# Gamma Knife consolidation therapy improves prognosis in patients with advanced epidermal growth factor receptor-mutant lung adenocarcinoma treated with first-generation epidermal growth factor receptor-tyrosine kinase inhibitors

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**Abstract.** Non-small cell lung carcinoma (NSCLC) accounts for most cancer-related deaths. Whilst epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) are effective in prolonging the survival of patients with EGFR mutations, resistance to these therapies inevitably emerges. The present study aimed to analyze the efficacy and safety of combining Gamma Knife therapy and first-generation EGFR-TKIs treatment in patients with advanced EGFR-mutant NSCLC. The present study was a retrospective analysis performed at a single center. The patients included in the analysis were histologically confirmed as inoperable stage III or IV lung adenocarcinoma with EGFR-sensitive mutations (19DEL or 21L858R). Patients received first-generation EGFR-TKIs treatment, including gefitinib, erlotinib and icotinib, then received Gamma Knife consolidation therapy for the treatment of residual lesions in the chest, with a total of 10-17 sessions administered five times a week. Each session delivered a fractionated dose between 3.0-5.5 Gy. The primary endpoint was progression-free survival (PFS) and overall survival (OS), and the secondary endpoints were objective response rate (ORR) and safety. Between October 2014 and November 2021, the 35 patients included in the follow-up analysis received Gamma Knife therapy combined with EGFR-TKIs treatment, with a follow-up visit in December 2023. The PFS and median OS were 20 (range, 17.6-22.4) and 39 (range, 32.0-46.0) months, respectively. The ORR was 77% and the incidence of grade III or higher radiation pneumonitis was 3%. Univariate analysis indicated an improved survival trend for patients with the following characteristics: Aged ≥62 years, carcinoembryonic antigen (CEA) level of <10 ng/ml and those with grade I or no radiation pneumonia; however, the differences were not statistically significant. Multivariate analysis demonstrated that non-smoking patients, those with a CEA level of <10 ng/ml, grade I or no radiation pneumonitis after treatment and those treated with icotinib had a statistically longer PFS. In conclusion, combining first-generation EGFR-TKIs with Gamma Knife therapy can delay EGFR resistance, extend PFS and OS, and result in a low incidence of toxic and side effects. However, further prospective randomized controlled studies are required to validate the results of the present study.

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## Introduction

The cancer with the highest mortality rate globally is lung cancer, accounting for ~18.7% of all cancer-associated deaths (1). Mutations in the epidermal growth factor receptor (EGFR) are among the typical driver gene alterations found in non-small cell lung carcinoma (NSCLC) (2). For patients with advanced NSCLC and sensitive EGFR mutations, tyrosine kinase inhibitors (TKIs) are recommended as first-line therapy by established guidelines (3-5). Targeted therapies can extend the survival of patients with advanced NSCLC and driver gene mutations, with life expectancy ranging from 12.9-21.9 months (6,7). Despite the common use of first- and second-generation EGFR-TKIs in treating patients with NSCLC, most patients eventually experience acquired resistance, resulting in disease recurrence and progression (8). The primary cause of this resistance is the T790M mutation. The ASPIRATION study demonstrated that adhering to the original targeted therapy after disease progression whilst on erlotinib could slow down disease progression, with a notable difference in progression-free survival (PFS). Specifically,

patients who continued with the original therapy achieved a PFS of 14.1 months, whereas those who discontinued the therapy experienced a shorter PFS of 11.0 months, with corresponding median overall survival (OS) of 33.6 and 22.5 months, respectively (9). Moreover, a study by Chaft *et al* (10) reported that among 61 cases, 14 experienced disease recurrence after discontinuing EGFR-TKIs, with a median recurrence time of 8 days. These findings underscore the possibility for the original targeted therapy to control disease in patients who develop resistance. Therefore, guidelines from Europe, America and China recommend that these patients continue with the original EGFR-TKI treatment regimen.

Certain patients exhibit oligometastasis, with metastasis limited to a few organs or regions. Generally, oligometastasis is categorized as inoperable stage III or IV; however, it is a unique condition between locally advanced and broadly disseminated stage IV. Guidelines recommend local treatment for these patients (11), and common local treatment methods include surgical resection, radiation therapy, microwave ablation, radiofrequency ablation, particle implantation and cryoablation (12,13).

