RESEARCH ARTICLE

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Impact of Waiting Times on Mortality in Advanced Stage Non-Small Cell Lung Cancer: A 10-Year Retrospective Cohort Study in Thailand

Voralak Vichapat[1]*, Panpicha Chantasartrassamee[2], Thanyanan Reungwetwattana[2]

Abstract

Objective: This study investigated the relationship between mortality and waiting times from diagnosis to first treatment while also considering other important risk factors associated with mortality. **Methods:** This is a cohort study including 497 patients diagnosed with advanced stage non-small cell lung cancer (NSCLC) between 1st January 2012 and 31st December 2021. The risk factors and waiting periods were analysed to determine their association with mortality. The waiting periods were recorded based on the timeline of patient visits, including the time between the 1st visit and imaging, the time between the 1st visit and tissue diagnosis, the time between the procedure and tissue diagnosis, the time between tissue diagnosis and treatment and the time from the 1st visit until treatment. The data were assessed using Cox regression with time-varying covariates. **Results:** Waiting time for tissue diagnosis had a modest effect on mortality, a waiting time of more than four weeks indicated poor prognosis both in univariate and multivariate analyses [HR 1.48 (95%CI 1.18-1.87), p = < 0.01), adjusted HR 1.007 (95%CI 1.002-1.010), p = 0.02]. Waiting time for other services was not shown to be associated with mortality. The mortality rate was 3 times higher in patients with poor ECOG performance status than good ECOG performance [adjusted HR 3.17(2.04-4.91)]. Patients with EGFR sensitizing mutation who were treated with EGFR TKI therapy had a lower risk of lung cancer death compared to those being treated with chemotherapy [adjusted HR 0.49 (0.33-0.72)]. **Conclusion:** Molecular testing for EGFR sensitizing mutation and the TKI treatment were fundamental changes that assisted in improving survival rates for patients diagnosed with advanced stage lung cancer over the 10-year period. However, poor ECOG performance status remained a strong risk factor for lung cancer death. Longer waiting time for tissue diagnosis might indicate a poor prognosis.

Keywords: Non-small cell lung cancer- advanced stage CA lung- waiting time- mortality rate

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Introduction

Cancer is the leading cause of death in Thailand. National public health statistics reported an overall cancer death rate of 120.5 people per 100,000 in 2017. Lung cancer is in the top five most common cancers, accounting for 14.1% of all types of cancer cases. The cases of lung cancer by gender were reported to be 22.7 men per 100,000 and 10.1 women per 100,000 (Virani et al., 2017). The majority of lung cancer cases were diagnosed at the advanced stage (70%) (Reungwetwattana et al., 2020). The five-year survival rate of lung cancer was only 22% which was the second lowest survival rate after hepatocellular carcinoma (Reungwetwattana et al., 2020).

Many risk factors were examined that contribute to the high rate of lung cancer mortality. The fact that it is usually diagnosed at the advanced stage is one of the leading risk factors for lung cancer death (Mountain, 2000). Tobacco smoking is a known risk factor for the development and increased risk of dying from lung cancer (Yoshino et al., 2006). Poor performance status as well as high tumour burden and metastasis to vital organs were reported to be associated with increased lung cancer-specific deaths (Obenauf and Massagué, 2015; Gómez et al., 2021; Owusuaa et al., 2022). The morphology of lung cancer such as squamous cell carcinoma was associated with a higher 5-year mortality rate than adenocarcinoma (94% and 81%, respectively) (Mäkitaro et al., 2002). In the Asian population, around 50% of those with adenocarcinoma histology harbour epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) sensitizing mutations (Shi et al., 2015). The prevalence of mutations reaches 59.6% among non-smokers (Shi et al., 2015).

*[1]Division of Medical Oncology, Department of Medicine, Saraburi Provincial Hospital, Thailand. [2]Division of Medical Oncology, Department of Medicine, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. *For Correspondence: voralak.vichapat@gmail.com*

Treatments for advanced lung cancer have been improved over the decade since the emergence of EGFR-TKIs and immune checkpoint inhibitors (Mok et al., 2009; Onoi et al., 2020; Vaid et al., 2021). The Thai healthcare policy was modified in 2020 to allow the reimbursement of the cost of EGFR-TKI drugs for all healthcare coverage schemes, including Universal Coverage (UC), Social Security Scheme (SSS) and Civil Servant Medical Benefit Scheme (CSMBS). Since then, patients with histology of adenocarcinoma were screened for EGFR sensitivity mutations and the drug was made accessible to the patient. Healthcare policy, technologies for investigations, diagnosis, as well as the accessibility to healthcare services have been much improved in the country (Khiewngam et al., 2023).

Delayed in cancer care may have contributed to increased mortality (Xolisile et al., 2002). Previous reports found an association between prolonged waiting time and mortality, but the evidence is inconsistent (Bozcuk and Martin, 2001; Gomez et al., 2015; Ha et al., 2018; Vichapat, 2021). Therefore, this study will investigate the risk factors for lung cancer death and evaluate time to service factors in a cohort of individuals diagnosed with advanced stage non-small cell lung cancer (NSCLC) during the past decade in Saraburi provincial hospital. The waiting time intervals that patients experienced in each step of the healthcare service will be investigated i.e., waiting time to diagnosis, time to imaging, time to procedure, and time to reception of systemic treatments.

