ARC Journal of Cancer Science
Volume 11, Issue 1, 2026, PP 1-8
ISSN (Online): 2455-6009
DOI: https://doi.org/10.20431/2455-6009.1101001
www.arcjournals.org

Role of Heterogeneity in Lung Cancer and its Implications for Personalized Oncology

Mawanda Anatoli[1, 2, 3*], Kakuba Frank[1, 2], Boaz Mwesigwa[1, 2], Betty A Kasiimo[4], Waiswa Ali[3], Musoke Sharrif[1], Alele David[1], Kalungi Sam[1, 2]

[1]*Department of Pathology, Mulago National Referral Hospital, Kampala, Uganda*

[2]*Department of Pathology, King Ceasor University, Kampala, Uganda*

[3]*Department of Pathology, Uganda Cancer Institute, Kampala, Uganda*

[4]*Department of Pathology, Busitema University, Mbale, Uganda*

Received: 22 December 2025 Accepted: 05 January 2026 Published: 09 February 2026

Corresponding Author:** ***Mawanda Anatoli, *Department of Pathology, Mulago National Referral Hospital, Kampala, Uganda*

Abstract

Tumor heterogeneity represents a major biological barrier to effective cancer treatment, arising from complex and dynamic interactions between genetic alterations, epigenetic regulation, and the tumor microenvironment. In lung cancer, which includes non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), this diversity is expressed across spatial and temporal dimensions, driving clonal evolution, therapeutic resistance, and disease progression. This review consolidates current evidence on the molecular and non-molecular mechanisms that generate heterogeneity in lung cancer, with particular emphasis on genomic instability, somatic mutation patterns, epigenetic plasticity, and immune interactions within the tumor microenvironment. We discuss how heterogeneity manifests differently in NSCLC and SCLC, highlighting subtype-specific cell states, immune escape mechanisms, and lineage plasticity. The clinical implications for personalized oncology are substantial, influencing both targeted therapy and immunotherapy outcomes. Despite advances in multi-omics profiling, challenges remain in accurately capturing heterogeneity and translating these insights into durable clinical benefit. Emerging approaches including single-cell technologies, spatial profiling, and adaptive therapeutic strategies offer promising avenues to address these challenges and improve individualized treatment outcomes for patients with lung cancer.

Keywords: *Tumor heterogeneity, Lung cancer, Therapy resistance, Personalized oncology*

1. INTRODUCTION

Lung cancer remains the deadliest malignancy worldwide, causing approximately 1.8 million deaths each year, according to recent global estimates (1). The disease is broadly classified into non-small cell lung cancer (NSCLC), which comprises approximately 85% of cases, and small cell lung cancer (SCLC), a neuroendocrine malignancy characterized by rapid growth and early dissemination (2,3). Although recent advances in targeted therapies and immune checkpoint inhibitors have improved outcomes for selected patient subgroups, long-term survival remains limited for most individuals (4). A central biological factor underlying these poor outcomes is tumor heterogeneity—the coexistence of multiple, biologically distinct cancer cell populations within a single tumor or across different tumor sites in the same patient (5). Historically, lung cancer was treated as a relatively uniform disease entity; however, the advent of next-generation sequencing and single-cell technologies has revealed extensive molecular and phenotypic diversity (6, 7). In NSCLC, driver alterations such as EGFR or KRAS mutations may be unevenly distributed across tumor regions, influencing sensitivity to targeted therapies (8). In SCLC, marked cellular plasticity enables transitions between neuroendocrine and non-neuroendocrine states, facilitating rapid adaptation to cytotoxic treatment (9, 10).

Personalized oncology aims to align therapeutic strategies with the molecular characteristics of individual tumors. However, the dynamic and heterogeneous nature of lung cancer complicates accurate tumor profiling and contributes to both intrinsic and acquired resistance. This review examines the mechanisms and manifestations of tumor heterogeneity in lung cancer and explores

their implications for diagnosis, therapeutic decision-making, and emerging precision oncology strategies.

2. Mechanisms Of Tumor Heterogeneity In Lung Cancer

Tumor heterogeneity in lung cancer arises from a convergence of genetic alterations, epigenetic regulation, and non-genetic influences exerted by the tumor microenvironment. Together, these processes generate diverse cellular populations that evolve over time and adapt to therapeutic pressure.

