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Original Article

Evaluating the Impact of Primary Tumor Resection on EGFR-TKI-treated Patients with Advanced Lung Cancer: A Multicenter Propensity-matched Study

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Abstract

Background: Nonsmall-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations is exceptionally sensitive to EGFR tyrosine kinase inhibitors (TKIs). Despite this, disease progression commonly occurs at the primary site, prompting debate on the potential advantages of incorporating primary tumor resection alongside standard maintenance therapy. **Materials and Methods:** This retrospective multicenter study enrolled NSCLC patients treated with EGFR-TKIs and categorized them into surgery and control groups based on primary tumor resection. The propensity score matching (PSM) method was used to ensure balanced comparisons, accounting for 12 covariates. Progression-free survival (PFS) and overall survival (OS) were evaluated, addressing immortal time bias. **Results:** Among 2151 EGFR-TKI-treated patients screened from 2010 to 2019, 57 (21 surgery group, 36 control group) were included post-PSM and accounting for immortal time bias. No cases of major complications (grade IIIa or higher based on Clavien-Dindo criteria) or 90-day mortality were noted in the surgery group. Pulmonary resection was significantly associated with longer PFS (58.6 vs. 14.1 months, $P = 0.001$) and OS (109.6 vs. 46.6 months, $P = 0.016$) compared to EGFR-TKI monotherapy. Positive outcomes were consistent across diverse subgroups. **Conclusion:** The addition of primary tumor resection in EGFR-mutant NSCLC patients receiving EGFR-TKI treatment was associated with improved PFS and OS compared to EGFR-TKI treatment alone. However, these results should be interpreted with caution due to potential selection bias in the analysis.

Keywords: Epidermal growth factor receptor, local consolidation therapy, nonsmall-cell lung cancer, primary tumor resection, progression-free survival, tyrosine kinase inhibitors

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Introduction

The clinical management of advanced nonsmall-cell lung cancer (NSCLC) has profoundly developed in recent years, primarily due to the identification of targetable oncogenic driver alterations. For patients harboring actionable gene mutations, targeted therapy has emerged as the contemporary standard of care, surpassing traditional chemotherapy in terms of clinical outcomes.[1-3] Epidermal growth factor receptor (EGFR)-mutated NSCLC is a targetable and predictive oncogenic driver alteration in lung cancer, demonstrating notable sensitivity to EGFR tyrosine kinase inhibitors (TKIs). While EGFR-TKIs provide an extended progression-free survival (PFS) compared to chemotherapy, the widespread occurrence of acquired resistance poses a significant challenge, ultimately resulting in disease progression in most patients.[1,4-8] This highlights the urgent need for effective strategies to prevent or delay the emergence of resistance and prolong survival.[9]

Prior research has indicated that the primary site is predominantly the site of initial progression, suggesting the existence of resistant cancer clones in the primary tumor that subsequently lead to radiological progression.[10,11] Therefore, incorporating primary tumor resection into the EGFR-TKI treatment regimen for primary residual tumors seems to be a promising and rational approach to prevent or delay the development of resistance.[12] Several retrospective studies have demonstrated that primary tumor resection may prolong PFS and overall survival (OS).[13,14] In addition, the NORTHSTAR randomized phase 2 clinical trial is currently underway and is investigating this issue (NCT03410043).[15,16]

Before data from prospective studies becoming available, the effectiveness and suitability of this strategy continue to be the subject of ongoing debate. Therefore, we performed this multicenter retrospective study to assess the prognostic implications of incorporating primary tumor resection in patients with NSCLC who had undergone first-line EGFR-TKI therapy, utilizing data from the Chang Gung Research Database (CGRD). To minimize selection bias and immortal time bias, we used a propensity score matching (PSM) approach and excluded patients from the control group who had disease progression before their matched surgery group underwent the operation. This rigorous methodology aimed to enhance comparability between the surgery and control groups, ensuring a more reliable evaluation of the prognostic implications of primary tumor resection in patients undergoing first-line EGFR-TKI therapy for NSCLC.

