RESEARCH ARTICLE

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Survival Analysis of Lung Cancer: A 10-Year Real-Life Experience in a Non-University-Based Hospital in Thailand (2012-2021)

Narongwit Nakwan*, Kittipong Kumsuk

Abstract

Background: Over the past decades, several studies have mostly revealed that the overall survival among patients with lung cancer in university hospitals remained poor. However, the data on real-world treatments in non-university tertiary hospitals in Thailand still needs to be discovered. The primary objective was to assess the 10-year real-life overall survival among patients with lung cancer in a non-university hospital. **Methods:** A retrospective cohort study assessed patients diagnosed with lung cancer from a hospital-based lung cancer registry from January 2012 to December 2021 at Hatyai Hospital, Songkhla, Thailand. The demographic data and treatment outcomes were recorded. Kaplan-Meier methods were used for overall survival (OS), and a Log-rank test was used to compare the differences in survival based on different categories of prognostic factors. The prognostic factors for OS were assessed using a Cox-proportional hazard model. **Results:** Of 1,528 patients, the median age was 63.2± 12.1years; 1,009 (66%) were male; 981 (64%) had a history of smoking; 1,433 (93.7)% were non–small-cell lung cancer (NSCLC); 1,327 (87%) presented with stage IV disease. The median OS was 7.8 months for all patients, eight months for those with NSCLC, and 6.4 months for those with small cell lung cancer (SCLC). The 1-year, 3-year, and 5-year cumulative survival rates with all patients were 38%, 11%, and 6%. With NSCLC, 39%, 12%, and 6%, whereas for those with SCLC, 29%, 5%, and 4%, respectively. Disease stage III/IV and male gender were significantly associated with an increased risk of death, whereas receiving 1-2 line systemic treatments and curative surgical resection was a significant factor for survival in lung cancer patients. **Conclusion:** In Thailand, the OS in patients with lung cancer has remained low over the decade. However, providing specific-lung cancer therapies and undergoing curative surgery remains a significant factor in improving their survival.

Keywords: Lung cancer- survival- lung carcinoma- non-small cell lung cancer

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Introduction

Lung cancer is the most commonly diagnosed malignancy and the leading cause of worldwide cancer-related mortality (WHO Cancer: fact sheet, 2022). In 2020, lung cancer was ranked the second most common cancer among men and the fourth most common among women in Thailand (International agency for research on cancer:fact sheet, 2020). It has been estimated that there are about 23,713 new lung cancer cases and 20,395 death annually (International agency for research on cancer:fact sheet, 2020). Its burden led to the second-highest mortality rate (18.7%), and rapid increases in mortality are now being observed. Over the past three decades, several studies in Thailand demonstrated varying survival outcomes among patients with lung cancer. During 1997-2001, the 1-and 3-year survival rates of NSCLC were 28.9% and 3.3%, respectively (Srisam-Ang et al., 2005), whereas 37.8% and 15.1% during 2013-2017, respectively (Musika et al., 2021). Despite the slight improvement of those rates over time, the patients primarily present with late-stage disease and die within eight months after diagnosis (Srisam-Ang et al., 2005; Musika et al., 2021). Regarding studies in Thailand, they were primarily studied in a university-based hospital or institution of cancer, which might not represent survival outcomes in a real-world environment.

Notably, lung cancer guidelines are updated yearly to raise public and professional awareness and recommend newer therapies, particularly immunotherapies, and novel targeted agents, to improve survival and life quality (National comprehensive cancer network guideline on Non-small cell lung cancer, 2020). In Thailand, several barriers have been issued, including poor access to early diagnosis and advanced drugs and even inadequate specialists, which lead to poor survival outcomes (Bhosai et al., 2011; Febbraro et al., 2022; Thongprasert and Permsuwan, 2014). Especially in non-university-based hospitals, which is a limited resource, but little is

*Division of Pulmonology, Department of Medicine, Hatyai Medical Education Center, Hatyai Hospital, Songkhla, Thailand. *For Correspondence: naronak@hotmail.com*

known regarding survival outcomes in patients with lung cancer. Therefore, disclosure of the gap may evaluate the availability and accessibility of quality care for patients with lung cancer as important advocacy and policy to ensure the future improvement of the health and well-being of those patients. This study aimed to explore real-world survival outcomes and identify the dependent factor for predicting survival in lung cancer patients in a non-university-based hospital during 2012-2021 in Thailand.

