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P K Kincaid, S M El-Saden, S H Park and B W Goy

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Cerebral Gangliogliomas: Preoperative Grading Using FDG-PET and ^{201}Tl-SPECT

Patricia K. Kincaid, Suzie M. El-Saden, Sung-Hye Park, and Barry W. Goy

PURPOSE: **To date there have been only scattered case reports comparing the nuclear medicine characteristics of gangliogliomas with their histologic grade. We sought to determine the relative usefulness of nuclear medicine scanning, CT, and MR imaging in predicting the histologic grade of these tumors.**

METHODS: **Eleven cases of pathologically proved ganglioglioma were analyzed retrospectively. Preoperative positron emission tomography with ^{18}-fluorodeoxyglucose (FDG-PET), thallium chloride Tl 201 single-photon emission computed tomography (^{201}Tl-SPECT), CT, and MR imaging studies were reviewed and compared with histologic tumor grade. FDG-PET scans were inspected visually for tumor metabolic activity relative to activity of normal gray and white matter. ^{201}Tl-SPECT scans were analyzed for tumor activity using regions of interest and activity ratios. CT and MR studies were reviewed for the presence of conventional radiologic features of malignancy (ie, enhancement and edema).**

RESULTS: **Eleven patients had a total of 15 nuclear scans. Eight of nine gangliogliomas scanned with FDG-PET showed tumor hypometabolism, the ninth was normal. All nine were low-grade gangliogliomas. Increased ^{201}Tl-SPECT activity was seen in two high-grade gangliogliomas. The third ^{201}Tl-SPECT scan, of a low-grade ganglioglioma, was normal. CT and MR studies showed enhancement in four gangliogliomas, of which two were high grade and two low grade. Edema was seen only in conjunction with the two high-grade gangliogliomas.**

CONCLUSION: **FDG-PET and ^{201}Tl-SPECT are 100% correlative in preoperative prediction of histologic grade of ganglioglioma. Tumors with decreased or normal PET or SPECT activity were low grade; tumors with increased SPECT activity were high grade. These results may be more reliable than CT and MR imaging findings in assessing tumor grade, and they may be of value for surgical planning and determining patient prognosis.**

Gangliogliomas are rare tumors of the CNS, accounting for 0.4% to 3.8% of all primary CNS neoplasms (1–5). Histologically, gangliogliomas are distinct in that they are composed of both neoplastic neuronal and neoplastic glial elements. Mature ganglion cells make up the neuronal component of the tumor, thus the name ganglioglioma. As the behavior of a ganglioglioma usually depends on the histologic characteristics of its glial (usually astrocytic) component, a grading scheme similar to that used for astrocytomas may be used (6–8). If the tumor shows anaplasia of its glial component, it is considered an anaplastic ganglioglioma (grade III) and tends to behave in a more aggressive fashion (9–11). Low-grade gangliogliomas are slow-growing tumors that generally have a favorable prognosis unless occurring in a nonresectable location (4, 12).

Gangliogliomas are more common in children and young adults and usually present with seizures (13–15). Because of the indolent nature of most gangliogliomas, patients often have a long history of seizure disorder. Few patients present with a focal neurologic deficit or evidence of increased intracranial pressure. Gangliogliomas can occur throughout the neuraxis but are most commonly found in the temporal lobe (1, 2, 4, 5, 11, 15).

Several articles have documented the features of ordinary gliomas and other tumors at positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) and thallium chloride Tl 201 single-photon emission computed tomography (^{201}Tl-SPECT) (16–22). These studies reported a direct correlation between glucose metabolism seen on FDG-PET studies

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From the Departments of Radiological Sciences (P.K.K., S.M.E.), Pathology (S-H.P.), and Radiation Oncology (B.W.G.), UCLA Center for the Health Sciences, Los Angeles.

Address reprint requests to Suzie M. El-Saden, MD, Department of Radiological Sciences, BL-122, University of California Los Angeles, Center for the Health Sciences, 10833 LeConte Ave, Los Angeles, CA 90095.

