# A Cross-sectional Study on Risk Factors, Symptoms, Treatment and Management Strategies of Lung Cancer in a Tertiary Care Cancer Hospital of Bangladesh

A project submitted

by

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This study is dedicated to my parents and my project supervisor for their unconditional inspiration and relentless support.

# Certification statement

This is to certify that, the project titled 'A cross-sectional study on risk factors, symptoms, treatment and management strategies of lung cancer in a tertiary care cancer hospital of Bangladesh' submitted for the completion of the precondition for the degree of Bachelor of Pharmacy from the Department of Pharmacy, BRAC University. This contains my personal work under the supervision of Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, BRAC University and proper acknowledgement goes to those from whom I got the ideas.

Signed,

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Counter signed by the supervisor,

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# Abstract

Lung cancer is the most common clinical problem of Bangladesh. Lung cancer is the uncontrolled, abnormal growth of cells that starts off in one or both lungs, usually in the air passages of cell lining. This study has represented the current scenario of lung cancer in the tertiary care hospital of Dhaka city, covering a range of parameters including age, gender, location, environment, education level, lifestyle, and family history, smoking or tobacco consumption habit, clinical features, mode of diagnosis, treatment received and medications prescribed to the in-patients of National Institute of Cancer Research & Hospital (NICRH). The study protocol was initially approved by Ethical Review board of National Institute of Cancer Research & Hospital (NICRH) to run this survey. This study was enrolled with 210 patients diagnosed with lung carcinoma. Majority of them were male patients. Around 89.522% of patients among 210 patients were male and only 10.48% were female. Lung carcinoma was observed more prevalent in age range of 51-60 years old and among rural people the risk was even higher. Among three types of lung carcinoma, non-small cell lung carcinoma diagnosed patients were in majority 62.86% . This study also found that coughing is the most reported and chest pain is the second most reported symptom by patients. In case of diagnostic tests, FNAC was the most referred test for patients by physicians. Chemotherapy was also given; around 80.48% patients received chemotherapy effectively. Besides surgery, radiography and target protein therapy were also recommended. Combination of alkylating agents and antimetabolites were also prescribed for chemotherapeutic drug cycles. Among this combination of cisplatin and paclitaxel was prescribed most (41.90%). From this study we can conclude that we need to be more careful, so that lung carcinoma can be diagnosed in initial stage. As it does not show any symptoms in early stage of lung carcinoma, regular health checkup of lung function each year might prove an effective way to minimize mortality rate. In this fact government peoples keen attention is in need.

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| ACRONYMS | FULL FORM |
|---|---|
| Brain MRI | Brain Magnetic Resonance Imaging |
| CT scan | Computerized Tomography scan |
| COPD | Chronic Obstructive Pulmonary Disease |
| EU | European Union |
| Eco | Echocardiography |
| EGFR | Epidermal Growth Factor Receptor |
| FNAC | Fine-Needle Aspiration Cytology |
| G | Grade |
| GLOBOCAN | Global Cancer Incidence, Mortality and Prevalence |
| LC | Lung Carcinoma |
| LCC | Large-cell Carcinoma |
| NICRH | National Institute of Cancer Research & Hospital |
| NSCLC | Non-Small Cell Lung Carcinoma |
| N | Nodes |
| M | Metastasis |
| PET | Positron emission tomography |
| RT | Radiation Therapy |
| SqCC | Squamous Cell Lung Carcinoma |
| SCLC | Small Cell Lung Carcinoma |
| T | Tumor |
| TB | Tuberculosis |
| USG | Ultrasonography |
| USA | United States of America |
| WHO | World Health Organization |

# Chapter 1: Introduction

**Chapter 1: Introduction**

In the modern context of science, words such as "epidemic" and "pandemic" are most normally utilized as a part of reference to contagious diseases. At a certain point, when a disease becomes so fatal, widespread, and capable of defeating bodily defense mechanism, it is referred to as an "epidemic". That epidemic does not create any boundaries bearing in mind about age, sex, ethnicity or socio-economic background. These descriptors without a doubt depicts lung cancer, a disease of worldwide geographic reach and considering over the past 100 years it can easily be termed as an epidemic disease. Unfortunately, it doesn"t cease to stop the death toll, even in the 21$^{st}$ century (Addario & Bonnie, 2015).

In the current world, lung carcinoma has been recognized to be the deadliest form of cancer throughout the globe; and the most malignant form particularly across Asia. The World Health Organization (WHO) has established and estimated around 51% of lung carcinoma cases to prevail in the Asian continent (Steward, Bernard and Wild, 2014) and a near estimate of 21% of deaths to occur from the cancer prevalence (WHO, 2013) . Lung cancer and its effects are a setback not only in Asia but also in Bangladesh, as a common clinical issue, ever since 1985 (Akhtar, Masud, Alam, & Begum, 2011).

Of all most common forms of deadly cancers known, lung cancer stands out to be most prevalent and lethal. Also known as lung carcinoma, this form of cancer causes uninhibited, abnormal growth of cells that habituates in the air passages of either one or both lungs. In healthy lung tissues, abnormal growth is not observed, whereas in mutagenic tissues they proliferated rapidly. These abnormal cells neither functions as healthy normal cells any longer nor carry out normal regular functions; rather they form a cell mass called tumor (D"Angelo & Pietanza, 2010).

Lung carcinoma arises when mutation begins to occur in the genes of lung cells. These mutations make the cells incapable to correcting the damages they found in their DNA; therefore cells lose their ability to promote apoptosis. Various reasons are present behind causing mutation. Most of the cancers in lung arise due to inhaling carcinogenic substances. Chemotherapy, surgery, radiotherapy, target site treatments and immunotherapy alone or in combination are mostly used to manage lung carcinoma. This whole study will represent the

current scenario of lung carcinoma in the tertiary care hospital of Dhaka city, based on different parameters; including age, gender, location, environment, education level, lifestyle, and family history, smoking/tobacco consumption habit, clinical features, mode of diagnosis, treatment received and medications prescribed to the in-patients of National Institute of Cancer Research & Hospital (NICRH).

## 1.1 Global scenario

Lung carcinoma is one of the most widely developed malignancy in both sexes around the world. One of the study of GLOBACON showed that lung carcinoma is accountable for around 14% of the aggregate growth analysis in 2012 among 1.8 million malignant patients (WHO, 2013). Due to the lack of clinical indications in the earlier times, most lung carcinoma cases can only be detected in advanced stages. The rate of survival in up to 5 years of malignancy is just 17%. GLOBACON statistics of 2012 claimed that among 1.8 million deaths, around 20% of it is due to carcinoma of lung (WHO, 2013). The rate of deaths in the USA owing to lung carcinoma in 2015 is 27% of all cancer deaths and in 2016 around 20% of lung carcinogenic deaths occurred in the EU (Siegel, Miller, & Jemal, 2017). The rate of lung carcinoma in under developed countries is higher than developing ones. Study discoveries have demonstrated that the ethnical and geographical appropriation of carcinoma in lung shifts in various parts of the world (Commonwealth, 2010). In case of male living in USA, North America, Europe and East Asia altogether have higher tendency to develop lung malignancy than sub-tropical Africa (Ghoncheh, Yousefi, Delaram, & Salehiniya, 2017).

## 1.2 Bangladesh perspective

The issue of lung carcinoma is extremely intense in Bangladesh. Considering male patients, lung carcinoma is a predominant malignancy in Bangladesh; including incidence rate of around 24.9% and mortality rate of 28.6% estimated by World Health Organization (WHO, 2013). For female patients, the estimation is around 5.6% among all carcinogenic disease (WHO, 2013). Study claimed population aged above thirty in Bangladesh are liable to it and around 196,000 were diagnosed with carcinoma in lung (Hussain & Sullivan, 2013). As per

the report of International Agency for Research on Cancer, in 2008 number of new cases of lung malignancy in Bangladesh were found almost 14,951 and the year wise counting of cases are evaluated to ascend up to 43,048 by 2030 (Islam et al., 2013).

## 1.3 The Gross anatomy of lungs:

The anatomy of the respiratory system comprises of two primary parts, the airway system and lung system. The lungs are made up of parenchyma cells.
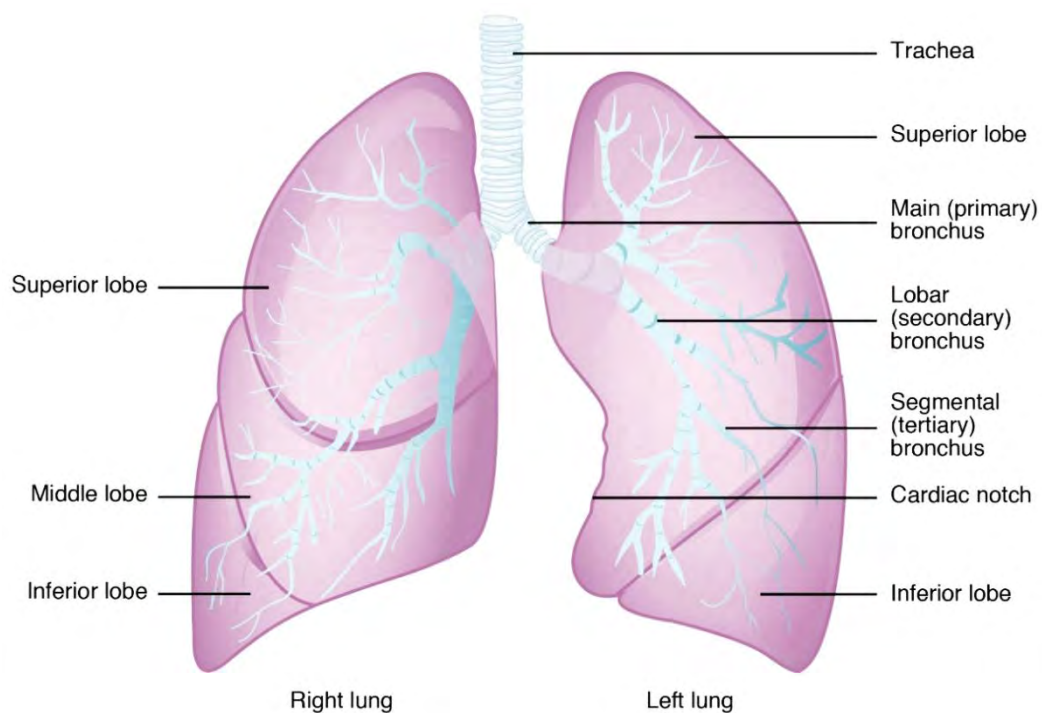


**Figure 1.1:  Anatomy of the Respiratory organ Lung** adapted from (Betts et. al, 2013).

Primary functions of those cells are to exchange gases, exchange from the alveolar region; and further partially involve in the conduction process. Lungs are paired organs that roughly adopt the shape of pyramids. They reside in the thoracic cavity of the human body (Moore, Dalley, & Agur, 2013).

The mediastinum separates right and left lung. Both are attached to the trachea with the aid of right and left bronchi; and further bounded by a diaphragm at the bottom of the cavity.
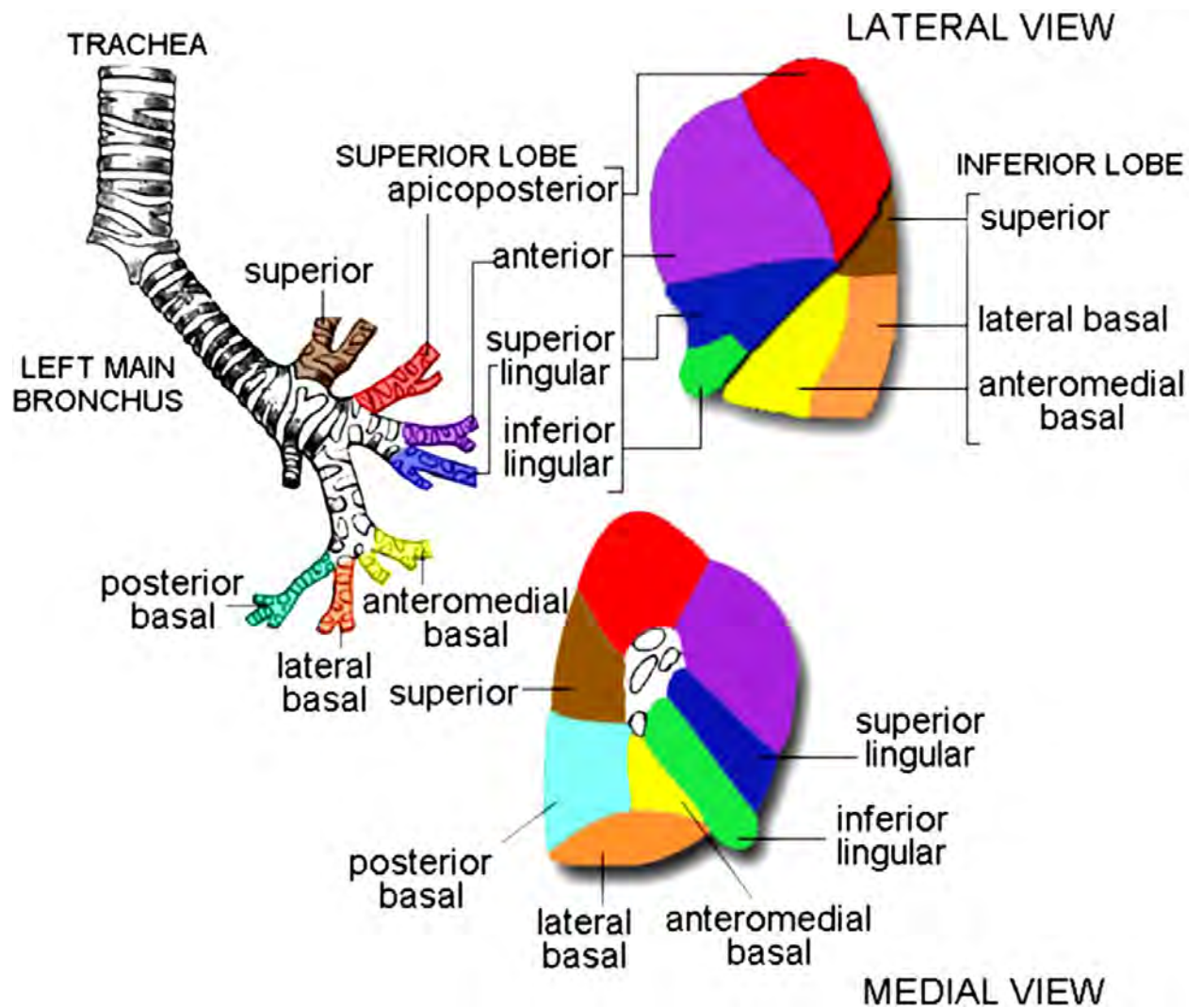


