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Novel Insights from Clinical Practice

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# Radiation-Associated Glioblastoma after Prophylactic Cranial Irradiation in a Patient of ALL: Review of Literature and Report of a Rare Case

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**Established Facts**

- Radiation-induced malignant glioma (RIMG) is a rare late complication of cranial or craniospinal radiotherapy (RT) with a cumulative incidence of 1–2% per decade after completion of RT.
- RIMG is an aggressive malignancy with a poor prognosis with reported overall survival usually less than a year despite multimodality management.

**Novel Insights**

- Though the average latency period before the development of radiation-induced malignant glioma (RIMG) is around 10 years, a shorter latency period may be observed in case of exposure to therapeutic RT at a very young age in a patient with haematolymphoid malignancy.
- Occasionally RIMG may run a fulminant and fatal course, characterized by diffuse leptomeningeal and subependymal dissemination, complicated by acute bacterial meningitis and brain abscess at the site of post-operative cavity.

**Keywords**
Cranial radiotherapy · Glioblastoma · Radiation-induced second malignancy · Radiation-induced malignant glioma

**Abstract**
***Introduction:*** The cumulative incidence of radiation-induced second malignancy is 1–2% per decade after radiotherapy (RT). Radiation-induced malignant glioma (RIMG) is a rare complication of cranial RT. ***Case Presentation:*** We herein describe a case of left frontal glioblastoma arising 5 years after prophylactic cranial irradiation (12.6 Gy/7 fractions/1.5 weeks) as a part of INCTR-02-04 protocol in a 3-year-old boy with B-cell ALL. He underwent gross total excision (GTE) of the tumour followed by post-operative intensity modulated RT (59.4 Gy/33 fractions/6.5 weeks) and concurrent and adjuvant (3 cycles) temozolomide. Thereafter, he had rapid disease progression, which entailed re-excision of the recurrent tumour. Subsequently, there was widespread subependymal and leptomeningeal spread of tumour, lead-

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ing to death 10.5 months after the initial diagnosis. ***Conclusion:*** RIMG is an aggressive malignancy with a dismal prognosis, and in spite of multimodality management, it exhibits relentless progression, occasionally characterized by subependymal and leptomeningeal dissemination, leading to eventual death within a year of diagnosis.



## Introduction

Cranial or craniospinal radiation (RT) is an important component of the therapeutic armamentarium in a plethora of solid as well as haematological malignancies. Like any treatment modality, cranial RT is associated with acute as well as late morbidities. The acute morbidities include fatigue, dermatitis, conjunctivitis, seizure, headache, and vomiting and are usually easily manageable. On the other hand, the late toxicities, for example, neurocognitive and neuroendocrine effects, cerebral vasculopathy, and radiation-induced second malignancy (RISM) are usually difficult to manage. Radiation-induced malignant glioma (RIMG) is an extremely rare complication of central nervous system (CNS)-directed radiation, and less than 200 cases have been described in medical literature [1]. In a systematic review of subsequent neoplasms of the CNS among survivors of childhood cancer, there was a linear correlation between the dose of cranial RT and the risk of subsequent high-grade glioma (HGG) [2]. The odds ratio (OR) for subsequent HGG increased with the dose of RT and peaked at exposure of 30–44.9 Gy (OR 21). Radiation-induced glioblastoma (RIG) is an aggressive tumour with a poor prognosis and despite multimodality management, the median overall survival (OS) is <1 year [1, 3]. We herein describe the management of a case of left frontal glioblastoma arising 5 years after prophylactic cranial irradiation (PCI) as a part of INCTR-02-04 protocol in a 3-year-old boy with B-cell ALL and review the pertinent literature.

