Efficacy and safety of online adaptive magnetic resonance-guided fractionated stereotactic radiotherapy for brain metastases in non-small cell lung cancer (GASTO-1075): a single-arm, phase 2 trial

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Summary

Background Brain metastases (BMs) in non-small cell lung cancer (NSCLC) are associated with poor prognosis and quality of life (QoL). This study aimed to evaluate the efficacy and safety of online adaptive MR-guided fractionated stereotactic radiotherapy (FSRT) using a 1.5 T MR-Linac in this subgroup of patients.

Methods This single-arm phase 2 trial was conducted at Sun Yat-sen University Cancer Centre. Patients aged 18–75 years with NSCLC, 1–10 BMs, and an ECOG status of 0–1 were included. Key exclusion criteria included inability to undergo contrast-enhanced MRI and contraindications to bevacizumab. Patients received 30 Gy adaptive FSRT in 5 daily fractions under real-time MR guidance, with bevacizumab before (day 1) and after (day 21) FSRT. The primary endpoint was 1-year intracranial progression-free survival (IPFS); secondary endpoints included objective response rate (ORR), 1-year progression-free survival (PFS), 1-year overall survival (OS), treatment-related toxicities, and QoL. All enrolled patients were included in primary and safety analyses. This trial is registered with Clinicaltrials.gov, NCT04946019.

Findings Between June 10th, 2021 and June 29th, 2023, 70 patients were assessed for eligibility and 55 patients were enrolled (median follow-up: 22.3 months). The median age was 58 years (IQR: 51–65), with 33% (18/55) female patients, and 82% (45/55) presenting with adenocarcinoma. The 1-year IPFS rate was 78.7% (95% CI, 68.2%–90.7%), with a median IPFS of 21.9 months (95% CI, 13.8–30.1 months). The 1-year PFS rate was 63.5% (95% CI: 51.8%–78.2%), and OS was 82.4% (95% CI: 72.6%–93.6%). The ORR reached 78% (95% CI: 65.0%–88.2%). Treatment-related toxicity was minimal, with only one case (2%) of grade 1 radiation necrosis. QoL improved steadily, with the Global Health Status score increasing from 65.67 ± 16.97 to 79.33 ± 8.79 at 6 months post FSRT ($p < 0.0001$).

Interpretation Online adaptive FSRT using a 1.5 T MR-Linac has demonstrated effectiveness and good tolerability for BMs in patients with NSCLC. However, the relatively small sample size and short follow-up may affect result generalizability. Further randomised studies are warranted to confirm these findings and establish optimal treatment protocols.

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Research in context

Evidence before this study

A comprehensive search of the PubMed database was conducted up to March 1, 2025. The search terms utilized were "brain metastases (BMs)", "non-small cell lung cancer (NSCLC)", and "stereotactic radiotherapy (SRT)", with no language restrictions imposed. The evidence has underscored the limitations associated with Whole-brain radiotherapy (WBRT). These limitations include the occurrence of neurocognitive decline and a reduction in the quality of life (QoL) of patients. As a consequence, there has been a discernible shift in the therapeutic approach towards stereotactic radiotherapy (SRT) or fractionated SRT (FSRT). In comparison to single fraction SRT, FSRT has demonstrated comparable local control and a reduction in the incidence of radiation necrosis. Intrafraction motion is typically not a major concern for BMs given the use of thermoplastic masks to immobilize the patient's head and negligible physiologic motion during FSRT. Nevertheless, inter-fractional variations in tumor dimensions can present challenges across a wide range of clinical scenarios. Magnetic resonance-guided radiation therapy (MRgRT) confers a distinct advantage in the daily visualization of tumors not only during the actual treatment delivery (intra-fractional) but also between treatment sessions (inter-fractional). This characteristic of MRgRT unlocks the possibility of leveraging real time information throughout the treatment course, which has the potential to impact patient outcomes.

Added value of this study

This phase II trial represents the initial attempt to assess the therapeutic effectiveness of online adaptive MR-guided FSRT carried out with a 1.5 T MR-Linac for the treatment of BMs in NSCLC patients. The research showed a promising 1-year intracranial progression-free survival (IPFS) rate of 78.7%. Additionally, the treatment related toxicity was tolerable, and the patients' QoL showed a consistent improvement after online adaptive MR-guided FSRT. By conducting an exploratory analysis of baseline MRI parameters, we determined K^{trans} to be a potential predictor of treatment response. Specifically, BM lesions with high K^{trans} values attained an objective response rate of 90%.

Implications of all the available evidence

Our study demonstrated that MR-guided adaptive FSRT could be a novel and promising approach in the management of BMs from NSCLC, optimizing outcomes while maintaining neurological function, which significantly enriches the existing evidence on NSCLC BMs treatment. Future research should prioritize randomized trials comparing MR-guided FSRT with standard linac-based approaches, validate imaging biomarkers in different populations, and explore combinations with targeted therapies or immunotherapy.

Introduction

Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases and is the leading cause of cancer-related mortality worldwide.[1] Brain metastases (BMs) develop in approximately 20%–50% of patients with NSCLC during disease progression, significantly impacting both prognosis and quality of life (QoL).[2] Due to the challenges posed by the blood–brain barrier (BBB) in limiting the effectiveness of conventional chemotherapy and early targeted therapies, radiotherapy has become a cornerstone in the management of BMs.[3] Whole-brain radiotherapy (WBRT) has traditionally been the standard treatment modality. However, numerous studies have associated extensive brain radiotherapy to adverse neuropsychological outcomes and a decline in overall QoL.[4–7] As a result, stereotactic radiotherapy (SRT) is becoming the preferred approach for treating BMs.[8]

While SRT has proven effective, determining the optimal dose and fractionation schedule that balances effective intracranial disease control with QoL preservation remains a challenge.[9] Evidence suggests a dose–response relationship, in which higher SRT doses improve local control but also increase the risk of toxicity.[10] Even with doses recommended by RTOG 9005, radiation-induced necrosis rates for large BMs can reach 24–38% within one year.[11,12] For larger lesions or those near critical structures, fractionated SRT (FSRT) is typically preferred, delivering 30–35 Gy over 3–5 fractions rather than as a single treatment.[13] Research indicates that FSRT may provide better local control and a lower risk of radiation necrosis compared to single-session SRT.[14] However, treatment-induced changes in tumor characteristics during therapy can affect targeting accuracy and treatment efficacy.[15] The need for re-

planning during FSRT for BMs has not been fully explored.

A major challenge in applying FSRT is the limited soft tissue contrast offered by cone beam computed tomography (CBCT), which hinders precise treatment delivery. In contrast, magnetic resonance imaging (MRI) provides superior soft tissue contrast, making it an essential tool for FSRT. In recent years, MR-guided radiotherapy has gained significant attention as a promising method for enhancing treatment precision.[16,17] The integration of MRI with linear accelerators, known as MR-Linac, has opened new possibilities for treating BMs. This innovative approach allows for daily position verification and enables adaptive radiotherapy, adjusting treatment plans based on real-time imaging feedback. The potential of MR-Linac to improve normal tissue protection and disease control has attracted significant interest.[17] Our previous research demonstrated that FSRT with MR-guidance led to significant tumor volume reductions and anatomical shifts, particularly in patients with multiple lesions or peritumoral edema.[18] This underscores the importance of adaptive planning, which not only improved target coverage but also reduced whole-brain dose compared to non-adaptive plans.[18]

Thus, we hypothesised that adaptive MR-guided FSRT could enhance treatment accuracy and improve patients' QoL. In this study, we evaluated the efficacy and safety of FSRT using a 1.5 T MR-Linac for BMs in patients with NSCLC.

