Optimal timing of stereotactic radiosurgery with first-line osimertinib in EGFR-mutant non-small cell lung cancer brain metastases: Immediate, early-consolidation and salvage strategies

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Abstract. The optimal timing for integrating stereotactic radiosurgery (SRS) with first-line osimertinib in EGFR-mutant non-small cell lung cancer (NSCLC) with brain metastases (BMs) is undefined. The present study compared outcomes of three distinct SRS timing strategies. In the present dual-center retrospective study, patients with EGFR-mutant NSCLC and 1-10 BMs receiving first-line osimertinib were categorized into immediate SRS (≤4 weeks; n=62), early-consolidation SRS (4-12 weeks; n=62) and salvage SRS (>12 weeks upon progression; n=62). The primary endpoint was intracranial progression-free survival (iPFS).With a median follow-up of 43.5 months, median iPFS demonstrated a significant gradient: 27.0 (immediate), 22.5 (early-consolidation) and 15.7 months (salvage; overall P<0.001). Compared with salvage SRS, immediate SRS reduced the risk of intracranial progression/mortality by 71% [hazard ratio (HR) =0.292; 95% confidence interval (CI), 0.191-0.448; P<0.001] and early-consolidation SRS by 60% (HR=0.398; 95% CI, 0.268-0.592; P<0.001). Immediate SRS also outperformed early-consolidation SRS (HR=0.569; 95% CI, 0.391-0.827; P=0.001). Overall survival and PFS demonstrated consistent benefits for earlier intervention. Grade ≥3 adverse events were similar between groups (P=0.824). Multivariable and propensity-score matched analyses confirmed the robustness of these findings. In conclusion, for EGFR-mutant NSCLC with BMs, upfront SRS integrated within the first 12 weeks of first-line osimertinib, particularly within 4 weeks, is associated with markedly superior intracranial control and survival compared with a salvage approach, without increasing severe toxicity.

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Abbreviations: NSCLC, non-small cell lung cancer; BMs, brain metastases; SRS, stereotactic radiosurgery; iPFS, intracranial progression-free survival; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; AE, adverse event; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Status; NGS, next-generation sequencing

Key words: EGFR-mutant non-small cell lung cancer, brain metastases, osimertinib, stereotactic radiosurgery, treatment timing, survival outcomes

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with ~2.2 million new cases and 1.8 million cancer-related mortalities reported annually; non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer diagnoses (1). The discovery of somatic mutations in the EGFR gene, which encodes a transmembrane tyrosine kinase receptor that drives constitutive activation of downstream proliferative signaling pathways, has revolutionized treatment paradigms by identifying a predictive biomarker for targeted therapy with EGFR tyrosine kinase inhibitors (TKIs) (2,3). EGFR mutations, particularly exon 19 deletions and exon 21 L858R point mutations, are prevalent in lung adenocarcinoma, with distinct ethnic distributions: 40-50% in East Asian populations and 10-15% in Caucasian populations (2,4). Women and never-smokers display higher mutation frequencies across ethnic groups. Osimertinib, a third-generation EGFR-TKI with potent central nervous system (CNS) penetration, has established itself as the standard first-line therapy for patients with advanced EGFR-mutant NSCLC, demonstrating superior efficacy over earlier-generation TKIs (5,6). First- and second-generation EGFR-TKIs are associated with higher rates of dose-limiting toxicities, primarily skin rash and diarrhea, due to non-selective inhibition of wild-type EGFR (7).

Despite this progress, the development of brain metastases (BMs) persists as a key clinical challenge and a frequent mode of treatment failure, occurring in 25-40% of patients with EGFR-mutant NSCLC (8,9). While osimertinib exhibits improved intracranial activity compared with its

predecessors, achieving objective response rates of 50-70%, a substantial proportion of patients still experience intracranial progression (10,11). This underscores an urgent need for more effective combinatorial strategies to achieve durable intracranial disease control.

Stereotactic radiosurgery (SRS) delivers precise, ablative radiation to metastatic brain lesions and is a cornerstone of modern BM management (12). Combining SRS with EGFR-TKIs presents a rational therapeutic approach, potentially yielding synergistic effects and overcoming the limitations of each modality alone (13). However, the optimal sequencing of this combination, specifically, the ideal timing of SRS relative to the initiation of systemic therapy, remains poorly defined and is not guided by robust prospective evidence (14).

Clinically, two contrasting strategies are employed: Early-consolidation SRS, administered upfront or shortly after TKI initiation to eradicate macroscopic disease, and salvage SRS, reserved for treating lesions that progress following initial TKI therapy (15). Preclinical rationale supports early combination, suggesting EGFR-TKIs may radiosensitize tumor cells (16). Furthermore, upfront local control of macroscopic BMs might prevent the emergence of resistant clones and subsequent CNS failure (17,18). Although several retrospective studies have suggested a potential benefit for concurrent TKI and radiotherapy over sequential approaches, direct comparative evidence specifically addressing the timing of SRS in the context of first-line osimertinib is scarce (19,20). The majority of available data is derived from heterogeneous cohorts involving various TKIs and radiotherapy techniques.