Materials and Methods

Study cohort and variables

We obtained data from 869 patients diagnosed with lung cancer between 1st January 2012 and 31st December 2021 from a Saraburi hospital-based cancer registry. Patients' information was retrospectively collected from the electronic database and the National Cancer Registry Thailand. The study included patients diagnosed with stage IV NSCLC according to the 8th edition of the AJCC-TNM classification (Goldstraw et al., 2016) or those who developed incurable recurrent diseases. Computerized tomography or chest radiographs were examined to confirm measurable lesions of metastasis. All patients were over the age of 15 years and were diagnosed with lung cancer by a histopathological or cytological examination of tissue biopsies. The clinical staging and pathological diagnosis of the disease were reviewed by two researchers for diagnostic confirmation. The patients all lived in the referral area and were treated in Saraburi Hospital. Other types of lung cancer such as small cell lung cancer and lung sarcoma as well as patients diagnosed with more than one cancer within six months were excluded due to shorter expected survival time. Patients without confirmation of tissue diagnosis were also excluded.

The variables for the analyses included age, gender, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) status (scale 0-2 refers to medically fit vs. scale 3-4 refers to frail), history of smoking, comorbidities, Thai healthcare schemes and tumour characteristics i.e., morphological type, grade, EGFR mutation and metastatic organs. Types of treatment were categorized as chemotherapy, TKI therapy, immunotherapy, and best supportive care, depending on which treatment was offered first. All EGFR-TKI drugs were 1st generation including Gefitinib and Erlotinib. The variable "EGFR mutation" was categorized to TKI responsive mutation (exon 19 and 21 mutation) and TKI non-responsive mutation (EGFR wild type, exon 18 and exon 20 mutation). Best supportive care refers to palliative care that does not involve any anti-cancer treatments.

Information regarding time was recorded as the following: date of the first visit, date of procedure, date of pathological report, date of imaging and date of treatment. These dates derived time-frame variables including time between first visit and imaging, time between first visit and tissue diagnosis, time between procedure and tissue diagnosis, time between tissue diagnosis and treatment, and overall waiting time between first visit and treatment. The categorization of waiting time intervals was based on optimal cutoff values derived from receiver operating characteristics (ROC) curves and was estimated using regression analysis of Liu's method. Various cutoff values were established for different time intervals. The time between the first visit and imaging had a cutoff value of 2.2 weeks, with an area under the ROC curve of 0.59, sensitivity of 0.58, and specificity of 0.60. The time between the first visit and tissue diagnosis was determined to be 3.8 weeks, with an area under the ROC curve of 0.75, sensitivity of 0.58, and specificity of 0.87. For the time between procedure and tissue diagnosis, the cutoff value was found to be 1.8 weeks, with an area under the ROC curve of 0.52, sensitivity of 0.47, and specificity of 0.56. Regarding the time between tissue diagnosis and treatment, the established cutoff value was 4.1 weeks, with an area under the ROC curve of 0.52, sensitivity of 0.44, and specificity of 0.61. Finally, the overall waiting time between the first visit and treatment was determined to be 5.7 weeks, with an area under the ROC curve of 0.67, sensitivity of 0.74, and specificity of 0.59. These cutoff values were rounded to one digit to align with the Thai National recommendations and facilitate categorization in the analysis.

Missing values were treated as a separate category i.e., "unknown". Date of death and cause of death were obtained from national death certificates from the provincial registration administration office, Saraburi Hospital Cancer registry and National Cancer Registry Thailand. The database included patients diagnosed with lung cancer between 2012 and 2021 with a follow-up time concerning vital status until the end of 2022. The proposed variables were analyzed according to periods of diagnosis which were 2012-2016 and 2017-2021 (Jansen et al., 2013).

Statistical analyses

Descriptive statistics were reported in mean and standard deviations (SD) if the data were normally distributed, whereas median and interquartile ranges (IQR) were reported for non-parametric data. Pearson chi-square test was used to compare categorical variables while Fisher's exact test was applied to examine small

sample sizes of less than 15 per group. The estimation of the 5-year survival rate was calculated based on a period analysis of survival estimates for the first period obtained from the survival experience in 2012-2016 and survival estimates for the latter period obtained from the survival experience in 2017-2021 (of patients diagnosed in 2012-2021) (Jansen et al., 2013). Cox regressions with time-varying covariates were used to determine which factors were associated with mortality (Ruhe, 2016). Univariate analyses examined each variable. The multivariate model derived from backward stepwise regression by gradually eliminating inappropriate variables from the regression model provided adjusted hazard ratios that best explain the association. All analyses and illustrations were performed using STATA version 17 (StataCorp, 2021).

Results

The full cohort comprises 497 patients as shown in Figure 1. The 1-year, 3-year, and 5-year mortality rates were 69%, 96.3% and 98.6%, respectively. The 5-year lung cancer-specific mortality rate for patients diagnosed during the period 2012-2016 was 1,260 (95%CI 1,080-1,490) per 1,000 person/year with median survival time of 27 weeks (IQR 9-41), compared to the period 2017-2021 for which the mortality rate was 1,050 (95%CI 930-1,120) per 1,000 person/year with a median survival time of 41 weeks (IQR 12.5-50). The 1-year lung cancer mortality estimates of patients diagnosed with advanced lung cancer over that year are depicted in figure 2. For example, the estimation for 2013 would be the 1-year mortality of patients diagnosed from 1st January 2013 till 31st December 2013 and so on.

