Egypt. J. Chem. **Vol. 68,** SI: Z. M. Nofal, pp. 619 - 630 (2025)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Squamous Cell Lung Cancer: Review of Biochemical Aspects, Cellular Signals, and Pharmacological Treatments

Sultan Suleiman Issa Al-Harb*, Sultan Mohammed Algfari, NAWAF SAKR ALMUTAIRI, Khaled Mohammed Alanazi , Fahad Saad Fahad Alanazi, NAIF FAISAL BEJAD ALBAQAMI, Owaidh Faisal Bejad Albaqami, ALOTAIBI MESHAL SAEED, Badr Talhab Al-Anzi, Fahd Sulaiman Al-Saif, ABDULLAH AYEDH DH ALHAFI, Khalid saeed oudah alahmari, Talal Ahmad Deifallah Al-Ghamdi, Abdullah Khatim R. Alanazi, Maryam Helal Rasheed Alanazi

National Guard Health Affairs, Jeddah, Saudi Arabia

Abstract

Background: Squamous cell carcinoma (SCC) of the lung is the second most common non-small cell lung cancer (NSCLC), strongly associated with smoking and central airway location. Despite declining incidence due to reduced smoking rates, it remains a major cause of cancer mortality, with unique histopathological and molecular features distinguishing it from other NSCLC subtypes.

Aim: This review examines the biochemical pathways, cellular signaling, diagnostic approaches, and evolving treatment paradigms for SCC, emphasizing recent advances in immunotherapy and targeted therapy.

Methods: A comprehensive analysis of peer-reviewed literature was conducted, focusing on SCC epidemiology, pathogenesis (particularly tobacco-induced carcinogenesis), diagnostic imaging/pathology criteria, and evidence-based treatment strategies across disease stages.

Results: SCC accounts for ~30% of NSCLCs, characterized by keratin pearls/intercellular bridges on histology. Diagnosis relies on CT/PET imaging and immunohistochemistry (p40/p63 positivity). Treatment is stage-dependent: surgery for early-stage (IA-IIB), chemoradiation for locally advanced (IIIA-IIIB), and platinum-based chemotherapy ± immunotherapy (pembrolizumab/cemiplimab) for metastatic disease. PD-L1 expression ≥50% predicts immunotherapy response. Unlike adenocarcinoma, targetable mutations (EGFR/ALK) are rare (<5%), though emerging agents show promise for FGFR1/PIK3CA alterations.

Conclusion: SCC management requires multidisciplinary integration of surgery, radiation, systemic therapy, and molecular profiling. Immunotherapy has improved survival in advanced disease, but limited targeted options underscore the need for biomarker discovery. Smoking cessation remains paramount for prevention.

Keywords: Squamous cell lung cancer, NSCLC, smoking-related cancer, PD-L1 immunotherapy, central lung tumors..

1. Introduction

Squamous cell carcinoma of the lung, commonly referred to as squamous cell lung cancer, represents one of the major forms of non-small cell lung cancer (NSCLC). Within the NSCLC group, adenocarcinoma is the most frequently diagnosed subtype, followed by squamous cell carcinoma, which is particularly noted among women. This trend has been linked to shifting smoking behaviors, although direct and conclusive evidence confirming this association remains lacking. Anatomically, squamous cell tumors are typically located in the central regions of the lung, often arising within the main airways such as the left or right bronchus. Cigarette smoking remains the primary etiological factor responsible for cellular transformation leading to this malignancy. Data suggest that nearly 80% of lung cancer cases in men and up to 90% of cases in women are directly linked to tobacco use. Compared with other NSCLC subtypes, squamous cell carcinoma demonstrates the strongest correlation with smoking. Additional contributing risk factors include advanced age, a positive family history of lung cancer, chronic exposure to second-hand smoke, and occupational contact with carcinogenic agents such as asbestos, metallic dust, and mineral particles [1][2][3]. The clinical manifestations of NSCLC, including squamous cell carcinoma, are diverse but commonly present as persistent cough, localized chest pain, progressive dyspnea, and hemoptysis. Patients may also experience audible wheezing, voice hoarseness, or recurrent chest infections such as pneumonia and bronchitis, which often prompt further evaluation. Systemic symptoms such as unintentional weight loss, diminished appetite, and generalized fatigue are also frequent. Upon clinical suspicion, diagnostic assessment is initiated, most often beginning with computed tomography (CT) imaging, which serves as a crucial tool in identifying and characterizing lesions provided the tumor is of sufficient size for radiological detection. Once an abnormality is noted, additional diagnostic procedures are employed. These include advanced imaging modalities for better delineation of tumor extent, histopathological examination for cellular characterization, and immunohistochemistry to confirm squamous histology and differentiate it from other lung malignancies. Tissue sampling is essential not only for establishing the diagnosis but also for staging the cancer, thereby determining the appropriate course of treatment [1][2][3].

*Corresponding author e-mail: *Al-Harbssi@gmail.com.*; (**Sultan Suleiman Issa Al-Harb**).
Receive Date: 04 July 2025, Revise Date: 27 August 2025, Accept Date: 05 September 2025
DOI: 10.21608/EJCHEM.2025.400356.11995

Management strategies for squamous cell carcinoma of the lung are highly dependent on the stage at which the disease is diagnosed. In early stages, surgical resection remains the preferred therapeutic approach, aiming to achieve complete removal of the tumor and involved tissues. For patients with locally advanced or metastatic disease, a multimodal strategy is generally required. This may involve a combination of chemotherapy and radiotherapy, with systemic therapy serving both curative and palliative objectives depending on disease burden. In recent years, immunotherapy has emerged as an important addition to treatment options, particularly for advanced-stage disease, with agents targeting immune checkpoints demonstrating significant survival benefits. Tailoring therapy to individual patients is crucial, as treatment tolerance, performance status, and comorbidities play substantial roles in clinical decision-making. Through the integration of diagnostic imaging, pathology, and modern therapeutic approaches, the management of squamous cell carcinoma of the lung continues to evolve. Early recognition of risk factors and presenting symptoms remains essential for timely diagnosis and intervention, which significantly impacts prognosis and survival outcomes [1][2].

Etiology

Lung cancer development is strongly linked to cigarette smoking, with epidemiological data indicating that nearly 80% of male cases and up to 90% of female cases are attributable to tobacco use [1][2]. Among the various subtypes of non-small cell lung cancer, squamous cell carcinoma shows the strongest correlation with smoking, highlighting its direct dependence on chronic exposure to carcinogenic compounds within tobacco smoke. The mechanisms through which smoking contributes to malignant transformation include the induction of DNA damage, promotion of mutagenesis, and impairment of normal cellular repair processes, all of which facilitate uncontrolled cell proliferation and tumor progression. Beyond smoking, additional risk determinants have been identified. Increasing age is a significant factor, as cumulative exposure to carcinogens and the decline in cellular repair capacity with aging enhance susceptibility. A positive family history of lung cancer also contributes to risk, suggesting a role for genetic predisposition in disease onset. Moreover, individuals who are regularly exposed to second-hand smoke remain at elevated risk, even in the absence of direct smoking, due to prolonged inhalation of carcinogenic particles. Occupational hazards further add to the etiological profile, with consistent evidence linking long-term exposure to asbestos fibers, metallic dust, and mineral particles to higher rates of squamous cell carcinoma. These exposures act synergistically with smoking, amplifying the likelihood of disease development and progression [1][2].

