

A RETROSPECTIVE COHORT STUDY ON OVERALL
SURVIVAL OF PATIENTS WITH NON SMALL CELL
LUNG CANCER (NSCLC) AND THE ASSOCIATED
FACTORS WITH MORTALITY IN HOSPITAL RAJA
PEREMPUAN ZAINAB II (HRPZ II)

DR. SOFIATULAKMAL BINTI ASHARI

DISSERTATION SUBMITTED IN PARTIAL
FULFILMENT OF THE REQUIREMENT FOR MASTER
OF MEDICINE (INTERNAL MEDICINE)



UNIVERSITI SAINS MALAYSIA

2022

ACKNOWLEDGEMENT

Bismillahirrahmanirrahim,

In the name of Allah, the most compassionate and the most merciful. Salutation to His Messenger, Prophet Muhammad (peace be upon him), his family companions. This dissertation is made possible with the kind with the kind support and help of many individuals. First and foremost, all praise and thanks be to Allah, the One True Almighty God who had given me strength, peace of mind, and good health that enabled me to complete this dissertation. I would like to extend my utmost gratitude and appreciation to my supervisor Dr. Nurashikin binti Mohammad, and my co supervisor Dr Azza Omar who provided me support, her expert opinion and guidance to complete my study. My thanks and appreciation to Dr Suhaily Mohd Hairon for his guidance in the statistical aspect. I would like to express my most profound appreciation to both my parents and siblings, for their encouragement and moral support.

TABLE OF CONTENTS

TITLE	
ACKNOWLEDGEMENT.....	ii
TABLE OF CONTENTS	iii
LIST OF ABBREVIATIONS	v
LIST OF TABLES	vi
LIST OF FIGURES	vii
LIST OF SYMBOLS	viii
ABSTRAK	ix
ABSTRACT	xi
CHAPTER 1:	
1.1 INTRODUCTION	1
1.1 PROBLEM STATEMENT	3
1.2 RATIONALE OF THE STUDY	4
1.3 RESEARCH QUESTIONS	5
1.4 RESEARCH HYPOTHESIS	5
1.5 OBJECTIVES :	
1.5.1 GENERAL OBJECTIVES	6
1.5.2 SPECIFIC OBJECTIVES	6
CHAPTER 2:	
2.1 LITERATURE REVIEW	7
2.2 CONCEPTUAL FRAMEWORK	17
CHAPTER 3:	
METHODOLOGY	
3.1 STUDY DESIGN	18
3.2 STUDY DURATION	18
3.3 STUDY AREA	18
3.4 REFERENCE POPULATION	18
3.5 SOURCE POPULATION	19
3.6 SAMPLING FRAME	19
3.7 STUDY SUBJECTS	19
3.8 SUBJECTS CRITERIA	19
3.9 SAMPLING METHOD	20
3.10 SAMPLE SIZE CALCULATION	20

3.11 STUDY/ RESEARCH TOOLS	21
3.12 OPERATIONAL DEFINITIONS OF STUDY VARIABLES	23
3. 13 STATISTICAL ANALYSES	26
3. 14 ETHICAL ISSUE CONSIDERATION	31
3.15 DATA COLLECTION METHOD	31
3.16 PRIVACY AND CONFIDENTIALITY	32
CHAPTER 4 : RESULTS	33
CHAPTER 5 : DISCUSSION	47
CHAPTER 6 : CONCLUSION, LIMITATION AND RECOMMENDATION	53
CHAPTER 7 : REFERENCES	54
CHAPTER 8 : APPENDICES	
APPENDIX 1 APPROVAL LETTER FROM JEPPEM	60
APPENDIX 2 APPROVAL LETTER FROM MREC	62
APPENDIX 3 APPROVAL LETTER FROM MEDICAL HEAD OF DEPARTMENT AND HOSPITAL DIRECTOR HRPZ II	64
APPENDIX 4 PROFORMA	66
APPENDIX 5 RAW DATA/CD	67

LIST OF ABBREVIATIONS

NSCLC	Non-Small Cell Lung Cancer
HRPZ II	Hospital Raja Perempuan Zainab II
CT	Computed Tomography
TNM	Tumour Nodal Metastasis
AD	Adenocarcinoma
SCC	Squamous Cell Carcinoma
LCC	Large Cell Carcinoma
ECOG PS	Eastern Cooperative Oncology Group Performance Status
BMI	Body Mass Index
NCD	Non-communicable Disease
EGFR	Epidermal Growth Factor Receptor
EGFR – TKIs	Epidermal Growth Factor Receptor - Tyrosine Kinase Inhibitors
PFS	Progression Free Survival
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
PTB	Pulmonary Tuberculosis

LIST OF TABLES

Table 3.1	Sample Size calculation	21
Table 3.2	Proforma / Data Collection Sheet	22
Table 3.3	Operational Definitions.	23
Table 4.1	Socio – Demographic of Non-Small Cell Lung Cancer (NSCLC) patients	34
Table 4.2	Disease and Clinical Characteristics of Non- Small Cell Lung Cancer (NSCLC) patients.	36
Table 4.3	Frequency and Association of Adenocarcinoma NSCLC According to Clinical Characteristic.	37
Table 4.4	Frequency and Association of Adenocarcinoma NSCLC EGFR Mutation According to Clinical Characteristic.	38
Table 4.5	Comparing the Frequency of EGFR Mutation by Gender/Sex	39
Table 4.6	Descriptive Statistics of Overall Survival Data in Non-Small Cell Lung Cancer (NSCLC) patients.	40
Table 4.7	Prognostic Factors of Mortality by Simple Cox Proportion Hazard Regression for Socio – Demographic of Non-Small Cell Lung Cancer (NSCLC) patients.	42
Table 4.8	Prognostic Factors of Mortality by Simple Cox Proportion Hazard Regression for Disease and Clinical Characteristics of Non-Small Cell Lung Cancer (NSCLC) patients.	43
Table 4.9	Prognostic Factors of Mortality by Multiple Cox Proportion Hazard Regression of Non-Small Cell Lung Cancer (NSCLC) patients.	45

