

**Malignant neoplasm of the lower respiratory tract  
at King Chulalongkorn Memorial Hospital:  
A retrospective study on histological  
diagnoses of 1,464 cases  
from 2000 to 2006**

Apisara Kulwongthanaroj\*

Chavit Chantranuwat\*

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- Introduction** : *With the advance in molecular targeted therapy on lung cancer, definite distinction of histological subtype becomes more important, which is not always possible in small biopsy. However, there is no well-documented study that describes the whole spectrum of diagnoses among all lung malignancies in Thailand.*
- Objectives** : *To describe the incidence of all pathological diagnoses given to lower respiratory tract malignancies at King Chulalongkorn Memorial Hospital from 2000 to 2006.*
- Materials and Methods** : *Histological diagnoses of 1,464 lower respiratory tract malignancies from King Chulalongkorn Memorial Hospital and affiliated laboratories from 2000 - 2006 were evaluated using the current classification scheme for lung cancer correlating with age, sex and types of specimen.*

**Results** : Of 1,464 cancers, there are 942 (64.3%) males (3-90 year) and 522 (35.7%) females (12 - 94 years old). There are 338 (23.1%) resections and 1,126 (76.9%) biopsies. Most patients (1,392 cases; 95.1%) were 40 years or older.

For patients who were 40 years or older, 92 cancers are of uncertain primary (0.9% from resection, 8.3% from biopsy). Unidentified non-small cell carcinoma is found only in biopsy group (10.7%). Discarding these two diagnoses, the five most common cancers in male were adenocarcinoma (43.9%), squamous cell carcinoma (29.9%), small cell carcinoma (9.5%), metastasis (6.0%), and large cell carcinoma (3.4%). The five most common cancers in female were adenocarcinoma (60.1%), squamous cell carcinoma (13.5%), metastasis (11.2%), small cell carcinoma (4.0%) and hematologic malignancy (3.3%). Slightly increasing trend of adenocarcinoma was noted in both genders.

In patients who were below 40 years old, the five most common cancers were adenocarcinoma (41.4%), metastasis (24.3%), carcinoma of the salivary gland type (7.1%), mesenchymal tumor (5.7%); and, two of the five most common malignant tumors were squamous cell carcinoma and hematologic malignancy (4.3% for each type).

**Conclusion** : Specimen type greatly affects the incidence of histological diagnosis. Diagnosis of unidentified non-small cell carcinoma is found in one-tenth of biopsy. Adenocarcinoma was the most common cancer in both age groups and relatively frequent in female with slightly increasing trend in both genders. Among those who were below 25 years old, mesenchymal tumor was the most common. Large cell neuroendocrine carcinoma was under-diagnosed. Relatively low incidences of small cell carcinoma and large cell carcinoma were noted. The study provided overall insight of lower respiratory tract malignancy in our institute and provides useful information for improving histological diagnosis in the future.

**Keywords** : Lower respiratory tract, Lung, Cancer, Malignancy, Histological diagnosis, Incidence.

อภิสรรา กุลวงศ์ธนโรจน์, ชวิษฐ์ จันทรานุกวัฒน์. การวินิจฉัยมะเร็งระบบทางเดินหายใจส่วนล่างชนิดต่าง ๆ ในโรงพยาบาลจุฬาลงกรณ์: การศึกษาย้อนหลังในผู้ป่วย 1,464 ราย ระหว่างปี พ.ศ. 2543 ถึง 2549. *จุฬาลงกรณ์เวชสาร* 2551 ก.ค. - ส.ค.; 52(4): 275 - 89

