Supratentorial Gangliogliomas: Histopathologic Grading and Tumor Recurrence in 184 Patients with a Median Follow-Up of 8 Years

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BACKGROUND. Supratentorial gangliogliomas (GGs) are rare tumors of the central nervous system and are commonly associated with chronic seizures. To date, only case reports and small series of patients with short-term follow-up have been available for the assessment of the potential of GGs to recur and progress.

METHODS. Data from 184 patients who underwent resection of GGs between 1988 and 2001 were available from the University of Bonn Epilepsy Surgery Center (Bonn, Germany). Analysis of factors that influenced tumor recurrence and patient survival, such as preoperative history, age at operation, tumor location, histopathologic findings (including immunohistochemical findings), extent of tumor resection, and recurrence evaluated on postoperative magnetic resonance imaging (MRI), was performed.

RESULTS. The median follow-up period was 8 years (range, 1–14 years). One hundred seventy-eight patients (97%) presented with long-term seizures ($\geq$ 2 years). The median age at surgery was 26 years (range, 2–65 years). Tumor location was temporal in 79% of patients and frontal in 12% of patients. Eleven tumors (6%) were classified as World Health Organization (WHO) Grade 2 lesions, and 2 tumors were classified as anaplastic WHO Grade 3 lesions. For 38 patients (21%), postoperative MRIs revealed residual tumors. Two years after surgery, 5 patients (3%) experienced tumor recurrence, which resulted in malignant progression in 3 patients (2%) and death in 2 patients (1%). Eighty-four percent of patients with epilepsy had complete and sustained seizure relief. The calculated 7.5-year recurrence-free survival rate was 97%. Lower rates of recurrence were found in patients with tumors classified as WHO Grade 1 lesions ($P < 0.0001$), patients with temporal lesions ($P < 0.0001$), patients who underwent complete tumor resection ($P = 0.0278$), and patients with long-standing epilepsy ($P < 0.0001$).

CONCLUSIONS. Supratentorial GGs are benign tumors, and the surgical goal for patients with GG should be complete resection. Residual tumor masses, frontal tumor location, and WHO Grade 2 or 3 lesions are associated with a greater risk of recurrence or malignant progression. Patients with such characteristics should be considered for long-term clinical follow-up using MRI. ***Cancer*** **2004;101:146–55.**

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Gangliogliomas (GG) are benign tumors that were first identified by Perkins in 1926 as a distinct type of intracranial neoplasm.[1] Morphologically, GGs are composed of dysplastic neurons and neoplastic glial cells. However, their biphasic morphologic pattern shows considerable variation.[2] Both cell populations may exhibit marked heterogeneity, with the morphologic spectrum of GGs ranging from

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variants with a predominantly neuronal phenotype to variants with a prominent glial population. Some GGs also may exhibit clear cell morphology, which makes the differential diagnosis of oligodendrogliomas or DNT difficult. The specific immunohistochemical profile of GGs (e.g., expression of the stem cell epitope CD34) typically allows more accurate distinctions to be made.[2–4]

GGs represent only 0.4% of central nervous system (CNS) neoplasms and 1.3% of brain tumors.[5] Patients usually suffer from seizures as a major clinical symptom,[2,5–12] and GGs can be identified as structural lesions underlying chronic temporal lobe epilepsy in 20–40% of patients in cohorts that undergo neurosurgery.[2,13–15] Accordingly, GGs occur throughout the entire CNS, with a prevalence in supratentorial (particularly temporomesial) locations.[7,10,12,14–17] Age at surgery varies but typically is ~20 years (range, from a few days to 67 years[2,12,18]). In addition, GGs are slightly more common among male patients.[2,12]

Because most series involve limited numbers of patients and short follow-up periods, few reports are available regarding postsurgical outcomes in patients with GG. Despite the usually benign biologic nature of the tumor, some reports have described the malignant transformation of low-grade GGs.[8,12,19–22] Primary diagnoses of atypical GG (World Health Organization [WHO] Grade 2) and anaplastic GG (WHO Grade 3) are rare and have not been described sufficiently by the WHO classification system of CNS tumors.[4,23–26] To our knowledge, the current series of patients with histopathologically confirmed GG and long-term follow-up data, including preoperative and postoperative magnetic resonance images (MRIs), is the largest one documented to date. Using data obtained from this unique patient cohort, we were able to evaluate correlations of clinical follow-up findings with morphologic and immunohistochemical findings, analyze factors that could influence tumor recurrence and survival, and assess the biologic nature of tumors that were histopathologically classified as atypical GG (WHO Grade 2) or anaplastic GG (WHO Grade 3).

