Original Article

Molecular epidemiology and outcomes of *EGFR* exon 20 insertion in Korean patients with non-small cell lung cancer

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Background: The treatment landscape for metastatic or advanced non-small cell lung cancer (aNSCLC) evolved with the development of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs). However, *EGFR* exon 20 insertion (E20ins) mutations remain challenging to target. This study delineates molecular epidemiology, clinical characteristics, treatments, and survival outcomes of patients with E20ins compared to other *EGFR* mutations.

Methods: Electronic medical records (EMRs) from three major hospitals in South Korea were analyzed retrospectively. Patients diagnosed with aNSCLC and confirmed *EGFR* mutations between 2014 and 2019 were included. Demographics, clinical characteristics, and treatment outcomes were analyzed to compare the impact of different *EGFR* mutations on patient outcomes.

Results: Among 2,209 patients with aNSCLC, 1,978 (89.5%) exhibited common *EGFR* mutations [exon 19 deletion (E19del) and a single point mutation from leucine to arginine at exon 21 (E21L858R)], and 53 (2.4%) had E20ins. E20ins patients demonstrated notably poorer survival outcomes, with median overall survival (OS) of 13.9 months [95% confidence interval (CI): 10.1–not reached] compared to 31.0 months (95% CI: 29.0–35.8) for those with common mutations. Among 810 aNSCLC patients tested by both next-generation sequencing (NGS) and polymerase chain reaction (PCR), 21 were positive for E20ins by NGS, and 13 were positive by PCR. Of the 21 E20ins positives detected by NGS, 10 (47.6%) were not detected by PCR, while 2 patients (0.3%) were only positive for E20ins by PCR.

Conclusions: E20ins represents a small but significant subset of *EGFR* mutations in aNSCLC, with worse survival outcomes. The study also highlighted superior sensitivity of NGS over PCR in detecting E20ins. This underscores necessity for improved detection strategies and effective treatments tailored to this mutation subgroup.

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Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (*EGFR*); exon 20 insertion (E20ins); tyrosine kinase inhibitors (TKIs); next-generation sequencing (NGS)

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Introduction

Non-small cell lung cancer (NSCLC) is a predominant cause of cancer-related mortality globally. The discovery of driver oncogenes, particularly epidermal growth factor receptor (*EGFR*) mutations, has significantly altered the therapeutic landscape of NSCLC. In Asia, *EGFR* mutations are detected in approximately 40–50% of advanced or metastatic NSCLC cases, with a notably high prevalence in Korean adenocarcinomas, ranging from 29% to 50%, similar to other Asian populations (1,2).

The majority of *EGFR* mutations involve either a single point mutation from leucine to arginine at exon 21 (E21L858R) or exon 19 deletion (E19del), collectively accounting for nearly 90% of cases (3). However, *EGFR* exon 20 insertion (E20ins), translating into amino acids at positions 762–823, remains relatively rare, comprising 4–12% of *EGFR* mutation cases (4). These insertions promote an active kinase conformation by forming a structural wedge at the end of the C-helix of *EGFR* (5-12). In the Asia-Pacific region, the prevalence of E21L858R, E19del, and E20ins mutations has been reported as 42%, 49%, and 2%, respectively, with other less common mutations, such as E18G719X or E21L861Q, contributing to 2–3% of cases (12,13).

Recent therapeutic advancements have seen the introduction of amivantamab, an *EGFR* and *MET* bispecific antibody, and the development of sunvozertinib (DZD9008) and furmonertinib (14), an irreversible and selective EGFR-tyrosine kinase inhibitor (TKI), which has demonstrated anti-tumor efficacy and received the Food and Drug Administration (FDA)'s breakthrough therapy designation (15,16). Given therapeutic advances, this study aims to provide a detailed account of the molecular epidemiology, clinical characteristics, detection methods, and treatment outcomes of E20ins in advanced or metastatic NSCLC within a real-world setting, highlighting the significant need for accurate molecular diagnosis and effective therapeutic strategies. We present this article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-1-1372/rc).

Highlight box

Key findings

- In South Korea, exon 20 insertion (E20ins) mutation prevalence in non-small cell lung cancer (NSCLC) was 2.4%, rising with next-generation sequencing (NGS) adoption.
- Patients with E20ins showed worse survival than common epidermal growth factor receptor (*EGFR*) mutations.
- NGS was more sensitive than polymerase chain reaction (PCR) for E20ins detection, emphasizing its earlier use.

What is known and what is new?

- E20ins in NSCLC is an uncommon alteration and has continued to be difficult to treat.
- This study demonstrated that E20ins was associated with poorer survival outcomes and emphasized the greater sensitivity of NGS compared to PCR in identifying E20ins.

What is the implication, and what should change now?

- Novel therapeutic approaches for E20ins are being developed, highlighting the importance of elucidating the molecular epidemiology, clinical profiles, treatment patterns, and survival outcomes of patients with E20ins in comparison with other EGFR mutations. This further emphasizes the need for enhanced diagnostic methods and optimized therapies specifically designed for this mutation subset.

