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Radiation-Induced Malignant Gliomas: A Current Review

Aladine A. Elsamadicy[1], Ranjith Babu[1], John P. Kirkpatrick[2], David Cory Adamson[1,3,4]

Key words
- Anaplastic astrocytoma
- Glioblastoma
- Malignant gliomas
- Radiation-induced malignant gliomas
- Radiotherapy
- Reirradiation

Abbreviations and Acronyms
ALL: Acute lymphoblastic leukemia
GBM: Glioblastoma multiforme
RIMG: Radiation-induced malignant glioma
RT: Radiotherapy

From the [1]Division of Neurosurgery, Department of Surgery, Duke University Medical Center; and [2]Department of Radiation Oncology, Duke Cancer Institute, and [3]Neurosurgery Section, Durham VA Medical Center, [4]Department of Neurobiology, Duke University Medical Center, Durham, North Carolina, USA

*To whom correspondence should be addressed: David Cory Adamson, M.D., Ph.D.
[E-mail: cory.adamson@duke.edu]*

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■ OBJECTIVE: **Radiation-induced malignant gliomas (RIMGs) are known uncommon risks of brain irradiation. We describe 4 cases of RIMG that occurred at our institution and conduct the largest comprehensive review of the literature to characterize RIMGs better.**

■ METHODS: **Patients were identified through the PubMed database. Pearson *R* linear correlation test was used to evaluate the correlation between radiotherapy (RT) dose and age and latency period. Student *t* test was used to evaluate differences between latency periods for original tumor lesions. A normalized biologic equivalent dose analysis was performed to indicate the minimum and maximum radiation threshold for neoplasia. A Kaplan-Meier analysis was used to illustrate the overall survival curves.**

■ RESULTS: **The analysis included 172 cases from the PubMed database and 4 cases occurring at our institution. The median RT dose administered was 35.6 Gy, with the most common dosage ranges being 21–30 Gy (31%) and 41–50 Gy (21.5%). Median latency period was 9 years until diagnosis of RIMG, and RIMG occurred within 15 years in 82% of the patients. There was no correlation between the age of the patient at the time RT was administered ($R^2 = 0.00081$) or amount of RT ($R^2 = 0.00005$) and latency period for RIMG. The mean biologic equivalent dose for neoplasia of a RIMG was 63.3 Gy. The median survival of patients with RIMG improved over time ($P = 0.004$), with median survival of 9 months before 2007 and 11.5 months after 2007.**

■ CONCLUSIONS: **The risk of RIMG appears to be the same for all age groups, histologies, and RT dosages. Although the risk is low, patients should be aware of RIMG as a possible complication of brain irradiation.**

INTRODUCTION

Radiotherapy (RT) is commonly used to treat various brain lesions. Although RT has proven to be a successful technique, side effects can occur owing to the radiation exposure, such as radiation necrosis, delayed cognitive changes, local scalp irritation, and radiation-induced malignant gliomas (RIMGs) (59, 80, 91). Although RIMGs are considered rare, many reports describe malignant gliomas (World Health Organization grade III or IV) arising after RT of histologically different tumors or lesions. Because of the rarity of these events, various characteristics, such as the latency time and correlation with radiation dosage or patient characteristics, have not been fully explored. We performed a comprehensive review of the literature to characterize RIMGs better. Because RT has greatly evolved in recent years, we set out to determine if the occurrence of RIMG has changed over time.

MATERIALS AND METHODS

Identification

A systematic review through a PubMed search was performed for articles related to RIMGs using key word phrases in combination to maximize the amount of related articles. "GBM," "malignant glioma," "glioblastoma," "brain tumor," and "anaplastic astrocytoma" were searched in combination with "after radiation," "radiation-induced," "radiosurgery-induced," "radiotherapy-induced," "SRS-induced," and "SRT-induced." Articles that presented cases involving patients undergoing RT for a brain tumor or lesion who were later diagnosed with a grade III or grade IV malignant glioma, including glioblastoma multiforme (GBM), anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma, were reviewed. We identified 172 published cases from 1960–2013 (Table 1), and we added 4 cases identified at our institution (2013). Various factors were collected, including patient age at initial diagnosis of brain lesion, age at second diagnosis of malignant tumor, gender, latency period from the time of RT to the second diagnosis of the malignant glioma, and the total RT dosage directed toward the lesion site.