Therefore, it is unknown whether proactive, early SRS integration offers a meaningful improvement in patient outcomes compared with vigilant monitoring and a salvage approach, thereby justifying its resource utilization and potential risks. Furthermore, the concept of 'early' intervention itself may be heterogeneous, and whether a very early intervention confers additional advantage over a slightly delayed consolidation intervention remains unexplored. The present study aimed to directly compare the efficacy and safety of three distinct SRS timing strategies: Immediate (≤4 weeks), early-consolidation (4-12 weeks) and salvage (>12 weeks upon progression), all combined with first-line osimertinib in patients with EGFR-mutant NSCLC and BMs. We hypothesized that an earlier SRS timing strategy would be associated with superior intracranial disease control and survival without a notable increase in severe toxicity.

Materials and methods

Study design and patient selection. The present study was a dual-center, non-randomized, retrospective comparative cohort study conducted at two institutions bound by a formal hospital-level collaboration framework: Tianjin Medical University Cancer Institute and Hospital (Tianjin, China), and Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei (Cangzhou, China), which is the officially designated Cangzhou Branch of Tianjin Medical University Cancer Institute and Hospital under the Beijing-Tianjin-Hebei regional medical collaboration initiative. The present study period spanned from January 2018 to December 2022, corresponding to the widespread clinical adoption of first-line osimertinib. Electronic medical records of all patients with advanced (stage IV) EGFR-mutant lung adenocarcinoma were screened, with data extraction and statistical analysis conducted from January 2024 to January 2025.

Key inclusion criteria were: i) Age ≥18 years; ii) histologically or cytologically confirmed lung adenocarcinoma with a sensitizing EGFR mutation (exon 19 deletion or 21 L858R point mutation) confirmed by clinically validated assays performed in certified molecular diagnostic laboratories. Formalin-fixed paraffin-embedded tumor tissue samples were tested using allele-specific quantitative PCR or targeted next-generation sequencing (NGS) panels covering exons 18-21 of the EGFR gene. Plasma circulating tumor DNA testing was performed using digital PCR or NGS for patients with insufficient or unavailable tumor tissue. All assays had a limit of detection of ≤1% variant allele frequency (21); iii) initiation of first-line osimertinib at a standard dose of 80 mg once daily at a participating institution; iv) presence of 1 to 10 newly diagnosed, measurable BMs on contrast-enhanced magnetic resonance imaging (MRI) performed within 4 weeks before starting osimertinib; and v) availability of complete medical records detailing treatment, radiographic assessments and follow-up. Key exclusion criteria included: i) Prior radiotherapy to the brain (SRS or whole-brain radiotherapy); ii) leptomeningeal disease at baseline; iii) prior systemic therapy for advanced disease, other active malignancies within the past 3 years; iv) inadequate organ function precluding osimertinib use; or v) insufficient radiological follow-up (<2 cranial MRI assessments after treatment initiation). The present study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of both participating centers: The Ethics Committee of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei (approval no. CZX2024180) and the Institutional Review Board of Tianjin Medical University Cancer Institute and Hospital (approval no. EK20250091). The requirement for written informed consent to participate in the present retrospective study was waived by both ethics committees.

Cohort definitions. Eligible patients were categorized into three mutually exclusive cohorts based on the timing of the first SRS procedure relative to osimertinib initiation: i) Immediate SRS cohort of patients who underwent SRS to all visible BMs within 4 weeks (≤28 days) after starting osimertinib; ii) early-consolidation SRS cohort of patients who underwent SRS between 4 and 12 weeks (29-84 days) after starting osimertinib, in the absence of intracranial progression; and iii) salvage SRS cohort of patients who received their first SRS >12 weeks (>84 days) after starting osimertinib, and only upon confirmed intracranial progression according to Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (22).

The 4-week and 12-week cut-off points were selected based on combined biological rationale and established clinical practice standards. The 4-week cut-off corresponds to the time when osimertinib reaches steady-state plasma and intracranial concentrations, and tumor cells remain maximally sensitized to ionizing radiation under TKI exposure. This timeframe is also consistent with the international standard window for

postoperative SRS, which is universally recommended to be performed within 4 weeks of surgical resection for optimal local control (23,24). The 12-week cut-off represents the first formal radiographic assessment time point per RANO-BM criteria, at which the intracranial response to osimertinib monotherapy can be definitively evaluated. Patients without intracranial progression at 12 weeks are typically managed with continued osimertinib monotherapy and close monitoring, reserving SRS for subsequent intracranial progression, which defines the standard salvage strategy in current clinical practice. Alternative cut-off points (such as 2 weeks or 8 weeks) were not selected as they do not align with either the pharmacokinetic profile of osimertinib or widely accepted clinical follow-up schedules.