LIST OF FIGURES

Figure 1	Conceptual Framework of the Study	17
----------	-----------------------------------	----

LIST OF SYMBOLS

Symbol	Description
α	0.05
Power (1-β)	0.80
R	The hazard ratio (Relative risk) of the control treatment relative to experimental treatment
A	Accrual time during which patient will be recruited
F	Additional follow up after end of recruitment
m1	Median survival time in control group
M	Ratio of control to experiment group
%	Percentage
>	More than
b	Regression coefficient
HR	Hazard ratio
CI	Confidence interval
Adj. b	Adjusted regression coefficient
Adj. HR	Adjusted hazard ratio

ABSTRAK

Latar belakang: Tujuan utama objektif kajian kami adalah untuk menentukan kadar kelangsungan hayat dalam masa setahun dan mengenalpasti faktor – faktor prognostik yang mempengaruhi kelangsungan hayat pesakit kanser paru – paru dalam kalangan rakyat Kelantan.

Kaedah: Kajian retrospektif ini melibatkan ulasan rekod perubatan pesakit kanser paru – paru antara 1hb Januari 2016 sehingga 31hb December 2020 di Klinik Respiratori HRPZ II. Data – data demografik pesakit, status ECOG, tahap kesihatan, jenis – jenis histologi, status mutasi EGFR, comorbid, jenis rawatan yang diberikan, dan komplikasi selepas rawatan telah diambil dan disimpan. Tarikh daripada keputusan ujian pengesahan histologi atau sitologi telah diambil sebagai tarikh permulaan sesuatu penyakit. Kadar kelangsungan hidup dikira daripada tarikh pengesahan permulaan penyakit sehingga tarikh kematian.

Keputusan: Seramai seratus lapan puluh pesakit telah menjalani analisa kelangsungan hayat. Pesakit *Non-Small Cell Lung Cancer (NSCLC)* kebanyakannya daripada lelaki, perokok, dan umur kurang daripada 65 tahun. *Adenocarcinoma* 154 (85.6%), merupakan jenis histologi *Non-Small Cell Lung Cancer (NSCLC)* yang paling kerap ditemukan jika dibandingkan dengan *non-adenocarcinoma* 26 (14.4%). Semua histologi *adenocarcinoma* telah menjalani ujian molekular *EGFR* dan keputusan menemukan bahwa mutasi pada *deletion exon 19* 34 (54.0%) adalah yang paling kerap ditemukan jika dibandingkan mutasi yang lain. Waktu kelangsungan hidup purata untuk pesakit *NSCLC* adalah 7.69 bulan. Kadar peratus kelangsungan hidup untuk setahun, 2 tahun dan 3 tahun adalah 28%, 10% dan 3%. Analisa *Multiple Cox Regression* telah memberikan dua faktor

prognostik yaitu mutasi *EGFR* dan jenis – jenis rawatan. *Exon 19 deletion*, *exon 21 T790M point mutation* dan *exon 21 L858R mutation* telah memberikan faktor prognostik yang baik untuk memperpanjangkan kelangsungan hayat untuk pesakit *NSCLC* dengan nisbah hazard 0.084 (95% CI; 0.021, 0.337; $P < 0.000$), 0.048 (95% CI; 0.009,0.268; $P < 0.001$) and 0.067 (95% CI; 0.015, 0.287; $P < 0.000$). Terapi *EGFR – TKIs* ejen sahaja dan gabungan terapi (kemoterapi dan *EGFR – TKIs*) juga telah memberikan faktor prognostik yang baik untuk memperpanjangkan kelangsungan hayat untuk pesakit *NSCLC* dengan nisbah hazard 0.021 (95% CI 0.006, 0.076; $P < 0.000$) dan 0.006 (95% CI 0.001, 0.026; $P < 0.000$).

Kesimpulan: Waktu kelangsungan hidup purata bagi pesakit *NSCLC* adalah sangat pendek. Terapi *EGFR – TKIs* sahaja dan gabungan terapi (kemoterapi dan *EGFR – TKIs*) telah dikenal pasti sebagai faktor prognostik yang bagus jika dibandingkan dengan terapi sokongan sahaja.

Kata kunci : Adenocarcinoma NSCLC, EGFR mutasi, kadar kelansungan hidup, kelansungan hidup purata, faktor – faktor, EGFR – TKIs

ABSTRACT

Background: The main objective in this study is to determine the 1 year overall survival rate and to describe prognostic factors that affected survival of lung cancer patients in Kelantan population.

Methods: This was a retrospective study of Non-Small Cell Lung Cancer (NSCLC) patients carried out from 1st January 2016 until 31st December 2020. Participants were recruited from Respiratory Clinic (RC) Hospital Raja Perempuan Zainab II (HRPZ II). Detailed demographic data, Eastern Cooperative Oncology Group Performance Status (ECOG PS), stage of disease, type of histology, presence of EGFR mutation, distance metastasis, co-morbid, type of treatment and post treatment complications were recorded. The date of histology or cytology confirmation test was used as the date of entry. Survival time was calculated from the date of entry to the date of death.

Results: One hundred and eighty participants were included for survival analysis. Non – Small Cell Lung Cancer (NSCLC) patients predominantly male, smokers and aged less 65 years old. Adenocarcinoma 154 (85.6%) is the most common NSCLC subtype as compared to non adenocarcinoma 26 (14.4%). All adenocarcinoma patients were tested for EGFR molecular test and the results showed deletion exon 19 34 (54.0 %) was the most common point mutation compared to other mutation. The overall median survival time was 7.69 months (95% CI: 6.176, 9.200). The probability of survival in 1-year, 2-years and 3-years periods were 28%, 10% and 3%, respectively. Multiple Cox Regression analysis revealed that two significant prognostic factors were sub type EGFR mutation and type of treatment. Exon 19 deletion, exon 20 T790M point mutation and exon 21 L858R mutation were a significant independent prolonged survival with hazard ratio

0.084 (95% CI; 0.021, 0.337; $P < 0.000$), 0.048 (95% CI; 0.009, 0.268; $P < 0.001$) and 0.067 (95% CI; 0.015, 0.287; $P < 0.000$) respectively. EGFR – TKIs alone and combination therapy (chemotherapy and EGFR – TKIs) were a significant independent prolonged survival with hazard ratio 0.021 (95% CI 0.006, 0.076; $P < 0.000$) and 0.006 (95% CI 0.001, 0.026; $P < 0.000$) respectively.

