Original Article

The Prevalence and Treatment Impact on Survival of Early Stage NSCLC: Phramongkutklao Hospital Experience

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Abstract:

Background: *In Thailand, one-fifth of non-small cell lung cancer (NSCLC) patients were diagnosed in early stage (stage I-IIIa), however disparity in stages of NSCLC may affect treatments and variable outcomes. We aimed to study the prevalence and determined the clinical characteristics of NSCLC, treatments by platinum-based chemotherapy, and prognostic factors on survival rates at Phramongkutklao Hospital.* ***Methods:*** *We reviewed the database of 216 patients who were diagnosed with early stage NSCLC between January 2003 and December 2013 at Phramongkutklao Hospital. The clinical characteristics, pathological features and treatments were collected and analyzed. Period prevalence was calculated by descriptive statistics, cox proportional hazards model and hazard ratios (HRs). A stepwise backward procedure were also used to estimate survival rates.* ***Results:*** *A total of 1,550 patients were diagnosed with NSCLC between January 2003 and December 2013 at Phramongkutklao Hospital, with 216 patients (14%) were diagnosed as early stage NSCLC. By stratifying by stage, there were stage Ia 35%, stage Ib 13%, stage IIa 8%, stage IIb 11% and stage IIIa 33%. The median follow-up time was 36.6 months. The 5-year disease free survival (DFS) rate was 33.8% and the overall survival (OS) rate was 48.9%. The univariate analysis revealed that total smoke of ≥ 20 pack-year, ECOG performance status of ≥ 2, stage IIIa, poorly differentiated histology grading, lymphatic-vascular & perineural invasion were associated with shorter OS and DFS, however, from multivariate analysis the only significant prognostic factors were stage IIIa disease and poorly differentiated histology grading. According to adjuvant chemotherapy treatments, there was no statistical difference between cisplatin and carboplatin-based regimens that affected survival rates (the 5-year OS of cisplatin-based and carboplatin-based were 43% and 36.6%, respectively).* ***Conclusions:*** *Only one-seventh of NSCLC patients at Phramongkutklao Hospital were found in early stage, however the 5-year OS rate remained poor. Factors that affected shorter survival rates were higher stage (stage IIIa) at diagnosis and poorly differentiated histology grading. In addition, adjuvant chemotherapy with platinum based-regimens could increase OS and DFS.*

Keywords: ● *Early stage non-small cell lung cancer (NSCLC)* ● *Adjuvant chemotherapy* ● *Cisplatin*

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นิพนธ์ต้นฉบับ

การศึกษาความชุกและวิธีการรักษาที่มีผลต่ออัตราการรอดชีวิตในผู้ป่วยมะเร็งปอดชนิดไม่ใช่เซลล์ขนาดเล็กระยะเริ่มต้นในโรงพยาบาลพระมงกุฎเกล้า

ปิยรัตน์ ลิมปวิทยากุล[1] ไนยรัฐ ประสงค์สุข[2] กสานติ์ สีตลารมณ์[2] และ สิริวิมล ไทรแจ่มจันทร์[2]

