Lung Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Prevalence of *EGFR* Mutations in Vietnamese Patients with Resected Early Stage Non-Small Cell Lung Cancer: EARLY-EGFR Study

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Introduction: Comprehensive profiling of mutations in the *EGFR* gene is vital for selecting patients eligible for *EGFR* targeted therapies.

Methods: We investigated the prevalence of *EGFR* mutations and treatment patterns in patients with early stage non-small cell lung cancer (NSCLC) in Vietnam as a part of EARLY-EGFR (Clinical Trial Identifier: NCT04742192), a global, real-world study. Consecutive patients with surgically resected stage IA-IIIB, non-squamous NSCLC were diagnosed from August 2021 to June 2022 and were prospectively enrolled from November 2021 to July 2022.

Results: A total 200 patients (age: median [range], 60.0 [30.0–80.0] years) were enrolled from 3 centers; 56.0% were males and 64.0% never smoked. The prevalence of *EGFR* mutations was 51.0% (102/200) including deletions in *exon-19* (49.0%) and *exon-21 L858R* mutations (33.3%). Females (73.9%, 65/88), patients aged ≥60 years (52.5%, 53/101), nonsmokers (61.2%, 63/103) and those with stage I (55.8%, 67/120) had higher prevalence of *EGFR* mutations. Multivariate analysis (adjusted odds ratio [aOR]) showed *EGFR* mutations to be significantly associated ($p < 0.05$) with female gender (aOR = 5.90), age ≥60 years (aOR = 1.05), and stage III disease (vs stage I) (aOR = 0.30).

Conclusion: These results underscore the need for *EGFR* testing early in management algorithm of NSCLC in Vietnam to identify patients eligible for targeted therapy in concordance with international guidelines.

Keywords: epidermal growth factor receptor mutations, EGFRm, early-stage resectable non-small cell lung cancer, targeted therapies, Vietnam

Introduction

Lung cancer accounted for 26,262 new cases and 23,797 deaths in 2020 in Vietnam, making it the second leading cause of cancer-related mortality and the third most prevalent cancer over a 5-year period.[1] The age-standardized incidence and mortality rates were 136.7 and 85.7 per lac population in Vietnam. In Vietnam, the lung cancer incidence and mortality rates have outpaced the global rates.[1–3] The aggregate 5-year lung cancer survival rate in Vietnam is considerably low at 14.8%,[4] compared with Surveillance, Epidemiology, and End Results (SEER), the US National Cancer registries (25.4%).[5] NSCLC, which constitutes 85% of all new lung cancer cases, is diagnosed at an early stage only in 30% of patients.[6] Surgical resection is the mainstay for managing early-stage NSCLC albeit a high recurrence rate is still observed among these patients.[7–10]

Targeted inhibition of epidermal growth factor receptor (*EGFR*) activity controls tumor cell growth, proliferation, and resistance to apoptosis.[11] With proven efficacy in advanced NSCLC with activating *EGFR* mutations, third-generation

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EGFR-tyrosine kinase inhibitors (TKIs) have demonstrated similar benefits in patients with early-stage disease harboring *exon-19 deletions* or *exon-21 L858R* mutations. The ADAURA trial has reported significant improvement in disease-free survival (hazard ratio [HR]: 0.20; 99.12% confidence interval [CI], 0.14 to 0.30; $p < 0.001$) and overall survival (HR: 0.49, 95% CI: 0.34–0.70; $p < 0.0001$) in patients with resected, stage IB to IIIA NSCLC who received adjuvant osimertinib treatment.[12] Based on these results, the National Comprehensive Cancer Network (NCCN®) Clinical Practice Guidelines in Oncology recommend osimertinib as an adjuvant therapy option for eligible patients with completely resected (R0) stage IB to IIIB (only T3, N2) *EGFR* mutation-positive NSCLC. The NCCN Guidelines® also recommend molecular testing for *EGFR* mutations when adjuvant TKI therapy is considered for NSCLC stage IB to IIIA and stage IIIB (T3, N2).[10]

The highest prevalence of *EGFR* mutations is reported in Asians (39%-51%) compared with other continents (11.9%–33.0%) for stage IIIB/IV NSCLC.[13] A meta-analysis of 456 studies, in patients with NSCLC estimated an *EGFR* prevalence of 29.9% to 34.0% in stage I to III disease. About 67% of the included studies were from Asia.[14] In Vietnam the prevalence of *EGFR* mutations is reported to be between 35.4% and 64.2% irrespective of stage of NSCLC.[15–20] The highest prevalence of EGFR mutations (64.2%) in Vietnamese population was reported in the PIONEER study in patients with stage IIIB/IV NSCLC.[18] In a recent study from Vietnam National Cancer Hospital, EGFR mutation rate was found to be 41% with higher frequency of mutations reported in females.[15] However, a majority of this data is available for patients with advanced NSCLC with meager data for early-stage disease.

