

A Follow Up Study on Lung Cancer Survival in the State Hospital in East Coast State of Pahang

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ABSTRACT

INTRODUCTION: There is lack of data of lung cancer survival in Malaysia. **MATERIAL AND METHODS:** This study was to determine the survival of lung cancer patients and factors affecting the survival in Kuantan, Pahang. A total of 170 lung cancer patients confirmed by histology from 1st January 2014 to 31 December 2017 were recruited in the study. Their demographic data, ECOG performance status, staging and treatment were recorded. Survival time was defined in weeks from the date of histological diagnosis made to the date of death of the patients. Kaplan-Meier curve was used to determine the median overall survival and log-rank test was used to test the survival differences between each subgroup. Multivariate analysis using COX regression was used to determine factors affecting its survival. **RESULTS:** The median age of the 170 patients was 63 years old, majority were males (74%) and smokers (64%). Adenocarcinoma (74.7%) was the most common histology followed by squamous cell carcinoma (18.8%). Almost all patient presented at the clinic at stage 3 or 4 (98%) but majority had ECOG 0-2 (64.3%). Median overall survival was 28.7 weeks. In the multivariate analysis, “supportive treatment” and “poor ECOG performance status” were independent predictors of death with the hazard ratio of 1.4 (95%CI 1.17 to 1.66) and 3.0 (95%CI 2.05 to 4.39) times respectively. **CONCLUSION:** Majority of lung cancer patients in Pahang presented with advanced disease with overall median survival of 28.7 weeks. Patients treated with supportive care and poor ECOG performance status were the two independent poor prognostic factors for survival.

Keywords

Lung cancer survival, HTAA, Pahang

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INTRODUCTION

According to World Health Organization, lung cancer is one of the commonest reported cancers worldwide with an incidence of 11.6% on top of highest reported mortality of 18.4% in year 2018.^{1,5,13,24} In Malaysia, lung cancer is the third commonest cancer (10.2%) and has poorest median survival time of 6.63 months in year 2007-2011 compared to other cancers.^{13,19,21} In Pahang, an east coast states, the median survival was significantly shorter at 4.5 months in year 2007-2010.⁷ Only 14.8% of lung cancer patients survived 1 year after diagnosis compared to the national data of 35.5%.^{6,13} as majority of the patients presented at the clinics at late stages with poor functional status, or low Eastern Cooperation Oncology Group (ECOG) score. Some opted for conservative treatment without chemotherapy, and many

were unable to afford targeted therapy due to financial constraints.⁶

The landscape of lung cancer management markedly changed in recent years with discoveries of oncogenes and new targeted therapy. Targeted therapy is advocated to patients who harboured activating driver mutation whereas patients without driver mutation but expressed high PDL-1, are treated with immunotherapy alone or with combination of chemotherapy. These targeted therapy and immunotherapy have been shown to prolong overall survival (OS).^{2,7,14,15,18,19,23} This is evidenced by the growing number of patients receiving targeted therapy from 2014 to 2017 and therefore are expected to have better survival. However, lung cancer survival in Malaysia

is not well studied especially after the emergent of these novel lung cancer treatments. Therefore, this study was intended to measure the 1 year survival of and median overall survival of lung cancer patients in Hospital Tengku Ampuan Afzan (HTAA), Kuantan and to determine factors that affect lung cancer survival.

MATERIALS AND METHODS

This was a three-year retrospective cohort study carried out at HTAA, Pahang from January 2014 to December 2019. HTAA is a tertiary government hospital which provides lung cancer treatment in Pahang. Currently another University hospital is also providing lung cancer treatment in Pahang; the Sultan Ahmad Shah Medical Centre. This study received the approval of the Malaysian Research Ethical Committee.

The methodology of this study is shown in Figure 1. Details of-demography, patient characteristics, and disease characteristic of patients were retrieved from hospital administration records, clinic Records, Endoscopic suite, and Histopathology laboratory registries and transcribed into clinical record form (CRF). The outcome of the condition of the patients were recorded for at least 2 years from date of diagnosis and it was retrieved from HTAA administration records, whereas for the patients without outcome record in hospital, the death dates were retrieved from National Registry Department (NRD).

The detailed demographic data of the patients, occupation, smoking history, number of smoking in packs year unit, underlying lung disease, staging, ECOG performance status, treatment and treatment outcome was recorded. Non-smokers were defined as those who have smoked less than 100 cigarettes before the date of diagnosis. Smokers further divided into group of those smoked more than 15 packs year and less than 15 packs year. Staging was based on the 7th TNM clinical staging using computerized tomography (CT) of thorax and abdomen, CT of brain, bone scan or PET Positron Emission Tomography (PET) scan. Endobronchial Ultrasonography (EBUS) or thoracoscopy was also used to obtain histology and the staging. The performance status of the patients at presentation was

classified according to the Eastern Cooperation Oncology Group (ECOG). Good ECOG performance was defined as ECOG performance status of 0 to 2 and poor ECOG was 3 to 4. The treatment of advanced lung cancer was divided into two groups: 1) Supportive care which included radiotherapy for symptomatic relief without treatment mentioned in no 2, and 2) definite treatment with either curative operation or chemotherapy or targeted therapy (Epidermal Growth Factor Receptor Thyrosine Kinase Inhibitors -EGFR TKI and Anaplastic Lymphoma Kinase - ALK Inhibitor) or immunotherapy or combination of treatment modality, with or without radiotherapy.