Materials and Methods

A retrospective cohort study of lung cancer was performed using the hospital-based lung cancer registry from Hatyai Hospital, a non-teaching government hospital in southern Thailand. The data source was retrieved from the database of the lung cancer registry and the patient's electronic medical records retrospectively from January 2012 to December 2021. All subjects have confirmed pathological diagnosis of primary lung cancer and were aged ≥ 18 years at diagnosis. Data extracted from medical records included demographic characteristics such as age, gender, smoking status, and clinical data associated with the diagnosis and investigation of lung cancer, including the type of histology, stage at diagnosis, and test results for molecular tests. Treatment modalities such as chemotherapy, radiotherapy, targeted therapy, surgery, immunotherapy, or best supportive treatment were also collected. The official pathological report date was considered the zero date. The subjects were followed-up until death or censored at the end of the study (December 31, 2021). All censored subjects' identification numbers were used to cross-check with the national registration data for their vital status (whether still dead or alive). The Institutional Review Board approved the protocol of Hatyai Hospital (Number 80/2560). The committee waived the need for individual consent due to no direct patient contact.

The mean and standard deviation were reported for continuous variables, while frequency and proportions were used for categorical variables. The Overall survival (OS) classified by diagnosis period, age group, gender, histology, disease stage, number of the line treatment, or all kinds of therapy was evaluated with the Kaplan-Meier method, and the log-rank test was used to compare the differences in survival rates. A Cox proportional hazard model was used to investigate the prognostic factors associated with the OS of lung cancer patients. A P value less than 0.05 in all statistical analyses was considered to indicate statistical significance.

Results

A total of 1,528 eligible patients were included in the analysis, and their details are summarized in Table 1. Most patients were more than 60 years old (60.5%), whereas 31.9% were between 45 and 60, and 7.6% were less than 45 years old. The mean age at diagnosis was 63.2±12.2 years. Sixty-six percent were male, and 64% had a history of smoking. Most (93.7%) had NSCLC; the histological subtypes were adenocarcinoma (60.2%), whereas small cell lung carcinoma was 6.3%. Most patients were diagnosed as advanced stage III/IV (96.4%). Of all tests for epidermal growth factor receptor gene (EGFR) mutation, 136 tests (48.9%) were detected, and most positive tests reported Exon 19 deletion (61.2%). Most patients (53.7%) received combined chemotherapy; almost half (41.6%) preferred the best supportive treatment. Sixty-five patients (4.2%) underwent curative surgical resection, and 170 (11.1%) received targeted therapy/immunotherapy.

Survival outcomes

All survival outcomes across the different factors are summarized in Table 2. The median OS for all patients was 7.8 months (95% CI, 7.1-8.5) (Figure 1A). Patients with NSCLC had a more prolonged median OS of 8 months (95% CI, 7.2-8.8) compared to SCLC of 6.4 months (95% CI, 4.9-6.9)(Figure 2). The patients of the female gender, diagnosed with NSCLC and presented with stage I and II diseases, showed a significantly longer survival time (Figure 2). Regarding treatments, those who received specific treatments, including chemotherapy, surgery, or