Conclusion: The overall median survival time among NSCLC patients in HRPZ II was revealed to be longer than previous study (7.69 months versus 4.5 months). EGFR – TKIs therapy alone and combination therapy (chemotherapy with EGFR – TKIs) were identified as independent good prognostic factors as compared to supportive therapy.

Keywords: Adenocarcinoma NSCLC, EGFR mutation, overall survival rate, median survival, factors, EGFR – TKIs.

CHAPTER 1

INTRODUCTION

1.1 Introduction

Cancer is the second leading cause of death worldwide behind cardiovascular diseases. Globally in 2015, there were 17.5 million cancer cases worldwide and 8.7 million deaths due to cancer (Fitzmaurice *et al.*, 2017). There were 2 million cases of lung cancer and 1.7 million death was reported worldwide.

Lung cancer was the second most common cancer in men accounting for 1.4 million cases in 2015, after prostate cancer with 1.6 million cases. However, lung cancer has become the most common cause of cancer deaths in men accounting for 1.21 million deaths (Fitzmaurice *et al.*, 2017). For women, lung cancer is the third common occurrence of cancer accounting for about 640 000 cases after breast and colorectal cancer. However, lung cancer is second cancer death accounting for 517 000 after breast cancer (Fitzmaurice *et al.*, 2017).

In Malaysia, lung cancer is the third most common cancer, accounting for 10.2% of all cancer cases (Rajadurai *et al.*, 2020). Adenocarcinoma NSCLC is the most common lung cancer type among Malaysians. Between 2007 – 2011, 66.4% of males and 70.4% of females lung cancer patients were diagnosed with Stage IV, inoperable locally advanced or metastatic disease (Azizah Ab M, 2015). In a study of lung cancer survival at a single referral hospital in Malaysia, all patients presented were either in stage III or stage IV of the disease (Rajadurai *et al.*, 2020). Most of the time, the treatment option for this group is chemotherapy, but majority patients refused treatment because of the side

effects of chemotherapy drugs. Thus, this contributes to higher death and mortality rate among lung cancer patients.

Epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein that is coded by a gene located at the short arm of chromosome 7 (Liam *et al.*, 2013). Mutations in EGFR causes continuous tyrosine kinase activities that can lead to uncontrolled cellular proliferation, differentiation, migration and survival which ultimately leads to lung cancer development. Presence of activating mutations in the epidermal growth factor receptor (EGFR) of Non-Small Cell Lung Cancer (NSCLC) predict clinical response to gefitinib and erlotinib.

Gefitinib and erlotinib are first generation reversible EGFR – tyrosine kinase inhibitors (EGFR – TKIs) (Liam *et al.*, 2014). These oral medication is very good in treating NSCLC patients especially for patients with EGFR mutation detected. Previous studies mentioned that first generation EGFR – TKIs are potential as first line therapy for NSCLC patients with EGFR mutation detected (deletion in exon 19 [Del19] or the exon 21 substitution, L858R) as it's has proven effective, improved mortality, prolonged overall survival and improved progressive free survival compared to chemotherapy (Fukuoka *et al.*, 2011; Y. L. Wu *et al.*, 2015; Abdullah *et al.*, 2016).

However, most patients will develop resistance to these agents after 10 to 14 months of treatment due to acquired resistance mechanisms (Gao *et al.*, 2019; Rajadurai *et al.*, 2019). Acquired resistance mechanisms can be classified in three categories: secondary EGFR point mutation such as acquired T790M mutation in exon 20, bypass signalling pathway activations and histologic changes such as small cell lung cancer transformation (Gao *et al.*, 2019; Gelatti, Drilon and Santini, 2019; Shah and Lester, 2020). Thus, these patients required second or third generations EGFR – TKIs.

Afatinib is the second generation EGFR – TKIs, an irreversible ErbB family blockers. Afatinib has been shown to be more effective compared to chemotherapy and first generation EGFR – TKIs for treatment in advanced NSCLC with EGFR mutation detected. Afatinib also indicated for advanced squamous cell carcinoma as a second line therapy after failed first line chemotherapy (Yang *et al.*, 2015; Ho *et al.*, 2019). Osimertinib is a third generation irreversible and wild – type sparing EGFR – TKIs. Osimertinib were indicated for advanced NSCLC patients with T790M mutation detected, patients who have developed disease progression with presence acquired T790M mutation and treatment failure after on treatment with first generation EGFR – TKIs (Gao *et al.*, 2019; Gelatti, Drilon and Santini, 2019; Shah and Lester, 2020).

1.2 Problem statement and study rational

1.2.1 Problem statement

Most of the lung cancer in Malaysia presents at the advanced stage, which is stage III and IV. The definitive treatment for early stage lung cancer is surgical operation, but surgery is no longer an option when the disease is in the advanced stage. Even among patients who are operable, more than half have refused surgery and opted for alternative treatment (Chan Siang and Kok Meng John, 2016).

Chemotherapy with or without radiotherapy is the treatment of choice in this group of patients but some patients refuse chemotherapy treatment as they fear of complications post chemotherapy. Some lung cancer patients are not suitable to receive chemotherapy treatment due to ECOG performance status (ECOG PS) more than three, fragile and have comorbid such Ischemic Heart Disease (IHD) and Chronic Hepatitis C Virus (HCV) which can worsen the condition of patients, subsequently post

chemotherapy complications such as hepatitis flare and cardiomyopathy. All these factors lead to early mortality and death among lung cancer patients.