Epidemiology

Lung cancer continues to represent one of the most significant health challenges worldwide due to its high incidence and mortality rates. According to the National Cancer Institute's Surveillance Epidemiology and End Results (NCI SEER) database, lung cancer ranked as the third most frequently diagnosed malignancy in the United States in 2023, while also maintaining its position as the leading cause of cancer-related deaths. The estimated number of new lung cancer cases reported during that year reached 238,340, corresponding to approximately 12% of the overall cancer burden in the country. These figures emphasize the sustained impact of lung cancer as a public health issue, underscoring the need for improved strategies in prevention, early detection, and therapeutic intervention [3]. Mortality data further highlight the severity of this malignancy. In 2023, lung cancer was responsible for an estimated 127,070 deaths in the United States, which accounted for nearly 21% of all cancer-related deaths. This disproportionate mortality burden compared with incidence rates reflects the aggressive nature of the disease, its frequent late-stage diagnosis, and the challenges associated with effective long-term management. Despite advances in screening techniques and targeted therapies, survival outcomes for lung cancer patients remain poor relative to other common cancers, reinforcing the urgency of refining diagnostic and therapeutic approaches [3].

In terms of histological distribution, approximately 85% of all lung cancers fall within the category of non-small cell lung cancers (NSCLCs), highlighting their predominance over small cell lung cancers. Among NSCLCs, adenocarcinoma emerges as the most common histological subtype, representing roughly 50% of cases. Squamous cell carcinoma follows as the second most prevalent subtype, constituting around 30% of NSCLC diagnoses [3]. This distribution pattern has important clinical implications, as differences in histology influence not only risk factors but also treatment responses and prognostic outcomes. For instance, adenocarcinoma tends to occur more frequently in non-smokers and women, while squamous cell carcinoma remains more strongly linked to smoking exposure. The epidemiological profile of lung cancer therefore illustrates both the scale of the disease burden and the critical necessity for ongoing research into preventive strategies, effective screening programs, and tailored treatment regimens. Understanding subtype-specific distributions and their associations with risk factors can contribute to improved clinical management and ultimately help reduce the global impact of this disease [3].

Pathophysiology

Squamous cell carcinoma (SCC) of the lung develops as a result of malignant transformation of the squamous epithelial cells that line the respiratory airways. These cells are normally thin and flat, serving as a protective lining in multiple organs, including the pulmonary system. In the context of lung cancer, the transformation most frequently occurs in the central regions of the lung, particularly within the primary airways such as the right or left bronchus. This central localization has clinical significance, as it often contributes to the early presentation of symptoms such as cough, hemoptysis, and airway obstruction [4]. The dominant etiological factor driving this transformation is chronic exposure to tobacco smoke. Tobacco contains more than 300 harmful chemical agents, with at least 40 of these identified as carcinogens capable of inducing mutations and cellular damage. Polycyclic aromatic hydrocarbons, nitrosamines, and heavy metals present in cigarette smoke directly interact with DNA, generating mutations that promote uncontrolled cellular proliferation. Repeated exposure over time leads to an accumulation of genetic alterations that progressively shift squamous cells from a state of normal differentiation to dysplasia, carcinoma in situ, and eventually invasive carcinoma. This stepwise process illustrates the multistage nature of lung carcinogenesis and explains why long-term smokers carry the highest risk of developing SCC [4].

At the histological level, transformed squamous cells demonstrate distinct morphological features that differentiate them from other lung cancer subtypes. Keratinization is a hallmark, marked by the production of keratin pearls within tumor

tissue, reflecting aberrant squamous differentiation. Another defining feature is the presence of intercellular bridges, which represent desmosomal connections between malignant squamous cells and provide a diagnostic clue during microscopic examination. In addition to these structural changes, SCC exhibits a high frequency of genetic mutations, particularly involving tumor suppressor genes and cell-cycle regulators, which further enhance its malignant potential [4]. The biological behavior of SCC is therefore rooted in a combination of environmental carcinogenic exposure and intrinsic cellular changes. The persistence of carcinogen-induced mutations, along with morphological transformation of airway squamous cells, drives the initiation and progression of disease. A deeper understanding of these processes not only provides insights into disease mechanisms but also informs the development of diagnostic markers and therapeutic targets specific to squamous cell carcinoma of the lung [4].

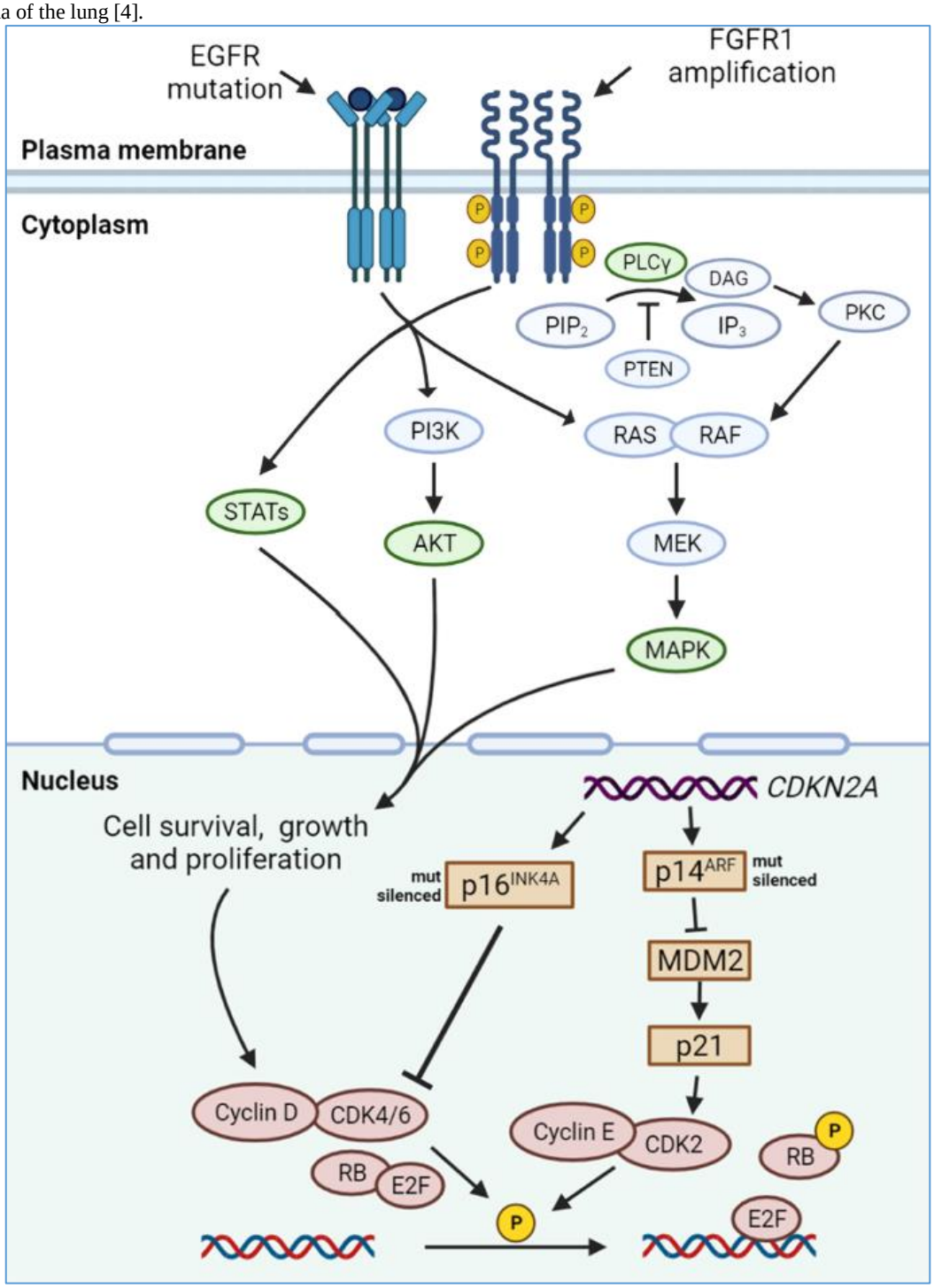

Figure 1: Signaling Pathway of lung squamous cell carcinoma.

