

# High-Grade Gliomas in Patients with Prior Systemic Malignancies

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**BACKGROUND.** The current study was conducted to characterize the impact of a prior malignancy on the diagnosis, treatment, and outcome of high-grade glioma. **METHODS.** A retrospective study of 21 patients with a histologic diagnosis of glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), or anaplastic oligodendroglioma (AO) after a prior diagnosis of solid tumor or hematologic malignancy was conducted. Glioma histology (GBM vs. AA/AO), patient age ( $\leq 60$  years vs.  $> 60$  years), and extent of resection (biopsy vs. subtotal vs. complete) were evaluated for their prognostic influence.

**RESULTS.** Of the 21 patients studied, 17 had GBM, 3 had AA, and 1 patient had high-grade AO. There were 25 systemic carcinomas diagnosed in 21 patients (18 solid tumors including breast carcinoma, prostate carcinoma, and melanoma and 7 hematologic malignancies). The glioma occurred within a previous radiation field in only three patients, two of whom had solid tumors and one of whom had a childhood hematologic malignancy. Surgical resection was the initial treatment for the brain tumor in 17 patients, and the majority of patients received radiation therapy and adjuvant chemotherapy. Four patients who initially were misdiagnosed as having brain metastases received whole brain radiation therapy as their initial treatment, thereby compromising optimal care. The overall median survival for all the patients in the current study was 14 months (range, 1–44 months) from the time of brain tumor diagnosis. The extent of resection was found to be the only prognostic variable that was associated with survival ( $P = 0.03$ ).

**CONCLUSIONS.** Secondary glioma may occur in patients as a consequence of therapy for a prior malignancy, but most often represents a sporadic event. The outcome and recommended treatment are identical to those for patients with primary gliomas. Accurate diagnosis is essential; neuroimaging often is suggestive of a primary brain tumor and should initiate surgical intervention so that histopathology can be obtained early and appropriate treatment instituted. *Cancer* 2002;94:3219–24. © 2002 American Cancer Society.

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**KEYWORDS:** glioma, glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), oligodendroglioma (AO), chemotherapy, radiation therapy, brain metastases.

High-grade gliomas are aggressive primary brain tumors with few known etiologic risk factors. Familial brain tumor syndromes and genetic disorders account for approximately 1–10% of all gliomas.<sup>1,2</sup> To our knowledge, ionizing radiation is the only known environmental risk factor for the development of high-grade gliomas,<sup>3</sup> but is reported to be a contributing etiologic factor in  $< 1\%$  of patients. Therefore, it appears that the majority of patients lack obvious risk factors. To our knowledge, in previous epidemiologic studies, prior systemic malignancies (other than hematologic malignancies<sup>4,5</sup>) have

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not been examined as potential risk factors for the development of a glioma.

Furthermore, to our knowledge, the affect of a prior cancer diagnosis on the diagnosis, treatment, and prognosis of patients with high-grade glioma has not previously been described to date. Patients with a history of another malignancy may be at risk of various impediments to treatment, including delayed diagnosis, inability to tolerate further aggressive therapy, and perceived poor prognosis. In the current study, we report 21 patients with high-grade glioma after a prior systemic malignancy with the purpose of characterizing the impact of a prior tumor and its treatment on the diagnosis, treatment, and outcome of a secondary high-grade glioma.

## **MATERIALS AND METHODS**

A query of the Memorial Sloan-Kettering Cancer Center (MSKCC) Neurology database identified 21 patients, treated between August 1993 and December 2000, who had a histologic diagnosis of glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), or anaplastic oligodendroglioma (AO) after a prior diagnosis of a solid tumor or hematologic malignancy. In the same time interval, a total of 703 patients with high-grade glioma were identified in the same database, indicating that these 21 patients represent approximately 3% of the malignant glioma patients seen at MSKCC. Basal cell carcinoma, squamous cell carcinoma of the skin, and *in situ* carcinoma of the cervix were not considered prior neoplasms. Hospital charts were reviewed for clinical information.