Data on the proportion of *EGFR* mutations in stage I–III NSCLC in the Vietnamese population is limited, except for the real-world KINDLE study that reported a prevalence of 20% in patients with stage III NSCLC.[21] With novel targeted agents approved for patients with early stage NSCLC, there is an urgent need for comprehensive profiling of *EGFR* mutations. It is essential to understand the prevalence of *EGFR* mutations in early-stage NSCLC to optimize the access to osimertinib in the country. We investigated the prevalence of *EGFR* mutations in Vietnam as a part of EARLY-EGFR (clinical trial identifier: NCT04742192), a global real-world study, determining the prevalence in 14 countries across Asia, Latin America, and the Middle East and North Africa.[22]

Methods

Study Design

The EARLY-EGFR study is a cross-sectional, non-interventional study. Vietnam Patients with surgically resected stage IA to IIIB NSCLC (per American Joint Committee on Cancer (AJCC) 8th edition,[23]) NSCLC were diagnosed from August 2021 to June 2022 and were prospectively recruited from 3 centers in Vietnam between 17 November 2021 and 1 July 2022. Institutional review boards/independent ethics committees of the participating centers approved the study protocol prior to initiation of study. All relevant guidelines including Declaration of Helsinki, International Council for Harmonisation and Good Clinical Practice were adhered while study conduct. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was utilized for the manuscript authoring.[24]

Study Population

Consecutive adult patients (≥18 years) with pathological stage IA to IIIB non-squamous NSCLC, with available medical records for the date of diagnosis and staging, who had undergone surgical resection between August 2021 and June 2022 and up to 12 weeks prior to the enrollment date, and those with the availability of formalin-fixed paraffin-embedded (FFPE) primary diagnostic sample or surgical tissue samples suitable for *EGFR* mutation testing were included. Tumors without primary origin in the lung and those with pure squamous cell histology, small cell, or large cell carcinoma origin without immunohistochemical evidence of adenocarcinoma differentiation were excluded.

Data on socio-demographics, clinical characteristics, and planned treatment patterns were collected from available medical records and were documented in electronic case report forms during patients' routine clinical care visits after obtaining written informed consent. *EGFR* mutation testing was conducted on the FFPE tissue specimens at validated local laboratories or a central laboratory and the results were recorded once available. Immunohistochemistry results for programmed cell death ligand 1 (PD-L1) and other mutation testing and/or next-generation sequencing (NGS) test results

were also recorded where applicable. Patients were followed up until the *EGFR* mutation status and planned treatment was recorded. In case of additional diagnostic and molecular analysis, follow-up was extended and the results were recorded.

Outcomes

The primary outcome was the frequency of *EGFR* mutations. The proportion of patients with *EGFR* mutations by histological subgroups, pathological stage, and sociodemographic and clinic-pathological characteristics was determined. Secondary outcomes included the frequency of *EGFR* mutation subtypes, clinicodemographic characteristics, treatment patterns and association of EGFR mutations with clinicodemographic characteristics.

Statistical Analysis

The sample size for the global cohort was estimated to be 600 based on the assumed frequency of *EGFR* mutations in early-stage NSCLC ranging from 0% to 50%. The Vietnam cohort planned to enroll 200 stage I to III patients to give similar precision of the mutation frequency. SAS9.4 was used for statistical analyses. Descriptive statistics were used to analyze patient demographics, clinical characteristics, *EGFR* mutation status, subtypes, and treatment patterns. The categorical variables were expressed using frequencies, and the continuous variables were defined using mean with standard deviation or median with a range. The clinicodemographic variables were compared with *EGFR* mutation status for association using Fisher's exact test with Monte Carlo. Multivariate regression was used to assess the association between clinicodemographic variables and *EGFR* mutation; results were presented with 95% confidence interval using Clopper-Pearson method.

