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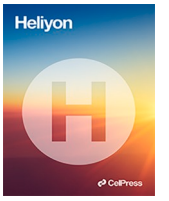

Effectiveness comparison of third-generation EGFR-TKI as initial and sequential therapy in adjuvant treatment for EGFR mutation-sensitive stage IIIA non-small cell lung cancer after surgery

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ABSTRACT

Introduction: Although third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) Osimertinib has been approved as adjuvant therapy for resected stage IIIA non-small cell lung cancer (NSCLC) with EGFR-sensitive mutations, the optimal treatment sequencing of EGFR-TKIs, particularly whether Osimertinib should be the initial or sequential therapy following the first-generation EGFR-TKIs remains uncertain.

Methods: A retrospective analysis was conducted on a cohort of patients with EGFR-mutated stage IIIA NSCLC who received treatment with either first-generation EGFR-TKIs or Osimertinib (third-generation) alone, or in sequential combination, at a single institution. The data analysis involved using the Kaplan-Meier method, log-rank test, and Cox regression.

Results: Out of the total 148 patients with stage IIIA NSCLC included in the study, 76 individuals underwent treatment with either first-generation EGFR-TKIs (referred to as subgroup "1″) or exclusively Osimertinib (subgroup "0 + 3″), or a sequential combination of the two (subgroup "1 + 3″) following surgery. Both univariate and multivariate analyses demonstrated that there were no discernible disparities in terms of disease-free survival and overall survival between subgroup " 1″ and " 1 + 3," nor between subgroup " 0 + 3″ and "1 + 3".

Conclusion: The findings from this study indicate that the introduction of third-generation EGFR-TKI Osimertinib did not yield enhanced survival benefits when compared to the first-generation drug in patients with stage IIIA completely resected NSCLC who were administered EGFR-TKIs as part of their postoperative adjuvant treatment. Additionally, within the observed sample size of this cohort, the sequential use of Osimertinib alongside first-generation EGFR-TKI did not demonstrate superiority over using either the first-generation EGFR-TKI or Osimertinib alone in terms of postoperative survival.

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1. Introduction

One of the most common oncogenic drivers in non-small cell lung cancer (NSCLC) is the presence of epidermal growth factor receptor (EGFR) mutations, which show varying prevalence among different racial and ethnic groups. Notably, the Asian population exhibits a high prevalence of EGFR mutations, with rates reaching approximately 50 % of lung adenocarcinoma cases [1–4].

First and second-generation EGFR tyrosine kinase inhibitors (TKIs) serve as primary therapeutic options for advanced NSCLC patients with sensitive EGFR mutations (e.g., EGFR exon 19 deletion mutation or exon 21 L858R point mutation). These treatments have shown significant improvements in median progression-free survival (PFS), a substantial advancement compared to chemotherapy [5–9]. However, disease progression remains inevitable, with the most prevalent cause being the emergence of secondary EGFR T790 M mutation [10]. To address this challenge, third-generation EGFR-TKIs have demonstrated their effectiveness in inhibiting the EGFR T790 M mutation, becoming the standard treatment for patients who develop this mutation following first or second-generation EGFR-TKI therapy. Notably, third-generation EGFR-TKIs exhibit pronounced improvements in both PFS [11–13] and overall survival (OS) [14,15] compared to their first-generation counterparts, thereby solidifying their position as the frontline standard treatment for patients diagnosed with advanced EGFR-mutated NSCLC.

Early and less advanced stage disease (stages I-IIIA) makes up about one-third of all NSCLC cases. In these instances, surgical resection is commonly given priority in accordance with established clinical guidelines. To improve the survival time and reduce the risk of recurrence after radical surgery, postoperative adjuvant treatment is recommended for stage IB-IIIA to eradicate residual micrometastases. Multiple clinical studies have illustrated the benefits of postoperative EGFR-TKIs for stage IB-IIIA NSCLC [16–18], although the PFS advantage did not translate to a significant OS difference. Recently, Osimertinib, a third-generation EGFR-TKI, has obtained approval for the management of stage IB-IIIA NSCLC patients with EGFR-sensitive mutations [15,19], providing additional compelling evidence that supports the efficacy of adjuvant EGFR-TKIs following surgical resection.

However, despite the significance of EGFR-TKI treatments in the postoperative setting, most clinical trials have primarily focused on either first- or third-generation EGFR-TKI therapies in isolation. There is a paucity of evidence to ascertain the optimal treatment strategy, specifically whether to employ third-generation EGFR-TKI as a primary treatment or as part of a sequential treatment approach after first-generation EGFR-TKIs. In a more recent phase II exploratory study of the APPLE trial, researchers found that in patients with advanced NSCLC carrying EGFR mutations, first-line Osimertinib treatment reduced the risk of brain metastasis compared to sequential treatment of first-generation gefitinib followed by Osimertinib (NCT02856893; Presented at: 2023 European Lung Cancer Congress). However, there was no significant difference in OS between the two groups, with the need for further studies to explore this matter in greater detail. It remains uncertain whether this observation holds true for NSCLC carrying EGFR mutations at less advanced stages (e.g., IB-IIIA) after surgery.

