

Latent Sarcomatous Consequences of Therapeutic Irradiation in Long-Term Brain Tumor Survivors: A Paradigm of Iatrogenic Complexity

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Abstract

Introduction: Radiation therapy is an essential component of cancer treatment and has substantially improved survival for patients with many primary brain tumors. However, exposure to ionizing radiation can, rarely, result in the development of secondary malignancies years after treatment. Radiation-induced sarcoma (RIS) represents an uncommon but clinically important late complication of radiotherapy and has been described as an iatrogenic consequence of successful cancer treatment. RIS accounts for approximately 3% of all soft-tissue sarcomas and has been reported in approximately 0.03%–0.3% of patients exposed to therapeutic radiation. Reported 5-year overall survival remains poor, ranging from approximately 10% to 36%. Beyond its clinical significance, RIS illustrates the temporal complexity of therapeutic risk, in which a treatment that provides substantial immediate benefit may contribute to a rare adverse outcome many years later. **Objective:** This study describes three cases of RIS arising after radiotherapy for primary intracranial tumors and examines their clinical characteristics, latency periods, histopathological features, management, and outcomes. The cases are additionally considered within broader perspectives of bioethics, survivorship medicine, biological time, and the long-term consequences of therapeutic interventions. **Methods:** A retrospective case series was conducted involving three patients who developed RIS following radiotherapy for primary intracranial tumors, including pituitary adenoma, ependymoma, and meningioma. Clinical presentation, radiological findings, histopathological characteristics, treatment, latency between radiotherapy and sarcoma development, and clinical outcomes were systematically reviewed. The cases were also examined from a conceptual perspective to explore the implications of delayed treatment-related harm in long-term cancer survivorship. **Results:** The patients were 19, 51, and 30 years old at the time of initial radiotherapy and subsequently developed RIS after latency periods of 9, 4, and 5 years, respectively. The secondary sarcomas were histologically distinct from the original tumors and comprised histiocytic sarcoma, undifferentiated high-grade sarcoma, and mesenchymal chondrosarcoma. All three tumors developed within previously irradiated fields. Surgical resection was performed in all patients, followed by adjuvant radiotherapy in two patients and adjuvant chemoradiotherapy in one. Post-RIS survival ranged from 1 to 2 years. One patient remained alive under regular follow-up at the time of reporting. **Conclusions:** These cases highlight radiation-induced sarcoma as a rare but serious late complication of therapeutic irradiation in patients with long-term survival after primary brain tumors. The variable histological presentations and relatively short survival following RIS underscore the need for sustained clinical vigilance during survivorship. Long-term follow-up should consider the possibility of secondary malignancies, particularly when new or progressive lesions arise within previously irradiated fields. A multidisciplinary survivorship approach may facilitate earlier recognition, appropriate diagnostic evaluation, and timely management of delayed treatment-related complications. From a bioethical perspective, RIS also illustrates the importance of recognizing therapeutic risk as temporally extended rather than confined to the period immediately surrounding treatment.

Keywords: Radiation-induced sarcoma, Secondary malignancy, Brain tumors, Radiotherapy, Cancer survivorship

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Introduction

Radiation therapy is a cornerstone of modern oncology and has substantially improved survival and disease control for patients with many intracranial tumors. However, ionizing radiation can also produce delayed biological effects in normal tissues, including the rare development of secondary malignancies. Radiation-induced sarcoma (RIS) is an uncommon but clinically important late complication of therapeutic irradiation, characterized by the development of a histologically distinct sarcoma within a previously irradiated field after an appropriate latency period [1-3]. These tumors may arise several years or even decades after the initial treatment and can be associated with poor clinical outcomes. Thus, RIS represents a particularly important example of a treatment-related complication whose clinical manifestation may occur long after the original therapeutic intervention.

The significance of RIS extends beyond its rarity. Improvements in the diagnosis and treatment of primary brain tumors have resulted in increasing numbers of long-term survivors who may remain at risk for delayed treatment-related complications. Consequently, the epidemiology of RIS is closely linked to the expanding population of cancer survivors. The emergence of a secondary malignancy after successful treatment does not necessarily indicate a failure of radiation oncology; rather, it illustrates the complex balance between the substantial therapeutic benefits of irradiation and its potential long-term risks. This temporal dimension of treatment-related harm presents an important challenge for survivorship care, particularly among patients who remain at risk for late complications many years after completion of therapy.

Radiation therapy is widely used in the management of intracranial tumors, and advances in treatment planning and delivery, including intensity-modulated radiation therapy (IMRT), three-dimensional conformal radiation therapy (3D-CRT), and stereotactic radiosurgery (SRS), have improved the ability to deliver therapeutic doses while limiting exposure to surrounding tissues [1-3]. Nevertheless, normal tissues within and adjacent to the radiation field may receive ionizing radiation and sustain molecular and cellular alterations. In a small proportion of exposed individuals, such changes may contribute to subsequent malignant transformation. Reported estimates of RIS incidence range from approximately 0.03% to 0.3%, and RIS accounts for approximately 3% of soft-tissue sarcomas [4, 5]. Although the absolute risk is low, the increasing number of long-term cancer survivors makes recognition of this late complication clinically relevant.

The diagnostic definition of radiation-induced malignancy is traditionally based on the criteria proposed by Cahan et al. in 1948 [6]. These criteria include a history of therapeutic irradiation, development of a secondary tumor within or adjacent to the previously irradiated field, a sufficient latency interval between irradiation and tumor development, and histological characteristics distinct from those of the original tumor. These principles remain

important in distinguishing RIS from local recurrence or progression of the primary neoplasm. In particular, the requirement for histological distinction emphasizes that the secondary tumor represents a separate malignant process rather than simply a recurrence of the original disease.

The development of RIS also highlights the temporal complexity of treatment-related risk. Unlike many acute adverse effects of cancer therapy, RIS may become clinically apparent only years after the initial therapeutic exposure, when the original disease may have been successfully controlled and the patient may no longer be receiving active oncological treatment. This prolonged interval can complicate both clinical recognition and the attribution of causality. It also emphasizes the importance of maintaining an appropriate awareness of late treatment effects within long-term survivorship programs.

From a systems-biology perspective, radiation-induced carcinogenesis is likely to involve interactions among DNA damage, genomic instability, cellular selection, tissue microenvironment, and individual host susceptibility [4,5]. Radiation exposure does not affect malignant cells exclusively; it may also alter surrounding stromal, vascular, and immune components of the treated tissue. The subsequent development of a sarcoma therefore reflects a complex biological process rather than a simple linear consequence of radiation exposure. The diversity of histological subtypes reported among RIS cases further illustrates this complexity.