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Antibodies used in immunohistochemical studies

Antibody	Clonality	Source	Dilution	Control Tissue
Synatophysin	Monoclonal	DAKO	1:200	Brain
NSE	Polyclonal	DAKO	1:200	Brain
SMI 31 (NF)	Monoclonal	Sternberger	1:1000	Brain
GFAP	Polyclonal	BioGenex	Prediluted	Brain

Note.—NSE, neuron-specific enolase; NF, neurofilament; GFAP, glial fibrillary acidic protein; SMI 31, Sternberger mouse monoclonol, 2 phosohorylated neurofilament (DAKO Corp, Carpenteria, CA; Sternberger monoclonal, Inc, Devon, UK; Biogenex, San Ramon, CA).

or activity seen on ^{201}Tl-SPECT scans and glioma grade and, subsequently, patient prognosis. A few case reports of low-grade gangliogliomas that include FDG-PET findings also exist in the literature (23–25). In these cases, the tumors each showed hypometabolism on FDG-PET scans. To date, however, no large clinical series of gangliogliomas have been evaluated with respect to their appearance on PET or SPECT scans.

In this retrospective analysis, we emphasize the preoperative findings on FDG-PET and ^{201}Tl-SPECT scans as they compare with histologic grade in a series of 11 cases of surgically treated, pathologically proved gangliogliomas. We also sought to determine the capability and accuracy of CT and MR imaging in predicting tumor grade in comparison with nuclear medicine studies. To this end, we chose to evaluate the CT and MR studies for conventional features of malignancy (ie, presence of tumor enhancement and associated edema).

Methods

Clinical Characteristics

Thirty-four patients with pathologically proved ganglioglioma were treated at our institution from 1969 to 1996. Eleven of these patients underwent preoperative FDG-PET and/or ^{201}Tl-SPECT and constitute our study group. The clinical charts of these patients were reviewed with regard to the patients' age, presenting signs and symptoms, age at pathologic diagnosis, and clinical outcome. Telephone interviews were conducted to obtain current follow-up information on patients who had not been seen recently at our institution.

Of the 11 patients, five were male and six were female. The median age at pathologic diagnosis was 22 years (range, 10 to 64 years). The median duration of symptoms before pathologic diagnosis was 8 years (range, 3 months to 28 years). Overall, 10 (91%) of the 11 patients presented with epilepsy. One patient presented with headache.

Radiologic Technique

Preoperative radiologic studies included MR imaging, CT, FDG-PET, and ^{201}Tl-SPECT. Nine patients had FDG-PET, three patients had ^{201}Tl-SPECT, and all had either CT or MR imaging. All of the CT and MR studies were initially interpreted by a neuroradiologist and reviewed for the presence of tumor enhancement and peritumoral edema by one of two authors. MR imaging performed at our institution was done on a 1.5-T magnet.

A nuclear medicine physician originally interpreted the FDG-PET scans of relative cerebral glucose metabolism and the ^{201}Tl-SPECT scans of cerebral blood flow and tumor activity. A neuroradiologist reviewed all PET and SPECT imaging reports and available scans. PET studies were performed after intravenous administration of 10 mCi/kg (adults) or 0.14 mCi/kg (children) of FDG. Scanning was performed on either a Siemens CTI 931 or 831 scanner and included 15 axial images of the brain at 6.75-mm intervals. FDG-PET scans were evaluated by visual inspection of glucose metabolism within the lesion in comparison with gray and white matter. If a tumor showed metabolic activity greater than or equal to gray matter it was labeled as hypermetabolic, suggesting high tumor grade. If a tumor showed metabolic activity less than or similar to white matter it was labeled as hypometabolic or isometabolic, respectively. Hypometabolism or isometabolism in a tumor suggests a low or intermediate tumor grade according to prior published reports comparing FDG-PET results with glioma tumor grade (16–22).

^{201}Tl-SPECT scans were obtained with a Siemens Orbiter, model 75, camera. Scanning was performed in the axial, sagittal, and coronal planes 5 minutes after intravenous injection of 4 mCi of ^{201}Tl. Preparatory to analyzing the ^{201}Tl-SPECT scans, two regions of interest were drawn, one over the lesion and the other in a corresponding location in the contralateral cerebral hemisphere, and computer-derived ratios of average number of counts/pixel per second were obtained. Ratios of tumor activity to contralateral brain activity of 1.5 or greater were considered to represent increased activity, suggesting high tumor grade. The ratio of 1.5 was chosen on the basis of prior studies correlating glioma tumor grade with activity on ^{201}Tl-SPECT scans (26).

