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Radiation-Induced Meningiomas Have an Aggressive Clinical Course: Genetic Signature Is Limited to *NF2* Alterations, and Epigenetic Signature Is H3K27me3 Loss

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ABSTRACT

Background: While the clinical course of radiation-induced meningioma (RIM) is considered to be more aggressive than that of sporadic meningioma (SM), the genetic predisposition for RIM is not established well. The present study aimed to analyze the clinical and genetic characteristics of RIMs to increase understanding of the tumorigenesis and prognosis of RIMs.
Methods: We investigated a database of 24 patients who met the RIM criteria between January 2000 and April 2023. Genetic analysis through next-generation sequencing with a targeted gene panel was performed on 10 RIM samples. Clinical, radiological, and pathological parameters were evaluated with genetic analyses.
Results: The median ages for receiving radiotherapy (RT) and RIM diagnosis were 8.0 and 27.5 years, respectively, with an interval of 17.5 years between RT and RIM diagnosis. RIMs tended to develop in non-skull bases and multifocal locations. Most primary pathologies included germ cell tumors and medulloblastoma. The tumor growth rate was 3.83 cm^3 per year, and the median doubling time was 0.8 years. All patients underwent surgical resection of RIMs. The histological grade of RIMs was World Health Organization grade 1 (64%) or 2 (36%). RIMs showed higher incidences in young-age (63%), high-dose (75%), and extended-field (79%) RT groups. The recurrence rate was 21%. Genetic analysis revealed *NF2* one copy loss in 90% of the patients, with truncating *NF2* mutations and additional copy number aberrations in grade 2 RIMs. *TERT* promoter mutation and *CDKN2A/B* deletion were not identified. Notably, loss of H3K27me3 was identified in 26% of RIMs. H3K27me3 loss was associated with a higher prevalence of grade 2 RIMs (67%) and high recurrence rates (33%).

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Disclosure

The authors have no potential conflicts of interest.

Author Contributions

Conceptualization: Kim TK, Lee JS, Park SH, Kim SK. Data curation: Kim TK, Lee JS. Formal analysis: Kim TK, Lee JS, Park SH. Funding acquisition: Park SH, Kim SK. Investigation: Kim TK, Lee JS, Kim SK. Methodology: Kim TK, Lee JS, Park SH, Kim SK. Software: Kim TK, Lee JS. Validation: Park SH, Kim SK. Visualization: Kim TK, Lee JS. Writing - original draft: Kim TK, Lee JS. Writing - review & editing: Kim TK, Lee JS, Phi JH, Choi SA, Kim JW, Park CK, Yun H, Park YS, Park SH, Kim SK.

Conclusion: The study reveals a higher prevalence of high-grade tumors among RIMs with more rapid growth and higher recurrences than SMs. Genetically, RIMs are primarily associated with *NF-2* alterations with chromosomal abnormalities in grade 2 tumors, along with a higher proportion of H3K27me3 loss.

Keywords: Brain Neoplasm; Genetic Testing; Meningioma; Pediatric; Radiation; H3K27me3

INTRODUCTION

Radiotherapy (RT) is an essential modality for treating intra- and extracranial tumors. However, RT has the risk of inducing secondary brain tumors, such as gliomas, sarcomas, and meningiomas.[1,2] Advances in therapeutic modalities and further understanding of cancer biology have drastically improved the survival of patients with childhood cancer,[3,4] which has led to a high chance of secondary brain tumors after RT. Therefore, detecting and diagnosing radiation-induced brain tumors has become important for cancer survivors, as has understanding the molecular biology of these tumors for accurate classification and appropriate treatment.[5]

Radiation-induced meningioma (RIM) is the most common secondary brain tumor after cranial irradiation.[6,7] RIM is defined as meningioma arising in the irradiated field with a sufficient latency period following radiation, usually over 5 years, and in patients with no familial history of phakomatosis.[1] Compared to sporadic meningiomas (SMs), RIMs are known as aggressive tumors with higher tumor grade and recurrences.[6,8] RIMs show a higher incidence of World Health Organization (WHO) grades 2 and 3 compared to SMs. RIMs have higher recurrence rates (18.3–25.6%) compared to SMs (3–11.4%).[2,4] However, RIMs share imaging and histological features with SMs, making it difficult to differentiate the two without detailed patient history and molecular analyses. Although RIMs tend to be more aggressive, treatment of RIMs has challenges, particularly for recurrent and malignant cases, due to limitations on using RT in previously irradiated areas. While genetic susceptibility to RIM development has been reported, the specific genetic predisposition is not as well established as SMs.[9,10] Especially, the genetic background that can explain the effects of radiation and the aggressive clinical course of RIMs remains obscure. This study aims to analyze the clinical and genetic characteristics of RIMs to gain further insight into RIM tumorigenesis and prognosis.

METHODS

Data and study population

The database of patients satisfying search terms 'meningioma' and 'RT' was queried retrospectively from January 2000 to April 2023 in the clinical data warehouse of the author's institution. We found 498 patients with pathologically confirmed meningioma who received RT. Of those, 421 patients undergoing RT after diagnosis of meningioma and 53 patients receiving extracranial RT were excluded; the remaining 24 patients met the established RIM criteria (**Fig. 1**): 1) tumor arising in the irradiated field, 2) different histology from previous neoplasm, 3) sufficient latency (usually > 5 years) following RT, 4) no family history of phakomatosis, 5) tumor not recurring or metastatic, and 6) tumor not present before RT.[1] None of the patients were diagnosed with NF-2.