Methods

Patients, design, and data collection

This multi-center, retrospective cohort study utilized electronic medical records (EMRs) from three large tertiary hospitals in South Korea—Asan Medical Center, Samsung Medical Center, and Severance Hospital of Yonsei University Health System. These hospitals represent approximately 20–25% of NSCLC cases diagnosed in South Korea between 2014 and 2019 (17,18). Data were extracted for patients aged ≥18 years with an initial diagnosis of advanced or metastatic (clinical stage IIIB/C or IV) NSCLC with *EGFR* mutation prior to the initiation of the first-line of treatment (LoT1). Exclusion criteria

included patients without histological confirmation, those with morphology code indicating small cell lung cancer, or other primary cancers from July 2013 to the end of the study period. Patients who were not treated during the study data period or did not receive any treatment within 6 months of diagnosis were also excluded.

EGFR mutation subtypes were identified based on the first *EGFR* mutation test conducted at or after the histologic diagnosis of advanced or metastatic NSCLC and prior to LoT1 initiation. Patients were categorized into four sub-cohorts based on activating *EGFR* mutation: (I) E19del; (II) E21L858R; (III) E20ins; and (IV) other uncommon mutations. The "uncommon mutations" category includes G719X, L861Q, S768I, E709X, and L747X. *EGFR* mutations E19del and E21L858R were grouped for comparison with E20ins mutation.

Baseline demographics, clinical characteristics, and treatment details were recorded, including age, sex, histology, smoking status, comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, tumor-node-metastasis (TNM) staging, number of therapy lines, and systemic anti-cancer therapies. Data collection was dependent on data availability, quality, and validity, which were assessed through rigorous data due diligence to ensure conformity, completeness, and plausibility (19). The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Boards of Asan Medical Center (No. S2020-1971-0002), Samsung Medical Center (No. SMC 2020-08-117), and Severance Hospital of Yonsei University Health System (No. 2020-1974-001). Individual consent for this retrospective analysis was waived.

EGFR mutation tests

Genetic test results, captured from diagnosis to the end of the study, were obtained using polymerase chain reaction (PCR) sequencing and/or in-house next-generation sequencing (NGS). Patients were considered to have a genetic mutation if any positive results were recorded during the collection period.

Outcomes and measurement

The primary outcomes included the incidence of *EGFR* mutation subtypes and proportion of genetic testing methods. Secondary outcomes encompassed clinical characteristics and treatment patterns by *EGFR* mutation subgroup, overall survival (OS) defined as the time from the initiation of LoT1 to the date of death or the end of follow-up, and time to treatment discontinuation (TTD) defined as date from LoT1 initiation to the date of LoT1 discontinuation.

Data analysis

Initially, site research teams analyzed de-identified patient-level data on-site, generating aggregated statistical summaries in a common format. These summaries were then shared with a central location and pooled using meta-analytic pooling. No patient-level data were shared outside each site. This strategy was designed to address data privacy concerns while enabling multi-site research collaboration.

Statistical analysis

Distributions of *EGFR* subtypes and tests performed were reported as counts and percentages. Baseline characteristics and treatments were summarized using descriptive statistics and compared using Student's *t*-test for normally distributed continuous variables and the Chi-squared test or Fisher's exact test (when any expected cell counts were <5) for categorical variables. OS and TTD were analyzed using the Kaplan-Meier (KM) approach, including median survival times, 95% confidence intervals (CIs), and P values from log-rank tests. Patients participating in clinical trials were excluded from all survival analyses.

The association between *EGFR* mutation subgroups and OS/TTD was assessed using multivariate Cox regression modeling, adjusting for confounding factors such as age at diagnosis, gender, smoking status, ECOG status, TNM staging, histology type, and underlying comorbidities [e.g., asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, tuberculosis, chronic liver disease, diabetes mellitus, ischemic heart disease, chronic hepatitis B, hypertension, previous cancer history]. A sensitivity analysis was performed with the Cox model adjusted for systemic chemotherapy regimens.

For the meta-analysis, direct estimates of the log-adjusted hazard ratios (aHRs) with standard errors from individual sites were pooled using a random-effects generic inverse variance meta-analysis (20,21). This model was chosen to account for potential heterogeneity among hospitals. Missing data were reported as numbers and percentages, with no imputation made for missing data. Analyses were performed using R version >4.0.0, and significance was determined using

two-sided tests at a significance level of 0.05.

Results

In total, 24,179 patients were identified with a primary diagnosis of NSCLC between 2014 and 2019. In total, 24,179 patients were identified with a primary diagnosis of NSCLC between 2014 and 2019. The date of data cut-off was March 31, 2020, and the maximum follow-up period for this study, from the beginning of the observation window to the data cut-off, was 69 months. After applying the eligibility criteria, 8,323 patients (34.4%) with stage IIIB/C–IV were noted. Of these, 2,209 patients (26.5%) with *EGFR* mutations between diagnosis and LoT1 initiation were included in the study.