As a result, there is a significant gap in the available data regarding whether Osimertinib should be prioritized as the initial choice for targeted treatment or considered in a sequential treatment approach following first-generation EGFR-TKIs for stage IIIA NSCLC patients with EGFR-sensitive mutations who have undergone complete resection in Asian patients. The lack of comprehensive studies comparing the effectiveness and sequencing strategies of these therapies leaves a critical question unanswered and underscores the need for further research to establish the optimal treatment strategy for patients with EGFR-mutated IIIA NSCLC after surgery.

This study, through the retrospective collection of clinical data, aims to provide empirical evidence to inform the optimal treatment pattern for stage IIIA NSCLC patients with EGFR-sensitive mutations who have undergone complete resection.

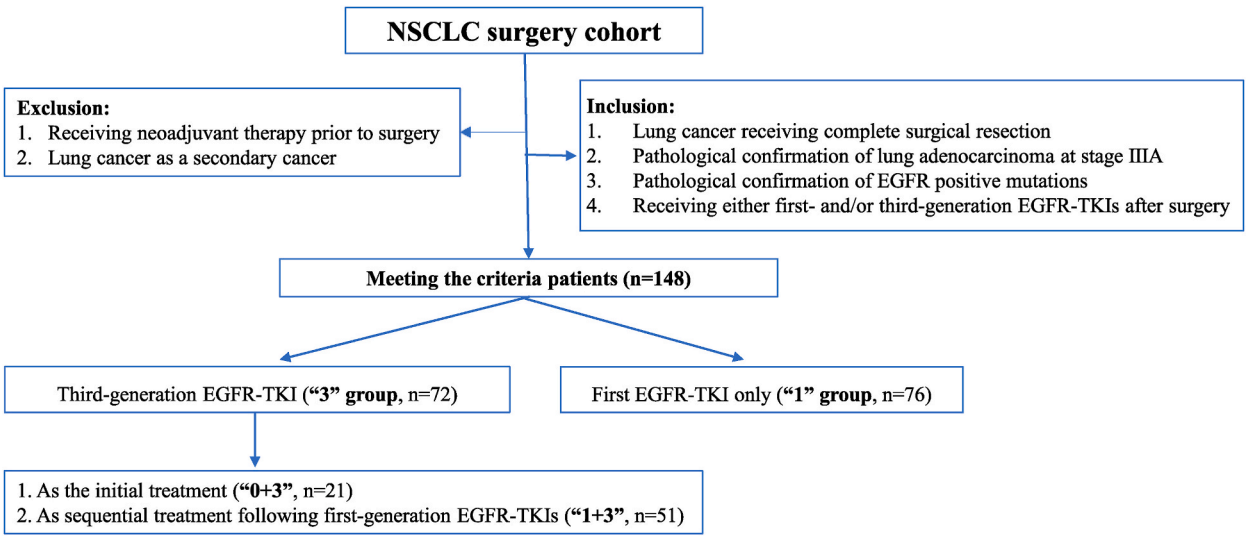

Fig. 1. The workflow of this study cohort.

2. Patients and methods

2.1. Study population and study design

The study population included patients at a single institution who underwent complete resection for stage IIIA NSCLC harboring sensitive EGFR mutation and received postoperative adjuvant treatment with either first-generation or third-generation EGFR-TKIs between January 1, 2015, and January 1, 2019 (Fig. 1). After obtaining approval from Shanghai Chest Hospital ethical review board (#KS(Y)21039), data were collected from the prospectively established cancer database according to the eligibility criteria. For information not available in the database, data were retrieved from the hospital electronic medical records using ID identification. The survival data were retrieved from the clinic records or telephone contact.

3. Preoperative examinations

The present study describes the comprehensive preoperative assessment conducted on all enrolled patients to ascertain the surgical resectability and safety. This evaluation encompassed a series of diagnostic procedures, including brain magnetic resonance imaging (MRI), contrast-enhanced chest computed tomography (CT) scan or positron emission tomography (PET)/CT scan, bronchoscopy, abdominal CT or ultrasonography examination, and/or whole-body bone scan [20,21].

Pathological confirmation of the suspected tumors was accomplished through tumor biopsies. Furthermore, the assessment of mediastinal nodal status was facilitated by employing PET-CT or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) techniques.

