

A RETROSPECTIVE HOSPITAL-BASED STUDY OF HISTOPATHOLOGICAL TYPES OF PRIMARY LUNG CANCER IN BAGHDAD TEACHING HOSPITAL

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ABSTRACT

Background: Lung cancer is considered as the leading cause of cancer death among both men and women. It is also one of the most common cancers in the world. The majority of lung cancers are related to smoking. **Objective:** This study was intended to identify the histopathological types of lung Cancer in relation to gender, age, and smoking habit in a sample of Iraqi patients. **Patients and method:** A total of 170 patients with histopathologically proved primary lung cancer were targeted by this study. All lung cancer cases diagnosed during a period of one year from January 2011 until December 2011 were retrospectively analyzed based on the data of the national center for early detection of cancer, Baghdad teaching hospital, and Ghazi Al-hariry hospital in the medical city complex in Baghdad. **Results:** There were 124 (72.9 %) males and 46 (27.1 %) females. The age of patients varied from 19 to 90 years and the mean age was 62.5 year. From the total number of cases 115 (67.6 %) patients were smokers while 55 (32.4 %) patients were non smokers. It was significant to find mean ages of each type of lung cancer are about the same (around 62 years) except younger (58.8 year) for large cell carcinoma. It was significant to find that most frequent type of primary lung carcinoma (47.1 %), followed by cell cancer is squamous adenocarcinoma (30.0%), then by small cell carcinoma (20%), while large cell contributed to small proportions of the sample (2.9%). Lung cancer among men was more often Squamous cell carcinoma (53.2%). Adenocarcinoma represents the most common type of lung cancer among women (43.4%). Among smokers squamous cell carcinoma was the most common type (51.30%) of primary lung cancer while adenocarcinoma was commonly seen in non smokers (41.8%). **Conclusions:** Males are more liable to have lung cancer than females. Most cases of primary lung cancer may be diagnosed after the age of 45 years. Squamous cell carcinoma represents the most common histological type of lung cancer in this sample of patients with significant predominance in males. Squamous cell carcinoma seems to occur mainly in smokers. These findings suggest that cigarette smoking is the main factor that influences the development and distribution of lung cancer with strong association between squamous cell carcinoma and smoking.

KEYWORDS: SCLC, NSCLC.

INTRODUCTION

Lung cancer has been the most common cancer in the world for several decades, and by 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers. It was also the most common cause of death from cancer, with 1.38 million deaths representing 18.2% of the total. In males, lung cancer is still the most common cancer worldwide with high rates in central-Eastern and Southern Europe, Northern America and Eastern Asia. Very low rates are still estimated in Middle and Western Africa. Incidence rates are generally lower in women, but, worldwide, lung cancer is now the fourth most frequent cancer of women with 516,000 cases and the second most common cause of death from cancer with 427,000 deaths.^[1] Malignant tumours of the lung are classified by the World Health Organization

(WHO)/International Association for the Study of Lung Cancer (IASLC).

There are two main types of lung cancer, including the following:

- ❖ Small cell lung cancer SCLC
- ❖ Non small cell lung cancer NSCLC

NSCLC is further divided into

- Squamous cell carcinoma.
- Adenocarcinoma.
- Large cell carcinoma.

There are numerous additional subtypes of decreasing frequency.^[2]

WHO/IASLC Histopathological Classification of NSCLC

I. Squamous cell carcinoma

- Papillary.
 - Clear cell.
 - Small cell.
 - Basaloid.
2. Adenocarcinoma
- Acinar.
 - Papillary.
 - Bronchioloalveolar carcinoma which includes the following subtypes
 - Nonmucinous.
 - Mucinous.
 - Mixed mucinous and nonmucinous or indeterminate cell type.
 - Solid adenocarcinoma with mucin.
 - Adenocarcinoma with mixed subtypes.
 - Variants which involves
 - Well-differentiated fetal adenocarcinoma.
 - Mucinous (colloid) adenocarcinoma.
 - Mucinous cystadenocarcinoma.
 - Signet ring adenocarcinoma.
 - Clear cell adenocarcinoma.
3. Large cell carcinoma.
- Variants which involves the following subtypes
 - Large cell neuroendocrine carcinoma (LCNEC).
 - Combined LCNEC.
 - Basaloid carcinoma.
 - Lymphoepithelioma-like carcinoma.
 - Clear cell carcinoma.
 - Large cell carcinoma with rhabdoid phenotype.
4. Adenosquamous carcinoma.
5. Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.
- Carcinomas with spindle and/or giant cells.
 - Spindle cell carcinoma.
 - Giant cell carcinoma.
 - Carcinosarcoma.
 - Pulmonary blastoma.
6. Carcinoid tumor.
- Typical carcinoid.
 - Atypical carcinoid.
7. Carcinomas of salivary gland type.
- Mucoepidermoid carcinoma.
 - Adenoid cystic carcinoma.
 - Others.

