

Pineal region germ cell tumors with secondary glioblastoma: A case report of long-term survival using chemoradiotherapy combined with TTFields

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Intracranial germ cell tumors (GCTs) primarily affect children and young adults, with favorable outcomes through radiotherapy and chemotherapy. However, radiation-induced secondary malignancies pose significant concerns in long-term survivors, particularly regarding optimal treatment strategies. We present a case of a 12-year-old Asian male initially diagnosed with pineal region GCTs who developed radiation-induced glioblastoma after 5 years of tumor-free survival. The secondary tumor was successfully treated with chemoradiotherapy combined with Tumor Treating Fields (TTFields), resulting in tumor regression and survival exceeding 3 years. This case demonstrates the potential efficacy of TTFields combined with chemoradiotherapy in treating radiation-induced glioblastoma in young patients and highlights the importance of long-term surveillance in pediatric tumor patients.

Intracranial germ cell tumors (GCTs) represent a unique challenge in pediatric neuro-oncology, with notable geographical variation in incidence. In Asian populations, GCTs account for 11–16% of primary central nervous system tumors in children and adolescents, predominantly occurring in the pineal region, suprasellar region, or thalamic basal ganglia.^{1–3} This stands in stark contrast to Western countries, where they constitute only 3–5% of cases.^{1–5} These tumors are broadly classified into germinomas and non-germinomatous germ cell tumors (NGGCTs), with the latter encompassing various subtypes including yolk sac tumors, choriocarcinomas, embryonal carcinomas, and teratomas (both mature and immature), as well as mixed variants.

The management of GCTs typically involves a multimodal approach combining surgery, radiotherapy, and chemotherapy. While treatment outcomes have improved significantly, with non-metastatic germinomas achieving impressive 10-year survival rates exceeding 90%.¹ Even in cases with

metastatic disease, survival rates range from 30% to 70%, necessitating careful attention to long-term complications, particularly in young survivors who receive cranial radiation therapy.⁶

Among secondary neoplasms following GCTs treatment, radiation-induced gliomas represent a particularly challenging entity.⁴ Despite their rarity, these secondary tumors pose significant therapeutic challenges and can dramatically impact long-term survival. The management of such cases remains poorly defined in current literature, especially regarding optimal treatment strategies and expected outcomes. Here, we present a unique case of radiation-induced glioblastoma following successful GCTs treatment, highlighting an innovative therapeutic approach using Tumor Treating Fields (TTFields) that achieved remarkable survival outcomes. This case not only adds to our understanding of secondary malignancies following GCTs treatment but also presents a potentially promising treatment strategy for similar cases in the future.

Case Presentation

A 12-year-old Asian male presented with a 1-month history of headache and progressive visual deterioration. Neurological examination revealed decreased visual acuity without other focal neurological deficits. Brain magnetic resonance imaging (MRI) demonstrated a well-defined mass in the pineal region measuring 3.7 × 3.1 × 2.8 cm with associated

obstructive hydrocephalus (Figure 1a). Laboratory investigations showed elevated serum alpha-fetoprotein (AFP) of 199.5 ug/L, while beta-human chorionic gonadotropin (β -HCG) remained within normal limits at 2.46 IU/L. Based on these findings, a diagnosis of pineal region GCTs was established.

The patient received multimodal therapy consisting of radiation treatment with whole ventricular irradiation (30 Gy) followed by a focal boost (20 Gy) to the tumor bed. Systemic chemotherapy comprised 6 cycles of alternating regimens of carboplatin plus etoposide and ifosfamide plus etoposide. Following the completion of chemotherapy, a residual tumor was observed in the pineal region, and a wait-and-watch approach was adopted given the patient's stable clinical status (Figure 1b). At 35 months post-chemotherapy, the patient presented with recurrent headaches and nausea. Although serum tumor markers remained within normal limits, a brain MRI revealed enlargement of the residual pineal tumor. Given these findings,

surgical intervention was deemed necessary, and the patient underwent tumor resection on August 30, 2019 (Figure 1c). Pathological examination of the surgical specimen confirmed the diagnosis of mature teratoma. Following completion of treatment, the patient achieved complete clinical remission and resumed normal school activities.