The stage of the primary tumor was categorized according to the American Joint Committee on Cancer (AJCC) cancer staging system<sup>6</sup> as locoregional (TNM0) or metastatic (TNM1). The treatment of the primary malignancy, including surgery, radiation therapy, chemotherapy, hormonal therapy, immunotherapy, or experimental agents, was recorded for each patient. Patients were considered to be free of the first malignancy if, at the time of the glioma diagnosis, clinical, laboratory, and radiographic evaluation had not revealed any evidence of systemic malignancy for at least 2 years. The interval between the first malignancy and the diagnosis of glioma was recorded in years. The date of the glioma diagnosis was the date of the first pathology diagnosis; otherwise the date of the first neuroimaging test was used.

Glioma resection was categorized according to the surgical report and postoperative imaging as biopsy, subtotal resection, or complete resection. Standard radiation therapy was used to treat all patients; no radiosurgery or hyperfractionated radiation therapy was administered. All chemotherapy agents adminis-

tered were recorded. Glioma histology (GBM vs. anaplastic glioma), patient age ( $\leq 60$  years vs.  $> 60$  years), and extent of resection (biopsy vs. subtotal resection vs. complete resection) were evaluated for prognostic influence.

Survival was calculated from the date of glioma diagnosis to the date of last follow-up or death. Survival was analyzed using the Kaplan-Meier product-limit method.<sup>7</sup> The Wilcoxon test was used to determine any significant difference in the median survival time according to the clinical prognostic variables on univariate analysis. All log-rank tests were assessed at a 5% significance level. The Cox logistic regression method was used for multivariate analysis.

## **RESULTS**

The 14 men and 7 women in the current study ranged in age from 23–75 years (median age, 60 years). Of these 21 patients, 17 had GBM, 3 patients had AA, and 1 patient had AO. Seven patients had first-degree relatives affected by cancer, seven had no contributory family history, and the family history was not properly recorded in seven patients. Of those family members with a history of cancer, only one had a brain tumor, and in two women with breast carcinoma there was a family history of breast carcinoma.

There were 25 systemic malignancies in 21 patients: 18 solid tumors and 7 hematologic malignancies (Table 1). Of the 15 patients with solid tumors, 13 had no evidence of active tumor at the time of glioma diagnosis and 2 patients had metastatic disease. The median age at the time of diagnosis of a primary solid malignancy was 57 years (range, 26–73 years), and the median time interval between the diagnosis of a systemic solid tumor and glioma was 6.5 years (range, 0.5–31 years). Glioma occurred within a previous radiation field in 2 patients; a 38-year-old man with liposarcoma of the left temple received 6600 centigrays (cGy) of focal brain radiation and developed a left frontal GBM 6 years later and a 58-year-old woman with breast carcinoma that was metastatic to the brain received whole brain radiotherapy 19 years prior to the development of a right parietal AO.

Seven patients had hematologic malignancies at a median age of 57 years (range, 15–63 years) followed by glioma at a median interval of 3 years (range, 1–31 years). Of these patients, 2 with childhood hematologic malignancies who were heavily exposed to chemotherapy including antimetabolites and cranial radiation therapy developed high-grade gliomas at a young age; 1 patient with acute lymphocytic leukemia (ALL) who received 2400 cGy of prophylactic cranial irradiation developed AA 8 years later at the age of 23

