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ORIGINAL ARTICLE

Outcomes of salvage lung resections in advanced *EGFR*-mutant lung adenocarcinomas under EGFR TKIs

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Keywords
Advanced stage; *EGFR* mutant; lung adenocarcinoma; salvage surgery; TKI.

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Abstract

Background: Studies regarding the outcomes of salvage lung resections of epidermal growth factor receptor (*EGFR*)-mutant advanced lung adenocarcinomas (ALAs) following treatment with *EGFR* tyrosine kinase inhibitors (TKIs) are limited, hence the objective of this study was to investigate such outcomes.

Methods: A total of 29 patients with *EGFR*-mutant ALA who underwent salvage surgery after *EGFR*-TKI treatment from October 2013 through January 2019 were enrolled. The patients were divided into two groups according to the surgical indications. Their perioperative parameters and surgical outcomes, including progression-free survival (PFS) and overall survival (OS), were then analyzed.

Results: The initial stages of the patients were stage IIIB (seven patients), IVA (17 patients), and IVB (five patients). Their surgical indications included residual tumor (25 patients) and progressive disease (PD) (four patients). They all underwent surgery via minimally invasive approaches and the median follow-up was 33.9 months. Within that follow-up duration, the median PFS after surgery was 36.4 months, and the median OS was still not reached. There were no significant differences in PFS or OS according to the different *EGFR*-TKIs used, the different durations of *EGFR*-TKI treatment before surgery, or the different surgical indications. However, the patients presenting with pleural seeding before *EGFR*-TKI treatment had significantly poorer PFS and OS than the other patients ($P < 0.001$).

Conclusions: Salvage surgery following *EGFR*-TKI treatment of ALAs is a safe procedure with acceptable intra- and postoperative results. However, studies involving more cases and longer follow-up periods are needed to clarify its benefits.

Key points

- Salvage surgery following EGFR-TKI treatment of ALAs is a safe procedure with acceptable intra- and postoperative results.
- Our results support the use of surgery following treatment with EGFR-TKIs such as afatinib in advanced lung cancer.

Introduction

Lung cancer is the leading cause of cancer death worldwide, resulting in more than 1.5 million deaths per year.[1] About 85% of lung cancer cases are due to non-small cell lung cancer (NSCLC), and the incidence of the adenocarcinoma type of NSCLC has been increasing in recent years, especially in non-smoking Asian women. Lung adenocarcinomas have now been divided into several molecular subsets according to their genetic alterations, such as alterations to *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, and others.[2]

Among them, *EGFR*-mutant lung adenocarcinomas are the most commonly occurring form of adenocarcinomas in east Asia, accounting for 47%–62% of lung adenocarcinomas.[3, 4] Various *EGFR*-tyrosine kinase inhibitors (TKIs), namely, gefitinib, erlotinib, and afatinib, have been proven in prospective randomized trials to result in longer progression-free survival (PFS) in *EGFR* mutation-positive advanced lung cancer than chemotherapy when used as a first-line therapy.[5–10] Some studies have also shown an overall survival (OS) benefit of these *EGFR*-TKIs in comparison with chemotherapy for advanced lung cancer with *EGFR* deletion 19 mutation.[11]

However, while such preferential responses of *EGFR*-mutant lung cancers to *EGFR*-TKIs are well evidenced, resistance to an *EGFR*-TKI tends to occur eventually, with the median PFS being around 11–13 months.[12] Use of the third-generation *EGFR*-TKI for T790M mutations after resistance to first- or second-generation *EGFR*-TKIs has extended the OS of advanced lung cancer in some patients up to 46 months.[13, 14] However, only about half of lung cancer patients who develop resistance to first- or second-generation *EGFR*-TKIs develop T790M mutations.[15, 16] Physicians should therefore do their best to prolong the use of the first- and second-generation *EGFR*-TKIs in order to maximize the PFS and improve the OS of *EGFR*-mutant lung cancer.

Aggressive surgery or some modality of local control for the primary site of lung cancer after systemic treatment may be beneficial in terms of long-term survival in certain stage IV lung cancer cases.[17–20] Local therapy for the oligoprogression of advanced lung cancer after treatment with TKIs has been shown to improve PFS and OS with the continued use of TKIs.[21] Local therapy has now been recommended in the National Comprehensive Cancer Network guidelines for the treatment of oligometastatic lung cancer following TKI treatment. However, as reported in a study by Hata *et al.* cancer cell experiments have indicated that acquired resistance caused by the *EGFR T790M* gatekeeper mutation can occur through either the selection of pre-existing *EGFR T790M*-positive cells or through the genetic evolution of initially *EGFR T790M*-negative drug-tolerant cells, with the response to the third-generation TKI being relatively poor if the resistance comes from initially *EGFR T790M*-negative drug-tolerant cells.[22] We believe that *EGFR*-TKI treatment is cytostatic rather than cytotoxic. As such, if we could resect the persistent lesions or residual tumors of a cancer relatively early, we could potentially eradicate the pre-existing *EGFR T790M*-positive cancer cells while also preventing the drug-tolerant cancer cells from developing the *EGFR T790M* mutation or some other mechanism of mutation.[23] This could, in turn, possibly extend the disease control of *EGFR*-TKIs. However, while previous studies have reported some promising results, there has only been a limited amount of research reporting the results of resections of residual tumors after *EGFR*-TKI treatment for *EGFR*-mutant advanced lung cancer.[24–26] Relatedly, while an early study of erlotinib as a neoadjuvant therapy for advanced lung cancer did not report positive results,[27, 28] a phase II trial (NCT01407822) of such use is currently being conducted because the previous trial did not exclude patients without *EGFR* mutations.

