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A Comprehensive Review of Non-Small Cell Lung Cancer: Pathogenesis, Diagnosis, and Innovative Therapeutic Approaches

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Abstract

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer, accounting for over 85% of all cases globally. It remains one of the primary causes of cancer-related death due to its rapid progression, few early symptoms, and late detection. The three main forms of non-small cell lung cancer (NSCLC) are adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma; each has a unique histology, prognosis, and response to treatment. While genetic mutations, occupational carcinogens, environmental pollutants, and chronic lung disorders all have a major role in the development of the disease, tobacco smoking is the main etiological component. The accuracy of early detection and staging has increased thanks to developments in diagnostic methods such bronchoscopy, endobronchial ultrasonography, CT, PET imaging, and genomic profiling. Recent therapeutic developments, including targeted therapies against EGFR, ALK, ROS1, MET, RET, and KRAS mutations, along with immunotherapy and antibody-drug conjugates, have transformed NSCLC management and improved patient survival outcomes. Emerging approaches involving personalized medicine, artificial intelligence, and precision oncology are expected to further optimize diagnosis and treatment strategies. This review highlights the epidemiology, pathogenesis, classification, diagnosis, current therapeutic approaches, complications, and future innovations in NSCLC management.

Keywords: Non-small cell lung cancer (NSCLC), adenocarcinoma, squamous cell carcinoma, large cell carcinoma, lung cancer, targeted therapy, EGFR inhibitors, ALK inhibitors, immunotherapy, precision medicine, molecular profiling, diagnosis, pathogenesis, chemotherapy, antibody-drug conjugates (ADCs)

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INTRODUCTION

The lung is one organ where cancer often spreads. For most patients with lung metastases, systematic therapy constitutes the mainstay of management [1]. Among all the cancers in the world, lung cancer has the greatest prevalence and death rate. It attacks both sexes and has a high death rate, accounting for almost 2.4 million new cancer cases globally and 484306 new cases in Europe per year [2]. Adenocarcinoma is the most common histological subtype of non-small cell lung cancer (NSCLC), which accounts for more than 80% of lung cancer cases. Twenty to thirty-five percent of NSCLC patients are diagnosed at stage III, and about fifty-three percent are diagnosed at stage IV with distant metastases. The 5-year survival rate for patients diagnosed at stage IV is around8.9%, whereas those diagnosed at stages IIIA, IIIB, and IIIC have survival rates of 36%, 26%, and 13%,

respectively [3]. Its broad classification is reflected in its various survival rates, which vary even within the same stage in terms of prognosis and therapeutic approach [4].

The two primary forms of lung cancer are small-cell lung carcinoma and non-small-cell lung cancer. Different treatment is given to these two categories. An abnormal growth of healthy lung cells that results in a mass known as a tumor, lesion, or nodule is the first indication of non-small cell lung cancer (NSCLC) [5]. Non-small cell lung cancer (NSCLC), which makes up around 85% of cases, and small cell lung cancer, which is becoming less common, are the two histologic classifications into which lung cancer is frequently divided. 75% to 90% of instances of lung cancer are caused by cigarette smoking, making it the most prevalent risk factor. Because lung cancer is so frequent, it ranks as the fifth most common cancer among those who have never smoked. The highest chance of recovery is provided by surgery with a curative intent, which is only available to patients in stages I, II, and some cases of stage III. However, only 30% of cases of NSCLC manifest early [6].

HISTORY AND PHYSICAL EXAMINATION

There are two types of non-small cell lung cancer clinical manifestations: intrathoracic and extrathoracic. Cough, hemoptysis, chest discomfort, dyspnea, or hoarseness are examples of intrathoracic effects that can be observed during a physical examination and history [7]. Shoulder pain is the hallmark of Pancoast syndrome, though it can also affect the forearm, scapula, or fingers. Squamous cell cancer can cause Horner syndrome, hand muscle atrophy, or bone destruction. Bone metastases can be suspected during the physical examination because they are present in roughly 20% of NSCLC cases at first presentation [8]. The most prevalent kind of adenocarcinoma is brain metastasis, which can cause localized neurologic problems, headache, vomiting, visual field insufficiency, or seizures [9].

The histologic diagnosis is a crucial component of a cancer diagnosis. Adenocarcinoma must be detected by neoplastic gland growth, intracytoplasmic mucin, or pneumocyte marker expression in the form of TTF-1 with or without napsin. Most of the neoplastic gland production is caused by acinar, papillary, or micropapillary, leptic, or solid growth patterns. To diagnose squamous cell carcinoma, tumor cells must produce keratin, which may involve intercellular desmosomes. Squamous cell carcinoma can express p40, p63, CK5, or desmoglein, according to immunohistochemistry (IHC).