**TABLE 1**  
Patient Characteristics, Treatment Received, And Outcome

Age (glioma dx)	Gender	Primary lesion	Glioma histology	Interval (yrs)	Prior CT	Prior cranial RT	Glioma treatment	Survival (mos)
58	F	Breast	AO	24	Yes	Yes	B	1 (D)
69	F	Breast	GBM	8	Yes	No	SB/RT/CT	14 (D)
68	F	Breast	GBM	9	No	No	C/RT/CT	13 (D)
64	F	Breast	GBM	7	Yes	No	SB/RT	8 (D)
63	F	Breast/melanoma	GBM	3/1	No	No	C/RT/CT	6 (AWD)
35	F	Melanoma	GBM	9	No	No	B/RT/CT	10 (D)
62	M	Melanoma	GBM	6	No	No	SB/RT/CT	6 (D)
64	M	Prostate	AA	7	No	No	SB/NA/NA	5 (AWD)
73	M	Prostate	GBM	1	No	No	C/RT/CT	5 (AWD)
75	M	Prostate	GBM	2	No	No	B/RT	7 (D)
44	M	Liposarcoma/prostate	GBM	6/2	No	Yes	SB/RT/CT	12 (AWD)
38	M	Liposarcoma <sup>a</sup>	GBM	1	No	No	SB/CT	8 (D)
60	M	Thyroid	GBM	0.5	No	No	C/RT/CT	13 (AWD)
67	M	Thyroid/renal	GBM	NA	No	No	B/NA/NA	29 (D)
65	M	CLL	GBM	3	No	No	SB/RT/CT	14 (D)
56	M	CLL	GBM	1	Yes	No	C/RT/CT	14 (D)
49	F	CLL/vulvar	AA	31/4	No	No	SB/CT	3 (AWD)
53	M	CML	GBM	2	Yes	No	C/RT/CT	3 (D)
23	M	ALL	AA	8	Yes	Yes	SB/RT/CT	11 (D)
35	M	HD	GBM	18	Yes	No	C/RT/CT	43 (D)
48	M	NHL	GBM	1	No	No	C/RT/CT	11 (D)

DX: diagnosis; CT: chemotherapy; RT: radiation therapy; F: female; AO: anaplastic oligodendroglioma; B: biopsy; D: died; GBM: glioblastoma multiforme; SB: subtotal resection; C: complete resection; AWD: alive with disease; M: male; AA: anaplastic astrocytoma; NA: not available; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; ALL: acute lymphocytic leukemia; HD: Hodgkin disease; NHL: non-Hodgkin lymphoma.

<sup>a</sup> Patient was infected with human immunodeficiency virus.

years and another patient with Hodgkin disease developed a GBM 18 years later at the age of 35 years.

Surgical resection was the initial treatment of the brain tumor in 17 patients; all patients had histologic confirmation of their glioma. Complete resection was achieved in nine patients, subtotal resection was performed in six patients, and two patients underwent a biopsy. Information regarding postsurgical treatment was available for 16 of these patients. Eleven patients received radiation therapy and adjuvant chemotherapy, 2 patients received adjuvant chemotherapy alone, 1 patient received radiation therapy alone, and 2 patients received no treatment. The most common cytotoxic agents used included carmustine, temozolomide, procarbazine, and the combination of procarbazine, lomustine, and vincristine (PCV).

Four patients had biopsy confirmation of their glioma after initial treatment for presumed brain metastases. All received whole brain radiation therapy as the initial treatment for intracranial lesions revealed by neuroimaging that were presumed to be metastatic on the basis of the patient's history of prior systemic malignancy. However, none of these patients had evidence of active systemic disease, and all were > 5 years from their original cancer diagnosis. A 62-year-

old man who was 6 years disease-free from a Clark Stage III melanoma developed an isolated brain lesion that was treated with concurrent whole brain radiation therapy (3600 cGy) and paclitaxel. A subsequent limited resection revealed a GBM and the patient died 6 months later from brain tumor progression. A 35-year-old woman with a diagnosis of resected melanoma 9 years prior to the appearance of an isolated left parietal mass was treated with 6000cGy whole brain radiation therapy. Subsequent MRIs were highly suspicious of a high-grade glioma as opposed to metastatic disease, and a biopsy revealed a GBM. This patient received carmustine and died 10 months after surgery. A 69-year-old woman with a prior diagnosis of Stage II breast carcinoma who was treated with surgery and adjuvant chemotherapy was diagnosed with an isolated brain lesion 8 years later and treated with whole brain radiation therapy. The pattern of radiographic progression raised a diagnostic concern and a subtotal tumor resection was performed, revealing GBM. The patient received additional postoperative radiation therapy as well as carmustine and procarbazine; however, despite undergoing a second resection, she died of progressive GBM 14 months after diagnosis. A 64-year-old woman with Stage II breast carci-