Gamma Knife is a type of stereotactic body radiation therapy (SBRT) radiotherapy technology. Through non-coplanar rotational irradiation, the radiation converges at a single focal point, creating an ellipsoidal high-dose region to cover the tumor target area. The dose in the central area of the tumor is markedly higher than that in the peripheral area. This design can more effectively kill hypoxic cells inside the tumor that are resistant to radiotherapy. The dose rapidly attenuates at the tumor periphery, and the notable focusing capability results in a smaller overall volume of normal lung tissue being irradiated and a lower irradiation dose, making it more suitable for treating multiple lesions. Gamma Knife is commonly used in Europe and the United States to treat brain tumors or brain metastases. However, in China, it is also used to treat primary and metastatic tumors in the body (14), with several studies indicating its notable efficacy (14-16). In 2006, Xia *et al* (14) reported marked results using Gamma Knife therapy for the treatment of early-stage lung cancer. Furthermore, Zhang *et al* (15) reported certain survival benefits using whole-body Gamma Knife radiotherapy combined with thermochemotherapy for locally advanced pancreatic cancer. For patients with oligometastatic NSCLC, systemic therapy combined with surgery or radiation treatment was reported to provide improved treatment effect compared with systemic therapy alone (17-19). Similarly, the adoption of first-generation EGFR-TKIs in conjunction with local consolidation therapy (LCT) has also been reported to demonstrate superior treatment effects compared with the TKI-only treatment group (20-24). However, most existing studies have focused on the combination of EGFR-TKIs with surgical interventions or radiotherapy for intracranial or other metastatic lesions (21,25,26). There are few reports on the combined treatment of primary lung lesions, with recent studies mostly concerning third-generation EGFR-TKIs in combination therapies (27,28). Therefore, the present retrospective study aimed to evaluate the impact of Gamma Knife therapy on primary pulmonary lesions combined with first-generation EGFR-TKIs treatment for advanced lung adenocarcinoma on disease control and survival of patients.

## Patients and methods

*Study population*. The present retrospective, single-arm study was performed on a small cohort of 35 patients diagnosed with advanced lung adenocarcinoma harboring EGFR-sensitive mutations. These patients underwent both targeted therapy and radiation at the 901st Hospital of the Joint Logistics Support Force of the People's Liberation Army (Hefei, China) between October 2014 and November 2021. The study was approved by the Hospital Ethics Commission and all patients signed informed consent prior to treatment.

*Patient selection criteria*. The inclusion criteria were as follows: i) Any sex or age; ii) pathologically confirmed diagnosis of lung adenocarcinoma; iii) history of post-surgical lung cancer recurrence; iv) prior exposure to adjuvant or neoadjuvant chemotherapy; v) genetic status indicating EGFR-sensitive mutations, specifically exon 19 deletion or exon 21 L858R mutation; vi) clinical staging of unresectable stage III or IV with oligometastatic; vii) use of the first generation EGFR-TKIs as a first-line treatment that achieved documented disease control; viii) resistance after first-generation EGFR-TKIs as first-line therapy, followed by Gamma Knife treatment for the primary lesions; ix) presence of at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria (29); and x) Eastern Cooperative Oncology Group (ECOG) performance status (30) ranging from 0-2.

The exclusion criteria were as follows: i) Co-existing malignancies; ii) severe underlying conditions such as cardiovascular diseases, liver disease or kidney disease; iii) presence of other genetic mutations, including EGFR 20 insertions, anaplastic lymphoma kinase, hepatocyte growth factor receptor and c-ROS oncogene 1; iv) concurrent use of other antitumor agents as part of first-line treatment, including anti-angiogenic agents, immunotherapy or chemotherapy; v) unmanageable adverse reactions to first-generation EGFR-TKIs; vi) disease not controlled following first-generation EGFR-TKI treatment due to primary resistance; and vii) presence of widespread systemic metastases.

*Treatment protocol*. Following disease control achieved through first-line treatment with first-generation EGFR-TKIs, lung lesions exhibited stability or slight progression without reaching progressive disease (PD). Consequently, patients underwent Gamma Knife radiosurgery for lung cancer for 10-17 sessions administered five times per week, with each session delivering a fractionated dose ranging from 3.0-5.5 Gy. The specific treatment protocol is detailed below.