As previously mentioned, 90% of instances of large cell carcinoma exhibit squamous, glandular, or neuroendocrine differentiation, making it an exclusionary diagnosis. Only when poorly differentiated carcinoma lacks distinguishing IHC markers that would rule it out as a separate subtype of lung cancer is it classified as large cell carcinoma.

THE MOST COMMON TYPES OF NSCLC ARE [10, 11]

- Squamous cell carcinoma (25% of lung cancers).
- Adenocarcinoma (40% of lung cancers).
- Large cell carcinoma (10% of lung cancers).

Squamous Cell Carcinoma

Most of lung squamous cell carcinomas occur in the lung's largest bronchi in the center. Squamous cell carcinomas are more strongly associated with smoking than other forms of non-small cell lung cancer. Lung squamous cell carcinoma has been less common in recent years.

The frequent histological heterogeneity of lung adenocarcinomas is one of the main issues. Tumors with a single pattern of acinar, papillary, bronchioloalveolar, and solid adenocarcinoma with mucin development are less prevalent than combinations of adenocarcinoma histological subtypes [12].

Lung Adenocarcinoma

Currently, the most prominent form of lung cancer among "never smokers" (lifelong nonsmokers) is adenocarcinoma. About 40% of lung malignancies are adenocarcinomas. In the past, small-cell lung

cancer and squamous-cell lung cancer were more frequently found in the middle of the lungs, but adenocarcinoma was more frequently seen in the periphery. However, recent research indicates that for both squamous-cell carcinoma and adenocarcinoma, the "ratio of centrally to peripherally occurring" lesions may be approaching unity.

The WHO/IASLC classification recognizes the following variations of adenocarcinoma:

- Fetal adenocarcinoma with excellent differentiation.
- Colloid mucinous adenocarcinoma.
- Cystadenocarcinoma mucinous.
- Signet ring adenocarcinoma.
- Adenocarcinoma with clear cells [13].

Large-Cell Lung Carcinoma

The varied class of undifferentiated malignant neoplasms known as large-cell lung carcinoma (LCLC) is caused by lung epithelial cells that have undergone transformation. Large-cell lung carcinomas used to account for about 10% of all non-small-cell lung cancers, but more recent diagnostic techniques seem to be identifying more poorly differentiated SCCs and adenocarcinomas rather than "classic" large-cell lung carcinomas. Large-cell lung carcinoma is essentially a "diagnosis of exclusion" because the tumor cells lack light microscopic characteristics that would classify the neoplasm as a small-cell carcinoma, squamous-cell carcinoma, adenocarcinoma, or another more specific histologic kind of lung cancer. The main characteristics that distinguish large-cell lung carcinoma from small-cell lung cancer are the anaplastic cells' bigger size, a higher cytoplasmic-to-nuclear size ratio and the absence of "salt-and-pepper" chromatin are the main characteristics that differentiate large-cell lung carcinoma from small-cell lung cancer [14].

The WHO/IASLC classification recognizes several rare variations in addition to the broad category of large cell carcinoma, such as [15]:

- large cell neuroendocrine carcinoma.
- Carcinoma basaloid.
- Carcinoma resembling lymphoepithelioma.
- Cancer with clear cells.
- Rhabdoid-like large cell cancer.

Adenocarcinomas may display a basaloid pattern, and basaloid carcinoma is also recognized as a variation of squamous cell carcinoma. Tumors lacking either of these characteristics are classified as a form of big cell carcinoma (Figure 1).

ETIOLOGY

About 80% to 90% of NSCLC cases are caused by tobacco smoking. Thousands of chemical carcinogens found in tobacco smoke can harm DNA over time [15–66]. The risk is directly correlated with the duration and intensity of smoking. The second most common cause of lung cancer overall and the primary cause among nonsmokers is radon gas. Radon is a naturally occurring radioactive gas that can build up inside and harm lung tissue if inhaled [67].

