Case Report: iMDT corner

Reirradiation using helical tomotherapy-based hypofractionated stereotactic radiotherapy for 19 brain metastases after the second recurrence of distant brain failure: a case report and literature review

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Background: A definitive optimal oncologic care regimen for recurrent multiple brain metastases (BMs) has yet to be established, and the accrual of high-quality evidence pertaining to helical tomotherapy-based stereotactic radiotherapy (HT-SRT) in patients with BMs is needed.

Case Description: We treated a 64-year-old male smoker initially diagnosed with non-small cell lung cancer (NSCLC) with BMs, and the initial schedule involved administering linear accelerator-based hypofractionated stereotactic radiotherapy (Linac-HSRT) targeting 6 intracranial lesions. Further chemotherapy was declined due to intolerance after one cycle of paclitaxel-albumin/carboplatin. Distant brain failure (DBF) and extracranial progression emerged 3 months subsequent to the initial SRT, and helical tomotherapy-based hypofractionated stereotactic radiotherapy (HT-HSRT) was replanned to 4 BMs, while helical tomotherapy-based intensity-modulated radiotherapy was employed for the extracranial lesions. Nevertheless, reirradiation with hippocampal-sparing HT-HSRT and simultaneous memantine approach were imminently delivered for confirmed DBF, as 19 newly identified intact intracranial lesions were observed at 5 months posttreatment. As assessed by the Hopkins Verbal Learning Test Revised Total Recall test, neither severe symptomatic radionecrosis (RN) nor neurocognitive dysfunction has manifested thus far, representing a survival period of 20.5 months. In the literature review, SRT delivery schedule to BMs, strategies for managing recurrent BMs and addressing RN, along with 6 summarized published studies of HT-SRT for BM were discussed.

Conclusions: We posit that the administration of repeated SRT for recurrent BMs in a short-term interval may be viable, yet randomized, robust analyses are imperative to ascertain the potential benefits of HT-SRT in preserving neurocognition and confirm the efficacy of memantine and hippocampal avoidance during SRT.

Keywords: Brain metastases (BMs); hypofractionated stereotactic radiotherapy (HSRT); helical tomotherapy (HT); radionecrosis (RN); case report

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Introduction

Approximately 40% of lung cancer cases develop brain metastases (BMs) during the course of treatment (1). Additionally, patients with lung adenosquamous carcinoma (ASC) with BMs have a median survival time of merely 4 months (2). With advances in radiation technologies that are steadily reducing toxicities, radiotherapy for the prophylaxis and treatment of BM is of continuing interest (3). Stereotactic radiotherapy (SRT) has advanced over the past half-century, with a gradual shift in perspective that challenges the conventional practice of whole-brain radiation therapy (WBRT) for BMs (4). SRT includes conventional single-fraction stereotactic radiosurgery (SF-SRS) and hypofractionated stereotactic radiotherapy (HSRT) (5). Repeat SRT ensures high local control (LC) rates, albeit with the undeniable risk of radionecrosis (RN) (6), which is typically secondary to neurocognitive defects and reduced quality of life (QOL) (7). A positive association between hippocampal avoidance (HA), memantine during WBRT, and neurocognitive protection has been observed (8). Helical tomotherapy (HT), a distinct category of intensity-modulated radiation therapy (IMRT) has shown promising results in HA-WBRT (9). With over 10 BMs or those near the hippocampi, the strategy of protecting the hippocampi during SRS planning needs to be adopted (10,11). In a context where HT-HSRT is in its infancy, dosimetric benefits for neurocognition should be considered, but there is no definitive evidence-based algorithm for adoption. Herein, we report a case of BMs from non-small cell lung cancer (NSCLC), in which twice-occurring distant brain failure (DBF) events were intervened upon via HT-HSRT within a short time frame, which was associated with a favorable survival of 20.5 months, incredible tumor control, a prolonged freedom from DBF, acceptable QOL and a relatively preserved neurocognition. Additionally, relevant prospective cohort studies, such as the FRACTIONATE trial (12) on the comparison of SF-SRS *vs.* HSRT for BM and the NRG-BN009 study (13) on whether to continue SRS in the patients with a relapsed intracranial disease and a high BM velocity after upfront SRS, are currently underway. We hope that this case will inspire further application of HT-SRT for BMs. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2024-1151/rc).

Highlight box

Key findings

- In the patient of this manuscript, repeated salvage stereotactic radiotherapy (SRT) for brain metastases (BMs) was appropriate and such a prolonged time of freedom from distant brain failure (DBF) was achieved after the final course of SRT. Helical tomotherapy-based hypofractionated stereotactic radiotherapy (HT-HSRT) addresses the need for effective and tolerable treatment of multiple intracranial and extracranial lesions. Hippocampal avoidance and memantine during SRT may preserve the neurocognition of the patient. Whole-brain radiation therapy was postponed in this case, and a favorable survival of 20.5 months was achieved.

What is known and what is new?

- Reirradiation is being increasingly adopted for patients with recurrent multiple BMs and DBF, and HSRT can reduce the risk of radionecrosis and ensure local control similar to that of single-fraction stereotactic radiosurgery (SF-SRS).
- Herein, we report a case of BMs from non-small cell lung cancer, in which twice-occurring DBF events were intervened by HT-HSRT within a short time frame, which was associated with acceptable quality of life and relatively preserved neurocognition.

What is the implication, and what should change now?

- The administration of repeated SRT for recurrent BMs in a short interval may be viable. Theoretically, the case should exhibit a more favorable prognosis, possible treatment targets or biomarkers need to be further explored and low-toxicity, well-tolerated agents should be prioritized, regardless of the systemic therapy administered, to improve therapeutic efficacy for the patient's follow-up treatment. Randomized robust analyses are required to confirm our results.

