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Pathophysiology, Diagnosis and Treatment of Lung Cancer: An Overview

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Abstract: Lung cancer is one of the most leading causes of cancer death in the world. Lung cancer, also known as lung carcinoma, is a malignant lung tumor characterized by uncontrolled cell growth in tissues of the lung. Lung cancer is the second most frequent cancer in both men and women. The major risk factor for lung cancer is smoking, which accounts for 75-80% of lung cancer-related deaths. If left untreated, this growth can spread beyond the lung by process of metastasis into nearby tissue or other parts of the body. Lung cancer can be broadly classified into 2 forms, small cell carcinomas and non-small cell carcinomas. Non-small cell lung cancer is more common, accounting for up to 75% of lung cancers. This review is comprehensive summary of study design, breath analytical methods, and suggested biomarkers in lung cancer. Various surgical and non-surgical therapeutic approaches including chemotherapy, immunotherapy, nanotechnology are employed in the treatment of lung cancer. This review will focus on the global variations and detail ideas of etiology, sign and symptoms, diagnosis and treatment of lung cancer.

Keywords: Carcinoma, Epidimiology, Chemotherapy, Immunotherapy, Nanotechnology, Etiology, Pathophysiology

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Introduction

Lung cancer, also known as lung carcinoma, is a malignant lung tumor marked by uncontrolled cell proliferation in the lungs. This makes it the leading cause of cancer-related death in men and the second leading cause of cancer related death in women, after breast cancer (Mohammad *et al.*, 2020). Lung cancer (LC) is one of the most common malignancies in the world today (Siragusa *et al.*, 2023). According to Global Cancer Statistic, there is an estimated 2.21 million new

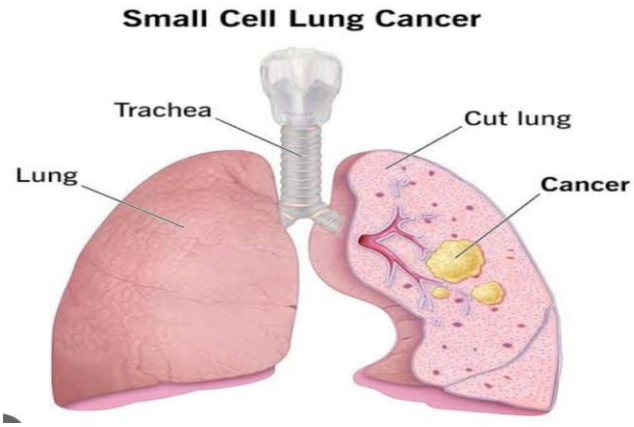

Fig. 1: Lung Cancer.

