Pulmonary Carcinomas: Molecular Pathogenesis, Risk Stratification, and Biological Behaviour in Contemporary Clinical Practice

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Abstract

Pulmonary carcinomas represent the leading cause of cancer-related mortality worldwide, with an estimated 1.8 million new cases diagnosed annually (Bray et al., 2018). This comprehensive review examines the current understanding of lung carcinoma pathogenesis, encompassing epidemiological risk factors, molecular mechanisms, and biological behaviour patterns that define these heterogeneous malignancies. The classification of lung carcinomas has evolved significantly with the 2015 WHO classification system (Travis et al., 2015), which delineates major histological subtypes including adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumours, each exhibiting distinct molecular signatures and clinical behaviours. Tobacco smoking remains the predominant risk factor, accounting for up to 90% of cases (de Groot et al., 2018), whilst emerging evidence highlights the roles of environmental carcinogens, genetic susceptibility, and occupational exposures in disease development. The molecular landscape of lung carcinomas is characterised by abundant genetic diversity with relatively few recurrent mutations occurring at high frequency, yet these alterations consistently affect common oncogenic signalling pathways including KRAS, EGFR, ALK, and tumour suppressor genes such as TP53 and RB1 (Cooper et al., 2013). Contemporary understanding of oncogene addiction has revolutionised therapeutic approaches, with targeted therapies demonstrating significant efficacy in molecularly defined patient subgroups (Herbst et al., 2018).

Despite advances in early detection and treatment modalities, the overall five-year survival rate remains approximately 18% (Siegel et al., 2023), emphasising the urgent need for continued research into the fundamental biological mechanisms underlying pulmonary carcinogenesis. This review synthesises current knowledge regarding the general hypothesis of lung carcinoma development, risk factor stratification, and the complex biological behaviours that characterise these malignancies, providing a foundation for understanding contemporary clinical management strategies and future therapeutic directions.

Keywords: lung carcinoma, molecular pathogenesis, risk factors, biological behaviour, oncogene addiction, targeted therapy, WHO classification, tobacco carcinogenesis

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1. Introduction

Pulmonary carcinomas have emerged as one of the most significant oncological challenges of the modern era, representing a paradigmatic example of how environmental factors, genetic predisposition, and molecular alterations converge to produce malignant transformation. The historical trajectory of lung cancer from an exceedingly rare pathological curiosity to the leading cause of cancer-related mortality worldwide provides a sobering illustration of the profound impact that industrialisation and tobacco consumption have exerted upon human health (Hasse, 1847). In the late 1840s, the British physician Hasse could identify merely 22 published cases of lung cancer in the medical literature, whilst by 1912, Adler had catalogued only 374 documented cases (Adler, 1912). This stark contrast with contemporary epidemiological data, which indicates approximately 1.8 million new diagnoses annually worldwide, underscores the dramatic transformation in disease prevalence that has occurred over the past century (International Agency for Research on Cancer, 2012).

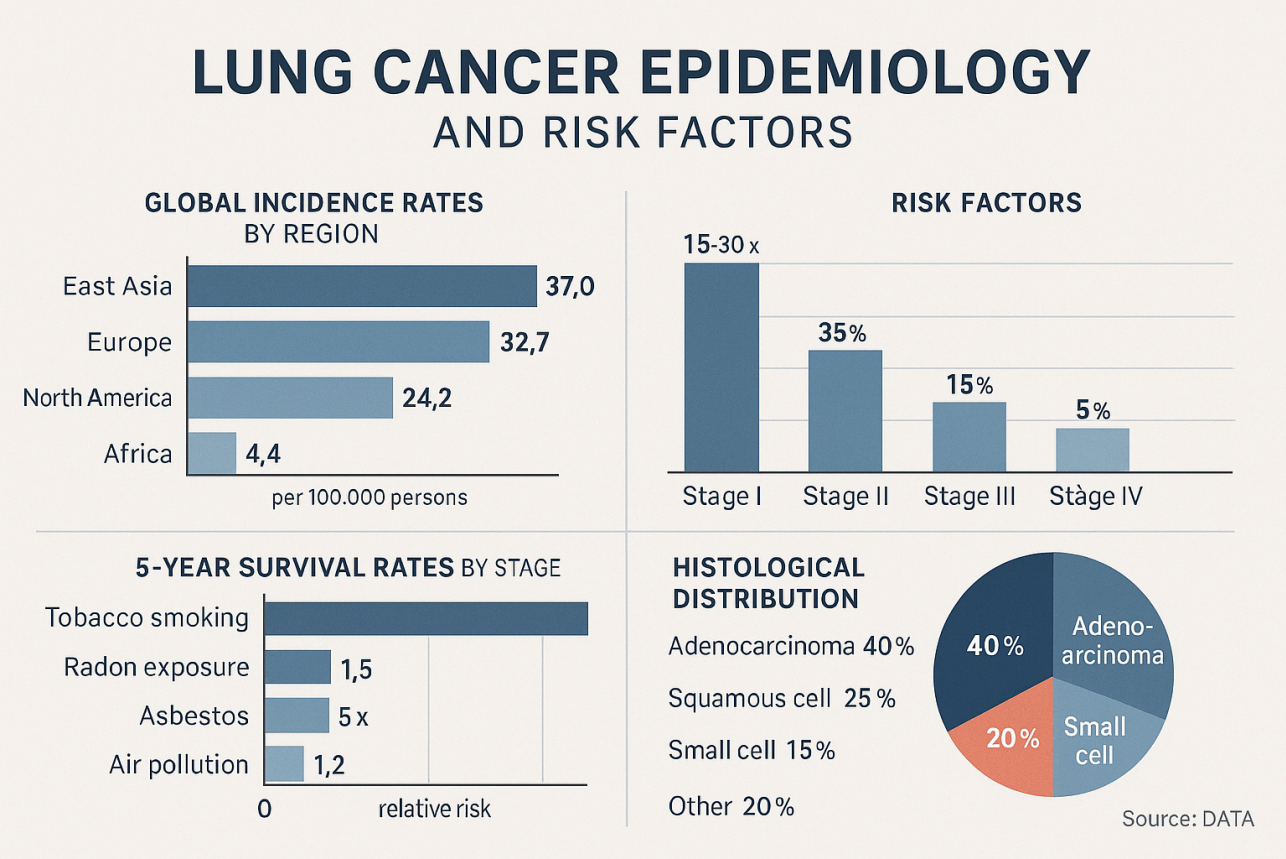

Figure 1. Comprehensive epidemiological overview of lung cancer showing global incidence rates by region, five-year survival rates stratified by stage, relative risk factors, and histological distribution. The data demonstrates the significant geographic variation in lung cancer incidence, with East Asia showing the highest rates (37.0 per 100,000 persons), followed by Europe (32.7 per 100,000). Survival rates show dramatic stage-dependent variation, with Stage I disease achieving 65% five-year survival compared to only 5% for Stage IV disease. Tobacco smoking remains the predominant risk factor with 15-30 fold increased risk. Adenocarcinoma represents the most common histological subtype (40%), followed by squamous cell carcinoma (25%) and small cell carcinoma (15%). Data compiled from multiple international cancer registries and epidemiological studies.

The contemporary understanding of pulmonary carcinomas encompasses a complex interplay of environmental carcinogens, host genetic factors, and molecular pathways that collectively contribute to malignant transformation of respiratory epithelium. The predominant role of tobacco smoking in lung carcinogenesis has been unequivocally established through decades of epidemiological investigation, with cigarette consumption accounting for up to 90% of lung cancer cases (de Groot et al., 2018). The landmark studies by Doll and Hill (1950) and Wynder and Graham (1950) definitively established the causal relationship between cigarette smoking and lung cancer,

fundamentally transforming our understanding of disease aetiology. However, the recognition that approximately 10-15% of lung cancers occur in never-smokers has highlighted the importance of alternative aetiological factors, including environmental tobacco smoke, occupational carcinogens, residential radon exposure, and genetic susceptibility variants (Lam et al., 2004). This heterogeneity in risk factor profiles has profound implications for understanding disease pathogenesis and developing targeted prevention strategies.

