Perspectives In Neuroscience

A Quarterly Publication for Continuing Medical Education

Central Illinois Neuroscience Foundation

Date or Original Release: April 1, 2001

Surgery of Brain Tumors Part I: Low Grade Astrocytomas

Emilio M. Nardone, M.D.

Division of Neurosurgery, Central Illinois Neuroscience Foundation

This quarterly publication is designed for primary care physicians, neurosurgeons, neurologists, neuroradiologists, and other practitioners. The purpose of this publication is to provide these physicians with current management strategies for dealing with a variety of disorders and conditions in the neurosciences, and to provide up-to-date diagnostic and prognostic information written by specialists in the field. It is estimated that it will take the physician 1 hour to complete the activity. The 10 questions at the end of each lesson are designed to test and evaluate the participants' comprehension of the topic. This CME program is sponsored by the Central Illinois Neuroscience Foundation and funded by grants and donations. This CME activity was planned in accordance with the essentials for Continuing Medical Education set forth by the Illinois State Medical Society. The Central Illinois Neuroscience Foundation is accredited by the Illinois State Medical Society to sponsor continuing medical education for physicians. The Central Illinois Neuroscience Foundation designates this activity for a maximum of 1 hour of Category I credit towards the American Medical Association's Physician Recognition Award. It is the intent of the Central Illinois Neuroscience Foundation to assure that its educational mission, and Continuing Medical Education activities in particular, is not influenced by the special interests of individuals associated with its program.

Dr. Emilio Nardone has no financial arrangements or affiliations that would constitute a conflict of interest with any corporate organization and this sponsoring institution.

OBJECTIVES

At the conclusion of this CME Activity, the participant should be able to:

1. Describe the behavior of low grade brain tumors.
2. Identify the current treatment modalities available to a patient with a low grade glioma.
3. Understand the expected prognosis associated with these types of tumors.

INTRODUCTION

The concept of a brain tumor is, for most individuals and physicians, one of the most dramatic forms of human illness. Brain tumors are the second most common form of malignancy in children and have a dramatic effect on their families. Among adults, primary tumors of the brain rank from 6th to 8th in frequency of all neoplasms. Metastatic tumors have become a more common complication of systemic cancer as methods for control of primary cancers become more effective. The advent of AIDS and immunosuppression associated with organ transplants have led to an increased incidence of lymphomas of the brain as well.

Although primary brain tumors account for only 2% of cancer deaths, they are responsible for 20% of malignant tumors diagnosed before the age of 15. In western society, about 30% of deaths are due to cancer. At autopsy, 1 in 5 cancer deaths will demonstrate intracranial metastatic deposits.

The revolutionary advances that have occurred in neuroimaging have led to an increased detection rate of brain tumors and a major increase in efficacy of surgical management. This is based on the exquisite detail of anatomical relationship afforded by modern imaging techniques. Additionally, there is evidence from epidemiologic studies that brain tumors are becoming increasingly more prevalent, especially as the population ages, and this increase appears to be in excess of the improvement of detection rates.

There has been an explosion in neurosciences related to molecular biology and genetics of brain tumors that should stimulate major advances in neuro-oncology. The advent of gene therapy is an exciting therapeutic frontier with major possibilities.

CLASSIFICATION

The original brain tumor classification was defined by Bailey and Cushing in 1929. Kernohan subsequently modified the approach to gliomas in 1951. He divided the gliomas into four grades showing an increasing degree of malignancy passing from grade I through IV. It clearly established the inverse relation between tumor grade and duration of survival. This general outline was maintained by the World Health Organization (WHO). In 1979 the WHO standardized the nomenclature of most human tumors, and in 1993 it expanded the classification of brain tumors. (Table 1)

GLIOMAS

The most common varieties of gliomas are astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, pylocytic astrocytoma, oligodendroglioma, and ependymoma.

Astrocytoma (WHO grade II)

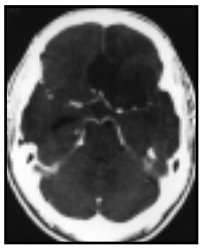
Astrocytoma (also called low grade astrocytoma) is a tumor of young adulthood with a median age of 35 years and a slight male predominance. Although it can involve all parts of the brain, the frontal and temporal lobes have been the most common locations. As with other brain tumors, low grade astrocytomas may produce signs and symptoms by several mechanisms:

1. By direct infiltration into and destruction of the neurons within a given area of the brain;
2. By local pressure upon neighboring structures;
3. By producing a generalized increase in intracranial pressure (ICP).