## Case Report

A 3-year-old boy presented with low-grade fever and bilateral lower limb pain for 1 month. With the exception of unilateral breast cancer in the paternal grandmother (diagnosed at 66 years), there was no history of cancer in his first-degree and second-degree relatives. Baseline full blood count showed haemoglobin 3.9 g/dL, total leucocyte count (TLC) 40,200/μL, differential count $N_3L_{22}E_2blasts_{73}$, and platelet count 78,000/μL, suggestive of acute leukaemia. Bone marrow aspirate and biopsy showed near total replacement of marrow by blasts, which were morphologically lymphoid and negative for myeloid peroxidase, suggestive of ALL. Flow cytometric analysis of peripheral blood revealed 45% blasts, which were immunopositive for CD45, CD34, CD10, CD19, CD38, and CD79a and immunonegative for CD3, CD13, CD20, and CD33, suggestive of B-lineage ALL. Hybrid transcript for BCR-ABL was not detected in the bone marrow leucocytes. Cerebrospinal fluid (CSF) cytology did not reveal any blast. He was started on INCTR-02-04 protocol. After induction 1 ($I_1$) chemotherapy with vincristine, daunorubicin, L-asparaginase, intrathecal methotrexate, and oral prednisone for 4 weeks, bone marrow aspirate and biopsy showed 1–2% blasts. This was followed by induction 2 ($I_2$) chemotherapy with vincristine, cytarabine, cyclophosphamide, L-asparaginase, intrathecal methotrexate, and oral 6-mercaptopurine for 4 weeks. Thereafter, he received repeat induction 1 ($RI_1$) and repeat induction 2 ($RI_2$) chemotherapy, each over 4 weeks, followed by interim maintenance chemotherapy with vincristine, L-asparaginase, intrathecal methotrexate, oral 6-mercaptopurine, dexamethasone, and methotrexate for 6 weeks. He received PCI 12.6 Gy/7 fractions/1.5 weeks as a part of CNS-directed therapy during the interim maintenance phase. Subsequently, he received repeat induction consolidation chemotherapy with vincristine, daunorubicin, L-asparaginase, intrathecal methotrexate, subcutaneous cytarabine, oral prednisone, and 6-mercaptopurine for 4 weeks, followed by 6 cycles of maintenance chemotherapy (M1–M6), each spanning over 3 months. After the completion of the planned treatment, he was in complete remission for 3.5 years (5 years from the date of completion of PCI). Then, he presented with headache and vomiting for 2 months. Contrast-enhanced magnetic resonance imaging (CMRI) of the brain and spine revealed an 8.2 × 5.5 × 6.6 cm solid cystic lesion in the left frontal lobe with mass effect, minimal perilesional oedema, and midline shift to the right by 1.2 cm (Fig. 1). He underwent gross total excision of the tumour in the neurosurgery department. Post-operative histopathology revealed glioblastoma, immunopositive for glial fibrillary acidic protein and p53 and immunonegative for IDH-1. Post-operative CMRI of the brain showed gliotic areas in the left frontal lobe with surrounding white matter oedema, areas of bleed, and peripheral contrast enhancement. He was planned for post-operative radiotherapy (RT) 59.4 Gy/33 fractions/6.5 weeks by fixed 8-field intensity modulated radiotherapy (IMRT) with 6 MV X-rays on Monaco treatment planning system version 5.11 (Fig. 2). The gross tumour volume included the pre-operative contrast enhancing solid cystic lesion and the post-operative cavity. The clinical target volume consisted of the gross tumour volume with an anatomically constrained expansion of 2 cm. A 0.3-cm isotropic margin was given to the clinical target volume to generate the planning target volume. The patient was treated on Elekta Synergy S medical linear accelerator (Elekta, Sweden) and received concurrent temozolomide 75 mg/m$^2$ OD through the course of RT. He tolerated the planned treatment well without any toxicity. Subsequently, adjuvant chemotherapy with temozolomide 150 (cycle 1) to 200 (cycle 2–3) mg/m$^2$ OD D1–D5 every 4 weeks was administered for 3 cycles. He tolerated adjuvant chemotherapy well and the toxicities included grade 1 neutropaenia. Three months after the completion of RT, CMRI brain showed heterogeneously enhancing nodular lesions in the wall of the post-operative cavity in the left frontal lobe extending to the body of the corpus callosum and a separate enhancing lesion in the frontal horn of the right lateral ventricle (Fig. 3a–d). On MR

