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Lung Cancer - A Review

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ABSTRACT

Lung cancer is the prime cause of cancer death among both men and women according to WHO report 2.09 million cases globally. It is also the chief cause of cancer death among men and the second leading cause of cancer death among women worldwide. The lung cancer classified into two different types are small-cell lung cancers (SCLC) and non-small-cell lung cancers (NSCLC). Non-small cell lung cancer is more common than small cell lung cancer. Treatment of lung cancer may involve a combination of surgery, chemotherapy, targeted therapy, immunotherapy, and radiation therapy. Therapeutic recommendations depend on several factors, including stage and type of cancer. Low- and middle-income countries now account for more than 50 % of lung cancer deaths each year the responses to current standard therapies are poor except for the most localized cancers. The purpose of this review is to sum up the types, epidemiology, detection, metastasis and the treatment of lung cancer.

Key words: WHO, SCLC, NSCLC, Epidemiology, Metastasis

INTRODUCTION

Cancer is not just one disease, but a generic term used to encompass a group of more than two hundred diseases sharing common characteristics. Cancers (carcinomas) are characterized by their unregulated growth and spread of cells to other parts of the body [1, 2].

Lung cancer is one of the most common cancers we have and a large number of people die of this disease every year. The disease is often discovered in a late stage, but also in earlier stages lung cancer patients have worse outcome than patients with other cancers. Even without spreading to other organs, during stage I, the survival rate of lung cancer is under 70%. In comparison, for example, breast cancer there is 95% survival in stage [3]

First location of spread in most of the lung cancer patients is lymph nodes. Pre-operative assessment of spread to lymph nodes is important for consideration of further treatment. Lymph nodes will be removed during surgery to be analyzed using light microscopy for review. If there are areas of tumor cells in lymph nodes, the patient is offered additional chemotherapy. In most cases the spread of cancer to lymph nodes remains unnoticed due to insensitivity of the clinical methods and the patients have low survival rate even after the diagnosis. More advanced and sensitive methods are needed to help this out. Lung Cancer, like all other cancers, results from an acquired abnormality in the body's basic unit of life, the cell. Normally, the body maintains a system of control mechanisms for cell

growth, so that cells divide to produce new cells only when new cells are needed [4] Disruption of this control system results in an uncontrolled division and proliferation of cells that eventually forms a mass known as a tumor. Although it can arise in any part of the lung; 90%-95% of the lung cancers arise from epithelial cells, bronchi and bronchioles Sometimes it may also arise from the other supporting tissues within the lungs like blood vessels5. Lung cancers arise through a multistep process involving many genetic and epigenetic changes that includes damage of many key cell-cycle genes [6].

The alterations may accumulate in bronchial epithelium leading to clonal cell expansion. In some cancer patients clonal cells does not exist only as malignant cells but also as histologically normal appearing areas adjacent to tumors[7,8]

Some cancer patients demonstrate chromosomal abnormalities that damage tumor suppressor genes or have mutations in oncogenes [9] The mutations are common at chromosome regions 3p (that includes the FHIT, a tumor suppressor gene mutated in over 70% lung cancers), 9p (that includes p16INK4a, p19ARF genes, which are involved in the RB signaling pathway), 13q (RB) and 17p (TP53)[10]

Classification of lung cancer [11]

Lung cancers are broadly classified into two types:

Small cell lung cancers (SCLC)

Non-small cell lung cancers (NSCLC)

Small cell lung cancer (SCLC):

It is one of the most aggressive and rapidly growing lung cancers comprising 20% of all lung cancers [12] This type of cancer is strongly related to cigarette smoking. SCLC often metastasizes rapidly too many sites and is discovered during late stages. These cancers have a specific cell appearance under the microscope, the cells being smaller than the cells of Non-Small Cell lung Cancer [13] SCLC often remains central to the lung and grows along the wall of large bronchus [14] the cells multiply quickly and form large tumors that spread throughout the body [15]

Non-small cell lung cancer (NSCLC): It is the most common type of lung cancers and accounts for about80% of all lung cancers. NSCLC can be divided into three main types:

Adenocarcinomas: This is found in the gland of the lung that produces mucous and is the most common type of NSCLC in Women and nonsmokers [16] Adenocarcinomas comprise up to 50 % of NonSmall Cell Lung cancers and it arises in the outer, or peripheral, areas of the lung. Asubtype of it is Bronchioloalveolar Carcinoma that develops frequently at multiple sites in the lungs and spreads along the preexisting alveolar walls [17] Sometimes adenocarcinomas arise around a scar tissue and are associated with asbestos exposure [18]

Squamous Cell Carcinomas: These are also known as epidermoid carcinomas and accounts for about 30-40% of primary lung tumors [19]. This type of cancer grows commonly in the central areas around major bronchi in a stratified or pseudoductal arrangement. The cells have an epithelial pearl formation with individual cell keratinization [20]

Large Cell Carcinomas:

The tumor cells are large and show no other specific morphological traits. Sometimes they are referred to as undifferentiated carcinomas, and they are the least common type of Non-Small Cell Lung Cancer. [21]

The prognosis and treatment options depend on how widespread the disease is when diagnosed. The TNM classification system is used to subgroup the patients according to the extent of the disease. The method classifies patients based on the size of primary tumor (T), degree of spread to lymph nodes (N) or distant spread at the

time of surgery (M). TNM classification is crucial for further treatment options and must be present before treatment is initiated. [22]

T-stage

This stage considers mainly the size of the primary tumor. From TX (positive cytology, but unknown tumor) and T0 (not detected primary tumor) to T3 (tumor> 7 cm) and T4 (tumor invading surrounding organ areas).

N-stage

- NX - Regional lymph nodes cannot be assessed
- N0 - no lymph node metastases
- N1 – The cancer has spread to lymph nodes within the lung and/or around the area where the bronchus enters the lung (hilar lymph nodes) Metastasis to lymph nodes is on the same side as the primary tumor. [23]
- N2 – The cancer has spread to lymph nodes around the carina (point where the windpipe splits into the left and right bronchi) or in the space behind the breast bone and in front of the heart (mediastinum. Metastasis to mediastinal nodes is on the same side as the primary tumor. [24]
- N3 - Metastasis to nodes on the opposite side of the lungs.

M-stage

- MX - distant spread cannot be assessed
- M0 - no distant metastases
- M1 - distant metastases
- M1a - distant spread to the lung on the opposite side of the main tumor
- M1b - distant metastases. [25]

Epidemiology

Lung Cancer is predominantly a disease of the elder persons. Nearly 70% of people diagnosed with lung cancer are above 65 years of age and less than 3% of lung cancers occur in the people below age of 45 years. [26] The incidence of lung cancer is strongly correlated with cigarette smoking, with 90 % of lung cancers arising because of tobacco use. The five-year survival rate is up to 65% among the patients of NSCLC where the disease is detected in early stages but the long-term survival rate is 1% for those having metastases. The prognosis for adenocarcinoma is poorer than for squamous cell carcinoma, whereas for large cell carcinoma it is poorest. Lung cancer is one of the commonest cancers and cause of cancer related deaths all over the world. It accounts for 13 per cent of all new cancer cases and 19 per cent of cancer related deaths worldwide. There were 1.8 million new lung cancer cases estimated to occur in 20121. In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes, It is the commonest cancer and cause of cancer related mortality in men, with the highest reported incidences from Mizoram in both males and females (Age adjusted rate 28.3 and28.7 per 100,000 population in males and females, respectively. The time trends of lung cancer show a significant rise in Delhi, Chennai and Bangalore in both sexes [27]

Clinical manifestation of Lung Cancer

There are several symptoms connected with the presence of Lung Cancer that vary depending upon where and how widespread the tumor is:

Symptoms related to the primary tumor:

The growth and invasion of cancer in the lung tissues and other surrounding areas may interfere with breathing that leads to some symptoms such as

- Cough,
- Shortness of breath,
- Wheezing,
- Chest pain
- Coughing up blood (hemoptysis).
- In case the cancer has invaded nerves it may cause
- Shoulder pain that travels down the arm (Pan Coast's syndrome) paralysis of the vocal cords leading to hoarseness.

- If it invades to esophagus
- It may cause difficulty in swallowing (dysphasia).

Symptoms related to metastasis:

If the lung cancer has spread to bones

- It may cause excruciating pain in the bones.
- In case of spreading to bones it causes number of neurologic symptoms that may include blurred vision, headaches, seizures, or, symptoms of stroke such as weakness or loss of sensation in parts of the body. [28]

Paraneoplastic symptoms:

Most frequently lung cancers are accompanied by symptoms that result from production of hormone-like substances by the tumor cells.