Given the limited amount of serial results of surgery for residual or persistent lung tumors after treatment with TKIs for locally advanced lung cancer in the literature, as well as the fact that most of the existing reports used gefitinib as the TKI treatment, this study was conducted to determine the outcomes of resections of residual lung tumors of *EGFR*-mutant advanced lung cancers following TKI treatment, especially treatment with the irreversible second-generation *EGFR*-TKI afatinib and the use of *EGFR*-TKIs as a neoadjuvant therapy.

Methods

We reviewed the data in the lung cancer database of National Cheng Kung University Hospital in Tainan, Taiwan, for patients who underwent both surgery and *EGFR*-TKI treatment for lung cancer. We excluded those patients who had no *EGFR* mutation analysis; whose lung cancer was clinical stage I, II, or IIIA; who had surgery before initiating *EGFR*-TKI treatment; or whose surgery was not a locoregionally curative surgery. Ultimately, the study included 29 patients with clinical stage IIIB or IV lung adenocarcinoma who underwent salvage surgery after *EGFR*-TKI treatment during the period from October 2013 to January 2019. The American Joint Cancer Committee seventh edition staging system was used for the lung cancer staging. The clinical stage of each patient was decided by the cancer multidisciplinary team in a thoracic tumor board conference according to chest computed tomography (CT), brain magnetic resonance imaging, bone scan or/and positron emission tomography images. If the staging was equivocal, the patient then underwent the appropriate invasive diagnostic procedure (eg, endobronchoscopic ultrasound-guided transbronchial needle aspiration, thoracoscopy, etc) to confirm his or her clinical stage. Moreover, all the patients were known to have a common *EGFR* mutation (such as an exon 19 deletion or exon 21 point mutation L858R) before starting the *EGFR*-TKI treatment. The treatment modality and strategy, including salvage surgery, were discussed and decided by the cancer multidisciplinary team.

The salvage surgery was well explained to all of the patients who all signed the necessary consent before undergoing surgery. Each salvage surgery was performed via a minimally invasive approach, including uniportal

(since March 2015) through triportal video-assisted or robotic-assisted thoracoscopic surgery (VATS-RATS). Each operation included at least the complete resection of the primary tumor and ipsilateral mediastinal lymph node dissection. If the lesion was stage IIIB, contralateral mediastinal lymph nodes dissection might be performed first to exclude unresectable lesions. Bilateral lung lesions were resected simultaneously if the patient had good performance, or in stages if the patient was old or had relatively poor pulmonary function. We classified the patients into two groups according to their surgical indications after undergoing the *EGFR*-TKI treatment: residual tumor and progressive disease (PD) after initial partial response groups. If all of the detected lung metastatic lesions and the main tumor were controlled by the *EGFR*-TKI treatment until they became localized lesions which could be resected by surgery (Fig 1, 2) and the patient could tolerate complete resection of all the lesions with good postoperative quality of life then at that point, those patients would be categorized in the residual disease group. For the patients in the residual disease group, we would perform salvage therapy and resect the remaining lesions unless the residual lesions were small ground-glass opacity nodules. Most of these patients had either stage IIIB or IVA cancer. For stage IVA (M1a, lung-to-lung metastasis) cancer, if the contralateral lung lesion could also be removed at the beginning, the patient underwent the operation directly instead of receiving the *EGFR*-TKI treatment first and was thus excluded from enrollment in this study. Other patients were operated on depending on the timing of the progression of the primary tumor after the *EGFR*-TKI treatment, and such patients were categorized into the PD group. For some patients with stage IVB with distant metastasis, the distant site should be well controlled. Usually these patients underwent surgery because of a complication of the primary tumor (such as hemoptysis). The histopathological responses of the primary tumors to the *EGFR*-TKIs were categorized into complete (no viable cancer cells), major (less than 10% viable cancer cells), and not major (more than 10% viable cancer cells).[29] All the patients were followed-up until their death or 30 April 2019, and OS was defined as the period from date of the