- *Second-Hand Smoke:* For nonsmokers, breathing in ambient tobacco smoke greatly increases their risk of developing lung cancer [68].
- *Occupational and Environmental Exposures:* The risk of non-small cell lung cancer (NSCLC) is increased by prolonged inhalation of specific carcinogens in industrial or residential settings. These include silica, diesel exhaust, chromium, nickel, beryllium, asbestos, and arsenic [69].
- *Air Pollution:* Long-term exposure to high ambient air pollution levels, especially fine particulate matter ($PM_{2.5}$), is known to cause lung cancer and cellular damage.
- *Pre-Existing Lung Conditions:* Because of ongoing inflammation and cellular turnover, chronic respiratory conditions such pulmonary fibrosis and Chronic Obstructive Pulmonary Disease (COPD) raise the risk of NSCLC [70].

- *Radiation Therapy:* Individuals who have received radiation therapy to the chest, such as for Hodgkin lymphoma or breast cancer, are at an increased risk of developing primary lung cancer in the future [71].

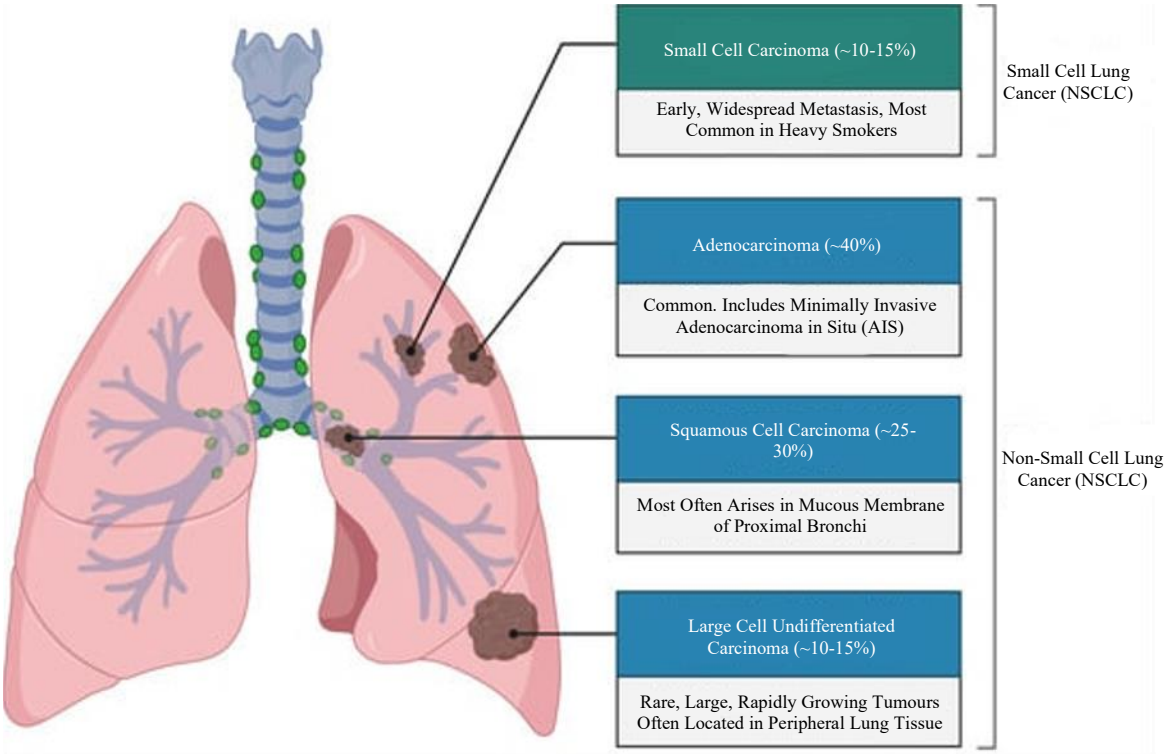

Figure 1. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the three primary subtypes of non-small cell lung cancer (NSCLC) [16].

The etiology of non-small cell lung cancer can be further categorized using preventable and unavoidable risk factors. The most well-known avoidable risk factor for non-small cell lung cancer is inhaled tobacco use. Lung cancer can also be caused by drinking alcohol, being around second-hand smoke, asbestos, radon, arsenic, chromium, nickel, ionizing radiation, and polycyclic aromatic hydrocarbons. Radiation therapy can cause primary lung cancer when it is used to treat other cancers such as Hodgkin lymphoma and breast cancer [72].