The present case series describes three patients who developed secondary intracranial sarcomas following radiotherapy for primary brain tumors. The cases involve different primary tumors, latency periods, and sarcomatous histologies, providing an opportunity to examine the clinical and pathological heterogeneity of RIS. In addition to describing the individual clinical courses, this report considers the implications of these cases for long-term surveillance and survivorship care. By examining RIS as both a rare clinical complication and a manifestation of delayed treatment-related risk, this study aims to emphasize the importance of sustained clinical vigilance in patients with a history of therapeutic irradiation.

The concept of iatrogenesis, particularly as articulated by Ivan Illich in *Medical Nemesis* (1976) and subsequently developed within bioethical scholarship, emphasizes that medical interventions can produce unintended forms of harm. Although Illich's broader framework was deliberately critical and polemical, the concept provides a useful perspective for understanding RIS as a treatment-related complication that may occur despite appropriate clinical decision-making. The sarcomas described in this case series were not attributable to negligence or technical failure; rather, they developed following radiation therapy administered as part of the treatment of the patients' primary intracranial tumors. In this context, RIS can be understood as a rare and delayed consequence of an intervention whose immediate therapeutic benefits may substantially outweigh its

long-term risks. This distinction is important because the occurrence of a treatment-related malignancy does not, in itself, imply inappropriate care. Instead, it illustrates the difficulty of balancing therapeutic benefit against adverse effects that may emerge only after a prolonged latency period.

The temporal dimension of RIS further distinguishes it from many other treatment-related complications. Therapeutic benefits and adverse effects are often evaluated within relatively defined clinical timeframes; however, secondary malignancies may become apparent years or decades after the initial exposure. In the present case series, the latency periods between radiotherapy and the diagnosis of RIS were 4, 5, and 9 years. During such intervals, patients may transition from active cancer treatment to long-term survivorship, and the connection between a previous therapeutic exposure and a newly developing malignancy may become less clinically apparent. This temporal separation presents challenges for long-term surveillance, informed consent, and causal attribution. It also emphasizes the importance of maintaining awareness of late treatment effects even after successful control of the primary tumor.

From a systems-biology perspective, RIS can be viewed as the result of complex interactions between radiation-induced cellular injury, genomic alterations, tissue microenvironment, and host-specific factors [4, 5, 7]. Ionizing radiation can produce DNA damage and other cellular alterations in both tumor and surrounding normal tissues. Subsequent biological responses may involve changes in stromal, vascular, and immune components of the irradiated tissue. In a small proportion of exposed individuals, these alterations may contribute to malignant transformation over time. The development of RIS should therefore not be conceptualized as a simple linear consequence of radiation exposure but as a multifactorial process influenced by characteristics of the host, the irradiated tissue, and the radiation exposure itself. Factors such as genetic susceptibility and radiation dose and volume may contribute to individual risk, although the precise mechanisms underlying RIS remain incompletely understood [4, 5, 7].

The histological diversity of RIS further illustrates the complexity of radiation-associated carcinogenesis. Reported secondary sarcomas include fibrosarcoma, osteosarcoma, leiomyosarcoma, and undifferentiated pleomorphic sarcoma, among other histological subtypes [8]. In intracranial cases, the tissues exposed to radiation may include the dura, leptomeninges, bone, and other mesenchymal components within or adjacent to the treatment field. The three cases presented in this report histiocytic sarcoma, undifferentiated high-grade sarcoma, and mesenchymal chondrosarcoma further demonstrate the histological heterogeneity that can occur among radiation-associated sarcomas. Their distinct morphological characteristics, combined with their occurrence within previously irradiated fields and the appropriate latency periods, support their classification as radiation-induced secondary malignancies.

The implications of RIS extend beyond diagnosis and

treatment to long-term cancer survivorship. The concept of an “iatrogenic disease of success” has been used to describe secondary malignancies that emerge among patients who survive long enough after successful treatment to experience delayed treatment-related complications [4]. As improvements in cancer treatment increase long-term survival, the clinical population requiring survivorship care also expands. Consequently, the management of patients with a history of therapeutic irradiation should extend beyond surveillance for recurrence of the primary tumor and should incorporate appropriate awareness of late treatment-related complications. This does not imply that all irradiated patients require intensive investigation for secondary malignancy; rather, it supports maintaining clinical vigilance when new or unexplained lesions develop within or near a previously irradiated field.

The three cases presented in this report illustrate this clinical and temporal complexity. Each patient had a distinct primary intracranial tumor, underwent therapeutic irradiation, and subsequently developed a histologically different sarcoma within the previously irradiated field after a latency period of several years. These features are consistent with the established diagnostic principles for RIS and demonstrate the heterogeneity of its clinical and pathological presentation. At the same time, the relatively short survival following diagnosis in these cases emphasizes the potential severity of this complication and the importance of timely recognition and multidisciplinary management.

Reporting rare cases such as these contributes to the broader understanding of treatment-related secondary malignancies and may help clinicians recognize patterns that are difficult to appreciate in individual practice. Although a three-case series cannot establish causal relationships or estimate the incidence of RIS, it can provide clinically relevant observations regarding latency, anatomical distribution, histological diversity, and management. More broadly, these cases highlight the importance of considering the entire temporal trajectory of cancer treatment from the initial therapeutic decision through long-term survivorship when evaluating the benefits and potential delayed consequences of radiation therapy.

Materials and Methods

This study employed a retrospective case series design to characterize radiation-induced sarcoma (RIS) arising after radiotherapy for primary intracranial tumors. Given the rarity of RIS, a case-series approach allows detailed examination of individual clinical trajectories, including the temporal relationship between the primary tumor, radiation exposure, subsequent sarcoma development, and clinical outcome. Although case series cannot establish causality or provide statistical generalizability, they can provide clinically relevant insights into rare complications that are difficult to investigate using large prospective studies.

Three patients who developed RIS following radiation therapy for primary intracranial tumors were identified,

and their available clinical records, radiological findings, histopathological reports, and treatment histories were retrospectively reviewed. The variables assessed included the type and date of the primary tumor, radiation technique and dose, interval between radiotherapy and diagnosis of RIS, anatomical location of the secondary tumor, histopathological characteristics, immunohistochemical findings where available, treatment administered after RIS diagnosis, and subsequent clinical outcome.

The diagnosis of RIS was assessed according to the established criteria proposed by Cahan et al., including a history of prior radiotherapy, development of the secondary tumor within or adjacent to the previously irradiated field, a sufficient latency period between radiation exposure and tumor development, and histological distinction between the primary and secondary tumors. Each case was reviewed individually, and the clinical course was presented chronologically to illustrate the relationship between the initial treatment and subsequent development of RIS.