*EGFR-TKI targeted therapy*. Patients received oral administration of either gefitinib (250 mg, once daily), erlotinib (150 mg, once daily) or icotinib (125 mg, thrice daily). Dose adjustments were permitted in response to any adverse events experienced by the patients. Drugs were preferentially selected according to the clinical features of the patients. For example, for patients with mild abnormal liver function, drugs mainly metabolized by the kidneys (such as gefitinib) were preferred; for patients with concurrent chronic lung diseases, the applicability of erlotinib was prioritized for evaluation considering its potentially lower risk of pulmonary adverse reactions. Additionally,

drugs that were economically affordable and easily accessible to patients were selected to improve long-term treatment compliance. Furthermore, all drug selections referred to the recommendations for first-generation EGFR-TKIs in the latest version of lung cancer diagnosis and treatment guidelines (such as National Comprehensive Cancer Network Guidelines and Chinese Society of Clinical Oncology Guidelines) (31,32). In scenarios where the guidelines did not clearly recommend a priority, a multidisciplinary team discussion model was adopted, and decisions were made jointly with the wishes of the patients. Finally, the balance of the distribution of baseline data on clinical characteristics was assessed among the three groups of patients taking gefitinib, erlotinib and icotinib. Table I indicates that the samples of patients receiving targeted therapy in the three groups were comparable in terms of sex, age, ECOG score, disease stage, gene mutation type and smoking status, with no significant differences demonstrated.

*Stereotactic radiation therapy*. The fourth-generation LUNA-260 Gamma Knife system (Shenzhen Yiti Medical Treatment Technology Co., Ltd.) was employed. Patients were positioned supine and secured using a vacuum bag. A helical CT scan (slice thickness, 3-5 mm) was performed on the lesion area, including the entire lung, to obtain localization images. The gross tumor volume (GTV) corresponded with the visibility of the tumor in the lung window; the clinical target volume (CTV) extended 5 mm beyond the GTV; and the planning target volume (PTV) extended a further 5 mm from the CTV. Regarding the determination of the radiation treatment target area, prior to Gamma Knife treatment, the operator instructed patients to maintain steady thoracic breathing (avoiding diaphragmatic breathing) to minimize irregular breathing. Additionally, the hospital department designed a set of devices to effectively reduce respiratory motion and positioning errors. These included extra anchoring points for positioning that were placed on the chest wall of the patient, and a hydrolyzed plastic body mold to cover the external thorax. Verification through 4-dimensional CT has shown that using a GTV + 10 mm margin can cover the risk of subclinical lesion extension whilst reducing the radiation dose to normal tissues (33). Therefore, the internal target volume region was no longer delineated separately. For lesions <3 cm, the 50% isodose line encompassed 100% of the PTV, the 60% isodose line encompassed 90% of the CTV and the 70% isodose line encompassed 80% of the GTV. In cases where the lesion was >5 cm, the 50-60% isodose line encompassed 100% of the GTV. The fractionated dose delivered per session ranged from 3.0-5.5 Gy and it was provided five times weekly for a total of 10-17 sessions, with a cumulative peripheral dose of 45-55 Gy.

*Treatment after progression*. If disease progression occurred after the combination of first-generation EGFR-TKI treatment and Gamma Knife therapy, subsequent treatment options were determined according to genetic testing results. These options included third-generation EGFR-TKIs, chemotherapy, anti-angiogenic therapy, immunotherapy and radiation therapy directed at metastatic lesions.

*Efficacy evaluation and prognostic analysis indicators*. Clinical data, including patient demographics, tumor characteristics, staging and radiological features, were recorded prior to treatment. Patients were followed up to gather radiological assessment results and details of any adverse events following therapy: Following completion of Gamma Knife treatment, patients underwent chest and abdominal CT scans after 1, 3, 6 and 12 months during the first year, and at 6-month intervals during the second year. RECIST 1.1 criteria were employed to assess the treatment efficacy. Short-term treatment outcomes were assessed within 3-6 months post-therapy. Patients were classified into 1/4 categories based on their response: Complete response (CR), partial response (PR), stable disease (SD) or PD. In the present study, the objective response rate (ORR), which equals CR + PR, was considered indicative of treatment effectiveness. For long-term outcomes, survival data, specifically PFS and OS, were collected until the follow-up cutoff date of December 31, 2023. Finally, any adverse reactions were recorded: The primary side effects of EGFR-TKIs included rash and diarrhea, whilst the main adverse reactions observed following lung Gamma Knife treatment were radiation pneumonitis.

