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Effects of Ethnicity on Outcomes of Patients With *EGFR* Mutation–Positive NSCLC Treated With EGFR Tyrosine Kinase Inhibitors and Surgical Resection

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ABSTRACT

Introduction: In addition to the higher prevalence of *EGFR* mutations found among lung cancer cases in East Asian patients, it is unclear whether there are differences in treatment outcomes by ethnicity—that is, East Asian versus non–East Asian.

Methods: Patients diagnosed with EGFR-mutant lung cancer between January 2004 and October 2014 at a single center were reviewed. Data captured included demographics, tumor and treatment information, and survival. Survival of patients of East Asian and non–East Asian ancestry was compared, including in the subgroup that received EGFR tyrosine kinase inhibitor (TKI) for advanced disease and in those with early-stage disease that underwent surgical resection.

Results: A total of 348 patients with EGFR-mutant NSCLC were identified. There was a higher proportion of non-smokers among those of East Asian ethnicity. No significant difference in survival was seen between patients of East Asian and non–East Asian ethnicity, median 6.7 years (95% confidence interval [CI]: 5.4–not applicable) and 5.4 years (95% CI: 4.1–7.2), respectively ($p = 0.09$). Among 196 patients that received treatment with EGFR TKI, the median survival from TKI initiation was also similar for those of East Asian and non–East Asian ethnicity, 3.0 years (95% CI: 2.1–3.5) and 2.7 years (95% CI: 2.2–3.5), respectively. Among the early-stage patients that underwent surgical resection (n = 163), those of East Asian ethnicity had similar median recurrence-free survival from surgery compared with non–East Asian patients, 5.3 years (95% CI: 3.5–not applicable) and 5.1 years (95% CI: 3.3–7.2), respectively.

Conclusions: In a cohort of patients with EGFR-mutant lung cancer with access to uniform standards of care, East Asian ethnicity was not associated with improved survival after treatment with EGFR TKI or surgical resection.

Introduction

Lung cancer management has evolved significantly over the past decade. Molecular testing for genomic alterations at the time of NSCLC diagnosis has become the standard of care along with the development and integration of molecularly targeted therapy. Tyrosine kinase inhibitors (TKIs) targeting activating mutations in the *EGFR* gene have become the standard of care in patients with advanced EGFR-mutant lung cancer with significant improvements in response rates, quality of life, lung cancer–specific symptoms, and progression-free survival (PFS) compared with chemotherapy.[1–4] In patients with early-stage NSCLC, surgical resection remains the optimal treatment for patients with good or low surgical risk, with improved relapse-free survival with adjuvant EGFR TKI in those with completely resected EGFR-mutant lung cancer (stages IB–IIIA).[5,6]

Among patients with advanced EGFR-mutant lung cancer treated with EGFR TKIs, varying levels of benefit have been observed in studies of different geographic and ethnic groups, such as the Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer study in Europe and Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer study in Asia.[1–4,7] Both trials compared outcomes with erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR-mutant lung cancer. Whereas both revealed superiority of the TKI over chemotherapy, patient outcomes varied. In the Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer study, patients receiving EGFR TKI had a median PFS of 9.7 months compared with 5.2 months with chemotherapy (hazard ratio [HR] = 0.37, 95% confidence interval [CI]: 0.25–0.54).1 In the Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer study, the median PFS with EGFR TKI was 13.1 months compared with 4.6 months with chemotherapy (HR = 0.16, 95% CI: 0.10–0.26).[7]

In the AZD9291 versus Gefitinib or Erlotinib in patients with locally advanced or metastatic non-small cell lung cancer study of first-line osimertinib versus first-generation EGFR TKI, subgroup analyses suggested greater benefit in patients of non-Asian ethnicity compared with those of Asian ethnicity, although both groups derived benefit.[8] Conflicting data exist regarding whether Asian patients with EGFR-mutant lung cancer have better outcomes than non-Asian patients.[1,7,9] Even in patients with early-stage NSCLC, ethnicity has been linked to differences in lung cancer stage at the time of resection, decisions to undergo surgery, and survival outcomes.[10–12]

It is unclear from the current literature whether ethnicity may be associated with outcomes in patients with EGFR-mutant lung cancer. In this single-center study with uniform treatment patterns for all patients, we explored whether differences exist in survival outcomes between patients with EGFR-mutant lung cancer of East Asian and non–East Asian ethnicity, including after treatment with EGFR TKIs for advanced disease or surgical resection for early stage.