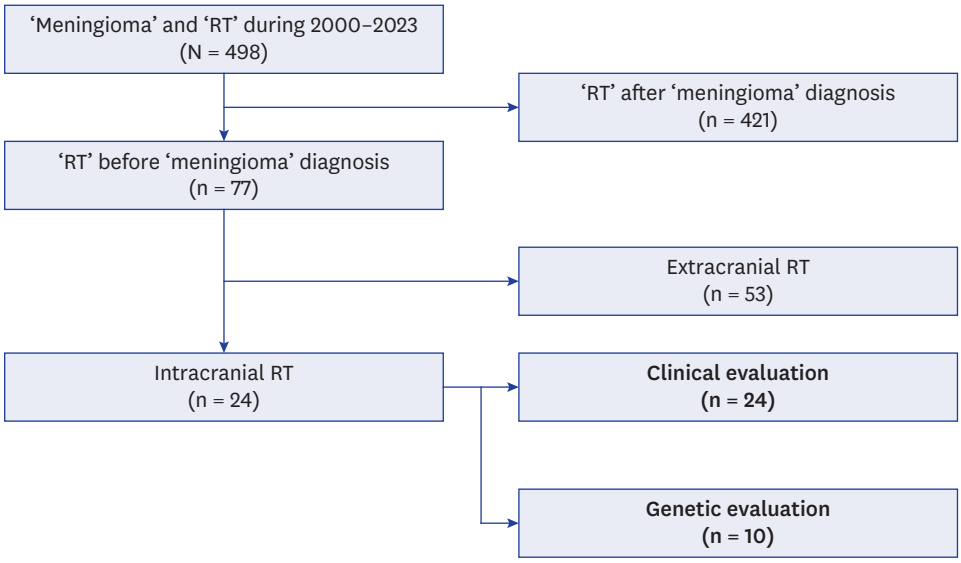

Fig. 1. Flowchart of the patient selection.
RT = radiotherapy.

The patients' medical records were reviewed, including operation, RT, neuroimaging, and pathological data. The preoperative tumor size was measured with magnetic resonance imaging using volumetry software (Xelis 1.0.6; INFINITT Healthcare Co., Ltd., Seoul, Korea). Tumor growth rate and doubling time were calculated using the formula: $T_d = (t_2 - t_1) \times \log(2)/\log(q_2/q_1)$, where t_1 and t_2 are the times at diagnosis and the last follow-up, and q_1 and q_2 are the volumes at baseline and the last follow-up, respectively.[11]

All patients underwent surgical resection of at least one RIM. The Simpson grade was used to evaluate the extent of resection.[12] Some patients concurrently presented with multiple RIMs, which were diagnosed radiologically without surgery. Pathological evaluation followed the 2021 WHO classification of central nervous system (CNS) tumors.[5] The BenchMark ULTRA automated immunostaining system (Roche Diagnostics, Rotkreuz, Switzerland) was used for immunohistochemical analysis. Mitotic rates in 10 high-power fields (HPFs) were determined using an anti-pHH3 antibody (Clone 369A-15, polyclonal; Cell Marque, Rocklin, CA, USA). Ki-67 (Clone M7240, monoclonal, 1:100; DAKO, Glostrup, Denmark) labeling indices were calculated using the SpectrumPlus Aperio morphometric algorithm. Loss of H3K27me3 (Clone C36B11, 1:100; Cell Signaling, Boston, MA, USA) was also evaluated.[13,14]

Patients were further divided into groups based on age at RT (young-age; < 10 years, old-age; ≥ 10 years), radiation dose (low-dose; < 30 Gy, high-dose; ≥ 30 Gy), and radiation field (extended-field; craniospinal irradiation [CSI] and whole brain radiotherapy [WBRT], involved-field; involved-field radiotherapy [IFRT]). Recurrence and mortality were evaluated during follow-up periods.

Next-generation sequencing (NGS) with customized brain tumor-targeted gene panels

Ten RIM samples were analyzed. We conducted NGS on tumor genomic DNA and RNA extracted from fresh frozen tumors using the Qiagen QIAamp DNA Mini Kit (Qiagen, Valencia, CA, USA) and RNeasy Plus Mini Kit (Qiagen), respectively. The yield and purity of

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the DNA and RNA were assessed using a 2100 Bioanalyzer (Agilent, Santa Clara, CA, USA). Sequencing was done on the NEXTSeq Dx505 platform with a customized brain tumor gene panel called 'the FiRST brain tumor panel, version 3.' This panel was established at our institution and approved by the Korea Food and Drug Administration (**Supplementary Table 1**). It is used in our clinical practice, covering meningioma-associated genes, such as *AKT1, BAP1, CDKN2A, CDKN2B, KLF4, NF2, PIK3CA, SMARCE1, SMO, TERT promoter*, and *TRAF7.*

The NGS data were analyzed using open-source Genome Analysis Toolkit (GATK) UnifiedGenotyper, SNVer, and LoFreq for SNV/InDel detection. Mutect 2 v4.1 was used for somatic mutations, Delly and Manta for translocation discovery, THetA2 for purity estimation, and CNVKit for CNV calling. Variants were annotated with SnpEf using RefSeq, COSMIC, dbSNP, ClinVar, OncoKB, and Genome Aggregation Database (gnomAD). Germline variants were filtered using population frequencies (> 0.01%) from the gnomAD and a 1000 Genomes panel provided by the GATK resource bundle. After calling somatic mutations, ANNOVAR was applied for variant annotation.

Statistical analysis

Statistical analyses were performed with R, and plots were constructed using the ggplot2 function. Continuous variables were analyzed using an independent *t*-test. Categorical variables were analyzed using the χ^2 test or Fischer's exact test. A *P* value less than 0.05 was considered to indicate statistical significance.

Ethics statement

The present study was reviewed and approved by the Institutional Review Board (IRB) of Seoul National University Hospital (IRB No. 2305-033-1429). Informed consent was obtained from patients for use of their tissue for research purposes according to the guidelines of the IRB.

RESULTS

Patient characteristics

Among 24 patients, 14 were male and 10 were female (**Table 1**). The most frequent primary pathology was germ cell tumors (GCTs, n = 9) and medulloblastomas (n = 7, **Supplementary Table 2**). The median age for receiving RT was 8.0 years (range 0–39 years). CSI was applied in 16 patients: 7 with GCT, 7 with medulloblastoma, 1 with ependymoma, and 1 with pilomyxoid astrocytoma. WBRT and IFRT were performed for 3 and 5 patients, respectively. The median age at RIM diagnosis and the median latency period to RIM diagnosis after RT were 27.5 years (range 12–55 years) and 17.5 years (range 6–32 years), respectively. Tumor removal was usually performed soon after detection (median 0 years, range 0–4 years) according to tumor-related symptoms, compressed brain parenchyma on neuroimages, or enlarging tumor sizes. The median postoperative follow-up period was 58 months (range 6–208 months).