The etiology of NSCLC can be further classified using risk factors that are preventable and those that are not. Inhaled tobacco usage is the most well-known preventable risk factor for non-small cell lung cancer. Other risk factors for lung cancer include alcohol consumption, exposure to second-hand smoking, asbestos, radon, arsenic, chromium, nickel, ionizing radiation, and polycyclic aromatic hydrocarbons. When radiation therapy is used to treat other diseases, like Hodgkin lymphoma and breast cancer, it can cause primary lung cancer. It has been demonstrated that people with pulmonary fibrosis have a seven-fold increased risk of lung cancer, and this risk is unaffected by cigarette usage. HIV patients have a higher risk of lung cancer than the overall population, regardless of whether they smoke or take antiretroviral drugs.

EPIDEMIOLOGY OF LUNG CANCER

Lung cancer is currently the most common malignant tumor to be diagnosed and the primary cause of cancer-related mortality globally. Lung cancer is the most prevalent kind of cancer in the globe. The following global cancer statistics by world regions for 2022 are based on updated projections from the International Agency for Research on Cancer (IARC). In 2022, there were approximately 20 million new instances of cancer (including non-melanoma skin cancers [NMSCs]) and 9.7 million cancer-

related deaths (including NMSCs) It is estimated that one in five men and women may have cancer at some point in their lives. Approximately one in nine men and one in twelve women die from cancer [63, 64]. Lung cancer was the most common type of cancer in 2022. 2.5 million additional cases, or one in eight cancer cases globally (12.4% of all cancer incidences), were impacted. The next most common cancers among women were breast cancer (11.6%), colorectal cancer (9.6%), prostate cancer (7.3%), and stomach cancer (4.9%). Lung cancer was also the leading cause of cancer-related mortality, with an estimated 1.8 million deaths (18.7%). The following positions were held by colorectal cancer (9.3%), liver cancer (7.8%), breast cancer in women (6.9%), and stomach cancer (6.8%). Lung cancer and breast cancer were the most common cancers in men and women, respectively, in terms of cases and deaths. Incidence rates (including NMSC) varied four to five times globally, ranging from over 500 in Australia/New Zealand (507.9 per 100,000) to less than 100 in West Africa (97.1 per 100,000). It ranged from over 400 among women in Australia/New Zealand (410.5 per 100,000) to almost 100 in South Central Asia (103.3 per 100,000) [73–75].

Tobacco use has been connected to over 90% of occurrences of lung cancer. Lung cancer is 20 times more common in patients who now smoke and have a history of smoking 40 packs annually than in non-smokers. This risk may increase if tobacco use is coupled with other lifestyle or environmental exposures such as asbestos exposure. Specifically, the invention of filter cigarettes in the 1960s is thought to have contributed to adenocarcinoma, albeit this has not been proven [65].

Globally, lung cancer is the leading cause of cancer-related deaths for men and the second most prevalent cause for women. The incidence of lung cancer varies greatly among populations depending on how common tobacco use is in different nations. There is a direct correlation between the rise or fall in smoking rates in various populations and the incidence of lung cancer. For example, reduced tobacco uses and anti-smoking initiatives are predicted to reduce the age-adjusted death rate in the United States by 79% between 2015 and 2065 [66].

PROGNOSIS

Lung cancer is extremely deadly. The average 5-year overall survival rate in the European Union between 2010 and 2014 was 15%, with individual country rates varying from 10% to 20%. The United States has the highest 5-year patient survival rates on record. The 5-year relative survival rate for lung cancer was 25%, according to the US data collected between 2013 and 2019. 4% show a gradual but consistent rise from 11.7% in 1975 [76]. However, the 5-year relative survival rate varies significantly based on the stage of the disease at diagnosis, as seen below:

- 61.8% in cases of localized illness.
- 34.8% for local illness.
- 8.2% for diseases with distant metastases [77].

Tumor, node, metastasis (TNM) staging, the patient's performance status, and comorbidities all affect the prognosis of non-small cell lung cancer (NSCLC). Reduced survival is linked to patients with poor performance status. Weight loss and reduced appetite are also negative prognostic indicators. Both occult lymph node metastases and lymphatic vessel invasion have a detrimental effect on prognosis. Patients with actionable mutations have been shown to have better prognosis. For instance, adenocarcinomas linked to women, Asian ancestry, and/or never smokers have activating EGFR mutations, which are often associated with a much better prognosis [78].

Metabolic activity on PET scans has been associated with a poor prognosis in stages I–IV NSCLC. After complete resection, 41% of cases have been recorded to return, with a median survival of 8.1 months and a median time to recurrence of 11.5 months. Shorter survival was associated with performance status, disease-free interval, distant metastases, and prior use of neoadjuvant chemotherapy or adjuvant radiation therapy [79].