Methods

Study design and participants

This is a prospective, phase II study conducted at Sun Yat-sen University Cancer Center. The inclusion criteria were: 1) age 18–75 years; 2) histological or cytological diagnosis of NSCLC; 3) 1–10 metastases on contrast-enhanced MRI; 4) Eastern Cooperative Oncology Group (ECOG) performance status score of 0–1; 5) all the BMs were measurable according to the RECIST criteria; 6) visible BMs on T2-weighted imaging; 7) at least one BM with a diameter greater than 2 cm; 8) stable extracranial disease; 9) adequate bone marrow, hepatic and renal function. The exclusion criteria were: 1) inability to undergo contrast-enhanced MRI; 2) contraindications to bevacizumab (Beva), including a history of cardiac or thromboembolic events, uncontrolled high blood pressure, or hemorrhagic brain metastasis; 3) prior brain metastasis surgery or radiotherapy; 4) presence of leptomeningeal metastases; 5) chemotherapy was either initiated within 7 days of patient enrollment or scheduled to coincide with the radiotherapy period; 6) prior malignancies (except curable non-melanoma skin cancer or cervical in situ).

The study received approval from the Clinical Research Ethics Committee of Sun Yat-sen University Cancer Center (B2022-126-01) and was carried out in compliance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. The study protocol is registered on ClinicalTrials.gov (NCT04946019).

Procedures

Bevacizumab was given intravenously at a dose of 7.5 mg/kg on Day 1 and Day 21 according to our previous study.[19] FSRT was initiated within one week off the first bevacizumab injection. Mannitol and dexamethasone were prescribed as needed to alleviate symptoms associated with cranial tumors.

For systemic therapies, patients were categorised into two groups based on their EGFR/ALK status: 1) EGFR/ALK-positive patients: Symptomatic patients started Beva + FSRT within one week of enrollment, continuing their targeted therapy concurrently. Asymptomatic patients received Beva + FSRT concurrently with their ongoing targeted therapy. 2) EGFR/ALK-negative patients: Symptomatic patients started Beva + FSRT within one week of enrollment, whereas asymptomatic patients began Beva + FSRT three weeks after their last systemic therapy. All patients were re-evaluated three weeks after Beva + FSRT to determine when to resume systemic treatment.

FSRT was delivered using a 1.5 T Elekta Unity MR-Linac (Elekta AB, Stockholm, Sweden). All patients received a prescribed dose of 30 Gy in five fractions, which is the standard radiotherapy for BMs in the United States.[20] The treatment strategy is illustrated in Supplementary Figure S1.

The MR-Linac workflow is illustrated in Supplementary Figure S2. Simulated CT and MRI scans were performed for all patients before treatment. The scans were acquired in the supine position with a slice thickness of 1 mm (Philips Brilliance™ CT and Ingenia 3.0 T MRI). Patient positioning was optimised using a head mask and customised foam devices. The MRI protocol included T1/T2-weighted sequences, gadolinium-enhanced T1-weighted imaging (T1C), and FLAIR imaging. The above images were transferred into the Monaco treatment planning system (TPS) (v5.40.02, Elekta AB). Simulated CT and MRI images were fused for registration. The gross tumor volume (GTV) and organs at risk (OARs) were outlined on CT images, with reference to T1C and T2 MRI scans. The planning target volume (PTV) was created by expanding the GTV by 2 mm in all directions.

During FSRT, online T2 images guided adaptive GTV delineation. Daily session MRI was integrated into the Monaco TPS for automated rigid registration with planning CT during adaptive planning. Manual fine-tuning was performed as needed. Elekta Unity's TPS offers two workflows: Adapt to Position (ATP) for aligning targets and OARs via virtual couch shifts, and

Adapt to Shape (ATS) for creating a new plan based on daily anatomy.[21] ATP or ATS was chosen depending on clinical necessity.

The refined plan was evaluation and approval by a radiation oncologist. Independent dose verification was performed using a second planning system (Raystation) without magnetic field interference to confirm significant changes. After validation, the plan was transferred to MOSAIQ and implemented on Unity MR-Linac. A post-treatment MRI was acquired after beam on.

The prescribed dose was 30 Gy in 5 daily fractions, ensuring 95% of the PTV and 99% of the GTV received the full dose, with the maximum dose kept below 110% of the prescribed level. OAR dose limits followed ICRU Report 83[22] and institutional FSRT guidelines: lens (5 Gy), and optic nerves (30 Gy). To minimize neurological toxicity, dose constraints for the brainstem were stratified based on the distance of metastases from the brainstem: 1. For metastases >1 cm away from the brainstem, the dose constraint was brainstem V20 <30% and Dmax <30 Gy; 2. For metastases ≤1 cm from the brainstem or located within the brainstem, the dose constraint was V30 <30% and Dmax <32 Gy.

Metrics for GTV and peritumoral edema variability during FSRT

GTV and edema volumes were assessed on all MR images. Relative volume change (ΔV) was calculated as the percentage difference from the simulation images, where negative values indicate shrinkage and positive values indicated growth:

$$\Delta V = \frac{V_{daily} - V_{reference}}{V_{reference}} \times 100\%$$

The dice similarity coefficient (DSC) was used to quantify the overlap between daily and reference contours from session MR and CT images. It is defined as:

$$DSC = \frac{2 \times (V_A \cap V_B)}{V_A + V_B}$$

where $V_A \cap V_B$ is the intersection of volumes A and B. A DSC of 0 indicates no overlap, and 1 indicates perfect overlap. Higher values represent better contour alignment.

Toxicity and adverse events

During weekly visits and post-treatment evaluations, treatment-related adverse events were meticulously recorded. Acute toxicities were evaluated from the start of Beva injections to 90 days post-treatment, with continued monitoring for late toxicities. Toxicities were graded according to the National Cancer Institute's CTCAE version 5.0. Radiation necrosis criteria included: 1) ring-enhancing lesions demonstrating enlargement with surrounding edema, and at least 2 follow-up MRIs showed no evidence of ongoing progressive disease (PD); 2) advanced MRI (including dynamic susceptibility contrast perfusion imaging or diffusion-weighted imaging) suggestive of radiation necrosis.[23,24] Radiation necrosis was graded 1–5 according to the CTCAE guidelines.

Response evaluation, quality of life, and follow-up

Two months after completing brain radiotherapy, treatment response was evaluated using contrast-enhanced MRI and diffusion imaging. Patients were monitored every 3 months for 2 years, every 6 months for 3–5 years, and annually thereafter. Each follow-up included a review of the medical history, conducting physical and neurological exams, performing contrast-enhanced brain MRI, and obtaining CT/PET-CT of the chest and abdomen. A senior radiation oncologist and radiologist reviewed brain MRI images. The RANO-BM criteria were used to evaluate the response of BM lesions, categorised as complete response (CR), partial response (PR), stable disease (SD), or PD. In-field tumor progression was defined as a ≥20% increase in the sum of the longest diameters (SLD) of measurable target lesions from baseline.

The EORTC QLQ-C30 v3.0 questionnaire was used to assess QoL at various time points: at enrollment, and at 1-, 3-, and 6-months post-treatment. Higher scores in general QoL measures indicate improved status, while higher symptom burden reflects poorer condition.