Material and Methods

This study was approved by the University Health Network research ethics board. Patients diagnosed with EGFR-mutant NSCLC between January 2004 and October 2014 were reviewed. Data captured included demographics, tumor and treatment characteristics, and survival. Patient ethnicity was abstracted from electronic medical records including patient self-report and physician consultation notes.

East Asian ethnicity was defined as the ancestral origin from the People's Republic of China, Taiwan, Hong Kong, Japan, Korea, Thailand, or the Philippines. Patients with ancestral origin from all other countries were classified as having non–East Asian ethnicity. For study inclusion, patients required a pathologicic diagnosis of NSCLC with evidence of *EGFR* mutation and documented report of ethnic status. The primary objective of the study was to compare the long-term survival between East Asian and non–East Asian patients after diagnosis of EGFR-mutant lung cancer. Secondary objectives included a comparison of survival between East Asians and non–East Asians after treatment with EGFR TKIs in those with advanced lung cancer and overall survival (OS) and recurrence-free
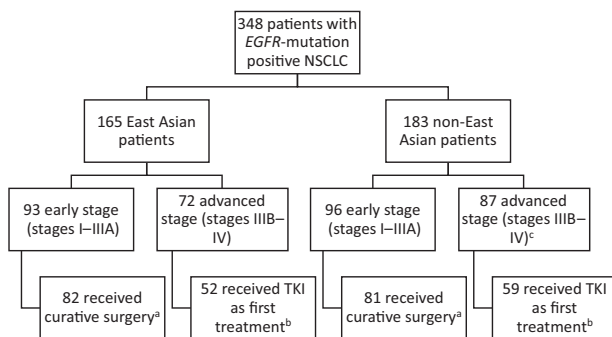
Figure 1. Flow diagram of study participants and treatment. [a]A total of 163 early-stage patients underwent curative surgery. [b]A total of 111 patients with de novo advanced lung cancer received EGFR TKI as initial therapy. [c]Three patients underwent surgery with an early clinical stage and were identified as stage IIIB (n = 1) and stage IV (n = 2) at diagnosis on pathologic stage. TKI, tyrosine kinase inhibitor.

Table 1. Demographic and Treatment Characteristics for All Study Participants

Characteristic	East Asian (n = 165)	Non-East Asian (n = 183)	p Value
Age at diagnosis			
Mean ± SD	65.0 ± 12.2	64.0 ± 11.9	0.47
Median (range)	64.6 (39.4-92.8)	64.6 (30.2-91.1)	
Sex, n (%)			
Female	106 (64.2)	129 (70.5)	0.21
Male	59 (35.8)	54 (29.5)	
Pathologic subtype, n (%)			
Adenocarcinoma	160 (97.0)	177 (96.7)	0.74
Squamous cell carcinoma	2 (1.2)	1 (0.5)	
Poorly differentiated carcinoma	1 (0.6)	3 (1.6)	
Other	2 (1.2)	2 (1.1)	
Stage at diagnosis, n (%)			
I	57 (34.5)	61 (33.3)	0.91
II	16 (9.7)	17 (9.3)	
III[a]	24 (14.5)	23 (12.6)	
IV	68 (41.2)	82 (44.8)	
Smoking, n (%)			
Current smoker	3 (1.8)	9 (4.9)	<0.0001
Former smoker	28 (17.0)	73 (39.9)	
Nonsmoker	134 (81.2)	101 (55.2)	
EGFR mutation variant, n (%)			
Exon 19 deletion	91 (55.2)	109 (59.6)	0.71
Exon 21 L858R	66 (40.0)	66 (36.1)	
Other[b]	8 (4.8)	8 (4.4)	
History of other malignancy, n (%)			
Yes	46 (27.9)	48 (26.4)	0.75
No	119 (72.1)	134 (73.6)	
Family history of lung cancer, n (%)			
Yes	29 (20.3)	25 (15.3)	0.26
No	114 (79.7)	138 (84.7)	
Non-TKI treatments received, n (%)			
Chemotherapy	12 (6.7)	19 (10.4)	0.19
Curative surgery	82 (49.7)	84 (45.9)	
Radical chemoradiation	8 (4.8)	12 (6.6)	
EGFR TKI (palliative), n (%)			
Any line[c]	91 (55.2)	105 (57.4)	
First line	78 (47.3)	81 (44.3)	0.31
Second line	9 (5.5)	16 (8.7)	
Third line or beyond	4 (2.4)	8 (4.4)	