Results

Baseline Characteristics

A total of 200 patients meeting the eligibility criteria were recruited. The median age (range) of patients was 60.0 (30.0–80.0) years, 56.0% (112/200) were males, 64.0% (103/161) were never smokers and 4.4% (8/183) had a family history of lung cancer. Approximately, 22% of patients first presented to clinical or medical oncologists. Most patients had adenocarcinoma (99.5%, 199/200) and had pathological stage I disease (60.0%, 120/200) at diagnosis. Majority of the tumors were classified as T1-T2 (77.0%, 154/200). Among patients with T2 stage (45.5%, 91/200), about one-third of patients had T2a tumors (35.0%, 70/200) and 10.5% (21/200) had T2b tumors. Sixty-three (31.5%) had T1 tumors (T1a: 3.5%, 7/200; T1b: 10.0%, 20/200; T1c:18.0%, 36/200), and 18.0% had T3 tumors (36/200), and 85% (170/200 had no lymph node metastases. Nearly 98.5% (194/197) of patients had public/government insurance (Table 1).

Table 1 Baseline Sociodemographic and Clinical Characteristics of Patients with NSCLC

Parameters	Number of Patients (N = 200), n (%)	EGFRm[a] n (%)
Age (years), mean (SD)	58.5 (8.84)	
Age categories (years)		
<60	99 (49.5)	49 (49.5)
60–80	101 (50.5)	53 (52.5)
Gender		
Male	112 (56.0)	37 (33.0)
Female	88 (44.0)	65 (73.9)
Tobacco smoking[b], n = 161, n (%)		
Current smoker	7 (4.3)	1 (14.3)
Ex-smoker	51 (31.7)	19 (37.3)
Never smoker	103 (64.0)	63 (61.2)

(*Continued*)

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Table 1 (Continued).

Parameters	Number of Patients (N = 200), n (%)	EGFRm[a] n (%)
Family history of lung cancer, n = 183, n (%)		
No	175 (95.6)	88 (50.3)
Yes	8 (4.4)	4 (50.0)
Histology		
Adenocarcinoma	199 (99.5)	101 (50.8)
Mixed	1 (0.5)	1 (100.0)
Pathological clinical stage		
Stage IA	58 (29.0)	33 (56.9)
Stage IB	62 (31.0)	34 (54.8)
Stage IIA	17 (8.5)	8 (47.1)
Stage IIB	37 (18.5)	18 (48.6)
Stage IIIA[c]	15 (7.5)	4 (26.7)
Stage IIIB	11 (5.5)	5 (45.5)
T stage		
T1	63 (31.5)	35 (55.6)
T2	91 (45.5)	49 (53.9)
T3	36 (18.0)	15 (41.7)
T4	10 (5.0)	3 (30.0)
Lymph node metastasis, n = 194, n (%)		
N0	170 (85.0)	87 (51.2)
N1	12 (6.0)	7 (58.3)
N2	18 (9.0)	8 (44.4)
Tumor site[d]		
Right lung	119 (59.5)	ND
Left lung	85 (42.5)	ND
Grade, n=98[*], n (%)		
1-low grade	48 (49.0)	27 (56.3)
2-moderately differentiated	14 (14.3)	11 (78.6)
3, 4-poorly differentiated	36 (36.7)	9 (25.0)
Surgery type[e]		
Lobectomy	203	104 (51.2)
Sublobar	10	5 (50.0)
Other	108	58 (53.7)
Resection type		
Complete resection (R0)	95	47 (49.5)
Microscopic residual disease (R1)	1	0
Not determined	112	60 (53.6)
Insurance		
Government insurance	194 (97.0)	-
Private insurance	1 (0.5)	-
Employer provided insurance	1 (0.5)	-
No insurance	1 (0.5)	-

Notes: The percentage was calculated based on the total number of patients available within each level. Unknown and missing data are not included. [a]Calculated from the number tested within the category. [b]Current and ex-smokers versus never smokers p = 0.001. [c]Stage I versus III p = 0.05. [d]Patients may have tumors on more than 1 side. [e]Patients may receive more than one surgery. [*]Applicable for the only for overall cohort.

Abbreviations: EGFRm, epidermal growth factor receptor mutations; N, Lymph node status; ND, Not determined; SD, standard deviation.