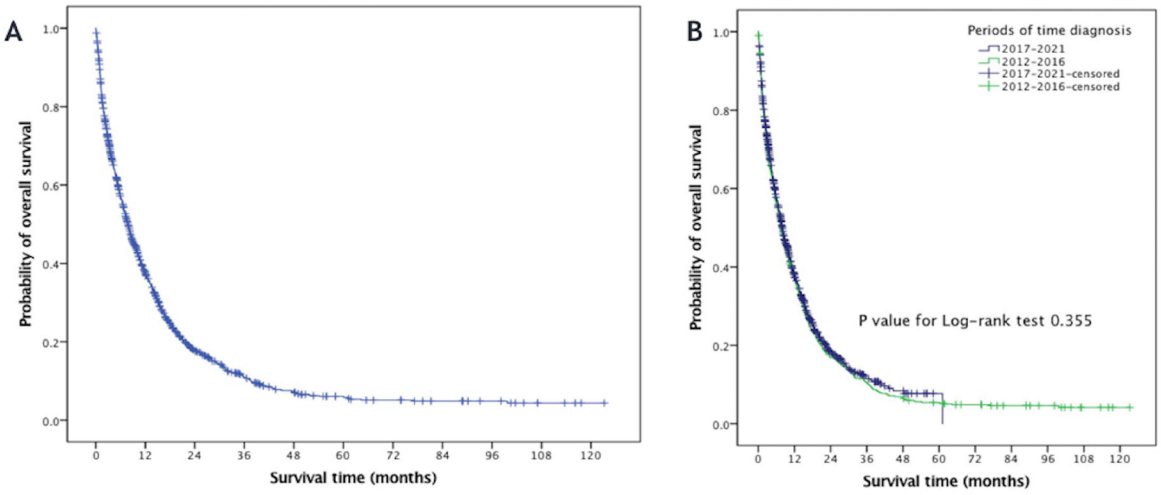

Figure 1. Kaplan-Meier Curves Show 1A) survival in lung cancer patients from January 2012-December 2021, and 1B) survival differences between 2012-2016 and 2017-2022.

Table 1. Baseline Demographics and Characteristics of the Study Population

Characteristic	Total (n=1,528)	2012-2016 (n=611)	2017-2021 (n=917)
Age - yr±SD, no. (%)	63.2±12.2	62.8±12.4	63.4±12.1
< 45 yr	116 (7.6)	48 (7.9)	68 (7.4)
45-60 yr	488 (31.9)	205 (33.6)	283 (30.9)
> 60 yr	924 (60.5)	358 (58.5)	566 (61.7)
Male sex - no. (%)	1,009 (66%)	412 (67.4)	597 (65.1)
Smoking- no. (%)			
Yes	981 (64.2)	389 (63.7)	592 (64.6)
No	541 (36.8)	222 (36.3)	325 (35.4)
Histopathology- no. (%)			
Non-small cell lung cancer	1,433 (93.7)	561 (91.8)	872 (94.9)
Adenocarcinoma	874 (60.2)	349 (62.3))	525 (60.3)
Squamous cell carcinoma	182 (12.7)	83 (14.7)	99 (11.4)
Non-specific carcinoma	368 (25.6)	125 (22.3)	243 (27.8)
Large cell carcinoma	2 (0.1)	1 (0.2)	1 (0.1)
Neuroendocrine carcinoma	7 (0.4)	3 (0.5)	4 (0.4)
Small cell lung cancer	95 (6.3)	50 (8.2)	45 (5.1)
Disease stage- no. (%)			
1	27 (1.8)	7 (1.1)	20 (2.2)
2	28 (1.8)	6 (1)	22 (2.4)
3	144 (9.4)	54 (8.8)	90 (9.8)
4	1329 (87)	544 (89)	785 (85.6)
Brain metastasis at first presentation - no. (%)	219 (14.3)	106 (17.3)	113 (12.3)
Sample tested for EGFR mutation- no. (%)	282	49	233
Positive	138 (48.9)	34 (69.3)	104 (44.6)
Negative	144 (51.1)	15 (30.7)	129 (55.4)
Type of EGFR mutation- no. (%)	138	34	104
Exon 19 deletion	83 (60.2)	17 (50)	66 (63.5)
Exon 21 (L858R)	37 (26.8)	8 (23.6)	29 (27.8)
Exon 21 insertion	6 (4.3)	2 (5.8)	4 (3.9)
Uncommon	1(0.7)	0	1 (0.9)
Exon 21 (790M)	11 (8)	7 (20.6)	4 (3.9)
Sample tested for ALK mutation- no. (%)	35	5	30
Positive	11 (31.4)	3 (60)	8 (22.7)
Negative	24 (68.6)	2 (40)	22 (73.3)
Treatment - no. (%)			
Best supportive care	637 (41.6)	231 (37.8)	406 (44.2)
Lobectomy	65 (4.2)	23 (3.7)	42 (4.5)
Chemotherapy	821 (53.7)	367 (60)	456 (49.7)
Targeted therapy/Immunotherapy	170 (11.1)	65 (10.6)	105 (11.4)