cases of lung cancer worldwide. Lung cancer has different histological subtypes, including small-cell lung cancer (SCLC) (Fig. 1) and non-SCLC (NSCLC), of which adenocarcinoma (AD) and squamous cell carcinoma (SQCC) are the two most common subtypes, accounting for >50% of cases (Han *et al*., 2023). It is well known that if the lung cancer can be treated surgically at an early stage, the prognosis will be significantly improved. However, early-stage lung cancer patients typically are asymptomatic, so that approximately 70% of patients have advanced disease at the time of diagnosis. Therefore, many medical and public health institutions have been committed to the early diagnosis and treatment of lung cancer through screening to ultimately reduce deaths from lung cancer (Li *et al*., 2021). Long-term tobacco smoking (85%) is contributing factor, with 10 to 15% of instances occurring in people who have never smoked. A combination of circumstances, including exposure to random gas, asbestos, secondhand smoke, or other form of air pollution, are frequently responsible for these cases (Mohammad *et al*., 2020). The incidence of lung cancer differs by geographic area, sex, age, and over time, reflecting the effect of the underlying distribution and trend in use of its principal determinant, tobacco smoking. Although 80% to 90% of lung cancer cases occur in current or past tobacco smokers, only a small fraction of smokers (1%-15%) develop lung cancer (Schmidt *et al*., 2022). Generally spoken, environmental tobacco smoke at home or at the workplace, radon, cooking oil vapor, indoor coal burning, hormonal replacement therapies, exposure to asbestos/heavy metals, infectious factors and air pollution have been linked to lung carcinogenesis in non-smokers (Smolle and Pichler, 2019). Understanding the molecular pathways behind cancer has benefited, in particular, from the research of uncommon high penetrance mutations. Tumor-suppressor genes have been found in autosomal-dominant diseases such as familial adenomatous polyposis and retino-blastoma (Kukita *et al*., 2016). Low-dose computed tomography (LDCT) was one of the promising areas that allowed for a 20% reduction in mortality rates. However, the National Comprehensive Cancer Network (NCCN) recommends this method for patients over 50 who are current or former smokers. Another significant limitation is the difficulty in determining the origin of pulmonary nodules. Therapy for immune checkpoint inhibitors and locally progressed and metastatic lung cancer is common. The most prevalent genetic variants, including those affecting EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3, MET, RET, and PD-L1 expression, should be tested for by law, according to NCCN guidelines. (Fig. 1) (Moskalenko *et al*., 2023). The main goal of this review is to identify and map all efforts in the field of lung cancer breath analysis methods and to report identified breath. Additionally, this study draws conclusion regarding the potential clinical value for early lung cancer detection or monitoring and suggests a

framework for future research (Schmidt *et al*., 2022).

Epidemiology:

Lung cancer is predominantly a disease of the elder persons. Nearly 70% of people diagnosed with lung cancer are 65 years of age and less than 3% of lung cancers occur in the people below age of 45 years. The incidence of lung cancer is strongly correlated with cigarette smoking (Sankar *et al*., 2023). The overall global ratio of lung cancer mortality to incidence is 22.4 and 18 per 100,000 with a relative lack of variability in survival in different world regions (Mcintyre and Ganti, 2017). Recent evidence has shown that low- dose computed tomography screening can reduce lung cancer – specific mortality by 62 events per 100000 person – years and is recommended by the US Preventive Services Task Force (grade B) for patients aged 55 to 80 years who have a 30 pack – year smoking history and currently smoke or have quit within the past 15 years (Arbour and Riely, 2019). More recent reports include those prepared by the International Agency for Research on Cancer in 2004, the 2004 and 2006 reports of the Surgeon General on active and passive smoking, respectively, and the 2010 report of the Surgeon General on the mechanistic basis of smoking-caused pathogenesis. The 2014 U.S. Surgeon General's Report commemorated the 50th anniversary of the landmark 1964 report and once again updated the evidence on the adverse health effects of cigarette smoking (Alberg *et al*., 2013). An estimated 75–80% of lung cancer-related deaths are due to smoking. A 1995 survey estimated that 47 million U.S. adults smoke. Smoking is more common among men (27%) than women (23%) (Cersosimo *et al*., 2002). South America has a wide range of lung cancer incidence across countries and markedly higher rates in men compared with women. The highest incidence and mortality in men can be found in Uruguay and in women of Venezuela and Argentina. Less populated countries such as Ecuador, Bolivia, and Guyana have very low age-standardized rates, just higher than those of central Africa and the Middle East. Asian countries closest to Eastern Europe such as Armenia, Turkey, and Kazakhstan have among the highest rates of lung cancer in the world. Korea and south-east Asia have slightly lower rates, and Middle Eastern countries including Yemen and Saudi Arabia have among the lowest lung cancer incidence rates in the world (Barta *et al*., 2019).

Both incidence and mortality rates reflect cigarette consumption in a given population about 20 years ago (Fig. 2) (Hammerschmidt and Wirtz, 2009). Examination of lung cancer trends, histologic types, and survival patterns can provide clues that can be investigated more fully in etiologic studies. There appears to be substantially different patterns in Western societies, compared with Asian countries, that are worthy of investigation (Brownson *et al*., 1998).