MR imaging, region of interest (ROI) delineation, and image analysis

MRI was performed at 3.0 T MRI scanner (Discovery MR750w 3.0 T, GE Medical System, Milwaukee, Wisconsin, USA). Except conventional MRI, DCE-MRI and DW-MRI were also conducted before treatment. The predictive value of MRI parameters for tumor response was evaluated. ROIs encompassing tumors were delineated on contrast-enhanced T1-weighted images by an experienced radiation oncologist and radiologist. In patients with multiple BMs, each metastasis was outlined as a separate ROI.

DWI images were analysed on the AW4.4 workstation (GE Healthcare, Milwaukee, WI) using Functool software, which automatically generated apparent diffusion coefficient (ADC) maps and calculated ADC values within the ROIs. Using the two-compartment Extended Tofts model in conjunction with DCE data and T1 maps, parametric metrics such as K^{trans}, K_{ep}, V_e, and V_p were derived on a DCE analysis workstation (United-Imaging Healthcare, Shanghai, China). Mean values of the above parameters were used for the analysis.

Outcomes

The primary outcome was to assess 1-year intracranial progression-free survival (IPFS), which was calculated

from the completion of radiotherapy to the first occurrence of either intracranial progression or death. The appearance of new brain lesions or tumor progression indicated intracranial progressive disease. The secondary endpoints included 1-year progression-free survival (PFS), 1-year overall survival (OS), objective response rate (ORR), toxicity, QoL, and target coverage and dose to normal tissues. All time-to-event endpoints (IPFS, PFS, and OS) were calculated from the completion of radiotherapy. ORR was defined as the proportion of patients achieving CR and PR, and the 95% CI was calculated via Clopper-Pearson exact method.

Statistical analysis

Previous studies reported a 43.3% 1-year IPFS for patients with NSCLC BMs following FSRT.[25] The study aimed to improve the 1-year IPFS to 62% based on our preliminary experience with MR-guided FSRT. Assuming a 1-year enrollment and a 1-year follow-up, with a one-sided $\alpha = 0.05$ and power $(1-\beta) = 0.90$,[26] a minimum of 50 patients was required. Accounting for a 10% dropout rate, 56 participants were planned for enrollment. Survival rates and median survival time with 95% confidence intervals (CI) were estimated using the Kaplan–Meier method in SPSS. The 95% CIs for the median were calculated according to SPSS's default settings. GTV, peritumoral edema volume, and QoL across varying time points were compared using the Wilcoxon matched-pairs signed-rank test. When the symmetry assumption was violated, the sign test was used instead. To conduct an exploratory analysis of the predictive performance of MRI parameters, receiver operating characteristic (ROC) analysis and the area under the ROC curve (AUC) were used. Optimal cut-off value for imaging biomarkers were identified via Youden's index using ROC curves. Statistical analyses were conducted using SPSS 22.0, with $p < 0.05$ considered statistically significant.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (B Q, DQ W, and H L) had full access to the dataset of the study and had final responsibility for the decision to submit for publication.

Results

Patient characteristics

Between June 10th, 2021 and June 29th, 2023, 70 patients were assessed for eligibility and 55 patients were enrolled (Fig. 1). The median age was 58 years (interquartile range [IQR]: 51–65), with the majority diagnosed with adenocarcinoma (45/55, 82%). EGFR or ALK mutations were identified in 28 patients (51%). Before treatment, 31 patients (56%) presented with symptomatic brain metastases. The median number of intracranial metastatic lesions was 2 (IQR: 1–3); 44 patients (80%) had fewer than 5 lesions. Additionally, 40 patients (73%) had no evidence of extracranial metastases. Patient characteristics are detailed in Table 1.

Systemic treatments

Details of the systemic treatments are provided in Supplementary Table S1. Among the 28 EGFR/ALK-positive patients, 89% (25/28) continued targeted therapy during FSRT, while 11% (3/28) began targeted

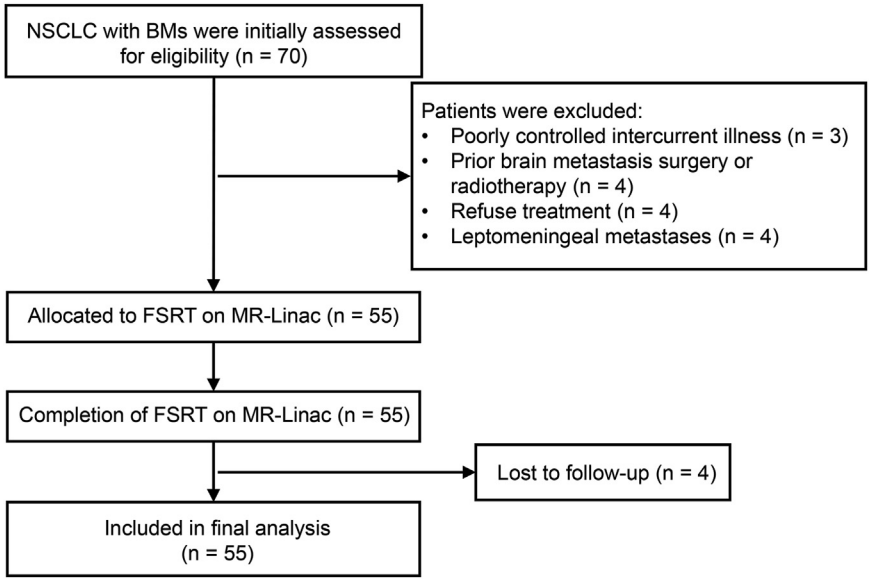


Fig. 1: Flow diagram of patient enrollment.

Characteristic	(No. %)
Patients	55
Lesions	163
Age	
Median, IQR, years	58 (51–65)
≥70	7 (13%)
<70	48 (87%)
Sex	
Female	18 (33%)
Male	37 (67%)
ECOG score	
0	38 (69%)
1	17 (31%)
Histology	
Adenocarcinoma	45 (82%)
Squamous cell	5 (9%)
Other	5 (9%)
EGFR/ALK mutation	
Positive	28 (51%)
Negative	27 (49%)
Symptomatic brain metastases	
Yes	31 (56%)
No	24 (44%)
Number of brain metastases	
≥5	11 (20%)
<5	44 (80%)
Extracranial metastases	
Yes	15 (27%)
No	40 (73%)
Presence of edema	
Yes	39 (71%)
No	16 (29%)
GTV	
Median, IQR, cm^3	9.11 (5.54–26.77)
≥10	25 (46%)
<10	30 (54%)
Distribution of brain metastases	
Supratentorial	137 (84%)
Infratentorial	26 (16%)

Abbreviations: IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume.

Table 1: **Clinical characteristics of included patients.**

therapy after completing FSRT. When these patients were initially diagnosed with NSCLC, the results of EGFR/ALK testing were pending. Since they presented with symptomatic brain metastases, immediate treatment was required. Given the urgency, we opted to initiate FSRT first. After the completion of FSRT, the EGFR/ALK test results became available, and we promptly administered the targeted drugs. This sequence of treatment was a result of the specific diagnostic situation and the need to address the symptomatic brain metastases promptly. It does not violate the overall treatment protocol. Of the 27 EGFR/ALK-negative patients, 19% (5/27) received chemotherapy or immunotherapy before FSRT due to concurrent extracranial metastases continuing systemic therapy thereafter. The remaining 70% (19/27) initiated systemic therapy exclusively after FSRT.

