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Survival Rate, Stage III Lung Cancer, Cancer Registry

RESEARCH ARTICLE

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Outcomes of Treatment, Survival Rates, and Factors related to Survival of Stage III Lung Cancer Patients Treated at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand

Nattaporn Raksasri[1], Supot Kamsa-ard[2,3]* Wachiraporn Musika[4], Chalongpon Santong[5], Anakapong Phunmanee[6]

Abstract

Background: Lung cancer (LC) is the leading cause of death worldwide. Stage III lung cancer (Stage III-LC) is characterized by local metastasis. The treatments for LC differ at each stage, while for stage IIIA and IIIB treatment various approaches have been tried with uncertain results. We determined the survival time of Stage III-LC patient and compared survival among multiple factors. **Methods:** Data were collected from the Srinagarind Hospital-Based Cancer Registry (2014 - 2019). 324 patients from Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, were followed up until December 31, 2021. The survival rate was estimated using Kaplan-Meier and the Log-rank test. In addition, hazard ratios (HR) and the 95% CI were estimated using Cox regression. **Results:** Of the 324 Stage III-LC patients, the total follow-up time was 447.3 person-years, and 288 cases died during the study, for a mortality rate of 64.4 per 100 person-years (95% CI: 57.40-72.27). The respective 1-, 3-, and 5-year survival rate was 44.1% (95% CI: 38.67-49.45), 16.2 (95% CI: 12.34-20.51), and 9.3 (95% CI: 6.14-13.31). The median survival time was 0.84 years (10.1 months) (95% CI: 0.73-1.00). After adjusting for sex and stage of disease, sequential chemoradiotherapy (SC) represented the most independent predictor of the risk of death (adjusted HR= 1.58; 95% CI: 1.41-2.18). Females had a mortality risk of 0.74-fold compared to males (adjusted HR = 0.74, 95% CI: 0.57-0.95). Stage of disease and stages IIIB and III (unknown and undefined) had a respective 1.33-fold (adjusted HR = 1.33, 95% CI: 1.00-1.84) and 1.48-fold (adjusted HR = 1.48, 95% CI: 1.09-2.00) risk of death compared to stage IIIA. **Conclusion:** Sex, stage of disease, and SC were related to stage III-LC survival, so physicians should emphasize combination therapy. Further research should focus on combination therapy and survival among Stage III-LC patients.

Keywords: Survival Rate- stage III Lung cancer- cancer registry

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Introduction

According to the 2020 worldwide cancer data, the number of deaths from lung cancer (LC) was 1,796,144 (18.0% of all cancer sites) (Global Cancer Observatory, 2020a). In Southeast Asia, the number of deaths for all cancer sites was 9.9 million. The most common causes of cancer death were LC (18.0%), colorectal cancer (9.4%), and liver cancer (8.3%) (Global Cancer Observatory, 2020b). In Thailand, in 2020, there were 114,199 cancer deaths and the most common causes were liver cancer (20.3%), LC (18.7%), and colon and rectal cancer (8.3%) (Global Cancer Observatory, 2020c).

The 2020 worldwide age-standardized rate (ASR) reveals that LC has the third highest incidence (ASR = 22.4 per 100,000), most commonly in males (ASR = 31.5 per 100,000), and the third rank among females (ASR = 14.6 per 100,000) (Global Cancer Observatory, 2020d).

In 2020, LC in Thailand had the second-highest incidence rate among males (ASR = 27.4 per 100,000) and fifth among females (ASR = 11.9 per 100,000) (Global Cancer Observatory., 2020d). According to the 2020 annual report for Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, LC constituted

*[1]The Khon Kaen Office of Disease Prevention and Control, Nai Mueang Subdistrict, Mueang District, Khon Kaen, Thailand. [2]Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand. [3]ASEAN Cancer Epidemiology and Prevention Research Group, Khon Kaen University, Khon Kaen, Thailand. [4]Bueng Khong Long Hospital, Bueng Khong Long District, Bueng Kan Province, Thailand. [5]Cancer Unit, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. [6]Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand. *For Correspondence: supot@kku.ac.th*

the highest incidence rate for both sexes. The number of new cases of LC was 7.6 %, the second highest after liver and bile duct cancer among males. While the fifth most common cancer contributed 5.7% among females, followed by breast cancer, liver and bile duct cancer, thyroid cancer, and colon and rectal cancer (KKU Cancer Unit, Srinagarind Hospital., 2020).

