

Lung Cancer: Clinical challenges, advanced diagnostics, and evolving therapeutic paradigm

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Abstract

Lung cancer remains the leading cause of cancer-related deaths worldwide, accounting for approximately 1.8 million deaths annually. Despite technological advancements, late diagnosis and poor prognosis persist, especially in resource-limited settings. This article presents an in-depth review of lung cancer, encompassing its historical context, pathophysiology, evolving diagnostic techniques such as PET-CT and liquid biopsy, and the current multidisciplinary treatment approaches including immunotherapy and targeted therapy. Two representative case studies are presented, highlighting diagnostic dilemmas, clinical decisions, and outcomes. The article emphasizes early recognition, tailored therapy, and community awareness as vital components in reducing lung cancer morbidity and mortality.

Keywords: Lung Cancer, NSCLC, Small Cell Lung Cancer, Immunotherapy, EGFR mutation, Case Study, India, Diagnostic Imaging, Histopathology, Community Awareness

Introduction

Lung cancer is one of the most aggressive and deadly forms of malignancy worldwide. It represents a major public health challenge due to its high incidence, late-stage diagnosis, and low survival rates. The disease was relatively uncommon in the early 20th century, but with the industrial revolution and a global rise in cigarette smoking, lung cancer incidence surged dramatically, becoming a dominant oncological concern.

It is broadly classified into two major histopathological types: Non-Small Cell Lung Cancer (NSCLC), which accounts for about 85% of cases, and Small Cell Lung Cancer (SCLC), comprising the remaining 15%. NSCLC includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, while SCLC is noted for its rapid growth and early metastasis.

Several risk factors contribute to lung cancer development. Cigarette smoking is the most significant and modifiable cause, responsible for over 85% of lung cancer deaths. However, a growing number of non-smoking individuals, particularly women, are being diagnosed, often linked to passive smoke exposure, air pollution, occupational hazards (asbestos, silica), and genetic susceptibility.

The disease typically presents late, often when curative treatment options are limited. The lack of specific symptoms in early stages contributes to delayed diagnoses. In India and other TB-endemic countries, lung cancer is frequently misdiagnosed as tuberculosis, leading to inappropriate treatments and lost opportunities for early intervention. Recent advances in diagnostics, such as low-dose CT screening, PET-CT imaging, and molecular testing, have improved early detection and allowed for personalized treatment. Despite this progress, the 5-year survival rate remains poor, particularly for advanced stages, underscoring the urgent need for public awareness, timely screening, and accessible healthcare infrastructure.

Historical Aspects and Background

The historical journey of lung cancer is closely tied to the global rise in tobacco use during the early and mid-20th

century. By the 1950s, landmark epidemiological studies had firmly established the causal relationship between cigarette smoking and lung cancer, prompting a shift in public health focus and cancer research. This period also marked the beginning of organized efforts in cancer prevention through tobacco control policies.

In the early decades, lung cancer was often diagnosed at an advanced stage, and treatment was limited to open surgical resection in operable cases and rudimentary chemotherapy with limited efficacy. The prognosis remained dismal for most patients, particularly for those with inoperable or metastatic disease.

Over time, technological advancements such as bronchoscopy, CT-guided needle biopsy, and high-resolution imaging revolutionized diagnostic accuracy. These tools made it possible to visualize central and peripheral lesions, obtain tissue samples safely, and stage the disease with greater precision.

A turning point in lung cancer management came with the discovery of genetic mutations and biomarkers associated with tumor growth. The development of molecular diagnostics allowed the identification of driver mutations like EGFR, ALK, and ROS1, enabling the use of targeted therapies such as tyrosine kinase inhibitors (TKIs). More recently, immune checkpoint inhibitors (like nivolumab and pembrolizumab) have shown significant survival benefits in selected patients.

Additionally, the introduction of stereotactic body radiotherapy (SBRT) and video-assisted thoracoscopic surgery (VATS) has improved outcomes in early-stage disease. Thus, the evolution of lung cancer care from conventional to personalized treatment represents one of the most transformative narratives in oncology.

