Neurosurg Rev (2018) 41:719–731
DOI 10.1007/s10143-016-0786-8

REVIEW

Radiation-induced gliomas: a comprehensive review and meta-analysis

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Received: 15 June 2016 / Revised: 25 August 2016 / Accepted: 19 September 2016 / Published online: 5 October 2016

Abstract By conducting a systemic search of the PubMed database, we performed a comprehensive literature review to characterize secondary gliomas following radiotherapy treatment and to determine the most appropriate treatment strategy. Our analysis included 296 cases of radiation-induced gliomas. The primary lesion was characterized as a hematological malignancy in 104 cases (35.1 %), pituitary adenoma in 35 (11.8 %), craniopharyngioma in 19 (6.4 %), medulloblastoma in 38 (12.8 %), germ cell tumor in 13 (4.3 %), low-grade glioma in 28 (9.4 %), cancer/sarcoma in 12 (4.0 %), scalp region disease in 15 (5.0 %), meningioma/schwannoma in 13 (4.3 %), metastatic brain tumor in 5 (1.6 %), and other types (e.g., arteriovenous malformations and angiomas) in 14 (4.7 %). The average age of onset for primary lesions was 16.0 ± 15.8 years, and the average radiation dose delivered to the primary lesion was 37.6 ± 20.0 Gy. Secondary gliomas could be divided into grade I (1), grade II (32), grade III (88), and grade IV (173) tumors. The median overall survival for all glioma cases was 11 months (95 % confidence interval [CI], 9–12), with a 2-year survival rate of 20.2 %. On multivariate analysis, combined modality treatment and the latency period from the radiotherapy treatment to the glioma diagnosis were variables associated with the overall survival of patients with grade III/IV secondary gliomas. For patients treated with cranial radiotherapy, the risk of secondary glioma incidence warrants a longer follow-up period beyond the standard time frame typically designated for determining the risk of primary tumor relapse. Moreover, combination therapy is a potential treatment option for radiation-induced gliomas.

Keywords Combined modality treatment · Glioma · Radiation-induced glioma · Radiation therapy

Introduction

Cranial radiotherapy is a mainstay modality for the treatment of intra- and extracranial tumors. Despite the overall improvement in survival rates, patients treated with radiotherapy are at risk of long-term neurological complications, such as the development of progressive leukoencephalopathy, arteritis, hypopituitarism, hypothalamic insufficiency, optic neuritis, and other secondary malignancies [77, 78, 125, 128, 156, 172]. Furthermore, radiation may have synergistic interactions with chemotherapeutic agents or genetic factors that are involved in the development of secondary gliomas.

Although radiation-induced intracranial tumors can occur within the brain, meninges, bones, and the connective tissue elements of the central nervous system, tumors such as meningiomas and gliomas are the most frequently reported secondary neoplasms [130, 175]. The cumulative risk of occurrence for secondary malignant brain tumors following treatment for pituitary adenomas is 2.7 % at 15 years [169] and 2.4 % at 20 years, which is 10.5 times higher than that seen in the general population [105].

Although evidence for the radiation-induced occurrence of secondary brain tumors is scanty, previous studies have shown an association between radiotherapy and the occurrence of

Electronic supplementary material The online version of this article (doi:10.1007/s10143-016-0786-8) contains supplementary material, which is available to authorized users.

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secondary brain tumors. Induction of oncogenesis by ionizing irradiation has also been widely demonstrated by using animal models [54, 71, 83, 91, 168]. Several other factors, such as genetic predisposition and additional chemotherapy, have also been suggested to play an important role in the development of secondary brain tumors [180].

Recently, several review articles have attempted to further examine radiation-induced gliomas [35, 141, 179]. However, these studies have been somewhat limited owing to their relatively small size (129–191 cases). In this review, we collected information on 296 cases of radiation-induced gliomas and conducted a systemic review to clarify the characteristics and outcomes of radiation-induced gliomas.

Methods

Literature search and selection

We conducted a systematic literature search for "radiation-induced glioma" related papers in the PubMed database through June 6, 2016. The terms used in the search were "radiation-induced glioma" combined with any of the following words: "glioma," "glioblastoma," "malignant glioma," "anaplastic astrocytoma," "radiotherapy-induced," and "radiation-induced." We obtained full copies of all articles that were considered potentially eligible for inclusion in our meta-analysis. The reference lists of all papers were also inspected to find any other eligible papers. Review articles not reporting original data were excluded but their reference lists were checked for potentially eligible studies.

This review includes original articles written in any language and there were no limitations with regard to publication date. Several parameters were collected, including patient age at diagnosis and sex, latency period from radiation therapy to the secondary glioma diagnosis, total radiation dosage and chemotherapy for the primary tumor, histopathology of the primary brain tumor and secondary glioma, the location of the secondary glioma, the treatment administered, and the overall survival (OS) time of the patients.