*Statistical methods*. Primary study endpoints included PFS and OS, whilst secondary endpoints included the ORR and safety. PFS was defined as the time from the initiation of EGFR-TKIs to the occurrence of disease progression, and OS was defined as the time from the initiation of EGFR-TKIs to death or the end of follow-up. SPSS 25 software (IBM Corp.) was used for analysis, with statistical methods including univariate linear regression (single-factor) and multivariate linear regression (multi-factor). The Kaplan-Meier method was adopted for assessing clinical treatment efficacy in patients. Moreover, Fisher's Exact Test or analysis of variance was used to assess the balanced distribution of baseline data for clinical characteristics (including sex, age, EGFR mutation subtype, tumor stage, ECOG performance status and smoking status) among the three groups of patients treated with gefitinib, erlotinib and icotinib. $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Patient characteristics*. A cohort of 35 patients was included in the final analysis. Fig. 1 illustrates the treatment plan for these patients. Detailed clinical characteristics of the patients are presented in Table II.

*Efficacy and survival*. Among the patients, 15 (43%) achieved CR, 12 (34%) had a PR, 8 (23%) showed SD and no patients exhibited PD, leading to an ORR of 77%. Moreover, according to the Radiation Therapy Oncology Group classification, radiation pneumonitis was graded as grade III in 1 patient (3%), grade II in 6 patients (17%) and grade I in 17 patients (49%), whilst no adverse reactions were observed in 11 patients (31%) (34).

*Outcomes of first-generation EGFR-TKIs combined with Gamma Knife therapy*. As of the December 2023 follow-up, descriptive statistics indicated the PFS was 20 months (range, 17.6-22.4 months) and the median OS was 39 months (range, 32.0-46.0 months) for the cohort of 35 patients. The corresponding PFS and median OS survival curve functions are presented in Figs. 2 and 3.

Table I. Analysis of baseline characteristics of patients in three groups of targeted therapy.

| Characteristic | Targeted drug | | | F | P-value |
|---|---|---|---|---|---|
| | Erlotinib (n=13) | Gefitinib (n=10) | Icotinib (n=12) | | |
| Sex | | | | - | 0.817 |
| Female | 9 (69.23) | 6 (60.00) | 9 (75.00) | | |
| Male | 4 (30.77) | 4 (40.00) | 3 (25.00) | | |
| Age | 62.23±12.52 | 62.40±12.56 | 62.25±13.96 | 0.001 | 0.999 |
| ECOG performance status | | | | - | 0.821 |
| 0 | 1 (7.69) | 1 (10.00) | 2 (16.67) | | |
| 1 | 12 (92.31) | 9 (90.00) | 10 (83.33) | | |
| Stage | | | | - | 0.821 |
| III | 1 (7.69) | 1 (10.00) | 2 (16.67) | | |
| IV | 12 (92.31) | 9 (90.00) | 10 (83.33) | | |
| Mutation type | | | | - | 0.228 |
| EGFR 19del | 10 (76.92) | 4 (40.00) | 8 (66.67) | | |
| EGFR exon21 L858R | 3 (23.08) | 6 (60.00) | 4 (33.33) | | |
| Smoking status | | | | - | 0.392 |
| No | 12 (92.31) | 7 (70.00) | 10 (83.33) | | |
| Yes | 1 (7.69) | 3 (30.00) | 2 (16.67) | | |

Data are presented as n (%) or mean ± standard deviation. ECOG, Eastern Cooperative Oncology Group.

