INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide with an overall 5-year survival rate of 17% after diagnoses. Indeed many patients tend to have a very poor prognosis, being diagnosed at an advanced stage ***(Andolfi et al., 2016).***

In 2012, lung cancer was the most frequently diagnosed cancer and the leading cause of cancer death in male populations. Among females, lung cancer was the leading cause of cancer death in more developed countries, and the second leading cause of cancer death in less developed countries ***(Torre et al., 2015)***.

In 2013 in the European Union, lung cancer mortality fell in men by 6% compared with 2009, while cancer death rates increased in women by 7%, thereby approaching male counterparts ***(Malvezzi et al., 2015).***

Tobacco smoking is still the main cause of lung cancer in most of the patients, and the geographic and temporal patterns of the disease largely reflect tobacco consumption during the previous decades ***(Jemal et al., 2012).***

Both smoking prevention and smoking cessation can lead to a reduction in a large fraction of human cancers. In countries with effective tobacco control measures, the incidence of new lung cancer has begun to decline in men and is reaching a

plateau for women ***(International Agency for Research on Cancer, 2016).***

To date, although tissue biopsy remains the gold standard for diagnosing malignant/premalignant airway disease and some techniques are still investigational, bronchoscopic technologies can be considered the safest and most accurate tools to evaluate both central and distal airway mucosa ***(Tremblay et al., 2016).***

Flexible bronchoscopy became the recommended procedure for all patient suspected of having lung cancer, showing a sensitivity for central airway lesions of 88% and overall sensitivity for all modalities in the diagnosis of peripheral disease of 78% (it varied from 36% to 88%, according to the biopsy method used) ***(Rivera et al., 2013).***

Symptoms do not usually occur until the cancer is advanced, and may include persistent cough, sputum streaked with blood, chest pain, and voice change, worsening shortness of breath, and recurrent pneumonia or bronchitis ***(Cancer Facts and Figures, 2015).***

AIM OF THE WORK

The aim of this work is to detect the predominant Clinical, Radiological, Bronchoscopic and Pathological presentations of lung cancer cases admitted to NICD at Imabab.

Chapter 1

LUNG CANCER

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Lung cancer was the most frequently diagnosed cancer and the leading cause of cancer death in male populations in 2012. Among females, lung cancer was the leading cause of cancer death in more developed countries, and the second leading cause of cancer death in less developed countries ***(Torre et al., 2015)***. In 2013 in the European Union, lung cancer mortality fell in males by 6% compared with 2009, while cancer death rates increased in females by 7%, so approaching male counterparts ***(Malvezzi et al., 2015).***

Worldwide lung cancer is the most common cancer among males in terms of both mortality and incidence. Among females has the third highest incidence, and is the second after breast cancer mortality. In 2012, there were 1.82 million new cases and 1.56 million deaths due to lung cancer, representing 19.4% of all deaths from cancer ***(WHO, 2014).***

The overall 5-year survival for lung cancer is still low ranging 10-20% due to the poor prognosis of many patients diagnosed at advanced stage despite the improvements in

diagnosis, staging and treatment. Screening and detection of early lung cancer is crucial for improving survival as patients with early stage lung cancer have a 5-year survival more than 70% ***(Allemani et al., 2015).***

Incidence and epidemiology

About 1.8 million people are diagnosed worldwide with lung cancer each year. This accounts for around 13% of total cancer diagnoses making it the most common cancer disease. Lung cancer has the highest mortality, killing approximately 1.6 million people annually. The highest incidence rates among males are in the Eastern Europe and United States whereas the highest among women are in North Europe and North America ***(Torre et al., 2016).***

Lung cancer incidence increases with age and about one-third of lung cancer deaths occur after the age of 75. Lung cancer before the age of 45 is rare and accounts only for about 3% of lung cancer deaths ***(Didkowska et al., 2016).***

The estimated new cases of lung cancer in the US for 2018 are 121,680 for men and 112,350 for women, for a total of 234,030 case, the equivalent of 641 lung cancers diagnosed per day ***(Siegel et al., 2018).***

