared to non-users. In the multivariable cox-proportional hazard model, participants with lymph node status of N2 (HR=4.9, 95% CI 1.0-23.6), N3 (HR=5.9, 95% CI 0.53-66.7), and NX (HR=31.7, 95% CI 2.8-354.7) had higher mortality risk compared to those with N1 status. Similarly, the number of metastatic sites (higher mortality risk in individuals with multiple metastases as compared to those without metastasis), ECOG Score (higher the score, higher the risk of mortality), and tumour size (larger the size, higher the mortality) were also associated with all-cause mortality.

Discussion:

We enrolled 761 patients with primary lung cancer in the registry. The mean age of the study population was around 65 years, with most patients in the age group between 55 and 75 years. Although we observed male preponderance, one in five participants was female. Adenocarcinoma was the most common pathologic type among males and females, followed by squamous and small-cell carcinoma. The median survival duration was around nine months, and the all-cause mortality rate was 6.38 per 100 person months. The number of metastatic sites, lymph node status**,** ECOG performance status, and tumour size were predictors of time to mortality.

The mean age of lung cancer in India is substantially lower than that of high-income countries. However, over the past 2-3 decades, there has been an increase in the mean age of diagnosed lung cancer patients in India. Our findings concur with more recent findings from India, where the mean age at diagnosis was 65 years. This increase in mean age may be attributed to a better quality of life and longevity among the Indian population.

The incidence and mortality of lung cancer are historically male predominated. However, the male-to-female ratio in our study is higher than that of the Indian Council of Medical Research (ICMR) cancer registry, showing a reducing trend from 4.5 in 2002 to 3.1 in 2021. A similar decrease in the male-to-female ratio is reported in many studies in the US, indicating that the incidence curve of females is plateauing while that for males is decreasing. However, in India, we observe an actual increase in the incidence of lung cancer among females.

Cigarette smoke inhalation is the primary cause of lung cancer, amounting to up to 90% of all reasons. Evidence from Western studies suggests that an increasing trend of female smokers results in identical risk between men and women. However, we find a lot of cases

of lung cancer in our registry without lifetime exposure to smoking tobacco. Although we could not assess exposure to second-hand smoke, our data suggest risk factors other than smoking associated with lung cancer. Older Indian studies show a predominance of squamous cell carcinoma over adenocarcinoma. However, our study is consistent with recent studies showing adenocarcinoma as the predominant form of lung cancer. This change in trend can be attributed to the changing smoking patterns and the increasing incidence of lung cancer in females and non-smokers.

Our multi-variable cox-proportional hazard model identified several predictors of all-cause mortality, such as the number of metastatic sites, lymph nodes, ECOG performance status, and tumour size. In the literature, multiple variables are highlighted as factors associated with mortality in lung cancer patients. In a study from South India, non-adenocarcinoma histology, ECOG performance status of more than two, and stage at diagnosis were associated with all-cause mortality in Non-Small Cell Lung Cancer (NSCLC). However, in small-cell lung cancer, younger age and early stage at diagnosis were associated with better survival outcomes. A lung cancer mapping project in Turkey (LCMPT) reviewed 4531 patients' data. In the multivariable analysis, age, sex, chronic obstructive pulmonary disease (COPD), weight loss, cavitation, histology, and stage at diagnosis were independent prognostic factors. A cohort study from Spain involving 505 early-stage non-small-cell lung cancer patients identified sex, age at diagnosis, type of treatment, ECOG status, and stage at diagnosis as potential predictors of mortality. However, comparing real biological associations across studies without well-established registries and standard variable definitions would be challenging.

The median survival time in our study was only nine months. Late diagnosis in the advanced stage of the disease is one of the prominent reasons for higher mortality in our study. There is consistent observation that early detection, aggressive treatment, and

appropriate disease management can improve survival outcomes for individuals with primary lung cancer. Given the aggressive nature and high mortality associated with this disease, timely interventions such as surgery, chemotherapy, radiation therapy, targeted therapies, and immunotherapy are crucial in combating tumour progression and improving outcomes. These treatments aim to reduce tumour burden and address potential metastases and complications, extending survival and enhancing the quality of life. Beyond medical interventions, holistic disease management involves supportive care, symptom management, and patient education, all contributing to better patient outcomes and prolonged survival in lung cancer.

Recommendations:

The findings of our study include significant implications for policy in cancer diagnosis and first health system contact for treatment. As it contributes to the highest mortality among all cancers, actions at the policy level are warranted. Lung cancer patients in India are at least a decade younger and in an advanced stage of the disease at the time of diagnosis when compared to their Western counterparts. Therefore, early detection of lung cancer is an important priority in Indian settings.

To effectively stratify risk in lung cancer beyond smoking history, comprehensive identification and assessment of potential predictors of mortality are crucial. Since more than one-third of all lung cancer cases in our study lack a history of smoking, understanding and elucidating alternative risk factors such as genetic predisposition, environmental pollutants, occupational exposures (e.g., asbestos, radon), and lifestyle factors (e.g., diet, physical activity) become important. Particularly in the context of rising lung cancer incidence among women, rigorous, long-term follow-up studies are essential. These studies should explore the incidence trends and the impact of emerging risk factors,

the effectiveness of early detection strategies, and the long-term outcomes of various treatment modalities. Such efforts are crucial for refining risk prediction models, optimizing prevention strategies, and improving overall survival outcomes in lung cancer patients beyond conventional smoking-related paradigms. There is a requirement for concerted endeavours to facilitate access to health care services with holistic cancer care to reduce mortality in lung cancer in developing countries like India.

Strengths and Limitations:

The prospective follow-up in a relatively large sample of consecutive lung cancer patients is a major strength. However, the number of study variables was limited as they were extracted from existing clinic records. Our study was restricted to one state of India; therefore, the findings' generalizability is limited to Kerala.

1 INTRODUCTION

1.1 DEFINITION AND CHARACTERISTICS OF NON-COMMUNICABLE DISEASES

Non-Communicable Diseases (NCDs), alternatively termed chronic conditions, often persist over extended periods and stem from a blend of genetic, physiological, environmental, and behavioural influences. Predominant NCD categories encompass cardiovascular issues (like infarction to myocardium and strokes), cancer, chronic lung-related ailments (such as chronic obstructive pulmonary disease and asthma), and diabetes. (WHO, World Health Organization, 2024) The attributes of NCDs include- intricate causative factors, numerous risk elements, extended periods of dormancy, non-transmissible sources, and prolonged duration resulting in functional limitations or incapacity.(CDC, 2023)

The World Health Organization (WHO) categorizes NCDs as "Group II Diseases," grouping various conditions and causes of death based on the “International Classification of Diseases, 11th Revision” (ICD-11) coding classification. These include malignant neoplasms, other types of tumours, neuro-psychiatric circumstances, sensory organ conditions, diabetes mellitus, endocrine conditions, cardio-vascular illnesses, respiratory illnesses, digestive disorders, genitourinary diseases, skin diseases, musculoskeletal disorders (such as rheumatoid arthritis), congenital anomalies (like cleft palate and Down syndrome), and oral conditions (such as dental caries). This classification distinguishes NCDs from “Group I (communicable, maternal, perinatal, and nutritional conditions)” and “Group III (unintentional and intentional injuries)”. (Bloom, 2011; Budreviciute et al., 2020; Matheson et al., 2013; World Health Organization, 2024)

1.2 RISK FACTORS OF NON-COMMUNICABLE DISEASES

A risk factor is “any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury”, - defined by WHO. (Non-Communicable Diseases, Rehabilitation and Disability, 2021) The health risk factors in any environment have the potential to cause injuries or illnesses. The potential for these elements to cause harm to human health exists whenever persons are exposed to them. In this context, risk refers to the probability of adverse effects on human health or ecological approaches from exposure to environmental stressors. Consequently, a human health hazard is the prospect that a specific contact or sequence of exposures could have caused or will cause harm to individuals' health. (Dovjak and Kukec, 2019)

The risk factors of NCDs are modifiable and non-modifiable.

The modifiable risk factors can be divided into metabolic and behavioural risk factors.

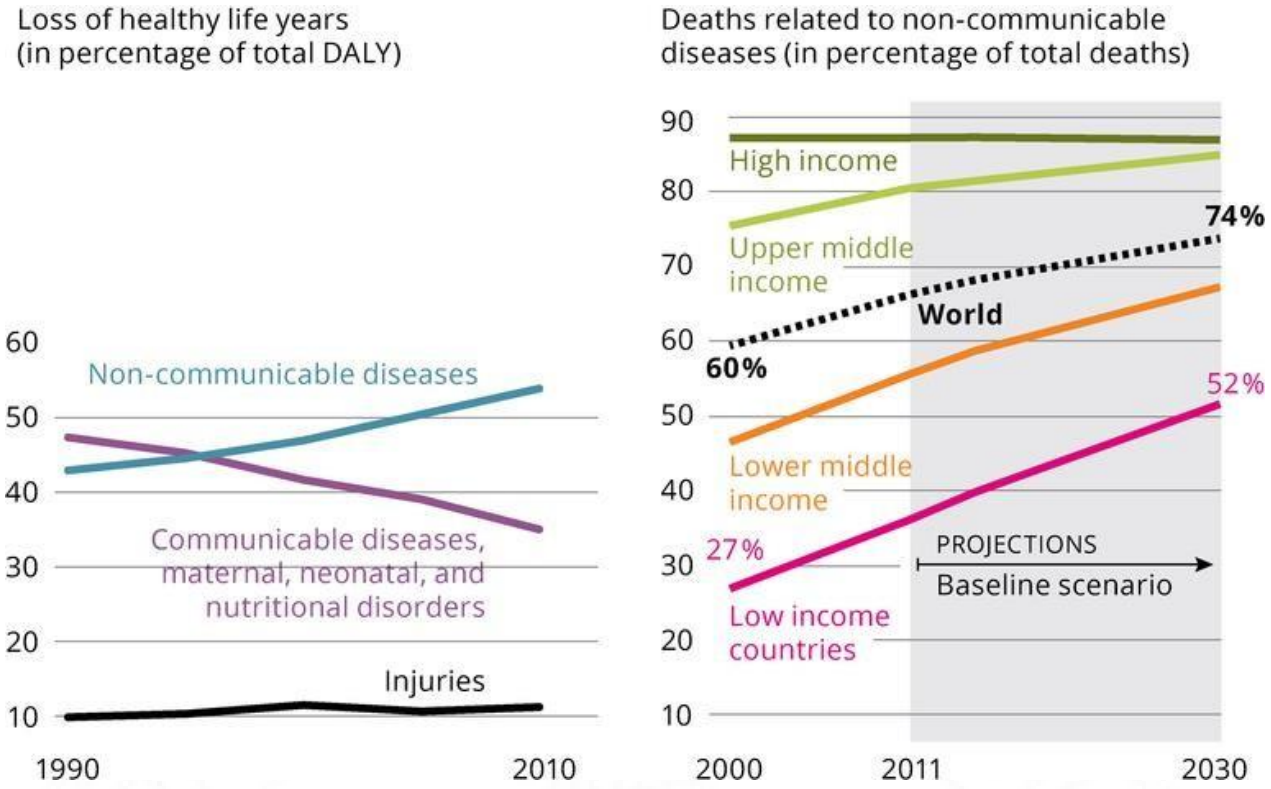
Metabolic risk factors of NCDs refer to certain physiological conditions or abnormalities predisposing individuals to developing chronic diseases. These factors are primarily related to disturbances in metabolism, which can contribute to the onset and progression of various NCDs.

Behavioural risk factors of NCDs are actions or habits that individuals engage in, which increase their susceptibility to developing chronic health conditions. These behaviours are often modifiable and can be influenced by individual choices, social environments, and cultural factors. (Olatona et al., 2018)

1.3 BURDEN OF NON-COMMUNICABLE DISEASES

Throughout history, communicable diseases (CDs) have posed substantial challenges to human health across all age groups during outbreaks. However, the mortality rates attributed to CDs have markedly declined in high-income countries since the early 1900s, mainly due to advancements in medicine, improved access to healthcare, and enhanced hygiene practices, particularly in combating diarrheal ailments and lower respiratory contaminations in the earlier two decades. The Industrial Revolution, accompanied by nutritional, epidemiological, and demographic shifts, profoundly influenced human ecology and biology, significantly altering life-history traits. Furthermore, genetic variations once advantageous for fitness may now influence the populace to NCDs, such as cancer, Alzheimer's disease, and coronary artery disease, due to antagonistic multifaceted impacts. Global epidemiological research underscores that chronic NCDs, including metabolic conditions and atherosclerosis, are the primary contributors to early death and illness. (Diem et al., 2016; *Lancet (London, England)*, 2016; *Nature Microbiology*, 2019; Murray et al., 2015; Omran, 2005) Figure 1 shows the transition in the burden from communicable to non-communicable diseases. (*European Environment Agency*, 2021)

Figure 1: Shift of burden of diseases. European Environment Agency 2021.



"Temporal coverage: 5-year intervals 1990-2010 (left panel); 2000, 2011, 2015, 2030 (right panel)

Geographical coverage: World (left panel); World, high income, upper middle income, lower middle income, low-income countries (right panel)"

1.3.1 INTERNATIONAL LEVEL

Significant shifts occurred in the global health landscape in the past three decades, driven by economic growth, population growth, aging demographics, increased longevity, unhealthy lifestyle choices, and environmental pollution. (Hong et al., 2023) These factors have collectively altered the pattern of disease burden. Epidemiological data indicate that NCDs have emerged as the primary causes of death and disability-adjusted life years (DALYs) on a global scale. (Bhattacharya et al., 2023) Furthermore, NCDs are no longer confined to affluent nations but impact countries across various socio-economic strata. (Diem et al., 2016; *Lancet (London, England)*, 2016; Murray et al., 2015; Omran, 2005)

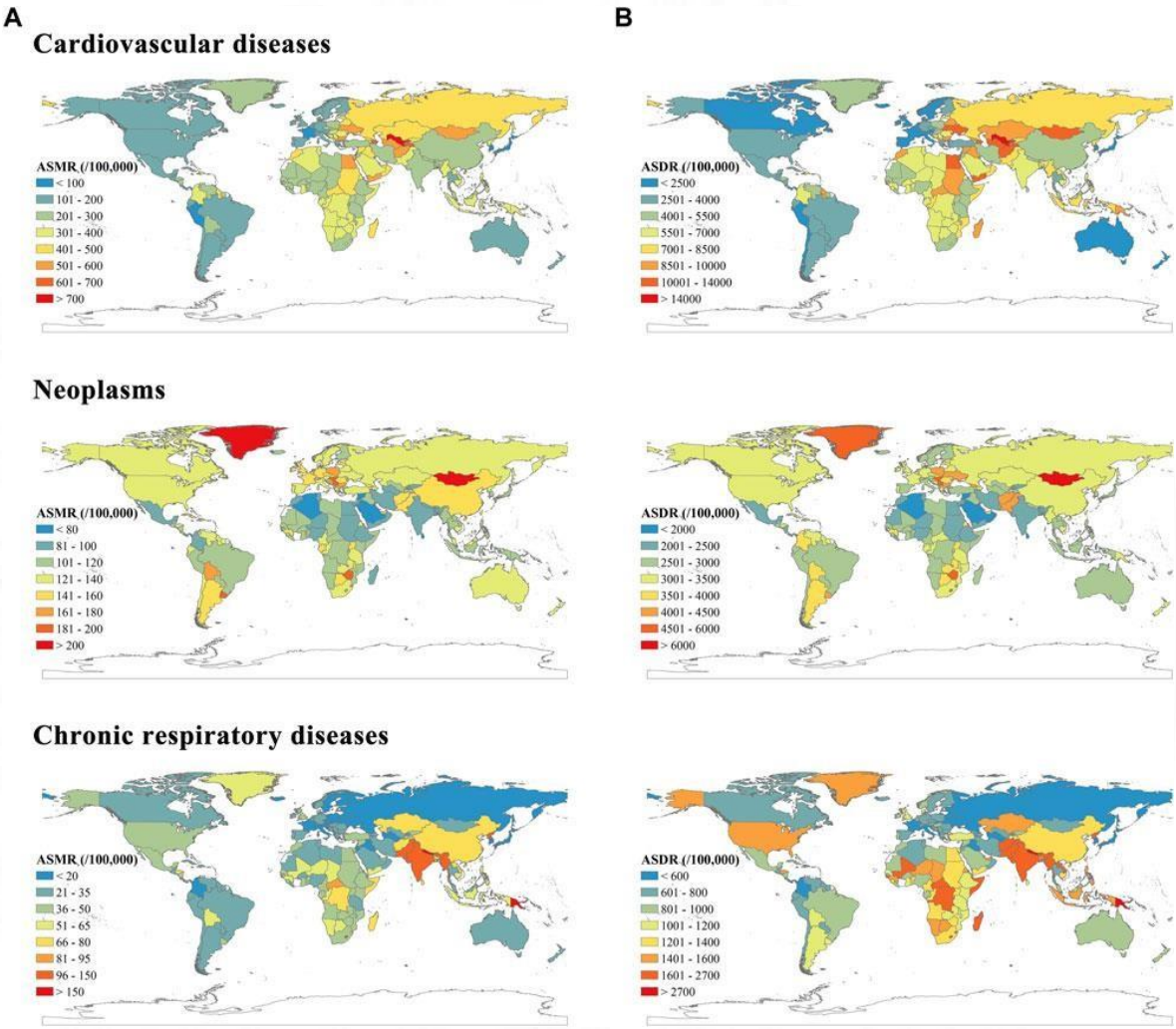
Approximately 41 million deaths worldwide, equivalent to nearly three out of every four deaths, can be attributed to NCDs. (NCD Countdown 2030 collaborators, 2018) Alarmingly, around 17 million of these deaths occur among individuals in their most productive years, with eight out of ten happening in developing middle/lower-income nations. Although NCD mortality rates are on the decline in high-income nations, the burden in LMICs is escalating due to the epidemiological transition, with these countries now bearing 85% of NCD-related deaths. (World Health Organization, 2020a; World Health Organization Geneva, 2024b) Cardiovascular illnesses, Diabetes mellitus, cancers, and chronic respiratory illnesses collectively contribute to approximately 80% of these fatalities. This burden is further compounded by shifts in nutrition, demographics, and economics within LMICs. (Budreviciute et al., 2020; Richards et al., 2016; World Health Organization, 2020; World Health Organization, 2024)

NCDs take the lives of 410 lakh people annually, comprising 74% of global mortality. Annually, 170 lakh people perish to NCDs before attaining 70 years, with 86% of these premature casualties happening in developing low/middle-income nations. Among all NCD fatalities, 77% are concentrated in LMICs. (Noncommunicable diseases: Mortality, 2022) Figure 2 depicts age-standardized mortality rate and disability rates per 100,000 populations.

Predominantly, cardio-vascular diseases lead to NCD-related deaths, affecting 179 lakh population annually, trailed by malignant cancers (93 lakh), chronic respiratory illnesses (41 lakh), and diabetes (0.2 lakh, including deaths from kidney ailment due to diabetes). These four disease categories contribute to over 80% of all premature NCD fatalities. Tobacco consumption, physical inactivity, extreme alcohol ingestion, poor dietary habits,

and air pollution heighten the risk of NCD mortality. Effective discovery, screening, and management of NCDs, alongside providing palliative care, are crucial to responding to NCDs. (World Health Organization, 2024)

Figure 2: Age-standardized mortality rates (A) and age-standardized disability-adjusted life year rate (B) of NCDs per 100,000 people with chronic illnesses. (Bai et al., 2023)



ASMR-Age Standardized Mortality Rates (A); ASDR- Age Standardized Disability-adjusted life years Rate (B).

1.3.2 NATIONAL LEVEL

In 2021, the global burden of disease report revealed that approximately 1.54 million deaths in India were attributed to high blood pressure, while worldwide, high blood pressure accounted for 10.4 million fatalities.(Ramesh and Kosalram, 2023) High blood pressure also resulted in 220.0 million disability-adjusted life years globally, with 38.1 million disability-adjusted life years in India.(Rapsomaniki et al., 2014) According to the recent report of the National Family Health Survey-5, approximately 21.3% of women and 24.0% of men in India exhibited elevated blood pressure (Systolic ≥140 mmHg and/or Diastolic ≥90 mmHg) or were under medication for hypertension control.(NFHS-5_Phase-II_0.)

1.4 CANCER BURDEN

1.4.1 CANCER BURDEN-GLOBALLY

In 2020, breast cancer and lung cancer were the most prevalent cancers globally, comprising 12.5 percent and 12.2 percent of the total number of recent cases detected, respectively. Colorectal cancer ranked as the 3rd most common cancer, with 1.9 million new cases reported, contributing upto 10.7 percent of new cases. (Bray et al., 2021; Gersten and Wilmoth, 2002; Omran, 1971; D World Health Organization, 2020b).

Cancer in men

In 2020, lung cancer emerged as the most common cancer among males globally, accounting for 15.4 percent of the total number of recent cases detected. (Ji et al., 2023;

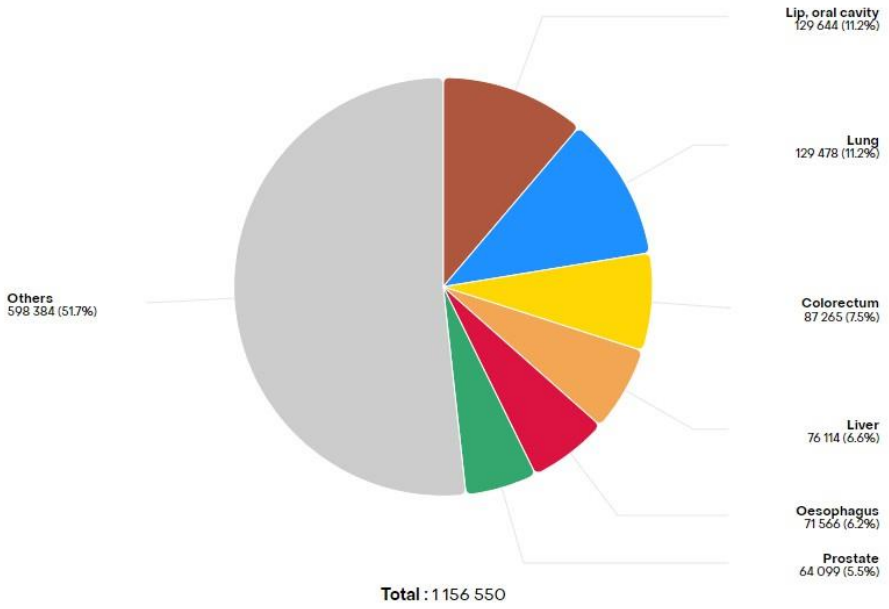
Sung, Ferlay, Rebecca L. Siegel, et al., 2021) The top three cancers in terms of incidence among men—lung, prostate, and colorectal cancers—collectively added to 41.9 percent of all cancers (ruling out non-melanoma skin cancer). Additionally, stomach and liver cancers were also prevalent, each contributing to more than 5% of new cancer subjects. (Worldwide cancer data | World Cancer Research Fund International, 2024)

Cancer in women

In 2020, breast cancer ranked as the most prevalent cancer among women globally, accounting for 25.8 percent of the total number of recent subjects detected. (Sung, Ferlay, Rebecca L. Siegel, et al., 2021). The top three cancers in terms of incidence among women are breast, colorectal, and lung cancers, collectively adding to about 44.5 percent of all cancers (ruling out non-melanoma skin cancer). Additionally, cervical cancer was the 4th most common cancer in female subjects, adding up to about 6.9 percent of the total number of recent cases detected in 2020. (Worldwide cancer data | World Cancer Research Fund International, 2022). Figure 3 depicts cancer incidence in the South East Asia Region in men and women.

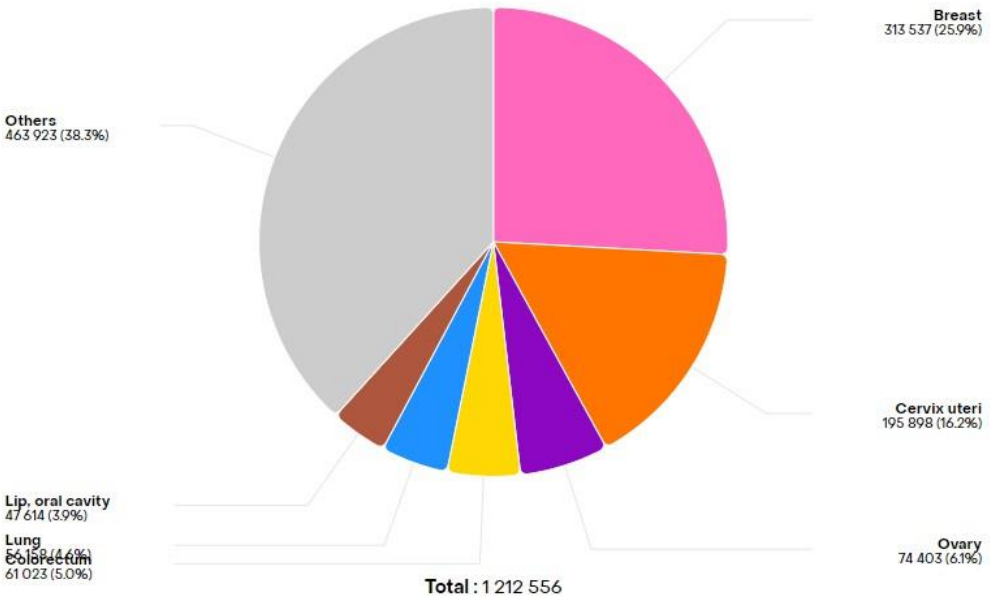
Figure 3: Cancer incidence in Southeast Asia region in men and women (GLOBOCAN 2020: New Global Cancer Data | UICC, 2022)

Absolute numbers, Incidence, Males, in 2022
WHO South-East Asia region (SEARO)



Total : 1 156 550

Absolute numbers, Incidence, Females, in 2022
WHO South-East Asia region (SEARO)

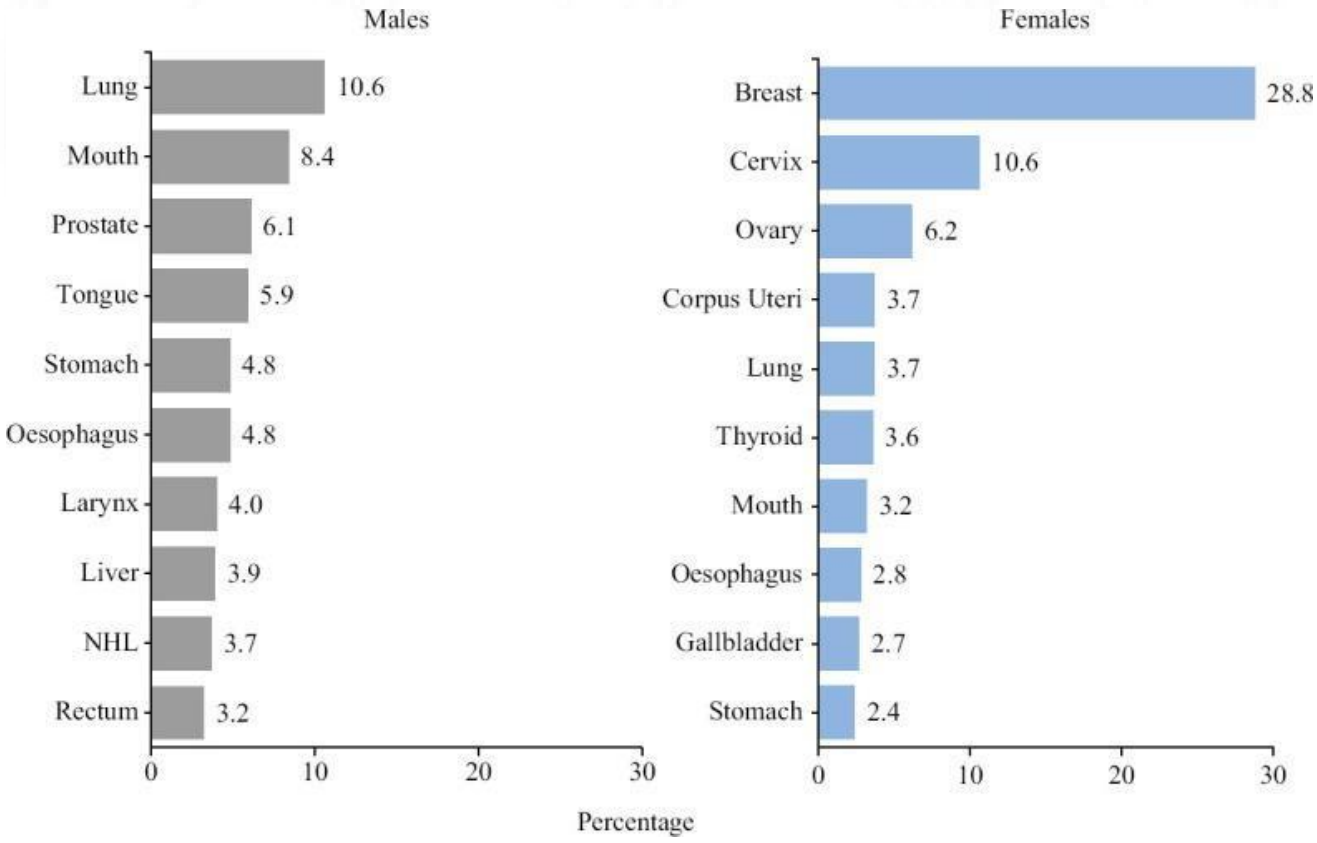


Total : 1 212 556

1.4.2 CANCER BURDEN-NATIONAL LEVEL

In India, in 2022, the number of recent cases was 1,461,427, with a crude rate of 100.4 per 100,000 individuals. One in nine people in India are expected to get cancer during their lifespan. Among males, lung cancer was the most common, while breast cancer ranked highest among females. Figure 4 shows cancer incidence in India for both sexes in 2022. Regarding childhood cancers (0-14 years), lymphoid leukaemia was the leading site, accounting for 29.2 percent of boys and 24.2 percent of girls. Cancer occurrence is projected to rise to 12.8 percent in 2025 compared to 2020. (Bray and Parkin, 2009; D'Souza et al., 2013; Murthy et al., 1990; Siegel et al., 2022; Sung, Ferlay, Rebecca L Siegel, et al., 2021; Swaminathan et al., 2011; Takiar and Shobana, 2009)

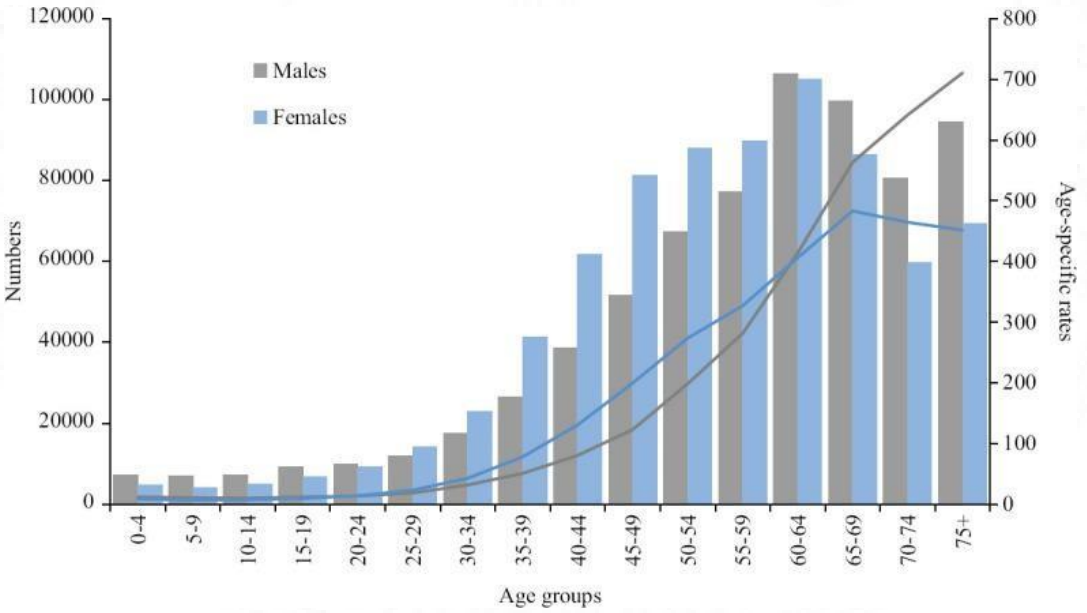
Figure 4: Estimated cancer incidence in India for both sexes in 2022. (Sathishkumar, Chaturvedi, Das, S. Stephen, et al., 2022)



In India, the estimated number of cancer cases for 2022 was 1,461,427. The crude incidence rate of cancer in India was 100.4 per 100,000 population. There were more cases among females, with 749,251 cases (105.4 per 100,000 women), compared to males, with 712,176 cases (95.6 per 1 lakh men). The assessed age-adjusted rate (AAR) for all locations of cancer in India was 107.0 per 1 lakh population. (Sathishkumar, Chaturvedi, Das, S. Stephen, et al., 2022). Figure 5 shows estimated age-wise cancer incidence rates.