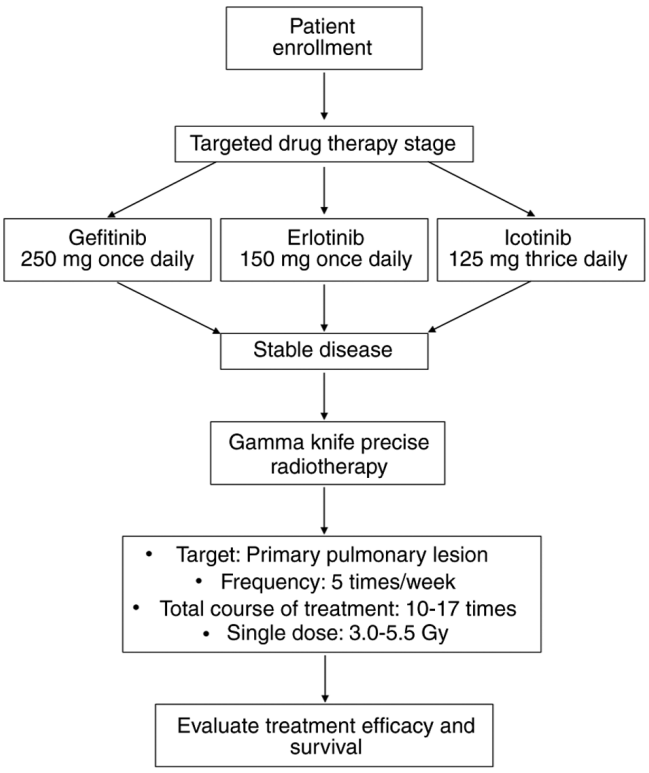


Figure 1. Treatment plan for patients during the complete observation period.

*Factors influencing the efficacy of Gamma Knife treatment*. Univariate and multivariate analyses were performed to evaluate the association between different factors on PFS, including sex, mutation type, cancer stage, visceral metastasis, age, carcinoembryonic antigen (CEA) levels, types of targeted therapies, ECOG performance status, size of lung lesions, smoking status and severity of radiation pneumonitis (Table III). Univariate analysis revealed a survival advantage among patients aged ≥62 years, with CEA <10 ng/ml and with grade I or no radiation pneumonitis; however, the differences were not statistically significant. Multivariate analysis demonstrated that non-smoking patients, CEA <10 ng/ml, grade I or no radiation pneumonitis after treatment, and treated with icotinib experienced significantly longer PFS (all P<0.05).

## Discussion

In the present study, Gamma Knife treatment extended both PFS and OS in patients with advanced EGFR-mutant lung adenocarcinoma receiving first-line EGFR-TKIs. Notably, enhanced survival benefits were observed in specific subgroups, such as non-smokers, patients with a CEA level of <10 ng/ml, grade I or no radiation pneumonitis after treatment, and those receiving icotinib. Previous studies have reported that integrating LCT with systemic treatments can boost survival rates in patients with oligometastatic NSCLC (18,35). Additionally, LCT has also been reported to extend survival for patients undergoing EGFR-TKIs or chemotherapy (12,18-20,36).

Moreover, previous studies have reported that radiation therapy or primary lung tumor resection combined with systemic treatment can yield survival benefits in patients with metastatic NSCLC (21,22,37,38). Takenaka *et al* (39) reported that salvage surgery can extend the median OS of patients treated with EGFR-TKI to ~66 months. Tseng *et al* (38) demonstrated that primary tumor resection (PTR) could increase the PFS and OS of patients to 25.1 and 56.8 months, respectively.

Table II. Characteristics of the 35 patients

| Characteristic | n (%) |
|---|---|
| Sex | |
| Male | 11 (31) |
| Female | 24 (69) |
| Age | |
| ≥62 years | 20 (57) |
| <62 years | 15 (43) |
| Stage | |
| III | 4 (11) |
| IV | 31 (89) |
| Visceral metastasis | |
| Present | 12 (34) |
| Absent | 23 (66) |
| CEA | |
| ≥10 ng/ml | 17 (49) |
| <10 ng/ml | 18 (51) |
| Smoking status | |
| Yes | 6 (17) |
| No | 29 (83) |
| ECOG performance status | |
| 0 | 4 (11) |
| 1 | 31 (89) |
| Mutation type | |
| Exon 19 Del | 22 (63) |
| Exon 21 L858R | 13 (37) |
| Type of EGFR-TKIs | |
| Gefitinib | 10 (29) |
| Afatinib | 12 (34) |
| Erlotinib | 13 (37) |
| Diameter of lung lesions treated with gamma knife | |
| ≥3 cm | 13 (37) |
| <3 cm | 22 (63) |

CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

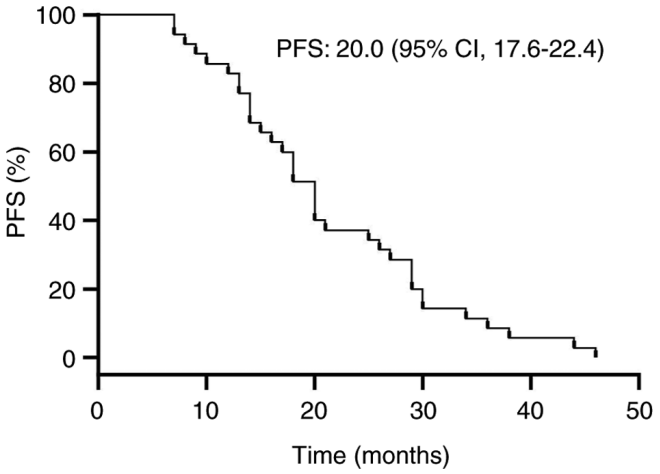


Figure 2. Kaplan-Meier curve for PFS. PFS, progression-free survival; CI, confidence interval.

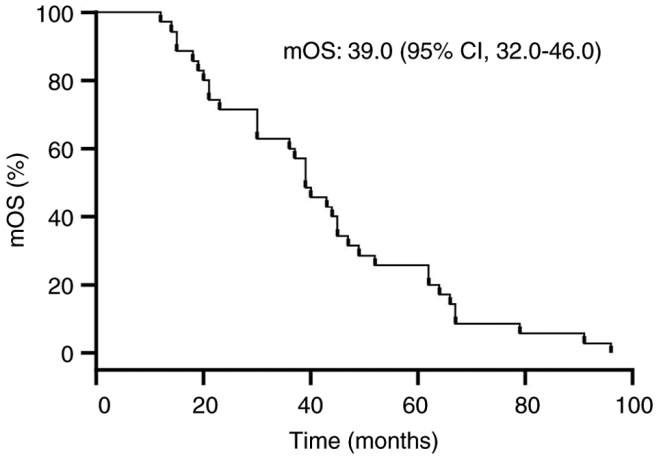


Figure 3. Kaplan-Meier curve for mOS. mOS, median overall survival; CI, confidence interval.

Kuo *et al* (21) reported that the median PFS of patients with stage IV EGFR-mutant NSCLC receiving PRT and first-line TKI treatment increased from 13.0 to 29.6 months, compared with patients not receiving PTR treatment. Furthermore, in the study by Hsu *et al* (22), compared with not receiving radiation therapy, first-generation EGFR-TKI treatment followed by radiation therapy for primary lung cancer increased PFS from 10.9 to 27.5 months and OS from 38.0 to not reached. Elamin *et al* (40) reported that oligometastatic disease (≤3 metastatic sites) occurred in 8/12 patients treated with TKIs and LCT. Of the 12 cases, 11 underwent radiation therapy and 1 underwent surgical resection. Furthermore, in comparison with TKIs alone, LCT following TKI treatment notably prolonged the PFS (14 vs. 36 months). Deng *et al* (41) assessed how synchronous radiation therapy (CPRT) impacts the primary tumor during first-line treatment with icotinib, and reported that the CPRT group achieved a median PFS of 13.6 months, compared with only 10.6 months in the non-CPRT group. Moreover, in a study by Peng *et al* (23), 13 patients with stage IV lung cancer who received EGFR-TKIs and SBRT to primary lung lesions had an median PFS of 27.3 months and an median OS of 49.1 months. Additionally, radiation therapy to the primary site alone offered improved benefits compared with radiation therapy targeted solely at metastatic sites or a combination of both approaches. Notably, osimertinib was not employed as the first-line treatment plan in any of the aforementioned studies.

Reducing the tumor burden in the primary site can enhance the efficacy of systemic therapy (42,43). Lin *et al* (44) demonstrated that salvage surgery performed before the disease advances can remove TKI-resistant subclones, thereby improving survival results. Furthermore. according to Al-Halabi *et al* (45), a notable number of patients receiving EGFR-TKIs initially experienced failure at the primary site,

Table III. Univariate and multivariate analyses associated with progression-free survival.