However, the previous study at Srinagarind Hospital, Khon Kaen, Thailand, revealed that the respective overall median survival time of patients with stage I-IV was 39.72, 21.84, 11.26, and 6.24 months. However, the later stages (stage III-IV) of lung cancer had the worst survival rates because most patients with LC have an advanced stage of cancer at diagnosis (Punjaruk et al., 2015).

This is because Stage III-LC (including stages IIIA and IIIB) has completely different staging between stage IIIA and stage IIIB. Additionally, metastasis and treatment are distinct for stage IIIA and IIIB of the disease. Therefore, the current study aimed to determine the survival rate of Stage III-LC patients at Srinagarind Hospital and to compare survival between various factors after diagnosis. The findings of this study may help policymakers and physicians at Srinagarind Hospital, a tertiary health care center, to design a more appropriate treatment plan for Stage III-LC patients. In addition, the study findings may also shed more light on lung cancer and advance clinical practice and treatment.

Materials and Methods

Cancer Registries and Case Ascertainment
Khon Kean Cancer Registry, KKCR

The Khon Kaen Cancer Registry (KKCR) was founded in 1984 at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University in northeastern Thailand. It includes hospital- and population-based registrations. The KKCR comprises 1.7 million people from Khon Kaen province. For cancer registration, the KKCR adheres to the standards and guidelines of the International Agency for Research on Cancer (IARC) for all types and sites of cancer (Esteban et al., 1995).

Case definitions

All Stage III-LC patients treated at Srinagarind Hospital were retrieved from the Srinagarind Hospital-based cancer registry (SHCR) database. Clinical staging was tracked from the medical records by following the TNM classification for Stage III-LC (Goldstraw et al., 2016). Diagnoses were obtained using the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3). LC is an ICD-O-3 diagnosis and only includes coding C34.0-C34.9 between January 1, 2014, and December 31, 2019 (World Health Organization, 2013).

Stage III-LC treatment can include various combinations of chemotherapy followed by radiation therapy (Sequential Chemoradiotherapy, SC). In addition, stage III-LC patients may receive radiation therapy or chemotherapy alone.

Statistical methods

Descriptive epidemiology of study patients

Patient characteristics were summarised using descriptive statistics. For continuous variables, means and standard deviations (SD), medians, and their ranges (minimum and maximum) were utilised; for categorical variables, frequency counts and percentages were used.

Survival analyses

A total of 324 cases with Stage III-LC were diagnosed at the SHCR with the ICD-O-3 codes C33.9 and C34.0-C34.9 (The International Classification of Diseases for Oncology (ICD-O-3).

The patients were followed up until December 31, 2021, to ascertain their vital status. The status was obtained by linking records from (1) the Mortality Registry of Thailand (National Health Office, 2017) and (2) the National Statistical Office (National Statistical Office Thailand). The vital status of each patient (alive, dead) included the date last seen and the cause of death.

The survival rate was estimated using the Kaplan-Meier method, and the survival rate, median survival time, and 95% confidence intervals (CIs) were reported. The Log-rank test was used to compare survival curves. Multivariable analysis was performed using Cox proportional hazards regression, after which Hazard ratios (HRs) were reported with their 95% CIs and p-values from the partial likelihood ratio test (Kleinbaum et al., 2012).

All test statistics were two-sided, and a p-value of < 0.05 was considered statistically significant.

Data processing

Data were recorded using the CanReg 5 software provided by the International Association of Cancer Registries (IARC) (IARC, 2019). The verification was performed with necessary corrections, including logic, range, and internal consistency, which were checked using statistical software. All analyses were performed using Stata release 10.0 (StataCorp LLC, College Station, TX, USA) (Stata Corp., 2007).

Ethical considerations

The Human Research and Ethics Committee of Khon Kaen University reviewed and approved this project (HE641492).

