Original Article

Advanced Non-Small-Cell Lung Cancer (NSCLC) Patients Treated at Phramongkutklao Hospital between 2011 and 2018: Comparison between Those With and Without Brain Metastases

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Background: Brain metastases (BM) remain a significant problem in NSCLC patients. The reports of factors associated with BM are varied in previous studies including age, histology subtypes, and oncogenic driver alterations.

Objective: To determine the prevalence and factors associated with BM in advanced NSCLC patients and to analyze the median overall survival (OS) of the patients that had BM at the time of diagnosis of NSCLC and during the course of the disease.

Materials and Methods: The medical records of 552 advanced NSCLC patients between 2011 and 2018 were reviewed. The prevalence of BM was calculated by descriptive statistics. Factors associated with BM were analyzed by using univariate and multivariate analyses. Kaplan-Meier methods were used to analyze the median OS of NSCLC patients with BM.

Results: Between January 2011 and December 2018, of the 552 patients newly diagnosed with advanced NSCLC, there were 164 patients who had BM. The prevalence of BM was 29.7%. In multivariate analysis, younger age (adjusted odd ratio [OR] 1.547, 95% confidence interval [CI] 1.049 to 2.280), and adenocarcinoma subtype (adjusted OR 2.529, 95% CI 1.262 to 5.067) were significantly associated with BM. The median OS of patients who had BM at time of advanced NSCLC diagnosis was 7.5 months (95% CI 6.4 to 8.5) and the median OS of patients who had BM during the course of disease was 14.4 months (95% CI 12.2 to 16.5).

Conclusion: One-third of the advanced NSCLC patients developed BM. Younger age and adenocarcinoma subtype were associated with BM. Patients who had BM during the course of diseases had better survival outcomes compared to those who had BM at the time of advanced NSCLC diagnosis.

Keywords: Advanced NSCLC; Brain metastases

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Lung cancer is the most common cancer-related death worldwide. In 2018, the International Agency for Research on Cancer reported 2.1 million new lung cancer cases and 1.8 million mortalities[1]. In 2016, Thailand's National Cancer Institute (NCI) reported 351 new lung cancer cases, with 67.5% of those identified as stage IV disease and 7.9% having brain metastases (BM)[2].

Non-small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer cases[3]. BM remains significant problems in patients with NSCLC for several reasons. First, they are frequently seen. About 30% to 50% of NSCLC patients will develop BM after treatment[4], which is a greater rate than the other malignancies. The incidence proportion of BM was high among patients with lung cancer (20%), melanoma (7%), renal cancer (7%), and breast cancer (5%)[5]. Second, the extensive use of imaging modalities such as magnetic resonance imaging (MRI), which has enhanced the identification of subclinical BM, has raised the incidence of BM[5]. Finally, when systemic therapies emerge, patients tend to survive longer, increasing their chances of developing BM[5]. However, the penetration of systemic therapies through blood-brain barrier (BBB) is restricted, resulting in poorer survival time as compared to the patients who do not have a BM[5]. NSCLC patients with BM typically have a dismal prognosis, with median survival times ranging from four to six months[6]. Brain MRI is now recommended

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by the National Comprehensive Cancer Network (NCCN) Guidelines Version 1.2020 for NSCLC patients with clinical stage II and higher to identify BM[7]. If an MRI is not accessible, a computed tomography (CT) scan might be used instead. At Phramongkutklao Hospital, the brain MRI or CT scan are not regularly performed in advanced NSCLC patients. Brain imaging was done in patients with neurological symptoms and suspected BM. The initial imaging option is a CT scan. The impact on survival outcomes is unknown.

The purpose of the present study was to determine the prevalence of BM in patients with newly diagnosed advanced NSCLC (AJCC 8th edition Stage IV)[7] and to explore clinical characteristics associated with BM. The authors also analyzed the median OS of the NSCLC patients with BM at Phramongkutklao Hospital.

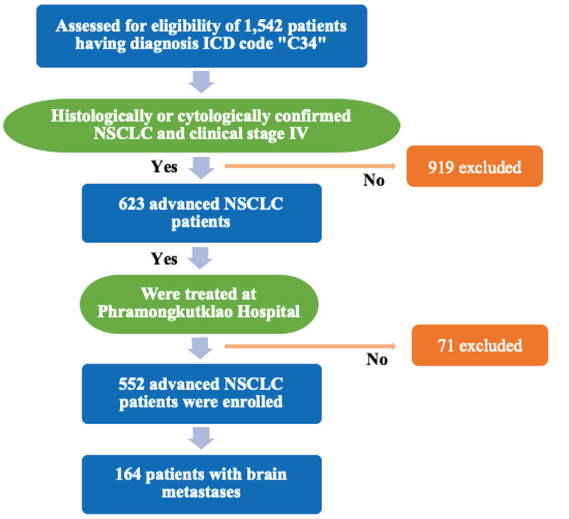

Figure 1. Flow diagram showing patients included in the study.