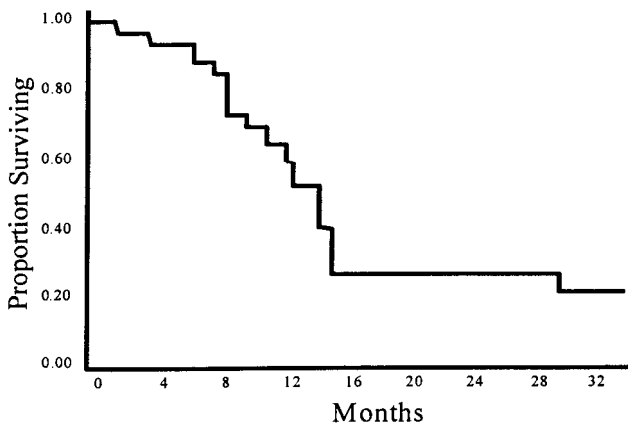


FIGURE 1. Survival distribution of 21 patients with a secondary glioma.

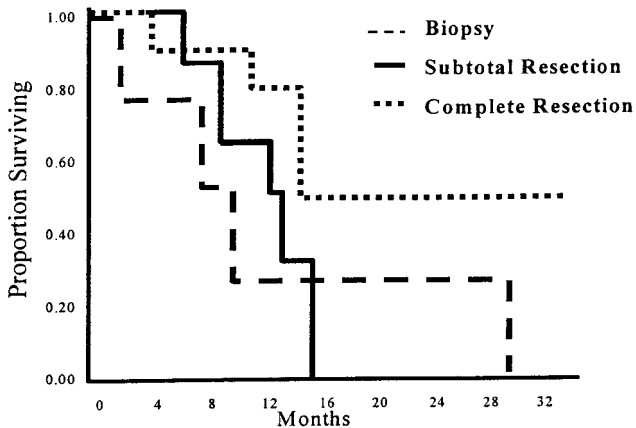


FIGURE 2. Survival distribution of 21 patients based on the extent of resection. The dashed line represents those patients who underwent a biopsy, the solid line represents those patients who underwent a subtotal resection, and the dotted line represents those patients who underwent a complete resection.

noma who was treated with surgery and adjuvant doxorubicin-based chemotherapy followed by tamoxifen developed 2 separate brain lesions 7 years later and was treated with whole brain radiation therapy with rapid disease progression. A subtotal resection revealed GBM, but due to poor neurologic status, no further treatment was given. The patient died 8 months later.

The median survival for all patients was 14 months (range, 1–44 months) from the time of diagnosis of the brain tumor (Fig. 1). The median survival for patients who underwent biopsy, subtotal resection, and optimal resection was 8 months (range, 1–29 months), 12 months (range, 3–14 months), and 14 months (range, 3–43 months), respectively ( $P = 0.09$ ) (Fig. 2). Patient age at the time of the diagnosis of high-grade glioma and tumor histology did not appear to be correlated with survival ( $P = 0.7$  and  $P = 0.7$ ,

respectively). Regression analysis demonstrated that the extent of resection was the only prognostic variable associated with survival time ( $P = 0.03$ ).

## DISCUSSION

In the current retrospective study of patients with secondary malignant gliomas, it would appear that the majority of gliomas develop as a sporadic event without any clear etiologic precipitant. The clinical outcome of this small series is similar to that observed in sporadic primary high-grade gliomas, suggesting that patients with secondary malignant gliomas merit the same treatment and have the same prognosis as those with no prior history of malignancy. Regression analysis found the extent of resection to be the only clinical variable associated with outcome ( $P = 0.03$ ). However, the small sample size and the heterogeneity of the patient population in the current study likely limited our ability to identify other prognostic factors known to affect outcome, such as patient age and tumor histology.