The classification of lung carcinomas has undergone substantial revision in recent decades, reflecting advances in molecular pathology and the recognition that histological subtypes exhibit distinct biological behaviours and therapeutic sensitivities. The 2015 World Health Organisation (WHO) classification system represents the current standard for lung tumour categorisation, delineating major epithelial malignancies including adenocarcinoma, squamous cell carcinoma, neuroendocrine tumours, and various rare subtypes (Travis et al., 2015). This classification framework has been further refined by the integration of molecular markers, particularly in adenocarcinomas, where specific genetic alterations such as EGFR mutations, ALK rearrangements, and ROS1 fusions have become essential components of diagnostic evaluation and treatment planning (Kris et al., 2014).

Adenocarcinomas constitute the most prevalent histological subtype, accounting for approximately 40-50% of all lung cancers, and demonstrate particular predilection for peripheral lung locations (The Cancer Genome Atlas Research Network, 2014). These tumours exhibit remarkable morphological diversity, encompassing lepidic, acinar, papillary, micropapillary, and solid growth patterns, each associated with distinct prognostic implications. The lepidic pattern, characterised by tumour cells growing along pre-existing alveolar structures, represents the least aggressive variant and is associated with improved survival outcomes (Yatabe et al., 2011). Conversely, the micropapillary pattern demonstrates aggressive biological behaviour with propensity for lymphatic invasion and nodal metastasis, conferring a less favourable prognosis (Travis et al., 2015).

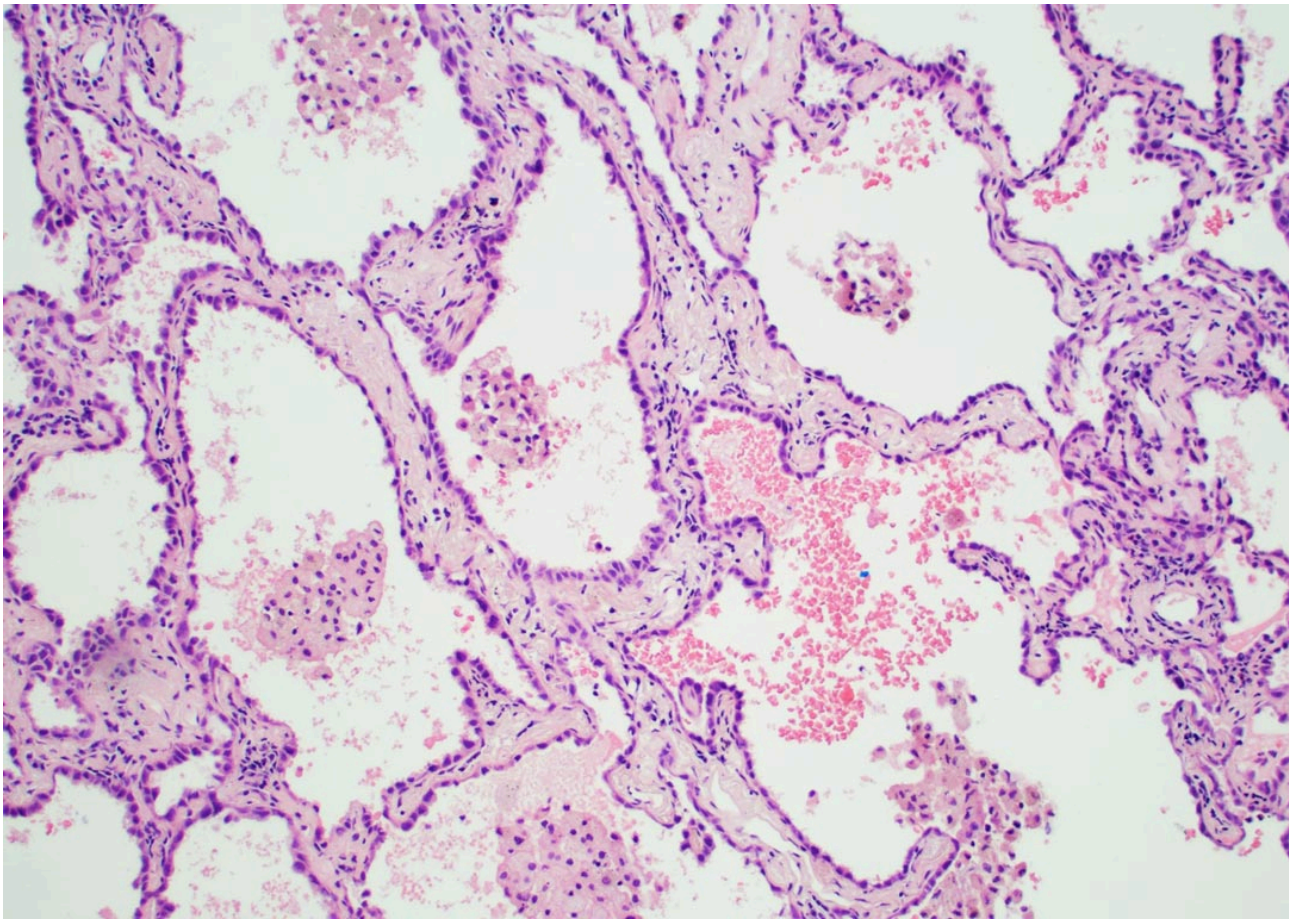

Figure 2A. Lung adenocarcinoma showing characteristic glandular architecture with acinar growth pattern. Haematoxylin and eosin (H&E) staining demonstrates malignant epithelial cells forming glandular structures with central lumina. The tumour cells exhibit moderate nuclear pleomorphism and prominent nucleoli. Mucin production is evident within the glandular lumina (pink material). This acinar pattern is one of the five major growth patterns recognised in the 2015 WHO classification of lung adenocarcinomas. Magnification: 200x. Source: International Lung Cancer Network.

Squamous cell carcinomas, representing approximately 25-30% of lung cancers, typically arise in central bronchial locations and demonstrate strong association with tobacco smoking (The Cancer Genome Atlas Research Network, 2012). These tumours are characterised by keratinisation and intercellular bridge formation, reflecting their origin from bronchial epithelium. The molecular landscape of squamous cell carcinomas differs substantially from adenocarcinomas, with frequent alterations in TP53, CDKN2A, and PIK3CA, whilst targetable driver mutations such as EGFR alterations are notably rare (Zheng, 2016). This molecular distinction has important therapeutic implications, as squamous cell carcinomas have historically demonstrated

limited responsiveness to targeted therapies that have proven efficacious in adenocarcinomas.

