"Pharmacological Convergence in Lung Carcinoma: Molecular Pathways, Therapeutic Targets, and Emerging Nanotechnological Interventions"

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Abstract

The leading cause of cancer-related death worldwide is still lung cancer, which is mostly caused by cigarette smoking but is also influenced by radiation exposure, occupational carcinogens, environmental contaminants, and genetics. The majority of patients continue to be diagnosed at advanced stages, leading to few curative options and low overall survival, despite significant advancements in clinical evaluation—including the development of the TNM classification system, minimally invasive biopsy procedures, and improved imaging modalities. Small cell lung cancer (SCLC) is primarily treated with chemoradiation because of its rapid progression and early metastatic potential, while non-small cell lung cancer (NSCLC) is treated with a combination of surgery, chemotherapy, radiotherapy, targeted molecular therapies, and immunotherapy. Immune checkpoint inhibitors and the identification of actionable genetic alterations have fundamentally changed therapy paradigms, providing better results for some patient populations. Additionally, new drug delivery methods based on nanotechnology, like liposomes, nanoparticles, and nanocomposites, have the potential to improve therapeutic selectivity, reduce systemic toxicity, and overcome resistance mechanisms. The overall prognosis is still difficult despite these developments, highlighting the need for effective preventative programs, early diagnosis techniques, individualized treatment plans, and ongoing research into cutting-edge therapeutic technology targeted at enhancing long-term survival.

Keywords – Lung cancer, Pathology, Epidemiology, Nanotechnology, Drug delivery

Introduction

Lung carcinoma has evolved over the past century from a rare and unknown illness to the most prevalent cancer worldwide and the lead ing cause of cancer deaths. There were only 22 documented occurrences of lung cancer in the late 1840s, according to British author Ha sse [1,2]. Adler found just 374 published cases in 1912 [3,4]. According to the most recent global statistical study, there were 1.6 millio n deaths and 1.8 million new cases diagnosed globally in 2012 [5]. In 2008, there were 1.4 million lung cancer deaths and 1.6 million n ew diagnoses [6]. Men's and women's incidence trends and geographic patterns differ, mostly reflecting regional, cultural, and historical variations in tobacco use [5]. An projected 234,030 people, or slightly less than a quarter of a million, would receive a new lung cancer diagnosis in the US in 2018 [7]. The known risk factors for lung cancer include genetic, behavioural, and environmental risk factors. These factors all influence a patient's ability to respond and contribute to the formation of tumors. Over the past few decades, there has been little change In the low overall 5-year survival rate for lung cancer [7-9].

Lung cancer ranks third in terms of cancer incidence and second in terms of cancer death among women globally, but it is the leading cause of major cancer incidence and mortality among men [10]. According to the American Cancer Society's 2010 forecast, lung cancer will be responsible for 157,300 cancer-related deaths and more than 222,520 new cases in the US.[11]. While the incidence of lung cancer in the United States appears to have plateaued for women, it started to fall for males in the early 1980s [11,12].

At the start of the 20th century, the phrase "lung cancer" was first used in clinical oncology. Although the names for lung tumors have changed over time, understanding the underlying causes of this disease type was essential to the development of medicine [13,14].

Classification

Histologic classification of lung cancer-

1. Preinvasive lesions
    - Squamous dysplasia/carcinoma in situ (CIS)
    - Atypical adenomatous hyperplasia (AAH)
    - Adenocarcinoma in situ (AIS) (nonmucinous, mucinous, or mixed nonmucinous/ mucinous)
    - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH)
2. Squamous cell carcinoma
    - Variants
        - Papillary
        - Clear cell
        - Small cell (probably should be discontinued)
        - Basaloid
3. Small cell carcinoma
    - Combined small cell carcinoma

4. Adenocarcinoma
    - Minimally invasive adenocarcinoma (MIA)

(<3 cm lepidic predominant tumor with

<5 mm invasion)

- Nonmucinous, mucinous, mixed mucinous/ nonmucinous
    - Invasive adenocarcinoma
        - Lepidic predominant (formerly nonmucinous bronchioloalveolar carcinoma (BAC) pattern, with >5 mm invasion)
        - Acinar predominant
        - Papillary predominant
        - Micropapillary predominant
        - Solid predominant with mucin
    - Variants of invasive adenocarcinoma
        - Invasive mucinous adenocarcinoma (formerly mucinous BAC)
        - Colloid
        - Fetal (low and high grade)
        - Enteric
5. Large cell carcinoma
    - Variants
    - Large cell neuroendocrine carcinoma (LCNEC)
        - Combined LCNEC
    - Basaloid carcinoma
    - Lymphoepithelioma-like carcinoma
    - Clear cell carcinoma
    - Large cell carcinoma with rhabdoid

Phenotype

6. Adenosquamous carcinoma
7. Sarcomatoid carcinomas
    - Pleomorphic carcinoma
    - Spindle cell carcinoma
    - Giant cell carcinoma
    - Carcinosarcoma
    - Pulmonary blastoma
    - Other
8. Carcinoid tumor
    - Typical carcinoid (TC)
    - Atypical carcinoid (AC)
9. Carcinomas of salivary gland type
    - Mucoepidermoid carcinoma
    - Adenoid cystic carcinoma
    - Epimyoepithelial carcinoma

A Modified from the 2004 WHO Classification [15] and the 2011 IASLC/ATS/ERS Classification of Lung Adenocarcinoma [16]. This classification primarily addresses histology in resected specimens.