Materials and Methods

Design, setting, and participants

The present retrospective study used data from the CGRD, which is the largest multicenter collection of electronic medical records in Taiwan.[17] Eligible participants for this study were individuals diagnosed with advanced NSCLC who had undergone EGFR-TKI therapy as a first-line treatment from January 2010 to December 2019. Patients who had undergone prior chemotherapy or radiation were excluded from the study. All participants had pathologically confirmed NSCLC and harbored EGFR mutations. The last follow-up date was December 2024.

The patient cohort was divided into two groups based on whether they underwent primary tumor resection (surgery group) or not (control group). Importantly, the surgery group excluded patients who underwent tumor resection due to disease progression (salvage surgery). We also excluded individuals who received targeted therapy for <3 months or underwent additional systemic therapy alongside targeted therapy.

The study protocol received approval from the Institutional Review Board of Chang Gung Memorial Hospital (reference number: 202201134B0, Approval date: July 26, 2022) and was granted a waiver for patient consent.

Data collection

Variables collected from the study participants encompassed age, gender, smoking status, tumor stage, performance status, EGFR mutation data, treatment-related information, and clinical outcomes. Lung cancer staging followed the eighth edition of the American Joint Committee on Cancer Staging Manual.[18] Tumor response was assessed using unidimensional measurements as defined by the Response Evaluation Criteria in Solid Tumors, version 1.1.

Surgical resection and postoperative treatment

The consideration for primary tumor resection was limited to patients treated with EGFR-TKIs who did not develop tumor progression. The surgeons assessed the resectability of primary tumors, ensuring adequate systemic control, evaluating pulmonary function, and verifying the absence of contraindications for surgery.

Most of the patients underwent anatomical resection combined with complete mediastinal lymph node dissection. However, a subset of the patients received limited resection due to intraoperative factors. In cases where metastatic spread to cervical or abdominal lymph nodes was identified, targeted dissection in the affected nodal stations was undertaken. EGFR-TKI therapy was consistently administered throughout the perioperative period. To facilitate the early detection of disease recurrence, follow-up computed tomography examinations of the chest and abdomen were conducted every 3−6 months postsurgery.

Definitions of outcomes

The Clavien-Dindo (CD) criteria were used to classify the severity of complications, of which grade IIIa or higher was considered severe.[19,20] PFS was defined as the duration from the initiation of EGFR-TKI therapy to the date when the first evidence of disease progression was observed. OS was calculated from the commencement of EGFR-TKI therapy to the date of death. Censoring was applied on the date of the last follow-up (administrative censoring).

Statistical analysis

To mitigate selection bias and minimize the impact of nonrandomized treatment allocation, we used PSM considering 12 potential confounding factors: age, sex, performance status, clinical stage (cT, cN, cM, and cStage), the presence of brain metastases, the number of distant metastases, the type of EGFR-TKI treatment, the type of EGFR mutation, and the best response after EGFR-TKI therapy. Subsequently, we generated a 1:2 propensity score-matched sample of patients who either underwent surgery or were observed. The matching process was based on the closest estimated value on the logit score.

The model's effectiveness in creating two balanced cohorts was assessed using the standardized mean difference (SMD), with an SMD value exceeding 20% defined as indicating a covariate imbalance. To address immortal time bias, patients from the control group who experienced disease progression before the matched surgery group underwent the operation were excluded. OS and PFS were the primary outcome measures. Survival curves were constructed using the Kaplan–Meier method and analyzed using the log-rank test.

Statistical analyses were conducted using SPSS (version 21.0; IBM, Armonk, NY, USA), SigmaPlot (version 12.5; Systat Software, San Jose, CA, USA), RStudio (version 4.0.3; PBC, Boston, MA, USA), and GraphPad Prism (version 9; GraphPad Inc., San Diego, CA, USA). The threshold for statistical significance was set at a two-tailed $P < 0.05$.