MATERIALS AND METHODS

Patients and Follow-Up

Data were extracted from our institution's epilepsy surgery database and neuropathologic tissue archive, both of which have been compiled prospectively since 1999. Between 1988 and 2001, 196 consecutive patients underwent surgery for supratentorial GGs at the Epilepsy Surgery Center at the University of Bonn (Bonn, Germany). Twelve patients were excluded—1 because of death due to unrelated causes, 4 because of unavailable follow-up data, and 7 because of missing postoperative MRI data. For the remaining 184 patients, complete and current follow-up data were available; follow-up data typically were obtained from the outpatient department, general practitioners and/or neurologists, or the patients themselves (via telephone interviews). The extent of tumor removal was determined for all patients using postoperative MRI data. For the purposes of the current study, a relational database was constructed by extracting data (most of which was collected prospectively) from the epilepsy surgery database, the neuropathologic tissue registry, and the epileptologic database. The following data were included and analyzed for possible influence on tumor outcome: duration of epilepsy, tumor location, age at surgery, date and mode of resection, histologic findings according to the 2000 WHO classification system for CNS tumors (including immunohistochemical findings), residual tumor evaluated on postoperative MRI, tumor recurrence, recent follow-up data for tumor outcome, and date and cause of death.[4]

Histopathology

Histopathologic specimens were retrieved from the histologic archives and were reviewed independently by three investigators (I.B., C.L., and O.D.W.) using routine staining with hematoxylin and eosin as well as a panel of reactions evaluating immunohistochemical markers. Among the evaluated markers were CD34 (QBend10; Immunotech, Marseille, France), a stem cell epitope that is not expressed in normal brain but is expressed in 80% of GGs; microtubule-associated protein 2C (MAP2C; clone C; Dr. Riederer, Institute of Cellular Biology, Lausanne, Switzerland); synaptophysin (SY38; Dako, Glostrup, Denmark); neurofilament protein (clone 2F11; Dako) and NeuN (clone A60; Chemicon, Temecula, CA), which were used to characterize the dysplastic nature of neurons in areas that were difficult to distinguish from preexisting brain parenchyma; glial fibrillary acidic protein (GFAP [polyclonal]; Dako), which was used to identify astrocytic elements; and Ki67 (Mib1; Dianova, Hamburg, Germany) epitope, which was used to identify proliferative activity in neoplastic cells.[2] Neuropathologic grading was based on the revised WHO classification system.[4] Fifty cases were included from an additional cohort of 207 patients with long-term epilepsy-associated tumors that previously were diagnosed as WHO Grade 1 pilocytic astrocytoma ($n = 25$), WHO Grade 2 diffuse astrocytoma ($n = 14$), or oligodendroglioma ($n = 11$). Most of these tumors were located in the temporal lobe (84%) and had to be reclassified as GG based on the 2000 WHO classification system as well

as the previously described specific immunohistochemical characteristics of GGs.[2]

The diagnosis of atypical GG (WHO Grade 2) was applied to tumors with presenting features of cellular atypia (i.e., increased cellularity or conspicuous nuclear pleomorphy in glial cell elements), prominent microvascular proliferation, and increased Mib1-positive proliferation of tumor cells (> 5%). Anaplastic GG (WHO Grade 3) exhibited additional features of tumor necrosis. Other frequently encountered morphologic characteristics of GGs (i.e., calcification, microglial and/or lymphocytic infiltration, microcystic vacuolation, and pilocytic or clear cell differentiation) were not considered to be attributes of atypical or anaplastic tumor variants.

Statistical Analysis

The influence of single (categorized) factors on tumor recurrence and survival was analyzed using chi-square tests or Fisher exact tests as necessary based on sample size. The method of Kaplan and Meier was used to calculate survival and recurrence rates,[27] and differences were analyzed using the log-rank test. Comparisons of quantitative variables (tumor location, age at surgery, WHO grade, range of resection, and long-term epilepsy) between groups of patients were made using the Wilcoxon–Mann–Whitney *U* test. Multifactorial analyses of relevant factors (i.e., factors for which $P < 0.05$) identified on one-factor analysis were calculated for every data set but yielded no reliable information, due to the limited numbers of events. All analyses were supported by SAS/STAT software (SAS Inc., Cary, NC).

Study Endpoints

The study endpoint was the time of tumor recurrence, death, or last examination. Data from follow-up examinations were updated for all patients until the year 2002.

RESULTS

Clinical Data

Clinical data from 184 patients with supratentorial GGs, including 104 males (57%) and 80 females (43%), are summarized in Table 1. The median patient age at the time of surgery was 26 years (range, 2–65 years). Seizures were the major preoperative symptom in 178 patients (97%), and 157 patients (85%) presented with long-term (≥ 2 years) epilepsy (median duration, 12 years; range, 2–45 years). Tumors were located predominantly in the temporal lobe (79%), and particularly in the temporomesial region (50%). Only 12% of all neoplasms were located in the frontal region. In 38 patients (21%), tumor resection was incomplete according to postoperative MRI. One hundred seventy-one tumors (93%) were classified histopathologically as GG (WHO Grade 1), 11 tumors (6%) were classified as atypical GG (WHO Grade 2), and 2 tumors were classified as anaplastic GG (WHO Grade 3). One year after surgery, 158 patients (86%) no longer experienced seizures, irrespective of the presence of residual tumor masses. There were no operative or postoperative deaths and no permanent morbidity. Adjuvant radiotherapy and/or chemotherapy were administered to only 4 patients (2%; after initial surgery [for WHO Grade 1 and Grade 3 disease, respectively] in 2 patients and after malignant progression in 2 patients). One child was treated with chemotherapy after undergoing incomplete resection of a WHO Grade 1 tumor. The median follow-up duration for the 184 patients examined was 8 years (range, 1–14 years), with a minimum follow-up duration in 157 patients