| | | | Univariate regression | | Multivariate regression | |
|---|---|---|---|---|---|---|
| Factor | n | Mean PFS, months | B[a] (95% CI) | P-value | B[a] (95%CI) | P-value |
| Age | | | | | | |
| <62 years | 15 | 18.47 | - | - | - | - |
| ≥62 years | 20 | 23.50 | 5.033 (-1.698-11.765) | 0.152 | 5.047 (-1.561-11.655) | 0.149 |
| Sex | | | | | | |
| Male | 11 | 21.91 | - | - | - | - |
| Female | 24 | 21.08 | -0.826 (-8.226-6.575) | 0.828 | -6.390 (-14.740-1.960) | 0.148 |
| ECOG performance status | | | | | | |
| 0 | 4 | 26.75 | - | - | - | - |
| 1 | 31 | 20.65 | -6.105 (-16.708-4.499) | 0.267 | -7.704 (-18.403-2.995) | 0.172 |
| Smoking status | | | | | | |
| No | 29 | 21.79 | - | - | - | - |
| Yes | 6 | 19.17 | -2.626 (-11.705-6.452) | 0.575 | -14.113 (-24.541-3.685) | 0.015[b] |
| Mutation type | | | | | | |
| Exon 19 Del | 22 | 22.45 | - | - | - | - |
| Exon 21 L858R | 13 | 19.46 | -2.993 (-10.035-4.049) | 0.411 | -1.608 (-8.518-5.303) | 0.653 |
| Stage | | | | | | |
| III | 4 | 20.75 | - | - | - | - |
| IV | 31 | 21.42 | 0.669 (-10.134-11.473) | 0.904 | 12.548 (0.566-24.529) | 0.052 |
| Visceral metastasis | | | | | | |
| No | 23 | 21.52 | - | - | - | - |
| Yes | 12 | 21.00 | -0.522 (-7.763-6.719) | 0.889 | -3.050 (-11.218-5.118) | 0.472 |
| CEA | | | | | | |
| <10 ng/ml | 18 | 24.17 | - | - | - | - |
| >10 ng/ml | 17 | 18.35 | -5.814 (-12.400-0.773) | 0.093 | -13.172 (-20.989-5.354) | 0.003[c] |
| Types of targeted drugs | | | | | | |
| Icotinib | 12 | 23.08 | - | - | - | - |
| Erlotinib | 13 | 19.66 | -3.468 (-11.648-4.712) | 0.412 | -9.219 (-16.598-1.840) | 0.023[b] |
| Gefitinib | 10 | 20.50 | -1.583 (-10.333-7.166) | 0.725 | -7.505 (-17.397-2.387) | 0.151 |
| Size of lung lesions | | | | | | |
| <3 cm | 22 | 20.45 | - | - | - | - |
| ≥3 cm | 13 | 22.85 | 2.392 (-4.677-9.460) | 0.512 | 6.673 (-0.701-14.046) | 0.090 |
| Radiation pneumonitis | | | | | | |
| Grade I + None | 28 | 22.46 | - | - | - | - |
| Grade II + III | 7 | 16.86 | -5.607 (-13.987-2.772) | 0.199 | -8.168 (-15.524-0.812) | 0.041[b] |

[a]B value represents the regression coefficient: A positive B value indicates that the factor has a positive effect on PFS, whilst a negative B value indicates a negative effect on PFS. The B value is meaningful only when P<0.05. [b]P<0.05; [c]P<0.01. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; CEA, carcinoembryonic antigen.

with a recurrence rate of 47.0% for primary tumors. The study by Hsu *et al* (22) also reported that the radiotherapy group had a reduced rate of primary tumor progression compared with the group not receiving radiation therapy. These findings indicate that integrating primary tumor control therapy (PTCT), whether through surgical resection or radiation therapy, enhances overall treatment outcomes and prolongs survival.

Additionally, research has demonstrated that combining EGFR-TKIs with radiotherapy can lead to improved survival in patients. Radiotherapy employs high-energy rays to target tumor cells and disrupt their genetic material. It can induce EGFR phosphorylation, which affects the efficacy of radiotherapy and may lead to resistance. Conversely, EGFR-TKIs can inhibit EGFR phosphorylation, thereby enhancing the effectiveness of radiotherapy (46). This synergistic mechanism provides a theoretical foundation for subsequent research. Furthermore, PTCT can restore immune function, reduce subclones of tumor stem cells and

decrease tumor heterogeneity, thereby enhancing the effect of EGFR-TKIs (22,38,47). In early studies, the values of PFS were smaller for patients with the L858R mutation than for those with the 19 deletions (19del) (48-50). In the present study, the PFS for the 19-exon deletion subgroup was 22.5 months, whereas for the L858R mutation subgroup it was 19.5 months, with no statistically significant difference observed. Factors such as sex, smoking status and cancer stage did not significantly affect PFS, indicating that all subgroups could benefit from Gamma Knife therapy.

