Safety and efficacy of consolidative stereotactic radiotherapy for oligo-residual EGFR-mutant non-small cell lung cancer after first-line third-generation EGFR-tyrosine kinase inhibitors: a single-arm, phase 2 trial

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Summary

Background Prospective data is limited on the efficacy and safety of consolidative stereotactic radiotherapy (SRT) in metastatic epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) patients harboring oligo-residual disease (ORD) after first-line third-generation EGFR-tyrosine kinase inhibitors (TKIs).

Methods In this single-arm, phase II trial, 61 patients from two academic centers were enrolled from March 2021 to March 2023. All these patients had metastatic EGFR-mutant NSCLC and harbored ORD after first-line third-generation EGFR-TKIs. Consolidative SRT was performed and EGFR-TKIs were not held during SRT. The primary endpoint was progression-free survival (PFS) and the secondary endpoints included overall survival and treatment-related adverse events (TRAEs). A prespecified propensity score matched (PSM) comparison was conducted with a contemporary cohort of patients who developed ORD but received EGFR-TKIs alone. This trial was registered with ClinicalTrails.gov, NCT04764214.

Findings All patients received consolidative SRT. With a median follow-up of 21.1 months, the median PFS was 29.9 (80% CI 22.4–32.4) months and the lower boundary exceeded the predefined threshold, meeting the primary endpoint. TRAEs occurred in 43 (70%) patients, with pneumonitis (27.9%) and esophagitis (26.2%) being the most common toxicities. Four patients (6.6%) reported grade ≥3 TRAEs, each for pneumonitis, esophagitis, leukopenia, and cranial radiation necrosis. PSM analysis showed significantly prolonged PFS in EGFR-TKI + SRT group compared to EGFR-TKI group (HR 0.46, 80% CI 0.20–0.61; $p = 0.002$).

Interpretation Consolidative SRT is associated with an encouraging PFS in first-line third-generation EGFR-TKI-treated metastatic NSCLC patients harboring ORD, with generally acceptable toxicities. Further confirmatory studies are warranted.

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Keywords: Non-small cell lung cancer (NSCLC); EGFR-Tyrosine kinase inhibitors (TKIs); Oligo-residual disease (ORD); Stereotactic radiotherapy (SRT)

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Research in context

Evidence before this study

We searched PubMed, Embase, Cochrane Library and Web of Science for relevant publications until March 2024, using the search terms ("non-small cell lung cancer" or "NSCLC"), and ("stereotactic radiotherapy" or "SRT"), and ("Tyrosine Kinase Inhibitors" or "TKI" or "EGFR-TKI" or "osimertinib" or "almonertinib"), and ("oligo*"). References of relevant studies were reviewed for additional articles. Our search yielded 7 studies, including 3 phase II trials focusing on oligo-progressive disease, 1 trial focusing on local ablative radiotherapy, and 3 retrospective studies from our group. In conclusion, prospective data is limited on the efficacy and safety of consolidative stereotactic radiotherapy (SRT) in metastatic EGFR-mutant NSCLC patients harboring oligo-residual disease (ORD) after first-line third-generation EGFR-TKIs.

Added value of this study

To our knowledge, our study is the first phase II trial reporting the efficacy and safety of consolidative SRT in metastatic EGFR-mutant NSCLC patients harboring ORD after first-line third-generation EGFR-TKIs. Our results demonstrated that the addition of consolidative SRT to first-line third-generation EGFR-TKI was associated with prolonged PFS and acceptable safety profiles among those harboring ORD.

Implications of all the available evidence

Consolidative SRT may be a promising treatment strategy for metastatic EGFR-mutant NSCLC patients harboring ORD after first-line third-generation EGFR-TKIs and future randomized control trials with large sample size are warranted to validate this hypothesis.

