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ONCOLOGY: RESEARCH ARTICLE

Treatment-related calvarial lesions in pediatric brain tumor survivors

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Abstract

Background: Despite improved survival, many pediatric brain tumor survivors receiving radiation therapy (RT) experience late effects.

Procedure: To study calvarial lesions in this population, we retrospectively reviewed records of patients undergoing neurosurgical evaluation for calvarial bone lesions detected in posttreatment follow-up imaging at St. Jude Children's Research Hospital. Primary tumor diagnosis, treatment, imaging, surgical intervention, and histopathology from patients with radiographic evidence of lesions followed for ≥2 years post-RT were studied.

Results: For 17 patients with 18 index lesions, median time to lesion manifestation was 2.34 years. Medulloblastoma patients developed lesions at a shorter interval from RT than ependymoma patients ($P = .05$). Twelve of 14 lesions requiring surgery were benign fibro-osseous or sclerotic. Two malignant lesions distinct from the primary tumor had genetic predisposition to malignancy.

Conclusion: Most calvarial lesions arising post-RT are benign and fibro-osseous. Serial imaging is recommended, and high index of suspicion for malignant lesions is warranted for patients genetically predisposed to cancer.

KEYWORDS
calvarial lesion, pediatric brain tumor, radiation therapy

1 | INTRODUCTION

Children with primary central nervous system (CNS) tumors frequently require multimodality care comprising surgical resection, radiation therapy (RT), and chemotherapy.[1] Advances in therapy have increased the number of long-term survivors of childhood CNS tumors.[2] However, they often experience late effects of therapy such as bone and soft tissue growth abnormalities, hearing loss, cognitive decline, endocrine and vascular complications, and secondary malignancies.[3–6]

Treatment-related bone changes in survivors of CNS tumors receiving RT are well documented, as they influence bone density, growth, and premature epiphyseal closure. However, hypo-ostotic lesions with localized bone destruction are not well reported.[7,8] These are often identified radiographically in asymptomatic patients. Determining whether these lesions are benign or malignant is difficult. These calvarial lesions are often asymptomatic, thus preventing clinical suspicion. Abnormal cranial/spinal imaging findings can cause anxiety to families and physicians, but few studies have addressed optimal management of these lesions. We systematically reviewed 17 cases of calvarial hypo-ostotic lesions for clinical history, imaging characteristics, and histopathology.

Abbreviation: CNS, central nervous system; CSI, craniospinal irradiation; LFS, Li–Fraumeni syndrome; MRI, magnetic resonance imaging; RT, radiation therapy.

2 | METHODS

2.1 | Study design

We retrospectively reviewed medical records (May 2001–August 2018) of children referred to the neurosurgery service at St. Jude Children's Research Hospital (St. Jude) for bony lesion in the cranial vault, detected by brain imaging as part of post-treatment surveillance

workup for primary CNS tumors. Records from patients with radiographic evidence of new calvarial lesions referred to the neurosurgical service for lesion evaluation were studied for primary CNS tumor diagnosis, treatment, and nuclear imaging. Date and nature of surgical intervention for calvarial lesions, follow-up imaging, and histopathology reports were collected. Diagnosis date of calvarial lesions was when they were first clearly defined in the radiology report. Children with lesions were periodically imaged, primarily by brain magnetic resonance imaging (MRI) every 2–3 months or as required by the treating physician. This study was approved by institutional review boards of St. Jude and Le Bonheur Children's Hospital.

2.2 | RT analysis

RT fields were studied by reviewing radiotherapy plans and/or radiotherapy portals for each field. Dose to the calvarial lesion was either estimated if only portals were available or calculated from co-registering the representative MRI or CT with the original dosimetric plan. RT fields were available for review in 15 of 17 cases. If patients received multiple RT courses, composite dose profiles were reviewed or cumulative dose inferred by field design and lesion location. If the RT plan was not amenable to dose accumulation, mean dose to the region was inferred by reviewing the radiotherapy plan and prescription.

2.3 | Statistical analysis

Distributions of variables of interest from data were summarized by descriptive statistics. Continuous data were summarized using measures of central tendency. Count and frequency data were compared and summarized by percentages and chi-square test, respectively. Continuous data across groups for time to lesion appearance were compared by Wilcoxon rank sum test.

