Bevacizumab is an effective treatment for symptomatic cerebral necrosis after carbon ion therapy for recurrent intracranial malignant tumours: A case report

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Abstract. Carbon ion therapy (CIT) is a form of particle therapy, which not only spares normal tissues but may also improve local control of recurrent intracranial tumours. Cerebral radiation necrosis (RN) is one of the most serious adverse reactions of recurrent brain tumours following reirradiation, which may lead to neurological decline or even death. Bevacizumab is an anti-vascular endothelial growth factor antibody, which has been used to treat symptomatic RN. However, studies on bevacizumab for the treatment of CIT-induced RN are sparse. The present study described two cases that were successfully treated with bevacizumab for symptomatic RN following CIT for recurrent intracranial malignant tumours. The two recurrent intracranial malignant tumours, a chondrosarcoma in the right cavernous sinus and an anaplastic meningioma in the right frontal lobe, were enrolled in a clinical trial of CIT. Both cases were treated intravenously with bevacizumab when deterioration that appeared to be symptomatic brain RN was observed. Just before CIT, enhanced magnetic resonance imaging (MRI) was performed in each case to confirm tumour recurrence. Both cases exhibited a deterioration in symptoms, as well as on MRI, at 12-month intervals following CIT. The first case underwent positron emission tomography/computed tomography to confirm no increase in fluorodeoxyglucose uptake in lesion areas. Both cases were diagnosed as having symptomatic brain RN and began intravenous administration of four cycles of 5 mg/kg bevacizumab biweekly. The patients responded well, with rapid and marked improvements on MRI, and in clinical symptoms. No tumour progression was observed 24 months after CIT. In conclusion, bevacizumab was revealed to exert marked effects on symptomatic brain RN following CIT. Notably, cycles of bevacizumab should be administered specifically based on the aim of treating brain necrosis, and long-term or prophylactic applications are not recommended.

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Introduction

Recurrent intracranial malignant tumours with complex pathological types may be difficult to treat surgically, due to their proximity to critical neurovascular structures of the skull base or previous administration of multi-modality treatment, such as surgery or radiotherapy (RT). The treatment options for recurrent intracranial malignant tumours are very limited. Although reoperation and standard-dose salvage chemotherapy are used in selected patients, they only provide palliative effects (1). In this context, reirradiation of the intracranial recurrent lesion may improve local control and prolong survival; however, caution is required due to cumulative late central nervous system toxicity and lack of a likely chance of a cure (2,3).

Photon-based RT remains the standard of care for the treatment of brain tumours. Notably, carbon ion therapy (CIT) is becoming more widely available for cranial irradiation (4). Radiation-induced brain necrosis is one of the most serious adverse events that can lead to neurological decline and even death (5). Its diagnosis usually requires advanced imaging techniques to quantify signal changes and differentiation from tumour recurrence (6). Bevacizumab is an anti-vascular endothelial growth factor (VEGF) antibody, which has been used to treat symptomatic cerebral radiation necrosis (RN) (7). However, to the best of our knowledge, there are no studies on the use of bevacizumab to treat CIT-induced RN.

A clinical trial (no. KJTJ2018013BOJI) to verify the safety and effectiveness of CIT was performed in Wuwei Heavy Ion Hospital (Wuwei, China), between November 2018 and February 2019. Prior to patient enrolment, the clinical trial was approved by the ethics committee of the Gansu Provincial Cancer Hospital (approval no. A201809200024;

Lanzhou, China). Written informed consent for publication of clinical data, including treatment, follow-up and any subsequent case reports, was obtained from all participants at the point of recruitment to the trial. A total of 47 subjects were recruited, including eight cases of recurrent intracranial malignant tumours. During follow-up 1 year after treatment, two patients were diagnosed with RN by magnetic resonance imaging (MRI). The present study reported on these two cases of symptomatic RN to verify the efficacy and optimal dose pattern of bevacizumab in the treatment of CIT-induced RN.

Case report

Case 1. A 28-year-old man was admitted to Wuwei Heavy Ion Hospital in November 2018, who presented with persistent headache, decreased visual acuity and visual field defect that had persisted for 1 year. A head gadolinium (Gd)-enhanced MRI brain scan revealed a mass that showed a hypointense signal in T1-weighted imaging (T1WI) and a diverse signal in T2WI. The mass measured 3.0x2.2x3.4 cm (antero-posterior x transverse x craniocaudal) and was located in the right parasellar region. Physical examination showed equally large and round bilateral pupils, light reflection, decreased binocular vision, visual field defect, restricted abduction in the right eye and right eyelid droop. The patient underwent a tumour biopsy in the right cavernous sinus area via the sphenoidal sinus under general anaesthesia by neuroendoscopic navigation in November 2018. The baseline neuro-ophthalmic assessment at this time showed no deterioration.