Etiology:

Tobacco use, especially cigarette smoking, accounts for up to 90% of all lung cancer deaths worldwide. Fewer than 20% of cigarette smokers, however, develop lung cancer, suggesting that other factors play a role in the disease. Other causes of lung cancer include environmental factors, such as tobacco smoke, radon, and various occupational exposures (Bilello *et al*., 2002). There are various etiologic factors for lung cancer apart from smoking, as it has been found that lung cancer is not only a concern for active smokers but also for nonsmokers with history of smoking and yet battling with lung cancer (Singh *et al*., 2022). The etiology of NSCLC can be further divided into risk factors that can be avoided and those that cannot be avoided. Inhaled tobacco smoking is the most well-known preventable risk factor for NSCLC. Other factors that contribute to lung cancer include alcohol consumption, secondhand smoke exposure, asbestos, radon, arsenic, chromium, nickel, ionizing radiation, and polycyclic aromatic hydrocarbons (Elsaka *et al*., 2022). Etiology may be age, genetic, gender,

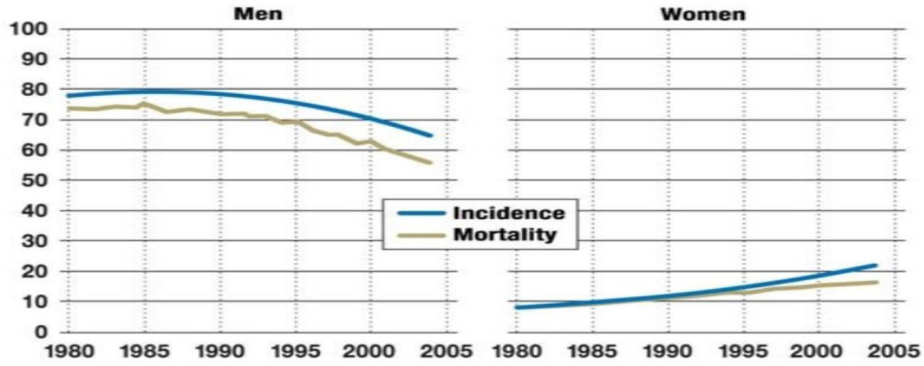

Fig. 2: Mortality rates.

environmental, ethnic, hormonal or viral factors. The primary factor attributed for the development of lung cancer is tobacco smoking. This does not come as a surprise given that tobacco has been known to contain varieties of carcinogens (Ahsan and Thomas, 2004). Primary cause of lung cancer is tobacco use, particularly with cigarettes. Approximately seventy-three recognized carcinogens, such as NNK, 1, 3-butadiene, and polonium-210. A radioactive isotope of polonium, are found in cigarette smoke. The term "passive smoking" describes breathing in someone else's smoke (Jaggi, 2017). The risk of lung cancer is related to smoking in all its forms in a dose-dependent manner. The risk of lung cancer rises with the amount of cigarettes smoked daily; it is 2.5 for people who smoke less than a pack and 32.8 for those who smoke more than two packs (Khudar *et al*., 1998). Due to their close proximity to smokers, people who live or work with smokers may inhale cigarette smoke. Smoke from cigarettes increases the risk of lung cancer when inhaled passively. Passive smoking is blamed for about one-third of lung cancer cases among nonsmokers who cohabitate with smokers (Cersosimo *et al*., 2002).

Sign and Symptoms:

Bulky involvement, typically in the mediastinum,

and clearly aberrant chest radiographs are the late signs of small cell lung cancer. The symptoms began to appear 8–12 weeks before the presentation, so they are brief. Cough, wheeze, dyspnea, and other symptoms may be caused by a localized intrapulmonary tumor growth (Cooper and Spiro, 2006). Refer people having a suspected cancer pathway referral (for appointment within 2 weeks) for lung cancer if they: (i) Have chest X-ray findings that suggest lung cancer or, (ii) Are aged 40 and over with unexplained haemoptysis.

