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Navigating Lung Cancer: Exploring Progress and Obstacles - A Comprehensive Review

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Abstract

Lung cancer persists as a significant global health dilemma, characterized by elevated incidence and mortality rates worldwide. Despite recent strides in diagnostic methodologies, screening approaches, and therapeutic modalities, lung cancer retains its status as the foremost cause of cancer-related fatalities internationally. The disease is predominantly

categorized into two primary forms: small-cell carcinomas and the notably more prevalent non-small-cell carcinomas, constituting approximately 85% of cases. While smoking stands as the primary risk factor for lung cancer, accounting for 80-90% of related deaths, other factors such as dietary habits, air pollution, genetic predisposition, and prior lung conditions play substantial roles. Diagnostic procedures encompass a range of techniques, including radiography, sputum cytology, bronchoscopy, biomarker analysis, among others. The imperative for progress and refinement in diagnostic tools, especially for early detection and monitoring in high-risk demographics, underscores the urgency. Continual research and enhancement of surgical, systemic, and localized treatments are indispensable in the battle against lung cancer. Despite advancements, challenges persist in achieving timely diagnoses, particularly in high-risk groups, and augmenting overall survival rates. This comprehensive review delves into current research advancements in lung cancer, with specific focus on classification, patient well-being, risk factors, diagnostic methodologies, and treatment options.

Keywords: Lung cancer, NSCLC, tobacco smoking, TNM staging, Biomarker analysis

Introduction

The global impact of lung cancer has been and continues to be a significant global health and economic concern. Lung cancer is the second most commonly diagnosed cancer accounting for 2.2 million or 11.4% of global cancer diagnoses, being recently surpassed by female breast cancer with 2.3 million or 11.7% new cases. Despite this shift in rankings, lung cancer continues to maintain its position as the primary cause of cancer-related deaths, contributing to an estimated 1.8 million fatalities or 18% of global cancer deaths (1,2). In the majority of instances, patients are diagnosed with advanced or metastatic disease at the time of diagnosis. The life expectancy following diagnosis and management is typically less than five years. The 5-year survival rate for patients diagnosed with lung cancer is merely 10% to 20% (1,3,4). Lung cancer can be broadly categorized into two main histological types: small-cell lung carcinoma (SCLC), accounting for around 15% of all lung cancer cases, and non-small-cell lung cancer (NSCLC), making up approximately 85% of all lung cancer diagnoses (5,6). Tobacco smoking stands as the primary culprit behind all primary histological types of lung cancer. The carcinogenic impact of tobacco smoke on the lungs has been long recognized by public health and regulatory authorities and proven through epidemiological studies (7–9). Nonetheless, numerous additional risk factors contribute to the development of

lung cancer. These encompass genetic predisposition, a diet rich in fried or well-done red meat, alcohol consumption, a history of lung disease, exposure to second-hand smoke or ionizing radiation, environmental factors like radon or air pollution, and occupational hazards (7). Despite recent progress in diagnostic tools like genomic sequencing, advancements in tumor markers, early diagnostic screening, the identification, and prevention of risk factors, the modification of environmental hazards, and the utilization of systemic therapy, lung cancer remains a significant global concern (3).

Classification

Lung cancers are traditionally subdivided into SCLC (15%) and NSLC (85%). The 2021 World Health Organization’s classification of thoracic tumors divide of lung cancers has been analyzed and comprehensively presented in Table 1.

Table 1. List of Lung Tumors according to 2021 WHO Classification of Thoracic Tumors (5)

Lung Cancer Classification	Most common subtypes
Epithelial Tumors	Adenocarcinomas Squamous Cell Carcinoma Large-Cell Carcinoma Pleomorphic Carcinoma and others
Lung Neuroendocrine Neoplasms	Small Cell Carcinoma Large Cell Neuroendocrine Carcinoma Carcinoid Tumors
Tumors of Ectopic Tissues	Melanoma
Mesenchymal Tumors Specific to the Pulmonary hamartoma Lung	
Hematolymphoid tumors	MALT lymphoma

This divide summarizes the sub-classification of lung cancer into various types and their respective subtypes, highlighting the prevalence of epithelial tumors and the subtypes within neuroendocrine tumors. Tumors of ectopic tissues, hematolymphoid tumors, and mesenchymal tumors are far less prevalent (5).

