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Spread through air spaces may predict early progression after salvage surgery for EGFR-mutant advanced lung adenocarcinoma treated with targeted therapy

Yu-Wei Liu[1], Wei-An Lai[2], Jen-Yu Hung[3], Yen-Lung Lee[1], Hung-Hsing Chiang[1], Jui-Ying Lee[1], Hsien-Pin Li[1], Shah-Hwa Chou[1] and Chih-Jen Yang[3,4*]

Abstract

Objective Salvage resection for residual lung cancer harboring epidermal growth factor receptor (EGFR) mutations following EGFR-tyrosine kinase inhibitor (TKI) treatment is gaining traction for its survival benefits. However, the impact of pathological factors on survival remains unclear.

Methods Between 2013 and 2023, we retrospectively reviewed 34 patients with advanced lung adenocarcinoma who received EGFR-TKI therapy. After a median TKI treatment duration of 9.1 months, all patients demonstrated either partial response ($n=27$) or stable disease ($n=7$) before salvage surgery. Demographic, pathological outcomes, progression-free survival (PFS), and overall survival (OS) were analyzed.

Results Among the 34 patients, six (17.6%) achieved a pathological complete response (pCR) and nine (26.5%) had a major pathological response (MPR). Additionally, 11 patients (32.4%) exhibited spread through air spaces (STAS), and lymphovascular invasion (LVI) was observed in nine patients (26.5%). The 3-year PFS and OS rates were 55.8% and 60.5%, respectively. No significant differences in PFS or OS were observed regarding mutation type, TKI generation, pCR, MPR, or LVI. However, Kaplan-Meier analysis revealed that STAS was associated with shorter PFS compared to non-STAS cases ($p=0.01$). In multivariate analysis, STAS was identified as an independent prognostic factor for PFS (hazard ratio: 2.83, 95% CI: 1.35–28.54, $p=0.02$). No significant prognosticators were found for OS in univariate or multivariate analyses.

Conclusion While salvage surgery following TKI treatment is feasible and prolongs survival by removing residual primary tumor with potential TKI resistance, STAS may contribute to a higher risk of early progression. This finding warrants further investigation and tailored treatment strategies.

Keywords Lung adenocarcinoma, Epidermal growth factor receptor, Tyrosine kinase inhibitor, Salvage surgery, Spread through air spaces

*Correspondence:
Chih-Jen Yang
chjeya@kmu.edu.tw

Full list of author information is available at the end of the article

Introduction

Previous studies have demonstrated that lung adenocarcinoma patients with actionable driver mutations, treated with matched tyrosine kinase inhibitors (TKIs), experience longer overall survival [1]. In Asia, approximately 50–60% of these patients have epidermal growth factor receptor (EGFR) mutations, with the most common being exon 19 deletions and exon 21 L858R mutations [2, 3]. Currently, EGFR-TKIs remain the standard first-line therapy for patients with advanced EGFR-mutant non-small cell lung cancer (NSCLC) [4, 5].

With the increasing adoption of multimodal treatment strategies in lung cancer, evidence supporting the efficacy of local consolidative therapy (LCT) has emerged in oligometastatic or oligo-progressive NSCLC patients treated with TKIs [6, 7]. Our previous study assessed the impact of LCT in EGFR-mutant patients receiving afatinib as first-line therapy [8], revealing that patients who underwent LCT had significantly longer progression-free survival (PFS) than those who did not (median PFS: 32.8 vs. 14.5 months, $p = 0.0008$). Additionally, LCT was associated with improved overall survival (OS) (median OS: 67.1 vs. 34.5 months, $p = 0.0011$). Salvage surgery is a common LCT intervention, but prognostic factors for successful outcomes remain unclear.

Recent studies have suggested expanding surgical resection for certain advanced NSCLC patients, particularly those with oligometastatic disease [9–12]. Several retrospective studies have demonstrated survival benefits from salvage surgery after TKI treatment in selected stage III and IV NSCLC patients [13–21]. Although surgery for regrown or residual tumors seems to provide good local control of the tumor burden and potentially prolong survival, some patients inevitably experience disease progression after primary tumor resection.

In recent years, studies investigating the correlation between specific pathological factors and outcomes in resected early-stage non-small cell lung cancer (NSCLC) have gained significant attention. Among these, spread through air spaces (STAS)– defined as tumor cells beyond the edge of the main tumor into the air spaces surrounding the tumor– has become one of the most widely discussed topics [22]. STAS has been confirmed as an independent prognostic factor regardless of lung cancer stage, although debates persist regarding the artifact hypothesis of STAS [23, 24]. Furthermore, studies examining the prognosis of completely resected early-stage lung cancer following neoadjuvant targeted therapy, based on histological grading systems, have highlighted its clinical significance [25]. Thus far, only one study has examined the pathological impact of treatment-resistant patterns on outcomes in advanced lung adenocarcinoma treated with TKIs and salvage resection [21]. Consequently, the influence of these pathological factors on oncological outcomes remains underexplored.

With this in mind, this retrospective cohort study primarily aims to evaluate surgico-pathological outcomes in patients with advanced EGFR-mutant lung adenocarcinoma who underwent salvage surgery following EGFR-TKI treatment. The secondary objective is to analyze prognostic factors and survival outcomes.

Materials and methods

Study design

This retrospective cohort study analyzed cases from January 2013 to July 2023 at a tertiary center in southern Taiwan. The study received approval from the Institutional Review Board of Kaohsiung Medical University Hospital, and the requirement for written informed consent was waived (KMUHIRB-E(I)-20240126).