Clinical features and surgical outcomes

Six of the 24 patients had multiple RIMs, with four having two RIMs and two having three RIMs in different locations (**Table 2**). The major locations of the 32 tumors were the convexity (n = 11), falx (n = 6), parasagittal (n = 6), skull base (n = 5), tentorium (n = 3), and cervical (n = 1) regions. The tumor sizes were 16.7 ± 24.8 (mean ± standard deviation) cm^3 and 36.7 ± 52.1 cm^3 at initial diagnosis and preoperatively, respectively. When serial changes

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Table 1. Characteristics of 24 patients with RIMs

No.	Sex	Age,[a] yr	Primary tumor	RT dose, Gy			Age,[b] yr	Latency, yr	Location of RIM	Initial size of RIM, cm^3	Age,[c] yr	Preop. size of RIM, cm^3	Preop. symptoms	Treatment	S-G	CNS WHO G of RIM	Mitotic rate, /10 HPF	Ki-67 index	H3K27me3	Rec	Survival	Adj
				CSI	WBRT	IFRT																
1	M	10	GCT (C+GE)	37.2	-	18.0	39	28	Falx, F	38.9	39	47.2	Hemiparesis	Surgery (craniotomy)	S-G2	G1	1	4.3	Retention	N	Alive	N
									Tentorium	1.8		2.3		Observation	-	-	-	-	-	-		-
2	M	12	GCT (GE)	-	-	54.0	34	21	Convexity, Cbll	2.4	34	2.7	None	Surgery (craniotomy)	S-G2	G1	0	6.8	Retention	N	Alive	N
3	M	17	GCT (GE)	-	-	45.0	37	20	Convexity, P	34.3	37	36.8	Seizure, dysphasia	Surgery (craniotomy)	S-G1	G1	1	4.4	Retention	N	Alive	N
4	M	12	GCT (imTE)	23.4	-	30.6	20	8	Parasagittal, F	8.2	21	12.0	None	Surgery (craniotomy)	S-G2	G2	7	16	Retention	Y	Alive	GKS
5	M	8	GCT (imTE)	23.4	-	30.6	19	10	Falx, F	1.4	20	8.5	None	Surgery (craniotomy)	S-G2	G1	1	5.2	Retention	N	Alive	N
6	F	8	GCT (GE+mTE)	36	-	19.8	27	18	Parasagittal, P	5.7	28	4.9	Hemiparesis	Surgery (craniotomy)	S-G2	G1	1	NA	NA	N	Alive	GKS
7	F	8	GCT (GE)	36	-	19.8	36	27	Convexity, T	12.5	36	15.7	Hemiparesis	Surgery (craniotomy)	S-G1	G2	5	24.2	Loss	Y	Alive	N
									Parasagittal, F	1.7		1.5		Observation	-	-	-	-	-	-		-
									Tentorium	0.6		0.4		Observation	-	-	-	-	-	-		-
8	M	9	GCT (GE+mTE)	36	-	18.0	21	11	Convexity, P	1.1	24	3.8	Seizure	Surgery (craniotomy)	S-G1	G1	2	14.6	Retention	N	Alive	N
9	M	30	GCT (imTE)	40.5	-	14.4	55	24	Falx, P	6.3	57	8.4	None	Surgery (craniotomy)	S-G1	G1	1	4.3	Retention	N	Alive	N
10	M	3	MB	23.4	-	30.6	16	12	Falx, P	0.9	17	2.5	None	Surgery (craniotomy)	S-G1	G2	10	24	Loss (weak +)	N	Alive	N
11	M	3	MB	16.2	-	28.8	13	9	Falx, P	0.5	13	0.5	None	Surgery (craniotomy)	S-G2	G1	0	4.3	Retention	N	Alive	N
							19	15	Tentorium	1.2	-	-	-	GKS	-	-	-	-	-	N		N
12	M	4	MB	23.4	-	30.6	22	17	Convexity, P	12.8	22	23.5	Hemiparesis	Surgery (craniotomy)	S-G2	G2	5	26.8	Retention	N	Alive	RT
13	M	4	MB	36	-	18.0	30	25	Convexity, T	74.2	30	70.7	None	Surgery (craniotomy)	S-G2	G2	11	28.4	Retention	N	Alive	N
14	F	8	MB	23.4	-	30.6	19	10	Parasagittal, F	0.6	22	3.2	None	Surgery (craniotomy)	S-G2	G1	1	3.3	Retention	Y	Alive	GKS
15	F	9	MB	36	-	19.8	26	16	Skull base, petroclival	0.8	30	6.0	CN 6, 7 palsy	Surgery (EEA)	S-G2	G2	4	11.8	Loss	N	Alive	N
16	F	13	MB	36	-	19.8	40	26	Cervical, C1–2	1.7	40	1.7	Paraparesis	Surgery (laminotomy)	S-G2	G1	2	3.8	Retention	N	Alive	N
17	F	22	PitNET	-	-	50.4	44	21	Skull base, sphenoid	40.0	44	42.8	Blindness	Surgery (craniotomy)	S-G2	G1	3	0	Loss	Y	Alive	GKS
18	M	39	PitNET	-	-	50.2	52	12	Convexity, T	13.6	52	18.3	Visual disturbance	Surgery (craniotomy)	S-G1	G2	8	15	Loss	N	Alive	N

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Table 1. (Continued) Characteristics of 24 patients with RIMs

No.	Sex	Age,[a] yr	Primary tumor	RT dose, Gy			Age,[b] yr	Latency, yr	Location of RIM	Initial size of RIM, cm^3	Age,[c] yr	Preop. size of RIM, cm^3	Preop. symptoms	Treatment	S-G	CNS WHO G of RIM	Mitotic rate, /10 HPF	Ki-67 index	H3K27me3	Rec	Survival	Adj
				CSI	WBRT	IFRT																
19	F	0	RB	-	-	50.4	12	11	Skull base, sphenoid	18.3	12	37.9	Visual disturbance	Surgery (craniotomy)	S-G4	G1	0	NA	-	Y	Alive	N
							14	13	Skull base, sphenoid	-	14	42.1	Headache	Surgery (craniotomy)	S-G4	G2	7	7	Retention	Y	Alive	GKS
							20	19	Skull base, sphenoid	-	20	210.8	None	Surgery (EEA)	S-G4	G2	2	7	-	Y	Alive	N
							21	20	Skull base, sphenoid	-	21	183.0	Ataxia	Surgery (EEA)	S-G4	G2	8	9.8	-	N	Dead	N
20	F	3	RB	-	30	20.0	36	32	Convexity, T	89.7	36	101.9	Headache	Surgery (craniotomy)	S-G1	G1	2	21.8	Retention	N	Alive	N
21	M	7	BL	-	18	-	28	19	Falx, P	37.0	28	38.9	None	Surgery (craniotomy)	S-G1	G1	1	1.5	Retention	N	Alive	N
22	F	16	EPN	36	-	19.8	36	19	Convexity, P	75.1	36	75.1	Rigidity	Surgery (craniotomy)	S-G2	G1	2	0.6	Retention	N	Alive	N
									Parasagittal, P	2.0		2.0		GKS	-	-	-	-	-	N	Alive	-
									Parasagittal, F	0.4		0.4		GKS	-	-	-	-	-	N		-
23	F	6	mNB	-	19.8	16.2	33	27	Convexity, F	16.9	33	14.8	Seizure	Surgery (craniotomy)	S-G1	G1	1	11.2	Loss	N	Alive	N
									Skull base, optic sheath	0.2		0.3		Observation	-	-	-	-	-	-		-
24	M	7	PMA	45	-	54.0	15	6	Convexity, T	0.1	15	5.0	None	Surgery (craniotomy)	S-G1	G2	13	12.4	Retention	N	Alive	N
				-	-	-	16	7	Skull base, sphenoid	1.4	18	7.8	None	Surgery (craniotomy)	S-G4	G2	-	-	-	N		N

