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Advancements in Diagnosis, Treatment, and Management of Lung Cancer: A Review Article

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Abstract *— The objective of this review is to provide a comprehensive overview of the recent advancements in the diagnosis, treatment, and management of lung cancer, highlighting the latest developments and innovations in the field. A systematic literature review was conducted using databases such as PubMed, Scopus, and Web of Science to gather relevant articles, clinical studies, and reviews published in the last decade. The search was focused on advancements in diagnostic techniques, treatment modalities, targeted therapies, immunotherapy, and supportive care in lung cancer. The review highlights significant advancements in the diagnosis of lung cancer, including the role of advanced imaging techniques, molecular biomarkers, and minimally invasive biopsy methods. In terms of treatment, the review discusses the latest developments in surgical procedures, chemotherapy, radiation therapy, targeted therapy, and immunotherapy, emphasizing the emergence of personalized medicine and novel therapeutic approaches. Additionally, the review addresses the importance of supportive and palliative care in the management of lung cancer, improving patient quality of life and overall survival rates. The review concludes with future perspectives and potential advancements in the field, emphasizing the ongoing research and clinical trials that are shaping the future of lung cancer diagnosis, treatment, and management.*

Keywords *— **Lung cancer, diagnosis, treatment, targeted therapy, immunotherapy, management, advancements.***

I. INTRODUCTION

Lung carcinoma has developed over the past century from a rare and obscure disease to the most frequent cancer worldwide and the leading cause of cancer-related death. Haste, a British author, was only able to locate 22 documented cases of lung cancer in the late 1840s (1,2). According to the most current global statistical analysis, 1.6 million people died and 1.8 million new cases were estimated to have been diagnosed globally in 2012 (3) . In 2008, there were 1.6 million new cases of lung cancer diagnosed, and 1.4 million deaths from the disease (4). Men and women experience differing trends in incidence and geographic patterns, which are mostly due to historical, cultural, and regional variations in tobacco use (3) . 2018 will likely see 234,030 new cases of lung cancer in the US, or slightly less than a quarter of a million new cases overall (5). Behavioral, environmental, and genetic risk factors are among the established risk factors for lung cancer; these factors influence tumor growth and the ability of each patient to respond. Lung cancer's poor overall 5-

year survival rate has barely changed over the past few decades (5-7).

EPIDEMIOLOGIC CHARACTERISTICS

Incidence and Mortality

Lung cancer ranks third in the world (after breast and colorectal cancers) and is the second most common cause of cancer-related deaths in women, after breast cancer. It is also the most common cancer worldwide and the primary cause of cancer-related deaths in men.
In 2012, there were over 1.8 million new instances of lung cancer diagnosed worldwide, or 12.9% of all cancer cases. In 2012, the global lung cancer mortality rate was 1.59 million deaths, or 19.4% of all cancer-related deaths (8) .

Since smoking is a recognized primary risk factor for lung cancer, lung cancer epidemiologic trends and their variations largely mirror historical changes in cigarette smoking.

About 20 years ago, the majority of US states passed laws prohibiting smoking in public places, and they have since kept their citizens informed about the dangers of smoking (9) . Since the tobacco-related epidemic has passed its peak in many states, lung cancer incidence and mortality rates are declining in many regions (10).

Lung adenocarcinoma has been increasingly common in males and notably in women during the past few decades, at a faster rate than squamous cell carcinoma (11) . Since 2004, adenocarcinoma has emerged as the most often diagnosed histologic cancer type worldwide, according to data from the World Health Organization (12) . The smoke from contemporary filtered cigarettes or the shift in historical tobacco usage patterns are most likely to blame for this tendency (11) . The historical variations in cigarette smoking rates between men and women over the past 50 years are also reflected in the disparities in lung cancer death patterns between the sexes.