A total of 59 patients with stage IIIB-IV primary lung adenocarcinoma who received TKI treatment followed by primary tumor resection were evaluated. We excluded patients who met the following criteria: ALK-TKI treatment ($n = 1$), non-first-line EGFR-TKI treatment with or without chemotherapy prior to surgery ($n = 5$), resection for re-examination of EGFR mutation due to clinical progressive disease ($n = 16$), or incomplete data for analysis ($n = 3$). This left 34 EGFR-mutant lung adenocarcinoma patients who received first-line TKI treatment and achieved a clinical partial response or stable disease for final analysis (Fig. 1).

Clinical staging was determined based on the American Joint Cancer Committee (AJCC) eighth edition guidelines for lung cancer staging. All patients had a pre-treatment histopathological diagnosis confirmed either by flexible bronchoscopy or CT-guided biopsy. Bone scans, brain magnetic resonance imaging (MRI), and optional positron emission tomography and CT (PET-CT) scans were conducted to exclude distant metastases. Additionally, patients were confirmed to have common EGFR mutations (such as exon 19 deletion or exon 21 point mutation L858R) using real-time PCR cobas® EGFR mutation test before initiating EGFR-TKI treatment. The treatment modality, including salvage surgery, was assessed preoperatively by multidisciplinary tumor boards to reach a consensus on the surgical treatment.

Indications of salvage surgery

Pulmonologists and thoracic surgeons were the key decision-makers in determining the inclusion criteria. Treatment plans for each patient were established during a multidisciplinary team (MDT) meeting. The strategy for salvage surgery was mainly concerned with the following criteria: (1) residual main tumor on CT scan showing partial response or stable disease by RECIST criteria, (2) all distant metastases were resolved on imaging studies

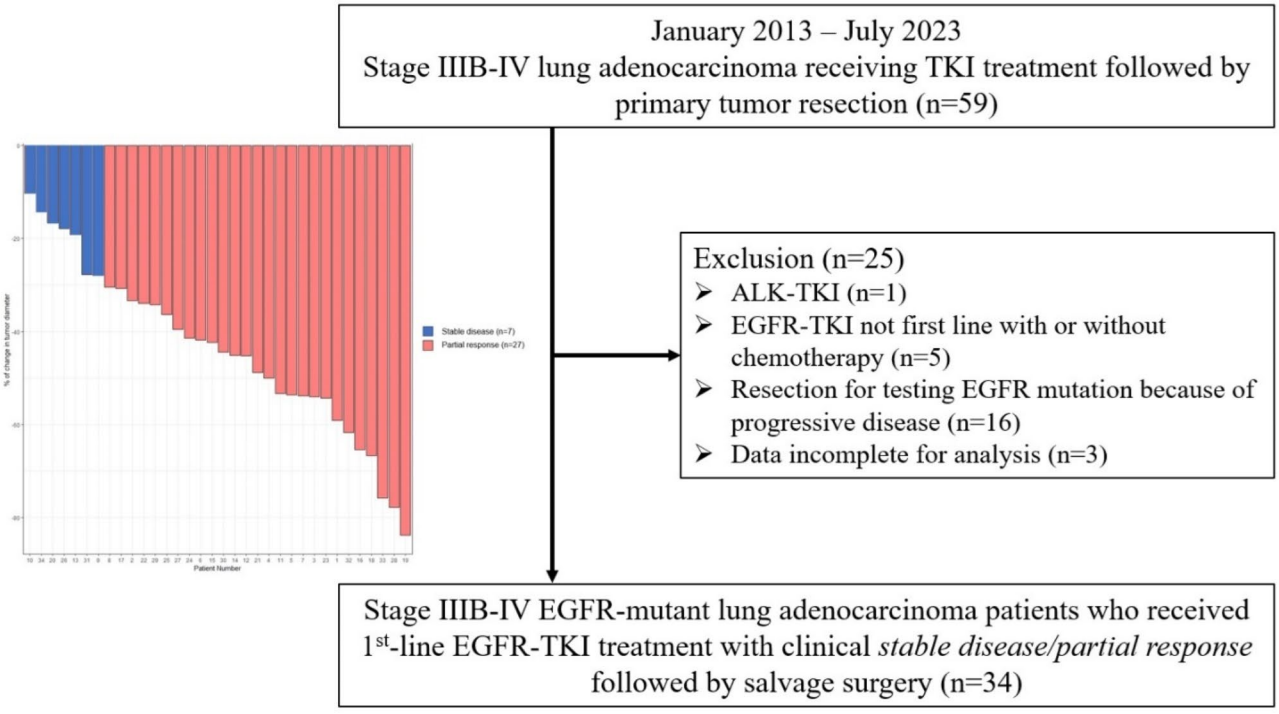

Fig. 1 Flow diagram of patient recruitment
TKI, *tyrosine kinase inhibitor*; ALK, *anaplastic lymphoma kinase*; EGFR, *Epidermal Growth Factor Receptor*

after EGFR-TKI treatment and/or received appropriate local control, (3) adequate patient performance status, and (4) tolerable cardiopulmonary reserve. For residual primary lesions that were large or centrally located, anatomical resections typically began with ligation of the lobar vein, followed by either the bronchus or the artery, allowing for safe execution of a non-stapled lobectomy. In patients who had undergone TKI treatment followed by salvage resection, dense hilar fibrosis and adhesions were occasionally present. These fibrotic changes complicated the separation of the pulmonary artery from the bronchus and made systematic mediastinal lymph node dissection more challenging. Given the difficulty in isolating individual hilar structures, direct division of the pulmonary artery was considered dangerous and could result in massive bleeding. To address this, we sometimes opted for simultaneous stapling of the remaining pulmonary artery and lobar bronchus using a black reload, ensuring a safer procedure (simultaneously stapled lobectomy) at the surgeon's discretion (see Supplemental Video 1) (Fig. 2A and D). We also employed absorbable PGA sheets (Neoveil) for additional bronchial stump coverage to ensure its integrity.