Introduction

Lung cancer remains the leading cause of cancer-related deaths, with non-small cell lung cancer (NSCLC) accounting for approximately 85% of cases.[1,2] Epidermal growth factor receptor (EGFR) mutations occur in 10–20% of Caucasians and at least 50% of Asians patients with NSCLC.[3,4] Third-generation EGFR-tyrosine kinase inhibitors (TKIs) have become the standard of care for first-line treatment of advanced EGFR-Mutant (EGFR-M) NSCLC, as they have shown improvements in progression-free survival (PFS) and overall survival (OS) compared to first-generation EGFR-TKIs.[5–8] However, the development of acquired resistance with diverse and complex underlying causes have posed challenges to EGFR-M NSCLC management.[9] Therefore, there is an urgent need to explore feasible treatments that can delay or overcome acquired resistance.

The term "oligometastasis" was coined in 1995 by Hellman and Weichselbaum, referring to an intermediate state between limited primary and polymetastatic cancers.[10] Since then, significant efforts have been made to redefine treatment approaches and therapeutic outcomes for these potentially curable patients. Oligo-residual disease (ORD), taking inspiration from oligometastasis, is a term used to describe a condition where a small amount of tumor cells remain in a limited number of sites after initial treatment. Evidence from prospective studies has shown that using of local consolidation therapy could improve treatment outcomes in patients with ORD after first-generation EGFR-TKIs.[11,12] In the era of third-generation EGFR-TKIs, our previous retrospective studies identified 26.8% of patients as candidates for consolidative stereotactic radiotherapy (SRT) at the time of maximal response to osimertinib,[13] and local therapies targeting ORD have shown improvements in PFS.[14] However, prospective data on the efficacy of consolidative local therapy for ORD after third-generation EGFR-TKIs is still limited.

To address this gap, we initiated a single-arm, phase II trial based on our previous findings.[12–17] The aim of this trial was to evaluate the efficacy and safety of consolidative SRT in patients with EGFR-M advanced NSCLC who developed ORD after first-line third-generation EGFR-TKIs. Additionally, a protocol-specified propensity score matched (PSM) comparison with a contemporary institutional cohort of patients who received first-line third-generation EGFR-TKIs alone was conducted to better assess the efficacy of this treatment approach.

Methods

Study design and participants

This is a single-arm, phase II trial (ClinicalTrials.gov identifier: NCT04764214) conducted at two centers in China. The study protocol was approved by the Institutional Review Board and ethics committees of Fudan University Shanghai Cancer Center (Reference Number. 2012228-4-2306A) and Tongji Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology. All patients provided written informed consent to participate.

Inclusion criteria were ≥18 and ≤75 years of age, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, pathologically confirmed stage IV NSCLC according to American Joint Committee on Cancer staging manual (8th Edition) and confirmed EGFR mutation of exon 19 deletion or exon 21 L858R mutation. Adequate baseline tumor assessment was required before the initiation of first-line third-generation EGFR-TKIs. Each patient should have at least one

measurable lesion according to Response Evaluation Criteria in Solid Tumors, version 1.1. The oligo-residual tumor lesions after first-line third-generation EGFR-TKIs should be amenable to consolidative SRT in the opinion of the investigators.

Exclusion criteria were history of or concurrent secondary malignancy, pregnancy or breastfeeding, general conditions that might affect compliance or ability to sign informed consent (including uncontrolled epilepsy, mental disorders, drug abuse and social conditions), and the residual tumors that were deemed not amenable to consolidative SRT.

Of note, patients with cranial- and/or extracranial ORD could be included. The definition of ORD was adjusted to the status of brain metastases (BMs). Extracranial ORD was defined as residual tumors limited to three organs and five lesions after effective third-generation EGFR-TKIs in patients without baseline BMs and those with intracranial complete response. In addition, lymph nodes with a short diameter of ≤ 1 cm and no obvious malignant signs (circular enhancement, uneven enhancement, positron emission tomography [PET]/computed tomography [CT] positive, etc.) are considered benign. Combined serous cavity effusion or multiple pleural/peritoneal nodules should be excluded from ORD. Bone metastases with clear boundaries and countable numbers should be included in the counting of lesions one by one. Meanwhile, cranial ORD was defined as the BMs limited to three lesions with a largest diameter of ≤ 3 cm after effective third-generation EGFR-TKIs, among those with residual BMs and without extracranial progressive disease (in this circumstance, extracranial ORD was not necessarily required). Based on the Response Assessment in Neuro-Oncology (RANO) standard, at least one BM lesion with a diameter >1 cm or a lesion with a diameter >0.5 cm on a 1.5 mm thick thin layer magnetic resonance imaging (MRI) was required for response evaluation.[18]