The lifetime aggregate risk of acquiring cancer between the ages of 0 and 74 was 1 in 9 people for all types of cancer in both genders. For males, the likelihood of getting lung cancer was 1 in 67, while for females, the likelihood of getting breast cancer was 1 in 29. (Sathishkumar, Chaturvedi, Das, S Stephen, et al., 2022)

Figure 5: Estimated age-wise cancer incidence rates (Sathishkumar, Chaturvedi, Das, S. Stephen, et al., 2022)



1.5 JUSTIFICATION/RATIONALE FOR THE STUDY:

Lung cancer stands out as a leading cause of mortality in India, marked by a challenging prognosis. Despite its significant impact, survival analysis studies on lung cancer remain sparse within the country due to the demanding nature of long-term follow-ups and the inadequacy of robust databases. Only a few studies investigated survival predictors of lung cancer among the Indian population. Indian Council of Medical Research has a cancer registry, but the registry does not collect survival data on lung cancer. The current registries in India collect cross-sectional data without follow-up. To address this gap, we established a lung cancer registry to study survival, leveraging a comprehensive socio-demographic, clinical, laboratory, and treatment-related factors analysis. We aimed to provide a better understanding of survival rates, thereby enhancing the assessment of current treatment protocols. Our research fills a critical knowledge gap that could potentially improve the prognosis of lung cancer patients in India. Our findings can inform clinical decision-making, risk stratification, and targeted intensive treatment. Furthermore, our research underscores the urgent need for investment in longitudinal data collection and research infrastructure to support ongoing cancer research and care efforts. Ultimately, leveraging multidisciplinary approaches and data-driven insights, we aspire to better clinical outcomes and quality of life for lung cancer patients across India.

1.6 **AIMS OF THE STUDY**

To assess the predictor variables of mortality in lung cancer patients

1.7 OBJECTIVES OF THE STUDY

1.7.1 PRIMARY OBJECTIVES

1 To assess the survival rates and median survival time among lung cancer patients in Kerala, India.

2 To identify the predictors of mortality outcomes among lung cancer patients in Kerala.

1.7.2 SECONDARY OBJECTIVES

1 To assess survival rates at six months, one year, and two years among lung cancer patients

2 To assess mortality per person-months among lung cancer patients

1.8 SCHEME OF THESIS

The succeeding chapters are structured schematically to cover the features of the study. A review of the literature on the topic (focusing on the most recent evidence) is presented first, followed by the material and methods used for the study. Findings emerging from the study are presented subsequently, after which the relevant discussions are narrated by comparing the findings with existing literature. Salient takeaways are summarized, along with conclusions and recommendations for the study.

2 REVIEW OF LITERATURE

A literature review of this study is being discussed under the following heads:

1. Cancer- definition and types
2. Lung cancer- epidemiology
3. Lung cancer- risk factors
4. Lung cancer-pathogenesis
5. Lung cancer- symptoms and staging
6. Lung cancer- diagnosis and treatment
7. Lung cancer- treatment
8. Survival status of lung cancer

2.1 CANCER- DEFINITION AND TYPES

Cancer, also known as malignant tumours or neoplasms, encompasses various illnesses that can develop in any section of the body. A defining characteristic of cancer is the swift proliferation of unusual cells that exceed their normal borders, leading to the invasion of surrounding tissues and potential spread to distant organs, a process known as metastasis. Metastasis to other body sections is often the primary cause of death in individuals with cancer. (Brown et al., 2023; Cooper, 2000)

Table 1 shows the various definitions of cancer. (Cancer | CDC, 2013; Cancer - Oxford Reference, 1919; Overview of Cancer - Cancer - Merck Manuals Consumer Version, 2023; What is cancer? | Cancer Research UK, 2023; Simpson et al., 2023; Webster, 1869)

Table 1: Definitions of cancer

Definition of cancer	**Source**	**Year**
In medicine, a roundish, hard, unequal, scirrhous tumour of the glands, which usually ulcerates, is very painful, and generally fatal.	An American Dictionary of the English Language. (Webster)	1828
A tumour is a new growth of tissue, which apparently originates and grows spontaneously, possesses an atypical architecture, does not subserve the uses of the organism, and reaches no definite termination of growth.	Textbook of General Pathological Anatomy and Pathogenesis (Ziegler)	1898
A malignant tumour eating the part it is in, spreading indefinitely, & recurring when removed.	Oxford Dictionary	1919
A tumour is an autonomous new growth of tissue.	Neoplastic Disease – a treatise on tumours (Ewing)	1919

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts.	National Cancer Institute	2023
Cancer isn't a single disease. Cancer is a group of diseases characterized by the uncontrolled proliferation of cells. Ignoring the body's signal to stop, malignant cells multiply to form tumours in organs and tissues or crowd out normal cells in the bloodstream and bone marrow in the case of blood cancers.	American Association for Cancer Research	2023
Cancer is when abnormal cells divide in an uncontrolled way. Some cancers may eventually spread into other tissues.	Cancer Research UK	2023
A group of diseases in which cells in the body change and grow out of control. Most types of cancer cells form a lump, or mass called a tumour.	American Cancer Society	2023
Cancer refers to diseases in which abnormal cells divide out of control and can invade other tissues. Cancer cells can spread to different body parts through the blood and lymph systems, which help the body get rid of toxins.	Centres for Disease Control and Prevention	2023

Cancer continues to be a prominent contributor to global mortality, accounting for around 10 million reported deaths in 2020. The predominant forms of cancer in terms of newly diagnosed cases in 2020 were:

- Breast cancer (2.26 million cases)
- Lung cancer (2.21 million cases)
- Colon and rectum cancer (1.93 million cases)
- Prostate cancer (1.41 million cases)
- Skin cancer (non-melanoma) (1.20 million cases)
- Stomach cancer (1.09 million cases)

In terms of cancer-related deaths in 2020, the most prevalent causes were:

- Lung cancer (1.80 million deaths)
- Colon and rectum cancer (916,000 deaths)
- Liver cancer (830,000 deaths)
- Stomach cancer (769,000 deaths)
- Breast cancer (685,000 deaths)

2.2 LUNG CANCER- EPIDEMIOLOGY

Lung cancer, also known as broncho-genic carcinoma, is the development of tumours in the lung tissue or bronchial tubes. There are two categories of lung cancer: “small cell lung cancer (SCLC) and non-small cell lung cancer” (NSCLC). Furthermore, there exists a less prevalent variant referred to as carcinoid lung cancer. ("Lung cancer, 2017; Types of Lung Cancer | American Lung Association", 2018; Siddiqui et al., 2023)

Types of lung cancer. (Types of lung cancer, 2021)

1. Small Cell Lung Cancer
2. Non-Small Cell Lung Cancer
    I. Adenocarcinoma
    II. Squamous Cell Carcinoma
    III. Large Cell Carcinoma
    IV. Undifferentiated Carcinoma

2.2.1 SMALL CELL LUNG CANCER

SCLC comprises two main subtypes: small cell carcinoma and mixed small/large cell cancer, also distinguished as merged small cell lung cancer. These types are differentiated

based on the types of cells in the tumour and their appearance under a microscope. It's crucial to note that small-cell lung cancer is convincingly linked with tobacco smoking, with most cases occurring in individuals with a history of tobacco use. (Types of Lung Cancer | American Lung Association, 2024) Treatment for small cell lung cancer typically involves chemotherapy, often in combination with other therapies such as radiation therapy. Early diagnosis and prompt treatment are essential for managing this aggressive form of lung cancer.

2.2.2 NON-SMALL CELL LUNG CANCER

NSCLC is more widespread, constituting approximately 80% of lung cancer situations. This variant typically progresses and metastasizes at a slower rate than SCLC. (Types of Lung Cancer | American Lung Association, 2024) There are four distinct subtypes of NSCLC:

- Adenocarcinoma: This type of NSCLC is commonly located in the external regions of the lung and originates in epithelial tissue cells, almost in line with various body cavities and surfaces, including gland formation.
- Squamous cell carcinoma: Noticed predominantly in the central areas of the lung adjacent to bronchial tubes, this non-small cell lung cancer arises from squamous epithelial cells.
- Large cell carcinoma: This subtype of NSCLC can develop in any section of the lung and exhibit more rapid growth and dissemination compared to adenocarcinoma or squamous cell carcinoma (SCC).
- Undifferentiated carcinoma: This can spread quickly in any part of the lung.

2.3 RISK FACTORS

The various risk factors in lung cancers include modifiable and non-modifiable factors. (Agents Classified by the IARC Monographs, Volumes 1–135 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans, 2024; Lung cancer, 2021; Lung Cancer Risk Factors | Johns Hopkins Medicine, 2024; Risks and causes of lung cancer | Cancer Research UK, 2023; Types of Lung Cancer | American Lung Association, 2024; What Are the Risk Factors for Lung Cancer? | CDC, 2023)

2.3.1 SMOKING

In the United Kingdom, smoking contributes to 71% of lung cancer cases through active smoking. In comparison, 1% is attributed to contact with environmental tobacco smoke (ETS), also identified as second-hand smoke. (Lung Cancer Risk Factors | Johns Hopkins Medicine, 2024) An estimated 86 percent of lung cancer deaths in the United Kingdom are linked to smoking tobacco. Studies have shown that the likelihood of mortality from lung cancer is almost 15 times greater in individuals who now smoke compared to those who have never smoked. This conclusion was drawn from a cohort study conducted on British males. Furthermore, the danger of developing lung cancer rises with both the extent and quantity of smoking, with duration having a more significant impact on risk. For instance, smoking one pack of cigarettes daily for 40 years poses a greater risk than smoking two packs daily for 20 years. The danger of lung cancer is substantially higher in folks who initiate habit-smoking at a younger age. For every five years younger at the onset of smoking, the risk of lung cancer death increases by 37%, as observed in a cohort study involving women. (Kenfield et al., 2010) Men who smoke 15-24 cigarettes daily face a risk of lung cancer, approximately 26 times higher than non-smokers. (Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-

control studies - PubMed, 2019). Moreover, the hazard of lung cancer mortality is about five times greater in individuals who smoke 1-4 cigarettes daily, approximately 12 times higher in those smoking 8 to 12 cigarettes daily, at least 24 times greater in individuals smoking 25 or more cigarettes daily, and 39 times higher in those smoking 42 or more cigarettes daily, compared to non-smokers. Smoking is mainly linked with a greater hazard of SCLC and SCC in comparison with other types of lung cancer, as indicated by meta-analyses and pooled analyses. Regarding water pipe tobacco smoking, meta-analyses primarily from African and Asian studies suggest that the risk of lung cancer is roughly twice as high compared to non-smokers; however, there may be confounding factors related to cigarette smoking.(Bjartveit and Tverdal, 2005; Darby et al., 2005a; Doll et al., 2005; Doll and Peto, 1978; Flanders et al., 2003; Kenfield et al., 2010a; Khuder, 2001; Lubin and Caporaso, 2006; Mamtani et al., 2017; Pesch et al., 2012; Peto et al., 2000; Pirie et al., 2013; Pope et al., 2011; Waziry et al., 2017; Wiencke et al., 1999)

India ranks 2nd largest consumer and 3rd -largest tobacco producer globally. Approximately 28.6 percent of the Indian populace habits tobacco products, with 42.4 percent being male subjects and 14.2 percent female subjects, resulting in an estimated 267 million tobacco users nationwide. (Singh et al., 2021). The impact of tobacco consumption on health, particularly cancer, is significant in India. According to the National Cancer Registry Programme (NCRP), tobacco-related malignancies account for 27 percent of all cancers in both males and females. However, this percentage varies widely across different country regions, ranging from 30% to 70% among males and 12% to 46% among females. (Singh et al., 2021b)

2.3.2 ENVIRONMENTAL TOBACCO SMOKE

Exposure to ETS, commonly identified as second-hand smoke, at home or in the workplace increases the hazard of lung cancer in non-smokers. A meta-analysis revealed

that individuals who have never smoked and are exposed to ETS have a 31% higher risk of getting lung cancer compared to those not exposed to environmental tobacco smoke. (Abazari et al., 2015b) Moreover, those with the highest levels of workplace ETS exposure have double the hazard of lung cancer compared to non-exposed individuals.

Specifically, the risk of SCLC in non-smokers is approximately three times higher in those exposed to environmental tobacco smoke compared to non-exposed individuals, as indicated by a meta-analysis. (Abazari et al., 2015b) Additionally, the risk of NSCLC is 28% higher in non-smokers open to ETS. For lung adenocarcinoma in situ/minimally invasive adenocarcinoma (AIS/MIA), the hazard is 45% higher in non-smokers exposed to environmental tobacco smoke in comparison to those not exposed. (Kim et al., 2015; Stayner et al., 2007)

Exposure to ETS during childhood, particularly from cigarette smoke, is strongly linked to an increased risk of lung cancer. Individuals exposed to ETS during childhood have a significantly greater hazard of developing lung cancer, with an odds ratio (OR) of 3.9 and a 95% confidence interval (CI) ranging from 1.9 to 8.2. (Gupta et al., 2002) This heightened risk is observed regardless of whether the exposure comes from a smoking father or mother, indicating that both parental smoking habits contribute to the excess risk of lung cancer in children. A study conducted in India suggests that the epidemiology of lung cancer in the country may be changing, as nearly 40% of lung cancer patients in the study were found to be non-smokers. This finding indicates a significant proportion of lung cancer cases in India are occurring in individuals who do not have a history of smoking. (Krishnamurthy et al., 2012; Rapiti et al., 1999)

2.3.3 ENVIRONMENTAL FACTORS

Environmental variables that increase cancer risk include ionizing and non-ionizing radiation like radon and UV radiation. Chemicals, including asbestos, dioxins, and metals like arsenic, chromium, nickel, and cobalt, as well as industrial pollution, domestic smoking, and second-hand smoke, contribute. Parental work exposure may also increase progeny cancer risk. (Parsa, 2012)

Lung cancer is associated with both environmental and occupational exposures. These exposures may range from widespread sources like outdoor and indoor air pollution to more localized exposure near specific industrial sites. Such exposures have been linked to various types of cancers, but lung cancer stands out as one of the most strongly associated malignancies. Occupational health risk factors are intimately tied to physical, biological, chemical, and factors present in the environment, with lung cancer being the most linked outcome, supported by robust evidence. (Shankar et al., 2019a) Bonner et al. conducted a study that found an increased occupational hazard ratio for individuals with the highest lifetime exposure to three specific chemicals used as pesticides. This increased exposure was associated with a higher risk of lung cancer. (Bonner et al., 2017b) (Bonner et al., 2017b)

A study conducted by the WHO revealed that promoting healthy living and working environments could prevent at least 1.7 million deaths from cancer annually. Unhealthy conditions are responsible for around 12.6 million deaths annually. This underscores the importance of environmental factors in shaping cancer outcomes. Changes in individual behaviour often occur alongside broader shifts in the environments where people live and work. (Alavanja et al., 2004; Bonner et al., 2017a; Hauptmann et al., 2020; Lichtenstein et al., 2000; Noronha et al., 2016; Samet, 2004; Thakur et al., 2018)

2.3.4 CHEMICAL EXPOSURE

There is compelling evidence suggesting that contact with industrial chemicals, manufacturing chemicals, unsafe pesticides, and aflatoxin can contribute to the development of cancer, particularly in our lives and working surroundings. Public health workers and Agricultural workers are particularly at risk of exposure to these hazardous substances during handling, dilution, and application.

Occupational contact with pesticide handling is linked to lung cancer. In some instances, the association is, however, not universal. In a study conducted by Bonner et al., elevated occupational hazard ratios [pendimethalin (1.50), dieldrin (1.93), and chlorimuron ethyl (1.74)] were observed in individuals with the highest lifetime exposure to three specific chemicals used as pesticides, indicating an association with lung cancer incidence. (Bonner et al., 2017b)

Pesticide groups such as chloro-phenols (CPs), dioxin combinations, and related phenoxy-acetic acids (PAs) are identified as having carcinogenic effects on the lungs. Diverse research studies have documented a broad spectrum of lung cancer cases occurrences in workplace settings. Meta-analyses examining longitudinal research have explored the factors contributing to lung cancer in workers who have been exposed to CP-related chemicals in plants. The data from 27,865 workers revealed a standardized mortality rate (SMR) for lung cancer of 1.18. (Boffetta et al., 2011; Burns et al., 2001; Collins, Bodner, Aylward, Wilken and Bodnar, 2009; Collins et al., 2009; Kogevinas et al., 1997; Manuwald et al., 2012; Ruder and Yiin, 2011; Singh et al., 2012; Walker et al., 2007; Zendehdel et al., 2014)

2.3.5 AIR POLLUTION

Many air contaminants are discharged from mining, industrial operations, waste from municipalities facilities, and insufficient domestic incineration. Moreover, motorized vehicles play a substantial role in the emission of air pollutants in metropolitan areas. Certain compounds included in automobile exhaust emissions are classified as cancerous to humans (group 1) and possibly cancer-causing to people (group 2A). Multiple research investigations have found that those living in metropolitan regions had a higher chance of developing lung cancer compared to those living in rural areas. Agricultural emissions primarily contribute to particulate matter (PM) 2.5 in the United States, Europe, Russia, and East Asia. Projections indicate that the effect of external air pollution on premature death could increase twofold by 2050. Higher concentrations of PM 2.5 in the environment are associated with an elevated risk of getting lung cancer. (Cohen, 2000; Lelieveld et al., 2015)

2.3.6 INDOOR AIR POLLUTION

Burning coal indoors for heating or cooking purposes emits particulate matter and gases that may contain various cancer-causing agents such as benzene, carbon monoxide, formaldehyde, and polycyclic aromatic hydrocarbons (PAHs). Internal or indoor air pollutants from household coal combustion are considered cancer-causing to humans (group 1). There is ample data to support the fact that home coal combustion is cancerous in people. Elevated levels of indoor smoke are linked with an increased danger of lung cancer (OR 1.62). (Lelieveld et al., 2015; Sapkota et al., 2008)

2.3.7 ASBESTOS

Asbestos, a type of fibrous silicate that occurs naturally, is widely used in several industries for its excellent properties in soundproofing and insulation from heat. These fibres can be classified into two groups: chrysotile and amphiboles, which consist of amosite, anthophyllite, crocidolite, actinolite, and tremolite fibres. Every type of asbestos is carcinogenic and has the potential to cause lung cancer and mesothelioma. (Kagan, 2013) Amphiboles exhibit more substantial biological effects on the pleura and peritoneum than chrysotile. Household exposure primarily affects immediate family members of asbestos workers through dust carried home on clothing, and it can also occur during the degradation, installation, and while asbestos-containing products are being removed and repaired.

Domestic exposure commonly occurs due to outdoor pollution caused by local asbestos mining or manufacturing processes, as well as exposure from nature resulting from the disintegration of rocks containing asbestos. Evaluating non-occupational asbestos contact is challenging due to generally low levels, poorly defined duration and frequency of exposure, and varied types of exposure. According to the International Agency for Research on Cancer (IARC), all forms of asbestos are carcinogenic to humans (Group 1) (Agents Classified by the IARC Monographs, Volumes 1–135 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans, 2024). The Environmental Protection Agency (EPA) also categorizes it as a Group A carcinogen. (Integrated Risk Information System | US EPA, 2024)

Research conducted on individuals who were heavily exposed to asbestos has revealed a significantly increased likelihood of developing lung cancer (relative risk (RR) 1.74).

Similarly, individuals with low exposure to asbestos over 20 years also exhibited a comparable increase in risk (RR 0.94). (Järvholm and Aström, 2014) The carcinogenicity of asbestos varies depending on fibre length, with longer and intermediate-length fibres (>5 μm) posing a higher risk to humans than shorter fibres. Autopsy research conducted on Italian shipyard workers found that chrysotile was the primary form of asbestos fiber present in lung plaques associated with asbestos exposure. Most of these fibers had a length of approximately 8 millimeters. (Järvholm et al., 1999) Despite health risks, asbestos use persists in many parts of Asia, Africa, and India. (Integrated Risk Information System | US EPA, 2024)

2.3.8 METALS

Arsenic presents both environmental and occupational hazards as a lung carcinogen regularly found in arsenite and arsenate forms. Workers in lead, gold, and copper ore mines and smelters face occupational exposure through dust inhalation. The IARC document suggests that arsenic inhalation increases the possibility of lung cancer. (Agents Classified by the IARC Monographs, Volumes 1–135 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans, 2024) Prior systematic reviews have determined that individuals who are exposed to elevated amounts of arsenic are at an increased risk of developing lung cancer. Nevertheless, the connection between the risk of developing lung cancer and low to moderate levels of arsenic concentration (<100 μg L–1) remains uncertain. (Lamm, Steven, 2018)

Both the EPA and IARC classify beryllium compounds as probable human carcinogens, supported by ample evidence linking them to lung cancer. (Agents Classified by the IARC Monographs, Volumes 1–135 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans, 2024; Integrated Risk Information System | US EPA, 2024)

Numerous studies demonstrated a considerably heightened hazard of lung cancer linked with hexavalent chromium exposure. (Gibb et al., 2000; Proctor et al., 2016; Sarlinova et al., 2015) Cumulative exposure to hexavalent chromium has been linked to increased lung cancer risk. (Gibb et al., 2000) While the EPA has not assessed nickel compounds as a class for possible cancer-causing effects on humans, exposure to certain substances in the workplace has been linked to lung cancer in various research studies. (Cantor and Lubin, 2007; Grimsrud et al., 2002; Lubin et al., 2008; Mosquin and Rothman, 2017)

2.3.9 IONIZING RADIATION

Environmental radiation arises from many different places, encompassing naturally present radioactive substances in soil, water, and air, such as Radon, a gas emitted naturally from rock and soil, serving as the principal natural radiation source. Ionizing radiation includes radon, X-rays, and gamma rays. However, radon presents a comparatively lower danger for lung cancer. A meta-analysis demonstrated a 16% increase in the chance of developing lung cancer for every 100 Becquerel per cubic meter (Bq/m3) increase in the average radon level found in residential houses. (Darby et al., 2005b)

While uranium contamination is frequently mentioned as a contributing factor in the study of ionizing radiation and its effects on public health, there is a lack of research investigating the relationship between radiation dose and its impact. Additionally, the methods used to quantify individual exposure to radiation in previous studies are generally insufficient. Moreover, differentiating between the radiotoxicity of uranium, its chemical toxicity, and the radio-toxicity of its offspring poses considerable difficulties. (Alavanja et al., 1999; Darby et al., 2006; Field et al., 2000; Krewski et al., 2006; Tirmarche et al., 2004)

2.3.10 FAMILY HISTORY

The risk of lung cancer is substantially elevated by familial history, with individuals having a sibling affected by lung cancer showing an 82% higher risk, while those with a parent afflicted have a 25-37% higher risk, according to a meta-analysis. Notably, this association remains independent of smoking status. (Coté et al., 2012)

2.3.11 OTHER MEDICAL CONDITIONS

Pneumonia: Individuals with a history of pneumonia face a 43-57% increased risk of lung cancer, with a slightly lower risk increase (35-36%) observed in non-smokers, as indicated by meta-analyses and pooled case-control studies. This elevated risk extends to both pneumococcal and community-acquired pneumonia. (Lin et al., 2014)

COPD: COPD encompasses various smoking-linked lung conditions like emphysema, chronic bronchitis, and chronic obstructive airway illness.

People with a history of emphysema exhibit a 104-144% higher risk of lung cancer, though this association may not apply to non-smokers, as suggested by meta-analyses. (Brenner et al., 2012)

Ever-smokers with a chronic bronchitis history face a 47-52% elevated lung cancer risk, while no such association is observed in non-smokers, according to meta- analyses. (Brenner et al., 2012; Denholm et al., 2014; Ibrahim et al., 2013; Lin et al., 2014; Zhan et al., 2011)

2.3.12 PATHOGENIC VIRUSES

Human Papillomavirus (HPV):

While HPV's primary association is with cervical cancer, it's also linked to certain lung cancers, especially among non-smokers and younger individuals. Strains like HPV types

16 and 18, which are considered high-risk, have been found in lung tumour samples. The development of HPV-related lung cancer likely involves the activity of viral oncoproteins like E6 and E7, which disrupt normal cell cycle regulation and encourage cell growth. (Karnosky et al., 2021; Xiong et al., 2017)

Epstein-Barr virus (EBV):

EBV, a herpes virus responsible for infectious mononucleosis, is implicated in various lymphomas and nasopharyngeal carcinoma. In lung cancer cases, EBV infection is identified, particularly in individuals with a history of COPD or interstitial lung disease. Lung cancers associated with EBV often display distinct histological features, such as a lymphoepithelioma-like appearance. (Becnel et al., 2021; Osorio et al., 2022)

2.4 LUNG CANCER- PATHOGENESIS

The underlying mechanisms of lung cancer involve the progression of abnormal cell growth and the disturbance of normal lung tissue function.

- Initiation: Lung cancer typically originates from genetic alterations in healthy lung cells' deoxyribonucleic acid (DNA). These changes may arise due to exposure to carcinogens like tobacco smoke, radon, asbestos, air pollution, or genetic predisposition. Such alterations can activate genes promoting cell growth (oncogenes) or deactivate genes inhibiting cell growth (tumour suppressor genes), leading to uncontrolled cell division.
- Cell Growth and Tumour Formation: Mutated cells multiply uncontrollably, forming an abnormal tissue mass called a tumour. Lung tumours are categorized as NSCLC or SCLC, based on their microscopic characteristics and behaviour.

- Formation of New Blood Vessels (Angiogenesis): Growing tumours require a blood supply to sustain their metabolism. They release signalling molecules prompting the creation of new blood vessels, ensuring an adequate oxygen and nutrient supply.
- Invasion and Spread (Metastasis): Cancer cells can infiltrate nearby tissues and spread to distant body parts, called metastasis. In lung cancer, metastases frequently occur in the brain, bones, regional lymph nodes, liver, and adrenal glands. Cancer cells move through the bloodstream or lymphatic system to establish secondary tumours.
- Evading the Immune System: Although the immune system is designed to detect and eradicate cancer cells, these cells can evade detection using various tactics, such as reducing immune recognition molecules and releasing immunosuppressive substances. This evasion allows cancer cells to proliferate unchecked and aids tumor progression.
- Paraneoplastic Syndromes: Lung cancer can produce substances causing systemic effects unrelated to the primary tumour or its metastases. These syndromes affect different organ systems, leading to symptoms like hypercalcemia, hyponatremia, neurological issues, and hormonal imbalances. (Aisner et al., 1990; Buche et al., 2017; Filosso et al., 2011; Kadota et al., 2014; Russo et al., 2000)

Understanding the pathophysiology of lung cancer is vital for developing targeted treatments that disrupt specific molecular pathways involved in tumour growth and metastasis, potentially enhancing outcomes for patients with this challenging condition.

2.4.1 NON-SMALL CELL LUNG CANCER

I. Adenocarcinoma

The growth of abnormal glands characterizes adenocarcinoma pathogenesis, specific markers such as thyroid transcription factor 1 (TTF-1) and napsin, and the presence of mucin within the cells. It is further classified according to the degree and arrangement of cancerous gland growth as either mucinous or non-mucinous. The non-mucinous subtypes consist of papillary, acinar, micro-papillary, lepidic, and solid. It is essential to identify these sub-groups in order to determine the prognosis. Solid, micro-papillary, and cribriform patterns in acinar non-mucinous adenocarcinoma are linked to worse prognoses. (Aisner et al., 1990)

Meanwhile, mucinous adenocarcinomas may exhibit micro-papillary, papillary, solid, and cribriform architecture, and less common forms of adenocarcinoma include enteric-like colloid, lymphoepithelial, and foetal types.