For peripherally located lesions with significant tumor shrinkage, sublobar resections were preferred. Due to the fibrotic and adhesive changes in the mediastinum, systematic mediastinal lymph node dissection was often difficult to perform. In such cases, lymph node sampling was typically carried out instead of systematic dissection.

Histological assessment after salvage surgery

The IASLC grading system for invasive pulmonary adenocarcinoma comprises three levels of invasion based on the tumor's histological subtype: well-differentiated adenocarcinomas (Grade 1), moderately differentiated adenocarcinomas (Grade 2), and poorly differentiated adenocarcinomas (Grade 3) [26]. According to current literature, the revised IASLC grading system offers optimal stage-independent prognostic stratification for invasive non-mucinous lung adenocarcinoma and is significantly associated with the prognosis of patients with lung adenocarcinoma [27–29]. Among the 34 patients included in this study, all resected tumors were microscopically reviewed and evaluated by two pathologists, one of whom specialized in pulmonary pathology, using the revised grading system. When disparities were encountered, consensus was reached through discussion. Histologic subtypes were classified into five categories (lepidic predominant, acinar predominant, papillary predominant, micropapillary predominant, and solid predominant) as per 2015 World Health Organization classification of thoracic tumor [30]. Notably, spread through air spaces (STAS), defined as tumor cells present within alveolar spaces in the lung parenchyma beyond the edge of the main tumor, has been introduced as a