2.1. Genetic Mechanisms

Persistent genomic instability plays a central role in shaping heterogeneity by promoting ongoing diversification of cancer cell populations (11). Chromosomal instability leads to widespread aneuploidy, copy number alterations, and structu ral rearrangements, phenomena observed in a large proportion of lung tumors (12). In NSCLC, elevated chromosomal instability has been associated with unfavorable clinical outcomes, reflecting its role in accelerating clonal evolution and disease progression. (13). Somatic mutations accumulate due to environmental exposures like smoking, resulting in high tumor mutational burden (14). Early clonal events frequently involve genes such as TP53, EGFR, or KRAS, whereas later-arising subclonal mutations contri bute to branching evolutionary trajectories (15). Mutant allele-specific imbalance further amplifies heteroge neity by increasing the dosage of oncogenic alleles through mechanisms such as loss of heterozygosity or copy-neutral alterations (16). In EGFR-mutant NSCLC, this phenomenon has been linked to adverse prognosis (17, 18). In SCLC, genetic heterogeneity is shaped by recurr ent alterations including MYC amplification and concurrent loss of TP53 and RB1, with additional subclonal changes emerging during metastatic dissemination (19).

2.2. Epigenetic Mechanisms

Beyond genetic alterations, epigenetic dysregulation introduces substantial non-genetic heterogeneity in lung cancer. Aberrant DNA methylation patterns can silence tumor suppressor genes or activate oncogenic pathways without altering the underlying DNA sequence. Regulatory non-coding RNAs, including microRNAs, further modulate gene expression programs associated with drug response and disease outcome (20, 21). In SCLC, epigenetic regulators like EZH2 suppress MHC class I expression via H3K27me3 marks, promoting immune evasion in neuroen docrine states (22, 23). Enzymes involved in chromatin remodeling, including Lysine-specific demethylase 1 (LSD1) and histone deacetylases, mai ntain cellular plasticity by enabling transitio ns between distinct transcriptional programs (24). This epigenetic flexibility allows tumor cells to dynamic ally shift phenotypes in response to environmen tal and therapeuticcues.

2.3. Microenvironmental and Non-Genetic Mechanisms

The tumor microenvironment imposes selective pressures that further expand heterogeneity by favoring the survival of specific cellular clones. Variations in oxygen tension, nutrient availability, acidity, and immune cell infiltration create spatially distinct ecological niches within tumors. Cancer stem-like cells contribute disproportionately to this diversity by generating hierarchically organi zed progeny with differing proliferative and drug-resistant capacities (25). In NSCLC, stem-like populations expressing markers such as CD133 or ALDH have been linked to resistance to chemotherapy (26). In SCLC, transcriptional regulators including ASCL1, NEUROD1, POU2 F3, and YAP1 define discrete cell states that coexist within tumors (27). Signaling path ways such as Notch and MYC-driven programs orches trate transitions between these states, reinforcing phenotypic plasticity and therapeutic escape (9).

3. Types Of Tumor Heterogeneity In Lung Cancer

Tumor heterogeneity in lung cancer can be conceptualized across multiple dimensions, including diversity within individual tumors, differences between lesions, spatial variation across tumor regions, and dynamic changes over time.

3.1. Intratumoral Heterogeneity (ITH)

Within a single lung tumor, multiple cellular populations often coexist, differing in genetic alterations, epigenetic states, phenotypes, and functional behavior an observation collectively described as intratumoral heterogeneity (Fig 1). In NSCLC, multi-region sequencing has revealed that up to 70% of somatic mutations can be subc lonal, with different regions harboring distinct driver mutations, such as alterations in EGFR, KRAS, or MET (28). In SCLC, ITH is characterized by the presence of co-existing neuroendocri ne (ASCL1/NEUROD1-high) and non-neuroend ocrine (YAP1/POU2F3-high) subt ypes within the same tumor, promoting rapid adaptation and contributing to chemoresistance (29).

3.2. Intertumoral Heterogeneity

Intertumoral heterogeneity describes the differences between tumors within the same

patient, particularly between primary and metastatic lesions or among multiple primary lung cancers (MPLC) (Fig 1). Metastases often arise from distinct subclones, leading to divergent molecular profiles. For example, lymph node metastases may lose EGFR mutations present in the primary NSCLC lesion, while brain metastases frequently acquire new alterations, such as PIK3CA or CDK4/6 amplifications (30).