Histopathologic Methods

A neuropathologist reviewed the surgical pathologic and biopsy specimens. Routine staining and immunohistochemical studies using commercially available primary antibodies in conjunction with the Vectastain Elite avidin-biotin complex kit (Vector) were carried out in paraffin-embedded sections. Primary antibodies included those against synaptophysin, neuron-specific enolase, neurofilament, and glial fibrillary acidic protein (GFAP) (see Table). Appropriate positive and negative control studies were performed in each case (Table). The tumors were graded by their glial component using the Daumas-Duport criteria for grading of astrocytoma (8). Subsequently, the tumors were grouped into two categories as either low-grade or high-grade ganglioglioma. Low-grade ganglioglioma corresponds to astrocytoma (grades I and II) in the WHO classification (6, 7). High-grade ganglioglioma includes anaplastic ganglioglioma and ganglioglioma with glioblastoma multiforme. Histologically, the former corresponds to astrocytoma grade III, and the latter to grade IV of the WHO classification.

Results

Imaging Findings

Most patients had tumors located in the periphery of the cerebrum, especially the temporal lobe (82%). One of these tumors was very large and extended into the frontal lobe as well. The other 18% (two cases) were in the occipital lobe.

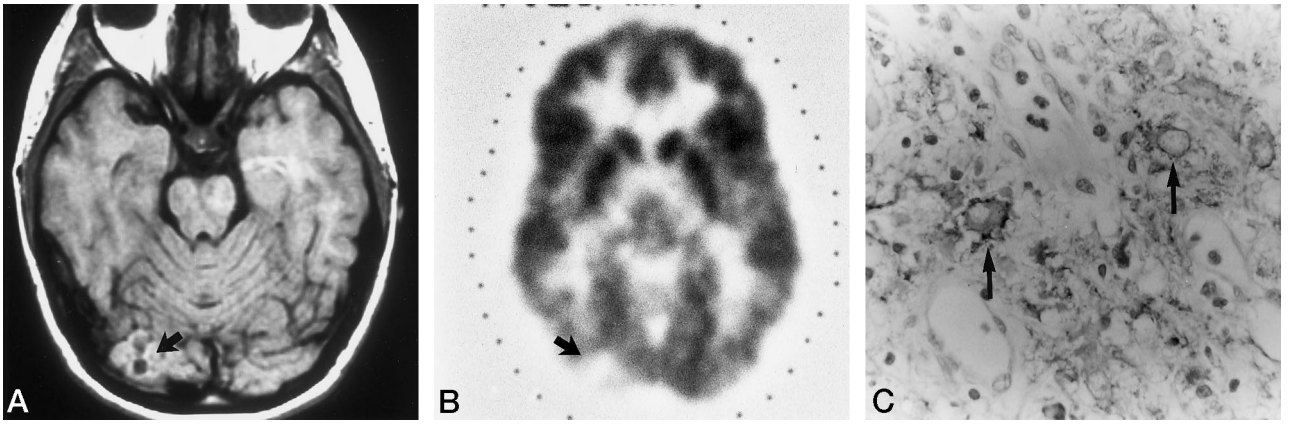

FIG 1. 22-year-old woman with seizures.

A, Axial T1-weighted (550/19/2) MR image shows a small hypointense mass in right occipital lobe (*arrow*).

B, FDG-PET scan shows hypometabolism in the right occipital pole (*arrow*), corresponding to location of this tiny low-grade ganglioglioma.

C, Photomicrograph of low-grade ganglioglioma. Synatophysin immunostain shows immunoreactivity in cytoplasm of ganglion cells with punctate accentuation along the cytoplasmic membrane (*arrows*) and granular immunoreactivity in the background neuropil (synatophysin immunostain with hematoxylin counterstain, original magnification ×400).