Note: Missing/unknown: history of other malignancy n = 1, family history of lung cancer n = 42.
[a]Includes patients with incurable stage III disease.
[b]Other mutations include exon 18 and exon 20.
[c]Includes patients with de novo incurable stage IIIB/IV (n = 111) and also recurrent M1 disease (n = 85).
TKI, tyrosine kinase inhibitor.

survival (RFS) after surgical resection in those with early-stage disease.

Statistical Analysis

Patient characteristics were summarized using descriptive statistics and compared between ethnicity groups using the chi-square test or Fisher's exact test for categorical variables and *t* test or Wilcoxon-Mann-Whitney test for continuous variables, when appropriate. OS and RFS were calculated using the Kaplan-Meier method, and log-rank test was used for testing the differences between ethnic groups. RFS was calculated from the date of surgery to the date of recurrence or death. OS was calculated from the date of diagnosis for all patients and also from the date of TKI initiation for patients receiving TKI treatment. Univariable and multivariable Cox regression was performed for both OS and RFS. Clinical factors included in the multivariable Cox model were age, sex, ethnicity, smoking status, and stage. Adjuvant chemotherapy receipt was also included in RFS analysis. The proportional hazards assumption was evaluated and satisfied. HR and 95% CI were
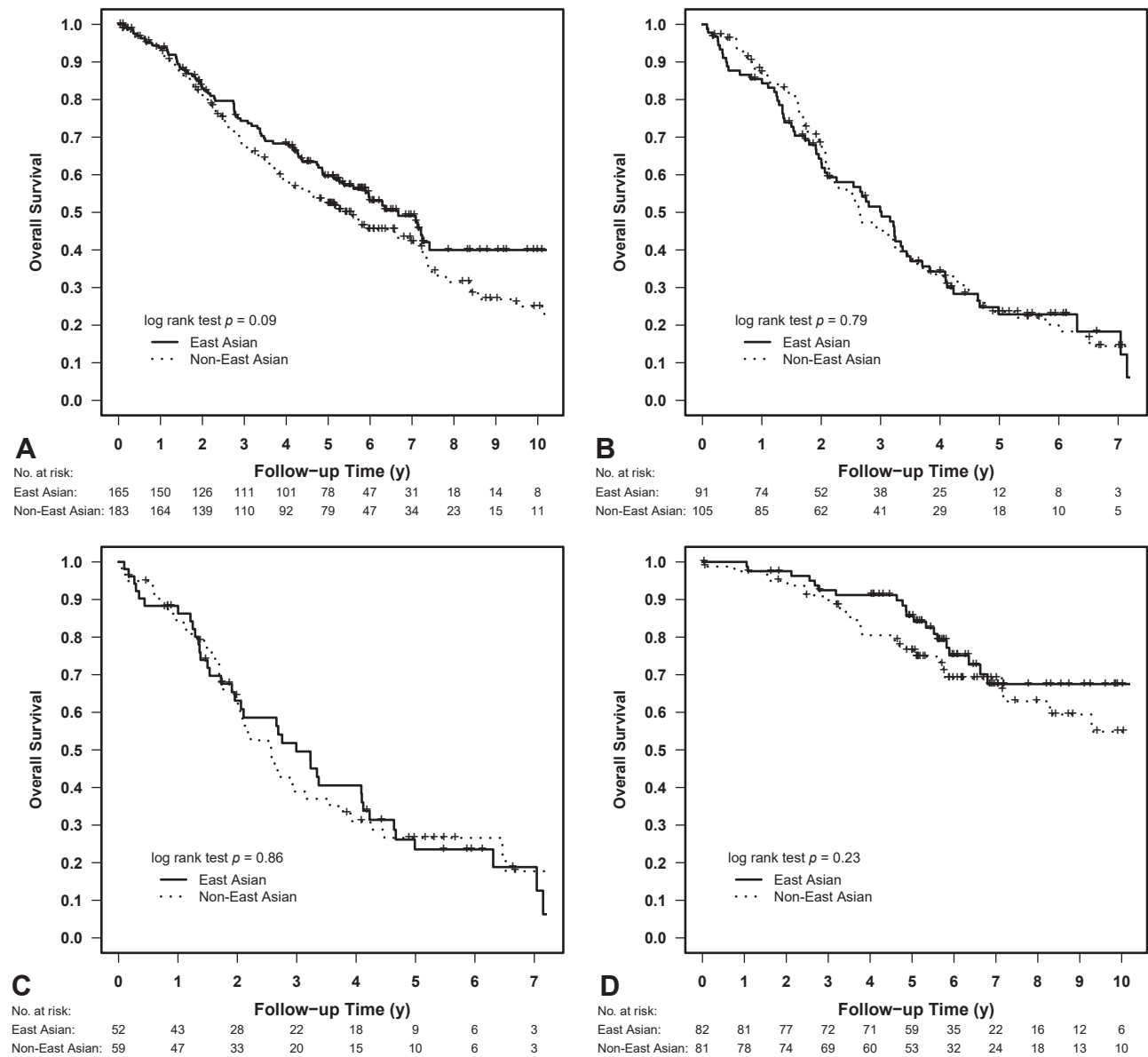