Epidemiology

The information regarding lung cancer epidemiology is presented using the Global Cancer Observatory (GLOBOCAN) 2020 data, which focuses on the incidence and mortality of cancers, developed by the International Agency for Research on Cancer. The occurrence of lung cancer is estimated at 2.2 million cases worldwide, constituting 11.4% of all cancer diagnoses. It is the most common cause of cancer-related deaths globally, accounting for an estimated 1.8 million (18%) deaths. In women, lung cancer is the third most frequently diagnosed cancer (11.4%), following breast cancer (11.7%) and colorectal cancer, and it is the second leading cause of cancer-related deaths in women (13.7%).

Among men, lung cancer is the most commonly diagnosed cancer (14.3%) and the leading cause of cancer-related deaths (21.5%). The incidence and mortality rates are approximately 2 times higher in men than in women. The rates of lung cancer incidence and mortality are 3 to 4 times higher in countries in the transformation period compared to those in transitional countries. Globally, the highest incidence rates for lung cancer in men are observed in Micronesia/Polynesia, Eastern and Southern Europe, East Asia, and West Asia, while Turkey has the highest rate among men worldwide. In women, the highest incidence rates are found in North America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand (1,10).

International variations in incidence and mortality reflect the magnitude of the tobacco smoking epidemic. In women, a less advanced tobacco epidemic is observed, resulting in a lower incidence rate compared to men (11,12). In most countries, the 5-year survival rate for patients diagnosed with lung cancer is only 10% (1,13).

Risk factors

Tobacco smoking

Tobacco smoking is the primary factor responsible for lung cancer. It is associated with about 80-90% of lung cancer cases and 66% of lung cancer deaths worldwide (1,9). This

in turn means that the differences in lung cancer rates and trends predominantly mirror the state of the tobacco use epidemic in the region (11). The trends in lung cancer mortality can be explained by analyzing the varying patterns of smoking prevalence among successive cohorts in different countries (14,15). A rise in tobacco consumption is often mirrored by a subsequent increase in lung cancer incidence a few decades later, while a decline in consumption tends to be associated with a decrease in incidence. Likewise, the temporal gap in the trends of lung cancer mortality between females and males mirrors historical distinctions in cigarette smoking habits among successive female and male cohorts (11,16). Historically a sharp rise in the incidence of lung cancer occurred after the widespread adoption of tobacco smoking among the male population in various high-income countries (17,18). The reduction in lung cancer rates occurred several decades after the peak of smoking prevalence and was initially noticed in younger birth cohorts (19). Hence, the reduction in mortality rates from lung cancer among men has been ongoing in recent years and is expected to persist in the foreseeable future (20). On the contrary, the tobacco epidemic among women is less developed and delineated, with many countries still experiencing an increasing incidence of lung cancer (11,21). The Global Burden of Disease Project reported an estimated 1.14 billion global smokers in 2019, a rise from just under a billion in 1990. Although the prevalence of smoking decreased during this period, the total number of smokers increased due to population growth (22). Notably in the majority of populations, smoking prevalence tends to be significantly higher among groups with lower levels of education or income (23). Continuous smokers face an excess risk of lung cancer that is 20 to 50 times higher compared to individuals who have never smoked. Among smokers, the duration of smoking is identified as the most influential factor in determining the risk of developing lung cancer (24).

Genetic risk factors

The presence of lung cancer in non-smokers and a familial history of the disease lends support to the hypothesis that there is a hereditary component associated with the risk of developing especially early-onset lung cancer (25,26). Lung cancers in never smokers account for 10-25% of all lung cancer cases, and are predominantly comprised of lung adenocarcinomas (27,28).