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บทคัดย่อ

วัตถุประสงค์ *ศึกษาความชุก และเปรียบเทียบประสิทธิภาพของยาเคมีบำบัดเสริมหลังการผ่าตัด รวมถึงศึกษาปัจจัยที่มีผลต่อการกลับเป็นซ้ำของโรคและอัตราการรอดชีวิตของผู้ป่วยมะเร็งปอดชนิดไม่ใช่เซลล์ขนาดเล็กระยะต้น (ระยะที่ 1-3 ตาม AJCC version 7) ในโรงพยาบาลพระมงกุฎเกล้า* ***รูปแบบการวิจัย*** *Retrospective study* ***วิธีการวิจัย*** *เก็บข้อมูลพื้นหลังได้แก่ เพศ อายุ ประวัติการสูบบุหรี่ ระยะของโรค ความสามารถในการใช้ชีวิตประจำวัน รูปแบบการผ่าตัด ผลชิ้นเนื้อ การรักษาเสริมหลังผ่าตัดโดยเฉพาะสูตรยาเคมีบำบัด ของผู้ป่วยมะเร็งปอดชนิดไม่ใช่เซลล์ขนาดเล็กระยะต้นตั้งแต่ มกราคม 2546 ถึง มกราคม 2556 จากฐานข้อมูลเวชระเบียนผู้ป่วยนอก โดยผู้ป่วยระยะลุกลามและแพร่กระจายจะถูกคัดออก พร้อมทั้งวิเคราะห์ปัจจัยที่มีผลต่ออัตราการกลับเป็นซ้ำและอัตราการรอดชีวิต ด้วยวิธี Cox proportional hazards model and hazard ratios (HRs)* ***ผลการวิจัย*** *มีผู้ป่วยมะเร็งปอดชนิดไม่ใช่เซลล์ขนาดเล็ก ทั้งหมด 216 คน จากทั้งหมด 1,550 คน คิดเป็นร้อยละ 14 จากระยะเวลาการติดตามโรค 36.6 เดือน พบอัตราการกลับเป็นซ้ำของโรคที่ 5 ปีร้อยละ 33.8 และอัตราการรอดชีวิตที่ 5 ปี ร้อยละ 48.9 จากการวิเคราะห์ทางสถิติด้วย Multivariated analysis พบว่าปัจจัยที่มีผลต่อการกลับเป็นซ้ำของโรคและอัตราการรอดชีวิตที่ลดลงได้แก่ ระยะที่ 3 และผลชิ้นเนื้อชนิด poorly differentiated โดยที่เมื่อเปรียบเทียบประสิทธิภาพของสูตรยาเคมีบำบัดที่ใช้ยาซิสพลาตินกับยาคาร์โบพลาติน พบว่าอัตราการรอดชีวิตที่ 5 ปี ที่ร้อยละ 43 และ 36 ตามลำดับ* ***สรุป*** *ความชุกของผู้ป่วยมะเร็งปอดชนิดไม่ใช่เซลล์ขนาดเล็กระยะต้นของโรงพยาบาลพระมงกุฎเกล้าใกล้เคียงกับการศึกษาอื่นในประเทศไทย และปัจจัยที่ส่งผลต่ออัตราการกลับเป็นซ้ำและอัตราการรอดชีวิตที่สั้นลงได้แก่ ระยะที่ 3 และชิ้นเนื้อชนิด poorly differentiated ทั้งนี้ประสิทธิภาพของยาเคมีบำบัดที่ใช้รักษาแต่ละชนิดไม่แตกต่างกัน*

คำสำคัญ: ● *Early stage non-small cell lung cancer (NSCLC)* ● *Adjuvant chemotherapy* ● *Cisplatin*

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ได้รับต้นฉบับ 19 กุมภาพันธ์ 2562 แก้ไขบทความ 8 เมษายน 2562 รับลงตีพิมพ์ 10 พฤษภาคม 2562

ต้องการสำเนาต้นฉบับติดต่อ นายสุรเชษฐ์ อ่อนเส็ง ภาคบริการโลหิตแห่งชาติที่ 9 จังหวัดพิษณุโลก สภากาชาดไทย ถ.พระองค์ดำ ต.ในเมือง อ.เมือง จ.พิษณุโลก 65000 E-mail: chedthnong@gmail.com

Introduction

The International Agency for Research on Cancer (GLOBOCAN) reported 1.8 million (12.9% of total) new cases of lung cancer worldwide in 2012, with 1.6 million deaths (19.4% of total)[1]. National Cancer Institute of Thailand (NCI) showed lung cancer incidence of 10.4% in 2012 and increased to 16.4% in 2015 with approxid mately 18.5% cancer deaths[2-6]

Non-small cell lung cancer (NSCLC) represents more than 80% of lung tumors, with 30% of NSCLC around the world was found in early stages (stage I-IIIa) and undergo surgery with curative intent[7]. In 2015, the prevalence of early stage NSCLC in Thailand was 20.83%[8]. The prognosis depends on stages of tumors at diagnosis (TNM staging, 6th AJCC edition)[9], and the 5-year survival rate of stage Ia is the longest when compared with others (60% versus 38%, 34%, 24% and 13%, respectively)[10]. In addition, histology, calcium level, weight loss, performance status, gender, age smoking habit are also important factors[11]. Despite surgery, about 40% of NSCLC patients with stage I, 60% with stage II, and 75% with stage IIIa disease die within 5 years[12,13].