Kaplan Meier survival curve used to describe the overall survival and subgroups. Log rank test was used to test the survival differences in each subgroup whereas multivariate analysis using Cox Regression hazard to determine the risk factor mortality and adjusted hazard ratio.

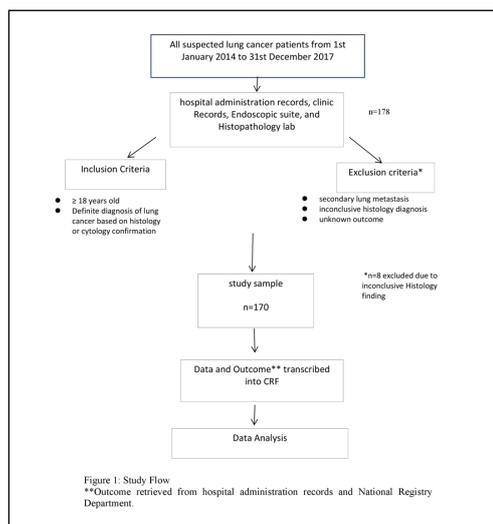


Figure 1: Study Flow
 **Outcome retrieved from hospital administration records and National Registry Department

RESULTS

Patient Characteristics

Data from a total number of 178 patients were included in this study. However, 8 of them were excluded because of inconclusive histology findings. The ages of patients ranged from 33 years to 86 years old with the median age of 63years old (IQR 9.4). Majority of them were males (74%). In all, Malays (69.4%) were most common

patients, followed by Chinese (25.9%), Aborigines (3%) and Indians (1.7%). Among those diagnosed with lung cancer, 64% were smokers (current active and ex-smoker). There were more male smokers (96.5%) than female smokers (3.5%).

Disease Characteristics

Majority of lung cancer patients in Kuantan were diagnosed with non-small cell lung carcinoma (NSCLC) which accounted for 98.2%, whereas small cell lung carcinoma was 1.8%. In subgroup of NSCLC, adenocarcinoma accounted for 74.7%, followed by Squamous cell carcinoma 18.8%, and NSCLC of Non otherwise specified -NOS accounts for 4.7%

There were only 2% of patients presenting with stage 2 and none in stage 1 lung cancer. Majority of patients presented with Stage 3 (18%) and stage 4 (80%). More than half of the numbers of patients presented with good ECOG (ECOG 1: 47.6%, ECOG 2: 16.5%), but only 46.7% (n=81) received definitive treatment; first-line treatment either targeted therapy n=36 (20.2%), or Chemotherapy n=34 (20%), or immunotherapy n=10 (5.9%) or operation n=1 (0.6%). Table I shows the demography and clinical presentation of the patients in the study.

Overall Survival

The median overall survival (MOS) for lung cancer patients in HTAA from year 2014 to year 2017 was 28.7 weeks (95% CI 15.7 ,41.7) and 1 year survival was 40.6%.

Patients who were diagnosed with adenocarcinoma had longer MOS 42.7weeks (95% CI 26.3, 59.2) compared to small cell lung cancer 14.4 weeks (95% CI 3.7, 25.2) and squamous cell carcinoma and others 14 weeks (95% CI 3.4, 24.6). Patients with good ECOG function had significant longer survival rate compared to those with poor ECOG function (MOS 62.2weeks vs 9.0 weeks, p <0.001) and patients who received definitive treatment lived longer compared with those received supportive treatment (75.4 weeks vs 10.6weeks, p<0.001). There was no significant difference in MOS for patients with different ages, gender, smoking status, frequency of

Table I: Demographic and basic characteristics of lung cancer patients in HTAA from year 2014-2017.

