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Etiology, Investigations, and Treatment in Cases of Non-Small Cell Lung Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Review Article

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ABSTRACT

Lung cancer is a diagnosis that has risen to the top of the global cancer death toll. Adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are all types of non-small cell lung cancer. This exercise examines the diagnosis and treatment of non-small cell lung cancer and emphasizes the importance of the interprofessional team inpatient care. This review article aims to: review the etiology of non-small cell lung cancer, describe the appropriate steps for non-small cell lung cancer evaluation, outline non-small cell lung cancer management options, and summarize the importance of collaboration and communication among the interprofessional team to improve care coordination for non-small cell lung cancer patients. Following the diagnosis, an interprofessional approach with medical oncology, radiation oncology, thoracic surgery, and pathology should be used to maximize the patient's treatment plan based on their TNM staging at the time of diagnosis.

Keywords: Chemotherapy; immunotherapy; non-small cell lung cancer (NSCLC); adenocarcinoma; squamous cell carcinoma; large cell carcinoma.

1. INTRODUCTION

Lung cancer is a disease that affects about 230,000 people in the United States each year. The number of people that die each year is believed to be around 135,000. Deaths from lung cancer have surpassed those from prostate, breast, brain, and colorectal cancer combined. It is now the leading cause of cancer death in men and the second leading cause in women. However, due to anti-smoking programs and decreased tobacco usage in the United States, this statistic is presently declining [1].

The foundation of lung tumor categorization is based on the 2015 World Health Organization (WHO) lung tumor classification. To better guide treatment and determine a prognosis course, this

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classification approach uses immunohistochemistry and light microscopy. Non-small cell lung cancer (NSCLC) refers to a group of lung cancers that includes adenocarcinoma, squamous cell carcinoma, and giant cell carcinoma, among others. The most frequent type of lung cancer in this category is adenocarcinoma, which accounts for half of all lung cancer cases. Squamous cell carcinoma is another kind of NSCLC that, until recently, was the most commonly diagnosed lung cancer. Squamous cell carcinoma (SCC) normally starts at the tracheobronchial tree's origin, although more cases are increasingly being found on the lung's periphery [2].

Large cell carcinoma is a diagnosis of exclusion that is a subgroup of NSCLC. Immunohistochemistry (IHC) and electron microscopy cannot further classify it since it is weakly differentiated. Squamous, glandular, or neuroendocrine differentiation will be seen in 90% of instances. Other types of lung cancer are included in NSCLC, which has a wide range of classifications and terminology. Adenosquamous carcinoma, sarcomatoid carcinoma, and non-small cell neuroendocrine tumors are examples of these [3].

2. PATHOPHYSIOLOGY

Lung cancer is assumed to be caused by both environmental and occupational exposure to specific chemicals, as well as an individual's vulnerability to these agents. Active smoking is responsible for nearly 90% of lung cancer incidences in the United States. About 9-15 percent of lung cancer cases are caused by occupational exposure to carcinogens. Exposure to carcinogens is a risk factor for cancer. Tobacco smoke contains over 300 hazardous chemicals, including at least 40 recognized carcinogens. In animal models, polyaromatic hydrocarbons and nicotine-derived nitrosamine ketone (NNK) have been shown to cause DNA damage through the formation of DNA adducts. Benzo-A-pyrine also appears to cause mutations in p53 and other tumor suppressor genes, as well as molecular pathways such as AKT. Asbestos exposure is the most common occupational risk factor for lung cancer. According to studies, radon exposure is linked to 10% of lung cancer incidences, whereas outdoor air pollution is responsible for 1-2 percent. Furthermore, nonmalignant lung illnesses such as chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, and tuberculosis have all been linked to an increased risk of lung cancer [4].

According to the current multiple hit theory, orderly genetic reproduction is disrupted by a sequence of harmful cellular insults. The uncontrolled disordered growth that interferes with local or distant anatomical or physiologic processes eventually causes symptoms. Ito et al. looked at the shift in lung cancer histologic types in Japan and the United States as a result of the switch from nonfiltered to filtered cigarettes. The study discovered that the change in cigarette kinds simply switched the most common type of lung cancer from SCC to adenocarcinoma [5].

Amplification of oncogenes and inactivation of tumor suppressor genes have been discovered in NSCLC using advanced molecular methods. Mutations in the ras family of oncogenes are the most common abnormalities found. H-ras, K-ras, and N-ras are the three members of the ras oncogene family. These genes code for a guanosine triphosphatase-active protein that is found on the inner surface of the cell membrane and may be involved in signal transduction. Ras mutations may play a role in the molecular etiology of NSCLC, according to mouse studies. Ras activation appears to contribute to tumor growth in people with lung cancer, according to human studies. Ras gene mutations are almost exclusively observed in adenocarcinoma, accounting for 30% of all cases. Adenocarcinomas that originated in people who did not smoke did not have these mutations. The K-ras mutation appears to be a prognostic factor on its own. There are currently studies underway to establish management plans based on the presence or absence of ras gene mutations. Mutations in the oncogenes c-myc and craf, as well as the tumor suppressor genes retinoblastoma (Rb) and p53, have been reported in NSCLC (Fig. 1) [6].

Early and extensive mutations in lung tumors have been identified in two investigations, resulting in considerable intratumor heterogeneity by the time these malignancies manifest clinically, helping to explain why these instances fail to react to treatment so frequently. Zhang and colleagues found 20 of the 21 known cancer gene alterations in all 11 locations of localized lung adenocarcinomas in research. Patients with postsurgical relapse exhibited a considerably higher percentage of subclonal mutations in their main tumors when they were followed upon. De Bruin and colleagues found

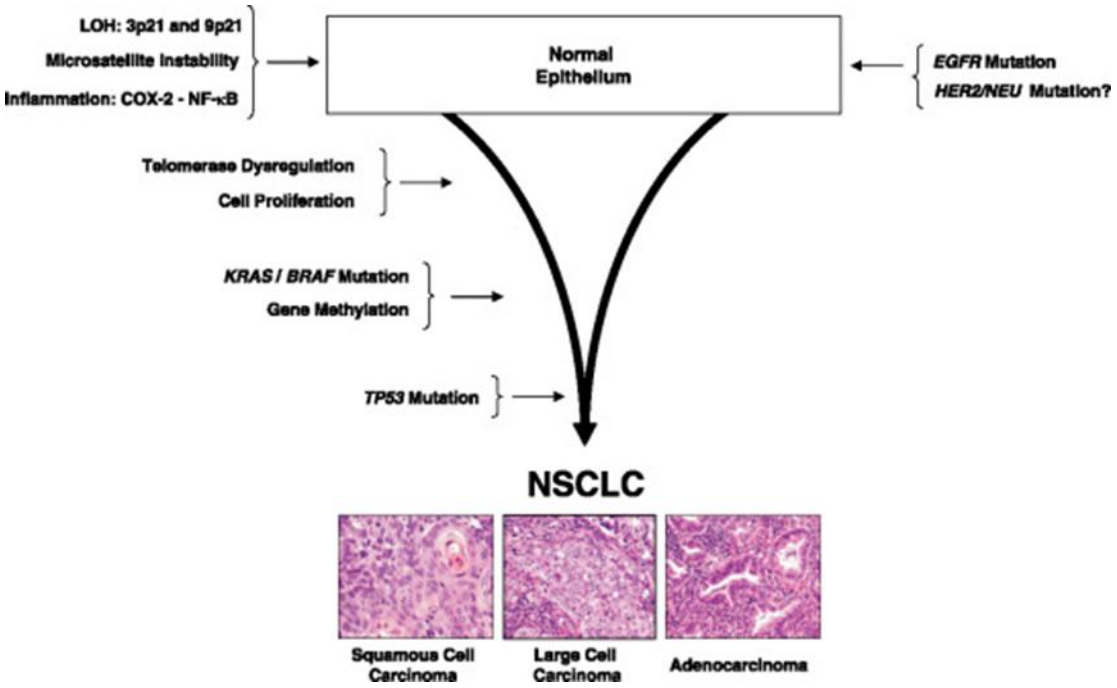

Fig. 1. The following is a summary of what we currently know about the pathophysiology of NSCLC: For squamous cell carcinoma histology, the sequence of pathologic and molecular changes involved in the pathogenesis of lung cancer is better known (left side of the panel). Chromosomal deletions, genetic instability, activation of inflammation-related molecules, cell proliferation, oncogene mutations (e.g., KRAS and BRAF), and inactivation of tumor suppressor genes are all examples of molecular alterations (e.g., P16 and TP53). Smoking (KRAS) and nonsmoking (EGFR and HER2/NEU)-related molecular pathways have been found for lung cancer (right side of the panel). HER2/NEU mutations have not been explored at the early stages of lung cancer formation, even though EGFR mutations have been found in normal respiratory epithelium [7]

that there was a considerable time of tumor latency between early mutations and clinical symptoms, which arose when subsequent mutations spurred rapid disease progression, in a study of seven operable NSCLCs. The earliest alterations in some ex-smokers might be traced back to when they were smoking cigarettes two decades ago. Those changes, however, grew less essential over time, with more recent mutations arising from a new process governed by a protein known as APOBEC [8].

3. ETIOLOGY

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. When radiation therapy is used to treat other cancers including breast cancer and Hodgkin lymphoma, it can also cause primary lung cancer. Patients with pulmonary fibrosis have a sevenfold increased risk of lung cancer, which has been demonstrated to be independent of cigarette usage. The incidence of lung cancer in HIV patients has also been reported to be higher than in the general population, and this has been proven to be irrespective of smoking status or the use of antiretroviral medication in the HIV population [9].

4. CLASSIFICATION OF LUNG CANCER

Lung malignancies are classified into two categories: SCLC and NSCLC. NSCLC accounts for over 85% of all lung cancer cases. Adenocarcinoma, SCC, and large cell carcinoma are the three types of NSCLC. Although they all have comparable treatment regimens and prognoses, their histologic and clinical characteristics differ (Fig. 2) [10].

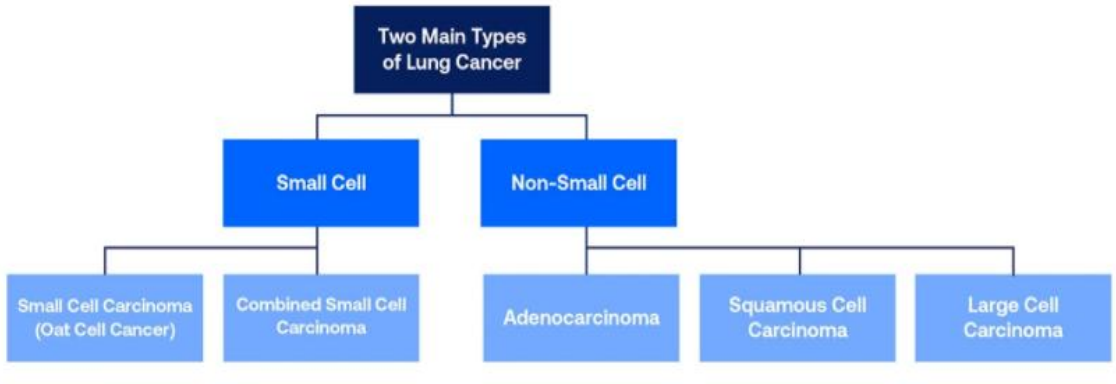

Fig. 2. Classification of Lung Cancer [11]

Adenocarcinoma: Adenocarcinoma is the most frequent NSCLC cancer in the United States, accounting for 35-40% of all lung cancers. It arises from the bronchial mucosal glands. It is the subtype that is most typically seen in nonsmokers. It typically develops in the lungs' periphery, sometimes at the site of pre-existing scars, lesions, or inflammation (eg, "scar carcinoma"). Bronchoalveolar carcinoma is a separate subtype of adenocarcinoma that shows up on a chest radiograph as interstitial lung disease. Type II pneumocytes give birth to bronchoalveolar carcinoma, which develops along alveolar septa. This subtype might present as a single peripheral nodule, multifocal illness, or a pneumonic form that progresses quickly. Voluminous watery sputum is a common sign in those with advanced illness [12].