TABLE 1
Data and Outcomes for 184 Patients with Supratentorial Gangliogliomas

Characteristic	No. of patients (%)		
	All patients	Patients with recurrences	Patients who died
Total	184 (100)	5 (3)	2 (1)
Gender			
Male	104 (57)	3 (3)	0 (—)
Female	80 (43)	2 (3)	2 (3)
Long-term epilepsy			
Yes	157 (85)	1 (1)	1 (1)
No	27 (15)	4 (15)	1 (4)
Duration of epilepsy (yrs)			
> 1	173 (94)	1 (1)	1 (1)
≤ 1	5 (3)	2 (40)	1 (20)
No seizures	6 (3)	2 (33)	1 (17)
Age at surgery (yrs)			
< 21	62 (34)	2 (1)	0 (—)
21–40	104 (57)	3 (3)	2 (2)
> 49	18 (10)	1 (6)	0 (—)
Tumor location			
Frontal	22 (12)	3 (14)	1 (5)
Temporomesial	93 (50)	0 (—)	0 (—)
Temporolateral	53 (29)	0 (—)	0 (—)
Insular	2 (1)	1 (50)	0 (—)
Basal ganglionic	1 (1)	1 (100)	1 (100)
Other	13 (7)	0 (—)	0 (—)
WHO grade			
1	171 (93)	1 (1)	1 (1)
2	11 (6)	3 (27)	1 (10)
3	2 (1)	1 (50)	0 (—)
Residual tumor			
Yes	38 (21)	3 (8)	1 (3)
No	146 (79)	2 (1)	1 (1)

WHO: World Health Organization.

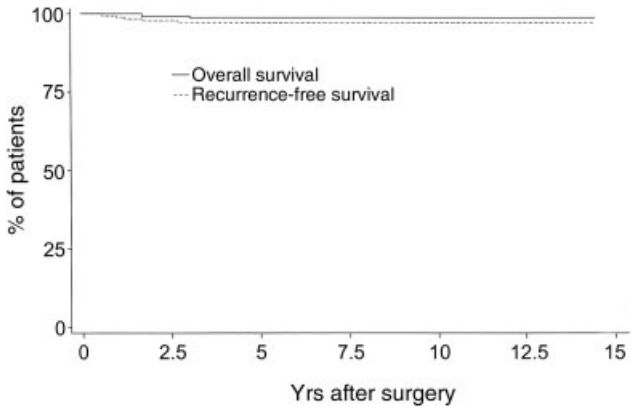

FIGURE 1. Kaplan–Meier plots showing recurrence-free (7.5-year recurrence-free survival rate, 97%) and overall survival data (7.5-year survival rate, 98%) for all 184 patients in the current study.

(84%) of 5 years. During follow-up, 5 patients developed recurrent tumors (3%), including 3 patients with malignant progression, and 2 patients died (1%) (Table 1). There were no recurrences among the 50 patients with epilepsy-associated tumors, which originally were identified as astrocytomas or oligodendrogliomas and were histopathologically reclassified as GG (see above). The calculated 7.5-year survival rate was 98%, and the 7.5-year recurrence-free survival rate was 97% (Fig. 1).

Neuropathologic Findings

Histopathologic evaluation of surgical specimens revealed a benign glioneuronal tumor (i.e., GG [WHO Grade 1]) in 171 patients. Characteristic radiographic and corresponding histopathologic features of this tumor are depicted in Figure 2. Although GGs display considerable morphologic heterogeneity with respect to neuronal and glial phenotypes, immunohistochemical detection of CD34, lack of glial MAP2 staining, and low Ki67 indices often can be used confirm the diagnosis. Eleven tumors exhibited conspicuous elements of atypia and were classified as WHO Grade 2 lesions. Increased cellularity was observed in 10 tumors, and nuclear pleomorphism was observed in the glial cell component in 3 tumors. Four WHO Grade 2 neoplasms exhibited elevated proliferation of the glial component ($>$ 5%). However, 1 GG with a low Ki67 labeling index recurred 1 year after surgery, with malignant progression to glioblastoma (WHO Grade 4) (Fig. 3). Because gemistocytic differentiation of the glial component was the only suspicious feature of the primary lesion, we propose that gemistocytic differentiation patterns in GG represent an additional feature of atypia. The two Grade 3 tumors (one of which is shown in Fig. 4) exhibited immunohistochemically detectable proliferation in $>$ 10% of cells as well as tumor necrosis.

Immunohistochemical analysis confirmed the expression of the stem cell epitope CD34 in 83% of all GGs. Whereas 85% of temporal tumors and 75% of frontal tumors expressed CD34, only 55% of WHO Grade 2 or 3 neoplasms and 2 of 4 tumors that malignantly progressed had this particular expression pattern. GFAP-immunoreactive neoplastic glial cells could be detected in all GGs, albeit with considerable variation. Dominant GFAP-expressing astrocytic cell populations that were suggestive of a gemistocytic phenotype were noted in 80% of tumors that later recurred and in 1 temporal WHO Grade 2 tumor that did not recur. All neuronal markers (i.e., MAP2, synaptophysin, and neurofilament protein) were detectable in the dysplastic neuronal components of the tumors.