The mean age at diagnosis of the total cohort was 63.7 years (SD±12.2). The average BMI was 21 kg/m^2 (SD±4.0). As shown in Table 1, patients in both periods had good ECOG performance status and did not have underlying diseases. Most of the patients had well-differentiated adenocarcinoma. Over 90% of patients in the period 2012-2016 did not have EGFR mutation testing while around 50% of patients in the period 2017-2021 had been checked for their EGFR status. Almost 45% of the patients did not receive a specific treatment for lung cancer during the first period. This number decreased to 35% in the latter period. Ninety-two patients refused to receive any treatments or had not been consulted to oncologists.

The median waiting time between the first visit and receiving treatment was 6 weeks (IQR: 4.6-11.7). The median waiting time between the first visit and imaging was 2.1 weeks (IQR: 0.9-6.0). Waiting time between first visit and tissue diagnosis was 3.7 weeks (IQR: 1.9-6.9). The median waiting time between procedure and tissue diagnosis was 1.8 weeks (IQR: 0.7-2.3) and 4.0 weeks between tissue diagnosis to treatment (IQR: 1.1-6.1). There were no statistically significant differences in waiting times between the two periods except for time to imaging where patients in the period 2017-2021 waited a week longer on average than patients in the period 2012-2016.

In univariate analyses, the risk of mortality was found to be associated with poor ECOG performance status, history of smoking, squamous morphology, no or unknown EGFR status, receiving best supportive care and having a prolonged waiting time for tissue diagnosis. Entitlement to government reimbursement and receiving EGFR-TKI therapy decreased the risk of mortality. However, we did not find an association between lung cancer mortality and age, gender, BMI, underlying disease, grade, and burden of diseases as well as waiting times in other healthcare service processes. Hazards ratios and confidence intervals for univariate analyses are shown in Table 2.

The adjusted hazard ratios in multivariate analysis (derived from model selections of Cox regression with time-varying covariates as shown in Table 2) were adjusted for age, gender, ECOG performance status, history of smoking, comorbidity, tumour morphology, grade, organ metastasis, types of palliative treatment and interval time between first visit and tissue diagnosis. EGFR mutation and receiving targeted therapy were found to be highly correlated (r = 0.88, pcorr = 0.007). Therefore, the variable "types of palliative treatment" was included in the multivariate model instead of "EGFR status" as it provides more information about management after the initial diagnosis. The analyses were confined to the 405 patients who had been assigned to treatments by oncologists. As a result, we found that patients with poor ECOG

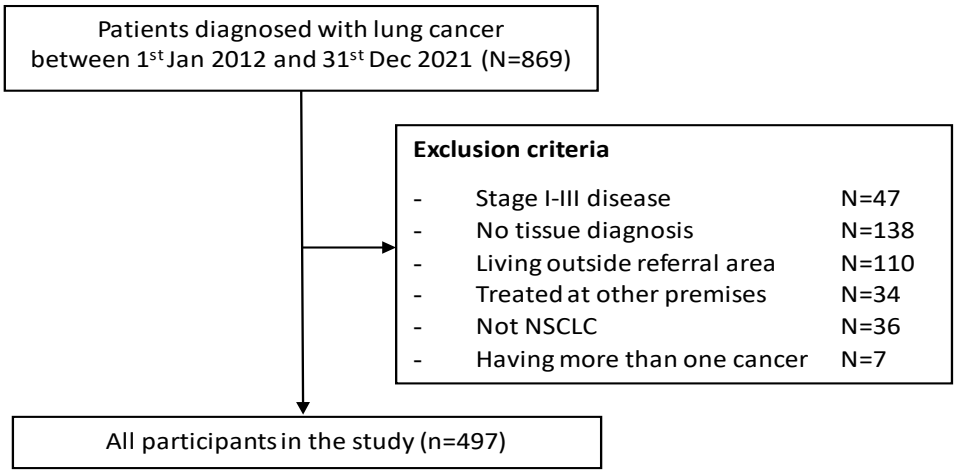

Figure 1. Flow Diagram of Patient Selection

Table 1. Demographics, Treatments and Waiting Time for 497 Patients According to Period of Diagnosis, p-value obtained from χ^2 test examining the difference in the distribution of patients' characteristics and calendar periods.