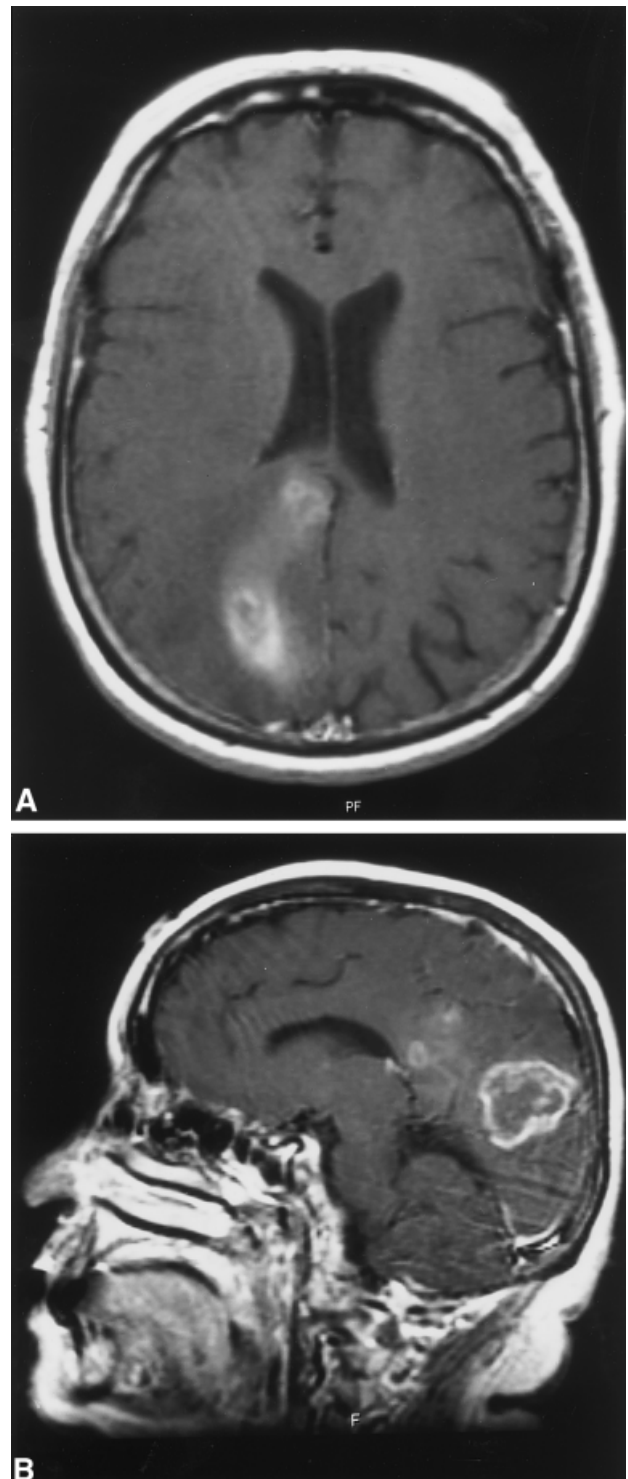
Carcinomas of the breast and prostate were the most common primary neoplasms observed in patients with secondary gliomas and, not coincidentally, are the most prevalent tumors affecting women and men, respectively. Both tumors usually affect patients age > 50 years and are associated with favorable long-term survival, thus “permitting” patients to develop a brain tumor at a later age. There was no obvious etiologic relation between the systemic tumor and the development of glioma in these patients. In a Swedish study of 154,414 patients, no correlation was found between breast carcinoma and the development of secondary gliomas.<sup>8</sup> None of the patients in the current study had lung carcinoma preceding glioma, despite the high incidence of lung carcinoma in the general population. This may be explained by the poor survival of most patients with small and nonsmall cell lung carcinoma,<sup>9,10</sup> so there is no “opportunity” for a brain tumor to become manifest. This hypothesis has been studied as a possible explanation for the apparent increasing incidence of brain tumors among the elderly. As other diseases that used to lead to early death become curable or controllable, patients live long enough to develop less common illnesses such as brain tumors that then appear to increase in incidence.<sup>11</sup>