- The paraneoplastic syndromes occur most commonly with SCLC but in some cases it may also be seen with some other type of tumor.
- A release of parathyroid hormone like substance is the most frequent paraneoplastic syndrome seen with NSCLC. The release of this substance leads to elevated levels of calcium in the blood stream [29]

Nonspecific symptoms:

Some nonspecific symptoms may be seen in lung cancer

Such as

- Weight loss,
- Weakness,
- Fatigue.
- Other psychological symptoms like depression and mood changes are also common.

No symptoms:

In around 25 % of patients with lung cancer the disease is discovered on a routine chest X-ray or CT scan as a solitary mass (coin lesion). Some of these patients with small, single masses show up no symptoms at the time cancer is discovered. [30]

Detection Strategies [31, 32]

Detection and Isolation of Lymph Nodes:

Lymph nodes are collected by the pathologists in the resection specimen by palpation and visual inspection. Following their detection lymph node biopsy is used to remove lymph nodes. The specimens are then formalin fixed and paraffin embedded. In this process lymph nodes are cut during the surgery of patients having lung cancer. The isolated lymph nodes are further analyzed for the presence or absence of tumor cells.

Detection of metastases in Lymph Nodes:

The sections of isolated lymph nodes are analyzed using various methods to follow the spread of the disease. Some of these methods are described below:

Routine analysis (H&Estainig)

Hematoxylin-eosin staining (H & E staining) is based on staining of tissue sections by hematoxylin and eosin dyes, making it easier to distinguish different types of cells visually. The method is not sensitive enough to detect small metastases but it can distinguish cancer cells from healthy cells by looking at the cells' shape, size and growth manner. Very small occurrences of cancer cells or single cells may be difficult to detect

Immunohistochemistry

Metastases in regional lymph nodes can also be detected using sensitive immunohistochemical (IHC) methods. The method is based on the binding of antibodies to epithelium-specific proteins on or inside the cancer cell. The cells are then stained and visually separated under microscope. Cancer cells are similar to the epithelial cells because they were originally epithelial cells, and these are not normally present in the lymph nodes.

Previous experiments have shown that this method is more sensitive than routine analysis based on H & E staining, since the color gives a greater contrast that makes the

cells be better separated from each other than with H & E staining.

Reverse-transcription PCR

Reverse transcription polymerase chain reaction (RT-PCR)-based detection of epithelium-specific mRNA is a fast and simple method for detecting metastases. The principle behind this method is that small amounts of cancer cells can be detected in clinical samples by amplifying specific mRNA that is expressed selectively in cancer cells, but not in the normal cells. The use of molecular markers in combination with RT-PCR defines a sensitive technology to detect even a small number of metastases in regional lymph nodes and blood.

Circulating Tumor Cells in Blood

Circulating tumor cells (CTCs) are the cancer cells that escape into circulator system from the primary tumor. While metastases directly lead to cancer recurrence, CTCs constitute a seed for metastases indicating the metastatic potential of the disease. Analyses of CTCs allow earlier detection of metastasis at an early stage. The molecular characterization of CTCs may enable the treatment to be more effective and the removal of CTCs from circulation minimizes the potential of metastases after surgery or therapy. Some previous studies have shown presence of CTCs in peripheral blood and bone marrow has a prognostic significance from many tumors. The measurement of burden of CTCs can be used to monitor treatment response or relapse

Enrichment methods

Density Gradient Separation: in this method CTCs and mononuclear cells are separated from blood cells and granulocytes on the basis of their density. CTCs have higher density (density <1.077 g/ml) than blood cells Immunomagnetic Separation: the method relies on the positive selection of CTCs from blood samples through their binding of antibodies coupled to magnetic beads targeting epithelial-specific antigens or tumor specific cell surface antigens

METASTASIS

Without treatment, lung cancer, almost without exception, eventually spread to other organs in the body, either via the lymphatic system (the system that produces, stores, and carries the cells that fight infections) or blood vessels. Spread to regional lymph nodes is the first and most common distribution system. Hematogen spread to other organs also occurs frequently, the most common localization is the other lung, bone, liver, adrenal glands and brain. Primary tumor can also spread by direct tumor growth into adjacent organs.