Squamous cell carcinoma (SCC) is the most common type of lung cancer, accounting for 25-30% of all cases. SCC tumors are found in the center sections of the lung, whereas adenocarcinoma tumors are situated on the periphery. A cavitary lesion in a proximal bronchus is the most common symptom. Because it tends to exfoliate, this kind is distinguished histologically by the presence of keratin pearls and can be recognized with cytologic investigations. It's the one most commonly linked to hypercalcemia [13].

Large cell carcinoma is the most common type of lung cancer, accounting for 10-15% of all cases. It appears as a large peripheral mass on a chest radiograph. This kind has sheets of extremely abnormal cells with focal necrosis and no signs of keratinization (as in SCC) or gland development histologically (as is typical of adenocarcinomas). Most NSCLCs that would previously have been classified as large-cell carcinomas are now categorized as undifferentiated adenocarcinomas or, less commonly, as SCCs, thanks to improved histopathologic methods and the use of electron microscopy. Large-cell undifferentiated tumors have the same prognosis as adenocarcinomas and are used in clinical studies alongside them [14].

5. PRESENTATION

Lung cancer is a sneaky disease that often goes unnoticed until it's too late. Lung cancer is identified in asymptomatic people in about 7-10% of instances when a chest radiograph taken for another cause reveals the disease. At the time of diagnosis, 20% of patients have localized illness, 25% of patients have regional metastases, and 55% of patients have distant spread of disease. The initial tumor, locoregional dissemination, metastatic illness, or ectopic hormone production can all cause symptoms in lung cancer patients. Lung cancer is said to have the most prevalent presenting symptom of cough. Dyspnea, chest discomfort and hemoptysis are some of the other respiratory symptoms. Hemoptysis has been identified as the one symptom that generally leads to a faster presentation [15].

Symptoms of a primary tumor: The symptoms caused by a primary tumor vary depending on where it is located (ie, central, peripheral). Squamous cell carcinomas (SCCs) are the most common type of central tumor and can cause cough, dyspnea, atelectasis, postobstructive pneumonia, wheezing, and hemoptysis. The majority of peripheral tumors are adenocarcinomas or large cell carcinomas, which can induce symptoms such as cough and dyspnea, as well as pleural effusion and severe

pain owing to infiltration of the parietal pleura and the chest wall. Because of their peripheral position, adenocarcinomas may not be seen until they have spread to other parts of the body. Patients may show clinical symptoms of bone spread or intracranial metastatic illness [16].

Symptoms of locoregional spread include superior vena cava obstruction, recurrent laryngeal nerve paralysis, and phrenic nerve palsy, all of which cause hoarseness and diaphragm paralysis; pressure on the sympathetic plexus, which causes Horner syndrome; dysphagia due to esophageal compression; and pericardial effusion. Compression of the brachial plexus roots as they exit the neural foramina can be caused by superior sulcus tumors (Pancoast tumors), resulting in acute, radiating neuropathic pain in the ipsilateral upper extremity [17].

Symptoms of cancer according to where it is found; Endobronchial malignancies might manifest themselves in the following ways: Cough (45-75 percent of patients), hemoptysis (57 percent), and bronchial obstruction are among the most common symptoms. Complications of obstructive pulmonary disease (eg, pneumonitis, pneumonia, effusion), The following signs and symptoms may occur as a result of mediastinal cancer: Dyspnea, coughing after eating (esophageal), Wheezing, a stairwell (upper airway obstruction, 2-18 percent), Hoarseness (2-18%), Chylothorax (left vocal cord paralysis owing to recurrent laryngeal nerve impingement) (thoracic duct), Palpitations are a type of heart palpitation that (pericardial), Dysphagia is a condition that affects people's ability to (enlargement of the subcarinal lymph nodes can cause dysphagia by compressing the middle third of the esophagus). The following signs and symptoms may occur as a result of pleural cancer: Chest discomfort (27-49 percent), dyspnea (37-58 percent), and cough (27-49 percent) are the most common symptoms (45-75 percent) [18].

The following are examples of neurologic signs and symptoms: Miosis, ptosis, and anhidrosis (cervical sympathetic chain, Horner syndrome), Dyspnea are all symptoms of brachial plexus impingement (secondary to phrenic nerve paralysis). Metastatic cancer can cause the following symptoms (8-68 percent of the time): Cachexia, weight loss The following are signs and symptoms of the central nervous system (CNS): Headache, altered mental status, seizure, meningismus, ataxia, and nausea and/or vomiting are some of the symptoms that can occur. The following are examples of vascular signs: Thromboembolism, Phlebitis (Trousseau syndrome), The following are examples of musculoskeletal manifestations: Bone discomfort (between 6 and 25 percent), as well as spinal cord impingement [19].

In 10-20% of patients, neoplastic syndromes develop. Small cell lung cancer is the most common cause of paraneoplastic disorders (SCLC). Non–small cell lung cancer (NSCLC) patients, on the other hand, experience a wide range of paraneoplastic symptoms. Here are a few examples: Patients with SCCs are more likely to develop hypercalcemia as a result of parathyroid-like hormone production. Adenocarcinomas are more likely to develop clubbing and hypertrophic pulmonary osteoarthritis, as well as the Trousseau syndrome of hypercoagulability. Irregular antidiuretic hormone production (SIADH) is more common in SCLC, but it can also happen in NSCLC. Cushing syndrome is more common in SCLC and bronchial carcinoid due to ectopic adrenocorticotropic hormone (ACTH) production [20].

6. COMPLICATIONS

NSCLC complications are determined by the local breadth of the disease process and the presence of cancer metastases. Malignant pleural effusion, which can cause dyspnea or respiratory failure depending on the extent of the pathology and associated diseases, is one example of an intrathoracic complication. Non-small cell lung cancer (NSCLC) is the most common cause of superior vena cava (SVC) syndrome, accounting for around half of all cases. Due to restriction of blood flow through the superior vena cava, this usually manifests as gradual face/neck swelling with dilated neck veins and upper extremity swelling [21].

7. DIFFERENTIAL DIAGNOSIS

When a patient presents with intrathoracic symptoms and a pulmonary nodule is discovered on a chest radiograph, the diagnosis of NSCLC is frequently suspected. The differential diagnosis can thus include: Bronchogenic carcinoma based on the intrathoracic symptoms and possible chest radiograph abnormalities (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, small cell carcinoma),

Breast cancer, head and neck cancer, melanoma, colon cancer, kidney cancer, germ cell tumors, and sarcoma are all examples of metastatic disease. Carcinoid of the lungs, Extranodal lymphoma, plasmacytoma, or schwannoma are all examples of extranodal lymphoma. Fibroma, neurofibroma, lipoma, hamartoma, leiomyoma, and angioma are examples of benign neoplasms. Hematoma, pulmonary infarction, and arteriovenous malformation are examples of vascular phenomena. cystic bronchospasm, Sarcoidosis, rheumatoid nodule, granulomatosis with polyangiitis, and other inflammatory findings Bacterial abscess, Aspergillus, Pseudotumor, and mucoid impaction are all examples of infectious granulomas (histoplasmosis, coccidioidomycosis, tuberculosis, atypical mycobacteria, cryptococcus, and blastomycosis) [22].

8. EPIDEMIOLOGY

Tobacco usage is thought to be responsible for 90 percent of all lung cancers. Patients who presently smoke and have smoked 40 packs per year have a twenty-fold higher risk of lung cancer than non-smokers. This risk can arise if additional environmental or lifestyle exposures, such as asbestos exposure, are combined with cigarette use. The creation of filter cigarettes in the 1960s is supposed to have triggered the development of adenocarcinoma, however, this has not been verified. Lung cancer is the most prevalent cause of cancer death in men and the second most common in women in the world. Based on the prevalence of tobacco smoking in various countries, there is a huge difference in lung cancer incidence across different populations. The rate of smoking in different groups has a direct relationship with the incidence of lung cancer. For example, in the United States, the age-adjusted mortality rate is projected to decrease by 79 percent between 2015 and 2065 due to decreased rates of tobacco use and anti-smoking campaigns (Fig. 3) [23].

9. PROGNOSIS

The tumor, node, and metastasis (TNM) staging, as well as the patient's performance status and comorbidities, all influence the prognosis of NSCLC. Patients with poor performance status have a shorter life expectancy. Weight loss and a lack of appetite are also negative prognostic

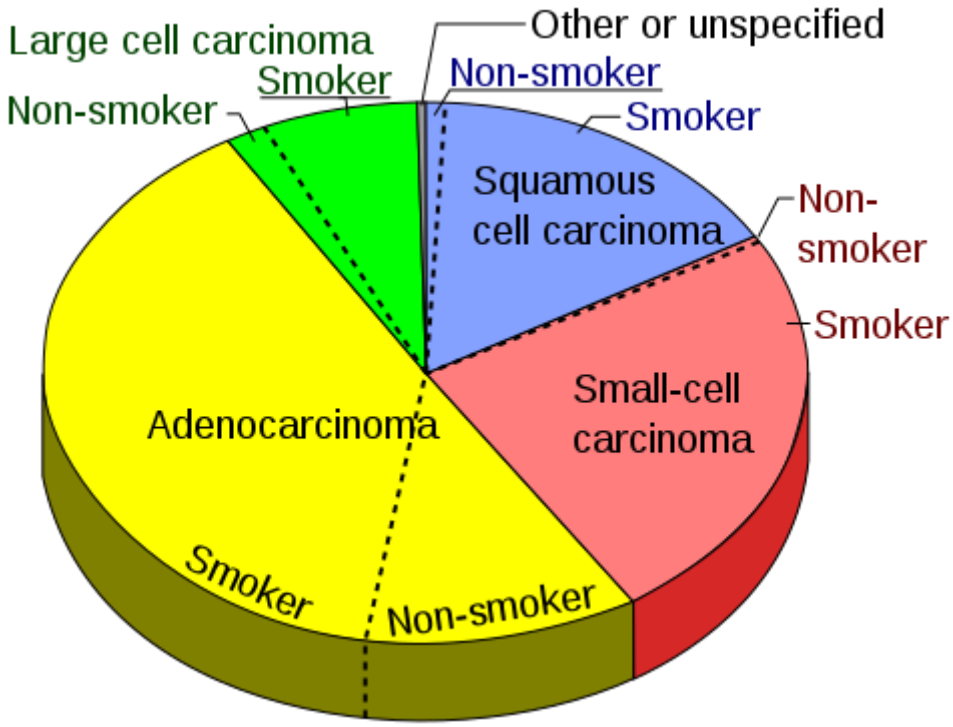

Fig. 3. Pie chart of lung cancer kinds, sorted by histological subtypes, then by non-smokers against smokers [24]

indicators. Lymphatic vascular invasion, as well as occult lymph node metastases, harm prognosis. Patients with actionable mutations had a better prognosis, according to research. Activating EGFR mutations, for example, are present in adenocarcinoma in never smokers, women, and/or Asian ancestry, and are associated with a considerably better prognosis. In stages I-IV NSCLC, metabolic activity on PET scan has been linked to a poor prognosis. The rate of recurrence following full resection is 41%, with a median time to recurrence of 11.5 months and a median survival of 8.1 months. Shorter survival depended on performance status, disease-free interval, the involvement of distant metastases, and prior use of neoadjuvant chemotherapy or adjuvant RT [25].

10. INVESTIGATIONS

The presence of persistent respiratory symptoms in a patient with a lengthy history of smoking or other lung cancer risk factors should trigger a chest radiograph. On radiographs, benign diseases and metastatic malignancies might seem like lung cancer, therefore histologic confirmation is required. Depending on the location of the tumor, this can be accomplished using sputum cytologic tests, bronchoscopy, or computed tomography (CT)-guided transthoracic needle biopsy of the mass (Fig. 4) [26].

All patients with non–small cell lung cancer (NSCLC) must be appropriately staged due to the importance of stage in the treatment decision-making process. To determine the extent of the disease, a thorough staging workup for NSCLC should be performed. CT, CBC, serum chemistry studies, alkaline phosphate, aspartate aminotransferase, pulmonary function test, and mediastinoscopy are the seven primary components of the standard staging workup for NSCLC in the United States. The results of these tests can then be used to inform future testing (eg, imaging studies). Patients who are candidates for potentially curative surgical resection may require invasive staging techniques such as mediastinoscopy and mediastinotomy to examine mediastinal lymph nodes. PET scans may be beneficial in detecting implicated nodes, the existence of which may influence operability decisions. According to Annema et al, a combination of endosonography and surgical staging demonstrated higher sensitivity for mediastinal nodal metastases in patients with suspected NSCLC than surgical staging alone. As a result, fewer unneeded thoracotomies were performed [28].