Offer an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over if they have 2 or more of the following unexplained symptoms, or if they have ever smoked and have 1 or more of the following unexplained symptoms: Cough, Fatigue, Shortness of breath, Chest pain, Weight loss, and Appetite loss. Consider an urgent chest X-ray (to be performed within 2 weeks) to assess for lung cancer in people aged 40 and over with any of the following:

(i) Persistent or recurrent chest infection

(ii) Finger clubbing

(iii) Supraclavicular lymphadenopathy or persistent cervical lymphadenopathy

(iv) Chest signs consistent with lung cancer

(v) Thrombocytosis. (Bradley *et al*., 2019).

Pathophysiology:

Lung cancers are classified into two main categories by the World Health Organization (WHO): non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Between the two, NSCLC is more common, accounting for about 80%

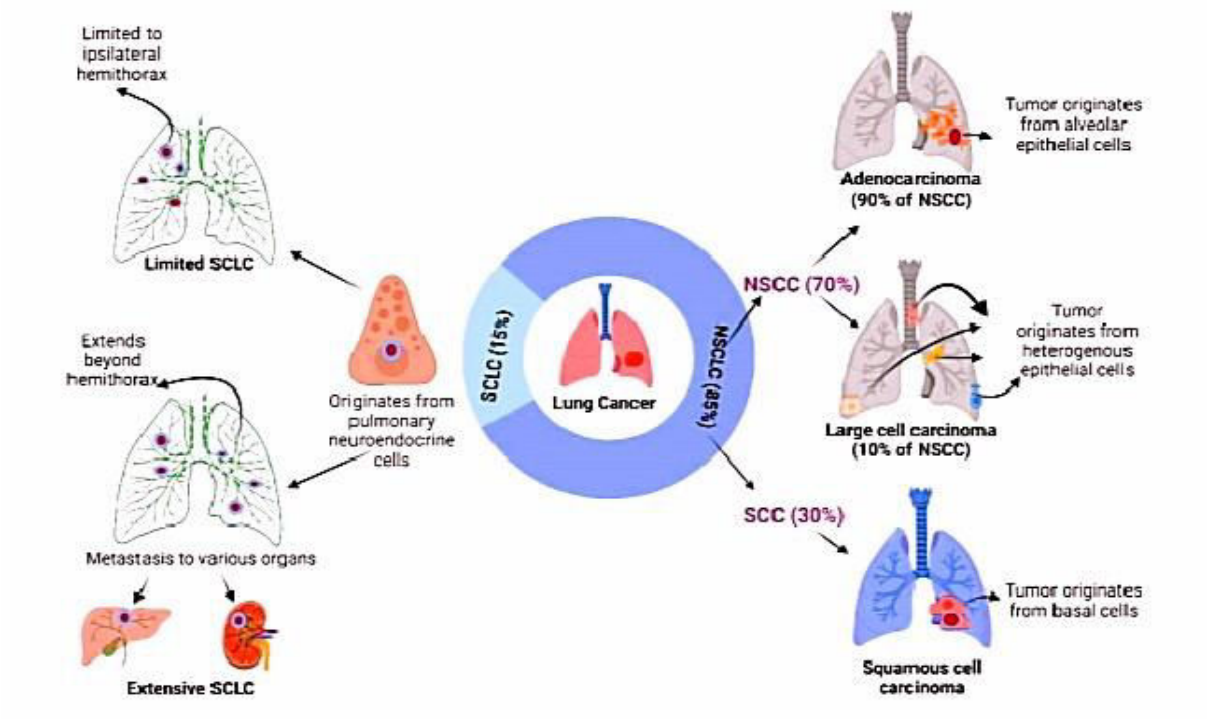

Fig. 3: Pathophysiological Classification of lung Cancer.

