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An Overview of Lung Cancer

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Abstract:- Lung cancer is characterised by unregulated cell growth. The most prevalent cancer killer worldwide is lung cancer. Lung cancer diagnoses and deaths are rising worldwide. Males and females over 70 have the highest lung cancer risk. Since 50% of lung cancer patients acquire a new cough, smokers or former smokers should be concerned. Lung cancer's complex pathogenesis is yet unknown. Smoking and carcinogen exposure can cause lung epithelial dysplasia. The most prevalent lung cancer diagnosis methods are flexible bronchoscopy and transthoracic sampling. Immunotherapy helps the immune system recognise and fight cancer cells as foreign intruders. Radiation and four to six chemotherapy cycles are usual for mediastinal or hilar lymph node LS-SCLC.

Keywords:- *Lung Cancer, Small Cell Carcinoma, Large Cell Carcinoma, PET-CT, Bronchoscopy, Programmed Death Receptor.*

I. INTRODUCTION

Lung cancer is characterised by unregulated cell growth. Physicians first documented lung cancer in the mid-1800s. It was rare before the outset of the 20th century, but by the end of the century, it had the highest mortality rate among men in over 25 industrialised nations. Since 1900, lung cancer has killed more people than all other cancers. It surpassed breast cancer as the leading cause of cancer deaths in women in developed countries in 2012.[1] The most prevalent cancer-related death worldwide is lung cancer, which rose rapidly after World War I due to increasing smoking. One reason is that it rarely develops symptoms until it's advanced. A recent study has shown that low-dose computed tomography (LDCT) lung cancer screening can cut mortality, and its use is rising. New standards help identify and grade lung cancer immediately after suspicion. We used to have no customised treatments, but now we treat by cancer subtype and stage. [2]

II. EPIDEMIOLOGY OF LUNG CANCER

Lung cancer diagnoses and deaths are rising worldwide. In 2018, it was the most frequent cancer and the leading cause of cancer deaths in men and women, with 2.09 million new cases (11.6%) and 1.76 million deaths (18.4%). This makes it the third most prevalent cancer type and the second largest cause of cancer death in women, surpassing the 2012 estimates of 1.8 million new cases and 1.6 million fatalities. Lung cancer incidence and demographic distribution vary widely among countries due to factors including smoking and economic development.[3] The recent growth in smoking in China, Indonesia, Eastern Europe, and Northern and Southern Africa is expected to increase lung cancer rates in developing regions, even if cancer statistics in developing nations are less reliable. Over half of lung cancer deaths occur in developing nations, and 80% of smokers live there. However, nations that "took up" smoking first and are implementing effective smoking cessation and avoidance programmes should see a decrease in lung cancer.[4] Countries like the US, UK, Nordic states, ANZ, Singapore, Germany, and Uruguay have high per capita incomes. Lung cancer in men accounts for most new cases worldwide, although female incidence are rising in most countries. Although breast cancer is the most common disease worldwide, lung cancer kills more women in the Americas, Western Europe, Australia, and New Zealand. Local smoking tendencies may explain these places' higher mortality rates. The WHO reports that 48% of men and 10% of women smoke worldwide. Men in rich and developing nations smoke approximately the same, whereas women in the former smoke much less. In places where women smoke less, non-smoking risk factors may affect lung cancer more. Even though Chinese women smoke less, charcoal, heating, and cooking smoke may explain why China's lung cancer rate is comparable to several European countries.[5,6]

- *Age*

Males and females over 70 have the highest lung cancer risk. Lung cancer is the most deadly cancer for men and women over 40 and 60. Lung cancer is most common in people aged 70–72, with a median death age of 72. Until 80–85, lung cancer mortality grows with age, but after that, heart disease kills both sexes more than cancer. A recent

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study found that young Hispanic and non-Hispanic white women aged 30–49 have a higher lung cancer rate than men. Smoking patterns likely contributed to the observed discrepancies, although the authors admitted that they did not entirely explain them. Lung cancer is more common in younger women, indicating a shift in "traditional" beliefs.[7]

➢ *Etiology*

The main cause of lung cancer is smoking. Most lung cancer cases (90%) are caused by smoking. Men who smoke are particularly vulnerable. Additional toxins, such asbestos, enhance risk. The amount of packs smoked annually does not affect lung cancer due to the complex interaction between smoking, environmental factors, and genetics. Secondhand smoke increases lung cancer risk 20-30%. Other than lung cancer, radiation treatment can treat breast cancer and non-Hodgkins lymphoma. Metal ions, polycyclic aromatic hydrocarbons, chromium, nickel, and arsenic enhance lung cancer risk. Independent of smoking, lung diseases including idiopathic pulmonary fibrosis increase lung cancer risk.[8]