Minimally invasive adenocarcinoma of the lung (MIA) is a term used to describe a tiny, single adenocarcinoma equal to or less than 3 cm in size. It is characterized by limited invasion, less than 5 mm depth, and a dominant lepidic growth pattern resembling progenitor glandular lesions. Lepidic-predominant adenocarcinoma is the term used when invasion surpasses 5 millimeters. Invasive mucinous adenocarcinoma, or mucinous bronchioloalveolar carcinoma, refers to mucinous tumors that are not categorized as minimally invasive adenocarcinoma (MIA). Lesions that exhibit both mucinous and non-mucinous development patterns, accounting for over ten percent of the lesion, are classified as mixed adenocarcinoma. (Aisner et al., 1990; Buche et al., 2017)

II. Adenosquamous carcinoma

Adeno-squamous carcinoma is a lung tumour characterized by glandular and squamous components, comprising more than 10% of the tumour. This particular form of lung cancer is uncommon and renowned for its highly aggressive characteristics. Current guidelines advocate the use of adjuvant chemotherapy for Stage I tumors that have been surgically excised, in addition to post-operative preventive radiation to the entire brain. It is recommended to use this method because adenosquamous carcinoma carries a high risk of recurrence and metastasis to the brain. (Aisner et al., 1990; Buche et al., 2017)

III. Squamous cell carcinoma

SCC is characterized by keratin and inter-cellular desmosomes observed through cytology or confirmed by immunohistochemistry (IHC) showing expression of markers such as p40, p63, CK5, CK5/6, or desmoglein. Different subtypes of squamous cell carcinoma include non-keratinizing, keratinizing, and basaloid variants. These carcinomas often exhibit widespread central necrosis, leading to cavitation. SCC may manifest as Pan coast tumors located in the superior sulcus of the lung and can also result in hypercalcemia. Pan coast tumors are associated with a high likelihood of recurrence in the brain following surgical intervention.

IV. Large cell carcinoma

Large cell carcinoma (LCC) is a malicious epithelial tumor that lacks cytological characteristics consistent with squamous, glandular, or neuroendocrine cancers. Typically, it does not express p40 and TTF-1 on immunohistochemistry or display small cell carcinoma cytological features. Large cell carcinoma normally comprises round to polygonal cells with prominent nucleoli. These cells are enormous and possess lavish cytoplasm without distinct defining features. Diagnosis of Large cell carcinoma is often made by excluding other types of lung cancer. (Filosso et al., 2011; Kadota et al., 2014)

2.4.2 SMALL CELL LUNG CARCINOMA

The SCLC comprises round, oval, or angulated cells with minimal cytoplasm and a size similar to a lymphocyte at rest. Distinct nucleoli are typically absent, and SCLCs often exhibit extensive necrosis. They commonly test positive for chromogranin or synaptophysin staining. Previously, the WHO categorized SCLC into three cell subtypes: oat cell, intermediate cell, and combined cell (SCLC with NSCLC component, squamous, or adenocarcinoma). However, recent studies indicate that such classification lacks significant clinical relevance or predictive value.

Lung cancer's pathogenesis is complicated. Repeated exposure to toxins like cigarette smoke may cause lung epithelial cell dysplasia. Genetic alterations affecting protein synthesis can arise from prolonged exposure to carcinogenesis, which results from the interruption of the cell cycle. MYC, BCL2, p53 for SCLC, EGFR, KRAS, and p16 for NSCLC are common lung cancer genetic variants. (Kadota et al., 2014; Russo et al., 2000)

2.5 LUNG CANCER- SYMPTOMS AND STAGING

2.5.1 SYMPTOMS

Lung cancer often presents with a variety of symptoms due to local tumour effects, metastasis, or paraneoplastic syndromes. However, specific signs and symptoms for lung cancer are lacking, and many patients are diagnosed at an advanced stage. Symptoms can arise from bronchial compression, distant metastasis, paraneoplastic syndromes, or underlying bronchopulmonary disease. Common symptoms include cough, which occurs in 50 to 75% of patients, and haemoptysis, present in 15 to 30% of cases. Roughly 20 to

40% of patients experienced chest pain, and up to 25 to 40% of cases involved the presence of dyspnoea at the time of identification. The presence of these symptoms may be indicative of either lung cancer or pre-existing broncho-pulmonary problems. (Kocher et al., 2015)

Pleural involvement may result in pleural thickening, nodules, or malignant pleural effusion, which occurs in about 10 to 15% of patients during their illness. Superior vena cava syndrome, illustrated by dilated neck veins, oedema, and a plethoric appearance, is common in SCLC and may be the primary presentation. Metastasis to bones, often symptomatic with bone pain, occurs in up to 20% of patients with NSCLC and 30 to 40% of those with small cell lung cancer. Brain metastasis is frequent in both small-cell and non-small-cell lung cancers. (Dixit et al., 2017; Husaini et al., 2009)

Paraneoplastic syndromes associated with lung cancer include hypercalcemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and various neurologic syndromes like Lambert Eaton Myasthenic Syndrome (LEMS) and ectopic adrenal corticotropin production causing Cushing syndrome. Other extrapulmonary manifestations include hypertrophic pulmonary osteoarthropathy, dermatomyositis, and polymyositis. (Kanaji et al., 2014; Soomro et al., 2020)

2.5.2 LUNG CANCER- STAGING

Lung carcinoma is broadly categorized into two main types: SCLC and NSCLC. SCLC typically originates as a central tumour arising from the submucosa of the airways, often presenting as a peri-hilar mass. Histological studies indicate this cancer arises from neuroendocrine cells within the basal bronchial epithelium. (Raso et al., 2021) SCLC cells

exhibit a tiny spindle, or circular shape with little cytoplasm. They also display granular chromatin and necrosis, which are frequently present. SCLC can exist either in a pure form or combined with sub-types of NSCLC. This cancer tends to metastasize to sites such as the liver, brain, and bone and is categorized into limited or extensive stages. Limited-stage SCLC is restricted to a single radiation site within the lung and may involve ipsilateral mediastinal or supra-clavicular lymph nodes. The presence of disease in supra clavicular lymph nodes is considered within the limited stage if it occurs on the same side as the cancer in the chest. Conversely, extensive-stage SCLC is not confined to a single radiation spot and can spread to the other lobe, lymph nodes, and other distant body sections, such as bone marrow. (Nooreldeen and Bach, 2021a)

NSCLC encompasses histological subtypes such as adenocarcinoma, large-cell carcinoma, and SCC, with staging determined by the Tumour, Node, Metastasis (TNM) staging system formulated by the American Joint Committee on Cancer (AJCC). (Moitra and Mandal, 2019; Sobin: TNM classification of malignant tumours - Google Scholar, n.d.) This system assesses the size of the primary tumour (T), the involvement of lymph nodes (N), and the presence of metastasis (M). The final TNM classification combines tumour characteristics (T1 to T4), lymph node involvement (N0-N3), and the presence (M1) or absence (M0) of metastasis. Table 2 depicts the TNM staging classification for lung cancer.

Table 2: TNM staging classification-8th Edition (International Association for Study of Lung Cancer)

TNM 8th - Primary tumor characteristics	
T_x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T_0	No evidence of tumor
T_{is}	Carcinoma in situ
T_1	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
$T_{1a(mi)}$	Minimally invasive carcinoma
T_{1a}	≤ 1 cm
T_{1b}	> 1 to ≤ 2 cm
T_{1c}	> 2 to ≤ 3 cm
T_2	> 3 to ≤ 5 cm *or* involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	>3 to ≤4cm
T_{2b}	>4 to ≤5cm
T_3	>5 to ≤7cm in greatest dimension *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe
T_4	> 7cm in greatest dimension *or* any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung
N_1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular
M_1	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M_{1c}	Multiple extrathoracic metastases in one or more organs

In the staging system TNM for lung carcinoma, tumour characteristics play a crucial role in determining the stage of the illness. In the T2 category, characteristic findings may include atelectasis or incomplete lung inflation affecting a portion of the lung. The tumour may invade the visceral pleura or extend to the main bronchus, located more than 2 cm from the carina. Progressing to T3, the extent of atelectasis may involve the entire lung. Additionally, the tumour can invade structures such as the phrenic nerve, diaphragm, chest wall, and mediastinal pleura. It may also approach closer to the main bronchus, within 2 cm from the carina. Stage T4, or the invasion stage, involves further invasion into mediastinal organs, vertebral bodies, and potentially the lung carina. Lymph node involvement, categorized as N0 to N3, varies from no lymph node involvement to ipsilateral or contralateral involvement, depending on the stage of the disease. Metastasis is staged based on the presence of M1, where bilateral lesions, distant metastasis, or malignant pleural effusion may be observed. Conversely, the absence of metastasis is classified as M0. (Blandin Knight et al., 2017; Chan and Coward, 2013; Edge and Compton, 2010; Goldstraw et al., 2016; Robbins et al., 2010; Travis, 2012)

2.6 LUNG CANCER- DIAGNOSIS

2.6.1 CHEST XRAY

Chest x-ray (CXR) is typically the initial diagnostic tool for evaluating suspected lung cancer. Its widespread use is due to accessibility, technical feasibility, low risk, and cost-effectiveness. When a suspicious lesion is identified on a chest x-ray, further detailed morphological information is necessary.

Lung tumors can manifest as central or peripheral masses, including in situ adenocarcinoma, which may present as an area of chronic airspace disease. The central tumour may exhibit features such as hilar lymph node enlargement, mediastinal invasion, or bronchial obstruction, potentially leading to partial or total lung collapse. Additionally, parenchymal consolidation or super-infection may be present, either masking or serving as the initial sign of an underlying neoplasm.

Mediastinal involvement of central neoplasms can be observed as an enlargement of the mediastinal profile on chest x-ray. However, more invasive features like invasion of the phrenic nerve or superior vena cava cannot be adequately evaluated via chest X-rays. Asymptomatic pulmonary neoplasms typically present as single or peripheral nodules with well-defined or spiculated margins. Internal nodularity and air crescents may also be observed occasionally. Without evidence of rib erosions, chest X-rays cannot reliably differentiate between benign and malignant masses. While it can detect pleural effusions, this alone does not allow for the determination of the lesion's benign or malignant nature.

2.6.2 COMPUTED TOMOGRAPHY

When a suspicious lesion is detected on a CXR, further evaluation with contrast-enhanced computed tomography (CT) is recommended for the complete staging of lung cancer. Computed tomography imaging helps identify lung abnormalities, especially in patients with chest pain, cough, and fever. It is also utilized to screen treatment reactions and aid in planning radiation therapy programs. Moreover, computed tomography has been indicated as a screening tool for select patient populations. Computed tomography is crucial in defining local invasiveness, with higher sensitivity than chest X-rays. However, it has limitations in evaluating mediastinal and thoracic pleural invasion.

Monitoring changes in lesion size over time on Computed tomography can provide valuable information about malignancy. A significant increase in diameter correlates with a substantial volume increase, indicating malignancy. Rapid doubling of nodule volume within seven days suggests a benign lesion, often indicative of inflammation or infection. Assessment of lymph node involvement on computed tomography is grounded on dimension-related standards, with involvement of lymph nodes typically detected when the short axis exceeds 10 millimeters. However, the sensitivity of computed tomography is limited when adenopathy is less than 10 mm in size. (Ganeshalingam and Koh, 2009) Evaluating distant metastasis, particularly in the adrenal glands and liver, is crucial, warranting the upper part of the abdomen in staging computed tomography scans. Detecting the current stage with computed tomography aids in determining the resectability of the lesion. (Hollings and Shaw, 2002) Neoplasms with a stage corresponding to or more advanced than IIIB are generally deemed unresectable. Radiology plays a pivotal role in managing lung cancer subjects by precisely delineating the magnitude of the disease and influencing treatment decisions.

A solitary pulmonary nodule indicates potential malignancy if it displays irregular or spiculated borders, is in the upper lung lobe, exhibits thick wall cavitation, contains a solid constituent within a ground glass lesion, or shows growth over time on follow-up imagery. Contrast-enhanced computed tomography scans of the chest can assist in determining the extent of invasion and assessing lymph node involvement. The presence of multiple nodules, particularly in individuals with a known extra-thoracic malignancy, strongly suggests pulmonary metastasis, indicating the spread of cancer from another primary site to the lungs. Therefore, careful examination and consideration of the patient's medical history are essential for accurate diagnosis and appropriate management of pulmonary nodules and metastases.

NSCLC can present as centrally positioned mass tissues occupying mediastinal structures or peripherally located lesions occupying the wall of the chest region. Tumors may exhibit smooth, lobulated, or irregular and spiculated margins. They can appear uniformly solid or may feature central necrosis and cavitation. Centrally located and cavitating tumors are more commonly associated with squamous histology. At times, tumors may resemble infective pathologies, presenting as areas of consolidation, ground-glass opacities, or a combination of both. This phenomenon is commonly seen in cases of adenocarcinoma and its subcategories. Characteristic features in broncho alveolar carcinomas, now known as adenocarcinoma in situ, include a combination of mixed density or pure ground-glass nodules and consolidation with air broncho-gram. (Kramer and Groen, 2003; Lewis et al., 1990; Nooreldeen and Bach, 2021b; Owonikoko et al., 2007; Panunzio and Sartori, 2020; Parkin et al., 2005; Saito et al., 2009; Silvestri et al., 2007; Sobue et al., 2002; Toyoda et al., 2008)

2.6.3 MAGNETIC RESONANCE IMAGING (MRI)

The MRI's sensitivity in detecting 5 to 11 mm nodules ranges from 85% to 95%. (Cavion et al., 2024) Despite Multi-detector CT's capability to identify nodules as minor as 1 or 2 millimeters, immediate action is advised only for lesions sizeable than 7 or 8 millimeters, depending on lung cancer risk assessment. (MacMahon et al., 2005) Evaluation of the primary tumour involves assessing its dimensions and the coverage of the mediastinal or involvement of the chest wall. Differentiating between T3 and T4 tumors is crucial. A T3 lesion is defined by its size (over 7 cm), chest wall invasion, or incidence of total lung collapse or invasion of the main bronchus without involving the carina of the trachea. T3 tumors are potentially resectable. Conversely, T4 tumors are deemed irresectable due to conquest of the mediastinum, heart, spine, great vessels, brachial plexus proximal to C7, or

carina of trachea. When CT criteria for invasion are inconclusive, MRI plays a role in defining lesser degrees of invasion. MRI surpasses CT in visualizing the heart, pericardium, and mediastinal vessels. It can be valuable for reviewing the spread of the extent of the myocardium, superior vena cava, or tumour extension into the left atrium via pulmonary veins. MRI also excels at noticing lung masses from adjoining atelectasis or consolidation and identifying masses from areas of consolidation or fibrosis post-radiotherapy. Post-obstructive atelectasis and pneumonitis often exhibit greater signal strengths than the central tumour on T2-weighted MRI. Accurately assessing lymph nodes in the mediastinum is crucial for treatment selection. Ipsilateral peri-bronchial or hilar nodes indicate N1 disease, while ipsilateral mediastinal or subcarinal lymphadenopathy indicates N2 disease, potentially resectable if involving only a single station. It is essential to differentiate between single-station N2 disease and multiple-station N2 disease or N3 sickness. N3 illness is characterized by pathological contralateral mediastinal, scalene, or supraclavicular nodes. This condition indicates that radical surgery is not recommended. PET-CT is preferred for pre-operative staging but can miss metastases in about 20% of cases. (Farsad, 2020a) MRI and PET exhibit comparable accuracy and efficacy for staging lung cancer. (Schmidt et al., 2005) Whole-body MRI is more effective in detecting brain and liver metastases. In contrast, PET-CT is particularly good at identifying bone and soft-tissue metastases or metastases in lymph nodes outside the chest. (Ohno et al., 2009) PET-CT sensitivity and specificity for adrenal gland metastases range from 80% to 100%. However, it may produce inaccurate results for masses smaller than 1 cm, leading to false negatives. (Ohno et al., 2009) Chemical-shift MRI aids in recognizing adrenal gland adenomas by revealing degraded signal strength in opposed phases, with high sensitivity and specificity for adenomas. The heightening of T1-weighted imageries and the lack of fat repression indicate malignancy in adrenal masses. Liver metastases appear as boosting

nodules on T1-weighted images. MRI's superior differentiation in the liver aids in lesion recognition. Similarly, enhancement on T1 weighted images in a bone lesion suggests malignancy. (Goldstraw, 2009; Hochhegger et al., 2011; Yi et al., 2008)

2.6.4 POSITRON EMISSION TOMOGRAPHY (PET)

18F-fluoro-de-oxy-glucose (18F-FDG) is an analogue of glucose and is the most utilized PET tracer for detecting solid tumors. This tracer gathers in tumour cells via membrane glucose-transporters (GLUT-1 and GLUT-3) due to elevated glucose metabolism. Upon phosphorylation by hexokinase, 18F-FDG produces a more polar product that can be trapped within tumour cells. The concentration of 18F-FDG within cells can then be visualized using PET imaging, reflecting the level of glucose metabolism. Consequently, 18F-FDG PET has emerged as a revolutionary imaging method in clinical practice for diagnosing, staging, planning treatment, and assessing the prognosis of tumors. Extensive research has been conducted on the prognostic and diagnostic measure of 18F-FDG PET in lung cancer subjects, with studies demonstrating its effectiveness in staging NSCLC. (Castello et al., 2020; Farsad, 2020b; Hong et al., 2019; Jadvar et al., 2009)

2.6.5 SPUTUM EXAMINATION

Another investigative approach for lung cancer involves a cytological assessment of sputum samples, particularly when multiple samples are collected. This method aids in detecting central tumors originating from the bigger bronchi, such as squamous and small cell carcinomas. However, sputum samples often fail to identify small adenocarcinomas (with a diameter of 2 centimeters or less) that arise from the airway ramifications, including small bronchi, bronchioles, and alveoli. This limitation has become more significant due to changes in cigarette exposure, such as the introduction of filters and

decreased nicotine content, which have led to a rise in adenocarcinomas and a reduction in squamous carcinomas. Based on screening studies, the sensitivity of sputum cytology for detecting early lung cancer is only in the range of 20 to 30%. (MacDougall and Weinerman, 1992; Risse et al., 1987b) Additionally, early research indicates the ability to detect premalignant conditions through sputum cytology based on variables such as the number and mode of cells in the airways. Overall, studies assumed that sputum cytology is not sufficiently sensitive or accurate to be routinely incorporated in the investigative workup of patients alleged to have lung cancer. (Tockman et al., 1988; Zhou et al., 1996)

2.6.6 BRONCHOSCOPY

White light bronchoscopy (WLB) is the primary investigative tool for getting a definitive histological lung cancer diagnosis. However, it has notable limitations when detecting pre-malignant masses. These lesions are visually challenging to identify as they consist of only scarce layers of cells, typically with a texture of 0.2 to 1 millimeter and a thickness of a few millimeters. Visualizing or detecting these small squamous lesions demands excellent expertise, as studies show that only 29 percent of cases were noticed by qualified bronchoscopists. (Nooreldeen and Bach, 2021c) To address this challenge, fluorescence bronchoscopy was developed, which could localize early invasive and in situ cancers but faced difficulties in detecting dysplasia. Additionally, the development of photodynamic diagnostic systems encountered obstacles related to sensitization issues and interference with tissue auto-fluorescence.

In order to address these difficulties, a novel laser photodynamic diagnostic technology was implemented. This system uses the fluorescence of tumor-specific drugs at a wavelength of 630 nm, which differs from the usual range of endogenous tissue fluorescence, which falls between 500 and 580 nm. The development of the LIFE-lung Fluorescence Endoscopy system was founded on the observation that dysplastic and

malignant tissues have lower levels of auto-fluorescence signals than normal tissues. Multiple studies have compared the diagnostic specificity and sensitivity of lung fluorescence endoscopy system bronchoscopy and White light bronchoscopy in diagnosing pre-invasive and early-invasive lesions. Most of these investigations have found that lung fluorescence endoscopy system bronchoscopy has a greater ability to detect pre-malignant and early malignant lesions. In contrast, it may have a poorer specificity, leading to more false positive results. The occurrence of pre-invasive and early lung cancer differs significantly among studies, potentially as a result of variations in the expertise levels of the health care staff performing the procedures.

A novel morphological condition called Angiogenic Squamous Dysplasia (ASD) was detected using lung fluorescence endoscopy system bronchoscopy. Angio-dysplasia alterations were commonly detected in pre-neoplastic and early malignant lesions in the bronchi, especially in smokers, as validated by morpho-logical studies. (Gazdar and Minna, 2000; Kennedy et al., 2000; Risse et al., 1987a; Venmans et al., 1998; Vermylen et al., 1999)

2.6.7 LUNG BIOPSY

Diagnosing lung nodules and masses can pose challenges and often necessitate invasive procedures. Lung biopsy is a widely accepted method for obtaining tissue samples to diagnose various pulmonary conditions. Different techniques are used to obtain lung tissue for histopathological examination:

Percutaneous Transthoracic Lung Biopsy (PTLB): Also known as percutaneous or transthoracic needle biopsy, this method involves inserting a needle through the chest wall under CT or fluoroscopic guidance to collect a tissue sample from the suspected area.

Open Lung Biopsy (OLB): This surgical procedure involves the removal of lung tissue under general anaesthesia for histopathological and microbiological analysis.

Video-Assisted Thoracic Surgery (VATS): Lung tissue is endoscopically removed via the chest wall using VATS, also known as endoscopic thoracic surgery.

Transbronchial Biopsy (TBLB): Flexible bronchoscopy is used via the trans-nasal or transoral route to obtain biopsy samples, typically preferred for accessible central lesions.

Cryobiopsy (Cryo-TBB): This technique involves freezing and extracting tissue using nitrous oxide and a specialized flexible probe during transbronchial biopsy.

Recent advancements include techniques such as Endobronchial Ultrasound (EBUS) biopsy, Electromagnetic Navigation Bronchoscopy, Cone Beam CT, and Robotic Bronchoscopy. (Gal, 2005; Georgiadou et al., 2013; Modi and Uppe, 2022)

2.6.8 LIQUID BIOPSY

Liquid biopsy refers to testing blood or bodily fluids for cancer cells. Blood is the primary liquid biopsy tested in clinical settings. This technique aids in understanding lung cancer characteristics by identifying tumour cells or tumour DNA released into the blood due to cancer cell growth or apoptosis. Utilizing highly sensitive technology, blood detection diagnoses cancer and reveals critical tumour characteristics like cancer type and major gene mutations.

Liquid biopsy offers a minimally invasive means of sample collection, primarily from body fluids, to detect molecular alterations, tumour cells, and metabolites. This emerging approach garners significant attention in clinical management, particularly for treatment

guidance and disease monitoring. In addition to its minimally invasive nature, liquid biopsy allows for serial sample collection, facilitating early detection of residual disease, relapses, and treatment resistance.

CTCs, ctDNA, exosomes, miRNA, peripheral blood circulating RNA, TEPs, and CTECs are common indicators in liquid biopsy. CTCs, ctDNA, and exosomes are the most common biomarkers. (Abbosh et al., 2017; Benlloch et al., 2006; Casagrande et al., 2023; Cescon et al., 2020; Chapman et al., 2007; Du et al., 2018; Fujii et al., 2017; Hanssen et al., 2016; Iqbal et al., 2019; Jia et al., 2017; Li et al., 2019; Moss et al., 2018; Seow et al., 2019; Sun et al., 2019; Tang et al., 2019; Yokota et al., 2007)

2.7 LUNG CANCER-TREATMENT

2.7.1 TREATMENT FOR NON-SMALL CELL LUNG CANCER

Stage I:

The primary treatment for stage I NSCLC involves surgery, typically lobectomy or pneumonectomy, with lymph node sampling. (Siddiqui et al., 2023b) Patients unfit for major surgery may undergo wedge resection or segmentectomy. While these alternatives carry a higher risk of local recurrence, survival rates remain comparable. Adjuvant therapy like radiation or chemotherapy did not show improved outcomes for stage I disease. (Siddiqui et al., 2023b)

Stage II:

Surgery followed by adjuvant chemotherapy is the preferred treatment for stage IIA and IIB NSCLC. For cases involving chest wall invasion or pancoast tumours, neoadjuvant

chemotherapy with concurrent radiotherapy is recommended. Survival rates vary depending on microscopic disease presence after surgery. (Siddiqui et al., 2023b)

Stage III:

This stage presents various tumour invasion and lymph node involvement scenarios. Surgery with adjuvant chemotherapy is preferred for stage IIIA with N1 lymph nodes, though many patients are found to have N2 disease post-resection. The optimal treatment for stage IIIA with N2/N3 lymph nodes remains debated. Concurrent chemo-radiotherapy yields better outcomes but can cause severe side effects. T4 tumours are often treated with chemoradiation, with surgery rarely considered. (Siddiqui et al., 2023b)

Stage IV:

Stage IV NSCLC is incurable, focusing on improving survival and symptom relief. Chemotherapy offers a small survival benefit, with targeted therapy and immunotherapy showing promise in select patients. (Siddiqui et al., 2023b)

Targeted Therapy:

Targeted therapy aims to block specific mutations (e.g., epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK)) critical for cancer cell growth. Checkpoint inhibitors like PD-1 antibodies (e.g., nivolumab, pembrolizumab) showed efficacy in certain NSCLC cases. (Créquit et al., 2017; Siddiqui et al., 2023b)

2.7.2 TREATMENT OF SMALL CELL LUNG CANCER:

SCLC, highly reactive to chemotherapy, is treated based on the disease stage. Limited-stage SCLC typically involves surgery followed by adjuvant chemotherapy or chemotherapy with radiation therapy. Extensive-stage SCLC, which includes distant metastasis, is primarily treated with platinum-based chemotherapy and radiation therapy, with limited survival outcomes. (Rudin et al., 2021; Siddiqui et al., 2023b)

Overall, treatment strategies for NSCLC and SCLC aim to balance therapeutic efficacy with patient tolerance and quality of life.

2.8 SURVIVAL STATUS OF LUNG CANCER

Bi et al. conducted a comprehensive analysis in 2024 to examine the worldwide trends and future direction of lung cancer survival. They utilized survival data from cancer registries and population-based studies that had been previously published. The study searched various databases, such as SinoMed, PubMed, Web of Science, EMBASE, and SEER, to gather all survival analyses from lung cancer studies based on cancer registry or population data. The search encompassed studies published until November 2022. Survival rates were obtained by analyzing data according to gender, time, and nation. The study examined observed, relative, and net survival rates of lung cancer to understand the pattern and changes from the latter part of the 1990s to the beginning of the 21st century. The age-standardized 5-year survival rate for lung cancer consistently remained at a low level, frequently ranging between 10 percent and 20 percent across most populations. Japan exhibited the most elevated age-standardized relative/net survival rate, standing at 32.9 percent, whereas India demonstrated the lowest rate, which was recorded at 3.7 percent. Females and younger persons in numerous nations exhibited greater 5-year age-standardized relative/net survival rates for lung cancer. Patients diagnosed with adenocarcinoma typically had a more positive outlook in terms of prognosis when compared to other histological categories. The highest 5-year overall survival rates were recorded in men and women in Jiangyin, China, with rates of 27.90 percent and 31.62 percent, respectively. (Bi et al., 2024)

In a study by Vlasceanu et al. in 2024, the clinical features and survival outcomes of 1369 patients diagnosed and treated at a single institution were assessed. The study examined

the factors that affect the prognosis and survival of individuals with non-small bronchopulmonary carcinoma. Univariate analysis identified multiple factors linked with a lower likelihood of survival. These aspects that were found to be linked with a higher risk of death include being male (with a hazard ratio [HR] of death 1.54 times higher in men), having a more advanced stage of the tumour (pT2, pT3, and pT4 tumours had progressively higher hazards of death compared to pT1 tumours), having a larger tumour size (each 10 mm increase in tumour size was associated with a 10% increase in the risk of death), having a lower degree of differentiation (grade 3 tumours were associated with a 2.16 times higher hazard of death compared to grade 1 tumours), and having a less successful resection (R1 B+, R1 V+, and R1 B+&V+ resections were associated with progressively higher risks of death compared to R0 resections). (Vlăsceanu et al., 2024)

Sheikh et al. (2023) did a study to examine the survival outcomes and predictive markers of patients with surgical removal of early-stage NSCLC in Central and Eastern Europe. Between 2007 and 2016, 2052 subjects diagnosed with stage I-IIIA NSCLC were recruited from nine medical centres in previous united Russia for the study. Patients were monitored every year till 2020. Throughout the designated observation period, a total of 1121 fatalities were documented, with 730 of these being specifically linked to cancer. The median survival time observed in the study was 4.9 years, and the overall survival rate at the end of 5 years was 49.5%. In the multivariable analysis, the study found that mortality rates were higher among elderly subjects (Hazard Ratio [HR] for each 10-year increase: 1.31, males (HR: 1.24), alcohol drinkers (HR: 1.22), individuals who experienced substantial weight loss (HR: 1.25), current smokers (HR: 1.30), and patients with enhanced stage tumours (HR for stage IIIA vs. I: 5.54). Nevertheless, variables such as level of education, chronic obstructive pulmonary disease (COPD), and the type of tumour did not show any correlation with the likelihood of mortality. In addition, all fundamental

measures of alcohol and smoking use showed a correlation with the risk of cancer-related death that increased as the amount consumed increased. This analysis considered various factors related to smoking and alcohol use. These factors were the quantity of smoking, the number of years of smoking, the number of pack years of cigarettes smoked, the amount of alcohol consumed in gram-days, the frequency of drinking, and the number of years of drinking. (Sheikh et al., 2023)

In 2023, Saed and Degu performed a study to gauge the mortality rates of lung cancer subjects who received treatment at Kenyatta National Hospital. A retrospective cohort study was undertaken at Kenyatta National Hospital to evaluate the survival results of 151 individuals diagnosed with lung cancer. Subjects were monitored retrospectively from the time of identification until their death or the most recent follow-up. The mean length of follow-up was 18.2 months, whereas the middle value, or median, was 17.5 months. Non-small cell lung cancer was the most prevalent type of cancer among 98% of the patients. The two-year survival rate was 66.7 percent, with 59.6 percent of patients developing distant metastases during the follow-up period and 25.1 percent of patients passing away. The median cancer-specific survival period was 18.0 ± 3.40 months. Patients who had distant metastasis had a mortality risk that was five times higher than those who did not have metastasis (Adjusted Hazard Ratio: 4.74). (Said and Degu, 2023)