Online adaptive MR-guided FSRT

All enrolled patients completed the FSRT protocol of 30 Gy in 5 fractions with the 1.5 T MR-Linac. The targets coverage and dose to OARs of the reference plan and adaptive plan are shown in Supplementary Table S2. Of the total 275 treatment fractions, 54.2% (149/275) were delivered with ATP, and 45.8% (126/275) used ATS. The distribution of ATP and ATS across the treatment fractions is shown in Supplementary Figure S3. The average daily MR-Linac-based adaptive FSRT treatment time was 21 min.

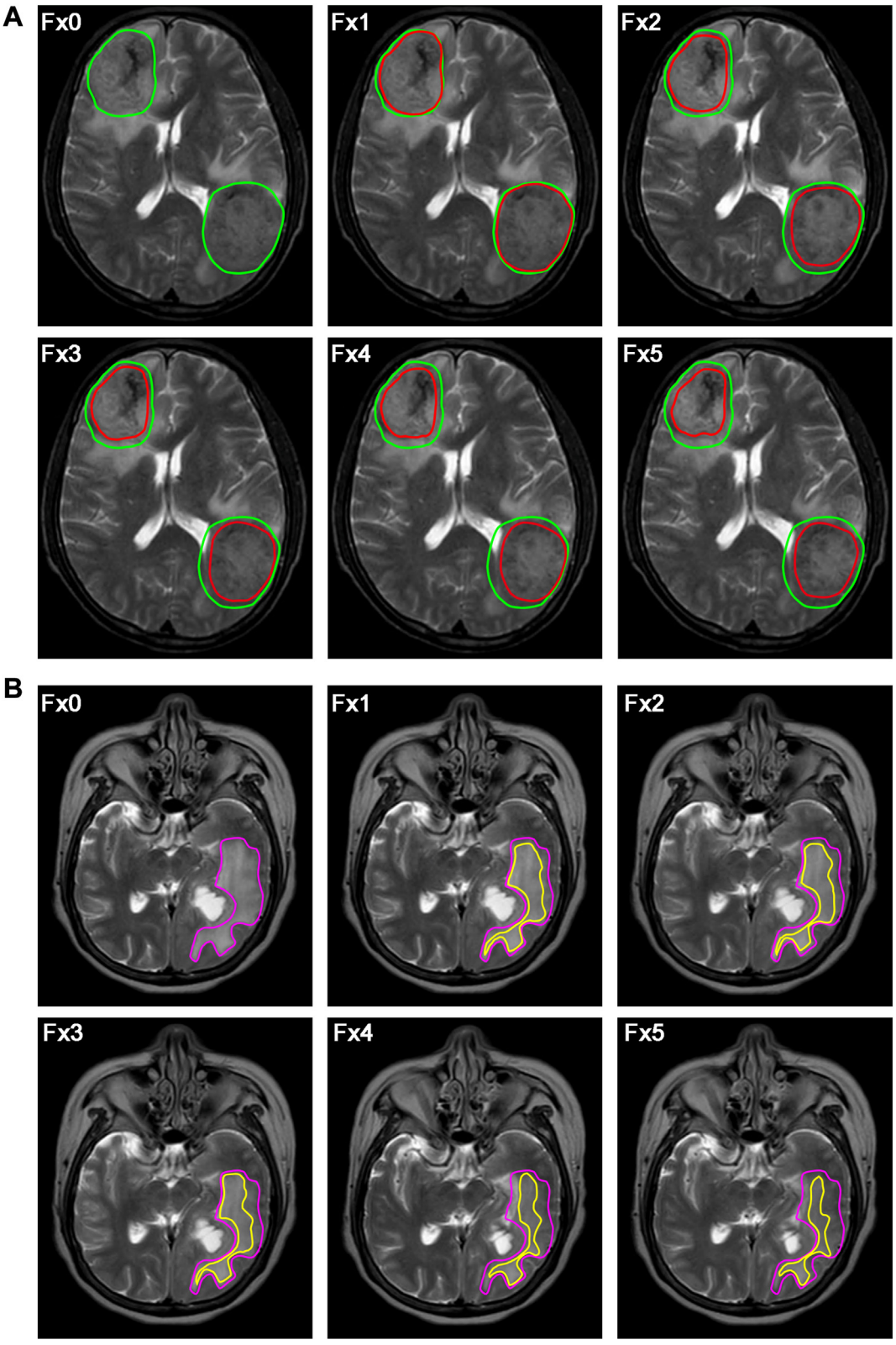
The median pre-treatment GTV was 9.11 cm^3 (IQR: 5.54–26.77 cm^3). From Fx2 to Fx5, compared to baseline (Fx0), the median reduction in GTV was 0.30 cm^3 (95% CI: 0.11–1.19) at Fx2, 0.47 cm^3 (95% CI: 0.34–1.89) at Fx3, 0.58 cm^3 (95% CI: 0.48–2.22) at Fx4, and 0.78 cm^3 (95% CI: 0.64–2.80) at Fx5. These reductions were statistically significant ($p = 0.020$ at Fx2, $p = 0.0052$ at Fx3, $p = 0.0028$ at Fx4, and $p = 0.0022$ at Fx5) (Supplementary Figure S4A, Fig. 2A). The median DSC index for GTV across fractions was 0.91 (IQR: 0.85–0.97) at Fx1, 0.83 (IQR: 0.81–0.93) at Fx2, 0.79 (IQR: 0.72–0.91) at Fx3, 0.77 (IQR: 0.69–0.89) at Fx4, and 0.73 (IQR: 0.68–0.88) at Fx5 (Supplementary Figure S4B).

Perilesional edema was present in 39 patients, with a median volume of 34.07 cm^3 (IQR: 6.38–82.05 cm^3) at Fx0. From Fx1 to Fx5, compared to baseline (Fx0), the median reduction in edema volume was 2.31 cm^3 (95% CI: 2.25–9.89) at Fx1, 3.72 cm^3 (95% CI: 3.55–11.95) at Fx2, 4.65 cm^3 (95% CI: 4.95–14.89) at Fx3, 5.98 cm^3 (95% CI: 6.82–17.93) at Fx4, and 6.59 cm^3 (95% CI: 8.33–21.05) at Fx5. These reductions were statistically significant ($p = 0.0026$ at Fx1, $p = 0.00060$ at Fx2, $p = 0.00030$ at Fx3, $p < 0.0001$ at Fx4 and Fx5) (Supplementary Figure S4C, Fig. 2B). The median DSC index for perilesional edema was 0.86 (IQR: 0.80–0.92) at Fx1, 0.82 (IQR: 0.75–0.86) at Fx2, 0.78 (IQR: 0.73–0.83) at Fx3, 0.74 (IQR: 0.70–0.83) at Fx4, and 0.73 (IQR: 0.67–0.79) at Fx5 (Supplementary Figure S4D).

Treatment efficacy and survival outcomes

At the 2-month post-treatment evaluation, 43 patients (78%) achieved a PR, while 12 patients (22%) had SD, resulting in an ORR of 78% (43/55, 95% CI: 65.0%–88.2%) (Fig. 3). Two patients developed progressive systemic disease despite ongoing systemic therapy following brain radiotherapy. Both fatalities were attributed to extracranial progression: Patient 1 to pulmonary metastases and Patient 2 to hepatic metastatic disease.