Other tests: An electrocardiogram (ECG) can be used to establish baseline findings and distinguish between clinical symptoms (eg, chest pain, dyspnea). ECG wave patterns are frequently altered by changes in lung hemodynamics. Peak expiratory flow tests performed at the bedside are good markers of substantial airflow blockage. Lung cancer is more closely associated with chronic obstructive pulmonary disease (COPD) with significant airway blockage than with COPD without severe airway obstruction [29].

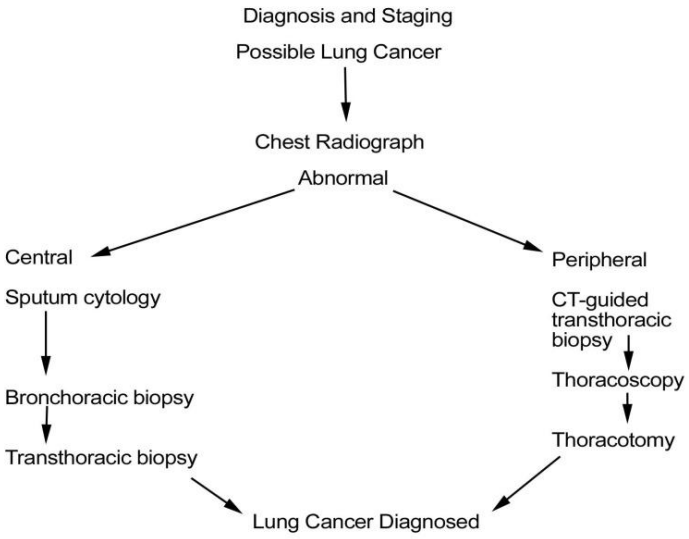

Fig. 4. Non–small cell lung cancer: Diagnostic approach for possible lung cancer [27]

11. LABORATORY STUDIES

A complete blood count (CBC) should be acquired in every patient for staging considerations, especially before starting chemotherapy. A CBC is not useful in the initial evaluation of an emergency. Obtain a complete blood count (CBC) in patients with extensively metastatic illness to help determine whether an infiltrate is infectious. Check for neutropenia (absolute neutrophil count 1000/L) in individuals with fever who have recently received chemotherapy. Lung cancer has a high risk of developing paraneoplastic syndromes. Assays of serum electrolytes, blood urea nitrogen (BUN), creatinine, calcium, and magnesium may be appropriate in such patients. Hypercalcemia is the most prevalent metabolic abnormality associated with NSCLC, which commonly occurs with squamous cell carcinoma and is caused by the tumor secreting parathyroid hormone-related peptide (PTH-rP). Normal serum parathyroid hormone (PTH) levels can be used to distinguish this from hyperparathyroidism [30].

Hyponatremia is another electrolyte abnormality that should be considered, in which case SIADH (syndrome of inappropriate antidiuretic hormone secretion) should be considered. Hyponatremia, a serum osmolality of less than 280 mOsm/kg, and high urine osmolality are the hallmarks of SIADH. Initial liver function tests (aspirate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyl transferase [GGT], prothrombin time [PT]/international normalised ratio [INR], prothrombin time [PT]/international normalised ratio [INR]) and alkaline phosphatase level) are usually ineffective. However, in patients with advanced disease, increased results could indicate hepatic and bone metastases, respectively. In sick individuals, arterial blood gas (ABG) levels are valuable in detecting respiratory failure (e.g., acidosis, hypercarbia, hypoxia). In patients with active systemic illnesses or abnormal laborious breathing, get ABG levels [31].

12. CHEST RADIOGRAPHY

When lung cancer is suspected, a chest radiograph is usually the first test ordered. The results of a chest radiograph may indicate the presence of lung cancer, but they may not be useful in determining a histologic subtype. Chest radiography can be used to assess response to therapy if the tumor is visible and quantifiable. Pulmonary nodule, mass, or infiltration, Mediastinal widening, Atelectasis, Hilar enlargement, and Pleural effusion are all possible findings on chest radiographs. Popcorn calcification is a radiologic feature of benign lesions in most cases. The number of patients diagnosed with lung cancer as a result of routine chest radiography has continuously been low. Screening chest radiographs do not prevent lung cancer mortality, according to randomized controlled trials (Figs. 5, 6) [32].

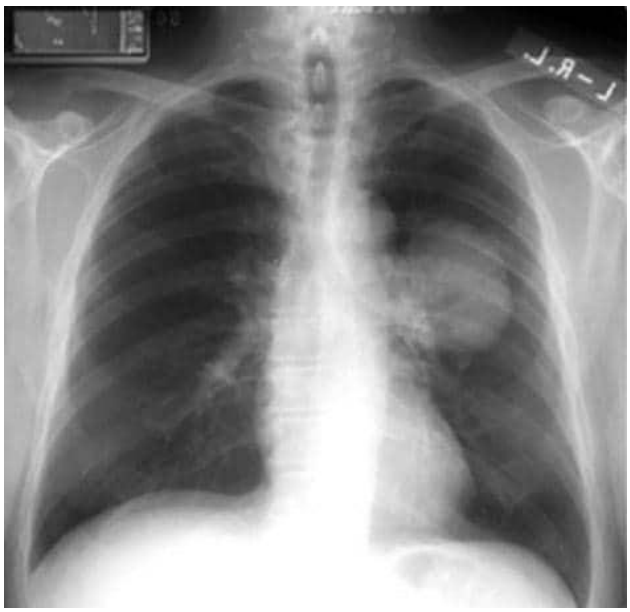

Fig. 5. A large central lesion was diagnosed as non–small cell carcinoma [33]

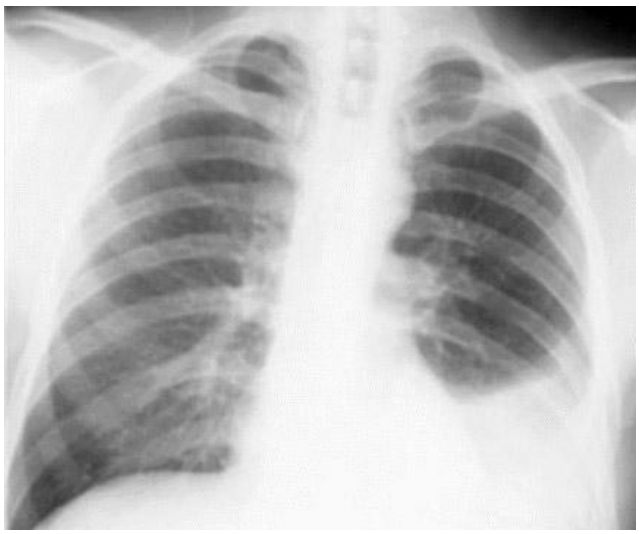

Fig. 6. Non–small cell lung cancer. Left pleural effusion and volume loss secondary to non–small cell carcinoma of the left lower lobe. The pleural effusion was sampled and found to be malignant; therefore, the lesion is inoperable [34]

13. COMPUTED TOMOGRAPHY

The standard for staging is a chest CT scan. CT scans of the chest and clinical signs and symptoms usually provide a presumptive distinction between NSCLC and small cell lung cancer (SCLC). Small cell carcinoma is frequently associated with massive lymphadenopathy and direct mediastinal invasion. A tumor in or close to the hilum is a common symptom of SCLC, appearing in roughly 78 percent of patients. The liver and adrenals are common locations of NSCLC spread, thus a CT scan of the chest and upper abdomen, which includes the liver and adrenals, is the minimal standard for a staging workup for someone newly diagnosed with NSCLC. Lung nodules seen by accident on an abdominal CT scan are frequently benign. If neurologic symptoms or signs (e.g., mental status change) are present, a CT scan or magnetic resonance imaging (MRI) scan of the brain may be required. Before attempting definitive resection of lung cancer, most thoracic surgeons undergo brain imaging (Fig. 7) [35].

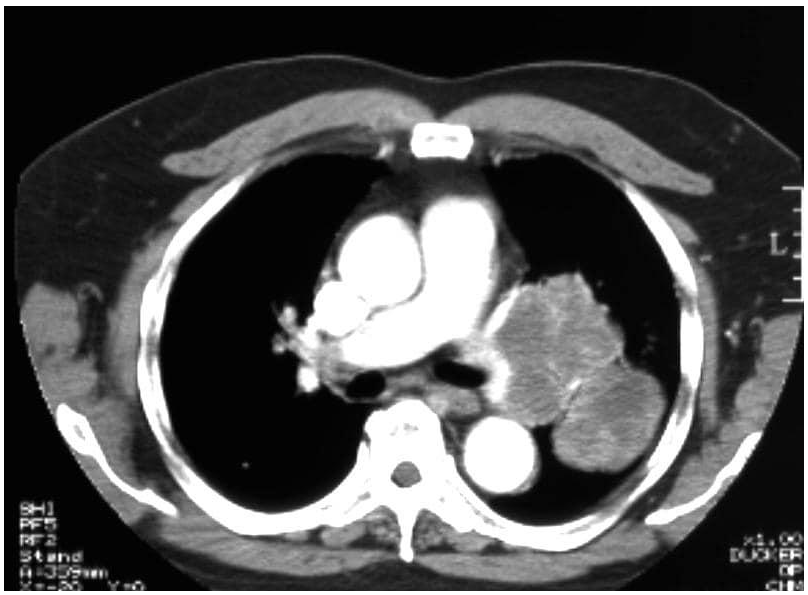

Fig. 7. Lung cancer, small cell. Contrast-enhanced CT scan of the chest shows a large left lung and a hilar mass, with invasion of the left pulmonary artery [36]

14. MAGNETIC RESONANCE IMAGING

When a patient's spinal cord compression is suspected, an MRI is most useful. Furthermore, when it comes to detecting central nervous system (CNS) metastases, brain MRI has a higher sensitivity than CT scan. When CT scan findings of the superior sulcus and brachial plexus tumors are ambiguous, MRI may be employed [37].

15. BONE SCINTIGRAPHY

Lung tumors frequently metastasize to the skeletal system. A bone scan should be obtained to screen for bone metastases if patients complain of bone pain or if their serum calcium and/or alkaline phosphatase levels are increased (Fig. 8) [38].

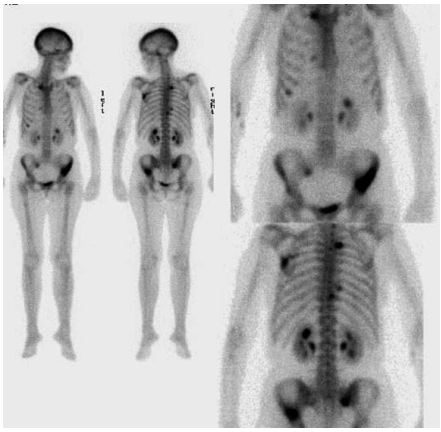

Fig. 8. Small cell lung cancer. Multiple aberrant areas of elevated radiotracer activity in the pelvis, spine, ribs and left scapula are revealed by whole-body nuclear medicine bone scanning with anterior and posterior pictures. These findings are in line with the diagnosis of bone metastatic illness. In patients with small-cell lung cancer, the bones are frequently damaged [39]

16. POSITRON EMISSION TOMOGRAPHY

PET scanning using fluoro-18–2-deoxyglucose (FDG) has proven to be an excellent method for examining solitary lung nodules, and the US Food and Drug Administration (FDA) has approved it for this indication. FDG-PET scanning's average sensitivity and specificity for diagnosing a tumor were 0.97 and 0.78, respectively. In comparison to places with nonendemic infectious lung disease, Deppen and colleagues observed that FDG-PET exhibited worse specificity for identifying cancers in areas with endemic infectious lung disease (Fig. 9) [40].

