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Review Article

UNDERSTANDING LUNG CARCINOMA: PATHOGENESIS, DIAGNOSTIC APPROACHES, AND THERAPEUTIC ADVANCES

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Abstract: *Lung carcinoma, originating in the bronchi or lung parenchyma, remains a leading cause of cancer-related morbidity and mortality worldwide. It accounts for approximately 2 million new cases and 1.8 million deaths annually. Factors such as tobacco consumption, environmental pollutants, genetic predispositions, and occupational exposures contribute significantly to its increasing prevalence. Lung carcinoma is broadly classified into small and non-small cell carcinoma, with subtypes such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. The pathogenesis of lung carcinoma involves genetic mutations, including alterations in tumor suppressor genes and proto-oncogenes such as K-RAS, EGFR, and ALK, leading to unchecked cell proliferation. Advances in genomic profiling and biomarker discovery have enabled the development of targeted therapies, such as EGFR inhibitors and tyrosine kinase inhibitors, revolutionizing the treatment landscape. Diagnosis relies on imaging techniques like CT and PET scans, histopathological analysis, and molecular tests. Early detection and personalized medicine approaches have improved survival rates, though challenges such as drug resistance and limited access to advanced treatments persist. Preventive measures, including smoking cessation programs and public health initiatives, remain critical in reducing lung carcinoma incidence. Palliative care plays a vital role in managing symptoms and enhancing the quality of life for advanced-stage patients. Despite advancements in therapeutic strategies, the prognosis varies significantly depending on cancer type, stage, and metastasis. Integrating immunotherapy and precision medicine holds promise for further improving patient outcomes.*

Keywords: Lung carcinoma, pathogenesis, genetic mutations, diagnostic approaches, targeted therapy, personalized medicine, immunotherapy

Introduction

Lung carcinoma refers to tumors that originate in the bronchi or lung parenchyma (1). It is the leading cause of incidence and death worldwide (2). The rates of occurrence and death due to lung carcinoma have been increasing consistently since the 1930s (3). It is estimated that lung carcinoma accounts for 2 million new cases and 1.8 million deaths across the world. It is the second most common cancer in both males and females, after prostate cancer and breast cancer, respectively. In the developing world, with the rise in industrialization and more access to tobacco, the occurrence of lung carcinoma has risen. The mean age of diagnosis is 70 years. Males are more likely to be diagnosed with lung carcinoma as compared to women because of increased consumption of tobacco. Among females, lung carcinoma occurs because of mutations of epidermal growth factor and the effects of estrogen (2). Other risk factors for lung carcinoma include exposure to asbestos, radon, domestic biomass fuels, and radiation; air pollution; poor diet and nutrition; and genetic factors (4). By 2050, it is projected that the burden of cancer will be twice, with lung carcinoma being first on the list (5). Lung carcinoma was a very rare condition about 150 years ago. Only 1% of all malignancies observed at autopsy in the Institute of Pathology at the University of Dresden, Germany, in 1878 were malignant lung tumors. (6). It was considered a reportable ailment a century ago, but today, it is the leading cause of cancer-related fatalities globally.

Pathogenesis:

Tumor suppressor genes can either be inactivated or activated, which causes unchecked cell proliferation and replication in the lungs and starts the pathogenesis of lung cancer. These genetic changes can result from a variety of causes, including exposure to toxins or inheritance from parents (12).

Specific gene mutations are linked to the pathophysiology of each type of lung cancer.(13) For instance, 10–30% of lung adenocarcinomas are caused by mutations in the K-ras proto-oncogenes, whereas mutations in the EML4-ALK tyrosine kinase.. cause 4% of non-small-cell lung carcinomas. (12).

The epidermal growth factor receptor (EGFR) controls angiogenesis, apoptosis, cell division, and tumor invasion. EGFR inhibitors are used in treating non-small cell lung carcinoma because genetic alterations that cause the overexpression of EGFR are frequently found in this illness. Additional genes that may contribute to the pathogenesis of lung cancer include BRAF, c-MET, NKX2-1, LKB1, and PIK3CA (12).

The pathogenesis of many occurrences of the disease is also closely linked to smoking and the other risk factors mentioned above. Cigarette smoke is known to include 70

recognized carcinogens (11), And there may be other ones that are not yet known. These include polonium-210, 1,3-butadiene, NNK, and benzopyrene (12).

Classification:

Lung carcinoma is broadly divided into two types:(14)

- Small Cell Carcinoma
- Non-Small Cell Carcinoma

Non-Small Cell Carcinoma is further divided into the following three types:(14)

- Adenocarcinoma
- Non-small Cell Carcinoma
- Small Cell Carcinoma

Morphology:

The initial lesions of lung carcinomas are usually tiny, hard, and gray-white. They can start as intraluminal masses, spread into the bronchial mucosa, or grow into the lung parenchyma next to them. (15).