The International Adjuvant Lung Trial (IALT) showed a significant 4% benefit at 5 years for cisplatin-based chemotherapy after curative surgery in stage Ia-IIIa NSCLC, and from subgroup analysis only stage IIIa derived benefits from adjuvant treatment[14]. The Cancer and Leukemia Group B (CALGB) 9,633 study reported a 12% reduction in mortality at 4 years with adjuvant carboplatin plus paclitaxel in stage Ib, unfortunately after follow-up for 6 years, it showed no survival improvei ment[15]. In addition, the Adjuvant Navelbine International Trialist Association (ANITA) showed an 8.6% improvet ment in overall survival (OS) at five years for cisplatin plus vinorelbine regimens in completely resected stage Ib-IIIa NSCLC, but in subgroup analysis the benefit is seen mainly in patients with stage II and IIIa diseases[16]. Similarly, JBR.10 trial that studied a benefit of adjuvant vinorelbine plus cisplatin in completely resected stage Ib or II NSCLC patients showed a 15% improvement in OS. However, only stage Ib patients who had tumor size ≥ 4 cm derived clinically meaningful benefits from chemotherapy[17].

Currently, the meta-analysis of Lung Adjuvant Cisplatin Evaluation (LACE) showed a 5-year absolute benefit of 5.4% of cisplatin-based chemotherapy which is not associated with combination regimens, and the subset analysis of stage II and IIIa disease revealed better benefits than that of stage I.[18] Indeed, adjuvant chemotherapy after surgical resection appears to reduce disease recurrence and improve survival[14-18].

According to the meta-analysis of metastasis NSCLC, carboplatin had a similar effect on survival rates but a different toxicity profile when compared with cisplatin[19,20]. However, there was no study that compared the efficacy of cisplatin and carboplatin-based chemotherapy in adjuvant setting.

In this retrospective study, we aimed to examine the prevalence of early stage NSCLC patients, the clinical characteristics and prognostic factors that affect survival rates, including the efficacy of cisplatin versus carboplatin based-chemotherapy at Phramongkutklao Hospital.

Materials and Methods

Patients

We reviewed the database of 216 patients who were diagnosed with early stage NSCLC between January 2003 and December 2013 at Phramongkutklao Hospital. We recorded the patient characteristics such as age, gender, body weight, history of smoking, ECOG performance status, tumor staging, histology subtypes, grading and treatment modalities including surgery, radiation and systemic chemotherapy. Patients who were diagnosed with advance and metastatic stages (stage IIIb-IV) were excluded. The last follow-up time was December 2016.

Objectives

The primary objective of this study was to evaluate the prevalence of early stage NSCLC (stage Ia-IIIa) over the last decade. The secondary objective was to study survival analysis of each stage and identify prognosis factors especially cisplatin and carboplatin-based adjuvant chemotherapy in Phramongkutklao Hospital.

Statistical analysis

We used descriptive statistics to identify baseline clinical characteristics of early stage NSCLC patients. The primary endpoint was the prevalence using means and standard error to calculate with 95% confidence interval. The secondary endpoints were OS, DFS (stratified by stage) using Kaplan-Meier methods and the log-rank test. The OS was defined as the date at diagnosis until death or the last follow-up date. The DFS was also defined as the date at diagnosis until disease recurrence, death from any cause, or the last follow-up date. The prognostic factors that affect survivals were performed using univariate analysis and cox proportional hazard model (HR).

Results

Between January 2003 and December 2013, we observed 1,550 patients who were diagnosed with NSCLC at any stages. From 1,550 patients, only 216 patients were diagnosed with early stage NSCLC (stage I, II, and IIIa). The prevalence of early stage NSCLC was 14% and the median follow up time was 36.67 months. In this study, there were 45 patients without the follow-up, accounted for 20% of 216 patients.

Of the 216 patients with early stage NSCLC, most of the patients were female (134/216, 62%) and the mean age was 63.31 ± 11.42 (SD) years (Table 1). Half of the patients never smoked (104/216, 48%) while the number of heavy smokers ≤ 20 pack-year) and light smokers (< 20 pack-year)[21] were 81 (37%) and 30 (13%), respectively.