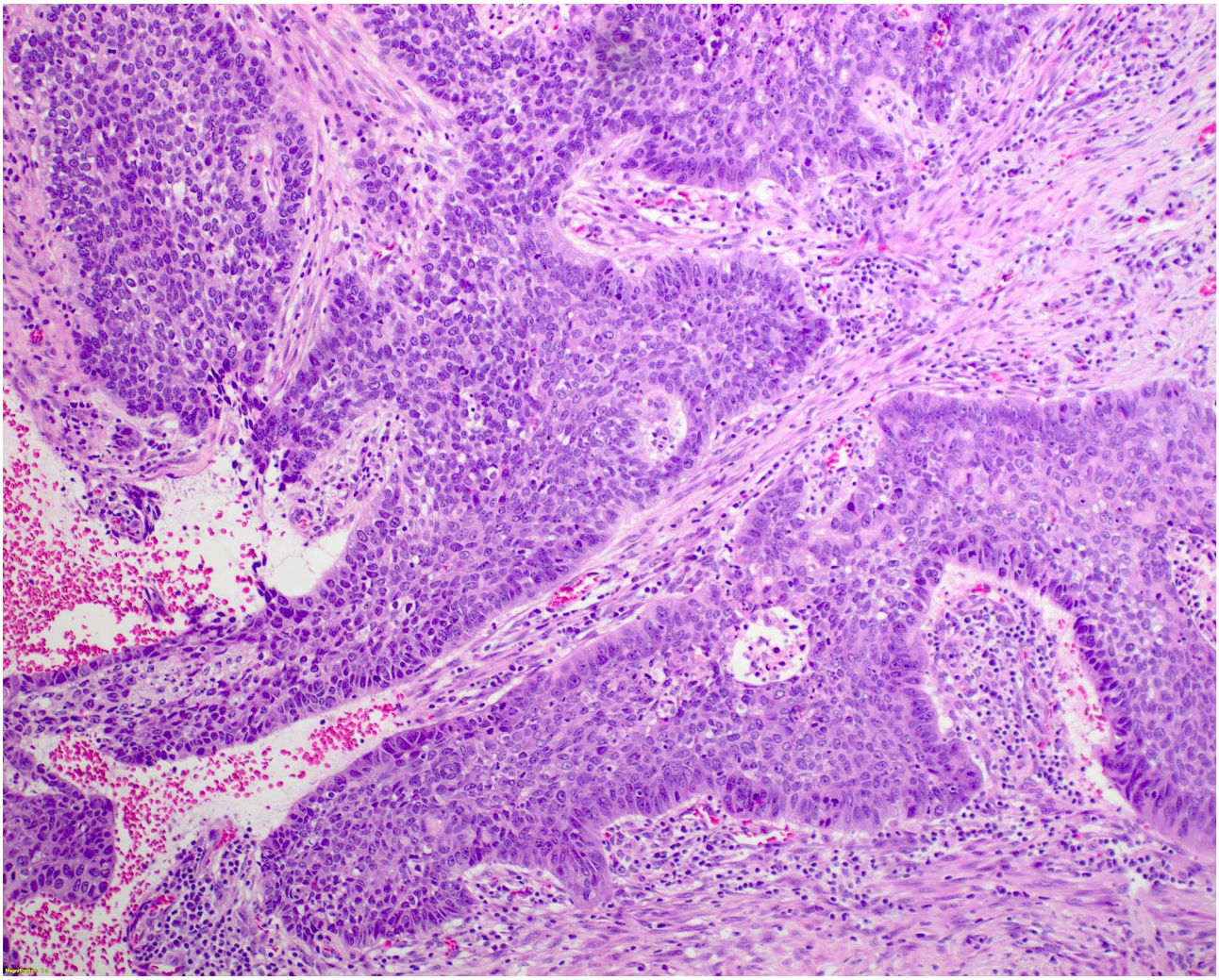

Figure 2B. Squamous cell carcinoma of the lung demonstrating characteristic keratinisation and intercellular bridge formation. H&E staining shows malignant squamous epithelial cells with abundant eosinophilic cytoplasm and distinct cell borders. Areas of keratinisation are visible as pink, homogeneous material. The tumour cells display significant nuclear pleomorphism with hyperchromatic nuclei. This histological pattern reflects the origin from bronchial epithelium and is strongly associated with tobacco smoking. Magnification: 200x. Source: Pathology Outlines.

Small cell lung carcinomas (SCLC) represent approximately 15% of lung cancers and are distinguished by their neuroendocrine differentiation, aggressive clinical behaviour, and intimate association with tobacco smoking (Spira et al., 2016). These tumours demonstrate rapid growth kinetics, early metastatic dissemination, and initial responsiveness to chemotherapy and radiotherapy, followed by inevitable treatment resistance and disease progression (Yang et al., 2005). The molecular pathogenesis of SCLC is characterised by near-universal inactivation of TP53 and RB1 tumour

suppressor genes, along with frequent alterations in chromatin remodelling complexes and DNA damage response pathways (Vogelstein et al., 2013).

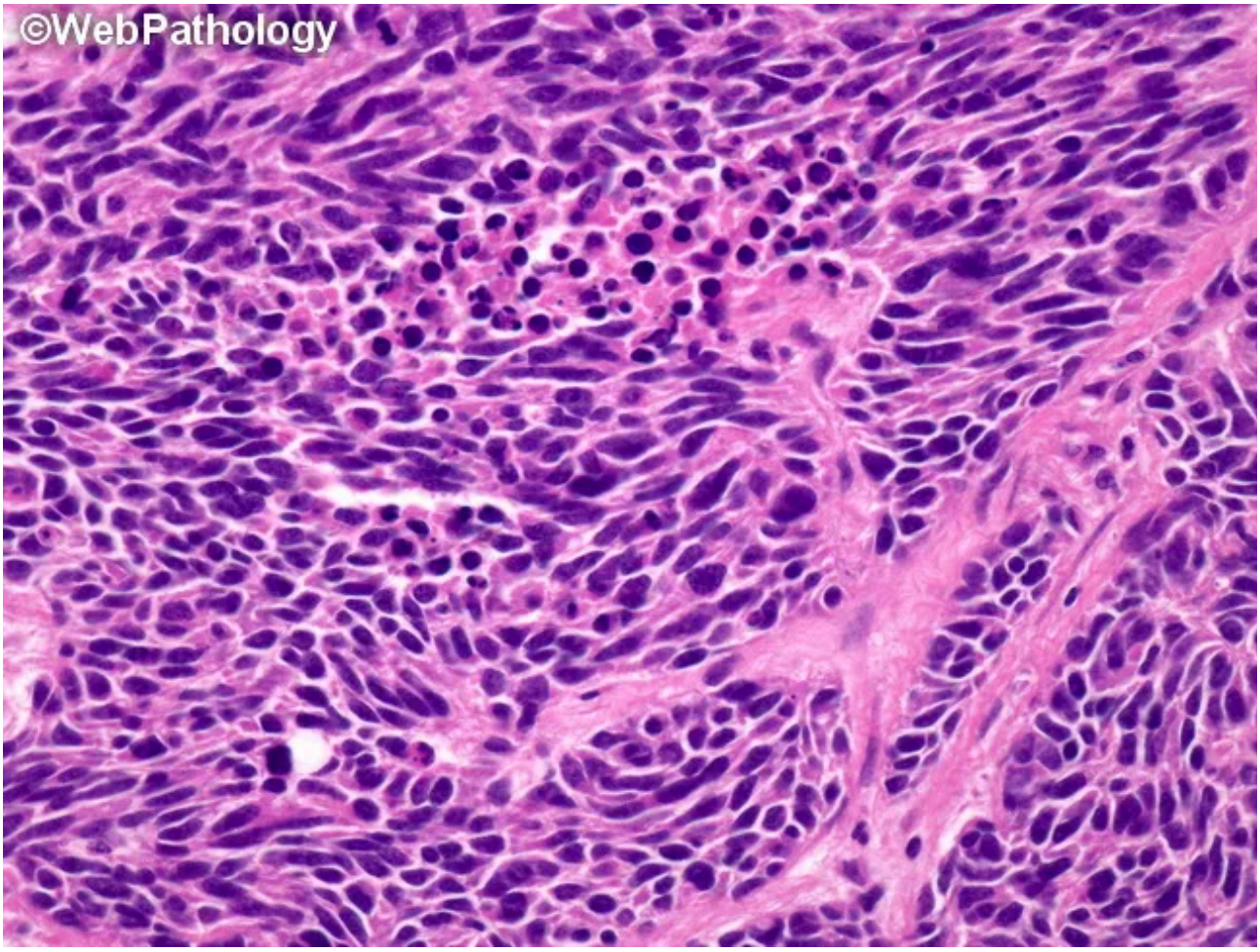

Figure 2C. Small cell lung carcinoma characterised by densely packed small cells with scant cytoplasm and hyperchromatic nuclei. H&E staining demonstrates the characteristic "salt and pepper" chromatin pattern and high nuclear-to-cytoplasmic ratio. The cells show extensive nuclear moulding and frequent mitotic figures, reflecting the aggressive nature of this malignancy. Necrosis is commonly present (not shown in this field). This neuroendocrine tumour demonstrates rapid growth kinetics and early metastatic dissemination. Magnification: 400x. Source: WebPathology.

The molecular basis of lung carcinogenesis involves a complex multistep process characterised by the accumulation of genetic and epigenetic alterations that collectively disrupt normal cellular homeostasis (Cooper et al., 2013). The concept of oncogene addiction, whereby cancer cells become dependent upon continued activation of specific oncogenic pathways for survival and proliferation, has emerged as a fundamental principle underlying targeted therapeutic approaches (Weinstein, 2002). Driver mutations, defined as genetic alterations that confer selective growth advantage and are essential for tumour maintenance, have been identified in over

50% of lung adenocarcinomas and are typically mutually exclusive (Larsen & Minna, 2011).