Treatment protocols. All patients received first-line osimertinib (80 mg orally, once daily) until disease progression, unacceptable toxicity, mortality or loss of follow-up. Dose modifications were permitted at the treating physician's discretion to manage adverse events (AEs). SRS was delivered using contemporary platforms: Gamma Knife® (Elekta Instrument AB), CyberKnife® (Accuray Incorporated) and linear accelerator-based systems using volumetric modulated arc therapy (Varian Medical Systems). Treatment planning was based on the co-registration of a high-resolution contrast-enhanced brain MRI with a thin-slice CT simulation scan. Radiation dose and fractionation were individualized per lesion based on maximum diameter and proximity to organs-at-risk, adhering to established international guidelines (23,24). Typical regimens were 20-24 Gy in 1 fraction for lesions ≤2.0 cm, 18-21 Gy in 1 fraction for lesions 2.1-3.0 cm and 24-27 Gy in 3 fractions for lesions >3.0 cm or located in critical anatomical sites such as the brainstem, optic apparatus (optic nerve and chiasm) and eloquent cortex.

Study endpoints and assessments. The primary endpoint was intracranial progression-free survival (iPFS), defined as the time from osimertinib initiation to the first objective documentation of intracranial progression per RANO-BM criteria or mortality from any cause. Key secondary endpoints included: i) Overall survival (OS) defined as the time from osimertinib initiation to mortality from any cause; ii) PFS defined as time from osimertinib initiation to radiographic progression (intracranial or extracranial) per RECIST version 1.1 (25) or mortality from any cause; iii) intracranial objective response rate (ORR) and disease control rate (DCR) assessed per RANO-BM; and iv) safety and tolerability, assessed by the incidence and severity of AEs graded according to the Common Terminology Criteria for Adverse Events version 5.0 (26). Tumor assessments were conducted at baseline and subsequently at scheduled intervals. Intracranial responses were evaluated by two independent, blinded radiologists using RANO-BM criteria. Extracranial disease was assessed using contrast-enhanced CT of the chest and abdomen per RECIST 1.1.

Patient follow-up. Patients were followed from osimertinib initiation until the data cut-off date (January 2025) or mortality. Follow-up included clinical evaluations and scheduled radiographic assessments. Cranial MRI was performed every 3 months for the first 2 years, then every 6 months thereafter. Extracranial imaging followed a comparable schedule. Survival status was verified through hospital records or telephone contact when necessary.

Statistical analysis. Categorical and continuous baseline variables were compared using χ^2 and Fisher's exact tests and Mann-Whitney U/Kruskal-Wallis tests, respectively. Time-to-event endpoints (iPFS, PFS and OS) were analyzed using the Kaplan-Meier method with log-rank tests for group comparisons; hazard ratios (HRs) with 95% confidence intervals (CIs) were derived from Cox proportional hazards models. Multivariable Cox models were adjusted for predefined baseline characteristics. Subgroup analyses were performed for the immediate vs. salvage SRS comparison, with the interaction tested via Cox models including an interaction term.

To address potential confounding, propensity score matching (PSM) was conducted as a sensitivity analysis. Separate 1:1 nearest-neighbor matching (caliper=0.2 x SD) was performed for 'immediate vs. salvage' and 'early-consolidation vs. salvage' comparisons based on seven baseline variables. Balance was assessed using standardized mean differences (SMDs; SMD <0.1 indicated good balance). All tests were two-sided, with $P<0.05$ considered to indicate a statistically significant difference. Analyses were performed using SPSS (v28.0; IBM Corp.) R (v4.2.1; Posit Software, PBC) and GraphPad Prism (v10.0; Dotmatics).

Results

Patient characteristics. A total of 186 patients with EGFR-mutant (exon 19 deletion or L858R) NSCLC and 1-10 newly diagnosed BMs were included in this dual-center retrospective analysis. All patients received first-line osimertinib (80 mg daily). Based on the timing of the first SRS relative to osimertinib initiation, patients were categorized into three cohorts of 62 patients each: The immediate SRS cohort (SRS within ≤4 weeks), the early-consolidation SRS cohort (SRS within 4-12 weeks) and the salvage SRS cohort (SRS >12 weeks after starting osimertinib and only upon intracranial progression). Baseline demographic and clinical characteristics were well-balanced across the three cohorts, with no statistically significant differences in age, sex, smoking history, Karnofsky Performance Status (KPS), EGFR mutation subtype, presence of extracranial metastases, number or volume of BMs or neurological symptoms at baseline (all $P>0.05$; Table I).

Survival outcomes. The primary endpoint, iPFS, differed significantly among the three cohorts (log-rank $\chi^2=62.98$; $P<0.001$). The median iPFS demonstrated a clear gradient: 27.0 months in the immediate SRS cohort, 22.5 months in the early-consolidation SRS cohort and 15.7 months in the salvage SRS cohort (Table II; Fig. 1). Pairwise comparisons are detailed in Table II. Compared with the salvage SRS strategy, the immediate SRS strategy was associated with a significantly reduced risk of intracranial progression or mortality (HR=0.292; 95% CI, 0.191-0.448; $P<0.001$). The early-consolidation SRS strategy also indicated a superior iPFS compared with the salvage strategy (HR=0.398; 95% CI, 0.268-0.592; $P<0.001$). Furthermore, the immediate SRS strategy was associated with

Table I. Baseline clinicopathological characteristics of patients in the immediate, early-consolidation and salvage SRS cohorts.