In 2023, Mir and colleagues undertook a study to ascertain the prevalence and clinic-pathological features of NSCLC (in Kashmir, a region in Northern India known for its high disease occurrence). The research was carried out at the Sher-I-Kashmir Institute of Medical Sciences, a specialized cancer treatment centre providing advanced care. They analyzed the clinical and demographic data of subjects with non-small cell lung cancer (NSCLC), encompassing demographic characteristics, clinical appearance, smoking stand, radio-logical features, histological type, and disease stage at the time of presentation. Most

patients (70 percent) resided in rural settings, with a median age of 58.0 years. The ratio of males to females was 3.7 to 1, and 77.39 percent of cases were smokers. Hookah was the predominant method of smoking, accounting for 65.06 percent of smokers. Squamous cell carcinoma (SCC) was more common than adenocarcinoma, with a ratio of 3.7 to 1 (67.5 percent vs. 24.9 percent). Most patients had advanced-stage disease, including Stage III and IV, which comprised 93 percent of all cases (30.6 percent and 62.7 percent, respectively). Squamous cell carcinoma exhibited a higher prevalence among individuals who smoked (74.3 percent), but adenocarcinoma was more frequently observed in individuals who did not smoke (44 percent). Most patients exhibited an Eastern Cooperative Oncology Group (ECOG) performance level ranging from one to two (79 percent patients). (Mir et al., 2023)

Bogere et al. (2022) conducted a study at the Uganda Cancer Institute and analyzed the baseline characteristics and survival outcomes of lung cancer patients. The study enacted a retrospective review of medical data that included all patients who had a confirmed histological analysis of lung cancer and were entered at the centre. Of the 207 registered subjects, 56.5 percent (n = 117) were female, and their median age was 60 years (ranging from 20 to 94). Out of the total number of participants, the majority (78.7%, n=163) were individuals who had never smoked, whereas a minor fraction (8.7%, n=18) were individuals living with Human Immunodeficiency Virus. Presumptive anti-tuberculosis treatment was administered to approximately 23.2% (n = 48) of the study participants. Most cases (96.6 percent, n = 200) were categorized as non-small cell lung cancer (NSCLC), with adenocarcinoma (74.5 percent, n=149) and SCC (19 percent, n=38) being the most prevalent subtypes. All patients exhibited advanced-stage illness, with 96.1 percent (n = 199) being identified at stage IV. The primary treatment modalities were chemotherapy (44.9 percent, n = 93) and biological therapy (34.8 percent, n = 72). The six-

month, one-year, two-year, and five-year survival rates were 41.7 percent, 29.7 percent, 11.8 percent, and 1.7 percent, respectively. The median survival time of 4.4 months did not demonstrate a statistically significant distinction between people with NSCLC or SCLC (4.5 versus 3.9 months, p = .335). (Bogere et al., 2022)

In 2022, Zhang et al. conducted a study to evaluate the time-dependent risks of death related to different causes and the likelihood of survival for individuals with lung cancer. The study collected data from the SEER database, which included 816,436 lung cancer cases diagnosed from 2000 to 2015. Following the removal of certain cases, 612,100 cases were considered for study. The study assessed overall survival, carcinoma-specific survival, and dynamic death hazards in this investigation. The researchers also analyzed the effects of immunotherapy, notably Nivolumab, approved by the FDA in 2015, on the survival rates of patients with metastatic cancer. They compared cases from 2016 to 2018 (during the period of immunotherapy, with a sample size of 7,135) to cases from 2013 to 2016 (before the era of immunotherapy, with a sample size of 42,061). The average age of these ladies was 68.30 years, with a standard deviation of 11.0 years. There were 252,558 instances of lung adenocarcinoma, 133,302 cases of lung SCC, and 78,700 cases of SCLC. The distribution of TNM stages was as follows: Stage I (140,518 cases), Stage II (38,225 cases), Stage III (159,095 cases), and Stage IV (274,262 patients). A total of 164,394 cases underwent surgical surgery. The 5-year total survival rate was 54.2 percent, whereas the 5-year cancer-specific survival rate was 73.8 percent. The 5-year conditional cancer-specific survival showed continuous improvement over time. Still, the conditional overall survival seemed to level off after a 5-year observation period. After eight years following the initial diagnosis, the danger of death from causes other than lung cancer became more significant than the risk of death, specifically from lung cancer. The survival rates for both cancer-specific and overall survival were considerably higher in metastatic patients who received

immunotherapy than those who did not (P<0.001). This suggests that immune-therapeutic intervention provides significant advantages for advanced lung cancer subjects. (Zhang et al., 2022)

In 2022, He et al. conducted a study to calculate the survival outcomes of subjects with lung cancer with varying pathological evaluations. The study aimed to investigate the predictive effects of these evaluations and offer insights for enhancing prognosis. A cohort of patients with primary lung cancer was recruited from 17 hospitals across three different tiers in China from 2011 to 2013. These patients were then monitored until 2020. Out of the 7,311 patients included in the study, the 5-year survival rates for overall and lung cancer-specific cases were 37.0% and 41.6%, respectively. The 5-year survival rates for patients at stages I, II, III, and IV were 76.9%, 56.1%, 32.6%, and 21.4%, correspondingly. The equivalent survival rates specifically for lung cancer were 82.3%, 59.7%, 37.2%, and 26.4%. Survival disparities remained statistically significant across histological classifications within each stage (P < 0.01). The 5-year survival rates for subjects with SCC, adenocarcinoma, and SCLC were 36.9%, 43.3%, and 27.9%, respectively. The comparable rates for survival specifically related to the disease were 41.5%, 48.6%, and 31.0%, respectively. At advanced stages, the observed differences were not statistically significant (P=0.09). Following adjustments for many variables, the stage and histological categorization continued to be significant predictors of lung cancer survival. (He et al., 2022)

In 2022, Vasudevan, Krishna, and Mehta conducted a study to examine the frequency, clinical features, driver mutations, and survival outcomes of lung cancer subjects treated in

tertiary centre, specifically focusing on the differences between non-smokers and smokers. They analyzed data from 724 consecutive lung cancer patients over two years. 40.9% of the study group consisted of individuals who did not smoke. Non-smokers exhibited a higher probability of experiencing illness initiation at a younger age and metastasis compared to smokers. The analysis of tumour histology revealed statistically significant variations ($P < 0.001$). Adenocarcinoma was found to be more prevalent among non-smokers (77.4%), whereas squamous and small cell histology were more prevalent among smokers (37.6 percent and 13.8 percent, respectively). The prevalence of EGFR mutation and ALK rearrangement was 23.3 percent and 10.1 percent, respectively, and was higher in patients who did not smoke. The 10-year survival rate was 7 percent overall, with non-smokers demonstrating considerably higher survival rates compared to smokers (median survival time of 15.13 vs. 10.17 months) (Vasudevan et al., 2022)

In their study, Bogos et al. (2021) examined the extended survival rates of Hungarian lung cancer patients by thoroughly reviewing the Health Insurance Fund database. The study performed a retrospective, longitudinal analysis on persons aged 20 years and older who were detected with lung cancer (ICD-10 C34). An analysis was conducted to determine the survival rates based on the patient's gender and age, year of diagnosis, and the morphology of lung cancer. The database recorded a total of 41,854 newly diagnosed instances of lung cancer. The average age of diagnosis varied from 64.7 to 65.9 years. The overall survival rates for the population at one and five years were 42.2% and 17.9%, respectively. Gender, age and the kind of lung cancer were found to have a substantial impact on survival outcomes. Among the patients, the survival rate of females (n = 16,362) was 23% higher (Hazard Ratio (HR): 0.77, than that of males. The 20-49 age group had the highest survival values, with a 5-year survival rate of 31.3%. Similarly, individuals with adenocarcinoma had a 5-year survival rate of 20.5%. We detected a 5.3% improvement (adjusted 9.2%) in

lung cancer survival rate between 2015-2016 and 2011-2012. This improvement was statistically significant, with a hazard ratio of 0.95 (CI: 0.92-0.97). The most notable gain in survival was seen in females under 60, with an adjusted hazard ratio of 0.79 (0.84-0.93). The examination of interactions revealed a noteworthy association between age and histological kinds. (Bogos et al., 2021)

Ekman et al. (2021) conducted a study to examine the patterns of OS in individuals diagnosed with NSCLC. From 2005 to 2015, 30,067 and 31,939 people with NSCLC were diagnosed in Sweden and Denmark, respectively. The predominant histological subtype observed was non-squamous cell carcinoma, accounting for 56.9% and 53.0% of cases. Stage at diagnosis of the disease in these studies were stage IV with 48.4% and 51.6% respectively. During the study period, there were notable advancements in the short-term survival (1 year) of patients with non-squamous cell carcinoma. Nevertheless, upgrading in extended-term survival (5 years) was solely noted in subjects diagnosed with stage 1st and 2nd illness. In contrast, patients with squamous cell histology showed short-term gains in survival, specifically for stage 1st disease in Sweden and stage 3A in Denmark. Notable progress in longer-term survival was observed exclusively for stage 3A NSCLC in both nations. (Ekman et al., 2021)

In a study by Mohan et al. 2020, the researchers examined lung cancer patients' demographic profile, histological distribution, molecular features, and survival outcomes over ten years. Analysed were the clinical statistics and survival outcomes. The study comprised 1862 individuals with an average age of 59 years. Most participants were male (82.9%) and smokers (76.2%). Adenocarcinoma accounted for the highest proportion (34%) among the histological types, followed by SCC and SCLC. During 10 years, the

incidence of ADC exhibited a consistent upward trajectory, whereas SCC and non-small cell lung cancer not otherwise specified (NSCLC-NOS) demonstrated a decline. An increasing percentage of women with lung cancer was observed. Most cases of NSCLC were detected at advanced stages. EGFR mutations and ALK rearrangements were detected in a significant number of patients with cancer. The median rate of overall survival was 8.8 months for the entire patient population and 12.57 months for those who received a particular treatment. Individuals who have never smoked, particularly those who are younger, female, and well-educated, exhibit a higher occurrence of adenocarcinoma and EGFR/ALK mutations, as well as improved survival rates. (Mohan et al., 2020)

Onal et al. (2020) did a study to evaluate how clinical and pathological indications at the time of diagnosis affect the overall survival of patients who have just been diagnosed with NSCLC. The analysis included a total of 518 individuals, consisting of 260 with SCC, 207 with adenocarcinoma, 50 with NSCLC not otherwise defined, and 1 with large cell carcinoma. The average life expectancy was 11.50 ± 1.40 months for SCC, 12.60 ± 1.59 months for adenocarcinoma, and 8.70 ± 1.87 months for other kinds. The projected 5-year relative survival rate for NSCLC was 8%, with a rate of 7% for males and 18% for women. In the analysis of multiple variables, the factors that were found to significantly predict a decrease in overall survival were being male (HR, 2.41; $P < 0.001$), having a prognostic status greater than 2 (1.70), having a more advanced stage of cancer (1.37;), having bone or liver metastasis (, 1.44, and 1.57; correspondingly), and not receiving radiotherapy (3.25;) or chemo-therapy (, 1.85). (Önal et al., 2020)

A study conducted by Abedi et al. in 2019 aimed to examine several statistical survival models and identify the survival rate and related features in patients with lung cancer. This study utilized retrospective cohort analysis to estimate the aggregate survival rate, median time of survival, and factors that impact the persistence of patients with lung cancer. The analysis employed Cox, Weibull, exponential, and Gompertz regression models. Out of the 102 individuals diagnosed with lung cancer, 74.5 percent were identified as male. During the entire duration of the follow-up period, a total of 80.4 percent of the patients passed away. The mortality rate among patients was estimated to be 3.9 (95 percent CI, 3.1 to 4.8) per 100 person-months. The 5-year survival rates for all patients, both males and females, patients with NSCLC, and patients with SCLC, were 17 percent, 13 percent, 29 percent, 21 percent, and 0 percent, respectively. The median survival time for all patients, male subjects, females, those with NSCLC, and those with SCLC was 12.7 months, 12.0 months, 16.0 months, 16.0 months, and 6.0 months, respectively. The multivariable analyses showed that the HR with 95% CI for being male (when compared to female), age (>60 yearrs when compared <60 years), and having SCLC (when compared to NSCLC) were 0.56 (0.33 to 0.93), 1.03 (1.01 to 1.05), and 2.91 (1.71 to 4.95), correspondingly. (Abedi et al., 2019)

In a study by Murali et al. in 2017, the researchers examined the results of lung cancer patients. The study aimed to evaluate the survival consequences of these patients and discover indicators that could predict their prognosis. The institute provided treatment to a total of 678 people diagnosed with lung cancer. The patients had a median age in years of 58 years, and 91% of them were diagnosed with NSCLC. Testing for mutations in the epidermal growth factor receptor was carried out in 132 out of 347 patients with NSCLC, and 61 of them (46%) tested positive. For patients with NSCLC, the median duration

without disease progression was 6.9 months, and the overall survival time was 7.6 months. In patients diagnosed with small-cell lung cancer, the median duration of time without disease progression was six months, and the overall time of survival was 7.2 months. Through multivariable analysis, it was found that numerous characteristics were strongly linked to a lower OS in NSCLC. These factors include histology other than adenocarcinoma, performance status larger than 2, and advanced stage of the disease. In contrast, younger age and earlier stage of presentation were found to be strongly correlated with improved survival outcomes in SCLC. (Murali et al., 2017)

In 2015, Abazari et al. did a study to evaluate the survival rates of Iranian individuals diagnosed with lung cancer and determine the prognostic factors linked to survival. The study encompassed a total of 355 patients who were hospitalized in hospitals in West Azerbaijan in the year 2007. Out of the total of 355 patients, 240 experienced mortality, while 115 were censored. The average and middle survival time was 13 and 4.8 months, respectively. As per the Kaplan-Meier survival curves, the survival rates at 1st, 2nd, and 3rd years were 39%, 18%, and 0.07%, respectively. Cox regression analysis demonstrated a significant association between ECOG performance status V and an increased risk of death (HR: 1.83). (Abazari et al., 2015a)

In 2014, Muallagolu et al. did a study to assess the epidemiological and clinicopathological features of NSCLC patients who have never smoked. The study specifically examined clinical risk factors and survival outcomes. A retrospective analysis was done on a cohort of 290 NSCLC patients diagnosed and treated between 2006 and 2011. Of the group, 243 individuals (83.8%) were classified as ever-smokers, while 47 individuals (16.2%) were classified as never-smokers. Within the group of individuals who have never smoked, the

majority were females (80.9%), and a significant proportion had adenocarcinomas (78.7%). During the analysis, a total of 143 patients, accounting for 49.3% of the sample, had deceased. The 5-year overall survival rates did not show a statistically significant difference between individuals who had never smoked and those who had ever smoked. The overall median survival (OS) was 26 months, with a 95% confidence interval (CI) of 16.8-35.2. Never-smokers had a median OS of 23 months, with a 95% CI of 11.8-34.2, while ever-smokers had a median OS of 30 months, with a 95% CI of 19.7-40.3. The p-value for the comparison between never-smokers and ever-smokers was 0.410. Non-smokers exhibited a higher prevalence of advanced disease ($p<0.004$) and generally had a higher age ($p<0.001$) in comparison to individuals who had smoked at some point in their lives. The hazard ratio for mortality was higher in individuals with a lower ECOG status of performance (ECOG 2=3), advanced stage (stage 3=4), and those who had not received treatment. Subjects with adenocarcinoma had a slightly reduced risk of death compared to those with SCC. (Muallaoglu et al., 2014)

In 2014, Arslan and colleagues conducted a study to evaluate the survival outcomes and prognostic markers of subjects with T4 locally progressed non-small cell lung cancer. The study included a large and diverse sample of patients and followed a novel staging system. The study retrospectively analyzed medical data from 122 individuals diagnosed with T4 N0-3 M0 LA-NSCLC, as determined by the new staging criteria. These patients were treated at two medical centres from November 2003 to June 2012. The patients had a median age of 60 years. The median time of overall survival (OS) was 18.3 months, with a one-year OS rate of 72% and a five-year OS rate of 28%. The univariate analysis identified several statistically significant determinants of survival, including ECOG-PS, age, T4 factor sub-group, stage, and initial treatment. The multivariate analysis for OS revealed

that ECOG-PS, diagnostic stage, and initial treatment were important predictors. Significantly, the median OS in patients who underwent non-curative treatment was 11.0 months. In contrast, 19.0 months in the group received standard radiotherapy and 26.6 months in the curative treatment category. There were significant differences in terms of treatment protocol that was used for these group of patients. Operating systems between the non-curative cluster and the clusters having definitive radiation therapy or curative procedures. The differences were significant statistically with p values of less than 0.05. Nevertheless, there was no substantial disparity observed between the cohorts undergoing definitive radiation therapy and curative surgeries. The median event-free survival (EFS) time was 9.9 months, with 46% and 19% rates after 3 and 5 years, respectively. The multivariate analysis for EFS revealed that primary therapy was the sole statistically significant predictor (p=0.001). Grade III/IV adverse effects were detected in 57 individuals (46.6%), with esophagitis being the most frequent among those who underwent final radiation. (Arslan et al., 2014)

In 2012, Zahir and Mirtalebi did a study in Yazd City, Iran, to evaluate the long-term survival of lung cancer subjects and the influence of several prognostic markers on their survival. This study was conducted to examine the medical records and follow-up data of 148 patients who were diagnosed with lung cancer through histological confirmation. It was a descriptive study that analyzed data from a specific point in time. The average survival time for all patients was 8.5 months after diagnosis, and there was no notable disparity in survival between males and females (p=0.958). The most common histological type was SCC, accounting for 35% of cases. The Kaplan-Meier analysis revealed a significantly higher mean survival time of 22.6 months for SCC compared to other

histological types, which had a survival time of less than ten months. While the results did not reach statistical significance, there was a noticeable pattern indicating a potential link between the histological type and the length of survival (p=0.08). (Zahir and Mirtalebi, 2012)

In a study by Lee et al. (2012), the researchers observed the survival rates of subjects with NSCLC who received radiofrequency ablation, surgery, or chemotherapy. The subjects were categorized based on the stage of their lung cancer. RFA was conducted on subjects who were considered medically ineligible for surgery or not suited for surgery due to advanced lung cancer or their reluctance to undergo surgery. Within the RFA group, 40 subjects diagnosed with inoperable NSCLC had RFA using CT guidance. This encompassed 16 subjects with stage one to two cancer and 24 subjects with stage 3 to 4 cancer who received RFA as an adjuvant treatment. The comparison cluster consisted of 37 individuals. Among them, 13 subjects had stage 1 to 2 cancer and underwent surgery, 18 subjects had stage 3 to 4 cancer and got chemotherapy, and six subjects had stage III to IV cancer but did not get any active treatment. The median survival durations for subjects who underwent surgery alone and radiofrequency ablation alone for stage 1 to 2 lung cancer were 33.8 and 28.2 months, respectively. The statistical analysis showed no difference between the two treatment groups. The median survival periods for subjects with stage 3 to 4 cancer who had chemotherapy alone and radiofrequency ablation with chemotherapy were 29 and 42 months, respectively. (Lee et al., 2012)

In their 2010 study, Kawaguchi et al. utilized data from the National Hospital Study Group. The study focused on categorizing patients based on their smoking status, distinguishing between never-smokers and ever-smokers. The study comprised 1,499

individuals who had never smoked and 3,455 individuals who had smoked at some point in their lives. These individuals had advanced stage IIIB and IV NSCLC and had undergone cytotoxic treatment. Non-smokers exhibited a higher proportion of females, younger individuals, those with better performance levels, and individuals with adenocarcinoma. The study found that smoking status was a significant predictor of outcomes. Never-smokers had a decreased hazard ratio (HR=0.88). In distinct multi-variate analyses conducted for those who have never smoked and those who have smoked, being female and having a higher performance status were identified as positive predictive factors for both groups ($p < 0.0001$). However, adenocarcinoma histology had a hazard ratio of 0.79 (CI: 1.02-1.47) compared to squamous cell carcinoma. Additionally, the period after 2000 had a hazard ratio of 0.85 compared to the period before 2000. These findings were observed only in individuals who never smoked. Exploratory research identified distinct predictor indicators like good ECOG PS, never smoker (versus ever smoker; hazard ratio = 0.935, 95% CI: 0.884-0.990; $p = 0.0205$), early stage of disease, female gender, and squamous cell carcinoma histology for survival (Kawaguchi, Takada, Kubo, Matsumura, Fukai, Tamura, Saito, Kawahara, et al., 2010)

Kawaguchi et al. (2010) conducted a study to evaluate the predictive importance of Performance Status (PS), considering other significant parameters. A retrospective analysis was performed utilizing the National Hospital Study Group for Lung registry database, covering the period from 1990 to 2005. One-third of participants (n=8137, 30.2%) were categorized as never smokers, with the majority being females (72.7%). Most individuals with a PS score of 0 exhibited stage I illness, accounting for 56.9% of cases. The percentage of individuals who had never smoked was highest in this category, at 36.7%. A notable difference in the median OS was noted between subjects with a performance status

(PS) of 0 and PS of 1 (51.5 months against 15.4 months, respectively). Additionally, substantial variations in survival were detected among patients with different PS within each specific AJCC on Cancer stage (all p values <0.0001). In addition, individuals who have never smoked showed a considerably hig9her median OS compared to those who had smoked at any point in their lives (30.0 months against 19.0 months, correspondingly. The multivariable analysis showed several characteristics independently associated with a favourable prognosis. These factors were good performance status, never smoking (compared to ever smoking), early-stage disease, female gender, squamous cell carcinoma histology, and treatment. The hazard ratio for never smoking was 0.935. (Kawaguchi, Takada, Kubo, Matsumura, Fukai, Tamura, Saito, Maruyama, et al., 2010b)

3 METHODOLOGY

3.1 FEATURES OF THE STUDY

3.1.1 STUDY SETTING:

The study was done in tertiary cancer care hospitals in Kerala, with a hospital-based Cancer registry program under NCRP of the Indian Council of Medical Research (ICMR). Six hospitals were selected from Kerala's north, central, and south zones. The hospitals were:

1. Amala Institute of Medical Sciences, Thrissur
2. Little Flower Hospital and Research Centre, Angamaly, Ernakulum
3. Lisie Hospital, Ernakulum
4. Prathyasa Cancer Research Centre, Cherthala
5. Malabar Cancer Centre, Thalassery
6. MVR Cancer Centre, Kozhikode

A registry of lung cancer patients was established in these hospitals. Our registry included consecutive patients from January 2017 to December 2019. A list of patients with lung cancer during the study period was extracted from the hospital records. Patients with metastatic lung disease (primary in another organ) were excluded using a screening tool.

3.1.2 STUDY TYPE/DESIGN:

The study design was a multi-centre lung cancer registry with follow-up for two years.

3.1.3 STUDY PERIOD:

Data for two years (2017-2019) were obtained from patient records. All consecutive patients diagnosed during the study period were included in the case registry. All patients were followed up further for a minimum period of two years from the date of diagnosis.

3.2 OPERATIONAL DEFINITIONS

1. **Case** – Patient with histologically proven primary lung cancer diagnosed from Jan 2017 to December 2019. Cases with secondary lung cancers and metastasis to the lung were excluded. Cases without histological diagnosis were also excluded.
2. **Registry** – A lung cancer registry established by including all consecutive cases histologically diagnosed during the study period from selected hospitals.
3. **Predictor** – A variable that is statistically associated with all-cause mortality.
4. **Study site** - Hospitals designated from three zones – north, central, and south of Kerala (six hospitals were included)
5. **BMI** – Body Mass Index (BMI) was derived from weight (kilograms) and height (meters). Using this, participants were categorized as underweight ($<18.5 kg/m^2$), normal weight (18.5-22.9 kg/m^2), overweight (23.0-24.9 kg/m^2) and obese ($\geq 25 kg/m^2$) based on consensus guidelines. (K.G. Sruthi et al., 2023)
6. **ECOG PS**- Eastern Cooperative Oncology Group Performance Status scores are 0-fully active, no performance restrictions, 1-strenuous physical activity restricted; fully ambulatory and able to carry out light work; 2- capable of self-care but unable to carry out any work activities, 3- capable of only limited self-care, 4- completely disabled; cannot carry out any self-care; confined to bed or chair. (Faisal Azam et al., 2019)

3.3 SAMPLE SIZE:

Sample size was estimated using STATA 13. The sample size was computed for Cox PH regression Wald test for detecting a minimum hazard ratio of 1.3. We assumed a probability of event of 0.60 for all-cause mortality among lung cancer patients, an alpha (two sided) of 0.05, and a standard deviation of the covariate under consideration of 0.50. The sample size and required number of events were estimated for 80% power. The required sample size was 761.

3.4 SAMPLE SELECTION PROCEDURES:

Consecutive primary lung cancer subjects diagnosed histologically (ICD code C 33 and C 36) from Jan 2017 to Dec 2019 were included in the study. A chart review was conducted to collect the data.

The file number of patients with lung cancer was taken from the hospital cancer registry and handed over to the medical records department of the hospital for retrieving the file. Individual patient files were taken from medical records, and data were collected using a structured data collection tool. There were four parts to the data collection tool. Part 1 of the data collection tool was filled out initially, and the subsequent forms were filled out if the patient was eligible for the study. Histological and lab data, available in the chart, were collected. Data regarding socio-demography, presenting complaints, investigations, past medical history, ECOG performance status at diagnosis, date and mode of diagnosis, treatment modalities, and treatment outcome were gathered from the subject chart. The last hospital visit date was obtained from the patient chart. Part IV of the data collection tool was filled by contacting the patient or caregiver. The patient/caregiver was contacted telephonically to assess the vital status at the time of data collection and every six months

till two years of diagnosis in the absence of the event of interest (all-cause mortality). If the patient/caregiver was not accessible by phone, the data collector tried to access the patient through the Primary Health Centre/Anganwadi Worker/accredited social health activist of the respective areas using the available address. Three attempts were made to collect relevant follow-up data from each patient or family member.

3.4.1 INCLUSION CRITERIA:

- All patients with histological diagnosis of primary lung cancer diagnosed during 2017-2019
- All age groups

3.4.2 EXCLUSION CRITERIA:

- Patients with secondary lung cancer (primary in other organs)

3.4.3 SAMPLING TECHNIQUE:

- All consecutive cases from the registry

3.4.4 DATA COLLECTION TECHNIQUES:

After obtaining written consent from the institution head and treating doctor, data were retrieved from the patient files of eligible patients. On behalf of the treating doctor, one of their team members contacted the patient or their relative and sought their verbal consent for a telephonic interview. A structured data extraction format was used to collect data from the files. The patient/caregiver was contacted to assess the patient's vital status.

3.4.5 ETHICAL CONSIDERATIONS:

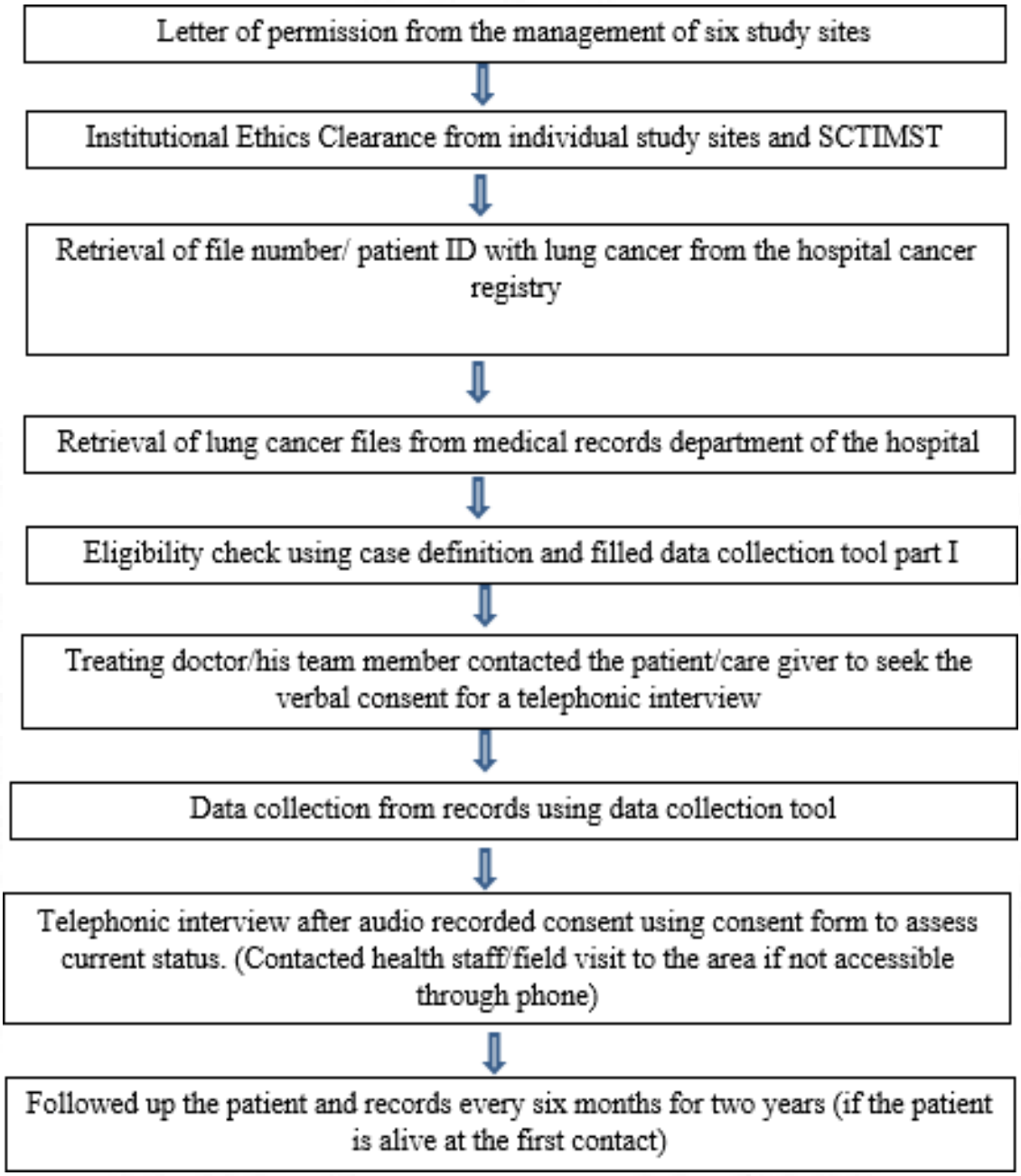
The study involved collecting secondary data from the patient chart and contacting the patient/caregiver to assess the vital status. Consent was from the institution head and treating doctor. All the personal information collected about the subjects was kept confidential, and a unique identity code was used to ensure the confidentiality of the data.