Results

Case Presentation

Case 1

In 2014, a 19-year-old female patient presented with a three-month history of intermittent headaches, nausea, and progressive blurred vision. She also reported irregular menstruation and galactorrhea. Magnetic resonance imaging (MRI) revealed a large, well-defined, lobulated mass within the pituitary fossa measuring $5.2 \times 4.0 \times 7.0$ cm. The lesion extended superiorly into the suprasellar cistern and caused compression of the third ventricle, optic chiasm, and brainstem, with extension toward the cerebellopontine angle.

The patient underwent craniotomy and tumor decompression, followed by adjuvant radiation therapy using intensity-modulated radiation therapy (IMRT), with a total dose of 50.4 Gy delivered in 28 fractions (Figure 1). Postoperative histopathological examination confirmed a pituitary adenoma. The patient subsequently received maintenance cabergoline therapy.

Follow-up MRI performed two years later, in 2016,

demonstrated a hyperintense lesion measuring $1.1 \times 1.8 \times 1.8$ cm in the right parasagittal region, extending into the suprasellar space and displacing the optic chiasm. The lesion was interpreted as probable residual disease with adjacent postoperative changes (Figure 2). Serum prolactin was greater than 200 ng/mL, and continuation of cabergoline therapy was recommended.

The patient was subsequently lost to follow-up. No clinical or radiological assessment was documented during the following seven years.

In April 2023, at 28 years of age, she returned with a six-month history of frontal headaches, unsteadiness, and disorganized speech. She also reported progressive visual deterioration. Neurological examination revealed right third cranial nerve palsy. Routine laboratory investigations, including serum prolactin and thyroid function tests, were within normal limits.

Brain MRI demonstrated a large solid-cystic lesion measuring $7.5 \times 5.6 \times 5.6$ cm in the left frontotemporal region. The lesion was located within the previously irradiated field (Figure 3). Given the substantial interval since radiotherapy, the distinct anatomical location, and the imaging characteristics of the new lesion, a secondary radiation-associated neoplasm was considered.

The patient underwent surgical excision of the lesion. Histopathological examination demonstrated a malignant neoplasm with features distinct from the original pituitary adenoma. The findings were consistent with a radiation-induced sarcoma.

The patient subsequently received the most recent follow-up

This case illustrates the intersection of biological temporality, diagnostic complexity, and patient autonomy. The patient's decision to decline salvage chemotherapy occurred after an extensive treatment trajectory that had begun with craniotomy at 19 years of age and culminated in the development of a second aggressive malignancy at 28 years. This decision highlights an important dimension of survivorship care: treatment decisions are shaped not only by tumor biology and available therapeutic options but also by individual preferences, treatment burden, and the patient's lived experience of illness. The ethical

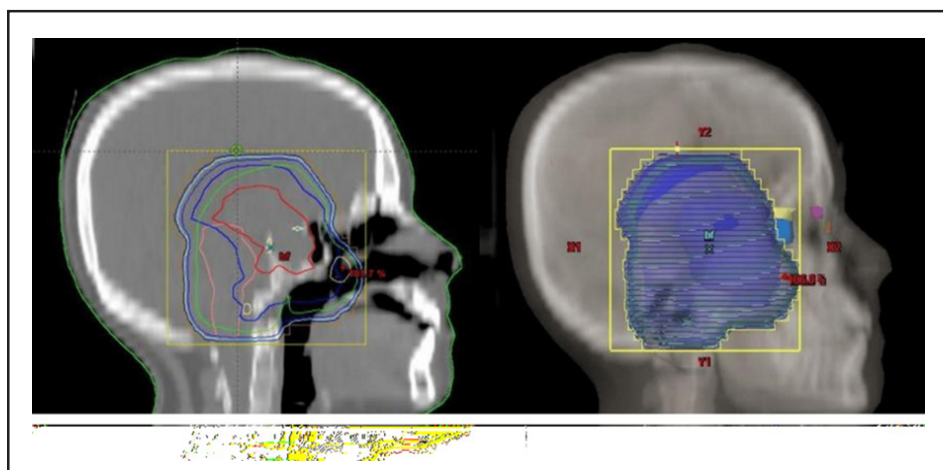


Figure 1. Adjuvant Radiotherapy Planning Image for Pituitary Adenoma (2014)

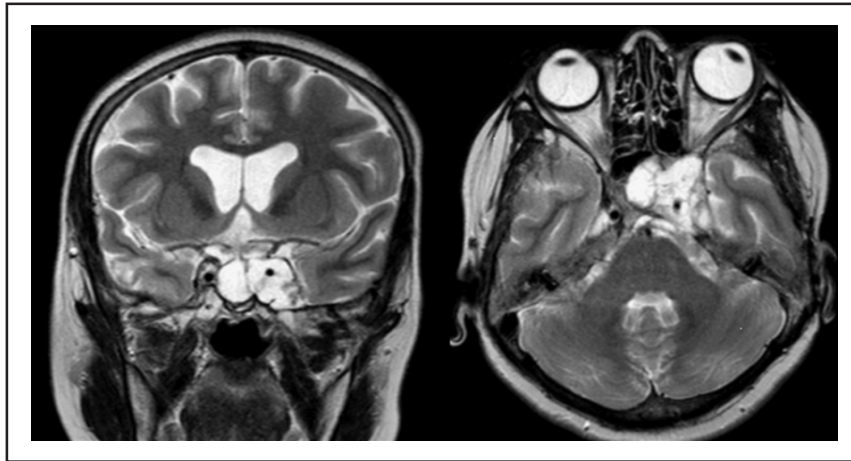


Figure 2. Brain MRI Showing a Residual Lesion with Adjacent Postoperative Changes in the Right Parasagittal Region, Extending into the Suprasellar Space and Displacing the Optic Chiasm (March 2016)

dimensions of survivorship are therefore not solely institutional; they are also personal and patient-centered (Figure 4).

Case 2

A 51-year-old woman presented in January 2014 with occipital headaches and bilateral visual impairment. Brain MRI revealed a right occipital space-occupying lesion (Figure 5a). She underwent gross total resection of the lesion. Postoperative histopathological examination and immunohistochemical analysis confirmed a World Health Organization Grade II right occipital ependymoma. The tumor cells were positive for glial fibrillary acidic protein (GFAP) and epithelial membrane antigen (EMA) and negative for cytokeratin and MIB-1 (Figure 5b). These findings were consistent with a well-defined glial neoplasm of intermediate grade.