Emergence of molecular biomarker testing such as Epidermal Growth Factor Receptor (EGFR) mutation and ALK arrangement in advance stage lung cancer especially in NSCLC is now considered standard of care and treatment. Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR - TKI) has been shown to improve overall survival of NSCLC patients with EGFR mutation detected. This targeted therapy in the oral form, is convenient for patients without hospital admission. However, despite the advantage of targeted therapy (EGFR – TKI) in advanced NSCLC, not all patients will respond well to EGFR – TKI therapy. It depends on mutation at the epidermal growth factor receptors. Deletion exon 19 is the most responsive with targeted therapy as compared to others mutations.

Some of the patients do not response well with EGFR – TKI which leads to treatment failure and disease progression. Thus this group needs to change treatment regime from first generation EGFR – TKI to second or third generation EGFR – TKIs or to chemotherapy regime as soon as possible to improve the survival of NSCLC patients. Unfortunately not all patients will opt for chemotherapy regime after treatment failure with targeted therapy.

1.2.2 Rationale of the study

Currently, there are no published study on survival of NSCLC patients in Kelantan. We hope to identify the survival and associated factors of mortality of NSCLC patients in our population that contribute to an early death. Consequently, we aim to improve the treatment options for lung cancer patients especially in advanced non- small

cell lung cancer (NSCLC) with EGFR mutation positive. In view of that majority of NSCLC patients presented at the later stage, there is a need to increase awareness among local population regarding early screening if they have respiratory symptoms to detect the diseases at an earlier stage. Thus, they can receive treatment and have a better chance of survival.

1.3 Research Questions

1. What is the proportion of adenocarcinoma NSCLC with EGFR mutation in HRPZ II ?
2. What are the demographic and clinical characteristics of NSCLC patients in HRPZ II ?
3. What is the overall survival rate at 1 year of diagnosis for NSCLC patients in HRPZ II ?
4. What are the factors associated with mortality in NSCLC among patients in HRPZ II ?

1.4 Research Hypothesis

1. There are association between the presence of EGFR mutation, the treatment type with mortality among NSCLC patients in HRPZ II.

1.5 Research Objectives

General Objective:

1. To determine overall survival of NSCLC patients at 1- year and the associated factors with mortality at Hospital Raja Perempuan Zainab II (HRPZ II).

Specific Objective:

1. To describe the proportion of Adenocarcinoma NSCLC with EGFR mutation in HRPZ II.
2. To describe the demographic and clinical characteristic of NSCLC patients in HRPZ II.
3. To determine overall survival rate at 1 – year diagnosis of NSCLC patients in HRPZ II.
4. To determine the factors associated with mortality of NSCLC patients in HRPZ II.

CHAPTER 2

LITERATURE REVIEW

2.1 Smoking or Tobacco Exposure Related with Gender/Sex

Cigarette smoking and tobacco exposure are the risk factors for developing lung cancer (Barta, Powell and Wisnivesky, 2019). A significant smoking history has an impact and outcome to lung cancer patients. The prevalence of smoking among Malaysians is very high despite having awareness campaigns on the effects of smoking by the Malaysia government. Nearly 90% of male lung cancer patients have a significant smoking history (Rajadurai *et al.*, 2020). However, compared to young female lung cancer patients, majority are non smokers (Cho *et al.*, 2017).

Many studies have mentioned that adenocarcinoma NSCLC was mostly found in women and not in patients who are smokers (Cho *et al.*, 2017; Lofling *et al.*, 2019). These two factors give a better outcome for NSCLC patients together with presence of driver mutation such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) (Cho *et al.*, 2017; Radkiewicz *et al.*, 2019). Compared to women, men with exposure to tobacco smoking had a poorer prognosis and increase mortality as compared to women regardless of the stage of disease in adenocarcinoma NSCLC (Radkiewicz *et al.*, 2019). Thus, a significant history of smoking is an independent poor prognostic factor and one of the risk factors that increases mortality in NSCLC.

2.2 ECOG Performance Status (PS)

Performance status is the assessment of patients' wellbeing. It measures the impact of tumour symptoms, together with other pre – existing medical condition with

patients' daily life and the ability of self care. The two common scales that are used in daily practice are the Karnofsky scale and the Eastern Cooperative Oncology Group scale (ECOG) performance status. These two scales are very useful in managing lung cancer to avoid the use of unnecessary harmful therapy in the end stage of life. ECOG performance status (ECOG PS) is an evaluation scale 0 – 5 based on the level of symptoms affecting normal activity and proportion of waking hours spent in bed (Sehgal *et al.*, 2021). ECOG performance status 3 – 4 score will cause early death, increase mortality and associated with poorer prognosis of lung cancer as compared to ECOG 1 – 2 (How *et al.*, 2015).

2.3 Non - Small Cell Lung Cancer (NSCLC)

Lung cancer can be divided into two subgroups, primary and secondary lung cancer. The primary lung cancer is diagnosed based on histopathology examination (HPE) and immune – histo chemical markers. For therapeutic purposes, two broad classes are distinguished based on the size and appearance of malignant cells: non-small cell lung cancer (NSCLC) and small-cell lung cancer (SCLC). The three main subtypes of NSCLC are adenocarcinoma, squamous-cell carcinoma and large cell carcinoma.

Non-small cell lung cancer (NSCLC) represents 85% of all lung cancers followed squamous cell carcinoma and large cell carcinoma (Moumtzi *et al.*, 2016). In NSCLC, adenocarcinoma is the most common subtype, have the best prognosis and outcome compared to squamous cell carcinoma and large cell carcinoma. Large cell carcinoma recorded the shortest survival compared to adenocarcinoma and squamous cell carcinoma (Molinier *et al.*, 2020).

Another study was done by Radkiewicz *et al.*, regarding sex related with survival in non-small cell lung cancer (NSCLC) patients. They do a comparison between

adenocarcinoma type and squamous cell carcinoma type in lung cancer patients. As we know that, adenocarcinoma histology type is the most good prognosis and outcome in lung cancer patients. However, in this study, they found that men gender with lung adenocarcinoma had a poorer prognosis compared to women regardless of stage (Radkiewicz *et al.*, 2019). Therefore, even though lung adenocarcinoma is the good prognostic factors in NSCLC, the men gender will give a significant poor prognostic factor in NSCLC compare to the female gender.