Procedures

For metastatic EGFR-M NSCLC patients receiving first-line third-generation EGFR-TKIs, evaluations for eligibility for consolidative SRT were scheduled one month after the initiation of treatment, and every two months for one year thereafter. Of note, the status of ORD was confirmed by PET/CT among potential candidates who were willing to participate.

Patients enrolled in this trial were treated with the intent to ablate all residual disease with consolidative SRT. The choice of dose-fractionation regimen was at the discretion of the treating radiation oncologist. Cranial SRT was mainly prescribed at 27 Gy in three fractions.[19] The dose and fractionation for extracranial ORD was referred to the regimens used in NRG-BR001 trial[20,21] (Supplemental Table S1). The third-generation EGFR-TKIs were continued during and after consolidative SRT until disease progression or intolerable toxicity occurred.

Follow-up visits were scheduled every three months for the first two years and every six months thereafter. Medical history, physical examination, chest CT scan, and abdominal ultrasound or CT scan were regularly assessed during each follow-up. Other tests, such as bone scanning and PET/CT, were performed at the discretion of the treating physicians. In patients without BMs, follow-up brain MRI scans were not mandatory and were performed at the discretion of treating physicians, typically after the appearance of indicative symptoms. In patients with BMs, brain MRI scans were regularly performed during each follow-up. Toxicity assessments were conducted at each follow-up.

Outcomes

The primary endpoint was PFS, which was defined as the time from the date of initiation of third-generation EGFR-TKIs to the time of disease progression or death. For patients who had no disease progression, PFS was censored on the date of the last follow-up.

Toxicity and OS were secondary endpoints. Toxicity was evaluated and recorded using the Common Terminology Criteria for Adverse Events, version 5.0. OS was defined as the time from the date of initiation of third-generation EGFR-TKIs to death from any cause. For patients alive, OS was censored on the date of last follow-up.

Statistical analyses

Due to the lack of prospective data about the survival outcomes of metastatic EGFR-M NSCLC patients with ORD after effective first-line third-generation EGFR-TKIs, a pooled analysis of three retrospective studies from our group was conducted and found a median PFS of 20.0 months for those harboring extracranial and/or cranial ORD after first-line third-generation EGFR-TKIs,[13,14,16] which served as the historical control of the current trial. The sample size calculation was based on the primary endpoint of PFS. Assuming that the PFS in metastatic EGFR-M NSCLC patients receiving first-line third-generation EGFR-TKIs and harboring ORD was 20.0 months, and that the addition of consolidative SRT would improve PFS with a hazard ratio (HR) of 0.65. All the participants would be enrolled in two years and the last participant would be followed-up for at least one year. Based on a one-sided alpha of 0.1 and a beta of 0.2, the total sample size was 55 patients. With a presumed dropout rate of 10% before the study evaluation, 61 subjects were needed in this trial.

In addition to reporting the endpoints of all enrolled patients, the protocol-prespecified PSM by a set of important factors was conducted with a contemporary cohort of patients with oligo-residual NSCLC after first-

line third-generation EGFR-TKIs but receiving EGFR-TKIs alone during the period of enrollment. PSM analysis was undertaken in an attempt to adjust for potential bias associated with prognostic factors related to treatment (EGFR-TKI + SRT vs. TKI alone). R package "MatchIt" was used for 1:1 nearest-neighbor PSM with institute, age, sex, smoking history, PS, TKI type, EGFR mutation type, status of baseline disease burden, presence of residual metastasis in lung, bone, and brain, respectively, and number of the residual involved lesions and organs. Of note, status of baseline disease burden was categorized as oligo-metastasis (limited to three organs and five lesions) and multi-metastasis.