Headache, lethargy, and personality changes are the most common symptoms produced by the third mechanism. The finding of papilledema is useful when it occurs in the setting of acute raised ICP or chronic raised ICP as caused by space occupying lesion(s).

The nature of the focal neurological deficit produced by local infiltration of tumor cells will depend on the location of the lesion. By far the most common presenting symptom is an epileptic seizure, which has been reported to occur in more than 50 % of all low grade astrocytoma patients.

The diagnostic procedures of choice are CT and MRI. Intraoperative ultrasonography is extremely helpful in outlining the extent of the lesion and guiding safe surgical resection. The typical CT scanning imaging of low grade astrocytomas reveals a non-enhancing lesion whose density is lower than that of the surrounding brain. (Figure 1)



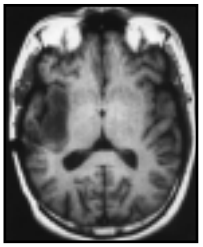


Figure 2 (left) *Typical MRI appearance of a low grade astrocytoma involving the right temporal-insular area. This T1-weighted image shows the tumor as decreased attenuation compared to surrounding brain.*

Figure 1 (above) *Post-contrast CT scan image of a typical low grade astrocytoma involving the left frontal and temporal lobes. The area shows decreased density compared to surrounding brain with no contrast enhancement. Note the enhancement of the major vessels of the brain.*

Table 1. World Health Organization proposed new classifications of CNS tumor

I. Tumors of neuroepithelial tissue
A. Astrocytic tumors
1. Astrocytoma; variants: fibrillary, protoplasmic, gemistocytic, mixed
2. Anaplastic (malignant) astrocytoma
3. Glioblastoma; variants: giant cell glioblastoma, gliosarcoma
4. Pilocytic astrocytoma
5. Pleomorphic xanthoastrocytoma
6. Subependymal giant cell astrocytoma
B. Oligodendroglial tumors
1. Oligodendroglioma
2. Anaplastic oligodendroglioma
C. Ependymal tumors
1. Ependymoma; variants: cellular papillary, epithelial, clear cell, mixed
2. Anaplastic (malignant) ependymoma
3. Myxopapillary ependymoma
4. Subependymoma
D. Mixed Gliomas
1. Mixed oligo-astrocytoma
2. Anaplastic (malignant) oligo-astrocytoma
3. Others
E. Choroid plexus tumors
1. Choroid plexus papilloma
2. Choroid plexus carcinoma
F. Neuroepithelial tumors of uncertain origin
1. Astroblastoma
2. Polar spongioblastoma
3. Gliomatosis cerebri
G. Neuronal and mixed neuronal-glial tumors
1. Gangliocytoma
2. Dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos
3. Desmoplastic infantile ganglioglioma
4. Dysembryoplastic neuroepithelia tumor
5. Ganglioglioma
6. Anaplastic ganglioglioma
H. Pineal tumors
1. Pineocytoma
2. Pineoblastoma
3. Mixed pineocytoma/pineoblastoma
I. Embryonal tumors
1. Medulloepithelioma
2. Neuroblastoma; variant: ganglioneuroblastoma
3. Ependymoblastoma
4. Retinoblastoma
5. Primitive neuroectodermal tumors (PNET) with multipotential differentiation neuronal, astrocytic, ependymal, muscle, melanocytic, etc.
a. Medulloblastoma; variants: desmoplastic, medullomyoblastoma, melanocytic medulloblastoma
b. Cerebral (supratentorial) and spinal PNETs

II. Tumors of cranial and spinal nerves
A. Schwannoma (syn: neurilemmoma, neurinoma) variants: cellular, plexiform, melanotic
B. Neurofibroma; variants: circumscribed (solitary), plexiform, mixed neurofibroma/schwannoma
C. Malignant peripheral nerve sheath tumor (MPNST) (syn: neurogenic sarcoma, anaplastic neurofibroma, malignant schwannoma) variants: epithelioid, MPNST with divergent mesenchymal and/or epithelial differentiation, melanotic