None of the 184 GGs exhibited nuclear immunoreactivity for p53 in a significant percentage of tumor cells (i.e., $>$ 5%). However, a glioblastoma that occurred 1 year after an atypical GG (WHO Grade 2) and was incompletely removed exhibited nuclear p53 accumulation.

Survival and Prognostic Factors

In 5 patients (3%), tumors recurred between 7 months and 3 years after surgery. Among these 5 patients were 3 (2%) who had histopathologic signs of malignant progression, including 2 patients who had histologically confirmed glioblastoma. Two of these 3 patients died 1–3 years after recurrence; the third patient, who had histologically confirmed glioblastoma, remained free of recurrence 1.5 years after undergoing surgery and receiving adjuvant radiotherapy and chemotherapy. The calculated 7.5-year survival rate for all 184 patients was 98%, with a 7.5-year recurrence-free survival rate of 97% (Fig. 1).

Among the five patients who developed recurrent tumors, three had tumors that were located in the frontal lobe, and two had deep-seated lesions (in the insula and basal ganglia, respectively) (Table 1). None of the 146 temporal tumors and only 1 of 157 lesions in patients with associated long-term epilepsy recurred. Tumor recurrence was noted in only 1% of patients with WHO Grade 1 lesions, compared with 18% of patients with Grade 2 lesions and 50% of patients with Grade 3 lesions (Table 1). One patient with an initial Grade 3 GG remained free of recurrence 11 years after surgery.

Kaplan–Meier plots demonstrated that the 7.5-year recurrence-free survival rate was significantly greater in patients who experienced epilepsy for $>$ 1