Regional Lymph Node Metastases

Metastasis means the spread of cancer. Cancer cells can break away from a primary tumor and enter the bloodstream or lymphatic system and spread to other parts of the body. When cancer cells spread and form a new tumor in a different organ, the new tumor is called a metastatic tumor. The cells in the metastatic tumor come from the original tumor. This means, for example, that if breast cancer spreads to the lungs, the metastatic tumor in the lung is made up of cancerous breast cells (not lung cells). In this case, the disease in the lungs is metastatic breast cancer (not lung cancer). Under a microscope, metastatic breast cancer cells generally look the same as the cancer cells in the breast.

Metastasis and Its impact

Regional lymph node involvement in lung cancer is heterogeneous. From micro metastases in intrapulmonary lymph nodes, coded as N1 (mi), to bulky contralateral nodal disease, coded as N3, the different situations in between vary in anatomic extent and prognosis. However, regardless of the amount of tumor burden in the regional lymph nodes, the present nodal staging of the tumor, node and metastases (TNM), described above, defines the extent

of nodal involvement solely via anatomic location.

Several studies have found that within every N category, there are prognostic modifiers. Thus, for pathologically staged I tumors, the number of removed lymph nodes at thoracotomy seems to have prognostic impact [28] the involvement of hilar (main bronchi) lymph nodes is closely associated with worse prognosis as compared to intrapulmonary lymph nodes in N1 patients. Other indicators of worse prognosis in these patients include macroscopic nodal involvement, involvement of multiple nodal and multiple nodal stations and metastatic involvement.

Some other factors of adverse prognosis include multilevel N2 disease and bulky disease, involvement of highest mediastinal lymph node and an extra nodal extension.

Treatment of lung cancer

There are several ways to treat lung cancer. The treatment depends on the type of lung cancer and how far it has spread. Treatments include surgery, chemotherapy, and radiation. People with lung cancer often get more than one kind of the following treatments

Surgery: Cancer tissues are removed by resection.

Chemotherapy [32]

This type of treatment involves the use of drugs to shrink or kill the cancer. The drugs could be tablets or medicines given through an IV (intravenous) tube chemotherapy drugs may be be classified as follows-

Alkylating agents (or) DNA- damaging agents

Alkylating agents act by chemically altering the cellular DNA. They add alkyl groups to the electronegative groups. Some examples include: Cisplatin, Oxaliplatin, Carboplatin, Chlorambucil, Cyclophosphamide, Mechloethamine and Melphalan.

Anti-metabolites

The anti- metabolic drugs function as the building blocks of DNA by imitating the role of purine or pyrimidine. These anti-metabolites stop cell division and are widely employed for their efficacy. Some of the important drugs include methotrexate, fludarabine, and cytarabine

Plant alkaloids and terpenoids

These plant-based chemicals block cell division by inhibiting microtubule function. The spindle fibers, made of microtubules, help to separate the chromatids during cell division. Examples are vinca alkaloids (derived from Catharanthus roseus) and taxanes.

The vinca alkaloids include: Vincristine, Vinorelbine, Vinblastine and Vindesine.

Podophyllotoxin

These plant-derived compounds are primarily extracted from Podophyllum peltatum (American mayapple). They prevent the cells from entering the G1 phase and also affects DNA synthesis. Two cytostatic drugs derived from podophyllotoxin are etoposide and teniposide

Taxanes

Taxanes are plant- based compounds that increase the stability of microtubules thereby preventing the separation of chromatids during mitotic anaphase.

Topoisomerase inhibitor

Topoisomerases are enzymes that are essential to maintain the topology of the DNA. Interfering with these enzymes prevents the normal functions of the DNA, such as

transcription, replication and repair

Type I inhibitors include irinotecan and topotecan

Type II inhibitors include amasacrine, etoposide phosphate and etoposide.

Antitumour antibiotics

Dactinomycin, daunorubicin, doxorubicin, idarubicin, and mitoxantrone are important drugs under this category.

Hormones
Prednisone and dexamethasone are examples of hormones which, in high doses, can damage lymphoma or lymphocytic leukemia cells.