Baseline characteristics and EGFR mutation subtypes

Among a total of 2,209 patients with *EGFR* mutations, the baseline characteristics of 2,031 patients, excluding 178 with uncommon *EGFR* mutations, are summarized in *Table 1*. The incidence of E20ins was a total of 2.6% (53 patients) and has gradually increased since 2017, correlating with South Korea's government reimbursement of NGS for advanced solid tumor patients since that year (22). Patients with E20ins were slightly younger (mean age: 58.8 *vs.* 62.3 years, P=0.02), and were less likely to have non-squamous carcinoma (94.3% *vs.* 97.2%, P=0.04) compared to those with common *EGFR* mutations. However, no significant differences were found in other baseline characteristics.

At diagnosis, approximately half of the patients had E19del (n=1,187, 53.7%), followed by E21L858R (n=791, 35.8%), E20ins (n=53, 2.4%), and other *EGFR* mutations (n=178, 8.1%). Common *EGFR* mutations accounted for 89.5% of all *EGFR* mutations identified. PCR sequencing detected more than 90% of *EGFR* mutation subtypes. However, the relative detection rate of NGS over PCR for E20ins was higher (9.4%) compared to E19del (3.2%), L858R (2.3%), and other mutations (7.3%) (*Figure 1*).

Among 787 advanced NSCLC (aNSCLC) patients tested by NGS and PCR, 21 and 13 patients were positive for E20ins by NGS and PCR, respectively. Of the 21 E20ins positives detected by NGS, 10 (47.6%) were not detected by PCR, while 2 patients (0.3%) were only positive for E20ins by PCR. Due to the limitations of PCR in detecting E20ins subtype, most patients with E20ins were unaware of their E20ins subtype (n=34/53, 64.2%). The E20ins (3dup) subtype was identified in 9 (17.0%) patients with E20ins, with other variants occurring at near-loop (n=6, 11.3%) and far-loop (n=4, 7.5%).

Pattern of systemic treatment and survival outcomes

Figure 2 details the first-line and second-line treatments by *EGFR* mutations. Fewer patients with E20ins (24.5% and 22.6%) received TKIs compared to those with common *EGFR* mutations (85.8% and 48.4%) at first- and second-line, respectively. Conversely, more patients with E20ins (62.3% and 22.6%) received platinum-based chemotherapy compared to those with common *EGFR* mutations (5.6% and 17.7%) as first- and second-line treatments, respectively.

Figure 3 illustrates OS from LoT1 by *EGFR* mutation subtypes. Detailed information on LoT is provided in Table S1. None of the patients with E20ins received sunvozertinib, zipalertinib, mobocertinib, or amivantamab. Patients with E20ins had a significantly shorter median OS (13.9 months; 95% CI: 10.1–not reached), compared to those with common *EGFR* mutations (31.0 months; 95% CI: 29.0–35.8). Patients with E20ins also had a two-fold higher risk of death from LoT1 (aHR: 2.2; 95% CI: 1.2–4.0; P=0.008) than those with common *EGFR* mutations, based on a multivariable analysis. However, upon adjusting for systemic chemotherapy regimen variables, this difference in risk of death was not significant (aHR: 1.5; 95% CI: 0.6–3.7; P=0.38) (Table S2).

Figure 4 shows TTD from LoT1 by *EGFR* mutation subgroups. Patients with E20ins had a significantly shorter median TTD (3.2 months; 95% CI: 2.5–5.6), compared to patients with common *EGFR* mutations (10.3 months; 95% CI: 9.7–11.0). Based on a multivariable analysis, patients with E20ins had a 2.5-fold higher risk of treatment discontinuation than those with common *EGFR* mutations (aHR: 2.5; 95% CI: 1.4–4.4; P=0.001). However, this difference became non-significant upon adjusting for systemic chemotherapy regimen variables (aHR: 1.3; 95% CI: 0.8–2.0; P=0.26) (Table S2).

Discussion

This study offers a comprehensive overview of the molecular epidemiology associated with *EGFR* mutation subtypes in advanced or metastatic NSCLC patients in South Korea from 2014 to 2019. The incidence of *EGFR* E20ins was 2.6%, and as the nationwide adoption of NGS became widespread, its incidence increased. Among 21

Table 1 Baseline characteristics stratified by E20ins *vs.* common *EGFR* mutations