- บทนำ** : จากวิวัฒนาการในการรักษามะเร็งที่จำเพาะเจาะจงกับชนิดของมะเร็งปอดมากขึ้น ส่งผลให้มีความสำคัญเพิ่มมากขึ้นในการวินิจฉัยแยกชนิดอย่างแม่นยำจากชิ้นเนื้อตัวอย่าง บางครั้งพยาธิแพทย์ไม่สามารถให้คำวินิจฉัยได้จากตัวอย่างชิ้นเนื้อ biopsy ที่ส่วนใหญ่มักมีขนาดเล็ก ปัจจุบันในประเทศไทยยังไม่มีการศึกษารวบรวมอุบัติการณ์ของการวินิจฉัยโดยรวมทั้งหมดของรอยโรคมะเร็งปอด
- วัตถุประสงค์** : เพื่อศึกษารวมอุบัติการณ์ของการวินิจฉัยมะเร็งของระบบทางเดินหายใจส่วนล่างชนิดต่างๆ ที่เกิดขึ้นในโรงพยาบาลจุฬาลงกรณ์ ระหว่างปี พ.ศ. 2543 ถึง 2549
- วิธีการทำวิจัย** : ผู้ป่วยมะเร็งระบบทางเดินหายใจส่วนล่างจากในโรงพยาบาลจุฬาลงกรณ์ และจากห้องปฏิบัติการที่เชื่อมโยงกับโรงพยาบาลตั้งแต่ปี พ.ศ. 2543 ถึง 2549 จำนวนทั้งหมด 1,464 ราย นำมาประมวลการวินิจฉัยแยกชนิดตาม *World Health Organization Histological Classification of Tumor of the Lung* ปีค.ศ. 2002
- ผลการวิจัย** : จากผู้ป่วยทั้งหมด 1,464 ราย ประกอบด้วยผู้ป่วยเพศชาย 942 ราย (อายุ 3 - 90 ปี) และผู้ป่วยเพศหญิง 522 ราย (อายุ 12 - 94 ปี) แบ่งผู้ป่วยออกเป็น 2 กลุ่มอายุ ผู้ป่วยส่วนใหญ่ (1,392 ราย) อยู่ในกลุ่มที่มีอายุตั้งแต่ 40 ปีขึ้นไป ในกลุ่มผู้ป่วยที่มีอายุตั้งแต่ 40 ปีขึ้นไปพบว่า มีเพียง 92 รายที่ไม่สามารถวินิจฉัยได้ว่าเป็นมะเร็งปฐมภูมิหรือทุติยภูมิ (0.9% ของตัวอย่างชิ้นเนื้อ resection และ 8.3% ของตัวอย่างชิ้นเนื้อ biopsy) ส่วนการวินิจฉัย unidentified non-small cell carcinoma พบในตัวอย่างชิ้นเนื้อ biopsy เท่านั้น (10.7% ของตัวอย่างชิ้นเนื้อ biopsy) นอกเหนือจากการวินิจฉัยสองกลุ่มดังกล่าวแล้วพบว่า มะเร็งที่พบบ่อยในผู้ชายห้าอันดับแรก ได้แก่ adenocarcinoma (43.9%), squamous cell carcinoma (29.9%), small cell carcinoma (9.5%), metastasis (6.0%), และ large cell carcinoma (3.4%) ในขณะที่ชนิดของมะเร็งที่พบบ่อยห้าอันดับแรกในผู้หญิง ได้แก่ adenocarcinoma (60.1%), squamous cell carcinoma (13.5%), metastasis (11.2%), small cell carcinoma (4.0%) และ hematologic malignancy (3.3%) นอกจากนี้ยังพบอีกว่าอุบัติการณ์ในการเกิดมะเร็งชนิด adenocarcinoma มีแนวโน้มเพิ่มขึ้นเล็กน้อย ทั้งในเพศชายและหญิง

- ชนิดของมะเร็งที่พบบ่อยห้าอันดับแรกในผู้ป่วยที่มีอายุต่ำกว่า 40 ปี ได้แก่ adenocarcinoma (41.4%), metastasis (24.3%), carcinoma of salivary gland type (7.1%), mesenchymal tumor (5.7%), squamous cell carcinoma (4.3%) และ hematologic malignancy (4.3%)
- บทสรุป** : ชนิดของตัวอย่างชิ้นเนื้อ resection หรือ biopsy มีผลต่ออุบัติการณ์ของการวินิจฉัยรอยโรคมะเร็งของระบบทางเดินหายใจส่วนล่างเป็นอย่างมาก ทั้งนี้ในการวินิจฉัย unidentified non-small cell carcinoma พบเพียงในตัวอย่างชิ้นเนื้อ biopsy เท่านั้น มะเร็งชนิด adenocarcinoma เป็นมะเร็งชนิดที่พบบ่อยสุดในกลุ่มผู้ป่วยที่มีอายุมากกว่าและน้อยกว่า 40 ปี และยังมีแนวโน้มของอุบัติการณ์ที่เพิ่มขึ้นเล็กน้อยทั้งในเพศชายและหญิง ในการศึกษาครั้งนี้ไม่พบการวินิจฉัยมะเร็งชนิด Large cell neuroendocrine carcinoma เลย ในกลุ่มผู้ป่วยที่มีอายุน้อยกว่า 25 ปี ชนิดของมะเร็งที่พบบ่อยที่สุดเป็นมะเร็งในกลุ่ม mesenchyma tumor พบอุบัติการณ์ของ small cell carcinoma และ large cell carcinoma ค่อนข้างต่ำ การศึกษานี้ช่วยให้เกิดความเข้าใจโดยรวมของการวินิจฉัยรอยโรคมะเร็งของระบบทางเดินหายใจส่วนล่าง และให้ข้อมูลที่เป็นประโยชน์ต่อการพัฒนาของการวินิจฉัยรอยโรคมะเร็งของระบบทางเดินหายใจส่วนล่างต่อไป
- คำสำคัญ** : การวินิจฉัย, มะเร็งทางเดินหายใจส่วนล่าง, มะเร็งปอด, อุบัติการณ์.