The chi-square test for categorical variables or t-test for continuous variables was used to assess the difference in distribution between the patients receiving EGFR-TKI + SRT and those receiving TKI alone after PSM. The Kaplan–Meier method was used to estimate time-to-event outcomes such as PFS and OS, with comparisons made with the log-rank test. Univariate and multivariate Cox analyses were used to explore the association between clinical characteristics and PFS in propensity score matched cohorts, and clinical characteristics with $p < 0.1$ in univariate analysis were included in multivariate analysis. SPSS (version 24), GraphPad Prism 9.0, and R software (version 4.2.2) were used for all analysis, and statistical significance was set at $p < 0.05$.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The current trial enrollment started in March 2021 and completed in March 2023, with the last follow-up date of March 31, 2024. The CONSORT flow diagram for this trial is shown in Fig. 1. 14 of the 75 patients assessed for eligibility were excluded for not meeting inclusion criteria or refusing to sign informed consent. A total of 61 patients were finally enrolled. The clinical characteristics of the patients enrolled are displayed in Table 1. Notably, 15 (68%) of the 22 patients with baseline BMs harbored cranial ORD and received cranial SRT. The rest seven (32%) patients had intracranial complete response and received extracranial SRT only. The SRT details were described in Supplemental Table S2. The median TKI duration before SRT was 3.7 months (IQR, 1.0–5.9 months).

With a median follow-up of 21.1 months (IQR, 19.0–23.2 months), 26 of the 61 patients developed progressive disease (PD). Among them, 5% (3/61) had intracranial PD, 36% (22/61) had extracranial PD, and 2% (1/61) had intracranial and extracranial PD simultaneously. The subsequent treatments in these patients were described in Supplemental Table S3. The median PFS in all patients was 29.9 months (80% confidence intervals [CI] 22.4–32.4, Fig. 2a), the lower boundary of which exceeded 20.0 months and the current trial met the primary endpoint. The 1- and 2-year PFS rates were 91.6% (80% CI 87.1%–96.3%) and 53.4% (80% CI 45.3%–65.1%), respectively. Meanwhile, among the 15 patients who received cranial SRT for residual BMs, one (7%) had intracranial PD, five (33%) had extracranial PD, and nine (60%) had no PD. The median PFS in this subgroup was 16.9 months (80% CI 16.3–NA, Figs. 2b)