**Figure 1.2: Broncho-pulmonary segments of the left lung** adapted from (Tu, Inthavong, & Ahmadi, 2013).

They have a spongy aerated texture and retain the brown color among the young; while adopting a black color in adults; due to deposition of carbon particles. The left lung usually

weighs around 550 grams when the right lung is about 600 grams (Betts et al., 2013). The right lung is little bit shorter and expanded; in contrast, the left lung occupies lesser volume.
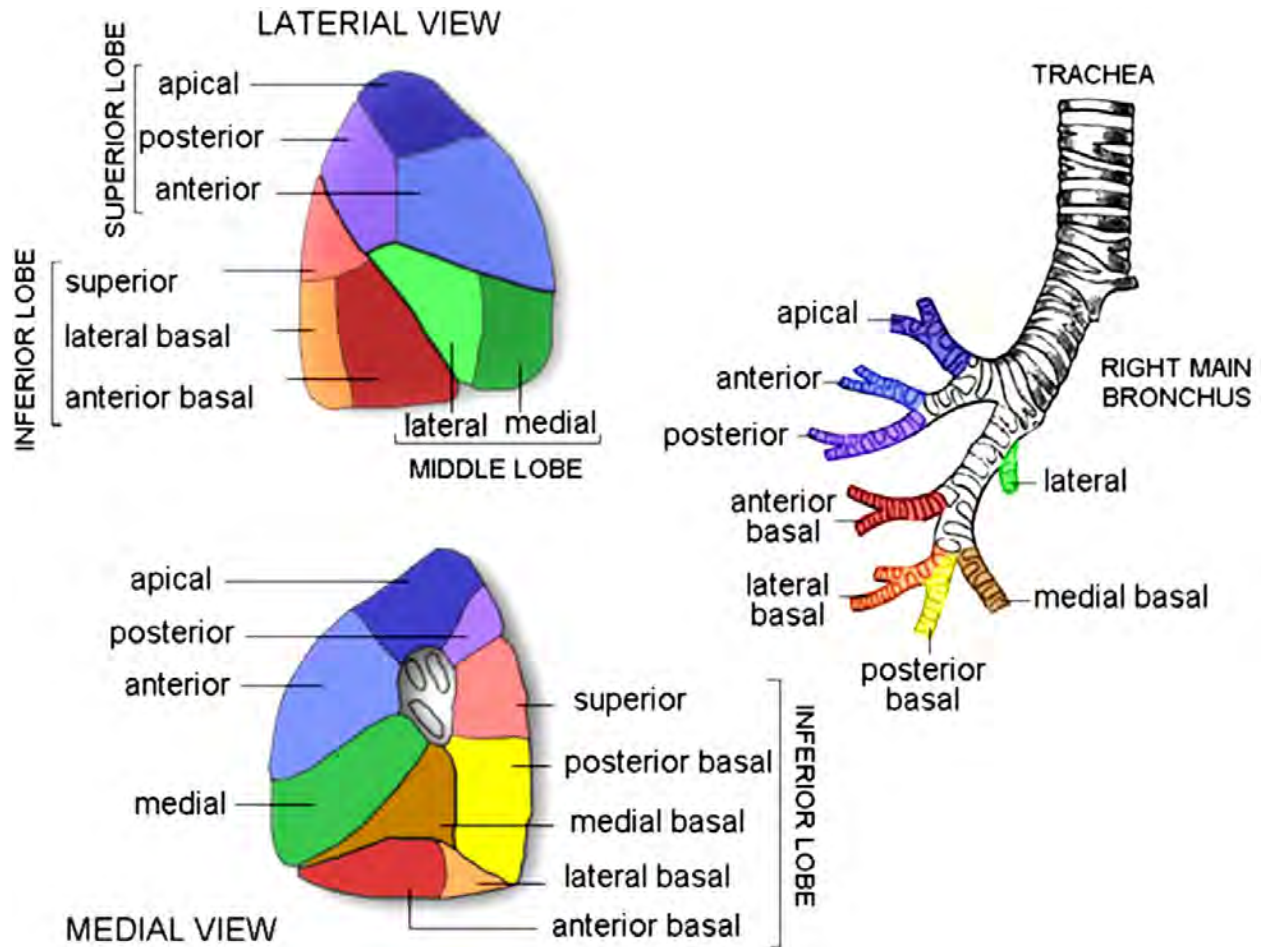


**Figure 1.3: Broncho-pulmonary segments of the right lung** adapted from (Tu, Inthavong, & Ahmadi, 2013).

The external portion of the left lung, there is an indention termed the cardiac notch; which functions to provide space for the heart. The lung"s most superior region is known as apex and at the inferior region – the base is situated, adjacent to the diaphragm. In addition, the ribs are situated in the lung"s coastal surface (Melorose, Perroy, & Careas, 2015).

Lungs originate from smaller units termed lobes; and these lobes are separated from one another by fissures. Three lobes are found in right lung. Lobes are- the superior, middle and inferior lobes. Besides, the left lung have only two lobes which are the superior and the inferior lobes (Moore et al., 2013) .

The lung further consists of autonomous, structural and functional units called broncho pulmonary segments; which exist as lobes by connective tissues. Each lobe contains multiple broncho-pulmonary segments. These segments receive air via a tertiary bronchus and are further provided with blood from their respective artery channels (Melorose et al., 2015). Despite the fact several diseases related to lungs affect at least one or more segments of broncho pulmonary apparatus; exceptional cases allow surgical removal of affected segments; with slight effects on the neighboring segments as a consequence (Melorose et al., 2015).

## 1.4 Lung carcinogen

The regular properties of cells are altered on a fundamental level; by a series of molecular events that results mainly from cancer. Cells of human body go through numerous physiological processes that include proper development of tissue and homeostasis. These processes require a balance among apoptosis of cell and proliferation of cell. All somatic class of cells of the body proliferates by the process of mitotic. That is maintained by through progression of the cell cycle. The apoptosis or programmed cell death happens widely in physiological settings. The role of apoptosis is to eliminate dangerous, impaired or unwanted cells. Cell cycle mainly develops and maintains a healthy cycle between apoptosis and the cell proliferation. Both processes are greatly exaggerated by regulators of cell cycle and apoptotic stimuli (Alenzi, 2004).

In case of cancer the normal control system of a cell becomes deactivated. The conventional control system functions for preventing over growth of cells and also the invasion of other tissues. Cancer cells proliferate and develop due to signals which usually controls cell grow and leads to apoptosis. Therefore those altered cells can no longer generate distinctive signals to induce the growth of the cells and rapid proliferation. Because of rapid

proliferation and new characteristics development; includes variation in so many aspects such as- variation in the structure of cell, decreases adhesion of cell; as well as production of new enzymes can occur (Akkurt & Karz, 2014).

Lung carcinoma mainly develops in epithelial cells that frame the inside covering to the lungs. The cancer in lung is not just only a single disease. Numerous sorts of lung carcinoma that shape in the lungs; a large portion of which can be easily seen by microscope. Lung cancer cells develop rapidly results replenish of the spaces and blockage of the thin tissues of lungs. The air becomes unable to pass through the areas. Small blockage in the lung does not create any remarkable effects because the lung is saturated with numerous air spaces. Depending of the severity of blockage, it can develop into a tumor and even more; chances increase to spread into different parts of the body before showing any symptoms (Prof & Peters, 2016).

In case of tumor there are two common terms one is „benign tumors" and the other „malignant tumors. Larger and increasing number of tumors suppresses the lung"s capacity to supply oxygen into the bloodstream. Benign tumors (not technically „cancer") usually accumulate in one place, in a localized mass of cells and do not spread. This kind of tumors is rarely risk to life and removal of it is not necessary. On the contrary, malignant tumors (cancer) are more dangerous since it contaminates in different region of the body; either via the lymphatic system or circulation system. Once malignancy spreads throughout, it becomes more difficult to treat efficaciously. Removal of it can be an effective footstep, but may breed back (Akkurt & Karz, 2014). Primary stages of cancer initiate in to it secondary stages. Initially it originates anywhere in the body, but later on, the cancer metastasizes and spreads throughout the lungs (Ellis, 2016).

**1.5 Types of lung carcinoma**

As indicated by American Cancer Society, there are three basic kinds of lung disease. Knowing the category of lung cancer of the patient is most imperative since the treatment choices depend on it and its prognosis. Depending on its microscopic appearance, three types are (Akkurt & Karz, 2014).

a. Small cell lung carcinoma,

b. Non-Small cell lung carcinoma and

c. Lung carcinoid tumor. These comprise of three broad types that further includes several sub types (Akkurt & Karz, 2014) .

### 1.5.1 Small cell lung carcinoma

It is the most rapid growing and most aggressive type of cancer in lung. By the estimation of American Cancer Society (2016), around 10 to 15 percent of the cancer is small cell carcinoma among all bronchogenic carcinomas.

**Table 1.1: Types of lung carcinoma**
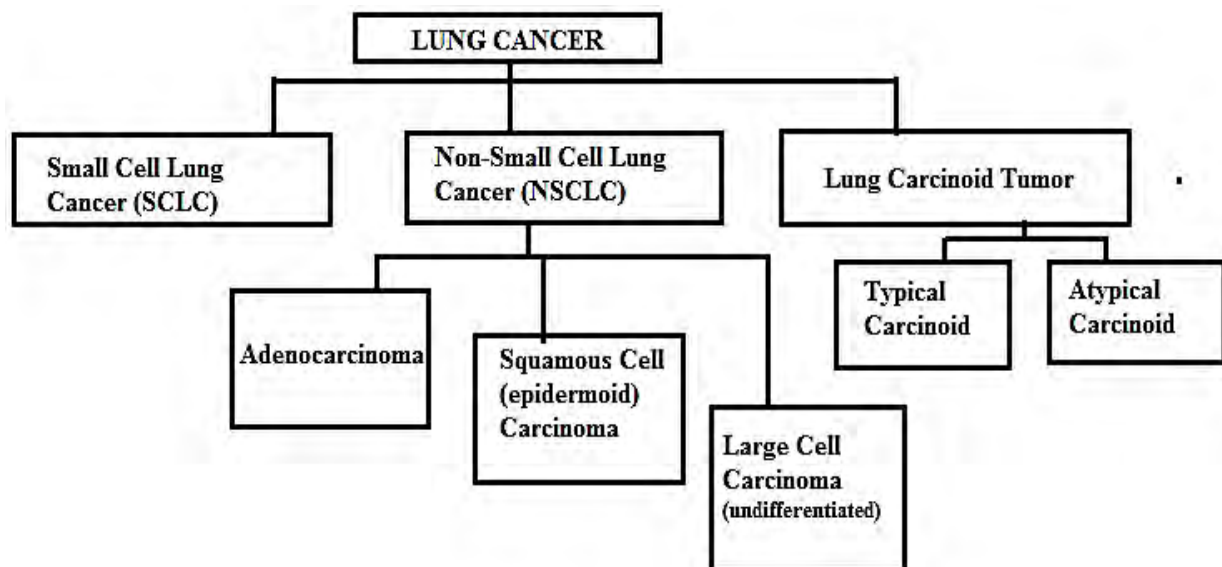


Considering characteristics of their clinical and biological angle, they are also identified as oat cell carcinoma (Wender et al., 2013). Small cell carcinoma contains unique biology that changes molecular and cellular configuration. According to study, this alterations leads to chromosomal changes, exhibits tumor suppressor genes dysregulations, alteration in signaling pathways and oncogenes (D‟Angelo & Pietanza, 2010). Small cell lung cancer can also be termed as neuroendocrine carcinoma, because they belong to the group of endocrine tumors. Those tumors are usually originate from neuroendocrine cells in the bronchus often they are called feyrter cells (Wender et al., 2013). Neuroendocrine cells are accountable for production and release of some specific peptide enzymes. It exhibits numerous changes,

including rapid proliferation, aggressive behavior, quick spread to different sites or parts of the body, sensitivity to chemotherapy and radiation, Associates para neoplastic syndromes, moreover Eaton-lambert syndrome, Cushing"s syndrome, hypercalcemia, inappropriate secretion of ADH (Antidiuretic hormone) and ACTH (Adrenocorticotropic hormone) syndrome etc. are also observed (D"Angelo & Pietanza, 2010).

