Radiation Oncology

CASE REPORT

Open Access

Proton beam therapy in a patient with secondary glioblastoma (32 years after postoperative irradiation of medulloblastoma): case report and literature review

Bai Jiwei[1†], Muyasha Abulimiti[2†], Jin Yonglong[3,4], Wang Jie[5], Zhang Shuyan[6], Liu Chao[6], Wang Zishen[5], Wang Wei[7], Li Yinuo[8], Wang Weiwei[6], Yang Lu[6] and Shosei Shimizu[6,8*]

Abstract

Objective This report details the experience of a patient who developed a second primary glioblastoma (GB), offering insights into the treatment process and reviewing relevant literature.

Case presentation A male patient, who was diagnosed with medulloblastoma at age 9, received treatment with cobalt-60 craniospinal irradiation (CSI) (36 Gy/20 fractions) and a tumor bed boost (total of 56 Gy). After 32 years, at age 41, an MRI revealed a space-occupying mass in the left cerebellar hemisphere. Surgical resection was performed, and postoperative pathology confirmed a diagnosis of radiation-induced glioblastoma (RIGB). Given the history of irradiation and the current tolerability of brainstem doses, proton beam therapy (PBT) combined with Temozolomide (75 mg/m^2) was chosen. The treatment plan included 60 Gy on the gross tumor bed and 54 Gy on the clinical target volume, delivered in 30 fractions. The patient underwent regular follow-up and achieved a complete response.

Clinical discussion For childhood cancer survivors, the development of a second primary tumor significantly impacts prognosis. RIGB is a rare form of secondary tumor with distinct molecular characteristics compared to primary GB and recurrent secondary GB. Molecular markers such as IDH and MGMT status can help differentiate between primary GB, recurrent secondary GB, and radiation-induced secondary GB in patients with a history of prior radiation therapy. Surgical resection remains a primary treatment option, while PBT is preferred for postoperative treatment due to its superior protection of normal tissues and the ability to deliver high-dose irradiation.

Conclusion RIGB is a rare second primary tumor that requires strategic molecular profiling and individualized management. Proton beam therapy provides effective high-dose irradiation in the postoperative phase and is the preferred treatment option for such cases.

†Bai Jiwei and Muyasha Abulimiti are co-first authors.

*Correspondence:
Shosei Shimizu
23s.showsay.shimizu@gmail.com

Full list of author information is available at the end of the article

Keywords Medulloblastoma, Second primary tumor, Radiation-induced glioblastoma, Proton beam radiotherapy

Introduction

Historically, the priority for treating medulloblastoma (MB) in children has been avoidance of undue side effects while achieving tumor control. As diagnostic and therapeutic techniques for such tumors increasingly have become more standardized, particularly through molecular subgroup stratification and multidisciplinary regimens (i.e., surgery, chemotherapy, and radiotherapy), the potential for survival or cure has significantly improved. At the same time, there has been an upturn in subsequent occurrences of second primary tumors (SPTs) [1]. The International Agency for Research on Cancer (IARC) [2] has defined in which a patient harbors two or more primary tumors simultaneously or successively. Initially diagnosed tumors are considered primary lesions, whereas those arising later are designated SPTs. Central nervous system (CNS) is the most frequent site for SPT emergence, followed by endocrine and hematologic systems [3]. However, there is less data on glioblastoma (GB) as a SPT and its preferred mode of therapy after treatment of MB.

The purpose of this article was to share our experience with a patient who developed a second primary GB. The latter occurred 32 years after previously administered craniospinal irradiation (CSI) for MB as a child. We intended to provide insights into the treatment process and review relevant publications in the literature.

Case presentation

In February 1991, our male patient (then 9 years old) presented with complaints of dizziness, vomiting, and loss of balance for 6 months. His condition had worsened recently, during the past month. Imaging studies disclosed a cerebellar tumor (30×25×25 mm) that was surgically removed on February 11, 1991. The pathology report confirmed MB, so cobalt-60 CSI (36 Gy/20 fractions) was delivered postoperatively, with a tumor bed boost (total of 56 Gy). He was monitored regularly thereafter, undergoing annual brain magnetic resonance imaging (MRI), but no chemotherapy was given.

In March 2023 (32 years later), a space-occupying mass of left cerebellar hemisphere was detected by MRI. By June 25, 2023, loss of balance and difficulty walking had developed. A subsequent brain MRI again showed a mass of left cerebellar hemisphere, roughly 50.3×47×51.1 mm in size (Fig. 1A). On July 6, 2023, left cerebellar hemispheric resection was performed using the prior incision line at left cerebellopontine angle. The tumor within was soft and richly vascularized, with no clearly demarcated borders. Once separated along its apparent boundaries, it measured approximately 50×50×45 mm. The brainstem was well protected, as were various cranial nerves (ipsilateral posterior group, facial, auditory, trigeminal, abducens) and other structures. Postsurgical recovery was event-free.