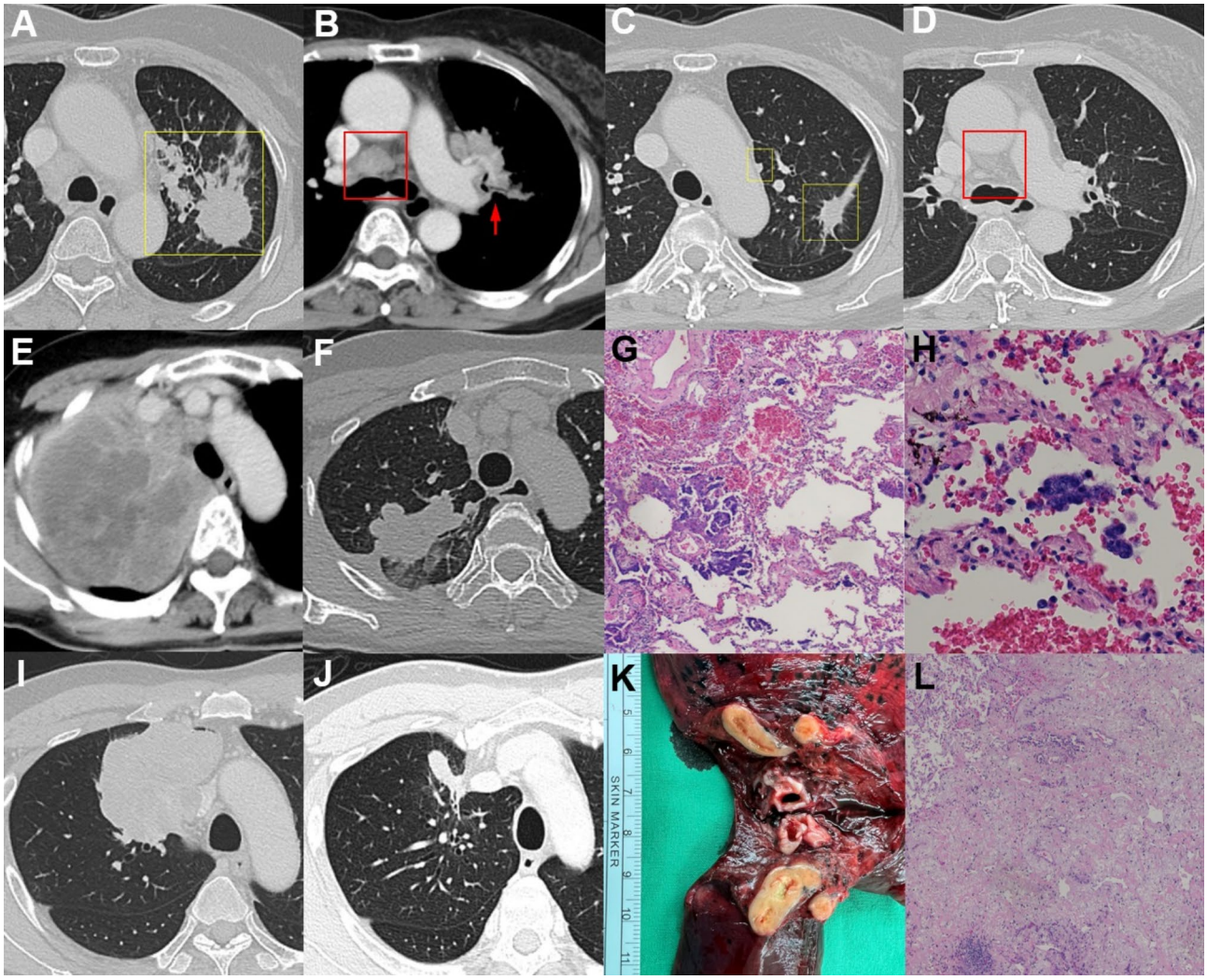

Fig. 2 Representative patients with (**A**-**D**) apparent radiological shrinkage of the main tumor (patient #19), (**E**-**H**) presence of spread through air spaces (patient #24), and (**I**-**L**) presence of pathological complete response (patient #16)
(**A**-**D**) Computed tomographic (CT) scan revealed a marked decrease of tumor size (*yellow squares*) and apparent shrinkage of mediastinal lymph nodes (*red squares*) after Erlotinib plus Bevacizumab treatment. Evident left pulmonary hilum invasion by tumor was also shown (*red arrow*) (see Supplemental Video 1). (**E**-**H**) CT scan revealed marked reduction of tumor size after Afatinib treatment. Pathologic examination showed spread through air spaces, with tumor cells in air spaces beyond the edge of the main tumor. (**I**-**L**) CT scan revealed marked decrease of tumor size after Osimertinib treatment. Pathologic examination showed extensive fibrosis and inflammation without viable tumor cells in the tumor bed area, indicating the pathological complete response. (Hematoxylin and eosin stain; G and L: original magnification x40; H: original magnification x200.)

novel mechanism of invasion from the pathologist's perspective [22] (Fig. 2G and H). Over the past decade, its importance as a significant prognostic factor for NSCLC has gained considerable attention, regardless of the tumor stage [31, 32]. In addition, lymphovascular invasion (LVI), another common factor, was also investigated. Evaluation of the treatment response was based on the recommendation of the International Association for the Study of Lung Cancer criteria proposed by Travis et al. [33], major pathologic response (MPR) is defined as 10% or less residual viable tumor following preoperative treatment, while pathologic complete response (pCR) is defined as the absence of residual viable tumor in all specimens, including the resected lung and lymph nodes (Fig. 2K and L).

Postoperative treatment and follow-up

EGFR-TKI therapy was maintained uninterrupted throughout the perioperative period, with most patients continuing the same regimen until disease progression. Upon progression, treatment was predominantly transitioned to second-line therapy with Osimertinib if a T790M mutation was detected in the rebiopsy specimen. In the absence of a confirmed T790M mutation, patients were managed with adjuvant chemotherapy (using a pemetrexed plus platinum doublet regimen as the

primary choice), radiotherapy, or a combination of both. Follow-up evaluations were conducted every 3 months using CT scans of the chest and upper abdomen. Contrast-enhanced magnetic resonance imaging (MRI) of the brain and nuclear bone scans were performed every 3 to 6 months, with additional PET-CT scans if necessary. Survival after surgery was assessed, along with the sites of disease progression.

Progression-free survival (PFS) was defined as the time from salvage surgery to confirmed disease progression, death, or the last follow-up. Overall survival (OS) was defined as the time from salvage surgery to death or the last follow-up. As of March 2024, a follow-up investigation was carried out to record either the date of death or the last follow-up for surviving patients.

Statistical analysis

Descriptive analysis was employed according to data normality, which was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median (range) according to data normality. Categorical variables were expressed as frequency (percentage [%]). The one-way ANOVA test was used to compare perioperative continuous variables. The Chi-square test and Fisher exact test were used to compare categorical variables. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method and log-rank test. Univariate and multivariate Cox regression analyses were applied to evaluate the effects of clinical factors on the prognosis of lung cancer patients who received TKI treatment. Variables with $P < 0.2$ in univariate analysis were included in multivariable analysis. The adjusted multivariate model was employed to identify factors predicting survivals. A P-value of less than 0.05 was considered significant. All statistical operations were conducted using SPSS Statistical Software (version 29.0; IBM Corp., Armonk, NY).

Results

Clinical and pathological characteristics

The demographic and clinical characteristics of the 34 enrolled patients are summarized in Table 1. The median age was 63 years (range: 40–81), with the majority of patients being female (64.7%) and nonsmokers (76.5%). Clinical staging at the start of TKI treatment was as follows: stage IIIB-IIIC in 5 patients (14.7%) and stage IV in 29 patients (85.3%). All patients had either an exon 21 (L858R) point mutation, an exon 19 deletion, or a combination of both. The EGFR-TKI agents used were gefitinib (17.6%), erlotinib (20.6%), afatinib (41.2%), and osimertinib (20.6%), with 6 patients (17.6%) receiving additional VEGF inhibitor therapy. Most patients (79.4%) achieved a partial response after a median TKI treatment duration of 9.1 months (range: 3.1–33.8 months). Regarding salvage surgery, the majority of patients underwent lobectomy (70.6%) via a VATS approach (91.2%). Positive surgical margins were noted in 2 patients (5.9%). The remaining perioperative outcomes and pathological findings are summarized in Table 1.

In terms of pathological response, 9 patients (26.5%) achieved a major pathological response (MPR), while 6 patients (17.6%) achieved a pathological complete response (pCR). Histological grade of tumor were classified as grade 2 (64.3%) and grade 3 (35.7%), respectively. Tumor subtypes were identified in 28 patients, with the majority (58.8%) having an acinar subtype. Other subtypes included micropapillary (2.9%), papillary (5.9%), and solid (14.7%). Additionally, 11 patients (32.4%) exhibited spread through air spaces (STAS), and lymphovascular invasion (LVI) was observed in 9 patients (26.5%).

Based on the presence of STAS, the demographic and pathological features of the available patients were analyzed (as shown in Supplemental Table 1). The STAS-positive group exhibited a higher proportion of histological grade 3 tumors (82%), increased prevalence of micropapillary and solid subtypes (9% and 46%, respectively), and a greater presence of lymphovascular invasion (LVI) (55%). Additionally, the STAS-positive group demonstrated a significantly higher rate of disease progression compared to the non-STAS group (73% vs. 12%, respectively).