2.4 Staging of the Lung Cancer

Clinical TNM (cTNM) staging plays a role in predicting survivor as well as definitive management in NSCLC patients. The tumour staging (T stage) is determined by the size of the primary tumour and its involvement with the adjacent structure. For T – stage, prognosis was analysed in patients with NSCLC, with or without nodal involvement, and without metastatic disease. From journal article by Lim *et al.*, they found that there is a poorer prognosis with each centimetre (cm) increase in tumour size. Thus, T staging more than T3 and above will give a poorer outcome and prognosis in lung cancer patients (Lim *et al.*, 2018). The nodal staging (N stage) is for assessment tumour nodal metastasis in the regional hilar and mediastinal nodes. The more nodal stations that are involved, the worse the prognosis. The metastasis staging (M staging) is defined by the presence of metastasis beyond the regional lymph nodes (Mirsadraee, 2012).

Based on the 7th edition of the International Association for the Study of Lung Cancer (IASLC)/ Union for International Cancer Control (UICC) TNM staging classification, advanced lung cancer is defined as stage III or locally advanced and stage IV or metastatic disease (Mirsadraee, 2012). However, stage III disease is further subdivided into IIIA and IIIB where it is classified into resectable/possible resectable and

unresectable primary tumours, respectively. Stage IIIB is defined as a primary tumour extension into extrapulmonary structures (T3 or T4) or mediastinal lymph node involvement (N2 or N3) without evidence of metastases (M0). Stage IV is defined as any T, any N with the presence of distant metastases beyond regional lymph nodes (M1) (Mirsadraee, 2012). However, the term ‘advanced’ in lung cancer refers to unresectable stages which is stage IIIB or stage IVA – C.

2.5 Distance Metastasis of the Lung Cancer.

Another condition we must be concerned with in lung cancer patients, is distant metastasis to another organ such as lung, pleural, liver, bone, brain, spleen, bone marrow, and adrenal gland. They are classified as M1 disease and represent terminal stage cancer (stage IV). The distant metastasis in lung cancer patients will give poorer outcome as it reduces the effectiveness of the treatment including chemotherapy, epidermal growth factor tyrosine kinase inhibitors (EGFR- TKIs), and immune checkpoint inhibitor (Shiroyama *et al.*, 2018).

In one retrospective study conducted by Li J *et al.*, it reported that multiple organ metastases are very common in NSCLC. For patients with isolated metastasis, bone was the most common metastases site, followed by contralateral lung, brain, liver in NSCLC (Li *et al.*, 2019). Majority of lung cancer patients suffer from bone metastases, mainly spine and rib involvement. Bone metastases was more common among adenocarcinoma. This bone metastases will involve significant morbidity, metabolic disorders such as hypercalcemia, pathologic fractures, and spinal cord compression. These complications substantially reduce quality of life, increase economic burden, give a poorer prognosis and increase risk of death (Cho *et al.*, 2019, Silva *et al.*, 2019).

In the survival analysis, they found that NSCLC patients with liver metastases had

the worst survival rate than those diagnosed with isolated metastases (Wu *et al.*, 2015). Another study by Chang *et al.* and Wu *et al.* also had similar findings with Li J *et al.* study (Chang *et al.*, 2017). The results showed that, presence of liver metastasis in stage IV EGFR –mutant NSCLC patients had a worse prognosis than those without liver metastasis (Chang *et al.*, 2017; Wu *et al.*, 2015). Patients with lung metastases had the best survival outcome, followed by bone metastases and brain metastases in NSCLC (Li *et al.*, 2019). Thus, distant metastasis has a worse prognostic factor and increases mortality in lung cancer patients.

2.6 Molecular Testing in Advanced Lung Cancer.

Lung tissue biopsy is mandatory to make an accurate initial diagnosis of lung cancer. It is very important to save sufficient tissue for determination of the histological subtype and molecular testing. Emergence of the epidermal growth factor receptor (EGFR) molecular biomarker testing of advanced-stage NSCLC is now considered standard of care and part of the diagnostic algorithm to identify subsets of patients for molecular – targeted treatment (Liam *et al.*, 2015).

Epidermal growth factor receptor (EGFR) is a plasma membrane glycoprotein that belongs to a family of four different tyrosine kinase receptors (EGFR(ErbB1), HER2/neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4)) (Othman and Nagoor, 2014). Dimerization and alteration of EGFR may result in cancer cell proliferation, inhibition of apoptosis, invasion, metastasis, and tumour induced neovascularization (Yoon *et al.*, 2020). Specific mutations and subsequent overexpression in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR) can be found in all histologic subtypes of NSCLC (Shim *et al.*, 2017).

Approximately 60% of patients with advanced adenocarcinoma subtype of NSCLC have an identified molecular alteration that may be beneficial with treatment EGFR – targeting tyrosine kinase inhibitors (EGFR – TKIs). Malaysian patients with NSCLC, the EGFR mutation rate was found to be nearly 40% of adenocarcinoma NSCLC, higher rates of EGFR mutations were found in women, as compared to men and higher incidence in non smokers compared to smokers (Liam *et al.*, 2014).

Causative genomic alteration in EGFR including exon 18 sensitizing mutations, deletion in exon 19, exon 20 T790M resistant mutation and point mutation in exon 21 L858R. Deletions in exon 19 and a point mutation in E21, are known to have favourable prognoses due to sensitivity to tyrosine kinase inhibitors. E19 deletions were the only significant factor that lowered mortality while an E21 mutation was the prognostic factor associated with the most increased mortality (Yoon *et al.*, 2020). The prognosis of other uncommon mutations are unclear.

2.7 Co – morbidities

Diabetes mellitus (DM) and cancer are common diseases with a rapidly increasing prevalence worldwide. The impact of DM on lung cancer survival is complicated. Some studies have reported an increase in survival, whereas others have reported a decrease in survival and risk of mortality (Zeng *et al.*, 2020). Hyperinsulinemia, hyperglycemia, and increased inflammatory cytokines in diabetic patients may cause cancer and promote cancer progression (Yu *et al.*, 2018). Hyperglycemia state can promote cancer proliferation via the induction of epidermal growth factor (EGF) expression and transactivation of the EGF receptor (Ogawa *et al.*, 2021). Thus, it is mandatory to do screening for diabetes in all cancer patients, treatment with proper anti diabetic agent

together with strict and proper glycemic control. This is because with strict and proper blood glucose control in diabetic patients diagnosed with lung cancer will have an impact and good prognosis in term of prolonging survival of patients (Bergamino *et al.*, 2019).