Epidemiology

Lung cancer is one of the most prevalent and deadly cancers worldwide. According to the Global Cancer Observatory (GLOBOCAN) 2020 report, it is the second most frequently diagnosed cancer (11.4% of total cases) and the leading

cause of cancer-related deaths, accounting for 18% of total cancer mortality. The global incidence of lung cancer continues to rise, especially in low- and middle-income countries due to increasing exposure to risk factors such as smoking, indoor air pollution, and occupational hazards.

In India, lung cancer constitutes approximately 5.9% of all cancers and is the most common cancer among men in many metropolitan cities including Delhi, Mumbai, and Kolkata. The Indian Council of Medical Research (ICMR) reports a sharp increase in lung cancer among both smokers and non-smokers, particularly among younger adults and women, often linked to secondhand smoke and biomass fuel exposure.

Maharashtra, particularly the urban areas like Mumbai, has reported increasing trends in lung cancer due to industrialization, vehicular emissions, smoking habits, and occupational exposures. Studies indicate that lung cancer incidence in men is nearly three times higher than in women, although the gap is narrowing due to changing lifestyle factors.

The most common histological subtype globally and in India is adenocarcinoma, followed by squamous cell carcinoma and small cell carcinoma. The trend has shifted from squamous cell dominance to adenocarcinoma in recent years, partly due to reduced smoking rates and increased detection in non-smokers.

The prognosis of lung cancer remains poor with a 5-year survival rate below 20% globally. In India, due to delays in diagnosis and limited access to specialized care, the outcomes are even more dismal. Early-stage detection through low-dose computed tomography (LDCT) screening and awareness campaigns has proven effective in reducing mortality in high-income countries, but its implementation in India remains limited.

Lung cancer in non-smokers is an emerging epidemiological concern. Nearly 20-25% of lung cancer cases globally now occur in individuals who have never smoked, and this proportion is higher in Asian countries. Environmental pollution, genetic susceptibility, chronic respiratory conditions, and infectious agents are under investigation as possible causes.

Given these trends, epidemiological surveillance, data collection, and investment in preventive healthcare are essential components of national cancer control strategies.

Academic Discussion

The management of lung cancer has undergone a significant transformation—from being primarily guided by histopathological classification to a more refined, precision medicine approach. While earlier decisions were based mainly on whether the tumor was small cell or non-small cell, molecular profiling has now become the cornerstone of modern lung cancer therapy. Identifying specific driver mutations like EGFR, ALK, ROS1, and PD-L1 expression allows for the use of targeted and immunotherapeutic agents, which significantly improve survival and quality of life.

Despite these scientific advances, resource-limited settings face numerous challenges in adopting precision oncology. Many patients still lack timely access to imaging tools like PET-CT and HRCT, and molecular testing is either unavailable locally or unaffordable. Even when testing is possible, delays in processing and reporting can postpone the start of effective treatment. Inconsistent drug availability

and high out-of-pocket expenses also contribute to treatment interruptions and poor adherence, adding to the disease burden.

Globally, low-dose computed tomography (LDCT) screening programs have demonstrated a significant reduction in lung cancer mortality among high-risk populations, particularly smokers. However, India has yet to implement such programs at scale, primarily due to a lack of infrastructure, funding, and awareness. Integrating LDCT screening into public health frameworks and increasing awareness among general practitioners could lead to earlier diagnoses and improved outcomes.

In conclusion, bridging the gap between cutting-edge science and ground-level implementation is essential to truly advance lung cancer care in India and similar settings.

Clinical Presentation and Diagnostic Challenges

Lung cancer often presents with non-specific respiratory and systemic symptoms, making early diagnosis challenging. The most common clinical features include a persistent cough, hemoptysis (coughing up blood), chest pain, unexplained weight loss, dyspnea (shortness of breath), and hoarseness of voice due to recurrent laryngeal nerve involvement. These symptoms can be mistaken for common respiratory infections, asthma, or chronic obstructive pulmonary disease (COPD), leading to under-recognition of the underlying malignancy.

A significant concern is that many patients remain asymptomatic in the early stages, with symptoms appearing only when the disease is locally advanced or has metastasized. In some cases, the first presentation may be due to paraneoplastic syndromes (such as hypercalcemia, SIADH, or neurological deficits), or distant metastases to the brain, liver, adrenal glands, or bones—making diagnosis even more complex.