As shown in Supplemental Table 2, a comparison among different generations of TKI treatment revealed no significant differences in clinical characteristics. However, third-generation TKIs showed numerically higher pCR and MPR rates (5/7, 71.4%) compared to the earlier generations, though the difference was not statistically significant.

Prognostic factors and outcomes after salvage surgery

Both the 3-year and 5-year PFS rates after salvage surgery were 55.8% (Fig. 3A), while the 3-year and 5-year OS rates were 60.5% (Fig. 3B).

Additionally, PFS and OS probabilities, calculated using the Kaplan-Meier method, for the STAS-negative, STAS-positive, and pCR groups are shown in Fig. 4. The STAS-positive group had significantly worse PFS compared to the STAS-negative group (HR: 5.7, 95% CI: 1.5–21.7, $p = 0.01$) although subgroup analyses were limited by small sample sizes (Fig. 4A). However, there were no significant differences in OS between the groups (Fig. 4B).

No significant differences in PFS or OS were observed based on EGFR mutation type, TKI generation, or other pathological factors, such as the presence of LVI, MPR, and pCR (Supplemental Figs. 1 and 2).

Table 2 presents the prognostic factors for PFS and OS based on univariate and multivariate analyses. After adjusting for relevant clinicopathological variables in the multivariate analysis, the presence of STAS remained an

Table 1 Demographic, clinical, and perioperative characteristics of the included patients

Variables	Patients ($n=34$)
Age, y, median (range)	63 (40–81)
Gender, N (%)	
Male	12 (35.3)
Female	22 (64.7)
Smoking, N (%)	8 (23.5)
Family history, N (%)	8 (23.5)
ECOG, N (%)	
0	17 (50.0)
1	17 (50.0)
AJCC stage (8th edition), N (%)	
IIIB-IIIC	5 (14.7)
IV	29 (85.3)
Clinical T, N (%)	
T1	2 (5.8)
T2	4 (11.6)
T3	10 (29.4)
T4	18 (52.9)
Clinical N, N (%)	
N0	5 (14.7)
N1	4 (11.8)
N2	8 (23.5)
N3	17 (50.0)
Clinical M1, N (%)	29 (85.3)
Metastatic site, N (%)	
Bone	10 (29.4)
Contralateral lung	11 (32.4)
Pleural	10 (29.4)
Brain	8 (23.5)
Others	6 (17.6)
yp T stage, N (%)	
T0	6 (17.6)
T1	12 (35.3)
T2	9 (26.5)
T3	5 (14.7)
T4	2 (5.9)
yp N stage, N (%)	
Nx	2 (5.9)
N0	21 (61.8)
N1	7 (20.6)
N2	3 (8.8)
N3	1 (2.9)
Preoperative CEA serum level	
≧5 ng/mL	7 (20.6)
< 5 ng/mL	27 (79.4)
Tumor diameter pre-TKI, cm, median (range)	4.2 (1.3–10.3)
Tumor diameter post-TKI, cm, median (range)	2.3 (0.5–6.8)
EGFR mutation, N (%)	
Exon 21 (L858R)	16 (47.1)
Exon 19 deletion	17 (50.0)
Exon 21 (L858R) + Exon 19 deletion	1 (2.9)
EGFR-TKI, N (%)	
Gefitinib	6 (17.6)

Table 1 (continued)

Variables	Patients (*n* = 34)
Erlotinib	7 (20.6)
Afatinib	14 (41.2)
Osimertinib	7 (20.6)
EGFR-TKI plus VEGF-i, N (%)	6 (17.6)
Duration from TKI to Surgery, months, median (range)	9.1 (3.1–33.8)
ASA grade, N (%)	
II	16 (47.1)
III	18 (52.9)
Type of resection, N (%)	
Lobectomy	24 (70.6)
Segmentectomy	5 (14.7)
Wedge resection	5 (14.7)
Operative approach, N (%)	
Open thoracotomy	3 (8.8)
VATS	28 (82.4)
Robotic VATS	3 (8.8)
Positive surgical margin (R1 resection), N (%)	2 (5.9)
Operative time, minutes, median (range)	180 (30–340)
Hospital stay, days, median (range)	4.5 (2–9)
Blood loss, mL, median (range)	20 (5–500)
Postoperative complication, N (%)	5 (14.6)
Grade II	4 (11.6)
Prolonged air leakage	2 (5.8)
Hoarseness	1 (2.9)
Postoperative atrial fibrillation	1 (2.9)
Grade IIIa	1 (2.9)
Cerebral ischemic stroke	1 (2.9)
30-day mortality, N (%)	0
N1 number, median (range)	2 (0–13)
N2 number, median (range)	4 (0–25)
Dissected LNs, median (range)	8.5 (0–30)
Pathological response, N (%)	
Major pathological response (MPR)	9 (26.5)
Non-MPR	19 (55.9)
Pathological complete response (pCR)	6 (17.6)
Spread through air space (STAS), N (%)	11 (32.4)
Lymphovascular invasion (LVI), N (%)	9 (26.5)
Subtype, N (%)	(*n* = 28)
Acinar	20 (58.8)
Papillary	2 (5.9)
Micropapillary	1 (2.9)
Solid	5 (14.7)
Histological grade, N (%)	(*n* = 28)
Grade 2	18 (64.3)
Grade 3	10 (35.7)
Disease progression after surgery, N (%)	11 (32.4)
Site of progression, N (%)	(*n* = 11)
Bone	2 (18.2)
Ipsilateral lung	1 (9.1)
Contralateral lung	2 (18.2)
N2 node	1 (9.1)
Thyroid	1 (9.1)

Table 1 (continued)

Variables	Patients ($n=34$)
Pleural effusion	2 (18.2)
Pleural and pericardial nodules	1 (9.1)
Brain	1 (9.1)
Death, N (%)	9 (26.5)
Follow-up, month, median (range)	33.5 (7.1–135.3)