Lung malignancy, including primary lung cancer and metastasis, is currently the most frequently diagnosed major cancers in the world and the most common cause of cancer mortality worldwide (12.6% of all new cancers, 17.8% of cancer deaths).<sup>(1)</sup> This is largely due to the carcinogenic effects of cigarette smoking. Over the coming decades, changes in smoking habits greatly influence incidence and mortality of lung cancer as well as the prevalence of various histological subtypes of the lung malignancy.<sup>(2-5, 6)</sup> By a yet unknown etiology, the incidence of lung cancer, especially adenocarcinoma is growing in women. Lung cancer has become the leading cause of cancer-related mortality in both men and women in most countries, with industrialized nations having the highest rates.<sup>(7)</sup>

Cancer of the lung occurs most often between the ages of 40 to 70 years old, with the peak incidence in the fifties or sixties. Only 2% of cases appear before the age of 40. <sup>(8, 9-11)</sup> Almost all lung cancers are carcinoma with other types of cancer comprising well less than 1%. Small cell carcinoma comprises approximately 20% of cases and large cell/undifferentiated carcinomas about 9%. As for carcinomas, the proportions of histological types differ by sex. Squamous cell carcinomas comprise 44% of lung cancers in men, and 25% in women, while adenocarcinomas comprise 28% of lung cancers in men and 42% in women. <sup>(1, 8, 12-14)</sup>

With the advance on molecular-targeted therapy, histological subtype of lung cancer has become more important and definite distinction is usually requested from the clinician. Pathologists could not always offer a definite diagnosis on histological subtype, especially from a small biopsy.

In Thailand, there is still no well-documented data regarding the incidence of histological diagnoses among all lung malignancies.

The aim of this study was to explore the demographic and incidence of all histological diagnoses of the malignant lower respiratory tract lesions in all age groups at King Chulalongkorn Memorial Hospital and affiliated laboratories during a 7-years period from 2000 to 2006 in order to gain an overall insight and potentially to improve the histological diagnosis approach in the future.

## Materials and Methods

A total number of 1,464 distinct cases of malignant lower respiratory tract lesion were recruited from King Chulalongkorn Memorial Hospital and its affiliated laboratories from 2000 to 2006. Information on gender, age, type of specimen, and histological diagnosis were obtained from the pathological reports. The specimens were categorized into resection (pneumonectomy, lobectomy, and wedge resection) and biopsy (transbronchial biopsy, bronchial biopsy, core biopsy, and pleural biopsy). The histological diagnoses were classified based on the 2002 World Health Organization's classification of the lung tumors. A review of pathology was performed in case the diagnosis was in doubt or inconclusive. In case of multiple biopsies were taken, the most specific diagnosis would be collected. If both the biopsy and resection were performed, the resection specimen would be chosen. To prevent confusion, the diagnosis of "unidentified non-small cell carcinoma" will be applied to a case of non-small cell carcinoma that could not be further sub-classified.

This study was approved by the Research Ethics Committee, Faculty of Medicine, Chulalongkorn University, Thailand.

## Results

Of 1,464 lower respiratory tract cancers, 942 (64.3%) cases were males and 522 (35.7%) cases were females (male to female ratio = 1.8:1). Their age ranged from 3 to 90 years old (mean = 57.6, SD = 8.3) in males and 12 to 94 years old (mean = 61.9, SD = 7.4) in females. The peak incidence was in the fifties and sixties. There were 338 (23.1%) resections and 1,126 (76.9%) biopsies. Most patients were in their forties or older ( $n = 1,392$ ; 95.1%), with the remaining 72 (4.9%) aged below 40 years old (Table 1).

## Patients 40 years or older (Table 2)

As for patients who were 40 years or older ( $n = 1,392$ ), there were 323 (23.2%) resections and 1,069 (76.8%) biopsies. The difference in types of specimen has great influence on the statistics of cancer subtypes. The diagnosis of adenocarcinoma was far more common in resection group ( $n = 206$ ; 63.8%) than biopsy ( $n = 383$ ; 35.8%). Large cell carcinoma was diagnosed in 16 (5.0%) resections, while the same diagnosis was made only in 18 (1.7%) biopsies. Adenosquamous carcinoma also offered the similar picture ( $n=7$ , 2.2% in resection group;  $n = 7$ , 0.7% in biopsy group). In addition, sarcomatoid carcinoma was diagnosed more commonly in resection ( $n=6$ , 1.9%), as compared to biopsy specimens ( $n = 4$ , 0.4%). On the other hand, small cell carcinoma

**Table 1.** General features.

	Male (case)	Female (case)
Gender	942 (64.3%)	522 (35.7%)
Age (year)	3-90	12-94
	Mean 61.9, SD=7.4	Mean 57.6, SD=8.3
Number of cases by age		
0-9	1	0
10-19	6	2
20-29	3	6
30-39	26	28
40-49	98	86
50-59	215	137
60-69	295	147
70-79	206	126
80-89	59	19
90-99	3	1
Type of specimen		
- Resection	207 (22.0%)	131 (25.1%)
- Biopsy	735 (78.0%)	391 (74.9%)

**Table 2.** Classification of the lower respiratory tract malignancy, according to sex and type of specimen in patients age 40 years or older.