Representative histologic preparations revealed a high-grade and diffusely infiltrating neuroepithelial tumor of left cerebellum. For the most part, this lesion was densely cellular, demonstrating marked pleomorphism and tumor giant cells in conjunction with microvascular proliferation and fenestrated necrosis. Its immunohistochemical and morphologic features were compatible with radiation-induced glioblastoma (RIGB), World Health Organization (WHO) Grade IV. Results of immunostaining are provided in Table 1, and additional evidence to support a diagnosis of RIGB is offered in Table 2.

Proton beam radiotherapy (PBT)

At this juncture, the patient was a 41-year-old man scoring 90 by Kanefsky Performance Scale. His medical history and past treatment did not preclude reirradiating the same area. Based on current and previous ranges of irradiation and the dosing tolerability of brainstem, proton beam therapy (PBT) was selected, hoping to minimize brainstem and spinal cord exposure. The patient received treatment on August 7, 2023, 1 month after surgery. We defined postoperative tumor bed area and contrast-enhanced volume in T1 fat-saturated contrast-enhanced MRI scan as gross tumor volume (GTVtb), adding a 5-mm clinical target volume (CTV) margin. Treatment planning relied on a RayStation platform (RaySearch Laboratories, Stockholm, Sweden) for inversely planned intensity-controlled (raster-scanned) proton delivery using two horizontal beams. GTVtb and CTV doses were 60 Gy and 54 Gy, respectively in 30 fractions each (Fig. 2). Maximum doses (Dmax values) to spinal cord and brain were 43.5 Gy and 53.5 Gy, respectively. Mean doses (Dmean values) to left and right hippocampus were 33 Gy and 0.95 Gy, respectively. Temozolomide (TMZ, 75 mg/m^2) was administered on days of radiotherapy, followed by postradiotherapy TMZ maintenance (200 mg/m^2 daily) for 5 days and cyclic dosing (every 28 days) for 6 months.

During the 32-year course of patient monitoring, multiple meningiomas had also arisen as SPTs, the first diagnosed in December 2008. One was removed in March 2009, but several non-resected meningiomas were under continued observation. To date, there is no evidence of recurrence or size increases, indicating stable disease. Likewise, MRI views of tumor bed remain devoid of high signal intensity nearly 1 year after completing radiotherapy. Aside from mild dizziness, the patient has