Case presentation

Patient characteristics

A 64-year-old male with a 40-year history of smoking was admitted to Radiation Oncology Department of China-Japan Union Hospital in August 2022 for weakness of the left upper limb, accompanied by a headache and nausea. Neurological examination identified blurred consciousness, diminished muscle strength in the left upper limb, and the absence of pathological reflexes. Subsequently, intravenous contrast-enhanced cranial magnetic resonance imaging (MRI) and chest computed tomography (CT) scans were conducted, revealing multiple intracranial lesions and a mass in the upper lobe of the left lung. Fluoro-D-glucose positron emission tomography (FDG-PET) further confirmed metastases to the left hilar lymph nodes and left adrenal gland, while also demonstrating the high metabolic response of the lesions previously identified on

MRI and CT scans. ASC was confirmed via pathological and immunohistochemistry results from the left lung biopsy. Genetic testing via fluorescence *in situ* hybridization and next-generation sequencing further attested to the positive mutations in *BRCA1*, *BRCA2*, and *KRAS*, as well as the positive expression of programmed cell death ligand 1 (PD-L1), with a tumor proportion score (TPS) >50% and a combined positive score (CPS) >50. According to the ninth edition of the Tumor Node Metastasis (TNM) Classification for Lung Cancer from the International Association for the Study of Lung Cancer (IASLC), the case was classified as T3N1M1c2 (stage IVB), with a poor Karnofsky Performance Status (KPS) <70, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 3, and a diagnosis-specific graded prognostic assessment (DS-GPA) score of 0.

The first course of SRT

Surgery was declined due to worsening neurological symptoms and poor PS. Pre-radiotherapy cranial MRI with intravenous contrast revealing varying degrees of enlargement of the six intracranial masses. With a dose of 52.5 Gy in 15 fractions for the 3.3 cm lesion in the right frontal lobe and 35 Gy in 5 fractions for the remaining lesions, linear accelerator-based SRT was imminently delivered using the Edge dedicated delivery device (Varian Inc., Palo Alto, CA, USA), and complete remission (CR) for the BMs was observed on the second positioning MRI. Subsequently, immune checkpoint inhibitors (ICIs) were rejected due to economic concerns, and one cycle of paclitaxel-albumin (200 mg, days 1–3, Q21d) and carboplatin (200 mg, days 1–3, Q21d) was applied after the first irradiation. However, grade 3 upper gastrointestinal symptoms, predominantly nausea, dysphagia, and vomiting, were noted based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, so the patient abandoned further systemic therapy to avoid the intolerable toxicity.

The second course of SRT

The first re-evaluation PET-CT revealed 4 new BMs, progression of previous extracranial lesions and a CR of previous 6 BMs after 3 months of the first SRT. Half a month later, the patient requested that the systemic lesions be controlled simultaneously via radiotherapy due to intolerance to chemotherapy, and a second SRT using HT was conducted, following the patient's informed consent. A thermoplastic mask (CIVCO, Orange City, IA, USA) was implemented prior to MRI and CT simulation in the supine position, and the high-resolution CT, MRI, and PET datasets were registered in a tomotherapy treatment planning system (Hi-Art version 5.1.3, Accuray, Madison, WI, USA) for target volume delineation, 5 fractions of 30 Gy for the mass in the brainstem and 5 fractions of 35 Gy for the other 3 BMs by HT-HSRT, while a dose of 50 Gy in 20 fractions was delivered to the extracranial lesions, including masses in the upper lobe of the left lung, the left hilar lymphatic area and the left adrenal gland by HT-IMRT. All the BMs were in CR after the two SRT courses, while the lung lesion remained, so the radiographic tumor response was assessed as a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1). *Figures 1*,*2* depict the location of the gross tumor volume (GTV) and organs at risk (OARs) for the first and second courses of SRT on MRI.

The third course of SRT

In July 2023, the patient presented with dizziness and a diagnostic cranial MRI showed no involvement of the regions irradiated in the previous two radiotherapy sessions, nor of the brainstem and other critical substructures, but new multiple intracranial masses, suggesting the second DBF. Only symptomatic treatment was given to relieve the cranial pressure. Two months later, further extensive deterioration of BMs was indicated by radiographic monitoring despite stabilization of extracranial lesions, which manifested as dysphasia. A multidisciplinary team consultation was performed, which clarified the 19 visible intact BMs, some of which were close to the bilateral hippocampi on positioning MRI, and other areas mentioned above remained uninvolved. The third SRT was prepared on September 7, 2023, with intervals of 11 and 6.5 months from the first and second SRT, respectively. Then, we contoured 19 intact intracranial masses, bilateral hippocampi, optic pathway, brainstem, cochlea and brain as per the Radiation Therapy Oncology Group (RTOG) protocol adhering to published dosimetric constraints. Notably, a 1-mm GTV and planning tumor volume (PTV) margin and the region for HA were set. Subsequently, a HT-HSRT schedule of 35 Gy in 5 fractions was planned. Treatment was planned to enclose the 95% of the PTV by the 90% isodose line of the maximum dose (95% of the PTV received 35 Gy). The mild dizziness, headache, and