As of the data cut-off date (July 17, 2024), the median follow-up duration was 22.3 months (IQR: 14.9–24.9 months). The study met its primary endpoint, achieving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a 1-year IPFS rate of 78.7% (95% CI, 68.2%–90.7%; one-side $p < 0.0001$, compared with the previous 1-year IPFS rate in literature) and a median IPFS of 21.9 months (95% CI: 13.8–30.1 months) (Fig. 4A). Regarding secondary endpoints, the 1-year PFS rate was 63.5% (95% CI: 51.8%–78.2%), with a median PFS of 19.6 months (95% CI: 11.6–27.7 months) (Fig. 4B). The 1-year OS rate was 82.4% (95% CI: 72.6%–93.6%), with a median OS of 28.4 months (95% CI: 19.0–37.9 months) (Fig. 4C). Censoring details for all endpoints are summarised in Supplementary Table S3.

Further analysis stratified patients by the EGFR/ALK mutation, assessing IPFS, PFS, and OS accordingly. As presented in the Supplementary Figure S5, results show no significant differences in treatment efficacy between the two groups.

Safety and quality of life

Among the included patients, 3 (5%) experienced grade 1 (G1) mild dizziness. Only one patient (2%) developed G1 radiation necrosis. No instances of meningeal or parenchymal hemorrhage were detected on MRI through the follow-up period.

The QLQ-C30 scores of the included patients, as shown in Fig. 5, indicate that their QoL continuously improved after treatment. The improvement was particularly notable in patients with symptomatic BMs. After 6 months post FSRT, patients' QoL significantly improved compared to baseline, with higher general QoL scores and reduced symptom burden (see Supplementary Table S4).

Failure pattens and salvage treatments

During the follow-up, intracranial progression was observed in 10 patients (18%), all of whom developed new lesions at novel sites. Subsequent management strategies included salvage FSRT for new lesions in 4 patients and a transition to alternative or higher-dose targeted therapies for 4 patients. 2 patients declined any form of salvage treatment (Fig. 3B).

Predictive value of baseline DCE-MRI and DW-MRI parameters for tumor response

A total of 26 patients with 46 BMs underwent DCE-MRI and DW-MRI scans. The baseline K^{trans}, K_{ep}, V_e, V_p, and ADC of BMs were $68.88 \pm 52.75 \times 10^{-3}$/min, $615.07 \pm 450.27 \times 10^{-3}$/min, $172.78 \pm 168.40 \times 10^{-3}$, $6.14 \pm 10.16 \times 10^{-3}$, and $1156.33 \pm 380.54 \times 10^{-6}$ mm^2/s, respectively. Supplementary Table S5 shows the ROC analysis of K^{trans}, K_{ep}, V_e, V_p, and ADC values to predict tumor response. The baseline K^{trans} value for BMs achieved the highest AUC at 0.78 (95% CI: 0.63–0.92, $p < 0.0001$) (Supplementary Figure S6). The AUC values for V_e and V_p were moderate, at 0.72 and 0.70, respectively. The statistically compared among the AUC values of different MRI parameters were listed in Supplementary Table S6. The optimal cut-off value for K^{trans} was 37.29×10^{-3}/min (sensitivity: 76.5%, [95% CI: 60.00%–87.56%]; specificity: 75.0%, [95% CI: 46.77%–91.11%]).

Based on the cut-off value of K^{trans}, BMs were classified into two groups: low-K^{trans} group (n = 17, $K^{trans} \leq 37.29 \times 10^{-3}$/min) and high-$K^{trans}$ group (n = 29, $K^{trans} > 37.29 \times 10^{-3}$/min). The high-$K^{trans}$ group showed a significantly higher ORR to FSRT compared to the low-K^{trans} group (90% [26/29, 95% CI: 72.6%–97.8%] vs 47% [8/17, 95% CI: 23.0%–72.2%], $p = 0.0010$). The following figures show DCE images and ADC map of a high-K^{trans} BM ($K^{trans} = 238.74 \times 10^{-3}$/min) and in a low-$K^{trans}$ BM ($K^{trans} = 6.32 \times 10^{-3}$/min) (Fig. 6A). The high-K^{trans} BM achieved PR after FSRT, while the low-K^{trans} BM achieved SD (Fig. 6B).

Discussion

This phase II study evaluated the therapeutic efficacy of online adaptive MR-guided FSRT using a 1.5 T MR-Linac for treating BMs in patients with NSCLC. The study demonstrated promising results, with an ORR of 78% (43/55), a median IPFS of 21.9 months, a median PFS of 19.6 months, and a median OS of 28.4 months. Treatment-related toxicities were minimal, with only one patient (2%) experiencing G1 radiation necrosis. Notable reductions in tumor and edema volumes led to improvements in neurological function and quality of life in patients with symptomatic brain metastases. To our knowledge, this is the first phase II study to assess the efficacy of daily adaptive MR-guided FSRT using a 1.5 T MR-Linac for patients with NSCLC BMs.

In our study, the median number of intracranial metastatic lesions was 2 (IQR: 1–3); at least one BM with a diameter greater than 2 cm and 44 patients (80%) had fewer than 5 lesions. stereotactic radiosurgery (SRS) and FSRT are increasingly favored for the treatment of multiple BMs in NSCLC due to their ability to achieve better local control while minimizing the neurocognitive decline associated with WBRT.[8,27] Retrospective study has shown that FSRT offers comparable intracranial control and survival rates to single-session SRT while reducing the risk of radiation necrosis, making it a preferred treatment option.[14] The results of administering radiosurgery alone are similar in patients with

Fig. 2: (A and B) Axial MRI slices from two patients illustrating changes in GTVs and perilesional edema over the course of treatment fractions. (A) The GTVs (green: baseline, red: fractions 1–5) demonstrated a marked reduction as treatment progressed. (B) The volumes of perilesional edema (purple: baseline, yellow: fractions 1–5) showed a significant decrease with continued treatment. For comparative analysis, baseline contours (fraction 0, Fx0) were co-registered to each daily MR scan. GTV, gross tumor volume.