## 1.5.2 Non-small cell lung carcinoma

Study from American Cancer Society (2016) found approximately 80- 85% of all lung carcinomas are non–small cell lung cancer (NSCLC). Non–small cell lung carcinoma typically develops and spreads more gradually considering small cell lung cancer. Histologically non–small cell lung cancer are divided into three types (The American Cancer Society, 2016). They are-

### 1.5.2.1 Adenocarcinomas

Around 40% of lung malignancies are adenocarcinomas (The American Cancer Society, 2016). This cancer begins in early forms of the cells that would typically emit mucus like substances. Adenocarcinomas are habitually originated in the external zone of the lung. This sort of lung cancer happens essentially in present or previous smokers, yet it is likewise the most widely recognized kind of lung carcinoma seen in non-smokers. It is more typical in female than in male, and probably happens in more young patients. Regardless of the way that it tends to grow slower than various sorts of lung cancer and will most likely be found before it has expand, this fluctuates from one patient to another. Individuals with a sort of adenocarcinoma called adenocarcinoma in situ (beforehand called bronchiole alveolar carcinoma) have a tendency to have a superior viewpoint than those with different kinds of lung carcinoma (Akhtar et al., 2011).

### 1.5.2.2 Squamous cell carcinomas

Squamous cell carcinoma originates habitually in central portion of lung, beside the bronchus air tube. Around 25% to 30% lung cancer are squamous cell carcinomas (The American Cancer Society, 2016). These growths begin in early forms of squamous cells.

Squamous cells are usually flat cells which mainly line up in the airways of the lungs (Wender et al., 2013).

### 1.5.2.3 Large cell carcinomas

Around 10-15% lung cancers are large cell carcinomas (The American Cancer Society, 2016). Large cell carcinomas could arise in almost any portion of the lung. It has a tendency to develop and spread rapidly, that become harder to manage. Large cell neuroendocrine carcinoma is the subtype of large cell carcinomas, is a quickly developing cancer and almost similar to small cell lung carcinomas (Wender et al., 2013).

### 1.5.3 Lung carcinoid tumor

Lung neuroendocrine cells sometimes experience certain progressions that reason them to become excessively and shape tumors. The tumors that create from neuroendocrine cells are termed as neuroendocrine tumors which are usually recognized as lung carcinoid tumor. This type can be further classified in 2 classes (Hendifar, Marchevsky, & Tuli, 2017) :

### 1.5.3.1 Typical Carcinoid

This type of tumor develops very slowly, moreover in rare case it spreads out of lungs. Typical carcinoid tumors have much better patient survival rates (Thomas, Tazelaar, Jett, & to, 2001).

### 1.5.3.2 Atypical Carcinoid

It is a rare subtype of carcinoid tumor and is aggressive in nature. Atypical carcinoid tumors are 9 times unusual, also slightly quick in developing tumor than typical carcinoid. This tumors have poor survival rates (Thomas et al., 2001) .

### 1.6 Staging of lung carcinomas

If a patient is diagnosed with carcinoma, physician"s first attempt is to identify how severe it has reached already. Staging of cancer is a way of ranking the state of the cancer. Staging is

a vital part for making strategy how the patient will be treated. Physicians go for numerous laboratory test that includes blood tests, imaging tests or biopsy; which helps to define the stage of cancer .To manage cancer of a patient, it is fundamental for physician to find out in which stage the patient is suffering from. Staging of cancer helps the physician to find (Detterbeck, Boffa, Kim, & Tanoue, 2017) the location of tumor, type of lung cancer, size or growth of the tumor, outlook of the tumor, extended to lymph nodes or not, extended to both lungs or not, extended to different body parts or not, survival chances and more (Detterbeck et al., 2017).

Staging is done twice among cancer patients. The primary ranking is prepared before receiving treatment and is recognized as the clinical stage. Then comes the second evaluation, is prepared after treatment, (for example, surgery), and is familiar as the pathologic stage. The pathologic stage is the most exact degree of the growth.

## 1.6.1 TNM System of Cancer Staging:

To analyze the stages of carcinoma, a physician's most preferable technique is the TNM staging system. In this framework, the letters T, N, and M portray an alternate region of malignancy development (Goldstraw & Street, 2010). In light of test outcomes, physicians will delegate a score to each letter.

> **T: Tumor**

The T score is related with primary level of tumor. This is the initial mass of malignant cell which can develop extensively for the lack of treatment. Tumor augmentation occurs when the cancer begins to spread; i.e. by crossing the tissue layers. When the carcinoma crosses the organ barrier, it can easily affect the surrounding nearby organs. T scoring is done based on three factors (Addario & Bonnie, 2015)-

   i.   Presence of primary tumor,
   ii.  Extension of the tumor and
   iii. Size of the primary tumor

> ➢ **N: Nodes**

The letter N is denoted when carcinoma has already moved to adjacent lymph nodes. The transparent liquid that exists in the tissue is lymph; which functions to supply water and nourishment to the cells and draw out all the waste matter out from the cells. It further transports WBC (white blood cell) which fights against foreign particles. This lymph is basically filtered by lymph nodes. Here, lymph nodes serve as defense body part. If carcinogen affected cells pass through the lymph vessels, they reach to the lymph nodes which will ultimately proliferate there and can show growth over there (Detterbeck et al., 2017). The N scoring are based on - existence of carcinoma to the adjacent lymph nodes and how many or which region of lymph nodes are cancerous.

> ➢ **M: Metastasis**

M scoring depicts whether the growth has extended to different distant parts of the body (AJCC, 2010). Carcinoma can even extend beyond adjacent lymph nodes.

The health care specialist also use some known terms, which are-

- In situ – Carcinoma cells are identified without any extend to adjacent tissues.
- Localized –Carcinoma has not extended beyond its initial origin location.
- Regional – Carcinoma has already extended to adjacent lymph nodes or nearby tissues.
- Distant – Carcinoma has extended through distant body parts.
- Unknown – Lack of evidence for proper staging.

**1.6.2 Staging system of Small cell lung carcinoma**

The TNM system of staging is more or less used for most of the type of lung carcinoma. After following the TNM system of staging, for more specific understanding, physician will utilize a two staging system. This two staging system is utilized if the cancer type is small cell carcinoma. Further staging divides small cell carcinoma into limited stage and extensive stage. This will enable the physician to understand the adaptation of aggressive treatments will be beneficial to patient or not.

**1.6.2.1 Limited stage**

The limited stage implies that the carcinoma is just in one part of the chest and radiation treatment could be a treatment alternative. Around one out of three individuals with small cell carcinoma have limited stage when initially analyzed (Kalemkerian & Gadgeel, 2013). On the other hand, analyzing on its initial stage is difficult, as it does not show any symptoms in its primary stage. If the patient is diagnosed in its limited stage, it increases more chances of survival.

**1.6.2.2 Extensive stage:**

This portrays carcinoma that has extended generally all through the lung or both lungs, to the lymph nodes on the opposite portion of the chest or into the distant body parts (involving bone marrow). In extensive stage, a physician also considers small cell carcinoma might extend to the fluid that surrounding the lungs. Around two out of three individuals with small cell lung carcinoma are in extensive stage when initially detected (Kalemkerian & Gadgeel, 2013).

**1.6.3 Staging system of Non-Small Cell lung carcinoma**

Numeric staging system is also widely followed by physicians. This staging system is denoted from 0 to IV. Staging descriptions are discussed below (Detterbeck et al., 2017) .

**A.** **Stage 0 :**

Features-

- In-situ disease,
- Localized malignancy,
- Did not extend to distant tissues or organs.


**B.** **Stage I:**

Features-

- Tumor is small in size,

- Did not expand to lymph nodes or nearby organs.

- Carcinoma may be found in main bronchus or visceral pleura.

- Divided into two sub stages (Detterbeck et al., 2017):

**Table 1.2: Sub-stages of stage I**  (Detterbeck et al., 2017).

| Stages | Characteristics |
|---|---|
| **Stage IA** | Tumor ≤3cm |
| **Stage IB** | 3cm <Tumor <4cm |

C.      **Stage II:**

Features-

- Carcinoma may have expanded to adjacent lymph nodes (Detterbeck et al., 2017).
- Sub stages are -

**Table 1.3: Sub-stages of stage II**  (Detterbeck et al., 2017).

| Stages | Characteristics |
|---|---|
| **Stage IIA** | 4cm < Tumor < 5cm (without involving adjacent lymph nodes.) |
| **Stage IIB** | Tumor ≤ 5cm (involving adjacent lymph nodes of affected lung.) |
| | Or, 5cm < Tumor <7cm (without involving adjacent lymph nodes.) |

D.      **Stage III:**

- Carcinoma affected lymph nodes and the middle of the chest(Roche, 2013).
- Sub stages are-

**Table 1.4: Sub-stages of stage IIIA** (Detterbeck et al., 2017).

| Stages | Characteristics |
|---|---|
| **Stage IIIA** | Tumor ≤ 5cm (involving lymph nodes present in the center of the chest.) |
| | Or, 5cm < Tumor < 7cm (with multiple tumor present in similar lobe of the lung.) |
| | Or, carcinoma extended to one or more sites, such as below areas-<br>· The chest wall of muscle, ribs or skin;<br>· Lung's adjacent nerve – the Phrenic nerve;<br>· Mediastinal pleura as well as parietal pericardium;<br>· Adjacent lymph nodes of the lung. |
| | Or, Tumor > 7cm (without involving lymph nodes but expand to more than one sites, such as –<br>· Diaphragm,<br>· Heart,<br>· Mediastinum,<br>· Oesophagus,<br>· Trachea,<br>· Blood vessel,<br>· Larynx,<br>· Spinal Bone,<br>· Carina. |
| | Or, carcinoma might expand to several lobes of the lung including lymph nodes |

**Table 1.5: Sub-stages of stage III (B, C)** (Detterbeck et al., 2017).

| Stages | Characteristics |
|---|---|
| **Stage III B** | 5cm < Tumor (involving lymph nodes of any areas given below- <br><br> · Other side of the chest from the affected lung. <br><br> · Above the collarbone. <br><br> · In the neck. |
| | Or, 5cm < Tumor < 7cm (involving lymph nodes of middle of the chest). |
| | Or, Carcinoma of any size might expand to lymph nodes of the middle of the chest, including at least one of the accompanying areas: <br><br> · Chest Wall, <br><br> · Mediastinal pleura and parietal pericardium, <br><br> · Diaphragm. |
| | Or, 7cm < Tumor |
| | Or, Expanded to major structure of chest, like- <br><br> · Blood vessel, <br><br> · Oesophagus, <br><br> · Trachea, <br><br> · The heart. |
| **Stage III C** | 5cm < Tumor < 7cm (involving- <br><br> · Phrenic nerve <br><br> · Parietal pericardium <br><br> Including lymph nodes as well – <br><br> · Middle of the chest, <br><br> · Other side of the affected lung, <br><br> · Top of the lung on the same / opposite side, <br><br> · Above the collarbone. |
| | Or, several tumors in numerous lobe of the lung. |

| | |
|---|---|
| | Or, Tumor > 7cm / expand to any of the following – <br>· Diaphragm, <br>· Mediastinum, <br>· Trachea, <br>· Blood vessel, <br>· The Heart, <br>· The recurrent laryngeal nerve, <br>· Oesophagus, <br>· The carina, <br>· Spinal bone. <br>Including lymph nodes of- <br>· Mid of the chest, <br>· Other side of the affected lung, <br>· Top of the lung on the same / opposite side, <br>· Above the collarbone. |
| | Or, several tumors in numerous lobe of the lung. |

**E. Stage IV:**

Stage IV is the last part of number system of staging. It also have sub-stages Stage IVA and Stage IVB (Detterbeck et al., 2017).