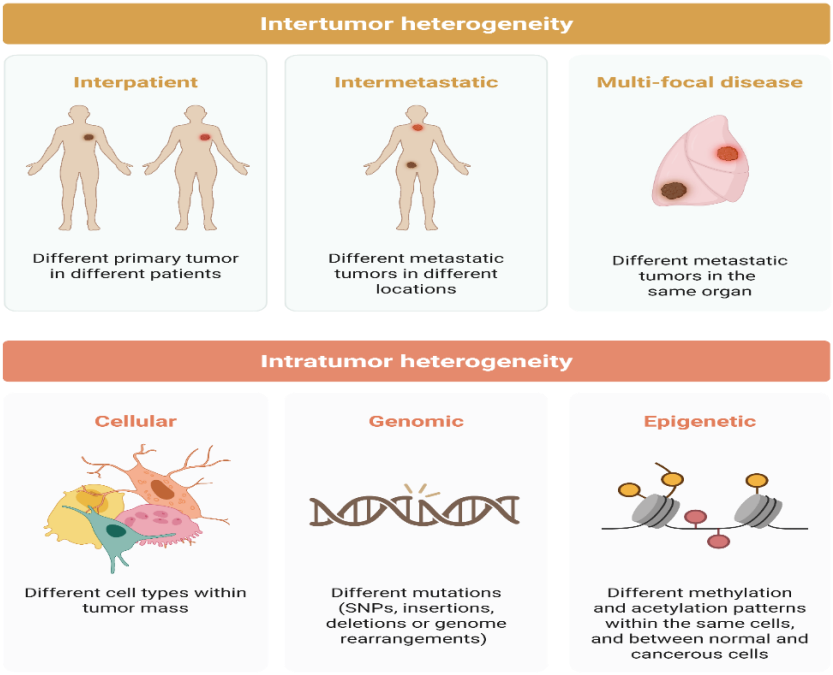

Figure 1. *Schematic representation of tumor heterogeneity. Created in BioRender. https://BioRender.com/64dckm2*

3.3. Spatial Heterogeneity

Spatial heterogeneity reflects geographic variation within a tumor or across lesions, influenced by gradients of hypoxia, pH, nutrient availability, and immune infiltration. In NSCLC, the tumor core is often hypoxic and immunosuppressive, referred to as "cold," while the invasive margin displays a higher density of CD8+ T cells, termed "hot."(31,32). Advances in radiomics and spatial transcriptomics have revealed distinct ecological habitats such as immune-inflamed, metabolic, or proliferative zones that correlate with prognosis and response to immunotherapy (33).

3.4. Temporal Heterogeneity

Temporal heterogeneity arises over time, particularly under therapeutic selection pressure. This phenomenon is most pronounced in EGFR-mutant NSCLC, which can undergo histological transformation to SCLC in approximately 5–15% of resistant cases (34,35). Additionally, relapsed SCLC often exhibits subtype switching (e.g., from ASCL1-high to YAP1-high). Longitudinal liquid biopsies demonstrate dynamic shifts in clonal architecture, with resistant subclones emerging following targeted therapy or immunotherapy (36–38).

4. Implications For Personalized Oncology

4.1. Therapy Resistance

Tumor heterogeneity is the primary driver of both intrinsic and acquired resistance in lung cancer (39). In EGFR-mutant non-small cell lung cancer (NSCLC), subclonal pretreatment populations harboring mutations such as T790M, MET amplification, or C797S emerge as dominant clones under the pressure of tyrosine kinase inhibitors (TKIs) (18). Additionally, histological transformation to small cell lung cancer (SCLC) occurs in 5–15% of cases. In KRAS-mutant tumors, co-occurring alterations in STK11 and KEAP1—often present as subclonal populations—confer primary resistance to both immunotherapy and chemotherapy (18, 40). The extreme plasticity of SCLC allows for rapid switching between neuroendocrine and non-neuroendocrine states (e.g., ASCL1-high to YAP1/POU2F3-high), rendering platinum-etoposide ineffective within a few months (41).

4.2. Targeted Therapies

The presence of heterogeneity necessitates multi-clone targeting strategies. Single-agent EGFR

TKIs are often ineffective when MET or HER2 bypass tracks are subclonal (42, 43). To preempt resistance, combinations such as upfront osimertinib with savolitinib or amivantamab are currently being explored. In ALK-rearranged NSCLC, sequential treatment with lorlatinib is more effective at delaying resistance compared to crizotinib, as it targets multiple known and unknown compound mutations simultaneously (44–46). The case of MET exon 14 skipping in NSCLC illustrates the impact of spatial heterogeneity: high-level focal amplification predicts durable responses to capmatinib or tepotinib, while cases with low-level amplification or polysomy tend to relapse early.

4.3. Immunotherapy

High levels of intratumoral heterogeneity are directly correlated with the failure of immunotherapy. Tumors characterized by dominant clonal neoantigens and a low subclonal burden tend to respond better to PD-1 blockade, while heterogeneous neoantigen landscapes often lead to immune editing and exhaustion (47). Priming strategies that combine EZH2 and LSD1 inhibitors with checkpoint blockade are currently entering clinical trials to reverse this resistance (48).

