



# Clinical Characteristics and Pathologic Profiles Correlation of Primary Lung Cancer: A 6-Year Retrospective Study in Thailand's Metropolitan Medical Center

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Vajira Med J. 2022; 66(1) : 1-10

<http://dx.doi.org/10.14456/vmj.2022.xx>

## Abstract

**Background:** Since 2018, the global incidence of lung cancer had increased to 2.1 million causing lung cancer to be a major leading cause of cancer-related mortality in worldwide, with 29 percent mortality rate. This is causing by an increasing tobacco consumption rate, especially in developing countries. For other risk factors that associate with lung cancer were sex, age and metropolitan people.

**Aim:** To study clinical characteristics and pathologic profiles correlation of primary lung cancer in Thailand's metropolitan medical center

**Method:** A retrospective study in Vajira hospital. The study population with diagnosed with primary lung cancer between January 2016, and May 2021. The information was collected: sex, age, pathologic profile, and stage.

**Results:** A total of 110 primary lung cancer patients were found at Vajira Hospital from January 2013 to June 2021, consisting of 52 males (47.3%) and 58 females (52.7%). The mean age for patients at the time of diagnosis was 62.93 years. Most common histologic type of lung cancer in both metropolitan and non-metropolitan residents were invasive adenocarcinoma (81.8% in total) with 41.8% and 40%, respectively. Most presentation of lung cancer staging were diagnosed at early stage.

**Conclusions:** This study revealed a growing incidence of adenocarcinoma, an increasing rate of female cases in both metropolitan and non-metropolitan nonsmoker female patients. However, further studies on risk factors of primary lung cancers emphasis on nonsmoker women are recommended.

**Keywords:** lung cancer, adenocarcinoma, metropolitan



# ความสัมพันธ์ทางคลินิกกับลักษณะทางพยาธิวิทยาของมะเร็งปอด: 6 ปีย้อนหลังในโรงพยาบาลโรงเรียนแพทย์ของกรุงเทพมหานคร ประเทศไทย

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Vajira Med J. 2022; 66(1) : 1-10

<http://dx.doi.org/10.14456/vmj.2022.xx>

## บทคัดย่อ

**บทนำ:** ตั้งแต่ปี พ.ศ. 2561 อุบัติการณ์ของโรคมะเร็งปอดทั่วโลกเพิ่มขึ้นเป็น 2.1 ล้านคน ทำให้มะเร็งปอดเป็นสาเหตุสำคัญของการเสียชีวิตที่เกี่ยวข้องกับมะเร็งทั่วโลก โดยมีอัตราการเสียชีวิตถึงร้อยละ 29 ซึ่งเป็นสาเหตุจากการสูบบุหรี่โดยเฉพาะในประเทศกำลังพัฒนา สำหรับปัจจัยเสี่ยงอื่นๆ ที่เกี่ยวข้องกับมะเร็งปอด ได้แก่ เพศ อายุ และการอาศัยอยู่ในเมืองใหญ่

**วัตถุประสงค์:** เพื่อศึกษาความสัมพันธ์ทางคลินิกกับลักษณะทางพยาธิวิทยาของมะเร็งปอดช่วง 6 ปีย้อนหลังในโรงพยาบาลโรงเรียนแพทย์ของกรุงเทพมหานคร ประเทศไทย

**วิธีดำเนินการวิจัย:** งานวิจัยนี้เป็นการศึกษาวิจัยแบบย้อนหลัง โดยศึกษาความสัมพันธ์ทางคลินิกกับลักษณะทางพยาธิวิทยาของมะเร็งปอดที่รับการผ่าตัดรักษา ในคณะแพทยศาสตร์วชิรพยาบาล ระหว่างเดือนมกราคม 2559 ถึง พฤษภาคม 2564