3 | RESULTS

3.1 | Patient characteristics

We studied 17 patients (12 male and five female) with 18 index lesions who met study criteria (Table 1). Primary CNS tumor diagnosis was medulloblastoma (N = 6), ependymoma (N = 5), retinoblastoma (N = 2), germinoma (N = 1), atypical teratoid rhabdoid tumor (N = 1), nongerminomatous germ cell tumor (N = 1), and other CNS embryonal tumors (N = 1). Median age at diagnosis of primary tumor was 7.6 years (range 0.99-19.18). Patients received cranial radiation (cranio-spinal irradiation [CSI] or focal RT) before developing the calvarial lesion after treatment for their incident primary CNS tumor.

3.2 | Lesion latency

Median time to lesion manifestation from RT on imaging was 2.34 years (range 1.04-13.56). Five patients were symptomatic and experienced pain in the lesion region. Four had multiple small calvarial lesions. Notably, one patient originally diagnosed with medulloblastoma developed two independent calvarial lesions 1.35 and 2.90 years from RT. All lesions were within the RT field.

Time to lesion development differed significantly by tumor type. Medulloblastoma patients developed lesions at a shorter interval from RT [median 1.61 years (range 1.04-5.38)] than ependymoma patients [median 7.18 years (range 1.69-9.39); $P = .055$]. Patients receiving large-field RT (craniospinal/cranial RT) trended toward reduced lesion latency from time of treatment (CSI, median 2.25 years [95% CI 1.55-NR] vs focal median 8.1 years [95% CI 6.08-NR]; $P = .065$). There were no significant differences by gender, race, or presence of a germline predisposition syndrome for lesion latency or incidence (Figure 1).

3.3 | Lesion management, histopathological findings, and interventions

Fourteen patients received surgical intervention as biopsy or lesion resection to determine histopathological diagnosis. Median time from diagnosis date of the lesion to surgical intervention was 92 days (range 8-964). Median area of lesions in MRI was 1.54 cm^2 (range 0.22-2.88). Of 14 patients, 12 showed benign fibro-osseous or sclerotic lesions (Figure 2). Two had a malignant lesion distinct from the primary tumor: one pleomorphic sarcoma, and the other high-grade sarcoma (Figure 3). Both had an underlying genetic predisposition for malignancy diagnosed before developing the calvarial lesion: one had Li–Fraumeni syndrome (LFS) and the other ataxia-telangiectasia (Table 1). Two patients with a benign calvarial lesion had a germline alteration in cancer predisposition genes *RB1* and *BRCA2*. At time of analysis, two patients died from complications unrelated to their calvarial lesion or resection: one from respiratory failure and the other due to glioblastoma, a secondary malignancy in the patient with LFS.

4 | DISCUSSION

RT is indispensable for treating several childhood CNS tumor types.[9–11] However, improved outcomes can come with adverse effects and damage to adjacent normal tissue, which might appear several years after treatment.[4–6] Newer RT delivery techniques may decrease some late effects.[4,12,13] Our study appraises the nature and progression of isolated bony skull lesions in brain and spinal cord tumor survivors given adjuvant RT after neurosurgical resection. Radiographically, after treatment, skull lesions appear as nonspecific lytic lesions with or without sclerosis. They show low-to-intermediate signal intensity on T1-weighted MRI, usually with enhancement, and intermediate-to-high signal intensity on T2-weighted images, but these findings are nonspecific.[8] Most lesions are small and patients may not perceive them. The radiologist often first notes them on surveillance imaging and may involve various differential diagnoses.

RT-induced osteitis and osteoradionecrosis result from altered blood supply to the bone and dysfunction of osteoblasts and osteoclasts.[14] Histopathology and pathogenesis of RT-induced fibrosis is better studied in soft tissues than calvarial lesions. RT

TABLE 1 Demographic, tumor, and treatment characteristics of pediatric patients with calvarial lesions