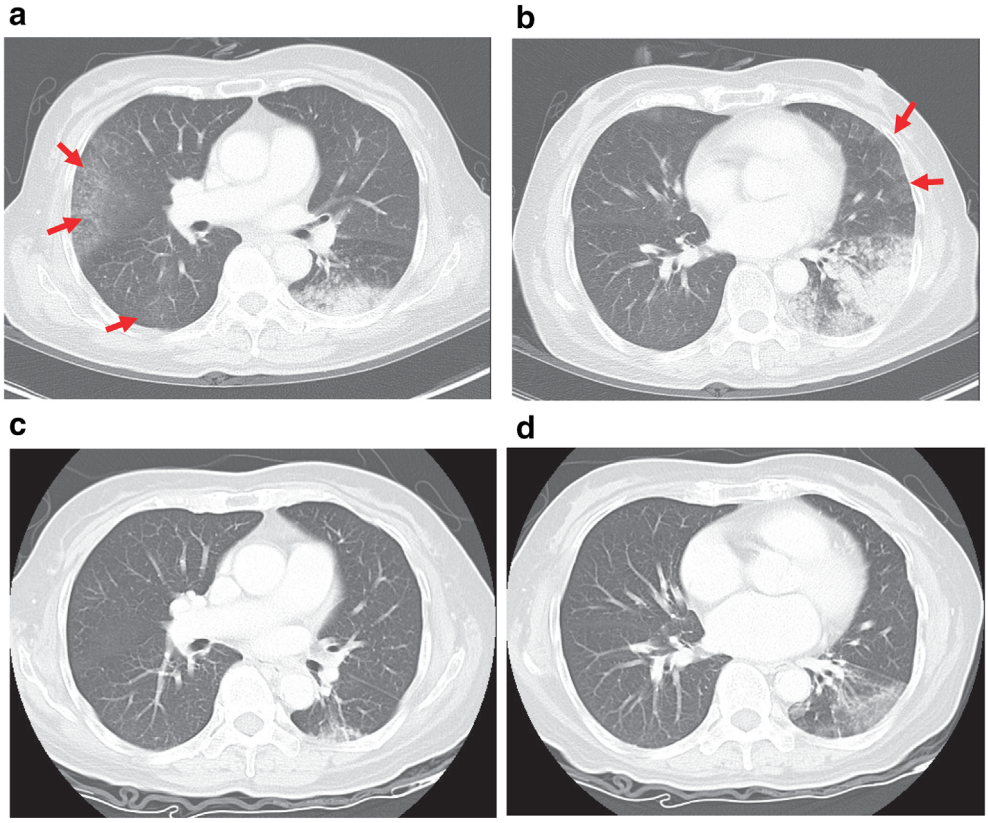


Figure 1 A 73-year-old female patient who had *EGFR*-mutant lung cancer (exon 19 deletion T4N3M1a stage IVA) and underwent targeted therapy with afatinib. (**a**, **b**) CT scans: Left lower lobe lobar invasion with multiple lung metastasis (red arrows); (**c**, **d**) CT scans: Shrinkage of main tumor and complete disappearance of lung metastasis. The patient remains under *EGFR*-TKI treatment and is free of recurrence 4.5 months after undergoing a left lower lobectomy.