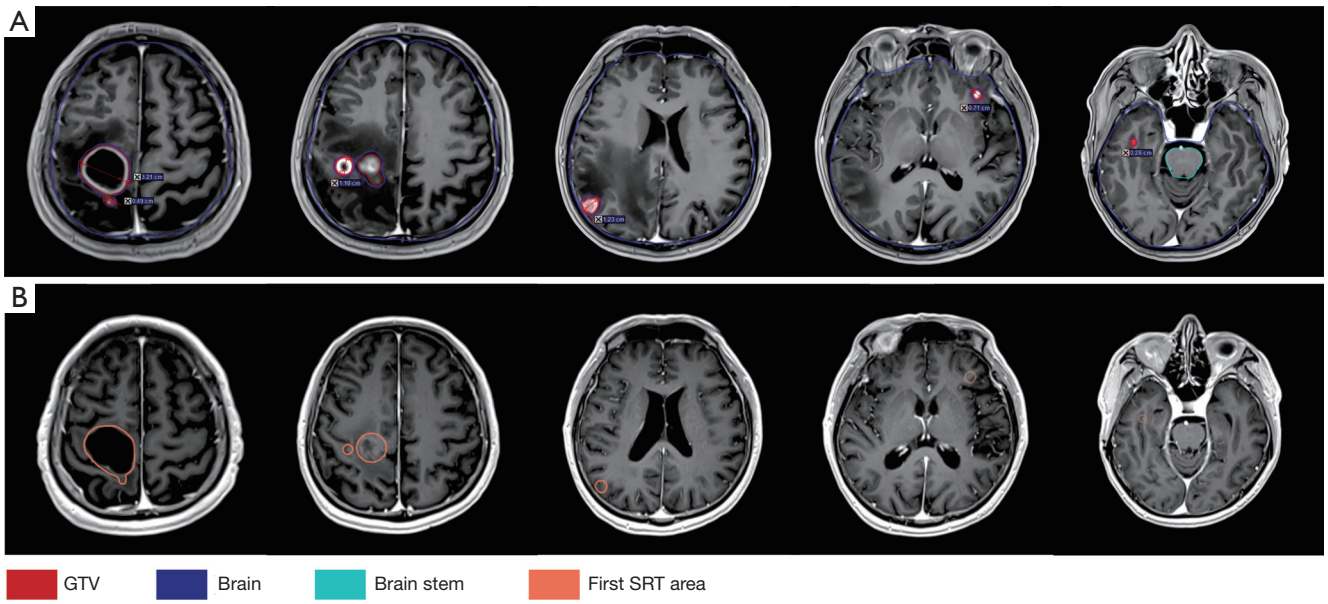

Figure 1 The changes in the initial 6 intracranial lesions and areas involved. (A) The location of the GTV and OARs for the first SRT from positioning MRI performed on September 15, 2022. (B) Positioning MRI that was performed on February 10, 2023 for the second SRT; the orange areas were the positions where the lesions were located during the first SRT course and were delineated to avoid reirradiation. GTV, gross tumor volume; SRT, stereotactic radiotherapy; OARs, organs at risk; MRI, magnetic resonance imaging.

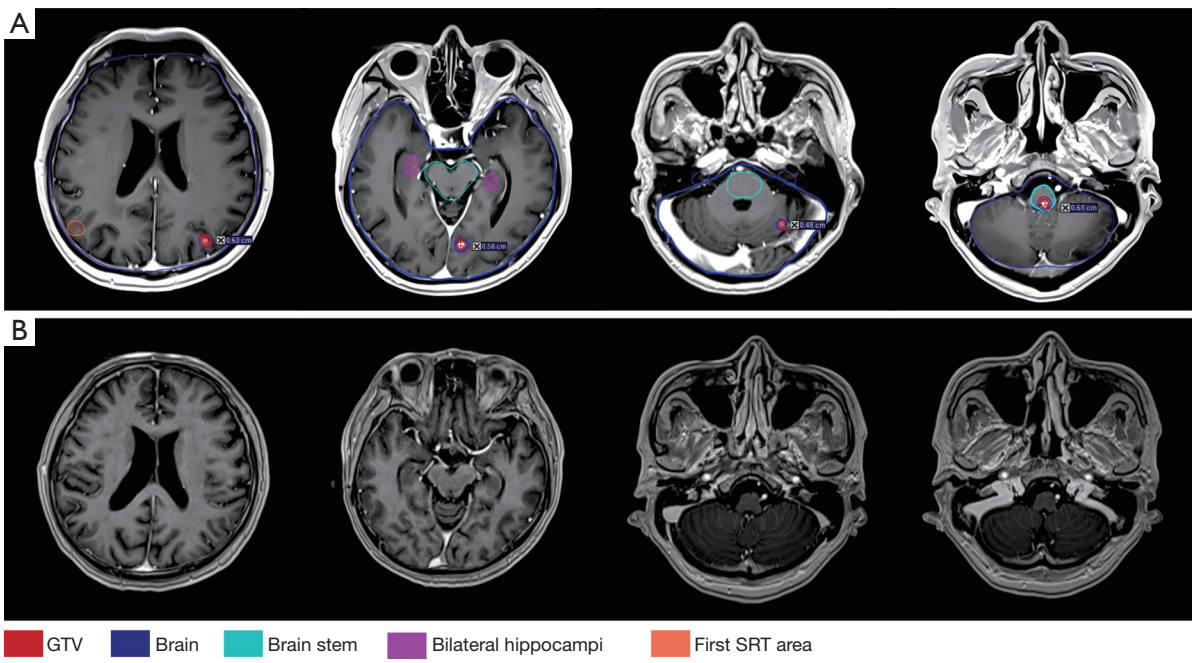

Figure 2 Changes in the 4 lesions after the first recurrence of distant brain failure. (A) The location of GTV and OARs for the second SRT from positioning MRI performed on February 10, 2023. (B) The intracranial lesion distribution on contrast-enhanced MRI performed on February 27, 2023, after the second SRT. GTV, gross tumor volume; SRT, stereotactic radiotherapy; OARs, organs at risk; MRI, magnetic resonance imaging.

Table 1 GTV volume and OAR dose of the radiotherapy treatment plans for BMs

Structure	Parameter	First SRT	Second SRT	Third SRT
GTV	Volume (cc), median [range]	1.3 [0.1–16.4]	0.2 [0.1–0.3]	0.2 [0.1–5.5]
	Total volume (cc)	17.4	0.8	19.5
Brain	V_{24} (cc)	56.2	40.8	943
Bilateral hippocampi	D_{max} (Gy)	19.4	7.3	34.0
Optic pathway	D_{max} (Gy)	21.2	4.7	30.1
Brainstem	D_{max} (Gy)	38.2	29.6	33.2
Cochlea	D_{max} (Gy)	18.5	8.4	28.6

GTV, gross tumor volume; OAR, organ at risk; BMs, brain metastases; V_{24}, volume of brain tissue exposed beyond 24 Gy; D_{max}, maximum point dose, with point defined as ≤0.035 cm^3; SRT, stereotactic radiotherapy.

hearing decline encountered by the patients during the third HSRT were alleviated after a short course of low-dose steroids. The intracranial tumor volume and the parameters of the critical structures, including the volume of brain tissue exposed beyond 24 Gy (V_{24}) as per the Hypofractionated Treatment Effects in the Clinic (HyTEC) protocol, in the three SRT schedules are listed in *Table 1*. After the third SRT course, symptomatic treatment primarily with steroids was administered, despite the decline to adopt ICIs or tailored targeted drugs for specific molecular drivers (BRCA1, 2, and KRAS), owing to economic constraints and stringent health insurance policies.

As indicated by the HVLT-R TR score measured in February 2024 and May 2024, after the administration of memantine, only slight radiation-induced neurocognitive sequelae were present. The location of GTV and OARs for the third course of SRT on MRI and the treatment course, follow-up and disease progression are illustrated in *Figure 3* and *Figure 4*, respectively.