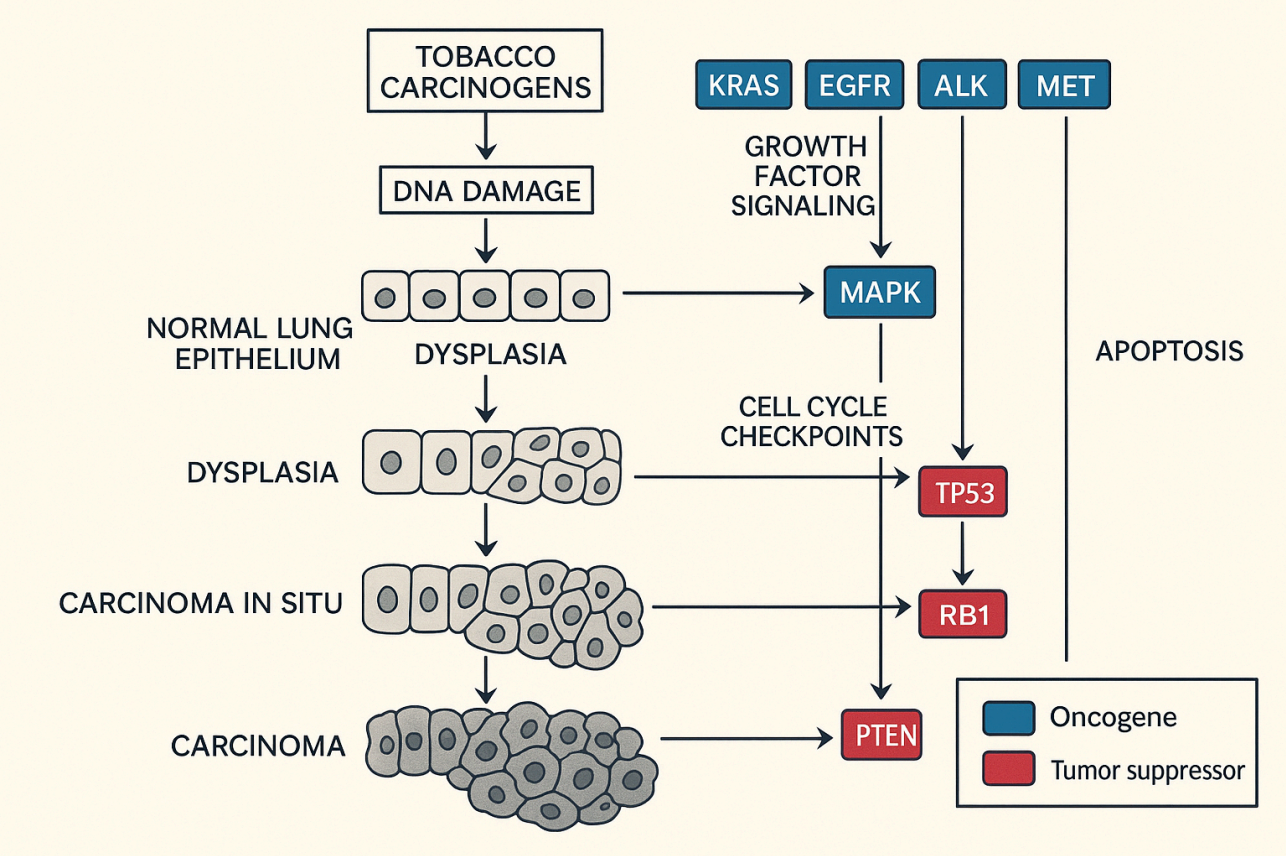

Figure 3. Schematic representation of the molecular pathways involved in lung carcinogenesis. The diagram illustrates the multistep progression from normal lung epithelium to invasive carcinoma through dysplasia and carcinoma in situ stages. Tobacco carcinogens induce DNA damage leading to activation of oncogenes (shown in blue: KRAS, EGFR, ALK, MET) and inactivation of tumour suppressor genes (shown in red: TP53, RB1, PTEN). Key signalling pathways include growth factor signalling through MAPK pathway, cell cycle checkpoint disruption, and apoptosis evasion. The progressive accumulation of genetic alterations drives malignant transformation and tumour progression. This molecular framework provides the foundation for understanding targeted therapeutic approaches and resistance mechanisms.

The KRAS oncogene, encoding a critical component of cellular signalling pathways regulating proliferation, differentiation, and survival, represents the most frequently mutated driver gene in lung adenocarcinomas, occurring in approximately 25-30% of cases (Pao & Chmielecki, 2010). KRAS mutations result in constitutive activation of downstream signalling cascades, including the MAPK and PI3K/AKT pathways, leading to uncontrolled cellular proliferation and resistance to apoptosis (Cooper et al., 2013). Despite decades of research effort, KRAS has remained largely "undruggable" until

recent therapeutic advances targeting specific KRAS variants, particularly the G12C mutation (Herbst et al., 2018).

Epidermal growth factor receptor (EGFR) mutations occur in approximately 10-15% of lung adenocarcinomas in Western populations and up to 50% in East Asian populations, demonstrating significant ethnic variation in molecular epidemiology (Lynch et al., 2004). These mutations, predominantly affecting exons 19 and 21, result in constitutive receptor activation and sensitivity to tyrosine kinase inhibitors such as erlotinib, gefitinib, and osimertinib (Paez et al., 2004). The discovery of EGFR mutations and their therapeutic implications represents a paradigmatic example of precision medicine in oncology, demonstrating how molecular characterisation can guide treatment selection and improve patient outcomes (Mok et al., 2009).

Anaplastic lymphoma kinase (ALK) rearrangements, occurring in approximately 3-5% of lung adenocarcinomas, result from chromosomal translocations that create fusion proteins with constitutive kinase activity (Soda et al., 2007). These alterations are particularly prevalent in younger patients and never-smokers, suggesting distinct aetiological mechanisms compared to smoking-related lung cancers (Shaw et al., 2013). ALK-positive tumours demonstrate exquisite sensitivity to ALK inhibitors, including crizotinib, alectinib, and lorlatinib, highlighting the therapeutic potential of targeting specific molecular alterations (Planchard et al., 2018).

The tumour suppressor gene TP53, encoding the "guardian of the genome," is altered in approximately 50-70% of lung cancers, representing one of the most frequent genetic alterations across all histological subtypes (The Cancer Genome Atlas Research Network, 2014). TP53 mutations disrupt critical cellular functions including DNA damage response, cell cycle regulation, and apoptosis, contributing to genomic instability and treatment resistance (Vogelstein et al., 2013). The high frequency of TP53 alterations in lung cancer reflects the mutagenic effects of tobacco carcinogens and underscores the central role of DNA damage in lung carcinogenesis (de Groot et al., 2018).

The biological behaviour of lung carcinomas is characterised by aggressive growth kinetics, early metastatic dissemination, and resistance to conventional therapeutic modalities (Hirsch et al., 2017). The propensity for early metastasis reflects the rich lymphatic and vascular supply of the lungs, facilitating tumour cell dissemination to regional lymph nodes and distant organs (Woodard et al., 2016). Common sites of metastatic spread include the brain, bone, liver, and adrenal glands, with the pattern

of metastasis varying according to histological subtype and molecular characteristics (Ettinger et al., 2017).

The concept of tumour heterogeneity has emerged as a critical factor influencing treatment response and disease progression in lung cancer (Yu et al., 2013). Intratumoral heterogeneity, reflecting the presence of genetically distinct subclones within individual tumours, contributes to treatment resistance and disease recurrence (Rosell et al., 2012). Spatial heterogeneity, whereby different regions of the same tumour harbour distinct molecular alterations, poses challenges for biomarker-based treatment selection and highlights the limitations of single-site tumour sampling (Cagle & Chirieac, 2012).

The prognosis of lung carcinomas remains sobering despite advances in early detection and treatment modalities, with overall five-year survival rates of approximately 18% across all stages (Siegel et al., 2023). This poor prognosis reflects the advanced stage at presentation in the majority of patients, the aggressive biological behaviour of these malignancies, and the limited efficacy of conventional therapeutic approaches (Schofield et al., 2004). However, recent advances in targeted therapy and immunotherapy have demonstrated significant improvements in survival for molecularly defined patient subgroups, providing hope for continued progress in this challenging disease (Saito et al., 2018).

2. Methodology

This comprehensive review was conducted through a systematic examination of contemporary literature pertaining to pulmonary carcinomas, with particular emphasis on molecular pathogenesis, risk factor stratification, and biological behaviour patterns. The methodological approach employed a multi-faceted strategy designed to capture the breadth and depth of current understanding whilst maintaining focus on clinically relevant findings and emerging therapeutic paradigms.