Materials and Methods

The present study was a single institution retrospective study that enrolled patient who were newly diagnosed with advanced NSCLC at Phramongkutklao Hospital between 2011 and 2018. The study protocol was approved by The Institutional Review Board of Royal Thai Army Medical Department (IRBRTA 267/2562). Eligible patients were age 18 or older with histologically or cytologically confirmed advanced NSCLC. The authors searched the hospital database and selected patients with C34 ICD-10 code. Of the 1,542 patients with C34 ICD-10 code, 623 patients were newly diagnosed with advanced NSCLC. Exclusion criteria were incomplete chart information.

The authors reviewed the data of 552 patients who were diagnosed with advanced NSCLC. One hundred sixty-four patients had BM. BM was diagnosed by MRI or CT scan. The BM were categorized into two groups between BM presented at the time of NSCLC presentation and BM developed during the course of disease. BM at the time of NSCLC presentation defined as the patients who had neurological symptoms and had imaging confirmed BM at the time of diagnosed NSCLC, and BM during the course of disease defined as the patients who had developed BM during the course of treatments. A flow diagram of the patients included in the present study is shown in Figure 1.

The authors examined baseline demographic information and clinical variables, including age, gender, the Eastern Cooperative Oncology Group (ECOG) performance status, tumor size, mediastinal node involvement, histology subtypes, treatment modalities, and metastatic sites at diagnosis. The number of brain lesions and BM treatment methods were also documented in patients with BM. The last follow-up time was December 2019.

The primary objective was the prevalence of BM in advanced NSCLC patients at Phramongkutklao Hospital. The secondary objective were factors that associated with BM, and the overall survival (OS) of NSCLC patients who had BM.

Descriptive statistics were used to identify baseline clinical characteristics of advanced NSCLC patients. Univariate and multivariate logistic regression analyses were used to explore the association of age at diagnosis, gender, histology subtypes, tumor size, metastatic sites, oncogenic driver alterations (EGFR and ALK), mediastinal node involvement, treatment modalities, and BM. Odds ratios (OR) were calculated with 95% confidence interval (CI), p-value of less than 0.05 was considered significant. The median OS was analyzed by Kaplan-Meier methods. OS was defined as the date at the time of diagnosis, to death from any causes or the last follow-up date. OS of BM at the time of NSCLC presentation was defined as the date at the time of diagnosed NSCLC with BM, to death from any cause or the last follow-up date. Finally, OS of BM during the course of disease was defined as the date at the time of diagnosed BM during the course of treatments, to death from any cause or the last follow-up date. All statistical data was performed by IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Between January 2011 and December 2018, the authors collected 552 patients diagnosed with advanced NSCLC. From the 552 patients, 164 patients were diagnosed of BM. The prevalence of BM in advanced NSCLC patients was 29.7%. Eleven-point-one percent of the patients had BM at the time of NSCLC presentation and 18.6% had BM during the course of disease. At the time of analysis, 97.1% of patients had died. The median follow-up time was 17.8 months. The baseline characteristics of advanced NSCLC patients are presented in Table 1. The mean age was 63.68 years (SD ±11.33). Most patients were men (68.5%), good ECOG PS (0-1) (86.2%), and most histologic subtypes were adenocarcinoma (83.2%). Thirty-six-point-six percent of patients with BM had a single brain lesion, 35.4% had two to three brain lesions, and 28% had more than three brain lesions. Treatment methods of BM were surgery, whole brain radiotherapy (WBRT), and surgery plus WBRT. Seventy-three-point-two percent of patients were treated by WBRT, 18.9% were treated by surgery plus WBRT, and 0.6% were treated by surgery alone. Twelve patients had no specific treatment for BM.

Factors associated BM

Based on univariate analysis, factors associated with BM were female, age less than 65 years, adenocarcinoma subtype, tumor size less than 3 cm, and treatment with targeted therapy (Table 2). In addition, a multivariate analysis was performed to identify factors associated with BM. The results showed that age less than 65 years and adenocarcinoma subtype were significantly associated with BM, adjusted OR 1.547, 95% CI 1.049 to 2.280, p=0.028 for age younger than 65 years and adjusted OR 2.529, 95% CI 1.262 to 5.067, p=0.009 for adenocarcinoma subtype (Table 3).