Table 1 The clinical characteristics of early stage NSCLC patients at Phramongkutklao Hospital

Patient characteristics	No. (%) (n = 216)
Gender	
Male	82 (37.9)
Female	134 (62.1)
Age	
< 60	79 (36.5)
≥ 60	137 (63.5)
Total of cigarettes smoking	
None	105 (48.7)
< 20 pack-year*	30 (13.8)
≥ 20 pack-year*	81 (37.5)
ECOG performance status	
ECOG 0-1	172 (79.6)
ECOG ≥ 2	44 (20.4)
TNM staging#	
Stage Ia	75 (34.7)
Stage Ib	28 (13.0)
Stage IIa	18 (8.3)
Stage IIb	25 (11.6)
Stage IIIa	70 (32.4)
Histology grading	
Well differentiated	116 (53.7)
Moderately differentiated	39 (18.1)
Poorly differentiated	38 (17.6)
Unknown	23 (10.6)
Histology subtype	
Adenocarcinoma	184 (85.2)
Squamous cell carcinoma	27 (12.5)
Large cell carcinoma	5 (2.3)
Invasion status	
No invasion	149 (69.0)
Lymphatic-vascular & perineural invasion	31 (14.4)
Unknown	36 (16.6)

*Total of cigarettes smoking defined as < 20 pack-year = light smoking and ≥ 20 pack-year = heavy smoking[21]

#TNM staging by 6th AJCC edition[9]

Almost all patients had ECOG performance status 0-1 172/216, 79.6%. Among patients with early stage NSCLC, the majority of patients was in stage Ia (75/216, 34%) and stage IIIa (70/216, 32%) while the rest was in stage Ib (28/216, 13%), stage IIb (25/216, 11%), and stage IIa (18/216, 8%). Well differentiated NSCLC was the most common histologic grading when compared with moderately and poorly differentiated NSCLC [116/216 (53%) vs 39/216 (18%) and 38/216 (17%), respectively]. In addition, adenocarcinomawas the most common histology subtype which was found about 184/216 (85%), while squamous cell carcinoma and large cell carcinoma were found in 27/216 (13%) and 5/216 (2%), respectively. Among known pathology reports of invasion status, most of the patients (149/216, 69%) had no invasion whereas only 31/216 (14%) had lymphatic-vascular and perineural invasion.

According to the treatment modalities in early stage NSCLC, surgery was the mainstay (Table 2). Most of themunderwent surgical resection (174/216, 80%), comprising of lobectomy (165/174, 95%), wedge resection (8/216, 4.6%), and only one patient receiving pneumonectomy. The systemic chemotherapy that we used in early stage comprised of neoadjuvant (14/216, 6.5%) and adjuvant chemotherapy (68/216, 31%). The adjuvant chemotherapy regimens, which are commonly used in adjuvant setting, were cisplatin-vinorelbine (19/68, 28%), cisplatin-etoposide (17/68, 25%), and carboplatin-vinorelbine (17/68, 25%). However, only one-third of patients received adjuvant radiotherapy.

As listed in table 1, 2 and 3 including clinical characteristics, treatment modalities, and pattern of disease recurrence, we conducted an analysis to determine the percentage. However, as listed in table 4 and 5 including univariate and multivariate analysis of prognostic factors that affect DFS and OS, we analyzed by Cox regression mode.

The efficacy of treatments

The median OS was 59.5 months (95% confidence interval (CI), 45.4 to 86.9). The 5-year survival rate was 48.9% (Figure 1), stratified by stages Ia, Ib, IIa, IIb and IIIa as 74.8%, 50.8%, 46.0%, 45.7%, and 14.8%, respecs

Table 2 Showed treatment modalities of early stage NSCLC patients at Phramongkutklao Hospital

Treatment modalities	No. (%) (n = 216)
Surgery (n = 174)	174/216 (80.5)
Lobectomy	165/174 (94.8)
Wedge resection	8/174 (4.6)
Pneumonectomy	1/174 (0.6)
Neoadjuvant chemotherapy regimens (n = 14)	14/216 (6.5)
Cisplatin Vinorelbine	1/14 (7.1)
Carboplatin Etoposide	1/14 (7.1)
Carboplatin Paclitaxel	12/14 (85.8)
Adjuvant chemotherapy regimens (n = 68)	68/216 (31.5)
Cisplatin based chemotherapy	37/68 (54.4)
Carboplatin based chemotherapy	31/68 (45.6)
Adjuvant radiotherapy (n = 70)	70/216 (32.5)