Statistical analyses

OS was calculated from the date of secondary glioma diagnosis to the date of death, regardless of the cause, or to the date of last follow-up. The Student's *t* test was used to evaluate differences between variables. A Kaplan-Meier analysis was used to illustrate the OS and the cumulative incidence for secondary gliomas. Statistical significance was assessed using a log-rank test. Odds ratios and 95 % confidence intervals (CI) from a logistic regression model were used to compare groups with respect to major clinical factors, which were assessed by both univariate analysis and multivariate analyses with stepwise variable selection. A p value <0.05 was considered to indicate statistical significance. We used JMP software (SAS Institute Inc., Tokyo, Japan) for all statistical calculations.

Results

Literature search of the database

We initially identified 315 cases of radiation-induced gliomas. Three cases were excluded because of the lack of histopathological diagnoses and eight cases were excluded because of the patients' known pre-existing genetic predispositions. Two cases were excluded because of the absence of a latency period between the radiotherapy treatment for the primary lesions and the onset of the gliomas. Six additional cases were excluded because the latency period from the radiotherapy treatment to the onset of gliomas was less than 2 years. Finally, 296 eligible radiation-induced glioma cases were included in our systematic review. Thirteen cases were histologically confirmed by autopsy and the remaining cases were confirmed by surgery or biopsy or autopsy. The selection steps and the underlying reasons for exclusion are summarized in Fig. 1.

The incidence of radiation-induced gliomas in the literature

In our review of the literature, we identified 296 (150 male patients, 129 female patients, and sex was not known in 17) cases of radiation-induced gliomas in the 1970–2015 period (Table 1; Supplementary Table 1) [1–18, 20, 22–24, 26–35, 37–53, 55–70, 72–74, 76, 79–82, 84–89, 92–97, 100, 101, 103–124, 126, 127, 129–135, 137–147, 149–151, 153–155, 157–167, 170–178, 181–190]. The primary tumor was characterized as a hematological malignancy in 104 patients (35.1 %), pituitary adenoma in 35 (11.8 %), craniopharyngioma in 19 (6.4 %), medulloblastoma in 38 (12.8 %), germ cell tumor in 13 (4.3 %), low-grade glioma in 28 (9.4 %), cancer/sarcoma in 12 (4.0 %), scalp region disease in 15 (5.0 %), meningioma/schwannoma in 13 (4.3 %), metastatic brain tumor in 5 (1.6 %), and other types (e.g., arteriovenous malformation [AVM] and angioma) in 14 (4.7 %).

The average age of onset for the primary lesion was 16.0 ± 15.8 years (range, 0–69) (Table 1). The average irradiation (IR) dose delivered to the primary lesion was 37.6 ± 20.0 Gy (range, 3–190) (Table 1). Secondary gliomas were found in the frontal lobe in 79 cases (32.7 %), in the temporal lobe in 65 (26.9 %), in the parietal lobe in 55 (22.8 %), in the occipital lobe in 16 (6.6 %), in the basal ganglia/thalamus in 10 (4.1 %), in the corpus callosum in 7 (2.9 %), in the chiasma in 5 (2 %),

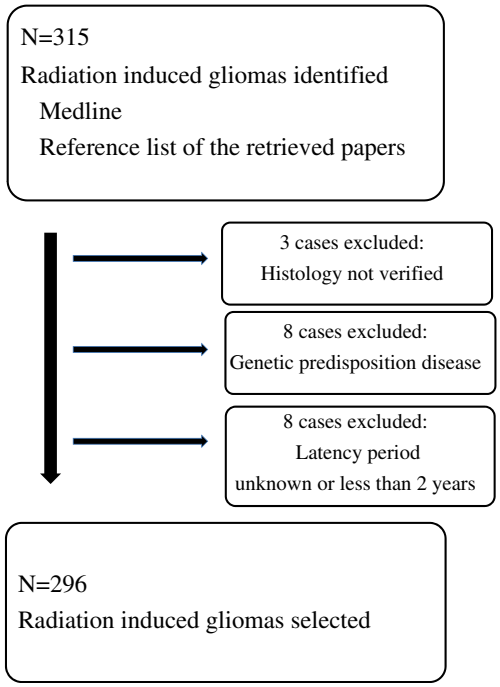

Fig. 1 Flowchart of the selection process for the studies included in the meta-analysis

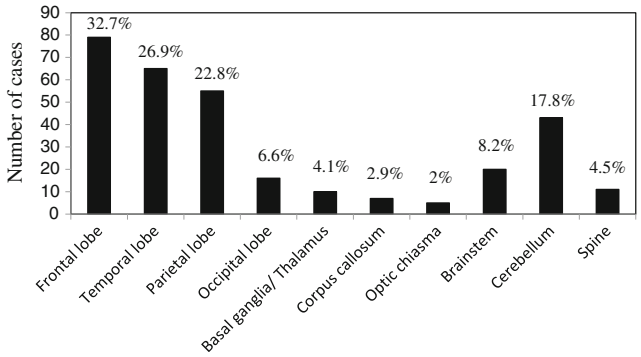

Fig. 2 The location of the secondary gliomas

in the brainstem in 20 (8.2 %), in the cerebellum in 43 (17.8 %), and in the spine in 11 (4.5 %) (Fig. 2).