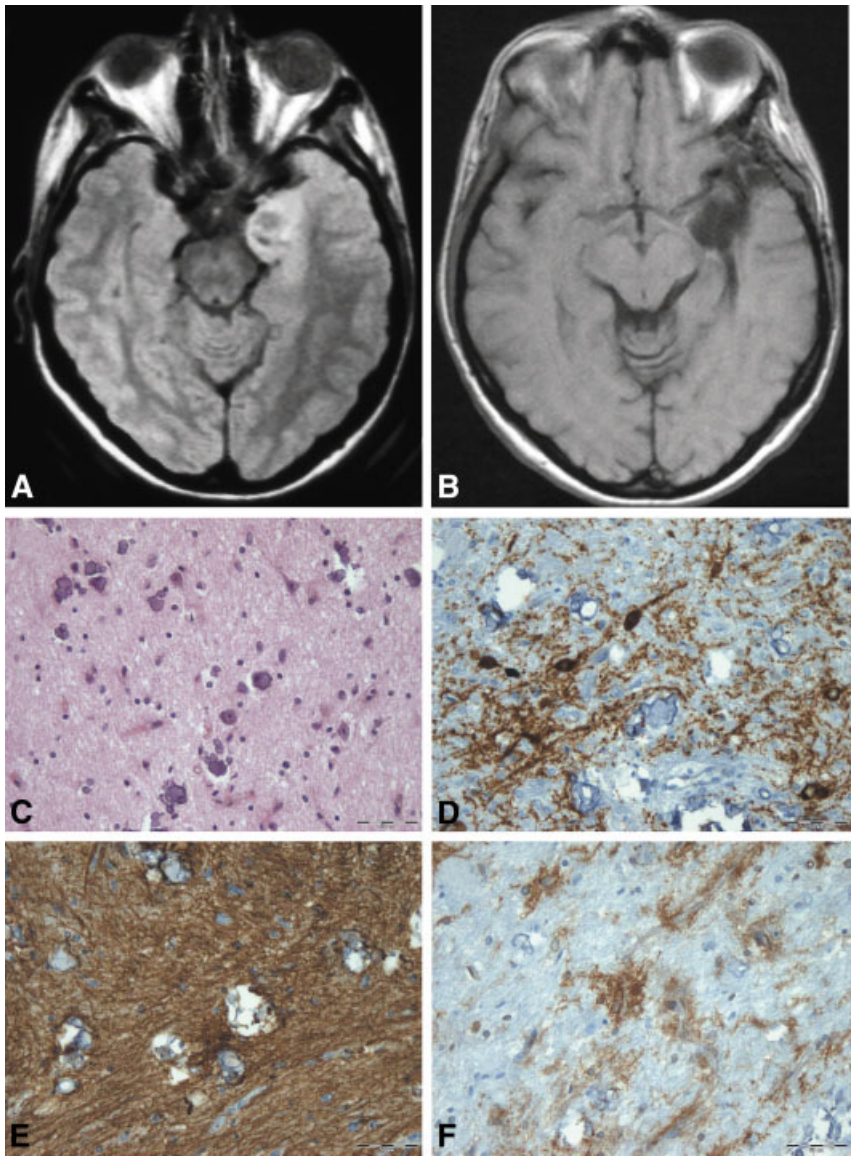

FIGURE 2. Radiographic and histopathologic findings in patients with World Health Organization Grade 1 gangliogliomas. (A) A preoperative magnetic resonance image (MRI) reveals a tumor mass in the left temporomesial region in a child age 4 years. (B) A postoperative MRI reveals complete resection. (C) The tumor specimen exhibits a biphasic differentiation pattern composed of glial and neuronal cellular elements. The cellularity is relatively low. Dystrophic calcification is encountered often in this tumor entity. (D) The dysplastic neuronal component can be visualized using microtubule-associated protein 2 immunohistochemical analysis; the glial element does not express this marker. (E) Intense staining for glial fibrillary acidic protein can be seen. (F) The majority of gangliogliomas exhibit CD34 immunoreactivity in patchy tumor cell clusters. To our knowledge, this distribution pattern has never been observed in normal brain tissue.

year (Fig. 5A). Among patients with lesions located in the temporal lobe (Figs. 2A, 5B), patients with WHO Grade 1 lesions (Figs. 2C–F, 5C), and patients for whom complete resection was possible (as confirmed by postoperative MRI), 7.5-year recurrence-free survival rates were significantly increased (Figs. 2B, 5D). Patient age at the time of surgery had no effect on the rate of tumor recurrence.

DISCUSSION

The current cohort study involved a comprehensive series of 184 patients with supratentorial GGs who had a mean follow-up duration of 8 years (range, 1–14 years). This series was assembled with the goal of systematically evaluating the factors that influence postoperative outcomes (i.e., rates of recurrence and death) in patients with GG, as well as the clinical and morphologic characteristics of the tumor itself.[3,5–7,9–12,18,23,28] Preoperative and postoperative MRI analyses appeared to be very helpful in defining the exact extent of resection.[29] Compared with other series of patients with GG,[5,7–9,11,22,30] the current series is unique in that only 1% of patients received adjuvant radiotherapy or chemotherapy after initial surgery.

Tumor Outcome

A median follow-up of 8 years revealed favorable outcomes for patients with supratentorial GGs, among whom only 5 recurrences and 3 tumors that exhibited malignant progression to glioblastoma were observed. This finding is in accordance with findings made in a recent series of patients with GG.[12] In contrast, earlier

