ORIGINAL ARTICLE

Genomic profiling of early-stage resectable non-small-cell lung cancer in a Malaysian private healthcare setting: Real-world clinical implications

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ABSTRACT

Introduction: The prevalence of oncogenic driver mutations in early-stage resectable non-small-cell lung cancer (rNSCLC) in Malaysia remains unknown. This information may guide treatment decisions, especially tyrosine kinase inhibitor (TKI) use. We characterised the genomic landscape of early-stage NSCLC in a surgical cohort and explored its impact on TKI administration, particularly osimertinib.

Materials and Methods: 146 patients who underwent curative resection for early-stage rNSCLC were included in this study. Real-time polymerase chain reaction (PCR) and next-generation sequencing (NGS) were used to identify genetic alterations in tumour samples. Associations between EGFR status and clinico-pathological characteristics were analysed using uni- and multivariate logistic regression.

Results: A majority of patients were female non-smokers of Chinese ethnicity with an incidental adenocarcinoma. EGFR mutations were detected in 62.3% (n=91) of patients, with 93.4% harbouring single-locus mutations, primarily in exons 19 and 21. Co-mutations occurred in 11% (n=10) of EGFR-mutant cases, most frequently involving TP53, and less commonly CTNNB1, HER2/ErbB2, and PTEN. Six (6.6%) patients had multi-loci EGFR mutations. Female sex and higher tumour histological grade were independent predictors for EGFR mutations, while former/never smokers showed higher odds on univariate analysis. Among patients tested for PD-L1 (78.8%), 46.6% had negative expression (tumour proportion score <1%), with no correlation to EGFR status.

Conclusion: This is the first genomic molecular profiling study to report exclusively on early-stage NSCLC in Malaysia. The high prevalence of EGFR mutations observed, predominantly involved sensitizing mutations at exons 19 and 21, and was associated with the female sex, a non-smoking status, higher tumour grade, but not PD-L1 expression. Early reflex genomic testing is vital to guide biomarker-driven peri-operative treatment strategies for rNSCLC.

KEYWORDS:
Early-Stage resectable NSCLC, Genomic Landscape, EGFR

INTRODUCTION

The treatment paradigm for early-stage resectable non-small-cell lung cancer (rNSCLC) has evolved considerably in recent years, particularly with the adoption of peri-operative systemic therapies and the integration of genomic insights into treatment planning. The incorporation of immune checkpoint inhibitors (ICIs) peri-operatively has improved patient outcomes with significant improvements in pathological complete response (pCR) rates that correlate with enhanced event-free survival (EFS), overall survival (OS) and reduced risk of recurrence for patients without driver mutations. Adjuvant administration of tyrosine kinase inhibitors (TKIs) has resulted in superior disease-free survival (DFS) and OS for patients with tumours harbouring actionable driver mutations.[1] Understanding tumour biology is now pivotal in selecting optimal bespoke treatment modalities, however, there remains a notable paucity of comprehensive genomic data for early-stage rNSCLC, in specific populations. This gap hampers the development of tailored treatment strategies and underscores the need for further research. Ongoing efforts to map the genomic landscape will help refine and personalise treatments, ultimately enhancing patient outcomes.

MATERIALS AND METHODS

Patients and data collection

This observational study utilized a universal sampling

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approach to retrospectively analyse 146 primary NSCLC patients who underwent curative resection from January 2021 to June 2025, at two private hospitals in Greater Kuala Lumpur, Malaysia. All patients were clinically staged pre-operatively with a PET-CT scan, and if indicated, a contrasted MRI brain scan. Demographic and clinico-pathologic data were collected from both physical and electronic medical records.

Surgical procedure
The standard operation in all patients was a curative-intent anatomical resection (lobectomy or segmentectomy) with concurrent systematic mediastinal lymph node dissection, performed with a minimally invasive uniportal approach under single lung ventilation general anaesthesia.

Tissue sampling and processing
Tissue samples were obtained by computed tomography (CT)-guided transthoracic needle biopsy or from the resected surgical specimen, then processed and preserved in formalin-fixed, paraffin-embedded (FFPE) tissue blocks.

Molecular testing and analysis
Next-generation sequencing (NGS) was used to identify genetic mutations and alterations. Programmed death-ligand 1 (PD-L1) expression was tested using the Dako 22C3 antibody on the Autostainer Link 48. The tumour proportion score (TPS) was used for reporting, indicating the percentage of tumour cells with membranous staining. Tests were performed in an ISO and CAP-certified laboratory.

Statistical analysis
Statistical analyses were performed using GraphPad Prism 10.0 and Jamovi (version 2.6.4). Descriptive statistics were used to analyse the demographic data. Continuous variables were presented as means, while categorical data were presented as frequencies or percentages. Logistic regression analysis was performed to identify predictors for an EGFR mutation. A p-value <0.05 was considered statistically significant.