III. Tumors of the meninges
A. Tumors of meninothelial cells
1. Meningioma
Histologic types:
a. Meningothelial (syncytial)
b. Transitional/mixed
c. Fibrous (fibroblastic)
d. Psammomatous
e. Angiomatous
f. Microcystic
g. Secretory
h. Clear cell
i. Chordoid
j. Lymphoplasmacyte-rich
k. Metaplastic variants (xanthomatous, myxoid, osseous, chondroid)
2. Atypical meningioma
3. Anaplastic meningioma; variants of a-k above, papillary
B. Mesenchymal, non-meningothelial tumors
Benign
1. Osteocartilagenous tumors
2. Lipoma
3. Fibrous histiocytoma
4. Others
Malignant
1. Mesenchymal chondrosarcoma
2. Malignant fibrous histiocytoma
3. Rhabdomyosarcoma
4. Meningeal sarcomatosis
5. Others
C. Primary melanocytic lesions
1. Diffuse melanosis
2. Melanocytoma
3. Malignant melanoma; variant: meningeal melanomatosis
D. Tumors of uncertain origin
1. Hemangiopericytoma
2. Capillary hemangioblastoma

IV. Hemopoietic neoplasms
1. Malignant lymphomas
2. Plasmacytoma
3. Granulocytic sarcoma
4. Others
V. Germ cell tumors
1. Germinoma
2. Embryonal carcinoma
3. Yolk sac tumor (endodermal sinus tumor)
4. Choriocarcinoma
5. Teratoma; variants: immature, teratoma with malignant transformation
6. Mixed germ cell tumors

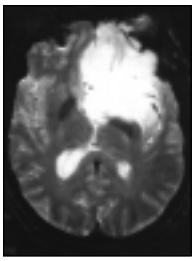
VI. Cysts and tumor-like lesions
A. Rathke's cleft cyst
B. Epidermoid cyst
C. Dermoid cyst
D. Colloid cyst of the third ventricle
E. Enterogenous cyst (syn: neuroenteric cyst)
F. Neuroglial cyst
G. Other cysts
H. Lipoma
I. Granular cell tumor (syn: choristoma, pituicytoma)
J. Hypothalamic neuronal hamartoma
K. Nasal glial heterotopias

VII. Tumors of the anterior pituitary
A. Pituitary adenoma
B. Pituitary carcinoma

VIII. Local extensions from regional tumors
A. Craniopharyngioma; variants: adamantinomatous, squamous papillary
B. Paraganglioma (syn:chemodectoma)
C. Chordoma; variant: chondroid chordoma
D. Chondroma
E. Chondrosarcoma
F. Adenoid cystic carcinoma (syn: cylindroma)
G. Others

IX. Metastatic tumors

On MRI they typically appear as non-enhancing low density areas on T1-weighted images, whereas there is almost always an increase in signal intensity on T2-weighted images. (Figure 2-3). A low grade glioma will be hypometabolic and therefore 'cold' on PET scanning. The typical histopathological feature is of rather plump astrocytes with unusually swollen cytoplasm. (Figure 4)



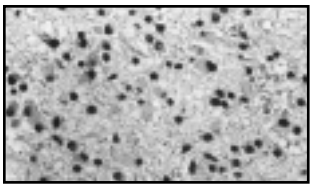


Figure 4 (above) *High power microscopic view of a low grade astrocytoma with plump astrocytes and swollen cytoplasm.*

Figure 3 (above left) *MRI appearance of a low grade astrocytoma involving the left frontal- temporal area spreading to deep cerebral structures. This T2-weighted image shows the tumor as high attenuation area compared to surrounding brain. Note how the lesion merges with the surrounding brain structures with no clear margins.*

It is well known that more than 50 % of low grade astrocytomas contain areas of anaplasia within the tumor. This consideration highlights the importance of tissue sampling. A low grade lesion with anaplastic foci within it follows the clinical behavior of its more malignant component.

The frequency of dedifferentiation, or change to a more malignant form, has also been very well studied. At the time of recurrence, more than 85% of the tumors were classified either as anaplastic astrocytomas or glioblastoma multiforme.