Epidemiology of Lung Cancer

Currently, lung cancer is the most common cause of cancer-related deaths worldwide and the most often diagnosed malignant tumor [17]. The most common type of cancer worldwide is lung cancer. According to the International Agency for Research on Cancer's (IARC) most recent estimates, the following are the global cancer statistics by world regions for 2022. Nearly 20 million new cases of cancer, including non-melanoma skin cancers [NMSCs], were reported in 2022, and 9.7 million people died from cancer, including NMSCs [18]. One in five men and women are predicted to have cancer at some point in their lives. Cancer claims the lives of one in nine men and one in twelve women. In 2022, lung cancer received the most diagnoses. It affected 2.5 million new cases, or one out of every eight cancer cases worldwide (12.4% of all cancer cases worldwide). With an anticipated 1.8 million deaths (18.7%), lung cancer was also the most common cause of cancer-related mortality [18].

Epidemiology of genetics

After adjusting for cigarette smoking, segregation studies show a 2.5-fold increased risk of lung cancer from family history, pointing to the existence of a rare autosomal dominant gene that predisposes to the disease (Amos et al, 1999). When lung cancer strikes non-smoker's, the familial relationship is easiest to find. However, genetic variations that are common in the population likely have minor but significant effects that account for the majority of inherited lung cancer risk [19].

When the activated carcinogens attach to DNA, they generate adducts that cause mutations, particularly G-to-T transversions, which can either be fixed, cause apoptosis, or endure. Based on the interactions between tobacco carcinogens, genetic polymorphisms involved in activating and detoxifying these carcinogens, and host cell efficiency in monitoring and repairing tobacco carcinogen-DNA damage, molecular epidemiology has demonstrated variations in smoking-related risk [20].

Pathogenesis of Lung Cancer

Lung cancer's molecular pathogenesis is a complex and heterogeneous process. Numerous genetic variables and epigenetic modifications, such as point mutations, amplifications, insertions, deletions, and translocations, can result in lung cancer. This is specifically linked to the suppression of tumor suppressor pathways and the activation of a pathway that stimulates growth (Figure 1).[21].

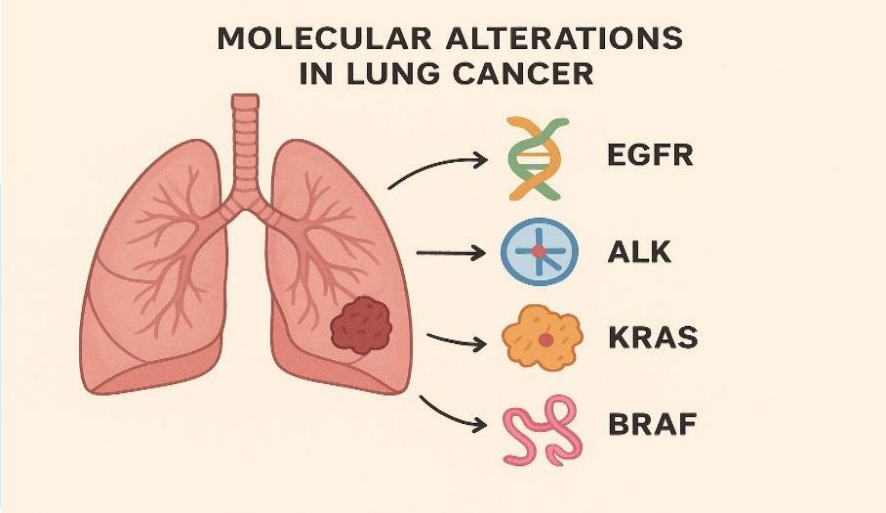

Figure 1. Molecular alterations in lung cancer

Research shows that squamous cell carcinomas and adenocarcinomas, two kinds of non-small cell lung cancer, are relatively uncommon and have different molecular traits [22,23]. Figure 2 lists the precursor mutations in NSCLC along with their prevalence's per histologic subtype.

The accumulation of several genetic and epigenetic alterations in the cell nucleus over an extended period of time should be interpreted as the biological underpinning of lung cancer [24] When a particular cell loses control over the processes that govern its division and placement, the cancer process begins. With the exception of not submitting to regulatory mechanisms and becoming insensitive to signals from other cells, its cell cycle is comparable to that of normal cells. Disorders in the expression of genes regulating the cell cycle play a vital part in all neoplastic transformation.

The following factors Impact the start and course of the neoplastic process:

- Cell cycle regulation abnormalities;
- Proto-oncogene and tumor suppressor gene mutations;
- DNA repair process disorders;
- Increased growth factor and angiogenesis expression;
- Avoidance of apoptosis (anti- and pro-apoptotic gene alterations);

Another significant factor is the instability of the entire cell genome, which happens at the start of the carcinogenesis process. It is the outcome of numerous genetic anomalies gradually building up. As a result, the DNA structure weakens and becomes more vulnerable to further mutations [25,26].

The MYC, RAS, and HER gene families are the proto-oncogenes that most frequently undergo mutations in lung cancer. Another crucial event is the rearrangement of the ALK gene [28].

The most frequently mutated suppressor genes in lung cancer cells are TP53, RB, and p16 [27]. The MYC, RAS, and HER gene families are the proto-oncogenes that most frequently undergo mutations in lung cancer. Another crucial event is the rearrangement of the ALK gene [28]. Because of their chaotic arrangement, fluctuating width, fragility, and brittleness, the vessels feeding the tumor may cause hemoptysis, one of the clinical symptoms. As such, the doctor treating such a patient should constantly be more oncologically vigilant. One key element in the pathophysiology of lung cancer is a decline in the cells' capacity to carry out apoptosis appropriately in response to environmental cues.

