



Global Burden of Lung Cancer: Prognosis, Symptom Management, And Challenges with Pulmonary Fibrosis

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ABSTRACT: Lung cancer represents a significant global health burden, accounting for the highest number of cancer-related deaths worldwide. Despite advancements in treatment modalities, the prognosis remains poor, with a low 5-year survival rate post-diagnosis and substantial mortality within the first year. Patients often experience debilitating symptoms such as fatigue, pain, dyspnea, and coughing, which severely impact their physical and psychological well-being. Pain management is particularly challenging and critical due to its potential leading to depression and anxiety. Lung cancer encompasses histological classifications such as adenocarcinoma, squamous cell carcinoma, large cell carcinoma and small cell lung cancer (SCLC), each with distinctive subtypes. Patients with idiopathic pulmonary fibrosis (IPF) face exacerbated challenges when they also develop lung cancer, impacting their prognosis significantly compared to those with lung cancer alone. The management of pulmonary fibrosis (PF) in lung cancer necessitates a multifaceted approach, incorporating supportive care, pharmacological interventions, and emerging therapies like molecular targeted therapies, gene therapy, and stem cell therapy. This comprehensive management requires collaboration among various healthcare professionals to optimize outcomes and enhance quality of life for affected patients. Despite considerable progress, managing fibrosis in lung cancer remains complex due to its heterogeneous nature and varied progression. Ongoing future research aims to identify biomarkers for early detection, refine treatment strategies, and explore novel therapies through clinical trials. This review highlights lung cancer's global burden, poor prognosis, and severe symptoms impacting patient well-being. It discusses histological types, compounded challenges with IPF, and the need for a multifaceted treatment approach. Emphasis is placed on ongoing research for early detection, refined treatments, and novel therapies to improve outcomes.

Keywords: Lung Cancer; Pulmonary Fibrosis; Radiotherapy Pain.

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I. INTRODUCTION

Globally, lung cancer is the most prevalent cause of cancer-related fatalities. The 5-year survival rate post-diagnosis is only approximately 16%, and nearly 82% of patients succumb within the first year after diagnosis, despite the availability of the most effective treatments.¹ As the disease progresses, patients experience severe symptoms due to both the cancer and its treatments. Key symptoms in advanced lung cancer, such as fatigue, pain, dyspnea, and coughing, significantly impair physical and psychological functioning, leading to a reduced quality of life.² An increasing number of lung cancer patients necessitate emergency care as they approach the end of their lives. The debilitating nature of pain can result in melancholy and anxiety, which is why it is particularly feared and distressing. The identification of a diverse array of mutations in a variety of lung malignancies, such as epidermal growth factor receptor (EGFR) mutations and ALK rearrangements, which serve as therapeutic targets, stresses the significance of managing these small specimens for molecular testing.³ As determined by histological analysis, the four primary varieties of lung cancer are squamous cell carcinoma, adenocarcinoma, malignant squamous cell, and large cell carcinoma.⁴ Subtypes of these primary types, including the basaloid variant of squamous cell carcinoma and the lepidic predominant subtype of adenocarcinoma, can be further distinguished. In the case of cystic fibrosis (CF), the predominant factor contributing to morbidity and mortality is lung disease.⁵ Lung disease is the primary cause of health complications and mortality in CF, a life-threatening autosomal recessive disorder that affects multiple organs and tissues. A dysfunctional protein is produced as a consequence of mutations in the CF Transmembrane Conductance Regulator (CFTR) gene, initiating a series of pathophysiological events that cause damage and remodelling of the airway epithelium.⁶ While some aspects of the wound repair pathophysiology in CF have been uncovered, more research is needed to completely understand the cellular and molecular processes involved and to enhance therapeutic strategies. PF is a concerning consequence of various lung diseases, leading to decreased lung compliance and capacity along with thicker alveolar walls.⁷ These alterations contribute to diminished lung function and difficult breathing for those affected. The underlying mechanisms of PF are intricate and not fully understood, owing to its diverse causes. The clinical characteristics of lung carcinoma in individuals with IPF are distinct from those without IPF.⁸ Regardless of the treatment method employed, individuals who have lung cancer and IPF typically have a worse prognosis than those who have lung cancer alone.⁹ Prior research has significant limitations, including the absence of a control group, the small patient sample sizes, and the emphasis on specific subgroups, such as patients undergoing surgery or with specific histopathological types.¹⁰ The prognosis for IPF is notably dismal, as it is a chronic, non-cancerous lung disease. The presence of common comorbidities, such as lung cancer, further worsens patient survival rates. Despite this, there is a significant gap in understanding regarding the diagnosis and treatment of patients who have both conditions. This review article discusses the primary challenges in managing patients with IPF and lung cancer and outlines potential future directions.