Characteristic	Immediate SRS (n=62)	Early-consolidation SRS (n=62)	Salvage SRS (n=62)	χ^2 value	P-value
Age, years				0.626	0.731
<65	44 (71.0)	46 (74.2)	42 (67.7)		
≥65	18 (29.0)	16 (25.8)	20 (32.3)		
Sex				0.131	0.936
Male	26 (41.9)	28 (45.2)	27 (43.5)		
Female	36 (58.1)	34 (54.8)	35 (56.5)		
Smoking history				0.607	0.738
Never	43 (69.4)	45 (72.6)	41 (66.1)		
Former/current	19 (30.6)	17 (27.4)	21 (33.9)		
KPS				0.779	0.678
≥80	49 (79.0)	51 (82.3)	47 (75.8)		
<80	13 (21.0)	11 (17.7)	15 (24.2)		
EGFR mutation subtype				0.305	0.858
Exon 19 deletion	36 (58.1)	33 (53.2)	35 (56.5)		
L858R	26 (41.9)	29 (46.8)	27 (43.5)		
Extracranial metastases at baseline				0.559	0.756
Absent	34 (54.8)	31 (50.0)	30 (48.4)		
Present	28 (45.2)	31 (50.0)	32 (51.6)		
Number of brain metastases				0.438	0.803
1-4	48 (77.4)	50 (80.6)	47 (75.8)		
5-10	14 (22.6)	12 (19.4)	15 (24.2)		
Largest brain metastasis diameter, cm				0.590	0.744
≤2.0	42 (67.7)	44 (71.0)	40 (64.5)		
>2.0	20 (32.3)	18 (29.0)	22 (35.5)		
Cumulative intracranial tumor volume, cm^3				0.564	0.754
<5	40 (64.5)	42 (67.7)	38 (61.3)		
≥5	22 (35.5)	20 (32.3)	24 (38.7)		
Neurological symptoms at baseline				0.576	0.750
Absent	41 (66.1)	43 (69.4)	39 (62.9)		
Present	21 (33.9)	19 (30.6)	23 (37.1)		

Data are presented as n (%). SRS, stereotactic radiosurgery; KPS, Karnofsky Performance Status.

a longer iPFS compared with the early-consolidation strategy (HR=0.569; 95% CI: 0.391-0.827; P<0.01). A consistent survival benefit for earlier SRS intervention was also observed for OS and PFS. For OS, the three-group comparison was significant (log-rank χ^2=32.12; P<0.001; Fig. 2), with median OS times of 42.2, 39.4 and 35.3 months for the immediate, early-consolidation and salvage cohorts, respectively. For PFS, the three-group comparison was also significant (log-rank χ^2=61.91; P<0.001; Fig. 3), with corresponding median PFS times of 25.3, 20.7 and 14.5 months. All pre-specified pairwise comparisons for both OS and PFS demonstrated significant differences favoring earlier SRS timing, with detailed HRs, CIs and P-values provided in Table II.

Intracranial tumor response. The depth of intracranial response, assessed per RANO-BM criteria, varied with the timing of SRS (Table III). The intracranial complete response (CR) rate was 25.8% (16/62) in the immediate SRS cohort, 16.1% (10/62) in the early-consolidation cohort and 8.1% (5/62) in the salvage cohort (P<0.05). Similarly, the ORR was 82.3, 77.4 and 62.9% in the immediate, early-consolidation and salvage cohorts, respectively (P<0.05).

Safety profile. The combination of osimertinib and SRS was well-tolerated across all cohorts (Table IV). The incidence of grade ≥3 AEs was similar among groups (immediate, 29.0%; early-consolidation, 25.8%; salvage, 24.2%; P>0.05). The rate of symptomatic radiation necrosis was low and not significantly different (immediate, 4.8%; early-consolidation, 3.2%; salvage, 3.2%; P>0.05). The profiles of common osimertinib-related AEs, such as rash, diarrhea and paronychia, were comparable.

Table II. Pairwise comparisons of survival outcomes (iPFS, OS and PFS) among the immediate, early-consolidation and salvage stereotactic radiosurgery cohorts.

Comparison	Endpoint	Median, months	HR	95% CI	P-value
Immediate vs. salvage	iPFS	27.0 vs. 15.7	0.292	0.191-0.448	<0.001
	OS	42.2 vs. 35.3	0.402	0.270-0.598	<0.001
	PFS	25.3 vs. 14.5	0.295	0.192-0.451	<0.001
Early-consolidation vs. salvage	iPFS	22.5 vs. 15.7	0.398	0.268-0.592	<0.001
	OS	39.4 vs. 35.3	0.521	0.357-0.760	<0.001
	PFS	20.7 vs. 14.5	0.409	0.276-0.606	<0.001
Immediate vs. early-consolidation	iPFS	27.0 vs. 22.5	0.569	0.391-0.827	0.001
	OS	42.2 vs. 39.4	0.632	0.433-0.923	0.012
	PFS	25.3 vs. 20.7	0.560	0.384-0.815	0.001

HR, hazard ratio; CI, confidence interval; iPFS, intracranial progression-free survival; OS, overall survival; PFS, progression-free survival.