Results

Baseline characteristics and treatment course of the surgery group

A total of 2151 patients with NSCLC harboring EGFR mutations and treated with front-line EGFR-TKIs were included in this study. Among them, 24 patients underwent primary tumor resection, forming the surgery group. Of the surgery group, 62.5% were men, and the median age was 56 years [Table 1]. These patients underwent primary tumor resection after a median duration of 6.55 months (interquartile range [IQR]: 4.21 − 9.89 months) of EGFR-TKI therapy. The majority (79.2%) underwent lobectomy using a minimally invasive approach, with no need for conversion to thoracotomy. The median operating time was 3 h, and the median length of hospital stay was 5 days. Two patients underwent combined surgical procedures: one had tumor excision along with pleural resection, and the other had tumor excision combined with hyperthermic intrathoracic chemotherapy. In the postoperative course, only two patients experienced complications. One developed postoperative pneumonia, while the other had persistent pleural effusion following surgery. Both complications were managed conservatively (CD grade II).

There were no surgical deaths or postoperative deaths within the first 90 days. Complete resection was achieved in 22 (91.7%) patients, while 2 (8.3%) showed no evidence of residual cancer on the surgical specimen (ypT0N0). The treatment course of each patient undergoing primary pulmonary resection is depicted in Figure 1.

Table 1: General characteristics of patients

Characteristics	Surgery group ($n=24$)
Age (years)	
Median (IQR)	56 (52.25−59)
Mean±SD	55.04±9.27
Sex, *n* (%)	
Male	15 (62.5)
Female	9 (37.5)
Smoking history, *n* (%)	7 (29.2)
Duration of EGFR-TKI treatment before surgery (months)	
Median (IQR)	6.55 (4.21−9.89)
Mean±SD	10.21±12.80
Surgical approach, *n* (%)	
Lobectomy	19 (79.2)
Segmentectomy	1 (4.2)
Wedge resection	4 (16.6)
Operating time (h)	
Median (IQR)	3.00 (2.45−8.14)
Mean±SD	3.29±1.19
Postoperative complications	
None	22 (81.7)
Minor	2 (8.3)
Major	0
Length of hospital stay (days)	
Median (IQR)	5.00 (4.00−6.00)
Mean±SD	5.33±2.26
90-day mortality, *n* (%)	0

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor, IQR: Interquartile range, SD: Standard deviation

Propensity-score matching and immortal time bias

Figure 2 provides an overview of patient flow throughout the study. Overall, before matching, the median OS among the 2127 patients treated without primary pulmonary resection and the 24 patients who underwent resection was 109.6 versus 20.3 months [$P < 0.001$, Figure 3a], while the median PFS was 46.5 versus 11.2 months [$P < 0.001$, Figure 3b].

Initially, a 1:2 propensity score-matched cohort was established, considering 12 potential confounding factors: age, sex, performance status, cT, cN, cM, cStage, the presence of brain metastases, number of distant metastases, type of EGFR-TKI treatment, type of EGFR mutation, and best response after EGFR-TKI therapy. To address immortal time bias, 12 patients in the control group who experienced disease progression before the matched surgery group underwent the operation were excluded. In addition, three patients in the surgery group who lacked a suitable match were also excluded. As a result, the final analysis included a total of 57 patients, with 21 in the surgical group and 36 in the control group. A detailed breakdown of data from both the original and final selected cohorts is presented in Table 2. Postselection, the baseline characteristics were considered to be balanced, as most SMDs were below 20%, with the exception of age. This