Histopathology

Accurate histological diagnosis of squamous cell carcinoma (SCC) of the lung has become increasingly significant in clinical practice, as histological subtyping may guide therapeutic choices and predict both treatment response and potential toxicity [5]. The confirmation of SCC relies on microscopic evaluation of resected tumor tissue. A definitive diagnosis is made when at least 10% of the tumor mass demonstrates classical features of squamous differentiation, such as keratinization or the presence of intracellular bridges. These structural changes are considered diagnostic hallmarks and allow pathologists to differentiate SCC from other subtypes of non-small cell lung cancer (NSCLC). In cases where squamous characteristics are present but in minimal amounts, and where tumor cells lack extensive differentiation, the lesion is classified as poorly differentiated SCC, reflecting a more aggressive biological behavior [5]. To improve diagnostic accuracy, immunohistochemistry (IHC) and ancillary staining techniques are widely applied. An IHC panel combined with mucin staining helps distinguish SCC from adenocarcinoma and other NSCLC variants. Squamous cell carcinoma consistently expresses squamous-specific biomarkers, with p63 and p40 proteins serving as highly sensitive and specific markers of squamous differentiation. The presence of these biomarkers provides essential diagnostic confirmation in cases where histological features alone may be insufficient for a conclusive classification [6].

In recognition of the heterogeneity within SCC, the World Health Organization (WHO) updated its classification in 2015, identifying three major histological variants of the disease [6]. The first is the keratinizing subtype, which is characterized by prominent keratin pearl formation and dense eosinophilic cytoplasm. The second is the nonkeratinizing variant, in which tumors lack overt keratinization but still demonstrate other defining squamous features. The third is the basaloid subtype, diagnosed when more than 50% of the tumor tissue displays basaloid morphology with only minimal squamous differentiation. Each of these variants presents distinct microscopic appearances, which can influence both clinical interpretation and management strategies [6]. Histopathological classification, therefore, plays a pivotal role not only in the accurate diagnosis of SCC but also in determining the most effective treatment pathways. By integrating morphological criteria with immunohistochemical profiling, pathologists provide clinicians with essential information that directly impacts therapeutic decisions and patient outcomes [6].

History and Physical

The clinical presentation of non-small cell lung cancers (NSCLCs), including squamous cell carcinoma, encompasses a wide spectrum of respiratory and systemic symptoms. Patients commonly report persistent cough, localized or diffuse chest pain, progressive shortness of breath, and hemoptysis. Wheezing and hoarseness are also characteristic, often resulting from airway obstruction or recurrent laryngeal nerve involvement. Repeated chest infections such as bronchitis or pneumonia may occur due to impaired airway clearance in regions obstructed by the tumor. Systemic manifestations, including unintentional weight loss, reduced appetite, and generalized fatigue, frequently accompany disease progression and often signal advanced stages. Despite these clinical features, it is important to recognize that many patients remain asymptomatic during the early stages of NSCLC, which contributes to delayed detection and diagnosis. A thorough social history often reveals risk factors that provide additional diagnostic clues. A significant smoking history remains the most common association, with long-term tobacco use serving as the primary contributor to disease onset. Occupational exposures are also relevant, particularly in individuals with prolonged contact with asbestos, radon gas, or heavy metals, all of which have established roles as carcinogenic agents. These environmental and occupational factors not only increase the risk of developing NSCLC but may also interact synergistically with tobacco exposure, amplifying disease susceptibility [5][6][7].

In advanced disease stages, metastasis becomes a key clinical concern. The spread of tumor cells beyond the lungs leads to secondary symptoms that vary depending on the site of metastatic involvement. Bone metastases often manifest localized pain, sometimes severe and persistent, which may require further imaging to confirm. Central nervous system involvement produces neurologic complications, including headaches, dizziness, seizures, and focal neurological deficits such as weakness or numbness of the limbs. Spinal cord compression, another potential consequence of metastatic spread, can present with back pain, progressive motor weakness, or sensory loss, requiring urgent evaluation and intervention. Taken together, the history and physical examination of patients with NSCLC provide critical insights into both local and systemic manifestations of the disease. While early detection remains difficult due to the absence of symptoms in many patients, careful assessment of presenting complaints, combined with a detailed exploration of risk factors and occupational exposures, allows clinicians to identify individuals at risk and initiate timely diagnostic investigations [5][6][7].

Evaluation

Diagnostic Imaging Studies

The evaluation of squamous cell carcinoma (SCC) of the lung relies heavily on imaging, which serves as a critical step in confirming the presence of a suspicious lesion, assessing its local impact, and guiding staging. Computed tomography (CT) remains the most frequently employed initial imaging modality following the clinical examination. Its value lies in its ability to detect central pulmonary lesions and associated changes in surrounding structures, provided that the tumor is large enough to be visualized. A classic radiological hallmark of SCC is the presence of a cavity within the tumor mass, which may contain either air or fluid and reflects the necrotic nature of this histological subtype [1]. Other features identified on CT may include discrete pulmonary nodules, larger masses or infiltrates, widening of the mediastinum, collapse of lung segments due to airway obstruction (atelectasis), hilar enlargement, and the presence of pleural effusion. Each of these findings helps guide further investigation and suggests disease extent [1]. In cases where incidental small nodules are discovered during chest CT, clinicians frequently turn to the Fleischner Society guidelines, which provide structured recommendations for follow-up imaging and management. When lung cancer is strongly suspected, the diagnostic strategy may prioritize staging rather than immediate biopsy. This approach enables the detection of metastatic sites that may be more easily accessible for tissue sampling, thereby facilitating both confirmation of malignancy and establishment of an advanced disease stage. This strategy is

particularly relevant when metastatic involvement alters the therapeutic approach, sparing patients unnecessary invasive procedures directed at the primary tumor [6][7].

Table 1: Diagnostic Workup for Squamous Cell Lung Cancer

Modality	Key Features	Clinical Utility
CT Chest	Central mass, cavitation, post-obstructive atelectasis	Initial tumor detection/local staging
PET/CT	FDG-avid primary/nodal metastases (SUVmax >2.5)	Metastatic evaluation (sensitivity ~85%)
Biopsy (EBUS/TBB)	p40/p63+ IHC; keratin pearls/intercellular bridges	Histologic confirmation
PD-L1 IHC	Tumor Proportion Score (TPS) ≥1% (22C3 antibody)	Predicts immunotherapy response

Positron emission tomography (PET) integrated with CT has become an indispensable tool in staging, providing both metabolic and anatomical information. PET/CT is especially valuable in identifying metastatic spread beyond the primary tumor site. Nevertheless, certain limitations persist. False positive findings can arise in the context of inflammatory or granulomatous conditions such as sarcoidosis, infections, or rheumatoid nodules, where increased metabolic activity mimics malignancy. Conversely, false negative results may occur in tumors with inherently low metabolic activity, such as carcinoid tumors, ground-glass opacities, or lesions smaller than 1 cm. The false negative rate for sub-centimeter lesions approaches 15%, reducing the sensitivity of PET in early disease. Accordingly, PET/CT is not routinely recommended for staging pure ground-glass opacities or very small peripheral tumors, particularly cT1a lesions [7]. Magnetic resonance imaging (MRI) of the brain plays a crucial role in evaluating patients for central nervous system metastasis. This modality is particularly recommended in patients with clinical stage II disease or higher, although it may also be considered in patients with stage IB disease, depending on clinical context. Detecting brain metastases at the time of staging is essential, as this significantly influences treatment planning and prognosis. Despite the sophistication of modern imaging, mediastinal staging frequently requires invasive confirmation. PET/CT alone has false positive and false negative rates of 15% to 20% for mediastinal lymph node involvement [7]. Therefore, invasive nodal evaluation remains indicated in a wide range of clinical scenarios. Such evaluation is generally recommended when CT imaging shows discrete enlargement of mediastinal nodes irrespective of PET activity, or when nodes appear normal on CT yet exhibit PET avidity. Conversely, invasive staging may be omitted in specific groups of patients, including those with established distant metastasis, small peripheral cT1a lesions, or obvious bulky mediastinal adenopathy where further confirmation may not alter the clinical decision-making [7].