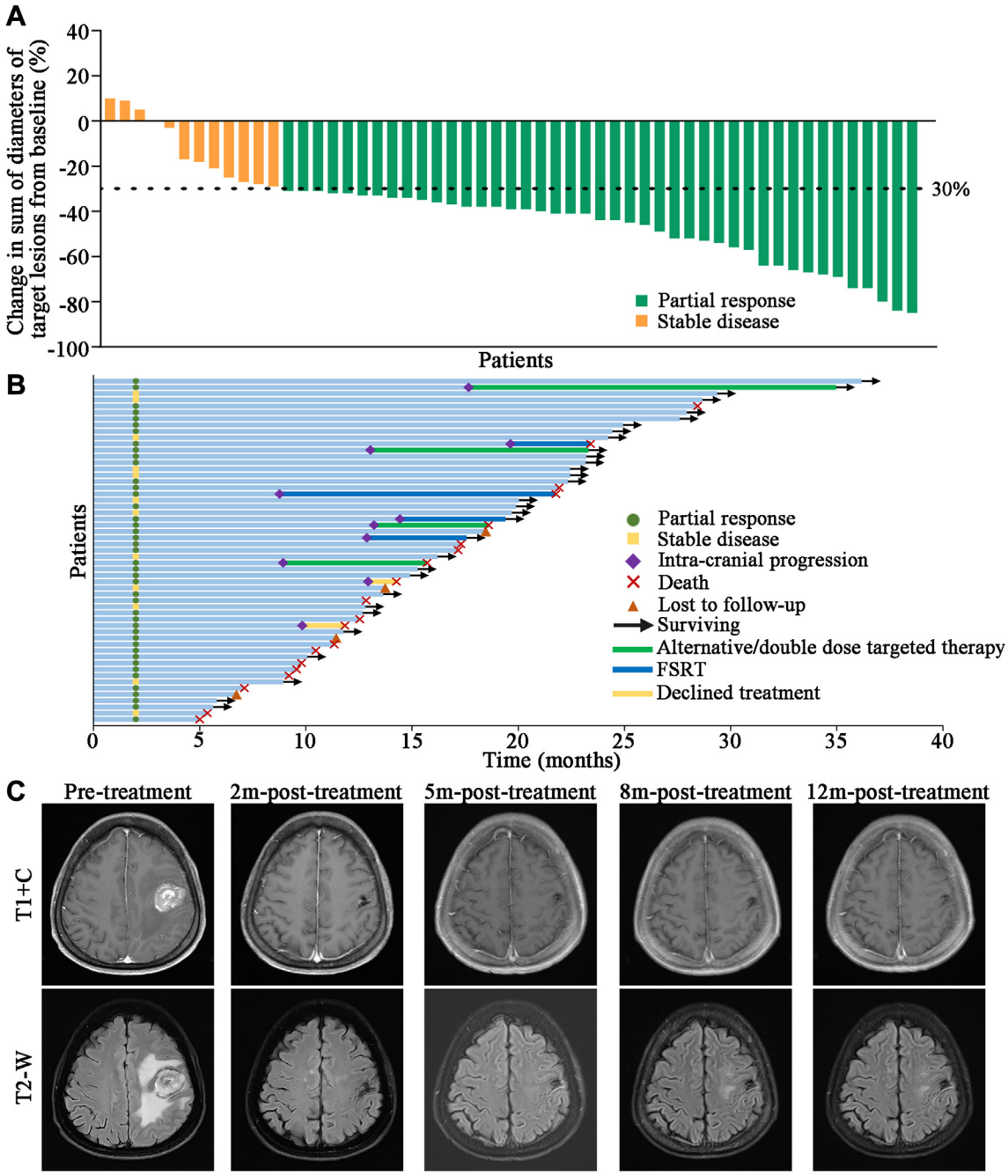

Fig. 3: (A) Waterfall plot illustrating the response of target BMs. The dashed horizontal line indicates the 30% tumor shrinkage threshold required for a partial response. (B) Swimming plot depicting intracranial response, survival, and subsequent salvage treatments following fractionated stereotactic radiotherapy (FSRT) with the MR-Linac. (C) Magnetic resonance imaging (MRI) of a patient with a left frontal lobe BM demonstrated a partial response (PR) 2 months after FSRT with the MR-Linac, with the lesion remaining locally stable at the 1-year follow-up. BMs, brain metastases.

5–10 metastases and in those with 2–4,[28] without differences in neurological toxicity between the two groups.[29] Even in selected patients with 10 or more metastases treated with radiosurgery, there was no difference in either outcome or neurological side effects compared to those with 2–9 metastases.[30] However, challenges remain, particularly the issue of interfractional target displacement and tumor regression

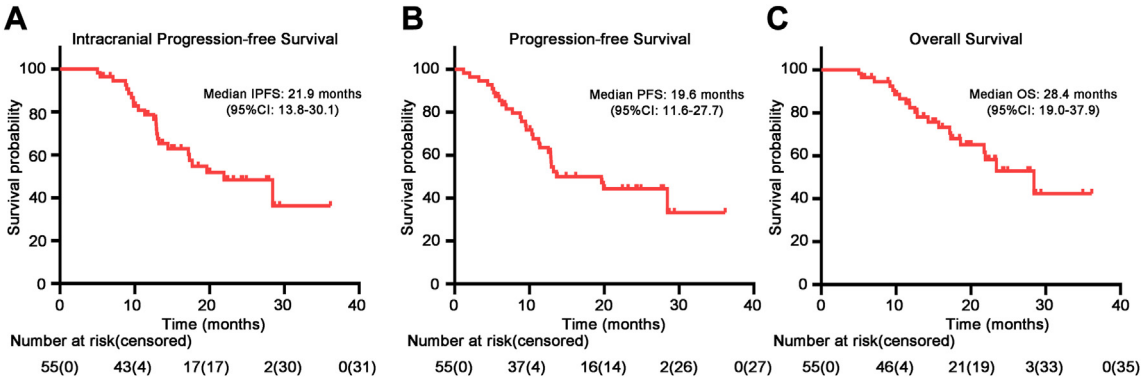

Fig. 4: Survival analyses of BMs patients received FSRT in MR-Linac. Kaplan–Meier survival curves for intracranial progression-free survival (A), progression-free survival (B), and overall survival (C). BMs, brain metastases.

during FSRT, which can affect treatment precision.[18,31,32] The incidence of radiation necrosis following SRS/FSRT ranges from 3% to 50%, with significant neurological symptoms occurring in approximately 50% of cases.[33–35] Our cohort demonstrated a 1-year IPFS of 78.7%. The enhanced precision of MR-guided FSRT, enabling daily adaptation to anatomic changes and intrafraction motion management, likely contributed to these improvements by reducing geographic misses and permitting tighter margins. This aligns with emerging data from the 1.5 T MR-Linac consortium, which only one patient (2%) developing G1 necrosis, suggesting that precise image guidance and adaptive volume adjustments may help mitigate the risk of toxicity.

Traditional imaging techniques, such as CBCT, are limited by their indistinct soft-tissue contrast, which can hinder accurate target delineation and adjustments in brain tissue. This limitation may have contributed to poor local control in some previous studies, especially in patients with multiple brain metastases.[36,37] Research has shown that tumor volume changes during FSRT can range widely, with significant shifts in tumor position over the course of treatment.[32] Furthermore, edema volume changes have been found to correlate with shifts in tumor position, which can affect treatment accuracy and target coverage.[38] In this context, MR-guided radiotherapy, particularly the use of MR-Linac, offers promising advancement, providing superior anatomical visualization and real-time adaptive planning.[39] Our previous study demonstrated that MR-guided FSRT resulted in significant tumor volume reductions, particularly in patients with multiple lesions, and improved target coverage compared to non-adaptive treatment plans, with lower doses to surrounding brain tissue.[18]

Extensive research has explored the cellular mechanisms of angiogenesis and the therapeutic potential of anti-angiogenic agents, particularly bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF). Lévy et al.[40] conducted the REBECA phase I trial, evaluating bevacizumab combined with WBRT in patients with unresectable brain metastases from solid tumors. Among 21 patients (primarily breast cancer, with others having lung, ovarian, or unknown primary malignancies), two (11%) experienced intra-lesional hemorrhage, with no cases of parenchymal brain hemorrhage. The 3-month response rate (53%) mirrored historical outcomes for WBRT alone. A potential biological paradox exists: while radiation-induced stress may promote angiogenesis, enhancing drug delivery, disrupting angiogenesis remains critical to curbing tumor growth. Preclinical models suggest that bevacizumab preconditioning prior to chemotherapy may optimise therapeutic efficacy.[41] Given bevacizumab's long half-life (21 days),[42] sequential administration strategies warrant further exploration. The REBECA trial proposed bevacizumab initiation two weeks before WBRT to induce vascular normalization and potentiate radiation effects.[40] Safety concerns, particularly intracranial hemorrhage risk, necessitate rigorous evaluation of bevacizumab combined with radiotherapy. In recurrent malignant gliomas, bevacizumab with salvage SRS improved progression-free survival by 3.1 months versus SRS alone, with comparable grade 3–4 toxicity rates.[43] These findings support further investigation of bevacizumab with SRS or FSRT in select patients, particularly those with favorable prognostic features (e.g. RPA or GPA).