Lung cancer is also linked to radon and asbestos. Asbestos exposure, especially at work, raises lung cancer risk, which varies by kind and amount. There is less information about asbestos exposure in non-work settings. The EPA's low-level acceptable nonoccupational asbestos exposure criteria say tenants in undisturbed buildings with no respirable particles pose no health risks. Radon-exposed uranium miners had a minor but considerable lung cancer risk. Radon can accumulate in homes from uranium and radium decay. A study of European research indicated that residential radon causes roughly 2% of lung cancer deaths in the region, notably among smokers.[9]

➢ *Clinical Manifestations*

Since 50% of lung cancer patients acquire a new cough, smokers or former smokers should be concerned. Recurrent pneumonia in the same anatomical region or repeated exacerbation of COPD may indicate a tumour. One-third to half of lung cancer patients develop dyspnea due to direct malignant airway, parenchymal, or pleural involvement. Patients may also have pneumothoraces, pleural effusions, pericardial effusions, and pulmonary emboli. Regional tumour invasion can induce chest pain, and recurrent laryngeal nerve involvement can produce hoarseness.[10] About 25% of lung cancer patients have hemoptysis, which is rarely serious. Superior vena cava syndrome, dysphagia, and arm/shoulder pain are some indications of intrathoracic spread caused by tissue mass effects. Patients can have symptoms from extrathoracic metastases.[11] The symptoms of lethargy, anorexia, and weariness are often unclear. Size and placement might cause neurologic issues from brain metastases, which are not necessarily painful. Bone metastases are more painful. Paraneoplastic disorders include bone metastases and parathyroid hormone-related protein release hypercalcemia. Cerebellar ataxia and Lambert-Eaton myasthenic syndrome are other neurologic syndromes.[12]

III. PATHOPHYSIOLOGY

Lung cancer's complex pathogenesis is yet unknown. Smoking and carcinogen exposure can cause lung epithelial dysplasia. Protein synthesis and genetic changes result from extended exposure. This disrupts the cell cycle and accelerates carcinogenesis. MYC, BCL2, and p53 mutations cause most small-cell lung cancer (SCLC). The most common NSCLC mutations are EGFR, KRAS, and p16.[11]

Histopathological classification, which uses cellular and molecular subgroups, helps diagnose and treat lung cancer. The WHO says histologic features, invasion depth, and dissemination mechanism are prognostic. Pathological evaluations should include air space tumour dissemination since it enhances recurrence after confined resections. The most recent WHO classification eliminated the clear cell, rhabdoid, and signet ring subtypes because they appear to be cytologic features that can occur in any adenocarcinoma. The World Health Organisation (WHO) classification relies on immunohistochemical labelling to classify cancers that may not show traditional cytologic markers under light microscopy. The 2015 WHO classification system reclassified poorly differentiated carcinomas as squamous cell carcinomas, adenocarcinomas with solid subtype, and neuroendocrine carcinomas based on thyroid transcription factor 1, p40, chromogranin, and synaptophysin expression.[13]

➢ *Precursor Glandular Lesions*

In situ adenocarcinoma and adverse adenomatous hyperplasia are examples. Usually 5 mm or smaller, AAH is a precursor to lung cancer. Whether mucinous or nonmucinous, adenocarcinoma in situ is a tiny, confined cancer under 3 cm. The "lepidic" pattern restricts alveolar development. It shows intact alveolar septae non-invasively.[14]

➢ *Adenocarcinoma*

Adenocarcinoma aetiology involves neoplastic gland growth, pneumocyte marker expression (TTF-1 with or without napkin), or intracytoplasmic mucin. The degree and structure of neoplastic gland development determine its mucinous or nonmucinous classification. Mucus-free subtypes include acinar, micropapillary, solid, lepidic, and papillary. Pathological confirmation of these subgroups is essential for prediction. Solid, micropapillary, and cribriform acinar nonmucinous adenocarcinomas have poor prognoses. Mucinous adenocarcinomas can be solid, micropapillary, papillary, or cribriform. According to the WHO, mucinous carcinomas should not be graded by tumour growth patterns. Rare adenocarcinomas include foetal, lymphoepithelial, enteric-like, and colloid. MIA is little, has no invasion (less than 5 mm), and grows epidemically. Like other precursor glandular lesions, it is present in solitary tumours under 3 cm. Adenocarcinoma with lepidic predominance invades above 5 mm. Previously known as mucinous bronchioloalveolar carcinoma, invasive mucinous adenocarcinoma encompasses non-MIA mucinous tumours. Mixed adenocarcinoma is diagnosed if the lesion