After a 5-year disease-free interval, at age 17, the patient developed new neurological symptoms including right-sided facial and hand numbness. MRI revealed a new mass involving the right thalamus and brainstem in the vicinity of the pineal region (Figure 1d). Although GCTs recurrence was initially suspected given the patient's history, both serum and cerebrospinal fluid tumor markers (AFP and β -HCG) were within normal limits. The tumor showed resistance to 7 cycles of chemotherapy, prompting further investigation (Figure 1e). A ROSA robot-assisted brain biopsy was performed, revealing high-grade glioma. Molecular profiling through Next Generation Sequencing demonstrated *IDH*-wildtype status, *MGMT* promoter methylation,

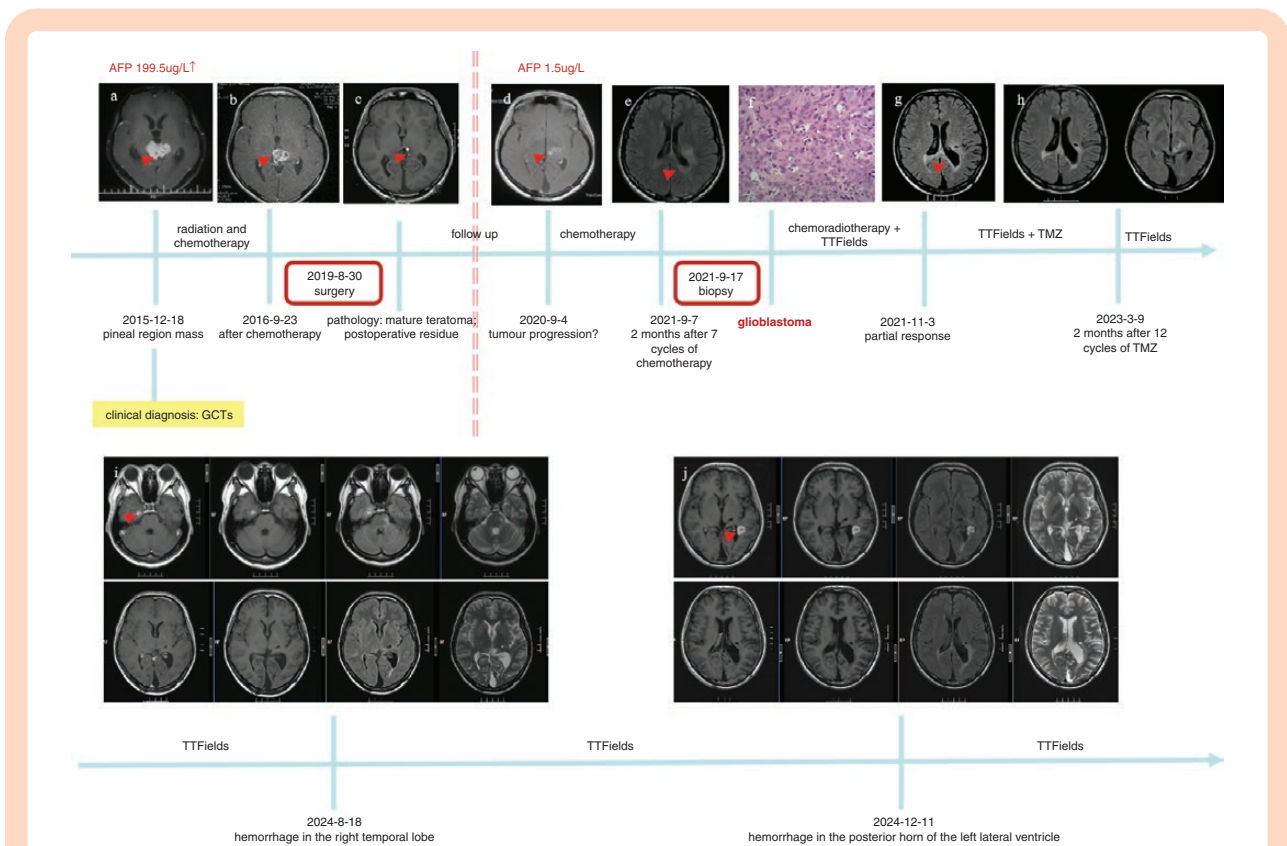


Figure 1. Sequential neuroimaging findings throughout the disease course. (a) Initial post-contrast T1-weighted MRI demonstrating a well-defined enhancing mass in the pineal region (arrow). (b) Post-treatment (radiation and chemotherapy) T1-weighted post-contrast MRI showing partial response with residual enhancement in the pineal region (arrow). (c) Post-surgical T1-weighted post-contrast MRI revealing minimal residual enhancement following subtotal resection (arrow). (d) T1-weighted post-contrast MRI demonstrating a new infiltrative mass involving the right thalamus and brainstem adjacent to the pineal region (arrow). (e) Following 7 cycles of chemotherapy, T2-FLAIR imaging showing extensive signal abnormality involving the brainstem, left thalamus, and posterior horn of the left lateral ventricle (arrow), despite reduced enhancement on post-contrast sequences. (f) Histopathological examination of the thalamic lesion confirming secondary glioblastoma. (g) T2-FLAIR imaging demonstrating partial response following combined chemoradiotherapy and TTFields treatment (arrow). (h) Follow-up T2-FLAIR imaging showing continued tumor regression in the brainstem, left thalamus, and posterior horn of the left lateral ventricle. (i) Multisequence MRI (T1-weighted pre- and post-contrast, T2-FLAIR, and T2-weighted) revealing a new vascular lesion with hemorrhage in the right temporal lobe (arrow), with sustained improvement in previously treated areas. (j) Surveillance imaging demonstrating a new chronic hemorrhagic focus in the posterior horn of the left lateral ventricle (arrow) on multisequence MRI, with stable T2-FLAIR signal abnormality in previously affected regions.