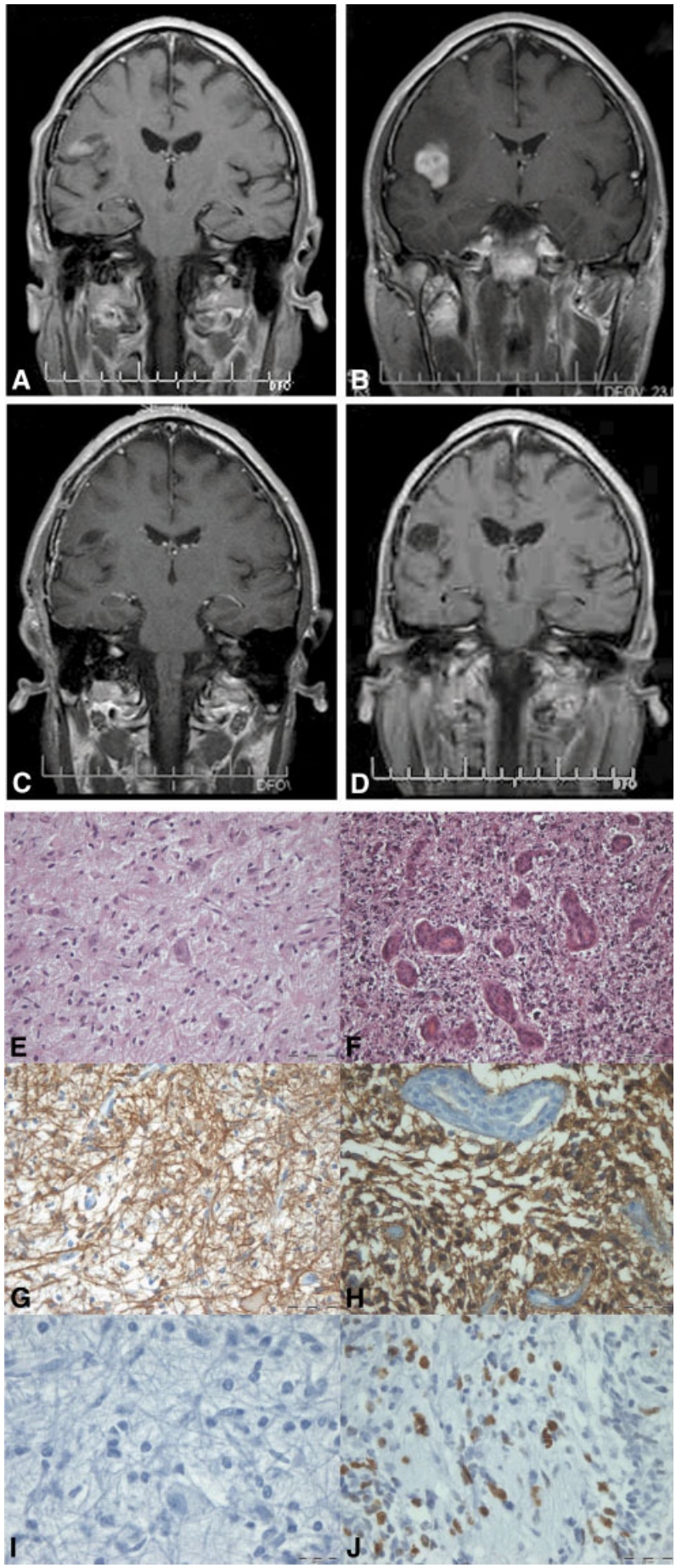

FIGURE 3. Radiographic findings in (A,C,E,G,I) an atypical ganglioglioma (World Health Organization [WHO] Grade 2) with malignant progression to (B,D,F,H,J) glioblastoma multiforme (WHO Grade 4). (A) A preoperative magnetic resonance image (MRI) reveals a tumor mass in the right frontal lobe in a male patient age 62 years. (B) An MRI reveals tumor recurrence in the same area 1 year after initial surgery. (C,D) Postoperative MRIs reveal complete resection. (E) Histologic findings in an atypical ganglioglioma (WHO Grade 2). Dysplastic neurons lack any anatomic orientation and are embedded within a glial matrix. (F) Histologic examination confirms the subsequent diagnosis of glioblastoma (WHO Grade 4). (G) Immunostaining for glial fibrillary acidic protein (GFAP) reveals prominent astroglial differentiation resembling gemistocytes. (H) Neoplastic astrocytes express GFAP as well as microtubule-associated protein 2C (not shown) and exhibit nuclear p53 accumulation (not shown). (I) Low proliferative activity (as assessed by Ki-67 immunoreactivity) in the atypical ganglioglioma specimen. (J) Significantly increased proliferative activity (affecting approximately 10% of tumor cells) in the glioblastoma multiforme specimen.