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has more than 10% mucinous and nonmucinous development.[15]

- *Adenosquamous Carcinoma*

Adenosquamous carcinomas are lung tumours with above 10% glandular and squamous cells. Even in Stage I severely resected lung cancers of this rare and aggressive subtype, adjuvant chemotherapy with whole-brain postoperative preventative irradiation is suggested due to the high risk of recurrence and brain metastasis.[14]

- *Squamous Cell Carcinoma*

Immunohistochemistry (IHC) can detect squamous cell disease as p40, p63, CK5, CK5/6, or desmoglein expression; cytology can show keratin and intercellular desmosomes. Squamous cell carcinoma has nonkeratinizing, keratinizing, and basaloid subtypes. Core necrosis and cavitation characterise squamous cell carcinomas. Squamous cell carcinoma can cause Pancoast tumours and hypercalcemia. Pancoast tumours are lung superior sulcus tumours. Pancoast tumours usually recur in the brain following surgery.[15]

- *Large-Cell Carcinoma*

Large cell carcinomas are malignant epithelial neoplasms without glandular, squamous, or neuroendocrine cytology. Small cell carcinoma-like cytology and immunohistochemistry showing p40 and TTF-1 are rare in them. Most LCCs are round or polygonal with conspicuous nucleoli. Large, featureless cytoplasmic cells define the organism. A diagnostic exclusion is LCC.[16]

- *Sarcomatoid Cancer*

Malignant epithelial components and sarcoma-like features characterise these rare carcinomas. Subtypes include pleomorphic cancer, lung blastoma, and carcinosarcoma.[17]

- *Small-Cell Carcinoma*

SCLC cells can be round, oval, or angulated and are about the size of a resting lymphocyte. They also have little cytoplasm. Non-visible nucleoli. Necrosis is common in SCLCs. They usually stain with synaptophysin or chromogranin. The WHO previously identified three SCLC cell subtypes: oat cell, intermediate cell, and mixed cell (SCLC with NSCLC component, squamous, or adenocarcinoma). However, evidence shows this categorization lacks clinical significance and predictive power.[18]

IV. BRIEF UPDATE ON THE EIGHTH EDITION TUMOR-NODE-METASTASIS

- *Classification of Lung Cancer*

The eighth edition of the lung cancer tumour-node-metastasis (TNM) classification has clinically significant advances. From 24 T descriptors, the "p" and "c" T-stage designators denote pathologic and clinical phases. A part-solid nodule's clinical size is dictated by its solid component, while its pathologic size is determined by its invasive component. Each cm of tumour size impacts prognosis in all T categories. The International Association for the Study of Lung Cancer recommends lung window tumour size measurement for valid radiographic T-stage evaluation. Minimally invasive adenocarcinoma is T1a, while carcinoma in situ (Tis) is non-metastatic. T2 and T3 endobronchial tumours had similar prognoses even with severe atelectasis and pneumonitis. Diaphragm-related T3 tumours are now T4. Like the N component, nodal disease must be quantified clinically and pathologically. In addition to seventh-edition N descriptors, prospective testing and validation use new subclass descriptors. A single pN1 node will be pN1a, while several will be pN1b. The designated node for a single pN2 nodal station that does not involve pN1 (skip pN2) is pN2a1, and for one that does, it is pN2a2. Finally, pN2b will affect several node stations.[19] Finally, the M component values metastasis number over location. Disease patterns characterise multi-lesion malignancies. With several primary tumours, each is classified by TNM. These eighth-edition TNM classification system upgrades will improve tumour categorization and stratification for lung cancer patients in future investigations.[20]