5. Challenges And Future Directions

5.1. Challenges

Significant challenges persist in standardizing heterogeneity assessment in cancer. Single biopsies often underestimate subclonal diversity, while liquid biopsies face limitations in spatial resolution (49). Additionally, the integration of radiomics and multi-omics data is hindered by reproducibility issues across different scanners and platforms (50,51). Therapeutic resistance, particularly driven by plasticity—such as subtype switching in small cell lung cancer (SCLC) and the transformation from non-small cell lung cancer (NSCLC) to SCLC—continues to restrict durable responses to targeted therapies and immunotherapy (52).

5.2. Future Directions

Future directions in cancer treatment include the routine adoption of single-cell sequencing (Fig 2) and spatial transcriptomics to effectively map tumor ecosystems (Fig 3). Additionally, AI-enhanced radiomics can facilitate non-invasive heterogeneity scoring and guide biopsy procedures (53,54). Serial monitoring of circulating tumor DNA (ctDNA) will enable real-time tracking of clonal evolution (55). Combination strategies that target plasticity, such as the use of EZH2 and LSD1 inhibitors, aim to restore antigen presentation and address common trunk alterations, showing considerable promise (56). Furthermore, adaptive clinical trials that incorporate dynamic treatment switching based on evolving tumor profiles, along with personalized neoantigen vaccines and next-generation CAR-T and NK cell therapies, provide hope for overcoming the barriers posed by tumor heterogeneity in the pursuit of a cure (56).

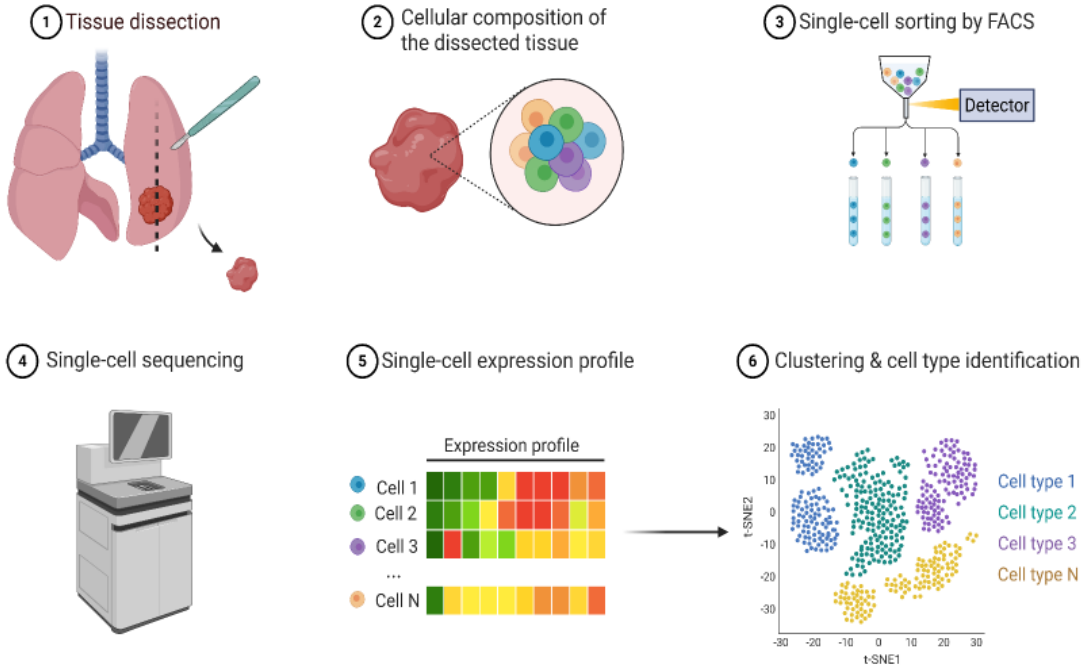

Figure 2. *Single cell sequencing work flow in lung cancer. Created in BioRender. https://BioRender.com/uorexws*