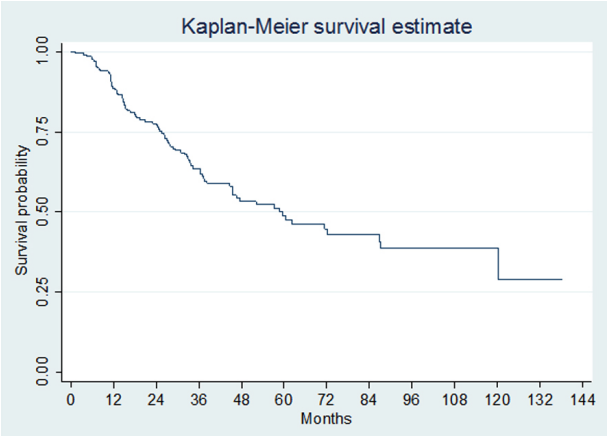

Figure 1 Showed the Kaplan-Meier survival analysis for OS of early stage NSCLC

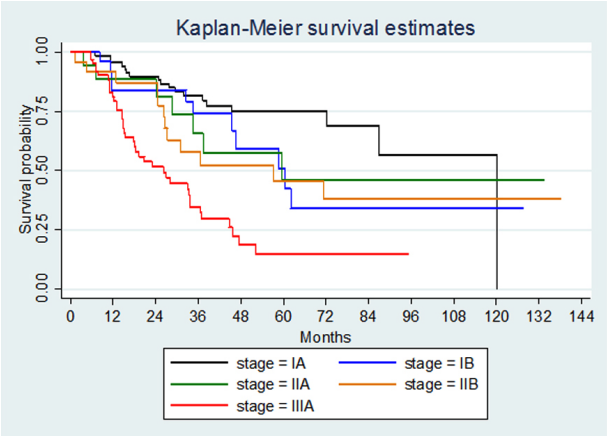

Figure 2 Showed the Kaplan-Meier survival analysis for OS of early stage NSCLC stratified by stages

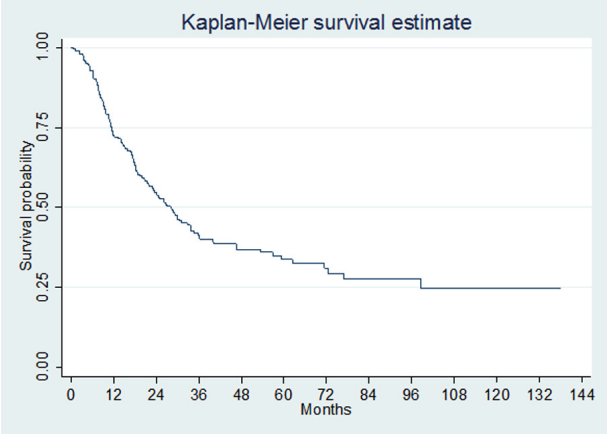

Figure 3 Showed the Kaplan-Meier analysis for DFS of early stage NSCLC.

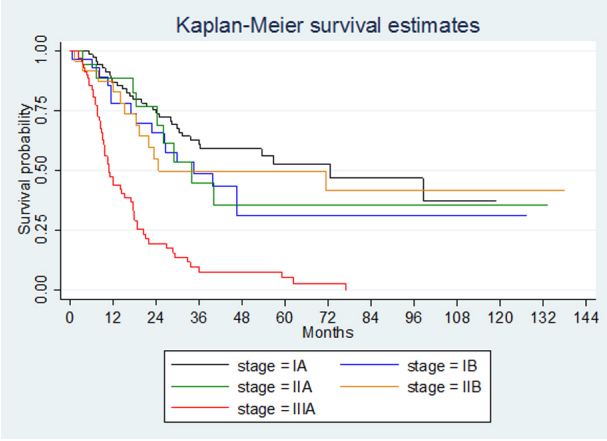

Figure 4 Showed the Kaplan-Meier survival analysis for DFS of early stage NSCLC stratified by stages

Table 3 Showed the pattern of disease recurrence of early stage NSCLC, stratified by stage

Pattern of recurrence	Stage I (n = 103) No. (%)	Stage II (n = 43) No. (%)	Stage IIIa (n = 70) No. (%)
Locoregional	12/103(11.6%)	3/43 (7.0%)	10/70 (14.3%)
Distant	31/103 (31.1%)	15/43 (34.9%)	40/70 (57.1%)

tively (Figure 2). The median DFS was 28.0 months (95%CI: 21.8 to 33.8). The 5-years DFS rate was 33.9% (Figure 3), stratified by stages Ia, Ib, IIa, IIb and IIIa as 52.8%, 31.1%, 35.8%, 49.9%, and 5.2%, respectively (Figure 4). Of 216 patients, 111 patients (51.4%) had recurrent disease. The common pattern of recurrence was distant metastases (8677.5% ,111/) (Table 3). The patients with stage IIIa was clearly found to recur more than stage I and II (40/70 (57.1%) vs 31/103 (3.1%) and 15/43 (34.9%), respectively).