- *Diagnosis and Staging*

The most prevalent lung cancer diagnosis methods are flexible bronchoscopy and transthoracic sampling. Bronchoscopic access is used for middle-third lesions, while transthoracic access is used for outside-third lesions. Although bronchoscopy services are concentrated in big cities in India, the frequency of these procedures has increased significantly over the previous decade. Several pulmonologists offer endobronchial ultrasonography and other bronchoscopic services. Interventional radiologists commonly employ ultrasonography or CT scans for transthoracic sampling. Right now, just 1% of Indian hospitals offer interventional radiology. Both methods can reach lesions in the centre one-third of the chest, depending on patient features and skill. Radial EBUS, virtual bronchoscopic navigation, electromagnetic navigation, and ultrathin bronchoscopy can sample peripheral lesions. These bronchoscopic treatments are difficult to access. An emerging transthoracic sampling method is PET-guided biopsy. PET-CT's metabolic characterization can target live tissue during collection, improving diagnostic yield. Even with ambiguous invasive samples, PET-CT-guided biopsy diagnosed all patients with thoracic lesions.[21] In advanced diseases, collecting adequate samples for histologic and molecular characterisation might be problematic, especially in smaller centres with few specialists. A liquid biopsy for driver mutation detection may be useful if tissue is insufficient for other tests. Patients' local and distant lung cancer spread is often determined by noninvasive imaging staging. Patients with resectable diseases need noninvasive staging. Whole-body PET-CT scans are the best noninvasive lung cancer staging tool. Since PET-CT cannot detect brain metastasis, staging evaluations usually include brain magnetic resonance imaging. Radionuclide bone scans are paired with contrast-enhanced CT scans of the upper abdomen, chest, liver, and adrenals in centres without PET-CT. Most Indian hospitals employ chest and upper abdomen contrast-enhanced CT scans to determine the stage. PET-CT or magnetic resonance imaging of the brain is rarely done if

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a clinical exam shows no metastatic illness. Most individuals with resectable disease undergo mediastinal invasive staging. Due to the danger of false-positive findings, invasive mediastinal staging is usually used to confirm imaging nodal involvement. Histological evidence of nodal involvement is critical in tuberculosis-endemic countries like India. Only a small fraction of peripheral stage IA patients without hilar or mediastinal involvement on PET-CT should undergo invasive mediastinal staging. India takes a different strategy. Although PET-CT may not always have a 100% negative predictive value, some facilities perform invasive mediastinal staging on all resectable patients. Some centres limit invasive mediastinal staging to patients with PETCT-detected N3 disease and urge liberal neoadjuvant chemotherapy (NACT) for all N2 patients.[21,22]

V. TREATMENT

➢ *Treatment of Non-Small Cell Lung Cancer (NSCLC)*

- *Stage I*

The best treatment for stage 1 NSCLC is surgery. Lobectomy or pneumonectomy with mediastinal lymph node sampling is recommended. 78% of IA patients survive 5 years, but 53% of IB patients do. Wedge resection or segmentectomy is less invasive than lobectomy or pneumonectomy for patients without enough lung capacity. Downside: increased local recurrence rate, although survival is unchanged. No evidence suggests adjuvant chemotherapy or local postoperative radiation therapy improves stage I cancer outcomes.[23]

- *Stage 2*

Stage IIA lungs survive and 36% of stage IIB lungs. Adjuvant chemotherapy following surgery is recommended. The chest wall should be removed immediately if a cancer spreads there. The pancoast tumour is unique among stage II tumours. This superior sulcus-originating disease is usually diagnosed at stage IIB or IIIA. Neoadjuvant chemotherapy with etoposide and cisplatin, radiation, and tumour excision is the conventional treatment for Pancoast tumours. Whether the resected specimen had microscopic disease affects overall survival, which ranges from 44% to 54%.[22]

- *Stage III*

This most diverse category includes tumour invasions and lymph node involvements.

Stage IIIA disease with N1 lymph nodes is best treated with surgery. Many patients are diagnosed with N2 diseases during resection, which is disappointing. The current plan is to perform surgery and then provide adjuvant chemotherapy. Patients with stage IIIA tumours and N2/N3 lymph nodes disagree on therapy. When performance is good and weight is stable, concurrent chemo-radiotherapy works well. Concurrent chemo and radiation can cause severe esophagitis and poor tolerability. Sequential treatment reduces side effects. Only 20% survive the fifth year, compared to 40% to 45% during the first two.

The normal treatment for T4 tumours is chemoradiation. Surgery is an option for T4 N0-1 carinal tumours. Cardinal resection has a 10%–15% operative mortality and a 20% survival rate. Surgery alone had a 20% five-year survival probability for T4 tumours with ipsilateral nonprimary lobe nodules and no mediastinal invasion.

Stage IIIB cancers are treated with chemo-radiotherapy like unresectable stage IIIA tumours. Some patients may choose surgery after induction chemo-radiotherapy. The survival rate of IBS patients is unknown because investigations on IB cancer survival included incurable IA tumours.[24]

- *Stage IV*

Since stage IV disease is incurable, treatment aims to improve survival and reduce symptoms. Only 10% to 30% of cancer patients respond to chemotherapy, and five-year survival rates are 1% to 3%. Patients with functional performance status can select one- or two-drug chemotherapy. Cancer survival is slightly better with chemotherapy. A small number of non-squamous non-small cell lung cancer (NSCLC) patients without hemoptysis or brain metastases may benefit from bevacizumab, a VEGF inhibitor.

