Original Article

Palliative surgery is effective in patients with *EGFR*-mutant lung adenocarcinoma with pleural metastasis

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Background: Pleural metastasis is a common metastatic pattern in patients with epidermal growth factor receptor-mutant lung adenocarcinoma (*EGFR*-LUADm); however, the value of palliative surgery for these patients remains controversial. The purpose of the present study aims to investigate whether palliative surgery benefits in stage IVA LUADm patients with pleural metastasis, who achieved complete remission of pleural lesions following targeted therapy.

Methods: From November 2014 to November 2023, patients with stage IVA *EGFR*-LUADm with pleural metastasis at Shanghai Pulmonary Hospital were retrospectively included in this study. All the patients received *EGFR*-tyrosine kinase inhibitor (TKI) monotherapy. The patients were divided into surgical- and non-surgical treatment subgroups. To reduce any selection bias, a 1:2 propensity score matching (PSM) was performed before comparing oncological outcomes between the two groups. The Kaplan-Meier method and log-rank test were used to identify the prognostic factors of these patients.

Results: A total of 134 patients who met the inclusion and exclusion criteria were enrolled in this study. Of the 134 patients, 13 received *EGFR*-TKI monotherapy followed by palliative surgical treatment (the surgical group), and 121 received *EGFR*-TKI monotherapy alone (the non-surgical group). No significant differences in the baseline characteristics were observed between the subgroups. After PSM, the surgical and non-surgical groups comprised 13 and 26 patients, respectively. The survival analysis showed that the patients in the surgical group had significantly better progression-free survival (PFS) than those in the non-surgical group {surgical *vs.* non-surgical: median PFS: 43 [95% confidence interval (CI): 30–not available] *vs.* 11 (95% CI: 10–26, P<0.001)}.

Conclusions: Compared with *EGFR*-TKI monotherapy, palliative surgery combined with *EGFR*-TKI

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treatment prolonged the PFS of pleural metastatic *EGFR*-LUADm patients. A subset of *EGFR*-LUADm patients with pleural metastasis might be suitable for palliative surgery.

Keywords: Lung adenocarcinoma; epidermal growth factor receptor (EGFR); target therapy; pleural metastasis; progression-free survival (PFS)

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Introduction

According to Global Cancer Statistics, there were an estimated 2.48 million new cases of lung cancer and 1.82 million lung cancer-related deaths worldwide in 2022, making it the leading cause of cancer-related mortality worldwide (1). Lung cancer is also the most common malignant tumor in China, with the highest incidence and mortality rates (2). More than half of lung cancer patients are diagnosed with stage III or IV disease (3). Non-small cell lung cancer (NSCLC) is the predominant pathological type of lung cancer, and accounts for approximately 85% of all lung cancer cases (4). In Asia, epidermal growth factor receptor (*EGFR*) is the most common driver gene in NSCLC (5,6). And EGFR mutations include the common Exon 19 Deletion (19DEL) and Exon 21 Leucine 858 to Arginine Mutation (L858R) and the less common Exon 18 Glycine 719 Substitution (G719X) and Exon 20 Serine 768 to Isoleucine Mutation (S768I) mutations and so on (7).

Patients with *EGFR* mutations treated with *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs) have significantly better survival than those treated with traditional chemotherapy alone (8). *EGFR*-TKIs have been recommended as the first-line therapeutic regimen for advanced *EGFR*-mutant NSCLC (*EGFR*-NSCLCm). *EGFR*-TKIs have also been recommend as the adjuvant treatment for locally advanced *EGFR*-NSCLCm postoperatively (9,10). However, resistance to *EGFR*-TKIs in *EGFR*-NSCLCm patients is inevitable (11-13); thus, the effective duration of targeted therapy needs to be extended.

With advancements in surgical techniques and improvements in drug efficacy, the range of patients who can achieve survival benefits from surgical treatment has significantly expanded. Previous studies have shown that surgical treatment can prolong the prognosis of NSCLC patients with oligometastasis who received *EGFR*-TKI therapy (14-16). However, controversy continues as to the efficacy of *EGFR*-TKIs combined with surgical treatment for advanced *EGFR*-NSCLCm patients (17,18). Therefore, research needs to be conducted to examine whether pleural metastatic *EGFR*-NSCLCm patients can benefit from *EGFR*-TKIs combined with surgical treatment.