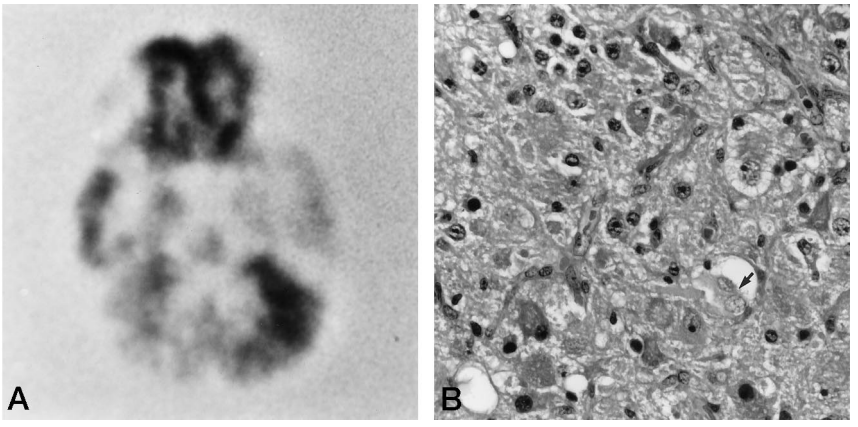

FIG 2. 10-year-old girl with an 8-year history of seizures.

A, Axial image from an FDG-PET scan shows a large region of hypometabolism in the left temporal lobe. Note also the remote effect of hypometabolism in the right cerebellar cortex, known as cross cerebellar diaschisis, a finding occasionally seen in association with cerebral lesions.

B, Photomicrograph of low-grade ganglioglioma. The tumor is composed of a mixture of moderately atypical ganglion cells and astrocytic cells. Some of the ganglion cells are binucleate (*arrow*), strongly suggestive of neoplastic transformation (hematoxylin-eosin, original magnification ×400).

Nine patients had preoperative FDG-PET examinations and three patients had ^{201}Tl-SPECT studies. The 11 patients underwent a total of 15 nuclear medicine scans, two of which were performed postoperatively for evaluation of tumor recurrence. Eight patients had a total of 10 FDG-PET scans, two patients had a total of three ^{201}Tl-SPECT scans, and one patient had both. In 10 of the 11 preoperative FDG-PET studies, an area of hypometabolism or ametabolism corresponding to the location of the tumor was seen (Figs 1 and 2). In the 11th case, the PET scan showed normal relative glucose metabolism (isometabolism) in the area of the tumor. All the patients scanned with FDG-PET had low-grade gangliogliomas. Two of the three patients who were imaged with ^{201}Tl-SPECT had high-grade gangliogliomas, both of which showed increased tumor activity (Fig 3C and D). One of these patients had a repeat scan after subtotal tumor resection that again showed increased activity in the residual tumor. The third patient who had a ^{201}Tl-SPECT study of the brain had a normal scan and a low-grade ganglioglioma.

On CT and MR studies, four gangliogliomas showed enhancement. Of these, two were high-grade anaplastic gangliogliomas and two were low-grade gangliogliomas. The patterns of enhancement were variable. One high-grade tumor showed relatively homogeneous solid enhancement (Fig 3B) and the other showed heterogeneous internal enhancement. Of the low-grade tumors, one had nodular enhancement and the other had a thin rim of marginal enhancement. The two high-grade gangliogliomas in this series also showed peritumoral edema at CT and MR imaging (Fig 3A). None of the nine low-grade gangliogliomas was associated with any significant edema pattern.

Histopathologic Findings

All 11 tumors showed the histologic characteristics diagnostic of ganglioglioma; namely, the presence of both neoplastic neuronal (ganglion) and neoplastic glial components (Figs 1–3). Immunohistochemical stains for neurofilament, neuronal-specific enolase, GFAP, and synaptophysin were used. The tumors were graded using the Daumas-Duport criteria for grading of astrocytomas (8). Nine of the specimens were subsequently categorized as low-grade ganglio-