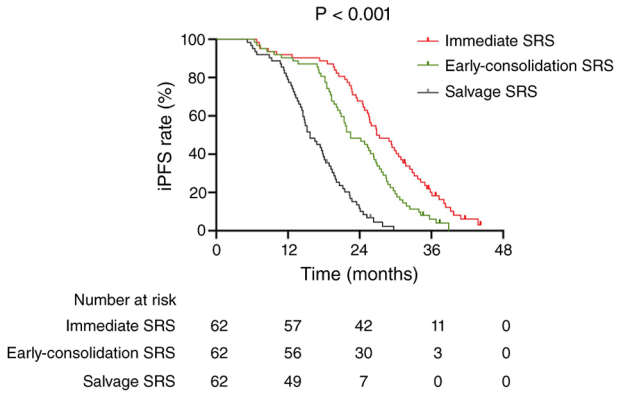

Figure 1. Kaplan-Meier curves for median iPFS. Immediate SRS, 27.0 months; early-consolidation SRS, 22.5 months; salvage SRS, 15.7 months (log-rank χ^2=62.98; P<0.001). SRS, stereotactic radiosurgery; iPFS, intracranial progression-free survival.

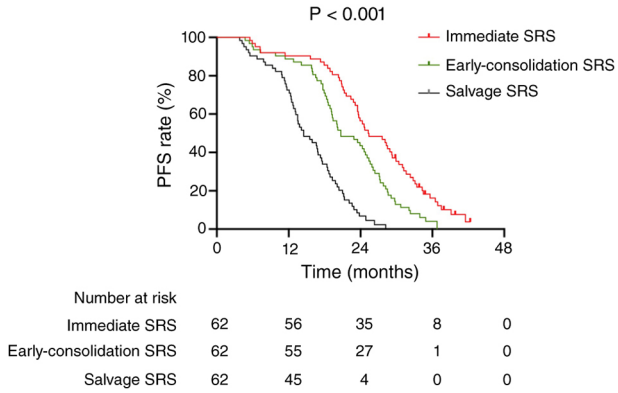

Figure 3. Kaplan-Meier curves for median PFS. Immediate SRS, 25.3 months; early-Consolidation SRS, 20.7 months; salvage SRS, 14.5 months (log-rank χ^2=61.91; P<0.001). PFS, progression-free survival; SRS, stereotactic radiosurgery.

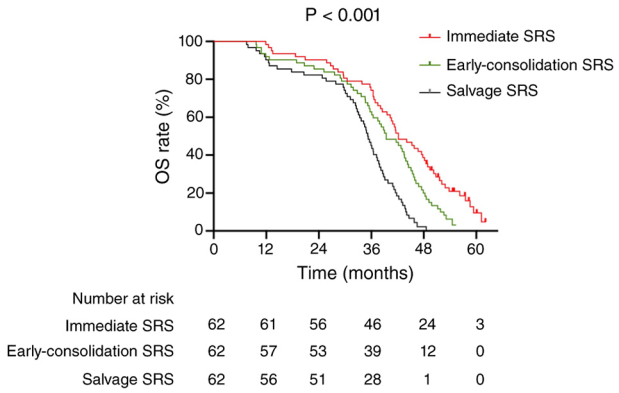

Figure 2. Kaplan-Meier curves for median OS. Immediate SRS, 42.2 months; early-consolidation SRS, 39.4 months; salvage SRS, 35.3 months (log-rank χ^2=32.12; P<0.001). OS, overall survival; SRS, stereotactic radiosurgery.

Multivariable and subgroup analyses. In a multivariable Cox regression model adjusting for age, sex, number of BMs, extracranial metastases, KPS, EGFR subtype and neurological symptoms, both the immediate SRS (adjusted HR=0.350; 95% CI: 0.220-0.556; P<0.001) and early-consolidation SRS (adjusted HR=0.475; 95% CI: 0.308-0.734; P<0.01) strategies remained independent predictors of longer iPFS compared with the salvage strategy (Table V). Similar independent protective effects were observed for OS and PFS (Tables SI and SII).

Prespecified subgroup analysis for the comparison of immediate vs. salvage SRS is presented in a forest plot (Fig. 4). The benefit of the immediate strategy (HR<1) was consistent across all subgroups analyzed. A significant interaction was observed (P<0.05), indicating a greater magnitude of benefit in patients with 1-4 BMs (HR=0.26; 95% CI, 0.17-0.40) compared with those with 5-10 metastases (HR=0.45; 95% CI, 0.26-0.78).

Sensitivity analysis with PSM. To account for potential baseline confounders, 1:1 PSM was performed separately for the comparisons of 'immediate vs. salvage' and 'early-consolidation vs. salvage' on seven key variables. After matching, all SMDs were <0.1, indicating good balance (Tables SIII and SIV). The survival benefits were robustly replicated in the matched cohorts. In the matched 'immediate vs. salvage' analysis (n=48 per group), the HR for iPFS was 0.300 (95% CI, 0.190-0.474; P<0.001). In the matched 'early-consolidation vs. salvage'

Table III. Best intracranial response per Response Assessment in Neuro-Oncology Brain Metastases criteria.