Ethical statement

All procedures performed in this study were in accordance with the Medical Ethics Committees of China-Japan Union Hospital of Jilin University and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

International multidisciplinary treatment (iMDT) discussion

Discussion for physicians from China-Japan Union Hospital of Jilin University

Well-established SRT for BM

As palliative therapies such as WBRT and steroids are no longer contraindicated for patients with BM, local therapy remains crucial for survival. Surgery offers limited potential survival benefits regardless of extracranial lesions, and we have had to postpone WBRT, which is recommended in the American Society of Clinical Oncology (ASCO)-Society for Neuro-Oncology (SNO)-American Society for Radiation Oncology (ASTRO) protocol (14). The landmark randomized controlled trial (RCT) assessed the complementary effect of WBRT when added to SRS, which provided and showed similar overall survival (OS), superior DBF, and a higher risk of neurocognitive toxicity (15). As SRS takes on increasing weight in small cell lung cancer (SCLC) BM management, the FIRE-SCLC cohort study evaluated outcomes for SCLC BM patients receiving first-line SRS and WBRT, revealing a shorter time to central nervous system (CNS) progression in the SRS arm without a decrease in OS, similar to results seen in established SRS settings (16). Additionally, ongoing prospective trials, including the NRG-CC009 study which compares adverse events, aim to assess the effectiveness of SRS *vs.* HA-WBRT in preventing memory and cognitive decline among SCLC BM patients (17). The development of SRS devices

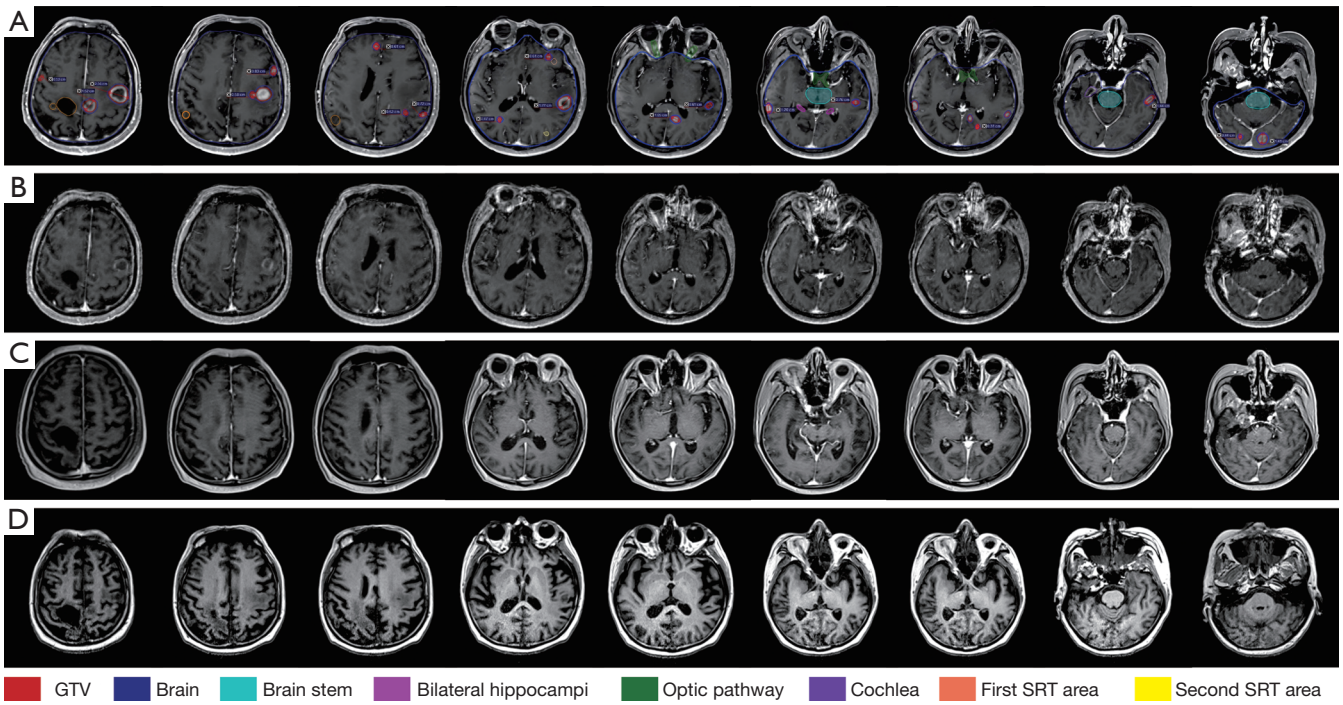

Figure 3 Changes in the 19 intracranial lesions after the second recurrence of distant brain failure. (A) The location of GTV and OARs for the second reirradiation of the HT-HSRT from positioning MRI performed on September 7, 2023. (B) Intracranial lesion distribution on contrast-enhanced MRI performed on October 3, 2023, after the third SRT. (C) The intracranial lesion distribution on the non-contrast-enhanced MRI in other institution performed on February 2, 2024. (D) The intracranial lesion distribution on contrast-enhanced MRI performed on May 31, 2024. GTV, gross tumor volume; SRT, stereotactic radiotherapy; OARs, organs at risk; HT-HSRT, helical tomotherapy-based hypofractionated stereotactic radiotherapy; MRI, magnetic resonance imaging.

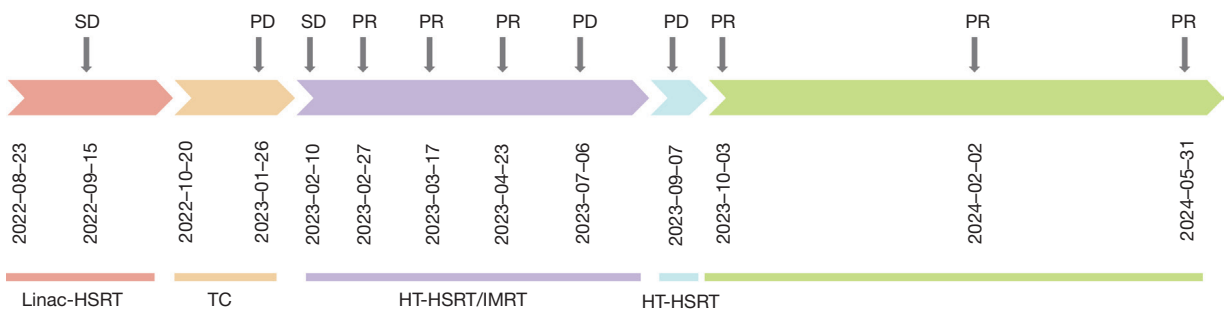

Figure 4 Treatment process and disease development. TC, paclitaxel-albumin/carboplatin; PR, partial response; PD, progressive disease; SD, stable disease; HT-HSRT, helical tomotherapy-based hypofractionated stereotactic radiotherapy; IMRT, intensity-modulated radiotherapy; Linac-HSRT, linear accelerator-based hypofractionated stereotactic radiotherapy.

and fractionated irradiation technology has freed SRT from traditional SF-SRS, with linear accelerators predominating. Ma *et al.* noted that volumetric-modulated arc therapy (VMAT) with robust frameless immobilization provides HSRT with unparalleled time-saving efficiency without compromising accuracy or increasing the risk of positioning error compared to the Gamma Knife (18). There is yet no substantial definitive evidence supporting the benefits of HT on LC and normal tissue complication probability (NTCP) in SRT for BMs, despite its excellent dosimetric properties (9).