RESULTS

Patient demographics and tumour characteristics
All patients but one had curative R0 resections with clear microscopic margins. There was no operative, in-hospital or 90-day mortality. Of the 146 patients evaluated, the mean patient age was 60.9 years, with a majority being females (n=81, 55.5%), of Chinese ethnicity (n=113, 77.4%) and never-smokers (n=102, 69.9%) (Table I). Ninety-five (65.1%) patients were asymptomatic with an incidental or screening-detected NSCLC. Patients who were symptomatic presented with cough, haemoptysis, weight loss, shortness of breath or chest pain. The predominant histology was adenocarcinoma in 141 (96.6%) patients (Table II). Of the 146 patients, 51 (34.9%) were diagnosed at stage IA, followed by stage IB (18.4%), stage IIA (14.4%), stage IIB (15.8%), stage IIIA (13.7%), and stage IIIB (2.8%). More than half of the patients (53.4%) had moderately differentiated (Grade II) tumours, followed by Grade I (34.9%) and Grade III (11.7%). In terms of tumour invasiveness, 37 (25.3%) patients had microscopic lymphovascular invasion (LVI), while visceral pleural invasion (VPI) (19.2%) and tumour spread through air space (STAS) (15.8%) were also reported, albeit at a lower rate. There were no microscopic features of tumour invasiveness in the remaining patients.

Overall mutational landscape, single gene mutation, and co-mutation profiles
The most common mutation detected in this study involved the EGFR gene, which was observed in 91 of 146 patients with a frequency of 62.3%. The next most frequent mutations were: TP53 (16.4%), HER2/ErbB2 (6.1%), ROS1 (5.5%), and ALK and RAS (4.8% each) (Figure 1(a)). The majority of the patients harboured a single gene mutation; EGFR mutations were the most frequent, identified in 71 patients (68.3%), followed by ROS1 (7.7%), ALK (6.7%), KRAS (5.7%), TP53 (5.7%), and other less commonly mutated genes (Figure 1(b)).

Co-mutations involving more than one gene were present in 26 of the 146 study patients (17.81%). The genes which co-mutated with EGFR include TP53 (10), CTNNB1 (3), HER2/ErbB2 (2), KEAP1 (1), PTEN (1) and NRAS (1) (Figure 2(a)). Another notable co-mutation pair was HER2/ErbB2 and TP53, present in 5 out of 7 patients who tested positive for HER2/ErbB2 mutations. Notably, 2 patients harboured two or more co-mutations, namely EGFR-TP53-FGFR2 and EGFR-TP53-PTEN-CDK4.

EGFR gene mutation subtypes
Exon 19 deletion and exon 21 L858R missense mutation were the most common, making up 84.6% of all the EGFR mutations detected in this study (Figure 2(b)). Other subtypes detected were exon 18 missense (5.2%), exon 20 insertion (4.1%) and exon 20 missense (T790M) (3.1%). The prevalence of rarer mutation subtypes such as exon 21 missense (L861Q), exon 19 insertion and exon 19 missense (I744M) was 1% each.

Univariate and multivariate logistic regression analysis for predictors of EGFR mutation
All 91 of our EGFR-mutated patients in this study had adenocarcinoma histology. The clinico-pathological characteristics of EGFR-mutated and EGFR-wild type patients are summarised in Table II. At univariate analysis, female gender, a former/never smoker status and tumour histological grade (grade III) were associated with a higher odds for harbouring an EGFR mutation (Table III). However, on multivariate analysis, only being female and a higher tumour grade were predictive (Table III). Although having a grade III tumour was significantly associated with EGFR mutation in both the univariate and multivariate models, the wide confidence interval (Table III) and the small number of cases (n=4) warrant cautious interpretation. (Tables II and III).

PD-L1 expression
PD-L1 testing was done in 115/146 (78.8%) of patients, either pre-operatively on the CT-guided diagnostic biopsy sample or on the resected surgical specimen. In patients who underwent PD-L1 testing, 68 (46.6%) had a negative score (TPS < 1%), 38 (26%) had a low score (TPS 1-49%), and 9 (6.2%) patients had a high expression (TPS > 50%) (Table II).

Table I: Demographics, smoking status, personal and family cancer history according to EGFR status