Patients' characteristics	Categories	Calendar Period 2012 to 2016 n = 173 (%)	Calendar Period 2017 to 2021 n= 324 (%)	p-value
Age in years	Mean (±SD)	63 (±13)	64 (±11.6)	
	< 65 years	91 (52.6 %)	160 (49.4 %)	0.49
	≥ 65 years	82 (47.4 %)	164 (50.6 %)	
Gender	Male	120 (69.4 %)	194 (59.9 %)	0.04
	Female	53 (30.6 %)	130 (40.1 %)	
Thai healthcare scheme	Universal coverage (UC)	124 (71.7 %)	228 (70.4 %)	0.42
	Social Security	17 (9.8 %)	43 (13.3 %)	
	Government	32 (18.5 %)	53 (16.3 %)	
Body mass	Mean (±SD)	21.1(±3.9)	21.4 (±4.0)	0.97
	< 18.5	45 (26.0 %)	86 (26.5 %)	
	18.5-22.9	72 (41.6 %)	133 (41.1 %)	
	> 22.9	56 (32.4 %)	105 (32.4 %)	
ECOG status	0-2	110 (63.6 %)	241 (74.4 %)	0.02
	3-4	63 (36.4 %)	83 (25.6 %)	
History of smoking	Never smoked	64 (37.0 %)	146 (45.1 %)	0.19
	Ever smoked	106 (61.3 %)	173 (53.4 %)	
	Unknown	3 (1.7 %)	5 (1.5 %)	
Co-morbidities	Pulmonary	24 (13.9 %)	59 (18.2 %)	0.44
	CVD	42 (24.3 %)	71 (21.9 %)	
	No	107 (61.8 %)	194 (59.9 %)	
Morphology	Adenocarcinoma	121 (69.9 %)	272 (83.9 %)	< 0.01
	Squamous cell	16 (9.3 %)	30 (9.3 %)	
	Others	36 (20.8 %)	22 (6.8 %)	
Grade	Well to moderately differentiation	138 (79.8 %)	251 (77.5 %)	0.55
	Poorly differentiation	35 (20.2 %)	73 (22.5 %)	
EGFR mutation	TKI responsive mutation	10 (5.8 %)	56 (17.3 %)	< 0.01
	TKI non-responsive mutation	2 (1.2 %)	107 (33.0 %)	
	No examination	161 (93.0 %)	161 (49.7 %)	
Metastatic organ	Single organ metastasis	91 (52.6 %)	117 (36.1 %)	< 0.01
	Multiple organ	60 (34.7 %)	141 (43.5 %)	
	Brain	22 (12.7 %)	66 (20.4 %)	
Treatment	Chemotherapy	86 (49.7 %)	152 (46.9 %)	< 0.01
	Targeted therapy	10 (5.8 %)	55 (17.0 %)	
	Immunotherapy	0 (0 %)	2 (0.6 %)	
	Best supportive care	77 (44.5 %)	115 (35.5 %)	
Time between 1st visit & imaging in weeks	≤ 2 weeks	81 (46.8 %)	117 (36.1 %)	0.02
	> 2 weeks	92 (53.2 %)	207 (63.9 %)	
Time between 1st visit & tissue diagnosis in weeks	≤ 4 weeks	103 (59.5 %)	175 (54.0%)	0.23
	> 4 weeks	70 (40.5%)	149 (46.0 %)	
Time between procedure & tissue diagnosis	≤ 2 weeks	169 (97.7 %)	295 (91.0 %)	< 0.01
	>2 weeks	4 (2.3%)	29 (9.0%)	
Patients who receive cancer-specific treatment (n=405)		(n=124)	(n=281)	
Time between tissue & treatment	≤ 4 weeks	81 (65.3 %)	186 (66.2 %)	0.86
	>4 weeks	43 (34.7 %)	95 (33.8%)	
Time between 1st visit & treatment	≤ 6 weeks	47 (37.9 %)	109 (38.8 %)	0.86
	> 6 weeks	77 (62.1 %)	172 (61.2%)	

Table 2. Univariate, Multivariate Hazard Ratios (HRs) and 95% Confidence Intervals (CI) for Prognostic Factors Associated with Lung Cancer Specific Mortality for 405 Participants who Received Cancer-Specific Treatments.

Patient's characteristics	Alive/death	Univariate		p-value	Multivariate*		p-value
		HR	95% CI		HR	95% CI	
Age in years							
< 65 years	50/158	1	Ref		1	Ref	
≥ 65 years	53/144	1.01	0.80 – 1.26	0.09	0.82	0.64 – 1.06	0.13
Sex							
Male	57/194	1	Ref		1	Ref	
Female	46/108	0.75	0.59 – 1.01	0.05	0.89	0.59 – 1.34	0.59
Thai healthcare scheme							
UC	69/207	1	Ref		-	-	-
SSS	8/42	1.21	0.86 - 1.68	0.26	-	-	-
Government	26/53	0.72	0.53 – 0.98	0.04	-	-	-
BMI							
< 18.5	29/79	1	Ref		-	-	-
18.5-22.9	47/128	0.79	0.59 – 1.05	0.1	-	-	-
> 22.9	27/95	0.8	0.59 – 1.09	0.16	-	-	-
ECOG							
0-2	83/254	1	Ref		1	Ref	
3-4	20/48	3.8	2.76 – 5.24	<0.01	3.17	2.04 – 4.91	< 0.01
History of smoking							
Never smoked	52/127	1	Ref		1	Ref	
Ever smoked	46/172	1.36	1.08 - 1.11	0.01	1.02	0.68 – 1.54	0.89
Unknown	5/3	0.35	0.11 - 1.11	0.07	0.26	0.08 – 0.83	0.02
Comorbidities							
No	15/55	1	Ref		1	Ref	
CVD	30/64	0.84	0.58 – 1.20	0.35	0.83	0.57 – 1.22	0.36
Pulmonary	58/183	1.1	0.81 – 1.49	0.53	0.98	0.72 – 1.35	0.94
Morphology							
Adenocarcinoma	88/242	1	Ref		1	Ref	
Squamous cell carcinoma	9/26	1.52	1.01 – 2.29	0.04	1.15	0.75 – 1.77	0.5
Others	6/34	1.34	0.93 – 1.92	0.11	1.23	0.83 – 1.82	0.29
EGFR mutation (Response to TKI)							
Response	30/36	1	Ref		-	-	-
Not response	13/77	2.81	1.86 – 4.21	<0.01	-	-	-
No examination	60/189	2.37	1.65 – 3.39	<0.01	-	-	-
Grade							
1-2	81/236	1	Ref		1	Ref	
3	22/66	0.9	0.68 – 1.18	0.46	0.93	0.70 – 1.24	0.64
Organ metastasis							
Single organ metastasis	50/126	1	Ref		1	Ref	
Multiple	32/117	1.14	0.89 – 1.33	0.27	1.21	0.96 – 1.39	0.09
Brain	21/59	1.14	0.83 – 1.56	0.41	1.04	0.75 – 1.44	0.79
Palliative treatments							
Chemotherapy	47/189	1	Ref		1	Ref	
Targeted therapy	29/36	0.48	0.33 – 0.68	<0.01	0.49	0.33 – 0.72	<0.01
Immunotherapy	1/1	0.35	0.04 – 2.46	0.29	0.45	0.62 – 3.24	0.42
BSC	26/76	2.06	1.57 – 2.70	<0.01	1.26	0.87 – 1.83	0.21
Time between 1st visit & imaging							
≤ 2 weeks	52/96	1	Ref		-	-	-
>2 weeks	51/206	0.96	0.75 – 1.22	0.75	-	-	-