She subsequently received adjuvant radiation therapy at a total dose of 54 Gy in 30 fractions using three-dimensional conformal radiation therapy (3D-CRT). The primary tumor remained controlled for four years, during which the patient was clinically and radiologically disease-free.

After four years of documented disease-free follow-up,

the patient re-presented with symptoms similar to those at her initial presentation. Brain MRI demonstrated a recurrent lesion in the right parietal region, measuring $3.9 \times 5.7 \times 5.2$ cm and located within the previously irradiated field (Figure 6). Given the anatomical proximity to the original tumor site and the similarity of the presenting symptoms, recurrent ependymoma was initially considered. However, the possibility of a radiation-induced secondary malignancy was subsequently considered because of the lesion's location within the prior radiation field and the four-year latency period.

She underwent right parieto-occipital craniotomy and excision of the lesion in August 2018. Postoperative histopathological examination confirmed that the lesion was not recurrent ependymoma but an undifferentiated high-grade sarcoma (Figure 7). This represented a histologically distinct malignancy of mesenchymal character arising within the previously irradiated tumor bed. The transformation from a controlled glial neoplasm to an undifferentiated, aggressive sarcoma within a four-year interval represents the shortest latency period in this case series. Notably, this case meets the minimum four-year latency criterion proposed by Cahan et al. for radiation-induced sarcoma, highlighting the potential

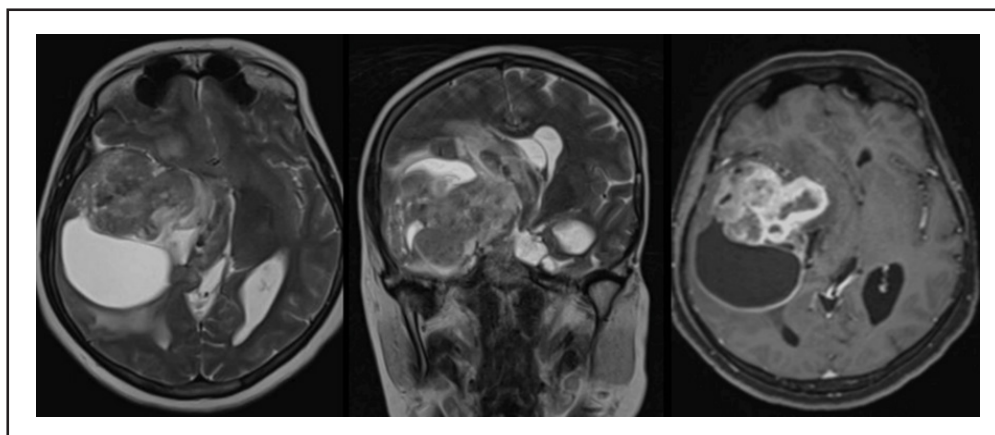


Figure 3. Brain MRI Demonstrating a Large Solid-Cystic Left Frontotemporal Lesion within the Previously Irradiated Field (April 2023)

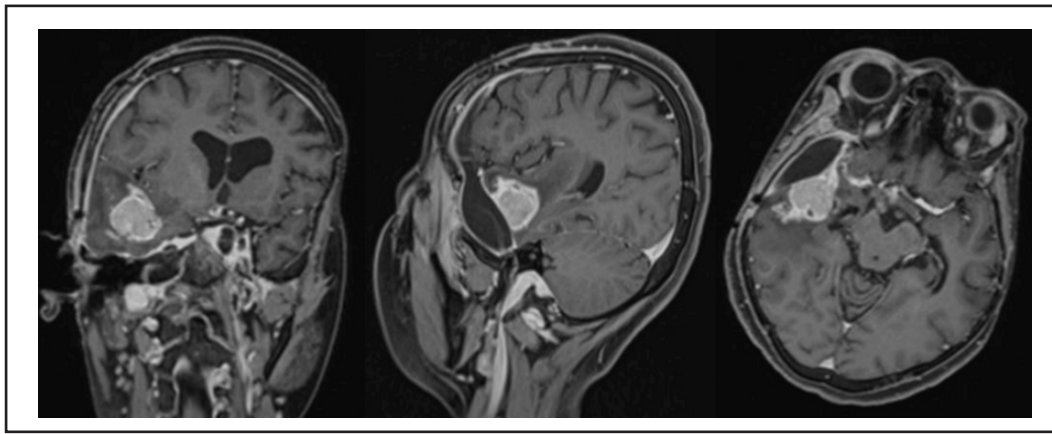


Figure 4. MRI Brain Showing Recurrence (January 2024)

variability of the latency period traditionally associated with RIS [6, 9].

Adjuvant chemoradiation was planned, consisting of radiation therapy at a total dose of 59.4 Gy in 33 fractions using 3D-CRT, with weekly vincristine. Although chemotherapy was discontinued because of treatment intolerance, the patient completed the prescribed radiation

course. The toxicity associated with treatment in an already compromised patient illustrates another dimension of the therapeutic paradox embodied by RIS: the primary modality used to treat the secondary malignancy may be the same modality implicated in its development. The patient was subsequently lost to follow-up and survived until July 2020, corresponding to an overall post-RIS

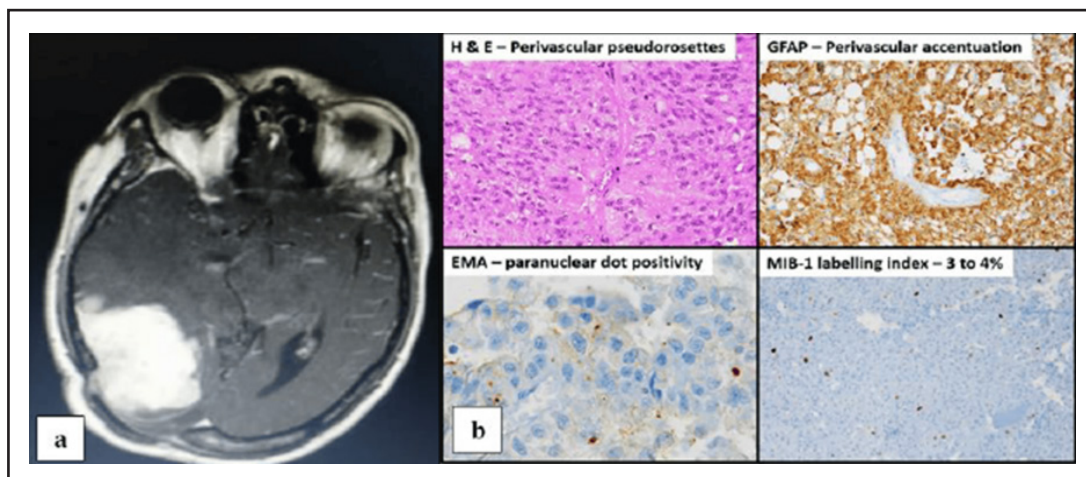


Figure 5. (a) Post-gadolinium contrast-enhanced T1-weighted MRI obtained postoperatively, showing diffuse edema. (b) Microscopic examination showing a glial neoplasm composed of plump cells with vesicular nuclei and glassy to pale eosinophilic cytoplasm arranged in papillary and sheet-like patterns. The tumor cells were positive for GFAP and EMA and negative for cytokeratin and MIB-1 on immunohistochemical staining.