Primary tumor	Tumor location	Age (years)	Race	Sex	Radiation field	Total radiation dose (Gy)	Adjuvant chemotherapy	Lesion location	Estimated RT dose to lesion (Gy)	Time to lesion (years)	Lesions size (cm^2)	PET[a] scan	Painful	Multiple lesions	Histopathology	Germline mutation
Medulloblastoma	Posterior fossa	7.6	AA	M	CSI	54	Yes	Sphenoid	40.0	1.67	1.80	Negative	No	No	Fibrosis and cystic changes	
Medulloblastoma	Posterior fossa	8.0	W	M	CSI	55.8	Yes	Frontal	23.0	2.41	0.22	–[b]	No	Yes	Pleomorphic sarcoma	TP53 (Li–Fraumeni)
Medulloblastoma	Posterior fossa	8.7	W	M	CSI	55.8	Yes	Parieto-occipital	39.6	1.04	1.2	–	Yes	No	Fibroblastic proliferation	
Medulloblastoma	Posterior fossa	10.8	W	M	CSI	55.8	Yes	Parietal	23.0	5.38	0.36	–	No	Yes	Fibroosseous lesion	
Medulloblastoma	Posterior fossa	14.0	W	F	CSI	54	Yes	Temporal	36.0	1.55	0.64	–	No	No		
Medulloblastoma	Posterior fossa	19.2	W	M	CSI	54	Yes	Fronto-parietal	39.6	1.35	0.66	–	Yes	Yes	Locally aggressive bland spindle cell tumor	
Ependymoma	Third ventricle	0.9	W	M	Focal	54	No	Occipital	30.0	6.08	1.68	Moderate uptake	No	No	Benign osteoid osteoma	
Ependymoma	Posterior fossa	2	W	M	CSI	59.4	No	Frontal	44.0	7.18	0.35	Negative	No	No		
Ependymoma	Posterior Fossa	4.2	W	F	Focal	59.4	No	Clivus/Sphenoid	50.0	1.69	0.81	Negative	No	No	Benign, fibrous dysplasia with inflammation	
Ependymoma	Right fronto-parietal lobe	5.1	W	F	Focal	59.4	Yes	Fronto-parietal	54.0	8.10	2.88	Mild uptake	Yes	No		
Ependymoma	Posterior fossa	9.8	W	F	CSI	59.4	Yes	Occipital	70.0	9.39	1.43	–	Yes	No	Sclerotic bone with inflammation	
CNS ET	Right frontal lobe	1.4	W	M	Focal	54	Yes	Frontal	–	8.48	1.91	–	No	No	High-grade sarcoma	ATM (heterozygous)
Retinoblastoma	Left and right eye	1.7	AA	M	Focal	44	Yes	Parietal	30.0	13.56	2.52	Increased uptake	Yes	No	Osteoblastoma	RB1
Retinoblastoma	Right eye	5.1	AA	M	WBRT	81	Yes	Fronto-parietal	45.0	2.34	1.75	–	No	No	Benign osteolytic fibroblastic lesion	
NSGCT	Third ventricle	10	W	M	CSI	54	Yes	Parietal	40.0	1.06	2.72	Negative	No	Yes	Fibroosseous lesion	*BRCA2*
Germinoma	Suprasellar/pineal	17.8	AA	M	CSI	45.2	Yes	Frontal	26.0	2.34	1.65	–	No	No	Osteoradionecrc	
ATRT	Right CPA	1.3	W	F	CSI	50.5	Yes	Sphenoid	–	2.15	2.88	–	No	No		

Abbreviations: AA, African American; ATM, ataxia-telangiectasia mutation; ATRT, atypical teratoid rhabdoid tumor; BRCA2, breast cancer gene 2; CNS ET, central nervous system embryonal tumor; CPA, central pontine angle; CSI, craniospinal irradiation; F, female; Gy, Gray; L, left; M, male; NSGCT, non-seminomatous germ cell tumor; PET, positron emission tomography; R, right; RB1, retinoblastoma 1 gene; RT, radiation therapy; TP53, tumor protein 53 gene; W, White; WBRT, whole brain radiotherapy.

[a]PET scan performed before surgical intervention.

[b]Dash (-): value not available.