Baseline Characteristics	All patients n = 146	EGFRm n = 91	EGFRwt n = 55
Age in years (mean ± S.D.)	60.9 ± 10.0	60.5 ± 9.2	61.6 ± 11.1
Age category (number (n), percentage (%))			
< 60	61 (41.8)	44 (48.3)	17 (30.9)
60-79	83 (56.9)	47 (51.7)	36 (65.5)
≥ 80	2 (1.3)	0 (0)	2 (3.6)
Gender (n, %)			
Male	65 (44.5)	30 (33.0)	35 (63.6)
Female	81 (55.5)	61 (67.0)	20 (36.4)
Race/ ethnicity (n, %)			
Malay	9 (6.2)	6 (6.6)	3 (5.5)
Chinese	113 (77.4)	69 (75.8)	44 (80.0)
Indian	10 (6.9)	5 (5.5)	5 (9.0)
Others	14 (9.5)	11 (12.1)	3 (5.5)
Smoking status (n, %)			
Current	16 (11.0)	4 (4.4)	12 (21.8)
Former	28 (19.1)	17 (18.7)	11 (20.0)
Never	102 (69.9)	70 (76.9)	32 (58.2)
Presenting symptoms (n, %)			
Asymptomatic	95 (65.1)	62 (68.1)	33 (60.0)
Cough	33 (22.6)	19 (20.9)	14 (25.5)
Hemoptysis	13 (8.9)	7 (7.7)	6 (10.9)
Weight loss	6 (4.1)	4 (4.4)	2 (3.6)
Shortness of breath	5 (3.4)	4 (4.4)	1 (1.8)
Chest pain and discomfort	5 (3.4)	3 (3.3)	2 (3.6)
Back pain and body ache	2 (1.4)	2 (2.2)	0 (0)
Dizziness	1 (0.7)	1 (1.1)	0 (0)
Palpitations	1 (0.7)	0 (0)	1 (1.8)
Personal cancer history (n, %)			
Yes	19 (13.0)	11 (12.1)	8 (14.6)
No	110 (75.3)	69 (75.8)	41 (74.5)
N/A	17 (11.7)	11 (12.1)	6 (10.9)
Family cancer history (n, %)			
Yes	49 (33.6)	34 (37.4)	15 (27.3)
No	80 (54.8)	44 (48.4)	36 (65.4)
N/A	17 (11.6)	13 (14.2)	4 (7.3)

EGFRm= EGFR mutation detected; EGFRwt= EGFR wild type; S.D.= Standard Deviation, N/A= not available

DISCUSSION

EGFR prevalence and reflex testing

NSCLC remains a major cause of cancer-related mortality globally. Sixty per cent of both new cases and mortalities occur in Asia, whilst in Malaysia, it is the second and third most prevalent male and female cancer respectively.[2] It is the most common cause of cancer-related mortality in Malaysian men, and in women, only breast cancer has a more fatal outcome. Approximately 30% of all NSCLC cases are amenable to surgery, offering the best long-term prognosis in terms of EFS, DFS and OS when combined with multimodal therapy. However, in Malaysia, lung cancer outcomes are particularly poor, with 95% of cases presenting at advanced stages. A considerable number of surgical patients will experience stage-dependent local or distant relapse due to micro-metastases. Despite surgery and adjuvant platinum-based chemotherapy (PBC), the five-year OS benefit over surgery alone remains modest at approximately 5%.[3,4]

EGFR mutation prevalence in Malaysia

Local genomic data in early-stage NSCLC is limited. Prior studies in Malaysian patients involved mostly stage III-IV adenocarcinoma, with reported EGFR mutation frequencies ranging from 39.5% to 46.5% with higher prevalence in females, never-smokers, and ethnic Chinese.[5,6] Our study observed an EGFR prevalence of 62.3%, exceeding previous local and regional reports, likely reflecting our patient composition of predominantly female, ethnic Chinese, non-smoking patients with earlier-stage adenocarcinoma. Globally, the prevalence of EGFR mutations varies widely, from 14.1% in Europe to 49.1% in Asia.[7-11] The EARLY-EGFR study demonstrated regional differences, with Singapore and Thailand reporting rates above 60%.[11] In our cohort, the majority of EGFR mutations were actionable: exon 19 deletions or exon 21 L858R missense mutations, consistent with patterns reported elsewhere.[11,12] In one study, the TP53 gene was the most common co-mutation identified, similar to our findings.[6]

The high proportion of druggable EGFR mutations (84.7%) underscores the need for reflex genomic testing at the start of the patient journey, upon initial histological diagnosis. Reflex testing expedites treatment planning, shortens turnaround times, and ensures patients receive timely,

Table II. Tumour characteristics according to EGFR status

Tumour characteristics	All patients n = 146	EGFRm n = 91	EGFRwt n = 55
Type of tumour (n, %)			
Squamous Cell Carcinoma	4 (2.7)	0 (0)	4 (7.3)
Adenosquamous Carcinoma	1 (0.7)	0 (0)	1 (1.8)
Adenocarcinoma	141 (96.6)	91 (100.0)	50 (90.9)
Pathologic stage (n, %)			
IA	51 (34.9)	36 (39.5)	15 (27.3)
IB	27 (18.4)	17 (18.7)	10 (18.2)
IIA	21 (14.4)	13 (14.3)	8 (14.5)
IIB	23 (15.8)	12 (13.2)	11 (20.0)
IIIA	20 (13.7)	12 (13.2)	8 (14.6)
IIIB	4 (2.8)	1 (1.1)	3 (5.5)
Tumour grade			
Well differentiated (I)	51 (34.9)	38 (41.8)	13 (23.6)
Moderately differentiated (II)	78 (53.4)	49 (53.8)	29 (52.7)
Poorly differentiated (III)	17 (11.7)	4 (4.4)	13 (23.7)
Tumour invasiveness			
Lymphovascular invasion	37 (25.3)	22 (24.2)	15 (27.3)
Spread through air space	23 (15.8)	13 (14.3)	10 (18.2)
Visceral pleural invasion	28 (19.2)	18 (19.8)	10 (18.2)
PD-L1			
Negative (TPS < 1%)	68 (46.6)	46 (50.5)	23 (41.8)
Low (TPS 1-49%)	38 (26.0)	22 (24.2)	15 (27.3)
High (TPS > 50%)	9 (6.2)	5 (5.5)	3 (5.5)
Not tested	31 (21.2)	18 (19.8)	14 (25.4)