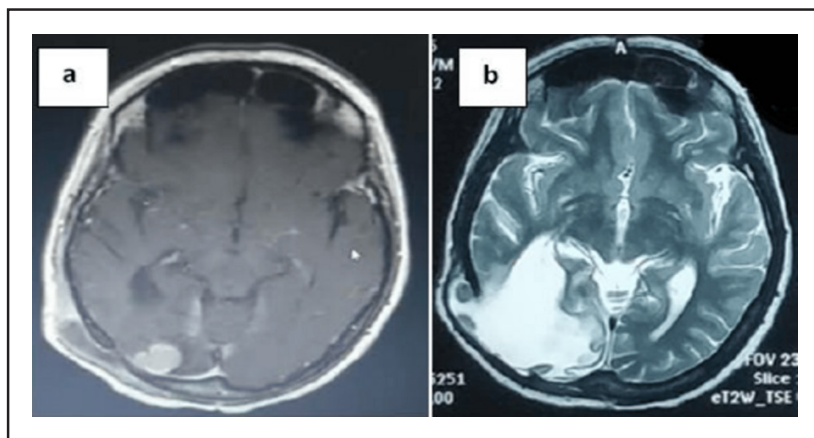


Figure 6. (a) Post-gadolinium contrast-enhanced T1-weighted MRI showing recurrence in the occipitoparietal region surrounded by edema. (b) T2-weighted MRI showing edema at the postoperative site following gadolinium contrast administration.

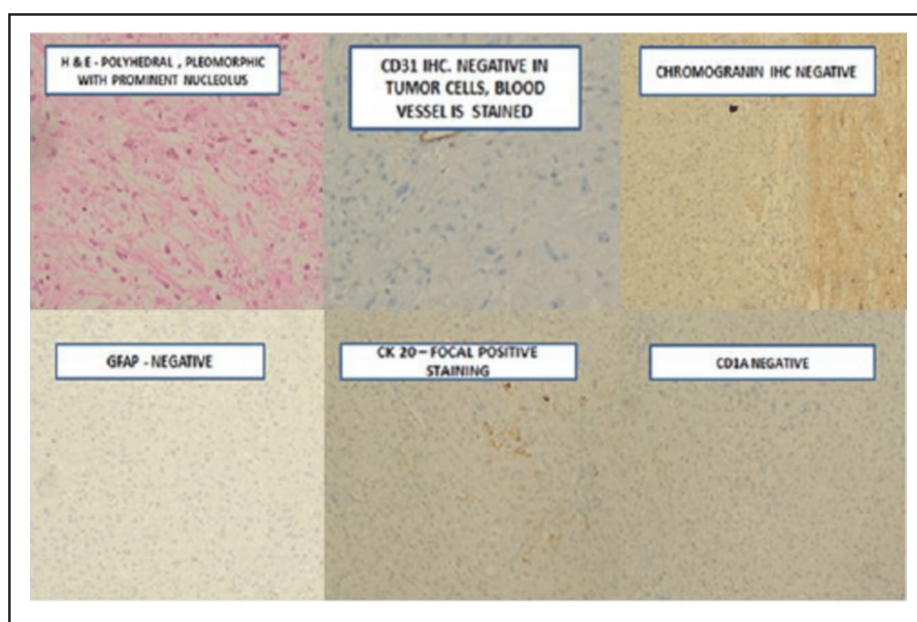


Figure 7. Round to Polyhedral Cells with Moderate Amounts of Granular Eosinophilic Cytoplasm, Pleomorphic Hyperchromatic Nuclei, and Prominent Nucleoli. Immunohistochemical staining was negative for GFAP, CD31, and CD1a and showed focal positivity for CK20, supporting a diagnosis of undifferentiated high-grade sarcoma.

survival of two years.

Case 3

In May 2014, a 30-year-old man presented with a one-year history of seizures and decreased sensation in the right lower limb. An MRI performed at an outside institution revealed a left parietal convexity meningioma closely associated with the superior sagittal sinus. Surgical excision was performed, and histopathological examination confirmed a World Health Organization Grade II meningioma of angiomatous and mixed type with a hemangiopericytomatous pattern. Postoperatively, the patient received adjuvant radiation therapy at a total dose of 60 Gy in 30 fractions using 3D-CRT in July 2014 (Figure 8).

This case introduces a radiobiological variable not present in the first two cases: the patient subsequently underwent a second course of radiation therapy. In May 2019, he presented with a three-month history of headaches. Contrast-enhanced brain MRI demonstrated a recurrent, irregularly enhancing lesion measuring $2.1 \times 1.9 \times 1.5$ cm in the right parasagittal region, compressing the superior sagittal sinus and showing calcification and mild diffusion restriction. Given the lesion characteristics and the patient's history, stereotactic radiosurgery (SRS) was planned and delivered at a dose of 16 Gy in a single fraction (Figure 9).

The decision to employ radiosurgery for recurrent meningioma was clinically rational and technically appropriate. From a biological perspective, however, this second irradiation event represents an additional radiation exposure within a tissue field that had already received a substantial dose five years earlier. The cumulative biological effects of sequential irradiation cannot be understood simply as an arithmetic sum of radiation doses.

Rather, they may reflect complex interactions involving cellular repair mechanisms, genomic instability, tissue microenvironment, and individual biological variability, which are not fully captured by current predictive models.