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; EGFR, Epidermal Growth Factor Receptor; TKI, Tyrosine Kinase Inhibitor; VEGF-I, Vascular endothelial growth factor inhibitor; LNs, Lymph Nodes; ASA, American Society of Anesthesiologists; VATS, video-assisted thoracoscopic surgery; MPR, Major Pathological Response; pCR, Pathological Complete Response; STAS, Spread through air space, and LVI, Lymphovascular Invasion

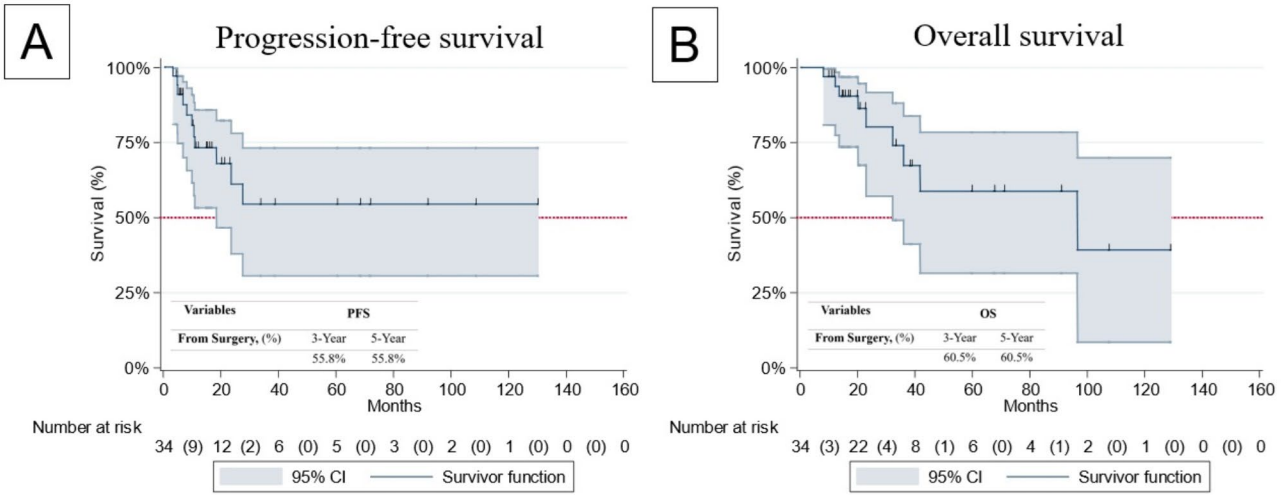

Fig. 3 Survival curves of PFS (**A**) and OS (**B**) after salvage surgery. PFS, *progression-free survival*; OS, *overall survival*

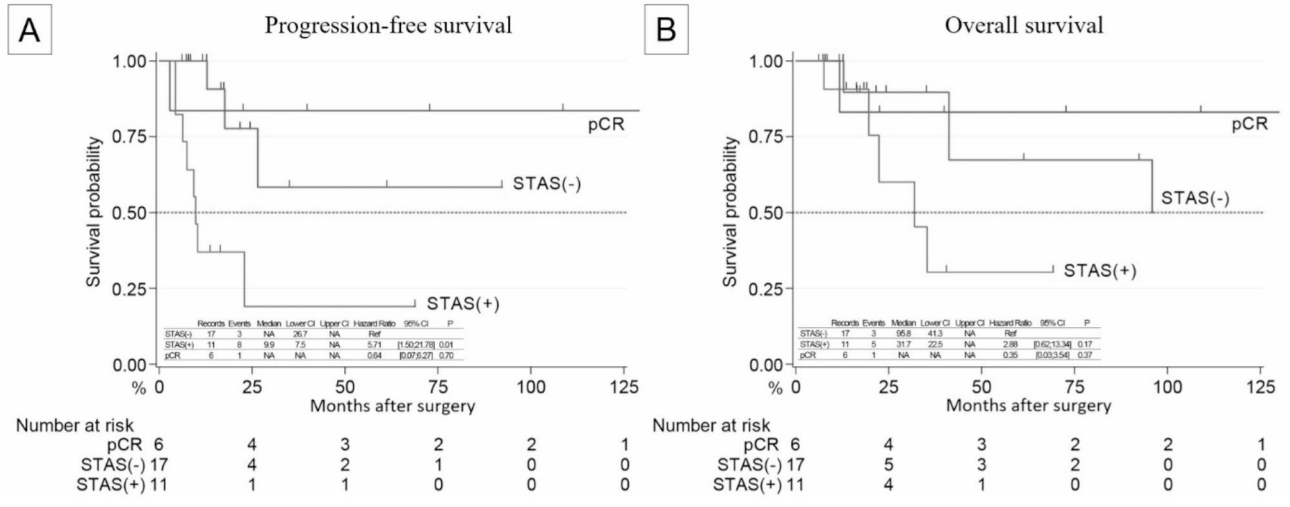

Fig. 4 Survival curves of patients after salvage surgery stratified by STAS
TKI, *tyrosine kinase inhibitor*; PCR, *pathological complete response*; STAS, *spread through air spaces*

independent predictor of PFS ($p=0.02$, HR: 2.83, 95% CI: 1.35–28.54). No significant prognostic factors were identified for OS.