Tumor biopsy revealed a highly differentiated chondrosarcoma in the right cavernous sinus. The immunohistochemistry results were as follows: CK (-), CK-19 (-), epithelial membrane antigen (EMA) (-), Ki-67 (8%+), S-100 (+), IDH-1 (-), Vimentin (+), neuron-specific enolase (-) and Brachyury (-), which supported the pathological diagnosis. The post-biopsy MRI showed local bone defects in the sellar base, sphenoid sinus and occipital slope, as well as structural disorder in the sellar region and patchy mixed T1WI and T2WI signal shadows with patchy rings under enhancement. Haemorrhage and partial fillings were observed in the operative area (Fig. 1A and D).

A total of 1 month after the biopsy, the patient applied to be enrolled in the clinical trial. After discussion by the expert group, the patient was considered to meet the inclusion criteria. In full communication with the patient and after signing the informed consent, the patient was officially enrolled in the clinical trial in December 2018. The patient had a definite diagnosis of chondrosarcoma in the right cavernous sinus, stage Ia with cT1N0M0, according to the American Joint Council on Cancer 8th edition staging (8). CIT was administered to the patient according to the protocol for chondrosarcoma of the skull base. The target volume was delineated based on the preoperative MRI and computed tomography (CT) imaging. The gross tumour volume (GTV) was defined as the primary tumour in MRI. The clinical target volume (CTV) included the GTV, parietal wall of the nasopharynx, cranial base slope, the small and great wings of the sphenoid bone, sella turcica, cavernous sinus, sphenoid sinus and the posterior ethmoid sinus. The planning target volume (PTV) was determined by adding 3-mm margins to the CTV. The patient was administered a PTV total prescription dose of 57.6 Gy [relative biological effectiveness (RBE)] in 16 fractions, 3.6 Gy (RBE) per fraction over 3.2 weeks (Fig. 2). The treatment process was uneventful, with no acute adverse events base on Radiation Therapy Oncology Group criteria (9). The patient reported relief of the symptoms of headache, diplopia and blurred vision after CIT completion.

After CIT, the patient entered regular follow-up and did not report any adverse events during the first year. However, 14 months after CIT, a follow-up MRI showed a mass with abnormal signal in the right temporal lobe, measuring ~18x28 mm in size. Gd-enhanced scans showed significant enhancement with a wreath shape in the lesion area, surrounded by a large area of high-signal oedema. The primary tumour in the right cavernous sinus had decreased in size (Fig. 1B and E). The patient experienced symptoms of olfactory hallucination, dizziness, nausea and petit mal epilepsy. Glucocorticoids and magnesium valproate were administered to reduce brain oedema and control the epilepsy. Fluorodeoxyglucose (FDG)-PET showed decreased tracer uptake in the lesions in the right temporal lobe, which indicated no progression in the tumor area. Thus, the aggravation of the clinical symptoms, combined with the FDG-PET and MRI findings, indicated RN rather than tumour progression.

Bevacizumab was proposed as the main treatment to control RN. Thereafter, the patient was administered 5 mg/kg bevacizumab biweekly for six cycles. MRI after four cycles showed marked improvement in both T1WI and T2WI. The symptoms of olfactory hallucination, dizziness and petit mal epilepsy were markedly improved with this treatment. MRI after six cycles showed that the abnormal signal mass and surrounding brain oedema had nearly disappeared and showed a further decrease in primary tumour size (Fig. 1C and F). Follow-up MRI performed 24 months after CIT showed no tumour progression with the patient in a stable state (data not shown).

Case 2. A 50-year-old man was admitted to Wuwei Heavy Ion Hospital in December 2018, who presented with a recurrent anaplastic meningioma for 9 years, for which he had undergone three surgeries and stereotactic RT. The patient first underwent intracranial tumour resection for an MRI diagnosis of meningioma in 2009, with the postoperative pathology indicating meningioma. No further adjuvant treatment was administered after the operation. In June 2015, follow-up MRI showed recurrence of left frontal meningioma, and a second surgical treatment was performed. The pathological findings indicated a grade 3 anaplastic meningioma based on the World Health Organisation (WHO) classification (10). Due to the presence of gross residual lesions, adjuvant stereotactic RT was performed in July 2015, with the 50% isodose line wrapped around the target volume, and prescribed doses of 30 Gy (5 fractions) in the centre and 15 Gy (5 fractions) at the edge. In April 2017, the patient developed frontal redness and swelling, headache and fever. MRI indicated a recurrent lesion. Surgery was performed for frontal sinus abscess removal and recurrent meningioma resection. The pathological diagnosis was meningioma in the right frontal area (WHO grade 2-3), with local bone invasion. The immunohistochemistry results were as follows: Vimentin (+), EMA (-), S-100 (-), CD34 (+), STAT6 (+), Ki-67 (20%+), and P53 (+), which support the pathological