Characteristics	All	E20ins	Common *EGFR* mutations	P value[†]
Total cohort	2,031 (100.0)	53 (2.6)	1,978 (97.4)	
Advanced diagnosis year				0.10
2014	186 (9.2)	3 (5.7)	183 (9.3)	
2015	288 (14.2)	<3 (<5.7)	286 (14.5)	
2016	376 (18.5)	8 (15.1)	368 (18.6)	
2017	422 (20.8)	13 (24.5)	409 (20.7)	
2018	401 (19.7)	13 (24.5)	388 (19.6)	
2019	358 (17.6)	14 (26.4)	344 (17.4)	
Age at aNSCLC diagnosis (years)	62.2±11.0	58.8±13.2	62.3±10.9	0.02*
Gender				0.32
Female	1,226 (60.4)	28 (52.8)	1,198 (60.6)	
Male	805 (39.6)	25 (47.2)	780 (39.4)	
Smoking status				0.22
Never smoker	1,344 (66.2)	30 (56.6)	1,314 (66.4)	
Former smoker	463 (22.8)	13 (24.5)	450 (22.8)	
Current smoker	218 (10.7)	10 (18.9)	208 (10.5)	
Missing/unknown	6 (0.3)	0 (0.0)	6 (0.3)	
Performance score ECOG at advanced diagnosis				0.13
0	481 (23.7)	10 (18.9)	471 (23.8)	
1	1,066 (52.5)	29 (54.7)	1,037 (52.4)	
2	128 (6.3)	5 (9.4)	123 (6.2)	
3 & 4	32 (1.6)	3 (5.7)	29 (1.5)	
Missing/unknown	324 (16.0)	6 (11.3)	318 (16.1)	
TNM classification at diagnosis				0.53
IIIB/C	112 (5.5)	4 (7.6)	108 (5.5)	
IV	1,919 (94.5)	49 (92.5)	1,870 (94.5)	
Histology				0.04*
Non-squamous carcinoma	1,973 (97.1)	50 (94.3)	1,923 (97.2)	
Squamous-cell carcinoma	26 (1.3)	0 (0.0)	26 (1.3)	
Other specified NSCLC carcinoma & not otherwise specified	32 (1.6)	3 (5.7)	29 (1.5)	

Data are presented as n (%) or mean ± SD. [†], comparison between E20ins and common types (E19del and E21L858R). Student's *t*-test was used to compare age at aNSCLC diagnosis between E20ins and common mutations groups. For categorical variables, Chi-squared test or Fisher's exact test was used when any of the expected cell counts were <5. *, P value <0.05 is considered as statistical significance. aNSCLC, advanced non-small cell lung cancer; E19del, exon 19 deletion; E20ins, exon 20 insertion; E21L858R, a single point mutation from leucine to arginine at exon 21; ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SD, standard deviation; TNM, tumor-node-metastasis.

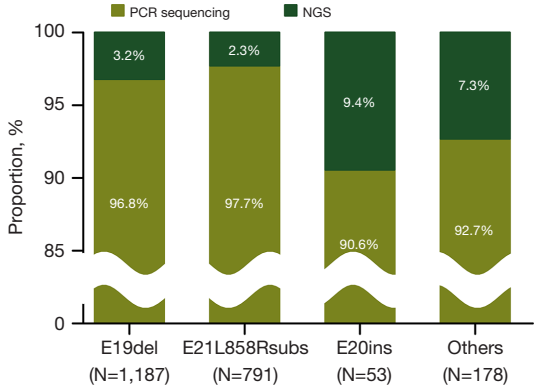

Figure 1 Incidence of *EGFR* mutations detected by PCR sequencing and/or NGS. The PCR sequencing subgroup includes *EGFR* mutations detected by PCR only or by both PCR and NGS. Whereas the NGS subgroup includes the *EGFR* mutations detected by NGS only. E19del, exon 19 deletion; E20ins, exon 20 insertion; E21L858R, a single point mutation from leucine to arginine at exon 21; *EGFR*, epidermal growth factor receptor; NGS, next-generation sequencing; PCR, polymerase chain reaction.

patients with *EGFR* E20ins who underwent both NGS and PCR, 10 (47.6%) were identified by NGS but not by *EGFR* single-gene PCR. Before the introduction of novel targeted therapies for *EGFR* E20ins, during the study period of 2014–2019, first-line palliative systemic chemotherapy for patients with *EGFR* E20ins aNSCLC consisted of EGFR-TKI (24.5%) and platinum-based chemotherapy (62.3%). The TTD of LoT1 was 3.2 months (95% CI: 2.5–5.6), which was significantly shorter than the LoT1 TTD of 10.3 months (95% CI: 9.7–11.0) observed in common *EGFR* mutations. Moreover, the median OS for *EGFR* E20ins-positive patients was 13.9 months (95% CI: 10.1–not reached), which was significantly worse compared to 31.0 months (95% CI: 29.0–35.8) in patients with common *EGFR* mutations. It highlights the evolving landscape of molecular testing, baseline characteristics, treatment patterns, and survival outcomes, with a particular focus on E20ins mutations. In this context, the significance of this study lies in its depiction of the natural clinical course of patients with *EGFR* E20ins and its proposal of an optimal molecular diagnosis strategy.