M = male, F = female, GCT = germ cell tumor, C = choriocarcinoma, GE = germinoma, imTE = immature teratoma, mTE = mature teratoma, MB = medulloblastoma, PitNET = pituitary neuroendocrine tumor, RB = retinoblastoma, BL = Burkitt lymphoma, EPN = ependymoma, mNB = metastatic neuroblastoma, PMA = pilomyxoid astrocytoma, RT = radiotherapy, Gy = gray, CSI = craniospinal irradiation, WBRT = whole brain radiotherapy, IFRT = involved-field radiotherapy, RIM = radiation-induced meningioma, F = frontal, T = temporal, P = parietal, Cbll = cerebellar, Preop. = preoperative, CN = cranial nerve, GKS = gamma knife surgery, EEA = endoscopic endonasal approach, S-G = Simpson grade, CNS = central nervous system, WHO = World Health Organization, HPF = high-power field, Rec = recurrence, Adj = adjuvant therapy, Y = yes, N = no, NA = not available.

[a]Data at surgery (primary tumor) and RT; [b]Data at the occurrence of RIM; [c]Data at the surgery of RIM.

Table 2. Perioperative findings and outcomes of patients with RIMs

Parameters	Measurement
Multiplicity[a]	32 tumors in 24 patients
Single tumor	18 (75%)
Multiple tumors	6 (25%)
Two tumors	4
Three tumors	2
Location	32 tumors in 24 patients
Convexity	11 (34.4%)
Temporal	5
Parietal	4
Frontal	1
Cerebellar	1
Falx	6 (18.8%)
Parietal	4
Frontal	2
Parasagittal	6 (18.8%)
Frontal	4
Parietal	2
Skull base	5 (15.6%)
Sphenoid wing	3
Petroclival	1
Optic nerve sheath	1
Tentorium	3 (9.4%)
Cervical	1 (3.1%)
Tumor growth	n = 17
Overall tumor growth in cm^3, mean (range)	2.51 (0–8.3)
Growth rate in cm^3 per year, mean, 95% CI (range)	3.83, 2.25–5.41 (0–45.6)
Tumor doubling time in years, median (IQR)	0.81 (1.06)
Simpson grade	28 surgeries[b] in 24 patients
Grade 1	10 (35.7%)
Grade 2	13 (46.4%)
Grade 4	5 (17.9%)
CNS WHO grade[c]	
Grade 1	16 (64%)
Grade 2	9 (36%)
Grade 3	0
Recurrence	5 (20.8%)
Expiration	1 (4.2%)

RIM = radiation-induced meningioma, CI = confidence interval, IQR = interquartile range, CNS = central nervous system, WHO = World Health Organization.
[a]Twenty-five tumors were surgically removed, 3 underwent gamma knife surgery, and 4 were observed.
[b]One patient repeated four surgeries for one recurrent RIM, and another patient underwent two surgeries for two RIMs in different locations.
[c]According to the 2021 WHO classification of tumors of the CNS (at the first surgery).

in tumor volume were evaluated for individual preoperative RIMs (n = 17), overall tumor growth was 2.51 cm^3 during the mean follow-up period of 26.4 months (range 2–61 months, **Fig. 2A**). The growth rate was 3.83 cm^3 per year, and the median tumor doubling time was 0.81 years. Seven tumors (41.2%) grew in a volume greater than 100% (**Fig. 2B**). They show no significant differences in tumor growth according to the tumor grade and the loss of H3K27me3 (**Fig. 2C and D**). Some RIMs were incidentally found as small tumors with no symptoms, but they rapidly grew and required surgical treatment (**Fig. 3**).

Twenty-five tumors were surgically removed in 28 surgeries. One patient underwent four surgeries for one recurrent RIM, and another patient underwent two surgeries for two different RIMs. The extent of surgical resection varied among Simpson grade 1 (n = 10), 2 (n = 13), and 4 (n = 5). Five patients received adjuvant gamma knife surgery, and one underwent