Additional Diagnostic Studies

Beyond imaging, mediastinal sampling techniques provide definitive histopathological evidence of nodal involvement, which is indispensable for accurate staging. These procedures are classified as surgical, endobronchial, or esophageal, each varying in accessibility to specific nodal stations and diagnostic accuracy. Surgical techniques include conventional mediastinoscopy, video-mediastinoscopy, anterior mediastinoscopy, and video-assisted thoracic surgery (VATS). Traditional mediastinoscopy allows access to nodal stations 1, 2R/L, 3, 4R/L, and 7. Video-assisted mediastinoscopy expands access to additional stations, including 5, 8, and 10R. The diagnostic reliability of surgical sampling is high, with reported false negative rates of approximately 2%, although outcomes are influenced by operator expertise and institutional experience [7]. Endobronchial ultrasound-guided needle aspiration (EBUS-NA) represents a minimally invasive alternative that has gained prominence in clinical practice. Using real-time ultrasound guidance, this technique enables sampling of nodal levels 2R/L, 3, 4R/L, 7, 10, 11, and 12. Similarly, esophageal ultrasound-guided needle aspiration (EUS-NA) provides access to nodal stations 4L, 5, 7, 8, and 9. Together, these two techniques can provide complementary coverage of the mediastinum, reducing the need for more invasive surgical procedures. However, their diagnostic accuracy depends heavily on operator skill and institutional experience, with false negative rates reported as high as 20% in less experienced hands. Despite this limitation, EBUS and EUS are typically the first-line approaches in patients requiring mediastinal nodal evaluation due to their minimally invasive nature and relatively low complication rates [6][7].

In addition to nodal assessment, functional testing is also integral to the pre-treatment evaluation of SCC. Pulmonary function testing (PFT) is particularly important for patients who are potential surgical candidates. By assessing lung capacity, diffusion capacity, and overall respiratory reserve, PFT provides essential data on whether a patient can safely tolerate surgical resection, especially lobectomy or pneumonectomy. Patients with borderline pulmonary reserve may require alternative therapeutic strategies to reduce perioperative risk [7]. Molecular profiling has also entered routine practice in the diagnostic evaluation of lung cancers, although its role in squamous cell carcinoma is somewhat limited compared to adenocarcinoma. Assessment of programmed death-ligand 1 (PD-L1) expression has become essential, as it predicts response to immune checkpoint inhibitors, which are now integral to the management of advanced SCC. Testing for epidermal growth factor receptor (EGFR) mutations is also routinely performed across NSCLC cases because targeted EGFR therapies can significantly alter outcomes. However, EGFR mutations are uncommon in squamous cell carcinoma, with prevalence estimated at less than 5% [7]. Nevertheless, documenting molecular alterations remains clinically relevant, especially when treatment options such as immunotherapy or clinical trial enrollment are being considered.

Together, these diagnostic tools—ranging from advanced imaging to invasive nodal sampling, functional testing, and molecular profiling—form the cornerstone of SCC evaluation. The combination of anatomical, metabolic, histological, and genetic information allows clinicians to establish not only a definitive diagnosis but also a precise disease stage. This, in turn, facilitates the development of individualized treatment strategies tailored to disease extent, biological behavior, and patient fitness. The reliance on a multimodal evaluation strategy reflects the complexity of lung cancer management, where accurate staging and molecular characterization directly determine prognosis and guide the integration of surgery, radiotherapy, chemotherapy, and immunotherapy [7][8].

Treatment / Management

The management of squamous cell carcinoma (SCC) of the lung is highly dependent on the stage at diagnosis, with treatment strategies ranging from surgical resection in early-stage disease to systemic therapy in advanced cases. In patients with stage I or II SCC, surgical intervention remains the cornerstone of curative intent therapy. For stage IA tumors, surgery alone is typically sufficient, and adjuvant chemotherapy is generally not indicated due to the low likelihood of microscopic residual disease. In contrast, stage IB tumors, particularly those larger than 4 cm, may benefit from surgical resection followed by adjuvant chemotherapy to reduce the risk of recurrence. Stage II disease is managed with surgical excision followed by systemic chemotherapy, with lobectomy preferred for patients who are surgical candidates. Sub-lobar resections may be considered in patients with compromised pulmonary function or other comorbidities that increase surgical risk. When postsurgical margins are positive or patients are not suitable candidates for surgery, radiation therapy provides an alternative modality to achieve local control. Stage III disease presents more complex challenges, as many tumors are unresectable. For stage IIIA SCC, definitive staging is often achieved during resection, though concurrent chemoradiation is the standard approach for most patients. Recent evidence supports the use of perioperative systemic therapy, combining chemotherapy with immunotherapy to enhance response rates and improve long-term outcomes. Patients with stage IIIB disease typically receive combined chemoradiation followed by maintenance immunotherapy for up to one year. For stage IV SCC, systemic therapy serves as the primary modality, often supplemented with palliative radiation to alleviate symptomatic tumor burden. Multiple randomized trials and meta-analyses have demonstrated the efficacy of combining chemotherapy with immunotherapy or utilizing single-agent immunotherapy in advanced NSCLC [2]. The choice of systemic therapy is increasingly informed by molecular profiling, which guides the use of targeted agents in tumors harboring actionable mutations.

Targeted Therapy

Targeted therapy has emerged as a critical component of treatment for advanced NSCLC, particularly when somatic driver mutations are identified [8]. Epidermal growth factor receptor (EGFR) mutations are targeted with tyrosine kinase inhibitors (TKIs) such as erlotinib, gefitinib, and afatinib. In patients lacking EGFR mutations, treatment decisions are influenced by programmed death-ligand 1 (PD-L1) expression. Immunotherapy, either alone or combined with chemotherapy, is considered based on PD-L1 status, while cisplatin-based regimens with agents such as paclitaxel, gemcitabine, or pemetrexed remain options for neoadjuvant or adjuvant therapy, particularly in non-squamous histologies. For patients unable to tolerate cisplatin, carboplatin combined with paclitaxel provides an effective alternative. Preoperative therapy, including chemoimmunotherapy with agents such as nivolumab or pembrolizumab, is recommended for tumors larger than 4 cm or in patients with positive nodal involvement. However, patients who cannot receive immune checkpoint inhibitors due to autoimmune disorders, immunosuppressive therapy, or the presence of EGFR or ALK alterations are managed with combination chemotherapy alone.

Molecular and genetic profiling is increasingly central to treatment selection in advanced SCC, guiding the use of targeted therapies for specific mutations. Patients with PD-L1 expression of ≥50% are eligible for first-line treatment with single-agent immunotherapy, including pembrolizumab, cemiplimab, or atezolizumab. Combination regimens that pair chemotherapy with immunotherapy are also approved for this population. Patients with PD-L1 expression between 1% and 49% typically receive combination chemotherapy and immunotherapy as first-line therapy. EGFR exon 19 deletions or exon 21 L858R mutations are preferentially treated with osimertinib, while progression after first-line TKIs such as erlotinib, gefitinib, afatinib, or dacomitinib may warrant switching to osimertinib upon confirmation of the T790M resistance mutation via liquid biopsy or tumor tissue sampling [9][10]. Other EGFR mutations, including S768I, L861Q, or G719X, are managed with afatinib or osimertinib. KRAS G12C mutations require initial therapy guided by PD-L1 status, with targeted inhibitors such as sotorasib or adagrasib reserved for disease progression [11][12]. In cases of ALK rearrangement, first-line therapy with TKIs, including alectinib, brigatinib, or lorlatinib, is preferred before initiating systemic chemotherapy [13][14][15]. ROS1 fusion-positive tumors are managed with entrectinib, crizotinib, or repotrectinib as first-line therapy [16]. BRAF V600E mutations are treated with combined BRAF/MEK inhibitors, including dabrafenib with trametinib or encorafenib with binimetinib [17]. NTRK fusions are targeted with larotrectinib or entrectinib [18][16], while MET exon 14 skipping mutations are managed with capmatinib or tepotinib [19][20]. RET rearrangements are treated with selpercatinib or pralsetinib [21], and HER2 mutations are addressed with trastuzumab deruxtecan in second-line settings after progression on first-line chemoimmunotherapy [22].