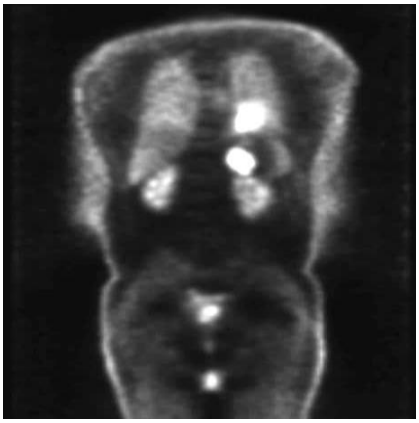

Fig. 9. Small cell lung cancer. A positron emission tomogram of the left hilar and left adrenal regions reveals aberrant areas of elevated metabolic activity, which is consistent with a hilar tumor with left adrenal metastases [41]

PET scanning has also been shown to be effective in the search for systemic spread when other diagnostic modalities fail to reveal an anomaly that could alter the patient's therapy. False-positive and false-negative results do, however, occur. Additional evidence has emerged that emphasizes the importance of PET scanning in NSCLC patients. PET scans for mediastinal disease staging tend to be more sensitive, specific, and accurate than CT scans. PET scans reveal the nature of the area under investigation, whereas radiography and CT scans offer images of structures. PET scans frequently detect abnormalities that are not visible on CT scans. According to published research, PET scan results may influence NSCLC staging in up to 60% of cases, and up to 25% of cases may be upstaged as a result of PET scanning. Caution is required when interpreting the results of PET scans in patients who may be denied potentially curative surgical resection based on PET results [42].

17. SPUTUM CYTOLOGIC STUDIES

Malignant cells may exfoliate into sputum from centrally positioned endobronchial malignancies. (Squamous cell carcinomas [SCCs] are the most common cancers with this site and tendency to exfoliate.) If the results are positive, sputum cytology can be a simple and inexpensive diagnostic test. The rate of false-positive sputum

cytology is 1%, but the rate of false-negative sputum cytology is as high as 40%. Sputum cytology is ineffective at distinguishing between various histologic subtypes. The cytologic and histologic findings of specimens acquired during bronchoscopy or transthoracic biopsy frequently disagree. Sputum cytology's diagnostic accuracy is dependent on thorough specimen sampling (at least 3 specimens) and preservation techniques, as well as the tumor's location (central versus peripheral) and size. Because the test detects 71% of central tumors but only 50% of peripheral cancers, additional testing is always required after a negative result [43].

Sputum cytology and chest radiography are not cost-effective in early detection in several big studies. A cytologic specimen was utilized to evaluate EGFR and KRAS mutations in one small study; however, this method still has to be verified. Sputum cytology is recommended for high-risk individuals who may be in danger from semi-invasive procedures like bronchoscopy or transthoracic needle aspiration. Sputum cytology is no longer routinely used in the diagnosis of NSCLC due to the development of improved x-ray imaging techniques and biopsy procedures [44].

18. BRONCHOSCOPY

Bronchoscopy allows direct visualization of the tumor, determination of the extent of airway obstruction, and collection of diagnostic material under direct visualization with direct biopsy of the visualized tumor, bronchial brushings and washings, and transbronchial biopsies when lung cancer is suspected. The decision to seek a diagnostic bronchoscopy for a suspected lung cancer lesion is mostly based on the location of the lesion (central vs peripheral). Bronchoscopy is the preferred test in patients with central malignancies, with an 88 percent combined sensitivity. When submucosal tumor spreads or peribronchial tumor is causing extrinsic compression, using transbronchial needle aspiration with endobronchial ultrasound to obtain cytology or histology samples boosts the sensitivity of bronchoscopy even further [45].

19. BIOPSY

Because peripheral tumors may not be accessible using a bronchoscope, a transthoracic needle biopsy guided by CT or fluoroscopy is suggested for tumors in the periphery of the lungs. A cancer positive finding is trustworthy; nevertheless, the false-negative rate is substantial (26%) and, as a result, the transthoracic biopsy is often ineffective in ruling out cancer. Other aberrant places can also provide diagnostic material (eg, enlarged palpable lymph nodes, liver, pleural or pericardial effusions, accessible bone lesions) [46].

20. NEEDLE THORACENTESIS (ULTRASOUND GUIDED)

In patients with respiratory distress, needle thoracentesis is both diagnostic and therapeutic. Thoracentesis has a sensitivity of just about 80% and a specificity of more than 90%. If the pleural fluid cytology finding is negative (after at least 2 thoracenteses) in patients suspected of having lung cancer who have an accessible pleural effusion, thoracoscopy is indicated as the next step to aid in diagnosis [46].

21. THORACOSCOPY AND MEDIASTINOSCOPY

Thoracoscopy is typically used to diagnose cancers that have not been identified by bronchoscopy or CT-guided biopsy. In the treatment of malignant pleural effusions, thoracoscopy is also useful. VATS is a recent technique for sampling tiny peripheral tumors (less than 2 cm in diameter), pleural tumors, and pleural effusions for diagnostic or staging purposes. It is safe and can provide a precise diagnosis with high accuracy while posing little risk to the patient. The stated sensitivity rates range from 0.80 to 0.99, the specificity rates from 0.93 to 1, and the negative predictive value from 0.93 to 0.96. The cost-effectiveness of assisted VATS is equivalent to that of comprehensive VATS. Tissue from malignancy that has entered the mediastinum can be obtained through mediastinoscopy. It is usually performed to evaluate the status of enlarged mediastinal lymph nodes before attempting definitive surgical resection of lung cancer [47].

22. MOLECULAR TESTING

Because very effective, less toxic, targeted treatments for NSCLC with particular molecular abnormalities have been available, molecular testing has become an important aspect of the entire pathologic evaluation of patients with metastatic non–small cell lung cancer (NSCLC). Epidermal growth factor receptor (EGFR) mutation, Anaplastic lymphoma kinase (ALK) rearrangement, BRAF V600E mutation, RET

rearrangement, ROS-1 rearrangement, NTRK 1/2/3 gene fusion, MET exon 14 skippings, KRAS G12C mutation, and PD-L1 expression should all be tested. Regardless of clinical variables such as sex, ethnicity, or smoking status, all lung cancer patients with adenocarcinomas should be tested for genetic abnormalities that indicate suitability for treatment with targeted agents, according to international evidence-based guidelines jointly published by the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP). Clinical trial data demonstrate that patients who are tested for these abnormalities and treated with the appropriate targeted therapy have better outcomes [47].

The Cobas EGFR Mutation Test, a companion diagnostic for erlotinib, was authorized by the US Food and Drug Administration (FDA) in 2013. This is the first companion diagnostic to be approved by the FDA for detecting EGFR gene mutations. Patients with NSCLC who are candidates for erlotinib as first-line therapy can be identified using the mutation test. With clinical data from the EURTAC study, the Cobas EGFR Mutation Test was found to be safe and effective, with patients with NSCLC who had specific types of EGFR mutations (exon 19 deletions or exon 21 [L858R] substitution mutations) surviving for 10.4 months when given erlotinib treatment, compared to 5.4 months for those given standard therapy. Ras mutation testing is also possible. Ras mutation is a marker for aggressive disease and poor prognosis. New agents and regimens to target this mutation (eg, selumetinib plus docetaxel) are currently under development, so these patients should be considered for enrollment in a clinical trial [48].

23. HISTOPATHOLOGY

A cancer diagnosis is incomplete without a histologic diagnosis. Evidence of neoplastic gland formation, pneumocyte marker expression in the form of TTF-1 with or without napsin, or intracytoplasmic mucin are all required for adenocarcinoma. Acinar, papillary, or micropapillary, leptic, or solid growth patterns make up the majority of neoplastic gland production. The presence of keratin synthesis by tumor cells, which can also include intercellular desmosomes, is used to diagnose squamous cell carcinoma. The expression of p40, p63, CK5, and desmoglein in squamous cell carcinoma is revealed by immunohistochemistry (IHC). Large cell carcinoma, as previously stated, is an exclusionary diagnosis that can show squamous, glandular, or neuroendocrine differentiation in 90 percent of cases. Only if there are no defining IHC markers that would rule out another subtype of lung cancer is a poorly differentiated carcinoma classified as big cell carcinoma [48].

24. STAGING

The TNM system, developed by the American Joint Committee on Cancer (AJCC), is the most commonly used staging approach for NSCLC. It is based on three main pieces of information: The main tumor's size and extension (T): What is the size of the tumor? Has it spread to neighboring organs or structures? Is there evidence of cancer spreading to neighboring lymph nodes (N)? The spread of cancer to distant places (metastasis): Cancer has progressed to other organs including the brain, bones, adrenal glands, liver, or lungs (Fig. 10) [49].

There are several other techniques for staging cancer, but the TNM approach is the most prevalent and suitable for most forms of cancer. The TNM classification system is maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) as a mechanism for doctors to stage many different types of cancer-based on common standards. The overall stage of cancer is assessed using the TNM approach after the cancer is given a letter or number to describe the tumor (T), node (N), and metastasis (M) categories. The initial (primary) tumor is denoted by the letter T. The number N indicates if the malignancy has spread to neighboring lymph nodes. M indicates if cancer has moved to other places of the body (metastasized) [50].

The primary tumor (T category): When doctors try to figure out how much cancer there is and where it is in the body, they start with the primary (principal) tumor, which is where cancer began. The tumor's size, location, and if it has spread to neighboring locations are all factors to consider. Doctors also look for additional malignancies in the area. A letter or a number can be allocated to the T category: TX indicates that there is no information or that the primary tumor cannot be measured. T0 denotes the absence of a primary tumor. This indicates that cancer cells are only growing in the layer of cells from which they originated, rather than spreading to deeper

layers. This is also known as pre-cancer or in situ cancer. A number after the T (such as T1, T2, T3, or T4) might describe the tumor size and/or amount of spread into nearby structures. The higher the T number, the larger the tumor and/or the more it has grown into nearby tissues [50].

Lymph nodes (N category): Lymph nodes close to the original tumor are typically tested to see if cancer has spread there. Lymph nodes are tiny groupings of immune cells in the shape of a bean. Before spreading to other regions of the body, many kinds of cancer frequently expand to surrounding lymph nodes. The N category is denoted by a letter or a number: NX indicates that there is no information or that the surrounding lymph nodes cannot be examined. N0 indicates that there is no malignancy in the lymph nodes nearby. The size, location, and/or the number of neighboring lymph nodes afflicted by cancer may be indicated by a number after the N (such as N1, N2, or N3). The greater cancer spread to neighboring lymph nodes, the higher the N number [50].

Doctors may examine other sections of the body to discover if cancer has spread. Metastasis (M category): Metastasis is the spread of cancer to other regions of the body from the initial tumor. A number is assigned to the M category: M0 indicates that there has been no evidence of distant cancer spread. M1 indicates that the malignancy has spread to further organs or tissues [50].

Because each cancer kind has its version of the TNM categories, letters and numbers don't always indicate the same thing. The T categories, for example, represent the size of the main tumor in certain types of cancer, while in others, they describe how deeply the tumor has grown into the organ it began in, or whether the tumor has expanded into neighboring structures (regardless of its size). TNM categories may contain subcategories for specific cancer types. After the category, these are denoted with lowercase letters. T3a or T3b, for example.Some cancer forms may also have fewer classification possibilities than others. Some tumors, for example, may not be classified as N3 [50].

The AJCC prognostic categories for NSCLC are divided into four stages, with each stage further subdivided into subtypes. The therapeutic and prognosis consequences of these stages will be examined later. The TNM system is divided into stages as follows (Table 1) [51]:

25. WORKUP FOR SPECIAL POPULATIONS

Patients with CNS metastases, immunosuppression, SVCS, Pancoast tumor, and/or Ogilvie intestinal pseudo-obstruction may require additional testing, as mentioned below. Discharge the patient with a prescription for continuing analgesic usage until follow-up care can be arranged with the patient's physician if no pathologic process is apparent. Head CT scanning, with and without contrast enhancement to illustrate masses, may be indicated in patients with CNS metastases and known malignancy. Obtain a consultation with a neurosurgeon. Admit patients for whole-brain irradiation or resection if necessary. Dexamethasone may help with headaches and brain edema (10 mg IV). Anticonvulsants are used to treat seizures, although patients with brain metastases and no history of seizures are usually not prescribed anticonvulsants [53].