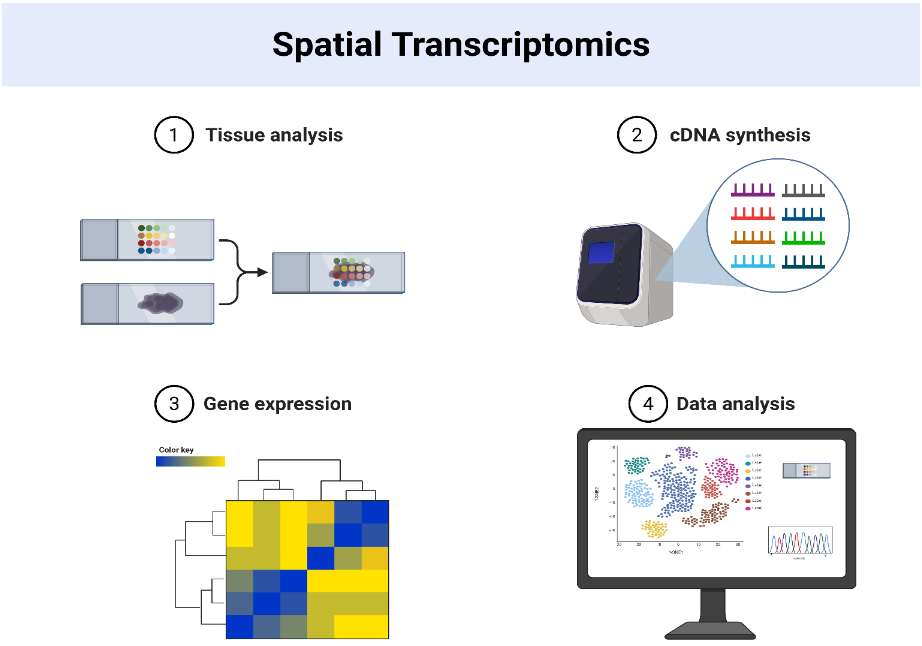

Figure 3. *A thin tissue slice is placed on a barcoded slide → mRNA from each cell sticks to the nearest barcode (1) → mRNA is turned into DNA (2) → sequencing reads the gene + its exact location barcode (3) → computer draws a color-coded map showing which genes are active (4). Created in BioRender.*

https://BioRender.com/mby84ai.

6. Conclusion

Tumor heterogeneity remains a significant obstacle to curing lung cancer. However, by embracing multi-modal profiling, adaptive therapies, agents that target plasticity, and individualized immunotherapy, personalized oncology has the potential to transform this challenge into an actionable roadmap. This approach can ultimately lead to durable responses and improved survival rates for patients

Abbreviations

ASCL1	Achaete-Scute Family BHLH Transcription Factor 1
ctDNA	Circulating Tumor DNA
EZH2	Enhancer of Zeste Homolog 2
ITH	Intratumoral Heterogeneity
LSD1	Major Histocompatibility Complex Class I
MHC-I	Major Histocompatibility Complex Class I
MPLC	Multiple Primary Lung Cancer
NEUROD1	Neuronal Differentiation 1
NSCLC	Non-Small Cell Lung Cancer
PD-1/PD-L1	Programmed Death-1/Programmed Death-Ligand 1
POU2F3	POU Class 2 Homeobox 3
SCLC	Small Cell Lung Cancer
TKI	Tyrosine Kinase Inhibitor
YAP1	Yes-Associated Protein 1

Ethics Approval And Consent To Participate

Not applicable.

Consent For Publication

The authors reviewed the results and approved the final version of the manuscript.

Conflict Of Interest Statement

The authors declare that there are no conflicts of interest related to this study.

Funding Information

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability

No datasets were generated or analyzed during The Current Study.

Author Contributions

M.A and **K.F** Conceptualization**, B.M**; methodology, writing, original draft preparation,

K.F., M.A., B.AK. M.S. and A.D.; review and editing, **K.S**- supervision, all authors have read and agreed to the published version of the manuscript.

REFERENCES

[1] Smolarz, B. *et al.* Lung Cancer—Epidemiology, Pathogenesis, Treatment and Molecular Aspect (Review of Literature). *International Journal of Molecular Sciences* vol. 26 Preprint at https://doi.org/10.3390/ijms26052049 (2025).

[2] Hernández de Córdoba, I. *et al.* Transformation to Neuroendocrine Phenotype in Non-Small-Cell Lung Carcinoma: A Literature Review. *International Journal of Molecular Sciences* vol. 26 Preprint at https://doi.org/10.3390/ijms26115096 (2025).

[3] Zhai, X. *et al.* Current and future therapies for small cell lung carcinoma. *Journal of Hematology and Oncology* vol. 18 Preprint at https://doi.org/10.1186/s13045-025-01690-6 (2025).

[4] Vicidomini, G. Current Challenges and Future Advances in Lung Cancer: Genetics, Instrumetal Diagnosis and Treatment. *Cancers* vol. 15 Preprint at https://doi.org/10.3390/cancers15143710 (2023).