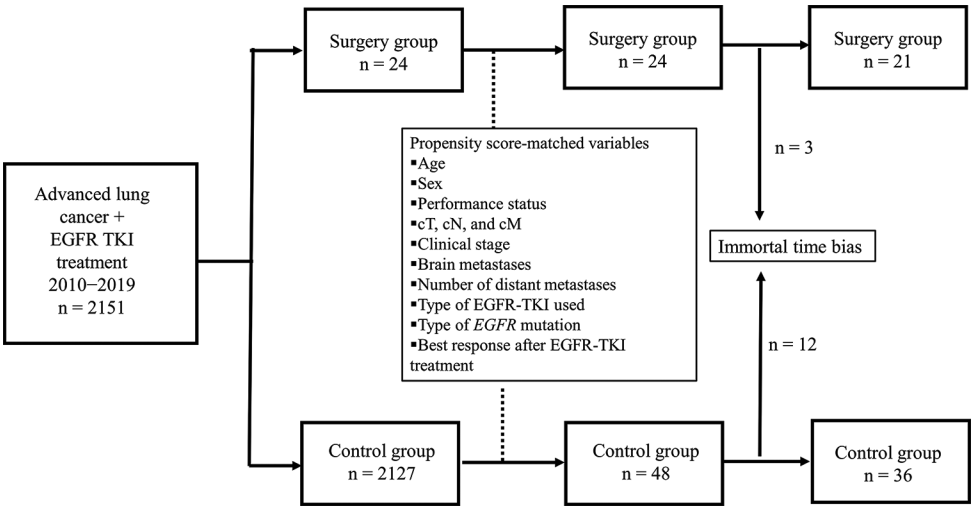

Figure 1: Swimmer plots illustrating the treatment course of each patient undergoing primary pulmonary resection included in the study

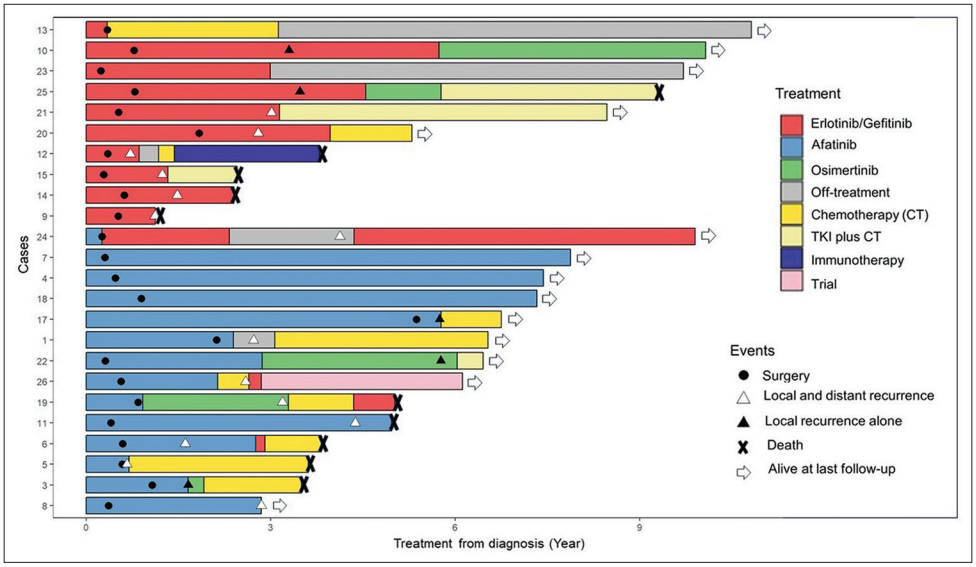

Figure 2: Study flowchart. Patients in the surgery group underwent primary tumor resection followed by epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) maintenance therapy. Conversely, the control group, which was carefully propensity score-matched based on 12 variables, received only EGFR-TKI therapy

indicated a well-matched cohort, reflecting effective patient selection.

Overall survival and progression-free survival in the matched cohort

After a median follow-up period of 46.2 months (IQR: 28.07 − 60.83 months), a total of 24 patients remained alive (12 in the surgery group and 12 in the control group). The addition of primary tumor resection to EGFR-TKI treatment resulted in a significantly longer OS compared to EGFR-TKI treatment alone [median: 109.6 vs. 46.6 months, respectively, $P = 0.016$; Figure 4a]. Disease progression was observed in 44 patients, with 11 in the surgery group, and 33 in the control group. The combination of pulmonary resection with EGFR-TKI treatment also led to a longer PFS compared to EGFR-TKI treatment alone [median: 58.6 vs. 14.1 months, respectively, $P = 0.001$; Figure 4b].

Subsequently, we explored whether specific subgroups would have the most or least advantage from primary tumor resection. As shown in Supplementary Figure 1, an association between surgery and OS was observed across various subgroups, however, these findings should be interpreted cautiously given the retrospective nature of this study and potential selection bias. This included the total patient population, both sexes, various tumor stages, differing ages, performance status, brain metastatic status, single-organ metastatic status, and EGFR mutation status, specifically the L858R mutation and exon 19 deletions.