Figure 2. Overall survival by ethnicity. (*A*) Survival of all patients from initial diagnosis (n = 348); (*B*) survival from EGFR TKI initiation as any line of therapy in advanced disease (n = 196); (*C*) survival from EGFR TKI initiation as first-line therapy in advanced disease (n = 111); (*D*) survival from the time of surgical resection for early-stage patients (n = 163). TKI, tyrosine kinase inhibitor.

reported. The statistical significance level was set at a *p* value less than 0.05.

Results

Patient Demographics

We identified 348 patients with EGFR-mutant lung cancer during the study period (Fig. 1). East Asian and non–East Asian patients had similar baseline characteristics including age, sex, stage, *EGFR* mutation variant, and first treatment type (Table 1). There was a higher proportion of never-smokers among East Asian patients

compared with non–East Asian patients (81.2% and 55.2%, respectively).

OS From Time of Diagnosis

In the entire patient population, the median follow-up from the date of diagnosis was 4.5 years (range: 0.05–14.8, interquartile range: 2.1–6.2). The median OS was 6.0 years in the entire cohort (95% CI: 5.2–7.2), and the 5-year and 10-year OS rates were 55.8% (95% CI: 50.5%–61.5%) and 31.0% (95% CI: 24.6%–39.0%), respectively. The 5-year OS rate of patients diagnosed

Table 2. Multivariable Analysis of Overall Survival From Time of Diagnosis (N = 348)