SURGICAL MANAGEMENT

The overall management plan for the patient diagnosed as having a low grade astrocytoma is controversial. A general rule of surgical oncology is that surgery should be carried out as early in the course of the malignancy as possible. However, many authors would agree that it has not been proven that earlier treatment of a low grade astrocytoma produces an increase in life span as measured from the time of diagnosis. Furthermore, because more and more patients are having their tumors detected while they are neurologically intact, and because operative intervention in some locations carry a significant risk of postoperative morbidity, some have made the case that surgery should be delayed in lesions that do not show a change in appearance on sequential radiological studies. More recently the goal of 'gross total' resection of the lesion has been supported by most authorities. In fact, life span seemed to be prolonged in such patients by preventing earlier recurrence and dedifferentiation.

One of the most important factors in surgical outcome is the operator experience in dealing with these lesions and with all possible adjuvant techniques. Versatility with the use of intraoperative ultrasound, cortical mapping and stimulation, neuro-navigation, awake craniotomy, and ultrasonic aspirator is definitely an important aspect of this type of surgery.

The possible surgical options include stereotactic biopsy, craniotomy for open biopsy or subtotal resection, and craniotomy for gross total resection.

Stereotactic biopsy

Advantages

Stereotactic biopsy has the advantage of being minimally invasive and well tolerated. Deeply located lesions can be easily reached with no disruption of adjacent areas.

Disadvantages

Because of possible tumor grade variability within the lesion itself and the small core sampling achievable with this technique, it may not reflect the possible higher-grade areas within the tumor that were not included in the biopsy. For this reason multiple biopsies directed into different areas of the tumor are generally performed. Disadvantages of multiple biopsies include its lack of effect on progress and the increase in vascular injury when the target is near a vascular structure.

Open biopsy or subtotal resection

Advantages

An open procedure usually avoids the potential tissue sampling error associated with stereotactic biopsy.

Disadvantages

It is a little more invasive than a stereotactic biopsy but usually well tolerated. Its main disadvantage is related to the lack of tumor resection.

Gross total resection

Advantages

There is evidence that survival is improved when the tumor is grossly excised. Seizures can become better controlled.

Disadvantages

Increased risk of neurological complications related to a more aggressive surgery.

In summary, a craniotomy for gross total resection should always been pursued if, according to location and size, the tumor can be safely excised. Otherwise stereotactic biopsy with multiple samplings would be the procedure of choice being minimally invasive, well tolerated and could be done on outpatient basis, making it also economically advantageous.

RADIATION THERAPY

Perhaps the most controversial area in the treatment of low grade astrocytomas is the question of whether post-operative radiation therapy should be used as an adjunctive form of treatment. The reason for this controversy is the lack of randomized, controlled, prospective clinical trials. Present guidance is based on major retrospective studies that have been published to date since no single neurosurgeon's experience is adequate to properly answer this question.

Though there is no general consensus on the efficacy of radiation therapy for the treatment of low grade astrocytomas, many reports in the literature demonstrate that post-operative radiation therapy at the dose of 50-60 Gy is beneficial in extending survival. Further studies are needed to provide a better understanding of the role of radiation therapy for low grade astrocytomas since our current assumption is based on retrospective, ill-defined studies.

Another important consideration when recommending radiation therapy to patients with low grade astrocytomas is the analysis of its potential side effects. The link between cognitive deficits and whole brain radiation in young and potentially long surviving patients is well known to neuro-oncologists. The development of radiation necrosis ranges between 1.5% at 55 Gy to 4% at 60 Gy.

CHEMOTHERAPY

At the present time, it appears that there is no proven beneficial effect of chemotherapy in the treatment of patients with low grade astrocytomas; however, ongoing trials are currently re-evaluating the plausibility of the potentially promising treatment modality.

OUTCOME

An algorithm has been developed for the treatment of low grade astrocytomas based on literature review and personal experience (Table 2).

Two studies indicate a current median survival of 7.5 years, with a 5-year survival of approximately 65% and a 10-year survival of approximately 40%. A retrospective analysis of 102 patients with histological diagnosis of low grade astrocytomas presented this year at the Fourth Congress of the European Association of Neuro-oncology showed a 5-year survival of 78% and a 10-year survival of 62%.