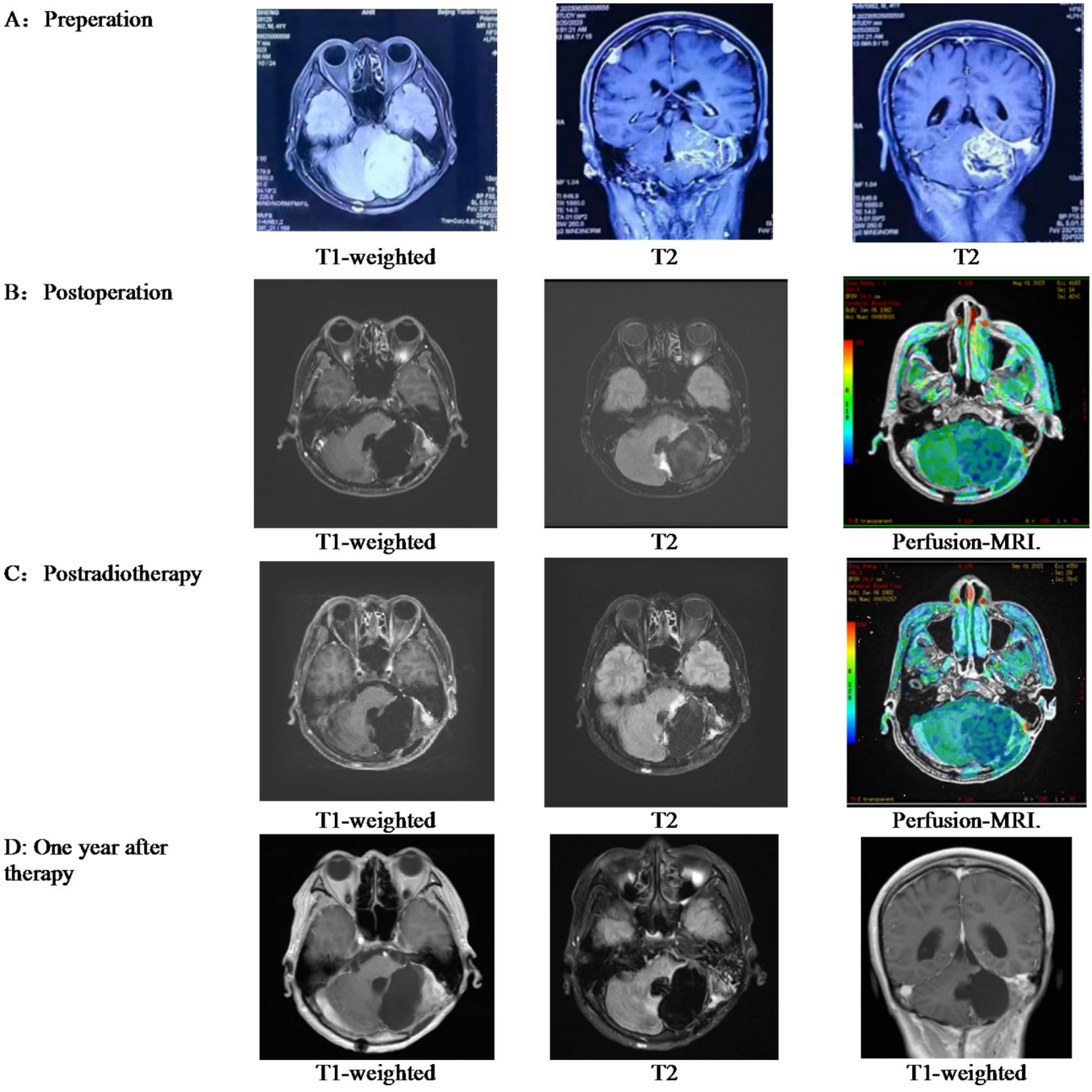

Fig. 1 Magnetic resonance imaging studies of 41-year-old male patient: **(A)** space-occupying mass of left cerebellar hemisphere (50.3 × 47 × 51.1 mm); **(B)** striated circumferential enhancement of tumor bed 1 month after surgery and 3D-arterial spin labeling (ASL) sequence showing localized, string-like, slightly hyperperfused operative margins; **(C)** less margin enhancement at operative site, compared with pretreatment baseline, but no real hyperperfusion of operative margins in 3D-ASL sequence; and **(D)** high intensity signal absent from tumor bed, 1 year after radiotherapy

experienced no other discomfort. A chronologic overview of the key medical events elaborated is included as Fig. 3.

Discussion

Herein, we have chronicled the medical course a childhood cancer survivor, including 32 years of follow-up after surgery and radiotherapy for MB and similar treatment imposed by a rare RIGB of later adult life. In this instance, PBT afforded access to high-dose, second-phase postoperative radiotherapy.

Second primary tumors (SPTs)

For survivors of childhood cancer, the cumulative incidence of SPTs arising within 30 years after initial tumor diagnoses ranges from 3 to 10% [3]. This is roughly 3–6 times higher than comparable rates in the general population. The most common SPTs encountered are breast

Table 1 Immunohistochemical features of primary and secondary glioblastoma

Tumor marker	Secondary GB [4]	Primary GB [5]	Present case
GFAP	**Positive (GFAP+)**	**Positive (GFAP+)**	**Positive (GFAP+)**
Olig-2	Positive (Olig-2+)	Positive (Olig-2+)	Positive (Olig-2+)
IDH1 R132H	Positive (IDH1 R132H+)	Negative (IDH1 R132H-)	**Negative (IDH1 R132H-)**
IDH2 R172K	Positive (IDH2 R172K+)	Negative (IDH2 R172K-)	**Negative (IDH2 R172K-)**
ATRX	Negative (ATRX-)	Positive/Negative (varies)	Negative (ATRX-)
p53	Positive (p53+)	Negative (p53-)	**Negative (p53-)**
Ki-67	Approximately 30%	Typically high (varies)	Approximately 30%
Synaptophysin	Positive (Syn+)	Positive/Negative (varies)	**Weak Positive (Syn weak +)**
H3K27M	Negative (H3K27M-)	Negative (H3K27M-)	Negative (H3K27M-)
H3K27me3	Typically retained	Typically retained	**Partial expression missing**
EZH2	Positive (EZH2+)	Variable (EZH2+)	**Negative (EZH2-)**
MTAP	Negative (MTAP-)	Negative (MTAP-)	Negative (MTAP-)
SOX11	Positive (SOX11+)	Variable (Positive/Negative)	Positive (SOX11+)
MSH6	Positive (MSH6+)	Positive (MSH6+)	Positive (MSH6+)
MSH2	Positive (MSH2+)	Positive (MSH2+)	Positive (MSH2+)
MLH1	Positive (MLH1+)	Positive (MLH1+)	Positive (MLH1+)
PMS2	Positive (PMS2+)	Positive (PMS2+)	Positive (PMS2+)
MGMT promoter methylation	**Methylated**	**Variable (methylated/non-methylated)**	**Methylated**
IDH1/IDH2	Mutant	Wild type	Wild type
1p/19q deletion	No deletion	No deletion	No deletion
EGFR amplification	No amplification	Often amplified	No amplification
CDKN2A deletion	Common (pure deletion)	Common	Pure deletion
CDKN2B deletion	Common (pure deletion)	Common	Pure deletion