Table 2. Continued

Patient's characteristics	Alive/death	Univariate		p-value	Multivariate*		p-value
		HR	95% CI		HR	95% CI	
Time between 1st visit & tissue diagnosis							
≤ 4 weeks	94/130	1	Ref		1	Ref	
>4 weeks	9/172	1.48	1.18 – 1.87	<0.01	1.007	1.002 – 1.010	0.02
Time between procedure & tissue diagnosis							
≤ 2 weeks	98/280	1	Ref		-	-	-
>2 weeks	5/22	1.29	0.83 – 1.99	0.25	-	-	-
Time between tissue & treatment							
≤ 4 weeks	70/197	1	Ref		-	-	-
>4 weeks	33/105	0.84	0.66 – 1.06	0.16	-	-	-
Time between 1st visit & treatment							
≤ 6 weeks	64/92	1	Ref		-	-	-
>6 weeks	39/210	1.05	0.82 – 1.35	0.67	-	-	-

*Multivariate model included age, gender, ECOG, smoking status, comorbidities, morphology, grade, organ metastasis, types of palliative treatments, and time interval between first visit and tissue diagnosis.

performance status had a higher risk of death from lung cancer than those with good performance status [adjusted HR 3.17 (95%CI 2.04-4.91)]. Patients who received the EGFR-TKI were more likely to survive compared to those who were treated with chemotherapy [adjusted HR 0.49 (95%CI 0.33-0.72)]. Although this result is modest, the risk of death from lung cancer was slightly higher when the waiting time between first visit and tissue diagnosis was more than 4 weeks compared to shorter waiting times [adjusted HR 1.007 (95%CI 1.002-1.010), p = 0.02]. Figure 3 shows Kaplan-Meier Curves estimated survival probability for these variables. The Log-Rank tests were calculated and showed statistically significant differences between groups.

We stratified the analyses by periods of diagnosis and found that poor ECOG performance status remained a strong risk factor for lung cancer mortality, while treatments with EGFR TKI demonstrated a protective effect on mortality in both periods. The waiting time between first visit and tissue diagnosis was significantly associated with mortality in both the univariate analyses and in the multivariate model (Table 3).

Discussion

This study was conducted in a 10-year follow-up cohort of patients diagnosed with and treated for advanced stage lung cancer in a tertiary referral cancer center. The current research investigated the risk factors for lung cancer mortality as previous research has found that longer waiting times between the first visit and receiving treatment increased the risk of mortality (Vichapat, 2021). In our study, we further evaluated the impact of waiting time intervals in each step of the patients' treatment on the risk of lung cancer death. We found that a longer waiting time for tissue diagnosis was associated with poor prognosis even though this effect was minimal in a multivariate analysis. This result suggests that waiting

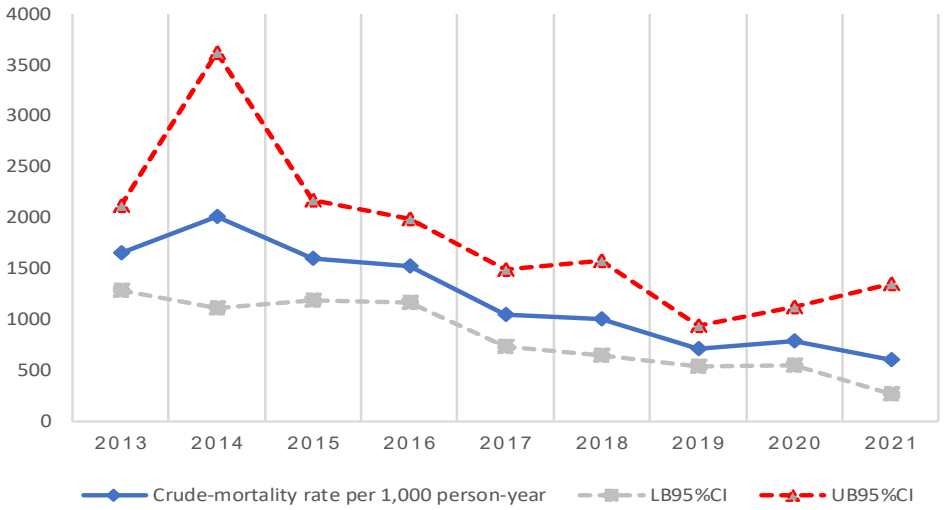

Figure 2. 1-Year Crude Mortality Estimates Per 1,000 Person/Year based on Data from Death Certificates among Patients Diagnosed with Advanced Stage Lung Cancer

Table 3. Univariate, Multivariate Hazard Ratios (HRs) and 95% Confidence Intervals (CI) for Factors Associated with 5-Year Lung Cancer Specific Mortality among 405 Patients who Received Treatment, Stratified by Period of Diagnosis