When we comparedthe efficacy on treatment between the cisplatin and carboplatin-based regimens, there were no statistical difference. The 5-year OS of cisplatin basedand carboplatin based were 43% and 36.6%, respectively (95%CI: 24.6 to 60.2 vs 95%CI: 17.78 to 55.78, p = 0.88) (Figure 5).

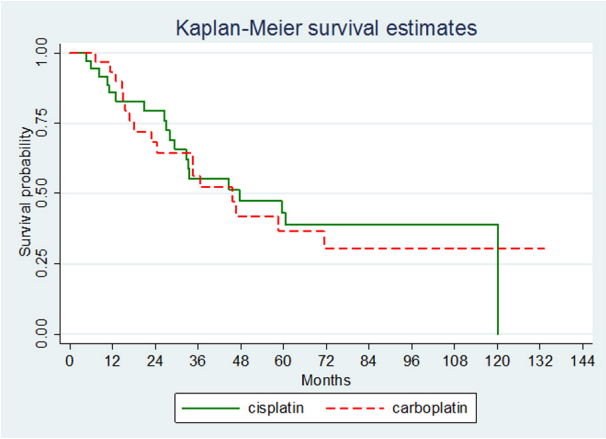

Figure 5 Showed the Kaplan-Meier survival analysis for OS of early stage NSCLC when compare between cisplatin and carboplatin-based adjuvant chemotherapy

The prognostic factors effect on survival

Early stage NSCLC patients, who had a history of heavy smoking, ECOG ≥ 2, stage IIIa, poorly differentiated histology grading and lymphatic-vascular & perineural, seemed to have a shorter survival rate (OS and DFS) than the others by univariate analysis, however, in the multivariate analysis only stage IIIa and poorly differentiated grading were associated with short survival rates (Table 4 and Table 5).

Discussion

The prevalence of early stage NSCLC at Phramongkutklao Hospital between 2003 and 2013 was 14%. It was

Table 4 Showed the univariate analysis and multivariate analysis of prognostic factors that effect on OS by Cox regression model

Variable	OS			
	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Total of cigarettes smoking				
Never	1.00		1.00	
< 20 pack-year	1.55 (0.84 - 2.86)	0.158	1.76 (0.87-3.60)	0.118
≥ 20 pack-year	1.60 (1.00 - 2.55)	0.048	1.56 (0.87-2.82)	0.137
ECOGperformance status				
ECOG 0-1	1.00		1.00	
ECOG ≥ 2	1.82 (1.11 - 2.99)	0.018	1.68 (0.88-3.26)	0.118
TNM staging				
Stage I	1.00		1.00	
Stage II	1.60 (0.90 - 2.85)	0.109	1.37 (0.75 - 2.53)	0.307
Stage IIIa	3.99 (2.45 - 6.49)	< 0.001	3.36 (1.97-5.74)	< 0.001
Histology grading				
Well-moderately differentiated	1.00		1.00	
Poorly differentiated	2.23 (1.35 - 3.67)	0.002	1.95 (1.18-3.24)	0.010
Lymphatic-vascular & Perineural Invasion				
Absent	1.00		1.00	
Present	1.95 (1.12 - 3.38)	0.018	1.69 (0.93-3.08)	0.086

Table 5 Showed the univariate analysis and multivariate analysis of prognostic factors that effect on DFS by Cox regression model

Variable	OS			
	Univariate		Multivariate	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Total of cigarettes smoking				
Never	1.00		1.00	
< 20 pack-year	1.21 (0.72 - 2.04)	0.474	0.93 (0.5 - 1.73)	0.827
≥ 20 pack-year	1.26 (0.86 - 1.86)	0.232	1.09 (0.68 - 1.73)	0.725
ECOGperformance status				
ECOG 0-1	1.00		1.00	
ECOG ≥ 2	1.70 (1.12 - 2.58)	0.013	1.41 (0.80-2.49)	0.231
TNM staging				
Stage I	1.00		1.00	
Stage II	1.21 (0.72 - 2.03)	0.464	0.88 (0.49 - 1.56)	0.657
Stage IIIa	4.73 (3.15 - 7.09)	<0.001	2.79 (1.34 - 5.79)	0.006
Histology grading				
Well-moderately differentiated	1.00		1.00	
Poorly differentiated	2.22 (1.44 - 3.43)	<0.001	2.70 (1.55 - 4.71)	<0.001
Lymphatic-vascular &Perineural Invasion				
Absent	1.00		1.00	
Present	2.03 (1.28 - 3.20)	0.002	1.56 (0.95 - 2.56)	0.077