Additionally, all patients who proceeded with the surgical intervention fulfilled specific eligibility criteria, including an Eastern Cooperative Oncology Group performance status of 0–1, normal organ function, and adequate lung function reserve suitable for the intended resection procedure. These stringent criteria ensured that the surgical candidates were in optimal health conditions, thereby promoting favorable surgical outcomes.

3.1. Surgical operation

The study implemented either a posterolateral thoracotomy (open) or video-assisted thoracic surgery (VATS) with systemic lymphadenectomy, chosen based on the patient's individual medical condition, their informed consent, and the preference of the operating surgeons. Throughout the surgical procedures, meticulous documentation of the operative approach, extent of resection, operative time, hospital length of stay, postoperative morbidity, and other relevant aspects related to the surgical experience were recorded. Pathological staging was based on the guidelines outlined by the American Joint Committee on Cancer (AJCC) for Lung Cancer Staging, 8th edition [22]. In the postoperative phase, all patients underwent adjuvant therapies encompassing EGFR-TKIs and/or chemotherapy.

3.2. Postoperative treatment subgroups

We compared the survival time of patients with and without third-generation EGFR-TKIs in the treatment regimens (Fig. 1).

1) Subgroup 1: First-generation ("1") EGFR-TKI alone vs. its sequential use with third-generation ("1 + 3") EGFR-TKI ("1" vs. "1 + 3");
2) Subgroup 2: Third-generation EGFR-TKI as initial ("0 + 3") vs. sequential ("1 + 3") therapy following first-generation EGFR-TKI ("0 + 3" vs. "1 + 3").

3.3. Survival analysis

The primary endpoint was overall survival (OS), defined as the interval between the day of surgery and the date of death from any cause or the last follow-up date (July 1st, 2023). In addition, we assessed disease-free survival (DFS) as secondary endpoint, defined as the duration from the day of surgery to the occurrence of either tumor relapse or death, whichever takes place first.

3.4. Statistical analysis

Baseline characteristics were compared using two-sample t-tests or the Mann–Whitney test for continuous variables, and chi-square or Fisher exact probability test for categorical variables [23]. The Kaplan–Meier method and log-rank test were performed to estimate DFS and OS and to examine the survival differences between the two groups, respectively. Cox's proportional hazard model was used to estimate the univariate and multivariate hazard ratios (HRs) with 95 % confidence intervals to identify the difference in effects between the two groups. Age, sex, surgical approaches, pathologic T and N stages, and whether chemotherapy constituted the initial treatment were all accounted for and adjusted in the multivariate Cox regression analysis. Akaike's information criterion (AIC) was used to compare the fit of different models. Akaike information criterion: $AIC = -2\log L + 2p$, where p is the number of estimated parameters and L is the likelihood function. A smaller AIC statistic suggests a better fit. Spearman (non-normally distributed) or Pearson (normally distributed) correlation analysis was used to measure the strengths of association between DFS and OS. Statistical analysis was performed using the R software (version 4.1.0, http://www.r project.org. $P < 0.05$ was considered statistically significant.

4. Results

4.1. Clinical characteristics

One hundred and forty-eight patients met our criteria. The most prevalent EGFR mutations were exon 19 deletion mutation (48.82 %) and exon 21 L858R point mutation (44.88 %). All patients received adjuvant chemotherapy, either as the first- or second-line treatment, during the postsurgical course in this cohort. Specifically, 123 patients received chemotherapy alone as the first-line treatment. The remaining 25 patients received EGFR-TKIs without chemotherapy as the first-line treatment. Adjuvant radiation therapy was given after disease recurrence.

One hundred and twenty-seven (127/148, 85.8 %) patients received first-generation EGFR-TKI as the initial targeted treatment, and the remaining 21 patients received third-generation EGFR-TKI targeted drugs as the first choice (Fig. 1). Of the 127 patients who received first-generation EGFR-TKIs, 76 patients (76/127, 59.8 %) were treated exclusively with one type of EGFR-TKIs, and 51 patients (51/127, 40.2 %) received first-generation EGFR-TKI drug following up third-generation EGFR-TKI during the treatment. The most commonly prescribed first EGFR-TKI targeted drugs were Ektinib (50.4 %), Gefitinib (40.16 %), followed by Erlotinib (9.45 %).

First-generation EGFR-TKI alone vs. its sequential use with third-generation EGFR-TKI ("1" vs. "1 + 3")

The baseline clinical characteristics of patients in subgroups "1" and "1 + 3" were presented in Table 1, which showed no significance. Brain metastasis was observed in 9 patients in the subgroup "1 + 3" (29.03 %), and 11 patients in the subgroup "1" group (30.56 %) without significance.

