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| RESEARCH ARTICLE

Oncogenic Addictions in Advanced NSCLC: Clinical Insights from Routine Molecular Profiling

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| ABSTRACT
Non-small cell lung cancer (NSCLC) exhibits significant molecular heterogeneity. Identifying oncogenic alterations is now a cornerstone of advanced disease management, facilitating access to targeted therapies. This study aimed to delineate the molecular landscape of NSCLC and evaluate the prevalence of major oncogenic drivers in our routine clinical practice. We conducted a retrospective analysis of 127 patients diagnosed with stage III or IV NSCLC between June 2023 and June 2025. Demographic, histological, and smoking history data were extracted. Molecular profiling focused primarily on EGFR mutations, alongside ALK and ROS1 rearrangements. The cohort had a mean age of 65.6 years (range: 30–88), with a strong male predominance (89.8%). Most patients (69.3%) reported a smoking history. Adenocarcinoma was the leading histology (70.1%), followed by squamous cell carcinoma (22.0%). Among the 59 patients tested for EGFR, mutations were detected in 16.9% (n=10). ALK and ROS1 rearrangements were identified in 7 and 6 patients, respectively, including 2 cases of ALK/ROS1 co-alteration. These results underscore the actionable mutational burden within this specific population. Systematic molecular profiling is imperative in advanced NSCLC. The detection of specific oncogenic drivers allows for the concrete integration of precision medicine and optimizes the selection of candidates for targeted therapies. Broadening the scope of routine molecular testing remains a critical priority to improve therapeutic outcomes.

| KEYWORDS

NSCLC; Oncogenic drivers; Precision medicine; Targeted therapy

| ARTICLE INFORMATION

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1. Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of all cases [Sung et al., 2021]. Despite advances in screening, a majority of patients still present with locally advanced or metastatic disease (stage III–IV) at diagnosis, rendering curative surgery unfeasible and necessitating systemic treatment [Wood et al., 2018].

Over the past two decades, the management of advanced NSCLC has shifted from a purely histology-based approach to a biomarker-driven paradigm. The concept of "oncogenic addiction" describes the dependency of certain tumors on a specific activated oncogene for their proliferation and survival [Sharma et al., 2007]. The identification of actionable genomic alterations—most notably epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) rearrangements, and ROS proto-oncogene 1 (*ROS1*) fusions—has revolutionized

therapeutic strategies [Mok et al., 2009]. Tyrosine kinase inhibitors (TKIs) targeting these drivers consistently demonstrate superior response rates and progression-free survival compared to conventional platinum-based chemotherapy [Soria et al., 2003; Solomon et al., 2014].

International guidelines, including those from the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN), strongly recommend comprehensive molecular profiling at diagnosis for all patients with advanced non-squamous NSCLC, and increasingly for squamous subtypes in specific clinical contexts [Planchard et al., 2018; Ettinger et al., 2022]. However, the implementation of these recommendations in routine clinical practice varies significantly across different regions and healthcare settings due to logistical, technical, and economic barriers [Lepage et al., 2022].

The primary objective of this study was to delineate the molecular landscape of locally advanced and metastatic NSCLC in our clinical practice and to evaluate the real-world prevalence of major oncogenic drivers (*EGFR*, *ALK*, *ROS1*) to better understand our local epidemiology and identify gaps in molecular testing.

2. Patients and Methods

2.1. Study Design and Setting

We conducted a retrospective, single-center, observational study. The medical records of patients diagnosed with NSCLC between June 2023 and June 2025 were systematically reviewed. The study was conducted in accordance with the Declaration of Helsinki, and due to the retrospective and anonymized nature of the data, the requirement for informed consent was waived by the local institutional ethics committee.

2.2. Study Population

Patients were included if they were aged 18 years or older, had a histologically or cytologically confirmed diagnosis of NSCLC classified as stage III (locally advanced) or stage IV (metastatic) according to the 8th edition of the TNM classification, and had available clinical and pathological data. Patients with missing staging information or insufficient tissue for pathology review were excluded.

2.3. Data Collection

Demographic and clinical data were extracted from electronic health records, including age at diagnosis, sex, and smoking history (categorized as never-smokers vs. ever-smokers). Histological subtypes were categorized as adenocarcinoma, squamous cell carcinoma, or "other" (including large cell carcinoma and not otherwise specified [NOS]).

2.4. Molecular Profiling

Molecular testing was performed on formalin-fixed paraffin-embedded (FFPE) tumor tissue samples or cytological cell blocks. *EGFR* mutational status was primarily assessed using real-time polymerase chain reaction (PCR). *ALK* and *ROS1* rearrangements were screened using immunohistochemistry (IHC), with positive results confirmed by fluorescence in situ hybridization (FISH) when sufficient material was available, in accordance with standard diagnostic algorithms [Lindeman et al., 2018].

2.5. Statistical Analysis

Descriptive statistics were used to summarize the data. Continuous variables were expressed as means with ranges, while categorical variables were presented as absolute frequencies and percentages. All statistical analyses were performed using SPSS software (version 26.0, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Baseline Demographics and Clinical Characteristics

A total of 127 patients met the inclusion criteria. The baseline characteristics of the cohort are summarized in Table 1. The mean age at diagnosis was 65.6 years (range: 30–88). There was a striking male predominance, with men representing 89.8% (n=114) of the population. A history of smoking was documented in 69.3% (n=88) of patients.