Apoptosis, sometimes referred to as physiological, active, suicidal, or programmed cell death, is a process that establishes the body's balance.

Etiology of Lung Cancer

Lung cancer is most frequently caused by smoking. Smoking is thought to be the cause of 90% of cases of lung cancer [29]. Male smokers are at the highest risk. Exposure to other carcinogens, such asbestos, increases the risk much more. Because of the intricate interactions between smoking, environmental variables, and genetics, there is no association between the number of packs smoked annually and lung cancer. There is a 20–30% increase in the risk of lung cancer due to passive smoking [29]. Radiation therapy for non-lung cancers, particularly non-Hodgkins lymphoma and breast cancer, is another factor [30]. Lung cancer is also linked to exposure to metals like arsenic, nickel, chromium, and polycyclic aromatic hydrocarbons.

Independent of smoking, lung conditions such as idiopathic pulmonary fibrosis raise the risk of lung cancer [31]. Additionally, radon and asbestos are known risk factors for lung cancer. Although it varies depending on the kind of asbestos fiber, exposure to asbestos, especially occupational exposure, raises the risk of lung cancer in a dose-dependent manner. The risk of non-occupational asbestos exposure is less clear. The Environmental Protection Agency (EPA) of the United States has established guidelines for low-level tolerable nonoccupational asbestos exposure, claiming that there is little health risk to building occupants if asbestos is left undisturbed and there are no respirable particles present [32].

Uranium miners who were exposed to radon had a slight but considerable risk of developing lung cancer [33]. It has also been demonstrated that radon builds up in dwellings as a by-product of uranium and radium decay. According to a meta-analysis of European research, home radon poses significant risks, especially to smokers, and accounts for around 2% of all lung cancer deaths in the continent [34].

Sign and Symptoms of Lung Cancer

The traditional physical examination for suspected lung cancer includes a comprehensive medical history, an evaluation of both active and passive tobacco smoke exposure, a family history of the disease, and occupational exposure to other known carcinogens. [35,36]

Enlargement of the heart silhouette, weakening of heart sounds, widening of the jugular veins, low amplitude of arterial pressure, and cardiac arrhythmias are the symptoms used to diagnose myocardial infiltration and the presence of fluid in the pericardial sac [37,38]. Superior vena cava syndrome symptoms, such as facial swelling, neck circumference enlargement, upper limb swelling, jugular vein and chest wall vein widening, and bruising of the facial skin and mucous membranes, are frequently seen in patients with advanced cancer [39, 40]. Table 1 presents the local and generalized clinical signs that accompany the formation of lung tumors.

Table 1. Local and general symptoms occurring in the course of lung cancer [41].

Local Symptoms of Lung Cancer	**General Symptoms of Lung Cancer**
Cough (especially a change in its character)	Arthralgia
Dyspnea	General weakness
Hemoptysis	Weight loss
Chest pain	Weight gain
Recurrent pneumonia	Superficial sensory disorders
Hoarseness	Symptoms of thrombophlebitis
Swallowing disorder	Symptoms of paraneoplastic syndromes: Wasting syndrome Exhaustion syndrome Syndrome of inappropriate antidiuretic Hormone secretion (SIADH) Cushing's syndrome Hypercalcemia Lambert–Eaton syndrome retinopathy Encephalopathy
Shoulder pain	
Superior vena cava syndrome	
Horner's syndrome	

Diagnosis and Staging of Lung Cancer

The state of the main tumor (feature T, tumor), regional lymph nodes (feature N, node), and organs where metastases may be present (feature M, metastasis) are all evaluated in order to determine the stage of lung cancer. The size, position, and relationship of the primary tumor to the surrounding anatomical structures (chest wall, pleura, diaphragm, heart, major arteries, and esophagus) as well as the state of the nearby lymph nodes are all important considerations for individuals who are eligible for radical treatment. Table 2 displays the collection of tests that are used to evaluate advancement. Table 4 determines the clinical stage of non-small cell lung cancer based on the combined evaluation of the T, N, and M features (Table 3).

The percentage of patients in stages I–II, III, and IV of NSCLC at diagnosis is roughly 25%, 35%, and 40%, respectively.

Table 2. Lists the tests used in the lung cancer staging process.

Primary Tumor Assessment	Lymph Node Assessment	Assessment of Distant Organs
• X-ray • CT (less often MRI) •Bronchofiberoscopy •Transbronchial biopsy ("blind", "semi-blind" transbronchial biopsy using radial ultrasound transducer, endobronchial ultrasonography, esophageal ultrasonography) • Chest wall biopsy (peripheral lesions) • Cryobiopsy of peripheral lesions • Pap smear examination of pleural or pericardial fluid	•Computed tomography (less often magnetic resonance) •Bronchofiberoscopy • Mediastinoscopy •Parasternal Mediastinoscopy • Positron emission tomography—computed tomography • Physical examination • Fine needle aspiration biopsy or surgical biopsy of suspected supraclavicular nodes • Thoracoscopy •Esophageal ultrasonography •Endobronchial ultrasonography	• Abdominal ultrasound or computed tomography • Biopsy of a single focus in the adrenal gland with suspected metastasis • Computed tomography or magnetic resonance imaging of the brain [SCLC—always; NSCLC—before planned radical treatment (see the text for details) and in case of clinical suspicion] •Bone scintigraphy (SCLC—planned combination therapy; NSCLC—Clinical Suspicion) • Positron emission tomography—computed tomography • Fine needle aspiration biopsy or surgical biopsy of suspicious lesions

Table 3. Classification of TNM in lung cancer (UICC, 2016) [42].