After a median follow-up period of 87.5 months for the subgroup "1 + 3" and 82.77 months for the subgroup "1", the 5-year DFS rates were 10 % and 18.5 %, respectively, for the two groups (Fig. 2A). The 5-year OS for the subgroup "1 + 3" was 71.1 % (95 % CI: 56.1%–81.8 %), while it was 61.5 % (95 % CI:49.3%–71.6 %) for the subgroup "1" (Fig. 2B).

Univariate and multivariate analysis did not show difference between "1" and "1 + 3" subgroups (Table 2).

Third-generation EGFR-TKI as initial vs. sequential therapy following first-generation EGFR-TKI ("0 + 3" vs. "1 + 3")

The baseline clinical characteristics of patients within these two subgroups were outlined in Table 3. The results predominantly indicated no significant differences, except for the average time lapse between surgery and the commencement of the initial EGFR-TKI treatment. This interval was 15.9 months in the "1 + 3″ subgroup, as opposed to 27.17 months in the "0 + 3″ subgroup, demonstrating a notable distinction (p-value = 0.0073).

Table 1
Clinical characteristics of patients receiving third-generation TKI as part of the sequential treatment (Subgroup "1") and those who did not (Subgroup "1 + 3").

	All (n = 127)	Subgroup "1" (n = 76)	Subgroup "1 + 3" (n = 51)	P value
Age at surgery, years, mean (SD)	58.19(9.2)	59.5(8.97)	56.28(9.17)	0.055
Sex, n (%)				
Female	78(61.42)	45(59.21)	33(64.71)	
Male	49(38.58)	31(40.79)	18(35.29)	
Surgery, n (%)				0.24
Lobectomy	124(97.64)	74(97.37)	50(98.04)	
Bilobectomy	1(0.79)	0(0)	1(1.96)	
Segmentectomy	2(1.57)	2 (2.63)	0 (0.00)	
Interval between surgery and EGFR-TKIs, month, Mean (SD)	16.37(12.17)	16.75(13.08)	15.9(12.17)	0.75
pN, n (%)				0.36
N0	3(2.36)	3(3.95)	0	
N1	15(11.81)	9(11.84)	6 (11.76)	
N2	109(85.83)	64(84.21)	45(88.24)	
pT, n (%)				0.61
T1	33(25.98)	19(25.00)	14(27.45)	
T2	60(47.24)	39(51.32)	21(41.18)	
T3	26(20.47)	13(17.11)	13(25.49)	
T4	8(6.3)	5 (6.58)	3(5.88)	
Metastatic site, n (%)				0.52
Brain	20(29.85)	11(30.56)	9(29.03)	
Lung	17(25.37)	11(30.56)	6(16.28)	
bone	13(19.4)	6(16.67)	7(22.58)	
Lymph nodes	6(8.96)	4(11.11)	2(6.45)	
Other sites	11(16.42)	4(11.1)	7(25.66)	
Adjuvant radiotherapy, n (%)				0.80
Yes	63(49.61)	37(48.68)	26(50.98)	
No	64(50.39)	39(51.32)	25(49.02)	
Adjuvant chemotherapy, n (%)				0.66
Yes	110(86.61)	65(85.53)	45(88.24)	
No	17(13.39)	11(14.47)	6(11.76)	
EGFR-TKIs as first-line, n (%)				0.69
Yes	22(17.32)	14(18.42)	8(15.69)	
No	105(82.68)	62(81.58)	43(84.31)	