Lung cancer has been rapidly rising in both incidence and mortality in developing nations like China. According to the annual report of the China National Cancer Registration, incidence of lung cancer was highest in men and second in women, but death rates were highest in both genders (13) The adenocarcinoma subtype has emerged as the predominant pathogenic type in both the smoking and non smoking populations. Thus, although the smoking pattern may be evolving, it may only account for a portion of the pathologic development of lung cancer. The prevalence of lung cancer may be correlated with air pollution brought on by immature and fast industrialization as well as persistently rising car use in urban areas.

Ethnic differences exist in lung cancer incidence and mortality rates. Hispanics had the lowest incidence rate of 28 per 100,000 and the lowest mortality rate of 19.4 per 100,000 in 2012, while Black Americans had the highest incidence rates of 62 per 100,000 and the highest mortality rates of 48.4 per 100,000. (14)

Lung Cancer in Never-Smokers

A rising percentage of incident lung cancer cases are found in never-smokers, who are generally regarded as having smoked fewer than 100 cigarettes in their lifetime. Between 15% and 25% of people with lung cancer fall into this category, and 300,000 of them pass away each year (15,16) . Adenocarcinoma is the most common type of cancer cell in this subset of people with lung cancer, and it is also more likely to be female .(17)

Environmental variables such as radon, indoor and outdoor air pollution, and second hand tobacco smoke have been associated to lung cancer in never-smokers (LCINS). Additionally, non smoking Chinese women with lung cancer commonly have human papillomavirus infection.(18)

II. RISK FACTORS

Tobacco

As a result of the widespread cigarette addiction worldwide, the prevalence of lung cancer has been verified (19) . Now that the tobacco-related epidemic has passed its height, the incidence and mortality rates of lung cancer are declining in many affluent nations 440 Mao et al (20) .

Tobacco is by far the most significant risk factor for the development of lung cancer as a single etiologic agent. Smoking is thought to be the primary cause of 80% of lung cancer cases in men and 50% in women worldwide each year (21) . The vast body of evidence demonstrating a dose-response connection and

biological plausibility lends credence to the theory that smoking causes lung cancer (22)

There is a similar connection between second-hand smoke, or passive smoking, and lung (23,24) .

Long-term cigarette smoking is associated with an increased risk of lung cancer in smokers; some research found that smoking duration had a greater impact than daily smoking quantity (25) Young smokers are more likely to continue smoking and to become heavier smokers. Long-term heavy smoking also significantly raises the risk of developing lung cancer. Consequently, it is clear that teen-targeted anti-smoking initiatives are important and successful in lowering the risk of lung cancer. In the interim, smokers can reduce their chance of developing lung cancer by giving up at any age (26).

According to recent studies, smoking filtered cigarettes can increase nitrosamine consumption while decreasing tar absorption. It might be a significant contributing element to the pathologic transition from squamous cell carcinoma (27) .

Air Pollution

A major environmental risk factor for lung cancer is air pollution, both indoors and outdoors. Prolonged exposure to air pollution from cars, factories, cooking smells, or formaldehyde from interior design all raise the risk of lung cancer (28) . Early ecological studies discovered that over 50% of lung cancer cases happened in cities, most likely as a result of car emissions and industrial air pollution rather than in rural areas. After adjusting for tobacco use and other possible risk variables, a number of case control and cohort studies revealed a strong correlation between air pollution and lung cancer (29-30) .

Radon

In the process of uranium decay, radium naturally gives rise to radon, an inert gas (31). Soil and construction materials are typically the source of indoor radon concentrations.

After smoking, radon is probably the second most common cause of lung cancer. In the US, radon exposure is thought to be a factor in 20,000 lung cancer deaths annually (32). Chronic radon exposure has been linked to lung cancer, according to three cohort studies done in China, North America, and Europe. In the measured radon concentrations more than 100 Bq/m3, the relative risk of lung cancer was 8% (95 CI, 3%–6%), 11% (95 CI, 0%–28%), and 13% (95 CI, 1%–36%), respectively (33-35).

Radiation

Low linear energy transfer radiation (such as gamma rays and x-rays) and high linear energy transfer radiation (such as radon and neutrons) are the two forms of radiation that are significant to lung cancer. According to epidemiologic research, lung cancer is linked to high radiation exposure levels 442 Mao et al. It is yet unknown, though, if low-dose radiation is connected to lung cancer (36).