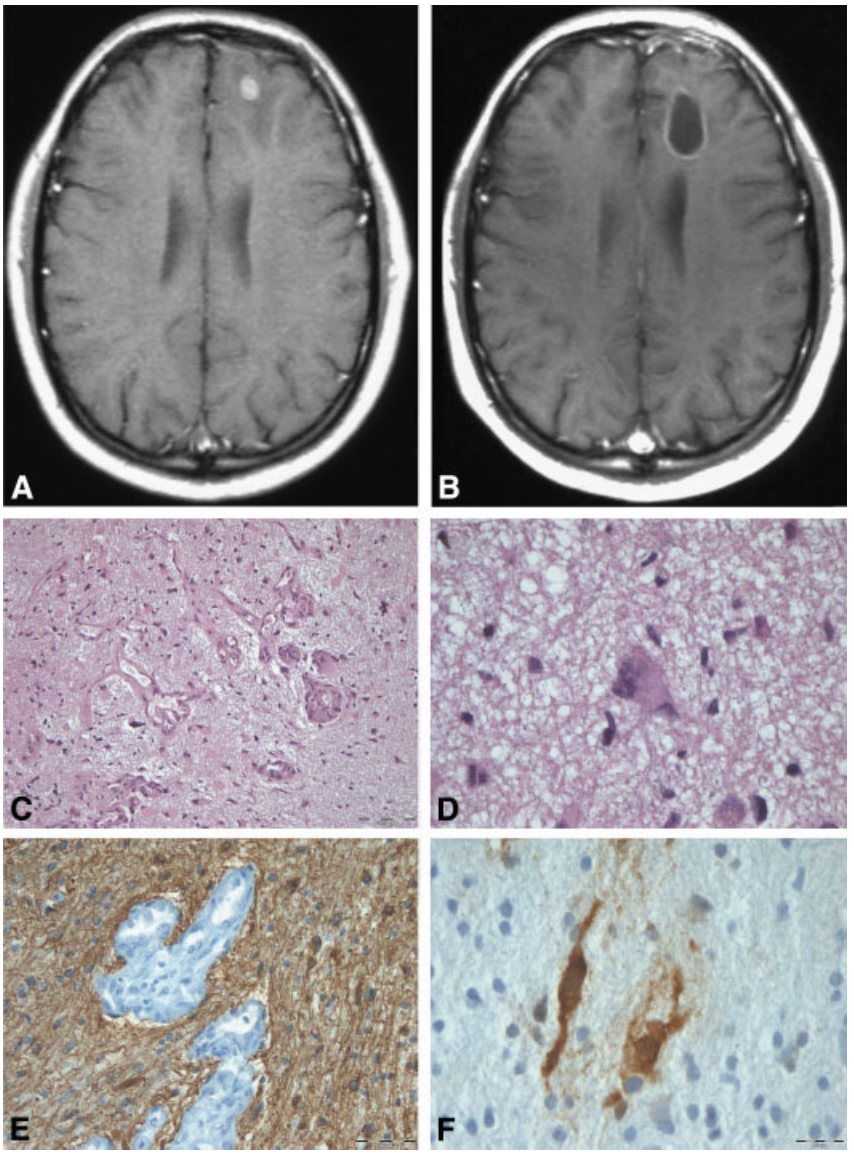

FIGURE 4. Radiographic and histopathologic findings in anaplastic ganglioglioma (World Health Organization [WHO] Grade 3). (A) A preoperative magnetic resonance image (MRI) reveals a tumor mass in the left frontal lobe in a male patient age 31 years. (B) A postoperative MRI reveals complete resection. (C) Prominent microvascular proliferation is a characteristic finding in this tumor specimen and supports the diagnosis of anaplastic ganglioglioma (WHO Grade 3). (D) Dysmorphic ganglion cells are encountered in many regions of the tumor. (E) The glial component can be identified by immunoreactivity for glial fibrillary acidic protein. (F) Dysmorphic neurons are identified using microtubule-associated protein 2 antibodies; in contrast, the glial component is not immunoreactive for this marker.

studies reported either higher recurrence rates, with progression-related deaths in 20%,[7] 23%,[8] 17%,[11] and 24%[22] of patients, or no recurrences other than primary anaplastic lesions (most likely because of the limited number of patients investigated).[9] In most series, recurrences were noted 1–3 years after surgery; however, later recurrences and malignant transformations occurring 5–11 years after surgery were described in 2 series.[5,21]

According to the results of the current study, histopathologic reevaluation of low-grade gliomas in patients with long-term epilepsy appears to be mandatory.[18,31,32] Neuropathologic inspection should address the degree of cellular atypia and the differential diagnosis of diffuse gliomas or pilocytic astrocytomas. In the current series, 50 tumors that previously were classified as pilocytic or diffuse astrocytomas or as oligodendrogliomas exhibited immunohistochemical features of GG, such as glioneuronal expression of CD34 and a lack of glial MAP2 expression.[33,34] These findings notwithstanding, the histologic spectrum of GG is very broad, and distinguishing GGs from low-grade gliomas often is difficult. Thus, previously published observations that temporal lobe epilepsy-associated astrocytomas predict more favorable clinical outcome and biologic behavior may necessitate careful neuropathologic reevaluation of the specimens in question.

Prognostic Factors

The results of the current study indicate that temporal tumor location[7,12,16] and long-term epilepsy[24] are as-