Prevalence of EGFR Mutations

In most cases (94.0%, 188/200), surgically resected tumor specimens were used for *EGFR* mutation testing using real-time polymerase chain reaction (PCR) (98.0%, 196/200); NGS was used in only 4 patients. Cobas® *EGFRm* test v2 testing kits by Roche molecular diagnostics (98.0%, 196/200) were employed predominantly. The *EGFR* mutation prevalence was 51.0% (102/200), comprising common mutations in 86.3% (88/102) patients—*exon-19* deletions (49.0%, 50/102), *exon-21 L858R* mutations (33.3%, 34/102), *exon-20 T790M* mutations (2.0%, 2/102), and *L858R+T790M* mutations (2.0%, 2/102). Uncommon mutations were found in 12.7% (13/102) patients, predominantly *G719X* mutations (5.9%, 6/102) and *L861Q* mutations (3.9%, 4/102), which were commonly reported in patients with stage I to II NSCLC. Compound mutation with *19-DEL/L858R/T790M* was reported in 1 patient with stage I NSCLC (Figure 1).

EGFR Mutations by Subgroups

Females (73.9%, 65/88) had a higher prevalence of *EGFR* mutations compared to males (33.0%, 37/112), patients of ≥60 years (52.5%, 53/102) versus those aged <60 years (49.5%, 49/99), nonsmokers (61.2%, 63/103) versus current/ex-smokers (34.5.%, 20/58), stage I (55.8%, 67/120) versus stage II (48.1%, 26/54) versus stage III (34.6%, 9/26), grade 2 (moderately differentiated) (78.6%, 11/14) versus grade 1 (low grade) tumor (56.3%, 27/48), lymph node status N1 (58.3%, 7/12) versus N0 (51.2%, 87/170) versus N2 (44.4%, 8/18), and T1 (55.6%, 35/63) versus T2 (53.9%, 49/91) versus T3 (41.7%, 15/36) versus T4 (30.0%, 3/10) (Table 1).

In the univariate logistic regression analysis, the female gender was associated with higher odds (odds ratio [OR]: 5.73, 95% CI: 3.09–10.62; $p < 0.001$), whereas smoking history was associated with lower odds (OR: 0.33, 95% CI: 0.17–0.65; $p = 0.001$) for *EGFR* mutations compared with males and those without smoking history, respectively. In the multivariate logistic regression, female gender (adjusted OR [aOR]: 5.90, 95% CI: 2.18–16.00; $p < 0.001$) and age ≥60 years (aOR: 1.05, 95% CI: 1.00–1.09; $p = 0.043$) and had higher odds compared with male gender and age <60 years, respectively, whereas stage III was associated with lower odds (aOR: 0.30, 95% CI: 0.10–0.93; $p = 0.038$) for *EGFR* mutations compared with stage I disease (Table 2).

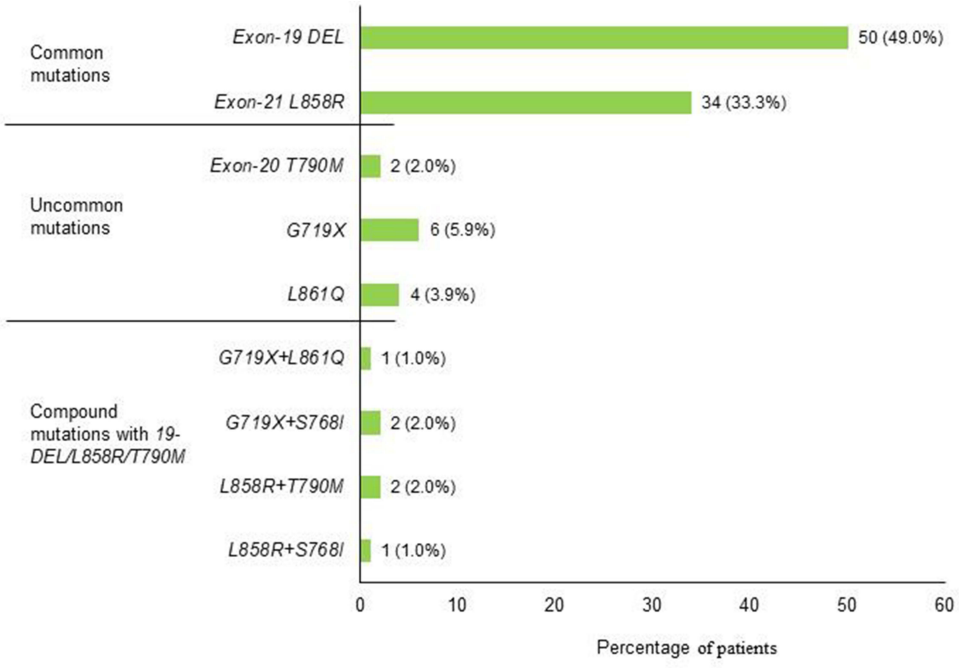

Figure 1 Epidermal Growth Factor Receptor Mutation and Subtypes.