Patient's characteristics	Alive/ death	Calendar Period 2012 to 2016 (n = 124)				p-value!	Alive/ death	Calendar Period 2017 to 2021 (n = 281)				p-value!
		Univariate		Multivariate*				Univariate		Multivariate*		
		HR	95% CI	HR	95% CI			HR	95% CI	HR	95% CI	
Age in years												
< 65 years	26/40	1	Ref	1	Ref		37/105	1	Ref	1	ref	
≥ 65 years	19/39	1.28	0.81 – 1.99	0.97	0.53 - 1.77	0.92	42/97	0.78	0.59 - 1.03	0.71	0.53 – 1.02	0.1
Sex												
Male	27/56	1	Ref	1	Ref		41/127	1	Ref	1	ref	
Female	18/23	0.76	0.46 - 1.24	2.59	0.73 - 9.02	0.14	38/75	0.75	0.56 - 1.00	0.87	0.56 - 1.36	0.56
Thai healthcare scheme												
UC	29/54	1	Ref	-	-	-	56/137	1	Ref	-	-	-
SSS	2/10	1.1	0.56 - 2.17	-	-	-	7/31	1.2	0.81 - 1.78	-	-	-
Government	14/15	0.78	0.44 - 1.39	-	-	-	16/34	0.63	0.43 - 0.93	-	-	-
BMI												
< 18.5	9/22	1	Ref	-	-	-	26/51	1	Ref	-	-	-
18.5-22.9	22/37	0.83	0.49 - 1.43	-	-	-	31/85	0.78	0.54 - 1.11	-	-	-
> 22.9	14/20	0.77	0.42 - 1.42	-	-	-	22/66	0.82	0.56 - 1.17	-	-	-
ECOG												
0-2	37/65	1	Ref	1	Ref		66/169	1	Ref	1	Ref	
3-4	8/14	3.22	1.77 - 5.82	9.04	3.02 - 27.0	<0.01	13/33	3.71	2.51 - 5.48	3.46	1.94 – 6.14	<0.01
History of smoking												
Never smoked	23/28	1	Ref	1	Ref		41/87	1	Ref	1	Ref	
Ever smoked	19/51	1.27	0.80 - 2.03	3.8	1.13 - 12.7	0.03	36/112	1.39	1.05 - 1.85	0.94	0.59 - 1.50	0.82
Unknown	3/0	-	-	-	-	-	2/3	0.91	0.28 - 2.90	0.42	0.12 - 1.40	0.16
Comorbidities												
No	3/16	1	Ref	1	Ref		12/39	1	Ref	1	Ref	
CVD	18/17	0.72	0.36 - 1.43	0.96	0.44 - 2.06	0.92	20/39	0.85	0.54 - 1.33	0.81	0.49 – 1.33	0.42
Pulmonary	24/46	1.05	0.59 - 1.86	1.22	0.66 - 2.26	0.51	47/124	1.19	0.83 - 1.71	0.96	0.66 – 1.42	0.88
Morphology												
Adenocarcinoma	38/56	1	Ref	1	Ref		66/170	1	Ref	1	Ref	
Squamous cell	5/4	0.75	0.27 - 2.09	0.67	0.22 - 2.09	0.5	7/19	1.65	1.02 - 2.68	1.24	0.75 - 2.05	0.39
Others	2/19	1.32	0.78 - 2.25	1.27	0.65 - 2.48	0.46	6/13	1.19	0.68 - 2.11	1.07	0.59 - 1.96	0.81
EGFR mutation (Response to TKI)												
Response	8/2	1	Ref	-	-	-	24/32	1	Ref	-	-	-
Not response	2/0	-	-	-	-	-	13/75	2.68	1.76 - 4.09	-	-	-
Not examination	35/77	3.66	0.89 - 14.0	-	-	-	43/94	2.25	1.50 - 3.38	-	-	-
Grade												
1-2	34/63	1	Ref	1	Ref		62/158	1	Ref	1	Ref	
3	11/16	0.66	0.38 - 1.15	0.63	0.34 - 1.19	0.16	17/44	1.11	0.79 - 1.55	1.24	0.87 - 1.76	0.22
Organ metastasis												
Single organ metastasis	32/35	1	Ref	1	Ref		32/77	1	Ref	1	Ref	
Multiple organ metastases	6/31	1.15	0.61 - 1.48	0.75	0.43 - 1.30	0.31	30/82	1.08	0.74 - 1.32	1.06	0.67 – 1.33	0.75
Brain	7/13	1.47	0.75 - 2.87	1.29	0.61 - 2.73	0.5	17/43	1.11	0.76 - 1.61	1.01	0.68 – 1.51	0.92
Palliative treatment												
Chemotherapy	26/59	1	Ref	1	Ref		38/113	1	Ref	1	Ref	
Targeted therapy	8/2	0.32	0.08 - 1.31	0.15	0.03 - 0.85	0.03	23/32	0.48	0.32 - 0.72	0.49	0.32 – 0.76	0.002
Immunotherapy	0/0	-	-	-	-	-	1/1	0.27	0.38 - 1.98	0.33	0.04 – 2.55	0.3
BSC	11/18	2.32	1.34 - 4.02	1.27	0.51 - 3.18	0.6	18/55	1.75	1.26 - 2.44	1.11	0.69 – 1.78	0.66
Time between 1st visit & imaging												
≤ 2 weeks	19/32	1	Ref	-	-	-	40/57	1	Ref	-	-	-
>2 weeks	26/47	0.91	0.57 - 1.44	-	-	-	40/144	0.94	0.69 - 1.28	-	-	-
Time between 1st visit & tissue diagnosis												
≤ 4 weeks	30/41	1	Ref	1	Ref		72/81	1	Ref	1	Ref	
>4 weeks	15/38	1.02	0.65 - 1.59	1	0.99 – 1.00	0.85	8/120	1.44	1.08 - 1.92	1.02	1.00 - 1.03	0.04