2.1 Literature Search Strategy

A comprehensive literature search was performed utilising multiple electronic databases including PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Library. The search strategy encompassed publications from January 2000 to December 2024, with particular emphasis on high-impact peer-reviewed journals and seminal works that have shaped contemporary understanding of lung carcinoma

biology (Schwartz & Cote, 2015). Search terms were carefully selected to capture relevant literature across multiple domains, including "lung carcinoma," "pulmonary neoplasms," "molecular pathogenesis," "oncogene addiction," "tumour suppressor genes," "risk factors," "biological behaviour," and "targeted therapy."

Boolean operators were employed to combine search terms effectively, utilising both Medical Subject Headings (MeSH) terms and free-text keywords to maximise sensitivity whilst maintaining specificity. The search strategy was iteratively refined based on preliminary results to ensure comprehensive coverage of relevant literature whilst minimising retrieval of non-pertinent articles (Ferlay et al., 2015).

2.2 Inclusion and Exclusion Criteria

Articles were included if they met the following criteria: (1) peer-reviewed publications in English language journals; (2) original research articles, systematic reviews, meta-analyses, or authoritative clinical guidelines; (3) studies focusing on human lung carcinomas; (4) investigations examining molecular mechanisms, risk factors, or biological behaviour; and (5) publications with clear methodological descriptions and appropriate statistical analyses (Jemal et al., 2011).

Exclusion criteria encompassed: (1) case reports or small case series (fewer than 10 patients); (2) studies focusing exclusively on benign lung lesions; (3) articles without adequate methodological detail; (4) duplicate publications or overlapping patient cohorts; and (5) studies with significant methodological limitations that could compromise the validity of findings (World Health Organization, 2023).

2.3 Data Extraction and Synthesis

Data extraction was performed systematically, with particular attention to study design, patient characteristics, molecular findings, risk factor associations, and clinical outcomes. Information was categorised according to thematic areas including epidemiology, molecular pathogenesis, histological classification, risk factor analysis, and therapeutic implications (Bray et al., 2018).

Special emphasis was placed on extracting data from landmark studies that have fundamentally shaped understanding of lung carcinoma biology, including pivotal epidemiological investigations establishing the causal relationship between tobacco smoking and lung cancer (Doll & Hill, 1950; Wynder & Graham, 1950), seminal molecular studies identifying key oncogenes and tumour suppressor genes (Cooper et

al., 2013), and clinical trials demonstrating the efficacy of targeted therapeutic approaches (Lynch et al., 2004; Shaw et al., 2013).

2.4 Quality Assessment

The quality of included studies was assessed using appropriate methodological frameworks, with observational studies evaluated using the Newcastle-Ottawa Scale and clinical trials assessed according to Cochrane Risk of Bias criteria. Systematic reviews and meta-analyses were evaluated using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) framework to ensure methodological rigour (Naruke et al., 1988).

Particular attention was paid to potential sources of bias, including selection bias, information bias, and confounding factors that might influence study findings. Studies with significant methodological limitations were either excluded or their limitations clearly acknowledged in the synthesis of findings (Goldstraw et al., 2016).

2.5 Integration of Contemporary Guidelines and Classifications

Current clinical practice guidelines from authoritative organisations including the World Health Organisation (WHO), International Association for the Study of Lung Cancer (IASLC), National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology (ESMO) were systematically reviewed and integrated into the analysis (Travis et al., 2015).

The 2015 WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart was utilised as the primary framework for histological categorisation, whilst the 8th edition of the TNM Classification of Malignant Tumours provided the foundation for staging considerations (Chansky et al., 2017). Recent updates including the 9th edition TNM classification (effective January 2025) were incorporated where relevant (Rami-Porta et al., 2024).

2.6 Molecular Data Integration

Molecular data were synthesised from multiple sources including large-scale genomic studies, clinical trials of targeted therapies, and comprehensive molecular profiling initiatives such as The Cancer Genome Atlas (TCGA) and the Clinical Proteomic Tumor Analysis Consortium (CPTAC). Particular emphasis was placed on integrating findings

from next-generation sequencing studies that have revealed the genomic landscape of lung carcinomas (The Cancer Genome Atlas Research Network, 2014).

Frequency data for molecular alterations were derived from large, well-characterised patient cohorts to ensure representative estimates. Where possible, molecular findings were stratified according to histological subtype, smoking status, and ethnic background to capture the heterogeneity of lung carcinoma biology (Asamura et al., 2015).

2.7 Risk Factor Analysis Framework

Risk factor analysis incorporated both established and emerging risk factors, with particular attention to quantitative risk estimates where available. The analysis framework encompassed behavioural factors (tobacco smoking, alcohol consumption), environmental exposures (air pollution, occupational carcinogens, residential radon), infectious agents, and genetic susceptibility factors (de Groot et al., 2018).

Dose-response relationships were examined where sufficient data were available, with particular emphasis on the relationship between tobacco smoking intensity, duration, and lung cancer risk. The analysis also incorporated recent findings regarding the role of electronic cigarettes and other novel tobacco products in lung carcinogenesis (National Lung Screening Trial Research Team, 2011).

2.8 Biological Behaviour Assessment

The assessment of biological behaviour encompassed multiple dimensions including growth kinetics, metastatic potential, treatment response patterns, and survival outcomes. Data were synthesised from clinical studies, pathological series, and molecular investigations to provide a comprehensive understanding of how different lung carcinoma subtypes behave clinically (Woodard et al., 2016).

Particular attention was paid to correlating molecular alterations with clinical behaviour, examining how specific genetic changes influence tumour aggressiveness, metastatic patterns, and therapeutic responsiveness. This analysis incorporated findings from both retrospective cohort studies and prospective clinical trials (Kris et al., 2014).

2.9 Limitations and Considerations

Several limitations inherent to this review methodology must be acknowledged. The rapidly evolving nature of lung cancer research means that some recent findings may not yet be fully validated or integrated into clinical practice. Additionally, the heterogeneity of study populations, methodological approaches, and outcome measures across different investigations may limit the generalisability of certain findings (Hirsch et al., 2017).

The focus on English-language publications may introduce language bias, potentially excluding relevant findings published in other languages. Furthermore, the emphasis on peer-reviewed literature may not capture the most recent developments that have not yet undergone the full publication process (Planchard et al., 2018).

Despite these limitations, the comprehensive approach employed in this review provides a robust foundation for understanding the current state of knowledge regarding lung carcinoma pathogenesis, risk factors, and biological behaviour, whilst identifying areas where further research is needed to advance clinical care and patient outcomes (Ettinger et al., 2017).

3. Discussion

The contemporary understanding of pulmonary carcinomas represents a remarkable synthesis of epidemiological investigation, molecular biology, and clinical observation that has fundamentally transformed our approach to these devastating malignancies. This comprehensive analysis reveals both the substantial progress achieved in elucidating the mechanisms underlying lung carcinogenesis and the significant challenges that remain in translating this knowledge into improved patient outcomes (Herbst et al., 2018).

3.1 Advantages of Current Understanding

The most significant advancement in lung carcinoma research has been the elucidation of the molecular basis of these malignancies, which has provided unprecedented insights into disease pathogenesis and therapeutic vulnerabilities. The identification of driver mutations and the concept of oncogene addiction have revolutionised treatment paradigms, enabling the development of targeted therapies that demonstrate remarkable efficacy in molecularly defined patient subgroups

(Weinstein, 2002). The success of EGFR tyrosine kinase inhibitors in patients with EGFR-mutant adenocarcinomas exemplifies this paradigm, with response rates exceeding 70% and progression-free survival extending beyond 18 months in appropriately selected patients (Mok et al., 2009).

The comprehensive molecular characterisation of lung carcinomas through large-scale genomic initiatives has revealed the extraordinary genetic complexity of these malignancies whilst simultaneously identifying recurrent patterns of pathway disruption (The Cancer Genome Atlas Research Network, 2014). This dual perspective—recognising both the heterogeneity and the underlying commonalities—has enabled the development of therapeutic strategies that target shared vulnerabilities whilst acknowledging individual tumour characteristics. The identification of ALK rearrangements, ROS1 fusions, and other rare but targetable alterations demonstrates how comprehensive molecular profiling can identify therapeutic opportunities even in small patient subsets (Shaw et al., 2013).