Classification	Resection		biopsy		Total	
	N (%)		N (%)		N (%)	
	Male	Female	Male	Female	Male	Female
Primary Lung Malignancy						
Small Cell Carcinoma	4 (2.0%)	0 (0.0%)	69 (9.8%)	17 (4.7%)	73 (8.1%)	17 (3.5%)
Unidentified non-small cell carcinoma	0 (0.0%)	0 (0.0%)	77 (10.9%)	37 (10.2%)	77 (8.5%)	37 (7.6%)
Non-small cell carcinoma						
Neuroendocrine Neoplasm						
Large cell neuroendo-crine carcinoma	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Carcinoid Tumor	2 (1.0%)	3 (2.4%)	7 (1.0%)	3 (0.8%)	9 (1.0%)	6 (1.2%)
Non-Neuroendocrine Neoplasm						
Adenocarcinoma	116 (58.6%)	90 (72.0%)	220 (31.1%)	163 (45.2%)	336 (37.0%)	253 (52.1%)
Squamous cell carcinoma	40 (20.2%)	9 (7.2%)	189 (26.7%)	48 (13.3%)	229 (25.2%)	57 (11.7%)
Large cell carcinoma	13 (6.6%)	3 (2.4%)	13 (1.8%)	5 (1.4%)	26 (2.9%)	8 (1.6%)
Adenosquamous carcinoma	4(2.0%)	3 (2.4%)	4(0.6%)	3 (0.8%)	8(0.9%)	6 (1.2%)
Sarcomatoid carcinoma	5(2.5%)	1 (0.8%)	4(0.6%)	0 (0.0%)	9(1.0%)	1 (0.2%)
Salivary gland typed carcinoma	2(1.0%)	0 (0.0%)	8(1.1%)	2 (0.6%)	10 (1.1%)	2 (0.4%)
Hematologic malignancy	1(0.5%)	0 (0.0%)	10 (1.4%)	14 (3.9%)	11 (1.2%)	14 (2.9%)
Mesenchymal tumors	1(0.5%)	3(2.4%)	7(1.0%)	7 (1.9%)	8 (0.9%)	10 (2.0%)
Secondary lung Malignancy (Metastasis)	9(4.6%)	11 (8.8%)	37 (5.2%)	36 (10.0%)	46 (5.1%)	47 (9.7%)
Malignant neoplasm of unknown origin (primary vs. secondary)						
Certain histological subtype	1(0.5%)	2 (1.6%)	3(0.4%)	0 (0.0%)	4(0.4%)	2 (0.4%)
Uncertain histological subtype	0(0.0%)	0(0.0%)	60(8.5%)	26(7.2%)	60(6.6%)	26(5.3%)
<b>TOTAL</b>	<b>198(100%)</b>	<b>125 (100%)</b>	<b>708 (100%)</b>	<b>361 (100%)</b>	<b>906 (100%)</b>	<b>486 (100%)</b>

diagnosis was far less common in resection ( $n = 4$ , 1.2%) than in biopsy specimens ( $n = 86$ , 8.0%). Similarly, the diagnosis of unidentified non-small cell carcinoma was not presented in resection specimens, but not uncommonly present in biopsy specimens ( $n = 114$ , 10.7%). As for squamous cell carcinoma, number of cases diagnosed in resection group ( $n = 49$ , 15.2%) was lower than the biopsy group ( $n=237$ , 22.2%). Other types of malignancy including hematologic malignancy, sarcoma, and metastasis, are also diagnosed more commonly in biopsy specimens. The percentages of carcinoid tumor and carcinoma of salivary gland type were comparable in both groups. Apparently, there was no case diagnosed as large cell neuroendocrine carcinoma (LNEC) in this study.

Of the 12 carcinomas of salivary gland type, 7 (58.3%) were adenoid cystic carcinoma and 5 (41.7%) were mucoepidermoid carcinoma.