PATHOPHYSIOLOGY

Lung cancer risk is said to be influenced by an individual's susceptibility to certain agents as well as exposure (occupational or environmental) to these agents. Roughly 90% of lung cancer cases in the US are caused by active smoking. Workplace exposure to carcinogens accounts for about 9–15% of lung cancer cases [17].

At least 40 known strong carcinogens are among the more than 300 dangerous compounds found in tobacco smoke. Polyaromatic hydrocarbons and nicotine-derived nitrosamine ketone (NNK) have been demonstrated to damage DNA in animal models by producing DNA adducts. Benzo-A-pyrine also seems to cause mutations in p53 and other tumor suppressor genes, as well as molecular pathways like AKT [18].

The most common occupational risk factor for lung cancer is asbestos exposure. According to studies, outdoor air pollution may be responsible for 1–2% of lung cancer cases, whereas radon exposure is linked to 10% of instances. Furthermore, it has been demonstrated that preexisting non-malignant lung conditions such tuberculosis, idiopathic pulmonary fibrosis, and chronic obstructive pulmonary disease are linked to higher incidences of lung cancer [19].

According to the current multiple hit theory, orderly genetic reproduction is disrupted by a sequence of harmful cellular insults. Uncontrolled, chaotic growth that disrupts distant or local anatomical or physiological processes is eventually the cause of symptoms [20].

Ito et al.'s study analyzed how the switch from unfiltered to filtered cigarettes affected the histologic kinds of lung cancer in Japan and the US. According to the study, the shift in cigarette kinds caused the most prevalent type of lung cancer to transition from SCC to adenocarcinoma [21].

Genetic susceptibility Oncogene amplification and tumor suppressor gene inactivation have been found in NSCLC using sophisticated molecular approaches. The most notable anomalies discovered are mutations involving the RAS family of oncogenes. H-RAS, K-RAS, and N-RAS are the three members of the RAS oncogene family. These genes encode a protein with guanosine triphosphatase activity on the inner surface of the cell membrane and may be involved in signal transduction [22].

RAS mutations may be involved in the molecular pathophysiology of NSCLC, according to research done on mice. Human studies indicate that RAS activation has a role in the development of lung cancer tumors.30 %of instances of adenocarcinoma have RAS gene mutations. Adenocarcinomas that developed in nonsmokers did not have these alterations. It seems that the K-RAS mutation is a separate prognostic factor.

Research is being done to create treatment options based on whether RAS gene mutations are present or not [23, 24].

SYMPTOMS OF NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer symptoms can include [25]:

- Chest pain.
- Chronic cough.
- Coughing up blood.
- Hoarseness.
- Loss of appetite.
- Shortness of breath.
- Tiredness.
- Wheezing.
- NSCLC may not constantly create symptoms.

Cigarette smoking is the main cause of NSCLC. Your chance of having NSCLC increases with the amount of smoking you do and the age at which you start. Second-hand smoke, exposure to chemicals at work, radiation exposure, environmental pollution, a family history of lung cancer, and prior HIV infection are additional risk factors (Figure 2).

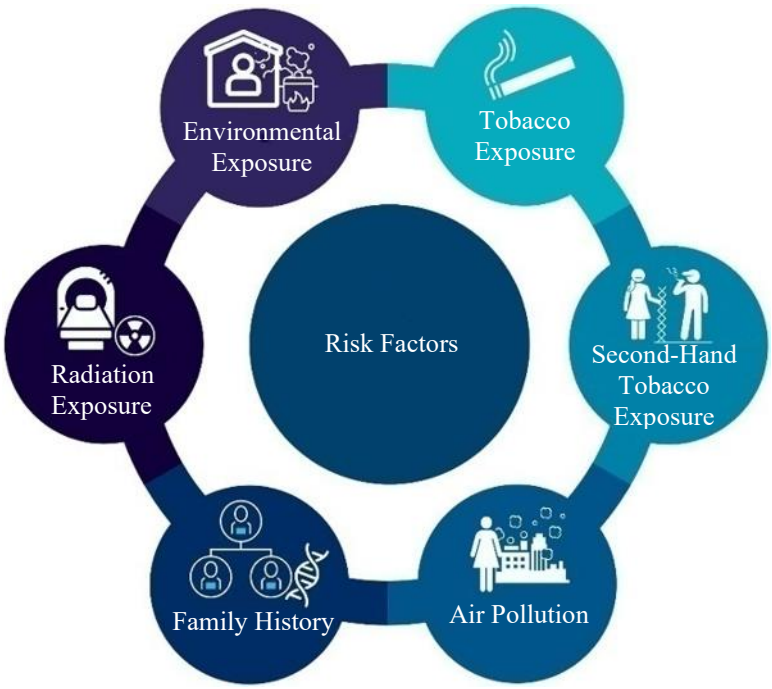

Figure 2. Represent Clockwise from top left: environmental exposure, tobacco exposure, second-hand tobacco exposure, air pollution, family history, radiation exposure [26].