The integration of molecularly targeted therapy, immunotherapy, and conventional chemotherapy has transformed the treatment landscape of SCC, particularly in advanced stages. Tailoring therapy based on tumor histology, genetic profile, and PD-L1 status optimizes therapeutic response and minimizes unnecessary toxicity. Surgical management remains fundamental for early-stage disease, but multimodal approaches combining chemotherapy, immunotherapy, and radiation are increasingly standard for locally advanced and metastatic disease. Ongoing research continues to refine treatment sequencing, identify new actionable mutations, and improve patient selection for specific targeted or immunotherapeutic agents. Neoadjuvant and adjuvant therapies have expanded the role of systemic treatment in early-stage SCC. Preoperative chemoimmunotherapy can shrink tumors, increase the likelihood of complete resection, and potentially improve long-term survival. Postoperative chemotherapy or radiation addresses residual disease and reduces recurrence risk in patients with positive margins or nodal

involvement. In patients unsuitable for surgery, definitive chemoradiation offers a curative-intent alternative, with subsequent maintenance immunotherapy for locally advanced disease providing improved outcomes.

In conclusion, the management of SCC of the lung requires a nuanced approach guided by disease stage, histological characteristics, and molecular profiling. Early-stage disease is optimally treated with surgical resection, with adjuvant therapy selectively applied based on tumor size and nodal status. Locally advanced disease requires multimodal therapy, integrating chemoradiation and immunotherapy, while systemic therapy forms the backbone of management in metastatic disease. Molecular testing for EGFR, ALK, ROS1, BRAF, NTRK, MET, RET, HER2, and PD-L1 is essential to guide targeted therapy and optimize outcomes. The evolving landscape of immunotherapy and targeted agents has markedly improved survival and quality of life for patients with SCC, underscoring the importance of individualized, precision-based treatment strategies. By integrating surgical, systemic, and targeted modalities, clinicians can provide comprehensive, stage-appropriate care that addresses both local and systemic disease while maximizing the potential for long-term disease control and improved patient outcomes.

Differential Diagnosis

Squamous cell carcinoma (SCC) of the lung requires careful differentiation from other primary lung malignancies to ensure accurate diagnosis and appropriate treatment. The main distinction is with small cell lung cancer (SCLC), which differs biologically, clinically, and in therapeutic approach. SCLC is typically more aggressive, centrally located, and associated with rapid growth and early metastasis, often necessitating systemic chemotherapy and radiotherapy rather than surgical resection. Among non-small cell lung cancers (NSCLCs), SCC must also be distinguished from adenocarcinoma and large cell carcinoma. Adenocarcinoma commonly arises in the peripheral lung fields, frequently occurs in non-smokers, and exhibits glandular differentiation, whereas large cell carcinoma is poorly differentiated, lacks specific histological features, and may present anywhere within the lung. Histopathological evaluation, immunohistochemistry, and molecular profiling are critical for distinguishing SCC from these entities, as accurate classification directly influences prognosis, staging, and treatment selection.

Surgical Oncology

Surgical resection remains the gold standard for the management of early-stage lung cancers in patients who are medically fit to undergo the procedure [23]. Traditionally, the upper limit for surgical intervention was considered stage IIIA (T3N1), beyond which surgery was often contraindicated due to poor outcomes. Anatomic pulmonary resection, most commonly in the form of a lobectomy, continues to be the preferred surgical approach for early-stage disease, offering optimal oncologic outcomes. Video-Assisted Thoracic Surgery (VATS) has emerged as the favored minimally invasive technique for performing anatomic lung resections. Compared with traditional open thoracotomy, VATS has been associated with reduced postoperative pain, shorter hospital stays, and faster recovery, while long-term oncologic outcomes, including overall survival and recurrence rates, appear equivalent to those achieved with open procedures [24][25]. Limited resections, such as segmentectomy or wedge resection, are occasionally performed for T1N0 NSCLC. While these approaches preserve pulmonary function and may be necessary in patients with limited pulmonary reserve, they are associated with higher local recurrence rates (approximately 18% versus 6% following lobectomy) and increased mortality. Such procedures may be considered in select scenarios, including small nodules less than or equal to 2 cm that are pure adenocarcinoma in situ (AIS), tumors with doubling times exceeding 400 days, or lesions demonstrating greater than 50% ground-glass opacity (GGO) on CT imaging [23][26]. Indications for VATS lobectomy generally include stage I to II disease, tumors less than 6 cm in diameter, lesions located at least 3 cm from the carina and more than 1 cm from the fissure line, and absence of mediastinal lymph node involvement.

Pneumonectomy, the complete removal of a lung, is reserved for centrally located tumors involving the mainstem bronchus or crossing major fissure lines. While it may be necessary to achieve oncologic control, pneumonectomy carries higher perioperative mortality and results in a substantial reduction in pulmonary reserve, making careful patient selection essential [27]. Regardless of the extent of resection, evaluation of representative N1 and ipsilateral N2 nodal stations is critical. At minimum, three N2 nodal stations should be sampled to ensure accurate pathologic staging, which directly influences the decision to administer adjuvant chemotherapy. More extensive T3 and T4 tumors may require en-bloc resection to achieve complete oncologic clearance. Preoperative assessment plays a pivotal role in identifying suitable surgical candidates. Comorbid conditions such as cardiac disease, prior lung resections, chronic obstructive pulmonary disease (COPD), bronchiectasis, chronic pulmonary infections including tuberculosis, interstitial lung disease, or pulmonary hypertension can significantly impact surgical risk. Assessing pulmonary reserve and predicting postoperative lung function are crucial to minimizing postoperative morbidity and mortality. A preoperative chest CT, which is routinely obtained during initial evaluation, provides essential information for surgical planning. The imaging allows precise counting of lung segments, determination of the extent of resection required, and estimation of postoperative lung volumes.

Quantitative pulmonary function testing (PFT) is a fundamental component of preoperative evaluation. Spirometry and diffusion capacity testing, particularly forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLCO), are strong predictors of postoperative complications. The American College of Chest Physicians (ACCP) endorses the use of these measures and provides an algorithm for further testing. Patients with FEV1 and DLCO values greater than or equal to 80% generally require no additional evaluation. When either measure falls below this threshold, predicted postoperative pulmonary function must be calculated, taking into account the number of lung segments to be resected and their relative contribution to overall function. Segment counting on CT is preferred for lobectomies, while lung scintigraphy is favored for pneumonectomies [28]. Predicted postoperative FEV1 or DLCO values above 60% typically indicate adequate pulmonary reserve, whereas values below 60% necessitate additional risk stratification using cardiopulmonary exercise testing or a simple walking test. Patients are classified as low, moderate, or high risk based on VO2max, with corresponding mortality rates of less than 1% for low-risk patients and exceeding 10% for high-risk patients.

Mortality following lobectomy ranges from 1.4% to 2.6% [29][30]. Common postoperative complications include persistent air leaks, occurring in 15% to 25% of patients, and atrial fibrillation, which can affect up to 40%. Postoperative pneumonia is reported in 2.5% to 6% of cases. Less frequent but serious complications include hemorrhage, chylothorax, phrenic nerve injury, recurrent laryngeal nerve injury, bronchopleural fistula, and right middle lobe torsion [29][30]. Pneumonectomy carries substantially higher risks. Mortality ranges from 5% to 11%, while morbidity can reach up to 60%. The most commonly reported complications include bronchopleural fistula, cardiac arrhythmias affecting approximately 19% of patients, pneumonia in 3.5%, and empyema in 4.8% [31][32]. The choice of surgical procedure, whether lobectomy, segmentectomy, wedge resection, or pneumonectomy, must balance oncologic efficacy with preservation of pulmonary function. Lobectomy remains the standard for most early-stage tumors, providing the best long-term survival and lowest recurrence rates. Limited resections are appropriate for select small lesions or patients with poor pulmonary reserve, while pneumonectomy is reserved for extensive central tumors where complete resection cannot be achieved otherwise. Accurate mediastinal nodal evaluation, both for pathologic staging and planning adjuvant therapy, is a critical adjunct to all surgical approaches.