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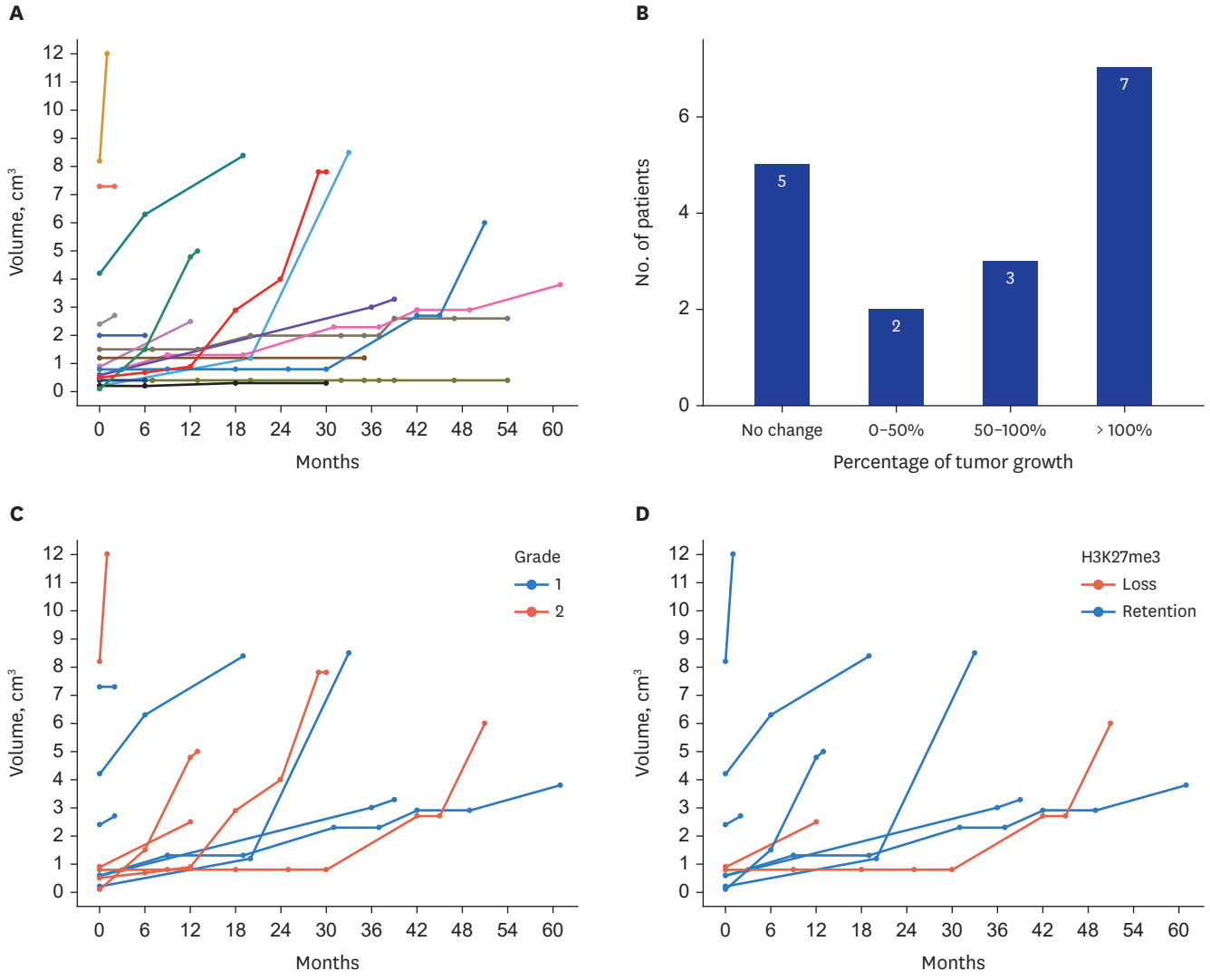

Fig. 2. Serial volume changes of radiation-induced meningiomas. (**A**) A plot of serial tumor volume for individual preoperative tumors (n = 17). Overall tumor growth was 2.51 cm^3 during the mean follow-up period of 26.4 months. The growth rate was 3.83 cm^3 per year, and the median tumor doubling time was 0.81 years. (**B**) A bar graph showing the percentage of tumor growth. Seven tumors (41.2%) grew in a volume greater than 100%. (**C**, **D**) Serial volume change of tumors according to the tumor grade (n = 11) and the loss of H3K27me3 (n = 9). They show no significant differences in tumor growth according to the tumor grade and the loss of H3K27me3.

adjuvant RT for residual or recurrent tumors. Five patients (20.8%) experienced recurrence. One patient with an RIM located in the right sphenoid wing (Case 19) experienced multiple recurrences. The tumor pathology was WHO grade 1, but the recurrent tumor became grade 2 two years later. Despite four surgeries, the tumor showed aggressive progression, and the patient died nine years after the diagnosis.

The characteristics of RIMs according to the patient's age upon receiving RT, the radiation dose, and the radiation field are shown in **Table 3**. The incidence of RIMs was higher in the young-age (62.5%), high-dose (75%), and extended-field RT (EFRT, 79.2%) groups. The high-dose RT group showed a greater multiplicity rate than the low-dose group ($P = 0.015$). The mean size of the RIM, the proportion of grade 2 tumors, and the recurrence rate were not significantly different among the groups.

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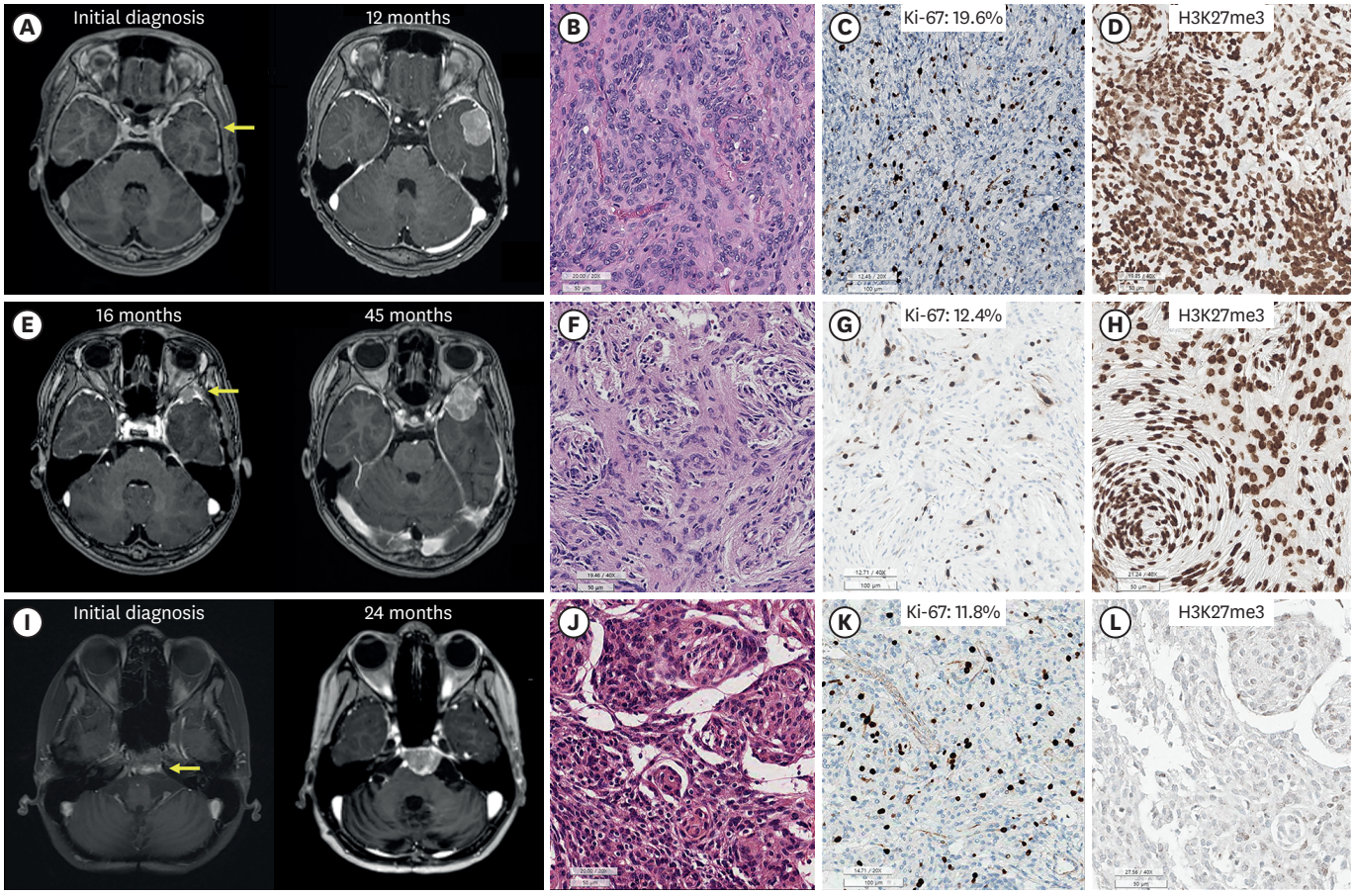