CDKN2A/B homozygous deletion, *EGFR* amplification, and chromosome 7 gain/chromosome 10 loss (+7/−10) signature, confirming the diagnosis of glioblastoma (Figure 1f).

Given the tumor's involvement in critical structures, surgical resection was deemed inappropriate. An innovative approach combining re-irradiation with TTFIELDS was implemented. As shown in Figure 1, the patient was treated with temozolomide (TMZ) chemotherapy and TTFIELDS during radiotherapy. After radiotherapy, TTFIELDS treatment and 12 cycles of TMZ chemotherapy were continued. This therapeutic strategy resulted in tumor regression, and the patient has maintained disease control for over 4 years since the diagnosis of secondary glioblastoma (Figure 1g and h). During routine follow-up, brain MRI on August 18, 2024, revealed a new vascular lesion with hemorrhage in the right temporal lobe, initially suspected to be a vascular malformation (Figure 1i). The patient remained clinically stable, and subsequent imaging demonstrated complete resolution of this temporal lesion. Further surveillance MRI on December 11, 2024, identified a new chronic hemorrhagic focus in the posterior horn of the left lateral ventricle (Figure 1j). Despite these radiological findings, the patient has maintained excellent clinical status, requiring only continued observation without additional intervention. The patient continues to survive with a good quality of life, representing an exceptional case of long-term survival in radiation-induced secondary glioblastoma treated with TTFIELDS. This case also highlights the importance of regular imaging surveillance in identifying and monitoring new radiological findings, even in the context of successful tumor control.

Discussion and Conclusions

Secondary malignancies following cranial radiation therapy represent a significant concern for long-term survivors of brain tumors, particularly in younger patients. Cahan established fundamental diagnostic criteria for radiation-induced malignancies, which have since gained widespread acceptance in the field. These criteria stipulate that the neoplasm must originate within the previously irradiated field and emerge following a substantial latency period, typically spanning several years post-radiation exposure.^{7,8} In addition, the secondary tumor must demonstrate distinct histological features from the primary malignancy, and the patient should have no documented history of cancer predisposition syndromes, such as Li-Fraumeni syndrome or neurofibromatosis.