The diagnostic process is further complicated in countries like India, where pulmonary tuberculosis (TB) is highly prevalent. Both TB and lung cancer can cause cavitory lesions, constitutional symptoms, and similar radiographic findings. As a result, many lung cancer patients receive empirical anti-TB treatment before a cancer diagnosis is considered—causing significant delays in appropriate investigations and treatment.

A high index of suspicion, supported by timely imaging (chest X-ray, HRCT) and tissue biopsy, is essential to differentiate malignancy from infections and avoid misdiagnosis. Early referral and use of advanced diagnostic modalities are critical for improving outcomes.

Advanced Diagnostic Modalities

Accurate diagnosis of lung cancer at an early stage is crucial for improving survival outcomes. Several advanced diagnostic tools and techniques have been developed in recent years to assist in detecting lung cancer, staging the disease, and determining the best treatment options. These technologies help doctors not only confirm the presence of cancer but also understand the specific type and genetic makeup of the tumor.

- 1. Low-Dose Computed Tomography (LDCT):** LDCT is a special type of chest CT scan that uses lower doses of radiation. It is widely used in high-risk individuals, such as long-term smokers, to detect lung cancer early. Studies have shown that LDCT can reduce lung cancer mortality by detecting tumors before symptoms appear.

2. **PET-CT Scan:** Positron Emission Tomography combined with CT scan is used to identify the metabolic activity of tumors. PET-CT helps in determining the stage of cancer, checking for spread to lymph nodes or distant organs, and guiding biopsy sites.
3. **Bronchoscopy with Endobronchial Ultrasound (EBUS):** This is a minimally invasive procedure that uses a flexible tube with a camera and ultrasound to look inside the lungs and airways. EBUS is helpful in sampling lymph nodes and masses near the bronchial tree without the need for open surgery.
4. **CT-Guided Needle Biopsy:** For tumors located deep in the lungs or near the chest wall, a needle is inserted through the skin under CT scan guidance to collect a tissue sample. This procedure is highly accurate and commonly used to confirm cancer diagnosis.
5. **Liquid Biopsy:** This modern technique detects cancer-related genetic mutations and markers in a blood sample. It is especially useful when traditional biopsy is not possible. Liquid biopsy can identify mutations like EGFR or ALK that help decide on targeted therapies.
6. **Immunohistochemistry (IHC) and Molecular Testing:** After a biopsy, tissue samples are tested in the lab to find proteins and genetic mutations. These tests reveal whether the tumor has specific mutations (like EGFR, ALK, ROS1) or expresses certain markers (like PD-L1) that help choose the best treatment.
7. **Artificial Intelligence in Imaging:** AI-based tools are being developed to read chest X-rays and CT scans with high accuracy. These technologies can flag suspicious lesions early and assist radiologists in faster diagnosis.
3. **Stereotactic Body Radiotherapy (SBRT):** SBRT delivers high doses of radiation precisely to the tumor, sparing healthy tissues. It is especially useful in early-stage lung cancers in patients who are not fit for surgery.
4. **Robotic and Minimally Invasive Surgery:** Advanced surgical methods such as Video-Assisted Thoracoscopic Surgery (VATS) and robotic surgery reduce recovery time, postoperative pain, and hospital stay compared to traditional open surgery.
5. **Chemotherapy Improvements:** Newer drug combinations and schedules are being used to minimize toxicity and increase effectiveness. Chemotherapy remains essential, especially in small cell lung cancer and in advanced NSCLC without targetable mutations.
6. **Personalized Medicine:** With advancements in genomics, treatments are now tailored to the genetic profile of each patient's tumor. This means that two patients with the same type of lung cancer might receive entirely different treatments based on their molecular reports.
7. **Palliative and Supportive Care:** Focus on quality of life through pain management, nutritional support, and psychosocial care has become an integral part of lung cancer treatment, especially in advanced or metastatic stages.

Differential Diagnosis

Differential diagnosis of lung cancer is critical due to its ability to mimic several other pulmonary conditions, especially in regions with a high burden of infectious and granulomatous diseases.