Table 1. Stage Groupings Based on the TNM classification of the Non- Small Cell Lung Cancer [51]

Overall Stage	T category	N category	M category
occult carcinoma	Tx	NO	M0
stage 0 (Figs. 11)	Tis	NO	M0
stage 1A (Figs. 12)	T1	NO	M0
stage 1B (Figs. 13)	T2	NO	M0
stage 2A (Figs. 14)	T1	N1	M0
stage 2B (Figs. 15, 16)	T2	N1	M0
	T3	NO	M0
stage 3A (Figs. 17, 18, 19)	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
stage 3B (Figs. 20, 21)	any T	N3	M0
	T4	any N	M0
stage 4 (Figs. 22, 23)	any T	any N	M1

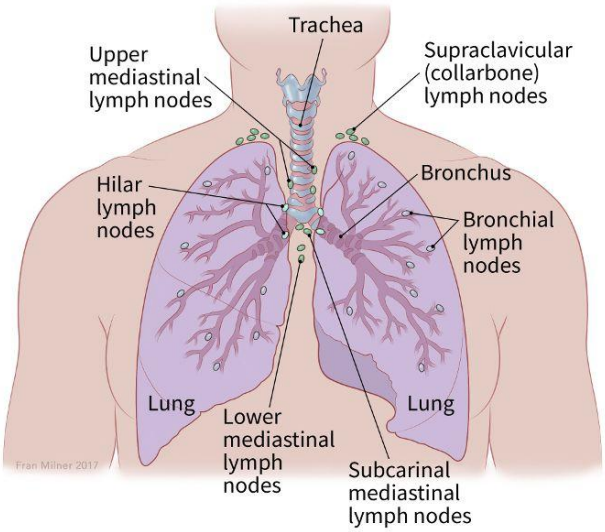

Fig. 10. Sites of lymph nodes [50]

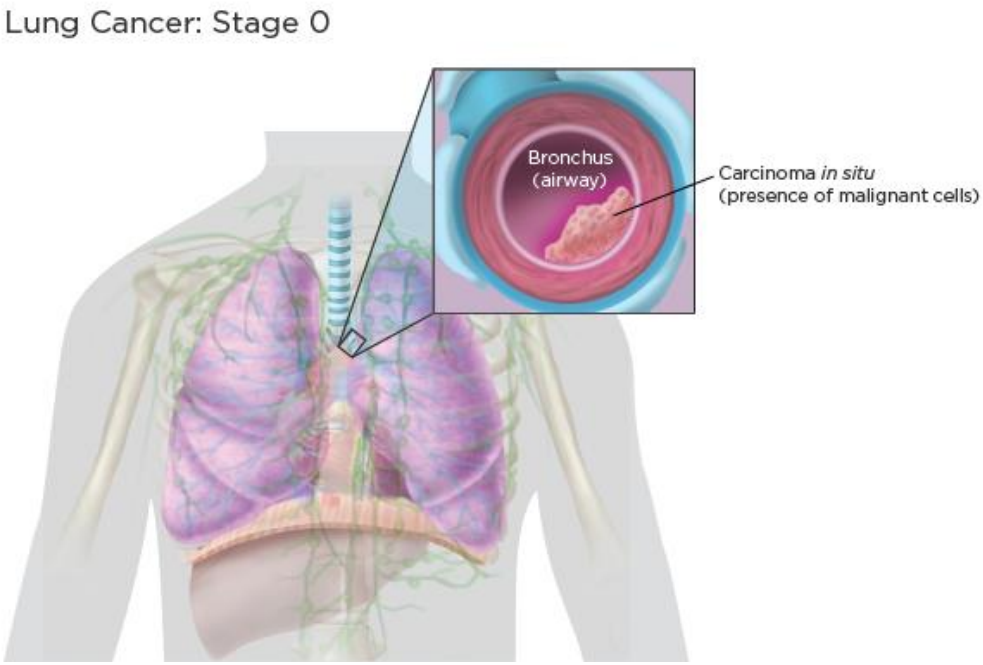

Fig. 11. Stage 0: This is called "in situ" disease, meaning that the cancer is “in place” and has not spread from where it first developed [51]

Patients with cancer and infections who are immunocompromised: Obtain a complete blood count (CBC) to check for neutropenia and other blood cell abnormalities. Check your electrolyte levels to see if you're dehydrated. The chest radiograph may only reveal a little infiltration. Perform urinalysis with culture, blood cultures with samples from peripheral locations, cultures with samples from indwelling catheters, and stool cultures for Clostridium difficile if diarrhea is present. Broad-spectrum empiric antibiotics and an aminoglycoside (e.g., piperacillin, gentamicin, second- or third-generation cephalosporin) should be given. Replace penicillin with a carbapenem (if mild penicillin allergy) or aztreonam if the patient has a penicillin allergy. Raising neutrophil counts may need treatment with granulocyte colony-stimulating factor (G-CSF). Before starting G-CSF therapy, you should speak with an oncologist [53].

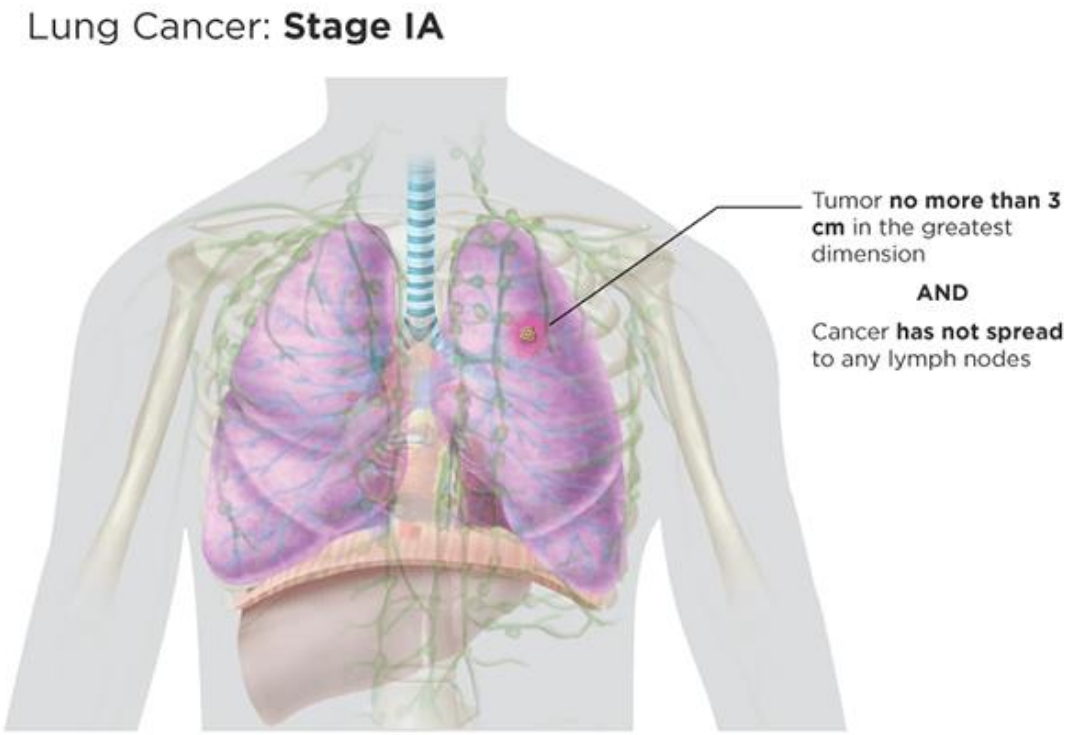

Fig. 12. Stage IA: Smaller tumors, those no more than 3 centimeters (cm) in the greatest dimension [51]

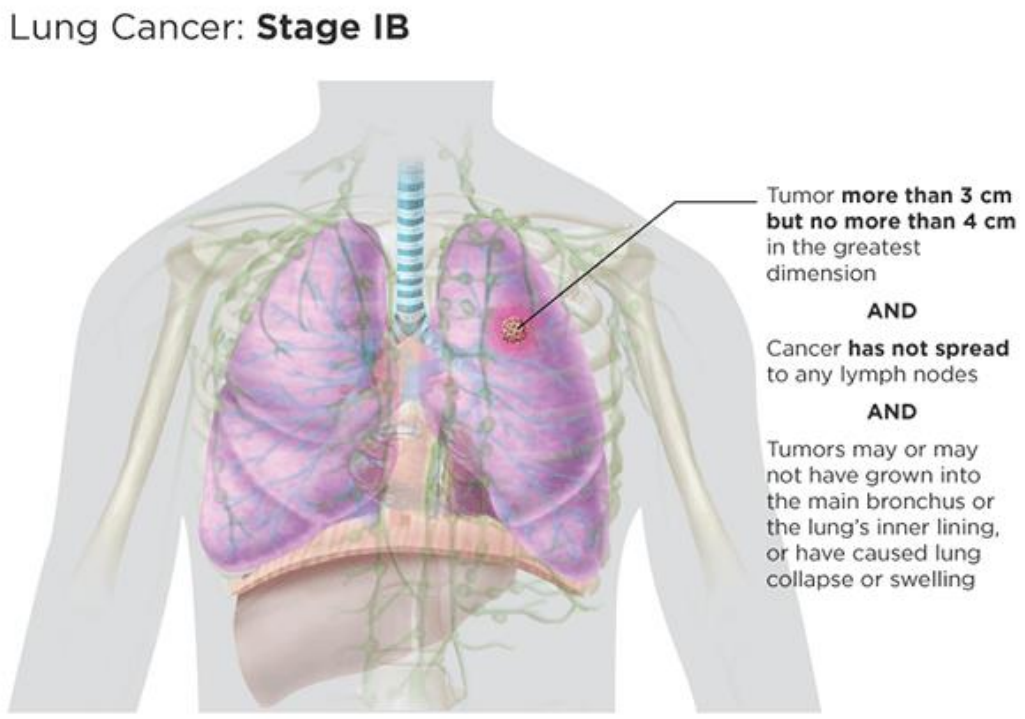

Fig. 13. Stage IB: Those are slightly larger, with a maximum dimension of more than 3 cm but less than 4 cm. Stage IB tumors may or may not have invaded the major bronchus or the inner lining of the lung, resulting in lung collapse or edema [51]

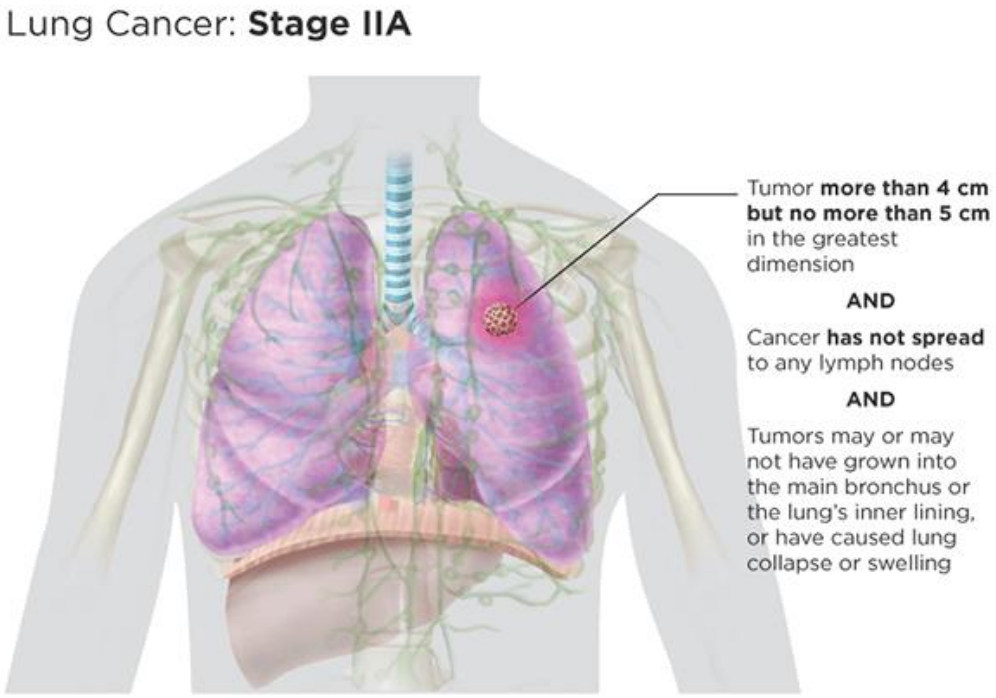

Fig. 14. Stage IIA: Tumors that are bigger than 4 cm in diameter but no larger than 5 cm in diameter have not spread to adjacent lymph nodes. The tumors could have developed into the main bronchus or the inner lining of the lung, causing lung collapse or edema [51]