The evolution of minimally invasive techniques such as VATS has significantly improved patient outcomes, reducing postoperative morbidity and shortening recovery periods without compromising oncologic efficacy. These advances, combined with rigorous preoperative assessment and careful patient selection, allow surgeons to tailor operative strategies to individual patient anatomy, comorbidities, and tumor characteristics. Quantitative preoperative assessment, including CT-based segment counting and functional testing, ensures that patients are neither undertreated nor exposed to undue perioperative risk. In summary, surgical oncology for SCC of the lung encompasses a spectrum of procedures designed to optimize oncologic outcomes while preserving pulmonary function. Lobectomy remains the gold standard, VATS provides minimally invasive access with equivalent long-term results, and limited resections or pneumonectomies are applied selectively based on tumor characteristics and patient fitness. Comprehensive preoperative assessment, including imaging and pulmonary function evaluation, is essential to stratify risk and guide surgical planning. Accurate nodal evaluation ensures proper staging and informs decisions regarding adjuvant therapy. Postoperative complications, including air leaks, arrhythmias, and infections, remain significant considerations, particularly in extensive resections such as pneumonectomy. Overall, the integration of meticulous preoperative evaluation, minimally invasive surgical techniques, and careful postoperative monitoring forms the cornerstone of effective surgical management in patients with early-stage and select locally advanced SCC of the lung [32].

Staging

Accurate staging is critical in the management of lung cancer, including squamous cell carcinoma (SCC), as it informs treatment decisions, predicts prognosis, and facilitates communication across multidisciplinary teams. The staging process relies predominantly on imaging studies, particularly computed tomography (CT) scans, to assess the primary tumor, regional lymph nodes, and distant metastatic spread. The eighth edition of the Tumor-Node-Metastasis (TNM) classification system, issued by the International Association for the Study of Lung Cancer (IASLC), provides the current standard for staging lung cancer, replacing the previous seventh edition [33]. This system categorizes tumors based on the size and extent of the primary lesion (T), regional nodal involvement (N), and the presence of distant metastases (M). Primary tumors are classified from T1 to T4 according to size and local invasion. T1 tumors include small lesions confined to the lung parenchyma and bronchial wall without invading adjacent structures. T1a describes uncommon superficial spreading tumors with invasion limited to the bronchial wall, which may extend proximally toward the main bronchus. T1 tumors also include solitary adenocarcinomas ≤3 cm with a predominantly lepidic pattern and ≤5 mm of invasion [33]. T2 tumors are subdivided into T2a and T2b, with T2a lesions measuring ≤4 cm or undetermined in size, and T2b lesions >4 cm but ≤5 cm in greatest dimension. Additional features, such as invasion into visceral pleura or partial main bronchus involvement, may also define T2 status. Tumor-associated pleural or pericardial effusions are included in staging unless extensive cytologic and clinical evaluation indicates the effusion is unrelated to the tumor [33].

Nodal involvement is classified as N0 to N3 based on the location and extent of regional lymph node metastasis. N0 indicates no regional lymph node involvement, whereas N1 describes ipsilateral peribronchial or hilar nodal spread. N2 involves ipsilateral mediastinal and/or subcarinal nodes, and N3 refers to contralateral mediastinal, contralateral hilar, or supraclavicular nodal involvement. The M category addresses distant metastases, with M0 indicating no distant spread and M1 describing the presence of metastatic disease, including a single distant node or involvement of organs such as the brain, liver, adrenal glands, and bones. Accurate classification of T, N, and M status is essential to determine treatment strategy, including the appropriateness of surgery, systemic therapy, or palliative measures [33].

Table 2: Stage-Directed Treatment Paradigms

Stage	Primary Treatment	5-Year Survival	Key Trials/Evidence
IA-IB	Lobectomy/VATS ± adjuvant chemo (if >4 cm)	60–80%	JCOG0802 (segmentectomy non-inferiority)
IIA-IIB	Lobectomy + adjuvant platinum-doublet	40–50%	ANITA trial
IIIA	Neoadjuvant chemoimmunotherapy →	30–40%	CheckMate 816 (nivolumab + chemo)

Stage	Primary Treatment	5-Year Survival	Key Trials/Evidence
	surgery		
IIIB	Concurrent chemoradiation → durvalumab	20–30%	PACIFIC trial
IV	Platinum-doublet + pembrolizumab (if PD-L1≥50%)	15–20% (2-year OS)	KEYNOTE-407

Prognosis

SCC of the lung exhibits a high propensity for metastasis, with common sites including the brain, spine, bones, adrenal glands, and liver. Prognosis is frequently poor due to the late stage at which the disease is often detected and the lower prevalence of targetable molecular mutations compared to adenocarcinoma or other NSCLCs. Nevertheless, in patients with advanced disease expressing high levels of programmed death-ligand 1 (PD-L1), immune checkpoint inhibitor therapy has shown improved and sustained responses relative to patients with nonsquamous histologies. Early detection remains the most significant determinant of prognosis, underscoring the importance of comprehensive staging and timely intervention[34].

Complications

SCC of the lung can result in multiple complications directly related to tumor growth and metastatic spread. Tumor obstruction of the central airways can cause shortness of breath or recurrent pulmonary infections, while pleural effusion secondary to tumor involvement may exacerbate dyspnea. Hemoptysis, or bleeding into the airway, can occur from tumor erosion of vascular structures. Metastatic disease can result in pain, neurologic deficits, or spinal cord compression, further contributing to morbidity and complicating management. Complications may necessitate urgent intervention, including palliative procedures, radiotherapy, or systemic therapy to alleviate symptoms and maintain quality of life [34].

Postoperative and Rehabilitation Care

Preoperative exercise programs and rehabilitation have demonstrated significant benefits in reducing postoperative pulmonary complications and improving functional outcomes [34]. Patients engaging in structured preoperative conditioning typically experience better postoperative exercise capacity and quicker recovery. Postoperative pulmonary rehabilitation alone, without preoperative conditioning, yields modest short-term improvements in exercise capacity, though the long-term impact on functional performance remains unclear [35]. Integration of preoperative and postoperative rehabilitation into the care plan is increasingly recognized as an essential component of optimizing outcomes in patients undergoing surgery for lung cancer.

Consultations

Effective management of SCC requires consultation with a range of specialists across multiple disciplines. Core consultations include pulmonology for airway evaluation and management, cardiothoracic and surgical oncology for operative planning, medical oncology for systemic therapy decisions, and palliative care for symptom management and quality-of-life considerations. Psychiatry may also be involved to address anxiety, depression, or other psychological challenges associated with a cancer diagnosis and treatment. Coordinated input from these specialists ensures comprehensive care addressing both disease control and patient well-being [35].

Patient Education

Patient education plays a crucial role in preventing SCC development and promoting early detection. Counseling on avoidance of tobacco products, including cigarettes and other inhaled substances, is essential to mitigate risk. Occupational exposures, such as inhalation of asbestos, metal dust, or other industrial particulates, should be minimized through the use of personal protective equipment and adherence to workplace safety protocols. Early cancer detection is facilitated by low-dose CT screening, particularly in high-risk populations such as long-term smokers or individuals with significant occupational exposure. Education should also include information on cancer staging, treatment options, and expected outcomes, ensuring patients understand the likelihood of cure in early stages and the role of palliative care in advanced disease. Structured counseling reduces patient and caregiver stress and enhances engagement with treatment plans [35].