Results

Descriptive epidemiology

A total of 324 Stage III-LC cases recorded between 2014 and 2019 were retrieved from the SHCR database. The database contained cases of lung cancer at Stage IIIA (n=69, 21.3%), Stage IIIB (n=103, 31.8%), and Stage III (unknown or undefined) (n=152, 46.9%). Of the 324 cases of Stage III-LC, the majority were males (n=223, 68.8%), and the mean age at diagnosis was 62.6 years (standard deviation = 10.1 years). Histology of the primary was the most common basis for the diagnosis of Stage III-LC (n=264, 81.5%), followed by cytology (n=30, 9.1%) and endoscopic biopsy (n=27, 8.2%).

Location of the LC

The highest was in the upper lobe (n=157; 48.5%),

Table 1. Characteristics of Stage III-LC Patients Diagnosed at Srinagarind Hospital between 2014 and 2019

Characteristic	Number (n = 324)	Percentage (%)
Year of diagnosis		
2014	80	24.7
2015	65	20.1
2016	74	22.8
2017	36	11.1
2018	34	10.5
2019	35	10.8
Sex		
Male	223	68.8
Female	101	31.2
Age at diagnosis (years)		
20-29	1	0.3
30-39	3	1
40-49	26	8
50-59	84	26
60-69	122	37.6
70-79	79	24.4
>80	9	2.7
Mean (SD)	62.9 (10.1)	
Median (minimum: maximum)	64.0 (29: 84)	
Marital status		
Single	5	1.5
Married	316	97.5
Monk	3	1
Basis of diagnosis		
X-ray / Endoscope/ Ultrasound (Endoscope and Radiology)	27	8.3
Cytology	30	9.3
Histology of metastasis	3	0.9
Histology of primary	264	81.5
Stage of disease		
Stage IIIA	69	21.3
Stage IIIB	103	31.8
Stage III (unknown or undefined)	152	46.9
Location		
Main bronchus	9	2.7
Upper lobe, lung	157	48.5
Middle lobe, lung	12	3.7
Lower lobe, lung	75	23.2
Overlapping lesion of lung	6	1.8
Lung, NOS	65	20.1
Histology		
Squamous cell carcinoma	34	11.6
Adenocarcinoma	169	57.7
Small cell carcinoma	4	1.4
Large cell carcinoma	1	0.3
Non-small cell carcinoma	25	8.5
Unspecified and other	91	28.1

Table 1. Continued

Characteristic	Number (n = 324)	Percentage (%)
Histology grading		
Well differentiated	13	4
Moderately differentiated	13	4
Poorly differentiated	41	12.7
Undifferentiated	4	1.2
Not known	253	78.1
Laterality		
Right	141	43.5
Left	98	30.3
Bilateral	6	1.8
Unknown	79	24.4
Metastasis		
Direct extension	3	0.9
Regional lymph	158	48.8
Unknown	163	50.3
Surgery		
Yes	33	10.2
No	291	89.8
Radiation		
Yes	75	23.2
No	249	76.8
Chemotherapy		
Yes	161	49.7
No	163	50.3
Targeted therapy		
Yes	4	1.2
No	320	98.8
Supportive care		
Yes	20	6.2
No	304	93.8
Palliative care consultation		
Yes	115	35.5
No	209	64.5
Adjuvant radiotherapy		
Yes	10	3.1
No	314	96.9
Adjuvant chemotherapy		
Yes	24	7.4
No	300	92.6
Neoadjuvant chemotherapy		
Yes	4	1.2
No	320	98.8
Concurrent chemoradiotherapy		
Yes	5	1.5
No	319	98.5
Sequential chemoradiotherapy		
Yes	54	16.7
No	270	83.3