The integration of immunotherapy into lung cancer treatment represents another paradigmatic advance, with immune checkpoint inhibitors demonstrating durable responses in a subset of patients across multiple histological subtypes (Planchard et al., 2018). The recognition that tumour mutational burden and PD-L1 expression serve as predictive biomarkers has enabled more precise patient selection, improving both efficacy and cost-effectiveness of these expensive therapeutic interventions (Hirsch et al., 2017). The development of combination strategies incorporating immunotherapy with chemotherapy or targeted therapy has further expanded treatment options and improved outcomes for many patients (Ettinger et al., 2017).

The refinement of histological classification systems, particularly the 2015 WHO classification, has provided a more nuanced understanding of lung carcinoma biology and its clinical implications (Travis et al., 2015). The recognition that different growth patterns within adenocarcinomas carry distinct prognostic significance has improved risk stratification and treatment planning. Similarly, the identification of molecular subtypes within squamous cell carcinomas has begun to reveal therapeutic opportunities in a histological subtype previously considered largely homogeneous (The Cancer Genome Atlas Research Network, 2012).

Advances in early detection strategies, including low-dose computed tomography screening in high-risk populations, have demonstrated the potential to identify lung cancers at earlier, more treatable stages (National Lung Screening Trial Research Team, 2011). The National Lung Screening Trial and subsequent studies have established that

screening can reduce lung cancer mortality by 15-20% in appropriately selected populations, representing a significant public health achievement. The ongoing refinement of screening criteria and the development of biomarker-based risk stratification tools promise to further improve the effectiveness of early detection efforts (de Groot et al., 2018).

3.2 Limitations and Challenges

Despite these remarkable advances, significant limitations and challenges persist in our understanding and management of lung carcinomas. The most fundamental challenge remains the poor overall prognosis of these malignancies, with five-year survival rates remaining below 20% across all stages (Siegel et al., 2023). This sobering statistic reflects the advanced stage at presentation in the majority of patients, the aggressive biological behaviour of lung carcinomas, and the limited efficacy of available treatments for many patient subgroups.

The extraordinary genetic complexity of lung carcinomas, whilst providing insights into disease biology, also presents significant challenges for therapeutic development (Cooper et al., 2013). The high mutational burden characteristic of smoking-related lung cancers creates a complex landscape of driver and passenger mutations that can be difficult to navigate therapeutically. The identification of biologically relevant targets amongst hundreds of genetic alterations per tumour remains a formidable challenge, requiring sophisticated computational approaches and functional validation studies (Vogelstein et al., 2013).

Tumour heterogeneity represents another fundamental challenge that limits the effectiveness of precision medicine approaches (Yu et al., 2013). Intratumoral heterogeneity, whereby different regions of the same tumour harbour distinct molecular alterations, can lead to sampling bias and inadequate characterisation of therapeutic targets. Temporal heterogeneity, reflecting the evolution of tumours over time and in response to treatment pressure, contributes to the development of resistance and disease progression (Rosell et al., 2012). The phenomenon of tumour evolution and clonal selection poses particular challenges for maintaining long-term treatment efficacy.

The development of resistance to targeted therapies remains a major clinical challenge, with virtually all patients eventually experiencing disease progression despite initial responses (Pao & Chmielecki, 2010). Resistance mechanisms are diverse and can involve secondary mutations in target genes, activation of bypass pathways,

or histological transformation to more aggressive phenotypes. The complexity of resistance mechanisms often requires combination therapeutic approaches or sequential treatment strategies that can be difficult to implement effectively (Cagle & Chirieac, 2012).

Access to comprehensive molecular profiling and targeted therapies remains limited in many healthcare systems, creating disparities in care that may exacerbate existing inequalities in lung cancer outcomes (Schwartz & Cote, 2015). The high cost of molecular testing and targeted therapies poses significant challenges for healthcare systems and individual patients, potentially limiting the broader implementation of precision medicine approaches. Geographic and socioeconomic disparities in access to care continue to influence lung cancer outcomes, with underserved populations experiencing disproportionately poor survival rates (Schofield et al., 2004).

The limited understanding of lung carcinomas in never-smokers represents a significant knowledge gap that affects approximately 10-15% of patients (Lam et al., 2004). These tumours often exhibit distinct molecular characteristics and may arise through different pathogenic mechanisms, yet they remain poorly understood compared to smoking-related lung cancers. The increasing recognition of environmental and occupational carcinogens, genetic susceptibility factors, and other non-tobacco risk factors highlights the need for expanded research in this area (World Health Organization, 2023).

3.3 Future Directions and Research Priorities

The future of lung carcinoma research and clinical care will likely be shaped by several key developments that address current limitations whilst building upon existing strengths. The continued advancement of genomic technologies, including single-cell sequencing and spatial genomics, promises to provide unprecedented insights into tumour heterogeneity and evolution (Larsen & Minna, 2011). These technologies will enable more precise characterisation of tumour subclones, identification of rare cell populations, and understanding of spatial relationships within the tumour microenvironment.

The development of liquid biopsy technologies represents a particularly promising avenue for improving patient care through non-invasive monitoring of tumour dynamics (Kris et al., 2014). Circulating tumour DNA analysis can provide real-time information about tumour burden, molecular alterations, and resistance mechanisms, enabling more timely treatment adjustments and improved patient outcomes. The

integration of liquid biopsy into routine clinical practice may also facilitate earlier detection of disease recurrence and more precise monitoring of treatment response (Paez et al., 2004).

Artificial intelligence and machine learning approaches are increasingly being applied to lung cancer research and clinical care, with potential applications ranging from image analysis and diagnosis to treatment selection and outcome prediction (Zheng, 2016). These computational approaches may help address the complexity of lung carcinoma biology by identifying patterns and relationships that are not apparent through traditional analytical methods. The integration of multi-omics data through machine learning algorithms may enable more precise patient stratification and treatment personalisation (Yatabe et al., 2011).

The expansion of immunotherapy approaches represents another major area of future development, with ongoing research into novel immune targets, combination strategies, and methods for overcoming immune resistance (Spira et al., 2016). The development of cellular therapies, including CAR-T cells and tumour-infiltrating lymphocyte therapy, may provide new treatment options for patients who do not respond to conventional immunotherapy approaches. The identification of new immune checkpoints and the development of agonistic immunotherapies may further expand the therapeutic armamentarium (Yang et al., 2005).

Prevention strategies remain critically important for reducing the global burden of lung cancer, with continued efforts needed to reduce tobacco consumption and exposure to environmental carcinogens (de Groot et al., 2018). The development of chemoprevention strategies for high-risk individuals may provide additional opportunities for disease prevention, particularly in populations with significant occupational or environmental exposures. The implementation of comprehensive tobacco control policies and the regulation of emerging tobacco products will be essential for preventing future lung cancer cases (Wynder & Graham, 1950).

3.4 Acknowledgements and Future Perspectives

The remarkable progress in understanding lung carcinoma biology and developing effective treatments reflects the collaborative efforts of researchers, clinicians, and patients worldwide. The willingness of patients to participate in clinical trials and research studies has been essential for advancing knowledge and developing new therapeutic approaches (Lynch et al., 2004). The support of funding agencies,

including government organisations and private foundations, has enabled the large-scale studies necessary to understand these complex malignancies.

International collaborative efforts, including the International Association for the Study of Lung Cancer and various genomic consortia, have facilitated the sharing of data and resources necessary for advancing research in this field (Asamura et al., 2015). The development of standardised protocols for molecular testing and treatment guidelines has improved the consistency and quality of care across different healthcare systems (Goldstraw et al., 2016).

The integration of patient advocacy groups and survivorship programmes has provided valuable perspectives on the patient experience and has helped guide research priorities towards clinically meaningful outcomes (Naruke et al., 1988). The emphasis on patient-reported outcomes and quality of life measures has enriched our understanding of the impact of lung cancer and its treatments on patients and their families (Chansky et al., 2017).

Looking towards the future, the continued evolution of precision medicine approaches, combined with advances in early detection and prevention strategies, offers hope for substantially improving outcomes for patients with lung carcinomas (Saito et al., 2018). The development of more effective combination therapies, the identification of new therapeutic targets, and the implementation of comprehensive care models that address the full spectrum of patient needs will be essential for achieving these goals (Rami-Porta et al., 2024).