**Table 1.6: Sub-stages of stage IV** (Detterbeck et al., 2017).

| Stages | Characteristics |
|---|---|
| Stage IVA | Carcinoma affected both of the lungs, in the pleura or pericardium, in the surrounding fluids of the lungs or the heart. |
| | Or, Carcinoma expanded to lymph nodes outside the chest or other organs like liver or bone. |
| Stage IVB | Carcinoma extended in different areas or more than organs. |

## 1.7 Histological grading system of lung carcinoma

The grading system is a histological technique for cancer which basically depends on morphological features. Typically based upon cytological (mitoses cell division) or architectural features or both (Travis, Brambilla, & Geisinger, 2016). Grading is a method of grouping malignant cells depending on their microscopic view. This provide us information about how rapidly or gradually the malignancy is developing and spreading. Grading spectrum is done from well differentiated scale to the most poorly differentiated scale. Grading is only applicable for non-small cell lung cancer (Travis et al., 2016).

**Table 1.7: Histological grading system G** (Travis et al., 2016).

| Stages | Differentiation Characteristics | Malignancy status |
|--------|--------------------------------|-------------------|
| GX | Grade of differentiation is not possible. | No malignancy |
| G1 | Well differentiated | Slow developing cancer cells, limited spreading. |
| G2 | Moderately differentiated | Abnormal in nature with tendency of spreading. |
| G3 | Poorly differentiated | Very abnormal cells with rapid growth and spread. |
| G4 | Undifferentiated | Highest grade malignancy. |

## 1.8 Risk factors influencing Lung Carcinoma

Risk factors that influence developing malignancy in the lung can be represent either by relative risk or by absolute risk. Relative risk resembles number of expose to the risk factor that influencing lung carcinoma rather than one who is not exposed to it. On the other hand absolute risk is one‟s own chance of rising carcinoma over a period of time(Zorbas, 2014). Most common factors that are involved in developing lung carcinoma are discussed below:

## 1.8.1 Active tobacco smoking

The puff of every cigarette (tobacco) conveys a blend of chemicals to the lungs, in which they become assimilated into circulatory system and conveyed to the distant organ of the body. A large number of chemicals present in tobacco harm DNA that controls cell replication and conducts cells to do distinctive tasks. These DNA damage causes cell mutation and uncontrolled growth, which leads to carcinogenesis. Each tobacco contains around 7,000 chemicals; among them 70 chemicals are responsible for causing malignancy (Sencer, 2010). Active smoking means direct contact to tobacco that one performs himself. Inhaling the tobacco fumes and drawing them deep into the lungs. This act leaving lethal and poisonous residues eventually causes serious health problems like malignancy. The study suggests that comparison between nonsmokers and current smokers the relative risk ratio is around 1: 9; and the relative risk ratio between nonsmokers and ex-smokers(at least one year of quitting) is around 1: 3.9 (Zorbas, 2014).Further study explains person who intake 20 cigarettes each day; have relative risk of 13.7 than nonsmokers. Moreover person who smoke more or less 10 cigarettes each day develops 1.4 times risks than nonsmokers (Zorbas, 2014).

## 1.8.2   Secondhand tobacco smoking

Smoke inhaled in indirect way like, from other person's cigarettes also considered as a factor for causing lung carcinoma. At a point when a man takes in secondhand smoke, resembles the person is smoking. Study shows in the United States, around 50 percent of children and 2 out of 5 adults are secondhand smokers and around 7,300 nonsmokers each year dies from lung cancer  because of secondhand  smoking (Sencer, 2010).

## 1.8.3   Radon

Radon is a radioactive gas. Exposure to it develops 1.6-3.8 times more chances of developing lung cancer than who never exposed to radon gas ever (Zorbas, 2014).

### 1.8.4  Arsenic

According to WHO, arsenic in water should be in safe level; otherwise it increases the risk of developing lung cancer. Arsenic level in water of Bangladesh is above 50ppb whereas WHO standard is only 10ppb; which is a great threat to the people of Bangladesh (Murcott, 2012)

### 1.8.5  Cadmium

The fumes or mist of cadmium contains relative risk of 2.1 compared with 0.7-1.0 when exposed to cadmium dust (Zorbas, 2014).

### 1.8.6  Asbestos

Exposure to asbestos have 1.3-2.0 times more chances to develop lung carcinoma than unexposed person (Zorbas, 2014).

### 1.8.7  Diet

Studies searched for any probable role of vitamin supplements that can reduce the risk of lung malignancy but the outcomes are frustrating. Indeed, 2 huge investigations found that smokers taking beta carotene supplements had an expanded risk of lung cancer. The aftereffects of these examinations recommend that smokers ought to abstain from taking beta carotene supplements (de Groot & Munden, 2012).

### 1.8.8  Family History

Family history can help to expand understanding of the risks the patient shared. Families share natural, behavioral and hereditary characteristics; and one‟s information of history of lung malignancy within their family. Genetic factors provide great influence in developing lung carcinoma. Study recommended that one who has a relative with lung malignancy is roughly twice as liable to create lung malignancy as someone without a family history of the malignancy. The outcomes recommend that the hazard shows up to be more huge if at least two person from family have had lung malignancy or if his/her mother had any history of lung carcinoma (Zorbas, 2014).

### 1.8.9  Personal history

If a person is previously diagnosed with following lung diseases have risk of developing lung carcinoma (Prof & Peters, 2016), including Chronic bronchitis, Emphysema, Asthma, Tuberculosis, Asbestosis, COPD (chronic obstructive pulmonary disease), Pneumonia, Lung fibrosis etc (Prof & Peters, 2016).

### 1.9  Symptoms of Lung Carcinoma

A person may experience some symptoms if he is affected by lung carcinoma. Several symptoms include Coughing (dry cough or productive cough), Coughing or spitting up blood, Hemoptysis, Chest pain, Dyspnea, Anorexia, Hoarseness of voice, Bone pain, Neurological manifestation, etc. In some cases symptoms do not always indicate that one have lung malignancy. Some of these conditions develop only for smoking. Symptoms are vague sometimes and malignancy is often identified in advanced condition. Furthermore, if malignancy does not show any symptoms and it is identified through diagnostic tests (like x-ray or CT scan). It has more chance of remaining in early stage of malignancy (Prof & Peters, 2016).

### 1.10 Diagnostic tests

Lung carcinoma is a troublesome carcinoma for diagnosing as it has lack of routine screening for its early detection. For a few individuals, lung carcinoma is detected when they go through for routine health checkups. On the other hand, some may have had symptoms for numerous months. Numerous imaging and pathology tests are used for accurate diagnosing and staging of lung carcinoma. The main purpose is to detect the type of lung carcinoma (NSCLC or SCLC) (Baird, 2011).

### 1.10.1 Medical history

To plan an accurate treatment for lung cancer patient it is vital to record patient‟s medical history. This medical history involves records of any previously diagnosed disease he was suffering from and medicines he took in his life. Physicians will also focus on symptoms connected to lung carcinoma. Various malignancy or health diseases flow in families. So

medical history of patient''s blood relatives (siblings, grandparents) will be also taken in consideration (Ferreiro, 2018).

## 1.10.2  Physical examination

Physical examination is done for signs present in the body due to illness. Initially basic examinations e.g. body temperature, systolic and diastolic rate for evaluating blood pressure, weight of the patient, stethoscope will be used by physicians to listen to know the condition of heart, lungs and gut (Ferreiro, 2018).

## 1.10.3 Blood tests

For treatment accuracy,  physician suggests for several blood tests that help them to plan for next treatment strategy for the patient''s wellbeing (Ferreiro, 2018).

## 1.10.3.1 Complete blood count

A CBC test is assigned for measuring the number of blood cells of patient''s blood sample. It gives counts of WBC, RBC, platelets and more (Kalemkerian & Gadgeel, 2013).

## 1.10.3.2 Chemistry Profile

Chemistry profile delivers result of presence of chemicals found in patient''s blood that may come from bones or liver or from other organs. Presence of abnormal levels may cause due to malignancy or other health issues (Kalemkerian & Gadgeel, 2013).

## 1.10.4 Diagnostic imaging

Diagnostic imaging tests are painless tests which capture images of the inside of body. These outputs clarify if one has lung carcinoma and if it has spread. This helps physician to plan the treatment procedure for his patient. Imaging test that are been widely used are:

## 1.10.4.1 Chest x-ray

Chest x-ray can display tumors more than 1 cm. Tiny or concealed tumors are not always is visible on x-ray, so further tests are needed to run (Prof & Peters, 2016).

### 1.10.4.2 Computerized Tomography scan

CT scan uses beam of x-ray for 3D images of the inside of body. CT scan can display tinnier tumors than X-ray detects. It can also display enlarged lymph nodes or tumors in distant parts of the body (Jocelyn & Mclean, 1997).

### 1.10.4.3 Positron Emission Tomography

PET is a specialized imaging test for diagnosing tumor in the lung where biopsy cannot be done. In this test a radioactive solution of glucose will be injected .It needs 30-90 minutes to spread all over the body. Then the scanning is done. „Hot spots" become visible in the scan where fluid remained, this occurs when there is presence of active cells, like carcinogenic cells (Prof & Peters, 2010).

### 1.10.4.4 Brain MRI

If any tiny tumors present in brain MRI can display it. For stage IA carcinoma, it is not preferred but for stage IB this test can be done. For stage II and stage III MRI is preferred and a mandatory test for stage IV (Ferreiro, 2018).

### 1.10.5 Biomarkers evaluation tests

Biomarkers evaluation tests are also suggested by physician to know the physical condition of the patient.

### 1.10.5.1 Sputum Cytology

This is a biomarker test where it examines liquid phlegm or mucus (sputum) collected from patient"s lungs. Sputum is collected coughing deeply and forcefully. This examination is done to find out any presence of abnormal cells (Jocelyn & Mclean, 1997).

### 1.10.5.2 Fine needle aspiration cytology

FNAC is the fastest, cheap and more precise form of biopsy test for classifying which type of lung carcinoma the patient is affected. FNAC involves utilizing a fine gauge (25-22G)

needle for collecting sample of lesion for further microscopic examination (Delamothe, 2004).

### 1.10.5.3 Bronchoscopy

Physicians can look directly into the bronchi by bronchoscopy. A bronchoscope (flexible tube) will be inserted via nose or mouth down to the trachea. A local anesthetic is sprayed for making the throat numb for less painful. Through this procedure tissue sample (biopsy) is collected by „brushing and washing" technique (Prof & Peters, 2016).

### 1.10.5.4 Endobronchial Ultrasound

EBUS allows physician to examine the bronchi and collect tissue sample through trachea. Tissue sample can be collected from nearby tumor or lymph nodes. Bronchoscope utilizes small amount of ultrasound probe .This probe helps to display images of that certain body part and displays position as well as size of the tumor (Jocelyn & Mclean, 1997).

### 1.10.5.5 Mediastinoscopy

Through this method sample collected from lymph nodes are examined. In this method tube is penetrated through a tiny cut nearby neck and passed to trachea for sample collection (Baird, 2011).

### 1.10.5.6 Thoracotomy

If other tests become unable to provide accurate detection, thoracotomy is performed. It is an operation using general anesthetic. This test has two ways to perform-

a. A tiny cut is done on the chest and a tiny camera is penetrated with surgical instruments known as thoracoscope.
b. A large cut is done by surgeon on the back to open the chest (Travis et al., 2016)

### 1.11 Treatment for lung carcinoma

NSCLC and SCLC are two major types of lung carcinoma. So treatment strategy will be different for different types and subtypes.

The subtypes of NSCLC are treated often with possible surgery or radiation therapy or chemotherapy or both, and/ or by targeted therapy. Depending on the stage of malignancy and type of carcinoma, a physician determines which treatment procedure he should follow.

**1.11.1 Surgery**

Removal of lung malignancy and its encompassing lung tissue, e.g. lymph nodes relies upon the size and expansion of the tumor and how much securely can be expelled (Respir, 2004). Surgery is considered as most curable path of treatment but only possible if patient is in either stage I or stage II tumors. For undergoing surgery good cardiopulmonary function are always preferred. Most common types of Lung surgery are mentioned in table 1.8 (Respir, 2004) :

**Table 1.8:  Types of surgical resection** (Respir, 2004)

| Types of Surgical Resection | Portion of excision |
|---|---|
| **a. Wedge Resection:** | Excision of less than one lobe of the lung. This resection is done by removing a small portion of pie shaped piece of lobe of the lung. |
| **b. Segmentectomy** | Excision of large portion of lobe of the lung. |
| **c. Lobectomy:** | Excision of lobe. |
| **d. Pneumonectomy:** | Expelling of entire left/ right lung. |

**1.11.2 Radiation therapy**

RT can be suggested by physicians before patient receive any surgery. RT is often given in combination with chemotherapy that provides a vital impact on reducing the size of the tumor and for easy removal of it. RT is also applicable after having any surgery; it can be combined with / without chemotherapy. RT is an external radiation beam where patient is

place on a table and beams passed from a linear accelerator machine. Beams are targeted on tumor and its contiguous cancerous tissues. Effective dose of this therapy can destroy malignant cells and helps patient healthy cells to recover. This whole procedure takes only 5 – 10 minutes (Bos, Hendriks, Strasser, Dolmer, & Kamermans, 2016).