Feature	Characteristics
T	
TX	Without the ability to be seen by imaging and bronchoscopy, the primary tumor cannot be assessed or its existence confirmed just by the presence of tumor cells in the bronchial secretion.
T0	Lack of the main characteristics of the tumor
Tis	carcinoma in situ
T1	A tumor that is no larger than 3 cm in diameter, encircled by pulmonary pleura or parenchyma, and free of major bronchial infiltrate
T1a(mi)	Adenocarcinoma < 3 cm, a single tumor, primarily lepidic growth type, with an invasive component ≤ 5 mm in the greatest dimension, is considered minimally invasive.
T1a	A rare primary tumor that spreads superficially and has an invasive component that is restricted to the bronchial wall, even if it arises in the main bronchi, and has a maximum size of 1 cm
T1b	Tumor that is larger than 1 cm but not larger than 2 cm.
T1c	Tumor that is larger than 1 cm but not larger than 2 cm. The greatest tumor is larger than 2 cm but not larger than 3 cm.
T2	A tumor that is larger than 3 cm but not larger than 5 cm, or one that has at least one of the following characteristics: -involvement of the main bronchi without involvement of the major spur -a visceral invasion of pleura -concurrent pneumonia or atelectasis that affects both the lung's central region and the entire lung
T2a	Tumor that is larger than 3 cm in diameter but not more than 4 cm.
T2b	A tumor that is larger than 4 cm but not larger than 5 cm.
T3	Any tumor that has infiltration of one of the following regions, or one that is larger than 5 cm but not larger than 7 cm in diameter: -the upper thoracic opening tumor is included in the chest wall -the phrenic nerve -pericardial wall or

	Tumor in the same lung lobe that coexists with satellite lesions
T4	Any size tumor that has infiltration in one of the following regions, or a tumor larger than 7 cm in diameter: - the mediastinum - diaphragm - heart - big dishes - the trachea - recurrent nerve of the larynx - esophagus - circles - the primary spur or Any size tumor that coexists with satellite lesions in a different lung lobe

Table 3. Cont.

Feature	Characteristics
N	
NX	Incapacity to evaluate the lymph nodes nearby
N0	There are no metastases in the nearby lymph nodes
N1	Intrapulmonary (including direct involvement by continuity from the side of the primary tumor) and peribronchial (or hilar) lymph node metastases on the side of the primary tumor
N2	Metastases in the tracheal bifurcation and/or mediastinal lymph nodes on the side of the original tumor
N3	Metastases on the contralateral side's mediastinal lymph nodes or hilum, behind the inclining muscle, and/or supraclavicular on the side opposite the initial tumor
M	
MX	Unable to evaluate metastases to other organs
M0	No distant metastases were found
M1	Distant metastases are present
M1a	There may be tumor cells in the pericardial fluid, pleura/pericardial nodules, or satellite lesions in the opposing lung
M1b	One distant metastasis in a single organ is present
M1c	One organ having several metastases, or several organs having metastases

Table 4. Stages of lung cancer (UICC, 2016)

Stages	Characteristics		
Occult cancer	TX	N0	M0
0	Tis		
IA1	T1a(mi), T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, T1b, T1c, T2a, T2b T3	N1 N1 N0	M0 M0 M0
IIIA	T1a, T1b, T1c, T2a, T2b T3 T4	N2 N2 N1 N0, N1	M0 M0 M0 M0
IIIB	T3, T4 T1a, T1b, T1c, T2a, T2b	N2 N3 N3	M0 M0 M0
IIIC	T3, T4	N3	M0
IVA	each T	each N	M1a, M1b
IVB	each T	each N	M1c

Treatment of Non-Small Cell Lung Cancer (NSCLC)

Stage I

The primary treatment for stage 1 NSCLC is surgery. Either lobectomy or pneumonectomy with mediastinal lymph node sampling are the preferred procedures. For IA and IB diseases, the 5-year survival rates are 78% and 53%, respectively. A more cautious strategy using wedge resection or segmentectomy can be used in patients who lack the pulmonary reserve to withstand pneumonectomy or lobectomy. While survival is the same, a higher local recurrence rate is a drawback. In stage I disease, there is little evidence that adjuvant chemotherapy or local postoperative radiation therapy improves prognosis.

Stage II

Stage IIA lung survival is 46%, whereas stage IIB lung survival is 36%. Adjuvant chemotherapy after surgery is the recommended course of treatment. An en-bloc excision of the chest wall is advised if the tumor has spread to the chest wall. A distinct type of stage II tumor is the pancoast tumor. It originates in the superior sulcus and is typically identified at stage IIB or IIIA. Neoadjuvant chemotherapy, typically with etoposide and cisplatin, and concomitant radiation, followed by excision, are the preferred treatments for Pancoast tumors. Depending on whether microscopic disease was present in the resected specimen after surgery, the overall survival rate ranges from 44% to 54%.

Stage III

There is no consensus on treatment for patients with stage IIIA tumors with N2/N3 lymph nodes; if the patient has good performance status and no weight loss, concurrent chemo-radiotherapy affords the best outcome; however, concurrent chemo-radiotherapy is not as tolerated and can cause severe esophagitis. This is the most heterogeneous group, with a wide variety of tumor invasion and lymph node involvement. Surgery with curative intent is the treatment of choice in stage IIIA disease with N1 lymph nodes; however, a considerable number of patients are found to have a N2 disease at the time of resection. Sequential treatment is more palatable. Five-year survival is barely 20%, compared to 40% to 45% in the first two years.