Genome-wide association studies of lung cancer have been able to identify multiple genetic polymorphisms underlying lung cancer risk. The most common genetic variations identified at 5p15.33, 6p21.33, and 15q25.1 exert an influence on lung cancer risk (29) (30)

(31). Notably, many less common susceptibility loci have also been reported, such as 3q28 (32–34), 17q24.3 (35), and 12q23.1 (36). Additionally, single-nucleotide polymorphisms at 22q12 and the 15q15.2 locus are strongly associated with an increased risk of lung cancer. Various genes involved in mechanisms such as carcinogen metabolism, nucleotide excision repair, base excision repair, and cell cycle control appear to play a role in the development of lung cancer (37,38).

Diet

Various studies suggest that high concentrations of beta carotene, vitamin A, and alpha-tocopherol, as well as a diet rich in vegetables and fruits, may have a protective effect against lung cancer (39–41). Fruits and vegetables contain a diverse range of antioxidants, that confer beneficial effects in mitigating inflammation induced by smoking, preventing oxidative DNA damage, and inhibiting squamous metaplasia in the lungs (42). Carcinogens such as nitrosamines formed during the process of cooking or frying red, or processed meat may be responsible for the increased risk of lung cancer (43–46). Coffee intake has been reported to be associated with lung cancer, however, because coffee drinkers are more likely to be smokers, no conclusive evidence was able to be drawn concerning coffee's impact on lung cancer incidence (7,47).

Alcohol consumption has been reported to increase the risk of lung cancer (48,49). However, there exists a strong connection observed in numerous populations between alcohol intake and tobacco use, therefore accurately determining the role of alcohol in the development of lung cancer becomes challenging, particularly when trying to effectively account for the potential influence of tobacco as a confounding factor.

Air pollution

Evidence from both human studies and experiments on animals suggests a link between the incidence of lung cancer, especially lung adenocarcinoma, and the concentration of particulate matter with a size less than 2.5 micrometers (PM_{2.5}) in outdoor air (50). The composition of atmospheric particulate matter includes benzene, dioxins, polycyclic aromatic hydrocarbons, along with various other organic and inorganic compounds, as well as metals. The International Agency for Research on Cancer has classified particulate matter in polluted air as a Group 1 carcinogen (51). Particles formed during combustion, upon entering the lungs, have the potential to induce chronic inflammation, damage cells, and promote their proliferation, deplete antioxidants, impair defense mechanisms, generate reactive oxygen

species, and contribute to genetic mutations (52,53). Vehicle emissions represent a significant contributor to outdoor air pollution, emitting both gaseous and particulate pollutants (54).

Previous lung disease

Several studies indicate that even non-smoking patients who have suffered from chronic obstructive pulmonary disease, asthma, tuberculosis, or pneumonia face a heightened risk of developing lung cancer (55,56). Especially chronic obstructive pulmonary disease was found to be a significant factor, increasing the risk of lung cancer. In smokers, suffering from chronic obstructive pulmonary disease the risk of lung cancer increases 5-fold (57). Patients diagnosed with pulmonary tuberculosis have been observed to face an elevated risk of developing lung cancer. In a particularly insightful study involving a substantial cohort of tuberculosis patients, those with a history of tuberculosis exhibited a relative risk of 1.5, which increased to 2.0 twenty years after the tuberculosis diagnosis. The correlation was also noted to be associated with the location of the tuberculosis lesions (58,59).

The heightened risk of lung cancer in individuals with respiratory diseases may be explained by inflammatory responses in the lung tissues. Chronic inflammation resulting from these respiratory conditions damages the lung tissues. The accelerated rate of cell division amplifies the risk of DNA damage, which, especially combined with smoking contributes to an increased rate of mutations, thereby elevating the likelihood of lung cancer (38,60).

Quality of life

Patients suffering from lung cancer often struggle with numerous difficulties that significantly impact their quality of life. This translates into frequent diagnoses being made at an advanced stage (40%), and high mortality rates, with 5-year survival rates accounting for only 10-14%. Among the most commonly reported problems are the presence of pain, sleep disorders, limitations in performing daily activities, fatigue, shortness of breath, and coughing (61–63). In a study conducted at Public Clinical Hospital No. 4 in Lublin, 111 patients treated with cytostatics for lung cancer were examined, and their quality of life was assessed using the QLQ-C30 and QLQ-L13 questionnaires. Chronic fatigue was present in 98% of the participants, 94% reported limitations in daily activities, and 79% experienced psychological tension. Resting dyspnea was reported by 47%, and coughing by 41% of the participants. The majority of those surveyed rated their quality of life as average. Most respondents were worried and irritated, anxiety and depression were observed in almost the entire group of