Enhancing Healthcare Team Outcomes

Optimal management of SCC requires an interprofessional team approach due to the complexity of care. The team typically includes primary care clinicians, pulmonologists, cardiothoracic surgeons, medical and surgical oncologists, radiation oncologists, palliative care specialists, nurses, pharmacists, and rehabilitation therapists. Effective communication and collaboration are essential to ensure that all team members have access to accurate and current patient information. Clinicians lead the overall management plan, while each specialty contributes expertise within its domain. Nurses play a pivotal role in patient assessment, perioperative support, postoperative care, chemotherapy administration, and ongoing counseling. Oncology-trained pharmacists oversee chemotherapeutic regimens, monitor for drug interactions, provide education, and track patient responses to therapy. Physical and respiratory therapists support pulmonary rehabilitation and functional recovery. Open communication and prompt reporting of concerns among team members are critical to reducing adverse events and optimizing patient outcomes [35]. The interprofessional approach enhances patient safety, facilitates coordinated care, and ensures that decisions regarding surgery, systemic therapy, and palliative interventions are evidence-based and patient-centered. By integrating expertise across disciplines, the healthcare team can effectively manage the multifaceted clinical, functional, and

psychosocial needs of patients with SCC, ultimately improving survival, quality of life, and overall care efficiency. In conclusion, staging SCC of the lung using the IASLC TNM system is essential for guiding treatment, predicting prognosis, and facilitating multidisciplinary collaboration. Comprehensive preoperative assessment, vigilant monitoring for complications, structured rehabilitation, and coordinated interprofessional care are integral to optimizing outcomes. Education and preventive strategies reduce risk and support early diagnosis, while staging and molecular profiling inform individualized treatment approaches. The integration of these strategies ensures evidence-based, patient-centered care, addressing both oncologic control and holistic patient well-being, and underpins contemporary standards for managing SCC of the lung [35].

Conclusion:

Squamous cell carcinoma (SCC) of the lung represents a distinct NSCLC subtype with complex molecular pathogenesis and clinical challenges. Its strong smoking association (80–90% of cases) underscores the persistent public health impact of tobacco, despite declining incidence in high-income countries. Central airway location and keratinizing histopathology differentiate SCC from peripherally predominant adenocarcinomas, contributing to classic symptoms like hemoptysis and post-obstructive pneumonia. Diagnostically, SCC is confirmed via biopsy with immunohistochemistry (p40/p63 positivity), while CT/PET imaging defines locoregional and metastatic spread. The IASLC TNM staging system guides prognosis and treatment: surgical resection (lobectomy/VATS) offers cure in stages I-IIIA, while unresectable locally advanced disease (IIIB) benefits from definitive chemoradiation followed by durvalumab consolidation. Metastatic SCC (stage IV) historically had limited options, but immune checkpoint inhibitors (pembrolizumab, cemiplimab) now improve survival in PD-L1-high tumors, with response rates of 30–45%. Unlike adenocarcinoma, targetable driver mutations (EGFR/ALK/ROS1) are rare in SCC, though emerging therapies for FGFR1 amplifications (e.g., erdafitinib) and PI3K/AKT pathway alterations show early promise. Key challenges persist. First, most SCCs lack actionable targets, emphasizing the need for biomarker discovery beyond PD-L1. Second, central tumors often complicate surgical resection, necessitating innovative techniques like sleeve lobectomy. Third, immunotherapy resistance mechanisms (e.g., T-cell exhaustion, tumor microenvironment suppression) require combinatorial strategies. Finally, disparities in access to molecular testing and novel therapies globally limit real-world outcomes. Prevention remains critical—screening high-risk smokers with low-dose CT reduces mortality, while smoking cessation programs are indispensable. For advanced disease, ongoing trials explore immunotherapy combinations (e.g., CTLA-4/PD-1 inhibitors), antibody-drug conjugates (e.g., sacituzumab govitecan), and adoptive cell therapies. In summary, SCC management demands a tailored, multidisciplinary approach integrating surgery, radiation, systemic therapy, and supportive care. While immunotherapy has transformed advanced-stage treatment, overcoming resistance and expanding targeted options are urgent priorities. Future progress hinges on elucidating SCC-specific molecular vulnerabilities and ensuring equitable access to precision oncology globally.

References:

1. Chaudhuri MR. Primary pulmonary cavitating carcinomas. Thorax. 1973 May;28(3):354-66.
2. Gridelli C, Ardizzoni A, Douillard JY, Hanna N, Manegold C, Perrone F, Pirker R, Rosell R, Shepherd FA, De Petris L, Di Maio M, de Marinis F. Recent issues in first-line treatment of advanced non-small-cell lung cancer: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. Lung Cancer. 2010 Jun;68(3):319-31.
3. Perez-Moreno P, Brambilla E, Thomas R, Soria JC. Squamous cell carcinoma of the lung: molecular subtypes and therapeutic opportunities. Clin Cancer Res. 2012 May 01;18(9):2443-51.
4. Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature. 2012 Sep 27;489(7417):519-25.
5. Dietel M, Bubendorf L, Dingemans AM, Dooms C, Elmberger G, García RC, Kerr KM, Lim E, López-Ríos F, Thunnissen E, Van Schil PE, von Laffert M. Diagnostic procedures for non-small-cell lung cancer (NSCLC): recommendations of the European Expert Group. Thorax. 2016 Feb;71(2):177-84.
6. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, Chirieac LR, Dacic S, Duhig E, Flieder DB, Geisinger K, Hirsch FR, Ishikawa Y, Kerr KM, Noguchi M, Pelosi G, Powell CA, Tsao MS, Wistuba I., WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol. 2015 Sep;10(9):1243-1260.
7. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, Harris LJ, Detterbeck FC. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e211S-e250S.
8. Lindeman NI, Cagle PT, Beasley MB, Chitale DA, Dacic S, Giaccone G, Jenkins RB, Kwiatkowski DJ, Saldivar JS, Squire J, Thunnissen E, Ladanyi M. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. J Thorac Oncol. 2013 Jul;8(7):823-59.
9. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, Dechaphunkul A, Imamura F, Nogami N, Kurata T, Okamoto I, Zhou C, Cho BC, Cheng Y, Cho EK, Voon PJ, Planchard D, Su WC, Gray JE, Lee SM, Hodge R, Marotti M, Rukazenkov Y, Ramalingam SS., FLAURA Investigators. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Jan 11;378(2):113-125.
10. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, Shepherd FA, He Y, Akamatsu H, Theelen WS, Lee CK, Sebastian M, Templeton A, Mann H, Marotti M, Ghiorghiu S, Papadimitrakopoulou VA., AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640.
11. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, Italiano A, Schuler M, Borghaei H, Barlesi F, Kato T, Curioni-Fontecedro A, Sacher A, Spira A, Ramalingam SS, Takahashi T, Besse B, Anderson A, Ang A, Tran Q, Mather