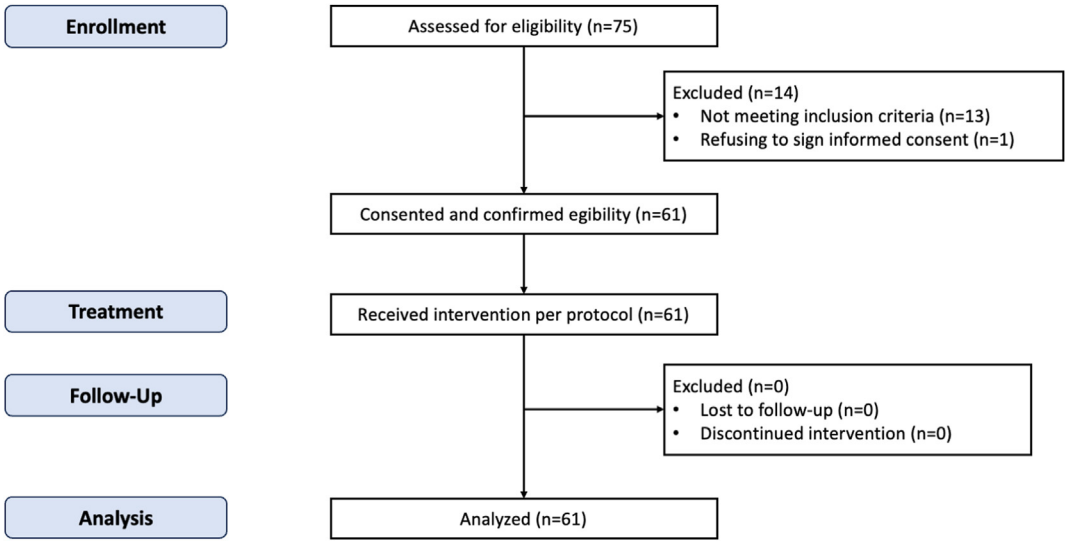

Fig. 1: **CONSORT flow diagram.**

Clinicopathological characteristics	Mean or no (%)
Age (years)	
Mean (range)	59 (33–75)
>60	28 (46)
≪60	33 (54)
Sex	
Male	28 (46)
Female	33 (54)
Smoking	
Current or ever	13 (21)
Never	48 (79)
ECOG PS	
0–1	50 (82)
2	11 (18)
TKI type	
Osimertinib	49 (80)
Almonertinib	12 (20)
EGFR Mutation	
L858R	29 (46)
19 Deletion	32 (54)
Baseline brain metastasis	
Positive	22 (36)
Negative	39 (64)
Status of baseline disease burden	
Oligo-metastasis	37 (61)
Multi-metastasis	24 (39)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; TKI, tyrosine kinase inhibitors; EGFR, epidermal growth factor receptor.

Table 1: **Clinicopathological characteristics (n = 61).**

and 1- and 2-year PFS rates were 86.7% (80% CI 66.9%–64.3%) and 48.4% (80% CI 31.9%–73.4%), respectively.

At the time of data lock, six patients died. The median OS had not been reached (80% CI, 33.6–NA months) and the 2-year OS rate was 86.4% (80% CI 79.2%–94.3%). In the patients receiving cranial SRT for residual BMs, only one patient died and the median OS had not been reached (80% CI NA).

Treatment-related adverse events (TRAE) were reported in 43 patients (70%; Table 2). The most common TRAE (any grade) was pneumonitis (27.9%) and esophagitis (26.2%), followed by paronychia (24.6%), diarrhea (24.6%), and platelet count decrease (18%). In the patients receiving thoracic SRT (n = 39), the rate of pneumonitis of any grade was 43.6%. Four patients (6.6%) reported grade ≥3 TRAEs, each for pneumonitis, esophagitis, leukopenia, and radiation cranial necrosis. None of AEs led to discontinuation of SRT or EGFR-TKIs.

A total of 1254 patients with metastatic EGFR-M NSCLC receiving first-line third-generation EGFR-TKIs during the period of enrollment were screened (Supplemental Figure S1). Among the 326 patients who developed ORD, 243 patients receiving EGFR-TKIs alone and having adequate follow-up served as the candidates for comparison cohort. After PSM, a comparison cohort with 61 patients was created and the disease burden before and after treatment in the EGFR-TKI + SRT group and the EGFR-TKI alone group was shown in Supplemental Table S4. The results in Supplemental Table S5 showed a satisfactory match with no significant differences in clinically relevant covariates between the two groups. By univariate and multivariate COX analyses, the addition of consolidative SRT to EGFR-TKI was identified as independent factor in better PFS with reference to EGFR-TKI alone (adjusted HR 0.47, 95% CI 0.27–0.82; $p < 0.01$, Supplemental Table S6).

In the EGFR-TKI alone group after PSM, the median PFS was 19.0 months (80% CI 18.0–24.1) in all the patients (n = 61, Fig. 3a) and 13.9 months (80% CI 10.9–18.0) in the patients with residual BMs (n = 18, Fig. 3b). The HR was 0.46 (80% CI 0.20–0.61, $p = 0.002$) for EGFR-TKI + SRT with reference to EGFR-TKI alone (Supplemental Figure S2a). For the patients with residual BMs, the addition of consolidative cranial SRT to EGFR-TKI brought significant improvement in PFS