Once patients are diagnosed with underlying malignancy, it is mandatory to do viral screening for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) infection and Pulmonary Tuberculosis (PTB) infection prior to giving treatment of lung cancer either chemotherapy or tyrosine kinase inhibitor (TKI) to avoid flare or reactivation of these disease. Many studies mentioned that an acute flare of viral hepatitis B and hepatitis C infection give a poorer outcome and increase in mortality due to chronic injury to the liver and could eventually lead to liver cirrhosis and organ failure (Peng *et al.*, 2015; Wu *et al.*, 2017).

Tuberculosis (TB) remains the most common infectious disease worldwide and leads to high mortality especially in developing countries. The incidence of reactivation of pulmonary tuberculosis (PTB) in lung cancer patients increases in trend, especially after undergoing treatment of lung cancer such as chemotherapy, EGFR – TKIs agents and immunotherapy agents. Besides that, the risk of TB in patients with malignancy is due to immunosuppression from the cancer itself and local structural changes due to inflammation and fibrosis in the lungs by primary lung cancer or metastasis (Shu *et al.*, 2019).

Usually lung cancer patients present with malnourish and typically are underweight. Body weight loss in cancer patients is generally known as cancer cachexia, which is characterized by inflammation and abnormalities in their metabolism rate. Body weight loss has been reported to increase morbidity and mortality, and decrease the quality of life (Nakagawa *et al.*, 2016). Being underweight (BMI < 18.5 kg/m²) at the

time of diagnosis of advanced NSCLC has been reported to be associated with poor outcomes and higher risk of death (Tsang *et al.*, 2016).

2.8 Treatment and Management of Lung Cancer.

The most effective option for treatment of lung cancer is curative surgical resection provided early stage. The curative surgical resection is advantageous for those patients with stage IA, IB, IIA and IIB in NSCLC. In most cases of early-stage NSCLC, removal of a lobe of the lung (lobectomy) is the surgical treatment of choice. The outcome of surgical resection treatment is very good as it can improve mortality (Chan Siang and Kok Meng John, 2016). However, most patients with lung cancer do not undergo surgical resection. The main reason is because, patients usually came in with late and due to late symptoms manifestations diagnosed in advanced stage of the disease. In Malaysia, most lung cancer cases are diagnosed late with either locally advanced disease or distant metastasis. 75-88% of lung cancer cases are diagnosed with stage III or IV; these patients can only be offered palliative chemotherapy therapy (Chan Siang and Kok Meng John, 2016).

The most common first line chemotherapy for patients with advanced non – small cell lung cancer (NSCLC) is platinum based (cisplatin) combined with gemcitabine (Goffin *et al.*, 2010). The platinum coordinated complex is widely used for the past two decades (Leow and Liam, 2005). However, usage of platinum based alone can cause drug resistance, leading to failure of treatment. Therefore, there is a need to combine with gemcitabine. Gemcitabine is a pyrimidine nucleoside antimetabolite. It has been shown to be an effective agent particularly when administered in combination regime. The aim of this treatment is to reduce the size of primary lesion and number of metastasis and/or

disappearance of cancer invasion and to improve the survival rate of these patients (Leow and Liam, 2005).

The recent management and treatment of lung cancer is a biologically targeted therapy, EGFR – Tyrosine Kinase Inhibitors (EGFR-TKIs) such as gefitinib, erlotinib and afatinib. These drugs, first generation EGFR-TKIs gefitinib and erlotinib function by selectively targeting the receptor via a competitive, reversible binding at the tyrosine kinase domain, thus leading to the inhibition of ATP binding and subsequent signal transduction and downstream functions (Zhang *et al.*, 2016). These drugs are very effective, improved outcome and survival, as well as be given as monotherapy treatment for those patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) compared to chemotherapy group (Y. L. Wu *et al.*, 2015; Abdullah *et al.*, 2016).

EGFR – TKIs agents can improve clinical outcome and improved overall survival as compared to chemotherapy alone in advanced NSCLC with EGFR detected patients. However, most patients will develop acquired resistance to these agents after 12 months of treatment and up to 30% advanced NSCLC EGFR detected patients do not respond to EGFR – TKIs agents and subsequent fall into disease progression stage. The most common symptoms of disease progression are cough and shortness of breath. The most common site of disease progression is the lung followed by central nervous system, pleural and bone (Gao *et al.*, 2018).