patients. Pain was reported by all participants, and the most common and troublesome symptom from the respiratory system was dyspnea during minimal physical activity. In patients treated with chemotherapy, physical, cognitive, emotional, and social functioning declined with the age of the participants. It was also observed that the greatest intensity of fatigue was present among patients treated with chemotherapy for more than 6 months but less than a year. Social role functioning was significantly worse in urban residents than in rural areas, and sleep quality deterioration more frequently affected women than men (64). In another study conducted by Leppert, on average, over half of the participants rated their health status and quality of life as very poor, with this assessment prevailing in outpatients compared to those in a stationary center (63). In a study conducted at the Palliative Medicine Department in Gdańsk, 51 individuals with lung or bronchial cancer were examined to compare the impact of treatment methods on the quality of life of patients. It was noted that for the majority of participants, regardless of whether chemotherapy or radiotherapy was used, there was a significant improvement in the sphere of mental and physical functioning (64). Despite advancements in the diagnosis and treatment of lung cancer, it remains one of the more poorly prognostic cancers, significantly affecting the mental and physical functioning of patients.

Diagnosis and screening

Unfortunately, the diagnosis of lung cancer often occurs during the advanced stages of the disease, as >75% of patients have a stage III or IV disease at the point of diagnosis, which contributes greatly to its high mortality (65). Timely diagnosis is critical, particularly in screening high-risk groups like smokers, and individuals exposed to fumes, oil fields, and toxic workplaces. Identifying novel biomarkers is urgently required to enhance early detection. Precise diagnosis is indispensable for tailoring optimal treatment strategies for individual lung cancer patients. Therefore, the pressing task is to discover sensitive and specific biomarkers for early identification.

Screening high-risk groups increases the chance of the early detection of lung cancer at stages that are treatable and curable. High-risk individuals in which screening for lung cancer is recommended include those with a history of heavy smoking exceeding 30 pack-years, current smokers, or those who quit smoking less than 15 years ago, particularly those aged between 55 and 74. At present, only a portion of the recommended population undergoes the screening process (65,66).

Staging

For SCLC staging The Veterans' Administration Lung Study Group (VALSG) classification scheme has been consistently employed since the 1950s (67). It is a two-stage system in which SCLC is classified either as a limited disease, limited to a single radiation port confined to the ipsilateral hemithorax, or supraclavicular lymph nodes if they can be included in the same radiation port as the primary tumor, or the extensive disease, unrestrained to a single radiation port in the lung and metastasizes to the second lung lobe, lymph nodes, and various distant sites (65,67,68).

NSCLC is categorized using the tumor-nodes-metastasis (TNM) staging system formulated by the American Joint Committee on Cancer (AJCC) (69). The TNM system aids in assessing the cancer stage by considering the size of the primary tumor (T), the extent of tumor involvement in lymph nodes (N), and the presence of metastasis (M). It has been presented in Table 2.

Table 2. The eighth edition of TNM staging of lung cancer: T, N, and M definitions (69,70)

Descriptor	Definition
T0	No evidence of a tumor
Tis	Carcinoma in situ
T1	
T1a(mi)	Minimally invasive carcinoma
T1a	$\leq \nabla \circ ?$
T1b	$> \nabla \circ ? \text{ } \text{ } \text{ } \leq \circ \circ ?$
T1c	$> \circ \circ ? \text{ } \text{ } \text{ } \leq \circ \circ ?$
T2	
T2a	$> \circ \circ ? \text{ } \text{ } \text{ } \leq \text{ } \circ \circ ?$
T2b	$> \text{ } \circ \circ ? \text{ } \text{ } \text{ } \leq \text{ } \text{ } \circ \circ ?$
T3	$> \text{ } \text{ } \circ \circ ? \text{ } \text{ } \text{ } \leq \text{ } \text{ } \circ \circ ?$
T4	$> 7\text{cm}$