of cases of lung cancer. In contrast to NSCLC, SCLC is more aggressive, develops more quickly, and is more likely to metastasize. Moreover, neuroendocrine cells are the source of SCLC. On the other hand, different kinds of epithelial cells are the source of NSCLC. NSCLC additionally large cell lung cancer, which is separated into histological groups, centrally located squamous cell carcinoma, and distantly located adenocarcinoma. NSCLC is more peripheral and basically originates in the epithelium of either bronchioles or alveoli, in contrast to SCLC, which is more central in location and has the bronchial epithelium as its common site of origin. Additionally, SCLC comes from neuroendocrine cells, while NSCLC comes from different kinds of epithelial cells. The classification of small cell lung cancer (SCLC) is based on two factors: either the cancer has spread beyond the thorax or its confined borders are restricted to the associated lymph nodes. All lung cancers, despite their diverse subtypes, proceed according to a common sequence of events caused by genetic mutations that typically follow exposure to carcinogens and are ultimately followed by clonal expansion of the implicated cell. Centrally located squamous cell carcinoma, and large cell lung cancer, varies in its whereabouts (Fig. 3) (Choudhary *et al*., 2023). Lung cancer can be diagnosed pathologically either by a histologic or cytological approach. The new International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/ European Respiratory Society (ERS) Lung Adenocarcinoma Classification has made major changes in how lung adenocarcinoma is diagnosed. It will significantly alter the structure of the previous 2004 World Health Organization (WHO) classification of lung tumor (Travis , 2011). It has been divided into oat cell or lymphocyte-like, polygonal, fusiform, or intermediate, and other or combined subtypes. In 1988, the Pathology Committee of the International Association for the Study of Lung Cancer (IASLC) reviewed the histopathological classification of SCLC and promoted a new nomenclature including the categories: small cell carcinoma, mixed small cell/large cell carcinoma, and combined small cell carcinoma. Recognizing that no prognostic

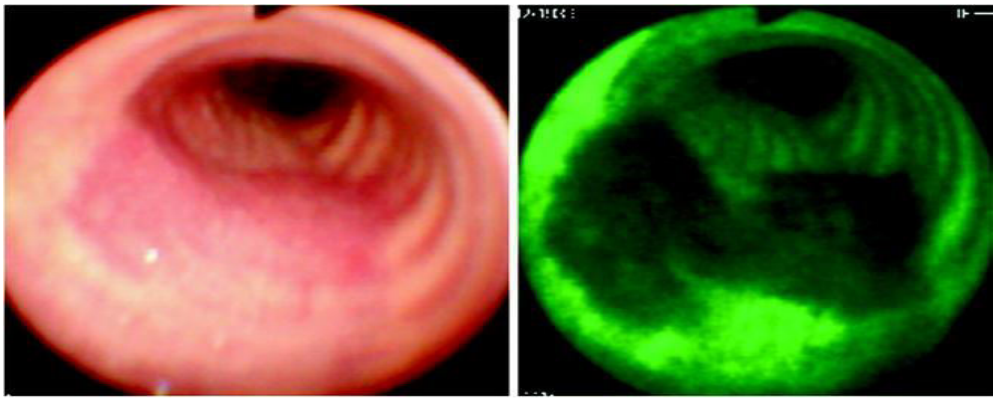

Fig. 4: Fluorescence bronchoscopy.

or therapeutic significance is imparted by the Division of SCLC into lymphocyte-like, oat cell, polygonal, fusiform, or intermediate patterns, the IASLC committee abolished these classifications and merged them into the category small cell carcinoma (Cook *et al*., 1993).

Diagnosis:

Fluorescence bronchoscopy:

This method, also referred to as auto fluorescence bronchoscopy, may aid medical professionals in detecting certain lung cancers early on, when they are probably easier to treat. A bronchoscope is inserted through the nose or mouth into the lungs in order to perform this test. Rather than a standard (white) light, the bronchoscope's end is illuminated with a unique fluorescent light (Fig. 4).