The histological distribution of the gliomas can be seen in Table 2. The secondary gliomas can be divided into grade I (1), grade II (32), grade III (88), and grade IV (173) tumors (Table 3). The mean radiation dose delivered to the primary lesion was 28.5 Gy for grade II, 39.3 Gy for grade III, and 37.2 Gy for grade IV gliomas (grade II vs. grade III, $p = 0.0137$; grade II vs. grade IV, $p = 0.0604$; Table 3).

The latency period from radiotherapy for primary lesions to the onset of gliomas

The mean latency period between radiotherapy for primary lesions and the onset of secondary gliomas, regardless of grade, was 9 years (95 % CI, 8–9.5) (Fig. 3a). The mean latency period until the onset of grade II, III, and IV gliomas was 9.6 years (95 % CI, 6–14), 9 years (95 % CI, 8–9.8), and 9 years (95 % CI, 8–10), respectively (differences not significant; Fig. 3b). The mean latency period from radiotherapy to acute lymphocytic leukemia (ALL), pituitary adenoma, or a scalp lesion was 8 years (95 % CI, 7–9), 10 years (95 % CI, 7.5–12.5), and 23 years (95 % CI, 6–25), respectively ($p < 0.0001$; Fig. 3c). When systemic chemotherapy was administered, the mean latency period was 8 years (95 % CI, 7–9), and when systemic chemotherapy was not administered, the latency period was 10 years (95 % CI, 9–12) ($p < 0.0001$; Fig. 3d). For patients who received no chemotherapy and an IR dose of ≥50, 50–25, or <25 Gy, the mean latency period was 9 years (95 % CI, 8–10.3), 13 years (95 % CI, 10–15), and

Table 1 Primary lesion of radiation-induced glioma (average ± standard deviation (95 % CI))

	Number of cases	Age	Gender (male %)	IR dose (Gy)	Latency (year)	OS (month)
Hematological malignancy	104	7.5 ± 6.7 (6.2–8.8)	63.8	23.1 ± 8.4 (21.5–24.8)	8.3 ± 3.8 (7.5–9.0)	12 (11–14)
Pituitary adenoma	35	35.6 ± 10.5 (32.0–39.3)	44.1	52.2 ± 11.2 (47.9–56.5)	12.1 ± 7.3 (9.6–14.6)	11 (3–14)
Craniopharyngioma	19	10.4 ± 5.9 (7.3–13.4)	58.8	59.5 ± 23.9 (48.0–71.0)	11.4 ± 6.0 (8.4–14.3)	4 (1–13)
Medulloblastoma	38	9.4 ± 7.5 (6.9–11.8)	55.5	51.3 ± 5.7 (49.1–53.5)	11.9 ± 7.9 (9.3–14.5)	9.5 (7–15)
Germ cell tumor	13	14.3 ± 10.2 (8.1–20.5)	61.5	50.4 ± 4.7 (47.0–53.0)	12.7 ± 10.1 (6.5–18.8)	8 (5–36)
Low-grade glioma	28	12.5 ± 15.4 (6.5–18.5)	39.2	49.1 ± 9.5 (44.7–53.6)	12.8 ± 7.2 (10.0–15.6)	10 (2–18)
Cancer/sarcoma	12	19.8 ± 18.0 (8.3–31.2)	41.6	54.8 ± 13.7 (46.1–63.5)	15.9 ± 15.0 (6.3–25.4)	12 (0.1–30)
Scalp region	15	20.8 ± 20.1 (9.7–32.0)	60	12.7 ± 12.5 (5.1–20.2)	21.4 ± 14.4 (13.4–29.4)	13.2 (2–NA)
Meningioma/schwannoma	13	46.7 ± 17.9 (35.3–56.1)	30.7	41.4 ± 20.6 (28.3–54.5)	6.7 ± 4.7 (3.6–9.6)	7 (1–NA)
Metastatic brain tumor	5	32.4 ± 9.9 (20.0–44.7)	25	46.8 ± 15.9 (21.4–72.3)	6.1 ± 2.4 (3.1–9.1)	8 (5–13)
Miscellaneous	14	23.9 ± 17.6 (13.2–34.6)	58.3	26.8 ± 16.2 (16.5–37.1)	11.5 ± 5.5 (8.3–14.6)	12 (1–NA)
Total	296	16.0 ± 15.8 (14.2–17.9)	53.7	37.5 ± 19.0 (35.1–39.8)	11.0 ± 7.8 (10.1–11.9)	11 (9–12)