➢ *Targeted Therapy for NSCLC*

In the 2000s, scientists discovered that some mutations code for proteins needed for cell growth and DNA replication. These alterations were called "driver mutations," and if we could halt them, lung cancer patients may survive. Currently, all advanced NSCLCs are examined for these mutations. Each mutation has a unique inhibitor:

- The EGFR mutation can be prevented by erlotinib, gefitinib, and afatinib.
- ALK inhibitors include crisetinib, ceritinib, and alectinib. Similar structure to ROS-1 mutation. Crizotinib was approved by the FDA to treat ROS-1-mutated cancers.[25]

➢ *Immunotherapy for NSCLC*

Immunotherapy helps the immune system recognise and fight cancer cells as foreign intruders. Checkpoints reduce autoimmunity, in which the immune system destroys its own. Cancer cells hijack these defences and instruct the immune system to ignore them. Recent interest has focused on programmed death receptor 1 (PD-1). PD-1 downregulates T-cells to promote self-tolerance. However, it reduces the immune system's ability to combat tumours. PD-1 interacts with PD-L1 and L2. Activated T-cells become inactive after binding. Antibodies have only been approved for PD-1 and PD-L1. They prevent activated T-cell inactivation by binding to PD-L1 or directly blocking PD-1. The IgG4 monoclonal antibody nivolumab targets PD-1. According to FDA approval, platinum-based chemotherapy can treat squamous and non-squamous NSCLC after progression. Patients with high or low PD-L1 expression can use it. Pembrolizumab targets PD-1 as an IgG4 monoclonal antibody. Patients with pre-treated metastatic NSCLC who express more than 50% PD-L1 and no EGFR or ALK

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mutations are eligible for this medication. It works against metastatic non-squamous NSCLC with less than 50% PD-L1 when combined with carboplatin and pemetrexed. The IgG1 antibody atezolizumab targets PD-L1. Metastatic, progressive NSCLC can be treated with it during or after platinum-based chemotherapy.[26] Patients with EGFR and ALK mutations who do not respond to targeted therapy may benefit. Immune treatments cannot include bevacizumab. It is an anti-angiogenesis antibody that blocks VEGF-A. It is usually used with platinum-based chemotherapy for non-squamous NSCLC. It is not advised for squamous cell non-small cell lung cancer due to severe and often fatal hemoptysis. It treats brain, kidney, colon, and breast malignancies.[24]

- *Treating Small Cell Lung Cancer*

SCLC is treatable, however, it recurs frequently. SCLC treatment severity increases with disease progression.

- *Treatment of Limited-stage Small Cell Lung Cancer*

Adjuvant chemotherapy is given to stage I LS-SCLC patients after lobectomy. SCLC appears as peripheral nodules rather than mediastinum or hilar lymph nodes. Be cautious when ruling out lymph node involvement. If PET-CT could not reveal lymph node size or FDG uptake, EBUS bronchoscopy or mediastinoscopy should be used.

Radiation and four to six chemotherapy cycles are usual for mediastinal or hilar lymph node LS-SCLC. Radiation is recommended to prevent recurrence since over 80% of SCLC will return locally without it. Multiple treatment options include concurrent, alternate, and sequential chemo-radiotherapy. Concurrent and alternate paths yield slightly better results but are more hazardous. Sequential treatment produces far fewer negative effects.

Remission patients receive prophylactic whole-brain radiation. Survival improves, and symptomatic brain metastases are rarer.[25,26]

- *Treatment of Extensive-stage Small Cell Lung Cancer (ES-SCLC)*

Symptoms of extensive stage small cell lung cancer include metastasis to other organs, malignant fluids around the heart or lungs, and involvement of lymph nodes on the opposite side. Platinum-based chemotherapy treats it. Prophylactic whole-brain irradiation after radiation treatment is recommended for 50%–60% remission rates. The typical survival time after ES-SCLC diagnosis is eight to thirteen months, and less than 5% survive the second year.[27]

VI. CONCLUSION

In conclusion, lung cancer is the greatest cause of cancer death worldwide, with smoking being the main cause but other factors contributing. Early detection and personalised therapy are essential to reducing lung cancer mortality. The text also discusses lung cancer's clinical symptoms, pathogenesis, histological categorization, and TNM classification advancements.

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