Institution Ethical Clearance was obtained from all six study sites and SCTIMST (SCT/IEC/1658/DECEMBER-2020), and the study was registered with the Clinical Trial Registry of India (CTRI/2021/ 02/031/031299).

3.4.6 DATA SOURCES

Data collection was conducted by health personnel who were trained and familiarized with the data collection tool. The staff nurse/ health worker collected the data at every site. The principal investigator (a trained physician with an MD degree) trained the data collectors at each study site and was present at every site's initial data collection stage. The principal investigator conducted site visits bi-monthly and reviewed all data points. Confidentiality of the data was maintained by blinding the individual’s identity and providing a unique identity code for each patient. Individual’s identity was not revealed in the data sheet sent for analysis or while publishing the data. The institution's identity was also not shown at any level of data retrieval. Figure 6 explains the data collection steps involved in the study.

Figure 6: Algorithmic Flow Chart: Data collection



3.5 DATA ANALYSIS PLAN

The data were inputted into an Excel spreadsheet and analyzed using STATA 13. The data for continuous measurements were reported as the mean and standard deviation, whereas the results for categorical measurements were provided as numbers and percentages. The primary outcome variable was all-cause mortality. The cumulative all-cause mortality data were reported at six months, 12 months, 18 months, and 24 months of follow-up. Furthermore, mortality data were also reported in person-months of follow-up. We also estimated the median survival time. Kaplan-Meier survival curves were generated, and the Log Rank Test was employed to compare the overall survival among study groups. A multi-variable Cox proportional hazard model was employed to evaluate the factors that predict all-cause death. The hazard ratios and their corresponding 95% confidence intervals were derived from the Cox-proportional hazard model.

3.5.1 KAPLAN-MEIER SURVIVAL ANALYSIS

The central statistical method utilized in this thesis was survival analysis, which involves examining the time until death occurs. Survival time is estimated as the number of months from the beginning of the individual follow-up until the death. Due to incomplete observation of survival time, data were right censored at 24 months of follow-up, allowing for a maximum follow-up period of 24 months for participants. Survival characteristics are summarised using survival probabilities or cumulative survival at specific time points

during follow-up. These probabilities are assumed to be consistent for the subjects recruited at different times during the study.

The survivor function, represented by S(t), denotes the likelihood of an individual's survival beyond a specific time 't' during the follow-up period. The hazard function, represented as h(t), quantifies the instantaneous rate at which an event is likely to happen within a specific time interval (one month) if the individual has already survived up to time 't.' The log-rank test is a frequently employed statistical method for comparing the survival rates of distinct groups. It evaluates the hypothesis that there is no disparity in the chance of surviving at any point over the whole follow-up period.

The Kaplan-Meier (KM) method was initially employed to summarize survival data for different categories. KM survival probabilities, represented as KM curves, were plotted as step functions for each ordered failure time (e.g., one month), starting with a horizontal line at a survival probability of 1 and, after that, stepping down to subsequent probabilities for each category of the baseline predictor variables. The available risk set was utilized to estimate survival probabilities at specific time points. A subject might not be included in the risk set at a given time if they had already died or lost to follow-up.

The log-rank test for multiple groups assessed whether KM curves for different categories of baseline predictor variables were statistically equivalent. This test compares observed versus expected cell counts over categories of mortality outcomes, using each ordered failure time for the analyzed dataset. However, the KM method has certain limitations. It primarily serves as a significance test and does not estimate effect size (i.e., the magnitude of difference.

Survival time is estimated as the months from individual follow-up to death. Due to differences in survival time observation between participants, data were right censored at

24 months, enabling participants a maximum follow-up of 24 months. Survival probabilities or cumulative survival at certain follow-up times summarize survival features.

The KM approach has drawbacks. It primarily tests significance and does not measure effect size by comparing groups. It cannot assess multivariable effects and can only analyze one element. Additionally, it cannot handle continuous predictor variables. (Bewick et al., 2004; Bland and Altman, 1998, 2004; Clark et al., 2003; Freedman, 1982; Pocock et al., 2002; Prinja et al., 2010; Stats_at_Square1.pdf, n.d.; Stel et al., 2011)

3.5.2 COX PROPORTIONAL HAZARDS MODELS

To analyze the influence of baseline predictor variables on mortality while adjusting for potential confounders, Cox proportional hazards (Cox PH) models were employed. The Cox PH model evaluated the risk of an event occurring at a time 't' for an individual based on a specified set of variables, assuming the individual has not experienced that event before time 't.'

The starting point hazard parameter in the Cox proportional hazards model represents the hazard rate when all covariates have a value of zero. In contrast to the Kaplan-Meier technique, the Cox model does not necessitate knowledge of absolute risk and solely calculates relative risk. In addition, the Cox model can handle discrete and continuous measurements of event timings.

Variables for the Cox models were selected using stepwise backward selection, where exposure variables with p-values less than 0.10 were retained, and others were excluded. If the linearity of the effect of an exposure variable on the outcome was uncertain, it was categorized into groups, often using quartiles or quintiles.

Semi-parametric Cox PH doesn't assume a survival distribution. However, it makes heavy assumptions about exposure variables and survival. The fundamental assumptions are the proportionality of hazard rates across time and the linear contribution of exposure factors and covariates to the natural log of the hazard ratio. The Cox PH model assumes a parametric form for predictor effects but not for the baseline hazard function. The Cox PH model's partial likelihood only works when there are no connections in the dataset, meaning no two subjects have the same event time. According to the proportional hazard (PH) assumption, HR remains constant throughout time, and the hazard for one person is comparable to the hazard for any other person. (Bender et al., 2005; Bradburn et al., 2003a, 2003b; Cox, 1972)

4 RESULTS

The results of the study are discussed under the following headings:

SOCIO-DEMOGRAPHIC CHARACTERISTICS

The mean age (completed years) was 65.11 (± 10.22), ranging from 14 to 93 years. In the study population, 258 (33.9%) were in the age group of 60-69 years, 235 (30.9%) in the 70-79 years group, 226 (29.7%) in the < 60 years group, and 42 (5.5%) in the ≥ 80 years of age group. Among the study participants, 617 (81.1%) were males, and 144 (18.9%) were females. Among them, 749 (98.4%) were currently married, and 12 (1.6%) were never married. Among the study participants, 292 (38.4%) were Hindu, 260 (34.2%) were Christian, and 209 (27.5%) were Muslim. Table 3 depicts the socio-demographic details of the study participants (Table 3).

Table 3: Socio-demo-graphic characteristics of the study participants (n=761)

Variables		Number	Percentage
Age	< 60 yrs	226	29.7
	60-69 yrs	258	33.9
	70-79 yrs	235	30.9
	≥80 yrs	42	5.5
Religion	Hindu	292	38.4
	Christian	260	34.2
	Muslim	209	27.4
Gender	Male	617	81.1
	Female	144	18.9
Marital status	Married	749	98.4
	Unmarried	12	1.6
BMI	Underweight	118	15.5
	Normal weight	258	33.9
	Overweight	78	10.2
	Obese	75	9.8
	Data not available	232	30.6

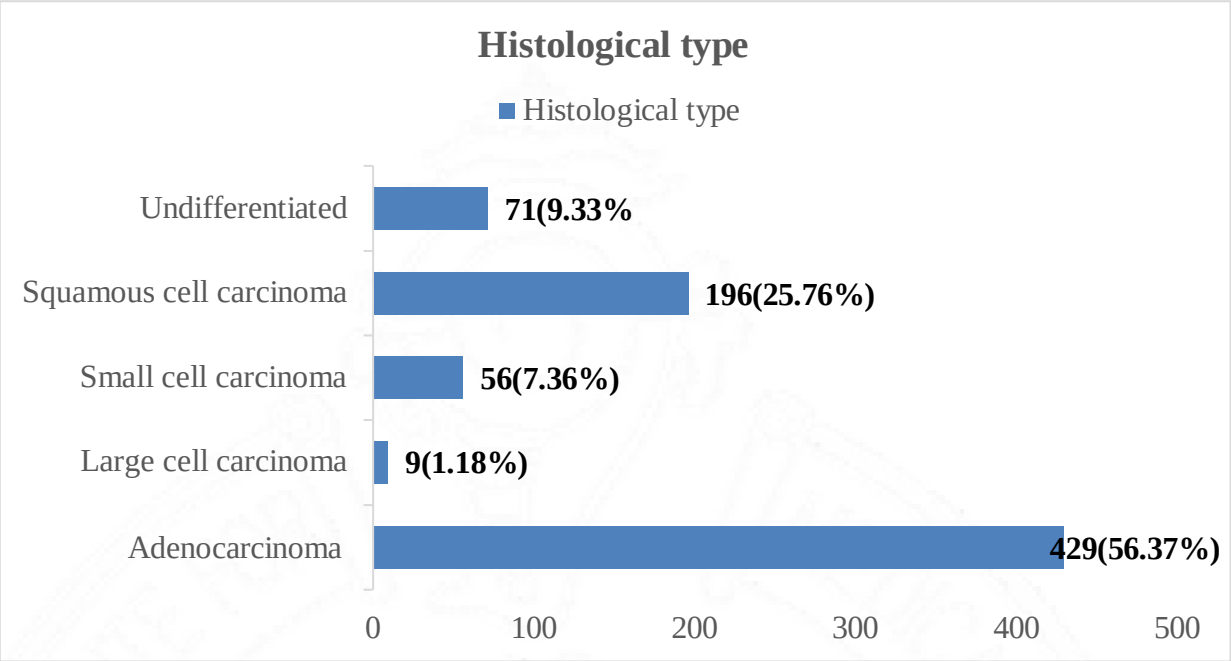
BMI- Body Mass Index

CLINICAL CHARACTERISTICS

Histological type

Among the study population, 429 (56.4%) had adenocarcinoma, and 196 (25.8%) had squamous cell carcinoma (Fig 7). Additionally, 71 (9.3%) patients were diagnosed with undifferentiated, 56 (7.4%) with small cell carcinoma, and 9 (1.2%) with large cell carcinoma.

Figure 7. Histological type of lung cancer (n=761)



Duration of symptoms to diagnosis and treatment

The median duration of symptoms to diagnosis in weeks was 4 with an Inter Quartile Range (IQR) of two to six weeks. The median duration of diagnosis to treatment was two (IQR 2-3) weeks.

Symptoms/signs of disease at presentation

Weight loss was reported in 79 participants (10.4% of the total). Additionally, 151 participants (19.8%) experienced dyspnea, and 152 participants (20%) reported weakness/fatigue. The participants also reported the following symptoms: cough (65.2% of the total), hemoptysis (17.2%), shortness of breath (35.7%), chest pain (19.5% of the

total), and difficulty swallowing (8.1%), and wheezing (1.3%). There was pleural effusion in 62 patients (8.1%) and hoarseness of voice in 33 patients (4.3%). Forty-nine participants (6.7%) reported feeling less hungry. Pain in the bones was reported in 20 patients (2.6%). (Table 4)

Table 4: Symptoms/signs at presentation among the study population (n=761)

Symptoms	Frequency	Percent
Cough	496	65.2
Breathlessness	272	35.7
Chest pain	194	25.5
Weakness	152	19.9
Dyspnoea	151	19.8
Haemoptysis	131	17.2
Fever	105	13.8
Weight loss	79	10.4
Pleural effusion	62	8.2
Loss of appetite	51	6.7
Hoarseness of voice	33	4.3
Bone pain	20	2.6
Wheezing	10	1.3
Difficulty in swallowing	8	1.1

Among the participants, 571 (75.0%) were diagnosed with stage 4 disease. Stage 3, stage 2, and stage 1 were diagnosed in 76 (9.9%), 72 (9.5%), and 42 (5.5%) participants, respectively. Similarly, T2, T3, and T4 status were reported in 280 (36.8%), 233 (30.6%), and 147 (19.3%) participants. One hundred and one (13.3%) participants were diagnosed with T1 tumor stages (Table 5). Based on the lymph node stages, 316 (41.5%) participants were diagnosed with N2. A similar number of participants (n=316) were diagnosed at the N3 stage. Ninety-three (12.2%) participants were diagnosed with the N1 stage, and 36 (4.7%) had Nx as the lymph node stage at the time of diagnosis.

Table 5: TNM staging of disease among the study population (n=761)

Variables		Number	Percentage
Tumour stages	T1	101	13.3
	T2	280	36.8
	T3	233	30.6
	T4	147	19.3
Node status	Nx	36	4.7
	N1	93	12.3
	N2	316	41.5
	N3	316	41.5
Metastasis	M0	190	25.0
	M1a	43	5.7
	M1b	202	26.5
	M1c	326	42.8
TNM staging	Stage1	42	5.5
	Stage 2	72	9.4
	Stage 3	76	9.9
	Stage 4	571	75.2

TNM-Tumour, Node, Metastasis

Among the participants, 548 (72.0%) had pleural involvement, and 355 (46.6%) had vessel invasion. Among the study population, 470 (61.8%) had bone metastasis. Furthermore, brain, liver, and adrenal metastasis were reported in 558 (73.3%), 678 (89.1%), and 607 (79.8%) participants, respectively (Table 6).

Table 6: Baseline clinical characteristics among the study population

Variables		Number	Percentage
Location of tumour	Right lung	468	61.5
	Left Lung	293	38.5
Lobe affected	Upper	410	53.8
	Middle	69	9.1
	Lower	282	37.1
Pleural invasion	Present	548	72.1
	Absent	213	27.9
Vessel invasion	Present	355	46.6
	Absent	406	53.4
Site of metastasis	Bone metastasis	470	61.8
	Brain metastasis	558	73.3
	Liver metastasis	678	89.1
	Adrenal metastasis	607	79.8
ECOG Score	1	313	41.1
	2	313	41.1
	3	133	17.5
	4	2	0.3

ECOG-Eastern Cooperative Oncology Group

BIOCHEMICAL CHARACTERISTICS

Haemogram

The mean hemoglobin was 12.04 (± 5.69), ranging from 4.9 to 149 g/dl. The mean leucocyte count was 434.7 (± 340.45), ranging from 6.5 to 3080 cells/cu.mm (Table 7). The mean neutrophil count was 73.79 (± 13.34), ranging from 7.74 to 97%. The mean lymphocyte count was 19.66 (± 10.98), ranging from 2% to 85%. The mean platelet count was 328 (± 138.2), ranging from 0.84 to 900 cells/cu.mm.

The mean serum protein was 6.8 (± 1.17) g/dl. The mean serum albumin was 3.48 (± 0.65) (Table 7). The mean serum globulin was 3.48 (± 0.74), ranging from 1.28 to 9.25 g/dl. The mean serum creatinine was 0.97 (± 0.62) mg/dl (Table 7).

Table 7. Haemogram of the study participants

Variables		**N**	**Mean**	**S.D.**
Haemogram	Haemoglobin	664	12.04	5.69
	Total leucocyte count	664	434.70	340.45
	Neutrophil count	664	73.79	13.34
	Lymphocyte count	664	19.66	10.98
	Platelet count	664	328.00	138.20
Protein count	Serum protein	530	6.80	1.17
	Serum albumin	537	3.48	0.65
	Serum globulin	519	3.48	0.74
	Serum creatinine	664	0.97	0.62

Liver function markers

The mean serum bilirubin was 1.76 (± 17.05), ranging from 0.1 to 370.3 mg/dl. The mean AST (SGOT) was 38.38 (± 111.54), ranging from 0.1 to 2437 mg/dl. The mean ALT (SGPT) was 33.78 (± 43), ranging from 4.48 to 522 mg/dl. The mean serum alkaline phosphatase was 131.4 (± 96.01), ranging from 0.5 to 1088 mg/dl. (Table 8) The mean serum calcium was 8.84 (± 1.16), ranging from 3.6 to 11.3 mg/dl. The mean serum phosphorus was 3.19 (± 1.2), ranging from 0.54 to 5.7 mg/dl. The mean serum sodium was

133.41 (± 5.92), from 109 to 148 mg/dl. The mean serum potassium was 4.13 (± 0.6), ranging from 2.29 to 6.5 mg/dl (Table 8).

Table 8. Liver function markers of the study population

Variables		N	Mean	S.D.
Liver function markers	Serum bilirubin	522	0.76	0.79
	AST (SGOT)	548	38.38	111.54
	ALT (SGPT)	555	33.78	43.00
	Serum alkaline phosphatase	664	131.40	96.01
	Serum calcium	116	8.84	1.16
	Serum phosphorous	16	3.19	1.20
S. Electrolytes	Serum Sodium	506	133.41	5.92
	Serum Potassium	507	4.13	0.60

Comorbidities

Hypertension (n=210, 27.6%) and diabetes (n=190, 25.0%) were reported in more than one-quarter of the study participants. Further, 126 participants (16.6%) reported other cardiac diseases. Dyslipidemia and renal disease were prevalent in 5.1% and 4.1% of the study population, respectively. Eighty-one patients (10.6%) reported a history of TB, and 175 (23.0%) had COPD (Table 9).

Table 9. Comorbidities of study participants

Comorbidities	Frequency	Percent
Hypertension	210	27.6
Diabetes mellitus	190	25.0
Dyslipidemia	39	5.1
Renal disease	26	4.1
Cardiac disease	126	16.6
History of MI	15	2.0
History of stroke	17	2.2
Respiratory disease	28	3.7
Asthma	12	1.6
TB	81	10.6
COPD	175	22.9

BEHVAIOURAL CHARACTERISTICS

Smoking and alcohol consumption history

Among the participants, 257 (33.8%) were nonsmokers, 219 (28.8%) were current smokers, 202 (26.5%) were past smokers, and 83 (10.9%) patients' data were not available (Table 10). The mean duration of smoking was 25.32 (± 10.59), ranging from 2 to 60 years. Among the study population, 465 (61.1%) did not report alcohol consumption. However, 205 (26.9%) participants reported consumption of alcohol. Alcohol data were not available in 91 (11.9%) participants.

Table 10. Smoking and alcohol consumption history (n=761)

Variables		Frequency	Percent
Smoking history	Non-smoker	257	33.8
	Current smoker	219	28.8
	Past smoker	202	26.5
	Data not available	83	10.9
Consumption of alcohol	Yes	205	26.9
	No	465	61.1
	Data not available	91	11.9

TREATMENT HISTORY DETAILS

Chemotherapy

Nearly half (n=376, 49.4%) of the study population underwent chemotherapy (Table 11). Among those who underwent chemotherapy, 191 (25.1%) and 183 (24.0%) had definitive and palliative chemotherapy, respectively. Two (0.3%) participants underwent neo-adjuvant chemotherapy, and another two participants (0.3%) had adjuvant chemotherapy. Paclitaxel (18.5%), carboplatin (30.2%), etoposide (8.8%), cisplatin (6.3%), pemetrexed (8.4%), gemcitabine (5.4%), vinorelbine (0.3%), and docetaxel (1.8%) were the main agents used in chemotherapy.

Table 11. Chemotherapy details

Variables		Frequency	Percent
Chemotherapy	Yes	376	49.4
	No	323	42.4
	Data not available	62	8.2
Type of chemotherapy	Definitive chemotherapy	190	25.1
	Palliative chemotherapy	182	24.1
	Neo-adjuvant chemotherapy	2	0.3
	Adjuvant chemotherapy	2	0.3
Chemotherapy drugs given	Paclitaxel	141	18.5
	Carboplatin	230	30.2
	Etoposide	67	8.8
	Cisplatin	48	6.3
	Pemetrexed	64	8.4
	Gemcitabine	41	5.4
	Docetaxel	14	1.8
	Gefitinib	75	9.9

Surgical treatment

In total, 52 (6.8%) patients underwent surgical treatment (36 lobectomies, four bi-lobectomy, two pneumonectomies, eight sleeve resections, and two wedge resections) (Table 12).

Table 12. Surgical treatment details

Variables		Frequency	Percent
Surgical treatment	Yes	52	6.8
	No	611	80.3
	Data not available	98	12.9
Type of surgical treatment	Lobectomy	36	4.7
	Bi-lobectomy	4	0.5
	Pneumonectomy	2	0.3
	Sleeve resection	8	1.1
	Wedge resection	2	0.3

Radiation

In total, 171 (22.5%) patients underwent radiation therapy (Table 13). Most of them (n=96, 12.6%) reported palliative treatment. Definitive therapy was reported in only three patients.

Table13: Radiation details

Variable		Frequency	Percent
Radiation	Yes	171	22.5
	No	500	65.7
	Data not available	90	11.8
Type of radiation	Palliative	142	18.6
	Definitive	3	0.4
	Prophylactic – cranial	2	0.3
	Adjuvant	18	2.4
	Concurrent	6	0.8

SURVIVAL ANALYSIS

All-cause mortality rate

The all-cause mortality rate per 100 person-months was 6.38, with a maximum at stage 4 contributing 10.01 events per 100 person-months (Table 14). In stage 1 disease, the all-cause mortality rate was only 0.7 per 100 person-months.

Table 14: Mortality event rate per 100-person months

Mortality event rate per 100 person-months (CI-95%)	
Overall	6.38 (3.03 - 12.97)
Stage 1	0.72 (0.1 - 4.99)
Stage 2	2.37 (0.72 - 7.54)
Stage 3	2.72 (0.88 - 8.05)
Stage 4	10.01 (5.53 - 17.44)

The number of deaths in the study population at the end of six months was 304. The cumulative mortality event in two years was 572 (75.1%).

Table 15: Mortality rate among the study participants

Mortality at the end of	Number of events	Percentage
Six months	304	39.95%
One year	440	57.82%
Two years	572	75.16%

Survival Analysis of Lung Cancer Patients

The median survival time was 8.57 (± 0.61) months, ranging from 7.38 to 9.75 months (Table 16).

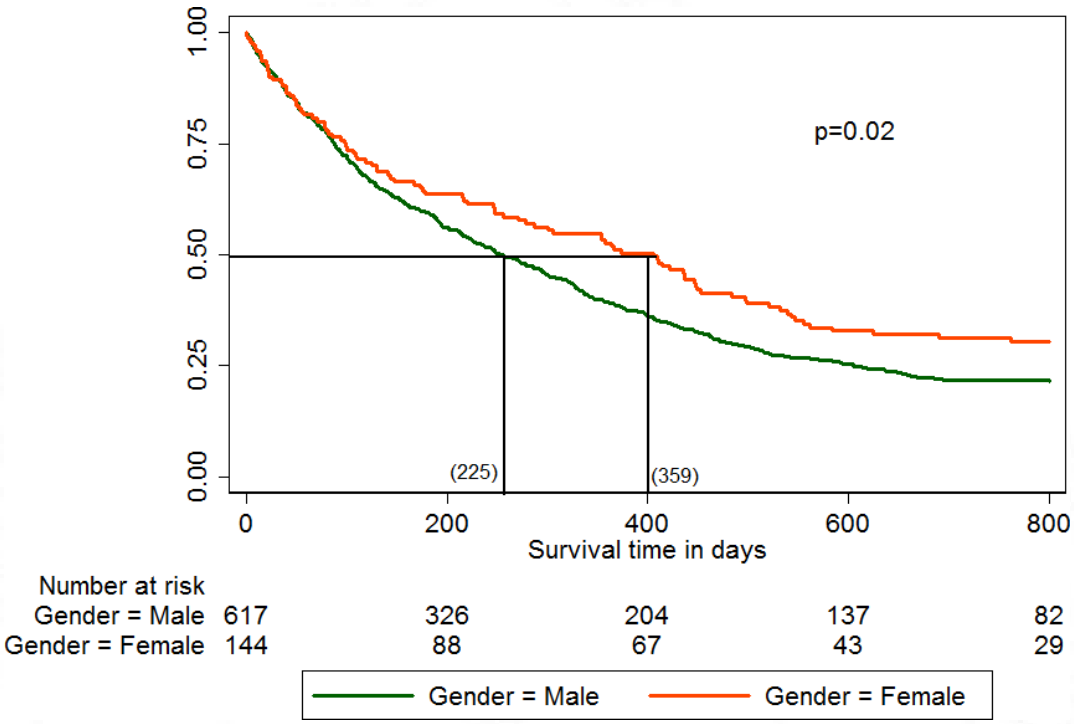
Table16. Median survival time of lung cancer patients

Median survival time (months)			
Estimate	**Std. Error**	**95% Confidence Interval**	
		Lower Bound	**Upper Bound**
8.567	0.606	7.380	9.754

Gender and Survival probability

The overall survival was better for women than men (Figure 8). Women had a median survival of 359 days, whereas males had 225 days.

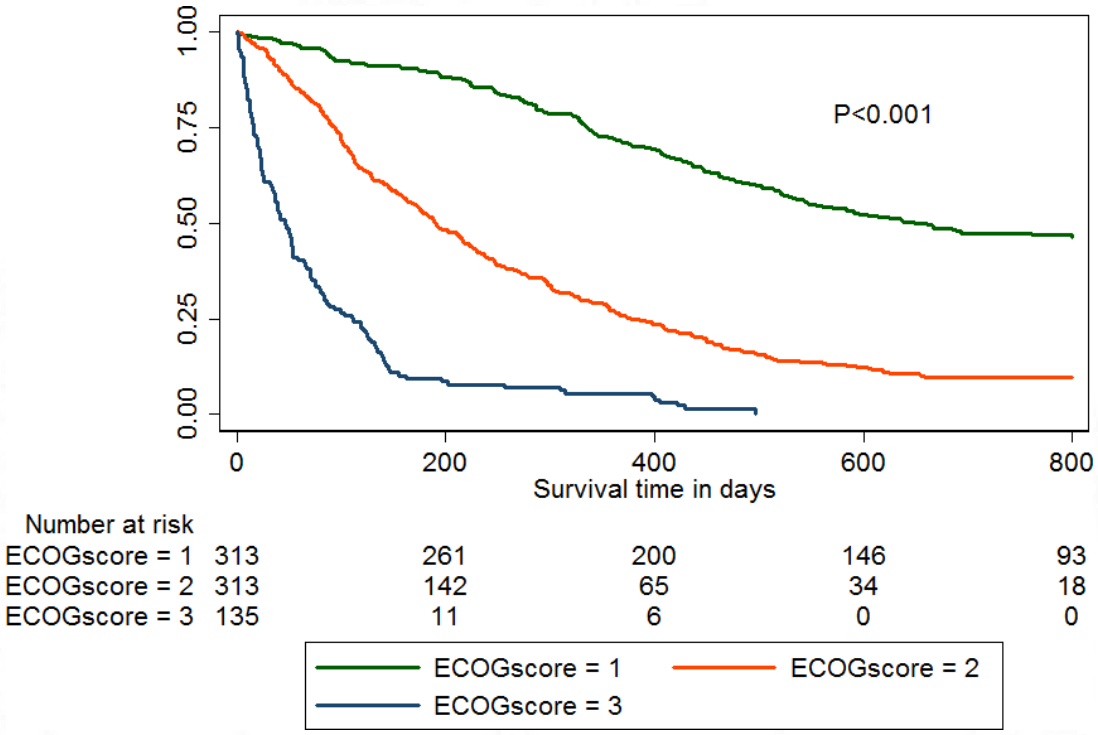
Figure 8: Gender and survival probability



ECOG Performance Score and Survival Probability

Overall survival was lowest in participants with an ECOG score of three (Fig 9) compared to ECOG scores 1 and 2 (log-rank p<0.001).

Figure 9: ECOG Score and survival probability

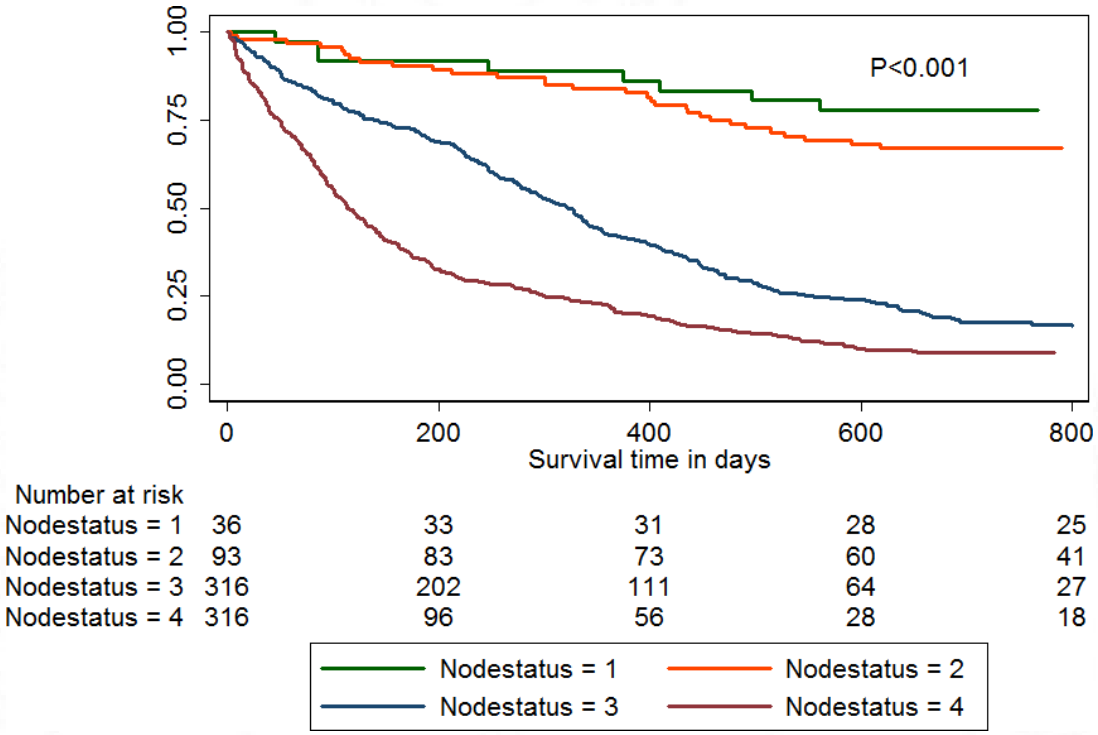


ECOG-Eastern Co-operative Oncology Group

Lymph node status and survival probability

The survival probability was lowest in individuals with lymph node status 4 (Fig 10) as compared to lymph node status 1, 2, and 3 (log-rank p<0.001).