As SF-SRS is constrained by the inadequate LC of large tumors, HSRT benefits from an advanced, dedicated delivery apparatus that provides similar precision to that of frame-based SRS, steep dose gradients, and narrow GTV-PTV margins while reducing the risk of RN and ensuring greater LC through potential radiobiological effects (19). The efficacy of SRT for patients with 1–4 BMs has been subjected to extensive and rigorous evaluation; for instance, in the JLGK 0901 study, the median OS (mOS) was 10.8 months for patients with 5–10 BMs (20). Indeed, over half of radiation oncologists favor SRT alone as the prescribed primary therapeutic modality for patients with >4 BMs (21). The ASCO-SNO-ASTRO guideline stipulates that HSRT should be employed when V_{12} >10 cc, irrespective of oncological setting and can serve as a substitute for SF-SRS (15). Minniti *et al.* reported 1-year cumulative LC rates of 77% *vs.* 91% for SF-SRS and HSRT groups, respectively, among patients with BMs >2 cm, along with 1-year cumulative RN rates of 18% *vs.* 9% (22). In this case, the six newly diagnosed intact BMs contained a mass of 3.3 cm. In addition, the V_{12} was very likely to exceed the limit attainable only with small, round BMs or low cumulative tumour volume. Given that published guidelines cannot accurately provide an appropriate radiotherapy regimen for specific individuals, HSRT is reasonable for this patient. The standardized and graded SRT schedules for BMs face constraints from various factors, including the number, size, location, and metastatic rate of lesions, as well as the PS score (23). It is inherently challenging to establish definitive thresholds for these factors solely through a purely evidence-based approach, as this can overlook the multitude of variables that may affect specialized treatment decisions.

The pronounced remission after the first course of SRT confirmed the effect intracranial local therapy, suggesting it is a feasible systemic therapy intervention; however, intolerable side effects led indirectly to DBF.

Management for recurrent BMs

There is no consensus on the treatment for recurrent BMs specifically for patients in whom DBF occurs following SRT. Given the rising rates of RN in repeat SRT for locally recurrent BM (6), neurosurgical procedures, laser interstitial thermal therapy (LITT), focused ultrasound, and magnetic hyperthermia therapy (MHT) may be alternatives (24). Reirradiation is being increasingly adopted for patients with DBF (25). As discussed above, supportive care should strive to avoid WBRT despite its historical status as the preferred treatment for recurrent BMs and its relatively lower rate of DBF compared to SRT (14). SRT is diminishing the importance of DBF and allows for greater focus on the potential for subsequent neurological decompensation, as the monitoring of recurrent BMs becomes more timely (23). Thus, in our case, reirradiation of SRT, in contrast to WBRT or the combination of SRT and WBRT, was prescribed based on the premise of preserving neurocognition despite the two prior DBF events. A 3-month interval before the second SRT, which is shorter than the interval recommended by the RTOG protocol, may justify an exemption due to dose gradient attenuation, brain tissue recovery, and lesion position variation. The ongoing prospective NRG-BN009 trial is evaluating the impact on repeat SRS or SRS + HA-WBRT for the patients after upfront SRS with DBF and a brain metastasis velocity (BMV) ≥4 new BMs/year. A 9.6 (4*12/5) and 32.6 (19*12/7) BMV for the first and second DBF periods, respectively, while a total 23 [(4+19)/1] BMV in this case were calculated following the equation given by NRG-BN009 trial (13). Significant differences in BMV changes between the two periods indeed necessitate a comparison of HA-WBRT + SRS to determine whether it can prolong BMV or intracranial progression-free survival (PFS).

The HT system, with its broadest coverage and multifield delivery modes, addresses the need for effective and tolerable treatment of intracranial and extracranial lesions, overcoming the impasse in providing whole-body lesions care (9). Selected retrospective studies (26-31) examining HT-SRT for BM are summarized in *Table 2*. The average number of BMs was less than 2 (354/194), with a median survival time ranging from 7 to 14.2 months in these studies. In contrast, with a number of 6, 4 and 19 BMs, an OS of 20.5 months in this case is quite satisfactory. Among them, three studies (26,27,30) reported the PS, with 82.2% (60/73) of patients having a PS ≤2, indicating that HT-HSRT is compatible with patients in relatively poor general condition. In the study by Tomita *et al.*, all patients exhibited extracranial active lesions, with seven undergoing WBRT + SRS (26). However, hippocampal sparing measures and evaluations of subsequent cognitive function were not mentioned in any of these studies. This omission may be due to the small number of lesions and exclusion of patients with hippocampal metastases. When the number of BMs is excessive, hippocampal sparing during SRS planning needs to be weighted (10,11). Only Koide *et al.* (30) reported two patients experiencing RN after HT-HSRT, and such a low