Chemoradiation is typically the only treatment used for T4 tumors. For T4 N0-1 tumors with carinal involvement, surgery can be a possibility. Carinal resection has a 10% to 15% surgical death rate and a 20% survival rate. Surgery alone results in a 20% five-year survival rate if the tumor is T4 and caused by ipsilateral nonprimary lobe nodules without mediastinal invasion.

Stage IIIB tumors are treated with concurrent chemotherapy and radiation therapy, same like unrespectable IIIA malignancies. After post-induction chemotherapy and radiation therapy, surgery may be an option for a small number of patients. Since inoperable IIIA tumors were included in the trials on the survival of individuals with IIIB tumors, it is unknown how well IIIB patients will fare.

Stage IV

Since stage IV disease is thought to be incurable, treatment focuses on enhancing survival and reducing symptoms. Five years after diagnosis, just 1% to 3% of patients survive, and only 10% to 30% of patients react to chemotherapy. Patients with functional performance status are provided chemotherapy based on one or two drugs. Chemotherapy has a slight survival advantage. Bevacizumab is a vascular endothelial growth factor (VEGF) inhibitor that may be useful in the treatment of non-squamous non-small cell lung cancer (NSCLC) in very specific patients who do not have hemoptysis or brain metastases. [43]

Targeted Therapy for NSCLC

Researchers found in the early 2000s that certain mutations encode essential proteins for cell division and proliferation. “Driver mutations” is the term given to these mutations. It was suggested that patients with lung cancer could have a higher chance of survival if certain mutation pathways were blocked. Every advanced non-small cell lung cancer is currently examined for the following mutations. There is a particular inhibitor available for each of these mutations:

1. Tyrosine kinase inhibitors erlotinib, gefitinib, and afatinib block a mutation in the EGFR (epidermal growth factor receptor). [44]
2. Crisotinib, ceritinib, and alectinib are selective inhibitors of anaplastic lymphoma kinase, or ALK. ROS-1 is a mutant that shares structural similarities. Crisotinib was recently approved by the FDA to treat malignancies that have ROS-1 mutations.

Immunotherapy for NSCLC

Immunotherapy strengthens the immune system, makes it more responsive, and aids in the recognition of cancer cells as alien. The immune system uses a number of checkpoints to reduce autoimmunity and cell autodestruction. These checkpoints are hijacked by cancerous cells, which then induce immunological tolerance. Programmed-death receptor 1 (PD-1) is one of these checkpoints that has garnered a lot of attention lately. PD-1 is crucial for promoting self-tolerance and suppressing T-cells. It also decreases the immune system’s ability to combat tumor cells, though. PD-L1 and PD-L2 are two proteins with which PD-1 interacts. Activated T-cells become inactive as a result of this binding. Only antibodies against PD-1 and its ligand, PD-L1, are currently approved.

An IgG4 monoclonal antibody that fights PD-1 is called nivolumab. The FDA has approved it for both squamous and non-squamous non-small cell lung cancer (NSCLC) that has advanced following platinum-based chemotherapy. Patients with high or low levels of PD-L1 expression can use it. Another IgG4 monoclonal antibody that fights PD-1 is pembrolizumab. It is authorized for use in pre-treated

metastatic non-small cell lung cancer (NSCLC) that has over 50% PD-L1 expression and is free of EGFR and ALK mutations. For metastatic non-squamous non-small cell lung cancer (NSCLC) with less than 50% PD-L1 expression, it is also used in conjunction with pemetrexed and carboplatin. An IgG1 antibody that targets PD-L1 is atezolizumab. It can be used in metastatic, progressing non-small cell lung cancer (NSCLC) either during or after platinum-based chemotherapy treatment.

Patients who express ALK and EGFR mutations and do not respond to targeted therapy may utilize it. Bevacizumab is not regarded as an immunological treatment. This antibody inhibits vascular endothelial growth factor A (VEGF-A) and is anti-angiogenesis. It is mostly used to treat non-squamous non-small cell lung cancer in conjunction with platinum-based chemotherapy. Because of the possibility of severe and frequently deadly hemoptysis, it is contraindicated in squamous cell non-small cell lung cancer. Additionally, it is used to treat brain, colon, kidney, and breast malignancies. [45] [46]

Small Cell Lung Cancer Treatment

Despite having a high recurrence rate, SCLC is extremely susceptible to chemotherapy. The course of treatment for SCLC depends on the disease's stage.

Treatment of Limited-stage Small Cell Lung Cancer

In stage I limited-stage small cell lung cancer (LS-SCLC), adjuvant chemotherapy is administered after lobectomy. One of these is SCLC that manifests as peripheral nodules devoid of hilar or mediastinal lymphadenopathy. The involvement of lymph nodes should be carefully ruled out. Even if PET-CT results for lymph node size or FDG uptake were negative, this is accomplished by sampling lymph nodes using EBUS bronchoscopy or mediastinoscopy.

Radiation therapy is used after four to six cycles of chemotherapy for LS-SCLC that involves mediastinal or hilar lymph nodes. Since about 80% of SCLC would recur locally without radiation therapy, it is recommended to prevent recurrence. Multiple treatment modalities are available, such as sequential treatments or concurrent and alternative chemo-radiotherapy. Alternative and concurrent pathways are more harmful than other methods, but their results are marginally better. Sequential treatment is far more well tolerated.

Prophylactic whole brain radiation is also administered to individuals who experience remission. This improves overall survival and drastically lowers symptomatic brain metastases.