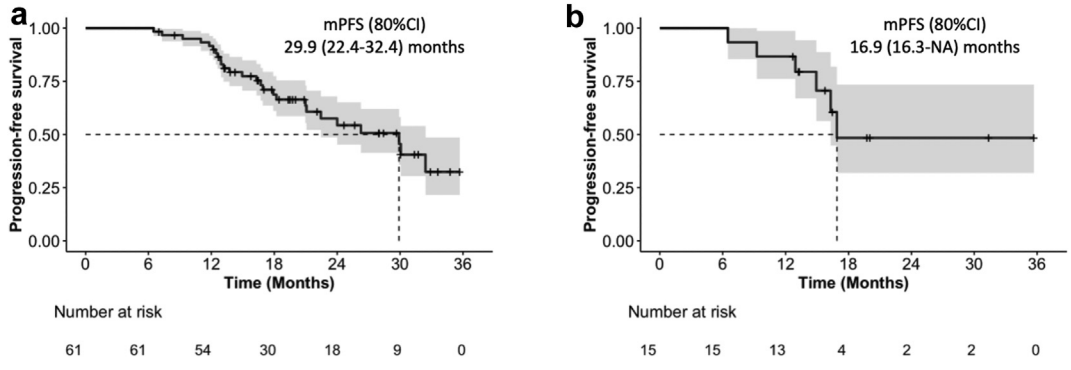

Fig. 2: **Progression-free survival**. (a) In all the patients (n = 61). (b) In the patients who received cranial SRT for residual BMs (n = 15). PFS, progression-free survival; SRT, stereotactic radiotherapy; BM, brain metastasis.

Adverse event, n (%)	EGFR-TKI + SRT (n = 61)			
	Any grade	Grade 1	Grade 2	Grade 3
Pneumonitis	17 (27.9)	10 (16.4)	6 (9.8)	1 (1.6)
Esophagitis	16 (26.2)	9 (14.8)	6 (9.8)	1 (1.6)
Paronychia	15 (24.6)	8 (13.1)	7 (11.5)	0
Diarrhea	15 (24.6)	11 (18)	4 (6.6)	0
Platelet count decrease	11 (18)	9 (14.8)	2 (3.3)	0
Dermatitis	9 (14.8)	7 (11.5)	2 (3.3)	0
Rash	8 (13.1)	7 (11.5)	1 (1.6)	0
Anemia	7 (11.5)	6 (9.8)	1 (1.6)	0
Leukopenia	6 (9.8)	4 (6.6)	1 (1.6)	1 (1.6)
Cranial radiation necrosis	5 (8.2)	3 (4.9)	1 (1.6)	1 (1.6)
Headache	3 (4.9)	2 (3.3)	1 (1.6)	0
Nausea	3 (4.9)	2 (3.3)	1 (1.6)	0
AST increase	2 (3.3)	2 (3.3)	0	0
ALT increase	2 (3.3)	2 (3.3)	0	0
Fatigue	1 (1.6)	1 (1.6)	0	0
Edema limbs	1 (1.6)	1 (1.6)	0	0

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; SRT, stereotactic radiotherapy.

Table 2: **Adverse events assessed by the investigators (the Common Terminology Criteria for Adverse Events, 5.0).**

with reference to EGFR-TKI alone (HR 0.39, 80% CI 0.21–0.93, $p = 0.046$, Supplemental Figure S2b).

Discussion

The LUNG-SORT trial is one of the first studies to explore the efficacy and safety of consolidative SRT in metastatic EGFR-M NSCLC patients harboring ORD after first-line third-generation EGFR-TKIs. Although the trial is single-arm, a per-protocol comparison was made with a contemporary cohort of patients who received first-line third-generation EGFR-TKI treatment alone to further evaluate the therapeutic efficacy. The results of the trial suggest that consolidative SRT may be a potential therapeutic strategy to prolong the duration of clinical benefit and delay the resistance to first-line third-generation EGFR-TKIs.

There are several rationales supporting the use of consolidative SRT to the oligo-residual lesions after EGFR-TKI treatment. Firstly, EGFR TKI-resistant subpopulations of NSCLC cells may present in the residual lesions, which could lead to future disease progression. With the involvement of SRT in eradicating the EGFR-TKI-resistant subpopulations, extended duration of EGFR-TKI treatment and improved PFS could be achieved. Secondly, there is an advantage of consolidative SRT for ORD over salvage SRT for progressive diseases. With the lowest tumor burden and fewest metastatic lesions at the time of maximal response to EGFR-TKIs, higher tumor control rates can be achieved by consolidative SRT with fewer side effects. Additionally, if the residual lesions progress, they can grow in size and number beyond critical levels, which may deprive the patients of the optimal opportunity to receive SRT.