PD-L1= Programmed Death-Ligand 1, TPS= Tumour Proportion Score

Table III: Univariate and Multivariate Logistic Regression Analysis of Predictors for EGFR Mutation in NSCLC Patients
Univariate Logistic Regression Analysis

Characteristic/ Variable	Odds Ratio (OR)	95% CI for OR		p-value
		Lower	Upper	
Age in years (mean, S.D.)				0.7224
Sex				
Female (vs male)	3.56	1.803	6.956	0.0005*
Race/ethnicity				
Malay	N.E.	-	-	-
Chinese	1.275	0.3401	4.836	> 0.999
Indian	2.000	0.3611	10.31	0.6499
Others	0.546	0.1037	3.001	0.6430
Smoking status				
Current	N.E.	-	-	-
Former	0.2157	0.066	0.7812	0.031*
Never	0.1524	0.052	0.4736	0.0015*
Cancer history				
No personal cancer history (vs personal cancer history)	0.8170	0.2955	2.227	0.7990
No family cancer history (vs family cancer history)	1.855	0.8582	3.819	0.1378
Pathologic stage				
IB (vs IA)	1.412	0.5586	3.863	0.6111
IIA (vs IA)	1.477	0.4698	4.079	0.5799
IIB (vs IA)	2.200	0.8391	5.724	0.1878
IIIA (vs IA)	1.600	0.5351	4.555	0.4109
IIIB (vs IA)	7.200	0.9670	95.52	0.0975
Tumour grade				
Well differentiated (I)	N.E.	-	-	-
Moderately differentiated (II)	1.730	0.8165	3.763	0.1836
Poorly differentiated (III)	9.500	2.620	29.27	0.0003*
Tumour invasiveness				
Lymphovascular invasion	N.E.	-	-	-
Spread through air space	1.128	0.3968	3.100	>0.999
Visceral pleural invasion	0.8148	0.3057	2.343	0.7988
PD-L1				
High	N.E.	-	-	-
Low	1.136	0.2315	4.790	> 0.999
Negative	0.8333	0.1912	3.373	> 0.999

S.D.= Standard Deviation, N.E.= Not evaluable
* Statistically significant (p < 0.05)

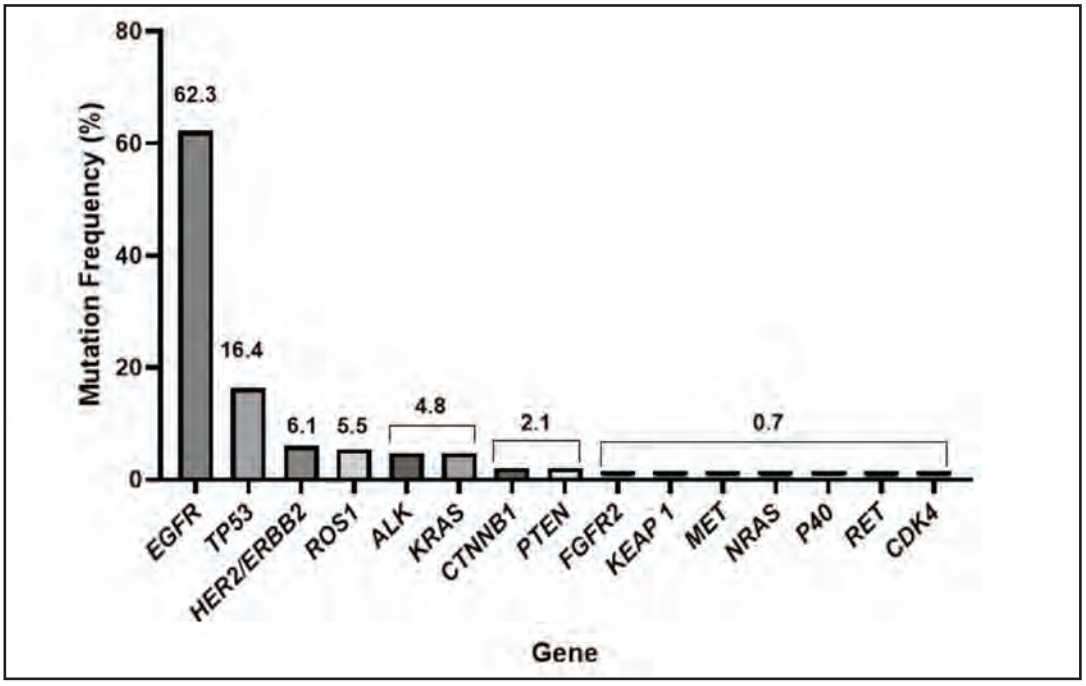

Fig. 1: A) Percentage frequency of gene mutations detected in early-stage, resectable NSCLC patients. Each bar represents the proportion of patients carrying mutations (mutant) for the respective genes.