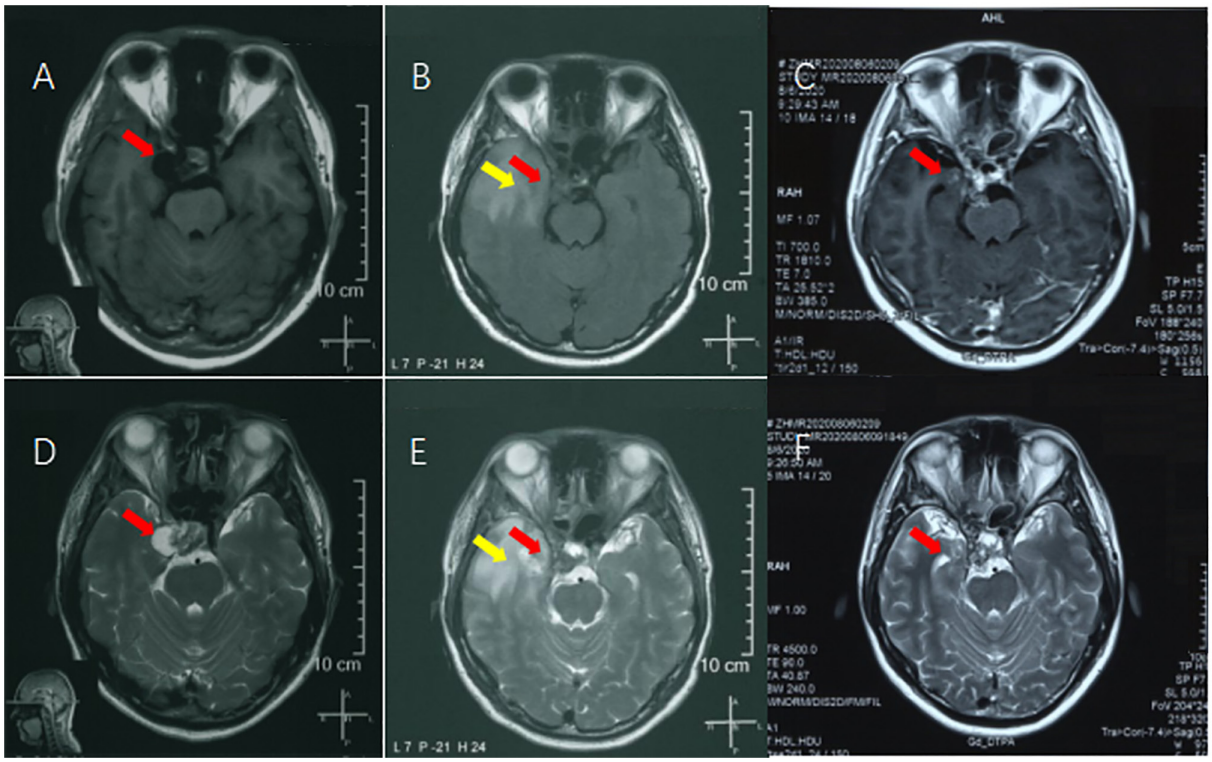

Figure 1. Periodic MRI changes in case 1 with chondrosarcoma. (A-C) T1-weighted MRI; (D-F) T2-weighted MRI. (A and D) Just prior to CIT; (B and E) 12 months after CIT and (C and F) 18 months after CIT (four cycles after initial bevacizumab treatment). The red arrows show the tumour area and the yellow arrows show the area of brain radiation necrosis.