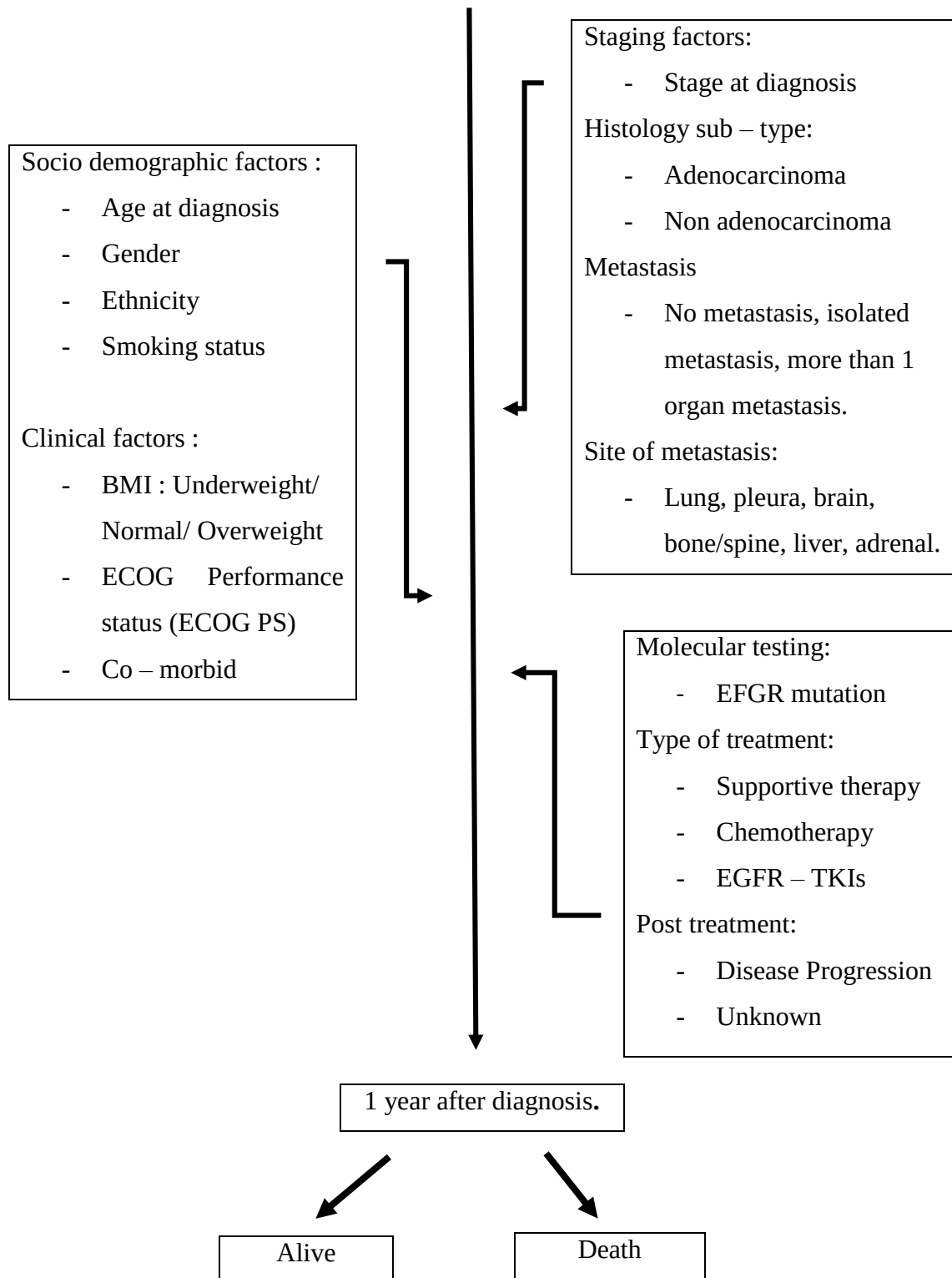
Thus, in view to overcome acquired resistance to EGFR-TKIs, a combination of EGFR – TKIs therapies with chemotherapy has been shown good results, improved clinical outcome and survival. Combination platinum – based chemotherapy with EGFR – TKIs can be given either in concurrent combinations or intercalated combinations (Rebuzzi *et al.*, 2020). These regime can be given in EGFR detected NSCLC patients or

unselected NSCLC patients. Based on previous study, they found that this regime is advantage to EGFR mutation detected NSCLC patients in term of improved overall survival and progressive- free survival compared to unselected NSCLC patients (Rebuzzi *et al.*, 2020). These finding demonstrated that the EGFR mutation status may serve as a biomarker to identify patients who can benefit from the combination therapy especially for those who have minimal benefit from EGFR – TKIs monotherapy (Wen *et al.*, 2018).

A randomized controlled trial was done by Han B *et al.*, regarding combination of platinum based chemotherapy and EGFR – TKIs (gefitinib) as first line treatment for patients with advanced lung adenocarcinoma with EGFR detected. From this study, the results showed a significant and promising finding. Patients who is received EGFR – TKIs (gefitinib) combined with platinum based chemotherapy had averaged 18 months progression-free survival (PFS), compared to 6 months for chemotherapy alone and 12 months with only EGFR – TKIs (gefitinib) (Han, B *et al.*, 2017). Gemcitabine is a cytotoxic agent used in NSCLC therapy. It also was used in combination therapy with EGFR – TKIs to produces a synergistic anti-cancer effect. Pemetrexed has recently been developed to suppress the metabolism of intracellular folic acid and thus prevent cell division. A combination of pemetrexed and EGFR – TKIs has been proven to overcome EGFR – TKIs acquired resistance (Yang Z *et al.*, 2018).

Conceptual Framework

All patients who were diagnosed as NSCLC confirmed by histopathology examination (HPE) or cytology examination.



CHAPTER 3

METHODOLOGY

3.1 Study Design

This is a retrospective cohort study involving a review of medical records of HRPZ II Lung Cancer patients who is registered and undergoing follow up in the Respiratory Clinic (RC) or admission to the general medical wards in HRPZ II.

3.2 Study Duration

Duration of cases were enrolled in this study between 1st January 2016 until 31st December 2020.

3.3 Study Area

This study was conducted at the Respiratory Clinic HRPZ II Kota Bharu, Kelantan which is the tertiary centre for referral of most respiratory patients from the different Kelantan districts.

3.4 Reference Population

Patients with lung cancer in Kelantan.

3.5 Source Population

All patients with Lung Cancer who have been registered under Respiratory Clinic (RC) HRPZ II Kota Bharu, Kelantan between 1st January 2016 until 31st December 2020.

3.6 Sampling frame

Lung cancer patients who have been registered under Respiratory Clinic (RC) HRPZ II Kota Bharu, Kelantan between 1st January 2016 until 31st December 2020 and who have fulfilled the inclusion and exclusion criteria.

3.7 Study Subjects

All lung cancer patients who fulfilled the inclusion and exclusion criteria and registered with Respiratory Clinic (RC) HRPZ II.

3.8 Subjects Criteria

3.8.1 Inclusion Criteria:

1. All patients age 18 years old and above
2. The definitive diagnosis of lung cancer was confirmed based on histological or cytological examinations and the result showed primary lung cancer with NSCLC.
3. Subjects were followed up Respiratory Clinic in HRPZ II.