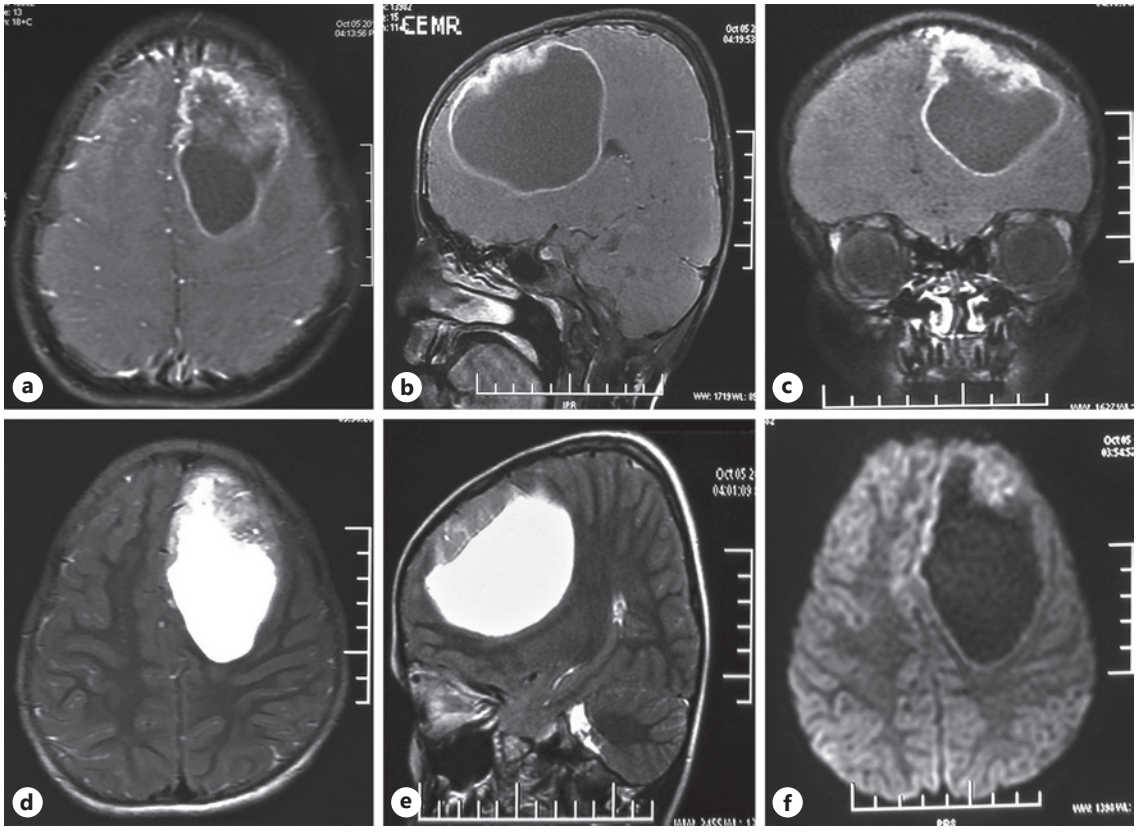


**Fig. 1.** T1-weighted post-contrast axial (**a**), sagittal (**b**), and coronal (**c**) and T2-weighted axial (**d**) and sagittal (**e**) baseline magnetic resonance images of the brain show an 8.2 × 5.5 × 6.6 cm solid cystic lesion in the left frontal lobe with mass effect, minimal perilesional oedema, and midline shift to the right. There was thick irregular post-contrast enhancement in the solid component of the lesion. Diffusion-weighted images (**f**) show restriction of diffusion of water molecules in the solid component of the lesion.

perfusion study, the lesions in the left frontal lobe showed hyperperfusion with increased relative cerebral blood volume and relative cerebral blood flow compared with normal brain parenchyma. Multi-voxel magnetic resonance spectroscopy showed choline peak and increased choline/N-acetyl aspartate ratio, suggestive of progressive disease. CMRI of the spine showed diffuse leptomeningeal enhancement. He was planned for lumbar puncture for CSF cytology, and he became mildly febrile and irritable on the day of the procedure. CSF cytology showed numerous polymorphs with occasional eosinophils, suggestive of acute meningitis. CSF analysis showed TLC 4,000/mm$^3$, differential leucocyte count 100% polymorphs, protein 528 mg/dL, and glucose 68 mg/dL. Full blood count showed neutrophilic leucocytosis (TLC 13,090/mm$^3$ and absolute neutrophil count 11,650/mm$^3$). He had altered sensorium, high-grade fever, and nuchal rigidity and was immediately admitted to the oncology ward for management of acute bacterial meningitis. He was started on empirical antibiotics Inj ceftriaxone 50 mg/kg IV 12 hourly, Inj vancomycin 15 mg/kg IV 6 hourly, and Inj dexamethasone 0.15 mg/kg IV 6 hourly (rapidly tapered after 4 days). As fever had not subsided after 3 days of antibiotherapy, lumbar puncture was repeated for CSF analysis and Inj meropenem 40 mg/kg IV 8 hourly was added. Contrast-enhanced computerized tomography of the brain revealed irregular nodular enhancing lesions in the wall of the post-operative cavity with mass effect; midline shift of 7.7 mm and subfalcine herniation; a 2.6 × 1.7 cm well-defined, heterogeneously enhancing, solid nodular lesion in the right basifrontal region; and a subependymal nodule in the right lateral ventricle. Blood and CSF samples for culture and sensitivity were sterile. Though fever subsided, he still had altered sensorium and right-sided hemiparesis. In view of subfalcine herniation, he underwent left frontal craniotomy, gross total excision of the recurrent tumour (in the left frontal lobe), and left frontal lobectomy. Intraoperative findings included a large left frontal abscess, recurrent tumour posteromedial to the abscess, and radiation necrosis. Pus for culture from the left frontal abscess was sterile. Post-operative histopathology revealed glioblastoma with areas of necrosis and calcification. The tumour was immunopositive for glial fibrillary acidic protein, p53, and chromogranin (focal) and immunonegative for IDH-1, cytokeratin, and leucocyte common antigen. Alpha-thalassemia mental retardation X-linked (*ATRX*) gene immunoexpression was retained. MIB-1 labelling index was 50% in the highest proliferating area. On cytogenetic analysis, both the tumour samples (primary and recurrent) revealed presence of EGFR amplification. Post-operative CMRI of the brain showed an ill-defined heterogeneously en-