[5] Oh, M. S. *et al.* Tumor Heterogeneity and the Immune Response in Non-Small Cell Lung Cancer: Emerging Insights and Implications for Immunotherapy. *Cancers* vol. 17 Preprint at https://doi.org/10.3390/cancers17061027 (2025).

[6] Huang, D. *et al.* Molecular Subtypes and Targeted Therapeutic Strategies in Small Cell Lung Cancer: Advances, Challenges, and Future Perspectives. Molecules vol. 30 Preprint at https://doi.org/10.3390/molecules30081731 (2025).

[7] Tagore, S. *et al.* Single-cell and spatial genomic landscape of non-small cell lung cancer brain metastases. *Nat Med* **31**, 1351–1363 (2025).

[8] Al Bakir, M. *et al.* Clonal driver neoantigen loss under EGFR TKI and immune selection pressures. *Nature* **639**, 1052–1059 (2025).

[9] Simpson, K. L., Rothwell, D. G., Blackhall, F. & Dive, C. Challenges of small cell lung cancer heterogeneity and phenotypic plasticity. *Nat Rev Cancer* **25**, 447–462 (2025).

[10] Duronio, G. N. & Sage, J. Tumor Heterogeneity and Plasticity in Small Cell Lung Cancer. *Lung Cancer: Targets and Therapy* vol. 16 125–138 Preprint at https://doi.org/10.2147/LCTT.S511789 (2025).

[11] Baumann, A. A., Buribayev, Z., Wolkenhauer, O., Salybekov, A. A. & Wolfien, M. Epigenomic Echoes—Decoding Genomic and Epigenetic Instability to Distinguish Lung Cancer Types and Predict Relapse. *Epigenomes* vol. 9 Preprint at https://doi.org/10.3390/epigenomes9010005 (2025).

[12] Zhang, C., Wu, B. Z. & Thu, K. L. Targeting Kinesins for Therapeutic Exploitation of Chromosomal Instability in Lung Cancer. *Cancers* vol. 17 Preprint at https://doi.org/10.3390/cancers17040685 (2025).

[13] Chen, X., Agustinus, A. S., Li, J., DiBona, M. & Bakhoum, S. F. Chromosomal instability as a driver of cancer progression. *Nat Rev Genet* **26**, 31–46 (2025).

[14] Mitrakas, A. G., Kakouratos, C., Lamprou, I., Xanthopoulou, E. & Koukourakis, M. I. Oncogenic Mutations and the Tumor Microenvironment: Drivers of Non-Small Cell Lung Cancer Progression. Cancers vol. 17 Preprint at https://doi.org/10.3390/cancers17050853 (2025)

[15] Nicoś, M. & Krawczyk, P. Genetic Clonality as the Hallmark Driving Evolution of Non-Small Cell Lung Cancer. Cancers vol. 14 Preprint at https://doi.org/10.3390/cancers14071813 (2022).

[16] Yu, C. C. *et al.* Mutant allele specific imbalance in oncogenes with copy number alterations: Occurrence, mechanisms, and potential clinical implications. *Cancer Lett* **384**, 86–93 (2017).

[17] Laface, C. *et al.* The Resistance to EGFR-TKIs in Non-Small Cell Lung Cancer: From Molecular Mechanisms to Clinical Application of New Therapeutic Strategies. *Pharmaceutics* vol. 15 Preprint at https://doi.org/10.3390/pharmaceutics15061604 (2023).

[18] Koulouris, A., Tsagkaris, C., Corriero, A. C., Metro, G. & Mountzios, G. Resistance to TKIs in EGFR-Mutated Non-Small Cell Lung Cancer: From Mechanisms to New Therapeutic Strategies. *Cancers* vol. 14 Preprint at https://doi.org/10.3390/cancers14143337 (2022).

[19] Keogh, A., Finn, S. & Radonic, T. Emerging Biomarkers and the Changing Landscape of Small Cell Lung Cancer. *Cancers* vol. 14 Preprint at https://doi.org/10.3390/cancers14153772 (2022).

[20] Sulewska, A. *et al.* A Systematic Review of Progress toward Unlocking the Power of Epigenetics in NSCLC: Latest Updates and Perspectives. *Cells* vol. 12 Preprint at https://doi.org/10.3390/cells12060905 (2023).

[21] Szejniuk, W. M., Robles, A. I., McCulloch, T., Falkmer, U. G. I. & Røe, O. D. Epigenetic predictive biomarkers for response or outcome to platinum-based chemotherapy in non-small cell lung cancer, current state-of-art. *Pharmacogenomics J* **19**, 5–14 (2019).