Values are shown as mean±SD or number (%); Abbreviations: EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SD, standard deviation; yr, year; no, number

targeted therapy, showed a significantly longer survival time than those who received only the best supportive care (Figure 2). According to diagnostic years, survival time was no different between 2012-2016 and 2017-2021 (p=0.355) (Fig 1B). The 1-year, 3-year, and 5-year survival cumulative rates by factors are shown in Table 2. Overall, 1-year, 3-year, and 5-year cumulative survival rates were 38%, 11%, and 6%, respectively. With NSCLC, 39%, 12%, and 6%, whereas for those with SCLC, 29%, 5%, and 4%, respectively. The patients, including those diagnosed as stages I and II, obtained curative surgical resection and received more than two specific treatments, reported 1-year cumulative survival rates of more than 80%.

Risk factors for lung cancer mortality

On multivariate analysis (Table 3), patients with male

Table 2. 1-Year, 3-Year, and 5-Year Cumulative Survival Rate and Median Survival

Characteristics	Median survival (months) (95% CI)	Log-rank test p=Value	1-year survival rate (%)	3-year survival rate (%)	5-year survival rate (%)
Overall	7.8 (7.1-8.5)		38	11	6
Year of diagnosis		0.355			
2012-2016	7.4 (7.1-9.1)		37	10	5
2017-2021	8.1 (6.5-8.3)		38	12	8
Age at diagnosis		0.083			
< 45 yr	10.6 (7.4-13.9)		44	10	8
45-60 yr	8.3 (7.1-9.5)		40	13	7
> 60 yr	7.2 (6.3-8.1)		36	11	5
Gender		<0.001			
Male	7.2 (6.5-8.0)		34	8	4
Female	9.8 (8.1-11.5)		45	18	11
Histopathology		0.02			
NSCLC	8.0 (7.2-8.8)		39	12	6
SCLC	6.4 (4.9-7.9)		29	5	4
Disease stage		<0.001			
I	not reached		88	62	62
II	40.2 (23.2-57.1)		84	52	32
III	10.1 (7.6-12.6)		45	14	11
IV	7.1 (6.4-7.8)		35	9	4
Chemotherapy		<0.001			
Yes	11.8 (10.7-12.9)		49	13	6
No	3.1 (2.7-3.6)		24	9	7
Surgery		<0.001			
Yes	48.1 (28.1-52.1)		87	59	48
No	7.3 (6.7-7.8)		36	9	4
Targeted therapy/Immunotherapy		<0.001			
Yes	23.4 (17.8-29.1)		76	32	7
No	6.7 (6.1-7.3)		33	9	6
Number line of systemic treatment (chemotherapy and/or targeted therapy/immunotherapy)		<0.001			
BSC	2.7 (2.3-3.2)		20	7	6
1-2 line treatments	10.9 (10.1-11.7)		46	11	6
>2 line treatments	29.9 (23.7-36.0)		86	39	9

Abbreviations: CI, confidential interval; NSCLC, non-small cell carcinoma; SCLC, small cell carcinoma; yr, year; BSC, best supportive care

gender (HR 1.22, 95%CI, 1.02-1.45) and disease stage III/IV (HR 3.6, 95% CI, 2.27-5.69) were associated with an increased risk of death. On the other hand, increasing the number of specific treatments could significantly reduce the risk of death (HR 0.62, 95% CI, 0.53-0.73), especially in patients who received 1-2 specific treatments (HR 0.49, 95% CI (0.31-0.76). However, receiving more than two specific treatments did not predict survival in lung cancer patients (HR 0.60, 95% CI, (0.30-1.21). Also, radical surgical resections were a significant factor related to survival (HR 0.26, 95% CI, 0.17-0.41). However, the risk of death was not reduced in patients who received chemotherapy (HR 0.93, 95% CI, 0.75-1.17) or EGFR tyrosine kinase inhibitor (TKI) (HR 0.91, 95% CI, 0.67-1.23).