Table 2 Selected studies on HT-SRT for brain metastasis

Parameter	Tomita 2008 (26)	Sanghera 2010 (27)	Nagai 2014 (28)	Barra 2015 (29)	Koide 2019 (30)	Cuccia 2023 (31)
No. pts	23	5	54	30	45	37
ECOG PS [No. pts]	>2 [8]; ≤2 [15]	>2 [1]; ≤2 [4]	NR	NR	>2 [4]; ≤2 [41]	NR
GPA	NR	NR	≥3 [9]; <3 [45]	>2 [21]; ≤2 [9]	NR	NR
Previous cranial radiotherapy [No. pts]	NR	4 (3 of WBRT, 1 of SRS)	NR	2	0	NR
Extracranial active lesion, No. pts (%)	23 (100.0)	1 (20.0)	NR	NR	13 (28.9)	5 (13.5)
Primary tumor [No. pts]	Lung [10]; breast [4]; colorectal [4]; others [5]	NSCLC [3]; renal [2]	Lung [46]; breast [4]; others [4]	Lung [12]; breast [10]; kidney [2]; ovary [2]; melanoma [2]; others [2]	Lung [11]; breast [10]; head and neck [6]; gynecology [6]; gastrointestinal [5]; renal [2]; others [5]	NSCLC [20]; colon [6]; breast [5]; others [6]
Total number of intracranial lesions	49	9	128; number of metastases: median 2 (range, 1–8)	46	58	64
Volume (cc), median [range]	6.0 [0.3–128.3]	NR	GTV: 1.9 [0.01–18]	CTV: 1.9 [0.18–13.81]	CTV: 7.2 [0.1–115.4]	CTV: 0.77 [0.3–17.86]
Prescription dose	35–37.5 Gy/5 f (7 patients combined with WBRT of 50 Gy/10 f)	30 Gy/5 f	28–28.8 Gy/4 f	21 Gy/1 f; 18 Gy/1 f; 15 Gy/1 f	35 Gy/5 f; 35–38.5 Gy/7 f; 30–33 Gy/5 f	30 Gy/5 f
Follow-up (mo), median [range]	4.6 [1–20]	NR	18 [3–34]	14 [4–31]	11.3 [1.7–93.9]	7 [1–38]
Median LC rate (%)	69 at 1 year	NR	96 at 6-mo; 91 at 12-mo; 88 at 18-mo	72 at 6-mo; 65 at 12-mo; 50 at 18-mo	64.7 at 1-year	92.5 at 1- and 2-year
OS						
OS (mo), median [range]	10 [1–20]	11	7	NR	14.2	NR
OS rate (%)	NR	NR	61 at 6-mo; 52 at 12-mo; 38 at 18-mo	60 at 12-mo; 44 at 18-mo	NR	54 at 1-year; 40 at 2-year
DBF						
Rate at 1-year (%)	NR	NR	NR	NR	13.3 (BM ≥3 cm); 27.3 (BM <3 cm)	NR
Median time (mo)			5.0		NR	
PFS, median [range] (mo)						
Intracranial	NR	NR	NR	NR	11.6	5 [1–17]
Overall					NR	3 [1–17]
Radiological response, acute, and late side effects, No. pts (%)	2 (8.7)	None	4 (7.4)	2 (6.7)	2 of RN (4.4)	2 (5.4)

HT-SRT, helical tomotherapy-based stereotactic radiotherapy; No. pts, number of patients; ECOG PS, Eastern Cooperative Oncology Group performance status; GPA, graded prognostic assessment; mo, months; LC, local control; OS, overall survival; DBF, distant brain failure; PFS, progression-free survival; NR, not reported; f, fractions; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; NSCLC, non-small cell lung cancer; GTV, gross tumor volume; CTV, clinical target volume; BM, brain metastasis; RN, radionecrosis.

incidence may be attributed to the small sample sizes of the individual studies and the lack of experience in diagnosing RN in earlier research. After excluding the case reports by Sanghera *et al.* (27), we observed extreme dispersion in the 1-year LC rates among the remaining five studies (26,28-31), which had a similar number of patients. The studies by Tomita *et al.* (26) and Koide *et al.* (30) focused on relatively large-volume BMs; and a prescribed dose of 35 Gy in 5 fractions did not deliver promising LC rates. Tomita *et al.* (26) suggested that HSRT was more suitable for large-volume or irregularly shaped BMs, excluding smaller, rounder tumors and recommending SF-SRS. Koide *et al.* (30) divided patients into subgroups based on tumor size (whether >3 cm) but found no statistical differences in mOS, LC, or median PFS between them. They also reported detailed recurrence patterns and subsequent treatment measures for 29 patients. Barra *et al.* (29) alone adopted SF-SRS with a localizer frame for immobilization, following RTOG criteria for dose delivery. The 1-year LC rates ranged from 64.7% to 67% in these three studies (26,29,30), compared to over 90% in the remaining two (28,31). Notably, Nagai *et al.* (28) reported the longest median follow-up and shortest mOS, potentially due to the largest average number of BMs among these studies. In this case, despite the median volume being relatively small compared to those in the studies, the total volumes of BMs across the three HSRT courses were 17.4, 0.8, and 19.5 cc, respectively. As a result, we administered a higher dose, ultimately achieving no local failure or RN. These studies are all confined to a limited number of patients with BM. There is paucity of robust RCTs and up-to-date practice to demonstrate the efficacy of HT-SRT for patients with >4 BMs.

RN, cognitive dysfunction and memantine

Biopsy as the gold standard for RN, combined with radiological evidence, facilitates screening and timely intervention for progressive and irreversible RN. Vascular injury and immune activation may be related to RN, implying the feasibility of anti-vascular endothelial growth factor (anti-VEGF) therapy and immunosuppressive agents (32). Resection removes causes of disease, relieves symptoms swiftly, and differentiates tumor progression from RN. LITT and hyperbaric oxygen therapy HBOT are alternatives to prolonged drug use, but their precise implications remain unclear (7,33).

V_{12} may be an independent predictor of RN after SF-SRS and is limited to 5–10 cc (34). Even a lower degree of fractionation could theoretically reduce the risk of RN (19). HyTEC suggests V_{24}, a readily available risk factor of RN for 5-fraction HSRT, at ≤20 or ≤30 cc, is associated with RN rates of ≤10% or ≤30%, respectively (6). Zhang *et al.* (35) analyzed 152 patients with 182 intact BMs following Linac-HSRT and reported a potential low-risk benefit, with a cumulative incidence of RN of 13.2%. However, Loi *et al.* (36) suggested a lack of a decreasing RN risk in HSRT *vs.* SF-SRS cohorts.