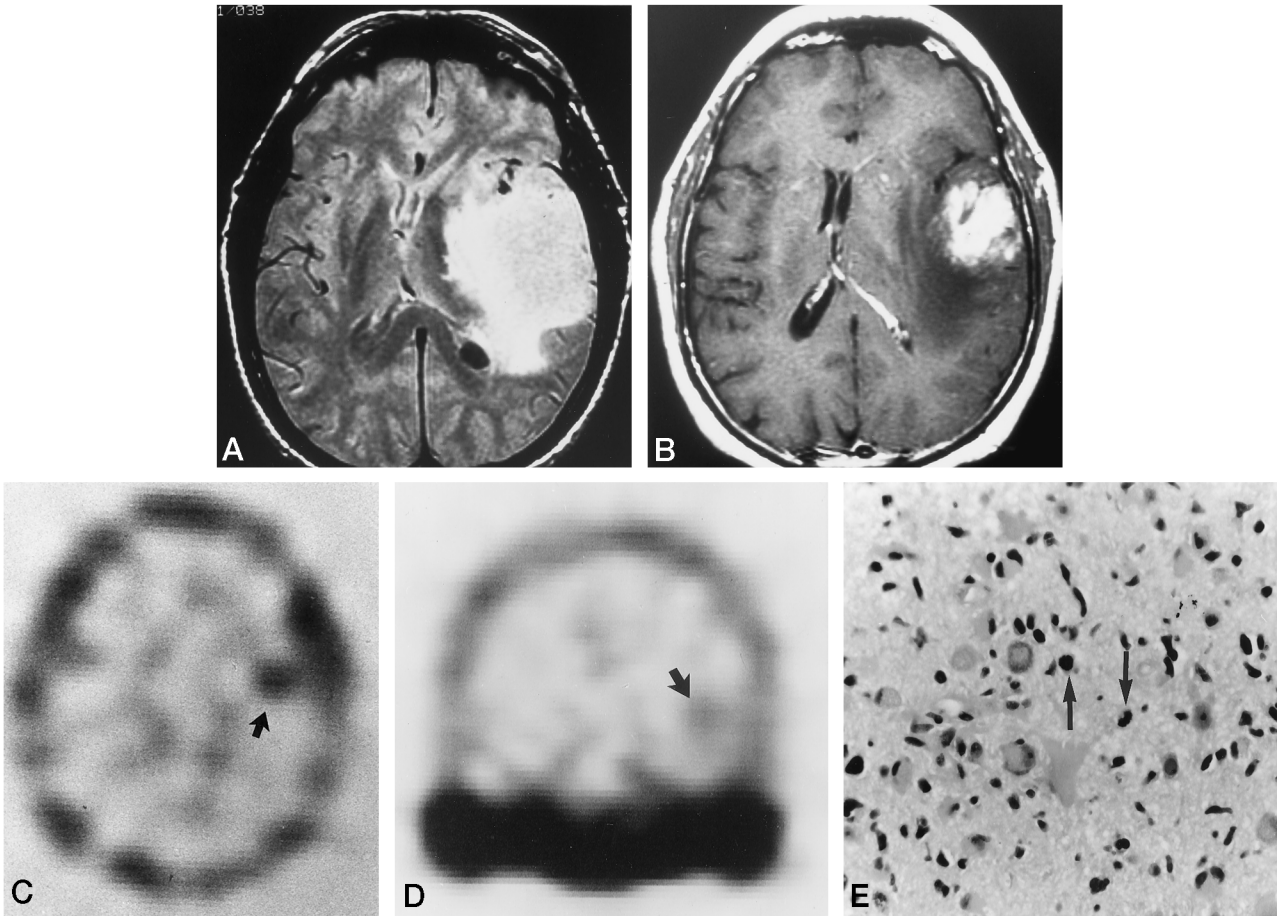

FIG 3. Anaplastic ganglioglioma of the temporal lobe.

Axial proton density–weighted (2200/30/1) (*A*) and contrast-enhanced T1-weighted (550/16/2) (*B*) MR images show solid tumor enhancement and significant peritumoral edema.

Axial (*C*) and coronal (*D*) ^{201}Tl-SPECT scans show increased thallium uptake (ratio $>$ 1.5) at the site of the tumor (*arrows*).

E, Photomicrograph of high-grade ganglioglioma. The tumor shows two components, ganglion cells and astrocytes; however, nuclei of astrocytic cells are pleomorphic and hyperchromatic. Two mitoses (*arrows*) are seen in this field (hematoxylin-eosin, original magnification $\times$400).

glioma (82%). Of these 11 low-grade gangliogliomas, the glial components were subclassified as low-grade astrocytoma in six, low-grade oligoastrocytoma in two, and low-grade oligodendroglioma in one. The remaining two specimens were high-grade gangliogliomas (18%). These high-grade tumors may also be categorized as anaplastic ganglioglioma or as ganglioglioma with grade 3 anaplasia of the astrocytic component.