Fig. 3. MRI and microscopic features of patients with rapidly growing RIMs. (under bar size of **B**, **D**, **F**, **H**, **J**, **L**: 50 μm, and **C**, **G**, **K**: 100 μm). (**A**-**D**) First-developed RIM (arrow) in patient 24. (**A**) Axial T1 contrast-enhanced MRI. For 12 months, the left temporal convexity meningioma is continuously enlarged, and surgical resection is performed. The tumor is diagnosed as grade 2 meningioma. (**B**) H&E shows highly cellular meningioma with a mitotic count of 4/10 HPFs. (**C**) The Ki-67 index is 19.6%. (**D**) H3K27me3 is retained. (**E**-**H**) Recurrent RIM in patient 24. (**E**) After postoperative 4 months, a newly enhanced tumor appears at the left sphenoid wing (arrow). For 29 months, the tumor is continuously enlarged, and surgical resection is performed. The tumor is diagnosed as grade 2 meningioma as well. (**F**) H&E looks like conventional meningioma with a whirling pattern and a mitotic count of 13/10 HPFs. (**G**) Ki-67 index is 12.4%. (**H**) H3K27me3 is retained in the nuclei. (**I**-**L**) First-developed RIM (arrow) in patient 15. (**I**) Axial T1 contrast-enhanced MRI. For 24 months, the clival meningioma is enlarged, slightly compressing the brainstem, and surgical resection is performed. The tumor is diagnosed as grade 2 meningioma. (**J**) H&E shows high cellularity and nuclear pleomorphism with a mitotic count of 4/10 HPFs. (**K**) Ki-67 index is 11.8%. (**L**) H3K27me3 loss is remarkable.
MRI = magnetic resonance imaging, RIM = radiation-induced meningioma, H&E = hematoxylin and eosin, HPF = high-power field.

Table 3. Characteristics of RIMs according to patient age at receiving RT, radiation dose, and radiation field

Characteristics	Age at RT			Radiation dose			Radiation field		
	< 10 yr	≥ 10 yr	*P* value	< 30 Gy	≥ 30 Gy	*P* value	Extended-field[a]	Involved-field	*P* value
No. of patients (n = 24)	15 (62.5)	9 (37.5)		6 (25.0)	18 (75.0)		19 (79.2)	5 (20.8)	
No. of RIMs (n = 32)	20 (62.5)	12 (37.5)		7 (21.9)	25 (78.1)		25 (78.1)	7 (21.9)	
Latency period,[b] yr	16.5 (6–32)	21 (8–28)	0.315	12 (8–19)	21 (6–32)	0.02	17.5 (6–32)	13.5 (8–19)	0.605
Multiplicity (n = 24)			1.0			0.015			1.0
Single tumor	11 (73.3)	7 (77.8)		14 (93.3)	4 (44.4)		14 (73.7)	4 (80)	
Two tumors	3 (20)	1 (11.1)		1 (6.7)	3 (33.3)		4 (21.1)	0	
Three tumors	1 (6.7)	1 (11.1)		0	2 (22.2)		1 (5.2)	1 (20)	
Tumor size, cm^3	17.5 ± 26.7	16.0 ± 25.8	0.477	11.7 ± 14.6	20.7 ± 27.6	0.347	17.7 ± 26.9	27.7 ± 16.8	0.468
CNS WHO grades (n = 25)			0.401			0.63			0.621
Grade 1	9 (56.3)	7 (77.8)		3 (50)	13 (68.4)		12 (60)	4 (80)	
Grade 2	7 (43.8)	2 (22.2)		3 (50)	6 (31.6)		8 (40)	1 (20)	
Recurrence (n = 5)	3 (20)	2 (22.2)	1.0	2 (33.3)	3 (16.7)	0.568	3 (15.8)	2 (40)	0.27

Values are presented as number (%), median (range), or mean ± standard deviation.
RIM = radiation-induced meningioma, RT = radiotherapy, Gy = gray, CNS = central nervous system, WHO = World Health Organization.
[a]Craniospinal irradiation or whole brain radiotherapy; [b]Duration to RIM diagnosis after RT.

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Pathological and genetic characteristics

Twenty-five tumors included 16 WHO grade 1 and 9 grade 2 RIMs. Pathological subtypes were transitional (56.5%, 13 cases), meningothelial (26.1%, 6 cases), and fibrous (17.4%, 4 cases). The mean mitotic rates and Ki-67 indices were 3.7 (range 0–13) and 11.1 (range 0.6–28.4), respectively (**Supplementary Fig. 1A and B**). Loss of H3K27me3 was identified in 6 of the 23 RIMs (26.1%, **Supplementary Fig. 1C and D**). Loss of H3K27me3 was found in almost half (4 of 9) of the grade 2 RIMs and 14.3% (2 of 14) of the grade 1 RIMs. It was identified in 40% (2 of 5) of recurrent RIMs and 22.2% (4 of 18) of nonrecurrent RIMs. Loss of H3K27me3 was associated with a higher prevalence of grade 2 RIMs (66.7% vs. 29.4%, $P = 0.162$) and higher recurrence rates (33.3% vs. 17.6%, $P = 0.576$) than retention of H3K27me3.