Table 2 Differing profiles of secondary GB (recurrent vs. radiation induced)

Characteristic	Recurrent secondary GB [6]	Radiation-induced secondary GB
Etiology	Progression from low-grade or intermediate-grade glioma	Development after radiotherapy for other conditions (e.g., leukemia, brain tumor)
IDH mutation	Common (especially IDH1 R132H mutation)	Rare
TP53 mutation	Common	Possible, but less frequent
ATRX inactivation	Common	Possible
MGMT promoter methylation	Common	Possible
TERT promoter mutation	Rare	Possible
1p/19q co-deletion	Rare	Rare
Typical patient age	Usually younger patients	Usually older patients
Medical history	History of low-grade or intermediate-grade glioma	History of radiotherapy for other tumors or diseases
Other chromosomal abnormalities	Common specific chromosomal mutation patterns	May have more heterogeneous chromosomal mutations and structural variations

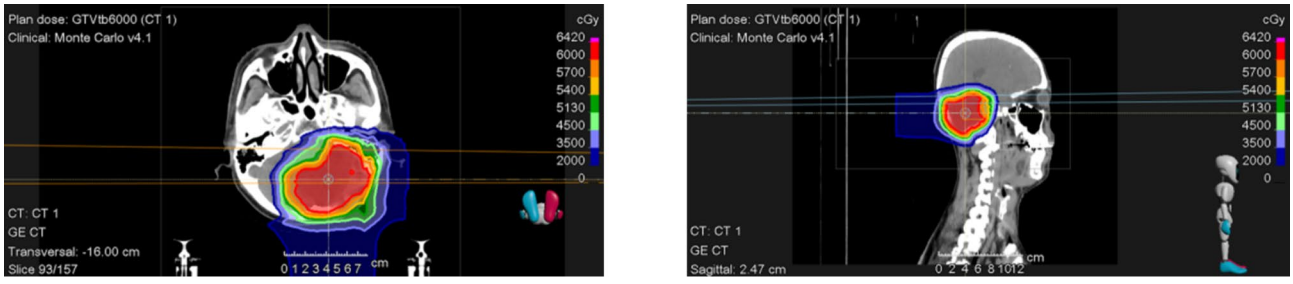

Fig. 2 Postoperative proton beam therapy plan (gross tumor volume [GTVtb] in red; clinical target volume [CTV] in dark green)