Survival analysis for patients with brain metastases

The median OS of advanced NSCLC patients was 13.5 months (95% CI 12.8 to 14.3), with 1-, and 5-year survival of 59.4% and 3.8% respectively. The median OS of NSCLC patients who had BM was 12.3 months (95% CI 10.4 to 14.3) and the median OS of patients without BM was 14.0 months (95% CI 13.1 to 15.0) (p<0.001).

Survival analysis for patients who had brain metastases stratified by time of brain metastases presentation

The median OS of patients who had BM at the time of advanced NSCLC presentation was 7.5

Table 1. Clinical characteristics of advanced NSCLC patients

Characteristics	Total (n=552); n (%)	Brain metastases (n=164); n (%)	No brain metastases (n=388); n (%)
Sex			
Male	378 (68.5)	99 (60.4)	279 (71.9)
Female	174 (31.5)	65 (39.6)	109 (28.1)
Age (year)			
<65	285 (51.6)	100 (61.0)	185 (47.7)
≥65	267 (48.4)	64 (39.0)	203 (52.3)
ECOG PS			
0 to 1	316 (57.2)	101 (61.6)	215 (55.4)
2	160 (29.0)	46 (28.0)	114 (29.4)
3 to 4	76 (13.8)	17 (10.4)	59 (15.2)
Histology subtypes			
Adenocarcinoma	459 (83.2)	152 (92.7)	307 (79.1)
Squamous cell carcinoma	90 (16.3)	11 (6.7)	79 (20.4)
Other	3 (0.5)	1 (0.6)	2 (0.5)
EGFR mutation			
Yes	75 (13.6)	24 (14.6)	51 (13.1)
No	104 (18.8)	23 (14.0)	81 (20.9)
Unknown	373 (67.6)	117 (71.4)	256 (66.0)
ALK rearrangement			
Yes	1 (0.2)	1 (0.6)	0 (0.0)
No	68 (12.3)	14 (8.5)	54 (13.9)
Unknown	483 (87.5)	149 (90.9)	334 (86.1)
Tumor size (cm)			
≤3	125 (22.6)	53 (32.3)	72 (18.6)
3.1 to 5.0	193 (35.0)	53 (32.3)	140 (36.1)
5.1 to 7.0	129 (23.4)	32 (19.5)	97 (25.0)
>7.0	105 (19.0)	26 (15.9)	79 (20.4)
Mediastinal node involvement			
Yes	462 (83.7)	139 (84.8)	323 (83.2)
No	90 (16.3)	25 (15.2)	65 (16.8)
Extracranial metastases			
Liver	69 (12.5)	23 (14.0)	46 (11.9)
Adrenal gland	43 (7.8)	12 (7.3)	31 (8.0)
Bone	181 (32.8)	53 (32.3)	128 (33.0)
Intrathoracic	378 (68.5)	106 (64.6)	272 (70.1)
Other	1 (0.2)	0 (0.0)	1 (0.3)
Systemic Treatment			
Chemotherapy	353 (63.9)	114 (69.5)	239 (61.6)
Targeted therapy	117 (21.2)	44 (26.8)	73 (18.8)
Immunotherapy	6 (1.1)	0 (0.0)	6 (1.5)
No treatment	128 (23.2)	37 (22.6)	91 (23.5)

ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor

Table 2. Univariate analysis of factors associated with brain metastases

Clinical factors	n	Brain metastases; n (%)	Odds ratio	95% CI	p-value
Sex					
Female	174	65 (37.3)	1.681	1.145 to 2.466	0.008*
Male	378	99 (26.2)	1	-	
Age (year)					
<65	285	100 (35.1)	1.715	1.182 to 2.360	0.004*
≥65	267	64 (24.0)	1	-	
ECOG PS					
0 to 1	316	101 (32.0)	1.63	0.905 to 2.938	0.104
2	160	46 (28.8)	1.4	0.739 to 2.653	0.302
3 to 4	76	17 (22.3)	1	-	
Histology					
Adenocarcinoma	459	152 (33.1)	2.020	1.663 to 2.453	<0.001
Squamous cell carcinoma	90	11 (12.2)	1	-	
EGFR mutation					
Yes	75	24 (32.0)	1.657	0.847 to 3.241	0.14
No	104	23 (22.1)	1	-	
ALK rearrangement					
Yes	1	1 (100)	-	-	0.217
No	68	14 (20.5)	-	-	
Tumor size (cm)					
≤3	125	53 (42.4)	2.237	1.268 to 3.946	0.005
3.1 to 5.0	193	53 (27.5)	1.15	0.667 to 1.982	0.614
5.1 to 7.0	129	32 (24.8)	1.002	0.552 to 1.82	0.994
>7.0	105	26 (24.7)	1	-	
Mediastinal node involvement					
Yes	462	139 (30.0)	2.324	1.905 to 2.835	0.661
No	90	25 (27.7)	1	-	
Systemic Treatment					
Chemotherapy	353	114 (32.2)	2.096	1.677 to 2.620	0.077
Targeted therapy	117	44 (37.6)	1.659	1.141 to 2.412	0.035
Immunotherapy	6	0	-	-	0.109
No treatment	128	37 (28.9)	2.459	1.678 to 3.604	0.82
Extracranial metastases					
Liver	69	23 (33.3)	2.000	1.212 to 3.299	0.481
Adrenal gland	43	12 (27.9)	2.583	1.327 to 5.030	0.788
Bone	181	53 (29.3)	1.614	1.452 to 1.795	0.878
Intrathoracic	378	106 (28.0)	2.566	2.050 to 3.212	0.206
Other	1	0 (0.0)	-	-	1.000