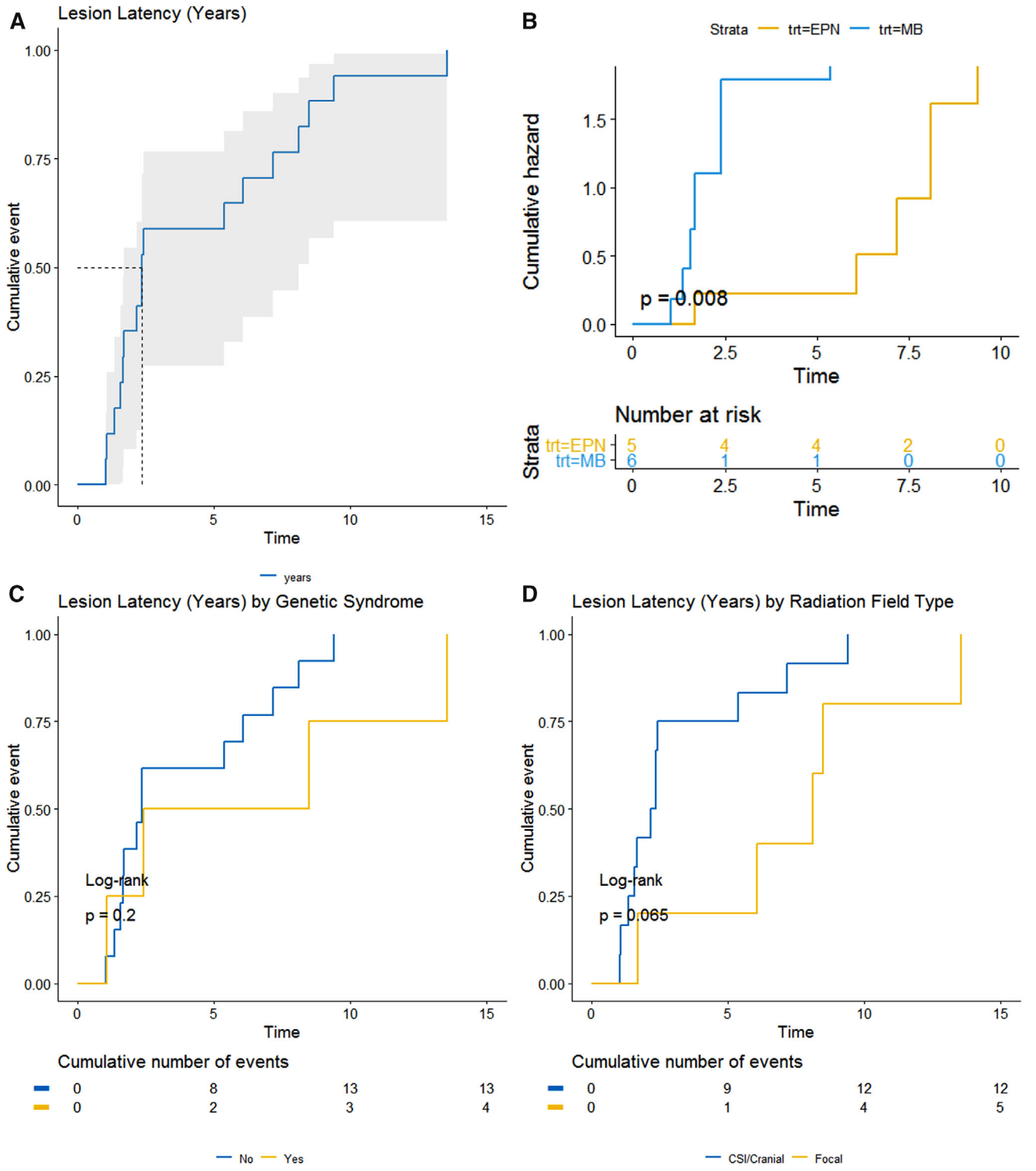

FIGURE 1 Latency of calvarial lesions. (A) Time-to-lesion diagnosis in all patients. (B) Time-to-lesion diagnosis by diagnosis. (C) Time to lesion by presence or absence of an underlying genetic syndrome, and (D) time to lesion diagnosis by radiation field type

triggers inflammation and differentiation of fibroblasts into myofibroblasts, which produces excessive collagen and extracellular matrix components,[15] and involves many proinflammatory cytokines, profibrotic cytokines, and chemokines. These events can be sustained for months or years after therapy completion.[16]

The treating physician should have a detailed understanding of treatment sequelae, which might be pathology specific, to monitor patients by appropriate imaging and at appropriate intervals. Strikingly, medulloblastoma patients tended to develop lesions sooner than ependymoma patients after RT (median 1.61 vs 7.18 years,