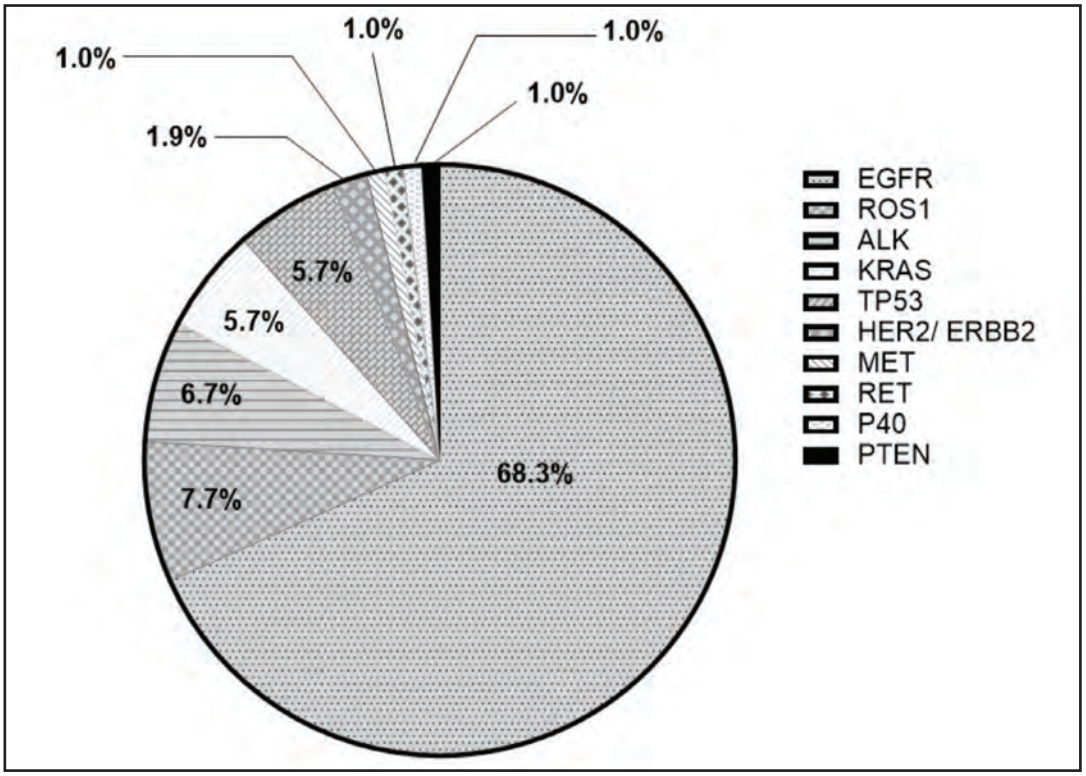

Fig. 1: B) Proportion of single gene mutations in early-stage, resectable NSCLC patients. The pie chart shows the percentage distribution of types of single-gene mutations in the patients.