2. COMMON SITES OF PAIN IN LUNG CANCER PATIENTS

Pain in patients typically arises from multiple factors, and it is

common for individuals to feel pain in various anatomical locations. Besides the underlying disease, treatments can also lead to significant pain conditions. The lumbar spine and thorax are the most frequently reported areas of pain, with 40% of patients experiencing pain in three or more distinct anatomical regions.¹¹ In lung cancer, the primary subtypes are nociceptive or somatic pain.¹² As a consequence, lung cancer patients are confronted with complex and diverse pain scenarios that are influenced by the severity of their disease and the treatments they receive. A number of syndromes have been identified as being associated with direct tumour involvement. Common causes of pain include pleural or visceral involvement, compression of neural structures, and bone metastases.¹³ The frequent and challenging complication of skeletal involvement is a common experience for many lung cancer patients. Pain typically manifests gradually over the course of weeks or months, escalating progressively. It is frequently increases at night or during weight-bearing activities and is typically restricted to a specific region.¹⁴ Pain that is persistent, sluggish, and continues to intensify is the most common description. In the affected area, pain may intensify when pressure is applied and may fluctuate in intensity in response to activities such as standing, walking, or seating. Visceral cancer pain is the result of lesions in parenchymal organs or lymph nodes, while somatic pain may be the result of parietal pleural involvement.¹⁵ The variability in responses to ischemia may be attributed to pre-existing conditions or mechanical distortions of parenchymal tissue caused by cancer. The localization of visceral discomfort is challenging, and it frequently refers to other regions of the thorax.

3. ETIOLOGIES OF PULMONARY FIBROSIS

PF remains a topic of continuous research due to its complex nature. This condition can arise from various causes, each involving distinct primary mechanisms that lead to the common outcome of fibrosis. For instance, individuals with acute respiratory distress syndrome (ARDS) may experience an overproduction of fibrotic factors, resulting in PF.¹⁶ Prolonged exposure to environmental irritants like asbestos or silica, or receiving thoracic radiation, can also lead to fibrosis. The lung's reaction to these irritants or conditions can either resolve and return to normal function or progress to fibrosis, causing a lasting decrease in lung capacity. Oxidative stress plays a significant role in the development of fibrosis as well. Inflammatory responses, including those involving neutrophil granules, and environmental exposures can lead to the excessive generation of reactive oxygen species (ROS).¹⁷ The lungs are particularly susceptible to oxidative stress because of their elevated oxygen levels in comparison to other body tissues. It is hypothesized that elevated ROS levels will induce epithelial cell death, increase the secretion of pro-fibrotic cytokines, and promote the differentiation of fibroblasts into myofibroblasts.¹⁸ It is important to note that severe COVID-19 patients frequently require ventilator support to facilitate respiration, which can increase their oxidative stress levels. Non-small cell lung cancer (NSCLC) and SCLC are the two primary histological forms of lung cancer. A comprehensive approach that includes surgery, radiotherapy, and/or chemotherapy is typically necessary for the treatment of NSCLC patients.¹⁹ The selection of treatment modalities is contingent upon the patient's overall health condition, cancer stage, and resectability. Peripheral neuropathy, which frequently manifests as painful sensations and a loss of sensibility in the hands and feet, is a potential consequence of chemotherapy, particularly when

administered with medications such as paclitaxel, cisplatin, and vinca alkaloids.²⁰ Tingling, sensory loss, and coordination difficulties are also frequent symptoms of sensory neuropathies associated with small-cell lung cancer. The fact that these neuropathies can manifest prior to the diagnosis of cancer and typically proceed irrespective of the tumor's progression is intriguing. In an early reported studies, both the IPF and no-IPF groups, the patients who underwent surgery, chemotherapy, and radiation therapy were comparable. Within the subsection of patients who received surgical treatment, a substantial proportion of patients underwent sub lobar resection. In patients with resectable NSCLC, the IPF group demonstrated a higher frequency of stereotactic radiosurgery and sub lobar resection in comparison to the no-IPF group. The IPF and no-IPF groups, however, demonstrated treatment similarities among patients with unresectable NSCLC.^{21,22} Similarly, the remedies administered to SCLC patients by the IPF and no-IPF groups did not demonstrate any discernible differences. The etiology

of lung fibrosis is complex and multifactorial, primarily driven by chronic inflammatory stimuli and repeated episodes of acute inflammation. Inflammatory stimuli, such as infections, autoimmune reactions, or exposure to harmful substances like silica and asbestos, initiate an inflammatory response in the lung tissue. When these stimuli persist, they lead to recurrent acute inflammation, which fails to resolve properly and transitions into chronic inflammation. This chronic inflammatory state activates fibroblasts, the cells responsible for producing extracellular matrix (ECM) components. Activated fibroblasts, also known as myofibroblasts, proliferate and synthesize excessive amounts of ECM proteins, including collagen, in an attempt to repair damaged tissue. However, in lung fibrosis, this process becomes dysregulated. The myofibroblasts resist apoptosis, leading to their accumulation and continuous ECM production. This results in the thickening and scarring of lung tissue, which impairs normal lung function and ultimately contributes to the progression of fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF).