Response	Immediate SRS (n=62)	Early-consolidation SRS (n=62)	Salvage SRS (n=62)	P-value
CR	16 (25.8)	10 (16.1)	5 (8.1)	0.030
PR	35 (56.5)	38 (61.3)	34 (54.8)	0.751
SD	10 (16.1)	13 (21.0)	18 (29.0)	0.216
PD	1 (1.6)	1 (1.6)	5 (8.1)	0.219
ORR	51 (82.3)	48 (77.4)	39 (62.9)	0.037
DCR	61 (98.4)	61 (98.4)	57 (91.9)	0.219

Data are presented as n (%). CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate; SRS, stereotactic radiosurgery.

Table IV. Incidence of grade ≥3 AEs.

AE	Immediate SRS (n=62)	Early-consolidation SRS (n=62)	Salvage SRS (n=62)	P-value
Any grade ≥3 AE	18 (29.0)	16 (25.8)	15 (24.2)	0.824
Symptomatic radiation necrosis	3 (4.8)	2 (3.2)	2 (3.2)	>0.999
Rash	6 (9.7)	7 (11.3)	5 (8.1)	0.832
Diarrhea	5 (8.1)	4 (6.5)	3 (4.8)	0.930
Paronychia	2 (3.2)	3 (4.8)	1 (1.6)	0.872
Oral mucositis	2 (3.2)	1 (1.6)	1 (1.6)	>0.999
Fatigue	3 (4.8)	2 (3.2)	4 (6.5)	0.910
Increased AST/ALT	2 (3.2)	3 (4.8)	2 (3.2)	>0.999
Interstitial lung disease (any grade)	1 (1.6)	0 (0.0)	1 (1.6)	>0.999

Data are presented as n (%). AE, adverse event; AST, aspartate aminotransferase; ALT, alanine aminotransferase; SRS, stereotactic radiosurgery.

analysis (n=48 per group), the HR for iPFS was 0.420 (95% CI, 0.270-0.653; P<0.001; Table SV).

Comparison with published clinical studies. To contextualize the findings, the present results were systematically compared with published studies evaluating SRS timing in combination with EGFR-TKIs for EGFR-mutant NSCLC BMs (27-31). As summarized in Table SVI, all included studies demonstrated a survival benefit for earlier SRS intervention compared with salvage therapy, consistent with the present results (27,29,30,31). Notably, the majority of previous studies grouped all early SRS interventions into a single 'upfront' category, without further stratifying by timing within the first 12 weeks of TKI initiation (29,30).

Discussion

The present dual-center retrospective cohort study provides novel and clinically relevant evidence addressing a pivotal question in the management of EGFR-mutant NSCLC with BMs: The optimal timing for integrating SRS with first-line osimertinib. By prospectively defining and comparing three distinct intervention windows: Immediate (≤4 weeks), early-consolidation (4-12 weeks) and salvage (>12 weeks upon progression), the present study demonstrates a clear, graded survival benefit favoring earlier SRS intervention. The core finding of the present study is that the 'immediate SRS' strategy, implemented within the first 4 weeks of TKI initiation, yields the most favorable outcomes, markedly surpassing not only the salvage approach but also the early-consolidation strategy within a 12-week window. This suggests the existence of a 'hyper-acute' therapeutic phase where combined modality therapy may be particularly synergistic.

The superiority of early local therapy combined with EGFR-TKIs for BMs has been suggested in the era of first- and second-generation TKIs (27,28). However, with the advent of osimertinib, which possesses superior CNS penetration, the necessity and optimal timing of upfront SRS became debated. Some retrospective analyses, such as the study by Yu *et al* (29) reported that upfront cranial radiotherapy improved iPFS in patients treated with osimertinib but did not stratify the 'early' period into more granular interval. Similarly, a study by Zhao *et al* (30) demonstrated that upfront cranial local therapy (including SRS and/or surgery) was associated with improved overall survival in patients receiving osimertinib, but that study combined various radiotherapy modalities and heterogeneous timing windows. The present study advances this field by quantitatively demonstrating that the benefit of early intervention is not binary, but exists on a continuum, with the greatest magnitude observed when SRS is delivered concurrently or in

Table V. Multivariable Cox regression analysis for intracranial progression-free survival.

Variable	Adjusted HR	95% CI	P-value
Treatment cohort			
Salvage SRS	1.000		
Immediate SRS	0.350	0.220-0.556	<0.001
Early-consolidation SRS	0.475	0.308-0.734	0.001
Age, years			
<65	1.000		
≥65	1.148	0.837-1.574	0.390
Sex			
Male	1.000		
Female	0.919	0.681-1.240	0.577
Number of brain metastases			
1-4	1.000		
5-10	1.523	1.101-2.105	0.011
Extracranial metastases			
Absent	1.000		
Present	1.315	0.975-1.775	0.072
KPS			
≥80	1.000		
<80	1.551	1.112-2.163	0.010
EGFR mutation subtype			
Exon 19 deletion	1.000		
L858R	1.080	0.802-1.454	0.624
Neurological symptoms at baseline			
Absent	1.000		
Present	1.211	0.889-1.650	0.226

CI, confidence interval; HR, hazard ratio; KPS, Karnofsky Performance Stastus; EGFR, epidermal growth factor receptor.

very close succession with osimertinib initiation (HR for iPFS, immediate vs. salvage=0.292). This finding challenges the notion that waiting 1-3 months to assess TKI response before considering SRS is a neutral strategy; instead, it may forfeit a notable portion of the potential survival gain. To the best of our knowledge, the present study is the first to demonstrate an additional benefit for SRS delivered within the first 4 weeks of osimertinib initiation compared with SRS delivered between 4 and 12 weeks. This finding suggests the existence of a narrow window of maximal therapeutic synergy between osimertinib and SRS, which has not been previously characterized.