### 1.11.3 Chemotherapy

Around half of the patients who are in initial stage can be cured by proper chemotherapeutic medications. In single hand chemotherapy can cure around 10% of all malignancy patients when the patients remain in advanced stage (Katzung & Trevor, 2012).

In easy words chemotherapy means treating with chemicals. In this therapy carcinomas are treated with anticancer or cytotoxic drugs which aim to destroy cancer cells along with normal healthy cells. As healthy cells are repairable, it plays imperative role in destroying malignant cells in the body. Chemotherapy can be given intravenously and some types are also available in tablet form. Chemotherapy can be suggested by physician with or without combining with any treatments. Combination forms are as follows (Baird, 2011) –

- Adjuvant: When chemotherapy is given after surgery.
- Concurrent: When Chemotherapy is given during Radiotherapy.
- Chemo-radiation: For treating primary stage lung carcinoma which is not operable are treated combining with radiotherapy.
- Palliative: When no cure is possible only to extend the survival times and to minimize symptoms (Baird, 2011) .

Chemotherapy treatment is designed as cycles, each cycle runs for three weeks. Intravenous chemotherapy might be given for some couple of days. Number of cycles that a patient will receive rely upon, with which type of carcinoma he is affected. Tablet form of chemotherapy might be suggested by physician for regular basis (Prof & Peters, 2010).

In case of lung cancer early detection and prevention is the most imperative part to keep it in control. Study explained patients remaining in IB, II and IIIA stages platinum based adjuvant chemotherapy are more effective to lengthening survival time. In advance stage,

physicians recommend systemic chemotherapy which includes carboplatin or cisplatin (platinum based agents). In addition the second drug is prescribed is paclitaxel and relbine for having independent histological activity. Antifolate pemetrexed ought to be utilized for non-squamous cell carcinoma and for squamous cell cancer gemcitabine is utilized. Moreover, after receiving 4 cycles of platinum based first line chemotherapy by a NSCLC affected patient but no improvements occurred .For better outcomes EGFR tyrosine kinase inhibitor, like – gefitinib or erlotinib are given for controlling EGFR mutations. As SCLC is the most aggressive and sensitive, platinum based combination of cisplatin and etoposide / cisplatin and irinotecan is initially given. Besides, if $2^{nd}$ line monotherapy is adapted topoisomerase I inhibitor topotecan is preferred (Katzung & Trevor, 2012).

### 1.11.4 Targeted Therapy

There are few sorts of chemotherapy known as targeted therapies which are not destructive to normal healthy cells. Physician will supply the biopsy sample of patient"s tumor for examination in the laboratory. This examination result will declare the type of cells, their gene mutation nature. Every cells have receptor on their surface, carcinoma cells have receptors as well. In targeted therapy those receptors are targeted for incorporating chemo-drugs. Such as- a patient suffering from adenocarcinoma may have an EGFR (Epidermal Growth Factor Receptor) gene mutation. By knowing this physician can recommend targeted therapy related to EGFR (Jocelyn & Mclean, 1997).

### 1.12 Anticancer Medications

Anticancer medication or antineoplastic medication, are those which shows quite successful results in treating malignancy or carcinoma. Numerous anticancer medications are prescribed, among them most potential classes are – alkylating agents, antimetabolites, natural products and some hormones (Miller et al., 2016).

### 1.12.1 Alkylating agents:

For more than six decades, alkylating agents are being utilized for treating lung carcinoma. Alkylating agents can demonstrate almost all phases of cell cycle, specifically on DNA, also

crosslinks the N-7 guanine residues, breaks down DNA strand, prompting abnormal base pairing, prevents proliferation of cells and in the end apoptosis occurs (Ralhan & Kaur, 2007). The structure of alkylating agents contains ethyleneimine, bis (choloroethyl) amine, or nitrosourea moiety (Katzung & Trevor, 2012). Most common alkylating agents that are prescribed by physicians are- carboplatin or cisplatin. In Table 1.9, details about some common alkylating medications are given:

**Table 1.9: Alkylating agents mostly prescribed by physicians** (Katzung & Trevor, 2012).

| Alkylating agent | Clinical application | Mechanism of action | Acute toxicity | Delayed toxicity |
|---|---|---|---|---|
| Cisplatin or Carboplatin<br><br>(Platinum based chemotherapy.) | NSCLC, SCLC | a. Inhibits DNA replication.<br><br>b. Interferes with DNA repairing mechanism that activates apoptosis mechanism for cancer cells.<br><br>c. Inhibits acceptance of mispairing of nucleotides prompting mutations. | Diarrhea, nausea, vomiting. | Nephro-toxicity, hepatic fibrosis, alopecia. |

**1.12.2 Antimetabolites:**

Antimetabolites usually interfere with purine or pyrimidine nucleotide precursors. They can prevent or interfere with the synthesis of DNA or RNA (Katzung & Trevor, 2012). Most common antimetabolites which are mostly prescribed are pemetrexate and gemcitabine. In table 1.10 most common antimetabolites are explained.

**Table 1.10: Antimetabolites mostly prescribed by physicians** (Katzung & Trevor, 2012).

| Anti-metabolites | Clinical application | Mechanism of action | Acute toxicity | Delayed toxicity |
|---|---|---|---|---|
| Pemetrexate | NSCLC | a.  Prevents TS, DHFR and purine nucleotide synthesis. | Diarrhea, Nausea, vomiting | Myelosuppression, diarrhea, mucositis, skin rash, fatigue, handfoot syndrome. |
| Gemcitabine | NSCLC | a.  Prevents synthesis and repairing of DNA, b.  Prevents ribonucleotide reductase with decreased formation of dNTPs. | Nausea, vomiting. | Myelosuppression |

## 1.12.3 Natural Product:

Natural chemotherapy also widely prescribed by the physicians in chemotherapy regiments. Most common natural products are discussed below in table 1.11 (Katzung & Trevor, 2012).

**Table 1.11: Natural chemotherapy for treating Lung Carcinoma** (Katzung & Trevor, 2012).

| Natural Chemo therapy | Clinical application | Mechanism of action | Acute toxicity | Delayed toxicity |
|---|---|---|---|---|
| Docetaxel (natural product) | NSCLC | c. Prevents cell mitosis. | Hyper-sensitivity | Neurotoxicity, myelosuppression with neutropenia, fluid retention |
| Doxorubicin (natural product) | NSCLC, SCLC | a. Single or double strand DNA splits due to bind between oxygen free radical and DNA. <br> b. Prevents topoisomerase II. <br> c. Intercalates into DNA. | Nausea, red urine. | Alopecia, myelosuppression, cardio toxicity, stomatitis. |
| Etoposide (natural product) | NSCLC, SCLC | a. Prevents topoisomerase II. | Nausea, hypotension, vomiting. | Myelosuppression, Alopecia. |

| | | | | |
|---|---|---|---|---|
| Irinotecan (natural product) | NSCLC, SCLC | a. Prevents topoisomerase II. | Diarrhea, vomiting, nausea | Myelosuppression, Anorexia, hemolytic-uremic syndrome, fatigue, mucositis. |
| Paclitaxel (natural product) | NSCLC, SCLC | a. Prevents cell mitosis. | Diarrhea, vomiting, nausea, hypotension, hyper-sensitivity, arrhythmias. | Myelosuppression, Anorexia, peripheral sensory neuropathy. |
| Topotecan (natural product) | SCLC | a. Prevents topoisomerase I. | Vomiting, nausea. | Myelosuppression. |
| Vinorelbine (natural product) | NSCLC | a. Prevents cell mitosis. | Diarrhea, vomiting, nausea | Myelosuppression, constipation, inappropriate ADH secretion syndrome. |

## 1.12.4 Antibiotics:

Antibiotics are also prescribed for lung carcinoma patients. In table 1.12, necessary details are given below (Katzung & Trevor, 2012).

**Table 1.12: Antibiotics for treating Lung Carcinoma** (Katzung & Trevor, 2012)**.**

| Antibiotics | Clinical Applications | Mechanism of actions | Acute toxicity | Delayed toxicity |
|---|---|---|---|---|
| Cephalo-sporin, Penicillin, Macrolide, Fluoro-quinolone | NSCLC, SCLC | a. Causes interaction with DNA in a wide range of ways that adds intercalation. <br> b. breakdown of DNA strand and hindrance with topoisomerase II enzyme | Nausea, seizures, vomiting. | alopecia, peripheral neuropathy, renal dysfunctions, antibiotic resistance. |

# Chapter 2: Objectives and Methodology

## 2.1 Objective

The main objective of this study was to acknowledge the present-day situation and treatment strategies of lung cancer in Bangladesh that would aid in development better treatment strategies to extend survival rate and maintain the best quality of life of patients.

In Bangladesh, adequate numbers of survey are neither emphasized nor performed on, by different health care organizations to exhibit the real scenario of lung carcinoma. Certain cases go undetected and some cases of lung carcinoma are not recorded in a proper data base. Even so, there is a need to conduct an adequate number of surveys to compare and illustrate lung carcinoma condition in Bangladesh with similar conditions in other countries. This study represented the current scenario of lung cancer in the tertiary care hospitals of Dhaka city; and focused on different parameters including age, gender, location, environment, education level, lifestyle, family history, smoking or tobacco consumption habit, clinical features, mode of diagnosis, treatment received and medications prescribed to the in-patients of National Institute of Cancer Research & Hospital (NICRH).

## 2.2 Methodology

### 2.2.1 Study site

The target site of interest was National Institute of Cancer Research and Hospital (NICRH), situated at Mohakhali, Dhaka. It is the only tertiary care cancer hospital in Bangladesh. Patients from different regions of Bangladesh come to this institution for treatment purpose. Therefore this institution was found most appropriate for the purpose of this survey.

### 2.2.2 Study design

This is a cross-sectional study, which was carried out amongst in-patient who were hospitalized due to lung carcinoma and admitted into department of epidemiology of National Institute of Cancer Research & Hospital (NICRH) from 10th January 2018 to 19th June, 2018. Protocol for the study was approved by ethical review board of National Institute of Cancer Research & Hospital (NICRH).

### 2.2.3 Data collection

Patients who demonstrated interest and responded and/or patient"s family member(s) shared patient history, clinical evaluation, previous treatment records including surgery, chemotherapy or radiation therapy, histopathology and other information. Chemotherapy and/or supportive symptomatic treatment carried out by the department was recorded and documented. All the information was collected in a standardized and structured questionnaire was which was further approved by the Ethical Review board of National Institute of Cancer Research & Hospital (NICRH). A brief description of collected information is enlisted in table 2.1.

### 2.2.4 Ethical consideration

The study protocol was approved by the Ethical Review board of National Institute of Cancer Research & Hospital (NICRH). The study was designed in such a way, that it would adhere and go hand in hand with all necessary guidelines of Bangladesh medical research council (BMRC); including a full written consent which was obtained from every research participant. In addition, protection of privacy and anonymity of the participant in the study was ensured. For the proposed study, data were collected individually and carefully. All types of communication in need of the study were done with honesty and transparency. Use of offensive, discriminatory or other unacceptable language was avoided in the preparation of the questionnaire and these instructions were further followed during interview sessions with research participants. Information provided by the research participants was kept strictly confidential.

### 2.2.5 Scope for error

The study was not laboratory based. Contrary to lab work, it involved thorough survey in a practical field at a target site of interest. All relevant and necessary information was gathered from answers provided by the research participants and via analysis of their medical reports. The chances of obtaining error were also less, had the participants not provided any accurate information.

**2.2.6 Data analysis**

All the sample data were initially compiled in a master spreadsheet, then undergone data analysis to obtain final results. In this regard, Microsoft Excel version -2010 and Graph Pad Prism 7.0 provided effective.

# Chapter 3: Results

**Chapter 3: Results**

Out of 210 patients, 89.522% patients were male and rests of 10.48% patients were female. Larger part of the patients was having a place with age bunch 51-60 which was 41.43%. Patients were going to both non-paying and paying expressions of NICRH. Among them 72.86% patients were from rural regions, 14.28% patients were from semi-urban territories and rest of 12.86% patients was from urban regions.