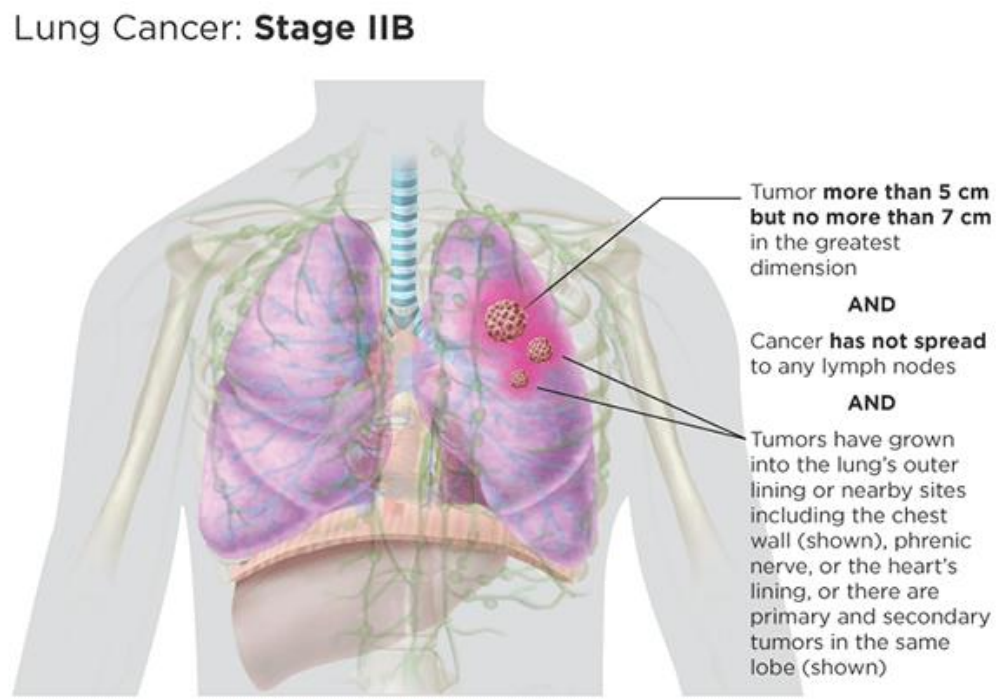

Fig. 15. Stage IIB: longer than 5 cm in length but less than 7 cm in width, and have not migrated to adjacent lymph nodes They've expanded into the outer lining of the lung, or neighboring places such as the chest wall, phrenic nerve, or the lining of the heart, or there are primary and secondary tumors in the same lobe [52]

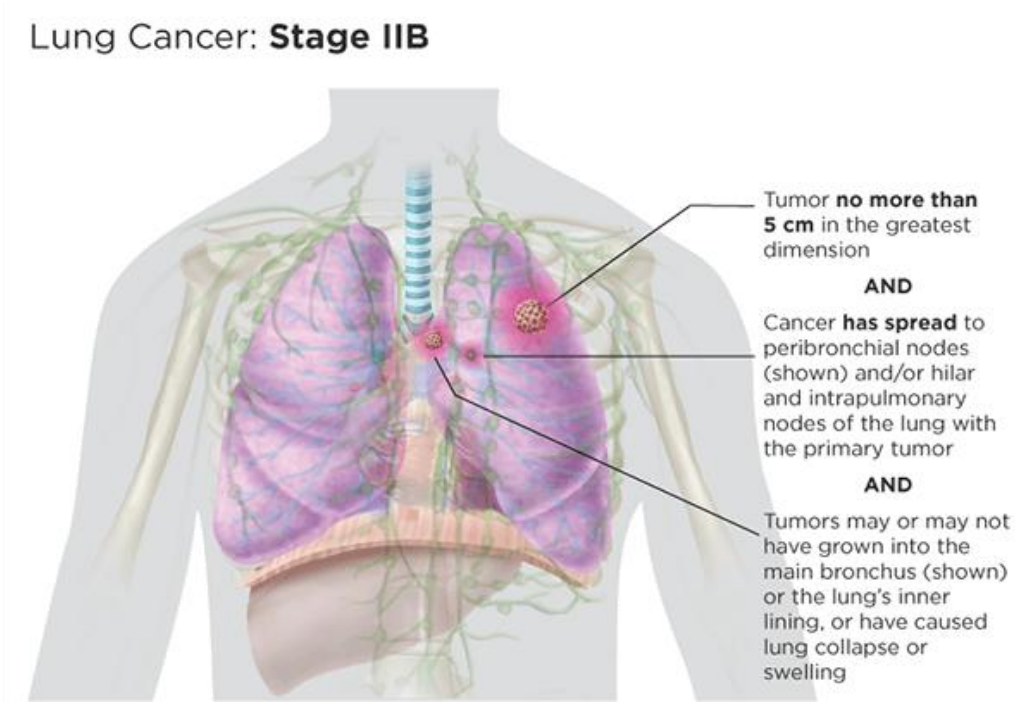

Fig. 16. Stage IIB: The initial tumour is no more than 5 cm in diameter and has spread to the peribronchial nodes and/or the hilar and intrapulmonary nodes of the lung. They could have developed into the main bronchus or the inner lining of the lung, resulting in lung collapse or edema [52]

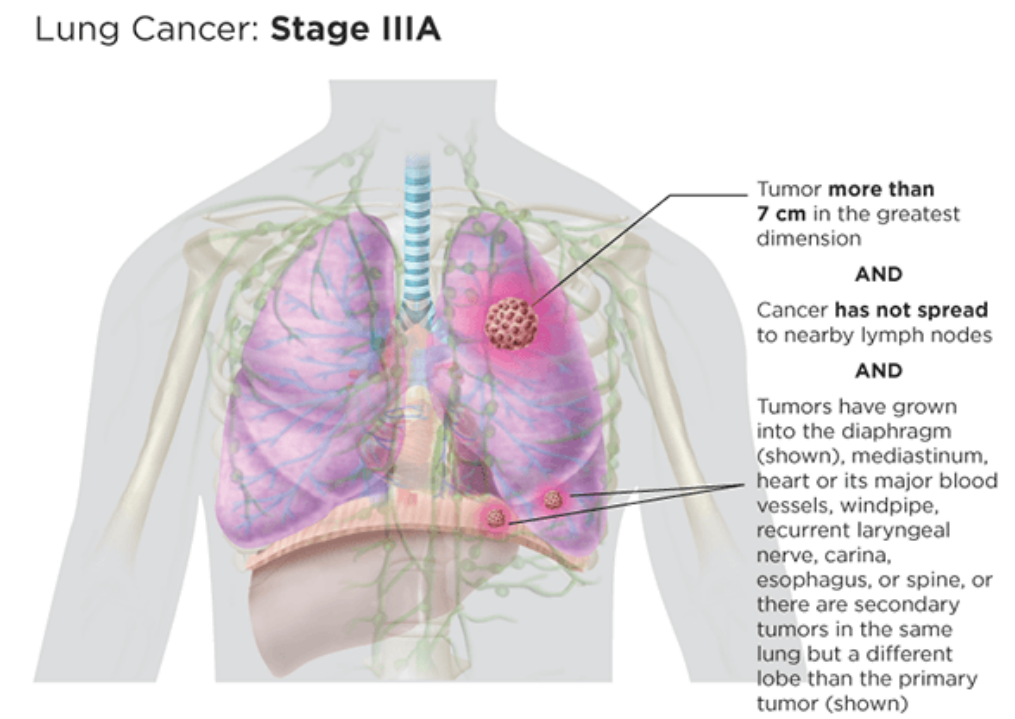

Fig. 17. Stage IIIA: The tumors are larger than 7 cm in diameter and have not migrated to adjacent lymph nodes. They may have developed into the diaphragm, mediastinum, heart or its major blood arteries, windpipe, recurrent laryngeal nerve, carina, esophagus, or spine, or there may be secondary tumors in the same lung but in a different lobe [52]

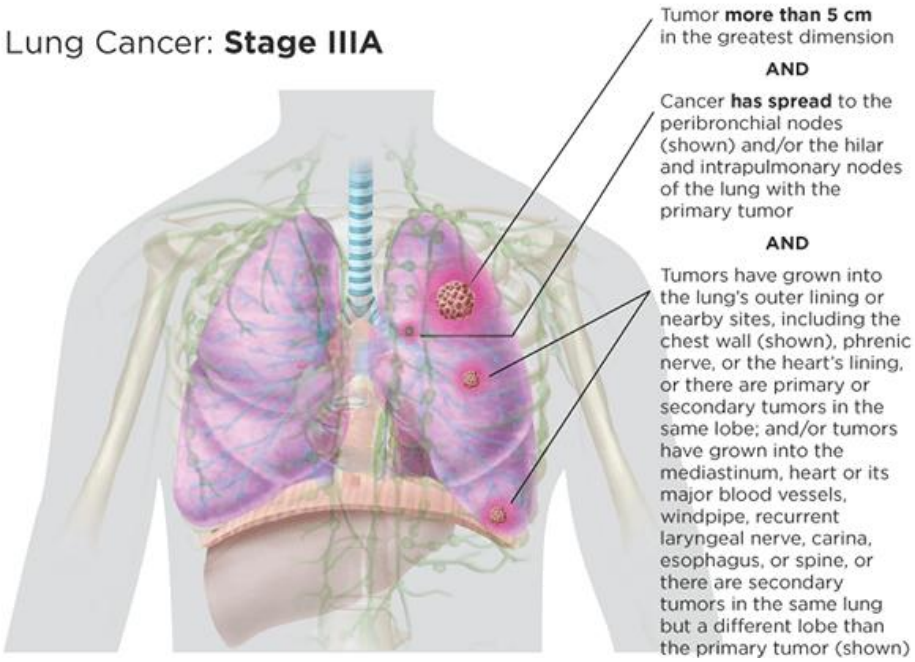

Fig. 18. Stage IIIA: The main tumor has spread to the peribronchial nodes and/or the hilar and intrapulmonary nodes of the lung with a diameter of more than 5 cm. Tumors have grown into the diaphragm, mediastinum, heart or its major blood vessels, windpipe, recurrent laryngeal nerve, carina, esophagus, or spine, or there are secondary tumors in the same lung but a different lobe than the primary tumor; and/or tumors have grown into the diaphragm, mediastinum, heart or its major blood vessels, windpipe, recurrent laryngeal nerve, carina [52]