DIAGNOSE NON-SMALL CELL LUNG CANCER

- *Lung Biopsies with Fine and Core Needles:* A tiny needle is used to take a sample of lung tissue or fluid. For precise guiding, CT or ultrasound imaging is utilized. While the patient is in the CT suite, a pathologist takes a needle sample and examines it to make sure there is enough diagnostic tissue. After that, the complete sample is sent to cytology for a final assessment to see whether cancer cells are present and what kind they are; if they are, the cells will be further examined for genetic anomalies [27].
- *Bronchoscopy:* A bronchoscopy examines the trachea and the lungs' main airways for anomalies. Through the mouth or nose, a bronchoscope is inserted into the trachea and lungs. A bronchoscope is a thin, tube-like instrument with a light and a viewing lens. It also has a device for extracting tissue samples that are analyzed under a microscope to determine whether cancer is present [28].
- *Endobronchial Ultrasound, or EBUS:* is a novel method that combines an ultrasound and bronchoscopy. This makes it possible for medical professionals to see lymph nodes with great sensitivity and to do a biopsy without making an incision [29, 30].
- *Navigational Bronchoscopy:* This novel technique uses a bronchoscope and a GPS-like guidance system to biopsy smaller and deeper lung regions [31].
- *Surgery:* Depending on where your node or tumor is located, a more involved procedure can be required to remove a tiny portion of the tumor. In certain instances, it is feasible to take a sample, examine it, and proceed with the necessary operation in a matter of minutes [32].

Evaluation

After the history and physical examination, the initial evaluation should include a complete blood count (CBC) and a complete metabolic panel (CMP) to further investigate any potential hematologic or electrolyte sequelae from NSCLC [80].

Examples of this include hypercalcemia or elevated alkaline phosphatase when bone metastases are present. A chest radiograph should be the initial imaging examination because the presentation of NSCLC may be vague. If lung cancer is suspected, further assessment with computed tomography (CT) imaging would likely be required to properly characterize the pathology seen on the chest radiograph [81].

A tissue sample will be needed for histopathologic and immunohistochemical investigation to diagnose NSCLC. After a diagnosis, a CT scan of the chest and upper abdomen, including the adrenal glands, should be conducted to screen for metastatic illness. A positron emission tomography (PET) scan can be used to further stage the patient for disease and treatment. To finish the disease staging, brain magnetic resonance imaging (MRI) is also required to check for brain metastases [82–85].

Treatment

Patients were examined at least once a week while getting treatment, four to six weeks thereafter, every three months for the next two years, and then every six months following that. Common Terminology Criteria version 3.0 was used to rate adverse occurrences. An interval medical history and physical examination, hematological tests, a chest X-ray, and a CT scan were all part of the initial follow-up visit.33

During the first three to four months following therapy, a follow-up PET scan was performed. PET tests were then alternated with CT and chest X-ray exams (Tables 1–7) [34].

CHEMOTHERAPY DRUGS NON-SMALL CELL LUNG CANCER [35–37]

Cisplatin or carboplatin is most likely to be taken together with at least one additional chemotherapy medication, such as:

- Pemetrexed.
- Vinorelbine.
- Gemcitabine.
- Paclitaxel (Taxol).
- Docetaxel (Taxotere).

INNOVATIONS IN TREATMENT PLANNING

Table 1. Innovations in radiotherapy treatment planning for NSCLC [38–39].

Category	Technique	Description	Key benefit
Advanced Imaging Techniques	Four-Dimensional CT (4D-CT)	Captures tumor motion during respiration to improve targeting accuracy	Reduces geographic miss and improves dose precision.
	MRI Integration	Provides superior soft-tissue contrast for better tumor and organ delineation	Improved tumor boundary identification.
Adaptive Radiotherapy	Real-Time Monitoring	Includes tumor tracking and respiratory gating during radiation delivery	Adjusts for patient movement and tumor position.
	Adaptive Replanning	Periodic imaging allows modification of treatment plans based on tumor changes	Enhances treatment effectiveness and safety.