Our study reveals a concerning median TTD of LoT1 of 3.2 months (95% CI: 2.5–5.6) for patients with E20ins mutations, reflecting the disappointing efficacy of first- and second-generation EGFR-TKIs and conventional chemotherapy in this population, revealing significant clinical unmet needs. In line with our nationwide findings from South Korea, real-world and population-based studies have consistently demonstrated that E20ins represent a rare but clinically aggressive subgroup of NSCLC. In a large multinational real-world analysis from Europe and the United States reported that immunotherapy or non-selective EGFR-TKIs did not result in meaningful improvements in OS or treatment durability compared with standard chemotherapy, underscoring the historical lack of effective frontline options for this population (23). However, a multicenter Spanish real-world study demonstrated that the introduction of targeted agents, including amivantamab, mobocertinib, and sunvozertinib, at any point during the treatment course was associated with a substantial improvement in median OS (24). The phase I CHRYSALIS study established the clinical activity of amivantamab in patients with E20ins progressed after platinum-based chemotherapy, demonstrating an objective response rate of approximately 40% and a median progression-free survival of 8.3 months (25). Encouragingly, PAPILLON trial, phase 3 trial comparing amivantamab plus pemetrexexd and carboplatin *vs.* pemetrexexd and carboplatin as comparator, resulted in superior PFS [median, 11.4 and 6.7 months; hazard ratio (HR) =0.40; 95% CI: 0.50–0.53; P<0.001] and became the first FDA approved treatment as the first-line treatment of patients with *EGFR* E20ins (26). Based on the findings of the PAPILLON trial, the first-line standard of treatment for patients with *EGFR* E20ins aNSCLC has now changed. More recently, real-world studies from early access programs and single-center cohorts have corroborated the effectiveness and manageable safety profile of amivantamab in routine clinical practice, reporting objective response rates of approximately 30–35% in heavily pretreated populations (27,28). Selective TKIs targeting E20ins mutations are also under active clinical development. Preclinical studies have shown that zipalertinib potently suppresses *EGFR* signaling and tumor cell proliferation in E20ins mutant cancer cell lines, while demonstrating enhanced selectivity for E20ins (29). In the REZILIENT1 trial, zipalertinib produced durable clinical responses in patients previously treated with amivantamab, with an objective response rate of approximately 30%. The ongoing two phase 3 trials (NCT05973773 and NCT05967689) are evaluating zipalertinib in combination with chemotherapy as first-line therapy and in patients with active or untreated brain metastases (30). In addition, early clinical data of sunvozertinib indicated meaningful

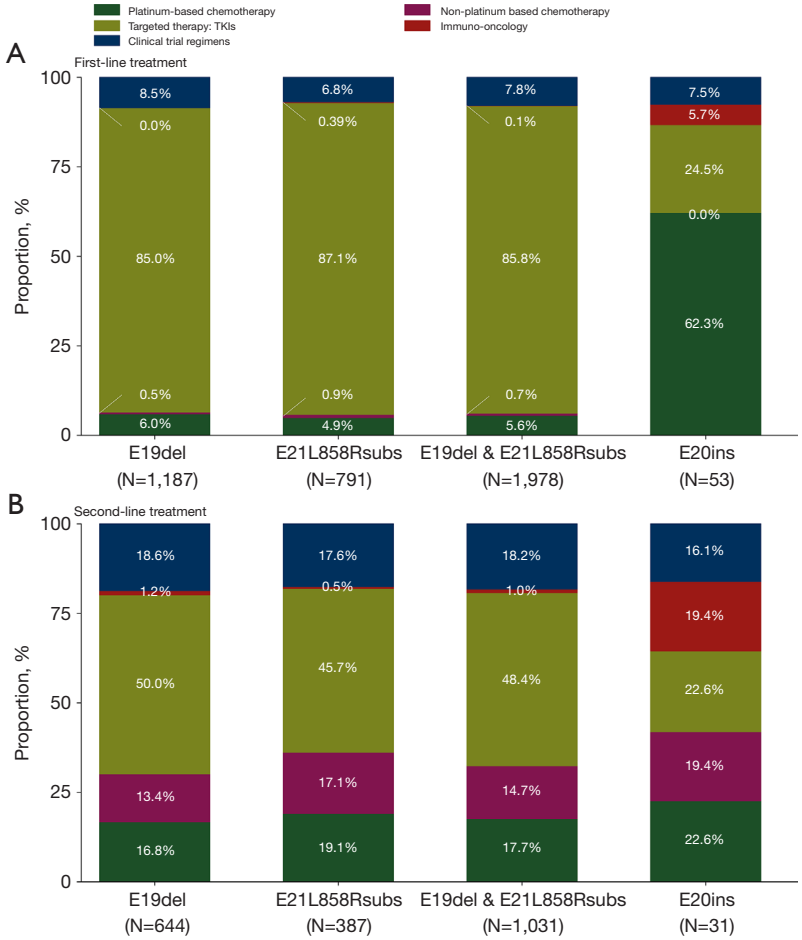

Figure 2 Treatment patterns of (A) first-line and (B) second-line treatment across E20ins and common *EGFR* mutations. E19del, exon 19 deletion; E20ins, exon 20 insertion; E21L858R, a single point mutation from leucine to arginine at exon 21; *EGFR*, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

antitumor activity in patients with E20ins previously received platinum-based chemotherapy, with an objective response rate reaching 46–47% and received accelerated approval from the FDA approval on July 2025 (31). In this context, the present study is noteworthy as it presented the real-world survival outcomes of prior treatments, including EGFR-TKIs and platinum-doublet chemotherapy, while also highlighting the diagnostic limitation of *EGFR* PCRs and demonstrating NGS as an optimal diagnostic strategy to overcome these challenges.