8. Unclassified carcinoma.

1. Squamous cell carcinoma

Most squamous cell carcinomas of the lung are located centrally, in the larger bronchi of the lung. Squamous cell carcinomas are linked more strongly with smoking than other forms of NSCLC.

2. Adenocarcinoma

Adenocarcinoma is now the most common histologic subtype in many countries, and sub classification of adenocarcinoma is important. One of the biggest problems with lung adenocarcinomas is the frequent histologic heterogeneity. In fact, mixtures of adenocarcinoma histologic subtypes are more common than tumours consisting purely of a single pattern of acinar, papillary, bronchioloalveolar, and solidadenocarcinoma with mucin formation. Criteria for the diagnosis of bronchiolo-alveolar carcinoma have varied widely in the past. The current WHO/IASLC definition is much more restrictive than that previously used by many pathologists because it is limited to only noninvasivetumors. If stromal, vascular, or pleural invasion are identified in an adenocarcinoma that has an extensive bronchioloalveolar carcinoma component, the classification would be an adenocarcinoma of mixed subtype with predominant bronchioloalveolar pattern and a focal acinar, solid, or papillary pattern, depending on which pattern is seen in the invasive component. However, the future of bronchioloalveolar carcinoma as a distinct clinical entity is unclear; a multidisciplinary expert panel representing the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) proposed a major revision of the classification of adenocarcinomas in 2011 that entails a reclassification of what was called bronchiolo-alveolar carcinoma into newly defined histopathological subgroups.

The following variants of adenocarcinoma are recognized in the WHO/IASLC classification:

- Well-differentiated foetal adenocarcinoma.
- Mucinous (colloid) adenocarcinoma.
- Mucinous cystadenocarcinoma.
- Signet ring adenocarcinoma.
- Clear cell adenocarcinoma.

3. Large cell carcinoma

In addition to the general category of large cell carcinoma, several uncommon variants are recognized in the WHO/IASLC classification, including the following:

- LCNEC.
- Basaloid carcinoma.
- Lymphoepithelioma-like carcinoma.
- Clear cell carcinoma.
- Large cell carcinoma with rhabdoid phenotype.

Basaloid carcinoma is also recognized as a variant of squamous cell carcinoma, and rarely, adenocarcinomas may have a basaloid pattern; however, in tumors without

either of these features, they are regarded as a variant of large cell carcinoma.

4. Neuroendocrine tumors

LCNEC is recognized as a histologically high-grade non-small cell carcinoma. It has a very poor prognosis similar to that of small cell lung cancer (SCLC). Atypical carcinoid is recognized as an intermediate-grade neuroendocrine tumor with a prognosis that falls between typical carcinoid and high-grade SCLC and LCNEC. Neuro-endocrine differentiation can be demonstrated by immunohistochemistry or electron microscopy in 10% to 20% of common NSCLCs that do not have any neuroendocrine morphology. These tumors are not formally recognized within the WHO/IASLC classification scheme because the clinical and therapeutic significance of neuroendocrine differentiation in NSCLC is not firmly established. These tumors are referred to collectively as NSCLC with neuroendocrine differentiation.

5. Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements

This is a group of rare tumors. Spindle cell carcinomas and giant cell carcinomas comprise only 0.4% of all lung malignancies, and carcinosarcomas comprise only 0.1% of all lung malignancies. In addition, this group of tumors reflects a continuum in histologic heterogeneity as well as epithelial and mesenchymal differentiation. On the basis of clinical and molecular data, biphasic pulmonary blastoma is regarded as part of the spectrum of carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements.

Aims of the study

The aim of this study was to study the distribution of histological types of primary lung cancer among Iraqi patients in relation to:

1. Age
2. Gender
3. Smoking

PATIENTS AND METHODS

This study had included 170 proven cases of lung cancer at medical city hospitals/Baghdad during the period from 1st of January to 31st of December 2011. This center is one of the largest medical centers in Iraq, and the referral area covers all parts of the country. Hospital-based lung cancer incidence data were analyzed retrospectively for histologic types occurring over the mentioned period. The diagnosis in each case was substantiated by histopathological surgical specimens, or biopsy or cytological preparations from the original tumor site in the lung. The histologic types were divided into four categories: small cell carcinoma, squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. SPSS version 18 used for data analysis. Continuous variables presented as mean \pm standard deviation. Discrete variables presented as numbers and percentages. Chi square test for goodness of fit used to verify the

significance of observed distributions. Chi-square test for independence used to test the significance of association between discrete variables, and condensation of cells was performed in any table with low expected frequencies. One-way ANOVA test used to test the significance of difference in mean for continuous variables in more than two independent samples. Findings with P-value less than 0.05 considered significant.