The notable difference in outcomes between the immediate and early-consolidation groups (43% reduction in intracranial progression risk) is a key and novel contribution. This suggests that the biological window for maximal synergy may be brief. Several non-mutually exclusive mechanisms could underpin this observation. First, initiating SRS when the tumor burden is at its nadir following rapid cytoreduction by osimertinib may allow for more effective eradication of residual, potentially resistant clones before they expand (32). Second, radiation-induced disruption of the blood-brain barrier in the hyper-acute phase may further enhance the delivery and intratumoral concentration of osimertinib (33). Third, there is preclinical evidence that EGFR-TKIs can act as radiosensitizers, and this effect might be most potent when tumor cells are actively proliferating under TKI pressure before entering a quiescent state (34). The significantly higher CR rate observed in the immediate group (25.8 vs. 16.1% in early-consolidation and 8.1% in salvage) provides clinical corroboration for a deeper and more robust tumor response with ultra-early combination.

The present results align with and extend the findings of the recent TURBO-NSCLC multi-institutional analysis, which concluded that upfront SRS with CNS-penetrant TKIs notably improved time to CNS progression compared with TKI monotherapy (31). However, the present study offers a higher resolution view within the upfront strategy, indicating that 'upfront' should ideally mean 'immediate'. Furthermore, the notable OS benefit associated with earlier SRS (median OS, 42.2, 39.4 and 35.3 months for immediate, early-consolidation and salvage groups, respectively) translates the intracranial control advantage into a tangible survival gain. This OS benefit may be mediated not only by delayed intracranial failure but also by the reduction in the subsequent need for salvage whole-brain radiotherapy, as suggested by other studies, thereby preserving neurocognitive function and quality of