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

Distant metastases, malignant pericardial or pleural effusions, contralateral hilar, or involvement of supraclavicular lymph nodes are all indicators of extensive stage small cell lung cancer (ES-SCLC). Platinum-based chemotherapy is used as treatment. Prophylactic whole-brain irradiation should be administered after radiation therapy, as up to 50% to 60% of patients exhibit remission. Just 5% of patients survive two years after diagnosis, and the median survival from the time of ES-SCLC diagnosis is approximately 8 to 13 months.

Nanotechnology in cancer therapeutics

The discipline of nanotechnology, which combines molecular science and technology, has the potential to revolutionize cancer therapies. New drug delivery techniques that improve the accuracy, efficacy, and success of cancer treatment can be developed using nanoscale materials. These tiny structures have a high degree of selectivity in targeting tumor cells, minimizing side effects and causing less harm to healthy tissues.

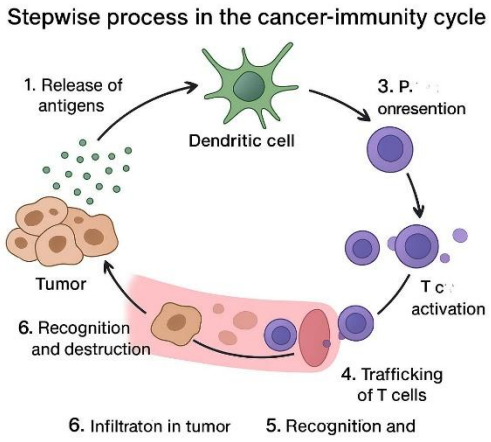

Figure 2. Stepwise process in the cancer-immunity cycle.

Liposomes

Scientists can create novel drug delivery systems that improve the precision, efficacy, and safety of cancer treatments by altering materials at the nanoscale level. At the intersection of molecular research and engineering, nanotechnology holds the potential to fundamentally alter cancer treatments. Lipid or fatty tissue-based nanovessels are intended to treat a range of diseases and immunological tests. Because of their high selectivity, these nanostructures can minimize side effects and lessen the impact of malignant cells on healthy tissues [47,48]. One kind of nanomedicine is liposomes, which are spherical NPs with a particular structure. Anticancer medications can be made more

selective, bioavailable, and biocompatible by encapsulating them in various liposome forms. Therapeutic liposomes come in a variety of forms, such as immunoliposomes and pH-sensitive liposomes.

"Targeting tumor cell and cancer tissue receptors" refers to the tactic of affixing particular molecules to the liposomes' membrane surface so that they can bind to particular receptors that are overexpressed on cancer cells.

Nanoparticles

Nanoparticles (NPs) are minuscule particles having special optical, conductivity, and durability qualities. These NPs act as drug carriers, or nanocarriers, altering the medication's pharmacokinetics and reducing its side effects. They are divided into two groups: inorganic and organic carriers[49] . NPs ought to be non-toxic, biodegradable, and biocompatible. Among the most often used nanocarriers in cancer treatment are polymers, which include solid lipid NPs, mineral NPs, hydrogel NPs, dendrimers, nano-spheres, nanocapsules, and polymersomes. The NPs enter the melanoma-covered microenvironment directly. Through a variety of methods, this inhibits cancer and prevents it from spreading from its original location. Although NPs come in a variety of forms, the drug NP conjugate is created when NPs and monoclonal antibodies are used together to target cancer cells [50,51] .These are connected to the cancer's active areas, which are extremely non-toxic and do not harm or destroy nearby healthy cells. Because of their potential for targeted tumor administration and improved tumor imaging capabilities, NPs are useful carriers for anticancer medicines.

Nano composites

NCs are nanoscale particles with functional specificity that are embedded in a matrix of another substance. These particles can be organic or other NPs. These NCs, a type of nanocarrier, are made up of several materials, each of which has at least one nanoscale dimension. They consist of nanostructures that enclose nanoscale particles in the matrix of another material [52] . When used to deliver a therapeutic payload, this NC should be released at or close to the intended location. There must be little nonspecific deposition of the therapeutic cargo along its journey from the administration site to the action site. NCs carrying therapeutic medicines should lessen nonspecific deposition as the cargo leaves the administration site in order to efficiently target malignancy with drug delivery. This method shields the medicinal substances from deterioration in the environment and stops chemotherapeutic medicines from causing toxicity or unfavorable reactions in healthy tissues [53,54].

This nanoscale composite's HA-encapsulated silver nanoparticles (AgNPs) limit tumor growth by reducing cytotoxicity and destroying mutant cells. By lowering membrane components, the redox conditions of the NC function as a ligand and reducing agent for CD44, promoting cell death[55] . Molybdenum NCs, which are employed in cancer research, readily bind to a variety of bodily indicators due to their optical characteristics, improving diagnosis and therapy via drug-release processes.

Quantum dot

Significant applications in bioimaging, targeted gene delivery, photodynamic treatment (PDT), biosensing, innovative drug discovery, and diagnostics have been demonstrated by the use of QDs in natural imaging and photography. For clinical resolution, fluorescence imaging technology is a useful tool. Because of their robust fluorescence emission and photochemical stability, QDs significantly improve fluorescence imaging. Cell transport mechanisms, cell functional heterogeneity, membrane transport protein diffusion movements, nonspecific signaling for imaging and detection, contrast in blood and lymph vessels (including microvessels), in vivo hepatoma diagnosis, intracellular delivery, internalization by live cells, probes in other bioassays, and many other applications are all explored by QDs in biomedical applications [56]. These QDs were discovered to be less dangerous and to enable quick and accurate fluorescence imaging. In vitro fluorescence pictures created by researchers utilizing QDs that depict adenocarcinoma, glioblastoma, ovarian, breast, pancreatic, hepatocellular, and glioblastoma malignancies. QDs that block the type-1 insulin-like growth factor receptor (IGF1R) offer a useful substitute for identifying and observing breast cancer cells.