In addition to the above theoretical rationales, our previous studies have laid groundwork for the current study. Firstly, we found that more than 25% of patients with metastatic EGFR-M NSCLC treated with first-line third-generation EGFR-TKIs rendered ORD status through retrospective review of serial scans.[13] In view of the high EGFR mutation rate in Asia, the patient population of EGFR-M NSCLC with ORD is considerable. Furthermore, pattern of failure analyses in the patients who didn't receive local consolidative therapy indicated that 76.2% of PD developed in the original oligo-residual lesions.[14] Besides, local consolidative therapies including SRT targeting oligo-residual lesions significantly improved PFS ($p = 0.01$) in a multicenter real-world study.[14] All these retrospective data suggested the potential clinical value of consolidative SRT in improving the local control and prolonging time to progression in this highly selected population. To provide prospective data in metastatic EGFR-M NSCLC patients harboring ORD after first-line third-generation

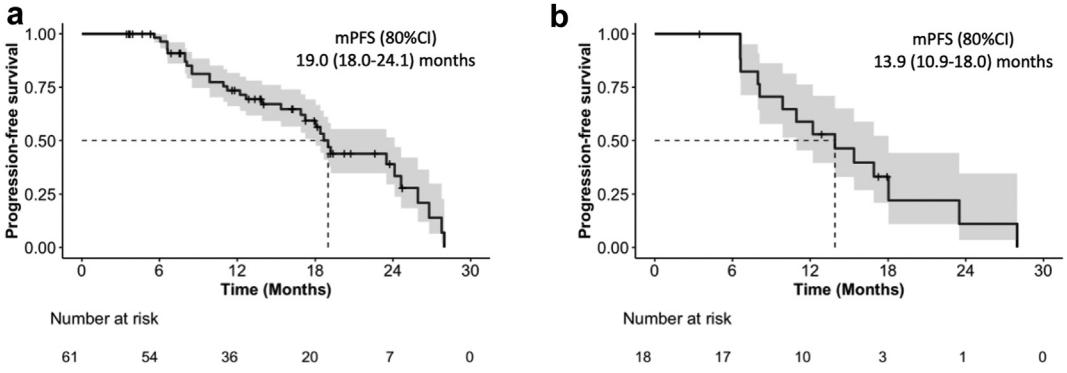

Fig. 3: **Progression-free survival in EGFR-TKI alone group after propensity score matching.** (a) In all the patients (n = 61). (b) In the patients with residual BMs (n = 18). PFS, progression-free survival; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors; BM, brain metastasis.

EGFR-TKIs, the present study was initiated and found a median PFS of 29.9 months (80% CI 22.4–32.4) with the lower boundary of 80% CI exceeding that in the historical control cohort, supporting the efficacy of this treatment approach. Recently, Sawsan Rashdan et al. evaluated the efficacy and safety of SBRT after 8-week induction of osimertinib in 43 patients with EGFR-mutant advanced NSCLC (NCT03667820).[22] With a smaller sample size and focusing on extracranial consolidative radiotherapy, they found a median PFS of 32.3 (95% CI 21.88–51.71) months, which was similar to our finding. Taken together, future randomized controlled trials (RCTs) are warranted to validated these promising results.

Meanwhile, our previous work has hinted the potential of consolidative cranial SRT in EGFR-M NSCLC with BMs treated with osimertinib. In this subgroup of patients, 40.2% of the initial PD involved the brain and 76.9% of the cranial PD developed at the original sites.[23] In those receiving first-line EGFR-TKIs, cranial SRT and/or surgery were associated with improved OS with reference to non-local therapy (38.9 vs. 26.7 months, HR 0.21, 95% CI 0.05–0.04; $p = 0.041$).[15] Additionally, the survival benefit provided by consolidative cranial SRT was more evident among patients with cranial ORD.[16] Based on these findings, we enrolled a subgroup of patients with cranial ORD in order to evaluate the efficacy of consolidative cranial SRT, which generated encouraging results. Hence, a multicenter RCT (BM-SORT, NCT06020066) has been initiated to further investigate the efficacy and safety of consolidative cranial SRT for oligo-residual cranial tumor lesions after first-line third-generation EGFR-TKI therapy in those with EGFR-M NSCLC and BMs.