CI confidence intervals, *IR* irradiation, *NA* not evaluated, *OS* overall survival

Table 2 Pathological type of secondary glioma

	Number of cases
Grade I	
Subependymoma	1
Grade II	
Astrocytoma	21
Oligoastrocytoma	1
Oligodendroglioma	3
Ependymoma	4
Diffuse astrocytoma	1
Low-grade glioma	2
Grade III	
Anaplastic astrocytoma	69
Anaplastic oligoastrocytoma	1
Anaplastic oligodendroglioma	6
Anaplastic ependymoma	3
Gliomatosis cerebri	2
Grade IV	
Glioblastoma	161
Gliosarcoma	7
Not specifically determined	
Glioma	2
Grade III glioma	2
High-grade astrocytoma	1
High-grade glioma	3
High-grade glioneuronal tumor	1
Malignant astrocytoma	5

11 years (95 % CI, 5–25), respectively ($p = 0.0484$; Fig. 3e). For patients who received systemic chemotherapy and whose IR dose was ≥50, 50–25, or <25 Gy, the mean latency period until the onset of gliomas was 8.5 (95 % CI, 5.5–10), 7.6 (95 % CI, 5.9–10), and 8 years (95 % CI, 6–9.2), respectively (differences not significant; Fig. 3f).

Radiation-induced gliomas in patients with genetic predispositions to disease

A total of eight patients (two male patients, six female patients) had known genetic predispositions to disease (Supplementary Table 2) [26, 89, 96, 98, 152]. Four patients were predisposed to retinoblastoma, three patients to type 1 neurofibromatosis, and one patient to tuberous sclerosis. The average age of patients with genetic predispositions and a primary tumor was lower than that of the patients with radiation-induced gliomas without known genetic predispositions to disease (6.1 ± 8.3 vs. 16.0 ± 15.8 years, $p = 0.0208$). In addition, we observed a tendency for the latency period between the primary tumor treatment and the secondary glioma diagnosis to be shorter in individuals with pre-existing genetic predispositions (6.8 ± 3.6 vs. 11.0 ± 7.8 years, $p = 0.1439$). All eight patients developed grade IV gliomas. The OS in these patients was 22.5 months (95 % CI, 4.5–80), and no significant differences in OS were observed between nonpredisposed and genetically predisposed patients.

Stereotactic radiosurgery-induced gliomas

Fifteen patients (2 male patients, 13 female patients) were identified with stereotactic radiosurgery (SRS)-induced gliomas (Supplementary Table 3) [2, 11, 13, 16, 64, 86, 100, 109, 137, 141, 146, 157, 178, 184, 186]. The primary lesions were identified as AVMs in five patients, vestibular schwannomas in five, meningiomas in two, metastatic brain tumors in two, and a cavernous angioma in one. The average patient age at onset of SRS-induced gliomas was higher than that seen in non-SRS-induced gliomas (42.7 ± 21.6 vs. 14.7 ± 14.3 years, $p < 0.0001$). The latency period from radiotherapy to secondary glioma diagnosis was shorter for SRS-induced gliomas (7.1 ± 4.1 vs. 11.2 ± 7.9 years, $p = 0.0069$). The marginal radiation dose delivered to primary lesions was 14.9 ± 9.5 Gy. Twelve patients developed glioblastomas and three patients developed anaplastic astrocytomas. The OS for SRS-induced glioma patients was 8 months (95 % CI, 1–12) and was not found to be significantly different from that for non-SRS-induced gliomas.

Treatments for radiation-induced gliomas

Various treatment options are available for secondary gliomas, including surgery, chemotherapy, and radiotherapy. In our study group, a total or partial tumor resection was performed in 164 patients and biopsies were obtained from 51 patients. Radiotherapy was performed in 98 patients, with an average

Table 3 Grade of radiation-induced glioma (average ± standard deviation (95 % CI))

	Number	Age	Gender (male %)	IR dose (Gy)	Latency (year)
Grade I	1	8	100	55 + 100	20
Grade II	32	14.0 ± 14.6 (8.3–19.7)	43.3	28.5 ± 17.5 (20.7–36.3)	12.5 ± 8.7 (9.3–15.7)
Grade III	88	15.8 ± 15.7 (12.4–19.1)	56.4	39.3 ± 16.4 (35.8–42.9)	10.9 ± 6.7 (9.5–12.3)
Grade IV	173	16.7 ± 16.3 (14.2–19.1)	53.4	37.2 ± 18.1 (34.3–40.1)	10.8 ± 8.2 (9.6–12.1)