Recent Advances in Treatment

The treatment of lung cancer has significantly evolved over the last decade. Traditional therapies like surgery, chemotherapy, and radiotherapy are now being complemented or replaced by advanced treatments based on genetic and immune profiling of the tumor. These personalized approaches improve the chances of survival and reduce side effects.

1. **Targeted Therapy:** This treatment uses drugs that specifically target cancer cell mutations without harming normal cells. Patients whose tumors have EGFR, ALK, ROS1, or other mutations can benefit from oral medications like Erlotinib, Osimertinib, Crizotinib, or Alectinib. These treatments are more effective and have fewer side effects compared to conventional chemotherapy.
2. **Immunotherapy:** This approach helps the patient's own immune system recognize and destroy cancer cells. Drugs like Nivolumab, Pembrolizumab, and Atezolizumab block the PD-1/PD-L1 pathway, allowing immune cells to attack tumors. Immunotherapy has shown remarkable benefits in patients with advanced NSCLC and improves long-term survival.
1. **Pulmonary Tuberculosis (TB):** In TB-endemic regions like India, lung cancer is often misinterpreted as tuberculosis due to overlapping symptoms such as chronic cough, hemoptysis, weight loss, and cavitary lesions on imaging. However, non-responsiveness to anti-TB treatment and presence of mass-like lesions should raise suspicion.
2. **Sarcoidosis:** This systemic granulomatous disease can cause bilateral hilar lymphadenopathy and pulmonary nodules, similar to malignancy. Diagnosis requires histological evidence of non-caseating granulomas and exclusion of infections and malignancies.
3. **Fungal Infections (e.g., Aspergillosis):** Chronic pulmonary aspergillosis can present with cavitary lung lesions resembling squamous cell carcinoma. A careful review of imaging, serologic tests, and fungal cultures is needed.
4. **Lymphoma:** Especially primary pulmonary lymphoma, can mimic lung cancer in imaging and symptoms. Biopsy with immunohistochemistry is essential for differentiation.
5. **Metastatic Cancer:** Lesions in the lung may originate from extrapulmonary primaries like breast, colorectal, or renal cancers. A thorough systemic evaluation and histopathological confirmation are necessary.

6. Inflammatory Pseudotumors and Hamartomas:

Benign conditions may appear as solitary pulmonary nodules and be mistaken for lung malignancy. CT features and tissue sampling are often required.

7. Bronchiectasis and Chronic Infections:

These may present with persistent symptoms and radiographic abnormalities. Clinical correlation and microbiological work-up help in ruling out malignancy.

Accurate diagnosis mandates a multidisciplinary approach involving radiologists, pulmonologists, oncologists, and pathologists. Tissue biopsy remains the gold standard for diagnosis and should be pursued aggressively in all suspicious cases.

Clinical and Public Health Difficulties

Lung cancer presents unique clinical and systemic challenges, particularly in developing countries. One of the most significant hurdles is misdiagnosis, especially in high tuberculosis (TB) burden settings like India. Due to overlapping symptoms such as chronic cough, weight loss, and hemoptysis, lung cancer is frequently mistaken for pulmonary TB. Patients are often started on empirical anti-TB therapy, delaying the correct diagnosis and timely initiation of cancer treatment.

Another major obstacle is the limited access to advanced diagnostics such as PET-CT scans and image-guided biopsies. These tools are essential for accurate staging and confirmation of malignancy, but are often unavailable or unaffordable in rural and resource-poor settings.

The financial burden of targeted therapies and immunotherapy is another critical barrier. Medications like EGFR inhibitors, ALK inhibitors, and immune checkpoint inhibitors have transformed outcomes in lung cancer, but remain beyond the reach of many patients due to high costs and limited inclusion in government health schemes.

In addition, delays in obtaining molecular testing results—due to logistic issues, sample transport, or centralized laboratory systems—further prolong treatment decisions, especially in aggressive cancers like small cell and advanced non-small cell lung carcinoma.