Characteristics	n=170
AGE, (in years)	
<60	53 (31%)
≥ 60	117(69%)
range	33yrs-86yrs
median	63yrs (IQR 9.4)
GENDER	n=170
Males	125 (74%)
Females	45 (26%)
RACE	n=170
Malay	118 (69.4%)
Chinese	44 (25.9%)
Others	8 (4.7%)
SMOKING STATUS	n=133
Smoker	85 (64%)
Non-Smoker	48 (36%)
SMOKING AMOUNT (in packs year)	n=91
≤ 15 packs year	56 (61.5%)
> 15 packs year	35 (38.5%)
HISTOLOGY	n=170
Non-Small Cancer Lung cancer	167 (98.2%)
Adenocarcinoma	127 (74.7%)
Squamous cell cancer	32 (18.8%)
Non-Otherwise Specified	8 (4.7%)
Small cell Lung cancer (SCLC)	3 (1.8%)
*ECOG	n=168
1	80 (47.6%)
2	28 (16.7%)
3	26 (15.5%)
4	34 (20.2%)
#CLINICAL STAGING, TNM	n=139
1	0
2	3 (2%)
3	25 (18%)
4	111 (80%)
Treatment	N=170
Definitive Therapy	81 (46.7%)
Targeted Therapy	36 (20.2%)
Immunotherapy	10 (5.9%)
Chemotherapy	34 (20.0%)
Operation	1 (0.6%)
Supportive therapy	89 (52.4%)

* ECOG: Eastern Cooperative Oncology Group - Functional Status

TNM - 7th lung cancer TNM classification and staging system

smoking and the stage of cancer (Table II). Kaplan Meier of overall survival, and different groups are shown in figure 2 and 3.

In multivariate analysis, only 2 factors are independently affecting the survival of lung cancer patients. Those were poor ECOG functional status with adjusted HR: 3.00, (95% CI 2.05 to 4.39, p<0.001) and supportive treatment with adjusted HR:1.4, (95% CI 1.17 to 1.66, p<0.001).

ECOG functional status and survival

Among the patients with good ECOG functional status who received definitive treatment, MOS was 79.1 weeks (95%CI 60.7, 97.6). On the other hand, patients with poor

Table II: Median Overall Survival (MOS) of lung cancer patients for various characteristics

	Med (weeks)	95% CI LL UL	X2 Logrank	df	P
Overall	28.7	15.7 - 41.7			
Age classification					
< 60years	45.6	34.0 - 57.1	1.368	1	0.242
≥60	21.3	10.9 - 31.7			
Sex					
Male	25.6	11.2 - 39.9	2.253	1	0.133
Female	61.3	30.7 - 91.8			
Race					
Malays	36.0	21.0 - 50.9	0.369	1	0.543
Non -Malays	25.6	4.4 - 46.8			
Smoking					
Ever smoked	26.1	10.1 - 42.2	1.034	1	0.309
Never smoked	41.1	22.4 - 59.9			
Smoking					
Non-smoker	41.1	22.9 - 56.7	3.000	2	0.223
≤15pack-years	74.6	-			
>15 pack-years	50.9	0.00- 105.9			
ECOG					
Good	62.3	49.0 - 75.5	61.11	1	<0.001
Poor	9.0	6.6 - 11.4			
Histology type					
SCLC	14.4	3.7 - 25.2	9.688	2	0.008
Adenocarcinoma	42.7	26.3 - 59.2			
Squamous cell and others	14.0	3.4 - 24.6			
Treatment					
Definitive	75.42	59.05 - 91.8	68.948	1	<0.001
Supportive Care	10.57	8.65 - 12.49			
Clinical Staging					
≤Stage 3	19.0	15.2 - 22.8	2.027	1	0.155
Stage 4	16.0	8.2 - 23.8			

ECOG, when treated with definitive treatment showed better MOS than those who were not (42.4 weeks vs 8.7 weeks).

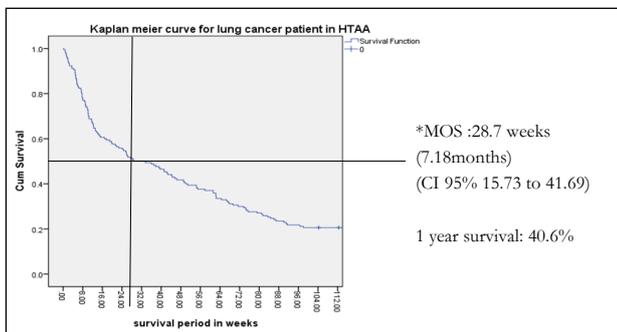


Figure 2: Overall Survival curve for lung cancer patient in HTAA from 2014-2017

Treatment modality and survival

Treatment modality is one of the independent predictors that affect survival of lung cancer patients. Among the patient who received definitive therapy those treated with immunotherapy had a longest MOS 83.4 weeks (95% CI 0.0, 167.1), followed by targeted therapy MOS 75.4 weeks (95% CI 49.4, 101.5), and chemotherapy MOS 64.5 weeks (95% CI 36.4, 92.8); (Table III)

DISCUSSION

The prevalence of lung cancer in Kuantan, Pahang was highest among Malay males, which is similar to the