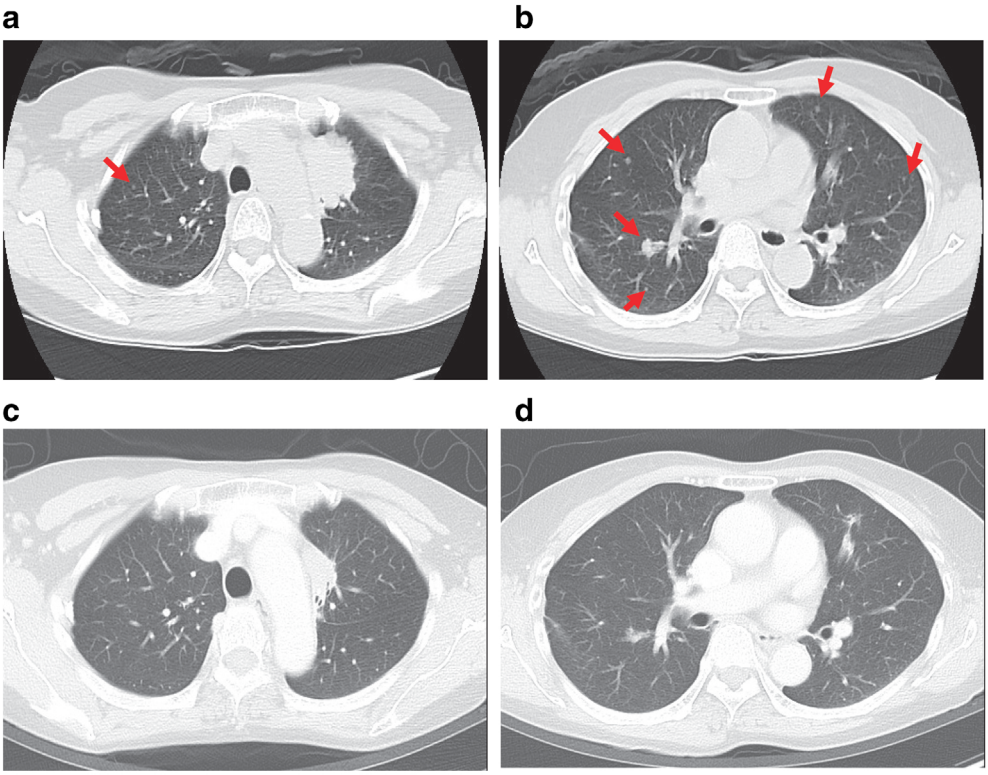


Figure 2 A 67-year-old female patient who had *EGFR*-mutant lung cancer (exon 19 deletion/21 L858R T4N2M1a stage IVA) and underwent targeted therapy with afatinib. (**a**, **b**) CT scans: A left upper lobe tumor with multiple lung-to-lung metastases (red arrows); (**c**, **d**) CT scans: Shrinkage of main tumor and disappearance of all the lung-to-lung metastases. The patient underwent a left upper lobe (LUL) lobectomy and mediastinal lymph node dissection. The patient remains under *EGFR*-TKI treatment and is free of disease recurrence 36 months after undergoing surgery.

operation to the last follow-up day, while PFS was defined as the period from the date of the operation to the day of recurrence or the last follow-up day. Tumor recurrence or progression within the initial hemithorax area, including in the ipsilateral lung, pleural cavity, or mediastinal lymph node, of the initial primary tumor was viewed as locoregional progression. Tumor recurrence or progression outside the initial hemithorax area, including in the contralateral hemithorax and other organs, was viewed as distant progression. This study was approved by the Institutional Review Board of our hospital (B-ER-108-324).

Statistical analysis

For the clinical data, the continuous variables are presented as medians (minimum-maximum) and the categorical variables are presented as frequencies (%). Differences between the compared groups were determined using Student's *t*-test and the Mann-Whitney U test for continuous variables and the X^2 test and Fisher's exact test for categorical variables. The PFS and OS were analyzed using the Kaplan-Meier method, and comparisons between the groups were analyzed using the log-rank test. A *P*-value of less than 0.05 was considered statistically significant. The analysis and figures were done in R (R Development Core Team, 2019) and the R package survminer.

Results

As shown in Table 1, the patients were predominantly female. Among them, two thirds had an exon 21 L858R mutation. The majority of the patients were stage IVA, with lung-to-lung metastasis (M1a_contra lung) being predominant. After targeted therapy, 31% of the patients had a histopathologically major response in the primary tumor (less than 10% viable tumor cells), but none had a complete tumor response. The second-generation *EGFR*-TKI afatinib was used in 55.2% of the total 29 patients. The median treatment interval before surgery was 5.0 months. The major indication for surgery was residual tumor (86.2%).

Table 2 shows the perioperative outcomes of the patients. The majority of the patients received lung anatomic resections after *EGFR*-TKI treatment, and lobectomy

Table 1 Characteristics of patients with *EGFR*-mutant advanced lung cancer who received surgery after *EGFR*-TKI treatment

Characteristics	Results (*N* = 29)
Age, years, median	62 (44–82)
Female, N (%)	22 (75.9)
Initial clinical stage, N (%)	
IIIB	7 (24.1)
IVA	17 (58.6)
Contralateral lung	14
Pleural dissemination	3
IVB	5 (17.3]
Histopathological response, N (%)	
Major	9 (31.0)
Not major	20 (69.0)
EGFR mutation, N (%)	
Exon 19 del	11 (37.9)
Exon 21 L858R	18 (62.1)
EGFR-TKI, N (%)	
Gefitinib	10 (34.5)
Erlotinib	3 (10.3)
Afatinib	16 (55.2)
Treatment duration before surgery, months, median	5.0 (1.9–46.2)
Surgical indication N (%)	
Residual tumor	25 (86.2)
Progression after initial response	4 (13.8)

Table 2 Perioperative variables and follow-up results of patients with *EGFR*-mutant advanced lung cancer who received surgery after *EGFR*-TKI treatment

Variables	Results (*N* = 29)
Surgical resection N (%)	
Lobectomy + segmentectomy	3 (10.3)
Lobectomy	19 (65.5)
Segmentectomy	5 (17.2)
Wedge resection	2 (7.0)
Approach method N (%)	
VATS	28 (96.6)
Uni–/ bi–/ tri–/ quadri-portal	15/ 4/ 8/ 1
RATS	1 (3.4)
Operation time, minutes median (range)	218 (43–660)
Blood loss, mL median (range)	100 (0–1600)
Dissected N1 number median (range)	8 (0–21)
Dissected N2 number median (range)	15 (0–47)
Intraoperative vascular injury N (%)	5 (17.2)
Conversion to open N (%)	2 (7.0)
Postoperative complication N (%)	5 (17.2)
Prolonged air leakage	4
Stress cardiomyopathy	1
Delayed empyema	1
Duration of pleural drainage, day median	3 (1–17)
Postoperative hospital stay, day median	5 (2–38)
Within 30-day mortality	0
Follow-up period, month median (range)	33.9 (3.8–66.0)
Recurrence/ progression N (%)	13 (50.0)
Locoregional	7 (24.1)
Pleural dissemination	4
Mediastinal LN	2
Bronchial stump	1
Distant	6 (20.7)
Contralateral lung	2
Extrathoracic lymph nodes	1

RATS, robotic-assisted thoracoscopic surgery; VATS, video-assisted thoracoscopic surgery.