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Table 2 Associations of Different Characteristics with Epidermal Growth Factor Receptor Mutations

Characteristics	*EGFRm* Rate (%)	Unadjusted OR[a] (95% CI)	p Value	Adjusted OR (95% CI)	p Value
Age (years) (≥60 vs <60)	52.5 vs 49.5	1.01 (0.98–1.04)	0.637	1.05 (1.00–1.09)	**0.043**
Gender (Female vs Male)	73.9 vs 33.0	5.73 (3.09–10.62)	**<0.001**	5.90 (2.18–16.00)	**<0.001**
Stage II vs I	48.1 vs 55.8	0.74 (0.39–1.40)	0.348	0.76 (0.34–1.70)	0.498
Stage III vs I	34.6 vs 55.8	0.42 (0.17–1.01)	0.054	0.30 (0.10–0.93)	**0.038**
Smoking history (Yes vs No)	34.5 vs 61.2	0.33 (0.17–0.65)	**0.001**	0.97 (0.35–2.65)	0.947
Family history of lung cancer (Yes vs No)	50.0 vs 50.3	0.99 (0.24–4.08)	0.987	1.09 (0.20–5.90)	0.917

Notes: Significant values are shown in bold. [a] Logistic regression was used to assess the association between variables and *EGFRm*.
Abbreviations: CI, confidence interval; *EGFRm*, epidermal growth factor receptor mutations; OR, odds ratio; vs, versus.

Other Mutations

Molecular testing for other genetic alterations was performed in 24 patients mainly for *ALK* (n = 5), *KRAS* (n = 4), *ROS1* (n = 5), *BRAF* (n = 4), *PI3KCA* (n = 4), *MET* (n = 1), and *RET* (n = 1) mutations; only *KRAS* mutations were observed in 2/4 (50%) of the patients tested. None of the patients were tested for PD-L1 expression.

Treatment Patterns

About 85% (165/195) of cases were discussed at the multidisciplinary team (MDT) meeting, with 54.5% (90/165) discussed prior to surgery, 40.0% (66/165) after surgery, and 5.5% (9/165) on both occasions. The majority (70.5%, 141/200) of the patients underwent only surgical resection without planned systemic therapy (stage IA-B, 77.5% [93/120]; stage IIA-B, 70.4% [38/54]; stage IIIA-B, 38.5% [10/26]). A total of 322 surgeries were performed; lobectomy was most common (63.0%). Of the 208 reported surgical outcomes, 95 (45.6%) were complete resections (Table 1). A total of 6.5% (13/200) underwent surgery and prescribed with adjuvant chemoradiotherapy; 22.0% (44/200) were prescribed with adjuvant chemotherapy. Of the 80 patients with stage IIA to IIIB, 32 (40.0%) received adjuvant systemic therapy (chemotherapy or chemoradiotherapy) (Figure 2). Among