Risk factors

Smoking, especially active smoking, is the biggest risk factor for lung cancer, however there is scientific evidence that passive smoking is equally significant. Eighty to ninety percent of instances of lung cancer are caused by smoking, and the lifetime risk of lung cancer is around 17% for men who smoke, 12% for women who smoke, and 1.5% for non-smokers [35,57]. Long-term exposure to substances like radon, asbestos, polycyclic aromatic hydrocarbons, arsenic, beryllium, cadmium, silicone, vinyl chloride, nickel and chromium compounds, and diesel engine exhaust is linked to an increased risk of lung cancer, according to the literature [58,59]. The aforementioned substances have a significant potential for genotoxicity, which leads to the development of various oxidative and nitrative damages. Furthermore, there is evidence of multidirectional activation of signal transduction pathways and the creation of the "cross-talk" phenomenon, which increases unchecked cellular proliferation [60]. Lung cancer risk is further increased by exposure to environmental pollutants and ionizing radiation used to treat other malignancies, such as breast cancer or early Hodgkin lymphoma [35]. Compared to the general population, first-degree relatives who have lung cancer are more likely to get the disease [61,62]. According to a research released by the American Society of Clinical Oncology (ASCO), smoking is the primary cause of lung cancer, but some people may have a genetic susceptibility. Researchers in the United States have demonstrated that patients with lung cancer may also develop pancreatic cancer, ovarian cancer in women, and prostate cancer in men due to the same tendency. They caution that the patient's closest family members might also be more vulnerable to cancer. The majority of lung cancers can be linked to smoking cigarettes and other environmental factors like asbestos exposure, according to experts from the American Society of Clinical Oncology. However, for thousands of patients, the disease is caused by inherited genetic factors. Up until now, it appeared that unfavorable environmental conditions and unhealthy lifestyle choices, most notably smoking, could be the source of harmful genetic alterations that lead to lung cancer. Nonetheless, certain individuals are more susceptible to this malignancy due to inherited genetic alterations. According to research conducted by American experts, identifying inherited genetic alterations known as pathogenic germline variations, or PGVs, is

crucial for estimating the risk of lung cancer. It has been determined that 15% of patients with lung cancer experience it. For these patients' closest relatives, this knowledge is also crucial. In addition to lowering the incidence of severe illness, early discovery of genetic predisposition enables even more effective treatment to be administered [63]. 1161 of the 7788 lung cancer patients in the study had inherited genetic alterations in 81 recognized cancer mutations. Approximately 95.1% of patients with these lesions potentially benefit from early illness detection or treatment with currently available medicines [63]. The lung cancer risk variables are as follows :

1. *Smoking*

Ninety percent of lung cancer cases in males and eighty percent in women are caused by smoking. Compared to non-smokers, smokers have a thirty-fold increased risk of dying from lung cancer. More than 7000 chemical components, including more than 70 carcinogenic chemicals, are concealed in cigarette smoke. Compared to those who are not exposed to tobacco smoke, second-hand smoke is also linked to an increased risk of lung cancer. Passive smokers are thought to be responsible for between 20 and 50 percent of lung cancer cases in "non-smokers" [64].

2. *Alcohol*

Lung cancer is more common among those who abuse alcohol, according to studies. Researchers estimate that smoking may be a contributing factor, although they do not provide precise statistics. People are more prone to seek for smokes after drinking, according to studies. Researchers from the University of Liverpool examined 47,967 Americans and 125,249 British drinkers. They have found up to six genes that they believe are linked to excessive alcohol use and, in turn, to lung cancer [65].

3. *Genetic predisposition*

It is yet unclear how hereditary factors play a part. A genetically determined propensity to either overactivate or eliminate carcinogenic chemicals from tobacco smoke from the body too slowly is linked to the high prevalence of lung cancer in some families. Additionally inherited is the propensity for respiratory epithelial cells to gradually repair DNA damage following carcinogen action. In conclusion, it may be said that the inherited syndrome is essentially a unique vulnerability to the harmful effects of tobacco. There are now no trustworthy genetic tests to identify the increased risk of lung cancer, and this inheritance is caused by polymorphisms (population variances) in numerous genes. According to research conducted by American experts, identifying inherited genetic alterations, also known as pathogenic germline variations, or PGV, is crucial for estimating the risk of lung cancer. It has been determined that 15% of people with lung cancer experience it, which is a rather substantial proportion [64].

4. *Occupational factors*

Lung disorders, including lung cancer, can occur as a result of exposure to numerous occupational variables. Heavy metals, silica, asbestos, and polycyclic aromatic hydrocarbons are the most significant occupational carcinogens [66]. Chrysotile is less potent than other kinds of asbestos, probably because it is more easily removed from the lungs, although both types of asbestos—including chrysotile and amphiboles like crocidolite, amosite, and tremolite—are carcinogenic. Asbestos exposure at work is still common in many developing nations [66,67]. Numerous industries and vocations linked to exposure to polycyclic aromatic hydrocarbons have been linked to an increased risk of lung cancer. These include the manufacturing of aluminum, coal gasification, coke, iron and steel foundries, tar distillation, roofing, and chimney cleaning. Additionally, it has been proposed that workers in a number of other industries, such as carbon electrode manufacture, wood impregnation, roofing, and shale oil extraction, are more susceptible to lung cancer [68].