The detection of *EGFR* E20ins presents unique challenges. Our findings highlight that PCR has limitations in detecting half of the E20ins cases. Hou *et al.* reported that E20ins were associated with a higher metastatic burden and significantly worse OS, therefore highlighting the importance of comprehensive NGS for accurate detection, as these mutations are frequently underrecognized by limited molecular assays (32). There has been an improved detection rate from 2017 onward, which aligns with the adoption of NGS under healthcare reimbursement policies. The rapid development of targeted therapies may exacerbate existing limitations in testing sensitivity, accessibility, turnaround times, and costs. Despite NGS becoming the standard molecular diagnostic tool for aNSCLC in Korea, its longer turnaround times (3–10 weeks) compared to PCR (3–4 days) remains a significant barrier in decision making of palliative first-line systemic treatment (22). Nonetheless, considering the limited efficacy data for novel E20ins-targeting agents in first-line settings, the implementation of upfront NGS is recommended as part of a comprehensive

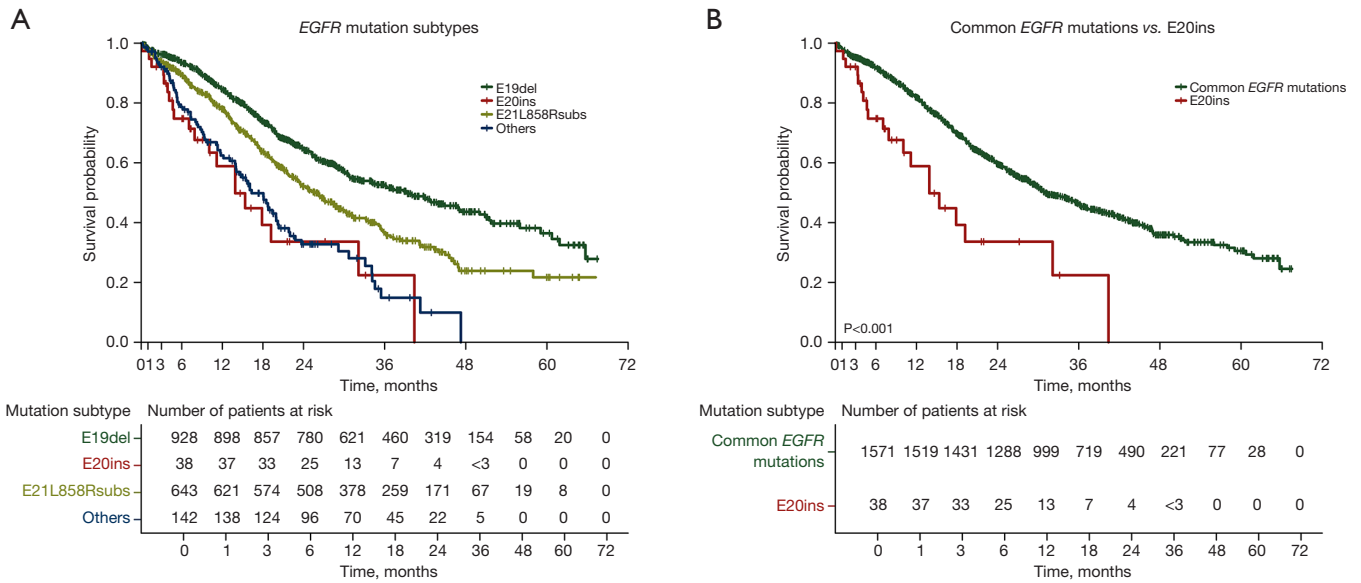

Figure 3 OS by (A) *EGFR* mutation subgroup, (B) common *EGFR* mutations *vs.* E20ins from the first-line systemic treatment. E19del, exon 19 deletion; E20ins, exon 20 insertion; E21L858R, a single point mutation from leucine to arginine at exon 21; *EGFR*, epidermal growth factor receptor; OS, overall survival.