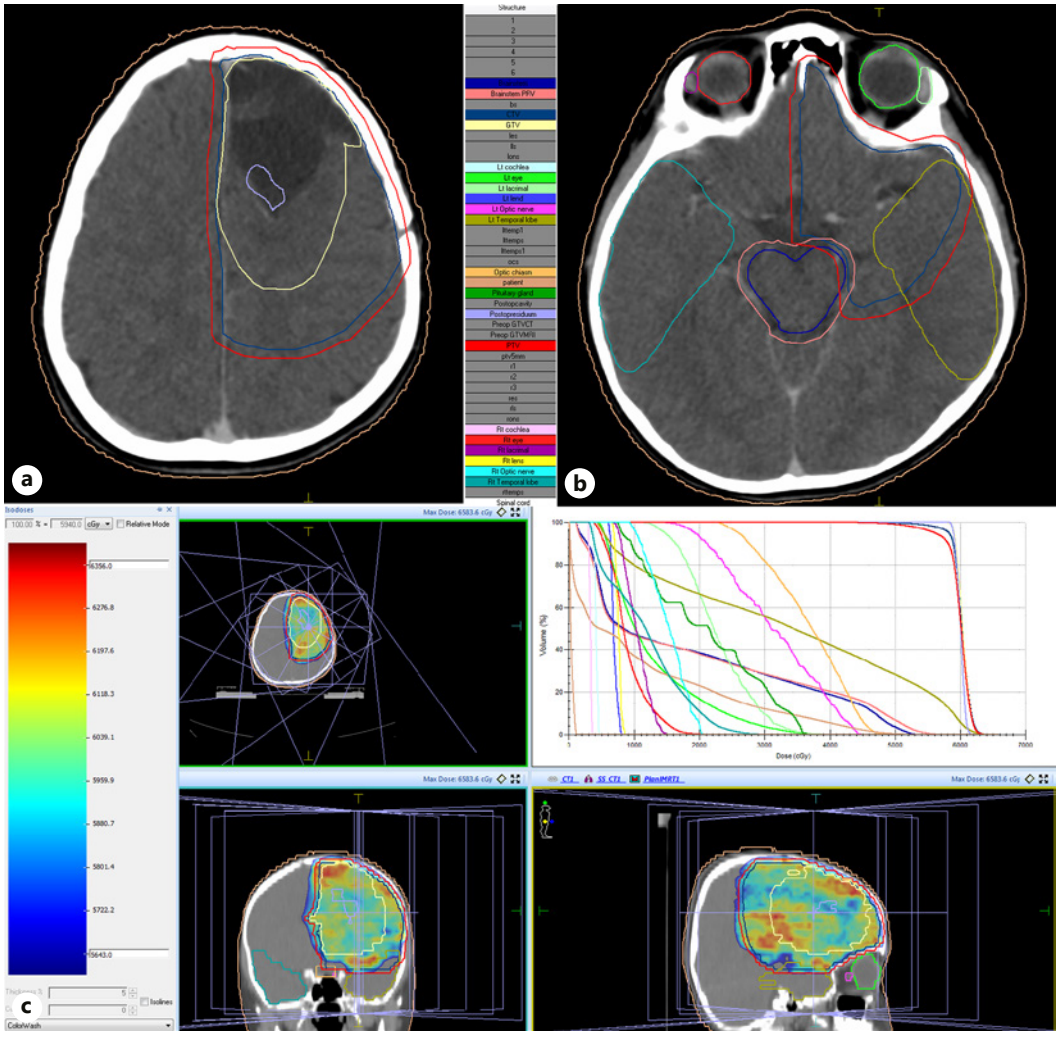


**Fig. 2. a**, **b** Contrast-enhanced radiation planning CT images of the brain show delineation of gross tumour volume (GTV), clinical target volume (CTV), planning target volume (PTV), and critical organs at risk (OARs), for example, bilateral temporal lobes, eyes, lacrimal glands, and brainstem. Dose of 59.4 Gy/33 fractions/6.5 weeks was prescribed to the PTV. **c** Radiation planning was done by fixed 8-field intensity modulated radiotherapy technique. Dose colour wash of ≥56.43 Gy (95% of the prescribed dose) is tightly sculpted around the target volumes on axial, coronal, and sagittal planning CT images with cumulative dose volume histogram showing satisfactory coverage of the GTV, CTV, and PTV with simultaneous sparing of the various critical OARs.

hancing butterfly lesion in bilateral fronto-parietal lobes involving the corpus callosum; multiple well-defined heterogeneously enhancing soft tissue lesions in the left frontal, right parietal, and right temporal lobes; hydrocephalus with irregular nodular enhancement of ependymal lining of all ventricles; nodular enhancement of meninges in bilateral cerebral and cerebellar hemispheres and brainstem, suggestive of subependymal and meningeal spread (Fig. 3g–i). In view of poor general health and absence of effective salvage treatment options in recurrent glioblastoma, he was kept on best supportive care and poor prognosis was explained to the guardians. Eventually he died due to progressive disease complicated by aspiration pneumonia 10.5 months after the initial diagnosis of glioblastoma.