In our previous study, the combination of FSRT with bevacizumab resulted in a 1-year IPFS of 82.9%[19] significantly higher than the 34.4%–74.2% range reported in previous studies using WBRT or SRS.[44,45] Recent studies showed that bevacizumab, a VEGF inhibitor, has significant efficacy in reducing peritumoral brain edema and lowering the incidence of radiation necrosis in NSCLC patients with BMs treated with radiotherapy.[46,47] By reducing the underlying pathophysiological processes such as edema and abnormal

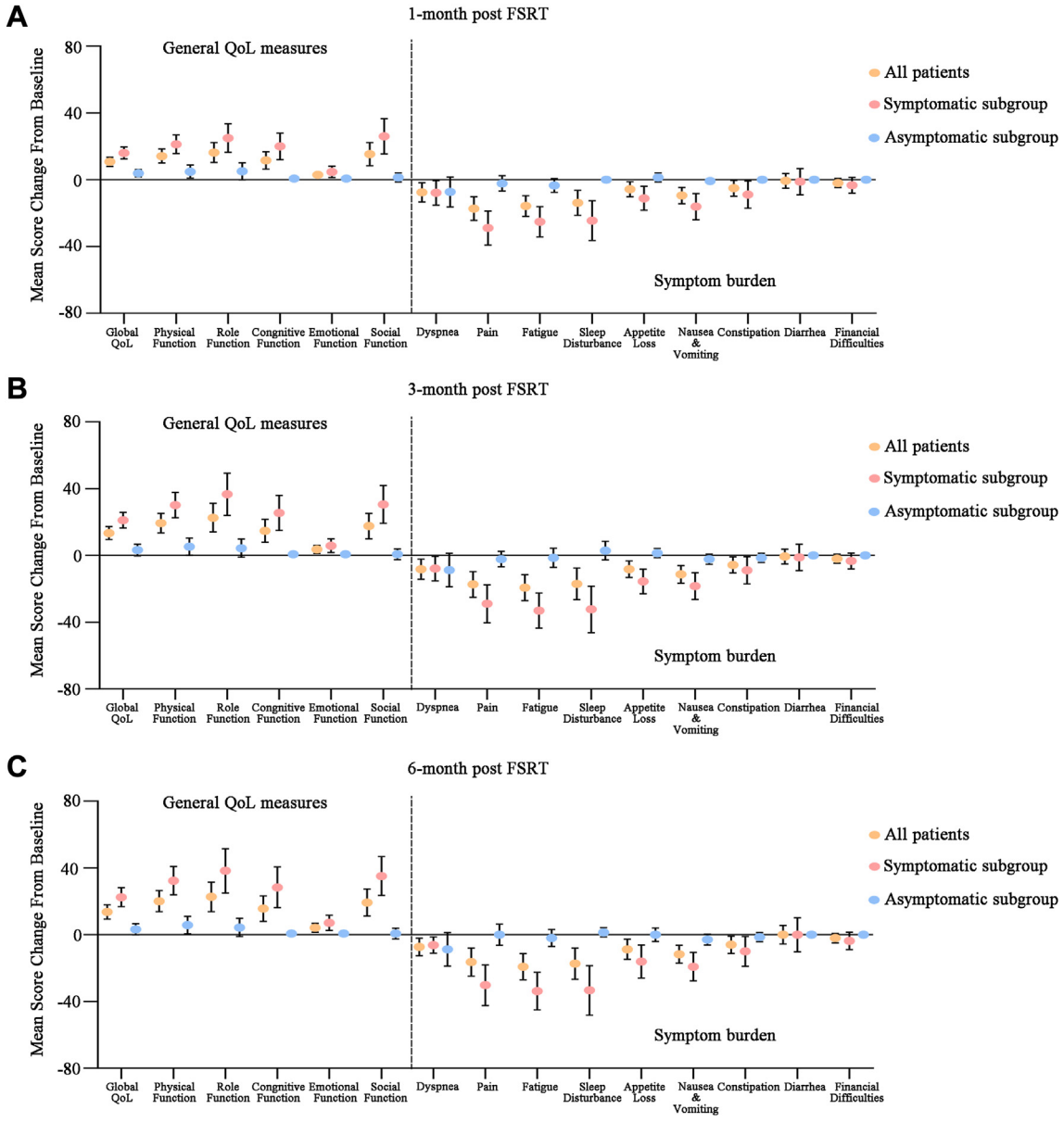

Fig. 5: The score changes of health-related QoL metrics at 1, 3, and 6-months after treatment compared to baseline (A–C). QoL improved across most metrics, with the most significant improvements observed in symptomatic patients. Error bars represent the 95% CI. QoL, quality of life.

perfusion, it provides real relief rather than masking the symptoms.[47–49] Our findings also demonstrated that MR-guided FSRT, in combination with bevacizumab, not only improved tumor control but also reduced peritumoral edema, suggesting a synergistic effect between precise MR-guided radiotherapy and anti-edema treatment. Our study also focused on patients with ≥2 cm lesions or perilesional edema, subgroups at elevated risk for symptomatic radiation necrosis, where bevacizumab may mitigate toxicity.

These results highlight the potential of MR-guided FSRT to improve both local disease control and the management of associated brain edema, thereby enhancing patient outcomes and QoL. The assessment of QoL has become increasingly important as survival rates improve for BM patients. Previous studies have shown that local treatments, including SRS or FSRT, generally offers better QoL outcomes than WBRT, which is associated with significant neurocognitive decline.[4–7] In our study, patients treated with MR-guided FSRT showed significant improvements in both QoL and neurological symptoms, particularly in those with symptomatic BMs. These improvements were likely due to substantial tumor shrinkage and reductions in