was the preferred operative procedure. More than 90% of the operations could be performed using a minimally invasive approach, ie, video-assisted or robotic-assisted thoracoscopic surgery. Only two patients in this series required conversion to a minithoracotomy approach, with the presence of fibrocalcified lymph nodes around vessels inducing intraoperative bleeding being the only reason for conversion. The surgical location and the interval from the initiation of the *EGFR*-TKI treatment to surgery for these two patients were the left upper lobe and 3.2 months, and the right upper lobe plus the superior segment and 7.7 months, respectively. Prolonged air leakage was the main complication after surgery. However, the incidence of this complication was not high (17.2%). No incision complications were noted. The median durations of chest tube drainage and postoperative hospital stay were three and five days, respectively. The average resected tumor number was 1.4. The majority of the patients continued to take their prior *EGFR*-TKIs after surgery, with the exception of three patients who discontinued their *EGFR*-TKI therapy due to intolerable adverse effects and did not receive any other treatments. The median follow-up duration was 33.9 months. A total of 45% of the patients developed disease progression in the form of either locoregional or distant metastasis (Table S1). There were nine patients who were further tested (tissue or blood sample) when their disease progressed after salvage surgery. Among the five tests conducted on the specimens from the salvage surgeries, one was found to have T790M, and another to have newly developed exon 21 L861Q. Six patients had a rebiopsy and were tested for recurrence; four had T790M, one had c-Met amplification, and one had small cell transformation. One T790M test was conducted using liquid biopsy at the time of disease progression, but the result was negative.

Four patients underwent surgery after oligoprogression of the main tumor. They received *EGFR*-TKI treatment for 10.8, 18.6, 22.7, and 46.2 months, respectively, before undergoing surgery. After surgery, the first three patients experienced recurrence at 8.7, 4, and 13.1 months in the pleura, pleura, and bronchial stump, respectively. The patients with recurrence in the pleura passed away at 20 and 13 months after surgery, respectively. The patient with recurrence in the bronchial stump is currently still alive with the disease at 52.1 months after undergoing

surgery. The last patient is still alive without the disease at 42.5 months after undergoing surgery.

As shown in Fig 3, the median PFS of the 29 patients was 36.4 months. Meanwhile, the OS had still not reached the median after 33.9 months of follow-up, but the estimated mean OS was 56.1 months.

As shown in Fig 4, the patients presenting with pleural seeding before *EGFR*-TKI treatment had significantly poorer PFS and OS than the patients presenting with other initial stages (median PFS: 5.2 months, $P < 0.001$; median OS: 14.5 months, $P < 0.001$). There were trends indicating that the patients undergoing the surgery on the indication of residual tumor had better PFS (median: 36.4 months vs. 8.7 months) and OS (median: not reached vs. 20.5 months), but the differences did not reach significance ($P = 0.12$ and $P = 0.094$, respectively). Trends were also observed in the outcomes according to the duration of *EGFR*-TKI treatment (>five months vs. ≤ five months, median PFS: not reached vs. 26.5 months, $P = 0.091$; median OS: both not reached, $P = 0.176$), but the differences were not significant. Also, there was no difference in PFS or OS between the first- and second-generation *EGFR*-TKIs ($P = 0.671$ and $P = 0.057$, respectively), or between mutant exon 21 and exon 19 ($P = 0.104$ and $P = 0.269$, respectively). The histopathological responses of the primary tumor (major response vs. not major response) also did not show any significant differences in terms of PFS or OS ($P = 0.145$ and $P = 0.578$, respectively) (Fig S1).

Discussion

Although surgery is still the standard treatment for lung cancer, most lung cancer patients present with advanced-stage cancer that cannot be eradicated by surgery alone. Kaira *et al.* suggested that TKI therapy plays an important role in long-term survival (that is, survival of more than five years) of advanced lung cancer.[30] However, when used as the first-line therapy, even the third-generation of *EGFR*-TKIs can only extend the median PFS to 18 months.[31] On the other hand, use of a first- or second-generation TKI followed by a third-generation TKI for advanced *EGFR*-mutant lung adenocarcinoma might extend survival to five years or more in some cases. In any case, it is clear that further efforts are needed to potentially prolong the survival of patients with *EGFR*-mutant advanced lung cancer.

Our reasons for selecting specific cases of locally advanced lung cancer in this study for surgery were based on our own clinical observations and the experimental study of Hata *et al.*[22] We have found some patients have a large residual primary tumor after undergoing TKI treatment. We thought that this was due to poor responsiveness to the given TKI. However, the post-surgical pathological reports of such patients in this study showed only adenocarcinoma in situ, minimally invasive adenocarcinoma, or even a complete response (Fig S1). This suggests that the assessments of responses to TKI therapy based on imaging might not be as accurate as we previously thought. As stated in the study by Mitsudomi *et al.* the value of a resection specimen is that it can provide the opportunity to detect the intratumoral heterogeneity of residual lung cancer.[32] This could be used as a part of precision medicine in the near future in cases in which a patient's lung cancer recurs. If we resect those residual lesions, which are full of tumor cells, we could also resect the drug-tolerant cells relatively early and prevent the late sequelae of developing resistance or new mutations on the tumor.[22] A residual tumor might also contain the cancer stem cells (CSCs). As Jones *et al.* reported, cytotoxic drugs are not effective against CSCs and those cells might respond poorly to