[22] Kirk, N. A., Kim, K. B. & Park, K. S. Effect of chromatin modifiers on the plasticity and immunogenicity of small-cell lung cancer. *Experimental and Molecular Medicine* vol. 54 2118–2127 Preprint at https://doi.org/10.1038/s12276-022-00905-x (2022).

[23] Mortezaee, K. EZH2 regulatory roles in cancer immunity and immunotherapy. *Pathol Res Pract* **270**, 155992 (2025).

[24] Fabrizio, F. P. Unlocking Lung Cancer Cell Dormancy: An Epigenetic Perspective.

International Journal of Molecular Sciences vol. 26 Preprint at https://doi.org/10.3390/ijms2622 10997 (2025).

[25] Hass, R., von der Ohe, J. & Ungefroren, H. Impact of the tumor microenvironment on tumor heterogeneity and consequences for cancer cell plasticity and stemness. *Cancers* vol. 12 1–20 Preprint at https://doi.org/10.3390/cancers1212 3716 (2020).

[26] Roudi, R., Korourian, A., Shariftabrizi, A. & Madjd, Z. Differential Expression of Cancer Stem Cell Markers ALDH1 and CD133 in Various Lung Cancer Subtypes. *Cancer Invest* **33**, 294–302 (2015).

[27] Baine, M. K. *et al.* SCLC Subtypes Defined by ASCL1, NEUROD1, POU2F3, and YAP1: A Comprehensive Immunohistochemical and Histopathologic Characterization. *Journal of Thoracic Oncology* **15**, 1823–1835 (2020).

[28] Zhang, Y. *et al.* Intratumor heterogeneity comparison among different subtypes of non-small-cell lung cancer through multi-region tissue and matched ctDNA sequencing. *Mol Cancer* **18**, 7 (2019).

[29] Megyesfalvi, Z. *et al.* Clinical insights into small cell lung cancer: Tumor heterogeneity, diagnosis, therapy, and future directions. *CA Cancer J Clin* **73**, 620–652 (2023).

[30] Shen, E. *et al.* A Need for More Molecular Profiling in Brain Metastases. *Frontiers in Oncology* vol. 11 Preprint at https://doi.org/10.3 389/fonc.2021.785064 (2022).

[31] Chen, H. *et al.* Integrative spatial analysis reveals tumor heterogeneity and immune colony niche related to clinical outcomes in small cell lung cancer. *Cancer Cell* **43**, 519-536.e5 (2025).

[32] Rahal, Z., El Darzi, R., Moghaddam, S. J., Cascone, T. & Kadara, H. Tumour and microenvironment crosstalk in NSCLC progression and response to therapy. *Nat Rev Clin Oncol* **22**, 463–482 (2025).

[33] Chen, H., Yang, H., Guo, L. & Sun, Q. The Role of Immune Checkpoint Inhibitors in Cancer Therapy: Mechanism and Therapeutic Advances. *MedComm (Beijing)* **6**, e70412 (2025).

[34] Megyesfalvi, Z. *et al.* Clinical insights into small cell lung cancer: Tumor heterogeneity, diagnosis, therapy, and future directions. *CA Cancer J Clin* **73**, 620–652 (2023).

[35] Cheng, X. & Chen, H. Tumor heterogeneity and resistance to EGFR-targeted therapy in advanced nonsmall cell lung cancer: Challenges and perspectives. *Onco Targets Ther* **7**, 1689–1704 (2014).

[36] Solta, A. *et al.* Small cells – big issues: biological implications and preclinical advancements in small cell lung cancer. *Mol Cancer* **23**, 41 (2024).

[37] Megyesfalvi, Z. *et al.* unfolding the secrets of small cell lung cancer progression: Novel approaches and insights through rapid autopsies. *Cancer Cell* **41**, 1535–1540 (2023).

[38] Huang, D. *et al.* Molecular Subtypes and Targeted Therapeutic Strategies in Small Cell Lung Cancer: Advances, Challenges, and Future Perspectives. Molecules vol. 30 Preprint at https://doi.org/10.3390/molecules30081731 (2025).

[39] Lim, Z.-F. & Ma, P. C. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. *J Hematol Oncol* **12**, 134 (2019).

[40] Ricciuti, B. *et al.* Diminished Efficacy of Programmed Death-(Ligand)1 Inhibition in STK11- and KEAP1-Mutant Lung Adenocarcinoma Is Affected by KRAS Mutation Status. *Journal of Thoracic Oncology* **17**, 399–410 (2022).