O, Henary H, Ngarmchamnanrith G, Friberg G, Velcheti V, Govindan R. Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation. N Engl J Med. 2021 Jun 24;384(25):2371-2381.
12. Jänne PA, Riely GJ, Gadgeel SM, Heist RS, Ou SI, Pacheco JM, Johnson ML, Sabari JK, Leventakos K, Yau E, Bazhenova L, Negrao MV, Pennell NA, Zhang J, Anderes K, Der-Torossian H, Kheoh T, Velastegui K, Yan X, Christensen JG, Chao RC, Spira AI. Adagrasib in Non-Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation. N Engl J Med. 2022 Jul 14;387(2):120-131.
13. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, Ou SI, Pérol M, Dziadziuszko R, Rosell R, Zeaiter A, Mitry E, Golding S, Balas B, Noe J, Morcos PN, Mok T., ALEX Trial Investigators. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Aug 31;377(9):829-838.
14. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, Hochmair MJ, Li JY, Chang GC, Lee KH, Gridelli C, Delmonte A, Garcia Campelo R, Kim DW, Bearz A, Griesinger F, Morabito A, Felip E, Califano R, Ghosh S, Spira A, Gettinger SN, Tiseo M, Gupta N, Haney J, Kerstein D, Popat S. Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2027-2039.
15. Shaw AT, Bauer TM, de Marinis F, Felip E, Goto Y, Liu G, Mazieres J, Kim DW, Mok T, Polli A, Thurm H, Calella AM, Peltz G, Solomon BJ., CROWN Trial Investigators. First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer. N Engl J Med. 2020 Nov 19;383(21):2018-2029.
16. Doebele RC, Drilon A, Paz-Ares L, Siena S, Shaw AT, Farago AF, Blakely CM, Seto T, Cho BC, Tosi D, Besse B, Chawla SP, Bazhenova L, Krauss JC, Chae YK, Barve M, Garrido-Laguna I, Liu SV, Conkling P, John T, Fakih M, Sigal D, Loong HH, Buchschacher GL, Garrido P, Nieva J, Steuer C, Overbeck TR, Bowles DW, Fox E, Riehl T, Chow-Maneval E, Simmons B, Cui N, Johnson A, Eng S, Wilson TR, Demetri GD., trial investigators. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020 Feb;21(2):271-282.
17. Planchard D, Besse B, Groen HJM, Hashemi SMS, Mazieres J, Kim TM, Quoix E, Souquet PJ, Barlesi F, Baik C, Villaruz LC, Kelly RJ, Zhang S, Tan M, Gasal E, Santarpia L, Johnson BE. Phase 2 Study of Dabrafenib Plus Trametinib in Patients With BRAF V600E-Mutant Metastatic NSCLC: Updated 5-Year Survival Rates and Genomic Analysis. J Thorac Oncol. 2022 Jan;17(1):103-115.
18. Drilon A, Laetsch TW, Kummar S, DuBois SG, Lassen UN, Demetri GD, Nathenson M, Doebele RC, Farago AF, Pappo AS, Turpin B, Dowlati A, Brose MS, Mascarenhas L, Federman N, Berlin J, El-Deiry WS, Baik C, Deeken J, Boni V, Nagasubramanian R, Taylor M, Rudzinski ER, Meric-Bernstam F, Sohal DPS, Ma PC, Raez LE, Hechtman JF, Benayed R, Ladanyi M, Tuch BB, Ebata K, Cruickshank S, Ku NC, Cox MC, Hawkins DS, Hong DS, Hyman DM. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. N Engl J Med. 2018 Feb 22;378(8):731-739.
19. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJM, Tan DSW, Hida T, de Jonge M, Orlov SV, Smit EF, Souquet PJ, Vansteenkiste J, Hochmair M, Felip E, Nishio M, Thomas M, Ohashi K, Toyozawa R, Overbeck TR, de Marinis F, Kim TM, Laack E, Robeva A, Le Mouhaer S, Waldron-Lynch M, Sankaran B, Balbin OA, Cui X, Giovannini M, Akimov M, Heist RS., GEOMETRY mono-1 Investigators. Capmatinib in *MET* Exon 14-Mutated or *MET*-Amplified Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Sep 03;383(10):944-957.
20. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, Mazieres J, Viteri S, Senellart H, Van Meerbeeck J, Raskin J, Reinmuth N, Conte P, Kowalski D, Cho BC, Patel JD, Horn L, Griesinger F, Han JY, Kim YC, Chang GC, Tsai CL, Yang JC, Chen YM, Smit EF, van der Wekken AJ, Kato T, Juraeva D, Stroh C, Bruns R, Straub J, Johne A, Scheele J, Heymach JV, Le X. Tepotinib in Non-Small-Cell Lung Cancer with *MET* Exon 14 Skipping Mutations. N Engl J Med. 2020 Sep 03;383(10):931-943.
21. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, McCoach CE, Gautschi O, Besse B, Cho BC, Peled N, Weiss J, Kim YJ, Ohe Y, Nishio M, Park K, Patel J, Seto T, Sakamoto T, Rosen E, Shah MH, Barlesi F, Cassier PA, Bazhenova L, De Braud F, Garralda E, Velcheti V, Satouchi M, Ohashi K, Pennell NA, Reckamp KL, Dy GK, Wolf J, Solomon B, Falchook G, Ebata K, Nguyen M, Nair B, Zhu EY, Yang L, Huang X, Olek E, Rothenberg SM, Goto K, Subbiah V. Efficacy of Selpercatinib in *RET* Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Aug 27;383(9):813-824.
22. Li BT, Smit EF, Goto Y, Nakagawa K, Udagawa H, Mazières J, Nagasaka M, Bazhenova L, Saltos AN, Felip E, Pacheco JM, Pérol M, Paz-Ares L, Saxena K, Shiga R, Cheng Y, Acharyya S, Vitazka P, Shahidi J, Planchard D, Jänne PA., DESTINY-Lung01 Trial Investigators. Trastuzumab Deruxtecan in *HER2*-Mutant Non-Small-Cell Lung Cancer. N Engl J Med. 2022 Jan 20;386(3):241-251.
23. Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman JR, Bharat A, Bruno DS, Chang JY, Chirieac LR, D'Amico TA, DeCamp M, Dilling TJ, Dowell J, Gettinger S, Grotz TE, Gubens MA, Hegde A, Lackner RP, Lanuti M, Lin J, Loo BW, Lovly CM, Maldonado F, Massarelli E, Morgensztern D, Ng T, Otterson GA, Pacheco JM, Patel SP, Riely GJ, Riess J, Schild SE, Shapiro TA, Singh AP, Stevenson J, Tam A, Tanvetyanon T, Yanagawa J, Yang SC, Yau E, Gregory K, Hughes M. Non-Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022 May;20(5):497-530.
24. Berry MF, D'Amico TA, Onaitis MW, Kelsey CR. Thoracoscopic approach to lobectomy for lung cancer does not compromise oncologic efficacy. Ann Thorac Surg. 2014 Jul;98(1):197-202.
25. Murakawa T, Ichinose J, Hino H, Kitano K, Konoeda C, Nakajima J. Long-term outcomes of open and video-assisted thoracoscopic lung lobectomy for the treatment of early stage non-small cell lung cancer are similar: a propensity-matched study. World J Surg. 2015 May;39(5):1084-91.

26. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995 Sep;60(3):615-22; discussion 622-3.
27. Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, Smith C, Chen Y, Livingston RB, Feins RH, Gandara DR, Fry WA, Darling G, Johnson DH, Green MR, Miller RC, Ley J, Sause WT, Cox JD. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet. 2009 Aug 01;374(9687):379-86.
28. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013 May;143(5 Suppl):e166S-e190S.
29. Ziarnik E, Grogan EL. Postlobectomy Early Complications. Thorac Surg Clin. 2015 Aug;25(3):355-64.
30. Darling GE, Allen MS, Decker PA, Ballman K, Malthaner RA, Inculet RI, Jones DR, McKenna RJ, Landreneau RJ, Rusch VW, Putnam JB. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg. 2011 Mar;141(3):662-70.
31. Joo JB, DeBord JR, Montgomery CE, Munns JR, Marshall JS, Paulsen JK, Anderson RC, Meyer LE, Estes NC. Perioperative factors as predictors of operative mortality and morbidity in pneumonectomy. Am Surg. 2001 Apr;67(4):318-21; discussion 321-2.
32. Klemperer J, Ginsberg RJ. Morbidity and mortality after pneumonectomy. Chest Surg Clin N Am. 1999 Aug;9(3):515-25, vii.
33. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, Nicholson AG, Groome P, Mitchell A, Bolejack V., International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016 Jan;11(1):39-51.
34. Sebio Garcia R, Yáñez Brage MI, Giménez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. Interact Cardiovasc Thorac Surg. 2016 Sep;23(3):486-97.
35. Sommer MS, Staerkind MEB, Christensen J, Vibe-Petersen J, Larsen KR, Holst Pedersen J, Langberg H. Effect of postsurgical rehabilitation programmes in patients operated for lung cancer: A systematic review and meta-analysis. J Rehabil Med. 2018 Feb 28;50(3):236-245.