Finally, palliative care services are inadequately integrated into cancer care in many regions. Patients in advanced stages often suffer from severe breathlessness, pain, and psychological distress with limited access to symptom relief, counseling, and end-of-life care. This highlights the need for comprehensive, equitable, and patient-centered cancer services across all levels of the healthcare system.

Case Study 1: Misdiagnosed as Tuberculosis

Patient: 52-year-old male, non-diabetic, chronic smoker

Presentation: Chronic cough for 4 months, weight loss, hemoptysis

Initial Diagnosis: Empirical anti-TB started at a private clinic

Investigations

- **Chest X-ray:** Right upper lobe cavitation
- **HRCT Thorax:** Spiculated mass with mediastinal

Lymphadenopathy

- **PET-CT:** Hypermetabolic lesion with skeletal metastasis
- **CT-guided biopsy:** Adenocarcinoma, EGFR-mutation positive

Treatment

- Erlotinib (TKI), Denosumab for bone metastasis
- Palliative care and family counselling

Outcome: Improved performance status for 9 months, then declined

Case Study 2: Young Female with ALK Mutation

Patient: 36-year-old non-smoking female software engineer

Symptoms: Progressive breathlessness, dry cough, pleuritic chest pain

Investigations

- **Chest CT:** Left hilar mass with pleural effusion
- **Pleural fluid:** Exudative, negative for TB or infection
- **Bronchoscopy and biopsy:** Adenocarcinoma with ALK rearrangement

Treatment

- Crizotinib, switched to Alectinib due to CNS metastasis
- CNS radiotherapy

Outcome: Alive and functioning well after 18 months

Conclusion

Lung cancer continues to be one of the most complex and fatal cancers globally, primarily due to its often-silent onset, late-stage diagnosis, and the need for costly, resource-intensive treatments. Despite significant advancements in diagnostic imaging, molecular testing, and personalized therapies, the overall survival rates remain low—particularly in countries with limited healthcare infrastructure.

One of the most important lessons in lung cancer care is the value of early detection. Implementation of low-dose CT screening for high-risk individuals can dramatically reduce mortality, but this strategy remains underutilized in many parts of the world, including India. Public health campaigns focused on education, tobacco cessation, and pollution control can play a significant role in both prevention and early intervention.

A multidisciplinary approach involving pulmonologists, oncologists, radiologists, pathologists, palliative care specialists, and social workers is essential to deliver holistic care. Such collaborative models ensure accurate diagnosis, individualized treatment, emotional support, and continuity of care through the cancer journey.

Equitable access to high-quality diagnostics and treatments must be prioritized through national cancer control strategies. Financial assistance schemes, decentralization of oncology services, and integration of digital health platforms can address disparities and improve outcomes for underserved populations.

The fight against lung cancer demands sustained efforts from clinicians, researchers, health systems, governments, and communities. Through innovation, awareness, and collaborative care, we can shift the narrative from despair to hope, from late detection to early cure, and from inequality to equity in lung cancer management.

Summary of Lung Cancer Case Series

This case series highlights the clinical diversity and diagnostic complexity associated with lung cancer through two contrasting but educational patient profiles.

Case 1: Misdiagnosed as Tuberculosis

- **Patient:** 52-year-old male, chronic smoker
- **Symptoms:** Chronic cough, weight loss, hemoptysis
- **Initial Diagnosis:** Empirical anti-TB treatment at a peripheral center
- **Imaging:** HRCT revealed a spiculated mass in the right upper lobe with mediastinal lymphadenopathy
- **Biopsy:** CT-guided FNAC confirmed adenocarcinoma; EGFR mutation positive
- **Treatment:** Started on EGFR TKI (Erlotinib) with bone metastasis management
- **Outcome:** Improved symptomatically for 9 months before clinical decline

Key Message: In TB-endemic areas, lung cancer is often misdiagnosed as tuberculosis. Non-response to anti-TB therapy must prompt imaging and biopsy to rule out malignancy.