Table 2. Overview of systemic therapy innovations in NSCLC [40–45, 86].

Therapy type	Molecular target	Prevalence in NSCLC	Clinical impact
Targeted Therapy	EGFR	10–15%	Improved PFS and OS with reduced toxicity.
Targeted Therapy	ALK	~5%	High response rates and CNS control.
Targeted Therapy	ROS1	1–2%	Durable responses and prolonged PFS.
Targeted Therapy	BRAF, MET, RET	<5% each	Personalized therapy with significant clinical benefit.

Table 3. EGFR inhibitors used in NSCLC [46–49, 86].

Generation	Examples	Mechanism of action	Clinical outcomes	Limitations
First	Erlotinib, Gefitinib	Reversible EGFR TKI	Improved PFS vs chemotherapy	Resistance (T790M mutation).
Second	Afatinib, Dacomitinib	Irreversible EGFR inhibition	Prolonged PFS	Increased toxicity.
Third	Osimertinib	Targets EGFR + T790M mutation	Superior PFS and OS; standard first-line therapy	Higher rate of serious adverse events.

Table 4. ALK inhibitors in NSCLC [50–52, 86].

Generation	Examples	Key features	Clinical benefit
First	Crizotinib	ALK inhibition	Improved PFS vs chemotherapy.
Second	Ceritinib, Alectinib, Brigatinib	Overcomes resistance; good CNS penetration	Longer PFS and CNS control.
Third	Lorlatinib	Targets multiple resistance mutations	Effective after second-generation failure.

Table 5. ROS1 inhibitors in NSCLC [53–55].

Drug Class	Examples	Characteristics	Clinical benefit
First-Generation	Crizotinib	Inhibits ROS1, ALK, MET	High response rates.
Second-Generation	Entrectinib, Lorlatinib	Better CNS penetration; resistance control	Longer PFS and CNS efficacy.

Table 6. Other targeted therapies in NSCLC [56–58].

Molecular target	Drugs	Mechanism	Clinical outcome
BRAF V600E	Dabrafenib + Trametinib	BRAF and MEK inhibition	Improved PFS and response rate.
MET exon 14	Capmatinib, Tepotinib	MET inhibition	Durable responses.
RET rearrangements	Selpercatinib, Pralsetinib	Selective RET inhibition	High efficacy and good tolerability.

Table 7. Combination and precision-based therapies in NSCLC [59].

Strategy	Description	Clinical significance
Targeted + Immunotherapy	EGFR inhibitors + checkpoint inhibitors	Potential synergistic antitumor effects.
Targeted + Chemotherapy	ALK inhibitors + chemotherapy	Delays resistance.
Precision Medicine	Genomic profiling via NGS	Personalized treatment selection.
Emerging Targets	HER2, NTRK, KRAS G12C	Expands treatment options.

COMPLICATION

The geographic breadth of the disease process and the presence of possible cancer metastases determine the complications associated with non-small cell lung cancer. Depending on the severity of the disease and associated conditions, malignant pleural effusion is one of the intrathoracic repercussions that may result in dyspnea or respiratory failure [87, 88]. Non-small cell lung cancer is the most frequent malignant etiology and accounts for almost half of all cases with superior vena cava (SVC) syndrome. This usually appears as a gradual development of swelling in the face and neck, accompanied by swollen neck veins and edema in the upper limbs, because of an obstruction of blood flow through the superior vena cava [89, 90].

Future Approaches: Antibody-Drug Conjugates

Antibody-drug conjugates (ADCs) have become a viable treatment option for non-small cell lung cancer (NSCLC). Monoclonal (targeted) antibodies and cytotoxic medications, referred to as the payload, are combined in ADCs. Compared to traditional chemotherapy, this strategy seeks to reduce toxicity. The most common payloads at the moment are extremely strong and either damage DNA or

interfere with microtubules, making them unsuitable for use as traditional chemotherapy. The drug-to-antibody ratio (DAR) is important in this situation. While a high DAR may result in excessive toxicity, a low DAR may reduce medication efficacy [91].

There are two kinds of linkers – cleavable and noncleavable – that join the medication and antibody. The medication is released through lysosomal breakdown in the former subgroup, which is more stable in the bloodstream. However, the latter subgroup relies on endosomes for drug release and is less stable in circulation. However, the possibility of a bystander effect is presented by extracellular drug release [92].