Parameter	Hazard Ratio	95% Confidence Interval	p Value
Age at diagnosis	1.01	0.99-1.02	0.41
Female sex	0.78	0.57-1.08	0.13
East Asian ethnicity	0.87	0.64-1.18	0.38
Ever-smoker[a]	1.06	0.76-1.47	0.74
Stage (reference = I)			<0.0001
Stage II	2.42	1.31-4.47	0.005
Stage III	3.51	2.05-6.01	<0.0001
Stage IV	7.71	4.97-11.96	<0.0001

[a]Ever-smoker (including current, former, and former light smokers of less than five pack-years) vs. never smoker.
TKI, tyrosine kinase inhibitor.

with earlier-stage disease (stage I–IIIA) was 76.6% (95% CI: 70.5%–83.1%) and 28.6% (95% CI: 21.9%–37.5%) for those diagnosed with advanced-stage (stage IIIB–IV) disease. The median OS was 10.2 years (95% CI: 7.4–not applicable [NA]) for those diagnosed with early-stage and 2.9 years (95% CI: 2.5–3.5) for advanced-stage patients.

The median OS (all stages) was 6.7 years (95% CI: 5.4–NA) among East Asian patients compared with 5.4 years (95% CI: 4.1–7.2) among patients of non–East Asian ethnicity. The 5-year OS rates were 59.6% (95% CI: 52.2%–68.1%) for East Asian patients and 52.2% (95% CI: 45.1%–60.4%) for non–East Asian patients (HR = 0.78, 95% CI: 0.58–1.04, log-rank p = 0.09; Fig. 2A). In univariable analysis, female sex was associated with longer survival (HR = 0.73, 95% CI: 0.54–0.99, p = 0.04), but in multivariable analysis, neither ethnicity nor sex was significantly associated with survival after adjusting for age at diagnosis, smoking status, and stage (Table 2). Only the stage at diagnosis remained prognostic in multivariable analysis (p < 0.0001). Former or current smokers of East Asian ancestry had numerically longer survival than those of non–East Asian ancestry, but this was not statistically significant (HR = 0.54, 95% CI: 0.27–1.08, p = 0.08). No difference was seen among never-smokers by ethnicity (HR = 1.08, 95% CI: 0.74–1.56, p = 0.70).

OS With EGFR TKI Treatment

The study identified 196 patients (56.3%) who received treatment with EGFR TKI as any line of systemic therapy for advanced disease. The median survival time from first TKI initiation (any line of therapy) was 2.8 years (95% CI: 2.4–3.3). Survival was similar between patients of East Asian and non–East Asian ethnicity, with a median OS of 3.0 years (95% CI: 2.1–3.5) and 2.7 years (95% CI: 2.2–3.5), respectively (log-rank p = 0.79; Fig. 2B). In multivariable analysis, patients who received EGFR TKI as first-line (HR = 0.34, 95% CI: 0.17–0.67, p = 0.002) or second-line (HR = 0.36, 95% CI: 0.17–0.79, p = 0.01) therapy for the advanced disease had more favorable outcomes

compared with those who received EGFR TKI therapy as third line and beyond (Supplementary Table 1 and Fig. 3). East Asian ethnicity was not associated with OS, (HR = 1.08, 95% CI: 0.76–1.53, p = 0.69), after adjusting for age at first TKI initiation, sex, smoking status, stage at diagnosis, and line of treatment.