In this study, we sought to compare the survival outcomes of patients with stage IVA *EGFR*-mutant LUAD (LUADm) with pleural metastasis who received *EGFR*-TKIs combined with palliative surgery to those who received targeted therapy alone. Our retrospective findings may be useful in clinical practice. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-140/rc).

Highlight box

Key findings

- Palliative surgery of primary tumor lesions can provide some therapeutic benefits for patients with pleural metastatic epidermal growth factor receptor (*EGFR*)-mutant lung adenocarcinoma (LUADm).

What is known, and what is new?

- Lung cancer patients with pleural metastasis have a poor prognosis.
- Palliative surgery may help patients achieve a better prognosis.

What is the implication, and what should change now?

- Multidisciplinary team discussions should be held to decide whether to perform palliative surgery for primary tumors in patients with *EGFR*-LUADm with pleural metastasis.

Methods

Study population

EGFR-LUADm patients with pleural metastasis treated at Shanghai Pulmonary Hospital from November 2014 to November 2023 were enrolled in this study. The pathological and *EGFR*-mutant diagnoses were confirmed

by percutaneous lung biopsy and polymerase chain reaction, respectively. The clinical staging was confirmed by positron emission tomography/computed tomography (PET-CT), chest CT, and brain magnetic resonance imaging (MRI). Pleural dissemination was defined as the presence of multiple pleural nodules with contrast enhancement on CT or increased flourodeoxyglucose (FDG) uptake [maximum standardized uptake value (SUVmax) ≥2.5] on PET-CT. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) *EGFR*-LUADm clinical stage IVA (based on the eighth version of the American Joint Committee on Cancer lung cancer staging system) with exclusive pleural metastasis; and (II) a complete response radiologically with pleural metastasis tumor after targeted therapy. The patients were divided into surgical and non-surgical groups. The surgical decision-making process was rigorously conducted by our institutional multidisciplinary tumor board (MDT), comprising thoracic surgeons, medical oncologists, radiologists, and pathologists. Surgical candidacy required fulfillment of all three core criteria: (I) complete response radiologically with pleural metastasis tumor after targeted therapy; (II) exclusion of new metastatic lesions via post-TKI; and (III) functional capacity meeting surgical risk thresholds. Final decisions required unanimous consensus from surgical and medical oncology teams. Patients in the surgical group underwent a pulmonary function test and brain MRI to ensure the feasibility of surgery. Patients were excluded from the study if they met any of the following exclusion criteria: (I) underwent a pneumonectomy; and/or (II) received other antineoplastic therapies in addition to the targeted therapy. The surgical approach was not restricted and included video-assisted thoracic surgery, open thoracic surgery, and robotic-assisted thoracic surgery. The follow-up of these patients continued until July 2024.

Clinical information collection

The clinical information of the eligible patients was retrospectively collected from the clinical database of Shanghai Pulmonary Hospital. The patients' characteristics were recorded, including diagnostic age, gender, smoking status, performance status based on the Eastern Cooperative Oncology Group Performance Status (ECOG PS), Programmed cell death ligand 1 (PD-L1) tumor expression, Tumor node metastasis classification (TNM) staging, *EGFR*-mutant status, targeted therapy details, surgical treatment, disease progression, and survival status.

Propensity score matching (PSM)

The patients were matched using PSM based on conventional prognostic factors affecting lung cancer (including ECOG score, smoke, age, N stage, and sex). The matching ratio was 1:2 (caliper: 0.05), such that two non-surgical patients were matched to each surgical patient.

Statistical analysis

The statistical analyses were conducted on the matched data. Fisher's exact test and the independent sample *t*-test were used to compare the categorical and continuous variables between the two subgroups, respectively. The median follow-up time was calculated using the reverse Kaplan-Meier method. Progression-free survival (PFS) was defined as the time from the initiation of *EGFR*-TKI therapy to disease progression, which was calculated using the Kaplan-Meier method, and the PFS difference between the two subgroups was compared using the log-rank test. The prognostic factors were identified by Cox proportional hazards regression analysis. All the statistical analyses were conducted using R (version 4.3.2) with a two-sided significance level.