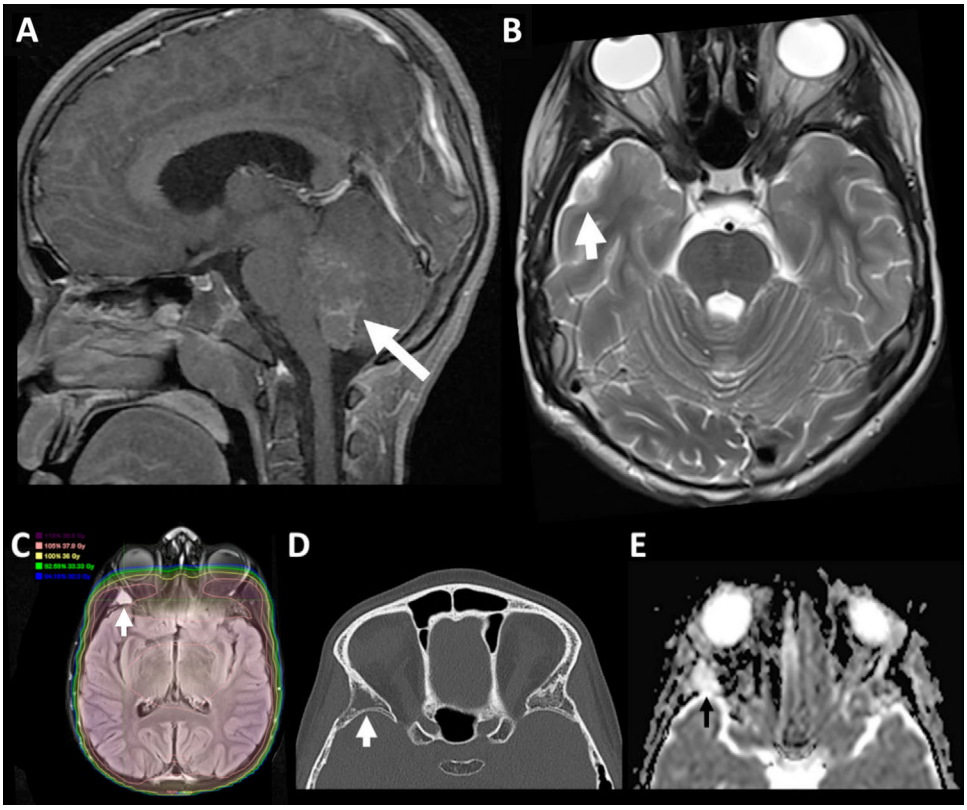

FIGURE 2 (A) Sagittal T1 postcontrast MR image at diagnosis of a 7-year-old African–American male with metastatic medulloblastoma desmoplastic nodular variant showing heterogeneously enhancing primary medulloblastoma in the posterior fossa (white arrow) and (B) transverse T2 postcontrast MR image showing one of the metastatic nodules (pretreatment; white arrow). He was treated with 36 Gy of CSI and an 18-Gy focal boost to the fourth ventricle and metastatic sites, followed by four cycles of adjuvant chemotherapy (NCT01878617). (C) Transverse T2 MR image showing hyperintensity and a heterogeneously enhancing lesion in the right sphenoid bone (white arrow) detected approximately 1.5 years after completing CSI. (D) CT scan showing the lytic lesion in the right sphenoid bone (white arrow), with thinning of the cortical bone, and (E) an associated high ADC score (black arrow). Histopathology of the bone lesion demonstrated fibrous dysplasia, para-trabecular fibrosis, and fatty changes with no evidence of malignancy