Cryobiopsy:

Apart from the navigation techniques that enhance the bronchoscopy localization of peripheral lesions, the diagnostic yield of bronchoscopy could be further enhanced by utilizing endobronchial cryobiopsy to facilitate the use of larger, higher-quality histopathological specimens. Using this method, a cryoprobe is directed onto the target tissue by passing it through the bronchoscope's instrument channel. After the cryoprobe is in place, pressurized gas is quickly passed through its end to cause an extreme temperature drop as low as -89 °C by using the Joule-Thomson effect. After being frozen, the tissue next to the probe's tip can be removed. (Fig. 5)(Mclean *et al*., 2018).

Treatment:

The current range of lung cancer treatment options can be divided into four main categories: surgical resection, radiotherapy, chemotherapy, and biological therapy. The most successful treatment for a lung tumor is surgical resection (Cryer and Thorley, 2019). Surgery, radiotherapy, or chemotherapy, or a combination of one or all of these, have been the mainstays of treatment for the past 50 years. In the first instance, Techniques, such as preoperative staging, have grown significantly refined as the primary method to offer a chance for cure (Mohammad *et al*., 2020). Asian patients seemed most likely to receive high-cost treatments like targeted therapy and chemotherapy, while Black patients and those with public insurance generally appeared to have the worst treatment outcomes. This could be partially explained by the lower rates of these types of expensive treatments and systemic treatments (Dwyer *et al*., 2023).

Immunotherapy in NSCLC:

Treatments known as immune checkpoint inhibitors, which block the PD-1 and PD-L1 pathway, have recently been developed, and they have completely altered the way that patients with

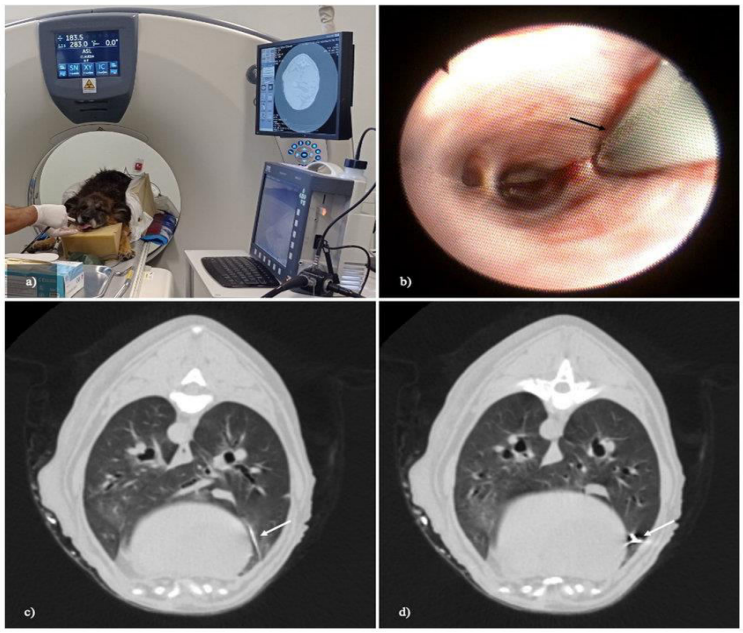

Fig. 5: Cryobiopsy of lung cancer.