In case of education level, 40.48% patients were illiterate, 29.52% patients did not continued their study after primary level, 27.62% patients were found completed higher secondary level and 2.38% patients were graduates or postgraduates and the levels of education have been shown in table . Among these 210 patients 91.90% patients were found exposed to hazardous environment during their work. Around 74.76% patients were exposed to dust , exposed to densely polluted air were 17.14%, industrial pollution exposure were 4.77% and chemical exposure were 3.33%. Among 210 patients ,9.52% were worked for less than 5 hours, 54.76%patients were worked for around 6-10hours and rest of the 33.33% patients worked for more than 10hours.Detailed patients" socio-demographic related information has been  shown in table 3.1.

In this investigation (table 3.2), around 5.24% were smokers and 73.33% were ex-smokers and rest of 17.62% was discovered non-smokers. Among them 46.19% patients were habituate to chewing tobacco, 8.57% patients were habituate to hookah. Additionally among 210 patients, 3.33% patients were discovered alcoholic, 51.42% patients were utilized to take tobacco users. This survey also found, 23.75% patients habituate to chewing tobacco, 4.40% on hookah users. In this study, E-cigarettes user patients were absent. Among the patients (cigarettes clients/used to take) per day of cigarette admission, under 10 cigarettes were 38.18%, 5.54% patients were utilized to take in excess of 10 cigarettes and around 61.21% patients were utilized to breathe in excess of 20 cigarettes. Among the nonsmokers, 69.52% of the patients relatives were discovered smokers.

**Table 3.1: Socio-demographic profile of the patients obtained in the study.**

| Variable | Percentage (%) |
|---|---|
| **Gender** | |
| Male | 89.522 |
| Female | 10.48 |
| **Age Groups (Years)** | |
| 20-30 | 2.38 |
| 31-40 | 6.19 |
| 41-50 | 23.81 |
| 51-60 | 41.43 |
| 61-70 | 20.95 |
| 71-80 | 5.24 |
| **Residential Status** | |
| Rural | 72.86 |
| Urban | 12.86 |
| Semi-urban | 14.28 |
| **Education level** | |
| Illiterate | 40.48 |
| Primary level | 29.52 |
| Secondary level | 27.62 |
| Graduation / post-graduation | 2.38 |
| **Working hazards** | |
| Yes | 91.90 |
| No | 8.10 |

| Condition | |
|---|---|
| **Condition** | |
| Chemical Exposure | 3.33 |
| Dust Exposure | 74.76 |
| Explosive Industry | 4.77 |
| Pollution | 17.14 |
| **Working hours** | |
| 1-5 hours | 9.52 |
| 6-10 hours | 54.76 |
| More than 10 hours | 33.33 |

**Table 3.2: Smoking, tobacco or other addiction history of the patients obtained in the study.**

| Variable | Percentage (%) |
|---|---|
| **Smoking status** | |
| Smoker | 5.24 |
| Ex-smoker | 73.33 |
| Non-smoker | 17.62 |
| Chewing tobacco | 23.75 |
| Hookah | 4.40 |
| Others | 23.27 |
| Tobacco users | 51.42 |
| E-cigarettes (with/without nicotine) | 00 |
| Alcohol users | 3.33 |
| **Cigarettes per day** | |
| Less than 10 cigarettes | 38.18 |
| 10+ | 5.45 |
| 20+ | 61.21 |
| Other Smokers at Home | 69.52 |

**Table 3.3: food habits and family history of the patients obtained in the study.**

| Variable | Percentage (%) |
|---|---|
| **Food habits** | |
| Regular | 89.05 |
| Irregular | 10.95 |
| **Family history** | |
| **Major illness of family members:** | |
| Yes | 41.43 |
| No | 58.57 |
| **Lung cancer among family members** | **13.81** |
| **Birth control pill taking records (Female)** | **40.91** |

As far as patients nourishment propensities 89.05% used to have regular eating regimen and 10.95% were discovered irregular eating routine showed in table 3.3. In case of family history, around 41.43% of patients" family members suffered from major illnesses and among 210 patients 13.81% of patients" family members were discovered diagnosed with lung cancer. Amongst the female patient only a handful number of female patients around 40.91% were subjected to the history of taking birth control pills.

In case of types of lung cancer, around 27.62% of patients were diagnosed with Small cell Lung Carcinoma, 62.86% of them were diagnosed with Non-small cell lung carcinoma and rests were found diagnosed with Lung carcinoid tumor 9.52%; which is showed in figure 3.1.
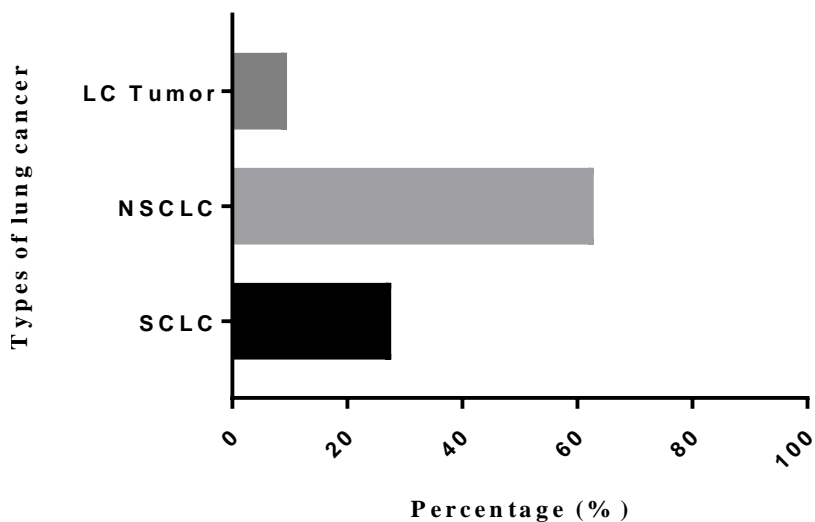
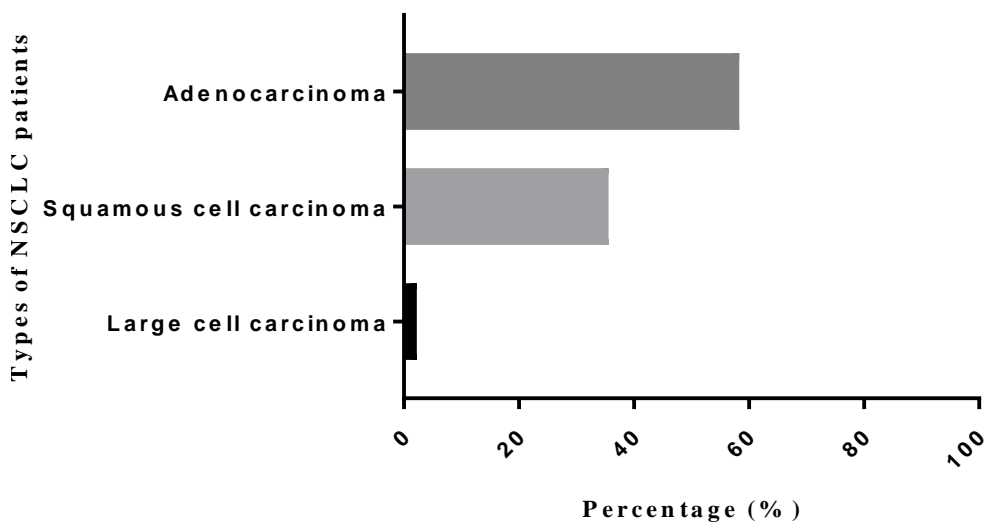**Figure 3.1: Percentage of different types of lung cancer patients.**



**Figure 3.2: Percentage of the sub-types of NSCLC lung cancer patients.**

As previously discussed non-small cell lung carcinoma have three sub types. Among 62.86% of NSCLC patients, 58.33% of them were diagnosed with Adenocarcinoma, 35.61% were found diagnosed with squamous cell carcinoma and rest of 2.27% were Large Cell Carcinoma affected patients, which is showed in figure 3.2.
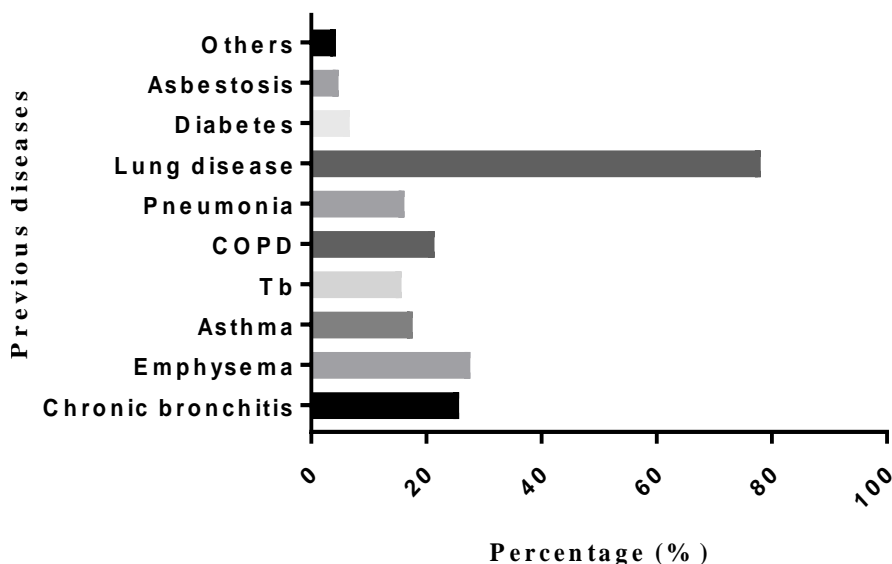


**Figure 3.3: Percentage of patients according to previous diseases.**

In terms of patients" previous history, 25.71% patients had previous history of chronic bronchitis, 27.62% patients had emphysema, 17.62% patients had asthma, 15.71% patients had tuberculosis, 21.43% patients had COPD, and 16.19% patients had pneumonia. In addition, 78.10% patients were diagnosed with lung disease previously, 6.67% patients had diabetes mellitus; 4.76% patients were suffering from asbestosis and 4.29% were diagnosed with other diseases.

Among the symptoms showed in figure 3.4, coughing is mostly reported symptom (94.29%) and chest pain is second most reported symptom which is 90.48%. In case of coughing different condition came out during the study. Patients who reported about coughing, among them 21.43% reported about dry coughing, 35.24% reported coughing with productive cough and 43.33% coughing with blood; which is showed in figure 3.5.
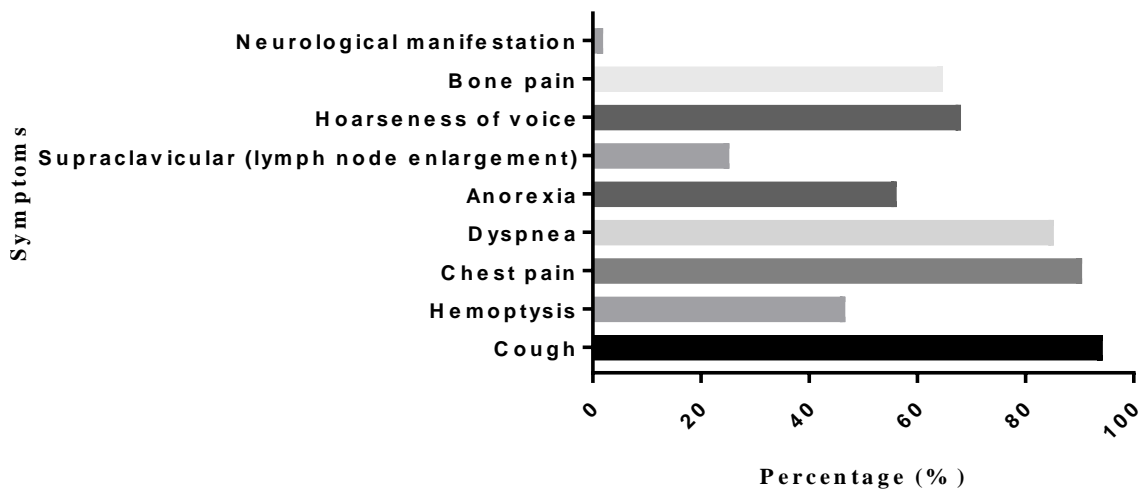
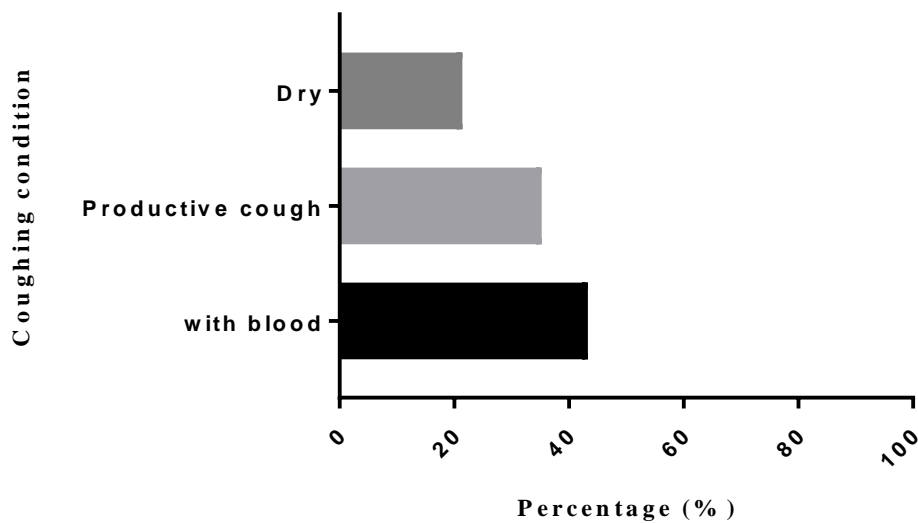**Figure 3.4: Percentage of symptoms reported by patients.**



**Figure 3.5: Percentage of coughing symptoms reported by patients.**

Hemoptysis was appeared in 46.67% patients, dyspnea was found 85.24%, anorexia was found common among 56.19% of patients and supraclavicular (lymph node enlargement) among 25.24% patients. Hoarseness of voice was appeared in 68.10% patients, bone pain was found in 64.76% and 1.90% were appeared with neurological manifestation.