Discussion

This study is the latest report to provide 10-year real-life information on the overall survival and predictive factors among lung cancer patients in a non-university-based Thailand hospital from 2012-2021. Our findings confirmed that the number of those with lung cancer significantly rose over time, particularly within the past five years (2016-2021). The characteristic of the population in this study was consistent with previous observational studies in Thailand (Srisam-Ang et al., 2005; Musika et al., 2021; Chang et al., 2018) and elsewhere in Southeast Asia (Toh et al., 2017; Kan and Chan, 2016; Sutandyo and Suratman, 2018). This study found that those with NSCLC were influential (92.7%);

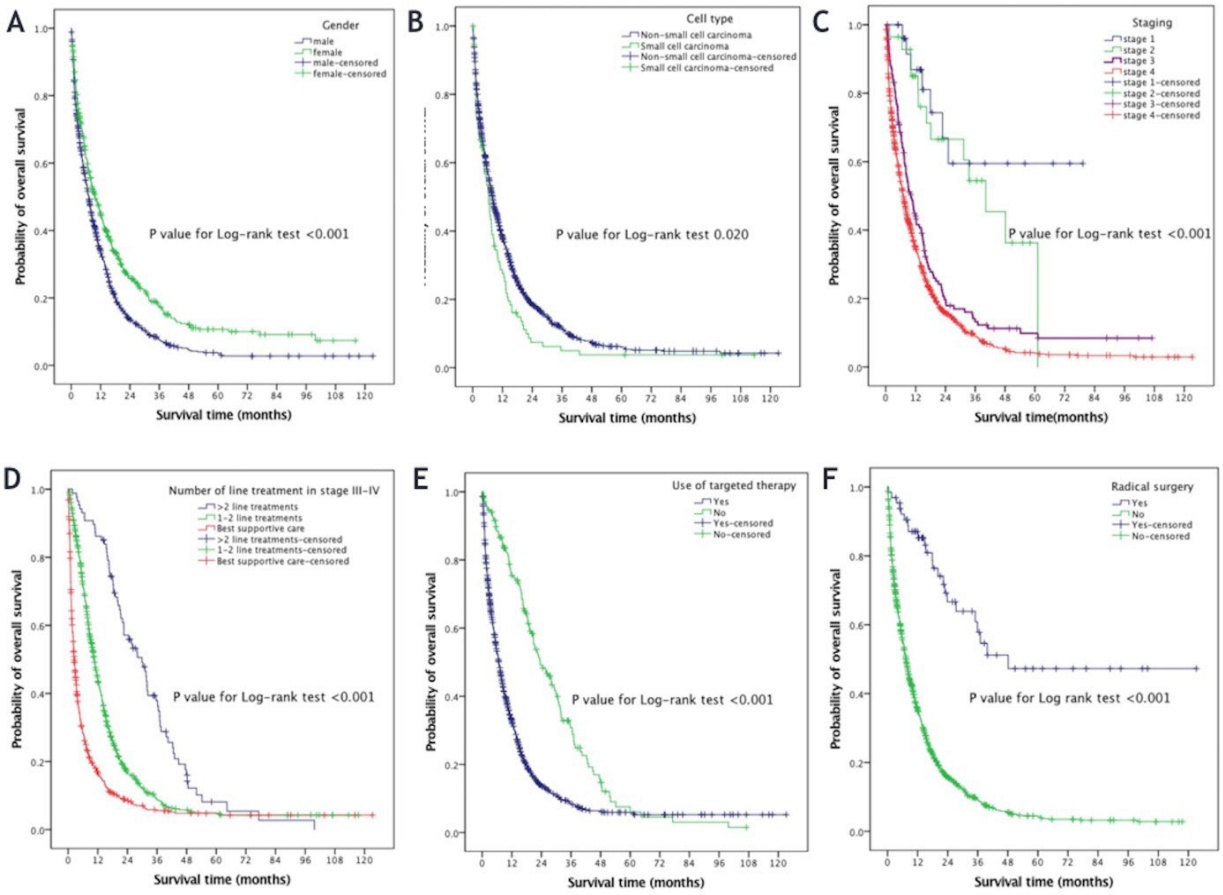

Figure 2. Kaplan-Meier Curves Showing Survival Differences Classified by A) gender, B) cell type, C) disease stage, D) the number of the line treatment, E) using targeted therapy, and F) radical surgery.