Figure 10: Lymph node status and survival probability

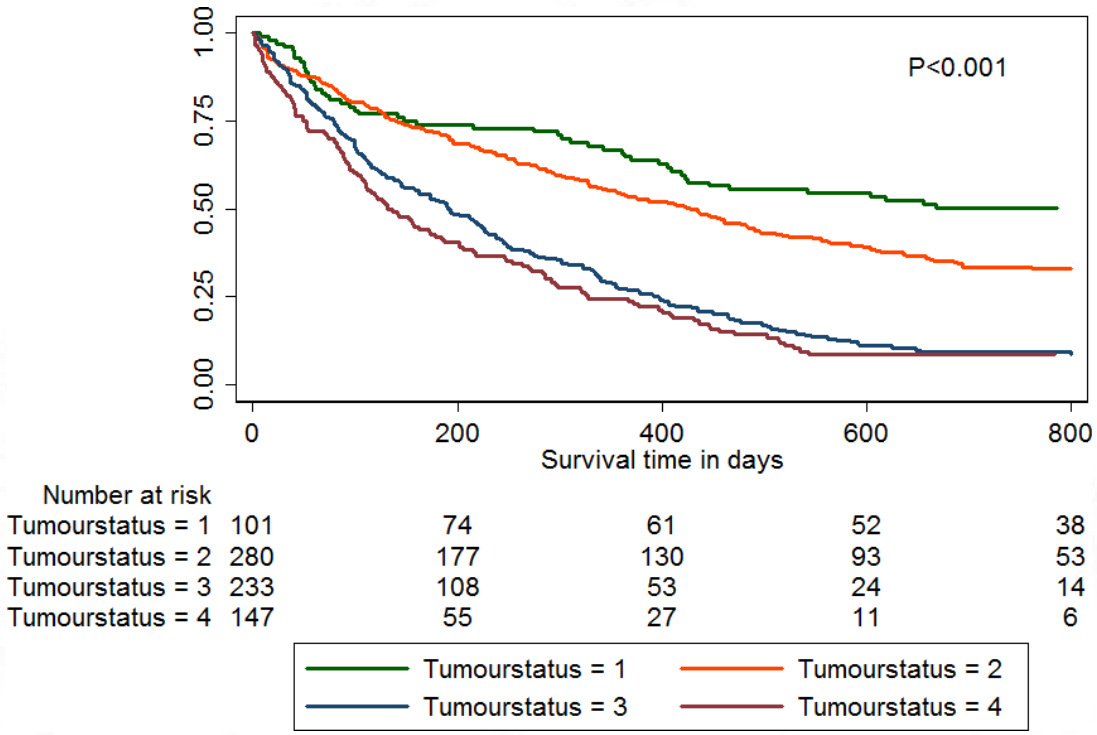


Node involvement 1- single lymph node affected, 2- two lymph nodes affected

Tumour stage and survival probability

As the size of the tumour increased from status 1 to 4 (Fig 11), the survival probability decreased (log-rank p<0.001).

Figure 11: Tumour stage and survival probability

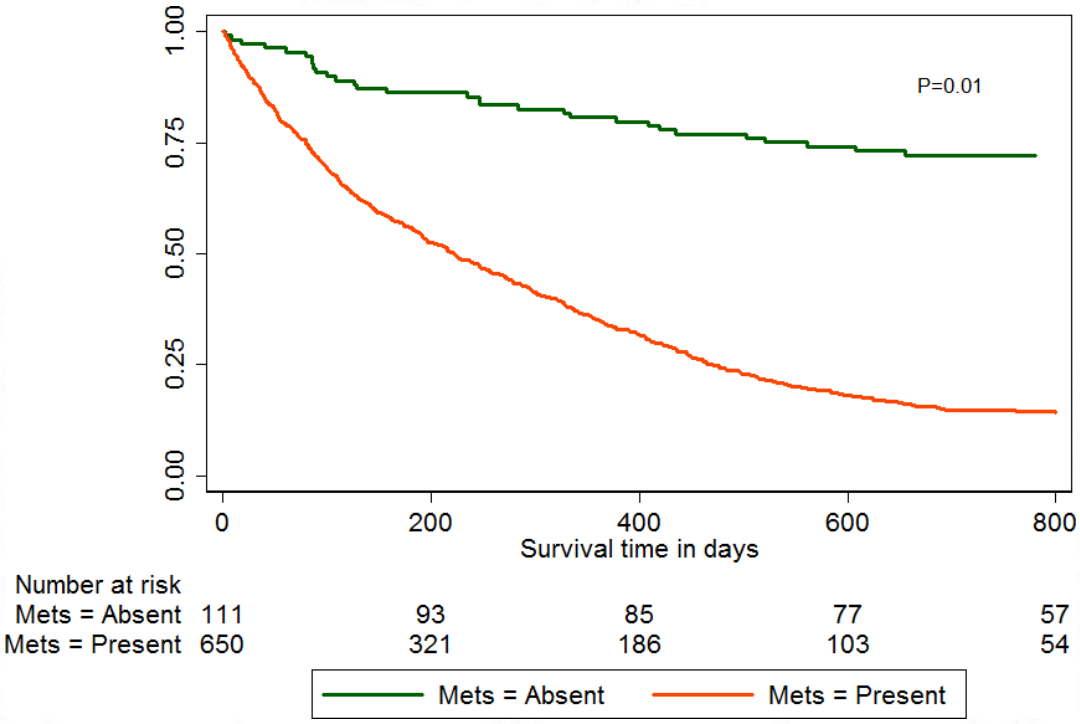


Tumour status 1- tumour stage 1 according to the size of the tumour

Metastasis and survival probability

Participants without metastasis had better survival (Fig 12) than participants with metastasis (log-rank p=0.01).

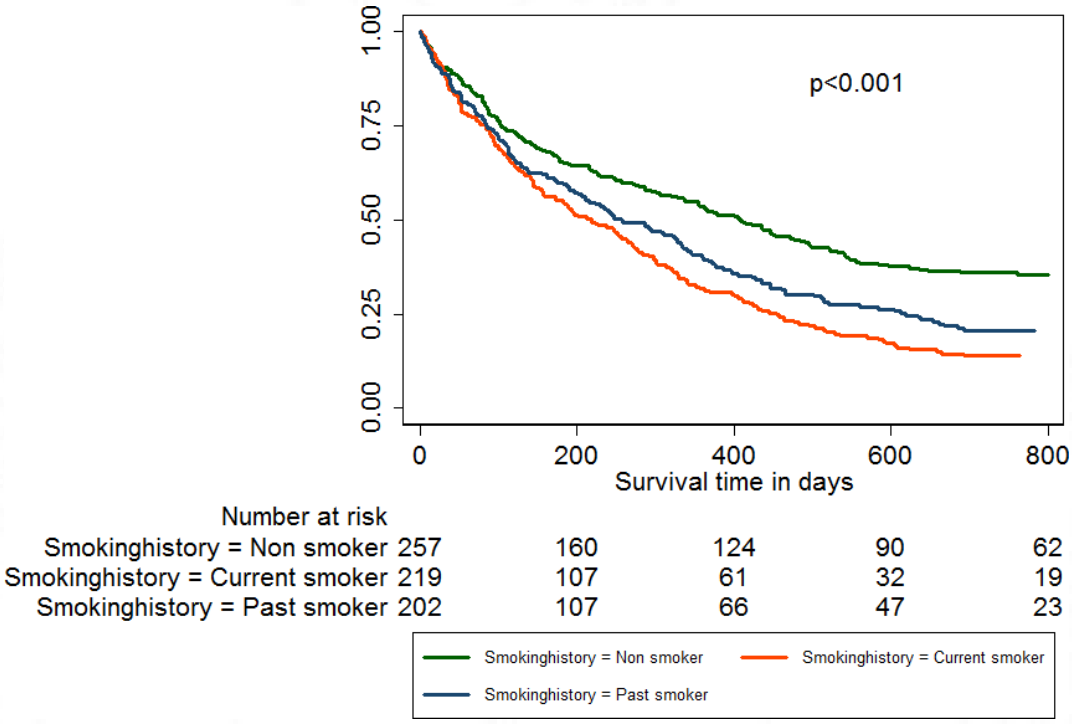
Figure 12: Metastasis and survival probability



Smoking history and survival probability

Current smokers had worse survival (Fig 13) compared to past smokers and non-smokers (log-rank p<0.001).

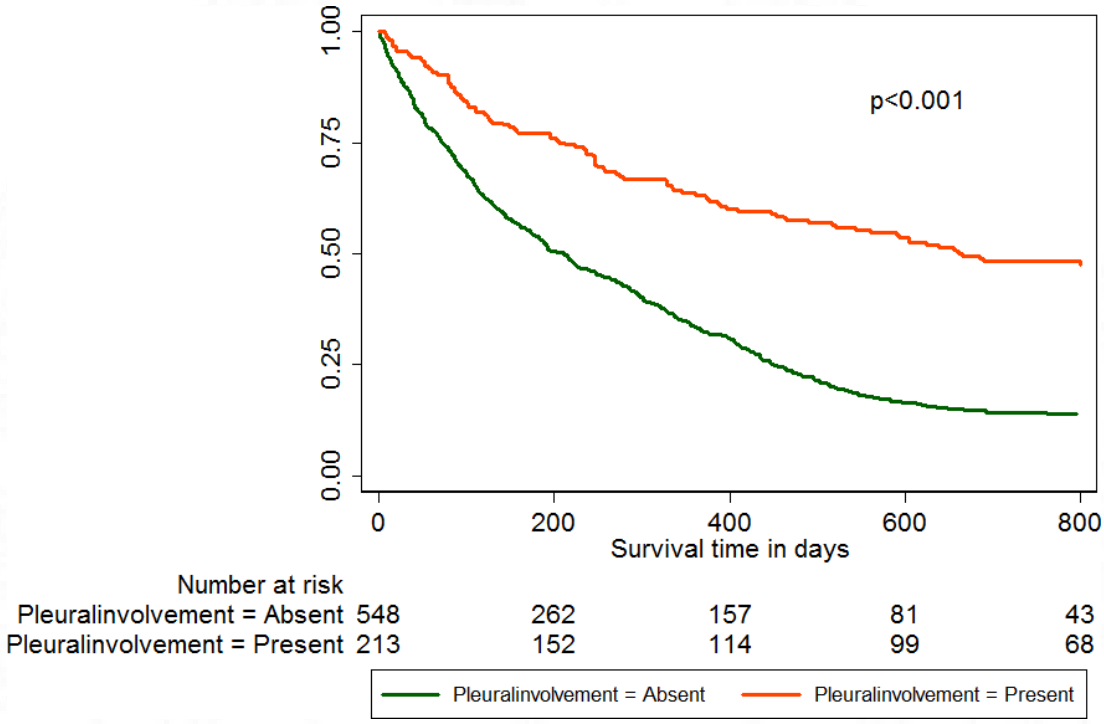
Figure 13: Smoking history and survival probability (n=678)



Pleural involvement and survival probability

Pleural involvement substantially reduced the overall survival (Fig 14) compared to individuals without pleural involvement (p<0.001).

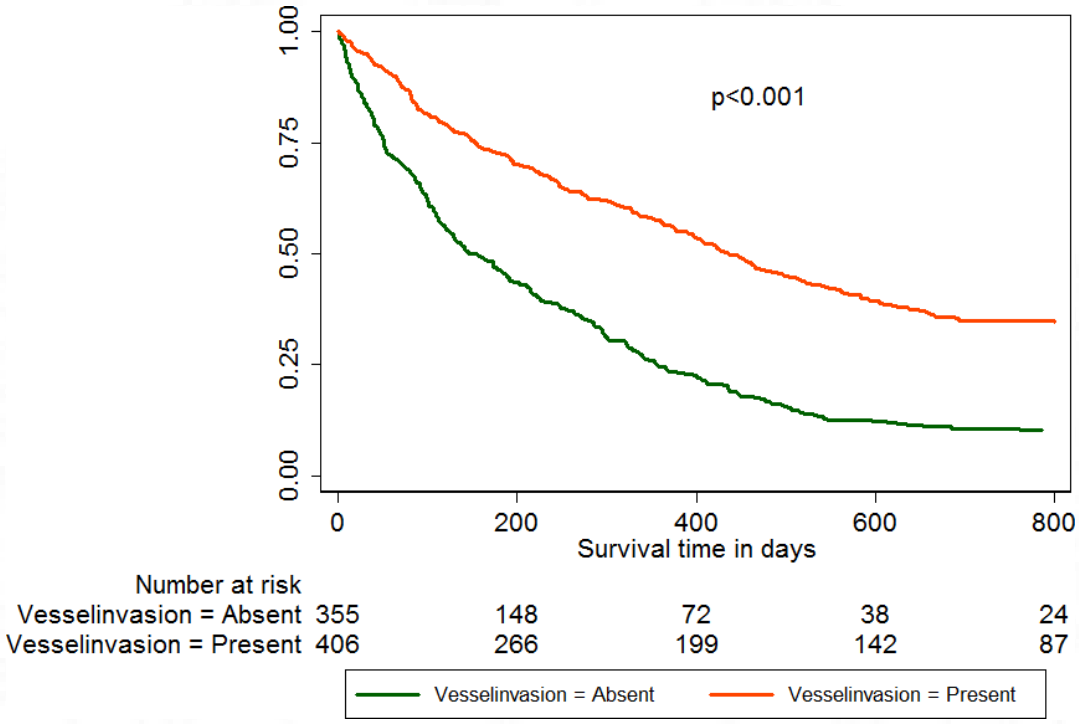
Figure 14: Pleural involvement and survival probability



Vessel Invasion and survival probability

Individuals with vessel invasion reported worse survival outcomes (Fig 15) compared to individuals without vessel invasion (log-rank p<0.001).

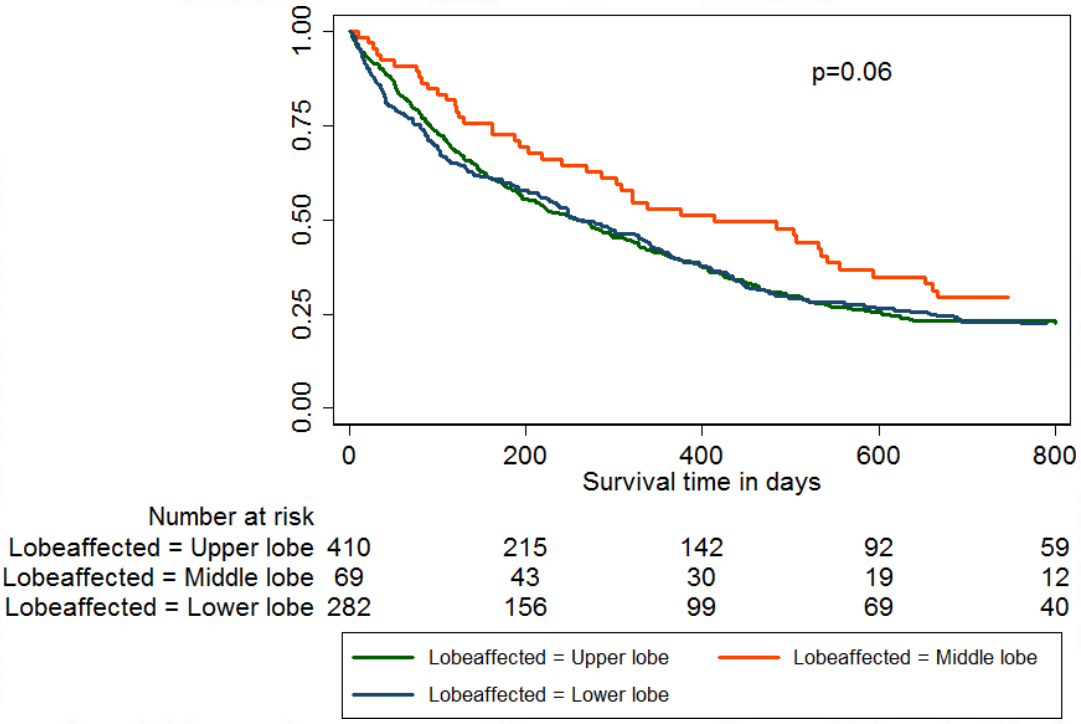
Figure 15: Vessel Invasion and survival probability



Lobe affected and survival probability.

Among the study participants, there was no significant difference in the survival probability and lobe affected in terms of upper, middle, or lower lobe (Fig 16).

Figure 16: Lobe affected and survival probability



Cox Regression for predicting survival of lung cancer patients

Males showed higher mortality risk with an unadjusted HR of 1.32 (p = 0.01) compared to females (Table 17). However, in the multivariable Cox-PH model (Table 18), this association was statistically non-significant after adjustment for other variables (Adjusted HR = 1.12, p = 0.39). Current smokers exhibited an increased risk of mortality compared to non-smokers with an HR of 1.54 (p = 0.001), which remains non-significant after adjustment for other variables (Adjusted HR = 1.03, p = 0.84). Past smokers showed an elevated risk for mortality compared to non-smokers, with an HR of 1.3 (p = 0.01). However, this association remained non-significant statistically after adjustment for other variables (Adjusted HR = 1.04, p = 0.77). The mortality risk was lower in large cell carcinoma with an HR of 0.3 compared to adenocarcinoma (p = 0.03), which remained non-significant after adjustment for other variables (Adjusted HR = 0.7, p = 0.54). The mortality risk was, however, higher in small cell carcinoma with an HR of 1.57 (p = 0.004). After adjustment, this association was statistically non-significant (Adjusted HR = 1.24, p = 0.18). Squamous cell carcinoma and undifferentiated tumours showed no difference in mortality compared to adenocarcinoma (Adjusted HR-0.6 CI: 0.7-0.54, p= 0.54)

T2, T3, and T4 stages were linked with an increased risk for all-cause mortality compared to T1, with HRs ranging from 1.49 to 3.41 (p < 0.01). The N2 and N3 stages were also linked with a greater risk for all-cause mortality than Nx, with HRs ranging from 6.94 to 11.92 (p < 0.01). Patients with metastasis were relatively at increased risk for all-cause mortality compared to patients without metastasis (HR of 2.44, p = 0.001). However, this association became non-significant after adjustment for other variables (Adjusted HR =

1.19, p = 0.13). Tumour size (tumour size increases by one cm, the hazard of mortality increases by 1%) and the number of metastatic sites were associated with a greater risk for all-cause mortality (p < 0.001).

Table 17. Cox-proportional hazard model of mortality in lung cancer (unadjusted Hazard Ratio)

Variables		**N(%)/mean (SD)**	**Unadjusted hazard ratio**	**95% CI**	**P value**
Age in completed years		65 (10.2)	1.02	1.01-1.03	0.001
Sex	Female	144 (18.9)	1		
	Male	617 (81.1)	1.32	1.06-1.65	0.011
Religion	Christian	260(34.1)	1		
	Hindu	292(38.3)	0.91	0.15-5.61	
	Muslim	209(27.4)	0.92	0.15-5.20	0.621
Consumption of alcohol	No	465(69.4)	1		
	Yes	205(30.6)	1.45	1.20-1.75	<0.001
Smoking history	Nonsmoker	340 (44.7)	1		
	Past smoker	202 (26.5)	1.32	1.06-1.59	0.010
	Current smoker	219 (28.8)	1.54	1.27-1.87	0.001
No of symptoms		2.3 (0.9)	1.14	1.05-1.25	
BMI		21.3(3.4)	0.91	0.89-0.95	<0.001
Number of metastatic sites		0.9 (0.8)	1.85	1.69-2.02	0.001
Vessel invasion	Absent	405(53.2)	1		
	Present	355(46.6)	2.29	1.93-2.71	<0.001
Pleural involvement	Absent	213(27.9)	1		
	Present	548(72.0)	2.49	2.02-3.01	<0.001

Lymph node status	Nx	36 (4.7)	1		
	N1	93(12.2)	1.95	0.91-4.19	
	N2	316(41.5)	6.94	3.43-14.05	<0.001
	N3	316(41.5)	11.92	5.89-24.13	
ECOG PS		1.7 (0.7)	3.51	3.09-3.97	
Tumour size in cms		5.8(14.8)	1.01	1.01-1.02	<0.001
Histological type	Adeno ca	429(56.3)	1		
	Large cell ca	9 (1.1)	0.31	0.10-0.93	
	Small cell ca	56(7.3)	1.57	1.16-2.13	0.003
	Squamous cell ca	196(25.7)	1.06	0.87-1.29	
	Undifferentiated	71(9.3)	1.31	1.0-1.73	
TNM stage	Stage1	42(5.5)	1		
	Stage2	72 (9.5)	0.82	0.23-2.95	
	Stage3	76 (10.0)	0.41	0.09-1.88	<0.001
	Stage4	571 (75.0)	0.88	0.25-3.12	

SD-Standard Deviation; CI-Confidence Interval; BMI-Body Mass Index; ECOG PS-Eastern Cooperative Oncology Group Performance Status

Table 18. Cox-proportional hazard model of mortality in lung cancer (adjusted HR)

Variables		**N(%)/mean (SD)**	**Adjusted hazard ratio**	**95% CI**	**P value**
Age in completed years		65 (10.2)	1.02	1.01-1.03	0.001
Sex	Female	144 (18.9)	1		
	Male	617 (81.0)	0.95	0.59-1.51	0.821
Consumption	No	465(69.4)	1		

of alcohol	Yes	205(30.6)	1.25	0.89-1.75	0.192
Smoking history	Nonsmoker	340 (44.7)	1		
	Past smoker	202 (26.5)	1.04	0.82-1.31	0.771
	Current smoker	219 (28.8)	1.03	0.79-1.34	0.845
No of symptoms		2.32 (0.9)	1.10	0.95-1.27	0.192
Number of metastatic sites		0.97 (0.8)	1.46	1.16-1.84	0.001
Vessel invasion	Absent	406 (53.2)	1		
	Present	355(46.6)	1.29	1.07-1.55	0.007
Pleural involvement	Absent	213(27.9)	1		
	Present	548(72.0)	1.19	0.95-1.51	0.13
Lymph Node status	N0	32(4.2)	1		
	N1	93(12.2)	1.51	0.69-3.25	0.30
	N2	316(41.5)	3.05	1.47-6.31	0.003
	N3	316(41.5)	4.52	2.16-9.37	0.001
ECOG PS		1.77 (0.7)	2.16	1.74-2.68	0.002
Tumour size in cms		5.86 (14.7)	1.07	1.01-1.12	0.02
Histological Type	Adenoca	429(56.3)	1		
	Large cell ca	9(1.2)	0.71	0.22-2.24	0.54
	Small cell ca	56(7.4)	1.24	0.91-1.71	0.18
	Squamous cell ca	196(25.8)	1.12	0.91-1.37	0.27
	Undifferentiated	71(9.3)	1.14	0.86-1.52	0.35

SD-Standard Deviation; CI-Confidence Interval; ECOG PS-Eastern Cooperative Oncology Group Performance Status

In the multi-variable Cox PH model, after adjustment for all other variables, the number of metastatic sites, vessel invasion status, lymph node status, ECOG PS, and tumour status were associated with all-cause mortality. With an increasing number of metastatic sites,

all-cause mortality was increased by 29 percent (HR=1.29, 95% CI 1.15-1.45, p=0.001),

and if vessel invasion by the tumor was present all-cause mortality was increased by 29% (HR=1.29, 95% CI 1.07-1.55, p=0.007). With increasing lymph node involvement, all- cause mortality increased by 50% (HR=4.52, 95% CI 1.47-2.68, p=0.001). A unit increase in ECOG performance status score increased all-cause mortality two times (HR=2.16, 95% CI 1.74-2.68, p=0.002). Each centimetre increase in tumor size was associated with a seven percent increase in all-cause mortality (HR=1.07, 95% CI 1.01-1.12, p=0.02).

5 DISCUSSION

The study's main aim is to assess the survival rates and the predictor variables of mortality outcomes among lung cancer patients in Kerala.

We enrolled 761 patients with primary lung cancer in the registry. The proportion of study participants who lost to follow-up was only 8%. The mean age was around 65 years, with most patients in the age group between 55 and 75 years. Although we observed male preponderance, one in five participants was female.

The mean age of lung cancer in India is substantially lower than that of high-income countries. However, over the past 2-3 decades, there has been an increase in the mean age of diagnosed lung cancer patients in India. Our findings concur with more recent findings from India, where the mean age at diagnosis was 65 years. This increase in mean age may be attributed to a better quality of life and longevity among the Indian population.

The male preponderance in lung cancer is well known. In a study in Kashmir, India, most study participants were males (92%). (Khan et al., 2006) A similar pattern of

predominantly male participants (83%) was also observed in a study conducted in a tertiary care centre. (Mohan et al., 2020) The male-to-female ratio was 3.5:1 in another study. (Noronha et al., 2012). The incidence of disease among females is increasing in India, which may be owing to risk factors of cancer other than smoking. In terms of histological type, adenocarcinoma was the most common pathologic type among males and females, followed by squamous cell and small-cell carcinoma. In a study done among hospitalized patients from Kashmir (Khan et al., 2006), the most prevalent histological type of tumor in both genders was SCC, followed by adenocarcinoma. Among smokers, the predominant histological subtypes of lung cancer were SCC and small cell carcinoma. It is observed that the prevalence of SCC (smoker's lung cancer) has been reduced, and other variants are increasing, which may be because of other risk factors of lung cancer. In a study based on the National Cancer Registry Programme, adenocarcinoma was the most common histological type of lung cancer, comprising 34% of cases in males. In females, adenocarcinoma constituted over half of the lung cancers, while SCC accounted for 11% of cases (Nath et al., 2022). These findings are consistent with our study.

In our study, stage four disease was observed in more than two-thirds of study participants at diagnosis. Tumour stages of T2 and T3 were observed in less than one-third of the participants. Around half of the participants had lymph node involvement of N2, and metastasis was present in more than 85% of subjects, with common sites being the liver, brain, and adrenal glands. Delayed diagnosis and advanced stage of disease at diagnosis are reported in several other studies from India. A study conducted in Delhi showed that in NSCLC cases, 57% were diagnosed with stage IV, while among SCLC cases, 72% presented with stage IV disease. (Rawat et al., 2009) In another study conducted in Uttarakhand, around 75% were detected at later stages of the disease (Stage 3B and 4). (Rawat et al., 2009). In India, lung cancer is often diagnosed at an advanced stage due to

the absence of screening and late presentation of the disease. Screening for lung cancer is not part of the National Program for Non-Communicable Diseases (NP-NCD), which may contribute to the higher number of cases diagnosed at a late stage. The screening tools used in HICs are not suitable for people in LMICs as communicable diseases may mimic lung cancer findings. (S P Blagden et al., 2003)

The median survival time among our study population was nine months, with 25% dying within three months and 60% within one year. In our survival analysis, the presence of bone or brain metastasis, squamous or undifferentiated carcinoma, pleural involvement, vessel invasion, and the advanced stage of cancer were predictors of time to mortality. In a study conducted at the Cancer Institute in Chennai, India, the median time of progression-free survival was around seven months, and overall survival was around eight months for subjects with NSCLC (Murali et al., 2017). For patients with small-cell lung cancer, the median time of progression-free survival was six months, and overall survival was 7.2 months. Upon multivariable analysis, factors associated with poor overall survival in NSCLC included non-adenocarcinoma histology, performance status greater than 2, and advanced stage of disease. In small-cell lung cancer, an earlier stage of presentation and younger age were associated with considerably better survival. (Murali et al., 2017). As the disease is often diagnosed at a later stage, the median survival is low in lung cancer patients from India. A critical factor for late diagnosis of this disease is late presentation. Symptoms/signs of the disease are primarily present after metastasis. Patients stay asymptomatic at an early stage of the disease, and this prevents opportunistic screening for lung cancer.

In our study participants the mortality rate at two years was 75.2%. In a study among 151 lung cancer patients, the mortality rate at two years was 66% (Said and Degu, 2023). The

median time of histological type-specific survival time was 18 months (Said and Degu, 2023), which is higher than that in our study population. Our survival rate was much lower than that reported from high-income countries (Murali et al., 2017). Similar findings are reported from studies conducted in other low and middle-income countries. Bogere et al., in 2022, reported an 88% mortality at two years in lung cancer patients in Uganda with a median survival time of 4.4 months. The differences in mortality across regions may be attributable to active screening approaches among high-risk populations and early diagnosis, the availability of better treatment facilities, and disease management modalities in high-income settings.

In lung cancer treatment, various strategies have been emerged. Neoadjuvant therapies, such as chemotherapy and radiation, are increasingly utilized to shrink tumors before surgery, improving the chances of successful resection. This approach not only targets the primary tumor but also addresses potential micrometastases, enhancing overall treatment outcomes. Immunomodulation has revolutionized lung cancer therapy by improving the body's immune system to recognize and destroy cancer cells. Checkpoint inhibitors like pembrolizumab and nivolumab have shown remarkable efficacy in certain subsets of patients, particularly those with PD-L1 expression, offering new hope for advanced or metastatic disease. Targeted therapies, directed at specific genetic mutations like EGFR or ALK, further personalize treatment, optimizing efficacy while minimizing side effects.

Survival research outcomes can differ due to a range of factors. These encompass variations in study populations stemming from regional demographics, lifestyle elements, and environmental factors. Discrepancies may also arise from distinctions in study design, diagnostic approaches, healthcare availability, and evolving trends in cancer treatment over time. Furthermore, reporting biases and statistical variations in small sample sizes can

affect the findings of survival studies. Therefore, it's essential to consider these factors when analyzing and contrasting survival data from different studies.

Limitations and Strengths

The registry data were extracted from patient records. Hence, data variables were limited, and the researcher did not have the choice to select variables for the study and adjust for pertinent confounding variables. Analysis was limited to one state of India, and the generalizability of the research findings is questionable as there is a huge difference in health indicators between South Indian and North Indian states. Relatively large sample size, representation of different regions of Kerala, multiple study sites, active follow-up till two years from the date of diagnosis, and an attrition rate of less than 10% are the key strengths of the study.

6 SUMMARY AND CONCLUSIONS

6.1.1 This study analyzed demographic and clinical characteristics among lung cancer patients, revealing several noteworthy findings and underscoring the multifaceted nature of the disease.

6.1.2 The predominance of males in the study aligns with existing literature, reflecting a gender disparity in lung cancer incidence. This observation emphasizes the importance of gender-specific considerations in disease management and the need for interventions targeting high-risk populations.

6.1.3 Histological subtype distribution, with adenocarcinoma and squamous cell carcinoma being the most prevalent, highlights the heterogeneity of lung cancer and the necessity of personalized treatment strategies based on tumour biology. Tumour localization predominantly affecting the right lung and upper lobes showed anatomical variability in disease presentation, influencing treatment planning and prognostication.