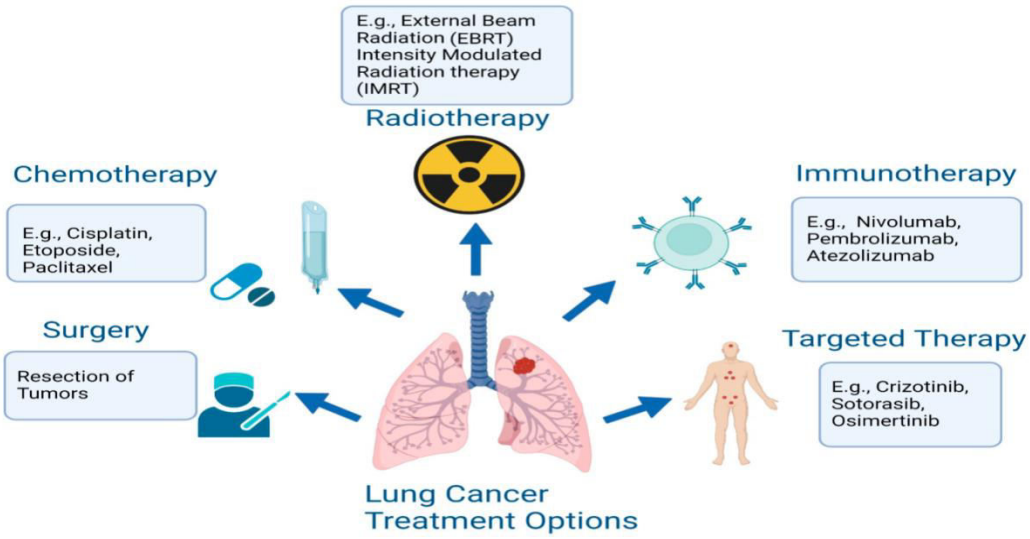

Fig. 6: Treatment of Lung Cancer.

metastatic NSCLC are managed. These medications are believed to activate T-cell function and target pertinent immune resistance mechanisms, such as immune inhibitory molecules in the tumor microenvironment, in order to enhance cell-mediated immunity's ability to identify and eliminate cancer cells. PD-L1 is one such inhibitory ligand that is commonly expressed in NSCLC (Arbour and Riely, 2019).

Chemotherapy of Lung Cancer:

Lack of target specificity, recurrence, and a flimsy extension of human lifespan are the primary drawbacks of the chemotherapy used today to treat lung cancer. Additionally, oral and intravenous administration of anti-cancer medications has a number of disadvantages, including the degradation of the drug molecule in the stomach's pH, changes in the drug molecule during liver metabolism, lack of specificity in conventional methods of treatment, and lack of

specificity that results in toxicity and side effects (Fig. 6)(Sivarajakumar *et al*., 2018).

Surgery in NSCLC:

Stage I or II NSCLC patients make up about 25% of the patient population. In these cases, the tumor is limited to the lung (T1–T2) and may metastasize to peribronchial lymph nodes (N0) or to other sites (N1). Cure is the aim of therapy for these patients, and it can be reached in 60% to 80% of cases with stage I and 40% to 50% of cases with stage II disease, respectively (Gadgeel *et al*., 2012).

Nanotechnology in Lung Cancer:

Considering the challenges in successfully treating lung cancer, nanotechnology can offer a different way to support conventional therapeutic methods. Nano-medicine is the use of nanotechnology to address medical issues, as was briefly mentioned in the introduction (Dwyer *et al*., 2023).

Conclusion

In this review we conclude overview of lung cancer with their pathophysiology, diagnosis and treatment. Lung cancer is the foremost reason for mortality in cancer patients. Improving early diagnosis of lung cancer is crucial to improving outcomes. The topic of lung cancer diagnosis in small biopsies and cytology is now addressed for the first time with an official standardized classification in which specific terminology and diagnostic criteria are proposed along with recommendations for strategic management of tissue and EGFR mutation testing in patients with advanced adenocarcinoma. The pathology of other lung cancers is also discussed such as large cell carcinoma, aggressive, carcinomas, and NE tumors, including small cell carcinoma and large cell NE carcinoma, as well as typical and atypical carcinoid tumors. Future directions must include improvements in early detection and technological advances in genomics and genetics to achieve a more personalized approach to therapy and ultimately improve lung cancer survival.

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