3.8.2 Exclusion Criteria:

1. Patients with diagnosis of lung secondary, mesothelioma, inconclusive histologic diagnosis or unknown outcome were excluded from this study.
2. Records with 20% of data missing, were excluded from this study.

3.9 Sampling Method

An initial screening of all lung cancer patients will be conducted by using the database registry of patients that have attended Respiratory Clinic in Hospital Raja Perempuan Zainab II (HRPZ II). Patients who were diagnosed with Non-small Cell Lung Cancer (NSCLC) from year 1st January 2016 until 31st December 2020 will be reviewed and screened based on the inclusion and exclusion criteria. Therefore, simple random sampling method was used.

3.10 Sample size calculation

3.10.1 Objective 2 and 3: To determine the overall survival rate at 1 year diagnosis and its associated factors with mortality among NSCLC patients in HRPZ II.

The sample size was calculated using Power and Sample Size (PS) software version 3.1.6 (Dupont and Plummer, Vanderbilt, USA; 2018). The sample size calculation was performed with the requirement for significant levels (α), 0.05 and power (1- β), 0.8 (80%) using Power and Sample Size Calculation (PS). Median survival time on the control treatment (m_1) and the ratio of control to experimental patients (m) was obtained from literature and clinical expert opinion. The accrual time during which the patient was

recruited (A) is 60 months, and additional follow up time after the end of recruitment (F) is 12 months.

Table 3.1: Sample Size calculation

Prognostic factor	R	m_1	M	N	n x m	Total sample	After adding additional 20%
ECOG PS (How et al., 2014)	1.8	5.5	1.8	38	68.4	106.4	127.70
Definitive treatment (How et al., 2014)	1.8	7.5	0.88	55	48.5	103.4	124.08
Gender Female (Liam et al., 2012)	1.8	9.75	1.08	53	57.24	110.24	132.28

Based on the calculation, the sample size required for this study is 124. After adding 20% anticipated drop – out due to missing data, the required sample size is 148.

3.11 Study/ Research tools

An initial survey based upon HRPZ II registration numbers was conducted to screen for potential and eligible patients that would be included in the study. Information on the relevant parameters was retrieved from the medical records of patients who fulfilled the inclusion and exclusion criteria and recorded in the proforma. The survival status was ascertained by checking in ‘Aplikasi Sistem Pengurusan Pesakit (SPP)’ and overall survival time was then calculated by manual calculation. The data in proforma were

subsequently transferred into SPSS data spreadsheet and stored in a password-protected computer folder which is totally inaccessible except to the principle investigator. This is to ensure no unintentional or intentional breach of a patients' confidentiality occurs during the course of the study.

Table 3.2 Proforma / Data Collection Sheet

Patients ID	Example : 001			
Age				
Sex	Male			
	Female			
Race	Malay			
	Non – Malay			
Smoking status	Non smoker			
	Smoker			
Weight (kg)				
Height (cm)				
Body mass index (BMI)	Underweight			
	Normal			
	Overweight			
ECOG PS				
Co Morbid	No			
	Yes	If Yes:		
Date of Diagnosis				
Histology/ cytology type	Adenocarcinoma			
	Non adenocarcinoma			
Staging at diagnosis	Stage IIIA Stage IIIB Stage IV			
Molecular testing - EGFR Mutation	No			
	Yes	If yes:		
		- Non detected		
		- Detected		
			- E18	
		- E 19		

			- E 20	
			- E 21	
Treatment option	Supportive therapy			
	Chemotherapy			
	Targeted therapy			
	Combination chemotherapy and targeted therapy			
Post treatment outcome/ complication	Unknown status			
	Disease Progression			
Date of death				

3.12 Operational Definitions of Study Variables

Table 3.3 Operational Definitions.

Event	Death of any causes within a determined study period.
Censored	Patients who is alive during the study period.
Date of tissue diagnosis	The date when the specimen was taken and confirmed histo/cyto pathological diagnosis.
Survival time	The number of months from the date of tissue diagnosis to the date in which patient died.
Median survival time	The first observed time at which the cumulative survival was 50% or less.
Age	Age was classified into 2 main groups, less 65 years old and more 65 years old.
Advanced stage	Advanced stage in lung cancer refers to unresectable stages which are stage IIIB or stage IV.
Smoker	Non – smoker is defined as they had never smoked during their lifetime. Smoker is defined as they had smoked in their lifetime or is still smoking.
Body Mass Index (BMI)	Body weight (kg) and height (m) of patients were documented during the 1 st presentation at Respiratory Clinical (RC) HRPZ II. BMI was

	calculated using formula $\text{weight (kg)} / \text{height (m}^2\text{)}$. The BMI classifications are based on the Western Pacific Regional Office (WPRO) of WHO. Underweight is $< 18.5 \text{ kg/m}^2$. Normal BMI is $18.5 - 22.9 \text{ kg/m}^2$. Overweight is $23.0 - 24.9 \text{ kg/m}^2$. Obesity is $> 25.0 \text{ kg/m}^2$.
Eastern Cooperative Oncology Group (ECOG) Performance Status	Patients' performance status at diagnosis was categorized in accordance with the Eastern Cooperative Oncology Group (ECOG) performance status. Scores 0: Fully active, able to carry on all pre – disease performance without restriction. Scores 1: Restricted in physical strenuous activity, but ambulatory and able to carry out light work and sedentary (lighthouse work, office work). Scores 2: Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours. Scores 3: Capable of only limited self care, confined to bed or chair more than 50% of waking hours. Scores 4: Completely disable. Cannot carry on any self care. Totally confined to bed or chair. Scores 5: Dead.
Comorbid:	No known medical illness is defined as patients did not have any medical illness during diagnosis was made. Non Communicable Disease included cardiovascular disease (such as Ischemic Heart Disease and stroke), all cancers, chronic respiratory disease (such as chronic obstructive pulmonary disease and asthma) and diabetes. Infectious disease included HIV infection, Chronic Hepatitis C and Chronic Hepatitis B. All haematological disorder included IDA, anaemia in chronic illness, Thalassemia.