Diet

Numerous particular micronutrients, like retinol and beta-carotene, that are believed to have anti carcinogenic effect have been discovered after decades of research on nutrition and lung cancer. Common sources of the majority of micronutrients include fruits and vegetables (37,38).

Consuming more fresh produce could lower the risk of developing lung cancer.

Others

Other risk factors for lung cancer include estrogen levels and human immunodeficiency virus infection. It has been debatable whether these factors actually increase the risk of lung cancer, and further research is required to reach a definitive conclusion.

Lung Cancer Staging

A quick explanation of staging is provided here to help you understand when to get screened for lung cancer and how the disease is progressing.

Small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC) are the two main subtypes of lung cancer.

SCLC phase. This is a peri-hilar mass, a core tumor emerging from the airway submucosa. According to histological investigations, neuroendocrine cells of the basal bronchial epithelium are the source of this particular type of cancer (39).

Necrosis is frequently seen, and the cells are tiny, spindle-shaped or spherical, with little cytoplasm and granular chromatin [40]. It is possible to subtype SCLC as pure or as mixed with NSCLC. This cancer is distinguished by its potential to spread to the liver, brain, and bone [39] and is categorized as either limited or extensive stages (41).

NSCLC phase. This kind of cancer is classified by phases and histologically separated into squamous cell carcinoma, large-cell carcinoma, and adenocarcinoma. The American Joint Committee on Cancer (AJCC) [42] developed the staging nomenclature, which is known as the TNM staging system. The TNM approach uses the size of the main tumor (T), the tumor's spread to lymph nodes (N), and the presence of metastases (M) to assist determine the stage of cancer.

Traditional Diagnosis and Screening

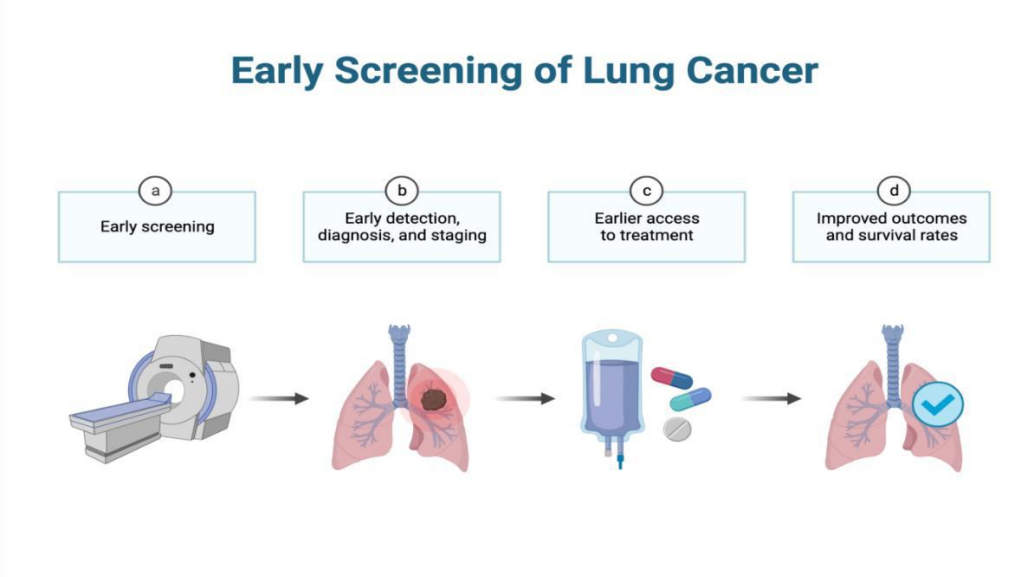

Fig.1

Screening High-Risk Groups

High-risk populations can be screened to enable early discovery at a stage that is treatable and curable.