ECOG PS=Eastern Cooperative Oncology Group performance status; EGFR=epidermal growth factor receptor; CI=confidence interval

months (95% CI 6.4 to 8.5), and during the course of disease was 14.4 months (95% CI 12.2 to 16.5), when compared with advanced NSCLC patients without brain metastasis was 14 months (95% CI 13.1 to 15.0) (p<0.001) (Figure 2).

Discussion

The present study is the first retrospective study that provided the data of prevalence and factors associated BM in advanced NSCLC at Phramongkutklao hospital. The prevalence of BM

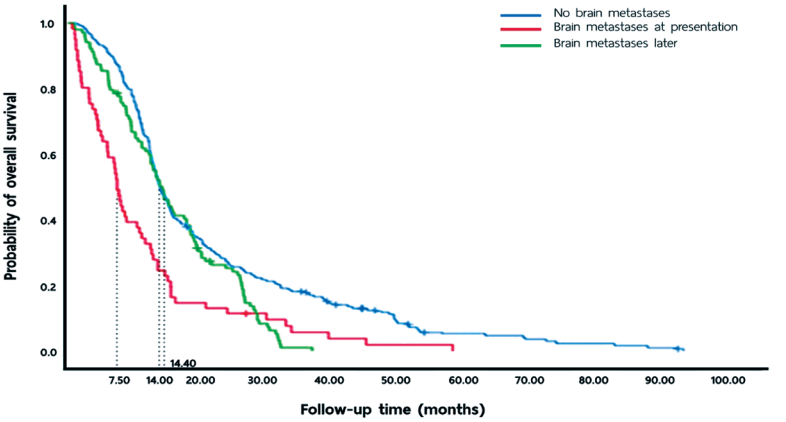

Figure 2. Kaplan-Meier curve analysis for median OS in advanced NSCLC patients stratified by time of brain metastases presentation.

Table 3. Multivariate analysis by adjusted odds ratio of factors associated with brain metastases

Clinical factors	Adjusted odds ratio	95% CI	p-value
Sex			
Female	1.463	0.981 to 2.182	0.062
Male	1	-	
Age (year)			
<65	1.547	1.049 to 2.280	0.028
≥65	1	-	
Histology			
Adenocarcinoma	2.529	1.262 to 5.067	0.009
Squamous cell carcinoma	1	-	
Tumor size (cm)			
≤3	1.889	0.987 to 3.339	0.064
3.1 to 5.0	1.053	0.597 to 1.858	0.859
5.1 to 7.0	0.961	0.516 to 1.787	0.899
>7.0	1	-	
Systemic treatment			
Targeted therapy	1.289	0.818 to 2.031	0.274

CI=confidence interval

in advanced NSCLC patients at Phramongkutklao Hospital between 2011 and 2018 was 29.7%. This was similar to previous reports such as the study by Waqar et al, which showed that the prevalence of BM was 26% in patients with advanced NSCLC[8]. In our study, the prevalence of BM at the time of NSCLC presentation was 11.1% and during the course of the disease was 18%. These results were similar to the previous reports by Schuette et al and by Ali et al, which showed BM at the time of NSCLC presentation was 7% to 10% and during the course of disease was 20%[9,10].