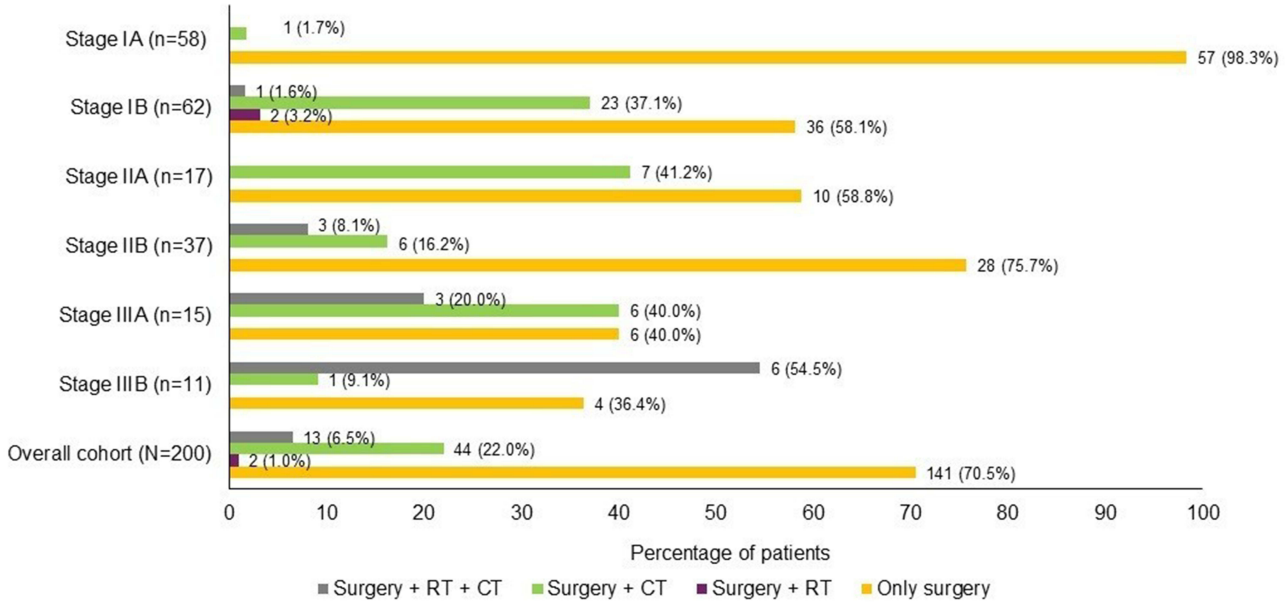

Figure 2 Treatment Patterns of Patients with Various Stages of Non-Small Cell Carcinoma.
Abbreviations: RT, Radiotherapy; CT, Chemotherapy.

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27.5% (55/200) patients who were prescribed with adjuvant systemic therapies, most (54/55, 98.2%) were prescribed platinum-based chemotherapy. Only 02/200 (1%) patients received neoadjuvant systemic chemotherapy (carboplatin-containing combination). Targeted therapy or immunotherapy was not planned in any patients (data not shown).

Discussion

Precision medicine is gaining importance in NSCLC with the advent of predictive and prognostic biomarkers. Recently results from ADAURA study confirming improved disease-free survival and overall survival[25] in stage I to III NSCLC prompted us to explore the burden of *EGFR* mutations in patients with early-stage NSCLC in Vietnam to expand the clinical benefit of EGFR-TKI in these patients. Our real-world study reported a prevalence of 51.0% in the Vietnamese subset of patients with early-stage resectable NSCLC. The prevalence in the Vietnamese subset was similar to the global EARLY-EGFR (51.0%) and Asian cohort (53%). The global cohort recruited almost 84% of patients from the Asian region, mostly from Vietnam.[26] Real-world studies from Vietnam (irrespective of stage) reported a lower prevalence of *EGFR* mutations than that observed in our study; 38.8% in patients with resected NSCLC,[27] 35.4% and 41% in patients with NSCLC using real-time PCR,[15,16] and 40.7% using Sanger sequencing.[17] The reported prevalence rates among Asian countries range from 32% in Japan,[28] 53.6% in China,[29] and 57.4% in Thailand[30] for both early and advanced NSCLC. The prevalence data in our study reflects the data available for Vietnamese population from the earlier studies in patients with NSCLC from Vietnam and Asia irrespective of the stage of NSCLC.