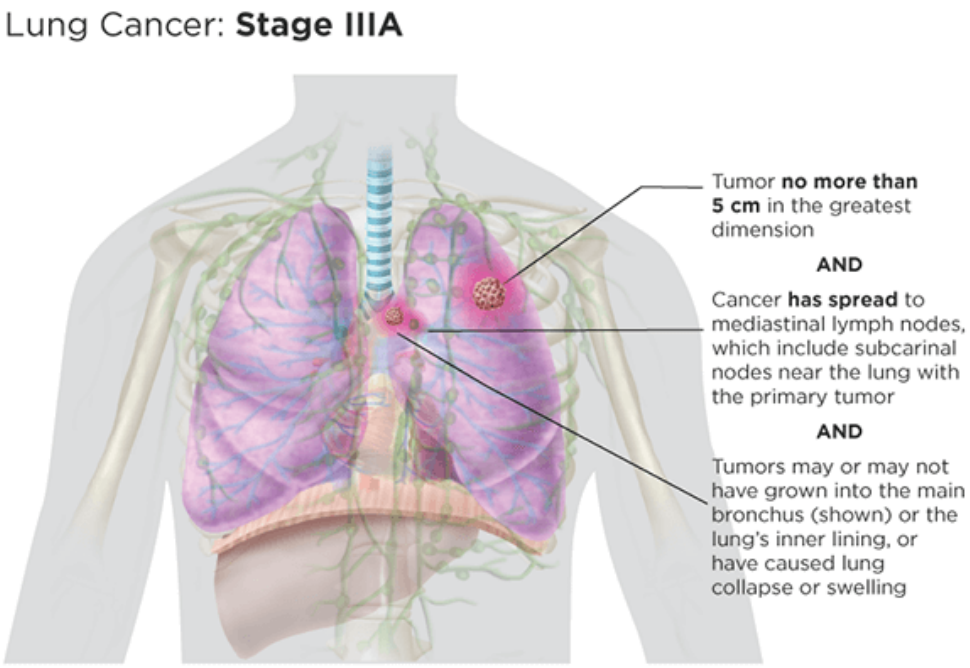

Fig. 19. Stage IIIA: They're no bigger than 5 cm in diameter and have expanded to mediastinal lymph nodes, including subcarinal nodes, near the main tumor. They may or may not have invaded the main bronchus or the inner lining of the lung, resulting in lung collapse or edema [52]

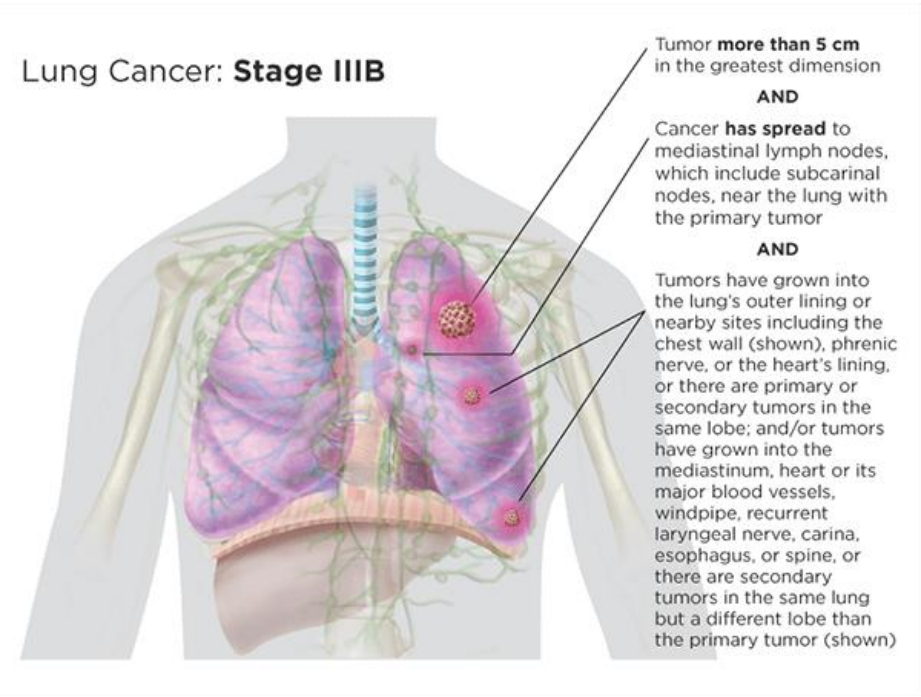

Fig. 20. Stage IIIB: greater than 5 cm in diameter and have migrated to mediastinal lymph nodes, including subcarinal nodes, near the main tumor's location. Tumors have grown in the diaphragm, mediastinum, heart or its major blood vessels, windpipe, recurrent laryngeal nerve, carina, esophagus, or spine, or there are secondary tumors in the same lung but a different lobe than the primary tumor; and/or tumors have grown in the diaphragm, mediastinum, heart or its major blood vessels, windpipe, recurrent laryngeal nerve, carina [52]

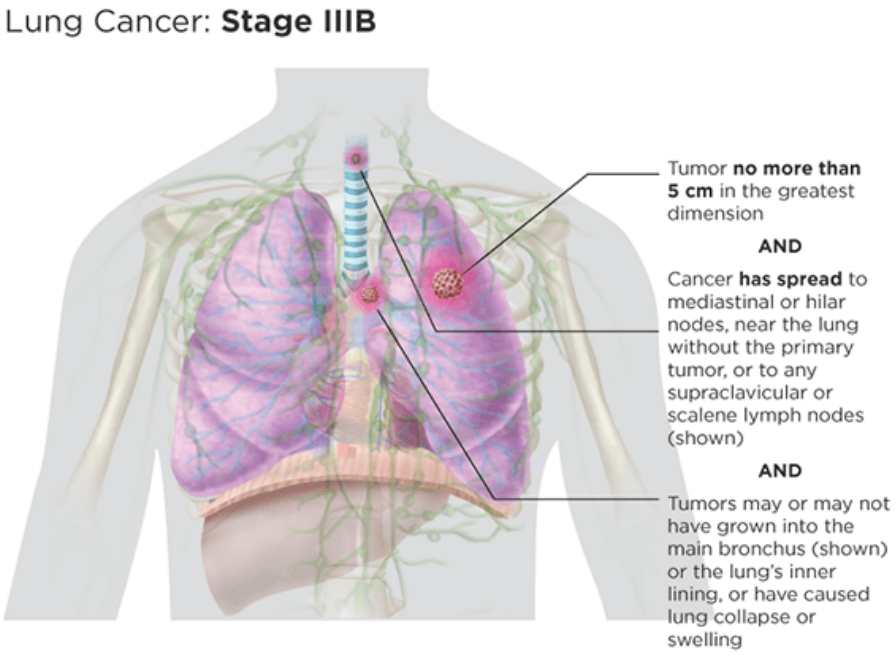

Fig. 21. Stage IIIB: Without the original tumor, the malignancy has migrated to the mediastinal or hilar nodes near the lung, as well as any supraclavicular or scalene lymph nodes. They may or may not have invaded the main bronchus or the inner lining of the lung, resulting in lung collapse or edema [52]

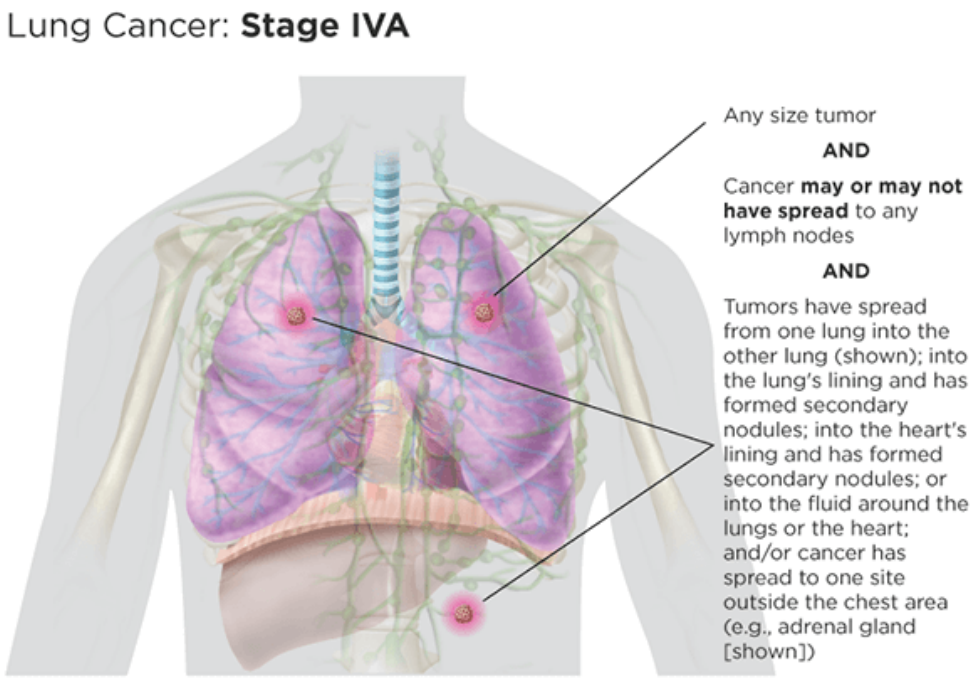

Fig. 22. Stage IVA: Tumors can be any size, have spread to lymph nodes or not, and have metastasized from one lung to the other, into the lung's lining (and formed secondary nodules), into the heart's lining (and formed secondary nodules), or into the fluid around the lungs or heart; and/or tumors have spread to one site outside the chest area (e.g., adrenal gland or bones) [53]

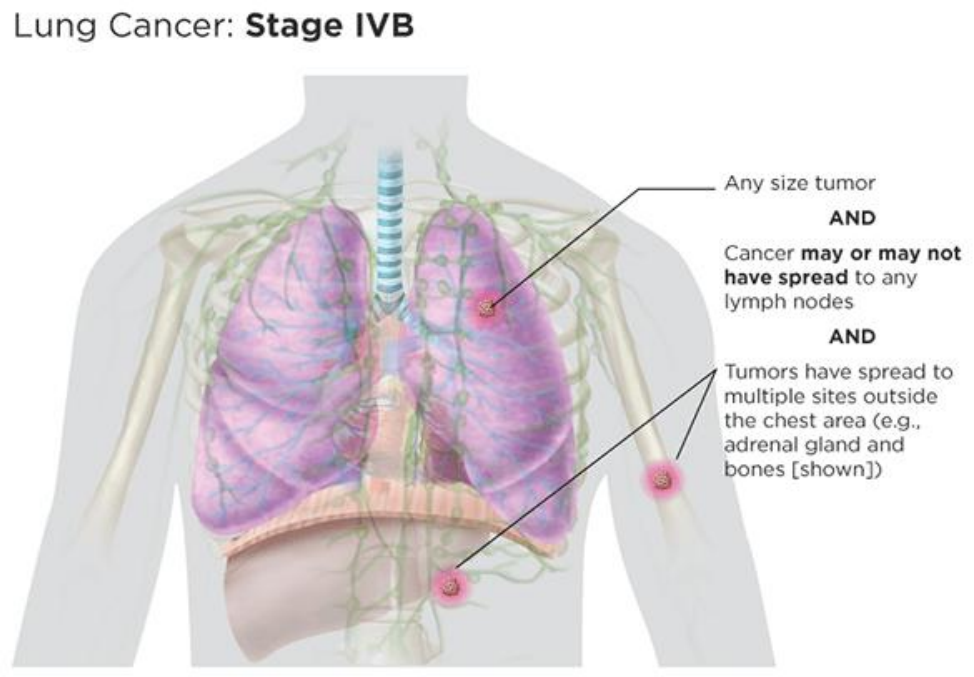

Fig. 23. Stage IVB: Tumors can be any size, have migrated to lymph nodes or not, and have spread to many locations outside the chest area (e.g., adrenal gland and bones) [53]

Patients with Pancoast tumors: An MRI shows superior sulcus tumors better than a CT scan. Transthoracic needle aspiration should be performed on the patient. If endobronchial involvement is suspected, bronchoscopy should be performed. SVCS patients: Lung cancer accounts for 60-80% of SVCS cases. Head elevation, judicious fluid administration, and supplemental oxygen are all recommended. Glucocorticoids (methylprednisolone 125 mg IV) and diuretics may aid with symptoms, although their roles are uncertain. Radiotherapy, chemotherapy, and/or vena caval stenting are frequently used as last treatments. Patients with Ogilvie pseudo-obstruction of the intestine: Massive dilatation of the colon and small intestine can be seen on an abdominal radiograph, with or without air-fluid levels. Check electrolyte levels and make any necessary adjustments. A nasogastric tube and a rectal tube should be placed. Admit the patient for possible colonic decompression and underlying cause treatment (eg, lung cancer-producing autoantibodies to the myenteric neural plexus). Opioid analgesics should be given to cancer patients who are in extreme pain and have advanced disease. Nasogastric tube and rectal tube placement may help with the pain [53].