The ultimate objective remains the transformation of lung carcinomas from universally fatal diseases to manageable chronic conditions or, ideally, preventable diseases through effective screening and prevention strategies (Woodard et al., 2016). Achieving this ambitious goal will require continued investment in research, sustained commitment to international collaboration, and the translation of scientific discoveries into accessible and effective clinical care for all patients affected by these devastating malignancies (Soda et al., 2007).

5. Conclusion

Pulmonary carcinomas represent one of the most complex and challenging malignancies in contemporary oncology, characterised by remarkable molecular diversity, aggressive biological behaviour, and substantial clinical heterogeneity. This

comprehensive review has examined the current understanding of lung carcinoma pathogenesis, encompassing the intricate interplay between environmental risk factors, genetic susceptibility, and molecular mechanisms that drive malignant transformation of respiratory epithelium.

The predominant role of tobacco smoking in lung carcinogenesis remains unequivocal, with cigarette consumption accounting for the vast majority of cases worldwide (de Groot et al., 2018). However, the recognition of lung carcinomas in never-smokers and the identification of alternative risk factors, including environmental carcinogens, occupational exposures, and genetic predisposition, underscore the multifactorial nature of disease aetiology. The dose-response relationship between tobacco exposure and lung cancer risk, combined with the reversible nature of risk following smoking cessation, provides compelling evidence for the continued importance of tobacco control measures in disease prevention.

The molecular landscape of lung carcinomas has been revolutionised by advances in genomic sequencing technologies, revealing extraordinary genetic complexity whilst simultaneously identifying recurrent patterns of pathway disruption (Cooper et al., 2013). The concept of oncogene addiction has emerged as a fundamental principle underlying targeted therapeutic approaches, with driver mutations in genes such as EGFR, ALK, and ROS1 providing therapeutic opportunities that have transformed outcomes for molecularly defined patient subgroups. The identification of tumour suppressor gene alterations, particularly in TP53 and RB1, has enhanced understanding of the mechanisms underlying genomic instability and treatment resistance.

The biological behaviour of lung carcinomas is characterised by aggressive growth kinetics, early metastatic dissemination, and remarkable adaptability that enables resistance to therapeutic interventions (Hirsch et al., 2017). The heterogeneity observed both between different tumours and within individual malignancies poses significant challenges for treatment selection and resistance prevention. The integration of immunotherapy into treatment paradigms has provided new therapeutic opportunities, particularly for patients with high mutational burden tumours, whilst highlighting the importance of the immune microenvironment in disease progression and treatment response.

Contemporary classification systems, particularly the 2015 WHO classification, have provided a more nuanced understanding of lung carcinoma biology and its clinical implications (Travis et al., 2015). The recognition that different histological subtypes

and growth patterns carry distinct prognostic significance has improved risk stratification and treatment planning. The integration of molecular markers into diagnostic algorithms has enabled more precise tumour characterisation and personalised treatment approaches.

Despite remarkable advances in understanding disease biology and developing targeted therapies, the overall prognosis of lung carcinomas remains sobering, with five-year survival rates below 20% across all stages (Siegel et al., 2023). This poor prognosis reflects the advanced stage at presentation in the majority of patients, the aggressive nature of these malignancies, and the limited efficacy of available treatments for many patient subgroups. The development of resistance to targeted therapies and the complexity of tumour evolution continue to pose significant clinical challenges.

Future research directions must address the fundamental challenges of tumour heterogeneity, treatment resistance, and early detection whilst building upon the substantial progress achieved in molecular characterisation and targeted therapy development. The continued advancement of genomic technologies, the development of liquid biopsy approaches, and the integration of artificial intelligence into clinical practice offer promising avenues for improving patient care. The expansion of immunotherapy strategies and the development of novel combination approaches may provide additional therapeutic opportunities for patients who do not benefit from current treatment modalities.

The ultimate goal of transforming lung carcinomas from universally fatal diseases to manageable chronic conditions requires sustained commitment to research, international collaboration, and the translation of scientific discoveries into accessible clinical care. The continued emphasis on prevention strategies, early detection programmes, and comprehensive care models that address the full spectrum of patient needs will be essential for achieving meaningful improvements in patient outcomes.

In conclusion, whilst significant challenges remain in the management of pulmonary carcinomas, the substantial progress achieved in understanding disease biology and developing effective treatments provides reason for cautious optimism. The continued evolution of precision medicine approaches, combined with advances in prevention and early detection strategies, offers hope for substantially improving outcomes for the millions of patients worldwide affected by these devastating malignancies.

7. References

Adler, I. (1912). Primary malignant growths of the lungs and bronchi: A pathological and clinical study. Longmans, Green and Company.

Asamura, H., Chansky, K., Crowley, J., Goldstraw, P., Rusch, V. W., Vansteenkiste, J. F., Watanabe, H., Wu, Y. L., Zielinski, M., Rami-Porta, R., & International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. (2015). The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology*, 10(12), 1675-1684.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68(6), 394-424.

Cagle, P. T., & Chirieac, L. R. (2012). Advances in treatment of lung cancer with targeted therapy. *Archives of Pathology & Laboratory Medicine*, 136(5), 504-509.

Chansky, K., Detterbeck, F. C., Nicholson, A. G., Rusch, V. W., Vallières, E., Groome, P., Kennedy, C., Krasnik, M., Peake, M., Shemanski, L., Bolejack, V., Crowley, J. J., Asamura, H., Rami-Porta, R., & IASLC Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions. (2017). The IASLC Lung Cancer Staging Project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM Classification of Lung Cancer. *Journal of Thoracic Oncology*, 12(7), 1109-1121.

Cooper, W. A., Lam, D. C., O'Toole, S. A., & Minna, J. D. (2013). Molecular biology of lung cancer. *Journal of Thoracic Disease*, 5(Suppl 5), S479-S490.

de Groot, P. M., Wu, C. C., Carter, B. W., & Munden, R. F. (2018). The epidemiology of lung cancer. *Translational Lung Cancer Research*, 7(3), 220-233.

Doll, R., & Hill, A. B. (1950). Smoking and carcinoma of the lung: preliminary report. *British Medical Journal*, 2(4682), 739-748.

Ettinger, D. S., Wood, D. E., Aisner, D. L., Akerley, W., Bauman, J., Chirieac, L. R., D'Amico, T. A., DeCamp, M. M., Dilling, T. J., Dobelbower, M., Doebele, R. C., Govindan, R., Gubens, M. A., Hennon, M., Horn, L., Komaki, R., Lackner, R. P., Lanuti, M., Leal, T. A.,

... Gregory, K. M. (2017). Non-small cell lung cancer, version 5.2017, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, 15(4), 504-535.

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D., & Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International Journal of Cancer*, 136(5), E359-E386.

Goldstraw, P., Chansky, K., Crowley, J., Rami-Porta, R., Asamura, H., Eberhardt, W. E., Nicholson, A. G., Groome, P., Mitchell, A., Bolejack, V., Ball, D., Beer, D. G., Beyruti, R., Detterbeck, F., Edwards, J., Galateau-Salle, F., Giroux, D., Gleeson, F., Huang, J., ... Yokoi, K. (2016). 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. *Journal of Thoracic Oncology*, 11(1), 39-51.

Hasse, C. (1847). Über primäre Lungenkrebse. *Virchows Archiv für Pathologische Anatomie und Physiologie*, 1(1), 83-96.

Herbst, R. S., Morgensztern, D., & Boshoff, C. (2018). The biology and management of non-small cell lung cancer. *Nature*, 553(7689), 446-454.

Hirsch, F. R., Scagliotti, G. V., Mulshine, J. L., Kwon, R., Curran Jr, W. J., Wu, Y. L., & Paz-Ares, L. (2017). Lung cancer: current therapies and new targeted treatments. *The Lancet*, 389(10066), 299-311.

International Agency for Research on Cancer. (2012). GLOBOCAN 2012: Estimated cancer incidence, mortality and prevalence worldwide in 2012. IARC Press.

Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. *CA: A Cancer Journal for Clinicians*, 61(2), 69-90.