## Discussion

*Radiation-Induced Second Malignancy*

The criteria for RISM were mostly developed on the basis of observation of development of sarcomas after irradiation of benign bone lesions [4]. They include (1) a new tumour in the field of radiation, (2) histological difference between initial and second tumour, (3) sufficient latency period (usually >5 years), (4) higher incidence of the tumour in an irradiated cohort than an adequate control group, and (5) existence of an animal model and/or

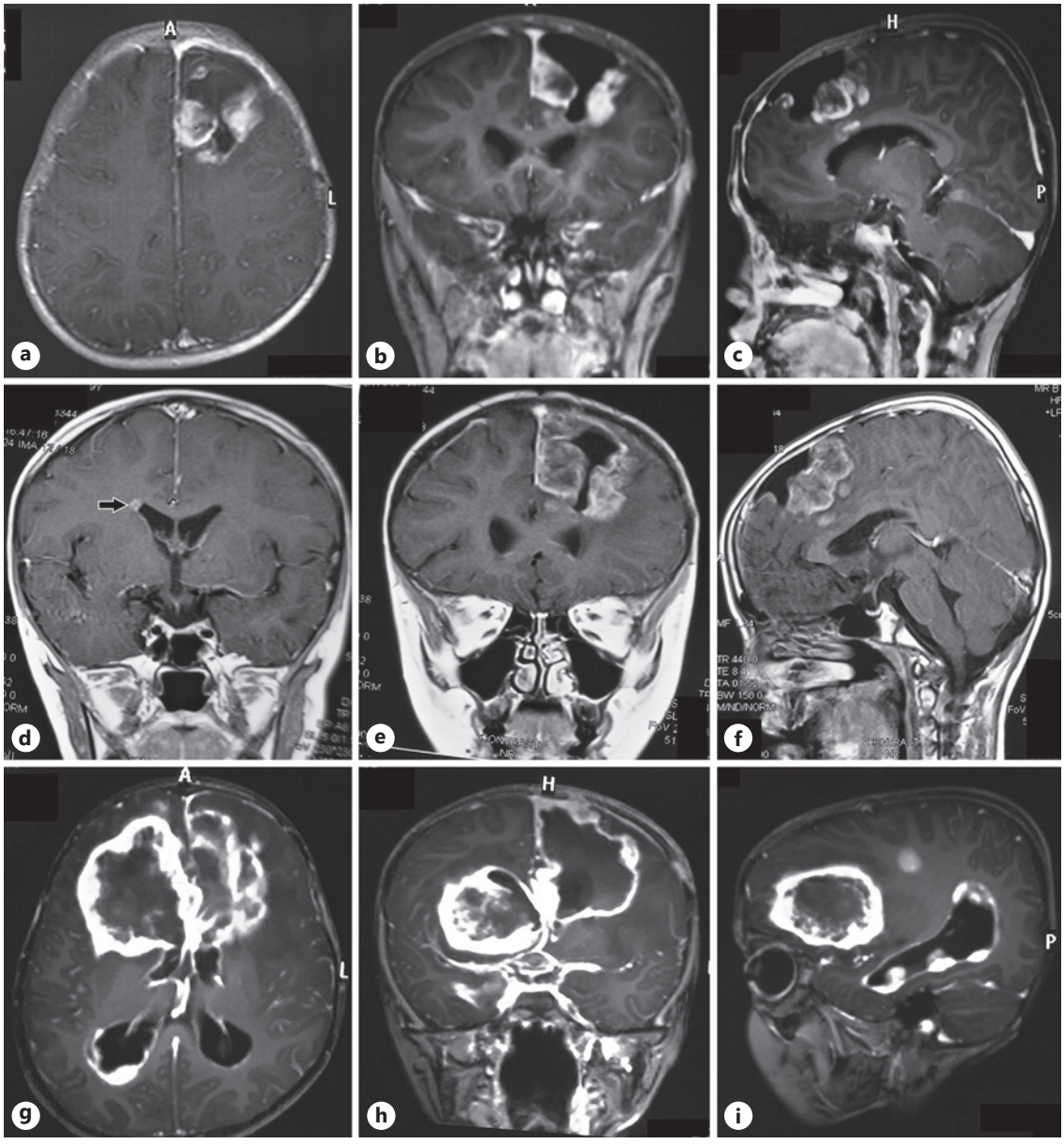


**Fig. 3.** Three months after the completion of radiotherapy, T1-weighted post-contrast axial (**a**), coronal (**b**), and sagittal (**c**) magnetic resonance images of the brain show heterogeneously enhancing nodular lesions in the wall of the post-operative cavity in the left frontal lobe extending to the body of the corpus callosum. **d** A separate enhancing lesion in the frontal horn of the right lateral ventricle was also discerned, suggestive of disease progression. **e**, **f** There was an increase in the size of the nodular enhancement in the abovementioned lesions on contrast-enhanced magnetic resonance images of the entire neuraxis, repeated after a week. Besides, there was diffuse leptomeningeal enhancement in the spinal cord. After repeat excision of the tumour in the left frontal lobe, T1-weighted post-contrast axial (**g**), coronal (**h**), and sagittal (**i**) magnetic resonance images of the brain showed an ill-defined heterogeneously enhancing butterfly lesion in bilateral fronto-parietal lobes involving the corpus callosum with hydrocephalus and diffuse subependymal and leptomeningeal spread.

dose-response relationship [4, 5]. Besides, patients should not have a mutator phenotype, for example, Li-Fraumeni syndrome (LFS) or retinoblastoma [6]. In general, paediatric patients are more susceptible to RISM compared to adults and younger the patient, the higher the incidence of and shorter the interval to RISM [7]. The rough estimate of RISM in adults treated with therapeutic radiation is 1–2% per decade after RT [8, 9]. Even in the modern

era of medical linear accelerator and IMRT, RISM continues to be a clinical issue perhaps due to increased low-dose bath and integral dose associated with these techniques [10].