The FLAURA trial reported that osimertinib achieved a PFS of 18.9 months and an OS of 38.6 months (51,52). In the present study, the PFS and OS data of Gamma Knife treatment combined with first-generation EGFR-TKI were broadly consistent with those of third-generation TKI monotherapy (such as osimertinib) in a similar population reported in the FLAURA trial, and the side effects were controllable; therefore, it is a viable option from a pharmacoeconomic perspective. However, it should be noted that the present study did not set up a third-generation TKI treatment group as a control. For patients eligible for Gamma Knife, the use of TKIs alone without local treatment (such as Stereotactic Radiosurgery/Gamma Knife) was not a routine or recommended practice in the 901st Hospital of the Joint Logistics Support Force of the People's Liberation Army. Therefore, among the concurrent, same-center patient population eligible for Gamma Knife, it was difficult for the present study to identify a sufficient number of suitable patients with comparable baseline characteristics who only received TKIs without any local treatment as the control group. Forcibly incorporating a poorly qualified control group would undermine the overall credibility of the research. Therefore, the current conclusion is based on a comparative analysis of indirect efficacy indicators among similar patient populations in different trials, rather than direct comparisons through head-to-head trials. Due to the differences in the treatment scenarios and patient screening criteria between the two, the statistical significance of the comparisons must be carefully interpreted. The main contribution of the present study lies in the description and preliminarily evaluation of a promising sequential treatment strategy, whose results need to be validated in future prospective controlled studies.

The focus of the present study was on consolidation therapy for the primary lesion of lung cancer (excluding metastatic lesions), which has not been systematically explored in existing studies, to the best of our knowledge. Current similar studies mainly focus on local treatment of metastatic lesions (12,26), lacking a specific analysis of the combination therapy of first-generation TKIs and Gamma Knife for the primary lesion. Through long-term follow-up data (PFS of 20 months and median OS of 39 months), the present efficacy and safety profile provide patients with one more treatment option.

Case inclusion in the present study preceded the subsequent regulatory approval of osimertinib for this indication (51). The treatment regimen of the present study may serve as an alternative option for situations in which third-generation TKIs cannot be used for treatment due to limited drug supply in certain developing countries or regions, insufficient financial affordability of patients, adverse reactions or contraindications. In the future, head-to-head research is needed to further compare the cost-effectiveness of first-generation TKIs combined with Gamma Knife, and of osimertinib monotherapy, in specific populations, providing more basis for individualized treatment.

Moreover, it should be noted that the present study has certain limitations. First, as it is a retrospective study without a control group, there may be selection bias. Second, a small sample size can lead to limited statistical power, which may affect the statistical significance of certain subgroup comparisons. Third, the follow-up time may have not been sufficient to obtain mature OS results from subgroup analyses and follow-up studies should extend the follow-up time to enhance the credibility of long-term interpretations. Large-scale prospective experiments are still needed to verify the findings proposed in the present study in the future.

In conclusion, combining first-generation EGFR-TKIs with Gamma Knife therapy can delay EGFR resistance and extend PFS and OS with a low incidence of toxicity and side effects. The results of the present study indicate that the combination of first-generation EGFR-TKIs and Gamma Knife therapy for the treatment of primary lung lesions is a viable therapeutic option for patients with advanced EGFR-sensitive mutations. Nevertheless, these results should be further verified in future prospective research.

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**Availability of data and materials**

The data generated in the present study may be requested from the corresponding author.

**Authors' contributions**

DLv was responsible for the study's conception and research protocol design. BX, DLu and ZL participated in study data acquisition, including data collection and patient management. DW, HM, LZ and ML analyzed the collected data and interpreted the results to derive key findings. DLv, BX, and DW collaborated on writing the manuscript's initial draft. All authors actively participated in the subsequent review and critical revisions, and all authors have read and approved the final manuscript. DLv and BX confirm the authenticity of all the raw data. All authors are accountable for the intellectual content of the work and agree to be responsible for all aspects of it.

**Ethics approval and consent to participate**

The present study was approved by the review board ethics committee of the 901st Hospital of the Joint Logistics Support Force of the People's Liberation Army (approval no. LYAHW2023BAc1003). The requirement for written

informed consent was waived due to the retrospective nature of the study. All data were anonymized prior to analysis and handled according to institutional and ethical standards.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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