The current study found that females had almost six times higher risk of *EGFR* mutations (aOR: 5.90, 95% CI: 2.18–16.00, $p < 0.001$) than males, and smokers had a 67% reduced risk of *EGFR* mutations (aOR: 0.33, 95% CI: 0.17–0.65, $p = 0.01$) compared with nonsmokers. In line with these findings, a meta-analysis reported a 2.7 times higher prevalence of *EGFR* mutations in females versus males (43.7% versus 24.0%; 95%, CI: 2.5–2.9), 3.7 times higher prevalence in nonsmokers versus past/current smokers (49.3% versus 21.5%; 95% CI: 3.4–4.0), and 4.1 times higher prevalence in patients with adenocarcinoma versus non-adenocarcinoma (38.0% versus 11.7%; 95% CI: 3.6–4.8).[13] In the PIONEER study exploring the epidemiology of *EGFR* mutations in Asian patients with newly diagnosed, advanced NSCLC (stage IIIB/IV) with adenocarcinoma histology determined significant association between females as well as nonsmokers with *EGFR* mutations.[18] Several other studies also found an association between *EGFR* mutations and female gender and nonsmoking status.[16,25,31,32] A Vietnamese study, sample tissue type and age along with female sex, non-smoker status, adenocarcinoma histology were also associated with *EGFR* mutations. This study did not find an association of EGFR mutations with the stage of the disease.[19] Additionally, a cross-sectional study by Thien et al reported that primary tumor status was associated with a higher prevalence of *EGFR* mutations (42.9%) compared with metastatic tumors (31.1%) in Vietnamese patients with NSCLC.[27] In our study, 65% of the cohort had stage I NSCLC, with more than half harboring an *EGFR* mutation (55.8%). Moreover, patients with stage III disease were less likely to have *EGFR* mutations than those with stage I (aOR: 0.30, 95% CI: 0.10–0.93, $p = 0.038$). In the PIONEER study, highest prevalence of EGFR mutations was reported in Vietnamese patients. The study found association of smoking history and ethnicity (people of Kinh-Vietnamese) with EGFR mutations.[18,33] Several epidemiology factors like ethnicity, geographical region, smoking, and gender has been established to be associated with the prevalence *EGFR* mutations.[34] Owing to high prevalence of *EGFR* mutations in Asian population, all patients with stage IIIB/IV adenocarcinoma and regular smokers, should be considered for *EGFR* testing.[18] However, considering the small sample size of the subgroup analysis, the results of these studies may not be conclusive as the association being evaluated as exploratory analysis. Future empirical studies may provide more conclusive results. We found *exon-19 deletions* (49.0%) and *exon-21 L858R* (33.3%) as predominant mutations. The results are concurrent with other studies, with prevalence ranging from 19% to 79.1% for *exon-19 deletions* and 7.1% to 57.2% for *exon-21 L858R* mutations.[16,19,25,27,35] Furthermore, a Vietnamese study reported 46 types of *EGFR* variant mutations, including six novel mutations reflecting broad spectrum of *EGFR* mutations in this population.[17]

In the present study, testing for other mutations was performed only for 24 patients; *KRAS* mutation was observed in only 2 out of 4 patients. In this study, we did not collect information about indications for further molecular analyses, such as *ALK* evaluation, in *EGFR* wild-type patients without a smoking history, although previous reports suggest that *ALK* abnormalities tend to be more common in non-smokers without *EGFR* mutations, especially in younger patients.[36]

Testing was not performed for PD-L1 expression, *HER2, MEK1, AKT1, KIF5B*, and *NTRK*. A study by Dang et al determined that the *EGFR* and *KRAS* were frequent mutations accounting for more than 50% of total patients, whereas *ALK* (6.6%), *ROS1* (3.1%), *BRAF* (2.3%), and *NRAS* (0.6%) mutations were minimal in Vietnam.[16] A recent report from the United States using COTA's oncology database in patients with stage 0 to IIIA NSCLC found an increased biomarker testing rate (55.3% to 88.1%) in the last decade with an *EGFR* mutation prevalence of 64%.[37] The guidelines from the College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology, and NCCN Guidelines (Version 1.2024) encourage molecular testing at diagnosis for patients presenting with early-stage disease in collaboration with its multidisciplinary oncology team.[10,38] The American Society of Clinical Oncology has recommended regular screening of driver gene mutations, including *EGFR, ALK, ROS1*, and *BRAF*, in clinical practice for NSCLC patients due to their profound impact on clinicopathological outcomes.[39] The NCCN Guidelines recommend NGS as a practical diagnostic tool for genomic sequencing.[10] Screening using NGS was performed in a few patients, which might have revealed more detailed information on unknown genetic mutations and deep sequencing. The unmet need for molecular screening and testing techniques can be combated by educating physicians and increasing patient access.

An MDT approach is integral to routine clinical practice and can facilitate decision-making in patients with NSCLC with heterogeneous mutation patterns. A study by Hung et al determined that the median survival of patients with advanced stage III NSCLC treated with the MDT approach was enhanced compared with optional MDT discussions (33.9 versus 25.7 months; $p = 0.003$).[40] In our study, more than three-fourths of the cases were discussed through MDT meetings and more than half were discussed before surgery, which complies with international guidelines.[10]