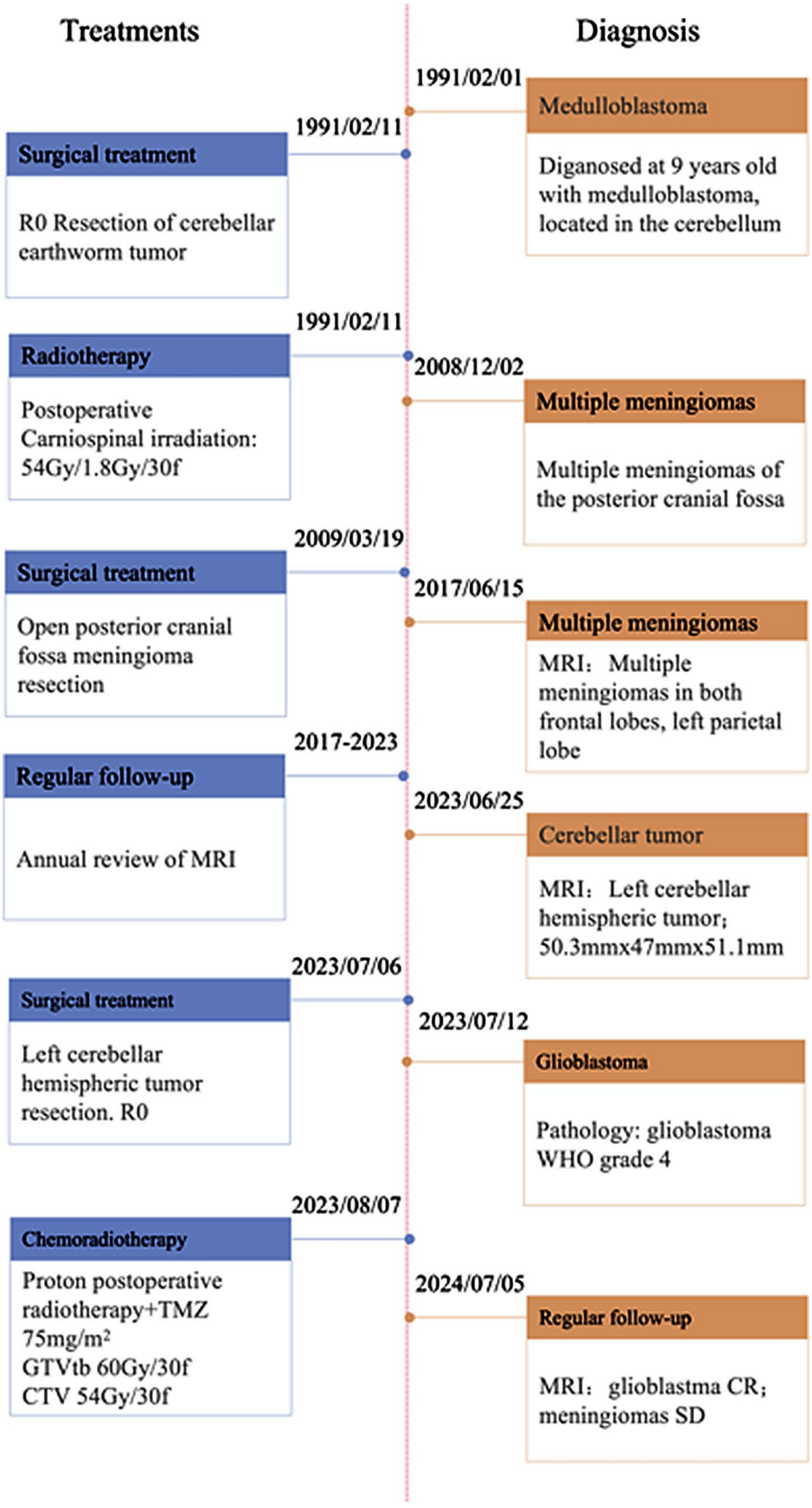

Fig. 3 Timeline of events during 32-year patient surveillance period

cancer for female survivors, ranging from 12 to 20%; thyroid cancer, estimated at 2–7%; and skin cancer, exceeding general population risk by 2–6 times [7, 8]. GB is a relatively rare SPT as such, but it is a recognized risk, particularly for recipients of cranial radiotherapy. More so than chemotherapy, irradiation is usually associated with a higher incidence of SPT (9.5% vs. 2.4%) [3], given its capacity to alter DNA methylation and methyltransferase activity and its deregulation of mRNA.

MB is a common childhood tumor, the overall survival of which has improved through combined use of radiotherapy, chemotherapy, and surgery. Current survival rates are ~80–85% for standard risk groups and ~65–70% for high-risk groups. However, long-term toxic effects (especially SPTs) are increasing as a result. In the aftermath of MB, CNS is reportedly the most common site of SPTs (63/146, 43.2%), followed by endocrine and hematologic systems. Similar outcomes have been documented during the Childhood Cancer Survivor Study and its British counterpart probe, likely due to whole brain and spinal axis targeting during CSI [7, 9]. The unique physical properties entailed have broadened the usage of PBT in treating childhood cancer. Proton doses are characterized by abrupt surges in energy release, called Bragg peaks. Such rapid dosing decays reduce radiation to nearby healthy tissues by a factor of 2–3. However, monitoring of treated patients for potential SPTs is a long-term proposition, and available research on SPT incidence by mode of MB treatment (proton vs. photon therapy) is currently lacking.

Raymond [10] has generated estimates of secondary cancer incidence using a model derived from Publication No. 60 of the International Commission on Radiologic Protection. Compared with intensity-modulated or conventional X-ray plans, proton beams lowered the expected incidence of radiation-induced secondary cancers after MB treatment by a factor of 8–15. An analysis of the SEER database from mid-2000s forward, ostensibly marked by greater PBT use, has also confirmed fewer SPTs as late effects [3]; and in another assessment according to treatment time frames (1973–1995 vs. 1995–2014), the SPT rate proved higher during earlier years (1973–1995) of more limited PBT use [11]. Matched adult populations ($n=558$ each) receiving proton or photon therapy have been followed as well (median interval: proton group, 6.7 years; photon group, 6.0 years) [12], recording SPT rates of 5.2% and 7.5%, respectively. Above findings imply a lower incidence of SPT after PBT of childhood MB. On the other hand, most present-day survivors of pediatric tumors have received photon therapy over a decade ago, so longer follow-up periods may be needed to ascertain SPT incidence in relation to PBT.