Monoclonal antibodies
Monoclonal antibodies attach themselves to tumour- specific antigens, thereby increasing immune response to tumour cell.Examples are- rituximab, cetuximab, trastuzumab. Some monoclonal antibodies, like imatinib mesylate, a tyrosine kinase inhibitor, targets an abnormality in certain cancer cells. Imatinib targets the philadelphia chromosome common to Chronic Myeloid Leukemia(CML). It is also used to treat gastrointestinal stromal tumors.

Chemotherapy of lung cancer [33]
Chemotherapy for small cell lung cancer
This is the main treatment for small cell lung cancer. Doctors use it because
This type of cancer responds very well to chemotherapy
Small cell lung cancer tends to have spread beyond the lung when it is diagnosed
Chemotherapy drugs circulate in the bloodstream around the body. So, they can treat cells that have broken away from the lung tumor and spread to other parts of the body even if they are too small to see on scans.
This microscopic spread often happens even in the early stages of small cell lung cancer. Treated with a combination of chemotherapy drugs, including either cisplatin or carboplatin (Paraplatin). The combinations include
EP – cisplatin and etoposide
Carboplatin and etoposide
GemCarbo (gemcitabine and carboplatin)
Small cell lung cancer usually responds well to these treatments. For cancer that has come back after treatment, may use one of the treatments above or one of the following chemotherapy combinations
CAV (cyclophosphamide, doxorubicin and vincristine)
CAVE (CAV plus etoposide)
ACE (doxorubicin, cyclophosphamide and etoposide

Chemotherapy for non-small cell lung cancer
Chemotherapy to treat non-small cell lung cancer in the following situations
After surgery for early-stage cancer
Before, after, or alongside radiotherapy treatment
For locally advanced lung cancer or cancer that has spread

Chemotherapy after surgery
For early-stage NSCLC, chemotherapy after surgery can help to lower the risk of the cancer coming back. Combinations of chemotherapy tend to work better than single drugs. Usually combine cisplatin or carboplatin (Paraplatin) with at least one other drug such as

Vinorelbine
Gemcitabine
Paclitaxel (Taxol)
Docetaxel (Taxotere)
Doxorubicin
Etoposide
Pemetrexed

Chemotherapy and radiotherapy
Giving chemotherapy before or after radiotherapy can sometimes help to get rid of early stage NSCLC in people who can't have surgery. The chemotherapy drugs will usually be the same as mentioned above.
These treatments can also help some people with advanced non-small cell lung cancer to live longer even if they are not likely to be cured of their cancer. If you are fairly fit, your doctor may suggest combined treatment with radiotherapy and chemotherapy (chemoradiation)

Chemotherapy for locally advanced NSCLC or cancer that has spread [34]
Locally advanced lung cancer means that the cancer has spread beyond the lung into surrounding tissues or nearby lymph nodes. Metastatic lung cancer means the cancer has

spread into other organs or lymph nodes far away in the body. Chemotherapy can help to shrink or slow the growth of locally advanced or metastatic NSCLC. It can also help to control symptoms for some people.
treatment with either cisplatin or carboplatin combined with one of the following drugs
Gemcitabine (Gemzar)
Paclitaxel (Taxol)
Vinorelbine (Navelbine)
Docetaxel (Taxotere)
Pemetrexed (Alimta)

Radiation [35]
The term for the treatment of cancer with x-rays. It works by killing cancer cells and often used on its own to treat lung cancer. It may also be given as part of a combined treatment with surgery and/or chemotherapy. It is usually given from outside the chest (external radiotherapy) by directing x-rays at the area needing treatment. The machines that are most commonly used for this are called linear accelerators. However, radiotherapy can also be given by putting a small amount of radiation directly inside the lung (brachytherapy).

CONCLUSION

In this article, we have briefly explained about the Lung Cancer, It is the leading cause of cancer death and the second most diagnosed cancer in both men and women. Cigarette smoking is the primary cause of lung cancer. Lung cancer also can be caused by using other types of tobacco (such as pipes or cigars), passive smoke, being exposed to substances such as asbestos or radon, and having a family history of lung cancer. Lung cancers typically start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli. About 80% to 85% of lung cancers are NSCLC. The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma the only recommended screening test for lung cancer is *low-dose computed tomography*. Lung cancer is treated in several ways, depending on the type and stage of lung cancer. People with non-small cell lung cancer can be treated with surgery, chemotherapy, radiation therapy, targeted therapy, or a combination of these treatments. People with small cell lung cancer are usually treated with radiation therapy and chemotherapy.

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