**ผลการวิจัย:** มีผู้ป่วยที่ได้รับการวินิจฉัยว่าเป็นมะเร็งปอดผู้ป่วยทั้งหมด 110 รายในช่วงเวลาที่ศึกษา คิดเป็น เพศหญิง 58 คน (ร้อยละ 52.7) และ ชาย 52 คน (ร้อยละ 47.3) ผู้ป่วยมีอายุเฉลี่ย 62.93 ปี ผลการตรวจทางจุลพยาธิวิทยาพบว่าส่วนใหญ่เป็นมะเร็งปอดชนิดต่อม (81.8%) ทั้งในเขตเมืองหลวง และเขตไม่ใช่เมืองหลวง คิดเป็น 41.8% และ 40% ตามลำดับ อีกทั้งระยะของมะเร็งที่พบในงานวิจัยนี้มักเป็นระยะเริ่มต้น

**สรุป:** การศึกษาชี้ให้เห็นอุบัติการณ์ของมะเร็งชนิดต่อมที่เพิ่มขึ้น ซึ่งมีอัตราที่เพิ่มขึ้นในผู้ป่วยสตรีที่ไม่สูบบุหรี่ทั้งในเขตเมืองหลวงและเขตไม่ใช่เมืองหลวง อย่างไรก็ตาม ในอนาคตควรมีการศึกษาเพิ่มเติมเกี่ยวกับปัจจัยเสี่ยงของมะเร็งปอดระยะแรกในกลุ่มสตรีที่ไม่สูบบุหรี่มากขึ้น

**คำสำคัญ:** มะเร็งปอด, มะเร็งชนิดต่อม, คนเมือง

## Introduction

Lung cancer is a major leading cause of cancer-related mortality worldwide in both males and females, including in Thailand<sup>1</sup>. The global incidence of lung cancer had increased from 1.95 million in 2014 to 2.1 million in 2018, with 29% mortality rate<sup>1</sup>.

Many epidemiological and clinical studies have proven several etiologies of lung cancer: tobacco smoking, air pollution, environmental pollutants such as asbestos, arsenic, and radiation<sup>2-4</sup>. These risk factors were associated with an individuals' geographic (non-metropolitan vs metropolitan), environmental, economic, and social characteristics such as sex, age<sup>5-7</sup>. For examples, increased lung cancer incidence and mortality rates were found associated with tobacco consumption especially in developing countries or in metropolitan areas especially non-small cell lung cancer (adenocarcinoma, squamous cell carcinoma, etc.) which had 1.2-2.3 times more likely to have lung cancer than non-metropolitan residents<sup>8-10</sup>.

Clinically, primary lung cancer is more common as age increased, generally after 40 years old<sup>5,8</sup> because there were more potential exposures and more unhealthy habits. Some of those things are out of our control. There was exposure to toxins, risk factor of cancer's exposure over time. These exposures might lead to mutations in cells that may evaded the immune system and develop into cancer. Most patients are asymptomatic in the early stages. The patients often have symptoms when the disease is in the advanced stage such as coughing or dyspnea caused by pleural effusion, large lung mass with or without metastasis to other sites<sup>11</sup>. Another problem is being a common metastatic site of other cancers which, several times, clinically presented first as lung lesions prior to the primary tumor manifestation. Hence, a correct pathological diagnosis is crucial for a proper management<sup>12</sup>. This requires all clinical information as well as a meticulous gross and microscopic pathologic examination to make a correct diagnosis.

Pathologically, lung cancer is characterized by abnormal cellular proliferation with high nucleus-to-cytoplasmic (N:C) ratio, hyperchromatic nucleus, high mitotic figure, and some cellular necrosis. A malignant lung tumor can also invade surrounding normal tissue and/or spread throughout the body (metastasis) via the circulatory or lymphatic systems. Sometimes, additional tests might be required to distinguish metastatic cancers and/or to confirm the diagnosis as well as type of cancer. According to Thoracic tumors WHO classification of Tumor, 5<sup>th</sup> edition 2021, pathologic diagnoses were categorized into 2 general groups of small cell lung cancers (SCLCs) and non-small cell lung cancers (NSCLCs)<sup>1,13-14</sup>. Non-small cell lung cancer is more common, accounting for 85% of all lung cancer. Each type has distinct clinical presentations, morphologic features, and treatment options. The management is based on the stage and possibility of surgical resectability (preferably complete resection). Chemotherapy, targeted therapy, immunotherapy and/or radiation would instead play major roles in more advanced or unresectable diseases<sup>14</sup>.