Of the 25 patients diagnosed with hematologic malignancy (one resection, 24 biopsies), almost all cases were non-Hodgkin lymphoma ( $n = 24$ , 96.0%). By morphological and immunohistochemical studies, there were five mucosal associated lymphoid tissue (MALT) lymphomas and four diffuse large B-cell lymphomas, with only one case of resection being MALT lymphoma. The remaining non-Hodgkin lymphomas lacked further immunohistochemical study for definite classification. There was only one case of Hodgkin lymphoma, which was a case of extension from the mediastinum.

There were 18 cases diagnosed as sarcoma (4 resections and 14 biopsies). The most common diagnosis was malignant mesenchymal tumor, which required additional investigation ( $n = 6$ , 33.3%). This

was followed by leiomyosarcoma ( $n = 5$ , 27.8%) and malignant fibrous histiocytoma ( $n = 2$ , 11.1%). Other diagnosis, included malignant peripheral nerve sheath tumor, rhabdomyosarcoma, dedifferentiated sarcoma, myxofibrosarcoma, and fibrosarcoma ( $n = 1$ , 5.6%, each).

In metastasis group ( $n=93$ ), the majority of the cases were metastatic adenocarcinoma ( $n = 48$ , 51.6%), of which 43 cases (89.6%) were adenocarcinoma originated from the colon and rectum. The second and third common metastases were ductal carcinoma of the breast ( $n = 13$ , 14.0%), and metastatic squamous cell carcinoma ( $n = 6$ , 6.5%). The remaining metastases were from nasopharyngeal carcinoma ( $n=5$ , 5.4%), hepatocellular carcinoma ( $n = 4$ , 4.3%), papillary thyroid carcinoma ( $n = 4$ , 4.3%), osteosarcoma ( $n = 3$ , 3.2%), and poorly differentiated carcinoma ( $n = 2$ , 2.2%), followed by one case each for renal cell carcinoma, choriocarcinoma, endometrial stromal tumor, chondrosarcoma, rhabdomyosarcoma, malignant nerve sheath tumor, malignant fibrous histiocytoma and metastatic phyllode tumor.

There are 92 cancers of uncertain primary, representing 6.6% of all cases. Only 3 cases were resection (0.9% of 323 resections), while 89 cases were biopsy (8.3% of 1,069 biopsies). All 114 (8.2%) unidentified non-small cell carcinomas were only found in biopsy group, comprising 10.7% of all biopsies. For more accurate incidence of each histological type of tumor and for comparison with other studies, these 206 confounding cases of uncertain diagnoses were disregarded. From the total number of 1,186 cases composed of 765 males and 421 females, the five most common malignant neoplasms of



the lower respiratory tract in the male patients were adenocarcinoma (43.9%), followed by squamous cell carcinoma (29.9%), small cell carcinoma (9.5%), metastasis (6.0%), and large cell carcinoma (3.4%). The five most common malignant neoplasms of the lower respiratory tract in the female patients were adenocarcinoma (60.1%), followed by squamous cell carcinoma (13.5%), metastasis (11.2%), small cell carcinoma (4.0%), and hematologic malignancy (3.3%).

**Patients under 40 years (Diagram 1)**

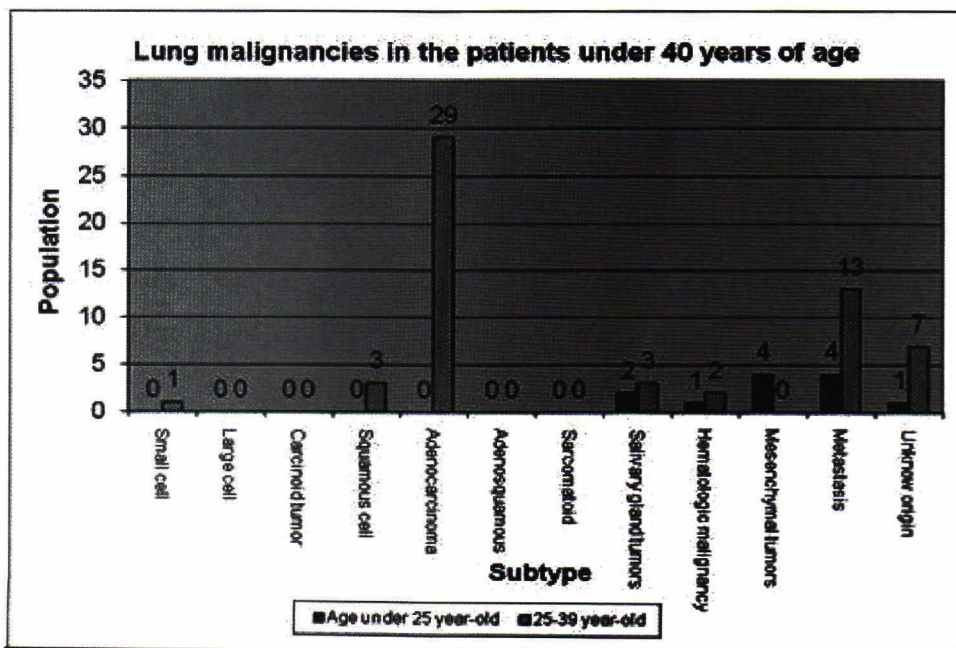
Of 72 cases (4.9% of study population) under the age of 40, there were two cases (2/72; 2.8%) of unidentified non-small cell carcinoma. Excluding these two cases, the five most common malignant neoplasms were adenocarcinoma (n = 29, 41.4%), metastasis (n = 17, 24.3%), carcinoma of salivary gland type (n = 5, 7.1%), sarcoma (n = 4, 5.7%), and