As previously indicated, high-risk individuals include those who have smoked heavily in the past (more than 30 packs per year), are smokers currently or who have quit within the last 15 years, and are between the ages of 55 and 80. Expanded lung cancer screening could save 30,000–60,000 lives annually in the United States, since the American Cancer Society projected 135,720 lung cancer deaths in 2020. The US Preventive Services Task Force (USPSTF) suggested reducing the smoking history requirements from 30 to 20 pack-years and the screening beginning age from 55 to 50 years. It has also been suggested by medical professionals to familiarize oneself with lung cancer screening recommendations and to prescribe these checks to individuals who are at high risk(43-45).

Radiographic Screening and Diagnosis

A study conducted in Japan found that yearly clinic-based chest X-ray screening for lung cancer decreased the mortality rate from the disease by 25% for those who underwent annual screenings [46]. Remarkably, a study conducted in Osaka, Japan, revealed that utilizing low-dose helical computed tomography (LDCT) for high-risk smoker screening resulted in a 20% lower incidence of lung cancer when compared to traditional radiography screening.(47).

When diagnosing lung cancer using chest radiography, the tumor's sensitivity for detection is about 1 cm in diameter, and it already contains over 109 cells that may have damaged the vascular and bronchial epithelia. CT is a more useful tool for identifying lung lesions in the periphery than traditional whole-lung tomography or plain radiography. Compared to plain radiography, spiral CT scans have better diagnostic accuracy, a quicker scanning time, and less radiation exposure since they can collect data constantly. After that, this method can quickly (one or two breath holds) photograph the entire chest, reducing artifacts and improving the quality of missing nodules in the process. Modern spiral CT imaging can show nodules as small as 1-2 mm. Screening for lung cancer is currently (46-47)

Bronchoscopy and Lung Tissue Biopsy

The most popular diagnostic method for determining a conclusive histological diagnosis of lung cancer is

white light bronchoscopy (WLB). For pre-malignant lesions, bronchoscopy has considerable diagnostic limits. These lesions consist of a few layers of cells that have a diameter of a few millimeters and a thickness of 0.2–1 mm, making them difficult to see with the naked eye.

As only 29% of the instances were identified by a skilled bronchoscopist, it would seem that a high level of training is necessary for the visualization or detection of these tiny squamous lesions. The introduction of fluorescence bronchoscopy removed this restriction. Though early invasive and in situ tumors may be localized using this approach, dysplasia detection remained a challenge. Furthermore, issues with tissue autofluorescence interference and sensitization impeded the development of photodynamic diagnostic systems. To get around this, a novel laser photodynamic diagnostic method that uses medication fluorescence unique to tumors at 630 nm wavelength was created. This wavelength is somewhat apart from the tissues' normal endogenous fluorescence, which occurs in the region of 500–580 nm (48).

Lung Tissue Biopsies

Tissue biopsy is the gold standard for confirming the presence of malignancy. Enough tissue material must be present in lung tissue biopsy samples for histopathology investigations to determine the subtype of lung cancer. The first biopsy is essential for confirming an early diagnosis, preventing the need for a second biopsy, which would raise the risk of complications and postpone the start of treatment. Numerous procedures are frequently used to diagnose lung cancer, such as endobronchial ultrasound, mediastinoscopy, pleural fluid analysis (thoracentesis), thoracoscopy, fiber optic bronchoscopy with or without transbronchial needle aspiration, image-guided trans-thoracic needle aspiration, and surgical approaches. These operations are expensive, prone to errors, and additional samples may be required (49).

Bridging between Traditional and New Screening Methods

By looking for mutations, the development of biomarker testing maximized the utility of lung tissue biopsies. Testing for the most prevalent targetable mutation in the EGFR gene, for which it has been routine procedure since 2011, is not regularly evaluated.

Reflex testing may shorten the time it takes to start treatment, according to some theories. Another drawback is that biopsies frequently yield tissue samples that are acceptable for diagnosis but insufficient for biomarker testing. This necessitates repeat biopsies, which can be difficult in terms of risk, expense, and patient choice. Technical issues could lead to test failures.

In order to ensure that enough tissue is retrieved for testing at diagnosis, a multidisciplinary system collaborating with pulmonology or interventional radiology is necessary for proper diagnosis (50-51).