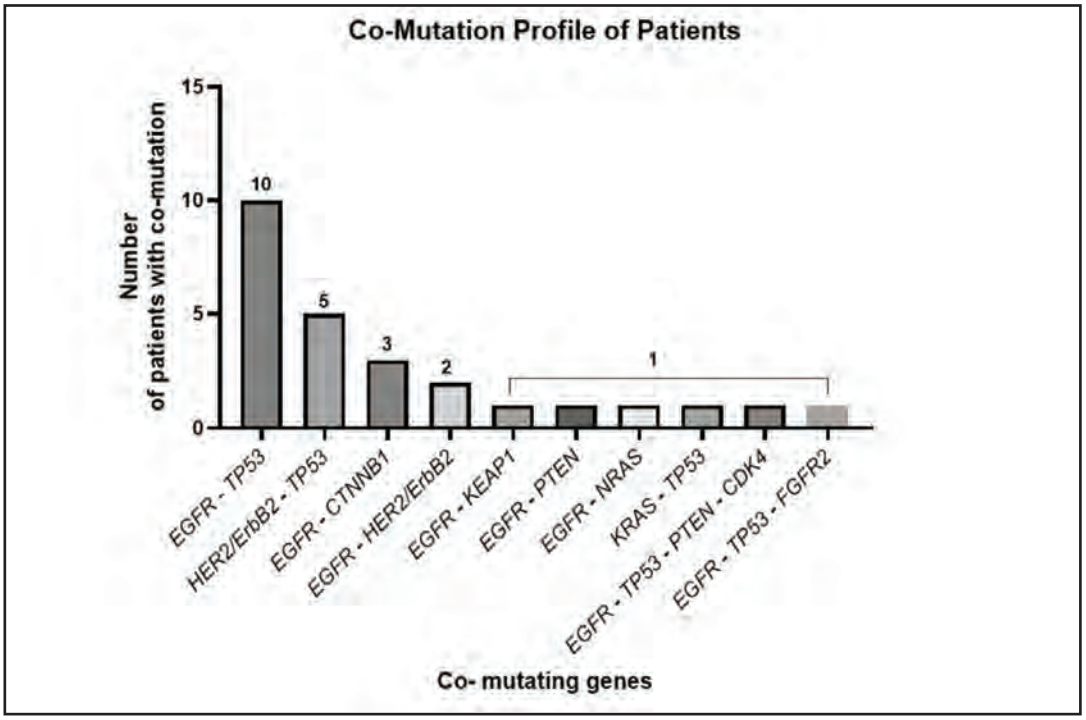

Fig. 2: A) Frequency of co-mutations in early-stage, resectable NSCLC patients. Each bar represents the number of patients with co-mutating genes, ranging from two to four.

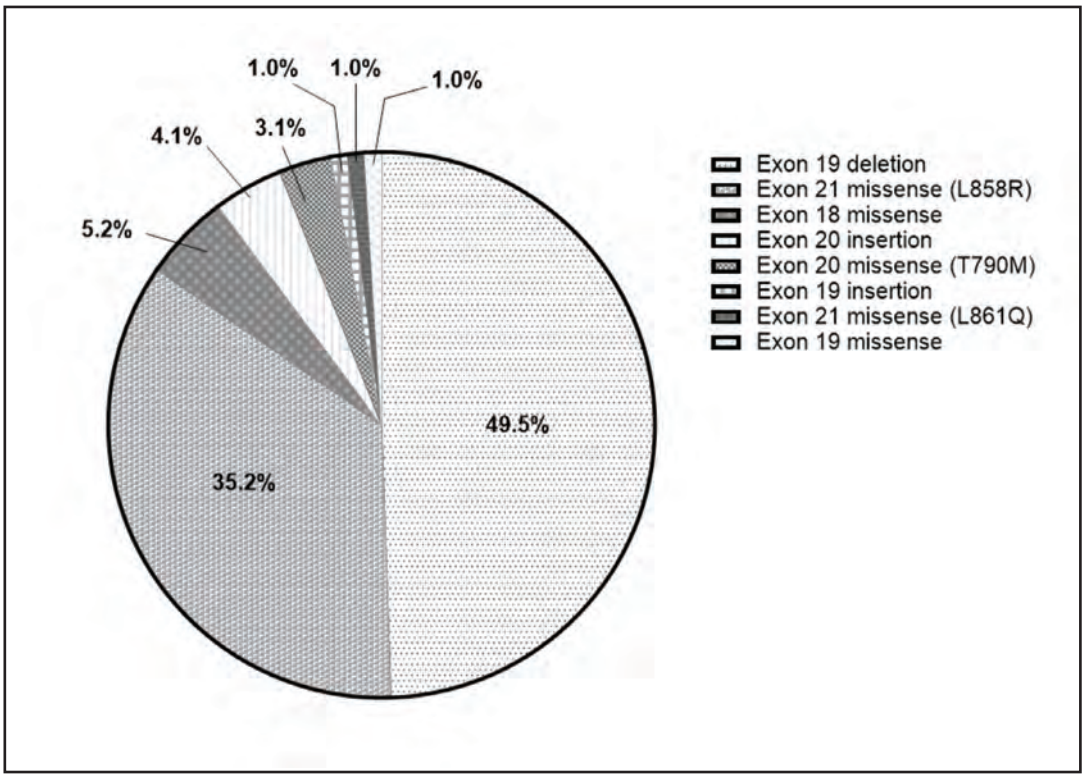

Fig. 2: B) Frequency of EGFR gene mutation subtypes in early-stage, resectable NSCLC patients. The pie chart shows the percentage distribution of subtypes of EGFR gene mutation in the patients.

appropriate biomarker-guided therapy. Pathologists should be empowered to initiate testing independently, ideally using NGS. Recently published clinical practice guidelines for early-stage NSCLC in Malaysia strongly encourage genomic molecular profiling as a reflex testing, at the start of the patient journey, where feasible, for stage IIA-IIIB-N2 NSCLC.[13] However, testing costs and variable insurance coverage remain barriers, highlighting the importance of informed consent and transparent discussions about potential out-of-pocket expenses.