Discussion

In this retrospective, multicenter investigation involving EGFR-mutated NSCLC patients undergoing first-line therapy with EGFR-TKIs, a subset of patients who underwent resection

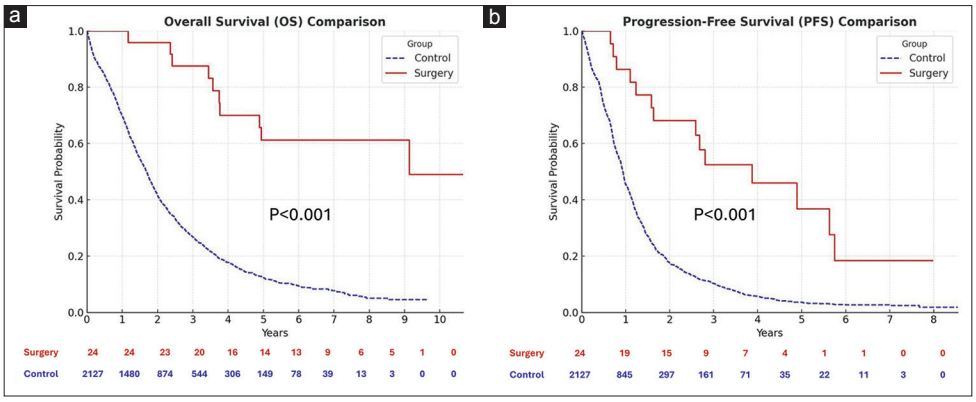

Figure 3: Kaplan–Meier plots of overall survival (a) and progression-free survival (b) observed in the surgery and control groups before propensity score matching

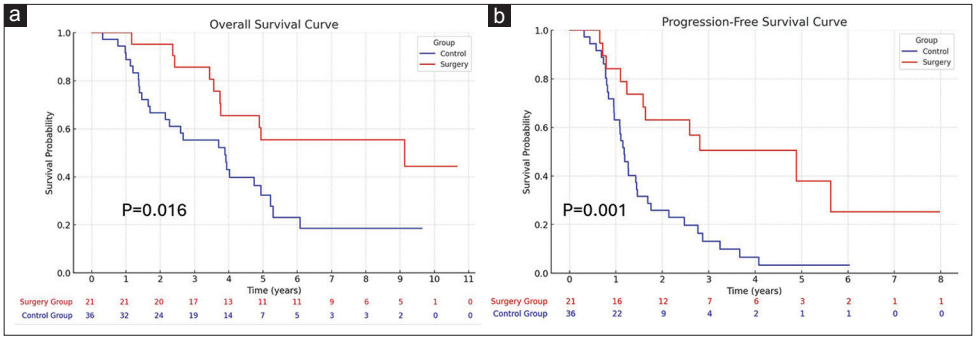

Figure 4: Kaplan–Meier plots of overall survival (a) and progression-free survival (b) observed in the surgery and control groups after propensity score matching

of their primary tumor had better PFS and OS compared to their nonsurgically treated counterparts. Our findings suggest that, for appropriately selected patients, achieving maximum locoregional control through surgical resection is not only possible but also a rational approach, considering that it can be achieved with minimal risk of postoperative mortality.

Although previous retrospective studies have reported similar results, the current study adds to the knowledge by addressing the limitations observed in prior research. Compared with these earlier investigations, the strength of our study lies in its rigorous approach to mitigating selection bias and minimizing the impact of nonrandomized treatment allocation. This was achieved through the implementation of a PSM approach. To specifically tackle the issue of immortal time bias – a challenge arising when the patients in the surgery group had to be free of progression before undergoing surgery – we implemented stringent exclusion criteria. First, patients from the control group who experienced disease progression before the time when their matched surgery group underwent the operation were excluded. In addition, patients who could not be adequately matched with a suitable control patient were also excluded. This meticulous methodology contributed to the robustness and reliability of the findings.