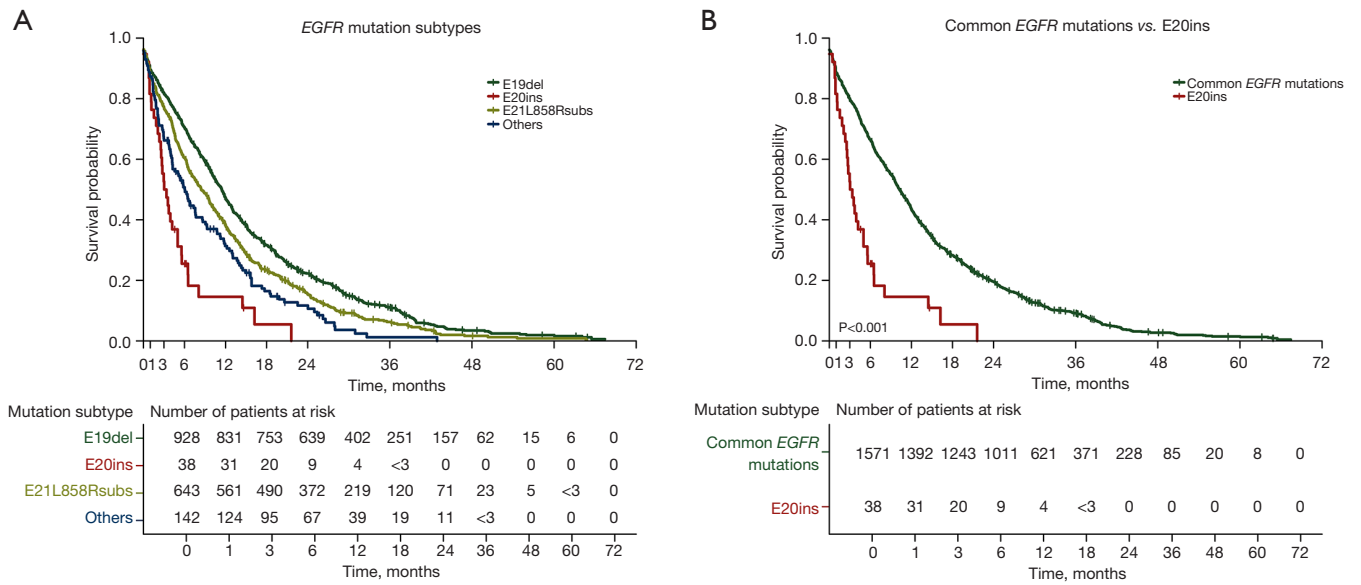

Figure 4 TTD from the first-line systemic treatment by (A) *EGFR* mutation subtype, (B) common *EGFR* mutations *vs.* E20ins. E19del, exon 19 deletion; E20ins, exon 20 insertion; E21L858R, a single point mutation from leucine to arginine at exon 21; *EGFR*, epidermal growth factor receptor; TTD, time to treatment discontinuation.

molecular diagnostic strategy at the time of diagnosis (33).

The *EGFR* exon 20 region, encoding amino acids 762 to 823, includes both the c-helix (AA762–823) and loop region (AA767–774) (34). This segment is critical because E20ins mutations, involving in-frame insertions and/or duplications of 3–21 bases typically between AA761 and AA775, exhibit over 60 pathogenic variants. As a result, *EGFR* E20ins represents a highly heterogeneous population with diverse mutational profiles and clinical behaviors. This molecular diversity was highlighted in the CHRYSTALIS trial, a phase I dose-escalation study of amivantamab that reported variable anti-tumor responses based on mutation sites within helical, near-loop, and far-loop regions, with overall response rates of 100%, 41%, and 25%, respectively (25). Such heterogeneity necessitates deeper genomic sequencing to accurately characterize these mutations, emphasizing precise identification of mutation site of *EGFR* E20ins by NGS.

Conclusions

Despite the rarity of E20ins mutations in aNSCLC patients in South Korea, similar to global trends, the lack of historical detection and the limited accessibility to NGS—which has been compounded by a lack of effective therapies—have likely contributed to underrepresentation. In the current treatment landscape, platinum-based chemotherapy combined with amivantamab is recommended as the preferred first-line therapy for patients with aNSCLC harboring E20ins mutations. Upon disease progression, targeted agents such as sunvozertinib or amivantamab are recommended as subsequent treatment options, followed by other systemic therapies according to prior exposure and clinical context. With the advent of targeted therapies for E20ins and more popular NGS use in routine clinics, there is a critical need to enhance the identification of these patients to improve clinical outcomes.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-1-1372/rc

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Boards of Asan Medical Center (No. S2020-1971-0002), Samsung Medical Center (No. SMC 2020-08-117), and Severance Hospital of Yonsei University Health System (No. 2020-1974-001). Individual consent for this retrospective analysis was waived.