Advances in adjuvant EGFR-TKI therapy and the role of mutation subtypes

The development of EGFR-TKIs has fundamentally transformed the management of EGFR-mutant NSCLC. The most important predictor of therapeutic benefit with TKI therapy is the EGFR mutation subtype. Osimertinib, a third-generation oral EGFR-TKI, is the current standard of care for EGFR-TKI sensitising (exon 19 deletion and L858R exon 21 missense) mutations. The ADAURA trial established osimertinib as a transformative adjuvant therapy, demonstrating significant DFS and OS improvements, including a 51% reduction in death risk at five years, following curative surgery.[14,15] In our study, 40/55 (72.7%) of eligible patients (stage 1B and above) received osimertinib (data not shown). Ongoing studies such as NeoADAURA,[16,17] ADAURA-2,[18] and TARGET[19] will further clarify the role of neoadjuvant and extended adjuvant EGFR-TKI therapy across disease stages.

In this study, NGS testing revealed that 84.6% of patients with EGFR-mutant NSCLC harboured sensitising mutations amenable to osimertinib treatment. This high prevalence highlights the importance of comprehensive molecular testing and profiling, locally, to guide appropriate biomarker-driven therapy. However, despite all our patients receiving an oncology review post-surgery, 27% of eligible patients did not receive Osimertinib (data not shown), suggesting cost and accessibility to therapy remain a real-world impediment even in an urban, private setting.

Identification of other mutations in NSCLC patients

Beyond EGFR, TP53, HER2/ErbB2, ROS1 and ALK were among the genetic mutations detected in our study population, either as a single mutation or a co-mutation. The most prevalent co-mutation in our EGFR-positive patients involved the TP53 gene, observed in 10 out of 20 patients with tumours that harboured co-mutations (50%). EGFR-mutant tumours with a TP53 co-mutation generally have a worse OS compared to wild-type TP53 patients receiving targeted therapy.[20]

While not all TP53 mutations are associated with a poorer prognosis, missense mutations, particularly on exon 8, have been shown to carry a worse progression-free survival (PFS), including those who developed T790M resistance mutations following treatment with osimertinib.[21,22] EGFR-mutant lung adenocarcinoma patients with TP53 co-mutation also had a higher tumour mutational burden and a worse recurrence-free survival compared to patients with only EGFR mutations.[23] Additionally, the presence of co-mutations of TP53 as well as other tumour suppressor genes such as RB1, NF1, ARID1A, BRCA1, and PTEN in patients with metastatic EGFR-mutant NSCLC has been associated with poor outcomes and reduced response when given EGFR TKIs.[24] Hence, such patients may potentially benefit from adjuvant chemotherapy in addition to TKI therapy and require closer follow-up as well as a low threshold for early re-biopsy in cases of suspected relapse.

HER2/ErbB2 mutations reported in 1-6% of NSCLC tumours often involve insertions in exon 20 of HER2/ErbB2 gene and are more common in female non-smokers. Our study findings (6.1%) align with this, where all but one patient with a HER2/ErbB2-mutated tumour harboured an exon 20 insertion or duplication. This is similar to another regional study that focused on Asians with non-squamous NSCLC.[25] Interestingly, five of our seven HER2/ErbB2 mutant patients also harboured a TP53 co-mutation, while two had concomitant EGFR mutations (Figure 3). Co-mutations of TP53 and HER2 are associated with a higher incidence of brain metastases in NSCLC patients, and shorter PFS and OS. Patients with these co-mutations also have a poorer response to targeted therapy.[26] In HER2-mutant lung cancers, TP53 is the most common co-mutation, whereas co-mutations of EGFR and HER2 are extremely rare. The existence of co-mutations may confer treatment resistance, which emerging treatments seek to surmount.

ROS proto-oncogene 1 (ROS1) rearrangements have been identified in 1- 2.6% of NSCLC patients and are sensitive to TKIs such as crizotinib, an approved first-line targeted therapy. ROS1 rearrangements are more commonly found in adenocarcinomas with distinct histological characteristics, women, young patients and light- or never-smokers.[27,28] The high frequency of ROS1 positivity (5.5%) we observed may be attributed to the predominance of female never-smokers with adenocarcinoma in our patient population.

Anaplastic lymphoma kinase (ALK) rearrangements were detected in approximately 5% of our patients, consistent with global estimates.[12] ALK-positive NSCLC patients tend to be younger, non-smokers, and present with predominantly adenocarcinoma.[29] Our ALK patients were slightly younger (mean 50.6 years), all non-smokers with more advanced disease (data not shown). Four of our seven patients commenced maintenance adjuvant alectinib (a second-generation ALK inhibitor). A recent phase III RCT (ALINA study) demonstrated significantly better DFS (88.3% (TKI) versus 53.3% platinum-based chemotherapy (PBC) at three years in fully resected ALK+ (stage II-IIIA) patients who received adjuvant alectinib 600mg twice daily for two years compared with PBC.[30] Patients who received alectinib in lieu of chemotherapy had a 76% reduction in the risk of disease recurrence. A similar DFS benefit was observed in the 'intention to treat' group, which included stage IB disease, driven by a better CNS disease-free survival (HR 0.22). Currently, OS data remains immature. These findings suggest that all resected IB-IIIA ALK-positive patients should be offered adjuvant alectinib for a minimum of two years. Meanwhile, the ongoing NAUTIKA1[31] and NEOLORA[32] trials studying neoadjuvant alectinib and lorlatinib (a third-generation ALK inhibitor), respectively, in stage IB-IIIB ALK-rearranged NSCLC will inform on the potential benefit of

upfront treatment. This again highlights the importance of reflex molecular genomic testing for any newly diagnosed early-stage rNSCLC.