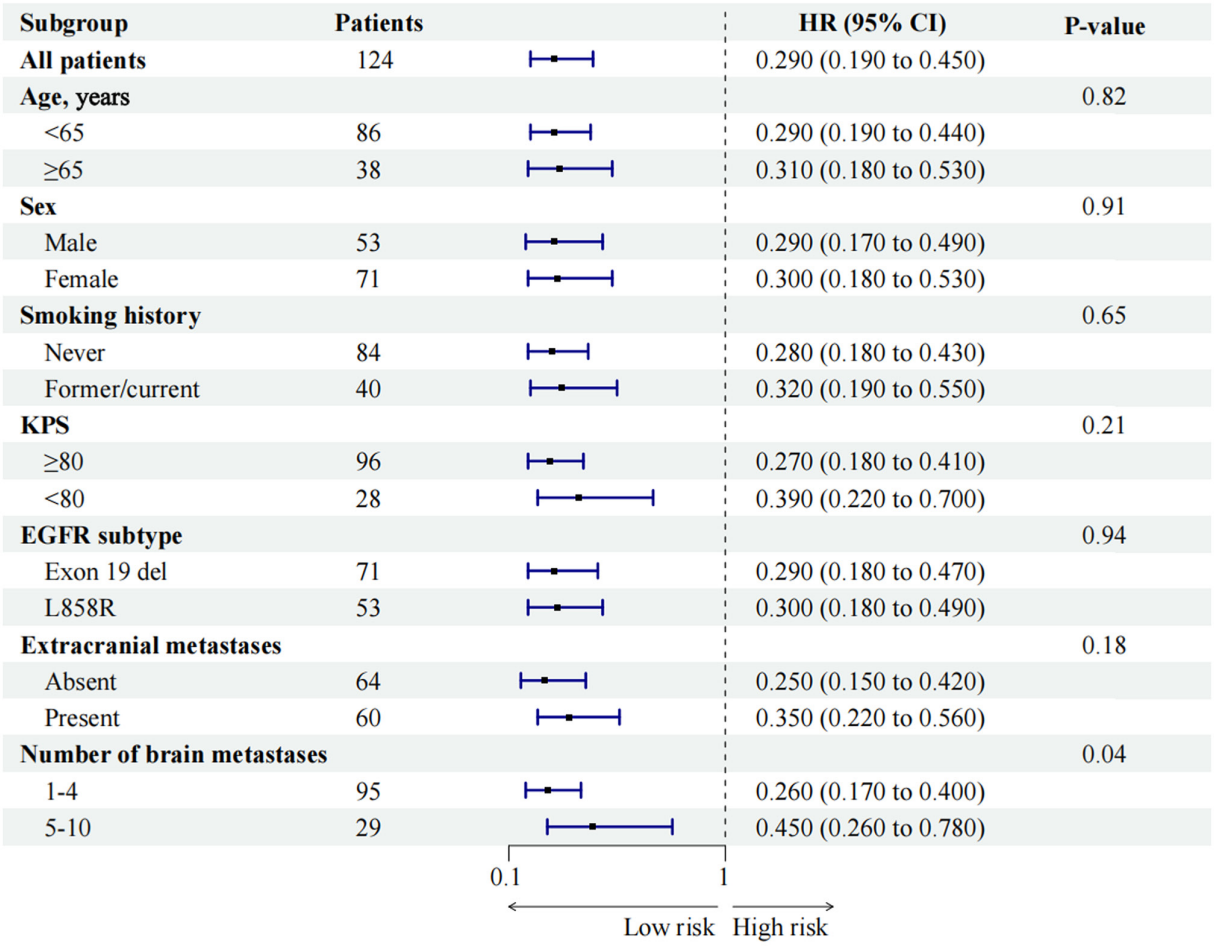

Figure 4. Forest plot of subgroup analyses for iPFS (immediate vs. salvage SRS). The benefit was consistent across subgroups. A significant interaction was observed for the number of brain metastases (interaction P=0.04), with a greater magnitude of benefit in patients with 1-4 metastases (HR=0.26; 95% CI: 0.17-0.40) than in those with 5-10 metastases (HR=0.45; 95% CI: 0.26-0.78). HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Status; Exon 19 del, exon 19 deletion.

life, which are crucial for maintaining effective systemic therapy (35-37).

The subgroup analysis revealed a more pronounced benefit for immediate SRS in patients with 1-4 BMs (interaction P=0.04) and is therefore clinically relevant. This finding supports a precision-based approach, suggesting that patients with limited intracranial disease burden stand to gain the most from an aggressive, ultra-early combined strategy. This is intuitive, as SRS is most logistically feasible and has the most favorable therapeutic index in the oligometastatic setting (38). The consistent benefit across all other subgroups reinforces the general applicability of the early intervention principle. The reassuring safety profile is paramount for adopting this strategy. The comparable rates of grade ≥3 AEs and symptomatic radiation necrosis across all three groups confirm that the addition of SRS, even in the immediate setting, does not incur unacceptable toxicity beyond that expected from either modality alone. This aligns with the growing body of literature affirming the safety of combining SRS with EGFR-TKIs (39,40).

The present study has several limitations inherent to its retrospective design. First, the sample size of 186 patients, while notable for this highly specific patient population (EGFR-mutant NSCLC with 1-10 newly diagnosed BMs receiving first-line osimertinib), is relatively modest. To mitigate potential selection bias and confounding, consecutive eligible patients from two centers were enrolled, and a strict, predefined inclusion and exclusion criteria was applied and performed rigorous multivariable Cox regression analysis as well as 1:1 PSM to balance baseline characteristics between groups. All SMDs after matching were <0.1, indicating good balance. Second, the specific timing within the salvage group was heterogeneous, reflecting real-world practice where intracranial progression occurs at varying intervals. Third, neurocognitive outcomes and detailed patient-reported quality of life measures were not systematically collected, which are important endpoints when evaluating brain-directed therapies. Finally, while the present dual-center design and long median follow-up of 43.5 months strengthen the validity of the present findings, validation in larger, prospective, multi-center trials is warranted. Additionally, the lack of large public datasets containing detailed intracranial treatment sequencing and efficacy data limits the ability to perform cross-population bioinformatic validation of the present results.

In conclusion, the present study provides compelling evidence that timing of SRS integration with first-line osimertinib is a key determinant of outcome for patients with EGFR-mutant NSCLC and BMs. An 'immediate' SRS strategy

(within 4 weeks) is associated with significantly superior intracranial control, OS and depth of response compared with both later early-consolidation and salvage approaches, without increasing severe toxicity. These findings strongly argue against a default strategy of deferring SRS and instead support proactive, ultra-early combined modality therapy as a new standard consideration, particularly for patients with limited brain metastatic burden. For patients with EGFR-mutant NSCLC and BMs, upfront SRS integrated within the first 12 weeks of first-line osimertinib, particularly within 4 weeks, is associated with superior intracranial control and survival compared to a salvage approach, without increasing severe toxicity. The present evidence should inform multidisciplinary decision-making and guide the design of future prospective trials aiming to optimize combination therapy sequencing.

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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

XZ and XL completed data curation, formal statistical analysis and methodology development, and wrote the original manuscript. XY was responsible for study conceptualization, funding acquisition, project administration and supervision of manuscript revision. JM participated in clinical assessment and eligibility screening of patients, independently verified the clinical accuracy of treatment and response-assessment data against original medical records, pathology and neuroimaging reports, contributed to clinical data interpretation, and critically revised the manuscript for clinical content. GH participated in research methodology design, and was responsible for result validation and data visualization. XZ and XY confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei (approval no. CZX2024180) and the Institutional Review Board of Tianjin Medical University Cancer Institute and Hospital (approval no. EK20250091). The requirement for informed consent to participate in this retrospective study was waived by the ethics committees.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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