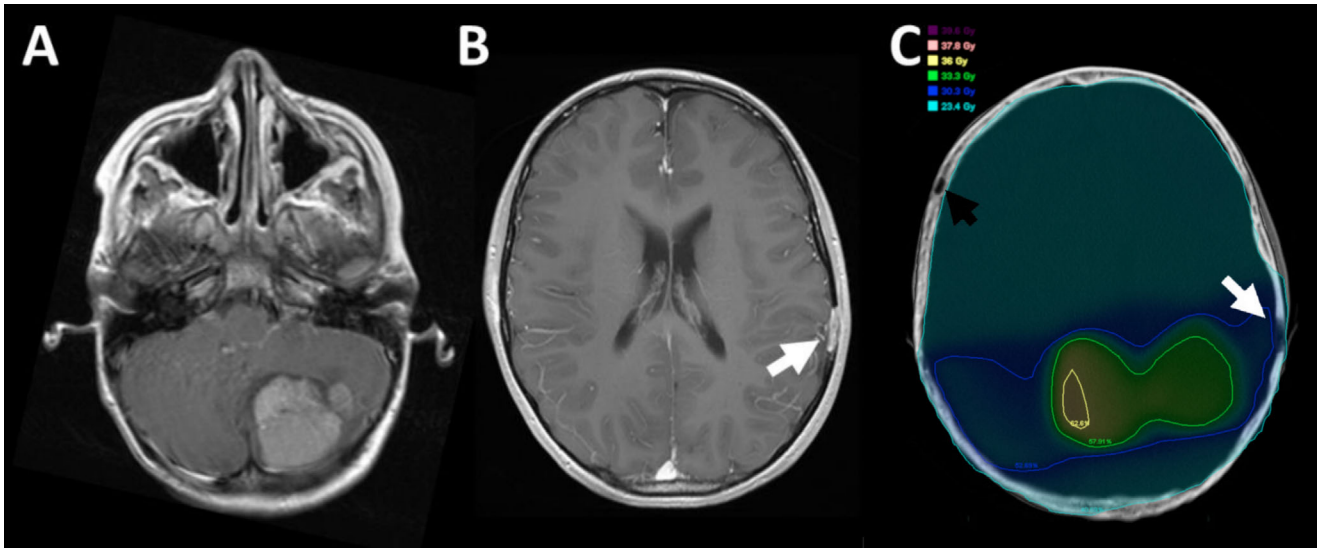

FIGURE 3 (A) Transverse T1 postcontrast MR images at diagnosis of a 7-year-old Caucasian male with a history of medulloblastoma anaplastic large cell, *MYCN*-amplified type, and a germline *TP53* mutation consistent with a diagnosis of Li–Fraumeni syndrome, showing the primary medulloblastoma in the left cerebellar hemisphere. (B) An enhancing lesion in the left temporal bone with (C) lytic and destructive bony changes on the CT scan (white arrows) detected 1.5 years after the initial diagnosis, and following treatment with 23.4 Gy CSI with a 32.4 Gy focal boost to the fourth ventricle and adjuvant chemotherapy (NCT0008520). An additional smaller lesion was noted in the right frontal bone (C, black arrow)

respectively). This is likely related to RT dose and route. Patients receiving CSI presented sooner than those receiving focal RT (median 2.25 vs 8.1 years, respectively).

Most patients had histologically benign skull lesions with nodular proliferation of fibroblasts and myofibroblasts. In the Childhood Cancer Survivor Study, 68 of 1877 patients with CNS malignancies developed second malignant neoplasms and received cranial RT ≥50 Gy. Cumulative incidence of secondary cancers in the CNS cohort was 7.1%.[17] Hence, a new lesion developing anywhere in the RT field, including the bony skull, can indicate the development of radiation-induced secondary malignancies.[18]

Germline predisposition might influence the development of subsequent treatment-related malignancies.[19] Interestingly, in our study, the two patients with malignant lesions had a genetic predisposition to cancer (LFS or ataxia-telangiectasia). Given the study's small sample size, we cannot unequivocally infer whether a genetic predisposition increased the risk of malignant skull lesions.

MRI findings did not differentiate between malignant and benign lesions, as evidenced in two cases. Also, the FDG-PET scan could not differentiate between the aggressiveness of lesions, but revealed negative uptake in lesions with histopathologic diagnosis of fibrotic and inflammatory changes. Analysis of future cases of RT-induced calvarial lesions will reveal relevance of the PET scan in this patient population.

Most calvarial lesions in patients post-RT are usually benign and require only close surveillance and reassurance to families. Children need not undergo invasive procedures, thereby reducing financial burden on the healthcare system and families. However, the treating physician should monitor all lytic calvarial lesions within the radiation field.

Given our study's limitations, we cannot make concrete recommendations for this patient population. First, due to small sample size and retrospective study design, we could not determine the true incidence of benign calvarial lesions developing after RT. Second, we included only patients referred to the neuro-surgery service for evaluating skull lesions found in routine surveillance imaging; therefore, we have no denominator for these patients. Hence, we might have missed other asymptomatic patients with similar lesions who were not given surgical intervention to determine the etiology of lesions.

Most patients with CNS tumors developing calvarial lesions post-RT have a benign fibro-osseous histopathology. Radiographically, it is often difficult to distinguish benign and malignant lesions, which clinically tend to be asymptomatic. Watchful waiting and follow-up imaging without surgical intervention suffices in most patients. Surgical intervention to exclude malignant lesions should be considered in patients with underlying genetic cancer predisposition or if regular follow-up cannot be ensured due to patient noncompliance.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the Supporting Information material of this article.

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