Generally, the additional of consolidative SRT to third-generation EGFR-TKI treatment has shown acceptable safety profiles. In the NRG-BR001 phase 1 trial, 18% (7/39) of the patients experienced grade ≥3 TRAEs evaluated by central reviw.[21] The incidence of grade ≥3 TRAEs was lower in the current study may due to that the patients enrolled had lower tumor burden and the majority of them received SRT for only one site. The occurrence of treatment-related pneumonitis (TRP) remains a concern in thoracic radiotherapy plus EGFR-TKI treatment.[24] A meta-analysis of 37 studies, involving 1143 NSCLC patients receiving combined therapy of thoracic radiotherapy and EGFR-TKIs, found an incidence of grade ≥3 TRP of 3.8% (95% CI, 1.8%–6.5%).[25] Compared to conventional radiotherapy, SRT results in less damage to normal tissues with the millimeter precision of radiation delivery, accounting for the low rate of grade ≥3 TRP in the current study. A multi-institutional retrospective case–control study of patients receiving stereotactic radiosurgery (SRS) found that the risk of cranial radiation necrosis was six times higher in the patients who used TKI than those who did not, and significantly higher in patients undergoing SRS after drug resistance than before drug resistance.[26] The timing of SRT before drug resistance and the low tumor burden may explain the low incidence (1.6%) of grade 3 cranial radiation necrosis observed in the current study.

There are several limitations that warrant discussion. Firstly, single-arm design makes it challenging to directly determine the superiority of EGFR-TKI + SRT to EGFR-TKI alone. To address this issue, a per-protocol comparison with a contemporary cohort of patients receiving first-line third-generation EGFR-TKIs alone was conducted and a 1:1 PSM analysis considering as many factors as possible was used to further minimize the potential selection bias. However, other covariates that might be associated with the outcomes were not available, such as the EGFR co-mutation.[27–29] As the current study is still hypothesis-generating, future RCTs are warranted in investigating the efficacy and safety of consolidative SRT in this disease population. Secondly, due to lack of prospective data on the PFS of patients with ORD after first-line third-generation EGFR-TKIs, the median PFS of 20.0 months from a pooled analysis of individual patient data was used as the historical control based on our previous work focusing on metastatic EGFR-M NSCLC patients who harbored extracranial and/or cranial ORD after first-line osimertinib.[13,14,16] The PFS of the comparison cohort deriving from a prospectively maintained database with a relatively large sample size, was generally consistent with the historical control, which demonstrated the robustness of our previous pooled analysis and could provide reference for future RCTs. Thirdly, target sites, dose fractionations and the timing of consolidative SRT varied in the current study. In order to identify the optimal schedule of consolidative SRT, temporal changes of extracranial and/or cranial tumor lesions after first-line third-generation EGFR-TKIs are being analyzed using comprehensive longitudinal radiographic data with a relatively large sample size.

Consolidative SRT is associated with an encouraging PFS in first-line third-generation EGFR-TKI-treated metastatic EGFR-M NSCLC patients harboring ORD, with manageable toxicities. Further confirmatory studies are needed to validate our findings.

Contributors

Conception and design: Ni J, Zhang L, and Zhu Z.

Provision of study materials or patients: Zhou Y, and Peng L.

Collection and assembly of data: Chu L, Chu X, Yang X, and Zhang J.

Data analysis and interpretation: Liang F, Wang Z, Guo T, Jiang S, and Pang Y.

Manuscript writing: All authors.

All authors had access to the data, participated in reviewing and editing of the manuscript, and approved the final version before submission. Two principal investigators (Zhou Y, and Peng L) verified the raw data of the study and had final responsibility for the decision to submit for publication.

Data sharing statement

Deidentified participant data and the protocol are available from the corresponding author on reasonable request.

Declaration of interests
All authors have no conflicts of interest to declare.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102853.

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