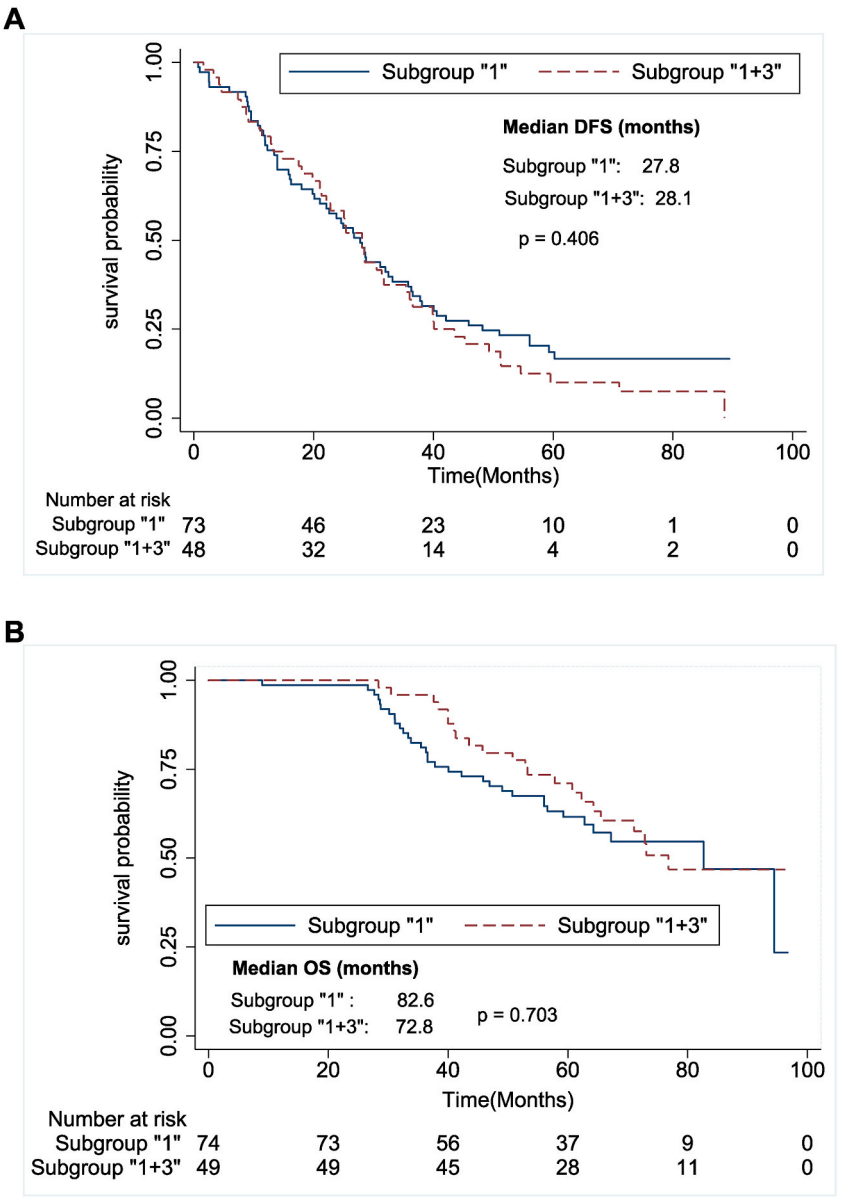

Fig. 2. The survival analysis entails a comparison between Subgroup "1" and Subgroup "1 + 3". Panel A: DFS (disease-free survival); panel B: OS (overall survival).

The median follow-up time was 87.5 months for the subgroup "1 + 3", and 97 months for the subgroup "0 + 3". The 5-year DFS rate were 10 % (95 % CI:5%–37.1 %) in the subgroup "1 + 3" and 8.7 % (95 % CI:3.5%–20.6 %) in the subgroup "0 + 3", respectively. In addition, the 5-year OS rates were 71.1 % (95 % CI:56.1%–81.8 %) and 61.6 % (95 % CI:37.6%–78.6 %) in the two groups, respectively. The median DFS was 28.1 months in the subgroup "1 + 3", and 27.9 months in the subgroup "0 + 3" (Fig. 3A). The median OS

Table 2
Univariate and multivariate survival analysis.

Comparison subgroups	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
"1" vs "1 + 3" (OS)[a]	0.91(0.56–1.48)	0.70	0.87(0.34–2.2)	0.76
"1" vs "1 + 3" (DFS)[a]	1.18(0.80–1.73)	0.41	0.66(0.34–1.2)	0.22

[a]The HR adjusted by age, metastasis site, type of surgery, pT, pN, sex, whether EGFR TKI using as first-line treatment in the Cox regression.
[b]The HR adjusted by age, metastasis site, type of surgery, pT, pN, sex, whether EGFR TKI using as first-line treatment in the Cox regression.

Table 3
Clinical characteristics between patients who received first-to third-generation TKIs sequencing (subgroup "0 + 3") and those who received third-generation TKIs as the initial EGFR-TKI (subgroup "1 + 3").

	All (n = 72)	Subgroup "1 + 3" (n = 51)	Subgroup "0 + 3" (n = 21)	P-value
Age at surgery, years, Mean (sd)	56.51(9.82)	56.3(9.2)	57.1(11.5)	0.77
Sex, n (%)				0.87
Female	47(65.28)	33(64.71)	14(66.67)	
Male	25(34.72)	18(35.29)	14(66.67)	
Surgery, n (%)				0.24
Lobectomy	70(97.22)	50(98.04)	20(95.24)	
Bilobectomy	1(1.39)	1(1.96)	0 (0)	
Segmentectomy	1(1.39)	0 (0)	1(4.76)	
Interval between surgery and EGFR-TKIs, month, Mean (SD)	18.62(13.5)	15.9(12.17)	27.17(14.24)	0.0073
pN, n (%)				0.78
N1	8(11.11)	6(11.76)	2(9.52)	
N2	64(88.89)	45(88.24)	19(90.48)	
pT, n (%)				0.31
T1	19(26.39)	14(27.45)	5(23.81)	
T2	32(44.44)	21(41.18)	11(52.38)	
T3	15(20.83)	13(25.49)	2(9.52)	
T3	6(8.33)	3(5.88)	3(14.29)	
Metastasis site, n (%)				0.56
Brain	16(37.21)	9(29.03)	7(58.33)	
Lung	7(16.28)	6(19.35)	1(8.33)	
bone	10(23.26)	7(22.58)	3(25)	
Lymph nodes	2(4.65)	2(6.45)	0	
Other sites	8(18.6)	7(22.58)	1(8.33)	
Adjuvant radiotherapy, n (%)				0.80
Yes	36(50.00)	26(50.98)	10(47.62)	
No	36(50.00)	25(49.02)	11(52.38)	
Adjuvant radiotherapy, n (%)				0.77
Yes	63(87.50)	45(88.24)	18(85.71)	
No	9(12.50)	6(11.76)	3(14.29)	
EGFR-TKIs as first–line, n (%)				0.88
Yes	11(15.28)	8(15.69)	3(14.29)	
No	61(84.72)	43(84.31)	18(85.71)	