Preplanned subgroup analysis was performed in patients diagnosed with de novo advanced lung cancer (stage IIIB/IV) who received EGFR TKI as initial first-line therapy (n = 111; Supplementary Table 2 and Fig. 2C). In multivariable analysis, no significant association was observed between survival and ethnicity (HR = 0.95, 95% CI: 0.61–1.49, p = 0.84), after adjusting for age (HR = 1.00, 95% CI: 0.99–1.02), female sex (HR = 0.73, 95% CI: 0.45–1.20), smoking (HR = 0.76, 95% CI: 0.45–1.30), and stage (stage IV versus IIIB, HR = 2.66, 95% CI: 0.64–10.94).
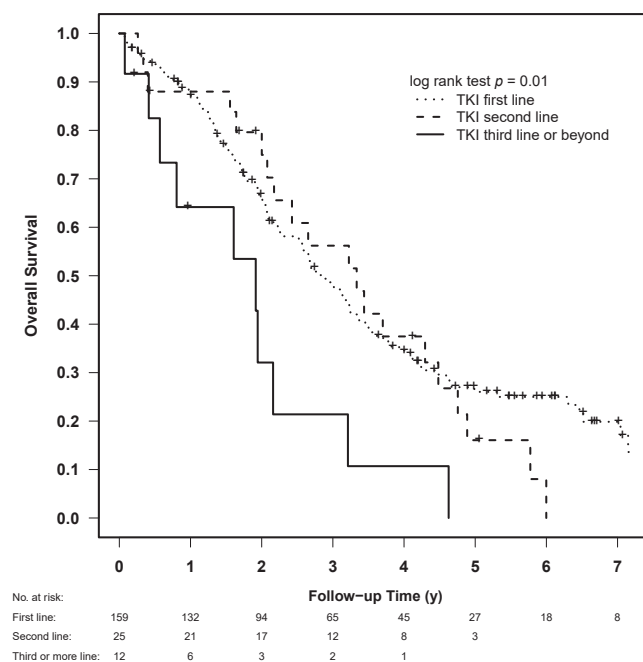
Figure 3. Overall survival by line of EGFR TKI therapy in patients with advanced-stage lung cancer (univariable analysis). TKI, tyrosine kinase inhibitor.
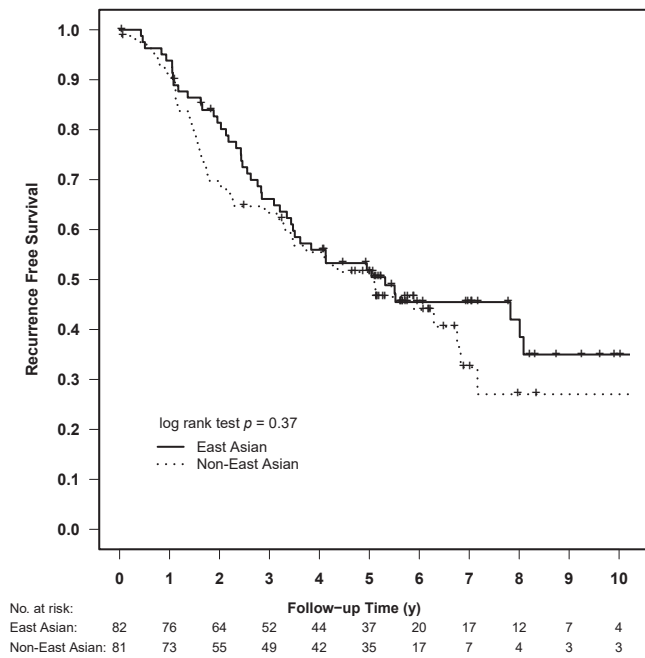
Figure 4. Recurrence-free survival after surgery in patients with early-stage lung cancer.

OS and RFS After Surgical Treatment

The study included 163 patients with stage I to IIIA EGFR-mutant lung cancer who underwent surgical resection with curative intent. The median follow-up time was 5.7 years from the date of surgery. The 5-year OS was 81.1% (95% CI: 75.1%–87.5%) among the entire surgical cohort, and the median OS was not reached. Patients of East Asian ethnicity had similar 5-year OS (85.6%, 95% CI: 78.0%–93.9%) compared with non–East Asian patients (76.4%, 95% CI: 67.4%–86.6%), as illustrated in Figure 2D, (log-rank $p = 0.23$).