The increasing incidence of lung cancer has a major impact on resources consumption which would, in turn, affects the national health budget allocation. A higher requirement is in areas where tobacco use, environmental hazards, or lung cancer incidence are higher. However, clinical characteristics and pathologic profiles of primary lung cancer in urban or metropolitan residents had not been adequately reported. Therefore, we collected clinical information and pathological data of patients with lung cancer who have received treatment in our hospital which is a tertiary center for cancer care in Bangkok Metropolitan.

## Methods

### Study settings

This study was conducted after obtaining approval from the institutional review board of the Faculty of Medicine Vajira Hospital (COA011/2564). Inclusion criteria were patients diagnosed with

primary lung cancer in our hospital between January 1, 2016, and May 31, 2021. Data retrieved from the medical records included age, gender, smoking status, underlying disease if available (such as hypertension, diabetes, pulmonary tuberculosis, COPD), history of other preceding cancers, histopathology, stage of cancer and current residence (urban vs non-urban). A stay in Bangkok or other urban areas for more than 3 years was regarded as urban or metropolitan citizen. A diagnosis of primary lung cancer was based on only surgical histopathological results of lung lesions. Information for tumor staging included histopathological and/or cytopathological results of other lung tissue distant from mainly lesion, lymph nodes, pleural tissue/effusion, pericardial tissue/effusion, etc.

Exclusion criteria included non-pathologically proven lung cancer, incomplete data, or no pathologic slides available for review.

### Statistical analysis

All statistical analysis was carried out using SPSS for Windows Evaluation Version 26.0 (IBM Corp. 2019, Armonk, NY). Continuous data were presented as mean and standard deviation for variables with normal distributions and median (IQR) for variables with non-normal distributions. Categorical data are expressed as absolute numbers and percentages. Correlations between the clinical characteristics and pathologic profile of each case were assessed. Clinical features of age, gender, and histological subtypes of cancer were studied according to the residence of patients (metropolitan vs non-metropolitan). Data were compared by Fisher's exact test or chi-square test as appropriate. P-value < 0.05 was considered statistically significant.

## Results

### General description

A total of 110 patients who had primary lung cancer were identified during the study period. The mean age of all patients at diagnosis was 62.9 years. Slightly more than half were females (n=58 patients, 52.7%). Having residence in metropolitan areas was

more common (n=59 patients, 53.6%) than the non-metropolitan, with a ratio of 1.16/1.

Female patients had significantly older age than male: mean age  $60.8 \pm 12.68$  years vs  $65.3 \pm 9.13$  years ( $p < 0.039$ ). At the time of diagnosis, a total of 27 (24.5%) patients were current or ex-smokers. Most primary lung cancer patients had no underlying disease nor history of previous cancers, 85 (77.3%) and 98 (89.1%) respectively. All demographic data of lung cancer patient were shown in Table 1

### Pathologic profile

The definitive pathologic diagnosis of malignancy was made according to the WHO classification of Tumor, 5th edition 2021<sup>1</sup>. Lung cancer was common at right side with 65.5% and predominately at lower lobe with 58.1%. The most histopathological subtype was invasive adenocarcinoma 81.8% (90 patients). Squamous cell carcinoma and other non-small cell lung cancer were found in equal numbers (n=6, 5.4% each). Majority had high grade tumors (n=81 patients having grade 2 and grade 3 tumors, 73.6%). The pathologic features of lung cancer in this study are summarized in Table 2.

History of smoking and histopathology were studied according to the residence (metropolitan vs non-metropolitan) (Table 3), it was determined that the incidence rates of primary lung cancer among male and female patients were different as shown in smoker and nonsmoker subgroups. Invasive adenocarcinoma was the most frequent tumor type among both male and female patients; in addition, adenocarcinoma was significantly higher among metropolitan female patients in our study. At the time of diagnosis, 83 (75%) were nonsmokers and only 17 (24.6%) were smokers in patients with invasive adenocarcinoma. The relationship between smoking status and tumor histologic type was evaluated as shown in table 3, among patients with invasive adenocarcinoma, the ratio of non-smokers male and current/ex-smoker male was 0.88/1 and was 11.5/1 in female.