was 76.8 months in the subgroup "1 + 3" and 66 months in the subgroup "0 + 3" (Fig. 3B). Univariate and multivariate analysis did not show difference between "1" and "1 + 3" subgroups (Table 4).

Additionally, in our study, we employed Spearman correlation coefficients to explore the relationship between OS and DFS. Specifically, the Spearman correlation coefficient between OS and DFS yielded a value of 0.12 for the entire population under investigation (Suppl. Fig. 1), indicating a weak correlation.

5. Discussion

The outcomes derived from this research elucidate that the incorporation of the third-generation EGFR-TKI Osimertinib failed to confer augmented advantages in terms of survival as compared to its first-generation counterpart. This pertains specifically to individuals afflicted with stage IIIA completely resected NSCLC who underwent administration of EGFR-TKIs within the framework of their postoperative adjuvant treatment regimen. Furthermore, within the confines of the observed sample magnitude in this particular cohort, the sequential administration of Osimertinib in conjunction with the first-generation EGFR-TKI exhibited an absence of superiority to the utilization of either the first-generation EGFR-TKI or Osimertinib in isolation, with respect to postoperative survival endpoints.

A pivotal concern pertains to the optimal timing of employing third-generation EGFR-TKIs, given the inherent challenge of therapy resistance across all generations of EGFR-TKIs. Analogous to the resistance mechanisms observed with first- and second-generation EGFR-TKIs, the currently documented modes of resistance to third-generation EGFR-TKIs predominantly encompass EGFR secondary mutations, bypass activation, and histological transformation [24–28]. Notably, the most prevalent mechanism of resistance to first- and second-generation EGFR-TKIs is rooted in the emergence of the secondary EGFR T790 M mutation (9), which can be effectively counteracted by Osimertinib [10]. However, it is important to highlight that there are presently no approved targeted therapies available to address resistance specifically arising from the use of third-generation EGFR-TKIs. This underscores the need for cautious consideration when selecting the appropriate generation of EGFR-TKIs for treatment, a decision that merits further thorough exploration.

Patients diagnosed with Stage III non-small cell lung cancer (NSCLC) are confronted with a substantial and concerning risk of developing brain metastases [29]. A pivotal investigation, recognized as the ADJUVANT trial [30], illuminated varying rates of recurrence for intracranial metastases among distinct treatment cohorts. Specifically, the subset administered gefitinib displayed a heightened recurrence incidence in contrast to their counterparts receiving vinorelbine plus cisplatin (27.4 % vs. 24.1 %). In contrast,