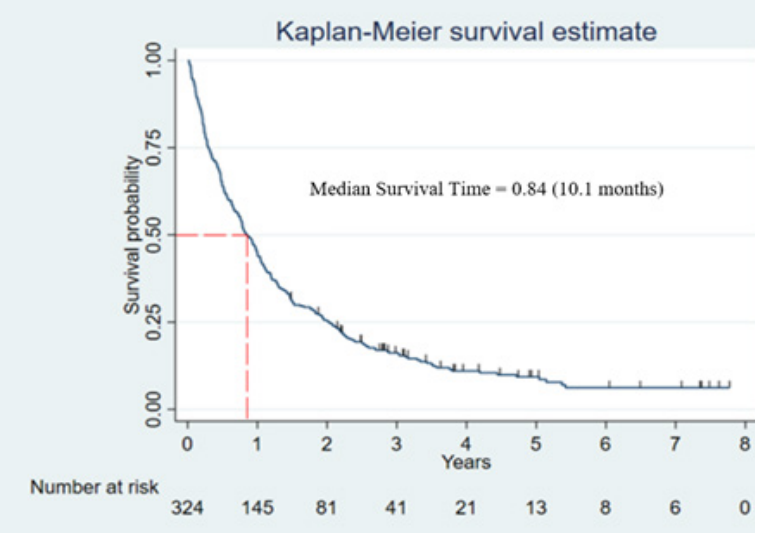

Figure 1. Survival Curve of Stage III-LC Patients Treated at Srinagarind Hospital between 2014 and 2019

Table 2. The 1-, 3-, and 5-Year Survival Rate for Stage III-LC after Diagnosis, Treated at Srinagarind Hospital between 2014 and 2019

Variable	Number		1-year	3-year	5-year
		Median time (95%CI)	Survival rate (95%CI)	Survival rate (95% CI)	Survival rate (95% CI)
Stage III LC	324	0.84 (0.73-1.00)	44.1 (38.67-49.45)	16.2 (12.34-20.51)	9.3 (6.14-13.31)

while the lowest was an overlapping lesion of the lung (n=6, 1.8%). The most common histological type was adenocarcinoma (n=169, 57.7%), while the least common was 'large cell carcinoma' (n=1, 0.3%). The most common treatment for Stage III-LC was chemotherapy (n=161, 49.7%), followed by palliative care consultation (n=115, 35.5%) and radiotherapy (n=75, 23.2%). For other characteristics, see more detail in Table 1.

SC was the most prevalent treatment modality (n=54, 16.7 percent), followed by adjuvant chemotherapy (n=24, 7.4%) and adjuvant radiotherapy (n=10, 3.1%) (Table 1).

Survival rate of Stage III-LC after diagnosis
Mortality rate and Median survival time

The 331 Stage III-LC patients had a total follow-up of 447.3 person-years. In total, 288 patients died during the study, corresponding to a mortality rate (case fatality) of 64.4 per 100 person-years (95%CI: 57.4 - 72.3). The median survival time was 0.84 years (10.1 months) (95%CI: 0.73-1.0). The respective 1-, 3-, and 5-year survival rate was 44.1 % (95% CI: 38.67 - 49.45%), 16.2 % (95%CI: 12.34 - 20.51), and 9.3% (95%CI: 6.14 - 13.31) (Table 2), (Figure 1).

Multivariable Cox regression analyses

After adjusting all variables in the model through multiple analyses, we found that sex, stage of disease, and SC affected patient survival after diagnosis (p-value < 0.05). The female mortality risk was 0.74–fold compared to males (adjusted HR=0.74, 95%CI: 0.57 - 0.95). Compared to stage IIIA, patients with stages IIIB and III (unknown or undefined) had a 1.33-fold (adjusted HR = 1.33, 95% CI: 1.00-1.84) and 1.48-fold (adjusted HR = 1.48, 95% CI: 1.09-2.00) increased risk of mortality, respectively. Treatment with SC was associated with a 1.58-fold increase compared to no SC treatment (adjusted HR =

Table 3. Multivariable Analysis for Stage III-LC after Diagnosis at Srinagarind Hospital between 2014 and 2019

Variable	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
Sex			0.018
Male	1	1	
Female	0.76 (0.59-0.97)	0.74 (0.57-0.95)	
Stage of disease			0.034
Stage IIIA	1	1	
Stage IIIB	1.36 (1.00-1.88)	1.33 (1.00-1.84)	
Stage III (unknown or undefined)	1.58 (1.17-2.13)	1.48 (1.09-2.00)	
Sequential Chemoradiotherapy, SC			0.004
Yes	1	1	
No	1.52 (1.15-2.00)	1.58 (1.41-2.18)	

1.58, 95% CI: 1.41 - 2.18) (Table 3).

Discussion

The current study compared the survival rate of patients diagnosed with Stage III-LC at Srinagarind Hospital between 2014 and 2019 based on several factors, as follows.

Overall Survival of Stage III-LC patients

This retrospective cohort study was conducted on patients with Stage III-LC. The SHCR was the source of the data. The mean age at diagnosis was 62.9 years (SD = 10.1 years) among the 324 cases in the study. Males outnumbered females by a ratio of 2.20 to 1.