SRT is linked to lower cognitive impairment risk compared to WBRT (15) However, the risk lingers, particularly in this complicated case. As multiple SRT courses were performed, several intracranial lesions adjacent to the hippocampus were revealed. Especially on the left side where, as Pospisil *et al.* showed, irradiation of the left hippocampus is more likely to cause cognitive risks (37). Taking the dose to the hippocampus into consideration, we measured the maximum point dose (D_{max}) of the bilateral hippocampi during the three SRT sessions as 19.4, 7.3, and 34.0 Gy, respectively. According to the RTOG-0933 study (8), the most commonly used hippocampal dose limit currently is a D_{max} of 16 Gy within a WBRT of a prescribed dose of 30 Gy in 10 fractions. If a direct comparison between the D_{max} of hippocampi of our patient and the limit is made, the total cumulative dose to the hippocampus clearly exceeds this threshold. Furthermore, a prospective trial involving 58 young patients with brain tumors and receiving stereotactic conformal radiotherapy at a dose of 54 Gy in 30 fractions evaluated hippocampal radiotherapy dose constraints to predict long-term neurocognitive outcomes, and recommended a mean dose limit of <30 Gy to the left hippocampus (38). After the conclusion of the third radiotherapy course, memantine was administered to mitigate potential cognitive decline, taking into account the aforementioned limitations. However, a crucial drawback that needs to be pointed out is the negligence in distinguishing and delineating the tissues of the left and right hippocampus, resulting in a situation where both the outlining and subsequent dosimetry have no choice but to be carried out on the hippocampus as a whole. Furthermore, the dose accumulation algorithm poses issues. While calculating the cumulative hippocampal dose for the final two radiotherapy treatments is straightforward, no adequate algorithm exists for accumulating the hippocampal dose from the first SRT due to the involvement of disparate treatment platforms and planning systems, which hinders the feasibility of accurately calculating the total cumulative hippocampal dose. However, the total cumulative dose to

the hippocampus, following a rough geometric estimation, is extremely dangerous relative to the two dose limits described above.

Maintaining neurocognitive health is a significant challenge, but countermeasures to address it are currently under investigation. Kirkpatrick *et al.* (39) reported that 1-mm or 3-mm GTV-PTV margins in SRT plans showed no LC disparity, prompting us to set the 1-mm margin in the expectation that it could mitigate RN risk despite the physical uncertainty. In the United States, 73% and 80% of patients subjected to WBRT receive HA-WBRT and memantine, respectively, which is rare in China due to limited experience and evidence (40). In the scenario where repeat SRT, instead of WBRT, is employed for BMs, applying HA or memantine to this specific patient appears unwarranted. Nevertheless, the potential for such application cannot be disregarded. The hippocampus, a critical component in maintaining the learning and memory function and protecting neural stem cell resources, is extremely vulnerable. Ionizing radiation has been shown to cause permanent damage to synaptic structures, particularly affecting dendritic spines rich in N-methyl-D-aspartate (NMDA) receptors in the hippocampus. This ultimately leads to a decrease in NMDA receptor density, which is mediated by post-radiation excitotoxicity, and then disrupts a process essential for memory formation, named long-term potentiation (41,42). The non-competitive NMDA open-channel blocker memantine has been demonstrated to prevent receptor remodeling and is prophylactically utilized to mitigate cognitive decline and restore cognitive function in patients post-cranial irradiation (43,44).

We must acknowledge that the administration of memantine in this case is merely a tentative and nascent strategy at the individual case level, as there is indeed scarcely any high-quality evidence directly supporting it. We hope that memantine can play a possible preventive role against cognitive impairment in such a context, just as its application in patients undergoing WBRT. In the absence of certainty regarding the comparative efficacy of the strategy of setting HA area and applying memantine in SRT with those in WBRT, or the potential benefit of this approach in enhancing NTCP, a heightened degree of caution was employed in its prescription for this specific patient. Further research is required to ascertain the necessity of that for SRT for lesions proximal to the hippocampus.

Follow-up treatment and prognosis

This case demonstrated the gradually extended period of freedom from DBF, but it should theoretically attain a more favorable prognosis due to the remarkable efficacy suggested by the multiple non-in situ intracranial recurrences post-SRT and the high radiosensitivity inherent to the characterized pathology. We hypothesize that DBF may be associated with subclinical lesions having early dissemination and being difficult to detect on imaging surveillance, and that all involved subclinical lesions, upon being promptly controlled by SRT, can avoid local recurrence. In addition, with the primary lesion under delayed control after irradiation, further progression of systemic lesions can be prevented.

Yuan *et al.* revealed that conditional survival of lung cancer with BM patients would change in real time based on the time survived, and the progressive increase in survival probability over time could mitigate patient anxiety, strengthen confidence in disease management and enhance overall QOL (45). Subsequent systemic therapy may ensure long-term survival even though attainment of CR is difficult according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria (46). We could not further analyze the pathological specimens for potential gene loci influencing tumor control, nor could we systematically monitor serum tumor markers, including several that could assess prognosis despite their dynamic changes not being significantly associated with the final outcome, such as carcinoembryonic antigen, cytokeratin-19 fragment, and neuron-specific enolase (47). We did not abandon systemic therapy considering its status in managing progression and prognosis for BM patients, though the patient did not accept such options due to extra economic burden. If subsequent WBRT proves feasible, simultaneous temozolomide therapy might further improve LC (14). Third-line therapy for patients with advanced NSCLC in China may be considered, as suggested by the ALTER 0303 study (48). ICIs show promising efficacy for advanced NSCLC, with an improvement in 5-year OS from 5% in the chemotherapy era to 16–23% (49). However, concurrent ICI therapy for patients with BMs from NSCLC with recent SRT, typically within 4 weeks, may increase the risk of RN (50). Well-tolerated agents with low toxicity should be prioritized regardless of the systemic therapy administered to improve therapeutic efficacy.

A favorable survival of 20.5 months, incredible tumor control, promising symptomatic RN, and manageable toxicity are noted for this case, which contrasts the previously reported median OS of 3.02 months of patients with BMs from NSCLC with 0–1 DS-GPA points (51).

Further investigation from the case

There is an absence of robust evidence on HT-SRT, repeat SRT for BM, and memantine for BM patients suffering from SRT. A single case study alone does not significantly add innovation in this field. For more definitive insights, examining a series of cases or a larger patient sample is essential. How to identify potential candidates for repeat salvage HSRT or timely WBRT after upfront SRT does matter, and we aim to draw lessons from this patient and, to the extent possible, propose feasible suggestions.

Numerous variable factors such as age, PS, diagnosis, molecular status with CNS penetrating drugs, extracranial disease control, previous treatment and intracranial tumor burden, which includes location, volume, number and velocity of metastases, among others, in BM patients have made it complex to implement the inclusion criteria for randomised prospective trials. Suspicious changes in local lesions post-SRT imply the dilemma of differentiating tumor progression from tumor necrosis. Diagnostic confirmation of local relapse, whether through pathology or advanced imaging techniques, indicates radioresistance (33). Given the uncertain efficacy of re-irradiation, local recurrent BM patients may be tentatively excluded from further exploration of appropriate radiotherapy modalities with a similar scenario in this case.