5. *Environmental factors*

According to data on air pollution, the incidence of lung cancer rises by 30–50% in regions with higher ambient air pollution levels than in those with lower levels [68,69]. The risk of lung cancer is significantly higher in highly industrialized, urbanized areas with a developed transportation system, especially one that relies on internal combustion engines, according to numerous studies conducted to date [36].

6. *Age*

The risk of acquiring lung cancer also increases with age. About half of lung cancer diagnoses in both sexes occur in those over 65, with the bulk of instances (96% in men and 95% in women) occurring after the age of 50. Men's risk of lung cancer rises in their eighth decade of life, while women's risk peaks at the beginning of their sixth and seventh decades [18].

Limitations

Globally, the poor prognosis of individuals with lung cancer is a problem. More effective primary prevention (reducing exposure to harmful products of tobacco combustion), early detection and efficient pathomorphological advancement and diagnosis, increasing the proportion of patients undergoing full surgical treatment, expanding the use of modern radiotherapy and radiochemotherapy techniques, and rationalizing systemic treatment are all opportunities to improve the situation. The utilization of accessible targeted pharmaceuticals in clinically justified settings and the appropriateness of chemotherapy (e.g., qualifying patients with genuine prospects of benefiting or modifying medications to the histological type) are two examples of rationalizing systemic treatment. Reducing the dangers of lung cancer is a difficult task. The creation of "centre's of excellence," or facilities with complete diagnostic and treatment capabilities, should be a priority. After an earlier diagnosis of lung cancer, the rate of full resections of the lung parenchyma must be increased. Additionally, the waiting period for pathomorphological examinations must be shortened, and the percentage of radiotherapy—especially combined care with chemotherapy and radiotherapy—must be increased. Systemic treatment should be used more rationally, which includes improving the likelihood of treatment targeted at molecular targets and appropriately qualifying and managing chemotherapy. The final issue is mostly related to the poor setup of molecular predictive factor testing (insufficient number of laboratories conducting tests in

compliance with standards and an inadequate method of financing molecular diagnostics). Increasing the likelihood that patients will take part in controlled clinical trials on novel treatment approaches and utilizing more contemporary techniques to assess the efficacy of novel medications are crucial components. Proper post-treatment care and early diagnosis of problems and recurrences are also crucial.

Conclusion

Lung cancer, despite being one of the most extensively studied malignancies, remains the leading cause of cancer-related morbidity and mortality worldwide. The burden is immense, with millions of new cases and deaths reported annually, making it a critical public health challenge. While smoking is the most significant etiological factor, environmental pollutants, occupational exposures, radiation, alcohol use, and genetic predisposition also contribute substantially to disease incidence. The complex interplay between these factors highlights the need for comprehensive prevention strategies focusing not only on tobacco control but also on reducing occupational hazards and environmental risks.

In terms of diagnosis and staging, remarkable advancements have been achieved through the TNM classification, imaging techniques, biopsies, and molecular testing. These tools enable clinicians to assess tumor size, lymph node involvement, and distant metastases with greater accuracy, facilitating more personalized treatment planning. However, a large proportion of cases are still diagnosed at advanced stages, which severely limits curative options and contributes to poor survival rates. This underlines the urgent need for improved early detection methods, including biomarker-driven screening and wider accessibility of low-dose CT scans in high-risk populations.

The treatment of lung cancer has evolved significantly. For non-small cell lung cancer (NSCLC), surgery remains the mainstay in early stages, while advanced stages rely on a combination of chemotherapy, radiotherapy, targeted therapy, and immunotherapy. The discovery of driver mutations such as EGFR, ALK, and ROS1 has revolutionized personalized medicine, with tyrosine kinase inhibitors (TKIs) offering meaningful survival benefits. Similarly, the advent of immunotherapies, particularly immune checkpoint inhibitors targeting PD-1/PD-L1, has transformed the therapeutic landscape, offering durable responses in subsets of patients. Small cell lung cancer (SCLC), although highly responsive to chemotherapy and radiotherapy, is associated with a high recurrence rate and poor long-term survival, emphasizing the need for novel therapeutic strategies.

Nanotechnology presents an exciting frontier in lung cancer management, providing opportunities for more precise drug delivery, reduced systemic toxicity, and improved therapeutic outcomes. Liposomes, nanoparticles, and nanocomposites offer innovative avenues for targeted therapy, potentially overcoming some of the limitations of conventional treatments. However, translating these advances into widespread clinical practice requires further research, safety validation, and cost-effectiveness analysis.

Despite these advancements, significant challenges remain. Globally, the prognosis for lung cancer patients is still poor, largely due to late detection and disease aggressiveness. Multidisciplinary approaches that integrate early screening, accurate staging, targeted systemic therapy, and advanced radiotherapy techniques are essential to improving outcomes. Equally important is the rational selection of therapies tailored to the histological type, genetic profile, and clinical condition of patients, ensuring that treatment is both effective and sustainable.

In conclusion, while substantial progress has been made in understanding the biology, classification, and management of lung cancer, the disease continues to pose major health challenges. Prevention through tobacco control, lifestyle modification, and environmental regulation remains the most effective strategy to reduce incidence. Concurrently, expanding access to early detection tools, investing in precision medicine, and advancing innovative therapies such as immunotherapy and nanotechnology hold the key to improving survival rates. Moving forward, a strong emphasis on multidisciplinary care, personalized treatment, and global health initiatives will be crucial in mitigating the devastating impact of lung cancer worldwide.

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