RESULTS

Patients aged below 40 were categorized as the young group and those between 40 and 65 as middle age group and those above 65 as old age group. It was significant to find majority of cases (60.6%) within the age group 40-65 years ($P < 0.05$) as shown in table (1).

Table (1): Age distribution of patients with primary lung cancer.

Age groups (years)	No. of patients	%
• <40	7	4.1
• <40-65	103	60.6
• >65	60	35.3
TOTAL	170	100

The number of male cases in this study was 124 (72.9%) and female cases was 46 (27.1%) with male to female ratio is 2.69: 1 as shown in figure (1)

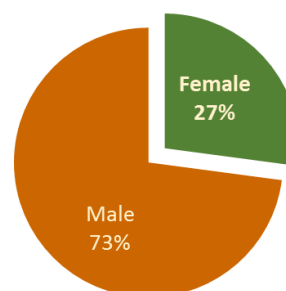


Figure 1: Sex distribution of patients with primary lung cancer.

Patients who had never smoked were classified as non-smokers, while all the remaining patients who either smoked at the time of diagnosis or had smoked in the past were categorized as smokers. The observed distribution of smoking status of patients with primary lung cancer was significant in this study ($P < 0.05$, table 2)

Table (2): Distribution of cases according to smoking status of patients with primary lung cancer.

Smoking status	Number (N)	Percent (%)
➤ Smoker	115	67.6
➤ Non smoker	55	32.4
Total	170	100

Histopathological types of primary lung cancer in the total sample of the study

It was significant to find that most frequent type of primary lung cancer is squamous cell carcinoma

(47.1%), followed by adenocarcinoma (30.0%) and small cell carcinoma (20.0%), while large cell carcinoma contributed to small proportion of the sample (2.9%) (P < 0.05, table 3).

Table (3): Distribution of cases with primary lung cancer according to the histological types.

Types of lung cancer	N	%
➤ Squamous cell carcinoma	80	47.1
➤ Adenocarcinoma	51	30.0
➤ Small cell carcinoma	34	20.0
➤ Large cell carcinoma	5	2.9
Total	170	100

Histological types of primary lung cancer in relation to age

Mean age distribution in relation to histological type of lung cancer is detailed in Table 4. It is significant to find

The mean ages of all types of lung cancer are about the same (around 60 years) except younger (58.8 year) for large cell carcinoma (P < 0.05, table 4).

Table (4): Descriptive statistics for age according to types of primary lung cancer.

Types of Lung cancer	N	Minimum	Maximum	Mean	SD
Squamous cell carcinoma	80	19	90	62.2	11.4
Adenocarcinoma	51	33	80	63.5	9.2
Small cell carcinoma	34	50	80	62.6	7.6
Large cell carcinoma	5	48	71	58.8	9.8
Total sample	170	19	90	62.5	10.0

Histological types of primary lung cancer in relation to gender

Squamous cell carcinoma is the commonest type of lung cancer among males (53.2 %), while in females the

adenocarcinoma represents the most common type(43.5%) as shown in table (5).

Table (5): Distribution of primary lung cancer types in both sexes.

Types of lung cancer	Male		Female	
	N	%	N	%
Squamous cell carcinoma	66	53.2	14	30.4
Adenocarcinoma	31	25	20	43.5
Small cell carcinoma	23	18.5	11	23.9
Large cell carcinoma	4	3.2	1	2.2

Histological types of primary lung cancer in relation to smoking status

Squamous cell carcinoma occur in smoker patients more than Non smokers (51.3%, 38% respectively), while

adenocarcinoma occur more in non-smoker patients than smokers (42.0%, 24.3% respectively). Other lung cancer types showed no significant smoking distribution (table 6).

Table (6): Distribution of lung cancer types according to smoking status of patients.