A review of the literature review identified two specific investigations that explicitly examined the potential advantages of pulmonary resection in combination with EGFR-TKI therapy.[13,14] Both studies concluded that pulmonary resection led to improved survival outcomes. Our investigation offers several advantages over previous research [Table 3]. First, our study is multi-institutional, utilizing a cancer registry that incorporates unbiased data from four different hospitals, encompassing both academic and nonacademic settings. This approach distinguishes our research from previous single-center-based studies. Second, although all of the studies used PSM, we used a much broader set of covariates. Our matching process considered not only factors influencing survival but also variables affecting the decision to undergo surgery, such as clinical stage and tumor response to EGFR-TKIs. Most importantly, our study is strengthened by addressing and correcting immortal time bias, a consideration not addressed in prior research.

Conditional landmark analysis, an effective method for mitigating the impact of immortal time bias, involves setting a predetermined point or "landmark" and excluding patients who died or experienced tumor progression before this time point. However, the choice of the landmark can be arbitrary. In our research, we introduced an additional criterion to the matching process, excluding patients from the control group if they developed disease progression before the matched surgery group received their operation. This methodological difference may have contributed to the disparity between our findings and those of Kuo *et al*.[13]

Table 2: General characteristics of the study patients before and after propensity score matching and mitigation of the immortal time bias

Characteristic	Original cohort					Post-propensity score matching and mitigation of the immortal time bias				
	Control group (*n*=2127)		Surgery group (*n*=24)		SMD	Control group (*n*=36)		Surgery group (*n*=21)		SMD
	Mean or *n*	SD or percentage	Mean or *n*	SD or percentage		Mean or *n*	SD or percentage	Mean or *n*	SD or percentage	
Age (years)	67.12	11	55.04	9.27	1.12	57.36	9.11	53.29	8.05	0.474
Sex										
Male	1290	60.65	15	37.5	0.476	25	69.44	14	66.67	
Female	837	39.35	9	62.5		11	30.56	7	33.33	
PS										0.104
<2	1659	78	23	95.83	0.548	35	97.22	20	95.24	
≥2	468	22	1	4.17		1	2.78	1	4.76	
cT										0.347
1	132	6.52	1	4.16	0.32	2	5.56	0	0	
2	353	17.45	7	29.17		11	30.56	7	33.33	
3	283	13.99	4	16.67		6	16.67	4	19.05	
4	1255	62.04	12	50		17	47.22	10	47.62	
cN										0.302
0	289	14.01	3	12.5	0.426	3	8.33	3	14.29	
1	164	7.95	0	0		0	0	0	0	
2	577	27.97	7	29.17		9	25	7	33.33	
3	1033	50.07	14	58.33		24	66.67	11	52.38	
cM										0.06
0	130	6.14	9	37.5	0.821	11	30.56	7	33.33	
1	1987	93.86	15	62.5		25	69.44	14	66.67	
Brain metastasis										0.103
No	1502	70.62	18	75	0.099	24	66.67	15	71.43	
Yes	625	29.38	6	25		12	33.33	6	28.57	
Number of organs involved (distant metastases)	2.06	1.14	1.6	1.06	0.418	1.64	1.08	1.64	1.08	0.003
Type of EGFR-TKI										0.024
Gefitinib/erlotinib	1513	71.13	11	45.83	0.531	15	41.67	9	42.86	
Afatinib	614	28.87	13	54.17	0.418	21	58.83	12	57.14	
EGFR mutation type										0.081
L858R	1126	52.94	7	29.17	0.498	9	25	6	28.57	
Exon 19	1001	47.06	17	70.83		27	75	15	57.13	
Best response to treatment										0.036
SD	317	16.54	2	8.33	0.547	2	5.56	1	4.76	
PR/CR	1420	74.11	22	91.67		34	94.44	20	95.24	
PD	179	9.34	0	0		0	0	0	0	

SD: Standard deviation, SMD: Standardized mean difference, PS: Performance status, EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor, SD: Stable disease, PR: Partial response, CR: Complete response, PD: Progressive disease

concerning the survival benefits of surgery in matched cohorts. We suggest that a more accurate assessment of the impact of surgery can be achieved by effectively mitigating immortal time bias. These methodological considerations underscore the relevance of our study to everyday clinical practice.