Five years after radiosurgery, in June 2023, the patient presented with seizures and progressive weakness of both the upper and lower limbs. MRI revealed a $5.0 \times 2.7 \times 3.6$ cm heterogeneously enhancing lesion in the left high frontal parasagittal region, initially interpreted as suggestive of recurrent meningioma (Figure 10). The clinical history, anatomical location, imaging

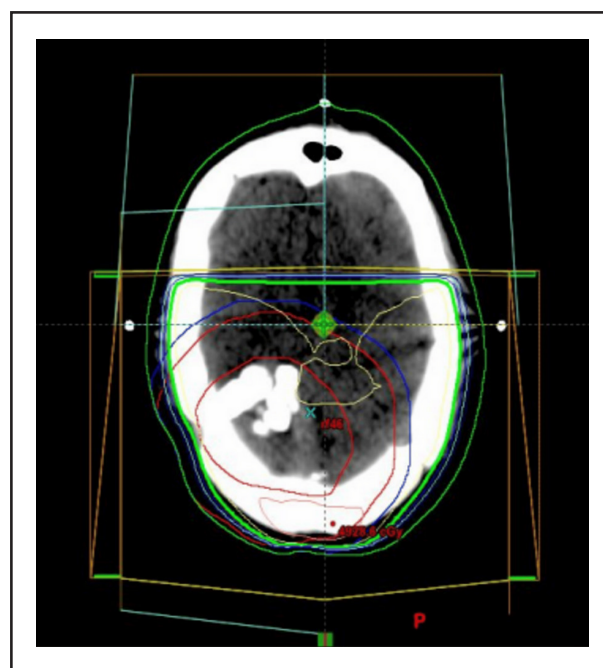


Figure 8. Adjuvant Radiation Therapy Planning Image (July 2014)

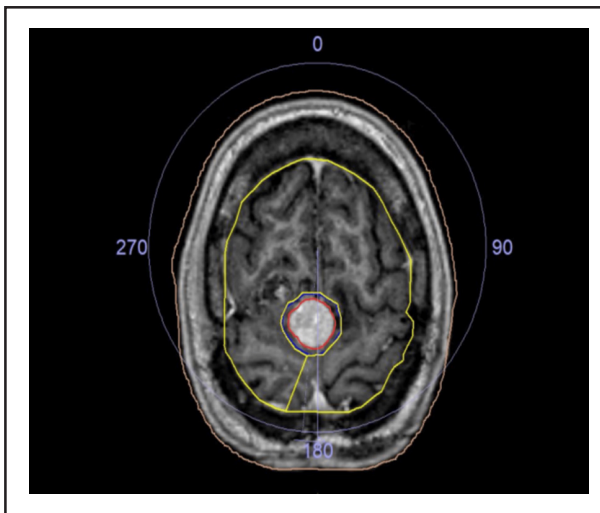


Figure 9. Stereotactic Radiosurgery Treatment-Planning Image (May 2019)

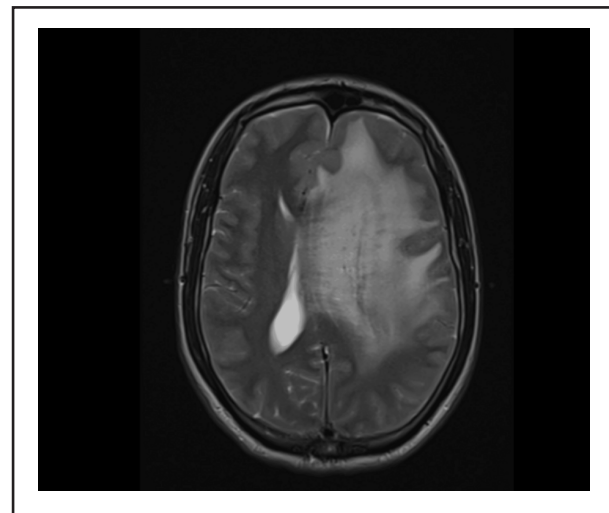


Figure 10. MRI Showing a Heterogeneously Enhancing Recurrent Lesion in the Left High Frontal Parasagittal Region (June 2023)

characteristics, and previous diagnosis all favored the familiar diagnosis of tumor recurrence. However, as in Case 2, subsequent histopathological examination demonstrated a different biological process.

The patient underwent bifrontal craniotomy and excision of the tumor. Postoperative histopathological examination revealed a mesenchymal chondrosarcoma, a rare and biologically distinctive sarcoma subtype that was histologically unrelated to the original meningioma. Adjuvant radiation therapy was planned at a total dose of 50 Gy in 25 fractions using IMRT, which the patient completed (Figure 11). He remains on regular follow-up, and the most recent MRI, performed in February 2025, showed no evidence of recurrent or residual disease.

Although this outcome is cautiously optimistic, it does not resolve the biological uncertainty inherent in this patient's case. It is possible that he has achieved durable control of the secondary malignancy. However, given the natural history of mesenchymal chondrosarcoma and the aggressive potential of RIS, the current disease-free state may represent a period of disease control rather than definitive cure. Continued vigilant follow-up is therefore essential, particularly in a patient whose treatment history includes two courses of irradiation and whose most recent

diagnosis was a rare and potentially aggressive sarcoma subtype.

Discussion

The Incidence Problem and What It Conceals

RIS is classified as a rare complication of radiation therapy, with a reported incidence ranging from 0.03% to 0.3% [5]. More recent studies suggest that RIS accounts for fewer than 4% of all sarcomas and occurs in approximately 0.19% and 0.10% of patients receiving radiation therapy for head and neck and breast cancers, respectively [10]. These figures are reassuring in absolute terms and support the conclusion that radiation therapy is generally safe for the vast majority of patients who receive it. Nevertheless, the rarity of RIS does not diminish the severity of its consequences for affected individuals or the clinical importance of recognizing and monitoring this late complication. As the global population of long-term cancer survivors continues to increase, the absolute number of patients who may eventually develop RIS is also expected to increase, even if its incidence remains relatively stable. The epidemiological significance of rare

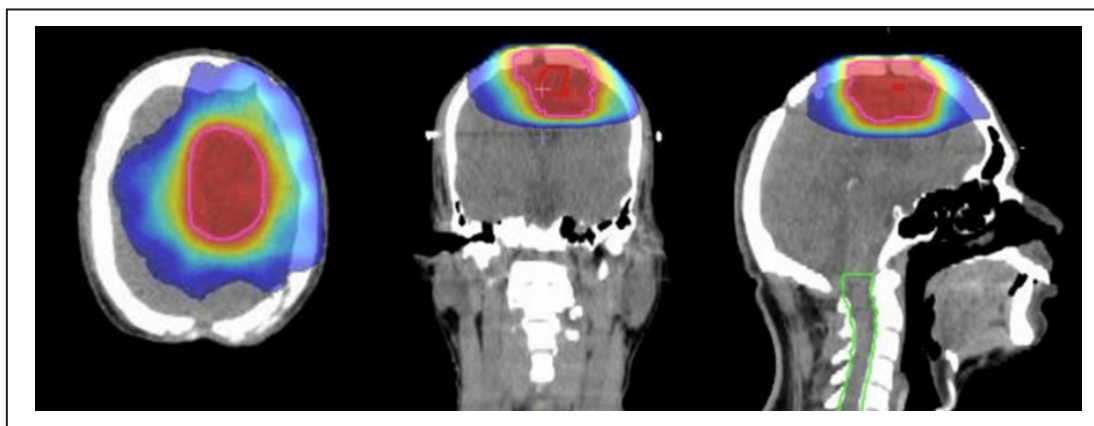


Figure 11. Adjuvant Radiation Therapy Planning Image (June 2023)

late treatment effects is therefore closely linked to the expanding population of cancer survivors.