Radiation-induced second primary glioblastoma (RIGB)

Classification of a second primary GB as radiation induced (rather than recurrent second primary) [13–15] is based on the following criteria: (1) tumor situated within the irradiated field; (2) sufficient latency between irradiation and tumor occurrence; (3) histological type different from that of original neoplasm; and (4) no pathology, such as Von Recklinghausen disease, favoring tumor development. The most common malignancies associated with RIGB are nasopharyngeal carcinoma (37%), primary intracranial germinoma (21%), and MB (16%) [16]. At 9 years of age, our patient with MB received postoperative CSI only. In analyzing 2771 patients with MB from the SEER-18 database, there were 146 patients (5.27%) who developed SPTs at 15 years. Rates of SPTs after radiotherapy only, radio- and chemotherapy, and chemotherapy only were 9.5%, 4.3%, and 2.4%, respectively [3]. Several studies have shown a 14-year mean latency between radiotherapy and diagnosis of RIGB, unlike the 32-year span in our patient that surpassed most previously published intervals [11, 14]. It is a widely held concept that the younger a patient is at primary treatment, the greater the risk of RIGB will be. Younger onset may therefore render patients especially vulnerable to radiation-induced gliomagenesis in later years due to an abundance of neurogenic stem cells and increased growth factor activity [17].

RIGB is a relatively rare SPT, with a molecular profile that distinguishes it from primary GB and recurrent secondary GB. Clinicians focus more on recurrent secondary GB, tending to overlook the specific and individualized treatment of RIGB. *IDH* mutation is a critical marker in glioma classification that helps differentiate recurrent and radiation-induced forms of secondary GB (Tables 1 and 2). *IDH* mutations are largely features of less ominous tumors (WHO grade II-III), whereas the *IDH* wild type primarily reflects aggressive disease (WHO grade IV), signaling a worse prognosis. In 2021, the latest WHO revision of GB grading was substantial, stipulating that only *IDH* wild-type lesions warrant a GB diagnosis [5]. Still, there are perhaps some GBs with *IDH* mutations. The latter have chiefly presented as secondary GBs, morphologically similar to primary GB but imparting a more favorable prognosis [18]. In patients with *IDH*-mutant GBs, median OS may be ~31 months, as opposed to 15 months for those with *IDH*-wildtype GBs [18, 19].

Among 39 patients with secondary GBs, the *IDH* mutation rate was found to be 60%, and the O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation rate was 68.8% [20]. MGMT is a direct DNA repair enzyme that eliminates the TMZ-produced genotoxic O6-methylguanine adduct in a single-step process. Because this restores the genomic integrity of tumors,

MGMT promoter methylation denotes a better prognosis. An earlier meta-analysis has determined a median OS (mOS) of 10 months in patients with RIGBs [Peter Y. M]. Across the spectrum of grade IV GBs, survival in patients with RIGBs (mOS, 4.8 months) was shorter than in instances of *de novo* GB (mOS, 19.2 months; $p<0.001$). These findings may be explained by the fact patients with *IDH* wild type were involved, and there was a lower percentage of MGMT promoter methylation [14]. Our patient with WHO grade IV GB exhibited both *IDH* mutation and MGMT promoter methylation, thus suggesting TMZ sensitivity and a better prognosis than anticipated for primary or recurrent secondary GB of *IDH* wild type.

RIGB treatment

Currently, there is no consensus on oncologic treatment in instances of RIGB. Studies have concluded that patients with secondary GBs experience significantly longer survival times if repeat resection is elected, instead of foregone [20]. Patients with good KPS scores and proper suitability for surgery should subsequently consider second-phase resection as a primary treatment option, although decisions on postoperative adjuvant therapy are comparatively more difficult. Physicians must weigh the perceived benefit of reirradiation against the risk of related brain damage.

In the past, the conventional dose limit for partial brain radiotherapy has been 60 Gy. Some sources have challenged this view, suggesting that reirradiated brain tissue may tolerate a fractionated (2 Gy/fr) cumulative normalized total dose of 100 Gy before necrosis ensues [13]. Paulino et al. have noted that among patients with radiotherapy-induced high-grade gliomas, those who received reirradiation of 50 Gy (35/85, 41%) displayed a 2-year overall survival (OS) rate of 21%. This was significantly better than the 3% rate recorded at 2 years in the absence of reirradiation [21]. Similarly, a meta-analysis has found that reirradiation (mean dose, 48 Gy) conferred a better 2-year OS rate (24%) than the rate achieved (9%) through different treatment. Upon examining factors linked to survival in the setting of grade III-IV RIGB, multimodality combination therapy (including radiotherapy) was identified as an independent prognostic factor ($p=0.002$) [16]. These observations suggest that in some patients with radiation-induced gliomas, a therapeutic strategy of reirradiation may serve to prolong disease control. However, the tolerance threshold is changing due to advances in radiotherapy technology, such as PBT. These improvements stand to mitigate the risk of late radiation effects. Despite a scarcity of data on PBT use for reirradiation of RIGB, we are encouraged by its successful application in patients with recurrent gliomas or other brain tumors. Scartoni et al. [22] have investigated 33 patients who completed questionnaires before starting PBT, on last day of treatment, and at every follow-up visit until disease progression. It appears that PBT is safe and well tolerated, ensuring stable quality-of-life parameters for the duration.