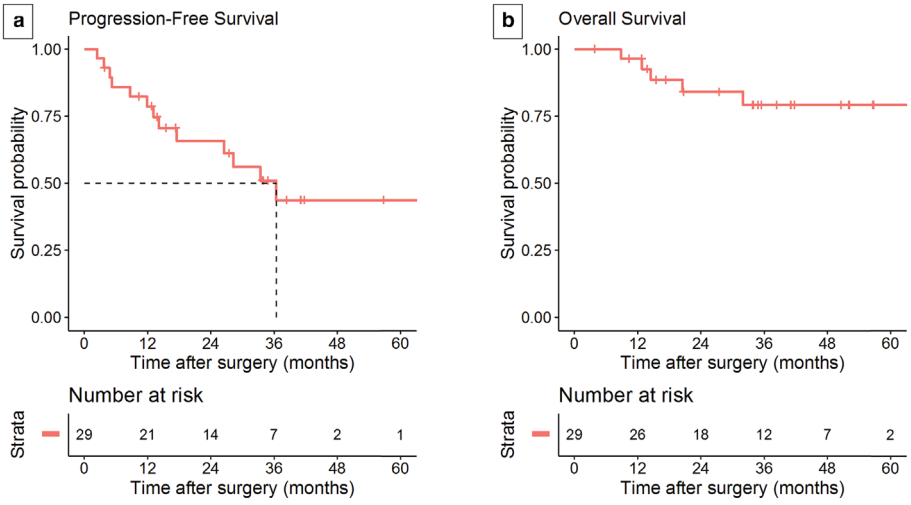
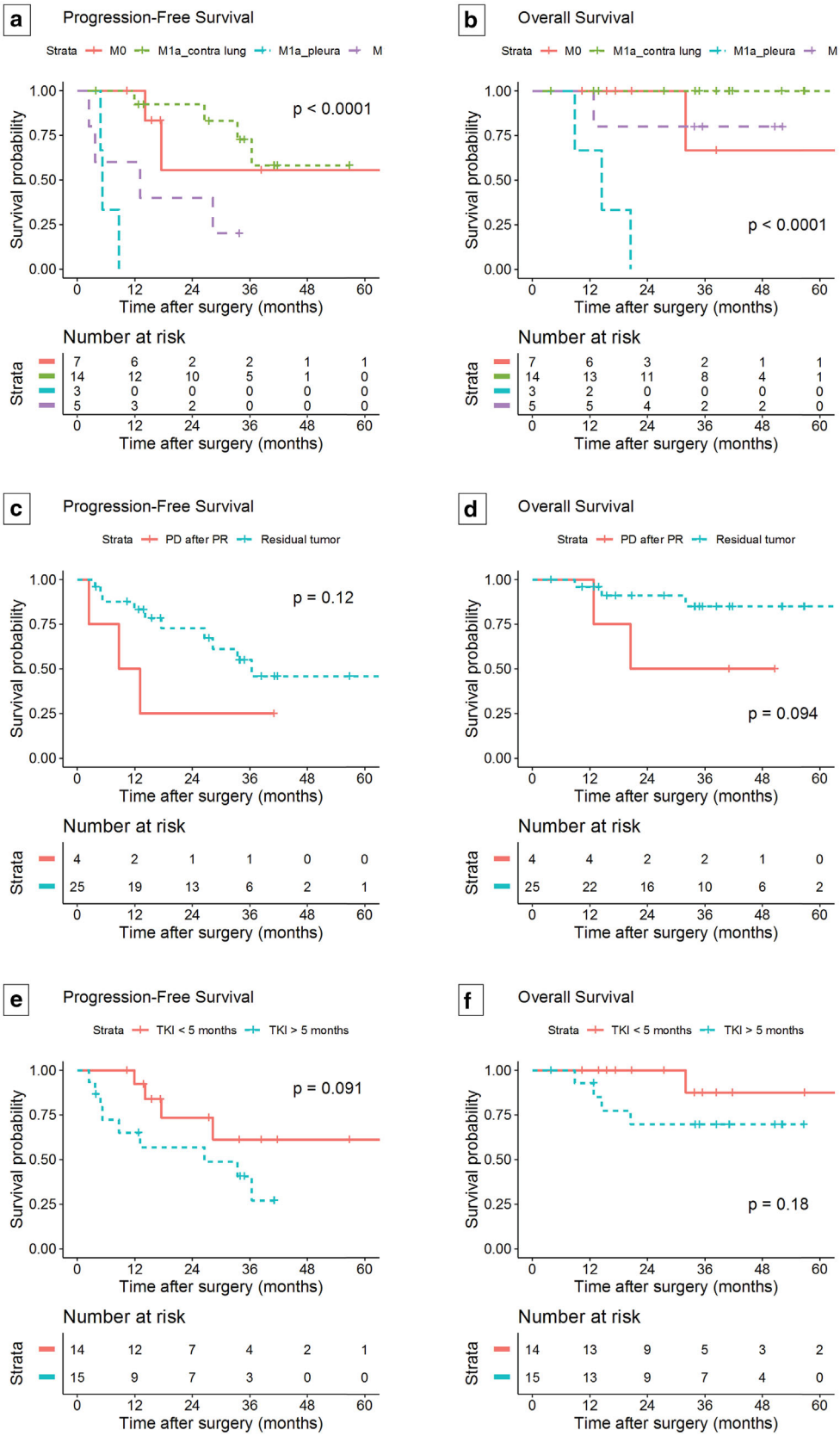