References

1. Lee JG, Kim HC, Choi CM. Recent Trends of Lung Cancer in Korea. Tuberc Respir Dis (Seoul) 2021;84:89-95.
2. Choi CM, Kim HC, Jung CY, et al. Report of the Korean Association of Lung Cancer Registry (KALC-R), 2014. Cancer Res Treat 2019;51:1400-10.
3. Leduc C, Merlio JP, Besse B, et al. Clinical and molecular characteristics of non-small-cell lung cancer (NSCLC) harboring EGFR mutation: results of the nationwide French Cooperative Thoracic Intergroup (IFCT) program. Ann Oncol 2017;28:2715-24.
4. Hou J, Li H, Ma S, et al. EGFR exon 20 insertion mutations in advanced non-small-cell lung cancer: current status and perspectives. Biomark Res 2022;10:21.
5. Gunter R, Szeto E, Jeong SH, et al. Cigarette Smoking in South Korea: A Narrative Review. Korean J Fam Med 2020;41:3-13.
6. Harrison PT, Vyse S, Huang PH. Rare epidermal growth factor receptor (EGFR) mutations in non-small cell lung cancer. Semin Cancer Biol 2020;61:167-79.
7. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. Ann Oncol 2014;25:126-31.
8. Wu JY, Wu SG, Yang CH, et al. Lung cancer with epidermal growth factor receptor exon 20 mutations is associated with poor gefitinib treatment response. Clin Cancer Res 2008;14:4877-82.
9. Naidoo J, Sima CS, Rodriguez K, et al. Epidermal growth factor receptor exon 20 insertions in advanced lung adenocarcinomas: Clinical outcomes and response to erlotinib. Cancer 2015;121:3212-20.
10. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. Mol Cancer Ther 2013;12:220-9.
11. Lund-Iversen M, Kleinberg L, Fjellbirkeland L, et al. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations. J Thorac Oncol 2012;7:1471-3.
12. Byeon S, Kim Y, Lim SW, et al. Clinical Outcomes of EGFR Exon 20 Insertion Mutations in Advanced Non-small Cell Lung Cancer in Korea. Cancer Res Treat 2019;51:623-31.
13. Pao W, Chmielecki J. Rational, biologically based treatment of EGFR-mutant non-small-cell lung cancer. Nat Rev Cancer 2010;10:760-74.
14. Han B, Zhou C, Zheng W, et al. OA03. 04 A phase 1b study of furmonertinib, an oral, brain penetrant, selective EGFR inhibitor, in patients with advanced NSCLC with EGFR exon 20 insertions. J Thorac Oncol 2023;18:S49.
15. U.S. Food and Drug Administration. FDA Approves First Targeted Therapy for Subset of Non-Small Cell Lung Cancer. 2021. Accessed 1 May 2023. Available online: https://www.prnewswire.com/news-releases/fda-approves-first-targeted-therapy-for-subset-of-non-small-cell-lung-cancer-301296998.html
16. U.S. Food and Drug Administration. FDA grants accelerated approval to mobocertinib for metastatic non-small cell lung cancer with EGFR exon 20 insertion mutations. 2021. Accessed 1 May 2023. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mobocertinib-metastatic-non-small-cell-lung-cancer-egfr-exon-20
17. Jung HA, Lee DH, Lim SM, et al. Epidemiology and Outcomes of Non-Small Cell Lung Cancer in South Korea. JAMA Netw Open 2024;7:e2355331.
18. National Cancer Center. Annual report of cancer statistics in Korea in 2019. 2021. Accessed 1 May 2023. Available online: https://ncc.re.kr/cancerStatsList.ncc?sea
19. Kahn MG, Callahan TJ, Barnard J, et al. A Harmonized Data Quality Assessment Terminology and Framework for the Secondary Use of Electronic Health Record Data. EGEMS (Wash DC) 2016;4:1244.
20. Higgins JPT, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. In: Higgins JPT, Thomas J, Chandler J et al., editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Hoboken: Wiley-Blackwell; 2019:143-76.
21. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
22. Yoon S, Kim M, Hong YS, et al. Recommendations for the Use of Next-Generation Sequencing and the Molecular

Tumor Board for Patients with Advanced Cancer: A Report from KSMO and KCSG Precision Medicine Networking Group. Cancer Res Treat 2022;54:1-9.
23. Chouaid C, Bosquet L, Knott C, et al. Real-world frontline treatments in patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor exon 20 insertions and adjusted comparisons versus amivantamab plus chemotherapy from the PAPILLON study. Lung Cancer 2025;203:108548.
24. Suay G, Martín-Martorell P, Aparisi F, et al. A real world study of clinical characteristics, treatment sequence and outcomes of patients with non-small cell lung cancer and EGFR exon 20 insertion mutations. Clin Transl Oncol 2025;27:2568-78.
25. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 2021;39:3391-402.
26. Zhou C, Tang KJ, Cho BC, et al. Amivantamab plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med 2023;389:2039-51.
27. Choi DH, Jung HA, Park S, et al. Effectiveness and safety of amivantamab in EGFR exon 20 insertion (E20I) mutations in non-small cell lung cancer (NSCLC). Transl Lung Cancer Res 2023;12:2448-59.
28. Pierret T, Greillier L, Guisier F, et al. Real-world efficacy and safety of amivantamab in EGFR exon-20-mutant non-small cell lung cancer in a French early-access program: Amexon 20 GFPC study. Lung Cancer 2025;209:108766.
29. Hasako S, Terasaka M, Abe N, et al. TAS6417, A Novel EGFR Inhibitor Targeting Exon 20 Insertion Mutations. Mol Cancer Ther 2018;17:1648-58.
30. Heymach JV, Yu HA, Besse B, et al. REZILIENT3: randomized phase III study of first-line zipalertinib plus chemotherapy in patients with EGFR exon 20 insertion-mutated NSCLC. Future Oncol 2025;21:549-56.
31. Yang JC, Wang M, Doucet L, et al. Phase II Dose-Randomized Study of Sunvozertinib in Platinum-Pretreated Non-Small Cell Lung Cancer With Epidermal Growth Factor Receptor Exon 20 Insertion Mutations (WU-KONG1B). J Clin Oncol 2025;43:3198-208.
32. Hou Y, Xue X, Zhang Z, et al. Genomic and clinical characterization of HER2 exon 20 mutations in non-small cell lung cancer: insights from a multicenter study in South China. BMC Cancer 2025;25:752.
33. Lee Y, Clark EW, Milan MSD, et al. Turnaround Time of Plasma Next-Generation Sequencing in Thoracic Oncology Patients: A Quality Improvement Analysis. JCO Precis Oncol 2020;4:PO.20.00121.
34. Tamirat MZ, Kurppa KJ, Elenius K, et al. Structural Basis for the Functional Changes by EGFR Exon 20 Insertion Mutations. Cancers (Basel) 2021;13:1120.

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