Ethics statement

This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. K24-495, 2024/8/9), and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all the patients or their family members.

Results

Patient characteristics

In total, 134 *EGFR*-LUADm patients with pleural metastasis in stage IVA were retrospectively included in this study. All patients received *EGFR*-TKI monotherapy as their first-line treatment after diagnosis. The surgical group comprised 13 patients, and the non-surgical group comprised 121 patients who received *EGFR*-TKI monotherapy only. Among 121 patients who did not undergo surgery, 99 (81.8%) experienced disease progression. The progression patterns were categorized as follows: primary lesion progression in 56 cases (56.6%), increased pleural metastasis or

development of other distant metastases in 21 cases (21.2%), lymph node progression in 4 cases (4.0%), and new-onset pleural effusion in 18 cases (18.2%). There were 65 19DEL and 56 non ex19 deletion mutant (N-19DEL) patients (including two patients with L858R + S768I mutation and one patient with G719X + S768I). Among 13 patients undergoing surgical resection following preoperative EGFR-TKI therapy (median duration 4 months), 10 (76.9%) received lobectomy and 3 (23.1%) underwent wedge resection. The objective response rate (ORR) to targeted therapy in the surgical cohort was 69.2%. All surgical resections were targeted at primary lesions, with concurrent systematic lymph node dissection performed in accordance with standard oncological principles. In surgery cohort, adjuvant therapy commenced within 30 days post-surgery. Patients in the surgery group were maintained on same TKI therapy and underwent surveillance chest CT at 3-month intervals for disease monitoring. After PSM at a 1:2 ratio, the surgical group comprised 13 patients, while the non-surgical group comprised 26 patients. The clinical and pathological characteristics of the patients before and after PSM are set out in *Table 1*. After PSM, in terms of targeted therapy, four surgical patients and two non-surgical patients received a third-generation *EGFR*-TKI. The majority of patients had an ECOG PS of 0 (76.9%). After PSM, no differences in the baseline characteristic variables were observed between the surgical and non-surgical subgroups; all the patients were never smokers. All patients had either the 19DEL or L858R mutation after PSM.

Prognostic factors

Before PSM, the univariate analysis revealed that surgical treatment significantly extended PFS for stage IVA *EGFR*-LUADm patients with pleural metastasis [hazard ratio (HR): 0.14, 95% confidence interval (CI): 0.056–0.36, P<0.001] (*Figure 1*). Additionally, patients with a diagnostic age ≥65 years had superior PFS than those with a younger diagnostic age (HR: 0.47, 95% CI: 0.282–0.79, P=0.004). Compared to the patients with T1 stage, those with T2 stage had significantly worse PFS (HR: 1.98, 95% CI: 1.019–3.84, P=0.044). Similarly, patients with Exon 19 Deletion (Ex19-Del) had significantly superior PFS than those without Ex19-Del (HR: 1.66, 95% CI: 1.082–2.55, P=0.02).

After PSM, the results of the survival analysis confirmed that the patients who received *EGFR*-TKI combined with surgical treatment had significantly better PFS than those who received *EGFR*-TKI monotherapy alone (HR: 0.15, 95% CI: 0.04–0.54, P=0.004) (*Figure 2*). Compared to the N0 patients, the N1 patients had a higher risk of recurrence (HR: 5.39, 95% CI: 1.053–27.65, P=0.043). Notably, this trend was not observed in the N2 patients (HR: 0.92, 95% CI: 0.314–2.71, P=0.88).

After PSM, the surgical and non-surgical groups comprised 13 and 26 patients. In the surgical group, there were five patients without recurrence; however, in the non-surgical group, there were only two patients without disease progression. As *Figure 3* shows, the PFS of the patients in the surgical group was significantly better than that of those in the non-surgical group [median PFS: 43 (95% CI: 30–not available) *vs.* 11 (95% CI: 10–26) months, P<0.001].