[41] Rubin, M. A., Bristow, R. G., Thienger, P. D., Dive, C. & Imielinski, M. Impact of Lineage Plasticity to and from a Neuroendocrine Phenotype on Progression and Response in Prostate and Lung Cancers. Mol Cell 80, 562–577 (2020).

[42] Sun, R., Hou, Z., Zhang, Y. & Jiang, B. Drug resistance mechanisms and progress in the treatment of EGFR-mutated lung adenocarcinoma (Review). *Oncol Lett* **24**, (2022).

[43] Yang, Z. & Tam, K. Y. Combination Strategies Using EGFR-TKi in NSCLC Therapy: Learning from the Gap between Pre-Clinical Results and Clinical Outcomes. *Int J Biol Sci* **14**, 204–216 (2018).

[44] Kowalski, D. M., Zaborowska-Szmit, M., Szmit, S., Jaśkiewicz, P. & Krzakowski, M. The combination of osimertinib and savolitinib as molecular inhibition of EGFR and MET receptors may be selected to provide maximum effectiveness and acceptable toxicity. *Translational Lung Cancer Research* vol. 13 1426–1431 Preprint at https://doi.org/10.210 37/tlcr-24-204 (2024).

[45] Romaniello, D., Morselli, A. & Marrocco, I. Strategies to Overcome Resistance to Osimertinib in EGFR-Mutated Lung Cancer. *International Journal of Molecular Sciences* vol. 26 Preprint at https://doi.org/10.3390/ijms260 72957 (2025).

[46] Shaw, A. T. *et al.* First-Line Lorlatinib or Crizotinib in Advanced ALK -Positive Lung Cancer. *New England Journal of Medicine* **383**, 2018–2029 (2020).

[47] Kim, R. *et al.* Differences in tumor microenvironments between primary lung tumors and brain metastases in lung cancer patients: Therapeutic implications for immune checkpoint inhibitors. *BMC Cancer* **19**, (2019).

[48] Nie, Y., Schalper, K. A. & Chiang, A. Mechanisms of immunotherapy resistance in small cell lung cancer. *Cancer Drug Resistance*

vol. 7 Preprint at https://doi.org/10.20517/cd r.2024.154 (2024).

[49] MacDonald, W. J. *et al.* Heterogeneity in Cancer. *Cancers* vol. 17 Preprint at https://doi.org/10.3390/cancers17030441 (2025).

[50] Teng, X. et al. Enhancing the Clinical Utility of Radiomics: Addressing the Challenges of Repeatability and Reproducibility in CT and MRI. Diagnostics vol. 14 Preprint at https://doi.org/10.3390/diagnostics14161835 (2024).

[51] Wu, X. & Polychronis, A. Application of radiomics and artificial intelligence in lung cancer immunotherapy: a guide and hurdles from clinical trials. Journal of Cancer Metastasis and Treatment vol. 9 Preprint at https://doi.org/10.20517/2394-4722.2023.10 (2023).

[52] Liang, X., Lin, A., Wang, Q., Zhang, J. & Luo, P. Cell plasticity in patients with NSCLC: The controversial origins of transformed SCLC. *Biomedicine and Pharmacotherapy* vol. 149 Preprint at https://doi.org/10.1016/j.biopha.2022.112909 (2022).

[53] Cherukuri, S. P. *et al.* Artificial Intelligence-Enhanced Liquid Biopsy and Radiomics in Early-Stage Lung Cancer Detection: A Precision Oncology Paradigm. *Cancers* vol. 17 Preprint at https://doi.org/10.3390/cancers17193165 (2025).

[54] Huang, D., Li, Z., Jiang, T., Yang, C. & Li, N. Artificial intelligence in lung cancer: current applications, future perspectives, and challenges. *Frontiers in Oncology* vol. 14 Preprint at https://doi.org/10.3389/fonc.2024.1486 310 (2024).

[55] Li, R. Y., Liang, Z. Y. & Wei, P. F. Circulating tumor DNA in lung cancer: Real-time monitoring of disease evolution and treatment response. *Chinese Medical Journal* vol. 133 2476–2485 Preprint at https://doi.org/10.1097/CM9.0000000000001097 (2020).

[56] Khadela, A. *et al.* A review of recent advances in the novel therapeutic targets and immunotherapy for lung cancer. *Medical Oncology* **40**, 152 (2023).

Citation: *Mawanda Anatoli et al. Role of Heterogeneity in Lung Cancer and its Implications for Personalized Oncology. ARC Journal of Cancer Science. 2026; 11(1):1-8. DOI: https://:doi.org/10.20431/ 2455-6009.1101001.*