Surgery with lobectomy was the preferred treatment choice among most Vietnamese patients. Around 27.5% were prescribed adjuvant therapies, and only 1.0% received neoadjuvant therapies in this study. Among 80 patients with stage IIA to IIIB NSCLC, 40% (n = 32) were prescribed systemic therapy. Despite the high frequency of *exon-19 deletions* and *exon-21 L858R* mutations in nearly half of the study population, none of the patients received EGFR-TKIs, particularly osimertinib, although being eligible to receive osimertinib, as per the current NCCN guidelines because, it was not approved during the study period. The ADAURA trial demonstrated improved OS rate and disease free survival (DFS) in patients with completely resected stage IB to IIIA NSCLC harboring *exon-19 deletions* or *exon-21 L858R* mutations with osimertinib as adjuvant treatment compared with placebo (5-year OS rate: 88% versus 78%, HR: 0.49; 95.03% CI, 0.34–0.70; $p < 0.001$; DFS: 89% versus 52%; HR: 0.20; 99.12% CI: 0.14–0.30; $p < 0.001$).[12,25] Furthermore, the ongoing NeoADAURA trial (NCT04351555) is evaluating the neoadjuvant osimertinib, as monotherapy or combination therapy with platinum-based chemotherapy in patients with *EGFR* mutated resectable, stage II to IIIB NSCLC.[41] In addition, evidence on neoadjuvant EGFR-TKI is currently under investigation. Although evaluated in small group of patients, an interim analysis from the single-arm NEOS trial, neoadjuvant osimertinib reported a response rate of 73.3% (11/15) and a disease control rate of 100% (15/15), in patients with resectable stage II to IIIB EGFR-mutated NSCLC supporting the advantage of osimertinib.[42] A meta-analysis conducted among patients with resected EGFR-mutant NSCLC reported that the DFS for osimertinib was significantly prolonged compared to the first-generation EGFR-TKIs (osimertinib versus gefitinib or erlotinib, HR: 0.20; 95% CI: 0.15–0.27 versus 0.53; 0.41–0.67; $p < 0.001$).[43]

The evolving treatment landscape can strengthen the rationale for routine assessment of *EGFR* mutations in all patients at initial diagnosis. The current Vietnam national guidelines recommend profiling of *EGFR* mutations for advanced NSCLC. Furthermore, *EGFR* testing coverage in early-stage NSCLC should be recommended in national guidelines to provide precision medicine and improve survival outcomes in this population. A survey suggests that only 50% reimbursement is available for first and second-line TKIs therapy (gefitinib, erlotinib, and afatinib) in advanced stage NSCLC and no reimbursement is approved for TKI therapy in early-stage disease.[4] There is an urgent need to adapt international treatment guidelines at the national level in Vietnam to incorporate genomic work-ups, develop appropriate treatment strategies involving the MDT in early-stage settings as well as to advocate for reimbursement policies for newer therapies.

The limitations of the study include a smaller sample size, and other inherent biases associated with real-world studies. Owing to the cross-sectional nature of the study, the data regarding adjuvant treatment may not be accurately recorded. Additionally, data were retrieved from available health records, resulting in a few missing data. Third, this

study identified a lower testing rate for other driver mutations, including PD-L1 expression resulting in inability to provide insights on co-mutations in early-stage NSCLC. As Vietnam does not have a screening program, most patients seek medical consultation when they experience symptoms such as persistent cough, chest pain, shortness of breath, or unexplained weight loss, followed by consultation with pulmonologist or oncologist. However, further studies are needed to evaluate data on the prevalence of *EGFR* mutations and its relationship with demographic characteristics. This data can provide insights into the genetic factors influencing lung cancer in the Vietnamese population and help tailor treatment strategies.

Conclusion

This real-world study provides the first evidence of a high prevalence of *EGFR* mutations among patients with stage I to III NSCLC in Vietnam. The results emphasize the need for upfront *EGFR* testing at index diagnosis to identify patients who may benefit from targeted therapy. The study identified factors associated with EGFR mutations in Vietnamese population. Considering the recent approvals for targeted and immunotherapeutic agents in patients with early-stage NSCLC, the treatment algorithm has undergone considerable change. With availability of prevalence data from our study and promising results from trials in patients with early-stage NSCLC, enhancing health insurance coverage plans for upfront *EGFR* testing in early-stage NSCLC in Vietnam is crucial. Our study also reported an unmet need for improving adherence to adjuvant treatment strategies in early-stage NSCLC.

Data Sharing Statement

The data for this study are available from the corresponding author, upon reasonable request. Data privacy and ethical reasons limit the public availability of the data.

Institutional Review Board Statement

Ethic Committee Name: Ministry of Health National Ethics committee in Biomedical research.

A written informed consent was taken from all the patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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