Discussion

Lung cancer is highly prevalent, and is frequently diagnosed as advanced stage disease that is not suitable for surgical treatment (3). In such cases, the therapeutic regimens aim to prolong the PFS of patients. This situation is particularly relevant to NSCLC patients harboring *EGFR* mutations, which is the most prevalent mutation in Aisa (5,6). Treatment adjustments are considered in multidisciplinary team discussions when resistance develops. As resistance to targeted therapy is inevitable (11-13), it is crucial to extend the resistance-free period, thereby prolonging PFS.

Tseng *et al.* reported that primary tumor resection in patients with advanced *EGFR*-LUADm undergoing *EGFR*-TKI therapy can result in a better prognosis (14). Ohtaki *et al.* found that salvage surgery in NSCLC patients receiving *EGFR*-TKI or Anaplastic Lymphoma Kinase-TKI (ALK-TKI) therapy is safe and feasible, and may extend overall survival by reducing the local tumor burden (15). Conversely, Hu *et al.* found that tumor resection did not improve the overall survival of patients receiving targeted therapy (HR: 0.649, P=0.38) (19).

In our study, both pre- and post-PSM, the results show that univariate analyses can detect a significant impact of surgery on patients' PFS (pre-PSM HR: 0.14, 95% CI: 0.056–0.36, P<0.001; post-PSM HR: 0.15, 95% CI: 0.04–0.54, P=0.004). This indicates that palliative surgery of the primary tumor lesion may provide some therapeutic benefits for patients with pleural metastatic LUAD.

The univariate analysis after PSM revealed that the presence of lymph node metastasis was more likely to lead to the development of resistance to targeted therapy. Meanwhile, patients with N1 staging were more prone

Table 1 Clinical characteristics of patients before and after PSM

Characteristics	Before PSM, n (%)			After PSM, n (%)		
	No surgery (N=121)	Surgery (N=13)	P value	No surgery (N=26)	Surgery (N=13)	P value
ECOG PS			0.10			>0.99
0	59 (48.8)	10 (76.9)		20 (76.9)	10 (76.9)	
1	62 (51.2)	3 (23.1)		6 (23.1)	3 (23.1)	
Smoker			0.45			NA
No	108 (89.3)	13 (100.0)		26 (100.0)	13 (100.0)	
Yes	13 (10.7)	0		–	–	
Age (years)			0.08			>0.99
<65	67 (55.4)	11 (84.6)		22 (84.6)	11 (84.6)	
≥65	54 (44.6)	2 (15.4)		4 (15.4)	2 (15.4)	
Sex			0.88			>0.99
Male	45 (37.2)	4 (30.8)		8 (30.8)	4 (30.8)	
Female	76 (62.8)	9 (69.2)		18 (69.2)	9 (69.2)	
T			0.19			0.09
T1	27 (22.3)	4 (30.8)		6 (23.1)	4 (30.8)	
T2	30 (24.8)	6 (46.2)		4 (15.4)	6 (46.2)	
T3	11 (9.1)	0		4 (15.4)	0	
T4	53 (43.8)	3 (23.1)		12 (46.2)	3 (23.1)	
N			0.88			>0.99
N0	20 (16.5)	3 (23.1)		6 (23.1)	3 (23.1)	
N1	14 (11.6)	2 (15.4)		4 (15.4)	2 (15.4)	
N2	62 (51.2)	6 (46.2)		12 (46.2)	6 (46.2)	
N3	25 (20.7)	2 (15.4)		4 (15.4)	2 (15.4)	
PD-L1			0.77			0.87
Negative	103 (85.1)	12 (92.3)		22 (84.6)	12 (92.3)	
Positive	18 (14.9)	1 (7.7)		4 (15.4)	1 (7.7)	
Mutation			>0.99			>0.99
19DEL	65 (53.7)	7 (53.8)		13 (50.0)	7 (53.8)	
N-19DEL	56 (46.3)	6 (46.2)		13 (50.0)	6 (46.2)	
3rd generation TKI			0.11			0.16
Yes	13 (10.7)	4 (30.8)		2 (7.7)	4 (30.8)	
No	108 (89.3)	9 (69.2)		24 (92.3)	9 (69.2)	

ECOG PS, Eastern Cooperative Oncology Group performance status; N-19DEL, non ex19 deletion mutant; PD-L1, programmed cell death ligand 1; PSM, propensity score matching; TKI, tyrosine kinase inhibitor.