Adenocarcinoma: Adenocarcinomas occur primarily in the periphery, though they can also occur closer to the hilum. It grows slowly, forms smaller masses, and spreads widely early on. Solid, acinar (gland-forming), papillary, mucinous (multifocal, pneumonia-like consolidation), and multifocal are some of the ways it can grow. Utilizing immunohistochemical stains for indicators such as TTF-1, a transcription factor that is comparatively specific for lung cancer, the diagnosis may be made (15).

Squamous Cell Carcinoma Typically, squamous cell carcinoma begins in the middle of the major bronchi and first spreads to adjacent hilar nodes. Dissemination occurs later on, away from the chest cavity. Core necrosis in big lesions can lead to cavitation. The condition that often precedes cancer in situ is bronchial squamous metaplasia or dysplasia. Cytologic sputum smears, bronchial lavage fluids, or brushings may reveal aberrant cells; however, at this stage, the lesion is asymptomatic and not evident on radiographs. Once a well-defined tumor mass obstructs the lumen of a central bronchus, the little tumor eventually reaches a symptomatic stage, often resulting in distal atelectasis and infection. Concurrently, the lesion spreads to the nearby lung. According to histologic analysis, these tumors range from poorly differentiated neoplasms with few squamous cell features to well-differentiated neoplasms with intercellular bridges and keratin pearls. (15).

More extensive Cell Carcinoma: Large cell carcinoma is an undifferentiated epithelial tumor that does not exhibit glandular or squamous differentiation and does not exhibit the cytologic characteristics of neuroendocrine carcinoma. Tumor cells are characteristic of having large nuclei, noticeable nucleoli, and modest amounts of cytoplasm. (15).

Small Cell Carcinoma: A pale grey tumor in the center that enters the lung parenchyma is the typical appearance of small cell carcinoma. There are metastases to the hilar and mediastinal lymph nodes. Cancer cells have spherical to rounded, fusiform, or round morphologies, with many mitotic figures, scant cytoplasm, and coarsely granular, salt-and-pepper-like chromatin. Owing to their fragility, the tumor cells often show signs of fragmentation and "crush artifact" in small biopsy samples, which results in the release of DNA-stained blue (Azzopardi effect). The expression of several neuroendocrine markers by these malignancies includes synaptophysin, chromogranin, and CD56. They could also create polypeptide hormones, which are responsible for paraneoplastic illnesses. Are attributes exclusive to tumor cells? (15).

Signs and symptoms:

The signs and symptoms include:

- A cough that doesn't go away or gets worse over time(16)
- Difficulty in breathing (dyspnea)(16)
- Chest pain or discomfort(16)
- Wheezing(16)
- Blood in cough (hemoptysis)(16)
- Hoarseness(16)
- Loss of appetite(16)
- Unexplained weight loss(16)
- Fatigue(16)
- Shoulder pain(16)
- Bone pain(17)
- Headache(17)
- Swelling of the face, neck, arms, and chest (superior vena cava syndrome)(16)
- Small pupil and drooping eyelid in one eye with little or no sweating on that side of your face (Horner's syndrome)(16)
- Difficulty in swallowing (dysphagia) and pain during swallowing (odynophagia)(18)
- Fingers becoming more curved or their ends becoming larger (finger clubbing)(18)
- Chest infections(18)
- Paraneoplastic syndromes, which include paraneoplastic endocrine syndromes (such as syndrome of **i**nappropriate anti-diuretic hormone, Cushing syndrome, and hypercalcemia) and paraneoplastic neurological syndrome (such as lambert-eaton syndrome, paraneoplastic cerebellar degeneration, and paraneoplastic limbic encephalitis)(19).

Diagnosis:

Lung cancer is diagnosed by using the following tests:

Blood tests: Blood tests are not used to diagnose lung carcinoma, but they can be used to check how the organs and other parts of the body are working (20).

Imaging techniques: The following imaging techniques are used to diagnose lung carcinoma:

- Chest X-ray(21)
- Computed Tomography Scan(21)
- Magnetic Resonance Imaging(22)
- Positron Emission Tomography Scan(21)

Sputum Cytology: Sputum, which is coughed up from the lungs, can be examined under a microscope and used to detect cancer cells.(22).

Bronchoscopy and Biopsy:

Biopsy: Techniques employed to determine the extent of lung cancer's spread or to make an initial diagnosis include (20).

- **Needle biopsy:** During this operation, the physician uses a needle to take tissue or fluid samples for testing.

- **Bronchoscopy, thoracoscopy, or video-assisted thoracic surgery (VATS):** To examine and remove tissue samples from specific areas of your lungs.
- **Thoracentesis:** This technique allows a medical professional to remove a fluid sample from your lungs so that it may be tested.
- **Endoscopic esophageal ultrasonography or endobronchial ultrasound:** A provider uses these techniques to examine and biopsy lymph nodes.
- **Mediastinoscopy or mediastinotomy:** To examine and collect tissue samples from the mediastinum, the space between your lungs.

Molecular tests: Gene mutations can occur in lung carcinoma and can be used for detection. These genes include (23).