followed by two of the five most common tumors including squamous cell carcinoma and hematologic malignancy (n = 3, 4.3%, each).

As for the 17 metastatic neoplasms found in the young age group, the most common metastasis was adenocarcinoma (n = 4, 23.5%). Three were originated in the colon and rectum and one was metastasis from the ovary. This is followed by two of the second most common metastases including ductal carcinoma of the breast and metastatic osteosarcoma (n = 2, 11.8%, each). The rest were metastases of mucoepidermoid carcinoma, lymphoepithelial carcinoma, papillary thyroid carcinoma, nephroblastoma, choriocarcinoma, seminoma, synovial sarcoma, malignant nerve sheath tumor, and osteosarcoma.

Five salivary gland type carcinomas comprised four cases of adenoid cystic carcinoma and one case of mucoepidermoid carcinoma.

**Diagram 1.** Lower respiratory tract malignancies in the patients under 40 years old.



As for the four cases of primary sarcoma of the lower respiratory tract, all occurred in patients under 25 years of age. The youngest patient was a 3-year-old boy diagnosed as pleuropulmonary blastoma. The rest included malignant solitary fibrous tumor, low-graded myofibroblastic tumor and synovial sarcoma.

Different patterns of malignancy could be appreciated in young-patient age group by dividing the patients into two subgroups, namely; those with less than 25 years of age, and from 25 to 39 years of age. Epithelial carcinomas, such as adenocarcinoma, squamous cell carcinoma, small cell carcinoma, were present only in the group of patients older than 25 years. Salivary gland typed carcinoma was present in both groups, but it was the only carcinoma found among patients below 25 years of age (one adenoid cystic carcinoma and one mucoepidermoid carcinoma). On the contrary, non-epithelial malignancies, for instance, sarcoma and hematologic malignancy, were principal malignancies in the patients who were below 25 years old.

## Discussion

Lung cancer occurs most often between the age of 40 and 70 years, with the peak incidence in the fifties or sixties. Only 2 to 3.1% of all cases appear before the age of 40.<sup>(8, 9-11,15)</sup> There is no difference when comparing the peak incidence to this series, of which peak the incidence is in the 7<sup>th</sup> decade of life (sixties). However, the percentage of the patients under 40 years in this study (4.9%) was slightly greater than the previous studies. This could be because our hospital is a tertiary referral center. The mean ages of the patients in male and female (57.6 and 61.9 years, respectively) are comparable to previous studies in

Thailand and other countries.<sup>(16 - 21)</sup> Of 1,464 lower respiratory tract cancers, 942 cases (64.3%) were males and 522 cases (35.7%) were females. The male to female ratio was 1.8:1, which was comparable to a previous study in Maharaj Nakorn Chiang Mai hospital (1.79:1) and in Lampang Provincial Hospital (1.84:1).<sup>(15)</sup>

Various factors may have influenced the incidence of each histological diagnosis. One of the most obvious factors is the type of specimen that the diagnosis was made from. This is largely due to intrinsic properties of the specimen. Problems such as sampling error, scantiness of tissue, or artifactual alteration on histomorphology are all commonly present in biopsy. In the group of patients aged 40 years or older, the incidence of adenocarcinoma, diagnosed in resection specimens (206/323; 63.8%) is much higher than in the biopsies (383/1,069; 35.8%). This could be explained by the fact that the diagnosis of adenocarcinoma was currently based on morphology, which was the presence of glandular structure or intra-cytoplasmic mucin. These features may not be present in a tissue biopsy from moderate and poorly differentiated adenocarcinomas.

The other important factor is the different treatment for different types of tumor. Our data showed that the diagnosis of small cell carcinoma had a distinct predilection for biopsy (86/1,069; 8.0%), as compared to the resection specimens (4/323; 1.2%). This is because small cell carcinoma is treated with chemotherapy and radiotherapy rather than resection.<sup>(8)</sup> Small cell carcinoma is initially highly responsive to chemotherapy and radiotherapy, therefore systemic chemotherapy and local radiotherapy is the best choice given, and resection is usually not performed.<sup>(22, 23)</sup> In this study, there were

four cases of small cell carcinoma found in resection group. One explanation was an inaccurate diagnosis of the biopsy prior to the resection. For example, a case of combined small cell carcinoma with squamous cell carcinoma was diagnosed initially as unidentified non-small cell carcinoma by biopsy.