SCLC was only 6.3%. SCLC constituted 4-10.8% of all lung cancers in Asia (Wang et al., 2017; Chen et al., 2005; How et al., 2015) but rose to 15-25% in Western countries (Dayen et al., 2017; Imperatori et al., 2006). In Thailand, the incidence rate of SCLC has fluctuated.

Table 3. Factors Associate with Mortality in Multivariate Cox Regression Analysis

Clinical predictors	HR (95%CI)	P-value
Age	0.99 (0.99-1.01)	0.555
Male gender	1.22 (1.02-1.45)	0.029
Number line of systemic treatment	0.62 (0.53-0.73)	<0.001
> 2 lines of systemic treatment vs BSC	0.60 (0.30-1.21)	0.153
1-2 lines of systemic treatment vs BSC	0.49 (0.31-0.76)	0.001
Disease staging	3.60 (2.27-5.69)	<0.001
Stage III-IV vs I-II		
Cell type		
NSCLC vs SCLC	0.88 (0.70-1.11)	0.275
Radical surgery		
Yes vs no	0.26 (0.17-0.41)	<0.001
EGFR TKI		
Yes vs no	0.91 (0.67-1.23)	0.55
Chemotherapy		
Yes vs no	0.93 (0.75-1.17)	0.574

Abbreviations: CI, confidential interval; NSCLC, non-small cell carcinoma; SCLC, small cell carcinoma;EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; BSC, best supportive care

4.9% was reported during 1990-2014 (Chang et al., 2018) and 2% during 2013-2017 (Musika et al., 2021). In addition, this study found that approximately 60% of histology was adenocarcinoma; this finding would confirm the previous projections suggesting that incidence rates of adenocarcinoma in Southern Thailand may continue to increase until 2030 (Chang et al., 2018). EGFR and anaplastic lymphoma kinase gene analysis has been widely used primarily to determine targeted therapy response; only 18.4% of sampling tissues were tested throughout this study, which may be reasoned as a limited resource and not reimbursed for those tests. Approximately 50% of tested EGFR analysis showed a favorable mutation, which is compatible with data on the study in the Asian population (Shi et al., 2015). The authors suggest that if all candidates' tissue is tested by molecular testing, it might affect the patient's survival to help inform future treatment decisions. According to received treatments, systemic chemotherapy is still a prominent option in our center, while treatment with targeted therapy carries only 10% of them. Based on the standard first-line treatment among lung cancer patients in Thailand before 2021 (National Health Security Office, 2018), platinum-based chemotherapy was still primarily used in the advanced lung cancer stage. In contrast, oral targeted drugs and immunotherapy with immune checkpoint inhibitors had been approved for reimbursement only by government officers based on second-line therapy. So, these real-world

variabilities in implementing treatment advances in lung Cancer might be pretty challenging to apply in the era of personalized medicine in lung cancer treatment. During 2013-2019, a recent study reported that OS in patients with EGFR mutation-positive lung cancer treated with EGFR-TKIs in Thailand remained beneficial at later points in the treatment timeline (Sukauichai et al., 2022); however, further data on lung cancer treatment will significantly differ due to new approval for reimbursing EGFR-TKI as a standard first-line drug in NSCLC treatment after 2021.