N0	No regional lymph nodes involved
N1	Ipsilateral peribronchial and/or ipsilateral hilar lymph nodes involved
N2	Ipsilateral mediastinal and/or subcarinal lymph nodes involved
N3	Contralateral mediastinal or hilar, ipsilateral/contralateral scalene/supraclavicular lymph nodes involved
M0	No distant metastasis
M1	
M1a	Separate tumor nodules in the contralateral lobe to the primary tumor, with pleural or pericardial effusion
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases

	Stage I		Stage II
A	T1, N0, M0	IA	T2b, N0, M0
B	T2a, N0, M0	IA	T1, N1, M0
		IA	T2a, N1, M0
		IB	T2b, N1, M0
		IB	T3, N0, M0

Imaging techniques

Given its wide accessibility, including for primary care physicians, the chest radiograph is frequently the initial imaging modality that may suggest the presence of lung cancer. Lung cancer can manifest as a clear-cut spiculated mass, but its indication may also be deduced from alternative presentations, such as persistent pneumonia or lobar collapse. In

the diagnosis of lung cancer through chest radiography, the sensitivity for detecting tumors is approximately 1 cm in diameter. However, computed tomography (CT) scanning of the chest is often necessary due to the limited sensitivity of chest radiographs in detecting mediastinal lymph node metastases, peripheral lung lesions, and mediastinal invasion (71,72).

Spiral CT scans have the capability to identify specific diagnostic features in lung nodules, and continuously acquire data, leading to shorter scanning times, reduced radiation exposure, and improved diagnostic accuracy compared to plain radiography. Spiral CT technology exhibits the capability to reveal nodules smaller than 5 mm in size. Nevertheless, the sensitivity of spiral CT for tumors situated in more central locations, particularly those of squamous cell carcinoma origin, is notably lower compared to its sensitivity for peripherally located tumors (65,73). Additionally, the false positive rates of low-dose CT screening were reported to be as high as 96% (74).

While CT demonstrates a sensitivity of 88% and specificity of 92% in mediastinal assessment, the staging process benefits from the addition of Positron Emission Tomography (PET). Integrated CT/PET scanners exhibit superior test characteristics compared to CT or PET alone (73,75,76). The use of low-dose CT has become a standard approach for lung cancer screening. However, there still remain significant obstacles hindering its widespread adoption among the general population in costs and issues related to accessibility.

Bronchoscopy

Flexible bronchoscopy has become the recommended procedure for all patients suspected of having lung cancer, demonstrating a sensitivity of 88% for central airway lesions (77). Moreover, flexible bronchoscopy enables accurate surgical planning by evaluating the tumor's surface, site, and extent, as well as assessing vocal cord motility and airway lumen (78). While white light bronchoscopy is the predominant diagnostic tool employed to establish a definitive histological diagnosis of lung cancer, it faces substantial diagnostic challenges when it comes to pre-malignant lesions. These lesions pose difficulties in visual detection due to their thickness of up to 1 mm, and a diameter measuring only a few millimeters (79–81).

Sputum analysis

Sputum is the most easily accessible biological fluid with a non-invasive collection process. Cigarette smokers typically produce higher quantities of sputum which contains

exfoliated cells from the bronchial tree (82). However, the sensitivity of sputum cytology for early lung cancer is limited, typically ranging from 20% to 30%. In addition, the increase in the incidence of adenocarcinomas has further decreased the validity of sputum cytology as a screening method since it exhibits a particularly low detection rate of adenocarcinomas (83,84).

Lung tissue biopsy

A biopsy of the lung tissue is the gold standard for cancer confirmation. For clinical diagnosis a tissue biopsy must be performed, to identify tumor histology and staging. The early confirmation of the diagnosis is crucial in the preparation and initiation of an optimized treatment plan (85,86). Most commonly employed procedures include surgical approach, flexible bronchoscopy with or without transbronchial needle aspiration, transthoracic needle aspiration, video-assisted thoracoscopy, and thoracentesis (65,68,77).