In EGYPT, lung cancer is one of the most common cancers, 5.0%-7.0% of all cancers. It's incidence increased during 1980-2014, from 11.9 to 63.3/100.000 populations for

men and from 3.7-13.8/100.000 populations for women. Lung cancer ranks the fifth in males and the ninth among females. Also, lung cancer is a leading cause of death (25% of all cancer deaths), ranks first in males and second in famales. Mortality rate increased from 9.1 to 32.4/100.000 populations and from 2.3 to 12.4/100.000 populations, between 2010 and 2014, among males and females, respectively ***(El-Moselhy et al., 2018).***

While small-cell lung cancer (SCLC) has been decreasing in frequency in many countries over the past two decades, Non-Small-Cell Lung Cancer (NSCLCs) accounts for 85-90% of lung cancers ***(Jemal et al., 2011)***. During the last 25 years, the distribution of histological types of NSCLC has changed: in the USA, squamous cell carcinoma (SCC), which was formally the predominant histotype) decreased, while adenocarcinoma has increased in both genders. In Europe, similar trends have occurred in men, while in women, both SCC and adenocarcinoma are still increasing ***(Forman et al., 2013).***

SCLC originates from neuroendocrine-cell precursors and is characterised by its rapid growth, its high response rates to chemotherapy and radiotherapy and development of treatment resistance in patients having metastatic disease. In the Western world, the proportion of patients with SCLC has decreased 13% ***(Govindan et al., 2006).***

Pathogenesis of lung cancer

Lung cancer results from the deregulation of cellular processes that control cell cycling and death, allowing unrestricted cell growth. Dysfunctional signaling pathways and proteins that promote carcinogenesis include guanosinetriphosphatases (GTPases) such as Ras, membrane-bound Receptor Tyrosine Kinases (RTKs) such as Epidermal Growth Factor Receptor (EGFR) and nuclear proteins that contribute to cell mitosis and abrogate the appropriate apoptotic (programmed cell death) pathway such as Myc and p53, respectively ***(Fishman, 2015).***

Lung cancer is initiated by inactivation of tumor suppressor genes or by activation of oncogenes ***(Cooper et al., 2013).*** EGFR regulates cell proliferation, apoptosis, angiogenesis, and tumor invasion ***(Herbst et al., 2008).***

Cancer develops following genetic damage to DNA and epigenetic changes. These changes alter the normal functions of the cell, including programmed cell death (apoptosis) and cell proliferation. As more damage accumulates, the risk of cancer increases ***(Brown et al., 2010).***

Mutations and amplification of EGFR are common in NSCLC and provide the basis for treatment with EGFR-inhibitors ***(Kumar et al., 2013).***

The identification of a variety of molecular and genetic alternations in NSCLC has provided the opportunity for

targeted therapy, such as EGFR Tyrosine Kinase Inhibitors (TKIs) for activating EGFR mutations in NSCLC, and the Anaplastic Lymphoma Kinase (ALK) inhibitor crizotinib for NSCLC harboring ALK fusions ***(Fishman, 2015).***

Risk Factors

Smoking

Tobacco smoking is still the main cause of lung cancer in most of the patients, and the geographic and temporal patterns of the disease reflect tobacco consumption during the previous decades ***(Jemal et al., 2012).***

Both smoking prevention and smoking cessation can lead to high reduction in a large fraction of human cancers. In countries with effective tobacco control measures, the incidence of new lung cancer has begun to decline in men and is reaching a plateau for women ***(International Agency for Research on Cancer, 2016).***

Prevalence of lung cancer in females without a history of tobacco smoking is estimated to represent 19%, compared with 9% of carcinoma in male lung in the USA ***(Novello et al., 2014).*** These new epidemiological data have resulted in 'non-smoking-associated lung cancer' being considered a distinct disease entity, where specific molecular and genetic tumour characteristics have been identified ***(Couraud et al., 2015).*** However, other clinical series do not report differences by sex

after adjusting for age and for the higher number of women >60 years who do not smoke compared with men. This could justify the different incidence, which may not be due to a real difference among genders specifically ***(ESMO, 2016).***