In the current analysis, it was noted that there was no difference in median OS among patients with lung cancer in 2012-2016 (7.4 months) compared to those in 2017-2021 (8.1 months); however, OS is better than in the previous studies in 2013-2017 of 5.51 months investigated in university-based hospital (Musika et al., 2021). These significant changes over the past decade may reflect improving Thailand's lung cancer management beyond several barriers, particularly in non-university hospitals not involved with the clinical trials. However, several studies previously suggested that healthcare outcomes among patients with cancer are better in research-active hospitals (Majumdar et al., Clarke and Loudon, 2011). In comparison to countries in Southeast Asia, 11.5 months (2013) of overall survival was reported in Singapore (Toh et al., 2017), with 4.5 months (2007-2010) in Malaysia (How et al., 2015). As expected, those diagnosed with TNM stage IV, male gender, NSCLC, and treated by best supportive care were significantly related to lower mean survival time. These findings were similar to those observed in previous studies (Srisam-Ang et al., 2005; Musika et al., 2021; Soares et al., 2020). The 1-year survival rates observed in our patients with 39% of NSCLC and 29% of SCLC in 2012-2021 are similar to rates reported from previous university hospital-based cancer registry in Thailand for those with 37.8% of NSCLC and 27.9% of SCLC in 2013-2017 (Musika et al., 2021), whereas 35.5% of 1-year survival rates were reported in Malaysia in 2018 (Rajadurai et al., 2020). Unfortunately, the 5-year survival rate in our results remained relatively poor at 6%, compared to 10.2% during 2013-2017 in Thailand (Musika et al., 2021), 11.5% in Malaysia (Rajadurai et al., 2020), and 15.5% in Viet Nam (Tran et al., 2021). Complete surgical resection offers the best chance and long-term survival consistent with our data providing a median survival time of 48.1 months and almost 50% of the 5-year survival rate among those who underwent surgical resection.

In the multivariate analysis of data for the entire cohort, male (HR 3.6, 95% CI 2.27-5.69; P <0.001) and disease stage III/IV (HR 1.22, 95% CI 1.02-1.45; P = 0.029) were associated with an increased risk of death, in agreement with the findings of previous study in Thailand showing these two factors had poor survival outcome (Srisam-Ang et al., 2005; Musika et al., 2021). As we know, local curative therapy should consider in patients with stage I or II diseases, or whether they are deemed inoperable and may be tolerated by minimally invasive surgery (National comprehensive cancer network guideline on Non-small cell lung cancer, 2020), this study also confirmed that surgical resection was a significant predictor for survival in lung cancer patients (HR 0.26, 95% CI 0.17-0.41; P < 0.001). Compared to the best supportive care, receiving 1-2 lines of systemic treatment show a significant benefit for survival (HR 0.49, 95% CI 0.31-0.76; P = 0.001), while receiving > 2 lines of systemic treatment had not reached this outcome (HR 0.60, 95% CI 0.30-1.21; P = 0.153). This finding would indicate raising an issue of additional clinical benefits beyond the last line of systemic treatment in patients with failure to standard regimens.

The limitations of our study are mainly due to its involvement in the retrospective data from a non-university referral hospital in southern Thailand. Therefore, all findings may not represent lung cancer patients throughout Thailand. Although this study was indicated as a real-life database, the results may not have external validity due to rapidly changing treatment strategies by immunotherapies and novel targeted agents. Further study requires a greater understanding of survival outcomes in lung cancer after these newer treatment options become available in Thailand. This study did not identify the data on chemotherapy regimens and clarify the sequencing in line with systemic treatment; these limitations may affect survival outcomes.

In conclusion, our study confirms an increasing trend in the number of lung cancer patients in Thailand, and the overall survival has remained low over the decade. Also, undergoing curative surgical resection and providing specific-lung cancer therapies remain significant factors in improving their survival. Male gender and disease stage III and IV were still significant factors for lung cancer mortality.

Author Contribution Statement

N.N. and K.K. had full access to all of the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, study design, data analysis and interpretation, the writing of the manuscript, and approval the final manuscript.

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Ethics approval and consent to participate

The protocol was approved by the Hatyai Hospital Ethics Committee (Number 80/2560).

Availability of data and material

The data set used in the study is available from the author upon reasonable request.

Competing interests

The author declares no conflicts of interest.

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