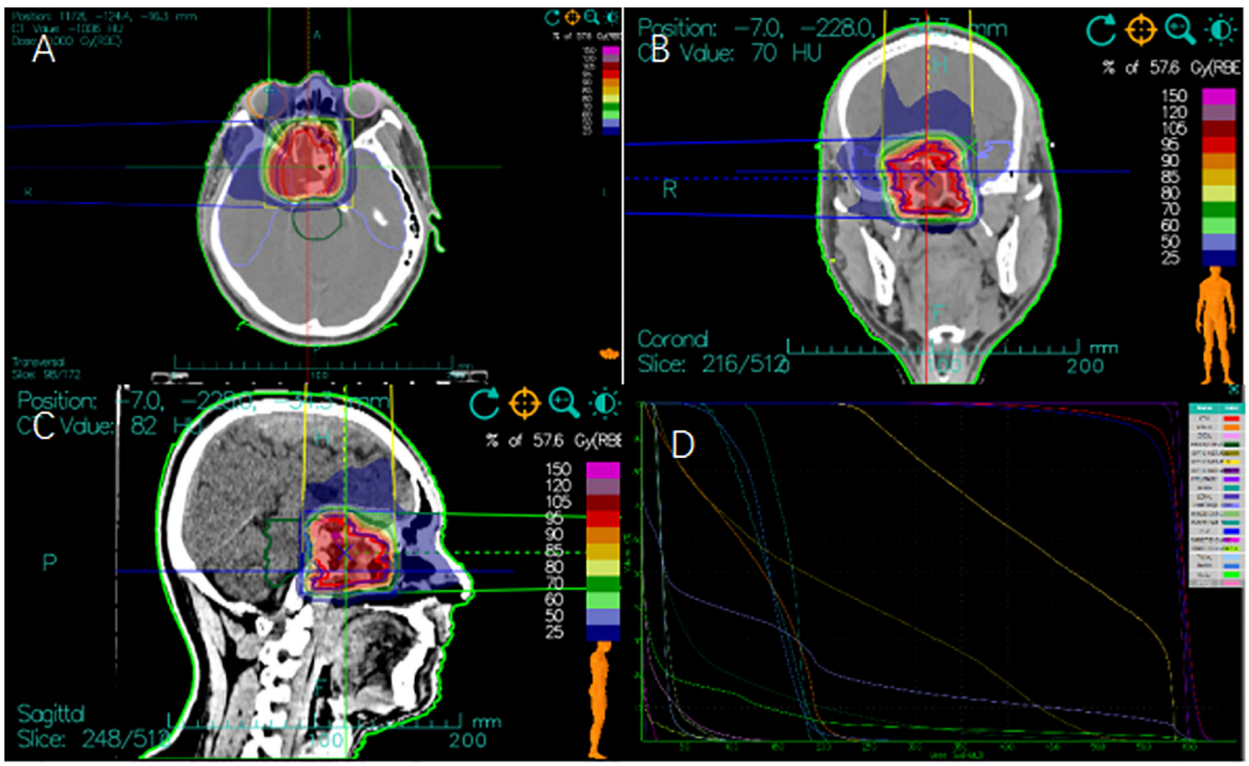

Figure 2. Target volume dose distribution in case 1. (A) Cross-sectional, (B) coronal and (C) sagittal planes. (D) Dose volume histogram.

diagnosis. In September 2018, the patient developed noticeable swelling in the left frontal area. Brain Gd-enhanced and FLAIR MRI confirmed a crescent-shaped T1-hyperintense and T2-hypointense signal mass measuring 5.7x1.8x4.0 cm (transverse x antero-posterior x craniocaudal) under the left frontal cranial plate. The anterior horn of the adjacent left