CI confidence intervals, *IR* irradiation

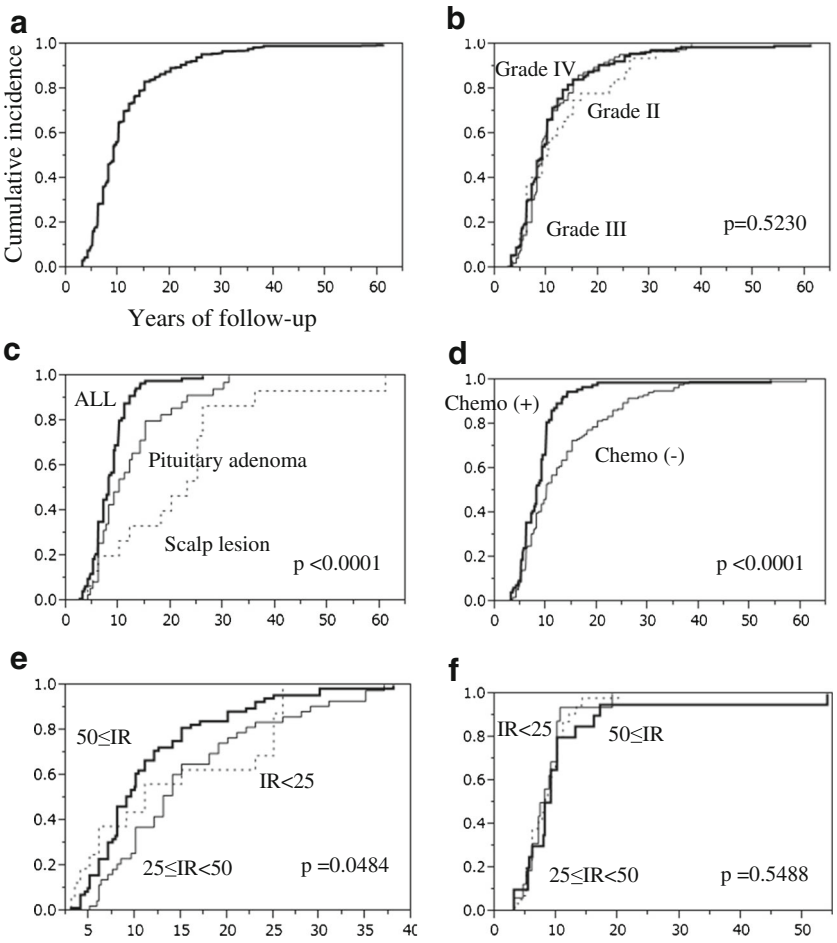

Fig. 3 Latency period from radiotherapy for the primary lesion to diagnosis of the secondary gliomas. **a** Overall cohort. **b** Comparing groups classified by grade. **c** Comparing groups by primary lesion classified as acute lymphocytic leukemia (*ALL*), pituitary adenomas, and scalp lesions. **d** Comparing groups classified as those treated with (*Chemo(+)*) and those treated without chemotherapy (*Chemo(−)*) for the primary lesion. **e** Comparing groups classified as those treated without systemic chemotherapy and an IR dose of ≥50, 50–25, or <25 Gy, for the primary lesion. **f** Comparing groups treated with systemic chemotherapy and an IR dose of ≥50, 50–25, or <25 Gy for the primary lesion

radiation dose of 48.3 (18–101) Gy. Eighty-seven patients were not treated with radiotherapy. Chemotherapy was prescribed for 104 patients, using a variety of protocols based on the physician's choice, and 81 patients did not receive any chemotherapy. The median overall survival for all glioma cases was 11 months (95 % CI, 9–12) with a 2-year survival rate of 20.2 % (Fig. 4a).

The median overall survival and 2-year survival rate for grade III and IV tumors were 11 months (95 % CI, 8–13) and 20.0 % and 10 months (95 % CI, 8–12) and 14.4 %, respectively (difference not significant; Fig. 4b). When dividing the patients into two groups, before ($n = 122$) and after ($n = 64$) 2007 (the year when temozolomide became available), the median OS and 2-year survival rate for grade III and IV tumors were 10 months (95 % CI, 8–12) and 13.2 % and 12 months (95 % CI, 8–14) and 22.1 %, respectively (difference not significant).

The median OS and 2-year survival rate for grade III and IV tumors where the primary lesion was ALL ($n = 82$), a medulloblastoma ($n = 32$), or a pituitary adenoma ($n = 29$) were 12 months (95 % CI, 11–17) and 21.2 %, 9.5 months (95 % CI, 7–14) and 8.3 %, and 11 months (95 % CI, 3–14) and 12.4 %, respectively (differences not significant).

The median OS and 2-year survival rate for grade III and IV tumors, grouped by their latency periods, were 10 months (95 % CI, 6–13) and 16.4 %, 10 months (95 % CI, 8–12) and 12.6 %, 12 months (95 % CI, 8–13) and 17.6 %, and 14 months (95 % CI, 7–19) and 24.9 %, for the <5 ($n = 18$), 5–10 ($n = 86$), 10–15 ($n = 46$), and 15 < year ($n = 36$) groups, respectively (differences not significant).