Electronic cigarettes are increasing in popularity as a tobacco-free alternative to regular smoking. Although this type of cigarette does not produce the harmful chemicals associated with tobacco combustion, the high temperature reached in the vapor can still generate dozens of toxic substances including polycyclic aromatic hydrocarbons (PAH) ***(Canistro et al., 2017).*** The long-term effects of electronic cigarette use remain to be determined ***(Shields et al., 2017).***

Radon

The U.S Environmental Protective Agency has determined radon to be the second leading cause of lung cancer after cigarette smoking. The increased risk is attributed to domestic exposure, due to diffusion of radon from the soil. High radon concentrations have been linked to increased risk of lung cancer in underground miners ***(Choi et al., 2017).***

The radioactive, naturally occurring noble gas radon-222 is responsible for about half of all non-medical exposure to ionizing radiation ***(Robertson et al., 2013).*** Radon exposure is considered to be the second most important risk factor for

developing lung cancer overall and the most important risk factor in negative smoker ***(Torres et al., 2014).***

Air Pollution

Cooking meals or heating homes by open fires with coal or biomass in poorly ventilated houses is commonplace in the developing world. The resulting fumes contain particles and gaseous chemicals that are carcinogenic ***(IARC working group, 2010).*** Concerning outdoor air pollution, one large study of 17 European patient cohorts suggests an association between to air pollution and risk for lung cancer ***(Raaschou et al., 2013).*** The International Agency for Research on Cancer (IARC) has classified outdoor air pollution as a lung carcinogen in humans ***(Loomis et al., 2014).***

Family History

It is reasonable to believe that this increased relative risk is partly due to genes that smoking behavior; however, most familial cases of lung cancer are not primarily due to shared smoking habits ***(Lorenzo et al., 2005).***

The evidence of familial aggregation of lung cancer suggests that certain genes are associated with lung cancer susceptibility. A linkage analysis has found a major susceptibility locus in chromosome 6q23-25 in lung cancer pedigrees ***(Baily-Wilson et al., 2004).***

Lung diseases (Pulmonary scarring)

It is a risk factor for a type of lung cancer called adenocarcinoma of the lung. Tuberculosis (TB) can make scar tissue form in the lungs.

The presence of certain diseases of the lung, notably chronic obstructive pulmonary disease (COPD), is associated with an increased risk (four to six times the risk of a non-smoker) for the development of lung cancer ***(Ferlay et al., 2004).***

Other factors

Several other factors have been described, including exposure to asbestos, arsenic, and non-tobacco-related polycyclic aromatic hydrocarbons. There is evidence that lung cancer rates are higher in cities than in rural settings, but many confounding factors other than outdoor air pollution may be responsible for this pattern ***(Straif et al., 2013).***

Pathology of lung cancer

Table (1): 2015 WHO Classification of Lung Tumor

Histologic Type and Subtypes
Epithelial tumors
Adenocarcinoma
Lepidic adenocarcinoma
Acinar adenocarcinoma
Papillary adenocarcinoma
Micropapillary adenocarcinoma
Solid adenocarcinoma
Invasive mucinous adenocarcinoma
Mixed invasive mucinous Nonmucinous adenocarcinoma
Colloid adenocarcinoma
Fetal adenocarcinoma
Enteric adenocarcinoma
Minimally invasive adenocarcinoma
Nonmucinous
Mucinous
Preinvasive lesions
Atypical adenomatous hyperplasia
Adenocarcinoma in situ
Nonmucinous
Mucinous
Squamous cell carcinoma
Keratinizing squamous cell carcinoma
Nonkeratinizing squamous cell carcinoma
Basaloid squamous cell carcinoma
Preinvasive lesion
Squamous cell carcinoma in situ
Neuroendocrine tumors
Small cell carcinoma
Combined small cell carcinoma
Large cell neuroendocrine carcinoma
Combined large cell neuroendocrine carcinoma.
Carcinoid tumors
Typical carcinoid tumor
Atypical carcinoid tumor
Preinvasive lesion
Diffuse idiopathic pulmonary neuroendocrinecell hyperplasia.
Large cell carcinoma
Adenosquamous carcinoma
Sarcomatoid carcinomas
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Other and Unclassified carcinomas
Lymphoepithelioma-like carcinoma
NUT carcinoma