The Proton Collaborative Group (PCG) has examined 45 patients from 12 PBT centers in the United States, all receiving photon radiotherapy initially at doses of 60 Gy. The median time between original diagnosis and recurrence was only 20 months, and the median total reirradiation dose was 46.2 Gy (range, 25–60 Gy), with a median of 2.2 Gy per fraction. Of these 45 patients, 40 (88.9%) had received an equivalent dose in 2 Gy fractions (EQD2) of >39 Gy. All patients had GB as their primary diagnosis. Median progression-free survival (PFS) time was 13.9 months, and median OS was 14.2 months. In terms of side effects, a total of five patients experienced grade 3 toxicity. One showed acute toxicity (ataxia), whereas late toxicity (neuropathy, cognitive disturbance, optic nerve disorder, or seizure) surfaced in the other four. No acute or delayed grade 4 or 5 toxicities were observed.

During a similar multicenter study, patients with GB were reirradiated at high dose, without serious side effects over a year's time, highlighting the utility of PBT for this purpose [23]. Another 20 patients who received proton reirradiation for recurrent gliomas also registered acceptable outcomes after high-dose radiotherapy. The mean initial dose was 59.4 Gy, and the mean reirradiation dose after a median of 15.3 months (range, 5.3-152.6 months) was 54 Gy [24]. Several earlier investigations have further reinforced the prospect of high-dose irradiation enabled by PBT.

When irradiating our patient (32 years after initial radiotherapy), we used a standard postoperative dose of 60 Gy, delivering a low dose to brainstem and hippocampus. The Dmax of brain scan was 53.5 Gy, the Dmean of left hippocampus was 33 Gy, and the Dmean of right hippocampus was 0.95 Gy. Although the prognosis of a grade IV RIGB is poor, lessening our concerns over later clinically significant necrosis, it is important for physicians to optimally protect a patient's cognitive function. The incidence of radiation necrosis typically peaks around 1–3 years after radiotherapy [25]. At 1 year after reirradiation, no signs of tumor recurrence or radiation necrosis have been detected as yet.

In summary, RIGB is a rare SPT determined by strategic molecular profiling and requiring individualized management. PBT is the preferred postoperative treatment.

Abbreviations

SPT	Second primary tumors
IARC	International Agency for Research on Cancer
CNS	Central Nervous System
CSI	Craniospinal Irradiation
MRI	Magnetic Resonance Imaging
CPA	Cerebellopontine Angle region

IHC	Immunohistochemistry
RIGB	Radiation-induced Glioblastoma
NPC	Nasopharyngeal Cancer
NOS	Not Otherwise Specified
WHO	World Health Organization
KPS	Karnofsky Performance Status
OS	Overall Survival
PFS	Progression-free Survival
PCG	Proton Collaborative Group
PBT	Proton beam therapy

Author contributions
Bai Jiwei and Shousei Shimizu contributed to formulating the surgical and radiotherapy treatment programs. Data collection and the first draft of the manuscript were written by MA. All authors provided comments on previous versions of the manuscript. Wang Jie, Zhang Shuyan, Liu Chao, and Wang Zishen contributed to the diagnosis and radiotherapy treatment. All authors read and approved the final manuscript.

Funding
Not applicable.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Consent for publication
Written informed consent for publication was obtained from all participants.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China
[2]Department of Radiation Oncology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba 305-8575, Japan
[3]Department of Radiotherapy, The Affiliated Hospital of Qingdao University, Qingdao, China
[4]School of Public Health, Qingdao University, Qingdao 266071, China
[5]Department of Radiotherapy Physics and Technology, Hebei Yizhou Cancer Hospital, Zhuozhou 072750, China
[6]Department of Pediatric Radiation Therapy Center/Pediatric Proton Beam Therapy Center, Hebei Yizhou Cancer Hospital, Zhuozhou 072750, China
[7]Department of Radiology, Hebei Yizhou Cancer Hospital, Zhuozhou 072750, China
[8]Department of Radiotherapy, University of Tsukuba Hospital, Tsukuba 305-8576, Japan

Received: 17 July 2024 / Accepted: 1 September 2024
Published online: 05 October 2024