*Radiation-Induced CNS Tumour*

Radiation-induced CNS tumours usually present at unusual ages and can be multiple in number [11]. The common radiation-induced CNS tumours are meningioma, schwannoma, malignant peripheral nerve sheath tumours, pituitary tumours, HGG, and sarcomas [12–14]. Radiation-induced meningioma mostly develops after low-dose radiation of scalp for tinea capitis but can also develop after moderate (10–20 Gy) and higher (>20 Gy) RT dose [15]. The lower the dose of RT, the longer the latency before the development of malignancy (meningioma). Radiation-induced glioma may occur after low-dose RT for tinea capitis or high-dose RT for treatment of a primary brain tumour [11, 16, 17]. In a study by Tsang et al. [16], the relative risk for secondary glioma after RT in patients with pituitary adenoma was 16 times higher than that in the general population of Ontario. The common RT-induced gliomas are glioblastoma, anaplastic astrocytoma, gliosarcoma, low-grade glioma, and oligodendroglioma [17]. The latency period for the development of RT-induced glioma varies from 5 to 25 years (average 9.6 years) [17]. Radiation-induced sarcomas most commonly include fibrosarcoma (58%), meningeal sarcoma (22%), osteosarcoma (14%), and often contain complex, mixed mesenchymal elements [11, 12].

*Radiation-Induced HGG*

Recent animal studies provide robust evidence that gliomas may be radiation-induced. Nine out of 11 primates developed glioblastoma at an interval of 2.9–8.3 years after receiving whole brain RT 35 Gy/10 fractions/2 weeks [18]. Comparative genomic hybridization revealed deletions in the primate chromosome (Ch.) corresponding to human Ch. 9. In a case series of 5 patients with RIG diagnosed in Children's Hospital, Denver, Colorado, from 1995 to 2006, the original diagnoses for which the patients received cranial RT were Burkitt's lymphoma, medulloblastoma, pilocytic astrocytoma, ependymoma, and ALL in 1 patient each [6]. The age at diagnoses of RIG ranged from 12 to 23 years. The latency period for the development of RIG ranged from 3 to 15 years. Unfortunately, all 5 patients died within 1–10 months after diagnoses of RIG. On immunohistochemistry, all showed high levels of TP53 immunostaining affecting >25% of tumour cells. The median MIB-1 labelling index was 42.1% (range 12.2–67.7%). There was no evidence of EGFR amplification in 4/4 informative cases. There was loss of 10q, including PTEN locus in 3/3 informative cases. All 3/3 informative cases showed highly complex tumour karyotype. Compared with paediatric glioblastoma, RIG showed 2-fold higher homogeneity on gene expression profile. On a molecular level, RIG showed more kinship with pilocytic astrocytoma (overlap in 39 of the 100 overexpressed genes on gene expression profile), suggesting a common precursor cell of origin. On the contrary, Brat et al. [19] assessed RT-induced HGG for possible genetic alterations in p53, PTEN, KRAS, EGFR, and p16 and the molecular alterations were similar to those seen in spontaneously arising primary (de novo) HGG with the exception of absence of PTEN mutation.

In a larger retrospective study of 92 patients with RIMG, the median age at the time of initial RT was 10 years and the initial conditions treated with cranial RT were brain tumours (40.2%), ALL (35.9%), benign conditions (12%), lymphoma (4.3%), retinoblastoma (3.3%), and other miscellaneous conditions (4.3%) [3]. The initial RT fields were partial brain in 41 (44.5%), whole brain in 42 (45.7%), and craniospinal in 9 (9.8%) patients. The median latency period before the diagnosis of RIMG was 8.75 years (6.5 years in ALL/lymphoma, 10 years in brain tumours and other malignant solid tumours, and 13 years in other benign conditions). The percentage of patients developing RIMG before 10 years from RT was 72.5 in patients who had undergone craniospinal or whole brain RT versus 51.2 in those who had undergone partial brain RT ($p = 0.035$). The subtypes of RIMG were glioblastoma in 69 (75%) patients and anaplastic astrocytoma in 23 (25%) patients. Ten patients had multifocal malignant glioma. The median OS after the diagnosis of RIMG in the entire cohort was 11 months (9 months in glioblastoma vs. 17 months in anaplastic astrocytoma; $p = 0.0013$). The 2- and 5-year estimates of OS were 13 and 4%, respectively, suggesting that clinical outcome in this group of patients is only slightly inferior to that in patients with spontaneously occurring malignant glioma.