With a similar OS compared with WBRT, expanded indications and a flexible schedule for repeat SRT, most clinical practices favor it for managing recurrent BM. The factors summarized from this case will facilitate the selection of suitable candidates for salvage SRT: (I) confirmed DBF with countable intact BMs and a reasonably acceptable KPS (generally >50); (II) passable baseline prognosis and life expectancy (generally >4 months); (III) requirement for the protection of neurocognitive function and subsequent QOL; (IV) metastasis in brainstem and hippocampus or greater than 2 cm (consider an alternative HSRT); (V) effective CNS-penetrating drugs for systemic therapy. However, WBRT application scenarios may be somewhat more extreme and consequently less complex, typically involving candidates with the poorest prognosis, and would be appropriate to meet the following conditions: (I) abysmal KPS and prognosis; (II) widespread dissemination and miliary BMs; (III) BM from primary germ cell tumor, small cell carcinoma or lymphoma; (IV) unbearable economic burden for multiple SRT; (V) to prioritize DBF, subclinical disease control, and mitigate recurrence risks in short intervals.

Several issues in the diagnosis and treatment of this patient remain

Should tomotherapy or Gamma Knife have been initially applied in this case? What would be the effect on the results had this been performed?

Expert opinion: Rafal Suwinski

In my opinion, there is no proven clinical advantage of tomotherapy/Gamma Knife or Cyber Knife over modern linear accelerator-based SRT in patients with BMs. Selection of each of these techniques is commonly based upon experience of the staff, availability and versions of the therapeutic and planning units, as well as imaging and immobilization techniques used. If multiple techniques are available, treatment plans for different techniques can be compared to select the best choice in a given individual case. The potential gain from use of Linac-HSRT or modern tomotherapy in patients with BMs is the apparent possibility of image-guided treatment (cone beam CT or MRI on magnetic resonance-guided unit). In the process of selection of a given treatment unit, it is also worthwhile to consider possible future treatments. Some treatment planning units (e.g., Varian Velocity) allows to combine the radiation dose distributions from the initial and retreatment SBRT plans. Such combination is, usually, possible providing the patient was treated on the same or compatible unit. The patient discussed was treated on two different units: linear accelerator (linac) and tomotherapy. My preference in this case would be therapy on one unit to make fusion of the consecutive plans readily available.

We noticed the positive mutations in *BRCA1*, *BRCA2*, and *KRAS* of the case, without common molecular drivers for NSCLC patients (such as *EGFR*, *ALK*, *ROSI*, *BRAF* V600). What is the way forward for targeted therapies in this case?

Expert opinion: Rafal Suwinski

Selection of a systemic treatment in a discussed case may be a subject of controversies. Among the reasons for this is a coexistence of *BRCA1* and *BRCA2* mutations in the same patient, which is a rare event (52) and the coexistence with *KRAS* mutation is, likely, even more uncommon. For this reason, in this case, selection of targeted therapy may not be based on strong clinical evidence or on the established clinical guidelines.

In my opinion, selection of a systemic treatment in NSCLC patients with BMs should be based on general

performance of the patient, necessity of steroids use (symptomatic *vs.* asymptomatic), pathological type of a tumour (squamous *vs.* adenocarcinoma), PD-L1 expression and the presence/absence of diver mutations.

In non-symptomatic patients with BMs, without targetable *EGFR* or *ALK* mutations immunotherapy (with or without chemotherapy) may be considered as a therapeutic option of documented efficacy. In patient with positive expression of PD-L1, with a tumour proportion score (TPS) >50%, such as in a discussed case, first-line immunotherapy with pembrolizumab might be a valid choice based on the outcome of a pivotal randomized trial (53). One may also consider that *KRAS*-driven lung cancer is, in general, associated with favourable responses to immune checkpoint blockade therapy. Other therapeutic options that incorporate immunocompetent drugs might also be considered (54). In a discussed case, ICIs were not used due to economic concerns, but it is rationale to assume that the clinical factors were also among the contributing factors.

The presence of *BRCA1* and *BRCA2* mutations may, potentially, suggest a possible activity of PARP inhibitors in a discussed case. These drugs are, at present, routinely used in therapy for breast and ovarian cancer patients with mutations in the *BRCA* gene. There are, however, only few case reports on use of PARP inhibitors in *BRCA*-mutated lung cancer (55). Lack of robust evidence for clinical activity and safety of PARP inhibitors in lung cancer preclude, in my opinion, use of these drugs in a daily clinical practice.

There is no information from the authors on the type of *KRAS* mutation that was found. The presence of *KRAS* G12C variant might prompt for use of sotorasib or adagrasib as a second line of systemic therapy in stage IV NSCLC (56,57). Both drugs have documented activity in patients with BM, although the clinical experience in such scenario is limited (58,59). Clearly, however, optimal combination of *KRAS* inhibitors with SRT for BMs is not well established.

What is the appropriate treatment for the intracranial lesions if there is another intracranial relapse in the future?

Expert opinion: Rafal Suwinski

In my opinion, another course of SRT may be considered, if allowed by adequate performance of the patient and if dose constraints for critical organs could be maintained. As mentioned before, selection of previously used stereotactic technique can make it easier to create and evaluate fusions of the current and previous radiation isodose distributions. Whole brain radiotherapy might be an option in case of multiple lesions. There appears to be limited evidence for routine use of third-line systemic therapies for NSCLC patients with multiple BMs. Use of anlotinib in the third-line systemic therapy for metastatic NSCLC raises, nevertheless, among the promising new options (48). For patients in adequate general condition, participation in a trial with novel drugs may, clearly, be a valuable option.

Conclusions

Use of WBRT has been consistently limited in this case, with it only being considered as a final option. An excessive cumulative dose from repeat SRT, within a condensed timeframe, should not be excessively avoided. It does not hinder mitigation in select individuals, suggesting HT-SRT is viable in this context. However, examining a series of cases to identify potential candidates for repeat salvage HSRT or timely WBRT after upfront SRT is essential. Factors to be considered include confirmed BM pathology, diagnosed distant intracranial recurrence, PS, baseline prognosis, intra- and extra-cranial tumor burden, as well as the specific aspirations or concerns of patients. Yet, robust randomized analyses are still needed to confirm the potential benefits of HT-SRT in preserving neurocognition and the tangible effects of HA and memantine during SRT.

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Footnote

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