26. SCREENING

The American Cancer Society (ACS), American College of Chest Physicians (ACCP), National Comprehensive Cancer Network (NCCN), and U.S. Preventive Services Task Force (USPSTF) recommend offering annual screening with low-dose computed tomography (LDCT) scanning to patients aged 55 to 74 years (the USPSTF extends the recommended age range to 80 years, and the NCCN extends to age 77) and who have at least a 30-pack-year smoking history and either continue or stop smoking When a patient has one of the following additional risk factors, the NCCN guidelines recommend starting screening at age 50 and decreasing the threshold to at least a 20 pack-year smoking history. Occupational exposure to carcinogens (e.g., silica, cadmium, asbestos, arsenic, beryllium, chromium, diesel fumes, nickel, coal smoke, soot), Radon exposure (confirmed persistent and substantially elevated), Cancer history (eg, lymphomas, head and neck cancer), First-degree relatives with a history of lung cancer, as well as disease history (chronic obstructive pulmonary disease [COPD] or pulmonary fibrosis) [54].

Patients who have not smoked for 15 years or who have developed a health condition that would significantly restrict their life expectancy, the feasibility of curative lung surgery, or their desire to undertake such an operation should not be screened. Cheung et al assessed the number of US smokers eligible for screening based on USPSTF criteria or the Lung Cancer Risk Assessment Tool, as well as the number of lung cancer deaths preventable with each method, using data from the National Health Interview Survey. They concluded that risk-based screening would result in more people being screened and fewer deaths. Risk-based screening would have saved 5000 lives in 2015 compared to USPSTF-based screening. However, that risk-based screening gives only minor and marginal benefits in terms of life-years, quality-adjusted life-years, and cost-effectiveness. A randomized trial that looked at the value of long-term lung cancer screening found that the benefit of LDCT screening improved after the fifth year, with a 58 percent lower risk of lung cancer mortality (HR 0.42; 95 percent CI 0.22–0.79) and a 32 percent lower risk of overall mortality (HR 0.68; 95 percent CI 0.49–0.94). Limitations of screening: In a 2013 analysis of data from the National Lung Screening Trial, Patz et al found that performing lung screens with LDCT scanning has a 22.5 percent chance of NSCLC overdiagnosis (ie, detection of indolent cancers) and an 18.5 percent chance of lung cancer overdiagnosis in general. Overdiagnosis, which can lead to higher treatment costs, anxiety, and treatment-related morbidity, should be considered by physicians when discussing the dangers of LDCT lung cancer screening. Following that, Patz et al found that patients with a negative initial LDCT scan have a decreased incidence of lung cancer and lung cancer-specific death in a retrospective cohort study of data from the National Lung Screening Trial participants. These authors proposed that a longer interval between screens might be warranted in patients whose initial LDCT screening scan is negative [54].

The 19,066 patients with a negative LDCT had a lung cancer incidence of 371.88 per 100,000 person-years, compared to 661.23 in the whole cohort of 26,231 participants. For the two cohorts, lung cancer-related death rates per 100 000 person-years were 185.82 and 277.20, respectively. In a study of 2106 individuals at Veterans Health Administration medical centers, Kinsinger et al found that LDCT detected nodules in 59.7% of screened patients, however, only 1.5

percent of patients had lung cancer diagnosed within 330 days. 97.5 percent of test findings were falsely positive. Implementing a lung cancer screening program for Veterans Health Administration patients "would potentially demand tremendous resources and effort by clinical staff and facilities for the unclear benefit of reduced lung cancer mortality," according to these authors [54].

Risk models for screening: A study by researchers from the National Cancer Institute (NCI) and the American Cancer Society that reviewed nine risk prediction models determined that the following four models were more accurate than the others for predicting lung cancer risk and for selecting patients who had ever-smoked for lung cancer screening: Bach model, Ovarian Cancer Screening Trial Model 2012 (PLCO-M2012), Lung Cancer Risk Assessment Tool (LCRAT), and Lung Cancer Death Risk Assessment Tool (LCDRAT) Although the researchers concluded that any of those models could be used to select US smokers who are at the greatest risk for lung cancer incidence or death, all the models have limitations. The Bach model does not account for race/ethnicity, family history of lung cancer, or presence of chronic obstructive pulmonary disease; the PLCO-M2012 model underestimated lung cancer risk in people of Hispanic descent by a factor of 2 to 3, and the LCRAT and LCDRAT models both underestimated risk in the "Asian/other" subgroup [54].

Biomarker screening: A collaborative study has developed and validated a panel of circulating protein biomarkers that could help with lung cancer risk assessment and could be used to determine CT screening eligibility. The Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer developed a risk assessment tool based on prediagnostic blood samples from patients at high risk for lung cancer. The panel of proteins included Cancer antigen 125, Carcinoembryonic antigen, Cytokeratin-19 fragment, and The precursor of surfactant protein B. An integrated risk prediction model that incorporated smoking exposure with the biomarker panel score detected 40 of the 63 lung cancer cases in a validation analysis of 63 ever-smoking patients with lung cancer and 90 matched controls, equating to a sensitivity of 0.63. The screening criteria developed by the US Preventive Services Task Force have a sensitivity of 0.42 for these instances [54].

27. TREATMENT

The most common treatments for NSCLC include surgery, systemic therapy, and radiation. Because most lung tumors are incurable with current therapeutic modalities, effective palliative care is an important aspect of the treatment of NSCLC patients. For stage I and stage II NSCLC, surgery is the treatment of choice. The following are some of the numerous forms of surgery that can be used: Wedge resection: removing part of a lobe, Pneumonectomy: removing the entire lung, and Lobectomy: removing a segment of the lung [55].

Systemic therapy: Approximately 80% of all lung cancer patients will be considered for systemic therapy at some time throughout their disease. Multiple randomized, controlled studies and comprehensive meta-analyses have all shown that combination chemotherapy regimens are superior to single-agent chemotherapy regimens for advanced NSCLC. The American Society for Clinical Oncology (ASCO) recommends using a platinum combination as the first-line treatment for NSCLC. Cisplatin is recommended in younger patients with high-performance status or the adjuvant setting, while carboplatin can be used in elderly patients or those with major comorbidities. Agents that target specific molecular aspects of the tumor have become commonplace. Systemic therapy regimens may include combinations of targeted drugs with chemotherapy or targeted agents alone, depending on the molecular aspects [55].

Radiation therapy is only recommended in the treatment of stage I and stage II NSCLC when surgical resection is not possible. For people who are not surgical candidates, stereotactic radiation is a viable choice for lung cancer treatment. In patients with NSCLC who are undergoing radiation, beta-blockers have been reported to improve overall survival, disease-free survival, and distant metastasis-free survival, but not locoregional progression-free survival [55].

For individuals with non–small cell lung cancer (NSCLC) stages I through IIIA, surgery is the treatment of choice. Furthermore, because patients with resected lung cancer have a significant risk of relapse, they are given adjuvant chemotherapy. Chemotherapy and surgery are generally administered to patients with stage IIIB

and IV NSCLC. In the treatment of advanced NSCLC, molecular-targeted therapy is becoming increasingly relevant. In patients who are not surgical candidates, radiation is a viable therapy option. The role of adjuvant radiation therapy after primary tumor excision is still debatable. Because most NSCLC patients cannot be cured with currently available treatments, effective palliative care is a vital aspect of the treatment plan. Palliative treatment should be offered concurrently with normal oncologic care when advanced NSCLC is first diagnosed, according to growing data. Patients with metastatic NSCLC who were assigned to early palliative care had a better quality of life and, interestingly, a longer median survival than those who were randomized to standard oncologic therapy alone, according to a clinical trial. Patients in the palliative care group also had fewer depression symptoms and received less aggressive end-of-life treatment [55].

28. OUTLINE OF TREATMENT OPTIONS BY STAGE

Treatment of NSCLC by stage is as follows: Stage IA - Surgery only; no adjuvant chemotherapy, Stage IB-IIIA - Surgery followed by adjuvant chemotherapy with four cycles of a cisplatin-based regimen and, in cases with an EGFR exon 19 deletion or exon 21 L858R mutation, adjuvant osimertinib, Stage II-IIIB - If surgically unresectable, chemoradiation plus durvalumab for one year if chemoradiation results in partial or complete response, and Stage IV - Treat based on histology (squamous or non-squamous). Treatment of stage IV squamous NSCLC is as follows: Cisplatin-based chemotherapy, If programmed death-ligand 1 (PD-L1) expression is 1-49%, chemotherapy plus pembrolizumab, If PD-L1 expression is > 50%, pembrolizumab alone. Treatment of stage IV non-squamous NSCLC is as follows: If PD-L1 expression is 1-49%, cisplatin-based chemotherapy plus pembrolizumab If PD-L1 expression is > 50%, pembrolizumab alone, Cisplatin-based chemotherapy plus bevacizumab is also a reasonable option, an oral tyrosine kinase inhibitor or other targeted therapy for tumors with treatable driver mutations (eg, EGFR, ALK, ROS1, RET, BRAF, NTRK gene fusion, MET exon 14) [56].

29. EMERGENCY TREATMENT

All individuals suspected of having lung cancer should be urged to see their primary care physician for follow-up care. Document and discuss the possible diagnosis with the patient in almost all circumstances. The emergency room cannot provide definitive treatment for the underlying malignancy (ED). Symptoms are used to guide emergency therapy. Admit the patient to the intensive care unit (ICU), prepare for intubation and/or cricothyrotomy, and seek otolaryngologic and/or surgical consultation for fiberoptic laryngoscopy or intraoperative tracheostomy in situations of upper airway obstruction. If hemoptysis is detected, give supplemental oxygen and suction the wound. Consider inserting a double-lumen endotracheal tube if there is a risk of death. Place the patient in a dependent position with the bleeding hemithorax. If the bleeding isn't minor, get an arterial blood gas (ABG) and a complete blood count (CBC) (type and crossmatching) coagulation test. Fiberoptic bronchoscopy may be required by a pulmonologist. Patients should be admitted to the ICU unless they are experiencing mild bleeding [56].

30. DISCUSSION

Small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC) are the two main types of lung cancer (NSCLC). NSCLC accounts for over 85% of all lung cancer cases. NSCLC is categorized into three types based on histology: adenocarcinoma, squamous cell carcinoma (SCC), and giant cell carcinoma. Lung cancer was once considered a rare disease in the early 1900s, but it has since become significantly more common. Lung cancer is only second to prostate cancer in males and breast cancer in women in terms of prevalence. Lung cancer had become the largest cause of preventable death in the United States by the end of the 1900s, and it had recently surpassed heart disease as the major cause of smoking-related mortality. Lung cancer is the top cause of cancer-related mortality in both men and women worldwide, not only in the United States. In the United States, the disease is anticipated to kill almost 132,000 people in 2021, more than colorectal, breast, and prostate cancers combined. Lung cancer forms have altered in the United States, as well as many other nations, during the last few decades, with adenocarcinoma becoming more common and SCC becoming less common [56].

The majority of lung carcinomas are discovered at an advanced stage, which means they have a bad prognosis. The importance of detecting lung cancer at an early and potentially treatable stage

is clear. Furthermore, the majority of patients with lung cancer are smokers, with smoking-related heart and lung damage, making severe surgical or multimodality therapy less viable possibilities. Lung cancer is a sneaky disease that often goes unnoticed until it's too late. Lung cancer is discovered by chance in about 7-10% of asymptomatic people when a chest radiograph is taken for another reason and the disease is discovered. NSCLC is linked to a variety of pulmonary symptoms. Weight loss that isn't explained and low-grade fever are examples of systemic abnormalities. Because stage is so important in the therapeutic decision-making process, all NSCLC patients must be properly staged. To determine the extent of the disease, a thorough staging workup for NSCLC should be performed. Surgery, chemotherapy, or radiation therapy are the most common treatments. Because most lung tumors are incurable with current therapeutic modalities, effective palliative care is an important aspect of the treatment of NSCLC patients [56].

31. CONCLUSION

The treatment of NSCLC necessitates an interdisciplinary approach to the patient's care. This starts with smoking cessation therapy, which the primary clinician plays an important role in. The main clinician also plays a critical role in the early detection of lung cancer by lung cancer screening before it progresses to advanced stages when the prognosis worsens. Following the diagnosis, an interprofessional approach with medical oncology, radiation oncology, thoracic surgery, and pathology should be used to maximize the patient's treatment plan based on their TNM staging at the time of diagnosis.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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