For analyses, we divided patients into 2 groups—before and after 2007. Patients who received their diagnosis in 2007 were included in the "after 2007" group. We chose 2007 because that seemed to be the most consistent time point to evaluate

Table 1. All Patients with a Diagnosis of Radiation-Induced Malignant Glioma from 1960—2013

Author, Year	Age (years)/Sex	Original Tumor	RT Dose (Gy)	Latency (years)	RIMG
Abedalthagafi and Bakhshwin, 2012 (1)	43/F	Clear cell renal cell carcinoma	unk	5	GBM
Ahn and Kim, 2012 (2)	4/F	EN rhabdomyosarcoma	45	13	sGBM
Amene et al., 2012 (3)	7/F	Juvenile pilocytic astrocytoma	unk	9	sGBM
Anderson and Treip, 1984 (4)	3/F	ALL	25	6	MG/III/IV
Bachman and Ostrow, 1978 (6)	1/F	Ependymoma	39.6	5	GBM
Balasubramaniam et al., 2007 (7)	60/F	Acoustic neuroma	50	5	GBM
Barnes et al., 1982 (8)	17/F	MB	40	6	GBM
Berman et al., 2007 (9)	34/F	AVM	15	9	GBM
Brat et al., 1999 (10)	18/F	Craniopharyngioma	55	11	GBM
	20/M	ALL	36	7	AA
	9/M	Rhabdomyosarcoma	54	11	GBM
	60/M	Pituitary adenoma	45	15	GBM
	28/F	Ependymoma	54	7	AA
	19/F	Lymphoblastic lymphoma	30	5	GBM
	31/F	Hodgkin disease	45	8	AA
	34/M	Pineal tumor	45.7	23	GBM
	13/M	ALL	24	8	GBM
Chung et al., 1981 (12)	2/M	ALL	24	5	GBM
Clifton et al., 1980 (13)	21/M	Hodgkin disease	49.7	6	sGBM
Dierssen et al., 1988 (15)	28/F	Pituitary adenoma	66	6	GBM
Donson et al., 2007 (16)	14/M	Burkitt lymphoma	unk	7	GBM
	11/M	MB	unk	3	GBM
	19/M	Low-grade astrocytoma	unk	15	GBM
	23/F	Ependymoma	unk	12	GBM
	14/F	ALL	unk	10	GBM
Enchev et al., 2009 (18)	18/F	Craniopharyngioma	49.3	22	AO
Flickinger et al., 1989 (19)	55/M	Pituitary adenoma	47.5	7.5	GBM
Fontana et al., 1987 (20)	6/M	ALL	24	11	GBM
	3/M	ALL	24	10	GBM
	6/M	ALL	24	10	GBM
Furuta et al., 1998 (22)	8/M	MB	40	15	AA
Gessi et al., 2008 (23)	7/M	MB	59.8	8	GBM
Grabb et al., 1996 (24)	20/F	Medullomyoblastoma	30	17	AA
Gutjahr and Dieterich, 1979 (25)	4/F	Craniopharyngioma	60	8	GBM
Hamasaki et al., 2010 (26)	5/M	MB	40	35	GBM
Hope et al., 2006 (27)	15/M	MB	40	23	AA
Huang et al., 1987 (28)	26/M	Pituitary adenoma	66	12	AO

RT, radiotherapy; RIMG, radiation-induced malignant glioma; F, female; unk, unknown; GBM, glioblastoma multiforme; EN, embryonal nasopharyngeal; s, spinal; ALL, acute lymphoblastic leukemia; MG/III/IV, malignant glioma World Health Organization grade 3 or 4; MB, medulloblastoma; AVM, arteriovenous malformation; M, male; AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; c, cerebellar; VHL, von Hippel-Lindau; MG/3, malignant glioma World Health Organization grade III; AML, acute myelogenous leukemia; VS, vestibular schwannomas.

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