The development of radiation-induced neoplasms has been well-documented in patients treated for intracranial GCTs. A comprehensive single-center retrospective analysis from Korea demonstrated that among 127 GCTs patients with long-term follow-up, 7 patients developed secondary tumors.² This observation is further supported by another study reporting a 6.0% cumulative incidence of secondary malignancies following GCTs treatment.⁹ Notably, age at initial radiation exposure appears to influence the type of secondary neoplasm, with younger patients more commonly developing lower-grade lesions such as meningiomas.⁸ Radiation-induced malignant

gliomas following GCTs treatment are particularly rare, with most cases documented through individual case reports. The temporal pattern of these secondary malignancies is distinctive, typically emerging after a latency period exceeding 5 years from initial treatment.^{2,7}

Further research has found that radiation-induced gliomas are genetically distinct from most other brain tumors, with the most common genetic alterations including *PDGFRA* amplifications, *TP53* mutations, *CDK4* amplifications, *CDKN2A* deletion, as well as chromosomal alterations such as 1q gain, 1p loss, 13q loss, and 14q loss.^{8,10} Our case report fulfills Cahan's criteria and demonstrates characteristic molecular features of radiation-induced brain tumors, specifically *CDKN2A* deletion and 1q gain. Furthermore, the patient has no documented history of cancer predisposition syndromes.

The management of radiation-induced secondary malignant gliomas presents unique therapeutic challenges. While the standard treatment protocol for primary glioblastoma in adults includes chemoradiotherapy combined with TTFIELDS, the optimal approach for secondary glioblastoma, particularly in younger patients, remains less well-defined.

The innovativeness of this study lies not in creating entirely novel therapeutic methods, but rather in the innovative combination of existing therapies and their remarkable efficacy in a unique patient population. This case involved a 17-year-old patient with radiation-induced secondary glioblastoma, a patient population for which well-established treatment protocols are currently lacking. Given that the tumor was located in critical brain structures preventing surgical resection, we implemented re-irradiation combined with chemotherapy and TTFIELDS, demonstrating both the feasibility and tolerability of this combination approach in young patients. The extended survival duration of over 3 years following glioblastoma diagnosis (approximately double the typical survival time while maintaining good quality of life throughout the treatment course) suggests enhanced therapeutic efficacy.

The biological characteristics of radiation-induced glioblastomas may differ from primary tumors, potentially influencing treatment response and clinical outcomes. Several factors warrant consideration in this context: the impact of prior radiation exposure on tumor biology, the potential role of genetic predisposition, and the influence of age-related factors on treatment tolerance and response. The exceptional response observed in our case raises important questions about the potential differential sensitivity of radiation-induced glioblastomas to TTFIELDS therapy.

In conclusion, this case highlights the importance of long-term surveillance for secondary malignancies in survivors of childhood brain tumors treated with radiation therapy. In this case, the application of TTFIELDS in combination with chemoradiotherapy for a patient with radiation-induced glioblastoma was associated with a prolonged survival of 3 years, which is encouraging and warrants further investigation, especially in younger patients. However, the following limitations should be recognized: First, as a single case report, our findings, while promising, cannot be generalized to all patients with radiation-induced secondary glioblastoma. Second, the long-term effects

and potential complications of combining re-irradiation with TTFields in young patients need additional study with longer follow-up periods. Future research should focus on elucidating the biological distinctions between primary and radiation-induced glioblastomas, which may inform more targeted treatment strategies. In addition, prospective studies are needed to validate the efficacy of TTFields in this specific patient population and to establish optimal treatment protocols. This case also underscores the potential for improved outcomes in secondary glioblastoma when innovative therapeutic approaches are carefully implemented within a multidisciplinary framework.

Keywords:

germ cell tumors | secondary glioblastoma | radiation-induced neoplasm | TumorTreating Fields | re-irradiation

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Conflict of interest statement

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Author Contributions

Conception and study design: Linbo Cai. Acquisition of data: Lian Chen, Yingying Zhou, Juan Li, Minting Ye, Ruyu Ai, LiChao Wang, and Yangqiong Zhang. Drafting of the first manuscript: Shaoqun Li. Critical revisions and writing: Shaoqun Li and Mingyao Lai. All authors read and approved the final manuscript.

Ethics Statement

This case report was conducted in accordance with ethical principles and was approved by the medical ethics committee of Guangdong Sanjiu Brain Hospital. The patient provided written

informed consent for the publication of his clinical details and any accompanying images. All efforts have been made to protect patient privacy.

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