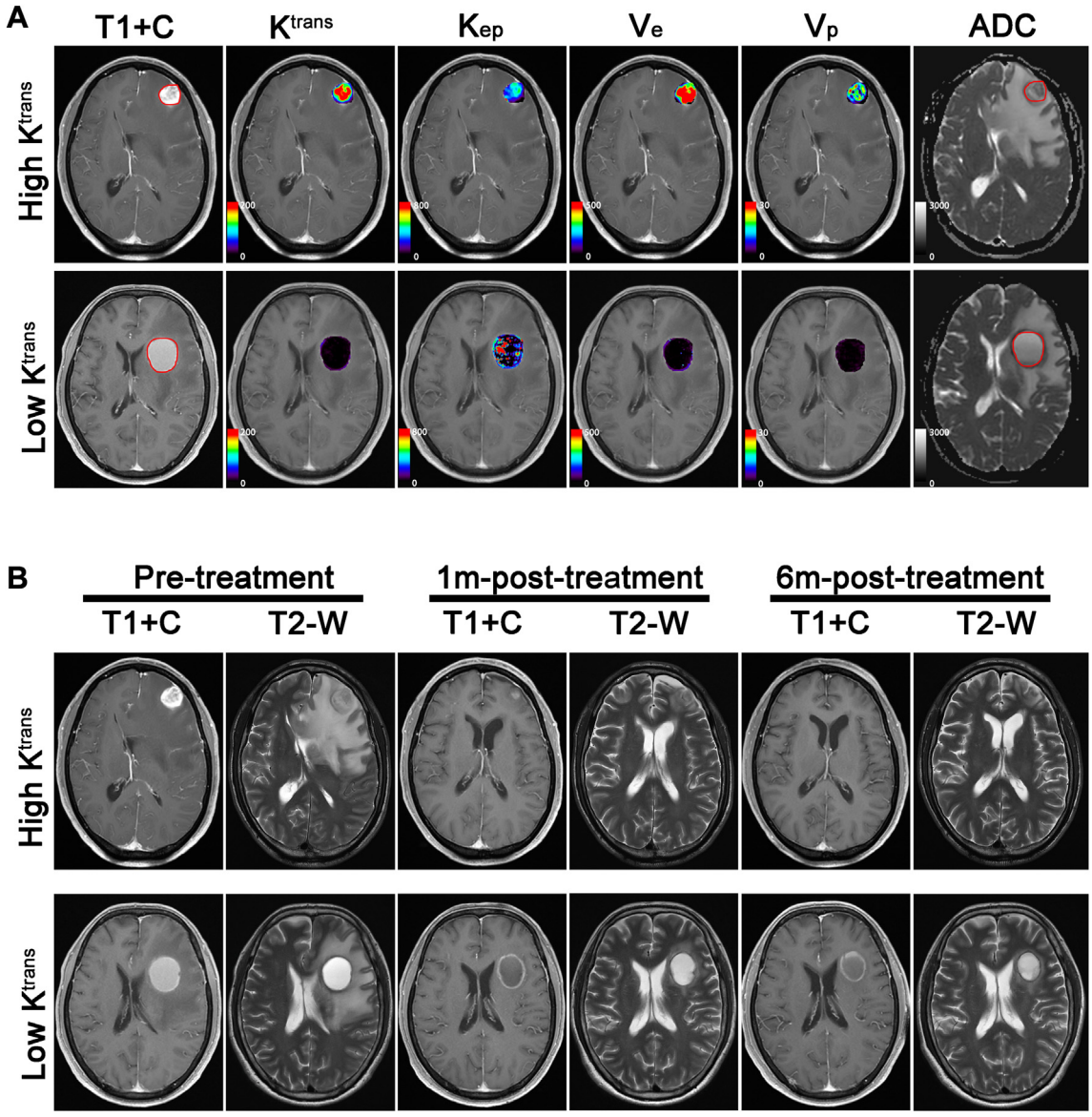

Fig. 6: (A) The baseline DCE images and ADC maps of two patients with NSCLC BMs, classified into high-K^{trans} and low-K^{trans} groups. (B) The high-K^{trans} BM lesion achieved partial response (PR) after FSRT, while the low-K^{trans} lesion remained stable disease (SD) during follow-up. FSRT, fractionated stereotactic radiotherapy; NSCLC, non-small cell lung cancer; BMs, brain metastases.

peritumoral edema, as well as favorable local control. The QLQ-C30 scores demonstrated continuous QoL improvement following treatment, with the most notable gains observed in patients with symptomatic BMs. These results underscore the importance of combining advanced MR-guided radiotherapy techniques with appropriate drug regimens to enhance both clinical outcomes and long-term QoL for NSCLC patients with BMs.

DCE-MRI is a valuable imaging technique that evaluates tumor microvascular function by assessing the pharmacokinetics of contrast agents.[50] One of the key parameters derived from DCE-MRI is K^{trans}, which reflects tumor perfusion and vascular permeability and has been identified as a potential predictor of radiotherapy response.[51] Several studies have explored the relationship between DCE-MRI parameters and tumor response to radiotherapy. Zahra et al. demonstrated that pre-treatment K^{trans} and K_{ep} significantly correlated with tumor response in cervical cancer.[52] Similarly, Ahn et al. observed that colorectal cancer xenografts with higher pre-treatment V_e and lower K_{ep} responded more favorably to therapy.[53] Consistent with these findings, our study identified pre-treatment K^{trans} as the most

predictive parameter for tumor response to MR-guided FSRT, with a sensitivity of 76.5% and specificity of 75.0%. Patients with higher pre-treatment K^{trans} values showed significantly better treatment responses, with an ORR of 90% (26/29) compared to 47% (8/17) in those with lower K^{trans} values. These results suggest the potential of K^{trans} as a biomarker to identify patients likely to benefit from MR-guided FSRT. The observed correlation between higher K^{trans} values and improved treatment response may support the hypothesis that increased tumor perfusion and oxygenation enhance radiosensitivity. Tumors with poor blood supply often experience chronic hypoxia, which diminishes oxygen free radical production and impairs the repair of radiation-induced DNA damage, fostering more resistant tumor subtypes.[54] In contrast, tumors with higher permeability, as indicated by elevated K^{trans} values, may be better oxygenated,[55] allowing for improved access to chemotherapeutic agents and enhanced radio-sensitivity.[51,56] These findings suggest a dual role for K^{trans} in predicting treatment response and guiding therapeutic strategies for patients undergoing MR-guided FSRT.

While these findings are promising, there are several limitations to this study: 1) The relatively small sample size and short follow-up period may have limited the statistical power of the analyses. 2) The absence of a comparison group treated with conventional linac-based radiotherapy necessitates further investigation. Many patients in this cohort had genetic mutations that could respond to targeted therapies, which may have influenced the outcomes. 3) The inclusion of patients with stable extracranial disease, who were able to tolerate treatment, may limit the generalizability of these findings to the broader population of NSCLC patients with brain metastases. 4) The treatment feasibility considerations influenced patient selection: the average daily MR-Linac-based adaptive FSRT treatment time was 21 min, necessitating pre-treatment evaluation to ensure patient tolerance. Consequently, the study population may have been enriched with patients experiencing mild symptoms, potentially impacting treatment outcomes. 5) The bevacizumab-FSRT combination remains investigational, this approach should be reserved for high-risk patients until validated in randomised trials and guiding future research. 6) Last but not least, since disease prevalence affects the ratio of true/false positives/negatives in their calculations, and NSCLC with BMs prevalence varies among populations, applying our results to different groups may lead to different positive predictive and negative predictive values. Further studies with larger cohorts and longer follow-up periods are needed to confirm these results and refine treatment strategies.

In conclusion, our study suggests that online adaptive FSRT using a 1.5 T MR-Linac offers a promising advancement in the management of BMs from NSCLC. The favorable results observed in IPFS and QoL, alongside a favorable toxicity profile, support the potential of this approach as a valuable addition to therapeutic options for NSCLC patients with BMs. Furthermore, high K^{trans} values in BM lesions may be correlated with a better ORR to FSRT. Larger randomised trials are required to confirm these findings and optimise treatment strategies.

Contributors

Conception of the study: B Q, DQ W, and H L. Data acquisition: All authors. Analysis of data: SY Z, SL D, BS L, YX X, B Q, DQ W, and H L. B Q, DQ W, and H L have access to and verify the underlying study data. Drafting the manuscript: All authors. Final approval of the manuscript: All authors.

Data sharing statement

The data are available upon reasonable request to the corresponding author when the publication is online.

Declaration of interests

The authors declare no potential conflicts of interest.

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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.2025.103189.

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