Table 3. Continued

Patient's characteristics	Alive/ death	Calendar Period 2012 to 2016 (n = 124)				p-value!	Alive/ death	Calendar Period 2017 to 2021 (n = 281)				p-value!
		Univariate		Multivariate*				Univariate		Multivariate*		
		HR	95% CI	HR	95% CI			HR	95% CI	HR	95% CI	
Time between procedure & tissue												
≤ 2 weeks	44/77	1	Ref	-	-	-	76/181	1	Ref	-	-	-
>2 weeks	1/2	1.15	0.28 - 4.71	-	-	-	4/20	1.21	0.76 – 1.93	-	-	-
Time between tissue & treatment												
≤ 4 weeks	33/48	1	Ref	-	-	-	52/134	1	Ref	-	-	-
>4 weeks	12/31	1.21	0.77 - 1.91	-	-	-	28/67	0.74	0.55 - 1.00	-	-	-
Time between 1st visit & treatment												
≤ 6 weeks	22/25	1	Ref	-	-	-	48/61	1	Ref	-	-	-
>6 weeks	23/54	0.95	0.59 - 1.54	-	-	-	32/140	1.02	0.75 - 1.39	-	-	-

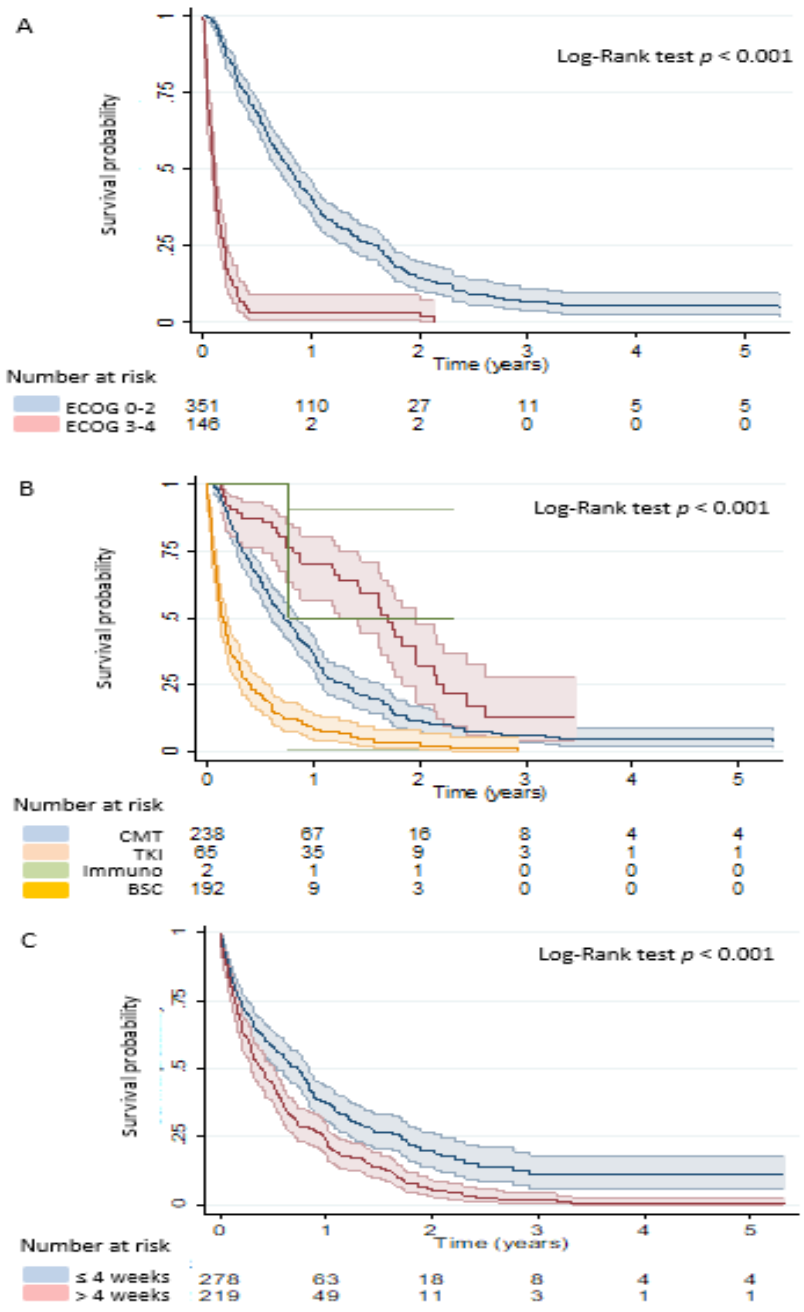

Figure 3. Kaplan Meier curves display survival estimates for (A) ECOG performance status, (B) types of palliative treatments and (C) waiting time between first visit to tissue diagnosis. The log-rank test indicates a statistically significant difference between the survival curves.

time should not exceed 4 weeks, in line with the Thai National recommendations.

Around 18% of the patients included in this study (92 in 497) whose tissue diagnosis was obtained were not assigned to any treatments. We reviewed the medical records and found that most of them died between processes and therefore did not receive cancer-specific treatment. Our research did not find a significant association between mortality and waiting times for treatment, imaging, procedure and pathological report. Information regarding the impact of waiting time to treatment was conflicting between studies with median waiting times of 6 to 12 weeks, which is consistent with the median time to treatment in our analysis (Bozcuk and Martin, 2001; Gomez et al., 2015; Ha et al., 2018; Vichapat, 2021; Chantasartrassamee and Vichapat, 2022). The conflicting results might be due to other risk factors such as ECOG performance status, tumour morphology, EGFR status, and treatments affecting the prognosis more than waiting time when the patients received a final diagnosis and proper treatments.