Table 1. Baseline Demographic and Histological Characteristics of the Study Population (N=127)

Characteristic	n (%)
Age (years)	
Mean (range)	65.6 (30–88)
Sex	
Male	114 (89.8)
Female	13 (10.2)
Smoking Status	
Ever-smoker	88 (69.3)
Never-smoker	39 (30.7)
Histological Subtype	
Adenocarcinoma	89 (70.1)
Squamous Cell Carcinoma	28 (22.0)
Other / NOS	10 (7.9)
TNM Stage at Diagnosis	
Stage III (Locally Advanced)	41 (32.3)
Stage IV (Metastatic)	86 (67.7)

NOS: Not otherwise specified.

Adenocarcinoma was the predominant histological subtype, accounting for 70.1% (n=89) of cases, followed by squamous cell carcinoma in 22.0% (n=28). The majority of patients (67.7%, n=86) presented with de novo metastatic disease (Stage IV).

3.2. Molecular Profiling and Oncogenic Drivers

Molecular profiling was not performed uniformly across the entire cohort due to clinical decision-making at the time of diagnosis (e.g., poor performance status, insufficient tissue). *EGFR* mutation testing was performed in 59 patients. The results of the molecular profiling are detailed in Table 2.

Table 2. Distribution of Molecular Alterations in Tested Patients

Biomarker	Patients Tested (n)	Positive Results n (%)
EGFR Mutations	59	10 (16.9)
ALK Rearrangements	42*	7 (16.6)
ROS1 Rearrangements	38*	6 (15.7)
ALK/ROS1 Co-alteration	-	2

Note: The number of patients tested for ALK and ROS1 varies due to sequential testing protocols and tissue availability.

Among the 59 patients tested for *EGFR*, mutations were identified in 10 cases (16.9%). When considering the total cohort of 127 patients, the overall prevalence of *EGFR* mutations was 7.9%.

Regarding *ALK* and *ROS1* rearrangements, positivity was found in 7 and 6 patients, respectively. Notably, 2 patients exhibited a rare co-occurrence of *ALK* and *ROS1* alterations. Overall, at least one actionable oncogenic driver was identified in a significant subset of the tested population, confirming the presence of a non-negligible mutational burden in this cohort.

4. Discussion

This retrospective study provides a real-world snapshot of the molecular landscape of advanced NSCLC in our clinical setting. Our findings reaffirm that advanced NSCLC is a heterogeneous disease where a substantial proportion of patients harbor actionable oncogenic drivers, thereby justifying the systematic implementation of precision medicine.

The demographic profile of our cohort, characterized by a high male predominance (89.8%) and a significant smoking rate (69.3%), is consistent with the classic epidemiological patterns of lung cancer observed in regions where tobacco control measures were historically implemented later than in Western countries [de Groot PM, 2019]. Despite the strong association between smoking and squamous cell carcinoma, adenocarcinoma remained the most frequent histological subtype (70.1%), mirroring the global epidemiological shift reported over the last two decades [Lortet-Tieulent et al., 2014].

The *EGFR* mutation rate among tested patients was 16.9%. While this is lower than the rates classically reported in East Asian populations (which can exceed 40-50%), it aligns closely with large-scale epidemiological data from Western and European cohorts, where *EGFR* mutations typically range between 10% and 15% [Midha et al., 2015; Barlesi et al., 2016]. Interestingly, our testing rate for *EGFR* (59 out of 127 patients) highlights a potential gap in routine clinical practice. International guidelines mandate molecular testing for all non-squamous NSCLC patients [Ettinger et al., 2022]. The fact that only 46.4% of our cohort—despite 70.1% having adenocarcinoma—underwent *EGFR* testing suggests that barriers such as inadequate tissue sampling, advanced age, or poor performance status are still impeding optimal biomarker evaluation in our center.

The identification of *ALK* (n=7) and *ROS1* (n=6) rearrangements further underscores the relevance of comprehensive profiling. While the absolute numbers are small, the proportion of positive cases among tested individuals is clinically significant. Furthermore, the observation of *ALK/ROS1* co-alterations in two patients is a notable finding. Although exceptionally rare, dual driver mutations have been documented in the literature and pose unique therapeutic challenges, often requiring next-generation sequencing (NGS) to fully elucidate complex genomic architectures rather than relying solely on sequential single-gene testing [Cai et al., 2019; Zhang et al., 2019].

The clinical implication of our findings is clear: the detection of these oncogenic addictions directly dictates the use of highly effective TKIs, which have demonstrated profound improvements in survival outcomes compared to chemotherapy [Soria et al., 2023; Solomon et al., 2014]. Missing these alterations means depriving patients of a chance at targeted therapy with better tolerability.

Our study has several limitations. First, its retrospective nature carries the inherent risk of selection bias and incomplete data collection. Second, the sample size is relatively small, and molecular testing was not uniformly applied to all eligible patients, which may underestimate the true prevalence of these drivers in the general population. Third, our testing strategy relied primarily on PCR and IHC/FISH; the lack of routine NGS limits our ability to detect rarer drivers (such as *BRAF*, *MET*, *NTRK*, or *KRAS* G12C) and understand the broader tumor mutational burden.

5. Conclusion

In conclusion, this study demonstrates that actionable oncogenic drivers are present in a clinically relevant proportion of patients with advanced NSCLC in our practice. The integration of precision medicine relies heavily on the initial step of systematic and comprehensive molecular profiling. Broadening access to routine testing, transitioning towards panel-based NGS where feasible, and ensuring adequate tissue acquisition during diagnostic procedures are critical priorities. These steps are essential to ensure that all eligible patients can benefit from the survival advantages offered by modern targeted therapies.

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