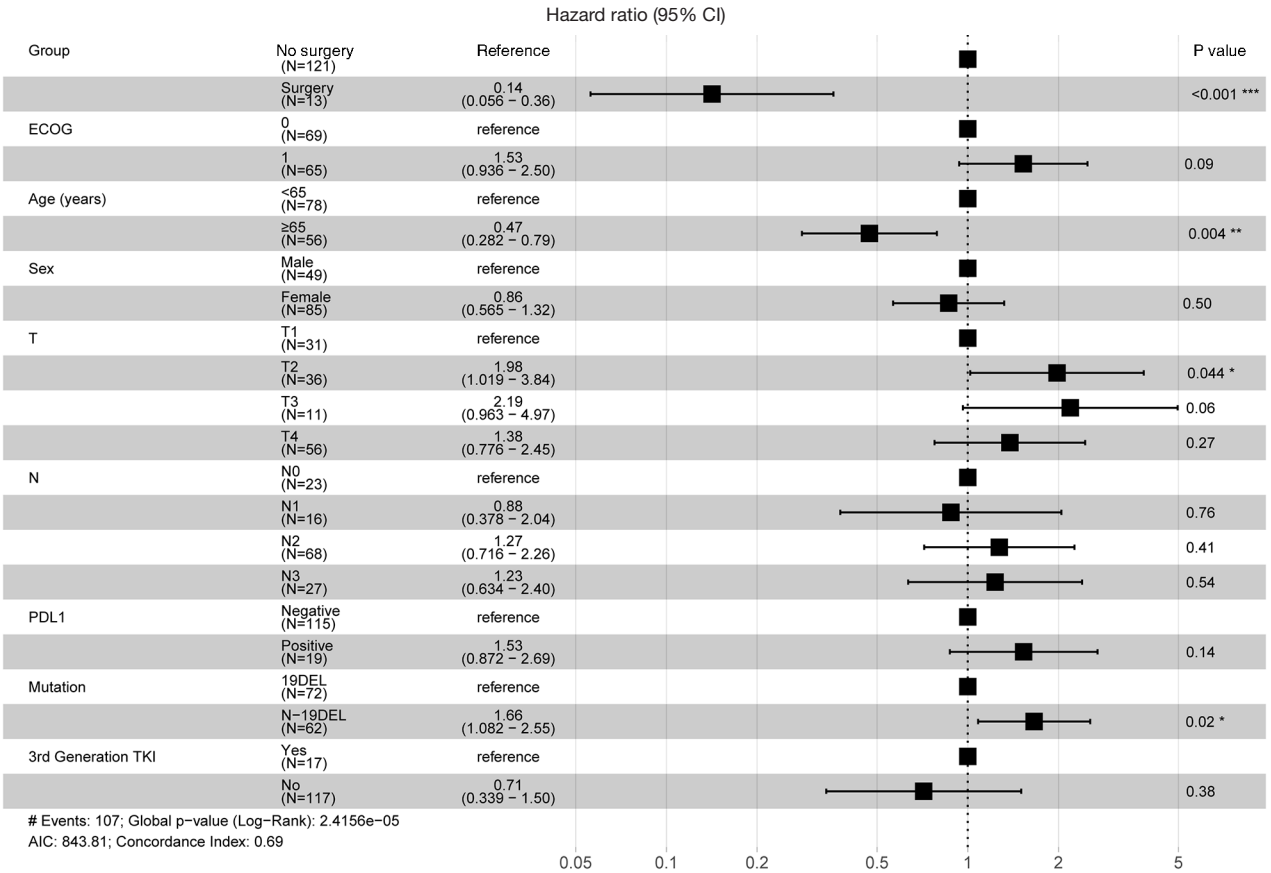

Figure 1 Univariate Cox regression analysis before PSM. Significance codes: ***, P<0.001; **, P<0.01; *, P<0.05. AIC, Akaike information criterion; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; N-19DEL, non ex19 deletion mutant; PD-L1, programmed cell death ligand 1; PSM, propensity score matching; TKI, tyrosine kinase inhibitor.