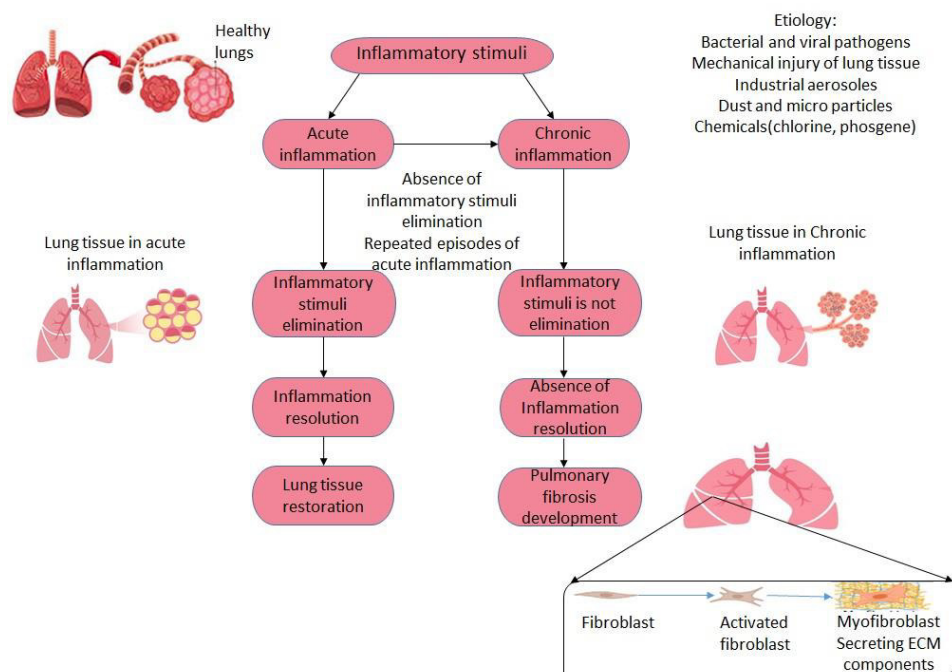


Fig 1: Etiologies of lung fibrosis (MDPI source²³)

4. RADIOTHERAPY PAIN

Radiotherapy has the potential to cause microinfarction of nerves by inducing direct toxicity to axons and vasa nervorum, resulting in nerve injury in the plexus.²⁴ Approximately 1% of cancer patients are affected by neoplastic plexopathy, with lung cancer being the most common cause of brachial plexopathy.²⁵ Radiation-induced brachial plexopathy can present as temporary or deteriorating symptoms that appear after a delay, typically occurring 3-4 months after radiation therapy. Common symptoms include hand muscle weakness and tingling sensations. Axillary tenderness is present in approximately 60% of instances. The syndrome typically improves within 4-7 months, although it can progress to paralysis. This is most likely the result of direct toxicity to Schwann cells, which results in demyelination. Rather than pain, the primary symptoms are sensory alterations and weakness, which are frequently accompanied by lymphedema and cutaneous lesions.²⁶ The condition's severity is inconsistent, ranging from mild discomfort to nearly complete arm paralysis. Sensory alterations may not be necessary for

the development of severe neuropathic pain. It is imperative to clinically distinguish between radiation plexopathy and neoplastic plexopathy, as the plexus area has been the site of radiotherapy for a significant number of cancer patients. Even so, it is possible for both conditions to coexist on occasion.²⁷ Radiation-induced plexopathy is diagnosed by the presence of patterns that exhibit aggregated or repetitive motor unit action potential discharges, which are comparable to myokymia. Tumor plexopathy frequently affects the lower plexus, resulting in sensory disturbances and pain in the elbow, medial forearm, and outer digits. In contrast, upper plexus infiltration by tumors is less common, leading to symptoms such as hand, shoulder, and lateral arm pain.²⁸ The protective effect of bony and soft tissues on the lower plexus is believed to be the cause of this discrepancy.