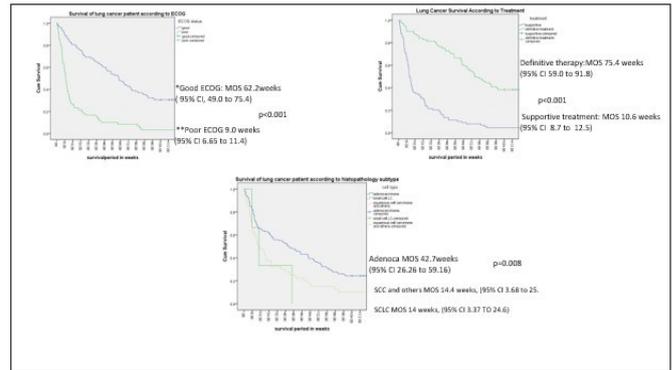


Figure 3: survival curve functional performance status (ECOG), survival curve for treatment type, and Lung cancer survival according to lung cancer histology sub-type

findings from previous national cancer registries.⁵ One of the reasons is that the smoking prevalence is highest among Malay males.¹¹ Among smokers, the ratio of male to female in this study was 27: 1, similar to the data from National Health and Morbidity Survey 2015 (31:1). This can be due to social norm where smoking habit by female is not well accepted in this part of Malaysia.¹¹ Majority of the patients (98%) in our study presented at advanced stage of lung cancer at diagnosis. This is similar to the data from a previous study that was conducted in HTAA Kuantan, Pahang a decade ago.⁶ In fact, the number of patients presented in early stage of disease in Malaysia including Pahang state is very low in comparison to any other developed countries. For example, data from United States of America between 1996-2003 was 16% of lung cancer patients presented with localized disease and the percentage improved to 20% in year 2015.²⁷ This is postulated to be due to the lack of free lung cancer screening program and lack of awareness about lung cancer in Malaysia.¹² Despite 65% of patients presented with good ECOG functional status, only 46.7% received definitive therapy.

The characteristics for both studies were similar for age, gender, racial distribution, ECOG on presentation, staging, and smoking status of patients compared to the

Table IV: Survival outcome of lung cancer patient based on treatment modality

Type of treatment	1 year survival (%)	MOS (Weeks)
supportive treatment	10.1	10.5
chemotherapy	67.7	64.5
Targeted therapy	83.3	75.4
Immunotherapy	60	83.4

study that was done 10 years ago. Compared to this previous study by How et al, there was a similar percentage of patient who received the definitive therapy, but the survival had improved by 60%. One of the reasons is that among the patients who were treated with definitive therapy in the current study, 44.4% received targeted therapy and 12.3% received Immunotherapy compared to a decade ago when chemotherapy was the only available first line treatment (table IV).

At the time of the previous study, the price of EGFR inhibitors (Gefitinib) was 50% more expensive than the current price, resulting in only a few patients who could afford this treatment, and the medication was only registered in Malaysia drug formulary (or known as the Blue Book) in year 2014. Furthermore, immunotherapy was not available at that time including the absence of readily available molecular testing to guide optimal treatment.

Compared to results from landmark clinical trials the survival rate of lung cancer patient in our study was slightly low MOS, (IPASS trial MOS 18.8 months vs 17.4 months for TKI whereas KEYNOTE-042 MOS of 20 months vs 19.1 months for immunotherapy) as our cohort included patients who had poor ECOG functional status.^{14,15}

The number of patients who underwent curative surgery was extremely low. Only 0.6% underwent surgery and they were all alive at the time of analysis. Patients who underwent curative surgery showed best survival however it is only advocated for early-stage lung cancer. Failure to detect lung cancer in early stage could be the leading cause for this. There is no effective lung cancer screening program nationwide in Malaysia. PEARLS study (Pilot Study for Early Lung Cancer Screening) intended to evaluate the feasibility and outcome of a single low-dose CT thorax as a screening modality was terminated prematurely due to low awareness among the general population, the refusal to be screened, and fear of lung cancer diagnosis.²²

The limitation of this study is that it is a single-centre retrospective study. Some data was not available i.e.

smoking status of patient, number of pack-year, details in subsequent treatment and reason why patients refused treatment.

Thus a multi-centre nationwide prospective study should be conducted to confirm our findings. We recommend that targeted therapy and immune checkpoint inhibitors should be made available in government hospitals as our data confirmed that newer treatment prolonged patients' survival. Education and counselling to patients and their relatives are important to avoid loss in the follow-up. With these measures, we hope the MOS of lung cancer will be further improved in the future.

In conclusion, 98% of lung cancer patients in HTAA Kuantan presented with advance stage. The independent predictor for lung cancer survival in HTAA were ECOG functional status and treatment modality. Good ECOG score and definitive treatment were associated with good overall survival. Patient with poor ECOG score were 3 times more likely to die than those with good functional status and those patients with supportive treatment were also 1.4 times likely to die than those on definitive treatment.

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