6.1.4 The high prevalence of metastatic spread and advanced disease stages at diagnosis emphasizes the challenges in early detection and the urgent need for improved screening modalities. The substantial proportion of patients with stage IV disease highlights the importance of integrating palliative care approaches into the management package to optimize symptom control and quality of life.

6.1.5 Treatment patterns varied, with chemotherapy being administered to many patients. However, the efficacy of chemotherapy varied, highlighting the need for individualized treatment approaches and the exploration of novel therapeutic modalities, including targeted therapies and immunotherapy, to improve treatment outcomes.

6.1.6 Survival analysis revealed a median survival time of 8.6 months, with females demonstrating a more prolonged median survival than males. Despite advances in treatment modalities, mortality rates remained high, with a significant proportion of patients experiencing disease progression and succumbing to the illness within six months or one year

6.1.7 The identification of predictors of mortality, including the age, number of metastatic sites, lymph node involvement, ECOG performance score, vessel invasion, pleural involvement, and tumour size, highlight the importance of comprehensive prognostic assessment in treatment decision-making.

6.2 RECOMMENDATIONS

Analyses of lung cancer patients' demographic and clinical characteristics offer valuable insights that can inform strategies for improving patient outcomes. Based on the findings of this study, the recommendations are:

6.2.1. Given the high prevalence of advanced-stage disease at diagnosis, there is a critical need to enhance efforts aimed at early detection and diagnosis of lung cancer. Public health initiatives should raise awareness about risk factors and symptoms, promote screening programs, and ensure timely access to diagnostic services.

6.2.2 The heterogeneity of lung cancer, as evidenced by the diverse histological subtypes and tumour characteristics observed in this study, highlights the importance of treatment approaches. Clinicians should prioritize molecular profiling and histological subtype testing to guide treatment decisions and optimize therapeutic outcomes. Additionally, efforts should be made to expand access to novel treatment modalities, such as targeted therapies and immunotherapy, particularly for patients with advanced disease.

6.2.3 Continued investment in lung cancer research is essential to drive innovation, advance scientific understanding, and improve diagnosis and treatment outcomes. Priority areas for research include the identification of screening tools and novel biomarkers, and the development of targeted therapies.

6.2.4 The findings indicate that a screening program for lung cancer must be incorporated into the national program so that early diagnosis and screening of high-risk groups can be ensured.

The above recommendations represent actionable strategies to improve lung cancer diagnosis, treatment, prevention, and supportive care. By implementing these recommendations in clinical practice and public health policy, stakeholders can work towards reducing the burden of lung cancer and improving the quality of life for affected individuals. Continued collaboration, innovation, and advocacy efforts are essential to effect meaningful change and improve outcomes for lung cancer patients.

6.3 WAY AHEAD

The following actions are in process consequent to the inferences derived from the study:

6.3.1 Building on the findings, national-level discussions have been initiated to develop and validate screening tools for lung cancer that leverage demographic and clinical characteristics to identify high-risk individuals for early detection

6.3.2 Exploration of targeted therapies for specific histological subtypes and molecular profiles of lung cancer is underway

6.3.3 The study highlights the need for expanding treatment options beyond conventional chemotherapy, emphasizing the importance of exploring novel therapeutic modalities, such as immunotherapy and targeted agents, to address the diverse needs of lung cancer patients.

6.3.4 The study emphasizes the need for a robust cancer registry in our country, especially longitudinal data for all highly prevalent cancers, to study the survival trends and plan further actions nationally.

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ANNEXURES

LIST OF PUBLICATIONS

1. Jose NK, Soman B, Thulaseedharan JV, Varghese BT, Thomas S, Tom JJ, et al. Demographic and clinical characteristics of primary lung cancer patients in Kerala: Analysis of data from six teaching centers. J Family Med Prim Care 2023;12:2501-6

2. Survival rates and predictors of mortality in lung cancer: a multi-centric study in Kerala IJCM_765_24 (in press)

CURRICULUM VITAE

PERSONAL PARTICULARS

Name : Nisha K Jose

Work Address:
Indian Council of Medical Research
Ansari Nagar
New delhi Pin: 110029
Mobile No: 09717660464

Home Address
Q 12, Tara Apartments
Alaknanda P O,
South Delhi, India. Pin: 110027
Mobile no:9495056174

Email : cathnisha@gmail,com

Date of Birth : 16/03/1978
Area of specialization : MD Community Medicine, PG Diploma Medical Ethics
Area of Interest : Non – Communicable Diseases

PROFESSIONAL EDUCATION

Year	Degree	Institution	University
2016	DNB Preventive and Social Medicine	National Board of Exams	National Board of Exams, Delhi
2015	MD Community Medicine	St. John's Medical College, Bangalore, India	Rajiv Gandhi University of Health Sciences, Bangalore, India
2014	Global Health	Global Health International Summer Program (full time student)	Ben Gurion University of Negev, Israel
2013	Post Graduate Diploma in Medical Law and Ethics	National Law School	National Law School of India University, Bangalore.
2008	Diploma in Religious Sciences	Carmel Jyothi Vidyabhavan	Pontifical Institute of Spirituality, Rome, Italy.
2006	MBBS	St. John's Medical College, Bangalore, India	Rajiv Gandhi University of Health Sciences, Bangalore, India
1996	Matriculation	Anitha Vidyalaya	Anitha Vidyalaya English

		English Medium School	Medium School, Kalady, Cochin, India

PROFESSIONAL EXPERIENCE

May 2006 – April 2007:	Compulsory Rotating Internship, St John's Medical College, Bangalore
March 2008- February 2009:	RMO in Vincent de Paul Hospital, Irinjalakuda, India
March 2009- February 2010:	CMO in MAGJ Hospital, Angamaly, India
March 2010 – December 2011:	Administrator in Marian Hospice, Nedumbassery, India
April 2012 – April 2015:	Tutor, St. John's Medical College, Bangalore, India
June 2015 – November 2015:	Assistant Professor, Amala Institute of Medical Sciences, Thrissur, Kerala
November 2015 – December 2017:	Surveillance Medical Officer, Sarguja Unit, National Public Health Surveillance Project, WHO
January 2018 – June 2019:	Assistant Professor, Amala Institute of Medical Sciences, Thrissur, Kerala
June 2019- May 2021:	Associate Professor, Amala Institute of Medical Sciences, Thrissur, Kerala
June 2021- till date	Scientist E (medical), ICMR, Hqrs

LICENSURE

Travancore-Cochin Medical Council (2015)

PAPERS/POSTORS GUIDED/CO-AUTHORED, AWARDS WON

1. **Guided** this paper and was awarded the **Best Paper Award** – Postgraduate category at National Conference on Postgraduate Medical Research, 2018
2. Prevalence of Triple Negative Breast Cancers from a Hospital Based Cancer Registry in a tertiary care hospital in Kerala, South India

Guided this paper and was awarded the **Best Paper Award** – Undergraduate category at South India workshop and conference, 2018

3. Trend Analysis of Cancers from an Institutional Based Cancer Registry In Kerala
   Guided this paper and was awarded the **Best Poster Award** – Undergraduate category at South India workshop and conference, 2018

MEMBERSHIP OF PROFESSIONAL ORGANIZATIONS / ASSOCIATIONS:

- Travancore-Cochin Medical Council, India
- Karnataka Association of Community Health, Bangalore, India
- Catholic Health Association of India (CHAI)
- Indian medical Association (IMA)

PUBLICATIONS

1. Neena Mary, **Catherin Nisha,** Kerline Jerome, Clint Vaz, Vijayalaxmi Nair. Prevalence of Triple Negative Breast Cancers from a Hospital-Based Cancer Registry in a Tertiary Care Hospital in Kerala, South India. Wor Jour of Pub Heal 2019;4(2): 43-46. doi: 10.11648/j.wjph.20190402.13.
2. Saju CR, **Catherin Nisha**, Jerry Rachel, Kerline Jerome, Subin Koshy, Vidhu J. Assessing risk factors of Non-Communicable Diseases using STEPS Survey in a rural area of Thrissur District, Kerala. Int Jour of Med Sci and Curr Resear. July-August 2019, (2) 4; 241-217
3. Shajan A, **Nisha C**. Anxiety and Depression among nurses working in a tertiary care hospital in South India. Int J Adv Med 2019;6:16115.
4. Ashlin Francy, **Catherin Nisha**, Joe Abraham. Prevalence of Shift Work Disorder among Nurses Working in a Tertiary Care Hospital in Thrissur District, Kerala, India. Inter Jour of Med Scien and Curr Rese. July-August 2019, 2(4); 320-325
5. Geetha K V, Sruthi M V, **Catherin Nisha**, Sesil Mariya, Vidhu Joshy. Health need assessment in an urban slum area of Thrissur District, Kerala, India. Indian Jour of Appl Resear. Nov – 2019; 9(11); 1-3.
6. Aswin M, **Catherin N**, Racheal J, Vaz C. Trend analysis of cancers from a hospital-based cancer registry in Kerala, India. Int J Non-Commun Dis 2020;5:11-5
7. Tom JJ, Vaz C, **Nisha C**. Screening for cervical dysplasia and reproductive tract infections in Kerala, India: A multicentric study. J Family Med Prim Care 2020;9:4107-11.
8. Iype RK, Vaz C, **Nisha C**. Survival rates among breast cancer patients from a hospital based Cancer registry, Thrissur, Kerala, India. J Surg Spec Rural Pract 2020;1:8-11.

9. Clint Vaz, **Nisha K. Jose**, Jeremiah Jacob Tom, Georgia R. Goodman, Jasper S. Lee, Rana Prathap Padappayil, Manjunath Madathil, Conall O'Cleirigh, Rashmi Rodrigues and Peter R. Chai. Formative acceptance of ingestible biosensors to measure adherence to TB medications. BMC Infectious Diseases 2022. 22:754.
10. **Jose NK**, Sruthi MV, Rachel J, Jerome K, Vaz C, Saju CR. Barriers and facilitators of noncommunicable disease (NCD) prevention in Kerala: A qualitative study. J Family Med Prim Care 2022;11:3109-14.
11. **Jose NK**, Vaz C, Chai PR, Rodrigues R. The Acceptability of Adherence Support via Mobile Phones for Antituberculosis Treatment in South India: Exploratory Study.JMIR Form Res 2022;6(5):e371 24.URL:https://formative.jmir.org/2022/5/e37124
12. **Jose NK**, Soman B, Thulaseedharan JV, Varghese BT, Thomas S, Tom JJ, et al. Demographic and clinical characteristics of primary lung cancer patients in Kerala: Analysis of data from six teaching centers. J Family Med Prim Care 2023;12:2501-6

FUNDED PROJECTS

1. 2018-2019: Principal Investigator: Acceptability of adherence support via mobile phones for anti-tuberculosis treatment in South India: An exploratory study. Funded by Tuberculosis Association of India, Delhi.
2. 2018-2019: Principal Investigator: Barriers and facilitators of NCD prevention in Kerala: A qualitative study. Funded by Government of Kerala, NCD Project.

PAPERS PRESENTED

1. Presented an oral paper on 'Demographic/ clinical/treatment characteristics of patients with primary lung cancer in Kerala' IAPSM CON, 3-5 March, 2022
2. .Presented an oral paper on 'Survival rates of primary lung cancer in Kerala-A multi centric study' IPHA CON, 23-25 September 2022

PROJECTS GUIDED:

1. Randomized control trial on skin to skin contact among mothers delivered in a rural maternity hospital, Karnataka, India.
2. Post-natal outcomes of MCH services provided by department of Community Health, St John's Medical College, Bangalore.
3. Prevalence of anxiety disorder among ante-natal mother attending a Taluk Hospital in South India
4. Absenteeism and its determinants among female plantation workers in South India

PG DISSERTATION: Title: "A Longitudinal Study of Morbidity among Nursing Assistants in a Tertiary Care Hospital in Bangalore."

Diploma Dissertation:

Indian spirituality and religious vows
Right to health as a human right
Ethical issues in palliative care and palliative care research

Technical Advisory Committee: TAC (AMCHSS)

Certificate of clearance

Title of the proposal: "Survival rates and predictors of mortality in lung cancer: a multi-centric study in Kerala"

***TAC-Registration No.*: AMCHSS /2020/6/021**

Principal Investigator (Name and address): Dr. Nisha K Jose, PhD student, AMCHSS, SCTIMST

*Coinvestigators/**Guide***: Dr Jeemon P, Assistant Professor, AMCHSS, SCTIMST

***Date of TAC Meeting**: Online review October23, 2020*

Reviewers: Dr Harikrishnan S, Dr R S Jayasree, Dr P S Sarma, Dr Ravi Prasad Varma and Dr Manju R Nair

Risk classification of the project: Minimum

Requirement of DSMB: Not required

Documents submitted:

1. Covering letter
2. TAC proposal
3. Participant information sheet
4. Consent form
5. Tool for screening for medical records

Documents reviewed: *All of the above*

Comments:

1. *The permissions from all the participating institutions are not attached*
2. *Page 8: The table provided does not indicate any primary data collection from patients, whereas it is mentioned in the proposal write up about telephonic interviews with patients. Please clarify*
3. *Study setting: Page 9, Section b mentions that hospitals are selected from three zones – north, central and south zones of Kerala. It is not clear which hospital is selected from the south zone*
4. *Is there an existing lung cancer registry? Page 10 mentions retrieval of file numbers from the hospital cancer registry? Please provide the details regarding the creation of the registry and whether it follows the NCDIR guidelines*

Recommendation for the consideration of IEC:

The principal investigator has responded to the comments satisfactorily and the proposal is cleared by the TAC

The research proposal is recommended for consideration by the IEC for expedited review.

Signature of Member Secretary:

Date: 17/11/2020

AMALA INSTITUTE OF MEDICAL SCIENCES

(An undertaking of Amala Cancer Hospital Society)
Amala Nagar, Thrissur - 680555, Kerala.

INSTITUTIONAL ETHICS COMMITTEE

REGISTRATION NO : ECR/653/Inst/KL/2014/RR-17
(Under Rule 122 DD of the Drugs & Cosmetics Rules 1945)

Decision of the Institutional Ethics Committee

AIMSIEC/2/2019

Dt. 18.02.2019

Protocol Title	Survival rates and predictors of mortality outcomes in lung cancer patients.
Principal Investigator	Dr.Nisha K.Jose, Assistant Professor of Community Medicine, Amala Institute of Medical Sciences, Thrissur
Guide	Dr.Jeemon P, Asst. Professor, SCTIMST.
Name and Address of the Institution	Amala Institute of Medical Sciences, Amala Nagar, Thrissur – 680 555, Kerala
Date of review	15.02.2019
Decision of the IEC • Approved • Pending revision • Rejected	Approved
Remarks	

- Inform IEC immediately in case of any adverse event.
- Inform IEC in case of any amendments to protocol, change of study procedure, site or investigator and premature termination of study with reasons.
- Six monthly and final reports to be submitted to IEC.

Member Secretary IEC

PRINCIPAL
AMALA INSTITUTE OF MEDICAL SCIENCES
AMALA NAGAR, THRISSUR-680 555

LISIE HOSPITAL
ERNAKULAM

INSTITUTIONAL ETHICS COMMITTEE

Registration No. : ECR/40/Inst/KL/2013/RR-16

LISIE/IEC/Jan-2020/01 **4 Feb 2020**

To,
Dr. Nisha K Jose (Sr. Catherene CMC)
Assistant Professor
Amala Institute of medical sciences
Trissur, Kerala

Ref: Survival Rates And Predictors Of Mortality Outcomes In Lung Cancer Patients.

Sub: Ethics Committee approval of the study documents for the above referenced study.

Dear Dr. Nisha K Jose,

We have received 13 copies of each of following study related documents from you with your letter-

No.	Documents
1.	Study Protocol
2.	Consent from Management
3.	Patient Information sheet (English)
4.	Questionnaire (English)

At the Ethics Committee meeting held on **28th Jan 2020**, your reference letter and the above documents were examined and discussed. After due consideration, the committee has decided to approve the conduct of the above mentioned study under your direction at **Lisie Hospital, P.B. #3053, Kochi – 682018, Kerala, India**.

Fax: 91-484-2403877, Phone: 2400812, 2400814, 2402044
Web: www.lisiehospital.org E-mail: contact@lisiehospital.org

LISIE HOSPITAL
ERNAKULAM

INSTITUTIONAL ETHICS COMMITTEE

Registration No. : ECR/40/inst/KL/2013/RR-16

The following members of the Ethics Committee were present in the meeting and were involved in the approval process of the above referenced study:

MEMBER'S NAME	DESIGNATION	GENDER	ROLE
Dr. Paul Puthooran	MBBS, MD	Male	Chairperson
Dr. Amel Antony	MD,DNB MNAMS	Male	Member secretary
Justice K. John Mathew	BSc Zoology BL	Male	Legal Person
Dr. Jabir Abdullakutty	MBBS, MD, DM	Male	Clinician
Dr. Sissy Thankachan	MBBS, MD	Female	Basic Medical Scientist
Dr. P P Mohanan	MBBS, MD, DM	Male	Clinician
Dr.Laliamma Jose	Msc. Phd	Female	Member
Rev.Fr.Dr.Joseph Kaniamparambil	B.Th, LPH,B.A Phd	Male	Theologian
Dr. T K Joseph	MD, FRCP	Male	Clinician
Dr. Usha Marath	PhD	Female	Member
Mr. Suresh Antony	SSLC	Male	Lay Person

It is also confirmed that neither you nor any of the study team members were present during the decision-making procedures of the Ethics Committee.

You are expected to report to the Ethics Committee the following:

- All deviations from, or changes to, the protocol to eliminate immediate hazards to the study subjects
- Changes that increase the risk to participating subjects and/or those that significantly affect the conduct of the study

Fax: 91-484-2403877, Phone: 2400812, 2400814, 2402044
Web: www.lisiehospital.org E-mail: contact@lisiehospital.org

- All serious adverse events
- New information that may affect adversely the safety of the subjects or the conduct of the study
- Any changes in the study document
- Progress of the study.

Also please provide a report to the Ethics Committee on the completion of the study.

Thanking You,

Yours sincerely,

Dr. Amel Antony
Member Secretary
Institutional Ethics Committee
Lisie Hospital, Kochi

Date: 4/Feb/2020

Dr. Amel Antony
Member Secretary
Institutional Ethics Committee
Lisie Hospital, Kochi, Kerala, Ind

ETHICAL COMMITTEE
LITTLE FLOWER HOSPITAL & RESEARCH CENTRE

P.O. Box No. 23 Angamaly - 683572
E-mail : enquiry@lfhospital.org, admin@lfhospital.org, Website : www.lfhospital.org
Tel:+91 484 - 2452546, 3096666, 3954000, Fax : +91 484 2452646

Decision of the Institutional Ethics Committee

Reg: Date .....

EC/22/2020

Dt.10.12.2020

Protocol Title	Survival rates and predictors of mortality in lung cancer: A multicentric study in Kerala
Principal Investigator	Dr.NishaK.Jose, Associate Professor, Amala Institute of Medical Sciences, Thrissur
Guide	Dr.Jeemon P, Assistant Professor, SCTIMST.
Name and Address of the Institution	Little Flower Hospital and Research Centre, SH 1, Angamaly, Kerala - 683572
Date of review	27.11.2020
Decision of the IEC Approved Pending revision Rejected	Approved
Remarks	➢ Inform IEC immediately in case of any adverse event ➢ Inform IEC in case of any amendments to protocol, change of study procedure, site or investigator and premature termination of study with reasons. ➢ Six monthly and final reports to be submitted to IEC

Fr. Shijo Konuparamban

Secretary IEC

MALABAR CANCER CENTRE

(an autonomous centre under Government of Kerala)

P. O. Moozhikkara, Thalassery,
Kannur - 670 103, Kerala, S. India

4772

Tel +91 490 2355881
Fax · +91 490 2355880
E-mail · mcctly@gmail.com
Website : www.mcc kerala.gov in

No. 1617/IRB-IEC/13/MCC/26-11-2020/ 6

Date: 22nd December 2020

DCG(I) Reg. No: ECR/780/Inst./KL/2015/RR-19

To

Dr Nisha K Jose
Associate Professor
Amala Institute of Medical Sciences
Thrissur, Kerala

Subject: IEC Approval Letter-Reg

Dear Dr Nisha,

The Institutional Ethics Committee reviewed and discussed your application dated 19th November 2020 to conduct the research study entitled "*Survival rates and predictors of mortality in lung cancer: A multi-centric study in Kerala*" during the Institutional Ethics Committee meeting held via tele -conferencing(Zoom meeting) on 26th November 2020 at 2 pm

The following documents were reviewed and approved

1. Study Protocol dated 19.11.2020
2. Investigator's Undertaking dated 19.11.2020
3. Patient information sheet and consent form dated 19.11.2020
4. CV, GCP certificate of Principal investigator and Co-investigators dated 19.11.2020

The following members of the IEC-MCC were present the tele- conferencing meeting held on 26th December 2020 at 2:00 PM.

No	Name	Position	Affiliation	Gender	Expertise
1	Dr T N Babu Ravindran	Chairman	Senior Medical Consultant Indira Gandhi Co-Operative Hospital,Manjodi, Thalassery,Kannur	Male	Medical consultant

2	Dr Sangeetha K. Nayanar	Member secretary	Professor &Head Department of Clinical service & Translational Research, Malabar Cancer Centre, Thalassery, Kerala	Female	Basic Medical Scientist
3	Dr. Balakrishnan Valliyot	Clinician	Professor of Medicine Head,Centre for Medical Research & Non-communicable diseases, Academy of Medical Sciences, Pariyaram, Kannur,	Male	Medicine
4	Dr. Jeeja M.C	Basic Medical Scientist	Additional Professor, Department of Pharmacology Govt, Medical College, Idukki,Kerala	Female	Pharmacologist
5	Dr Biju George	Clinician	Associate Professor in Community Medicine, Govt. Medical College, Kozhikode, Kerala	Male	Basic Medical Scientist
6.	Adv Preethi Parambath	Legal expert	Addl Govt Pleader & Public Prosecuter, Kannur District Court, Thalassery,Kerala	Female	Legal expert
7	Adv John Joseph	Legal Expert	Advocate, near District Court, Thalassery "Thalackal" House Nangarath Peedika,Temple Gate Thalassery, Kerala	Male	Legal Expert
8	Dr K R Vasudevan	Clinician	Consultant Physician "*ARCHANA*", Kovilakam Road, Nilambur (P.O),Malappuram, Kerala	Male	Medical consultant
9	Rev.Fr Thomas Thengumpally	Social Scientist	Chancellor Archdiocese, Arch Bishop House, Thalassery, PB No. 70 Kerala	Male	Social Scientist

10.	Mr. G.V. Rakesh	Lay Person	Correspondent Mathrubhumi Daily G.V. House, Ponniam P.O.,Thalassery, Kannur, Kerala	Male	Lay Person

The study is approved in the present form for a period of 18 months till 30th June 2022. The principal investigator should submit continuing review application/ annual status report on or before 31st December 2021.You may request for extension of validity in the submission of continuing review application/annual status report. In order to ensure that there is no lapse in the IEC approval period, it is mandatory to submit study status report prior to lapse of the study validity.

The study should be initiated only after-

- Registration of the study with clinical trials registry India (CTRI)

Following points must be noted:

1. IEC has approved recruitment of 400 lung cancer patients on this study
2. IEC has approved the conduct of the study at MCC
3. Principal investigator and study team should be GCP trained
4. IEC mandates that details of any funding received as part of educational/unconditionally support and /or other extramural funding obtained for the conduct of the study needs to be initiated to the IEC along with appropriate documents: Eg-CTA/MoU etc as the PI is privy to the information.
5. PI and other investigators should notify initiation of the study. Principal investigator should intimate the IEC after accrual of first 10 participants in the study or after 6 months of initiation of study whichever is earlier.
6. PI and other investigators should co operate fully with data and safety monitoring board(DSMB), who will monitor the study from time to time
7. The decision was arrived at through consensus/unanimous or majority opinion amongst the voting members of IEC. Member(s) of the committee who is/are listed as investigator(s) on a research proposal opted out from all deliberations on the proposal and did not participate in decision making. Neither PI nor any of proposed study team members participated during the decision making of the IEC.
8. At the time of PI's retirement/intention to leave the institute, study responsibility should be transferred to colleagues after obtaining clearance from HOD or head of the Institution. Status report, including accounts details should be submitted to HoD and extramural sponsors.
9. The IEC function in accordance with its SOP and is complaint with the New Drugs & clinical Trail rules,2019,ICMR guidelines and Indian /ICH GCP

10 In the events of any protocol amendments, IEC must be informed and the amendments should be highlighted in clear terms as follows:

a) The exact of any protocol amendments, IEC must be informed and the amendments should be the original project(Page no, clause no etc)
b) Alternation in the budgetary status should be clearly indicated and the revised budget from should be submitted
c) If the amendments require a change in the consent form, the copy of revised consent form should be submitted to Institutional Ethics Committee for approval
d) If the amendment demands a relook at the toxicity or side effects to patients, the same should be documents
e) If there are any amendments in the study design, there must be incorporated in the protocol, and other study comments. These revised documents should be submitted for approval of the IEC, only then can they be implements
f) Approval of amendment changes must be obtained prior to implementation of changes. Without including all the above points, the amendment is unlikely to be approved by the IEC

11 Any serious Adverse events(SAEs) occurring on the study should be reported to IEC
12 Any deviation/violation/waiver in the protocol must be informed the IEC
13 PI should conduct the study in accordance with the IEC approval
14. The PI should submit a report to the IEC at the time of study completion/premature termination/suspension/discontinuation, as is applicable
15. PI should comply with regulations and guidelines as applicable

Thanking you,

Yours Sincerely

Dr.Sangeetha K Nayanar

IEC-Member Secretary, MCC

Institutional Ethics Committee
Malabar Cancer Centre
Thalassery, Kerala-670 103

INSTITUTIONAL REVIEW BOARD
THALASSERY
KERALA
MALABAR CANCER CENTRE

MVR
CANCER CENTRE & RESEARCH INSTITUTE

INSTITUTIONAL ETHICS COMMITTEE

(Reg.No.ECR/1259/Inst/KL/2019)

Certificate of approval

Date: 17/12/2021

EC Ref No. : IEC2021/III/01

Principal Investigator :Dr.NarayanankuttyWarrier Medical Director & Senior Consultant, Medical Oncology, MVRCCRI

Co-Principal investigators:1) Dr. Nisha K Jose, ICMR Scientist, New Delhi & Ph.D Scholar SCTIMST, Trivandrum

2)Dr. Jeemon P, Asst Professor, SCTIMST, Trivandrum

Subject: Approval of the research study "Survival rates and predictors of mortality in lung cancer: a multicentric study in Kerala" by the Institute Ethics committee of MVR Cancer Centre & Research Institute.

Dear Dr.Narayanankutty Warrier,

The Institutional Ethics committee of MVR Cancer Centre & Research Institute has reviewed and discussed your application to conduct the above mentioned research project in the department of Medical oncology with yourself as the Principal investigator.

The Following documents have been reviewed and approved:

1. IEC application
2. Research Proposal
3. Informed Consent forms (both English &Malayalam)
4. Questionnaires

The members who attended this meeting held on 29 Dec 2020 at which the above mentioned document was discussed are listed below

Sl. No	Name	Role in the Ethics Committee
1	Dr N C Cherian	Chairperson
2	Dr Shaik Ubedulla	Biomedical Scientist/Pharmacology
3	Adv. Dineshan M.K	Legal Person
4	Ms Sreeja V.P	Lay person
5	Fr. (Dr.) Anish T	Social Scientist/ Philosopher
6	Dr Chandini R	Biomedical Scientist
7	Dr M Haridas	Basic Scientist
8	Dr P S Sreedharan	Clinician
9	Dr Dileep Damodaran	Clinician
10	Dr Lineesh M C	Biostatistician
11	Dr Thulaseedharan N K	Clinician

We provisionally approve the research study to be conducted in the presented form. None of the Investigator and co-investigator participating in this study took part in the decision making and voting procedure for this study

The institutional Ethics committee expects to be informed about the progress of the study (semiannually), any serious adverse event (SAE) occurring in the course of the study, any revision in the protocol and patient information/informed consent and ask to be provided a copy of the final report.

Yours Sincerely,

Dr. P S Sreedharan
Member Secretary
Institute Ethics Committee
MVR Cancer Centre & Research Institute
Kerala, India.

INSTITUTE ETHICS COMMITTEE MVR REG. NO. ECR/1259/INST/KL/2019

Member Secretary
Institute Ethics Committee
MVR Cancer Centre & Research Institute
Veilalassery P.O., Calicut, Kerala - 673 601

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM - 695 011, KERALA, INDIA
(एक राष्ट्रीय महत्व का संस्थान, विज्ञान एवं प्रौद्योगिकी विभाग, भारत सरकार)
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/IEC-1658/DECEMBER-2020 19.12.2020

Dr K.Nisha K Jose
Amala Institute of Medical Sciences Thrissur, Kerala

Dear Dr K.Nisha K Jose ,

Thank you for submitting documents related to your proposal titled "**"Survival rates and predictors of mortality in lung cancer: a multi-centric study in Kerala"** (IEC/IEC-1658)" to the IEC for review.

The following documents were reviewed:

1. Checklist
2. Covering letter addressed to the Chairman, IEC, SCTIMST
3. TAC Approval Letter
4. IEC Application Form
5. TAC Submission
6. Proposal
7. CV of Dr Nisha Jose with TCMC registration number
8. CV of DrJeemon, Asst. Professor, AMCHSS, SCTIMST without signature
9. Patient Information Sheet (English)
10. Informed Consent (English)
11. Informed Consent (Malayalam)
12. Medical Record Screening for eligibility Part-1
13. Medical Record Screening for eligibility Part-II
14. IEC Approval from Amala Institute

IEC Recommendations

1. Please ensure that all listed centres give approval for being in the registry
2. Mentioning information relating to death rates as part of a consent process might hamper their morale. While this information needs to be conveyed, could it be done in a less alarming manner by referring to survival rates?
3. Induction of a General Physician/Pulmonologist/Pathologist as Co-PI may be beneficial to the study.

The following members of the Institutional Ethics Committee participated in the discussions held virtually on Dec 18 2020, at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person(Chairman)	No
2.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Dr. K R S Krishnan	M.E., Ph.D.	Male	Medical Technology	No
5.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	Medical Technology	Yes
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	No
7.	Dr. Anand Kumar A	MD, DM	Male	Clinician	No
8.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	No
9.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
10.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
11	Dr.Raman Kutty V	MD (Padiatrics), Mphil, MPH	Male	Health Science Expert/Clinician	No
12.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
13.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
14.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
15.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study with the conditions listed under IEC Recommendations.