Kris, M. G., Johnson, B. E., Berry, L. D., Kwiatkowski, D. J., Iafrate, A. J., Wistuba, I. I., Varella-Garcia, M., Franklin, W. A., Aronson, S. L., Su, P. F., Shyr, Y., Camidge, D. R., Sequist, L. V., Glisson, B. S., Khuri, F. R., Garon, E. B., Pao, W., Rudin, C., Schiller, J., ... Bunn Jr, P. A. (2014). Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA*, 311(19), 1998-2006.

Lam, W. K., White, N. W., & Chan-Yeung, M. M. (2004). Lung cancer epidemiology and risk factors in Asia and Africa. *The International Journal of Tuberculosis and Lung Disease*, 8(9), 1045-1057.

Larsen, J. E., & Minna, J. D. (2011). Molecular biology of lung cancer: clinical implications. *Clinics in Chest Medicine*, 32(4), 703-740.

Lynch, T. J., Bell, D. W., Sordella, R., Gurubhagavatula, S., Okimoto, R. A., Brannigan, B. W., Harris, P. L., Haserlat, S. M., Supko, J. G., Haluska, F. G., Louis, D. N., Christiani, D. C., Settleman, J., & Haber, D. A. (2004). Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *New England Journal of Medicine*, 350(21), 2129-2139.

Mok, T. S., Wu, Y. L., Thongprasert, S., Yang, C. H., Chu, D. T., Saijo, N., Sunpaweravong, P., Han, B., Margono, B., Ichinose, Y., Nishiwaki, Y., Ohe, Y., Yang, J. J., Chewaskulyong, B., Jiang, H., Duffield, E. L., Watkins, C. L., Armour, A. A., & Fukuoka, M. (2009). Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *New England Journal of Medicine*, 361(10), 947-957.

Naruke, T., Goya, T., Tsuchiya, R., & Suemasu, K. (1988). Prognosis and survival in resected lung carcinoma based on the new international staging system. *The Journal of Thoracic and Cardiovascular Surgery*, 96(3), 440-447.

National Lung Screening Trial Research Team. (2011). Reduced lung-cancer mortality with low-dose computed tomographic screening. *New England Journal of Medicine*, 365(5), 395-409.

Paez, J. G., Jänne, P. A., Lee, J. C., Tracy, S., Greulich, H., Gabriel, S., Herman, P., Kaye, F. J., Lindeman, N., Boggon, T. J., Naoki, K., Sasaki, H., Fujii, Y., Eck, M. J., Sellers, W. R., Johnson, B. E., & Meyerson, M. (2004). EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science*, 304(5676), 1497-1500.

Pao, W., & Chmielecki, J. (2010). Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. *Nature Reviews Cancer*, 10(11), 760-774.

Planchard, D., Popat, S., Kerr, K., Novello, S., Smit, E. F., Faivre-Finn, C., Mok, T. S., Reck, M., Van Schil, P. E., Hellmann, M. D., & Peters, S. (2018). Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 29(Supplement 4), iv192-iv237.

Rami-Porta, R., Nishimura, K. K., Giroux, D. J., Chansky, K., Crowley, J., Detterbeck, F. C., Donington, J., Kernstine, K., Nicholson, A. G., Ruffini, E., Tsuboi, M., Yatabe, Y., Groome, P., Kennedy, C., Krasnik, M., Peake, M., Shemanski, L., Bolejack, V., Lyons, G., ... Asamura, H. (2024). The International Association for the Study of Lung Cancer lung

cancer staging project: proposals for revision of the TNM stage groups in the forthcoming (ninth) edition of the TNM classification for lung cancer. *Journal of Thoracic Oncology*, 19(5), 786-800.

Rosell, R., Carcereny, E., Gervais, R., Vergnenegre, A., Massuti, B., Felip, E., Palmero, R., Garcia-Gomez, R., Pallares, C., Sanchez, J. M., Porta, R., Cobo, M., Garrido, P., Longo, F., Moran, T., Insa, A., De Marinis, F., Corre, R., Bover, I., ... Paz-Ares, L. (2012). Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *The Lancet Oncology*, 13(3), 239-246.

Saito, M., Suzuki, H., Kono, K., Takenoshita, S., & Kohno, T. (2018). Treatment of lung adenocarcinoma by molecular-targeted therapy and immunotherapy. *Surgery Today*, 48(1), 1-8.

Schofield, P., Ball, D., Smith, J. G., Borland, R., O'Brien, P., Davis, S., Olver, I., Ryan, G., & Joseph, D. (2004). Optimism and survival in lung carcinoma patients. *Cancer*, 100(6), 1276-1282.

Schwartz, A. G., & Cote, M. L. (2015). Epidemiology of lung cancer. In *Lung cancer and personalized medicine* (pp. 21-41). Springer.

Shaw, A. T., Kim, D. W., Nakagawa, K., Seto, T., Crinó, L., Ahn, M. J., De Pas, T., Besse, B., Solomon, B. J., Blackhall, F., Wu, Y. L., Thomas, M., O'Byrne, K. J., Moro-Sibilot, D., Camidge, D. R., Mok, T., Hirsh, V., Riely, G. J., Iyer, S., ... Engelman, J. A. (2013). Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *New England Journal of Medicine*, 368(25), 2385-2394.

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*, 73(1), 233-254.

Soda, M., Choi, Y. L., Enomoto, M., Takada, S., Yamashita, Y., Ishikawa, S., Fujiwara, S., Watanabe, H., Kurashina, K., Hatanaka, H., Bando, M., Ohno, S., Ishikawa, Y., Aburatani, H., Niki, T., Sohara, Y., Sugiyama, Y., & Mano, H. (2007). Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature*, 448(7153), 561-566.

Spira, A., Halmos, B., & Powell, C. A. (2016). Update in lung cancer 2015. *American Journal of Respiratory and Critical Care Medicine*, 194(6), 661-671.

The Cancer Genome Atlas Research Network. (2012). Comprehensive genomic characterization of squamous cell lung cancers. *Nature*, 489(7417), 519-525.

The Cancer Genome Atlas Research Network. (2014). Comprehensive molecular profiling of lung adenocarcinoma. *Nature*, 511(7511), 543-550.

Travis, W. D., Brambilla, E., Nicholson, A. G., Yatabe, Y., Austin, J. H., Beasley, M. B., Chirieac, L. R., Dacic, S., Duhig, E., Flieder, D. B., Geisinger, K., Hirsch, F. R., Ishikawa, Y., Kerr, K. M., Noguchi, M., Pelosi, G., Powell, C. A., Tsao, M. S., Wistuba, I., & WHO Panel. (2015). The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *Journal of Thoracic Oncology*, 10(9), 1243-1260.

Vogelstein, B., Papadopoulos, N., Velculescu, V. E., Zhou, S., Diaz Jr, L. A., & Kinzler, K. W. (2013). Cancer genome landscapes. *Science*, 339(6127), 1546-1558.

Weinstein, I. B. (2002). Cancer: addiction to oncogenes—the Achilles heal of cancer. *Science*, 297(5578), 63-64.

Woodard, G. A., Jones, K. D., & Jablons, D. M. (2016). Lung cancer staging and prognosis. In *Lung cancer: treatment and research* (pp. 47-75). Springer.

World Health Organization. (2023). Lung cancer fact sheet. Retrieved from https://www.who.int/news-room/fact-sheets/detail/lung-cancer

Wynder, E. L., & Graham, E. A. (1950). Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma: a study of 684 proved cases. *Journal of the American Medical Association*, 143(4), 329-336.

Yang, P., Allen, M. S., Aubry, M. C., Wampfler, J. A., Marks, R. S., Edell, E. S., Thibodeau, S., Adjei, A. A., Jett, J., & Cassivi, S. D. (2005). Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest*, 128(1), 452-462.

Yatabe, Y., Borczuk, A. C., & Powell, C. A. (2011). Do all lung adenocarcinomas follow a stepwise progression? *Lung Cancer*, 74(1), 7-11.

Yu, H. A., Arcila, M. E., Rekhtman, N., Sima, C. S., Zakowski, M. F., Pao, W., Kris, M. G., Miller, V. A., Ladanyi, M., & Riely, G. J. (2013). Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clinical Cancer Research*, 19(8), 2240-2247.

Zheng, M. (2016). Classification and pathology of lung cancer. *Surgical Oncology Clinics of North America*, 25(3), 447-468.