References

1. Turcotte LM, Neglia JP, Reulen RC, et al. Risk, risk factors, and surveillance of subsequent malignant neoplasms in survivors of childhood cancer: a review. J Clin Oncol. 2018;36:2145.
2. Report WG. International rules for multiple primary cancers (ICD-0 third edition). Eur J cancer Prevention: Official J Eur Cancer Prev Organisation (ECP). 2005;14:307–8.
3. Nantavithya C, Paulino AC, Liao K, et al. Development of second primary tumors and outcomes in medulloblastoma by treatment modality: a surveillance, epidemiology, and end results analysis. Pediatr Blood Cancer. 2020;67:e28373.
4. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013;19:764–72.
5. Mahajan S, Suri V, Sahu S, et al. World Health Organization Classification of Tumors of the central nervous system 5th Edition (WHO CNS5): what's new? Indian J Pathol Microbiol. 2022;65:S5–13.
6. Kleihues P, Ohgaki H. Primary and secondary glioblastomas: from concept to clinical diagnosis. Neurooncology. 1999;1:44–51.
7. Reulen RC, Frobisher C, Winter DL, et al. Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA. 2011;305:2311–9.
8. Turcotte LM, Whitton JA, Friedman DL, et al. Risk of subsequent neoplasms during the fifth and sixth decades of life in the childhood cancer survivor study cohort. J Clin Oncol. 2015;33:3568.
9. Turcotte LM, Liu Q, Yasui Y, et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year survivors of childhood cancer, 1970–2015. JAMA. 2017;317:814–24.
10. Miralbell R, Lomax A, Cella L, Schneider U. Potential reduction of the incidence of radiation-induced second cancers by using proton beams in the treatment of pediatric tumors. Int J Radiation Oncology* Biology* Phys. 2002;54:824–9.
11. Nantavithya C, Paulino AC, Liao K, et al. Observed-to-expected incidence ratios of second malignant neoplasms after radiation therapy for medulloblastoma: a Surveillance, Epidemiology, and end results analysis. Cancer. 2021;127:2368–75.
12. Chung CS, Yock TI, Nelson K, et al. Incidence of second malignancies among patients treated with proton versus photon radiation. Int J Radiation Oncology* Biology* Phys. 2013;87:46–52.
13. Salvati M, Artico M, Caruso R, et al. A report on radiation-induced gliomas. Cancer. 1991;67:392–7.
14. Woo PY, Lee JW, Lam SW, et al. Radiotherapy-induced glioblastoma: distinct differences in overall survival, tumor location, pMGMT methylation and primary tumor epidemiology in Hong Kong Chinese patients. Br J Neurosurg. 2024;38:385–92.
15. Cahan WG, Woodard HQ, Higinbotham NL, et al. Sarcoma arising in irradiated bone: report of eleven cases. Cancer: Interdisciplinary Int J Am Cancer Soc. 1998;82:8–34.
16. Yamanaka R, Hayano A, Kanayama T. Radiation-induced gliomas: a comprehensive review and meta-analysis. Neurosurg Rev. 2018;41:719–31.
17. Tubiana M. Can we reduce the incidence of second primary malignancies occurring after radiotherapy? A critical review. Radiother Oncol. 2009;91:4–15.
18. Juratli TA, Kirsch M, Geiger K, et al. The prognostic value of IDH mutations and MGMT promoter status in secondary high-grade gliomas. J Neurooncol. 2012;110:325–33.
19. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360:765–73.
20. Hamisch C, Ruge M, Kellermann S, et al. Impact of treatment on survival of patients with secondary glioblastoma. J Neurooncol. 2017;133:309–13.
21. Paulino AC, Mai WY, Chintagumpala M, et al. Radiation-induced malignant gliomas: is there a role for reirradiation? Int J Radiation Oncology* Biology* Phys. 2008;71:1381–7.
22. Scartoni D, Amelio D, Palumbo P, et al. Proton therapy re-irradiation preserves health-related quality of life in large recurrent glioblastoma. J Cancer Res Clin Oncol. 2020;146:1615–22.
23. Saeed AM, Khairnar R, Sharma AM, et al. Clinical outcomes in patients with recurrent glioblastoma treated with proton beam therapy reirradiation: analysis of the multi-institutional Proton Collaborative Group Registry. Adv Radiation Oncol. 2020;5:978–83.
24. Galle JO, McDonald MW, Simoneaux V, Buchsbaum JC. Reirradiation with Proton Therapy for Recurrent Gliomas. Int J Part Therapy. 2015;2:11–8.
25. Strenger V, Lackner H, Mayer R, Sminia P, Sovinz P, Mokry M, Pilhatsch A, Benesch M, Schwinger W, Seidel M, Sperl D, Schmidt S, Urban C. Incidence and clinical course of radionecrosis in children with brain tumors. A 20-year longitudinal observational study. Strahlenther Onkol. 2013;189(9):759–64.

Publisher's note