In terms of diagnostic tests, fine needle aspiration cytology was performed mostly around 97.14% patients. Chest X ray was done for 64.29% patients and computed tomography scan was done for 64.76%, positron emission tomography test was only done for 0.476% patient. Among 210 patients 1.90% patient were tested with brain MRI , 3.33% patients with sputum cytology, 8.10% patients with bronchoscopy, ultrasonography test was done for 83.81% patients. In addition, hematology test was done for 69.52% patients; biochemistry test with 53.33% patients; thoracotomy and ECO were tested among 0.476% and 6.67% patients. Histopathology test and endoscopy was performed with 1.43% and 3.33% patients only; which is showed in figure 3.6.
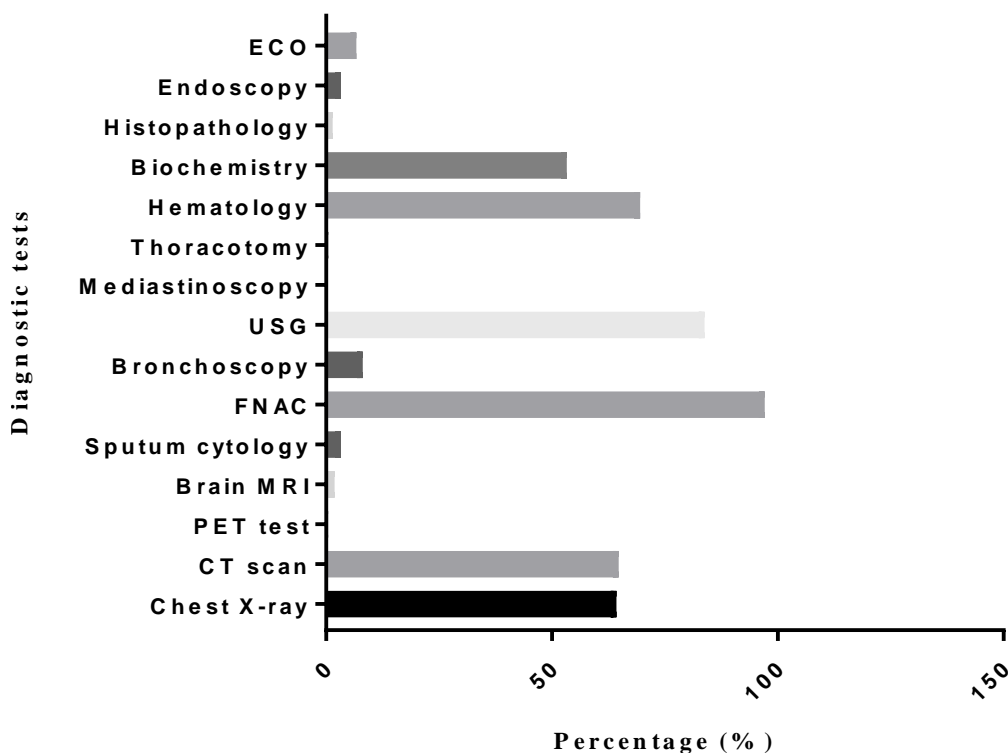


**Figure 3.6: Percentage of patients receiving different diagnostic tests.**
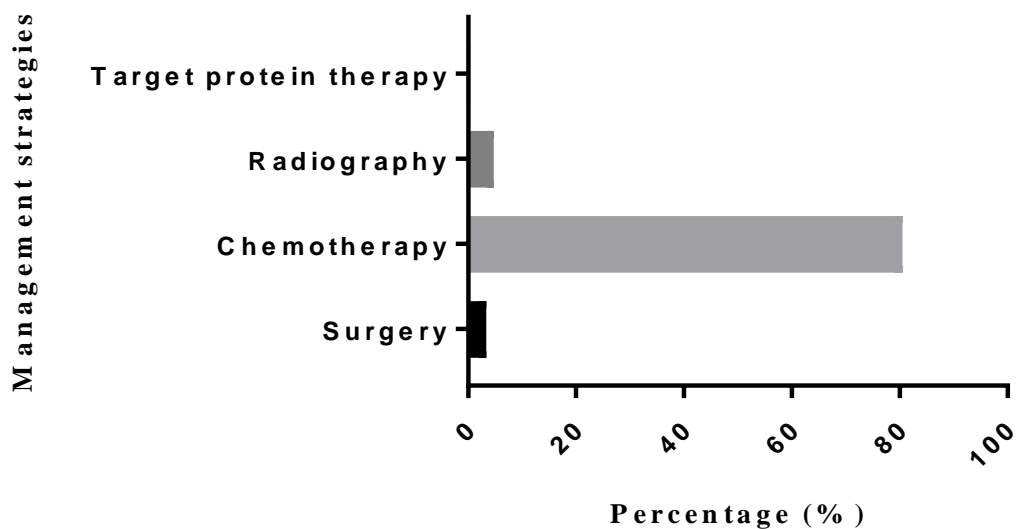
**Figure 3.7: Percentage of patients receiving different treatments.**

Considering treatment procedures that physicians followed to treat their patients among them chemotherapy was given on 80.48% patients, radiography was given on 4.76%, surgery had been received by 3.33% patients and rest 0.476% patient received target protein therapy, which is showed in this figure 3.7.
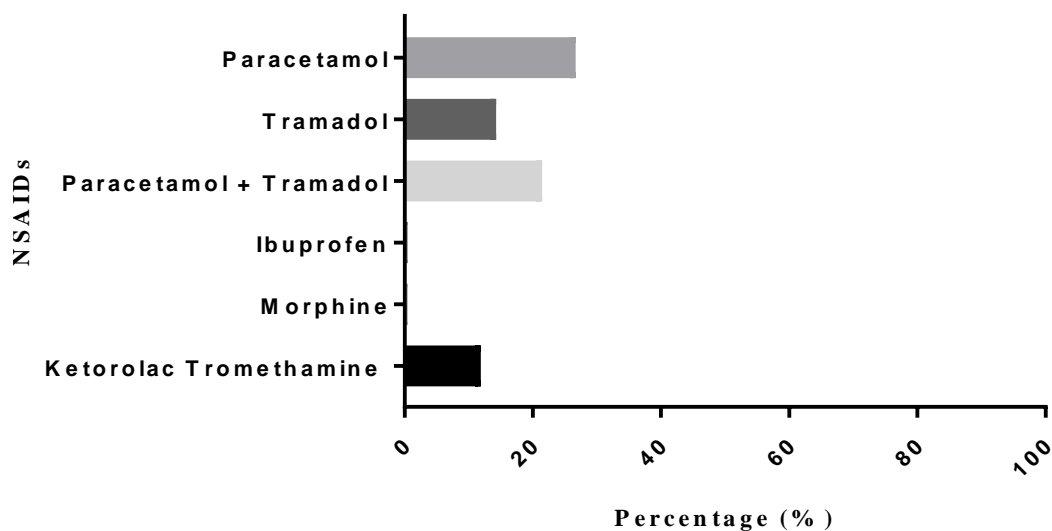


**Figure 3.8: Percentage of patients receiving analgesics.**

In figure 3.8, among various analgesic medications paracetamol was prescribed on 26.67% patients, tramadol on 14.29% patients and combination of paracetamol and tramadol was prescribed on around 21.43% patients. In addition, ketorolac tromethamine was received by 11.90% and ibuprofen and morphine were received by 0.476% and 0.476% patients.
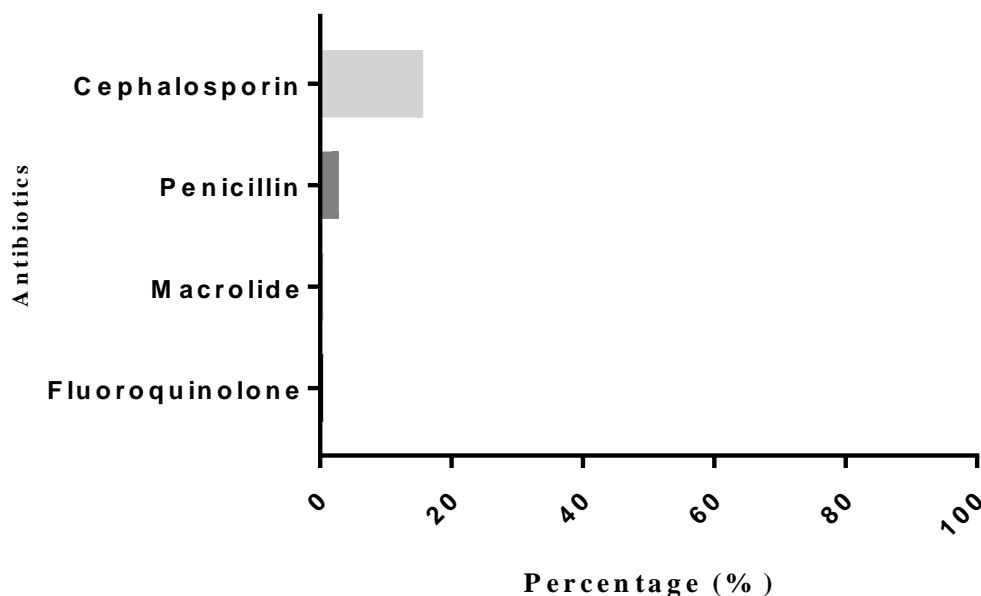


**Figure 3.9: Percentage of patients receiving antibiotics.**

In terms of antibiotic drugs (figure 3.9), among 210 patients; cephalosporin was individually received by 15.71% patients, penicillin was received by 2.86% patients, and lastly macrolide and fluoroquinolone was received by 0.476% and 0.467% patients.

An adequate number of corticosteroids variants were used basing on their mode of action and longevity of action. Among them interpretation of the figure 3.11, gives us insight that about 94.29% of the corticosteroids were elucidated intermediate action were only a diminutive number encircles the short acting drugs.
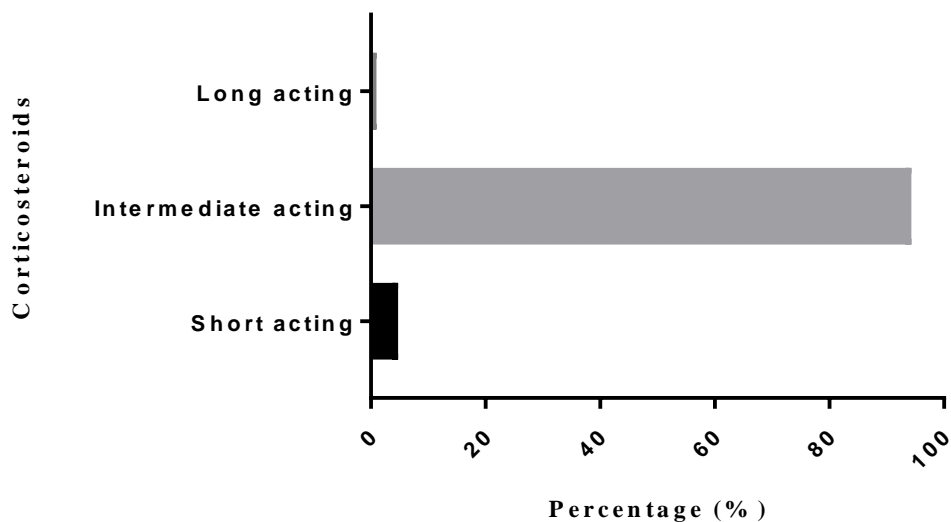
**Figure 3.10: Percentage of patients receiving corticosteroids.**