similar to that of NCI of Thailand in 2015 (about 20.8%)[9] and Shanghai in 2011 (13%)[22], but different from that of American Lung Association Epidemiology and Statistics Unit in 2014 and Europe National Lung Cancer Audit annual report in 2016 of 37% and 38%, respectively[23,24]. The reason that the prevalence of early stage NSCLC in Asia was lower than that of the Unites States of America (U.S.A.) and Europe may be because the patients are not concerned with alarming symptoms such as chronic cough and weight loss, leading to advance stage cancer[25], and may be due to low screening rates in Asia.

From our data of clinical characteristics, females were slightly predominant than males, while males were predominant in other studies such as Shanghai[22], U.S.A.[23], Europe[24], Korea[26] and Taiwan[27]. The mean age of patients was 63.31 years, consistent with that in Shanghai (62 years), but the mean age of the study from Europe was higher[24]. The history of smoking was also interesting. The patients who had smoked more than 20 pack per year were found equally between Asia and U.S.A., accounted for 32-38%[28,29]. The behavior of smoking does not correlate with racial. Stratified by stages, half of our patients were in stage I (48%), similar to the study in Shanghai and Europe (47%)[22,24]. The most common histologic grading was well and moderately differentiated NSCLC which was found equally with the study

in U.S.A. and Japan (about 70%)[30,31]. Adenocarcinoma was the major subtype histology (~85%), which was similar to other studies[22,26,27], and lymphovascular invaw sion (LVI) & perineural invasion (PNI) was found at 14.4%, which was equal to the study in Korea (15.8%)[26] and U.S.A. (12%)[31].

Most curative surgery technique in our study was lobectomy (94.8%), which was slightly higher than the studies in U.S.A. (80%)[31] and in Taiwan (87%)[27]. Adjuvant chemotherapy was reported around 31.5%, which was slightly lower than that in Shanghai (43%)[22]. One half of chemotherapy regimens were cisplatin-based, which was similar to another study[32]. However, we administered carboplatin instead of cisplatin in the patients who had impaired kidney function (GFR ≤ 60)[33].

More than half of the patients with stage IIIa (71.4%) experienced recurrence during the period, and 80% had distant metastases, which were similar to the studies in U.S.A. and China (about 80%)[34,35].

According to our study, the 5-year OS rates stratified by stages (Ia, Ib, IIa, IIb and IIIa) were 74.8%, 50.8%, 46.0%, 45.7%, and 14.8%, respectively, which were similar to studies in Asian countries such as shanghai[22], Korea[26], and Taiwan[27], and in U.S.A.[36], except stage IIIa that showed higher 5-year OS rates about 36%[36]. The lower survival rate of stage IIIa (only 14%) in our study may be from the small number of patients (n = 70) and only one-third of patients received adjuvant chemotherapy.

We analyzed the factors affecting survival rates by univariate analysis and found that the patients who smoked ≥ 20 pack-years, ECOG ≥ 2, stage IIIa, poorly differentiated histology grading and lymphatic-vascular & perineural invasion seemed to have a shorter survival rate. The patients who smoked ≥ 20 pack-years were associated with worse OS (HR 1.60; 95%CI: 1.00-2.55), which was consistent witha retrospective cohort study by Bryant A. et al. who demonstrated a shorter 5-year OS rate of patients who smoked ≥ 20 pack-years (35%) when compared with others (63%)[37]. Indeed, cigarettes contain mutagenic and carcinogenetic chemicals that cause mutations in tumor suppressor genes such as *p53* and *KRAS* mutations, and then cause poor survival outcome[38]. Interestingly, LVI/PNI was the factor that had an impact on survival rates which was consistent with other studies[26,39,40]. It has already been demonstrated to be a prognostic pathological marker for survival in many cancers such as breast, colorectal, and head and neck cancers[26], and adverse prognostic factor for NSCLC recurrence[39,40]. Park et al. reported LVI as an adverse prognostic factor for NSCLC recurrence[39,40]. Park et al. reported LVI as an adverse prognostic factor for the development of distant recurrence in their study of patients with NSCLC in stage Ia to IIIa with HR 4.76 (95%CI: 2.08-10.90)[26], and Yoshihisa Shimada et al. reported that LVI had an association with disease recurrent in stage Ia with HR 1.58 (95%CI: 1.02-2.45)[39]. In our study, the results showed that LVI/PNI was a strong prognostic factor for tumor recurrence (HR 1.95; 95%CI: 1.18-3.24) in any stage of completely resected NSCLC.