Other than the genes described, EGFR co-mutations were observed with CTNNB1, KEAP1 and PTEN. CTNNB1 mutation has been associated with poor recurrence-free survival in patients with EGFR-mutant lung adenocarcinoma.[33,34] Similarly, mutation in KEAP1 was associated with shorter DFS and a negative prognosticator for patients with advanced-stage tumours.[35] PTEN loss is another mutation associated with shorter PFS and OS.[36] All these genes are involved in the development of off-target resistance to osimertinib and in such patients, a more cautious approach is required.

PD-L1 expression and challenges with predictive biomarkers

We did not observe any correlation between PD-L1 expression and EGFR mutation status, similar to the findings from the EARLY-EGFR study.[11] PD-L1 expression is part of a complex dynamic tumour microenvironment, and intra-tumoural heterogeneity further complicates interpretation: in our small sample of paired biopsies, discordance was observed in 83% of cases (data not shown). This variability limits the predictive utility of PD-L1 expression for therapeutic response to ICI therapy. Complementary biomarkers, such as circulating tumour DNA (ctDNA), may help refine patient selection, including safe adjuvant therapy de-escalation in appropriate patients, thereby mitigating unnecessary toxicity and costs.

Financial toxicity and access to targeted therapy

Affordability remains a critical barrier to treatment access. In the EARLY-EGFR study, only 8.2% of eligible patients received a TKI.[11] While a majority (73%) of our patients were able to start osimertinib, this likely reflects our private urban practice. A lower compliance with standard-of-care adjuvant osimertinib can be expected in non-private and rural settings. Nationally, financial hardship is common, with over half of Malaysian households reporting catastrophic expenditure within a year of a cancer diagnosis.[37] Ensuring equitable access to effective but high-cost targeted therapies must be a healthcare priority. Despite being an approved first-line therapy since 2018, many Malaysians with advanced EGFR-mutant NSCLC still have poor access to osimertinib and are instead prescribed more affordable first and second-generation EGFR-TKIs.[38] Patients who progressed often still did not have access to osimertinib and were offered chemotherapy. This lack of accessibility impacts their time on treatment and overall prognosis.

Implications for Contemporary Clinical Practice

Our findings support routine reflex genomic profiling in all non-squamous NSCLC upon diagnosis, including for early-stage resectable disease. Timely identification of actionable mutations will inform optimal treatment strategies, including adjuvant TKI use and neoadjuvant ICI use for non-oncogene-driven stage-dependent NSCLC, pre-operatively. Additionally, reliance solely on a tobacco history will overlook a substantial proportion of early-stage lung cancer in asymptomatic never-smokers, underscoring the need to broaden screening criteria with emphasis on a salient family history for the disease. Cost remains a real-world impediment and precludes many eligible patients from proven standard-of-care adjuvant therapy. Future healthcare financing strategies must ensure that highly efficacious drugs are affordable and accessible.

LIMITATIONS

This was a contemporary but small retrospective observational study from a private urban setting with a predominantly Chinese, female, non-smoking population. Therefore, our findings may not be generalizable to the wider Malaysian population. Larger, multicentre studies involving more diverse groups of patients are needed to validate these findings and establish true national genomic prevalence patterns.

CONCLUSION

Our study highlights the high prevalence of actionable EGFR mutations in early-stage Malaysian NSCLC patients. Reflex genomic testing at the start of the patient journey and equitable access to targeted therapies are critical to improving outcomes. Future work should focus on broader screening strategies including targeting high-risk non-smokers, better funding mechanisms, and the integration of novel biomarkers into routine care.

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ETHICS DECLARATIONS

Conflict of Interest Disclosures

Professor A. Sachithanandan is on the thoracic advisory board for AstraZeneca, Bristol Myers Squibb, Roche, and Merck Sharp & Dohme. Professor R. Pathmanathan is on the advisory board of several pharmaceutical (Merck Sharp & Dohme, AstraZeneca, Roche) and laboratory equipment manufacturers (ThermoFisher, Agilent, Roche, BioRad). The remaining authors have no disclosures or conflicts of interest.

ETHICAL APPROVAL

This study was approved by the respective Independent Research Ethics Committees of Sunway Medical Centre and Subang Jaya Medical Centre, which waived the requirement for informed consent owing to the retrospective nature of the study. This research was conducted in accordance with the principles of the Declaration of Helsinki and its later amendments or comparable ethical standards.

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