In figure 3.11, only two variants of antiemetic drugs were seen to be prescribed that being Domperidon and Ondansetron. In 55.71% cases Ondansetron was prescribed on the contrary a significant number of times Domperidon which encompasses about 44.29% of the total number of patients.
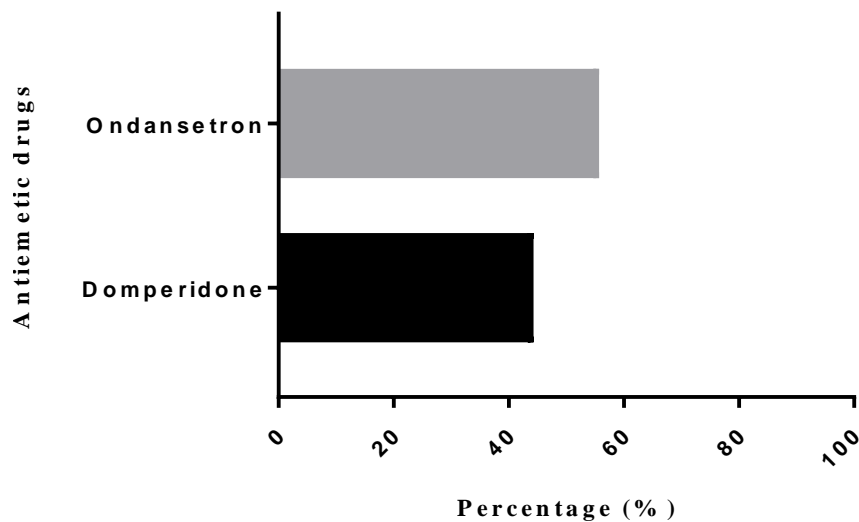


**Figure 3.11: Percentage of patients receiving antiemetic drugs**.

**Figure 3.12: Percentage of Patients receiving chemotherapy drugs.**

The figure 3.12, interprets the equal and maximized usage of two variants that being Cisplatin and Placitaxel (41.90%); and Cisplatin and Etoposide (40.95%) over the other variant which was Cisplatin and Gemcitabine combination was rare (0.476%) to be implemented at all.

# Chapter 4: Discussion

**Chapter 4: Discussion**

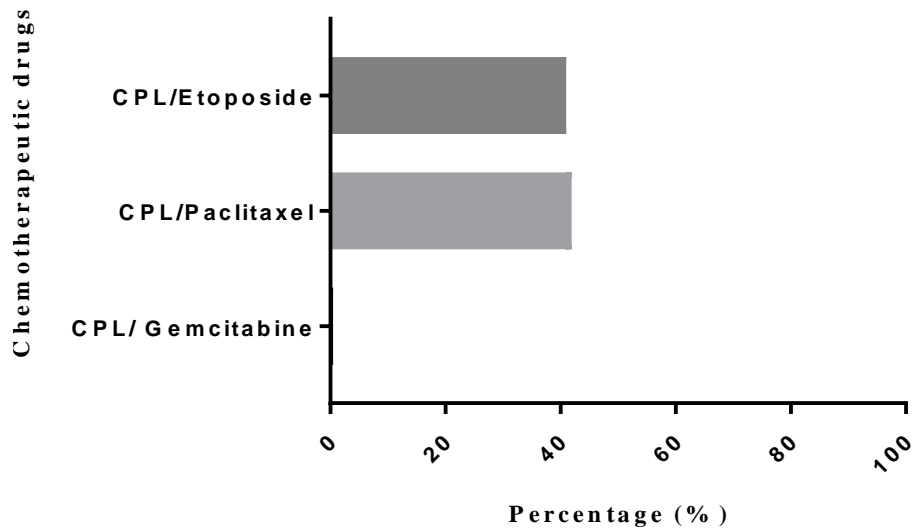This entire study conducted at the National Institute of Cancer Research & Hospital (NICRH), comprised of 210 in-patients of this hospital. These in-patients were diagnosed with carcinoma of lung. This survey based study was carried out to find; risk factors, symptoms, and treatment and management strategies of lung cancer in a tertiary hospital of Bangladesh. This study has been done due to lack of vast study on lung cancer in Bangladesh, though it creates the foremost mortality in the world. Through this study I wanted to identify the current situation and treatment strategies of lung carcinoma in Bangladesh which will ultimately help us to find out the lacking present in our health care support. Recovery of those lacking will progress better treatment strategies to extend survival rate and preserve the best quality of life of patients.

The socio-demographic profile study of the patients reflected that, among them percentage of the male patients was 89.522% and around 10.48% female patients. The ratio of male and female stands 8.54:1. India showcases a different scenario regarding male: female ratio, the proportion being roughly 3.5:1 (Noronha et al., 2012). According to this study, it can be stated that male patients develop higher risk than female patients. Considering age, risk of lung carcinoma was comparatively high after 40 years and greater frequency was found in the age group 51-60 years. On the other hand, the study shows decreasing value after 60 years. So the result shows after 60 years the risk of having lung carcinoma is comparatively less. The percentage of patients in this age group was around 41.43% and other data's have been shown in table 1. It has been observe that the percentage of lung carcinoma patients is quite higher in rural regions of Bangladesh rather than any other regions of Bangladesh, which were around 72.86% patients. In case of education level, most of the patients were illiterate (40.48%); detailed information have been given in table 3.1. Demographic data concerning age, residence and education in a similar study in India (Noronha et al., 2012), showed more or less similar results. On risk assessment, present study found 91.90% patients were exposed to hazardous environment in their working stations and exposure to dust was the most common scene among patients. Around 54.76% patients were found working for 6-10 hours regularly; other detailed information has been included in table 3.1.

In case of lung carcinoma, smoking is considered one of the greatest risks. This study found 73.33% patients were smokers; they left smoking when they were diagnosed with lung carcinoma. This study also found that around 5.24% patients were smokers and they could not quit smoking even after they had been diagnosed with lung carcinoma. This study also demonstrated around 51.42% patients were tobacco users which includes chewing tobacco, hookah and others; detailed information has been given in table 3.2.

In this investigation (Figure 3.1), among the three main types of lung carcinoma, non-small cell lung carcinoma prevailed in 62.86% patients, which was the majority.  This study found lower than the range from the American cancer society (2016) expects. In case of small cell lung carcinoma 27.62% patients were found, which is within the range 25-30% declared by the American cancer society (2016). This survey reveals 9.52% patients among 210 patients were diagnosed with Lung Carcinoid Tumor. Figure 3.2 displays the patients with Adenocarcinoma (subtype Of NSCLC) was around 58.33%; which was the majority subtype of NSCLC. In this study the percentage we found is slightly higher than the American cancer society's consideration which was around 40% (The American Cancer Society, 2016). Squamous cell carcinoma and large cell carcinoma according to the present study is, 35.61% and 2.27%. According to the American Cancer Society, the percentage is slightly higher than the range (25-30%) but large cell carcinoma is below than the range (10-15%).

This study also tried to find out any significant disease, the patient was diagnosed before or not. Knowing previous disease history of a patient is really necessary for early diagnosis of Lung Carcinoma. It is because the symptoms of lung carcinoma are quite similar to chronic bronchitis and pulmonary tuberculosis. If the physician becomes unable to find out previous disease history, it will delay the diagnosis of lung carcinoma. Moreover if the patient was previously diagnosed with COPD or other cardiovascular cases, he will be incapable for going through any surgery for treating lung carcinoma. In our investigation, chronic bronchitis had 25.71% patients, 27.62% patients had emphysema, 17.62% patients had asthma, 15.71% patients had tuberculosis, 21.43% patients had COPD, and 16.19% patients had pneumonia (Figure 3.3).

During this analysis of symptoms, persistent coughing was the most common. Around 94.29% of patients had conveyed about this symptom Figure 3.4. Patients reported about different condition they had gone through during coughing. Patients also reported about dry coughing; around 21.43%patients had suffered from dry coughing, 35.24% reported coughing with productive cough and 43.33% coughing with blood; which is showed in Figure 3.5. In lung carcinoma coughing is one of the major symptoms but some people do not experience coughing in initial stage of lung carcinoma. Experiencing a persistent cough can be distressing, and cough turn out to be more prevalent as lung cancer turn out to be more advanced. For coughing, palliative care is more preferable. Besides coughing, around 90.48% patients reported chest pain. Around 46.65% Patients conveyed about hemoptysis; dyspnea was reported by 85.24%, anorexia was common among 56.19% of patients and supraclavicular (lymph node enlargement) among 25.24% patients. Also, another symptom hoarseness of voice was reported by 68.10% patients, bone pain was found in 64.76% and 1.90% were appeared with neurological manifestation.

In this survey, diagnostic tests were also included to find out those physicians of that tertiary hospital is following proper screening to diagnose or to understand the level of development of lung carcinoma among patients. Around 97.14% patients were examined by fine needle aspiration cytology. Chest X ray was done for 64.29% patients and computed tomography scan was done for 64.76%, positron emission tomography test was only done for 0.476% patient. Here, physicians did not refer about PET test in some cases, but PET test is the only way to diagnose tumor where biopsy cannot be done. More details have been showed in figure 3.6. Chemotherapy is one of the effective steps for treating cancer; around 80.48% patients were treated with chemotherapy. Radiography was given for 4.76% and surgery had been received by 3.33% patients (Figure 3.7). Carcinoma growths cannot be evacuated totally by surgical procedure. Our study also found combination treatments such as after surgery, chemotherapy cycle was referred. Also, combination of chemotherapy and radiotherapy was given. This study found a single patient who was treated with EGFR inhibitor which is a target protein therapy.

Pain is a standout amongst the most common side effect of treatments in patients determined to have lung carcinoma. Pain can emerge due to chemotherapy, radiography or for surgical procedure. It can be seen from Figure 3.8, among different pain relieving medications paracetamol was recommended on 26.67% patients, Tramadol on 14.29% patients and combination of paracetamol and tramadol was endorsed on around 21.43% patients. Moreover, ketorolac tromethamine, ibuprofen and morphine were also seen prescribed by physicians. As with the prescription of antibiotic drugs, among 210 patients; cephalosporin was prescribed for 15.71% patients, penicillin was recommended to 2.86% patients, and ultimately macrolide and fluoroquinolone was received by only 0.476% and 0.467% patients respectively. Corticosteroids also had been prescribed for patients; it was widely prescribed by Physicians. Corticosteroids may assume a potential part in diminishing the risk of lung disease among individuals with COPD. Corticosteroids also can decrease markers of inflammation, such as, C-responsive protein and diminish inflammation of airways (Wang et al., 2016). Study found around 94.29% patients received intermediate acting corticosteroid (Dexamethasone) and short acting (4.76%) and long acting (0.95%) corticosteroids also had been prescribed by physicians. Antiemetic drugs strongly prevent nausea and vomiting caused by platinum based chemotherapeutic drugs. In figure 3.11, ondansetron and domperidon information has been displayed. The imperative part of this study is chemotherapeutic drug prescription (Figure 3.12). cisplatin is an alkylating agent and paclitaxel is a natural antimetabolite. Combinations of these two drugs were recommended for around 41.90% patients. Most prescribed regimens for the management of non-small cell lung carcinoma; and combination of cisplatin (alkylating agent) and etoposide (natural antimetabolite) was prescribed for 40.95% patients. Moreover, combination of cisplatin (alkylating agent) and gemcitabine (antimetabolite) was prescribed for 0.476% patients. Chemotherapy enhances rate of survival as well as quality of life.

# Chapter 5: Conclusion

**Chapter 5: Conclusion**

The scrutiny of this study concludes that we should be more careful; with the goal that lung carcinoma can be analyzed in introductory stage. As it does not demonstrate any symptoms in beginning time of it, general wellbeing checkup of lung function every year may demonstrate a compelling method to limit death rate. Moreover, according to this study as male patients were higher in number, they should be more careful about their smoking habits. Risk level also remains high with the increasing age number. People more than 40years age, keeps higher risk than below 40years in age. Smoking habit should be strictly handled by individual and by society. Previously diagnosed disease of patients should be kept in mind by the physicians so treatment strategies can be set in more effective way. Diagnostic tests should be done following international guidelines which will give them better understanding about patient"s condition. Skipping some tests might not give them clear understanding. Treatment strategy must be done considering the physical condition of patients and side effects should be handled providing palliative care. That will reduce their side effects without harming patients" health condition. Proper recognition of symptoms and contacting the physicians without wasting time can reduce the mortality rate and increase survival rate with better quality life.

# Chapter 6: Future work

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No previous cross sectional study on lung carcinoma has been found in Bangladesh. This study, first of its kind in our country reflects risk factors, symptoms, treatments and management strategies which were collected from the patients diagnosed with lung carcinoma. During this study, due to time limitations, follow up the patients was not possible. In our future plan, we wish to conduct another study to observe the rate of survival of patients after receiving the treatments. In addition, another study could be carried out to observe how increasing application of target protein therapy can prove beneficial to lung cancer patients.

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