Radiologic and Clinical Follow-up

Postoperative studies (CT or MR imaging) performed for the evaluation of residual tumor, recurrent tumor, or progression of disease were obtained in all patients. Time to follow-up scanning ranged from the same day as surgery to more than 5 years after surgery (mean, 31 months). Three of the patients had tumor on late follow-up scans, two of whom had recurrence of an anaplastic ganglioglioma. The third patient with tumor seen on the follow-up study had undergone a subtotal resection of a low-grade ganglioglioma because of its involvement of eloquent brain tissue (basal ganglia).

Clinical follow-up intervals ranged from 15 months to 7 years (mean, 4 years). The majority of patients have done very well after treatment, with marked improvement or complete resolution of epilepsy. Many patients remain seizure free on lower doses of seizure medication, and doses are being gradually tapered with the goal of drug discontinuation. The two patients with high-grade gangliogliomas had poor outcomes. One patient had continued growth of tumor on follow-up studies; he subsequently had his care transferred to another institution and was lost to follow-up. The other patient in whom an initial diagnosis of anaplastic ganglioglioma was made also had progression of tumor on follow-up studies, prompting a second operation. In the interim, this tumor evolved histologically from anaplastic ganglioglioma to glioblastoma multiforme, and the patient subsequently died.

Discussion

Clinical Characteristics

Gangliogliomas are rare tumors of the CNS. Reported frequency varies among series, ranging from

0.4% to 3.8% (1–5). The prevalence is higher in children, as great as 14% in some large pediatric series (13–15). Generally considered a tumor of children and young adults, up to 80% of gangliogliomas are seen in patients younger than 30 years old (2). In this series, roughly 64% were diagnosed within the first three decades of life. The tumor can occur at any age, with ranges reported in the literature from 20 days to 80 years (2). We found a roughly equal sex predilection, similar to previous reports (1, 4, 27), although other published series describe both male (2, 13, 15) and female (5) preponderance.

In this series, the time from symptom onset to pathologic diagnosis ranged from 3 months to 28 years, similar to other studies (1, 2, 4, 27). Epilepsy is, by far, the most common clinical presentation of ganglioglioma (1–5, 10, 11, 13–15, 27, 28), and was the presenting symptom in 91% of our patients. Focal neurologic deficits and signs of increased intracranial pressure are less common. A presentation with focal neurologic deficit has been reported to correspond to tumor located in the parietal lobe or in deeper locations, such as the thalamus, brain stem, or spinal cord (29). The fact that epilepsy is the main clinical presentation of ganglioglioma in part reflects its typical temporal lobe location. In our series, 82% of the tumors were located in the temporal lobe, 18% were in the occipital lobe, and one tumor extended from the temporal lobe into the frontal lobe. Many of the tumors involved cortex, probably contributing to the tumor's epileptogenic effect.

Pathologic Characteristics

Ganglioglioma is histopathologically diagnosed on the basis of findings of a neoplasm of mixed cellularity, composed of both neoplastic neuronal and glial elements. Ganglion cells make up the neuronal component whereas the glial component is astrocytic in most cases (2, 9, 12). Less commonly, the glial component is oligodendroglial; rarely, it is ependymal. Other tumors or lesions that are similarly composed of neuronal and glial elements and that constitute the histopathologic differential diagnosis include gangliocytoma, desmoplastic infantile ganglioglioma, dysembryoplastic neuroepithelial tumor, central neurocytoma, and cortical dysplasia (6, 7).

Miller et al (9) published a series of 63 gangliogliomas in 1993 and demonstrated that four histopathologic "features represent important clues to the correct diagnosis: 1) clusters of large cells potentially representing neurons (without such cells the tumor cannot be classified as a ganglioglioma); 2) no perineuronal clustering of the glial cells around the alleged neoplastic neurons; 3) fibrosis (desmoplasia); and 4) calcification." These authors concluded that tumors meeting these criteria require confirmation by special stains to distinguish them from other gliomas. A recently developed monoclonal antibody marker for synaptophysin has proved to be a sensitive and specific stain for neurons and neoplastic ganglion cells seen in ganglioglioma (9, 12). Astrocytic components may be verified by immunoreactivity with GFAP (2, 9, 12).