In our study, the control group had favorable median PFS and OS outcomes, with durations of 14.3 and 47.3 months, respectively. These outcomes surpassed those observed in previous real-world studies and can be attributed to the exclusion of high-risk patients through the implementation of PSM and the mitigation of immortal time bias. Even though the control group showed improved outcomes, the role of primary surgery remains crucial as it has the potential to extend survival, particularly among carefully selected subjects. Furthermore, the low surgical complication rate and no cases of mortality within the first 90 days highlight the feasibility and safety of primary surgery, even for patients with advanced lung cancer.

In the current study, the median duration from initiating EGFR-TKI treatment to primary tumor resection was 6.55 months, which

Table 3: Comparison between the current study and previously published series

	Kuo *et al*.[13]		Chen *et al*.[14]		Current study	
	Surgery group	Control group	Surgery group	Control group	Surgery group	Control group
Number of patients	56	224	53	53	21	36
	Single-center		Single-center		Multicenter	
Propensity score-matched variables	Age Performance status Number of distant metastases		Age Sex Brain metastases EGFR mutations		Age Sex Performance status cT, cN, and cM Clinical stage Brain metastases Number of distant metastases Type of EGFR-TKI used Type of EGFR mutation Best response after EGFR-TKI treatment	
Impact of immortal time bias	**Not addressed**		**Not addressed**		**Mitigated**	
Stage						
III B/C (*n*)	0	0	NA	NA	7	11
IV (*n*)	56	224	NA	NA	14	25
Mutation type						
L858R mutation	18	99	33	33	6	9
Exon 19 deletion	32	93	20	20	15	27
Other mutations	6	30	0	0	0	0
EGFR-TKI type						
Gefitinib/erlotinib	38	168	16	NA	9	15
Afatinib	14	41	28	NA	12	21
PFS (months), median	32.5	18.0	52	9.8	58.6	14.1
OS (months), median	NR	60.0	NR	30.6	109.6	46.6

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor, NA: Not available, PFS: Progression-free survival, OS: Overall survival, NR: Not reached

aligns with our clinical practice. Typically, in our clinical setting, tumors noticeably decrease in size within the first 3 months of initiating EGFR-TKI treatment, with clinicians anticipating a deeper response in the subsequent 3 months. However, the tumor size tends to remain stable thereafter. The optimal timing for primary tumor resection remains unknown. Based on clinical experience, tumors tend to achieve a maximal response approximately 3 months after initiating EGFR-TKI treatment, suggesting that this period may be optimal for incorporating primary tumor resection. The ongoing NORTHSTAR trial is designed to address this question and patients without disease progression after 6–12 weeks of induction osimertinib will be randomized 1:1 to continue osimertinib or continue osimertinib with local consolidation therapy.[15,16]

In metastatic NSCLC, the disease can manifest as either oligometastatic or polymetastatic, depending on whether the patient presents with a limited number of metastases (oligometastatic) or multiple metastases (polymetastatic). Oligometastasis refers to a clinical stage where patients have a limited number of metastases, often resulting in a better prognosis. In NSCLC, the incidence is estimated to be 20%–50%, with varying criteria for defining oligometastatic disease.[21] Existing evidence indicates that treating patients with limited or oligometastases may significantly enhance outcomes.[22] The decision for local consolidative treatment, whether surgery (metastasectomy) or radiotherapy,[23,24] depends on factors including age, performance status, comorbidities, metastatic timing, lesion number and location, primary tumor extension, and lymph node involvement. In contrast, we specifically assessed the impact of primary tumor resection, excluding an evaluation of local consolidative treatment for oligometastases, as systemic metastases were predominantly managed with EGFR-TKIs. Therefore, polymetastatic NSCLC was included in the current study.