It increases drug efficacy by directly cytotoxically affecting nearby cells when paired with transmembrane diffusion following internalization. Despite being intended as targeted agents, 119 ADCs are highly toxic and cause additional adverse effects. Premature drug release can lead to off-target toxicity, especially when the intended bystander impact is present. The binding of ADCs to noncancerous cells that express the target antigen is associated with on-target toxicity. Additionally, antibody-dependent cellular toxicity and local inflammation in the TME affect general toxicity. Hematologic toxicity, hepatitis, keratitis, and particularly interstitial lung disease are pertinent ADC-associated toxicities [93, 94].

Trophoblast cell surface antigen 2 (TROP2), MET, or carcinoembryonic antigen–related cell adhesion molecule 5 (CEACAM5) are targets that are presently being studied in nononcogenic addicted NSCLC. The phase III TROPION-Lung01 experiment examined datopotamab-deruxtecan (Dato-DXd) that targets TROP2. A total of 604 patients were randomized to either docetaxel or Dato-DXd. While OS was not yet mature (HR, 0.90 [0.72–1.13]), the research reached its first coprimary end objective PFS (HR, 0.75 [0.62–0.91], P = .004) in an intermediate analysis. In contrast to SQ histology, which favored docetaxel (HR, 1.38 [0.94–2.02]), patients with NSQ histology demonstrated a significant PFS advantage (HR, 0.63 [0.51–0.78]) [95–97].

The CEACAM5-directed ADC tusamitamab-ravtansine was evaluated against docetaxel in the phase III CARMEN-LC03 study. Early in December 2023, the study was discontinued after a preliminary analysis revealed that the first coprimary end target of PFS was futile. Second, the major end point of OS was not met in the phase III EVOKE-01 trial comparing sacitzumab-govitecan with docetaxel. Both studies' outcomes have not yet been made public [98–101].

FUTURE DIRECTIONS IN NSCLC RESEARCH AND TREATMENT DEVELOPMENT

Personalized Medicine

Personalized medicine, that develops treatments customized to the distinct genetic and molecular composition of each patient's tumor, is the key to the future of treating non-small cell lung cancer. Accurately identifying actionable mutations and biomarkers is becoming possible thanks to advancements in genomic profiling and liquid biopsy procedures. By using this approach, physicians can select the best course of action, minimizing needless treatments and their adverse effects. The goal of current research is to incorporate comprehensive genomic data into clinical judgments, opening the door to more successful and customized treatment regimens [60].

Machine Learning and Artificial Intelligence (AI)

Research and treatment for NSCLC could be revolutionized by AI and machine learning. These state-of-the-art systems are excellent at identifying patterns, processing enormous datasets, and producing extremely precise forecasts. AI helps in NSCLC diagnosis, staging, and therapy response prediction. In the meantime, machine learning algorithms are being developed to improve treatment planning, increasing the accuracy of radiotherapy and the selection of targeted medicines. By improving diagnostic precision and expediting treatment processes, AI integration in clinical settings has the potential to enhance patient outcomes [61].

Novel Therapeutic Targets

New therapy options for NSCLC are continuously being uncovered by research activities. Focusing on the tumor's microenvironment, cancer stem cells, and metabolic pathways are examples of emerging research areas. Research is being conducted on treatments that modify the immunological milieu, such as drugs, that target T-cell engagers and macrophages. Furthermore, studying the metabolic requirements of cancer cells – such as the use of glutaminase inhibitors – offers a fascinating line of inquiry. These cutting-edge methods may be able to address resistance mechanisms and open up new treatment options [62].

CONCLUSION

Due to its high incidence and fatality rates, non-small cell lung cancer continues to be a significant worldwide health burden. Significant progress has been made in comprehending the molecular biology and clinical behavior of non-small cell lung cancer (NSCLC), despite major obstacles related to delayed diagnosis and tumor heterogeneity. Patients' quality of life, survival rates, and illness management have all greatly improved because to specialized therapy approaches and modern diagnostic techniques. Treatment selection now heavily relies on personalized medicine based on molecular profiling, which enables more accurate and efficient treatments with lower toxicity.

The future of NSCLC treatment is also quite promising due to current developments in immunotherapy, antibody-drug conjugates, genomic technology, and artificial intelligence. To significantly lower the worldwide burden of NSCLC and enhance long-term patient outcomes, ongoing research, early screening initiatives, smoking cessation education, and the creation of innovative targeted medicines are crucial.

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