In a more comprehensive systematic review of RIMG ($n = 176$), the 5 most common index lesions treated with RT were ALL (31.8%), medulloblastoma (13%), pituitary adenoma (10.8%), craniopharyngioma (8%), and tinea capitis (4%) [1]. The median age of the patients receiving RT for primary tumour was 11 years and the median RT dose was 35.6 Gy. The median latency period before the diagnosis of RIMG was 9 years. There was no correlation between the latency period and the dose of RT or the age at RT. Survival data were available for 155 patients, and after 2007,

the median OS in patients with glioblastoma and anaplastic astrocytoma were 11.5 and 16.5 months, respectively.

A case of anaplastic astrocytoma of the posterior fossa arising 10 years after PCI (18 Gy/10 fractions/2 weeks) in a case of ALL has been previously reported from our institute [20]. The patient underwent midline suboccipital craniotomy and gross total excision of the tumour, followed by post-operative RT 60 Gy/30 fractions/6 weeks by 3-dimensional conformal RT technique. Six weeks after the completion of post-operative RT, he had residual/recurrent disease and was started on salvage temozolomide. The illustrative case is only the second patient with RIMG at our centre in a decade. The age at RT (PCI) was 3.5 years, and the latency period before the diagnosis of RIG was only 5 years.

*Second Malignancy in Patients with ALL*

The cumulative incidence of second malignancy in patients with ALL is 2.5–4% at 15 years and 6% at 30 years [21, 22]. The most commonly observed second malignancies include CNS tumour, leukaemia, lymphoma, and skin cancer [20–22]. The risk factors for the development of second malignancies in patients with ALL are age at diagnosis less than 5 years, female sex, use of cranial or craniospinal irradiation, and disease relapse [20–22]. The possible pathogenesis for second malignancy in ALL may include intrinsic factors, for example, pleiotropic gene action, cytogenetic abnormalities, and immunoregulatory dysfunction, and extrinsic factors, for example, common carcinogen and iatrogenic causes [23]. In a cohort of 9,720 patients with ALL treated as per the CCSG protocol between 1972 and 1988, a total of 43 second neoplasms were diagnosed 3 months to 13.2 years (median 6 years) after the initial diagnosis of ALL [21]. In 43 patients with second malignancy, 24 (56%) patients had CNS tumour (OR 21.7) and 14/24 patients had HGG. All CNS tumours occurred in younger patients who had undergone cranial RT or total body irradiation before bone marrow transplant. Similarly a 20-fold excess of brain tumour has been noted in the UK among children with leukaemia as first cancer [24]. In an analysis of 1,612 patients treated on sequential institutional protocols for newly diagnosed ALL at St. Jude Children's Research Hospital from 1967 to 1988, 22 brain tumours (10 HGG [4 glioblastoma, 2 anaplastic astrocytoma, and 4 other HGG], 1 low-grade glioma, and 11 meningiomas) were diagnosed in 21 patients, leading to a cumulative incidence of brain tumour at 20 years of 1.39% [25]. The risk factors for the development of secondary brain tumour were CNS leukaemia at diagnosis, treatment on Total X Therapy Programme (containing teniposide and modified CNS-directed treatment, i.e., increased use of intrathecal methotrexate and randomization of low-risk patients to low-dose RT [18 Gy] vs. no RT in Era 3 (1979–1983]) and use of cranial RT. Increasing doses of cranial RT were associated with an increased risk of secondary brain tumours in general and HGG specifically in this study. Age <6 years was associated with an increased risk of developing HGG. The outcome was particularly poor in patients with HGG, with a median OS of only 7 months.

*Cancer Susceptibility Syndromes Predisposing to ALL and HGG*

LFS (SBLA syndrome) is a rare autosomal dominant hereditary disorder, characterized by germline mutation of the *p53* tumour suppressor gene, which predisposes to development of multiple cancers, that is, soft tissue sarcoma (20%), bone sarcoma (15%), breast cancer (25%), leukaemia, adrenocortical carcinoma, and brain tumour (13%), for example, glioblastoma, medulloblastoma, and choroid plexus carcinoma [26, 27]. This mutation can be inherited or can arise de novo (in 20–25% cases) in one of the parent's germ cells or early in embryogenesis [27]. In the classical LFS families, 60–80% harbour detectable germline *p53* mutations, the majority of which are missense mutations in the DNA-binding domain of the gene [26]. In the illustrative case, though there was no strong family history of cancer (with the exception of unilateral breast cancer at 66 years in paternal grandmother), it is notable that both the primary and recurrent glioblastoma samples were diffusely immunopositive for p53. It is a known fact that p53 immunohistochemistry is a moderately sensitive and highly specific marker to predict *p53* mutation (particularly, missense mutations) in gliomas [28]. However, protein-truncating mutations of the *p53* gene (20% of all mutations), for example, deletions, nonsense mutations, and intronic mutations may escape detection by immunohistochemistry [28]. Hence, molecular testing, for example, DNA sequencing of the *p53* gene from frozen tissue samples, which is currently done only in research setting at our institute, would have provided a more accurate prediction of *p53* mutation.