In Thailand, treatments for the adenocarcinoma subtype have been developed over time, especially for those with EGFR genetic mutations. The cost of molecular testing and TKI drugs has been reimbursed to patients who hold CSMBS since 2018. In 2020, the policy was expanded to allow patients who hold UC and SSS to be reimbursed as well. In this analysis, we observed that the 1-year mortality rates gradually decreased. Furthermore, the 5-year lung cancer-specific mortality for the period 2012-2016 dropped from 1,260 per 1,000 person/year to 1,050 per 1,000 person/year for the period 2017-2021. This improvement in survival rate could be explained by many factors, but in our study, the effect of TKI treatments for patients with expression of EGFR sensitizing mutations on mortality-risk reduction were observed in all analyses. This finding was consistent with the outcomes of a multicenter study in Thailand, which showed that EGFR-TKI treatment improved the overall survival of patients with EGFR-responsive mutations (Sukauichai et al., 2022; Khiewngam et al., 2023).

In our cohort, the prevalence of EGFR sensitizing mutation among the adenocarcinoma subtype was 60% (66/109) which was consistent with previous reports in the Asian population (Shi et al., 2015). Although 93% of patients in the period 2012-2016 were not evaluated for genetic mutations, this number decreased to 49.7% in the period 2017-2021. We did not find anaplastic lymphoma kinase (ALK) gene rearrangement in our cohort. This might be due to the test for ALK alteration currently being restricted to CSMBS only. Other biomarkers and genetic mutation testing such as PD-L1, ROS1, BRAF, NTRK, RET and HER2 could not be reimbursed in any healthcare schemes at the time of this analysis.

Squamous cell lung cancer is a notoriously histologic subtype which is associated with lung cancer death (Mäkitaro et al., 2002). This was consistent with the finding in our study that squamous cell carcinoma presented a higher risk of lung cancer death than adenocarcinoma in a univariate analysis. However, the risk was reduced and did not reach statistical significance in a multivariate model. In Thailand, molecular testing in squamous cell lung cancer is not routinely examined in clinical practice and is not reimbursed in any healthcare coverage schemes. Immunotherapy also could not be reimbursed and is too costly for self-paying patients; therefore chemotherapy has been the only treatment option for the squamous histological subtype in the past 10 years. We did not find any difference in the risk of death between the period 2012-2016 and the period 2017-2021 among patients who were diagnosed with squamous cell carcinoma.

Poor ECOG status has been reported to be related to death from lung cancer (Obenauf and Massagué, 2015; Gómez et al., 2021; Owusuaa et al., 2022). Best supportive care was more likely to be assigned to patients with poor ECOG performance status as chemotherapy does not increase chances of survival in medical practice (Murakawa et al., 2019). This creates a treatment bias that commonly occurs in retrospective studies to which participants were not randomly allocated. Multivariate regressions were used to adjust for such bias and an independent effect of poor ECOG performance status on lung cancer mortality was found. Best supportive care was not strongly associated with mortality when the analyses were adjusted for treatment types. High tumour burden was neither found to be associated with poor ECOG performance status ($r = 0.40$, $p_{corr} = 0.35$) nor mortality. Ageing was not associated with mortality in our analyses.

All information regarding patients' characteristics, follow-up, management, and death was obtained by two physicians from the electronic medical database and the Thai Cancer Base (TCB) which is a National Cancer Registry. Information regarding death date and cause-specific death were reviewed in correspondence with the population-based registry. Hence, the level of data completeness is over 90%. Our information on 1-year, 3-year, and 5-year mortality rates is consistent with the National statistical report (Virani et al., 2017; Reungwetwattana et al., 2020). Since the data we retrieved was for patients who had a confirmed final diagnosis by the histological or cytological report, not including patients who did not receive a tissue diagnosis is an unavoidable limitation of this study. The cohort of this study comprises patients referred from provinces in central Thailand across a 10-year span, which arguably makes the study representative of the national population of Thailand.

In conclusion, poor ECOG performance status is an independent risk factor for lung cancer-specific death. Treatment with TKI drugs among EGFR sensitizing mutations decreases the risk of death from lung cancer. The reimbursement for molecular testing and EGFR-TKI treatments may have assisted in reducing mortality rates for advanced stage lung cancer patients over the past decade. A longer waiting time for tissue diagnosis showed a modest risk for poor prognosis.

Author Contribution Statement

All the authors have reviewed and approved the final manuscript. The contributions of each author to this

research are as follows:

a. Voralak Vichapat: The corresponding author contributed of 90% to the work including conceptualization, planning, and designing methodology, data collection, data management, analysis, literature review, manuscript writing and revision, and obtaining ethical approval. b. Panpicha Chantasartrassamee: Data collection and validation; c. Thanyanan Reungwetwattana: Supervision and manuscript mentoring

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Ethical considerations

This study adhered to all relevant ethical guidelines and was conducted with the approval of the Saraburi Hospital Ethics Committee (project code SRBR63-044). This ethical review board conforms to international standards according to the Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the international conference on Harmonization in Good Clinical Practice, ICH-GCP.

Conflict of interest

There are no conflicts of interest to be disclosed regarding this research.

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