The Cahan Criteria as a Diagnostic and Temporal Framework

The diagnostic criteria proposed by Cahan et al. in 1948 for identifying radiation-induced malignancies established four key requirements: a documented history of radiation therapy, development of a second tumor within the previously irradiated field, absence of the secondary tumor at the time of the initial treatment, a latency period of at least four years, and histological distinction between the secondary tumor and the original malignancy [6]. All three cases in the present series fulfill these criteria.

Beyond their diagnostic utility, the Cahan criteria provide a temporal framework for linking a present malignancy with a previous therapeutic exposure. Establishing such a relationship requires reconstruction of the patient's clinical history across several years, integrating previous imaging, treatment records, radiation fields, and pathological findings. In this sense, the diagnosis of RIS requires not only current pathological evidence but also an accurate reconstruction of the patient's prior treatment history.

The patients in our case series had a mean age of 33 years at the time of initial radiation therapy, which is broadly comparable to the median ages reported by Callesen et al. (32 years), Patel et al. (34 years), and Hanna et al. (46 years) [9, 11, 12]. The relatively young age of these patients emphasizes the long-term implications of radiation-associated complications. Radiation therapy administered to patients aged 19, 30, or 51 years may be followed by several decades of survivorship, during which late treatment-related complications may emerge. Consequently, the potential for RIS represents an important component of long-term survivorship considerations.

Latency as a Biological and Clinical Concept

RIS typically develops after a prolonged latency period, with reported intervals commonly ranging from approximately 8 to 14 years [9]. In the present series, the latency periods were 9, 4, and 5 years, respectively, with a mean of 6 years. These intervals are toward the shorter end of the range reported in the literature, although the four-year interval in Case 2 corresponds precisely to the minimum latency specified in the Cahan criteria [6].

Latency should not be regarded as a fixed biological interval. It may be influenced by multiple interacting factors, including radiation dose and fractionation, the radiosensitivity of the affected tissue, individual genetic susceptibility, the local immune and stromal microenvironment, and potentially exposure to other oncogenic treatments [7]. Given the small sample size of the present case series, however, no conclusions can be drawn regarding factors that may have contributed to the relatively short latency periods observed in these patients.

The temporal characteristics of RIS also present challenges for conventional oncological surveillance. Follow-up protocols are generally designed around the natural history of the primary tumor, with particular

emphasis on local recurrence, metastatic disease, and treatment-related complications during the period of greatest expected risk. As time from treatment increases, surveillance intensity may decrease. However, RIS can emerge years after the primary disease has been controlled, potentially outside the conventional surveillance window. This temporal mismatch highlights the importance of maintaining awareness of previous radiation exposure when evaluating new lesions arising within a previously irradiated field, even after prolonged disease-free intervals.

Histological Diversity and the Mesenchymal Origin of RIS

Sarcomas are malignant tumors of mesenchymal origin and encompass a broad range of histological subtypes, including fibrosarcoma, chondrosarcoma, and spindle cell sarcoma. Radiation-induced CNS sarcomas are thought to arise from mesenchymal tissues within or adjacent to the irradiated field, including the scalp, subcutaneous tissue, dura, bone, and leptomeninges [7]. The histological diversity of RIS may therefore reflect the biological heterogeneity of the tissues exposed to radiation and the different cellular populations capable of undergoing malignant transformation.

Commonly reported histological subtypes of RIS include malignant fibrous histiocytoma, osteosarcoma, leiomyosarcoma, and both high- and low-grade sarcomas [8]. In contrast, the three cases in the present series involved less common entities: histiocytic sarcoma, undifferentiated high-grade sarcoma, and mesenchymal chondrosarcoma. The occurrence of these uncommon subtypes within an already rare clinical entity further emphasizes the diagnostic challenges associated with RIS and the importance of comprehensive histopathological and immunohistochemical assessment of new lesions arising within previously irradiated fields.

The initial diagnosis of xanthocytic astrocytoma in Case 1, subsequently revised to histiocytic sarcoma following immunohistochemical evaluation, illustrates the potential diagnostic complexity of these lesions. In patients with a history of radiation therapy, a new mass within the irradiated field should therefore prompt consideration of both recurrence of the primary tumor and a possible radiation-associated secondary malignancy.

Genetic predisposition and exposure to other anticancer therapies, including chemotherapy, have also been proposed as potential contributors to the development of secondary malignancies [7]. However, the present case series does not provide sufficient evidence to determine the contribution of these factors in the individual patients. The different histological subtypes and clinical outcomes observed in the three cases further illustrate the biological heterogeneity of RIS and the limitations of applying a uniform prognostic model to these uncommon tumors.

The Rare Subtypes and Their Clinical Significance

The histiocytic sarcoma in Case 1 developed nine years after radiation therapy for pituitary adenoma, and the patient survived for approximately one year following diagnosis of RIS. This observation is consistent with reports describing radiation-associated sarcomas

following treatment of intracranial tumors as uncommon but potentially aggressive secondary malignancies [13]. The tumor demonstrated positivity for CD68, CD163, vimentin, and BRAF, supporting histiocytic differentiation. These findings also emphasize the importance of immunohistochemical characterization when the morphology of a secondary tumor is not readily distinguishable from that of other intracranial neoplasms.

In Case 2, the original Grade II ependymoma was followed four years later by the development of an undifferentiated high-grade sarcoma within the previously irradiated field. This observation is consistent with reports emphasizing the rarity and clinical significance of sarcomatous transformation following treatment of intracranial tumors [14]. The term “ependymosarcoma,” described in the literature, reflects the unusual coexistence or sequential development of glial and sarcomatous components in certain cases. However, in the present case, the secondary lesion was classified histopathologically as an undifferentiated high-grade sarcoma and should therefore be interpreted as a distinct secondary malignancy rather than assumed to represent a specific hybrid entity.