Genetic analysis was conducted in 5 grade 1 and 5 grade 2 RIMs (**Fig. 4**). The genetic findings revealed *NF2* one copy loss in 9 RIMs (90%). Within this group, 3 cases showed *NF2* mutations (E465fs, Y217*, and Y101*), and all three cases had a primary tumor of medulloblastoma. The remaining one case involved a confirmed *NF2* mutation (K40* only) without any copy number aberrations. Among 5 grade 2 RIMs, three showed additional copy

Patients No.[a]	3 (8)	8 (20)	9 (23)	6 (14)	4 (11)	5 (13)	2 (7)	1 (4)	7 (19)	10 (24)
Age of primary tumor dx, yr	9	3	6	8	3	4	8	12	0	7
Age of RIM dx, yr	21	36	33	19	13	30	36	20	12	15
Latency, yr	11	32	27	10	9	25	27	8	11	6
Primary tumor	GCT	RB	NB	MB	MB	MB	GCT	GCT	RB	PMA
Grade of RIM	G1	G1	G1	G1	G1	G2	G2	G2	G2	G2
Location of RIM	P	T	F	F	P	T	T	F	Sphenoid	T
22q loss										
NF2 loss										
NF2 mutation[b]				E465fs	K40*	Y217*				Y101*
CNV (loss)								6, 14q	1p	1p, 14q
TERTp mutation *CDKN2A/B* deletion	No	No	No	No	No	No	No	No	No	No
H3K27me3 IHC	Retention	Retention	Loss	Retention	Retention	Retention	Loss	Retention	Retention	Retention
Follow-up duration, mon	27	25	30	65	98	23	47	11	116	37
Outcomes	NED	NED	NED	Recur	NED	NED	Recur	Recur	Recur	NED

Fig. 4. Genetic profile of RIMs with clinical information.
Dx = diagnosis, RIM = radiation-induced meningioma, CNV = copy number variation, IHC = immunohistochemistry, GCT = (central nervous system) germ cell tumor, RB = retinoblastoma, NB = neuroblastoma, MB = medulloblastoma, PMA = pilomyxoid astrocytoma, G = grade, P = parietal, T = temporal, F = frontal, NED = no evidence of disease.
[a]The serial numbers of patients in **Table 1** are in parentheses.
[b]*NF2* mutation, variant allele frequency (VAF): E465fs, c.1393delG, 44.71%; K40*, c.118A>T, 17.56%; Y217*, c.651C>G, 33.11%; Y101*, c.303T>G, 65.03%.

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number aberrations: chromosome 6 and 14q loss (1 case), 1p loss (1 case), and 1p and 14q loss (1 case). *SMARCE1*, *BAP1*, and *KLF4*/*TFAF7* mutations, known biomarkers associated with the classification of meningiomas, were not identified. *TERT* promoter mutation and deletion of *CDKN2A*/*B*, suggestive of malignant meningiomas, were not identified.

DISCUSSION

RIMs exhibit distinct clinical features from SMs, including earlier onset, female predominance, and a greater incidence of multiple tumors[2,15-20] with higher tumor grade and recurrences.[8,21,22] Recent studies have emphasized genetic predispositions contributing to these features.[8,10,23] We aim to specify the clinical characteristics of RIMs and to identify their genetic characteristics using a gene panel that is easily used in clinical practice. Our findings reveal a higher prevalence of high-grade tumors among RIMs with more rapid growth and higher recurrences than SMs. RIMs are more prevalent in the young-age, high-dose, and EFRT groups. Genetically, RIMs are primarily associated with *NF-2* alterations with chromosomal abnormalities in grade 2 tumors, along with a higher proportion of H3K27me3 loss. This article is of clinical importance since there has been a lack of studies comprehensively discussing the genetic and clinical characteristics of RIMs.

Previous studies reported median ages at RT between 6 and 8 years[17,19] and latency period of 12 to 49 years.[16,19,20,22,24] RIM multiplicity ranged from 4.6–29%,[2,22] with only 12.9–14.1% occurring at the skull base,[16,19] whereas SM multiplicity ranged from 0.6–2.4% and skull base SMs accounted for 70%. Our study found median ages at RT and latency periods of 8.0 and 27.5 years, with a 25% multiplicity rate. We detected 72% of the RIMs at the non-skull base. Also, previous studies showed higher incidences of RIMs in patients receiving RT before 10 years of age and doses over 24 Gy.[24] Another study demonstrated that radiation doses over 30 Gy resulted in a higher incidence of high-grade and multiple tumors than low radiation doses (≤ 15 Gy).[20] Our study showed a higher prevalence of RIMs in the young-age, high-dose, and EFRT groups. However, while some studies showed a female predominance in RIMs,[20] others, including ours, found a slight male predominance[21,25] with different constitutions of primary tumors. RIMs usually develop in patients with leukemia, medulloblastoma, low-grade glioma, and GCT, which have considerable long-term survival.[3,17,20,26-28] Our study, focusing only on pathologically confirmed RIMs, showed a high prevalence of CNS GCTs in South Korea.[29]

The growth rate of RIM has been documented in only a few studies, measured at 0.19 cm^3 and 0.62 cm^3 per year in different studies.[30,31] Younger age at diagnosis correlated with rapid tumor growth. In our study, the RIM growth rate was 3.83 cm^3 per year, significantly faster than SMs, which grew at 0.3 to 0.5 cm^3 per year.[11] Tumor doubling time was also shorter in RIMs (0.81 in our study vs. 18.7 years in SMs).[11] Our results support that surgical RIMs grow faster than non-surgical RIMs and SMs.

Pathological findings support the aggressive features of RIMs. Previous studies reported 70.8%, 23.8%, and 5.4% of RIMs as grade 1, 2, and 3, respectively,[16] with similar proportions in other studies (68.3%, 26.8%, and 5.9%, respectively),[20] whereas over 90% of SMs are grade 1.[32] The recurrence rate was higher in RIMs (25.6%) compared to SMs (11.4%).[18] Our study found 64% grade 1, 36% grade 2, and 0% grade 3 RIMs, with a recurrence rate of 20.8%. In previous studies, more than 95% of SMs exhibited fewer than

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4 mitoses (per 10 HPF),[33] and mitoses < 4 or a KI-67 index < 5% suggested better progression-free survival. Our results show mitosis exceeding 4 in 37.5% and Ki-67 exceeding 5% in 60.9% of cases.