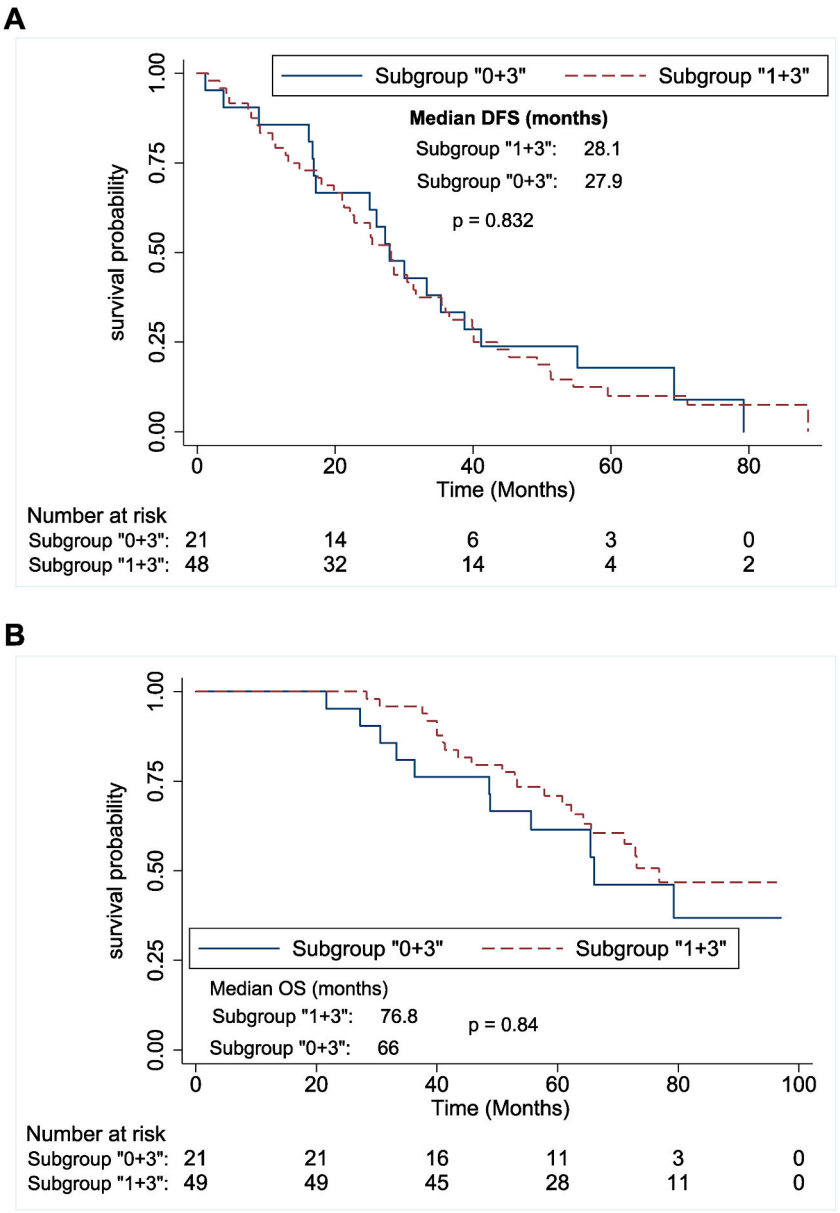

Fig. 3. The survival analysis entails a comparison between Subgroup "0 + 3" and Subgroup "1 + 3"
Panel A: DFS (disease-free survival); panel B: OS (overall survival).

Table 4
Univariate and multivariate survival analysis.

Comparison subgroups	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P-value	HR (95%CI)	P-value
"1 + 3" vs "0 + 3"(OS)[b]	1.37(0.66–2.82)	0.84	1.87(0.64–5.47)	0.25
"1 + 3" vs "0 + 3"(DFS)[b]	0.94(0.55–0.62)	0.83	2.49(0.69–8.96)	0.16

[a]The HR adjusted by age, metastasis site, type of surgery, pT, pN, sex, whether EGFR TKI using as first-line treatment in the Cox regression.
[b]The HR adjusted by age, metastasis site, type of surgery, pT, pN, sex, whether EGFR TKI using as first-line treatment in the Cox regression.

the occurrences of treatment failure stemming from intracranial metastasis stood at 6.1 %, 7.5 %, and 3.9 % for the first-generation EGFR-TKIs gefitinib, erlotinib, and icotinib, respectively [31]. This discernible pattern can likely be ascribed to the constrained capacity of first-generation EGFR-TKI medications to effectively breach the blood-brain barrier.

In stark contrast, the third-generation EGFR-TKI, Osimertinib, exhibits a heightened efficacy in navigating the intricate blood-brain barrier. A notably remarkable revelation emerged from the ADAURA trial [19], showcasing that the inclusion of adjuvant Osimertinib therapy precipitated a substantial 82 % reduction in the incidence of metastases towards the central nervous system, encompassing brain metastases. Moreover, this therapeutic intervention distinctly curtailed the peril of mortality when juxtaposed with a placebo (HR = 0.18, 95 % CI = 0.10–0.33). Hence, for postoperative stage III NSCLC patients harboring EGFR-sensitive mutations, the preferable recommendation is to consider adjuvant therapy with Osimertinib [32].

Despite the significance attributed to EGFR-TKI treatments within the postoperative context, a predominant focus of most clinical trials has been directed towards the independent assessment of either first- or third-generation EGFR-TKI therapies. This has resulted in an insufficiency of substantive evidence necessary to delineate an optimal treatment strategy, specifically in terms of determining whether the implementation of third-generation EGFR-TKI is more judicious as a primary intervention or as a constituent element within a sequential treatment regimen subsequent to the administration of first-generation EGFR-TKIs.