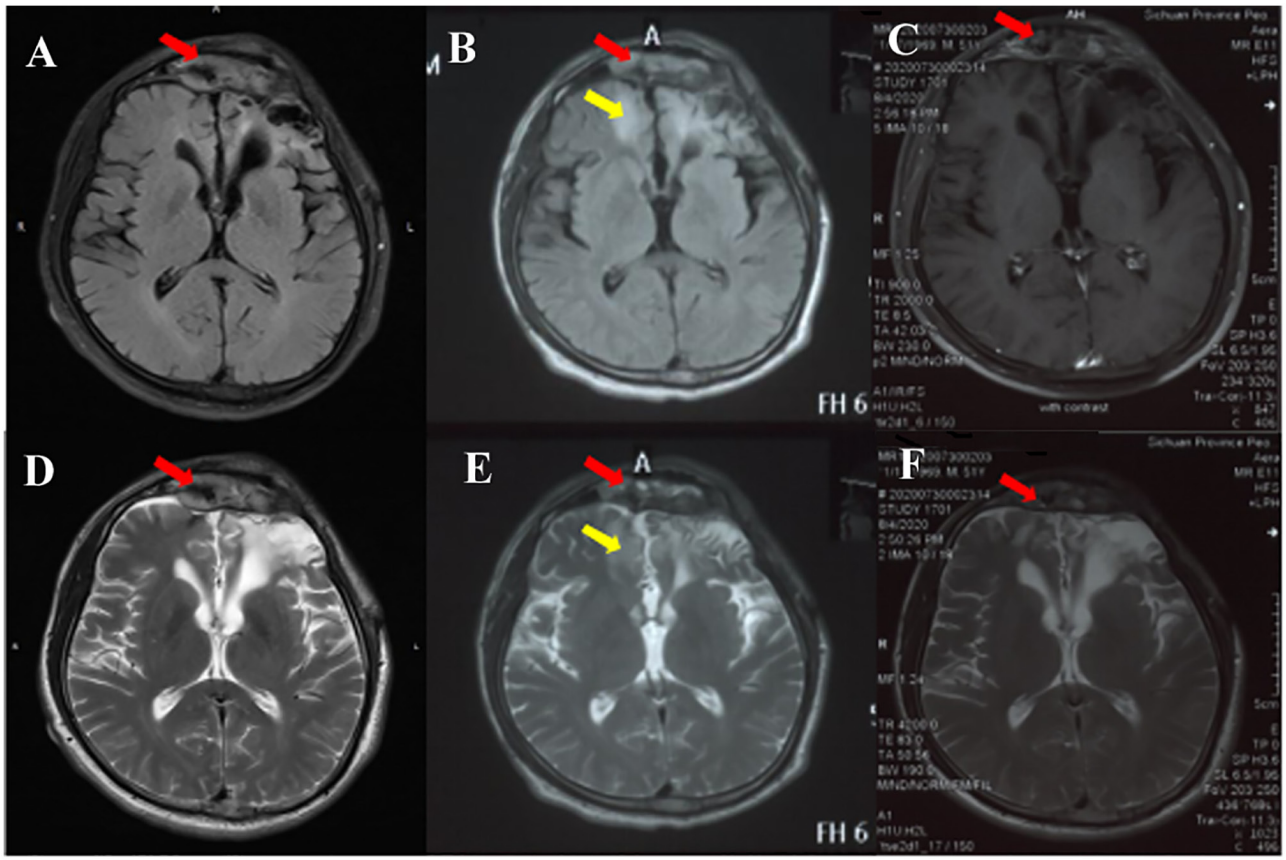

Figure 3. Periodic MRI changes in case 2 with recurrent anaplastic meningioma. (A-C) FLAIR MRI; (D-F) T2-weighted MRI. (A and D) Just prior to CIT, (B and E) 12 months after CIT and (C and F) 18 months after CIT (four cycles after initial bevacizumab treatment). The red arrows show the tumour area and the yellow arrows show the area of brain radiation necrosis.

ventricle was broadened and obtuse. The proposed diagnosis was a recurrence of the meningioma (Fig. 3A and D). On physical examination, the left eyebrow arch was slightly raised with local swelling and the bilateral pupils were equally large and round. Light reflection and normal binocular vision were also observed.

The patient applied to be enrolled in the clinical trial and was administered CIT according to the approved protocol. The target volume was delineated based on MRI and CT imaging. The GTV included the enhanced lesions observed in MRI. The planning GTV (PGTV) was generated by adding a 3-mm margin to the GTV. The CTV included the GTV and tumour bed area. The PTV was generated by applying 10-mm margins to the CTV. The PTV or PGTV were shrunk in the presence of bony structures or parts beyond the body. The patient received the total prescription dose of 52 Gy (RBE) in 13 fractions to the PTV and 64 Gy (RBE) in 16 fractions to the PGTV, at 4 Gy (RBE) per fraction over 3.2 weeks (Fig. 4). The treatment course was smooth and the patient reported relief of the symptoms of headache with grade 1 adverse events, including alopecia and cutaneous pigmentation, when finishing CIT.

After CIT, the patient entered regular follow-up and did not report any severe adverse events during the first year. The follow-up MRI performed at 13 months showed large areas with long T1 and T2 signals in the bilateral frontal lobes; Gd-enhanced imaging showed significant enhancement with multiple nodules. The anterior horn of the left lateral ventricle was also enlarged (Fig. 3B and E). The primary meningioma in the frontal lobe was stable. The patient experienced mild dizziness, nausea and headache. Combined with their medical history and MRI characteristics, the patient was considered to have developed RN.

Bevacizumab was proposed as the main treatment for RN control. Thereafter, the patient was administered 5 mg/kg bevacizumab biweekly for four cycles. Subsequent MRI showed reduction of the Gd-enhanced areas in the bilateral frontal lobes (Fig. 3C and F). In addition, the symptoms of mild dizziness, nausea and headache improved markedly with the treatment. Follow-up MRI performed 24 months after CIT showed no RN and no tumour progression, and the patient was in a stable state (data not shown).