During the median follow-up period of 33.5 months (range: 7.1–135.3), disease progression occurred in 11 patients (32.4%). Progression sites included bone, ipsilateral lung, contralateral lung, N2 nodes, thyroid, pleura, and brain. Nine patients (26.5%) died during the study period. A Swimmer's plot was generated to visually represent each patient's postoperative treatments

Table 2 Uni and multivariate Cox regression analysis of predictors for PFS and OS

Variables	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age ≧ 65 y (Ref < 65 y)	0.42 (0.12–1.48)	0.28	-	-	0.41 (0.1–1.64)	0.21	-	-
Female patients (Ref = Male)	0.68 (0.19–2.57)	0.57	-	-	0.63 (0.10–3.83)	0.59	-	-
ECOG PS 1 (Ref = PS 0)	4.22 (1.10–16.19)	0.03	9.23 (0.49–36.32)	0.72	10.3 (1.28–83.1)	0.09	18.7 (1.63–92.1)	0.72
Smoking (Ref = No smoking)	0.32 (0.04–2.53)	0.32	-	-	0.96 (0.19–4.7)	0.96	-	-
Family history (Ref = No family history)	1.78 (0.51–6.01)	0.37	-	-	2.3 (0.61–8.62)	0.22	-	-
Preoperative serum CEA level ≧ 5 ng/mL (Ref < 5 ng/mL)	1.13 (0.82–5.73)	0.24	-	-	2.57 (1.24–9.87)	0.51	-	-
Stage IVA or IVB (Ref = III)	2.1 (0.27–16.58)	0.48	-	-	27.9 (0.012–6224)	0.39	-	-
19 deletion (Ref = 21 L858R)	4.17 (0.90–19.29)	0.07	8.22 (0.36–48.57)	0.47	3.03 (0.62–14.9)	0.17	15.6 (0.97–45.82)	0.45
2nd & 3rd Generation TKI (Ref = 1st generation)	0.95 (0.26–3.57)	0.95	-	-	1.75 (0.24–12.78)	0.58	-	-
Duration of pre-op TKI ≥ 9 months (Ref < 9 months)	0.71 (0.22–2.36)	0.58	-	-	1.1 (0.29–4.17)	0.89	-	-
Histological grade 3 (Ref = grade 2)	4.21 (1.41–12.28)	0.04	4.84 (0.52–16.71)	0.26	3.84 (0.54–31.25)	0.32	-	-
STAS (Ref = no STAS)	8.04 (2.90–15.87)	0.002	2.83 (1.35–28.54)	***0.02***	3.74 (0.88–15.8)	0.07	7.44 (1.67–18.62)	0.31
LVI (Ref = no LVI)	1.89 (0.53–6.69)	0.33	-	-	1.12 (0.22–5.71)	0.89	-	-

PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen; TKI, Tyrosine Kinase Inhibitor; STAS, Spread through air space, and LVI, Lymphovascular Invasion

and outcomes following salvage surgery (Supplemental Fig. 3).

Discussion

Over the past decade, several retrospective studies have demonstrated the feasibility and safety of salvage surgery following TKI treatment in patients with advanced NSCLC [13–18]. However, the small sample sizes, variations in disease stage and mutation types, non-first-line treatments, and differing surgical indications for regrown or residual tumors in these studies likely introduced potential bias in the reported outcomes. Recently, two large case-control studies compared data between patients who underwent residual tumor resection and those who did not, using propensity score matching [19, 20]. These studies consistently showed that combining EGFR-TKI treatment with primary tumor resection provides better PFS and OS than EGFR-TKI therapy alone. However, few studies have examined the impact of pathological factors or mutation profiles on patient outcomes [16, 20, 21].

In our 10-year study, we evaluated the clinicopathological characteristics and survival outcomes of 34 patients with stage IIIB-IV lung adenocarcinoma who underwent salvage surgery after first-line EGFR-TKI treatment. All patients were confirmed to have common EGFR exon 19 deletions or exon 21 point mutations (L858R) and had achieved either a clinical partial response ($n = 27$) or stable disease ($n = 7$) before undergoing salvage surgery.

Our study yielded several key findings. First, among the 34 patients, six (17.6%) achieved a pathological complete response (pCR), and nine (26.5%) achieved a major pathological response (MPR). The rates of pCR and MPR in our study were higher than those reported in previous studies, where pCR rates ranged from 0 to 11.4% and MPR rates from 17 to 44% in patients undergoing salvage surgery [13–15, 20]. Additionally, the median duration of preoperative TKI therapy in our study was slightly longer, at 9.1 months. While some studies suggest that six months of treatment may be optimal for minimizing coexisting genomic alterations and improving PFS [19], there is no consensus on the ideal duration of preoperative TKI therapy. Reported treatment durations in the literature range from 5 to 14 months [16–21].

Second, univariate and multivariate analyses identified the presence of STAS as the only adverse prognostic factor for PFS, while other variables such as age, mutation type, TKI generation, duration of preoperative TKI treatment, and preoperative serum CEA levels had no significant impact on PFS or OS. Regarding prognostic factors, previous studies have shown that disease progression during TKI therapy, preoperative CEA levels (≥ 5 ng/mL), and pleural seeding at pre-treatment stage are associated with worse OS [12, 14, 17]. Other studies have identified older age at treatment initiation (≥ 70 years), more advanced pathological T stage (T2-T4 vs. T0-T1), pleural seeding, and more advanced preoperative stage (stage III vs. I-II) as predictors of inferior PFS [14, 17, 18]. In

our retrospective study, which included carefully selected patients, we did not find significant prognostic factors for OS or the aforementioned factors. However, we identified the presence of STAS as an independent predictor of worse PFS. To our knowledge, this is the first study to demonstrate the important role of STAS in patients with advanced lung adenocarcinoma treated with salvage surgery following EGFR-TKI therapy.