- KRAS
- EGFR
- ALK
- ROS1
- BRAF
- RET
- MET
- HER2
- NTRK

Differential Diagnoses:

Differential diagnoses include (1).

- Bacterial pneumonia
- Bronchitis
- Mycoplasmal pneumonia
- Pleural effusion
- Pneumothorax
- Tuberculosis
- Viral pneumonia
- Fungal pneumonia

Staging:

TNM is a staging method used by clinicians for lung cancer. These three factors include (24).

- T indicates the tumor's (cancerous tissue's) size.
- N explains how the cancer migrated to the lymph nodes.
- M explains whether metastasis, the spread of cancer to another part of the body, has occurred.

Palliative care:

Hemoptysis, weariness, appetite loss, dyspnea, and weight loss are among the many symptoms that a large percentage of lung cancer patients encounter. Patients with metastatic non-small cell lung cancer (NSCLC) who received early palliative care in addition to normal oncologic care had higher median survival, less depressive symptoms, a better quality of life, and fewer needs for aggressive end-of-life care. Megestrol acetate (MA), an appetite stimulant, is one of the adjuvant medicines that has shown promise in treating cancer-related anorexia (CRA) and improving quality of life (28).

Prevention:

The process of lung carcinogenesis is long-term and involves multiple genetic, cellular, and local tissue alterations. When preneoplastic cells develop into malignant cells, they experience modifications such as damage to DNA, changes in genetic and epigenetic patterns, and relentless cell division and invasion beyond the boundaries of local tissues. These changes are referred to as metastases. Exposure to certain carcinogens alters normal cells, even before invasive malignant tumors show clinical symptoms. The largest risk factor for lung cancer is smoking cigarettes, with an attributable risk of 85% to 90% and a relative risk of 20 to 25. The three primary risk factors for lung cancer that are still present are ambient tobacco smoke, occupational exposure to asbestos and radon, and diet. Lung cancer mortality can be reduced by reducing or quitting smoking, treating the disease, chemoprevention, and early detection. Only programs aimed at preventing and quitting smoking have been shown to reduce the incidence of lung cancer among all of these. (29).

Prognosis:

Relative survival rates by types:

Non-small-cell lung cancer (NSCLC): This kind of lung cancer accounts for around 90% of cases. The database maintained by the National Cancer Institute classifies malignancies according to the extent of tumor dissemination. These relative survival rates represent the typical percentages of patients who survive five years after diagnosis. These include the following (30).

- **Localised:** 60% (cases are localised or limited to one lung)
- **Regional:** 33% (cancer has moved to lymph nodes or outside the lung)
- **Distant:** 6% (cancer has spread to other parts of the body, including the brain, other lung, and bones)
- **All stages:** 23%

Small-cell lung cancer (SCLC): This lung carcinoma is more aggressive while being rare. The survival rates are the following (30).

- **Localised:** 29%
- **Regional:** 15%
- **Distant:** 3%
- **All stages:** 6%

Relative survival rates by stages: These rates represent the actual proportion of a sample of individuals who received a diagnosis of either SCLC or NSCLC and were alive at two and five years of age. Survival rates by stages are the following (30).

- **Stage IA1:** 97% (2 years); 90% (5 years)
- **Stage IA2:** 94%; 85%
- **Stage IA3:** 92%; 80%
- **Stage IB:** 89%; 73%
- **Stage IIA:** 82%; 65%
- **Stage IIB:** 76%; 56%
- **Stage IA:** 65%; 41%
- **Stage IB:** 47%; 24%
- **Stage IC:** 30%; 12%

Advancement in lung carcinoma research:

Lung cancer is a problematic ailment that necessitates specific therapy procedures because of its wide variety of types and stages. With an emphasis on recent findings and their implications for prevention, diagnosis, and therapy, this in-depth examination explores the intricate subject of lung cancer research. The development of

tailored medications that successfully target cancer cells while minimizing harm to healthy tissues has been made possible by genomic profiling and biomarker discovery, ushering in the era of personalized medicine. Investigating the link between pulmonary tuberculosis and lung cancer could lead to the discovery of possible pathways connecting these two conditions. Early therapies are essential since patient outcomes have significantly improved with early detection technology like low-dose computed tomography scans. A common surgical procedure for early-stage lung cancer is segmentectomy, which has grown in popularity recently. Immunotherapy, a revolutionary approach, targets and eliminates cancer cells by harnessing the body's immune system. When paired with other established therapies like chemotherapy and targeted medications, immunotherapy is more effective in treating the heterogeneity of the disease and overcoming drug resistance. The development of targeted therapies, such as tyrosine kinase inhibitors, enables patients to get personalized treatment regimens by applying precision medicine and genomic profiling. Interdisciplinary collaboration and innovative technologies such as artificial intelligence are essential in light of persistent issues like drug resistance and limited access to innovative treatments. Notwithstanding challenges, ongoing interdisciplinary collaboration and technological advancements offer hope for a future in which lung cancer is treated and prevented, reducing the global burden on patients and healthcare systems (31).

Declarations

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