Tumor staging and poorly differentiated histologic gradingwereindependent significant prognosis factors forsurvival in multivariate analysis, which was consistent with previous studies[41-43]. We found that patients withstage IIIa had a higher risk of recurrence and death as reported in studiesby Dziedzic et al. and Cruz et al.[41,42]. In addition, a study bySun Z. et al. demonstrated that patients with poorly differentiated or undifferentiated carcinoma had a HR 1.71 (95%CI: 1.49-1.95) of death, compared with well-differentiated patients[43], and a study by Kobayashi et al. about risk factors for recurrence and unfavorable prognosis in patients with stage I NSCLC reported that poorly differentiated carcinoma was the only independent factor associated with an unfavorable OS (HR 3.61; 95%CI:

1.24-10.51) and DFS (HR 4.94; 95%CI: 1.01-24.21)[44]. In our study, poorly differentiated NSCLC was the prognostic factor for OS and DFS with HR 1.95 (95%CI: 1.18-3.24) and 2.70 (95%CI: 1.55-4.71), respectively.

We focused on the chemotherapy treatment regimens which may have an impact on survival rates by cisplatin-based and carboplatin-based adjuvant chemoe therapy. Reports from studies of IALT[14], ANITA[16], JBR.10[17], and LACE meta-analysis[18] showed the absolute clinical benefit of 5% of adjuvant chemotherapy predominantly cisplatin-based regimens such as cisplatin/vinorelbine and cisplatin/etoposide. For our patients with impaired kidney function, we administered carboplatin instead of cisplatin and it showed no statistical difference on survival rates between both regimens. However, this cannot be concluded because it is a retrospective study with a small number of patients, however, prospective studies may confirm this result. In addition, a previous study by Valerie Couillard-Montminy et al. on the efficacy of carboplatin instead of cisplatin in NSCLC patients with stage Ib-IIIb conducted in three groups including the cisplatin-vinorelbine group (CISV), the carboplatin-vinorelbine group (CBV), and the combination group which included patients who started their chemotherapy with cisplatin-vinorelbine but were switched to carboplatin-vinorelbine (CISV/CBV), and showed no difference in DFS and OS between these groups[32].

From univariate and multivariate analyses, we found that patients who smoked ≥ 20 pack-years, ECOG ≥ 2, stage IIIa, poorly differentiated histology and lymphatic-vascular & perineural invasion had poor prognosis, especially those in stage III NSCLC had a higher risk to recurrence and shorter survival rates, independent to chemotherapy regimen treatment. In addition, we may develop a method to detect early-stage NSCLC including low dose CT scan for high risk populations[45], a campaign of smoking cessation, and educate people about early signs and symptoms of NSCLC.

Our study had several limitations. The first limitav tion is the retrospective nature of the analysis, which means we cannot make an evidence-based conclusion that several risk factors were poor prognostic factors of overall survival. The second limitation is the small number of patients who received adjuvant chemotherapy, so this explains why this study found no statistically significant difference between cisplatin and carboplatin-based adjuvant chemotherapy. The third limitation is previous data for a complete follow up in some patients. Lastly, the duration of follow-up time is short, thus, a long-term follow-up is required to determine the survival rates of patients with early stage NSCLC.

Conclusions

Only one-seventh of NSCLC patients were found in early stage, however the 5-year OS rate remained poor. The patients who underwent a complete resection often experienced recurrences, especially distant metastases resulting from unfavorable prognosis factors such as history of heavy smoking, poor ECOG performance status, poorly differentiated histology grading, lympho-vascular& perineural invasion and stage IIIa disease at diagnosis. Adjuvant chemotherapy regimens with platinum-based could increase OS and DFS. However, cisplatin and carboplatin-based adjuvant chemotherapy showed no difference in DFS and OS. We may use carboplatin instead of cisplatin in patients with impair kidney function, but we may need more prospective studies to confirm this result.

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