Salivary gland-typetumors
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Epithelial-myoepithelial carcinoma
Pleomorphic adenoma
Papillomas
Squamous cell papilloma
Exophytic
Inverted
Glandular papilloma
Mixed squamous andglandular papilloma
Adenomas
Sclerosingpneumocytoma
Alveolar adenoma
Papillary adenoma
Mucinous cystadenoma
Mucous gland adenoma
Mesenchymal tumors
Pulmonary hamartoma
Chondroma
PEComatous tumors
Lymphangioleiomyomatosis
PEComa, benign
Clear cell tumor
PEComa, malignant
Congenital peribronchialmyofibroblastic tumor
Diffuse pulmonary lymphangiomatosis
Inflammatory myofibroblastic tumor
Epithelioidhemangioendothelioma
Pleuropulmonaryblastoma
Synovial sarcoma
Pulmonary artery intimal sarcoma
Pulmonary myxoid sarcoma with EWSR1–CREB1 translocation
Myoepithelial tumors
Myoepithelioma
Myoepithelial carcinoma
Lymphohistiocytic tumors
Extranodal marginal zone lymphomas of mucosa-associatedLymphoid tissue (MALT lymphoma).
Diffuse large cell lymphoma
Lymphomatoidgranulomatosis
Intravascular large B cell lymphoma
Pulmonary Langerhans cell histiocytosis
Erdheim–Chester disease
Tumors of ectopic origin
Germ cell tumors
Teratoma, mature
Teratoma, immature
Intrapulmonary thymoma
Melanoma
Meningioma, NOS
Metastatic tumors

(WHO, 2015)

The 2015 World Health Organization (WHO) Classification of Tumors of the Lung, Pleura, Thymus and Heart has just been published. This follows previous WHO Classification of Lung Tumors in 1967 and 1981, of Lung and Pleural Tumors in 1999 and Tumors of the Lung, Pleura. Thymus and Heart in 2004.

Updates about Lung Adenocarcinoma WHO 2015 included the following changes:

Added:

- Adenocarcinoma in situ.
- Minimally invasive adenocarcinoma.
- Invasive mucinous adenocarcinoma.

Discontinued:

- Bronchoalveolar carcinoma.
- Mixed subtype adenocarcinoma.
- Clear and signet ring cell carcinoma.

(WHO, 2015).

Squamous cell carcinoma is defined by the identification of keratinization or by prescence of intercellular bridges. ***Adenocarcinoma*** is either characterized by mucus formation, which may be discrete or intracellular, or by distinct growth patterns such as glandular/acinar growth, papillar

differentiation, or a single-layer, wallpaper-like spread along the alveolar septum and bronchioles; the latter is characteristic for bronchioloalveolar carcinoma.

Large cell carcinoma is an exclusion diagnosis; the term refers to a barely differentiated, non–small cell cancer with a poor prognosis, in which neither the characteristics of squamous cell carcinoma nor those of adenocarcinoma are detectable.

Small cell carcinoma represents the other extreme of a poorly differentiated lung cancer and has a poor prognosis. On the one hand it is a tumor with a high proliferative activity and small tumor cells, which can- not be larger than three lymphocytes; and on the other hand, neuroendocrine differentiation has been identified ***(Travis et al., 2015).***

Staging of lung cancer

TNM classification and revised international staging of lung cancer

The International Association for the Study of Lung Cancer (IASLC) Staging and Prognostic Factors Committee has collected a new database of 94,708 cases donated from 35 sources in 16 countries around the globe. This has now been analysed by statistical partners at Cancer Research And Biostatistics and, in close collaboration with the members of the committee proposals have been developed for the T, N, and