The mesenchymal chondrosarcoma in Case 3 developed five years after radiation therapy for meningioma. This finding is compatible with previous reports of secondary sarcoma following radiation therapy for brain tumors, including studies describing substantially longer and highly variable latency periods [7]. Mesenchymal chondrosarcoma is a rare sarcoma subtype with recognized potential for local recurrence and distant metastasis. Accordingly, the absence of recurrent or residual disease on the most recent follow-up MRI should be interpreted as evidence of the patient’s current disease status rather than definitive evidence of cure.

Taken together, these three cases demonstrate the substantial clinical and histological heterogeneity of radiation-induced sarcomas arising after treatment of intracranial tumors. They also emphasize the importance of maintaining diagnostic vigilance when a new lesion develops within a previously irradiated field, particularly when the imaging appearance resembles recurrence of the original tumor. Long-term clinical surveillance, careful review of prior radiation exposure, and appropriate histopathological and immunohistochemical evaluation remain essential components of the management of these rare secondary malignancies.

Survival, Prognosis, and the Limits of Treatment

The five-year overall survival of patients with radiation-induced sarcoma (RIS) has been reported to be approximately 45% [15]. In our case series, post-RIS survival was 1 year, 2 years, and ongoing at 2 years, respectively. These outcomes reflect the aggressive clinical behavior of the tumors encountered in this series, although meaningful comparison with published survival estimates is limited by the small sample size and heterogeneity of RIS. Intracranial RIS may present particular therapeutic challenges because the anatomical constraints of the central nervous system can limit the extent of surgical resection, while previous irradiation restricts the feasibility

and dose of subsequent radiation because of cumulative toxicity. The delivery and effectiveness of systemic chemotherapy may also be influenced by the biological and anatomical characteristics of intracranial disease.

The refusal of salvage chemotherapy by the patient in Case 1 and the chemotherapy intolerance documented in Case 2 are clinically relevant aspects of treatment outcome. These observations illustrate that treatment feasibility in RIS depends not only on tumor biology and available therapeutic modalities but also on individual patient factors, including treatment tolerance, cumulative treatment burden, functional status, and personal preferences. A complete assessment of outcomes in RIS should therefore consider these patient-centered dimensions alongside conventional measures of tumor control and survival.

The Expanding Obligation of Survivorship Care

Advances in cancer treatment have resulted in a growing population of long-term survivors who may subsequently experience delayed treatment-related complications. Continued surveillance and appropriate diagnostic evaluation can facilitate recognition of rare secondary malignancies arising within previously irradiated fields. Reporting such cases contributes to the collective clinical knowledge required to improve recognition and management of these uncommon tumors.

The value of this case series extends beyond the individual patients described. It highlights the importance of maintaining long-term clinical awareness of RIS, particularly when a new lesion develops within a previously irradiated field. Such awareness requires an appropriate index of suspicion, careful review of the patient’s treatment history, and comprehensive histopathological and immunohistochemical assessment when clinically indicated. It also supports a survivorship framework that extends beyond surveillance for recurrence of the primary tumor and considers the possibility of delayed treatment-related neoplasms.

Larger multicenter studies and systematic analyses are required to better define the incidence, latency, prognostic factors, molecular characteristics, and optimal management of intracranial RIS. Until stronger evidence becomes available, careful individualized assessment remains essential. In particular, a new lesion arising within a previously irradiated field should not automatically be presumed to represent recurrence of the original tumor. Definitive pathological evaluation is important when the clinical and radiological findings permit, especially because the distinction between recurrent primary disease and RIS has direct implications for treatment planning and prognosis.

In conclusion, radiation-induced sarcomas represent a rare but clinically important late complication of radiation therapy and illustrate the complex temporal relationship between therapeutic benefit and delayed treatment-related harm. The three cases presented in this series demonstrate several characteristic features of RIS, including development within a previously irradiated field, histological distinction from the primary

tumor, a latency period of several years, and aggressive clinical behavior after diagnosis. The cases also illustrate considerable histological diversity, with Histiocytic sarcoma, Undifferentiated high-grade sarcoma, and Mesenchymal chondrosarcoma occurring after irradiation for pituitary adenoma, ependymoma, and meningioma, respectively.

The latency periods in this series ranged from 4 to 9 years, with a mean of 6 years. Although these intervals are shorter than the 8–14-year range commonly reported in some studies [6], the small number of cases does not permit conclusions regarding whether these patients represent a distinct latency pattern. Nevertheless, the cases demonstrate that RIS may occur within relatively short intervals after radiation therapy and reinforce the importance of sustained clinical awareness beyond the period of routine surveillance for the primary tumor.

The principal clinical lesson is that a new lesion arising within a previously irradiated field warrants careful consideration of RIS in the differential diagnosis. Although recurrent primary disease may be the most likely clinical interpretation, histopathological and immunohistochemical evaluation is essential when feasible because RIS may closely mimic recurrence radiologically and clinically. In all three cases presented here, the final diagnosis differed from the initial clinical or radiological expectation. Accurate distinction between recurrent primary disease and RIS is therefore important because these entities differ in biological behavior, treatment considerations, and prognosis.

The cases also highlight the importance of long-term survivorship care after cranial irradiation. Such care should extend beyond monitoring for recurrence of the original tumor and should incorporate awareness of delayed treatment-related complications, including secondary malignancies. The appropriate duration and intensity of surveillance should remain individualized according to the patient's primary diagnosis, age at treatment, radiation exposure, subsequent treatment history, and overall clinical context. Particular attention should be given to new or progressively enlarging lesions arising within previously irradiated anatomical regions.

From a broader bioethical perspective, RIS illustrates the temporal complexity of therapeutic risk. Radiation therapy may provide substantial and sometimes life-saving benefit while simultaneously introducing a small risk of delayed malignancy. The occurrence of RIS should not be interpreted as evidence of inappropriate treatment or therapeutic failure; rather, it represents one of the recognized long-term risks that accompany an intervention whose benefits can be substantial. The ethical responsibility therefore lies not in eliminating a risk that cannot currently be reduced to zero, but in communicating clinically meaningful risks appropriately, maintaining long-term vigilance, and ensuring that survivors remain connected to systems capable of recognizing and managing delayed complications.

Ultimately, the significance of these cases extends beyond their rarity. They emphasize that the consequences of cancer treatment may unfold across years rather

than within the immediate period surrounding therapy. A survivorship model that recognizes this temporal dimension can provide a more comprehensive approach to patients who have received cranial irradiation. Continued reporting of rare cases, combined with multicenter data collection and molecular characterization, may help clarify the mechanisms, risk factors, and optimal management strategies for RIS and strengthen the evidence base for long-term follow-up of cancer survivors.

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Conflict of interest

Author declares no conflict of interest

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