In the present study, the authors aim to identify clinical characteristics that associated with BM in advanced NSCLC patients, including age, gender, ECOG performance status, tumor size, mediastinal node involvement, histology subtypes, treatment modalities, and metastatic sites at diagnoses. Based on multivariate analysis, age less than 65 years and adenocarcinoma histology were associated with BM. The present study results were consistent with the previous study by Waqar et al, which using the SEER database on clinical risk factors to predict the development of brain metastasis, they revealed that younger age or less than 70 years, adenocarcinoma, or large cell histology, tumor size larger than 3 cm, tumor grade at or above II, and node-positive disease were associated with BM[8]. Ceresoli et al studied about factors associated with the incidence of BM in 112 locally advanced NSCLC patients and showed that age less than 60 years was associated with increased risk of BM[11]. Mujoomdar et al published a retrospective study about clinical predictors of BM in 264 NSCLC patients (stage I to IV), and found that BM positively correlated with larger size of the primary tumor, adenocarcinoma and undifferentiated cell type, and the increased of lymph node stage[12]. In addition, Hubbs et al published a study that defined the risk of developing BM after definitive treatment of locally advanced NSCLC. They found that younger age, larger tumor size, lymphovascular space invasion, and hilar lymph node involvement were associated with an increased risk of developing BM[3]. Bajard et al also studied about factors associated BM in a group of stages I-III NSCLC patients and demonstrated that factors predictive of brain progression were age less than 62 years, T4 tumor status, N2-3 status, and

adenocarcinoma[13].

Furthermore, the authors also examine the molecular biomarkers including ALK and EGFR alterations. In the present study, EGFR mutation and ALK rearrangement were not associated with BM in NSCLC patients. These findings contradicted the recent research, which found that patients with EGFR mutations or ALK rearrangements have a greater prevalence of BM. Up to 50% to 60% of patients with these oncogenic driver alterations will develop BM during the course of diseases[14,15]. The inconsistency could be due to the present study's modest number of EGFR and ALK tests. Only 32% and 12.5% of patients, had their EGFR and ALK tested respectively. In the last ten years, new treatments have been developed, including targeted therapy and immunotherapy. Patients with BM had a much better survival rate after receiving targeted therapy[16,17]. Most patients in the present study had no known EGFR mutation or ALK rearrangement status and were not treated with targeted therapy.

As a result, the overall survival outcome in the present study appeared to be lower than that of Okamoto et al who presented real-world data on survival outcomes in advanced NSCLC and found that the median OS was 25.2 months[18]. The authors focused on the survival of patients with BM. The median OS of patients who had BM at the time of advanced NSCLC presentation was 7.5 months and during the course of disease was 14.4 months. The median OS of patients who had BM at the time of NSCLC presentation seem to be shorter. These results in the present study were comparable to the previous study by Ali et al, which reported the survival of NSCLC patients with brain at presentation and late BM at 6.2 months and 14.3 months, respectively[10]. However, the treatments of BM between the two groups were not different, including surgery, WBRT, and surgery plus WBRT.

Based on the present study, brain imaging including CT scan or MRI may be considered more actively at the time of advanced NSCLC diagnosis, especially in patients with clinical factors that increase risk of BM including age less than 65 years and adenocarcinoma cell type. Early diagnosis of BM and early treatment lead to prolong progression free survived (PFS) and OS in advanced NSCLC patients.

The present study has limitations. First, the study is a retrospective study. To identify factors associated with BM in NSCLC, the prospective study still needed to make a conclusion. Second, brain imaging was only performed in NSCLC patients who had neurological symptoms, so, the present study could miss asymptomatic patients who had BM at presentation. Third, the present study has a small number of the advanced NSCLC patients who had BM at the time of diagnosis, thus it is difficult to summarize the impact on survival. Finally, not all patients had a EGFR and ALK test leading to low prevalence of EGFR and ALK positive patients. It might cause a low possibility to detect any association between these mutation and BM.

Conclusion

The prevalence of BM was about one-third of advanced NSCLC patients at Phramongkutklao Hospital, which 11% had BM at the time of diagnosis and 18% had BM during the course of disease. The factors associated with BM were age less than 65 years and adenocarcinoma subtype. However, the EGFR mutation and ALK rearrangement were not associated with BM due to the small number of tests. The local treatment of the patients who had BM included surgery, WBRT, and surgery plus WBRT. The median OS of patients who had BM at time of diagnosis of advanced NSCLC was shorter than patients who had BM during the course of disease.

What is already known on this topic?

NSCLC with brain metastasis is the most common central nervous system malignancy. Studies have shown that clinical factors such as age, stage, and histology are associated with brain metastasis in NSCLC patients.

What this study adds?

In this study, younger than 65 years and adenocarcinoma subtype are associated with BM in advanced NSCLC. The finding correlated to the previous studies. Brain imaging should be considered in these high-risk patients at the time of NSCLC diagnosis to detect BM. Early detection of BM could prevent patients from deterioration by early appropriate treatment. Further prospective studies are required.

Conflicts of interest

There are no conflicts of interest.

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