Discussion

Limited evidence shows no obvious histological difference between RN and pseudoprogression (psPD). Notably, psPD often occurs within the first 2 months of treatment completion, whereas RN may show a latency of >3 months to years after RT (11). Thus, during the follow-up of patients with a history of brain malignancy and RT, inexperienced physicians may conclude that the disease has actually progressed if abnormal lesions are observed on radiography. Both of the present cases were diagnosed with disease progression by a radiologist based on abnormal signals in the tumour bed and oedema in the surrounding area using conventional MRI protocols, as

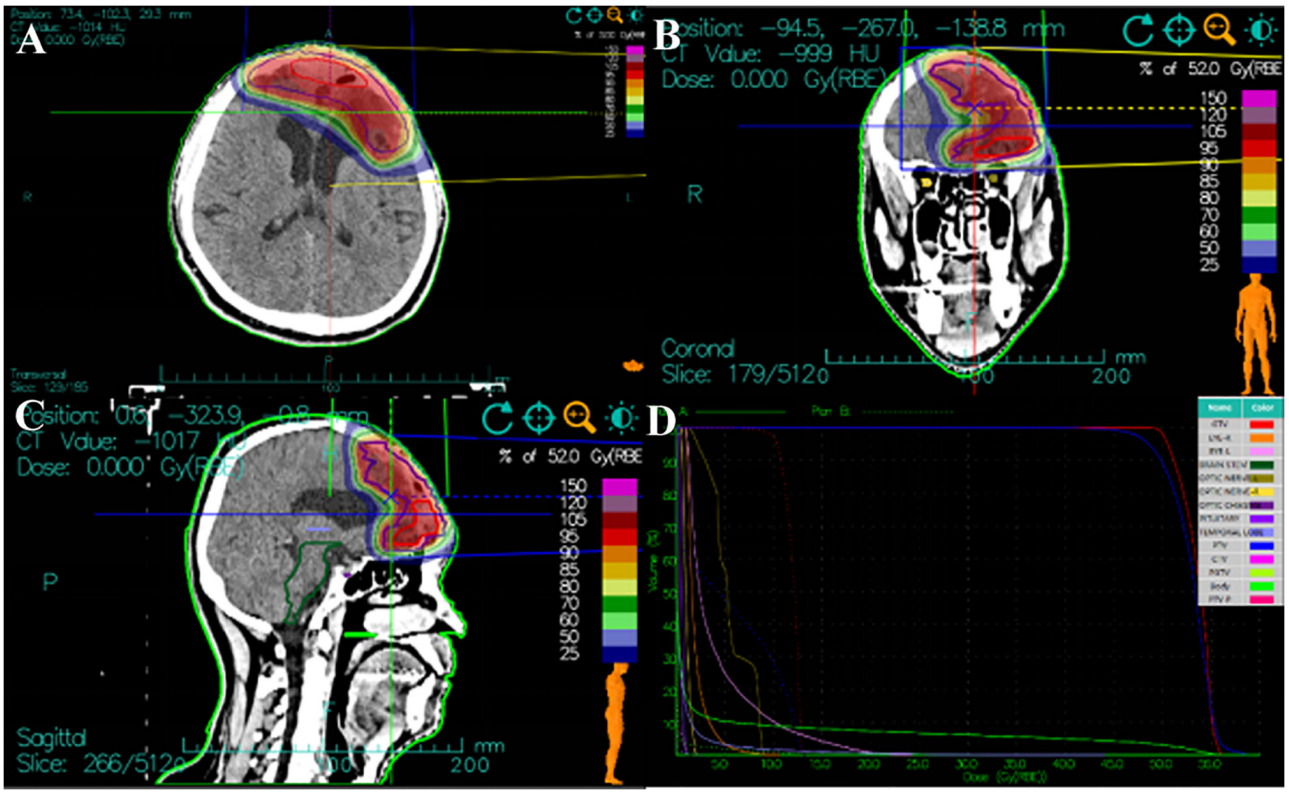

Figure 4. Target volume dose distribution in case 2. (A) Cross-sectional, (B) coronal and (C) sagittal planes. (D) Dose volume histogram.

these non-specific findings may also be observed in tumour progression. For patients with malignant brain tumours after RT, distinguishing between progressive disease and RN is key for the timely administration of the correct treatment regimen.