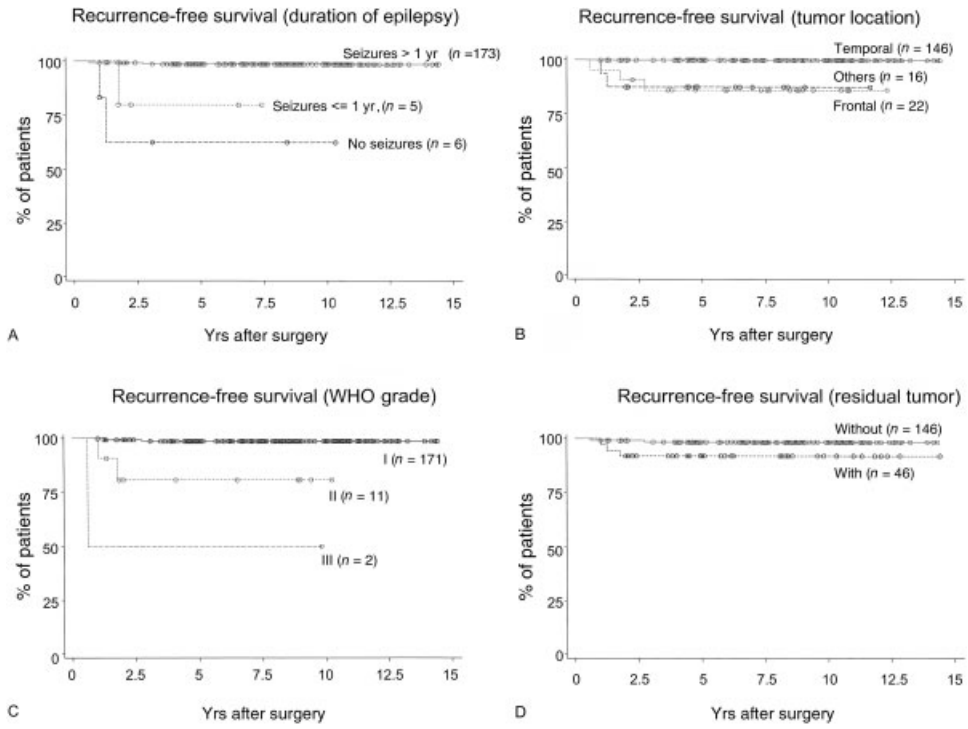

FIGURE 5. Kaplan–Meier plots showing recurrence and survival rates according to length of seizure history, tumor location, World Health Organization (WHO) tumor grade, and residual tumor. (A) A significantly higher 7.5-year recurrence-free survival rate is evident among patients who had epilepsy for $>$ 2 years (97%) compared with patients who did not have seizures (63%) and patients who had preoperative epilepsy for $<$ 1 year (80%). $P < 0.0001$ (log-rank test). (B) None of the patients with temporal lesions experienced disease recurrence. In contrast, patients with frontal lesions had a 7.5-year recurrence-free survival rate of 84%, and patients with lesions in other locations had a 7.5-year recurrence-free survival rate of 86%. $P < 0.0001$ (log-rank test). (C) WHO grade was significantly associated with recurrence-free survival. The highest recurrence-free survival rate was observed among patients who had Grade 1 tumors (98%). In contrast, patients with Grade 2 tumors had a recurrence-free survival rate of 80%, and patients with Grade 3 tumors had a recurrence-free survival rate of 50%. $P < 0.0001$ (log-rank test). (D) A significantly higher 7.5-year recurrence-free survival rate was observed among patients whose tumors were removed completely (99%) compared with patients who had residual tumor masses (92%) on postoperative magnetic resonance imaging. $P = 0.0278$ (log-rank test).

sociated with a more favorable postoperative outcome and that residual tumor masses are associated with higher recurrence rates.[9,12] Only Lang et al.[17] and Rumana et al.[22] did not report this latter finding, although postoperative MRI data were not incorporated into those studies. Unlike the outcomes of patients with other neuroepithelial neoplasms, the outcomes of patients with GGs were not influenced by patient age at the time of surgery.[12] Cellular atypia may be weakly associated with unfavorable outcome,[11,12] although the described histopathologic criteria for atypia will require confirmation in additional neuropathologic studies that employ similar immunohistochemical protocols in independent patient series.[2,3,21]

Despite the large number of patients included in the current study, we could not determine whether long-term epilepsy and temporal location were associated with more favorable outcome. Even in the current study, the absolute number of WHO Grade 2 and Grade 3 GGs was too small to allow multifactorial analysis.

The finding that residual tumor masses detected on postoperative MRIs were associated with a higher recurrence rate indicates that GGs should be removed completely if possible. In contrast, adjuvant treatment, such as postoperative radiotherapy, did not appear to be beneficial for patients with WHO Grade 1 or 2 tumors.[5,7,8,11,22,30] Nonetheless, collaborative efforts are warranted to recruit sufficient numbers of patients and implement matched protocols to systematically analyze long-term follow-up data as well as histopathologic and molecular genetic features within the broad spectrum of GGs and their atypical and anaplastic variants.

Differential Diagnosis of GG

GGs have an immunohistochemical profile that is different from that of low-grade gliomas.[2,33] Among the

most useful differences are the presence of CD34 immunoreactivity in almost 80% of GGs and the lack of MAP2 immunoreactivity in neoplastically transformed glial cell elements. The latter feature can be identified in the majority of diffuse astrocytomas, oligodendrogliomas, and pilocytic astrocytomas.[34] In the current series, considerable numbers of tumors that previously were identified as long-term epilepsy-associated gliomas (pilocytic astrocytomas, diffuse astrocytomas, and oligodendrogliomas) were reevaluated. Fifty tumor specimens had immunohistochemical features of GG, and the accompanying favorable long-term follow-up data (median follow-up duration, 8 years) supported our diagnostic estimation. However, with respect to the prognosis of atypical and anaplastic tumor variants and the malignant progression of low-grade variants, we have not yet established consistent histopathologic parameters. In fact, GGs appear to behave differently from WHO Grade 2 or Grade 3 gliomas, and common criteria for anaplasia (i.e., cellularity, necrosis, mitosis, and proliferation of microvessels) do not appear to play an equivalent role in GG compared with glioma. Even glioblastomas with gangliomatous components appear to behave differently from gliomas. Thus, future studies should address the comparative molecular genetics of GGs with defined histopathologic phenotypes. Because the inactivation of p53 and other glioma-related tumor suppressor genes and the activation of oncogenes do not appear to play a role in GG,[2] it is likely that developmentally regulated signaling cascades are involved.[35,36] It is tempting to speculate that future molecular biologic studies will help to distinguish specific clinicopathologic variants from each other.[34,36]

Conclusions

Only a minority of supratentorial GGs bear a risk of recurrence and malignant transformation within the first 3 years after surgery. Long-term epilepsy, temporal tumor location, a benign histopathologic phenotype (WHO Grade 1), and complete resection (as defined by postoperative MRI) were associated with a significantly reduced risk of tumor recurrence. Therefore, complete tumor resection should be achieved via neurosurgical treatment. The benefit of radiotherapy remains to be elucidated, as radiotherapy may not be as critical in GG as it is in diffuse gliomas. Patients with frontal tumor location, WHO Grade 2 or 3 disease, a short period of preoperative symptom recurrence, or a residual tumor mass require consecutive clinical monitoring. Immunohistochemical investigations are helpful for distinguishing GGs from other low-grade neuroepithelial tumors but still cannot predict malignant transformation. Despite the large number of patients included in the current study, multifactorial analysis was not helpful in identifying which factors affected recurrence and death. Therefore, we recommend the establishment of an international consortium to characterize clinicopathologic phenotypes of GG.

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