The median OS and 2-year survival rate for grade III and IV tumors grouped by IR dose were 12 months (95 % CI, 10–17) and 22.4 %, 10 months (95 % CI, 7–13) and 12.5 %, and 9 months (95 % CI, 6–12) and 13.7 % for the <25 ($n = 71$), 25–50 ($n = 42$), 50 < Gy ($n = 66$) groups, respectively (not significant). The median OS and 2-year survival rate for grade III and IV tumors grouped based on the administration ($n = 62$) or lack ($n = 84$) of chemotherapy were 12 months (95 % CI, 9–13) and 18.0 % and 8 months (95 % CI, 7–12) and 15.0 %, respectively (differences not significant).

Survival was also estimated based on the treatment modality administered to grade III/IV gliomas. The median survival following radiotherapy ($n = 78$) was 14 months (95 % CI, 12–18.5) with a 2-year survival rate of 23.7 %, whereas patients who did not receive radiation ($n = 72$) had a median survival

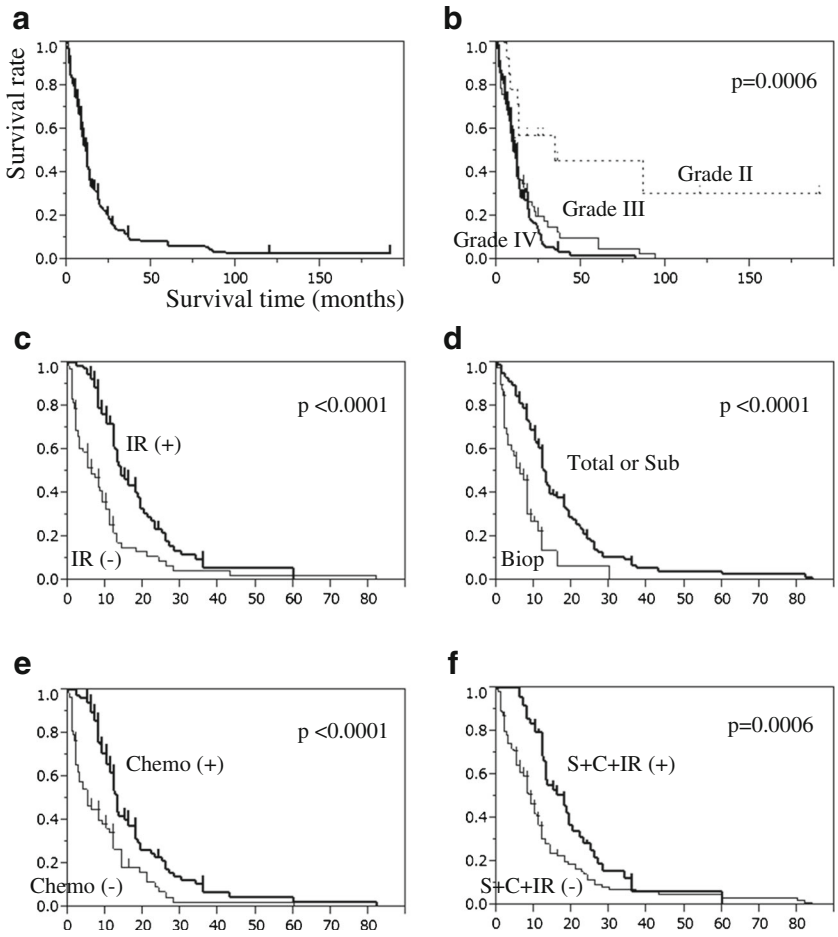

Fig. 4 Kaplan-Meier survival analysis in patients with secondary gliomas. **a** Overall cohort. **b** Comparing groups classified by grade. Survival was also estimated based on the treatment modality administered to grade III/IV gliomas. **c** Comparing groups classified as those treated with radiation therapy (*IR(+)*) and those treated without radiation therapy (*IR(−)*). **d** Comparing groups classified according to total or subtotal removal (*Total* or *Sub*) and biopsy (*Biop*). **e** Comparing groups classified as those treated with chemotherapy (*Chemo(+)*) and those treated without chemotherapy (*Chemo(−)*). **f** Comparing groups classified as those treated with surgery, chemotherapy, and radiation therapy (*S+ C+ IR(+)*) and those treated without these three modalities (*S+ C+ IR(−)*)

of 6 months (95 % CI, 3–9) with a 2-year survival rate of 8.7 % ($p < 0.0001$; Fig. 4c). The median survival for patients who underwent total or partial tumor resection ($n = 126$) was 13 months (95 % CI, 12–14) with a 2-year survival rate of 19.1 %. For patients who underwent only biopsy ($n = 40$), the median survival rate was 6 months (95 % CI, 3–8) and the 2-year survival rates were 6.8 %, respectively ($p < 0.0001$, Fig. 4d). The median survival in patients who received chemotherapy ($n = 86$) was 13 months (95 % CI, 12–16) with a 2-year survival rate of 23.0 %, while patients who did not receive chemotherapy ($n = 65$) had a median survival of 5 months (95 % CI, 2.5–9) and a 2-year survival rate of 6.9 % ($p < 0.0001$, Fig. 4e).