The incidence of RN is influenced by numerous factors, including RT modality, total dose, dose fractionation, intracranial pathology and diagnostic imaging modality. A previous study reported an RN incidence of 14-15% based on conventional RT modalities (12). Precision RT techniques, such as intensity-modulated RT, image-guided RT, stereotactic radiosurgery (SRS) and particle beam RT have minimized the risk of RN by decreasing the radiation injury to normal tissue (13). As a type of high linear energy transfer (LET) ray, CIT is considered more suitable for the treatment of radiation-resistant and recurrent tumours, due to its physical and biological advantages. CIT can be used to produce highly compact dose distributions that significantly reduce exposure to normal tissues compared with traditional photon RT. Carbon ion beam dose depositions follow the so-called Bragg curve as a function of tissue depth (14,15); therefore, because of the higher density of ionization events along the direction of carbon ions entering into tissue, CIT is a fundamentally different form of radiation with regard to its biological effects (16). Because of this, numerous uncertainties exist regarding the clinical and physical properties of carbon ions (17-19). Previous studies have investigated the robustness of scanned ion therapy, as well as uncertainties in treatment planning, treatment delivery and patient alignment (20,21). For example, if a patient is offset or the tumour volume changes during the treatment course, ion Bragg peaks may miss the planned target location, resulting in a potential underdose or overdose to critical structures outside the target. These uncertainties may lead to more severe damage to organs at risk (OARs) or tumour recurrence. Another phenomenon that cannot be ignored is the trailing effect of the carbon ion dose deposition curve. Particularly for large-volume tumours, the widening of the spread-out Bragg peak (SOBP) leads to an increased dose at the tail of the dose curve, which may also lead to increased toxicity to the OARs behind the tumour (22). Due to limited clinical experiences with CIT, more attention should be paid to its toxicities in clinical practice. In the present two cases, RN occurred 1 year after CIT, despite the very low radiation dose in the necrotic area according to the dose distribution and dose-volume histogram in the treatment plan.

Animal models of proton- or carbon-induced RN are notably sparse. In one study, researchers irradiated the right hemisphere of rat brains with large single-fraction doses of proton or helium ion beams. The animals were then subjected to continuous MRI (23). T2WI showed abnormal lesions consistent with the histological analysis findings of necrotic changes. Similar studies have been conducted with carbon ions (24,25), in which physical doses of 30 and 50 Gy with carbon particles (290 MeV/nucleon; 5 mm SOBP) in a single fraction were delivered to the left cerebral hemispheres of adult Sprague-Dawley rat brains. Histological examination revealed necrotic tissue damage, haemorrhage in the thalamus and vasodilatations around the necrotic region a total of 8 weeks after 50 Gy irradiation. The damaged tissue regions correlated well with those expected from the radiation-dose distribution, thus suggesting an advantage of charged carbon particles for irradiating restricted brain regions. While such experimental setups are complex, the use of fractionated radiation, and spatial correlation of imaging and histological changes with dose and LET may improve knowledge on carbon-induced neurotoxicity (26).

The utility of CIT is majorly limited by RN, since administering large doses in hypo-fractions or reirradiation of recurrent tumours are expected to result in significant RN. Mayer and Sminia (27) reported a cumulative dose of >100 Gy for reirradiation to be the threshold beyond which RN occurred. To reduce the incidence of RN, the real-time dose distribution should be evaluated, in addition to paying close attention to the RT history of the patient and estimated cumulative doses of the tumour target volume and OARs.

Among theories on the development of RN in the brain, the role of VEGF and hypoxia-inducible factor-1α (HIF-1α) in the pathogenesis of RN has become increasingly obvious. Radiation exposure damages vascular tissue around the tumour, subsequently leading to impaired oxygen diffusion between the tissue and blood vessels, and tissue hypoxia, which can initiate increased HIF-1α expression. Secondly, hypoxia and increased HIF-1α expression in tumour tissues stimulate reactive astrocytes to secrete VEGF, which is an angiogenic factor. High VEGF expression can lead to abnormal neovascularization, in which the vessels lack normal vascular structure, and exhibit structural disorder, fragility and high permeability. Abnormal neovascularization also promotes blood plasma exudation to the surrounding tissue and brain oedema. In turn, local high intracranial pressure can be caused by cerebral oedema, which can induce ischemia and hypoxia, forming a vicious cycle of local hypoxia, eventually progressing to RN (5,28,29).