Case 2: Young Female Non-Smoker with ALK Mutation

- **Patient:** 36-year-old female, software engineer, non-smoker
- **Symptoms:** Progressive dry cough, pleuritic chest pain, and mild dyspnea
- **Investigations:** CT scan showed a left hilar mass with pleural effusion; EBUS biopsy confirmed adenocarcinoma with ALK rearrangement
- **Treatment:** Initiated on Crizotinib, later switched to Alectinib due to CNS metastases
- **Outcome:** Stable disease with functional independence at 18 months follow-up

Key Message: Even non-smokers, particularly women, may develop lung cancer. ALK-positive cases respond well to targeted therapy and require molecular testing as standard of care.

Overall Insights

- Both cases underline the importance of early and accurate diagnosis, the role of molecular profiling, and the impact of targeted therapies on survival and quality of life.
- They also emphasize the need to move beyond the traditional smoker-centric model of lung cancer risk assessment.
- Delay in diagnosis, especially in resource-limited settings, leads to poor outcomes and missed therapeutic windows.

Key Messages**For the Community**

- Do not ignore warning signs such as chronic cough, chest pain, unexplained weight loss, hoarseness, or coughing up blood—especially if you're a smoker or have prolonged exposure to dust, smoke, or air pollution.
- Seek early medical attention if symptoms persist for more than 2–3 weeks. Lung cancer diagnosed early is more treatable and curable.
- Avoid self-medication or unconfirmed TB treatment—misdiagnosis is common in TB-endemic areas and delays proper cancer treatment.
- Quit tobacco in all forms (smoking or chewing). It is the single most effective way to prevent lung cancer.

Seek support from tobacco cessation clinics or helplines.

- Get vulnerable groups screened: Elderly family members, women using firewood, and workers in dusty environments should have regular lung health check-ups—even if they don't smoke.
- Stay informed and aware by participating in community awareness programs about lung cancer, risk factors, and prevention strategies.

For Healthcare Workers (HCWs)

- Maintain high suspicion for lung cancer in patients with chronic respiratory symptoms not improving with conventional therapy.
- Always rule out malignancy in TB-negative individuals, especially in cases with persistent symptoms or atypical radiology.
- Facilitate timely investigations such as chest X-rays, HRCT, PET-CT, and biopsy. Delay in diagnosis directly affects survival outcomes.
- Encourage molecular profiling (EGFR, ALK, ROS1, PD-L1) in all eligible lung cancer patients to guide targeted and immunotherapy.
- Provide empathetic counseling and simplify complex information to help patients and families make informed treatment decisions.
- Record environmental, occupational, and lifestyle exposures comprehensively to identify at-risk populations.
- Collaborate through multidisciplinary teams for personalized, evidence-based care and better long-term outcomes.

For Policymakers and Health Administrators

- Include lung cancer in public health NCD programs, especially for high-risk populations like smokers, factory workers, and urban poor.
- Fund and implement LDCT screening in government hospitals for early detection of lung cancer in chronic smokers or high-risk groups.
- Ensure universal access to biomarker testing (EGFR, ALK, PD-L1) and newer therapies by expanding insurance coverage or subsidies.
- Decentralize cancer care to tier 2/3 cities and rural areas through tele-oncology units, mobile diagnostics, and regional cancer centers.
- Reduce environmental and occupational exposure to carcinogens through stricter air pollution controls and workplace safety regulations.
- Run multilingual mass awareness campaigns on the early signs of lung cancer, anti-tobacco messages, and available support services.
- **Invest in data systems and research:** Strengthen cancer registries, epidemiological surveillance, and promote local research to guide action.

References

1. Bray F, *et al.* Global Cancer Statistics 2020. GLOBOCAN estimates. CA Cancer J Clin. 2021.
2. National Cancer Registry Programme, ICMR. Consolidated Report, 2020.
3. Herbst RS, *et al.* The biology management of non-small cell lung cancer. Nature, 2018.

4. Indian Journal of Cancer, Lung cancer trends in India: Epidemiological insights, 2022.
5. Planchard D, *et al.* ESMO Clinical Practice Guidelines. Ann Oncol, 2019.
6. NCCN Guidelines on NSCLC, Version 3, 2024.
7. Ganti AK, *et al.* Small Cell Lung Cancer: 2022 Update. J Thorac Oncol, 2022.
8. Reck M, *et al.* Immunotherapy for lung cancer: Progress challenges. Nat Rev Drug Discov, 2023.