to disease progression than patients with other N stages; however, the reasons for its rapid progression are not yet known. There may be two possible reasons for this outcome. First, it may be related to the small sample size of the study. Second, it may be that the malignancy level differs due to varying metastasis patterns. Research of other cancers has shown that patients with hematogenous metastasis are at higher risk than those with lymphatic metastasis (20). Thus, LUAD with predominantly hematogenous metastasis may have a higher malignancy level. We speculate that in patients with N1 lymph node metastasis and concurrent pleural metastasis, the primary metastatic routes are likely hematogenous metastasis.

After PSM, all smoking patients were excluded from the study. Of the total 13 smoking patients, none underwent surgery [which suggests that the effect of *EGFR*-TKI may be worse in smokers (21)]; 10 experienced disease progression (median PFS: 15.1 months), and three did not experience disease progression. These patients had follow-up times of 16, 17, and 21 months, respectively. The overall PFS of the smoking patients was better than that of non-smoking patients (median PFS: smokers, 15.1 months; non-smokers, 11 months), but this is likely due to the small sample size of this study.

Among the eight patients who experienced postoperative recurrence (seven of whom had N2/3 stage), four showed pleural carcinoma recurrence, while the other four showed pulmonary carcinoma recurrence. However, the underlying causes of this phenomenon remain unclear; thus, further research needs to be conducted to explore the reasons behind it.

In the non-surgical group, disease progression was observed in 99 patients, with primary lesion progression accounting for 56.6% of cases (56/99). These findings suggest a potential therapeutic advantage of palliative resection. Therefore, in surgical candidates with preserved