In the current study, the survival rate of stage III-LC after diagnosis was poor. The 5-year survival rate after diagnosis was 9.3% (95%CI: 6.1 - 13.3). The median survival time was 0.84 years (95% CI: 0.7 - 1.0) (10.1 months), consistent with previous studies. Musika et al. (2021) found that the 5-year survival rate of all stages of LC after diagnosis was 10.2% (95%CI: 8.7 - 11.7), and the median survival time was 0.46 years (95% CI: 0.4-0.5). According to Zemanova et al. (2020), the median Stage III-LC survival time was 16.8 months (95% CI: 15.3-18.5). The respective 1-, 3-, and 5-year survival rate was 65.1 % (95% CI: 61.3 - 69.1%), 31.4 % (95%CI: 30.4 - 38.2), and 21.0% (95%CI: 17.3 - 25.4) (Zemanova et al., 2020).

The outcome of the present study differs from a study conducted in China (Shanghai). For example, the respective 1-year survival rate of stage III and IIIB/IV LC after diagnosis (in Shanghai) was 78.8 % (95% CI: 74.1 - 83.5%) and 58.9 % (95%CI: 56.1 - 61.7). Moreover, Beksisa et al. reported that the respective 2-, 3-, and 5-year survival rate was 57.1 % (95% CI:43.4 - 72.2%), 38.9 % (95%CI: 19.3 - 59.6), and 22.1% (95%CI: 0.0 - 36.7). The median survival time was 28.0 months (95% CI: 22.0 - 40.0). Patient characteristics, such as stage of disease and metastasis, can influence the variation in patient survival rates (Beksisa et al., 2020).

Generally, patients diagnosed with stage IIIA had better survival than stage IIIB and Stage III (unspecified). In contrast, the current study revealed that the survival of patients diagnosed with stage IIIA was poorer than those diagnosed with Stage IIIB and Stage III (unspecified). The reason may be that the number of patients in Stage IIIA was less than Stage IIIB and Unspec. (IIIA n=69, 21.3%) vs. Stage IIIB and Stage III (unspecified) (n=255, 78.7%) . Currently, the best treatment for Stage III-LC is multimodal, including chemotherapy and radiotherapy. In addition, the best treatment is chemoradiotherapy, followed by sequential chemoradiation and radiation or chemotherapy alone. Radiation or chemotherapy alone can be the appropriate treatment for Stage III-LC patients who are often weak and ailing, so do not tolerate a multimodal approach. In the current study, the small number of concurrent chemoradiation (5, 5.0%) and sequential chemoradiation (54, 16.7%) was due to the poor survival of Stage III-LC patients in this area (Table 1).

Survival factors of Stage III- LC patients

Sex

The current study revealed a significant association between sex and survival rate (p-value = 0.018). After adjusting for all variables in the model, it was discovered that the female mortality risk is 0.74-fold compared to the male risk (adjusted HR = 0.74, 95%CI: 0.57-0.95). Thus, females survive longer than males. Our findings are consistent with prior research. For all stages of LC patients diagnosed at Srinagarind Hospital, it was discovered that sex influenced patient survival (p-value < 0.05). After adjusting for all variables in the model, females had a mortality risk of 0.78-fold compared to males (adjusted HR = 0.78, 95%CI: 0.68-0.89) (Musika et al., 2021). Consistent with a Japanese study, the association between sex and survival rate was statistically significant (p-value < 0.001). Male mortality risk was 1.19-fold times that of the female mortality risk (adjusted HR = 1.19, 95% CI: 1.16-1.21) (Kinoshita et al., 2017). In addition, a Swedish study reported that sex was strongly associated with the survival rate (p-value < 0.001). The female mortality risk was 0.73-fold compared to that of males (adjusted HR = 0.73, 95% CI: 0.67-0.79) (Sachs et al., 2021).