Remarks:

1. **The PI is required to self-certify that all the conditions required by the IEC have been fully and fairly met with. The declaration should include the listed IEC suggestions and the revisions made. A revised copy of the complete submission including the self-declaration should be submitted as a single pdf file to the email id of the Member Secretary – iec.mem.sec@sctimst.ac.in/iec@sctimst.ac.in**
   The study shall be commenced only after the submission of the revised protocols with the self-declaration.
2. The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.
3. There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1658/AUGUST/2022

03.09.2022

Dr. Nisha K Jose
Part Time Ph D Student
AMCHSS
SCTIMST, Thiruvananthapuram

Dear Dr. Nisha K Jose,

The Institutional Ethics Committee held on 20th August, 2022, reviewed and discussed your application to conduct the study titled "**SURVIVAL RATES AND PREDICTORS OF MORTALITY IN LUNG CANCER: A MULTI-CENTRIC STUDY IN KERALA**" (IEC/1658).

The following members of the Ethics Committee were present at the meeting held on 20th August, 2022

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. C.C. Kartha	MBBS,MD	Male	Basic Medical Scientist (Chairman)	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
5.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
8.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
9.	Dr. Harikrishna Varma PR	Ph.D (Materials Science)	Male	Medical Technology	Yes
10.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
11.	Dr. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
12.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
13.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

1. *Checklist Form*
2. *Covering letter addressed to the Member Secretary, IEC, SCTIMST*
3. *TAC Approval letter*
4. *IEC Application Form*
5. *Project proposal*
6. *CV of PI and Co-PIs*
7. *Informed Consent Form in English and Malayalam*
8. *Proforma*
9. *Institutional Ethics Committee approval letter from Amala Institute of Medical Sciences, Thrissur dated 18.02.20*
10. *Institutional Ethics Committee approval letter from Lisie Hospital, Kochi dated 04.02.2020*
11. *Institutional Ethics Committee approval letter from Little Flower Hospital and Research Centre, Angamaly dated 10.12.2020*
12. *Institutional Ethics Committee approval letter from Malabar Cancer Centre, Thalassery dated 22.12.2020*
13. *Institutional Ethics Committee approval letter from MVR Cancer Centre and Research Institute dated 17.12.2021*
14. *Covering letter addressed to the Rev Fr Sebastian Kalapurackal Director Little Flower Hospital Angamaly from Dr Nisha K Jose (Sr Catherene CMC) Assistant Professor Amala Institute of Medical Sciences Thrissur*
15. *Covering letter addressed to the Director Prathyasa Cancer Centre Cherthala from Dr Nisha K Jose (Sr Catherene CMC) Assistant Professor Amala Institute of Medical Sciences Thrissur*
16. *Copy of IEC Approval letter dated 19.12.2020*

IEC Decision

The IEC approved inclusion of MVR cancer centre as a study site. Personal details in the proforma are to be removed.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

Original Article

Demographic and clinical characteristics of primary lung cancer patients in Kerala: Analysis of data from six teaching centers

Nisha K. Jose[1], Biju Soman[2], Jissa V. Thulaseedharan[2], Bipin T. Varghese[2], Shaji Thomas[2], Jeremiah J. Tom[3], Narayanankutty Warrier[4], Manuprasad Avaronnan[5], Panniyammakal Jeemon[2]

[1]NCD Division, Indian Council of Medical Research, New Delhi, India, [2]Associate Professor, Sree Chitra Tirunal Institute of Medical Sciences and Technology, Thiruvananthapuram, Kerala, India, [3]Resident, Amala Institute of Medical Sciences, Thrissur, Kerala, India, [4]Director, MVR Cancer Centre, Poolacode, Kerala, India, [5]Professor, Malabar Cancer Centre, Thalassery, Kerala, India

Abstract

Background: Lung cancer continues to be the leading cause of cancer-related deaths in men and women. A breakdown by level of economic development shows no differences in cancer deaths in men but a higher rate of lung cancer deaths in women in industrialized countries as compared with developing nations. The risk factors for lung cancer most commonly include lifestyle, environmental, and occupational exposures. The role these factors play varies depending on geographic location, sex and race characteristics, genetic predisposition, as well as their synergistic interactions. **Materials and Methods:** It was a hospital-based registry, wherein hospitals were selected from three zones—north, central, and south zones of Kerala. The study was registered with clinical trial registry of India with Registration No. CTRI/2021/02/031299. Registry of lung cancer patients was prepared at all sites and institutional ethical clearance was received from all sites. All patients with primary lung cancer, histologically proven of all age groups were included in the study. **Results:** A total of 761 patients were registered from six teaching hospitals in Kerala who were diagnosed with primary lung cancer during the period 2017–2019. The mean age of the study population was 65.1 ± 10.2 years. Of all, 81.1% of them were males and 18.9% were females. Histologically, 56.4% had adenocarcinoma and 25.6% had squamous cell carcinoma. **Conclusion:** It was observed that the proportion of females diagnosed with primary lung cancer is increasing. Patients get diagnosed at a later stage of the disease, which calls for screening and early detection of lung cancer. As it accounts for the highest mortality among all other cancers, there is high scope for prevention and screening strategies.

Keywords: Adenocarcinoma, Kerala, lung cancer patients, primary lung cancer

Introduction

Lung cancer is one of the leading causes of cancer deaths in the world. GLOBOCAN 2018 database shows that approximately 2.1 million people were affected with lung cancer in 2018, with a reported estimate of 1.8 million deaths.[1] In India, lung cancer constitutes 9.3% of all cancer-related deaths.[2] Lung cancer is the leading cause of cancer among men and the second leading cause

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in women. Developed countries show an increase in the women population with cancer explained by the increased population of women smokers coming to par with men. However, a decrease in rates of smoking among men in developed countries, explains plateauing of lung cancer rates in men.[2] Since first described in 1912, the major cause of lung cancer is cigarette smoke inhalation; amounting to up to 90% of all causes of lung cancer.[3] A study in New Mexico by Humble CG *et al.* showed that the cumulative risk of lung cancer in heavy smokers is approximately 30% compared with a less than 1% risk in nonsmokers.[4] Other major risk factors include occupational asbestos exposure, radon, indoor smoke from cooking and heating, chronic obstructive pulmonary disease (COPD), and genetic factors.

In developing countries like India, patients reach the primary care physician with symptoms and are then referred to higher centers. First-level investigations and symptom management happen at the primary care level. Although cases may be detected incidentally, clinical manifestations of lung cancer are very common. Clinical symptoms include cough, dyspnea, hemoptysis, chest pain, hoarseness of voice, fever, and loss of weight/appetite. Lung cancer is also associated with metastatic symptoms and paraneoplastic syndromes. The diagnostic evaluation involves assessing the stage of the disease, histological grading and genotype, presence of metastasis, and associated paraneoplastic syndromes.

This study focuses to describe the demographic and clinical characteristics of lung cancer patients in teaching hospitals in Kerala, India.

Materials and Methods

It was a hospital-based registry, wherein hospitals were selected from three zones of Kerala—north, central, and south zones. A total of six tertiary care hospitals were selected. Patients of pathologically (biopsy or cytology) proven lung cancer, (ICD code: C 33 and C 36) were recruited in this study and a registry was prepared. Patients diagnosed with lung cancer from January 2017 to December 2019 were included in the registry. All patients were followed up for 2 years from the date of diagnosis and the outcome was assessed. Patients with thoracic metastatic lung disease from nonpulmonary primary cancer were excluded. Informed consent was taken from the patient/caregiver. Institutional ethical clearance from all six sites was taken (SCT/IEC/1658/DECEMBER-2020). The study was registered with the clinical trial registry of India with Registration No. CTRI/2021/02/031299. Data regarding sociodemography, presenting complaints, performance status at diagnosis using the Eastern Cooperative Oncology Group scale (ECOG), date and mode of diagnosis, investigations, past medical history, treatment modalities, and treatment outcome were collected from the patient chart using a predesigned structured proforma.

Statistical analysis

The data were entered into an Excel worksheet and analysis was performed using the Statistical Package for the Social Sciences (SPSS) 23. Data on continuous measurements were presented as mean and standard deviation and results on categorical measurements were presented in number (%).

Results

A total of 761 patients with primary lung cancer in the period of 2017–2019 were included in the study. The mean age of the study population was 65.1 ± 10.2 years. The study included a wide range of age groups, which showed the highest population (37.8%) in the age group of 65–74 years followed by 32.5% in the age group of 55–64 years. Our study also shows lung cancer is mostly seen in males (81.1%) when compared with females (18.9%), with a male: female ratio (M: F) of 4.28:1. The calculated body mass index (BMI) showed that most patients belonged to the "normal weight" category (33.9%) followed by "underweight" category (15.5%) with the lowest number of patients in the obese category (9.8%). ECOG performance scoring evaluation showed 40.9% of patients to have a score of 1 and 41.1% of patients to have a score of 2 and only 0.3% to have a score of 4.

With regard to smoking history, data is not available for 10% (81) of our study population. On assessing the available smoking history data, 420 males (55%) and 1 (0.13%) female have smoked in their lifetime. Table 1 shows that 219 patients continue to smoke after a diagnosis of lung cancer was made and 202 patients stopped smoking thereafter. It also shows that 259 (34%) patients with lung cancer have never smoked in their lifetime.

Our study shows that 61% of the patients have the tumor located in the right lung and upper lobe to be involved in 53.8% of the patients. The most common pathological type was adenocarcinoma (56.4%) and it was the most common among both males and females; followed by squamous cell carcinoma (25.6%) and small cell carcinoma (7.3%). Large cell carcinoma was the least common (1.3%) and was only present in males. Metastasis to multiple sites were studied and showed predominant bone (38%) and brain (27%) metastasis followed by adrenal (20.2%) and liver (10.9%).

Table 2 shows a list of presenting symptoms of lung cancer and its metastasis, with cough (present in 65%) and breathlessness (present in 35%) being the predominant ones. Other noted symptoms include chest pain (25.4%), weakness (19.9%), hemoptysis (17.2%), fever (13.7%), weight loss (10.3%), pleural effusion (8.1%), loss of appetite (6.7%), hoarseness of voice (4.3%), and bone pain (2.6%).

Table 3 shows the past history of diseases of the study population. Data shows hypertension to be the most common past history overall (27%) and among females. This was followed by diabetes mellitus (24.9%), COPD (22.9%), and cardiac diseases (16.5%). However, COPD was the most common among males (27.7%) with only few females (2.7%) affected.

Table 1: Demographic and baseline characteristics of lung cancer patients (*n*=761)

Variables	Male (%)	Female (%)	Total
Age<55 years	83 (66.9)	41 (33.1)	124
55–64 years	205 (82.6)	43 (17.4)	248
65–74 years	244 (84.7)	44 (15.3)	288
>75 years	85 (84.1)	16 (15.9)	101
Sex	617 (81.0)	144 (19.0)	761
Smoking history			
Current smoker	219 (100)	0	219
Past smoker	201 (99.5)	1 (0.5)	202
Never smoker	116 (44.7)	143 (55.3)	259
Data not available	81 (100)	0	81
Location of tumor			
Left lung	242 (82.5)	51 (17.5)	293
Right lung	357 (76.2)	93 (23.8)	468
Lobe affected			
Lower	218 (77.3)	64 (22.7)	282
Middle	54 (78.2)	15 (21.8)	69
Upper	345 (84.1)	65 (15.9)	410
Pathological type			
Adenocarcinoma	310 (72.2)	119 (27.8)	429
Squamous cell	182 (93.3)	13 (6.7)	195
carcinoma	52 (92.8)	4 (7.2)	56
Small cell carcinoma	10 (100)	0	10
Large cell carcinoma			
ECOG performance			
1	251 (80.4)	62 (19.6)	312
2	256 (81.7)	57 (18.3)	313
3	108 (81.2)	25 (18.8)	133
4	2 (66.6)	1 (33.4)	3
Metastasis			
Bone	233 (80.0)	58 (20.0)	291
Brain	166 (81.7)	37 (18.3)	203
Liver	65 (78.3)	18 (21.7)	83
Adrenals	127 (82.4)	27 (17.6)	154
BMI			
Underweight	100 (84.7)	18 (15.3)	118
Normal weight	211 (81.7)	47 (18.3)	258
Preobese	64 (82.0)	14 (18.0)	78
Obese	60 (80.0)	15 (20.0)	75

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group scale

Table 2: Symptomatology of patients with lung cancer

Symptoms	Male (%)	Female (%)	Total
Weight loss	69 (87.3)	10 (12.7)	79
Weakness	122 (80.2)	30 (19.8)	152
Cough	405 (81.6)	91 (18.4)	496
Hemoptysis	123 (93.8)	8 (6.2)	131
Breathlessness	219 (80.5)	53 (19.5)	272
Chest pain	156 (80.4)	38 (19.6)	194
Hoarseness of voice	32 (96.9)	1 (3.1)	33
Pleural effusion	39 (69.5)	23 (30.5)	62
Loss of appetite	39 (76.4)	12 (23.6)	51
Fever	87 (82.8)	18 (17.2)	105
Bone pain	15 (75.0)	5 (25.0)	20

Table 4 shows the distribution and differences between genders in Tumour, Nodes & Metastasis (TNM) staging at the time of diagnosis. Analysis of our study data shows that most of the patients (31%) were diagnosed at stage T3 after significant tumor growth. It also shows that 95% of the patients had nodal metastasis and 83% were found to have extensive nodal metastasis at the time of diagnosis. A significant majority (85%) of the patients had distant metastasis and 69% of the study population had at least one extra thoracic metastasis during presentation.

Discussion

Our study aims to analyze the epidemiology, demographic, clinical, and histological profile of primary lung cancer by collecting data from hospital-based registries from six tertiary care teaching centers located in the north, central, and south zones of Kerala. The mean age of the study population was 65.1 ± 10.2 years, with the least patients in the ages of <55 years and >75 years. Over the decades, there is an increase in the mean age group of diagnosed lung cancer patients. It was 52.1 years before 1985 and increased to 54.6 years after 1985.[5] Recent studies in India show their mean age group similar to our study indicating that the occurrence is most common in the elderly age groups.[6-8] This is in line with the latest US preventive task force recommendation of screening for lung cancer in smokers from 50 to 80 years.[9] The incidence and mortality have historically always been male-predominated and continue to be so according to the global cancer statistics 2020.[10] Our study data showed 81.1% males and 18.9% females with M:F ratio of 4.28. The M:F ratio in our study is higher than the Indian Council of Medical Research (ICMR) cancer registry data showing a decreasing trend in M:F ratio from 4.5 in 2002 to 3.1 in 2021.[11] This similar decrease in M:F ratio is supported by many studies in the United States indicating that the incidence curve of females is plateauing while that for males is decreasing.[12-14]

Since first described in 1912, cigarette smoke inhalation is the major cause of lung cancer amounting to up to 90% of all causes.[3,4,15,16]In addition, 55.3% of the patients were smokers with a large majority being males (55.1%) and just 0.13% constituting females. A study done by Kshetrimayum *et al.* in Lucknow showed a similar drastic difference between male and female smokers in India.[17] However, Western studies show that an increasing trend of female smokers is resulting in identical risk between men and women.[2] In addition, 52% of the smokers in our study population continue to smoke, which can increase the all-cause mortality, recurrence, and development of new primary cancers.[18] Our study also shows that 34% were nonsmokers; among which; incidence of lung cancer in females (55.2%) was higher than in males (44.7%). Wakelee HA *et al.* conducted a pooled analysis of six prospective cohort studies that showed similar higher incidence rates of nonsmoking-related lung cancer in females than in males.[19] Nonsmoking-related lung cancers can be attributed to other etiologies like second-hand smoke, occupational asbestos exposure, radon, indoor smoke from cooking and heating, COPD, previous history of chemoradiation, genetic, and environment factors. However, more research is required in this area as no clear etiology and screening guidelines are stated for nonsmokers, despite their increasing incidence rates.[20] Similar to other studies demonstrated before,[21,22] our

Table 3: Past history of diseases of the study population

Past history	Male (%)	Female (%)	Total
Hypertension	143 (68.0)	67 (32.0)	210
Diabetes mellitus	147 (77.3)	43 (22.7)	190
Dyslipidemia	25 (64.1)	14 (35.9)	39
Renal diseases	26 (100)	0 (0)	26
Cardiac diseases	109 (86.5)	17 (13.5)	126
History of TB	73 (90.1)	8 (9.9)	81
COPD	171 (97.7)	4 (2.3)	175

COPD, chronic obstructive pulmonary disease; TB, tuberculosis

Table 4: Distribution according to TNM staging (*n*=761)

Staging of lung cancer	Male (%)	Female (%)	Total
T1a	2 (50.0)	2 (50.0)	4
T1b	15 (68.1)	7 (31.9)	22
T1c	45 (69.2)	20 (30.8)	65
T2a	88 (81.4)	20 (18.6)	108
T2b	132 (78.1)	37 (21.9)	169
T3	193 (81.7)	43 (18.3)	236
T4	142 (90.4)	15 (9.6)	157
NX	3 (75.0)	1 (25.0)	4
N0	25 (78.1)	7 (21.9)	32
N1	69 (74.1)	24 (25.9)	93
N2	266 (84.1)	50 (15.9)	316
N3	254 (80.3)	62 (19.7)	316
M0	94 (84.6)	17 (15.4)	111
M1a	97 (79.5)	25 (20.5)	122
M1b	156 (77.2)	46 (22.8)	202
M1c	270 (82.8)	56 (17.2)	326

study showed that tumor most frequently develops in the right lung and upper lobe. In addition, 40.9% of patients had a good ECOG of 1, 41.1% of patients had ECOG score of 2, and only 0.3% had score of 4. However, this is lower compared with other Indian[23] and Western reports.[24] This could be due to increased detection of lung cancer at a later stage. Developing countries does not have screening tools for cancer detection, which leads to late diagnosis. Screening facilities at primary care level can help in early diagnosis and better survival.

Most patients present with symptoms due to the locoregional spread, metastasis, or paraneoplastic syndromes. Our study data showed that the most common symptoms were cough (65%), breathlessness (35%), chest pain (25.4%), weakness (19.9%), hemoptysis (17.2%), fever (13.7%), and weight loss (10.3%). Other associated presentations were pleural effusion (8.1%), loss of appetite (6.7%), hoarseness of voice (4.3%), and bone pain (2.6%). Studies done in India[17,25,26] and internationally[27] showed cough and breathlessness to be the most common presentations followed by chest pain and weight loss. This showed a similar pattern of symptoms in our study compared with other studies. However, one limitation of our study was that it did not analyze the correlation of symptoms with pathological type to lung cancer as multiple studies[27,28] has shown that cough is present in 50%–75% of the patients with small cell carcinoma and squamous cell carcinoma.

Adenocarcinoma (56.4%) was the most common pathological type overall among both males and females; followed by squamous cell carcinoma (25.6%) and small cell carcinoma (7.3%). Large cell carcinoma was the least common (1.3%) and was only present in males. Older Indian studies have shown predominance of squamous cell carcinoma over adenocarcinoma.[29,30] However, our study is consistent with many recent studies showing that adenocarcinoma has surpassed squamous cell carcinoma.[17,31,32] This change in trend can be attributed to the changing smoking patterns and the increasing incidence of lung cancer in females and nonsmokers.[17,31,33]

Metastasis to distant sites like the liver, bone, brain, adrenals is common due to the aggressive nature of the disease.[34,35] This study showed that metastasis to bone (38%) and brain (27%) was the most common followed by metastasis to adrenal (20.2%) and liver (10.9%). This is contradicted by studies showing liver to be the most common site for metastasis.[17] However, the work by Riihimaki M, *et al.*[36] and other analysis show that liver and brain metastasis is most commonly seen in small cell carcinoma, whereas bone metastasis is commonly seen in adenocarcinoma.[17,37] The limitation of our study was its inability to define such a correlation of pathological subtype of lung cancer to site of metastasis.

Conclusion

The major concern our study shows is that lung cancer continues to be detected at a later stage when the tumor size is large and after nodal or distant metastasis. In addition, 31% of the patients were diagnosed at stage T3 after significant tumor growth, 95% had nodal metastasis, and 83% were found to have extensive nodal metastasis at the time of diagnosis. This is consistent with the ICMR cancer registry data[11] and multiple studies in different parts of the country.[21-23,38] This could be due to a lack of screening in high-risk individuals, nature of disease to be asymptomatic till the advanced stage; and lack of screening guidelines.

Acknowledgment

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Nil.

Conflicts of interest

There are no conflicts of interest.

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PART I

Medical record screening for eligibility

1. Patient ID			
2. Unique ID code:			
3. Date of chart review:			
4. Date of diagnosis:			
5. Name:			
6. Age in completed years:			
7.Primary lung cancer	Yes	No	
8. Histological diagnosis available	Yes	No	

9. Histological type (tick the option)

Non-Small Cell Lung Cancer	
Adenocarcinoma	
Squamous cell carcinoma	
Large cell carcinoma	
Undifferentiated	
Small Cell Lung Cancer	
Carcinoid tumour	
Other details, if any	

(If Q 7 & 8 are YES go to part II)

PART II
Detailed chart review

Unique ID code

A. SOCIO-DEMOGRAPHY –

1. Complete Address:
House name/ House No:
Place :
Post office :
District :
Phone number :
2. Name of husband / wife:

3. Name of father / guardian:

4. Age at diagnosis (in completed years):

5. Date of diagnosis	date:	month:	year:

6. Gender (circle the option)	Male	Female

7. Religion (circle the option)	Hindu	Christian	Muslim	Other

8. Marital status (tick the option)

Never married	Currently married
Separated	Divorced
Widow/widower	Data not available

B.PRESENTING SIGNS/SYMPTOMS

9. Duration of symptoms to diagnosis (in weeks):			
10.Duration of diagnosis to treatment (in weeks):			
11.Height (in cms)		12.Weight at diagnosis (in kgs)	

13. Presence of following symptoms/signs at diagnosis. (tick multiple options if appropriate)	
a. Weight loss of more than 10kg in 6 mts	b. Dyspnoea
c. Weakness:	d. Cough:
e. Coughing out off blood (haemoptysis):	f. Breathlessness:
g. Chest pain:	h. Difficulty in swallowing:
i. Wheezing:	j. Strider:
k. Hoarseness of voice:	l. Pleural effusion:
m. Loss of appetite:	n. Fever:
o. Bone pain	p. Asymptomatic

14. Tumour size with maximum diameter (in cms)
15. Lymph node status: (tick the option below)
NX (cannot be assessed)
N0 (no nodal metastasis)
N1 (ipsilateral - peribroncial/hilar/intrapulmonary)
N2 (ipsilateral - mediastinal/subcarinal)
N3 (contralateral or supraclavicular)

16. Metastasis (tick the option below)

MO (no distant metastasis)
M1a (separate nodule in contralateral lobe/pleural/pericardial/nodule/ malignant pleural effusion)
M1b (single extra thoracic organ metastasis)
M1c (multiple extra thoracic metastasis)

17. Location of tumour	Right lung	Left lung	
18. Lobe affected	Upper	Middle	Lower
19. Number of metastatic sites (write number)			
20. If metastasized to other organs, please mention			

21. Pleural involvement	Present	Absent

22. Vessel Invasion	Present	Absent

C. INVESTIGATIONS (pre-treatment)

23. Haemoglobin (gm/dl)			
24. Total Leucocyte count (cells/cu.mm)			
25. Neutrophil count (%)			
26. Lymphocyte count (%)			
27. Platelet count (cell/cu.mm)			
28. S Creatinine (mg%)			
29. S. Total Protein (gm%)			
30. S. Albumin (gm%)			
31. S. Globulin (gm%)			
32. S. Calcium (mg%)			
33. S. Phosphorus (mg%)			
34. S. Alkaline Phosphatase (K.A.U)			
35. S. Total Bilirubin (mg%)			
36. AST (SGOT)(U/L)			
37. ALT (SGPT)(U/L)			
38. Sodium (mmol/l)			
39. Potassium (mmol/l)			
40. C reactive protein (mg/mL)			
41. S. Lactate Dehydrogenase((IU/L)			
42. IHC Markers	CK7	CK5/6	CK
	CK20	P40	P63
(mark -1 positive, 2 -negative, 3- not done)	NapsinA	TTF1	CD5
	Others		

D. Diagnosis (tick appropriate option)

1. **Sputum cytology**	positive	negative	not done
2. **Pleural fluid cytology**	positive	negative	not done
3. **Broncoscopy**			
bronchial brush	positive	negative	not done
bronchial wash	positive	negative	not done
bronchial biopsy	positive	negative	not done
broncho alveolar lavage (BAL)	positive	negative	not done
4.**Thorcoscopic** biopsy	positive	negative	not done
5. **FNAC**			
lymph node	positive	negative	not done
primary lesion	positive	negative	not done
6. **CT guided Biopsy**	positive	negative	not done
7. **PET Scan**	positive	negative	not done
8. **EBUS** -endobroncial biopsy	positive	negative	not done

E. PAST HISTORY (tick appropriate option)

43. Hypertension	yes	no
44. Diabetes mellitus	yes	no
45. Dyslipidaemia	yes	no
46. Renal disease	yes	no
47. Cardiac disease	yes	no
48. Liver disease	yes	no
49. History of (heart attack) MI	yes	no
50. History of stroke	yes	no
51. Psychiatric illness	yes	no
52. Respiratory disease	yes	no
53. Asthma :	yes	no
54. Tuberculosis (TB)	yes	no
55. Chronic Obstructive Pulmonary Disease (COPD)	yes	no
56. Interstitial Lung Disease	yes	no
57. Others –	yes	no
(If yes specify)		
58. Any cancer other than lung	yes	no
59. Family history of lung cancer	yes	no
60. History of drug allergy	yes	no
61. Mutation studies conducted.	yes	no
If yes details (circle options) EGFR	ALK	ROS1 Others
62. ECOG Performance Score (0-5)		

F. PERSONAL HISTORY

63. Smoking history			
Never smoker		Current smoker	
Past smoker		Data not available	
64. Duration of smoking (in years) :			
65. Consumption of alcohol –	yes	no	data not available

PART III
Treatment Details

Unique ID code:

Treatment modality used (tick appropriate option)

1.**Chemotherapy**	Yes	No	No data
Type	1.Definitive		2.Palliative
	3. Neodjuvant		4. Adjuvant

Medicines used	No. Of cycles (write number)
Paclitaxel	
Carboplatin	
Etoposide	
Cisplatin	
Pemetrexed	
Gemcitabine	
Vinorelbine	
Docetaxel	
Geftinib	
Crizotinib	
Erlotinib	
Ramucirumab	
Gemcitabine	
Irinotecan	
Others (specify)	

2. **Surgical treatment**	Yes	No	No data
Lobectomy			
Bilobectomy			
Pneumonectomy			
Segmentectomy			
Sleeve resection			
Wedge resection			
Others (specify)			
3. **Radiation**	Yes	No	No data
palliative therapy			
neoadjuvant therapy			
adjuvant therapy			
prophylactic therapy(cranial)			
concurrent therapy			
Gray	Fraction		
4. **Palliative treatment**	Yes	No	No data

PART IV

Current Status

1.	Unique ID code :			
2.	Name of patient:			
3.	Phone number :			
4.	Date of diagnosis	Date:	Month:	Year:
5.	Date of last review	Date:	Month:	Year:
6.	Duration of review in the hospital from the date of diagnosis (in months) :			
7.	Person contacted :-	patient	care giver	file review
8.	Mode of contact –	phone	field visit	health staff / file review
9.	Current status	Alive:	Dead:	Unknown:
10.	Date of death			
11.	If alive, date of last contact			
12.	Duration of survival from the date of diagnosis (in months)			

A. PATIENT INFORMATION SHEET

I, Dr Nisha K Jose, Part time PhD student at Achutha Menon Centre for Health Sciences Studies, SCTIMST, Trivandrum would like to conduct a research study on "**Survival rates and predictors of mortality in lung cancer: a multi-centric study in Kerala**" among lung cancer patients from 2020 December - 2022 November under the guidance of Dr Jeemon P, Assistant Professor, Achutha Menon Centre for Health Sciences Studies, SCTIMST, Trivandrum. The study is conducted for assessing mortality rates and predictors of mortality among lung cancer patients. I would like to include you in to the study and collect data from your hospital file under this research. I will be assessing mortality rates, predictors of mortality and associated factors as per following conditions.

1. Information given by you, will remain strictly confidential.
2. You may not receive any personal benefit by participating in this research study.
3. You will not be debited any extra charges for the study.
4. No invasive procedure is involved in this study.
5. You are assured that there will be no harm or risk to you by participating in this study
6. Participation in this study is voluntary and you are free to withdraw from this study at any time without giving reasons and that it will not anyway affect your medical care or legal rights.
7. Confidentiality of the data collected from records will be maintained by blinding the individual's identity and providing unique identity code. Individual's identity will not be revealed in the data sheet sending for analysis.
8. The study may be published in approved journals, but without revealing your identity.

Read by me and understood / Read to me and made understood*

Place: Signature/Thumb Impression of Participant:

Date: Name and complete address of participant:

Place: Signature of Principal Investigator:

Date: Name of Principal Investigator:

Phone number:

B. INFORMED CONSENT FORM (ICF)

I confirm that I have read and understood the information sheet dated _____ for the study "**Survival rates and predictors of mortality in lung cancer: a multi-centric study in Kerala**", and have had the opportunity to ask questions.

(i) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

(ii) I understand that the investigator will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.

(iii) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)

(iv) I agree to take part in the above study.

Place: Signature/Thumb Impression of Participant:

Date: Name and complete address:

Phone number:

Place: Signature of Principal Investigator:

Date: Name of Principal Investigator:

Phone number:

If you have any further questions, please ask Dr. Nisha K Jose, Part time PhD student, SCTIMST or Dr. Jeemon P (tel: 0484 2462045/ 9495056174/ 0471 2524250) or email: nisha@sctimst.ac.in

For any clarifications regarding the study's ethics clearance you may contact the Member Secretary of the SCTIMST-IEC. The phone number is: 0471 2524234 and the email id is iec.mem.sec@sctimst.ac.in

Supplementary Table

Table: 1 Cox-Proportional Hazard Assumptions checks (Schoenfeld residuals)

Proportional hazards assumption was checked and P value was 0.06. Assumption of proportionality is met.

		chi2	df	Prob>chi2
Global	test	25.28	16	0.065

NKJ_PhD_rev

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