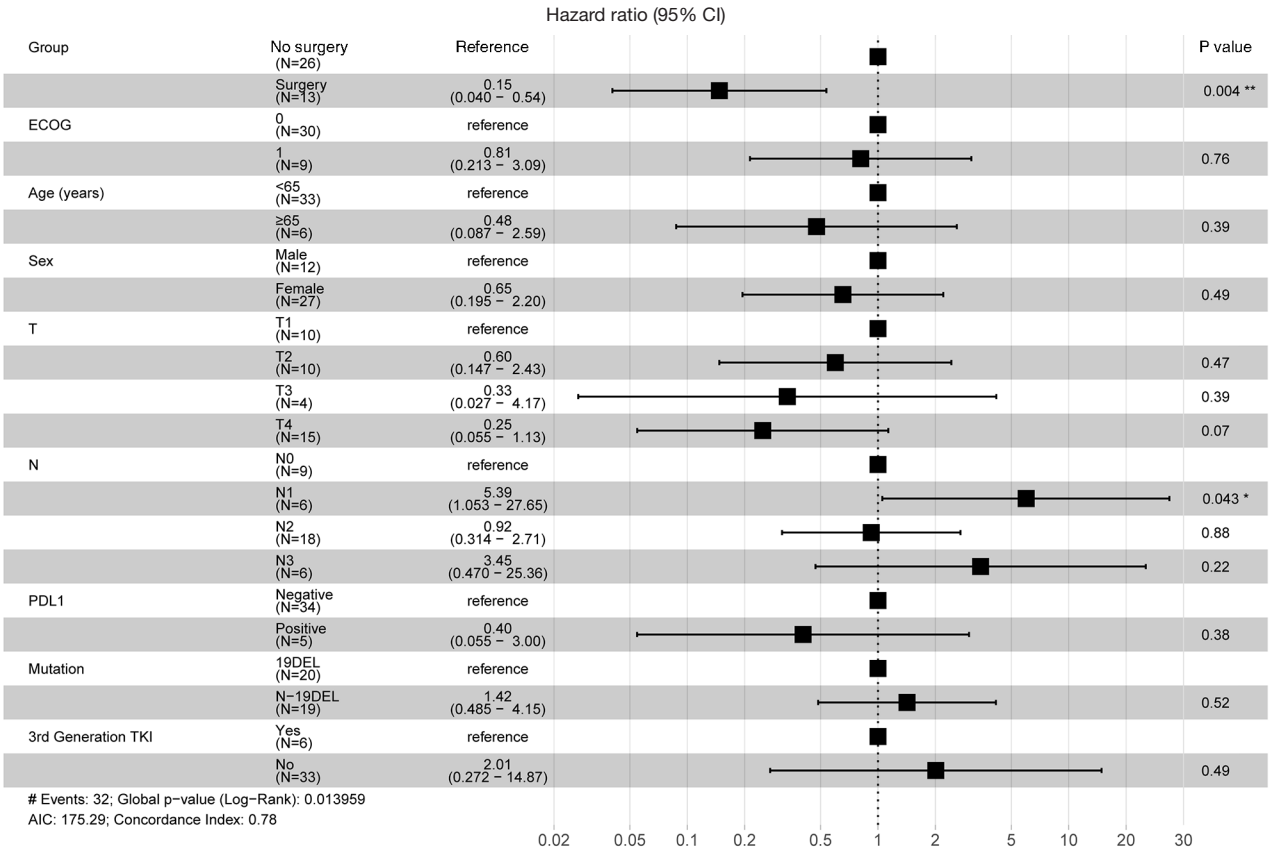

Figure 2 Univariate Cox regression analysis after PSM. Significance codes: **, P<0.01; *, P<0.05. AIC, Akaike information criterion; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; N-19DEL, non ex19 deletion mutant; PD-L1, programmed cell death ligand 1; PSM, propensity score matching; TKI, tyrosine kinase inhibitor.

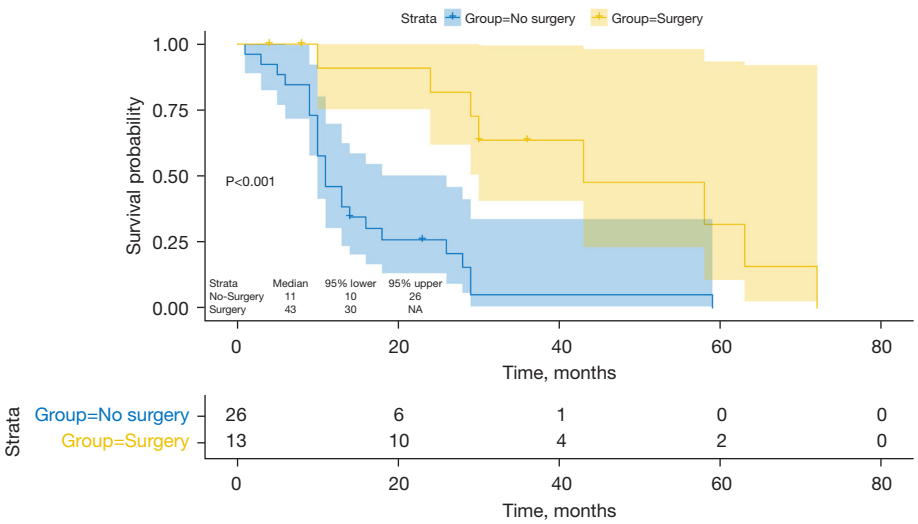

Figure 3 After PSM, PFS comparison between the surgical and non-surgical groups. NA, not available; PFS, progression-free survival; PSM, propensity score matching.

functional status, proactive resection of primary lesions through palliative surgery should be considered to optimize oncological outcomes.

This study had several limitations. First, some biases were inevitable because of the retrospective and single-center nature of this study. The decision to perform surgery was solely determined by the multidisciplinary team at our hospital. Additionally, the sample size was not large, which might be due to the strict inclusion criteria, which limited the number of eligible patients. And the 134 patients included thus far have had a mortality rate of less than 5%. It remains unclear whether surgical intervention would impact survival, which will be the focus of our subsequent research.

Conclusions

We found that palliative surgery of the primary tumor lesion provided some therapeutic benefits for pleural metastatic LUAD patients, and may delay the *EGFR*-TKI therapy resistance.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-140/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-140/dss

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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. This study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. K24-495, 2024/8/9), and the study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from all the patients or their family members.

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