III. CURRENT TREATMENT OPTIONS

Surgery

If a patient can tolerate surgery and the tumor is determined to be resectable, patients with stage I, II, and IIIA NSCLC usually have surgery to remove the tumor. A lobe or portion of the lung containing the tumor may be removed by surgeons. Biopsies and imaging examinations are performed, and patient variables are assessed to evaluate operability and if the tumor is resectable. These days, a lot of surgeons use video-assisted thorascopic surgery (VATS), which involves making a tiny incision in the patient's chest and inserting a thorascope. With the use of a scope, a lobe can be removed through this tiny incision, avoiding the need for a bigger one (52).

Adjuvant

Adjuvant therapy may be beneficial for certain patients who have had resection surgery in terms of lowering the risk of lung cancer relapse. Radiation, chemotherapy, and targeted therapy are examples of adjuvant therapy. Chemotherapy is typically used following surgery to patients with stage IIA, IIB, and IIIA NSCLC in order to eradicate any cancer cells that may still be present and extend survival (53).

Chemotherapy

Roughly 40% of patients with lung cancer who receive a new diagnosis are in stage IV. Reducing adverse events connected to the disease and increasing survival are the main objectives of treatment for these patients. The first-line treatment

for stage IV NSCLC is cytotoxic combination chemotherapy, which may be impacted by histology, age in relation to comorbidity, and state of performance (PS) (54). According to the American Society of Clinical Oncology, a platinum treatment regimen (cisplatin or carboplatin) plus paclitaxel, gemcitabine, docetaxel, vinorelbine, irinotecan, or pemetrexed is recommended for patients with a PS of 0 or 1 (55). Similar findings have been obtained from four sizable multicenter randomized clinical trials examining the aforementioned drugs in combination with either carboplatin or platinum.

The findings of these investigations have revealed that no regimen stood out as being noticeably better than any other combination. In these investigations, the patients' median overall survival was roughly 8–10 months (56-59).

Radiotherapy

High-energy beams are used in radiotherapy to cause DNA damage in cancer cells, ultimately leading to their destruction. Tumors at particular body places may be controlled or completely removed with the aid of this therapy. Individuals who have locally advanced non-small cell lung cancer (NSCLC) who are not suitable candidates for surgical resection might benefit from radiation treatment. In order to improve the quality of life for NSCLC patients who do not react to surgery or chemotherapy, radiotherapy can potentially be used as part of palliative treatment (60).

Patients with early-stage non-small cell lung cancer (NSCLC) who have a single tiny lung nodule and no lymph nodes nearby that have metastasized are treated with a procedure known as stereotactic body radiation therapy (SBRT). This method ensures that the tracking device is placed correctly and locates the tumor using an advanced coordinate system. This makes it possible to administer radiation therapy that is highly concentrated and focused. In a meta-analysis of photon, proton, and carbon-ion radiation therapy's efficacy for non-small cell lung cancer, it was discovered that SBRT provided higher rates of 2-year overall survival, reduced expenses, and improved patient convenience (61). The 50-month results of 70 medically inoperable patients getting SBRT in a prospective phase II research shown that receiving SBRT led to high rates of local control in medically inoperable patients with Stage (62).

Immunotherapy

Exploring immunomodulation as a potential way to combat cancer is currently being pursued. It has been discovered that oligonucleotides with particular CpG sequence patterns can activate the immune system through the Toll-like receptor 9 (TLR9) signaling pathway, which has antitumor effects (64). These immunostimulatory oligonucleotides have been demonstrated in in vitro models to have strong antitumor effects as well as to augment the effects of chemotherapy drugs like gemcitabine and pembranedib (65). Despite having a sound scientific foundation and being technically feasible, other immunotherapy methods, such as lung cancer vaccines, are still in the very early preclinical and phases I and II stages .Developing less expensive and labor-intensive vaccinations and simpler regimens, standardizing biological test monitoring, and defining the immunological response that correlates with clinical response are some of the challenges (65).

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