Biomarkers

Overcoming impediments to early lung cancer screening and diagnosis through conventional methods (as previously discussed) may be achieved by implementing the usage of the numerous biomarkers that are now surfacing as effective tools for early detection. Especially in recent years with the integration of next-generation sequencing technologies alongside advancements in bronchoscopic and imaging techniques a diverse set of molecular biomarkers for lung carcinoma has been identified (87).

Treatment and management

Treatment of early-stage (stage I and Stage II) Non-Small-Cell Lung Cancer

For early-stage lung cancer, surgical resection is the preferred treatment (88). This method provides the best option for long-term survival. Five-year survival rates after surgical resection are 60%-80% for stage I NSCLC and 30%-50% for stage II NSCLC patients (89). The degree of surgical removal is contingent upon the tumor's size and location, along with the patient's preoperative pulmonary capacity. While adjuvant chemotherapy is advised for completely removed stage II NSCLC and is the recommended treatment strategy for completely resected patients, it is typically not recommended for stage I. Post-surgery

radiation is not suggested unless the resection is incomplete. For individuals with unresectable tumors or those refusing surgery primary radiotherapy can be used such as stereotactic body radiotherapy (SBRT). (90). Another option for selecting peripheral tumors instead of SABR is percutaneous ablation. However, there is limited evidence of effectiveness and a notable occurrence of pneumothorax. Transbronchial ablation may present specific advantages and is presently undergoing investigative phases (91,92).

Treatment of Stage III Non-Small-Cell Lung Cancer

Stage III NSCLC is a heterogeneous condition and varies from resectable tumors with microscopic metastases to lymph nodes to unresectable, bulky disease involving multiple nodal locations (89). Patients with limited nodal (N1) involvement may be suitable for initial surgical resection, followed by chemotherapy and/or radiation (93). Patients with more advanced nodal (N2) involvement may still be eligible for surgery, typically after receiving induction therapy, as consistently favorable outcomes have been observed with this approach. However, it remains uncertain whether tri-modality therapy (involving surgery, chemotherapy, and radiation) offers greater benefits compared to chemo-radiation alone, necessitating further investigations, especially in subgroups of patients with N2 disease (94). Patients in which the primary tumor has directly infiltrated neighboring structures beyond the lung (T3-T4), and/or the cancer has extended to mediastinal lymph nodes (N2-N3) are not suitable for primary surgical removal (95).

Treatment of Stage IV Non-Small Cell Lung Cancer

The foundation of treating patients with advanced NSCLC lies in platinum-based chemotherapy (eg. cisplatin, carboplatin). However, the selection of treatment for individuals with stage IV NSCLC is contingent on various factors such as comorbidity, PS, histology, and molecular genetic characteristics of the cancer. It is generally advisable to conduct tests on tumor tissue to detect mutations in the epidermal growth factor receptor gene, rearrangements in the anaplastic lymphoma kinase gene, rearrangements in the reactive oxygen species proto-oncogene-1 gene, point mutations in the B-raf proto-oncogene, and point mutations in the KRAS proto-oncogene (KRAS) (93). The existence of these genetic modifications can influence the selection of targeted treatments, as they can forecast the effectiveness or ineffectiveness of specific agents. Moreover, evaluating programmed death

ligand-1 expression levels can assist in determining the appropriate use of certain immunotherapies.

In addition to systemic therapy, localized treatment may be necessary in stage IV disease. It is necessary when the metastasis causes local symptoms (96).

Treatment of Small Cell Lung Cancer

SCLC is a highly aggressive cancer distinguished by neuroendocrine differentiation, early metastasis, and initial responsiveness to treatment (97). SCLC is managed in a more straightforward manner compared to NSCLC, with all patients undergoing systemic therapy. For those with confirmed limited-stage disease, radiation is also administered. Patients initially treated for extensive disease receive systemic therapy alone, with the option of palliative radiation at sites causing significant symptoms due to tumor burden. Surgical resection is rarely considered, typically for less than 5% of SCLC cases involving stage I disease confirmed by invasive nodal staging and PET scan (98). Even in these instances, adjuvant postoperative chemotherapy is included. Prophylactic cranial irradiation is commonly recommended for all patients showing some response to therapy, irrespective of their initial stage, as it has been shown to improve overall survival (99).

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