Gangliogliomas are graded as either ganglioglioma (low grade) or anaplastic ganglioglioma (high grade) (6, 7). The presence of malignant features is almost always confined to the astrocytic component of the tumor. In this series, the glial component was graded on the basis of standard histopathologic criteria used for astrocytomas (Daumas-Duport) (8). An anaplastic ganglioglioma, then, possesses features consistent with at least a grade III astrocytoma within its glial component. In our series, 18% of the gangliogliomas met or exceeded these criteria (ie, showed either anaplasia or frank glioblastoma multiforme). Low-grade gangliogliomas accounted for 82% of the cases, with the most common histopathologic subclassification of the glial component being low-grade astrocytoma.

Radiologic Characteristics

The histologic grade of gliomas has been reported to correlate with metabolic activity on FDG-PET and ^{201}Tl-SPECT scans (16–22). Until now, only isolated case reports of gangliogliomas have been published that incidentally include information on nuclear medicine findings (23–25). In this series of 11 gangliogliomas, we demonstrated a definite correlation between histologic grade and tumor metabolic activity on FDG-PET and ^{201}Tl-SPECT scans. Of the nine low-grade gangliogliomas in this study, none showed increased metabolic activity on FDG-PET scans, a finding that has previously been associated with high-grade tumors (16–22). Unfortunately, the two patients in our series with histologically proved high-grade gangliogliomas did not undergo FDG-PET scanning preoperatively. These patients instead had ^{201}Tl-SPECT scanning that showed increased tumor activity relative to normal brain (ratio greater than 1.5). Only one patient had both FDG-PET and ^{201}Tl-SPECT scanning. This patient had a low-grade ganglioglioma that was hypometabolic on PET and showed normal activity on ^{201}Tl-SPECT scans. Taken together, these findings represent a 100% correlation between histologic tumor grade and results of nuclear medicine scanning. That is, tumors that showed increased activity on ^{201}Tl-SPECT (ratio $>$ 1.5) were high grade and tumors that showed isometabolism or hypometabolism on FDG-PET or had decreased or normal activity on ^{201}Tl-SPECT were low grade. Therefore, findings at preoperative nuclear medicine scanning with FDG-PET and/or ^{201}Tl-SPECT can positively predict histologic grade of ganglioglioma and, thereby, patient outcome.

We found that CT and MR imaging data were also somewhat helpful in predicting tumor grade, although less consistent than the nuclear medicine scan results. We found an excellent correlation between the presence of edema and high histologic grade of tumor (two of two). Conversely, none of the low-grade gangliogliomas showed surrounding edema. These results

suggest that the presence of edema in association with a ganglioglioma may predict a higher tumor grade.

Overall, four gangliogliomas enhanced (36%). Histologically, these enhancing tumors were divided evenly between low and high grade. We are well aware that the small numbers in this study preclude any meaningful statistical analysis of the data. However, the combined presence of both peritumoral edema and tumor enhancement on the CT and MR studies of ganglioglioma may yield greater accuracy in the prediction of high tumor grade.

Conclusion

A combined radiologic approach to gangliogliomas will be of greater prognostic utility and accuracy in the preoperative evaluation. CT and MR imaging offer the best anatomic resolution, with MR imaging having the advantage or multiplanar display, which is especially helpful in evaluating temporal lobe lesions, a common location of gangliogliomas. FDG-PET and ^{201}Tl-SPECT techniques provide accurate preoperative assessment of tumor grade. Low-grade gangliogliomas uniformly showed hypometabolism or isometabolism on FDG-PET scans and decreased or normal activity on ^{201}Tl-SPECT scans in our series. Moreover, they showed no perilesional edema and variable enhancement on CT and MR studies. Clinically, low-grade gangliogliomas behave in a benign fashion, are typically curable by surgery, and carry an excellent prognosis. High-grade gangliogliomas showed increased activity (ratios greater than 1.5) on ^{201}Tl-SPECT scans and were associated with both the presence of peritumoral edema and tumor enhancement on CT and MR studies. High-grade gangliogliomas may evolve further to glioblastoma multiforme and typically have a poor clinical prognosis.

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