As for large cell carcinoma, the diagnosis technically could not be made from biopsy, since it was the diagnosis of exclusion, which required resection specimen. The eighteen large cell carcinomas diagnosed in the biopsy group were likely due to three causes. The first was using the term "large cell carcinoma" in the meaning of tumor with non-small cell histology. This practice should be avoided since it often creates a misunderstanding that the case is specific type of carcinoma. The second was a misdiagnosis which came about from not using the stringent diagnostic criteria, which is the exclusion of other specific types of carcinoma. The third was because no further investigation was taken, such as stain for mucin not performed. Furthermore, the incidence of 5.0% (16 of 323 resections) in this study was relatively lower than the 9 to 15% of large cell carcinoma in other studies.<sup>(1,8)</sup> This is largely because some large cell carcinomas were diagnosed to be other types of tumor by non-definite criteria. For example, some squamous cell carcinomas were diagnosed when tumor cells only show polygonal shape without definite evidence of squamous differentiation (intercellular bridge or true cytoplasmic keratinization). As for adenocarcinoma, degenerative loosening or necrotic drop out of tumor cells in tumor nest could result in gland-like appearance.

The diagnosis of adenosquamous carcinoma that presents more commonly in resections also

reflects sampling problem of biopsy. In small specimen, only one component of tumor might be present. This makes pathologist give diagnosis only on squamous or adenocarcinomatous component, when the tumor is actually carcinoma of mixed histologic type. This is not the case in resection specimen, from which the pathologist can take adequate representative tissue to make the correct diagnosis.

Salivary gland neoplasms comprise less than 1% of all lower respiratory tract malignancies.<sup>(1)</sup> The salivary gland type carcinomas have been reported in the lower respiratory tract include adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma and epithelial-myoepithelial carcinoma. Our incidence of this type of carcinoma is similarly low (0.9%), but we found only adenoid cystic carcinoma (7; 58.3%) and mucoepidermoid carcinoma (5; 41.7%).

Primary pulmonary lymphomas account for less than 0.5% of primary lower respiratory tract malignancy. The two most common of hematologic malignancies were MALT lymphoma, which comprised of 70 - 90% of the cases, followed by diffuse large B-cell lymphoma, which were account for 5 - 20% of the cases.<sup>(1)</sup> According to this study, there were 25 cases (1.8%) of hematologic malignancy. Almost all were non-Hodgkin lymphoma (24 cases), with only one case of Hodgkin lymphoma. Cases with complete immunohistochemical study included four cases of MALT lymphoma and four cases of diffuse large B-cell lymphoma. Since the history of patients' illness was not completely provided in all patients, the larger incidence of lymphoma in the current study was likely resulted from inclusion of both primary pulmonary lymphoma and secondary involvement together.

Also noted is that the incidence of lymphoma was obviously lower in the resection group (0.3% vs. 2.2%), reflecting the principle therapy for lymphoma which is chemotherapy rather than resection. The only one resection case of lymphoma was a pulmonary MALT lymphoma. The low incidence of lymphoma case diagnosed from resection was also noted by a previous study.<sup>(24)</sup>

The terms "non-small cell carcinoma" can be applied in two meanings. The first is a major group of tumor as classified into small cell (neuroendocrine) carcinoma and non-small cell carcinoma. The second is the diagnosis given to a carcinoma showing large neoplastic cells but without morphologic information sufficient to permit further specific diagnosis. In the second sense, we applied the term "unidentified non-small cell carcinoma". In this study it is composed 10.7% of the biopsies (114/1,069). This group reflects problems in tissue sampling and artifact of the biopsy, which limit morphology based evaluation. There is a study that attempted to further classify this group of unidentified non-small cell carcinoma into specific histological diagnosis by using immunostaining for TTF-1, CK-7, 34betaE12, and CD56 and a decent result was obtained.<sup>(25)</sup>