Figure 3 Outcomes of 29 patients after surgery. (**a**) Progression-free survival: Median and mean ± SD: 36.4 and 38.5 ± 5.1 months; (**b**) Overall survival (mean ± SD): 56.1 ± 4.0 months.



targeted therapy.[33] Therefore, if we could also resect these cells, then it is possible that the disease control of *EGFR*-TKIs against lung cancer could be extended.

In this series, we sought to select advanced *EGFR*-mutant lung adenocarcinoma patients for surgery in order to apply surgery as a partner to *EGFR*-TKI therapy. In comparison with our previous report, which found a median PFS of 9.8–12.7 months after *EGFR*-TKI therapy,[34] resection of the residual lung tumor or oligoprogression in this study extended the median PFS up to 36.4 months with an average estimated OS of 56.1 months, with the median OS still not having been reached. These results were even better than those of Yu *et al.* who reported a PFS of 22 months and OS of 41 months after local therapy for acquired resistance after TKI therapy.[21] In this series, complications were relatively rare and no wound healing problems were found, which is consistent with the previous literature.[25] The operations in this series could generally be performed using minimally invasive surgery (video-assisted thoracoscopic surgery or robotic-assisted thoracoscopic surgery). However, two of six patients, who had calcified adherent lymph nodes around lobar vessels, required conversion of the minimally invasive approach to minithoracotomy. We have, however, adapted a new technique for use when encountering adherent or calcified lymph nodes around vessels to prevent the need for conversion.[35] In any event, no surgical mortality occurred among the patients in this study, and overall, our results suggest that anatomic resections after *EGFR*-TKI therapy are safe and effective.

In this series, most of the patients with advanced lung cancer who received surgical resection had stage IIIB or IVA cancer. The series included five patients with stage IVB cancer who underwent surgical resection; two had brain metastasis, two had bone metastasis, and the fifth had both liver and bone metastases. Four of them experienced disease progression, usually within or around one year. There was a trend in which the PFS of extrathoracic metastasis was worse than that of cases involving lung metastasis or cases without metastasis, but there was no significant difference in OS. The literature shows that when oligometastasis, whether with or without EGFR mutation, is aggressively treated, brain metastasis is a positive prognostic factor, while bone metastasis is a negative prognostic factor.[19, 36–38] Because the number of our cases was too small, we could not further compare the results between bone or brain metastasis. If this group of stage IVB patients are to be aggressively treated with surgery, they must be carefully selected. It may be better to observe such patients for a little longer under systemic treatment to determine whether there are no new or progressed metastatic lesions, and whether a better prognosis may be obtained. For stage IVA disease, as our results show, we did not suggest that those patients with an initial presentation of pleural seeding undergo surgery. This is because we had previously found that even if preoperative images and intraoperative frozen sections showed no pleural seeding after *EGFR*-TKI in such patients, the pleural seeding tended to recur soon after surgery and the survival time was diminished. The best candidates for surgery after *EGFR*-TKI therapy are shown in Fig 1, 2. In these patients, multiple lung metastases or multiple patches of lung metastasis could not initially be completely eradicated. However, after *EGFR*-TKI treatment yielded good responses in terms of cancer control, we could resect all the lesions that remained in the lungs. This kind of patient should benefit in terms of PFS and might have the chance to have prolonged survival of more than five years.

In previous reports, first-generation TKIs were used for lung resection after TKI therapy.[21, 24, 25] This study, meanwhile reports the first series of patients who underwent surgery after using the second-generation irreversible *EGFR*-TKI afatinib. The FDA of Taiwan approved this second-generation *EGFR*-TKI for use as a first-line therapy for advanced lung cancer in July of 2014. Since then, 16 of the 29 patients included in this study were selected for surgery after treatment with afatinib. Overall from the literature, afatinib produced better objective and subjective tumor responses in comparison with the first-generation *EGFR*-TKIs, although the differences were not significant, especially among the patients with exon 21 L858R-mutant advanced lung cancer. In this series, 62% of the patients had an exon 21 mutation. The incidence rates of this mutation among the patients selected for surgery who were treated with gefitinib or afatinib exhibited no significant difference. This might be due to patient selection bias. Thus far, however, our results suggest that use of the first- or second-generation EGFR-TKIs followed by surgery could achieve the same results in terms of PFS and OS.