In 4 of the 21 patients studied (19%), there was a possible correlation between glioma development and prior therapy. Three patients (14%) developed malignant glioma within a prior radiotherapy port, a known cause for gliomas. One patient with Hodgkin disease who was heavily exposed to antimetabolites, a suspected risk factor,<sup>12</sup> developed GBM. The dose of cra-

nial radiation therapy was different for all patients, although all patients received doses known to predispose to glioma formation. In addition ALL itself is a risk factor for glioma formation,<sup>13</sup> independent of the administration of cranial radiation therapy.<sup>4,5</sup> The cumulative 20-year risk of developing secondary high-grade gliomas in patients with ALL was reported to be 0.7%, and the median interval from the time of ALL diagnosis to the appearance of a high-glioma was 9.1 years.<sup>3</sup> Bhatia et al. also have demonstrated a higher incidence of secondary gliomas in patients with childhood Hodgkin disease treated with chemotherapy and radiation therapy.<sup>14</sup>

The most important clinical observation is the risk of misdiagnosis of brain metastases in patients with a prior history of systemic malignancy. In the current study, four patients who were misdiagnosed with brain metastases received inappropriate whole brain radiation therapy, and complete surgical resection was compromised by the delay. Several radiographic and clinical factors may be helpful in differentiating between a brain metastasis and a new primary brain tumor. The lack of active systemic disease (particularly lung metastases<sup>12</sup>), a long disease-free interval between the first malignancy and the appearance of the brain lesion, a primary neoplasm that does not usually metastasize to the brain (e.g., prostate carcinoma), and prior exposure to cranial radiation therapy should raise the suspicion of a primary brain tumor. Of equal importance, the magnetic resonance imaging (MRI) characteristics of the lesion may provide direct clues that the lesion is a primary brain tumor and not metastatic. Infiltrative lesions with involvement of the corpus callosum, lesions involving deep white matter structures as opposed to the gray-white cortical junction, and extensive infiltration involving gray matter and not just white matter all suggest a glioma (Fig. 3). If clinical and MRI findings are suggestive of glioma, a surgical procedure should be considered to obtain a pathologic diagnosis and delineate optimal therapy. In those patients in whom radiographic features are consistent with either a primary or metastatic lesion and the clinical situation does not clarify the issue, resection therefore is indicated. Macroscopic total resection prolongs survival for patients with gliomas<sup>15</sup> and patients with single brain metastasis as well.<sup>16</sup> Therefore, therapeutic benefit is achieved as well as diagnosis in either situation.

Our conclusions are limited by the small sample size in the current study and the fact that this was a retrospective review from a single institution. The clinical outcome of the patients with secondary malignancies in the current study was identical to that for patients with primary gliomas despite the prior malig-



**FIGURE 3.** Gadolinium-enhanced (A) axial and (B) sagittal magnetic resonance imaging scan of a breast carcinoma patient treated with suboptimal radiation doses for misdiagnosed brain metastasis. This scan demonstrates infiltration of the corpus callosum that would be extremely unusual for a metastatic lesion.

nancy and treatment of the patients herein. However, accurate diagnosis is essential and usually suggestive on neuroimaging; biopsy or resection is critical in these patients and should be performed early so appropriate treatment can be instituted. To determine whether patients with solid tumor, particularly those with breast and prostate carcinomas, are at increased risk of developing a secondary glioma would require a larger epidemiologic study.

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