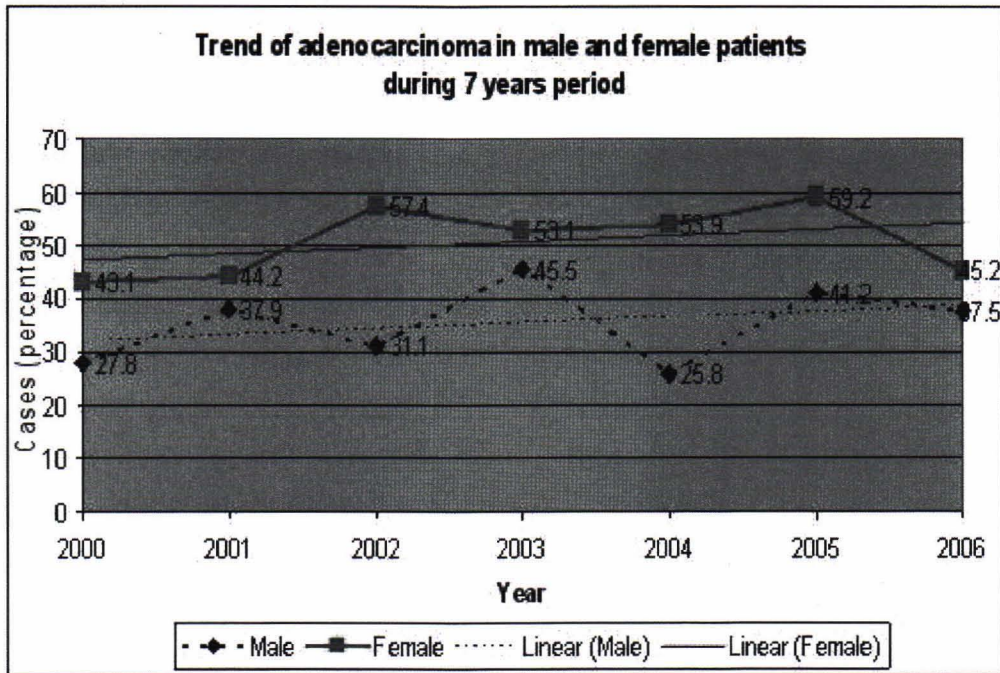
Some discrepancies to previous study are noted. The incidence of adenocarcinoma in our study (43.9% in males and 60.1% in females) is higher than the incidences in several studies (25 to 40%) in both genders.<sup>(1,8,12-14)</sup> This difference among the studies is largely due to difference in the study populations and types of specimen, possible genetic predisposition among different races, and smoking habits in different populations. As for small cell carcinoma and large cell carcinoma categories, our incidences (9.5% and

4.0% for small cell carcinoma in men and women, respectively; 3.4% and 1.9% for large cell carcinoma in men and women, respectively) are lower than other studies in which comprised approximately 20% of small cell carcinoma and 9 to 15% of large cell carcinoma.<sup>(1,8)</sup> As for the lack of LNEC in our series, it was very likely due to under-diagnosis. Since the diagnosis of LNEC is rare and not familiar to general pathologist, it was overlooked and immunohistochemical study for neuroendocrine markers was not in consideration.

We have noticed a subtle trend of increasing incidence of adenocarcinoma during the period of the study in both genders (Diagram 2, linear regression). This could be a result of changing in smoking pattern of our population, urbanization that exposes the patients to pollution with a yet uncertain carcinogen, and the advance in molecular-targeted therapy for a subset of adenocarcinoma making pathologists more aware on making such the diagnosis.

Previous study found that, in patients aged less than 40 years, the four most common lung cancers are adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma, respectively.<sup>(15, 26-29, )</sup> On the contrary, our five most common malignancies were adenocarcinoma, metastasis, carcinoma of salivary gland type, mesenchymal tumor, followed by two of the five common malignant tumors including squamous cell carcinoma and hematologic malignancy. Similarly, the most common cancer in the young is adenocarcinoma. Thus, there might be other factors than smoking that contribute to develop lung cancer in the young such as genetic predisposition<sup>(20, 30)</sup> or exposure to a yet uncertain environmental factors. In addition, our

**Diagram 2.** Trend of adenocarcinoma in male and female patients during 7-year period.



study provides information that the most common malignancy in young patients less than 25 years old is malignant mesenchymal neoplasm.

**Conclusion**

Our study showed that the type of specimen greatly affects the incidence of histological diagnosis. Unidentified non-small cell carcinoma, found in one-tenth of biopsy specimen and cancers of uncertain primary found approximately 8% overall provide opportunity for future improvement by other means of investigation, such as immunohistochemical or molecular study. Difference in the patterns of lower respiratory tract malignancy is noted according to sex and age group, as divided into less than 25, 25-39 and more than 39 years. We noted that adenocarcinoma was the most common cancers in both age groups. It was relatively high in our population, and significantly higher in females with

slightly increasing trend in both sexes. As for patients who were below 25 years old, mesenchymal tumor was the most common malignancy, and salivary gland type carcinoma was the only type of carcinoma presented. The lack of LNEC in our study reflects under-diagnosis; therefore the awareness of this type of malignancy should be exercised. Relatively low incidences of small cell carcinoma and large cell carcinoma are noted with uncertain explanation. The study provides an overall insight of lower respiratory tract malignancy in our institute and gives information useful for improving histological diagnosis in the future.

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