Third, in the present study, the 3- and 5-year PFS rates after initial TKI treatment were both 55.5%, while the 3- and 5-year OS rates were 73.2% and 59.3%, respectively. These data are comparable to previously reported rates in the literature, with 3-year PFS and OS rates ranging from 22 to 34.5% and 76%, respectively [17, 21].

There is compelling evidence in the literature linking STAS to lower survival rates and identifying it as an independent prognostic factor, regardless of lung cancer stage [31]. In our study, as detailed in Supplemental Table 1, the STAS group exhibited a higher frequency of coexisting micropapillary and solid components compared to the non-STAS group. This finding is consistent with previously reported associations between STAS and histological subtypes, which highlight its significant correlation with high-grade histological patterns, particularly the solid and micropapillary subtypes of lung adenocarcinoma [31, 34]. Furthermore, large cohort studies and meta-analyses have shown that STAS is a significant prognosticator for surgical patients with stage I-IV NSCLC [32, 34]. Recent literature on STAS and epithelial-mesenchymal transition (EMT)—a biological process that promotes tumor cell migration and invasiveness—provides one of the possible insights. Ikeda et al. [35] investigated the role of the EMT phenotype in the occurrence of STAS and found that the EMT phenotype is associated with an increased frequency of STAS and a higher risk of recurrence following lung carcinoma resection. This suggests that patients exhibiting STAS may gradually develop resistance mechanisms, such as EMT, which might occur concurrently in STAS patients. Moreover, a recent study by Lin et al. [21] highlighted the presence of morphologically treatment-resistant tumor regions with acquired T790M mutations and histologic transformations, indicating the existence of resistant subclones in TKI-treated tumors prior to disease progression. These findings underscore the value of timely resection of residual primary tumors in selected patients, potentially improving survival by removing TKI-resistant subclones before progression.

The current literature on salvage surgery primarily focuses on recurrent or persistent disease following definitive chemoradiation. A recent study [36] examining lung resections for NSCLC after initial nonoperative treatments (including targeted therapy, chemotherapy, radiotherapy, and immunotherapy), which affirmed the safety of salvage surgery and reported favorable perioperative outcomes. However, the study highlighted that prior radiation therapy was associated with worse outcomes. Notably, the rate of major complication (grade 3 or greater) in patients with a history of radiation was 11%, comparable to previous studies on salvage surgery after radiation, which reported major morbidity ranging from 16 to 18% [37]. These findings may indirectly reflect the technical challenges posed during surgery in such cases.

Although direct comparisons with earlier studies involving different treatment modalities are challenging, our results suggest an encouraging prognosis, with perioperative morbidity rates remaining comparable. No mortality occurred within 30 days of surgery, and the overall incidence of postoperative complications was 14.6% (5/34), with only 3% (1/34) classified as grade 3 or higher. As documented in previous literature, tissue fibrosis and adhesions resulting from post-TKI treatment responses often increase the technical complexity of surgery [16]. Nevertheless, these challenges did not significantly impact postoperative outcomes when addressed by experienced surgeons employing appropriate surgical techniques [16, 21].

In our opinion, salvage surgeries following TKI treatment were not associated with increased morbidity. In fact, they facilitate more accurate pathological and genomic analyses without significantly increasing complications in carefully selected cases. Although non-surgical local consolidative therapies remain essential for treating oligometastatic NSCLC in patients on TKIs, as shown in our prior experience [8], surgery offers a major advantage over radiation therapy by providing entire tissue samples for pathological and genetic analysis. Assessing TKI efficacy by determining the fraction of remnant viable tumor, MPR, pCR, and other pathological prognostic factors (e.g., STAS) allows for more accurate prognoses and the development of further treatment strategies.

This study has several limitations. Although it is one of the larger studies evaluating clinicopathological factors in patients undergoing TKI therapy followed by salvage resection, its retrospective nature and relatively small sample size introduce potential bias. First, we acknowledge that chemotherapy and other postoperative treatments have undergone significant changes over the past decade, which may have influenced survival outcomes. Regarding survival predictors, we identified STAS as an independent prognostic factor for PFS but not for OS. Unlike PFS, OS is affected by a multitude of complex factors, including the administration of second-line or third-line treatments following disease progression or recurrence. These treatment decisions are often guided by the distinct resistance mechanisms identified through next-generation sequencing (NGS) analysis. Second, the

optimal timing between the initiation of TKI therapy and surgery remains uncertain, especially given the varying treatment efficacy across first- to third-generation TKIs. Third, we did not include data from patients with similar oncological profiles who did not undergo surgical intervention. Lastly, long-term outcomes and extended follow-up data are still lacking, even though certain survival outcomes showed differences when stratified by pathological factors. Whether the aforementioned factors have a decisive impact on survival requires confirmation through longer follow-up periods.

In conclusion, salvage surgery for treating EGFR-mutant advanced NSCLC is proven to be both safe and effective, providing benefits such as local tumor control and prolonged survival outcomes. Our study specifically highlights that STAS is a significant adverse prognostic factor for PFS in patients treated with TKI therapy followed by salvage surgery. Identifying patients with STAS may help guide postoperative multimodality treatment strategies and reduce the risk of early progression. Further large-scale, prospective studies are warranted to confirm the prognostic significance of STAS in these patients.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Kaohsiung Medical University Hospital (approval no. KMUHIRB-E(I)-20240126).

Consent for publication
The need for informed consent for publication was waived according to the policy of our IRB.

Competing interests
The authors declare no competing interests.

Author details
[1]Division of Thoracic Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
[2]Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan
[4]School of Post-Baccalaureate Medicine, College of Medicine, Kaohsiung Medical University, No. 100, Tzyou 1st Road, Kaohsiung 80756, Taiwan

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