Recent data from the phase III FLAURA trial demonstrated that first-line Osimertinib is superior to first-generation EGFR-TKIs in PFS [13], and a significant but less pronounced OS (HR, 0.80 (95 % CI, 0.64 to 1.00); P = 0.046)) data were also reported [33], thus supporting Osimertinib as the new first-line standard of care for NSCLC patients with EGFR-mutation at advanced stages. However, whether their data could be reproduced in real world remains to be determined given the low crossover rate: one-third of patients in the control arm did not receive any subsequent anticancer therapy at progression [34]. In our study that focused on stage IIIA NSCLC receiving surgery, we found no significant difference in the effectiveness of OS and DFS in the sequencing group of third-generation EGFR-TKI, compared to the first- or third-generation EGFR-TKI alone.

The APPLE trial (EORTC-1613-APPLE) was conducted to assess the viability of longitudinally monitoring plasma EGFR T790 M levels for determining the optimal sequencing strategy involving Gefitinib and Osimertinib for patients diagnosed with EGFR-sensitive, treatment-naive non-small cell lung cancer (NSCLC). The trial encompassed three distinct arms: 1) Arm A: Administering upfront Osimertinib until RECIST-defined disease progression; 2) Arm B: Employing Gefitinib until the emergence of EGFR T790 M mutation in circulating tumor DNA (ctDNA) or RECIST-defined disease progression; 3) Arm C: Using Gefitinib until RECIST-defined disease progression, followed by a switch to Osimertinib in both arms. As of now, only the outcomes from arms B and C have been published [35]. The conclusive survival analysis for arms A versus B/C is still pending. Recently, the updated outcomes of APPLE trial was released at 2023 European Lung Cancer Congress. The investigation underscored that the initiation of Osimertinib as the primary treatment modality exhibited a proclivity for attenuating the vulnerability to brain metastasis when juxtaposed against a sequential therapeutic schema involving the successive administration of first-generation gefitinib, followed by Osimertinib. Nonetheless, notwithstanding this observed correlation, no statistically noteworthy disparities manifested in relation to OS outcomes between the two cohorts subjected to scrutiny. As a consequence, it becomes evident that a more thoroughgoing inquiry is indispensable to comprehensively elucidate this subject matter.

Additionally, DFS is generally used as a surrogate endpoint for OS [36,37]. However, in multiple clinical studies that have investigated the benefits of postoperative EGFR-TKIs for stage IB-IIIA NSCLC [16–18], the observed DFS advantage did not translate to a significant OS difference. Similarly, within this retrospective cohort, DFS does not serve as a robust surrogate endpoint for OS, and this necessitates further investigation. This observation may be attributed to the imprecise determination of the date of tumor relapse in retrospective settings, as it often depends on patient-initiated follow-up surveillance after surgery, which may not adhere to a regular schedule. Moreover, the limited sample size and relatively short follow-up duration in this cohort introduces the potential for bias in the analysis.

Our study is subject to several limitations, foremost among which are the inherent biases associated with a retrospective research design and the constraint imposed by a relatively small sample size. Specifically, the cohort receiving Osimertinib in combination with first-generation EGFR-TKIs consisted of a comparably diminished sample size in relation to the comparative group, a factor that could have potentially influenced the resultant findings. Furthermore, we did not stratify whether patients underwent administration of EGFR-TKIs as primary or secondary treatment during the postsurgical course, which varies considerably in the retrospective setting [38]. This lack of differentiation is noteworthy, as evidenced by a retrospective investigation that explored sequential treatment transitioning from first-generation EGFR-TKIs to third-generation EGFR-TKIs. This inquiry indicated that the efficacy of Osimertinib might not exhibit significant attenuation when deployed as a second-line therapeutic approach among patients with advanced NSCLC [39].

6. Conclusions

The conclusions drawn from this study suggest that the incorporation of the third-generation EGFR-TKI Osimertinib did not lead to improved survival advantages in contrast to the first-generation counterpart. This is evident among patients diagnosed with stage IIIA completely resected NSCLC, who were subjected to EGFR-TKI administration as a component of their postoperative adjuvant therapeutic regimen. Furthermore, within the scope of the observed sample size within this cohort, the sequential administration of Osimertinib in conjunction with the first-generation EGFR-TKI did not exhibit a superior performance compared to the utilization of either the first-generation EGFR-TKI or Osimertinib independently, in relation to postoperative survival outcomes. Additionally, OS and DFS exhibit a weak correlation within this cohort, suggesting DFS is a not strong surrogate endpoint for OS, which warrants further investigations.

Ethics statement

This study has obtained approval from Shanghai Chest Hospital ethical review board (#KS(Y)21039). The participants gave informed consent before taking part.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Wenyan Ma: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ziyi Sheng:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. **Yongliang Niu:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Bo Yan:** Data curation, Formal analysis, Investigation, Writing – original draft. **Yong Chen:** Conceptualization, Data curation, Formal analysis, Validation, Writing – original draft, Writing – review & editing. **Haitang Yang:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Rong Li:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors have declared that no competing interest exists.

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Appendix A. Supplementary data

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