5. MANAGEMENT OF FIBROSIS IN LUNG CANCER

The management of fibrosis in lung cancer presents a complex challenge requiring a comprehensive and integrated approach

to effectively address its impact on patients' respiratory function and overall well-being. Fibrosis can manifest in lung cancer patients as a result of the disease itself, treatments such as radiation therapy or certain chemotherapeutic agents, or as a secondary complication of pre-existing lung conditions.²⁹ The objectives of the management strategies are to not only alleviate symptoms but also to delay the progression of the disease and enhance the quality of life. Diagnosis of fibrosis in lung cancer patients begins with a thorough evaluation of clinical symptoms, which typically include progressive dyspnea (shortness of breath), chronic cough, and decreased exercise tolerance.³⁰ The extent and severity of fibrotic alterations in the lungs can be visualized through imaging studies, including chest X-rays and high-resolution computed tomography (HRCT) examinations.³¹ Pulmonary function tests (PFTs) provide valuable information about lung function and capacity. In some cases, a lung biopsy may be necessary to confirm the presence of fibrosis and to rule out other potential causes. The cornerstone of managing fibrosis in lung cancer involves supportive care measures aimed at improving respiratory function and overall quality of life. Supplemental oxygen therapy is often prescribed to alleviate symptoms of hypoxemia and improve oxygenation.³² Pulmonary rehabilitation programs play a crucial role, offering structured exercise regimens, education on breathing techniques, and behavioural interventions aimed at enhancing functional capacity and reducing respiratory symptoms. Nutritional support is also essential to maintain strength, support immune function, and optimize overall health. Pharmacological interventions are another key component of treatment for fibrosis in lung cancer. Doxycycline has demonstrated anti-inflammatory effects by decreasing the production of pro-inflammatory cytokines, which are implicated in the pathogenesis of pulmonary fibrosis. Its ability to inhibit pathways involved in fibrosis, such as the transforming growth factor-beta (TGF- β) signaling pathway, further underscores its potential utility.³³ Although these findings are promising, the clinical efficacy of doxycycline in lung fibrosis requires more extensive investigation through well-designed clinical trials to fully establish its role and optimize its use in therapeutic protocols for patients suffering from conditions like idiopathic pulmonary fibrosis (IPF). Anti-fibrotic agents such as pirfenidone and nintedanib have demonstrated efficacy in managing fibrosis associated with IPF and are increasingly being explored in the context of fibrosis related to lung cancer.³⁴ Corticosteroids may be used to reduce inflammation and manage symptoms, although their long-term use is limited by potential side effects. Emerging therapeutic strategies offer promising avenues for managing fibrosis in lung cancer. Molecular targeted therapies, including inhibitors of pathways such as TGF- β , are being investigated for their potential to halt or slow fibrosis progression. Gene therapy approaches, such as CRISPR-Cas9 technology, hold promise for correcting genetic abnormalities that contribute to fibrosis development.³⁵ Stem cell therapy, particularly the use of mesenchymal stem cells (MSCs) for their anti-inflammatory

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and tissue repair capacity, is also under investigation as a potential treatment option. A multidisciplinary approach is crucial in the management of fibrosis in lung cancer, involving collaboration among pulmonologists, oncologists, radiologists, nurses, respiratory therapists, and other healthcare professionals. A comprehensive evaluation, personalized treatment planning, and ongoing monitoring of disease progression and treatment response are guaranteed by this team-based approach. Despite advancements, managing fibrosis in lung cancer remains challenging due to its heterogeneous nature and variable progression. Ongoing research efforts are focused on identifying biomarkers for early detection, refining treatment strategies, and developing novel therapies aimed at improving outcomes and quality of life for patients affected by fibrosis in the context of lung cancer. Clinical trials investigating new treatments and combination therapies offer hope for continued progress in addressing this complex aspect of lung cancer management.

6. CONCLUSION

Managing fibrosis in lung cancer is a multifaceted endeavor requiring an integrated approach to mitigate its impact on respiratory function and overall patient well-being. From early diagnosis through advanced treatment strategies, the focus is on alleviating symptoms, slowing disease progression, and improving quality of life. Diagnostic tools such as imaging studies and pulmonary function tests play a pivotal role in assessing fibrotic changes and guiding therapeutic decisions. Supportive care measures like supplemental oxygen, pulmonary rehabilitation, and nutritional support are essential components of management. Pharmacological interventions including anti-fibrotic agents and corticosteroids aim to manage inflammation and symptoms effectively. Future treatment options are promisingly represented by emerging therapies, including molecular targeted therapies, gene therapy, and stem cell therapy. A multidisciplinary approach that includes pulmonologists, oncologists, radiologists, and other specialists guarantees a comprehensive evaluation and personalized treatment plans that are unique to each patient's requirements. Despite challenges posed by the complex nature of fibrosis in lung cancer, ongoing research efforts continue to advance our understanding and treatment options. Identification of biomarkers, refinement of therapeutic strategies, and exploration of novel therapies through clinical trials remain pivotal in enhancing outcomes and quality of life for patients affected by fibrosis in the context of lung cancer.

7. AUTHORS CONTRIBUTION STATEMENT

Dr. Anand Mohan Jha, Dr. Anil Kumar wrote the initial draft. Dr. John Abraham and Dr Huma Firdaus contributed to critical revision and supervision. All authors reviewed the manuscript.

8. CONFLICT OF INTEREST

Conflict of interest declared none.

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