Types of lung cancer	Non smoker		Smoker		Total Number
	N	%	N	%	
Squamous cell carcinoma	21	38.0	59	51.3	80
Adenocarcinoma	23	42.0	28	24.3	51
Small cell carcinoma	10	18.0	24	21.0	34
Large cell carcinoma	1	2.0	4	3.4	5

DISCUSSION

This study revealed that most of those afflicted by lung cancer were males consisting 72.9% of patients. This finding regarding male predominance in liability for lung cancer is compatible with the previously well known

male predominance in lung cancer susceptibility^[3] Active cigarette smoking is the most well documented cause of lung cancer and has a stronger association with squamous cell carcinoma than other types of lung cancer.^[4] The fact that the risk of squamous cell

carcinoma falls more rapidly after cessation of smoking than the risk of adenocarcinoma also reflects the stronger link between squamous cell carcinoma and smoking.^[5] In men aged 40 and over, squamous cell carcinoma still accounted for the majority of lung cancers. Adenocarcinoma was the most common type in men younger than 40. The high incidence of adenocarcinoma in the younger group is similar to findings in other published studies.^[6-9] Adenocarcinoma was also the predominant type among older male nonsmokers. Induction of squamous cell carcinoma perhaps requires long exposure to carcinogens, and therefore occurs less frequently in the young. Cigarette smoking seems to be an important causative factor in the development of lung cancer even in younger individuals⁽¹⁰⁾. However, this cannot explain the occurrence of lung cancer in patients less than 40 years or women in this study who developed lung cancer without a smoking history. In Our study, for each major histological type of lung cancer, the mean age was approximately 62 years. El-hassany^[28] on 750 patients with lung cancer showed men to women ratio 4.4:1 squamous Cell carcinoma 37%, adenocarcinoma 27%, small cell carcinoma 21%, large cell carcinoma 6%. AL- Saleem et.al⁽²⁹⁾ .(344) slide were re-examined for patients with lung Cancer from 1976-1982 the results were men to women ratio was (7:1) Squamous cell carcinoma 48%, adenocarcinoma 13%, large cell Carcinoma 7% there were men predominant in all types. Al- Alusi^[30] 1519 patients with lung cancer studied men to women ratio were (4.5:1), 90% smokers, squamous Cell carcinoma 42% adenocarcinoma 24.5% ,small cell carcinoma 17.8% and large cell carcinoma 5.5%. Some large population-based studies.^[11-13] have obtained that adenocarcinoma of the lung showed a significant increase in both men and women, and adenocarcinoma has become the most prevalent type in both sexes⁽¹⁵⁾

There are several etiological factors responsible for the increasing incidence of adenocarcinoma

1. Advances in histopathological diagnosis resulting in reclassification of other cell types as adenocarcinoma, especially large undifferentiated carcinoma (47% of undifferentiated carcinomas were reclassified as adenocarcinoma by Valaitis et al.^[15]
2. An increase in female patients, who have a predilection for adenocarcinoma;
3. Improvement of diagnostic methods for detecting peripheral lesions.^[15-16]
4. The role of passive smoking.^[17-19] However, lung cancers among younger men, non-smoking older men and women were more often adenocarcinoma in our study, suggesting the influence of factors other than tobacco.
5. Some factors including diet.^[20] hormones.^[21] family history.^[22] and occupational exposure.^[23] have been proposed.

Advances in molecular biology show promise for correlating specific genetic changes with exposure to

carcinogens.^[24,25] El-Torky et al.^[26] observed an increase in the frequency of small cell carcinoma among women through a review of 4928 cases of lung cancer. An autopsy study in Japan also revealed a similar trend.^[27] but this was attributed to a change in the criteria of lung cancer histology from undifferentiated carcinoma to small cell carcinoma. In our study undifferentiated large cell carcinoma showed low incidence the reason for this is unclear, but rates over the period of study undetermined carcinoma which cannot be identified easily by cytopathology or even histopathology may have decreased as a result of improvements in electron microscopy and immunohistochemistry. There is no doubt that the proportion of adenocarcinoma among lung cancers and the proportion of women with lung cancer are high, the reasons for the development of adenocarcinoma in the lungs of non-smokers of either sex are still unknown. Small cell carcinoma has demonstrated a higher distribution among males than females reflecting strong association with smoking. Therefore the influence of factors other than tobacco causing lung carcinoma awaits further investigation.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

1. There was predominance of males among primary lung cancer patients and this might be due to more prevalent smoking habit males.
2. The majority of lung cancer patients were in the age range of 40-65 years.
3. Squamous cell carcinoma was the most common type of lung cancer among patients in this study.
4. Squamous cell carcinoma was the most common type of lung cancer among smoker males reflecting the strong association between smoking and this type of lung cancer.
5. Adenocarcinoma showed higher incidence in women and non smoker males suggesting the presence of risk factors other than tobacco in the development of lung cancer.

Recommendations

4. Further studies that including the data of many years are needed to describe the precise incidence of each type of lung cancer in our country.
5. Further detailed studies are needed to assess the role of passive smoking in the development of lung cancer.
6. Other studies are needed to demarcate risky thresholds for smoking duration and heaviness and their effect on the type of lung cancer.
7. Further large sampled studies are needed to evaluate other factors that influence the type of lung cancer like occupational exposures to carcinogens and area of residence.

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