Constitutional mismatch repair-deficiency syndrome is a rare, autosomal recessive cancer predisposition syndrome, characterized by biallelic germline mutations of mismatch repair genes, that is, *MLH1*, *MSH2*, *MSH6,* and *PMS2*, leading to early onset, often, multiple tumours, that is, paediatric brain tumour (glioblastoma, other astrocytic tumours, primitive neuroectodermal tumour, and medulloblastoma), ALL, acute myeloid leukaemia, lymphoma, early onset gastrointestinal and gynaecologi-

cal cancers, and a phenotype that is reminiscent of neurofibromatosis type 1 (NF1), in particular, café-au-lait macules [27, 29]. The illustrative patient did not have any stigmata of neurofibromatosis type 1. Majority of the patients with HGG associated with constitutional mismatch repair-deficiency syndrome have developmental brain vascular anomalies on radiology and giant multinucleated cells on histology, and these particular findings were also absent in this case [30]. However, in hindsight, genetic testing for *p53* and mismatch repair genes would have been worthwhile in this illustrative patient.

*Treatment of RIMG*

The first-line treatment of RIMG is maximal safe resection of the tumour. The reluctance on the part of the physicians to aggressively treat RIMG with reirradiation is understandable [10]. However, in a retrospective analysis of 85 patients with RIMG by Paulino et al. [3], 35 patients underwent reirradiation (median dose 50 Gy and range 30–70 Gy) and had 2-year OS rate of 20.5% in contradistinction to 3% ($p = 0.0009$) in 50 patients who were not irradiated. Traditionally, the tolerance of whole and partial brain is considered to be 45 and 60 Gy, respectively [31]. However, in the setting of reirradiation, reirradiated normal brain tissue can tolerate cumulative normalized total dose of >100 Gy in conventional fractionation [10, 32]. With the use of linear accelerator-based stereotactic radiosurgery (SRS), the tolerated cumulative normalized total dose of normal brain tissue is as high as 135 Gy [10, 32]. Intensity modulated proton therapy using active scanning may further reduce the exit dose in the healthy brain tissue and may be a worthwhile treatment option for reirradiation in paediatric patients with brain tumour [10]. In suitable patients with RIG, systemic chemotherapy in the form of concurrent and adjuvant temozolomide should be considered. In the study by Paulino et al. [3], 31/85 (36.5%) patients with RIMG underwent chemotherapy. However, no significant difference in OS was noted in patients who underwent chemotherapy versus those who did not. However, in an updated systematic review of RIMG, the median OS before and after 2007 (pre- and post-temozolomide era) was 9 and 11.5 months, respectively, suggesting the fact that survival outcome in patients with RIMG has gradually improved over time ($p = 0.004$) [1]. For patients with recurrent or progressive disease after frontline treatment, surgical resection should be attempted whenever feasible. In the study by Paulino et al. [3], surgery alone (in 24/85 patients) was the most common salvage treatment modality. In patients with unresectable tumour, reirradiation using ultraprecise techniques, for example, stereotactic radiosurgery or radiotherapy, may be considered. Antiangiogenic therapy using bevacizumab is also an acceptable treatment option in this scenario. After the diagnosis of RIG, the illustrative patient underwent multimodality treatment in the form of gross total resection of the tumour, followed by postoperative IMRT (59.4 Gy) and concurrent and adjuvant temozolomide (3 cycles) but had relentless disease progression, characterized by diffuse subependymal and leptomeningeal spread and complicated by acute bacterial meningitis and brain abscess. Kleinschmidt-DeMasters et al. [11] had reported a similar case of diffuse subependymal and leptomeningeal spread, complicated by brain abscess at the site of the post-operative cavity in a young adult male with high-grade complex CNS sarcoma, diagnosed 10 years after radiation for glioblastoma. Our patient underwent re-excision of the recurrent tumour and left frontal lobectomy but eventually died of progressive disease 10.5 months after the diagnosis of RIG.

## Conclusion

RIMG is an aggressive malignancy with a dismal prognosis. In spite of state of the art multimodality management, it exhibits relentless disease progression, occasionally characterized by subependymal and leptomeningeal dissemination, leading to eventual death within a year of diagnosis. Though RIMG is an extremely rare complication of cranial RT, it should be prevented whenever possible by appropriate selection of patients for cranial RT using a risk-adapted strategy.

## Statement of Ethics

Written informed consent was obtained from the patient's guardian before surgery and administration of radiotherapy and chemotherapy. Also written informed consent for publication of data and images was obtained from the patient's guardian.

## Conflict of Interest Statement

On behalf of all of the authors, the corresponding author states that there are no conflicts of interests.

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There is no source of funding to declare.

## Author Contributions

A.B.: clinical care of the patient during RT and chemotherapy (temozolomide) for glioblastoma, clinical care of the patient during prophylactic cranial RT for ALL, and review of literature and drafting of the manuscript. L.K.: clinical care of the patient during RT and chemotherapy (temozolomide) for glioblastoma and review of literature. S.B.: clinical care of the patient during chemotherapy (INCTR-02-04 protocol) for ALL and appraisal of the manuscript.

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