Steroids have been effectively applied to treat RN and have been used to provide prompt relief of symptoms. Notably, steroids can reduce cytokine levels and inflammatory responses, not only improving brain oedema, but also reducing the risk of subsequent blood vessel changes and inflammation (30). Thus, for decades, steroids have been recommended as the front-line therapeutic strategy, including pulse-dose intravenous steroids, which are more effective than oral steroids (31). While the conventional treatment with steroids is dehydration combined with immunosuppressants (such as glucocorticoids), the reported response rate is only 20-30% and the long-term use of glucocorticoids can cause a series of adverse reactions, including metabolic disorders, gastrointestinal bleeding and immunosuppression-associated infection (31,32). Bevacizumab, as an antagonist of VEGF binding to its receptor, serves a role in vascular pruning, regulating vascular permeability, reducing brain oedema caused by brain necrosis and treating brain necrosis; however, its effect on RN has been reported only in small-sample clinical studies (33). Levin *et al* (34) conducted a randomized double-blind placebo-controlled trial of bevacizumab for the treatment of symptomatic radiation necrosis of the brain in 14 patients, reporting that all of the bevacizumab-treated patients, but none of the placebo-treated patients, exhibited an improvement in neurological symptoms. In addition to several case reports, studies have further established the clinical efficacy of bevacizumab for the treatment of brain RN, concluding that bevacizumab exhibits good short-term efficacy for RN, no matter whether SRS was applied to brain metastases or if conventional fraction RT was applied to high-grade glioma (33,35). However, the optimization of bevacizumab administration is a complex issue, involving dose, treatment course and discontinuation criteria. Researchers have administered various doses of bevacizumab (2.5-10 mg/kg) but the field has not yet produced a consensus on doses. Due to the vascular mechanisms of brain necrosis and the features of anti-angiogenic therapy, most experts recommend low-dose bevacizumab (2.5-5 mg/kg) in clinical practice, because of the associated treatment costs and treatment goals (36-38). Regarding treatment course, patients in previous studies typically received at least two doses of bevacizumab every 2-4 weeks (no maximum) (39,40). As the goal of bevacizumab treatment is symptom relief, not prolonging survival, treatment should be provided until symptoms are relieved and imaging improves, rather than being given as a long-term treatment (25).

The use of bevacizumab in the treatment of CIT-induced RN has rarely been reported (33). In the present two cases, bevacizumab doses of 5 mg/kg were administered every 2 weeks for four cycles. Both patients achieved good symptom remission and imaging improvement, with no recurrence of brain necrosis observed after 2 years of follow-up. Since bevacizumab was effective in the treatment of CIT-induced RN, it remains to be determined if it should be administered as early as possible to prevent the occurrence of RN. This administration remains controversial based on the results of published studies on the use of bevacizumab to prevent photon radiation-induced RN. Two studies have reported anti-angiogenic drug resistance (41,42), and premature or intermittent administration has been shown to increase bevacizumab resistance in patients with radiation brain necrosis. Moreover, Jeyaretna *et al* (43) reported that excess bevacizumab treatment may cause excessive vessel pruning, thereby aggravating localized ischemia and hypoxia of the necrotic area, and resulting in brain necrosis recurrence. Therefore, administrating bevacizumab to patients that have undergone brain radiation prior to the progression of brain necrosis may do more harm than good.

In conclusion, CIT differs fundamentally from photon radiation in both physical and biological characteristics. Data comparing the effects of different types of radiation on the occurrence of RN are surprisingly limited. Notably few, if any, studies of normal tissue toxicity following CIT have attempted to link biological effects to physical factors, not just dose. In addition, considering the trend of hypofractionation with CIT, an evaluation of various fractionation schemes is required. Notably, early treatment is necessary once symptomatic brain necrosis occurs. Bevacizumab is currently recognized as one of the best medicines for the control of RN based on the principle of anti-angiogenesis. The available evidence suggests that the number of administered cycles of bevacizumab should be based on the purpose of RN treatment, and long-term or prophylactic applications are not recommended; this is considered to be the best strategy to reduce the incidence of RN through protecting critical structures and avoiding severe damage in a clinical setting.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RL performed the patient treatment plans and analyzed the image data, and was a major contributor in writing the manuscript. QZ designed clinical trial protocol, and analyzed and interpreted data. HL, YG and XZ were the attending physicians of these two cases, who formulated the diagnosis and treatment plans, observed efficacy, followed up and collected medical data. ZL and SS were responsible for dose calibration, quality control and implementation of carbon ion radiotherapy. XW contributed to design and conception. RL and QZ confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient consented to the collection of data and images for the purpose of research and for their publication.

Competing interests

The authors declare that they have no competing interests.

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