In patients who received a combination of surgery, chemotherapy, and radiotherapy ($n = 50$), the median survival was 18 months (95 % CI, 13–20) with a 2-year survival rate of 28.5 %, whereas for the remainder of the patients who did not receive combined modality therapy ($n = 126$), the median survival was 9 months (95 % CI, 8–10.5), while the 2-year survival rate was 11.9 % ($p = 0.0006$; Fig. 4f). Those variables were then analyzed via multivariate factor analysis. Combined modality treatment was the significant variables retained in the model (Table 4).

Discussion

Cahan et al. [25] established the diagnostic criteria for radiation-induced brain tumors based on the following parameters: (1) the tumor must occur within the irradiated field, (2) a sufficient latency period must exist between irradiation and tumor incidence, (3) the radiation-induced tumor must be proven to be of a different histological type from that of the original neoplasm, and (4) the patient must not have any pathologies favoring the development of tumors such as von Recklinghausen disease, Li-Fraumeni disease, tuberous sclerosis, xeroderma pigmentosum, retinoblastoma, or neurofibromatosis. In this series, all 296 cases fulfilled the criteria required for radiation-induced gliomas.

In terms of cases studied, this review is currently the largest study of this type. All observed gliomas occurred within the irradiated field, a sufficient latency period was observed between irradiation and glioma incidence, and the gliomas were proven to be of a different histological type compared to the original neoplasm. Patients who were identified as having known genetic predispositions favoring tumor development were excluded from the main analysis. Thirty-nine secondary gliomas were identified where the latency period from

Table 4 Factors associated with OS in grade III and IV radiation-induced gliomas

Variable	Univariate		Multivariate	
	OR (95 % CI)	*P* value	OR (95 % CI)	*P* value
Age	1.17 (0.60–2.18)	0.63		
Gender	1.01 (0.73–1.41)	0.94		
IR dose for primary lesion	1.26 (0.54–2.87)	0.58	0.99 (0.98–1.00)	0.63
Latency period from IR to glioma diagnosis	0.34 (0.08–1.23)	0.11	0.97 (0.95–1.00)	0.08
Primary lesion type	1.49 (0.84–2.52)	0.71		
Chemotherapy for primary lesion	0.86 (0.59–1.23)	0.42	0.81 (0.51–1.27)	0.53
Before and after 2007	0.91 (0.65–1.27)	0.61		
Multimodality combined therapy	0.53 (0.36–0.77)	0.0006	0.54 (0.36–0.80)	0.002

CI confidence intervals, *IR* irradiation, *OR* odds ratio, *OS* overall survival

radiotherapy to glioma occurrence was less than 5 years. Among these cases, the occurrence rate of grade III and IV gliomas was 79 %. Therefore, we considered a 2-year latency period to be sufficient to exclude the possibility of malignant gliomas that might predate the primary lesions.

Radiation-induced gliomas occurred in patients of all ages and in both sexes. Hematological malignancies were the most frequent primary lesion seen in radiation-induced gliomas, while medulloblastomas and pituitary adenomas were also commonly observed. Spontaneous high-grade gliomas typically affect adults and are preferentially located in the cerebral hemispheres [75]. However, the age of onset of radiation-induced gliomas is lower than that of spontaneous high-grade gliomas; in spontaneous cases, only 1 % of diagnosed patients are younger than 20 years old [75]. Radiation-induced gliomas are frequently located in the cerebellum and spinal cord, whereas these sites are rare for spontaneous high-grade gliomas [75].

Various chemotherapeutic agents produce double-stranded breaks in DNA, which can induce carcinogenesis. A cumulative effect of independent doses of etoposide, cyclophosphamide, 6-mercaptopurine, and epipodophyllotoxins has been associated with the development of secondary malignant neoplasms [20, 90, 130]. There is also the possibility of a potential synergistic effect between chemo- and radiotherapy, because we found that the latency period of secondary glioma occurrence was shortened in patients treated with a combination of radiation and chemotherapy. Relling et al. [130] reported that intensive systemic antimetabolic chemotherapy during cranial radiotherapy could increase the incidence of secondary brain tumors in ALL patients. In patients who were not treated with chemotherapy for their primary tumor, dose cumulative effects of radiotherapy were clearly present. However, dose cumulative effects of radiotherapy were not observed in patients whose primary tumor had been treated with chemotherapy.