Stage of disease

The current study revealed a significant relationship between the stage of disease and survival rate (p-value < 0.001). After adjusting for all variables in the model, stage IIIB and III LC patients (unknown and undefined) were associated with a 1.33– and 1.48–fold mortality risk (adjusted HR = 1.33, 95% CI: 1.00-1.84 vs. 1.48, 95% CI: 1.09-2.00) compared to stage IIIA. Consistent with a study conducted in Ubon Ratchathani, Thailand, the survival rates of patients in the metastasis stage of the disease were significantly different (p < 0.001). After adjusting for all variables in the model, stage IIIB and IV LC patients had an increased risk of mortality compared with stage IIIA (adjusted HR = 2.00, 95% CI: 1.23-3.31) and stage IV as 3.20 (adjusted HR = 3.20, 95% CI: 1.96-5.17) (Srisam-ang et al., 2005). In addition, a study at Srinagarind Hospital revealed an association between the TNM stage and patient survival (p < 0.001). After adjusting for sex, histologic type, and chemotherapy, stage III and IV LC patients had an increased mortality risk than those with stage I and II (adjusted HR = 6.35, 95% CI: 4.05-9.95) and stage IV as 8.32 (adjusted HR = 8.32, 95% CI: 5.36-12.90), respectively (Musika et al., 2021).

In the current study, the TNM staging system for LC (seventh edition) was adapted from the eighth edition (Lababede et al., 2018); however, the clinical staging was used to determine the stage of the disease. As a result of imprecise clinical staging that can impact survival (Navani et al., 2019), patients with stage IIIB and III LC who have "unknown and undefined" conditions may have a poorer survival rate.

Sequential Chemoradiotherapy (SC)

In the present study, SC was statistically associated with the Stage III-LC survival rate (p-value < 0.029). After adjusting for sex and stage of disease, we found that those without SC had a 1.58–fold higher risk of

mortality than those with SC (adjusted HR = 1.58, 95% CI: 1.41-2.18). Compared to patients treated with SC as a reference group (n=54), those treated with radiation alone (n=16) and chemotherapy alone (n=102) had a 1.40 (adjusted HR=1.14; 95%CI:0.76–2.56) and 1.15 (adjusted HR=1.15; 95%CI: 0.79–1.65)-fold increased risk of mortality (Data not shown). Consistent with prior research, SC was associated with a 0.51–fold increase in mortality risk compared to no SC (adjusted HR = 0.51, 95%CI: 0.28-0.91) (Sakin et al., 2021). Our findings are comparable to those of David et al., (2016) who reported that chemotherapy alone for LC was associated with a 0.40–fold mortality risk compared to no-treatment (adjusted HR=0.40; 95%CI: 0.39 - 0.42). Additionally, Urvay et al. reported that sequential chemoradiotherapy (n=26) vs. concurrent chemoradiotherapy (n=122) were factors affecting survival. The combination therapy was significantly associated with a higher rate of Stage III-LC survival (p-value = 0.025) (Urvay et al., 2016). After adjusting for all variables in the model, concurrent chemoradiotherapy for Stage III-LC was associated with a 0.50–fold increased mortality risk compared to sequential chemoradiotherapy (adjusted HR = 0.50, 95% CI: 0.30-0.90). Specifically, stage III-LC was treated by chemoradiotherapy, the standard for Stage II-LC, while concurrent chemoradiotherapy was limited. Sequential chemotherapy is, therefore, flexible for the treatment because most of the analyzed data come from existing medical records. The combination of treatments has superior survival than no treatment.

Furthermore, vis-à-vis the current study, performance status is another factor affecting Stage III-LC. However, we cannot provide an analysis due to a lack of data from the cancer registry.

Advantages and Disadvantages of the study

Advantages

According to the SHCR, the current study is the most recent examination of Stage III-LC post-diagnosis survival factors between 2014 and 2019. In this study, Stage III-LC was treated with chemoradiation and radiation therapy.

Disadvantages

Our study has certain limitations, such as incomplete pathological data, as some patients were diagnosed without pathological confirmation because most patients delay seeing a doctor and are diagnosed at a late stage.

In conclusion, the current study demonstrated that sex, disease stage, and SC are associated with Stage III-LC patient survival. Therefore, further research into the factors affecting LC survival in northeastern Thailand should centre on combination therapy.

Author Contribution Statement

NR was the principal investigator and provided project management supervision. SK and CS provided advice about the study design and statistical analyses. WM was involved in exploratory analysis and data quality. AP was a physician and operated on patients with apparent LC and assisted in the final diagnoses of the cases.

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Statement conflict of interest

The authors declare that they have no conflicts of interest.

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