Figure 4 Outcomes of the 29 patients according to the M status. (**a**) There was a significant difference of shorter PFS if patients' had pleural seeding in the initial stage before receiving *EGFR*-TKI treatment: $P < 0.001$. (**b**) The OS was also significantly poorer in the patients with initial pleural seeding in comparison with the others: $P < 0.001$. Outcomes according to the surgical indications: Although there was a trend in which resection according to the indication of residual tumor had better (**c**) PFS; and (**d**) OS, the differences between the indications were not significant; $P = 0.117$ and $P = 0.094$, respectively. Outcomes according to the preoperative duration of EGFR-TKI treatment: There was a trend in which operation within a duration of five months had better (**e**) PFS; and (**f**) OS, but the differences between within and after five months were not significant; $P = 0.091$ and $P = 0.18$, respectively.

Several issues require further research. First of all, what is the best timing for surgery after *EGFR*-TKI therapy? According to our results, it is better not to wait until tumor oligoprogression to remove the main tumor. At that time, drug-resistant genes may have developed within the tumor, potentially as a new nidus of metastasis, so the PFS after surgery was only eight months, which was shorter than the 36.4 months of the residual tumor group. Even if the preoperative treatment time is added (around 12–18 months), the result is still relatively poor. Drug-resistant genes were also found in two (50%) excised specimens from the PD group. For those patients with residual disease, we usually waited for four–six months to make sure that the residual lesions were stabilized and that the metastatic lesions had disappeared, or were resectable. It is better to remove the main tumor and the resectable lesions four–six months after the drug. The pretreatment time of the *EGFR*-TKI therapy influenced the prognosis. This was because the longer the duration of *EGFR*-TKI treatment, the more likely it is that subclinical drug-resistant tumor cells will develop and grow. If these tumor cells metastasize, it will affect the patient's prognosis. In addition the longer the period of waiting, the more difficult it is to manage the adherent lymph nodes. In this study, it was found that, among the excised specimens, only 31% had a major response, with nearly 70% of the resected main tumors still having more than 10% viable tumor cells. Therefore, the removal of the main tumor and other resectable metastases may indeed remove the reservoir of drug-tolerant and drug-resistant tumor cells, thereby achieving the purpose of prolonging PFS and OS. The second issue requiring further investigation is, should we resect all the residual lesions? Typically, we try to resect all the residual lesions if possible either concomitantly, or in stages unless small residual ground-glass opacity lesions are present in the center of the affected lobe. However, we could also wait for lesion progression and for better recovery of the patient for any further surgery. The third issue requiring further investigation is, should we stop the *EGFR*-TKI therapy after the surgery? Based on our experience, we believe that long-term *EGFR*-TKI therapy is required for all advanced lung cancer patients. Most of the patients in this series who stopped taking an *EGFR*-TKI ultimately developed recurrence.

This study did have some limitations. First, it was not a randomized trial. Therefore we cannot tell if patients who have a good response to *EGFR*-TKI therapy and then do not receive surgery would have a similar PFS or OS to those of the patients in this study. Furthermore, selection bias of patients for surgery was present between the doctors who prescribed EGFR-TKIs for advanced lung cancer and surgeons, and the total number of patients was limited. The treatment of stage IIIB patients in this series did not represent the current standard of care for primary lung cancer; it was an alternative option for patients who refused traditional chemotherapy or chemoradiation. More evidence is needed to verify the efficacy of *EGFR*-TKI as a treatment for stage IIIB disease.

In conclusion, this study reports the first series of patients who underwent lung resection following treatment with the second-generation *EGFR*-TKI afatinib, as well as the first series of patients who underwent the resection of residual lesions following treatment with various *EGFR*-TKIs. The median PFS of the patients who underwent surgery after receiving *EGFR*-TKI treatment was extended to 36.4 months, and the patients had an average estimated OS of 56.1 months. Our results provide support for the use of surgery following treatment with *EGFR*-TKIs such as afatinib in advanced lung cancer. However, we still need to investigate more cases and make more precise comparisons to patients without surgery to better determine the role of salvage surgery and which types of patient can benefit from surgery.

Disclosure

The authors declare that there are no conflicts of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

Figure S1 Outcomes of the 29 patients according to different *EGFR*-TKIs (a, progression-free survival; b, overall survival), different mutation locations (c, progression-free survival; d, overall survival), and the histopathological responses of the primary tumor to the *EGFR*-TKIs (e, progression-free survival; f, overall survival).

Figure S2 A 65-year-old female patient who had *EGFR*-mutant lung cancer (exon 21 L858R T4N1M0 stage IIIA) underwent targeted neoadjuvant therapy with erlotinib. (a–b) CT scan: A 10 cm tumor over the right lower lobe with interlobar lymph nodes metastasis; (center) PET scan: Tumor and interlobar lymph nodes exhibiting positive uptake; (d–d) CT scan: Shrinkage of main tumor and interlobar lymph nodes. The pathological report for the resected specimen revealed a complete response without cancer. The patient received follow-up assessments without further *EGFR*-TKI treatment and had brain metastasis six months after undergoing surgery.

Table S1 The detailed data of all patients