There is a concept of "mutagenicity versus cytotoxicity." This concept postulates that high doses of radiation might kill tumor cells, which results in the elimination of potential carcinogenic mutations, and thereby reduces the risk of tumor induction [53]. Errors in DNA repair might lead to the cellular transformation of the cells that survived radiation therapy or chemotherapy. Patients with a genetic predisposition for disease have pre-existing abnormalities in tumor suppressor genes and are therefore at a greater risk of developing radiation-induced gliomas. The Late Effects Study Group reported that 17 % of radiation-induced tumors originate from the edge of the radiation field where lower radiation doses are delivered [102]. Based on our data, even low doses can be associated with secondary neoplasms [25, 136], because approximately 10 % of cases developed secondary gliomas following radiotherapy treatment with less than 16 Gy. There is an increasing rate of the development of radiation-induced neoplasms up to a maximum peak dose between 3 and 10 Gy [19]. Therefore, the occurrence of secondary tumors is of vital importance, as they can occur even when neighboring tissues receive low radiation doses.

More than 500,000 patients have been treated with SRS worldwide. However, only 15 cases of SRS-induced gliomas have been reported so far. Radiosurgery and fractionated stereotactic radiotherapy, which reduces the volume of normal brain tissue receiving high radiation doses, have been considered the main contributors in reducing the incidence of secondary brain tumors. Despite this, the possible risk of radiosurgery might be underestimated because of its relatively recent introduction. In addition, certain types of patients (e.g., patients with metastatic brain tumor who usually receive SRS treatment) have shortened life expectancies, possibly too short to develop secondary gliomas. Radiation passes through the head via multiple trajectories when Gamma Knife radiosurgery is used. Thus, even distant areas of the brain are exposed to low doses of radiation, which may cause secondary gliomas [148]. The risk of radiation-induced tumors following radiosurgery treatment may not differ significantly from conventional radiotherapy.

Therefore, the incidence of secondary tumors should always be a point to consider even in case of SRS, as they can occur even when neighboring tissues receive low radiation doses.

Activation of oncogenes or inactivation of tumor suppressor genes via DNA strand breaks has been hypothesized as the main mechanism driving the development of secondary tumors after radiotherapy. Somatic *p53* gene mutations have been identified in radiation-induced tumors [21, 163]. An initial mutation to a single allele might occur after radiotherapy, and an additional mutation to the wild-type allele might occur after several years, leading to tumorigenesis. However, reports concerning genetic alterations in radiation-induced gliomas are limited. Using animal models, Lonser et al. reported deletions of the chromosomal regions corresponding to human chromosomes 9, 17p (*p53*), 5q31 (*EGFR*, *interleukin-5*, and *interleukin-6* genes), 14, and 15, and also gains of the chromosomal regions corresponding to humans chromosome 8q (*c-myc*) [91]. A 3-bp homozygous deletion in exon 7 of the *p53* gene was reported to exist in radiation-induced gliomas [163]. Nine radiation-induced high-grade gliomas were investigated for molecular alterations in *p53*, *PTEN*, *KRAS*, *EGFR*, and *p16* [23]. Genetic alterations similar to those described in spontaneous high-grade gliomas, with the exception of *PTEN* mutations, were observed in the radiation-induced gliomas. However, a more wide-scale analysis, using a larger series, is required to truly address these issues.

Radiation-induced glioma is difficult to treat; radiotherapy is not always a therapeutic option as the patient may have already had prior exposure. However, Mayer and Sminia found that re-irradiated normal brain tissue could tolerate a cumulative total dose of more than 100 Gy using conventional fractionation [36]. These observations indicate that therapeutic approaches using methods such as re-irradiation might allow for prolonged disease control in some patients with radiation-induced gliomas. In radiation-induced glioma cases as a whole, several patients have been reported to have achieved a sustained remission following only chemotherapy or chemoradiotherapy. A dramatic response and prolonged survival were reported following the administration of carmustine, nimustine hydrochloride, and temozolomide [72, 81, 99, 108]. Such intensive chemotherapeutic approaches may also allow for prolonged disease control in certain radiation-induced glioma patients. Overt chemo- and radiosensitivity should be further investigated as a potential avenue for the treatment of radiation-induced gliomas.

There are limitations to this study, since the data were obtained from retrospective case reports and case series. However, our data supports the need for more aggressive treatment methods for patients with secondary gliomas [180]. Future studies should focus on genetic profiling of secondary gliomas to elucidate features that might aid in the development of targeted therapies.

Conclusion

The risk of secondary gliomas should be considered before patients undergo radiotherapy for treating primary lesions. In addition, we suggest long-term follow-up for patients who undergo brain radiotherapy. Moreover, combination therapy should be considered a potential avenue of treatment for radiation-induced gliomas. Extensive molecular pathological research on radiation-induced gliomas is warranted.

Acknowledgments This study had no funding source.

Compliance with ethical standards

Funding No funding was received for this research.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a retrospective review so for this type of study formal consent is not required.

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