There are several limitations to this study, including the retrospective design, the meticulous selection of surgical patients, and the challenge of determining the genuine intention-to-treat among the patients who were not surgically treated. Despite rigorous selection criteria and PSM, our study remains subject to selection bias, as patients undergoing surgery were highly selected based on clinical factors. The observed survival advantage may reflect the impact of these factors rather than the effect of surgery itself. Future randomized controlled trials are necessary to clarify the role of primary tumor resection in this setting. In addition, we enrolled heterogeneous stage III and stage IV cohorts, leading to an initial imbalance in the data. To rectify this, we performed

PSM. Furthermore, in subgroup analysis to differentiate between stage III and stage IV, we consistently observed that primary resection improved outcomes in both stages. Another limitation is that we only included first-and second-generation EGFR-TKIs. The impact of osimertinib treatment remains unknown as it was not indicated for front-line therapy during the study period. However, a prospective randomized phase 2 trial (NORTHSTAR, NCT03410043) is currently underway to evaluate the role of primary surgery in patients receiving osimertinib. Despite the multicenter nature of our study, the sample size was small, and larger longitudinal investigations are necessary to confirm our results. Due to the limited sample size, further stratified analysis based on the year of diagnosis and treatment initiation was not feasible. While OS may have been influenced by advances in systemic therapy over time, PFS is less likely to be significantly affected, as it primarily reflects the efficacy of first-line EGFR-TKI therapy. Despite these limitations, the current literature provides limited information on pulmonary resection during EGFR-TKI treatment. Hence, this study represents a timely examination of a question that has been gaining clinical significance.

Conclusion

In the context of this retrospective, multicenter investigation, particularly when applying PSM and mitigating immortal time bias, our findings suggest that primary tumor resection in carefully selected patients with EGFR-mutant NSCLC undergoing EGFR-TKI therapy was associated with improved PFS and OS. Among highly selected patients, primary tumor resection may be a feasible approach to enhance locoregional control. However, given the retrospective nature of this study and the highly selected patient cohort, these results should be interpreted with caution. Further prospective studies are required to establish the role of primary tumor resection in this setting.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

Dr. Chiao-En Wu, an editorial board member at Journal of Cancer Research and Practice, had no role in the peer review process of or decision to publish this article. All authors declared no conflicts of interest in writing this paper.

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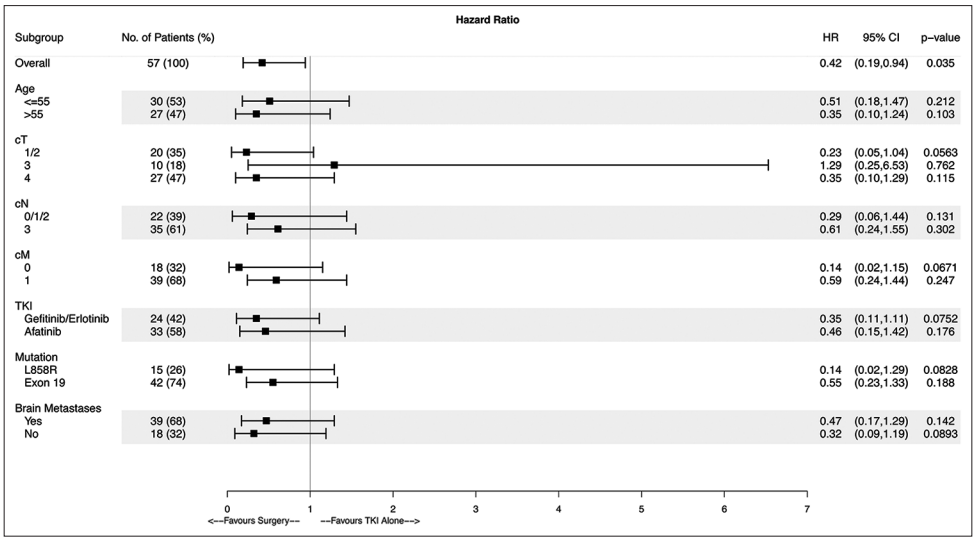

Supplementary Figure 1: Forest plot of subgroup analyses comparing overall survival between patients who underwent primary tumor resection versus those treated with EGFR-TKI alone. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional hazards models for each subgroup. Values less than 1 indicate a survival benefit associated with surgery. Subgroups include age, clinical T/N/M stage, EGFR-TKI agent, mutation subtype, and presence of brain metastases