**Table 1:**

Clinical characteristics of patients with lung cancer (n=110)

Variable	Number, % (n=110)
Age (Mean $\pm$ SD)	62.93 $\pm$ 11.32
<b>Gender</b>	
male	52 (47.3)
female	58 (52.7)
<b>Smoking status</b>	
non-smoker	83 (75.5)
current/ex-smoker	27 (24.5)
<b>Underlying disease</b>	
absent	85 (77.3)
present	25 (22.7)
<b>History of previous malignancy</b>	
absent	98 (89.1)
present	12 (10.9)
<b>Residence</b>	
metropolitan	59 (53.6)
non-metropolitan	51 (46.4)

**Table 2:**

Pathologic profile of patients with lung cancer (n=110)

Variable	n, % (n=110)
<b>Tumor size (median), cm (IQR)</b>	2.5 (1.95, 3.85)
<b>Tumor laterality</b>	
right side	72 (65.5)
left side	38 (34.5)
<b>Main location</b>	
<i>upper lobe</i>	
right	15 (13.6)
left	23 (20.9)
<i>middle lobe (right)</i>	8 (7.3)
<i>lower lobe</i>	
right	49 (44.5)
left	15 (13.6)
<b>Histologic type</b>	
<i>non-small cell carcinoma</i>	
adenocarcinoma in situ	3 (2.7)
invasive adenocarcinoma	90 (81.8)
squamous cell carcinoma	6 (5.4)
other non-small cell lung carcinoma*	6 (5.4)
<i>small cell lung carcinoma</i>	5 (4.5)
<b>Histologic grade</b>	
1 (well differentiated)	29 (26.4)
2 (moderately differentiated)	67 (60.9)
3 (poorly differentiated)	14 (12.7)
<b>Lymphovascular invasion</b>	
not identified	72 (65.5)
present	38 (34.5)
<b>Visceral pleura invasion</b>	
not identified	70 (63.6)
present	40 (36.4)
<b>Spread through air spaces (n=105)</b>	
not identified	65 (61.9)
present	40 (38.1)

\*Other: non-small cell lung cancer included adenosquamous carcinoma (4 cases, 3.6%) and pleomorphic carcinoma (2 cases, 1.8%)

**Table 3:**

Comparison of histologic type between gender, status smoking in each address group (n=110)

Variable	Address		p-value				
	metropolitan n, % (59, 53.6%)	non-metropolitan n, % (51, 46.4%)					
<b>Male (52, 47.3%)</b>							
nonsmoker	19 (17.2)	10 (9.1)	0.007				
current/ex-smoker	8 (7.3)	15 (13.7)					
<b>Female (58, 52.7%)</b>							
nonsmoker	29 (26.4)	25 (22.7)	0.043				
current/ex-smoker	3 (2.7)	1 (0.9)					
<b>Male (52, 47.3%)</b>							
Histologic type	nonsmoker	smoker	nonsmoker	smoker	0.043		
	adenocarcinoma in situ	-	-	-		1 (0.9)	
	invasive adenocarcinoma	15 (13.7)	4 (3.6)	9 (8.2)		12 (10.9)	
	squamous cell carcinoma	1 (0.9)	1 (0.9)	0		1 (0.9)	
	non-small cell lung carcinoma, other*	2 (1.8)	2 (1.8)	1 (0.9)		-	
small cell lung carcinoma	1 (0.9)	1 (0.9)	-	1 (0.9)			
<b>Female (58, 52.7%)</b>							
Histologic type	nonsmoker	smoker	nonsmoker	smoker		0.043	
	adenocarcinoma in situ	1 (0.9)	-	1 (0.9)			-
	invasive adenocarcinoma	24 (21.8)	3 (2.7)	22 (20)			1 (0.9)
	squamous cell carcinoma	2 (1.8)	-	1 (0.9)	0		
	non-small cell lung carcinoma, other*	1 (0.9)	-	-	-		
small cell lung carcinoma	1 (0.9)	-	1 (0.9)	-			

\*Other: non-small cell lung cancer included adenosquamous carcinoma (4 cases, 3.6%) and pleomorphic carcinoma (2 cases, 1.8%)

The majority of our patients were diagnosed with early-stage diseases. More than half of lung cancer patients were present stage I lung cancer with 51.8%. For incidence of other stage were shown in table 4.