Genetically, *NF2* is a key gene in the pathogenesis of SMs,[5,34,35] along with other gene, such as *AKT1*, *BAP1*, *KLF4*, *PIK3C*, *SMARCE1*, *SMO,* and *TRAF7*, depending on the subtype. Mutations in the *TERT* promoter and *CDKN2A/B,* and H3K27me3 loss are known to play essential roles in high-grade meningiomas.[5] Several studies have been conducted to identify differences in genetic landscapes between RIMs and SMs (**Supplementary Table 3**).[1,8,34,36-38] Sahm et al.[37] performed whole-genome sequencing of 20 RIMs and concluded that RIMs harbor *NF2* alterations and DNA methylation profiles similar to those of *NF2*-altered SMs. They also found that RIMs exhibited genetic variants affecting the *NF2* gene. However, others suggested that *NF2* inactivation and chromosome 22q deletions are far less frequent in RIMs.[8,23] Other chromosomal lesions, especially loss of 1p, possibly induced by irradiation, might be more important in the tumor development, followed by changes in chromosomal locations 9p, 19q, and 22q.[39] A recent study by Paramasivam et al.,[36] which performed multiplatform genetic analyses, showed that RIMs had higher mutational load and chromosomal instability with a higher prevalence of *NF2* structural variants.

Our gene panel study found that *NF2* loss or *NF2* mutation was common, and loss of chromosomal segments in 1p, 6, and 14q was identified in grade 2 RIMs. No mutations were found in *AKT1*, *TRAF7*, *SMO*, *PIK3C*, *KLF4*, *SMARCE1*, and *BAP1*, consistent with previous RIM studies.[34] *TERT* promoter mutations and *CDKN2A/B* deletions associated with high-grade SMs,[40,41] were also absent. Notably, in our study, loss of H3K27me3 was prevalent in RIMs. In a previous study, the prevalence of H3K27me3 loss in SMs was 4.7%.[13] In another meta-analysis, the pooled prevalence of H3K27me3 loss in SMs was 16%, with point prevalence ranging from 4% to 51%.[14] In those studies, H3K27me3 loss significantly increased with higher tumor grade: 3.1%, 10.4%, and 17.7% for grades 1, 2, and 3 SMs,[13] and 6%, 20%, and 37% for grades 1, 2, and 3 SMs, respectively.[14] SMs with H3K27me3 loss show higher recurrence rates than SMs with H3K27me3 retention (49.1% vs. 19.9%). In our study, the prevalence of H3K27me3 loss was higher (26.1%), and H3K27me3 loss was identified in 14.3% and 44.4% of grade 1 and 2 RIMs, respectively. RIMs with H3K27me3 loss showed higher recurrence rates than RIMs with H3K27me3 retention (33.3% vs. 17.6%). Our results support that RIMs possess a greater proportion of H3K27me3 loss than SMs, consistent with the aggressive clinical features of RIMs.

On the other hand, a recent study described four molecular groups (MG1–MG4) of meningiomas identified through an integrative multiplatform analysis involving whole-exome sequencing, copy number analysis, DNA methylation, and RNA sequencing.[42] Based on 149 patients with meningiomas, whose data can be accessed with The Cancer Genome Atlas data through cBioPortal (cBioportal.org), four distinct molecular groups (MG1–MG4) with unique clinical and genetic characteristics were identified.[43] Clinically, MG3 and MG4 tumors showed more aggressive behavior compared to MG1 and MG2. MG3 tumors had higher recurrence rates than MG1 and MG2, while MG4 tumors demonstrated the poorest prognosis with the shortest recurrence-free survival. Genetically, MG3 and MG4 meningiomas were highly aneuploid, with frequent losses in chromosomes 1p (77% and 89%, respectively), 6q (30% and 38%), 14 (47% and 35%), and 18 (19% and 38%). MG4 tumors showed a higher prevalence of 1q gain and 10 losses, which were uncommon in MG3 tumors. In our study, RIMs showed aggressive clinical course and chromosomal abnormalities of 1p,

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6, and 14q losses, which were characteristic features of M3 and M4 tumors. In our tissue, there were no mutations in *TRAF7, AKT1*, or *KLF4*, which were found only in MG2 tumors. Our findings suggest that RIMs appear to align closely with MG3 (hypermetabolic) and MG4 (proliferative) meningiomas. The high genetic disruption and mutation load observed in RIMs are consistent with the characteristics of these MG3 and MG4 molecular groups. In the future, it is expected that a more specific molecular subtype of RIMs can be defined through multiplatform genetic analysis on additional RIM samples.

Our study has several limitations. First, the study was retrospective with a limited sample size. However, RIMs have a long latency period, and our cohort included patients over a long period. Second, genetic mutations not included in the targeted gene panel could not be identified by our NGS analysis. However, all well-known meningioma-associated genes were included in this panel that is actively used in clinical settings. We additionally performed an immunohistochemical evaluation of H3K27me3.

In conclusion, with a latency period from RT to RIM development of 17.5 years, extended monitoring is required for childhood cancer survivors receiving RT. The incidence of RIMs is greater in the young-age, high-dose, and EFRT groups. The histopathology of RIMs shifts to higher WHO grades than SMs, with a higher recurrence rate. The key genetic landscape of RIMs is unique and limited to the *NF2* alterations, while chromosomal abnormalities such as 1p and 14q loss are identified in grade 2 RIMs. Their epigenetic signature is characterized by a high prevalence of H3K27me3 loss.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

List of the FIRST brain tumor panel established by the Department of Pathology at the author's institution, including 272 genes for DNA sequencing and 151 fusion genes for RNA sequencing

Supplementary Table 2

Histopathological diagnosis of primary tumors (N = 24)

Supplementary Table 3

Previous studies analyzing genetic features of RIMs and/or SMs

Supplementary Fig. 1

Immunohistochemical evaluation of radiation-induced meningiomas (under bar size of **A-D**: 50 μm). (**A**, **B**) Ki-67 labeling indices are determined by calculating positive nuclei per 500 tumor cells. (**C**, **D**) H3K27me3 loss, inlets of (**C**, **D**): positive control of H3K27me3. Internal positive control is positive nuclei of the endothelial cells or entrapped normal cells (arrows).

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