The median RFS was similar between patients of East Asian and non–East Asian ethnicity, 5.3 years (95% CI: 3.5–NA) and 5.1 years (95% CI: 3.3–7.2), respectively (log-rank $p = 0.37$; Fig. 4). The higher stage at the time of diagnosis was significantly associated with shorter RFS, with HR equal to 3.15 (95% CI: 1.57–6.32) for stage II versus stage I and HR equal to 4.41 (95% CI: 2.20–8.82) for stage IIIA versus stage I; both had p values of less than or equal to 0.001. Female sex (HR = 0.61, 95% CI: 0.39–0.96, p = 0.03) was significantly associated with RFS after adjusting for age at surgical resection, smoking status, and adjuvant chemotherapy. East Asian ethnicity was not significantly associated with RFS (HR = 0.78, 95% CI: 0.50–1.21, $p = 0.26$).

Discussion

Although cross-study comparisons may suggest potential differences in outcomes in patients with EGFR-mutant lung cancer by ethnicity,[13–16] the results of this single-center study reveal similar survival outcomes between East Asian and non–East Asian patients. No differences were seen by ethnicity in the subgroup of de novo stage IV NSCLC patients who received first-line EGFR TKI in the study nor the subgroup of patients with resected early-stage disease with similar RFS among the two groups. Thus, external factors, such as differences in treatment access and patterns in different geographic areas, may influence the appearance of differential outcomes by ethnicity seen in cross-trial or within-trial comparisons.

Although smoking status has been previously found to be an independent prognosticator of a favorable outcome in advanced-disease patients, we did not observe this in our study among patients receiving EGFR TKI for advanced disease.[13] Other studies have found that smoking status is predictive of prognosis after surgery for lung cancer, though conflicting data exist.[17–19] The range of effects of cigarette smoking on tumor burden and outcomes after surgery may reflect differences in age of smoking initiation, lung function, smoking intensity, and use of filtered versus unfiltered cigarettes in various geographic regions.[20–22] Nevertheless, we found that patients of East Asian and non–East Asian ethnicities had similar outcomes after surgical resection under standardized access and treatment practices at our single cancer center, irrespective of smoking history.

One interesting finding in our study is that patients who underwent systemic treatment with EGFR TKI soon after palliative diagnosis had improved survival compared with those who received EGFR TKI in the third line and beyond. This supports the current recommendation for reflex testing at diagnosis and first-line initiation of EGFR TKI for patients with EGFR-mutant lung cancer.

Limitations of this study include its limited sample size, with all patients treated at a single tertiary cancer center, especially after stratification by ethnicity. However, patient recruitment from a single center may provide benefits in limiting the number of potential confounding variables. Because of the retrospective study design, ethnicity information was obtained through both physician notes and patient self-report. Patients with missing ethnicity information were not included in the current study. In addition, information on smoking cessation duration was not available for a significant proportion of patients, which may have been an important confounder in our analysis. Finally, patients of South Asian descent were categorized as non–East Asian for the purposes of this study. However, this population of patients may have distinct outcomes with EGFR TKI treatment that are not captured in the current study.

In a setting in which health care access and quality of care are standardized and potential confounding factors are limited, this single-center study revealed similar survival outcomes between patients with EGFR-mutant lung cancer of East Asian and non–East Asian ethnicity. Therefore, extrinsic factors such as regional differences in

treatment access and disease management may play a significant role in outcome discrepancies perceived in published literature.

CRediT Authorship Contribution Statement

Mike R. Sung: Conceptualization, Methodology, Data curation, Writing - original draft, Visualization.

Pascale Tomasini: Conceptualization, Methodology, Data curation, Writing - original draft.

Lisa W. Le: Methodology, Formal analysis, Writing - review & editing, Visualization.

Suzanne Kamel-Reid, Ming-Sound Tsao, Geoffrey Liu, Penelope A. Bradbury, Frances A. Shepherd, Ronald Feld: Writing - review & editing, Supervision.

Janice J.N. Li: Data curation, Writing - original draft.

Natasha B. Leighl: Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration.

Informed Consent Statement

This study was approved by the institutional research ethics board, is a chart review, and only aggregate data are presented. No personal identifying information were obtained nor presented in this manuscript.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100259.

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