**Discussion**

In our study, the age range of the patients included in our study (62.93 ± 11.32) was similar with previous study which reported 60.57±12.31 years<sup>15</sup>.

There was a female predominance; increase was observed in the rate of female metropolitan patients. These findings were consistent with global changes in the gender distribution of lung cancer. The global male predominance in lung cancer was mainly attributed to greater prevalence of smoking

**Table 4:**

Stage classification of patients with lung cancer (n=110)

Stage classification	Number, % (total n=110)
I	57 (51.8)
II	18 (16.4)
III	15 (13.6)
IV	20 (18.2)

in men. Lung adenocarcinoma, unlike other types of lung cancer, is also associated with non-smokers – especially female non-smokers<sup>12</sup>. However, the rate

of lung cancer in women is gradually rising especially in Asia people<sup>8,15,17-21</sup>. In the United States, approximately 10% of patients with lung cancer was never-smokers<sup>22</sup>, while in Asia, >30% of patients with lung cancer were never-smokers and more than 50 percent of lung cancers occur in never-smoker women. The reason is a nonsmoker in Asia females tend to have a gene mutation especially EGFR mutation<sup>23-24</sup>.

Majority of the patients in this study population are from metropolitan area (53.6%). The ratio of primary lung cancer in the male and female among metropolitan versus non-metropolitan area was 1.16: 1. The finding is similar to the international epidemiology evidence in many previous studies<sup>5,8,15-20</sup>.

All of the various histological type, the most common type of histology was adenocarcinoma in both metro and non-metropolitan whereas the least common type was small cell carcinoma. However, in the literature was reported the most common type was squamous cell carcinoma which associated with smoking behaviors. We believe that the reason was because the health promotion of smoking cessation in Thailand for the past recent years<sup>8, 15-16, 25-26</sup>. Therefore, the rate of squamous cell carcinoma should be reduced accordingly. Tumor size was correlated with early stage. Most common histologic grade was moderately differentiated that was similar with previous studies<sup>27-30</sup>.

Visceral pleural invasion was diagnosed as positive in 40 cases (36.4%). Visceral pleural invasion was also significantly associated with a higher frequency of LVI as shown in previous studies<sup>29-30</sup>, but not shown in our study.

Spread through air spaces (STAS) was a phenomenon of lung cancer spread, was first named by Kadota and colleagues<sup>31</sup> in 2015. STAS was defined as tumor cells within air spaces in the lung parenchyma beyond the edge of the main tumor. STAS was initially observed in adenocarcinomas. However, with recent in-depth studies, STAS was identified in other types of lung cancer including squamous cell carcinoma<sup>31-33</sup>. In our study, STAS (was analyzed only in non-small cell lung carcinoma, totally 105 cases) was observed in 40 cases (38.1%). Our result is correlated with previous studies<sup>31-33</sup>.

Our study had some limitations, the sample size involved in the present study was small, especially for squamous cell carcinoma, and the patients were from only our institution and had an information loss in some cases. In the future, genetic testing, which screens actionable genetic alterations including *ALK* and *EGFR* mutations for targeted therapy<sup>34-35</sup>, will likely provide important information about the treatment and prognosis of lung cancer although the immunotherapy appears set to offer new modes of treatment for non-small cell lung cancer, even for patients with advanced disease.

## Conclusions

A study of primary lung cancers in Vajira Hospital last 6 years revealed the growing incidence of adenocarcinoma, an increasing rate of female cases, Adenocarcinoma, in comparison with squamous cell carcinoma, other NSCLCs and SCLC, was more prevalent among all metropolitan and non-metropolitan nonsmoker women patients, Also, further studies on risk factors of primary lung cancers emphasis on nonsmoker women are recommended.

## Ethics approval

This study was conducted with the approval of the Institutional Review Board of Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA 011/2564). No informed consent to participants was required as a retrospective study.

## Disclosure

The authors declare that they have no competing interests.

## Acknowledgments

The authors wish to thank Miss. Kannika Yodaun for data and glass slide collected management and the staff of the Department of Anatomical Pathology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University for all their support and help.

## Funding

This study was supported by Navamindradhiraj University Research Fund.

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