Pilocytic astrocytoma (WHO Grade I)

Pilocytic astrocytomas occur most frequently in children and young adults. They arise at all levels of neuroaxis, however, these tumors are characteristically located in the midline structures, e.g., cerebellum, third ventricular region, optic pathways, brainstem and spinal cord. Compared to the diffusely infiltrating astrocytomas previously discussed, pilocytic astrocytomas are less biologically aggressive, relatively well-circumscribed tumors, which displace rather than infiltrate the surrounding brain. The most common form of pilocytic astrocytoma is the one involving the cerebellum. This accounts for 55% of low grade astrocytomas in childhood and usually presents with clinical features related to hydrocephalus. These include headache (usually bifrontal and occipital), nausea, vomiting, somnolence, papilledema, and sixth nerve palsy.

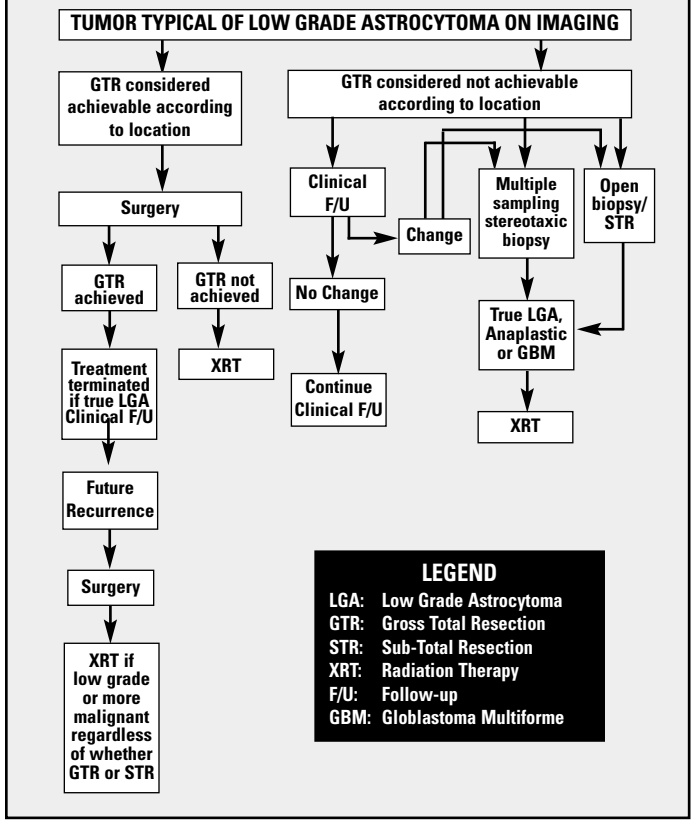
CT and MRI show a tumor arising from within the vermis or cerebellar hemispheres. Typically there is a large cyst with a single enhancing mural nodule, although they can have multiple cysts or be completely solid. The solid component enhances briskly. (Figures 5-6-7-8)

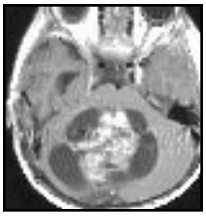
Surgery is the most valid treatment option for these lesions. If the tumor can be safely and completely removed, the chance for a cure is high. This is usually achievable in cerebellar pilocytic astrocytomas that do not involve the brain stem. Long-term survival beyond 10 years is not an uncommon feature even with subtotal resections.

Adjuvant therapies in the form of radiation and/or chemotherapy are usually reserved for recurrences into a more malignant grade or for resilient, non-resectable lesions that continue to show growth potentials.

Table 2.

Algorithm for the Treatment of Low-Grade Astrocytomas





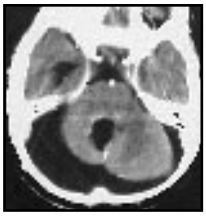
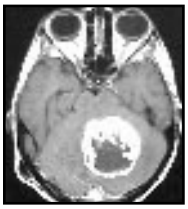


Figure 5. (left) *Post-contrast MRI shows large midline posterior fossa pilocytic astrocytoma. Multiple cysts surround the enhancing lesion.*

Figure 6. (above right) *Post-operative CT scan shows complete resection of the lesion with cerebrospinal fluid filling the space left by the tumor. Note that the fourth ventricle is seen again.*



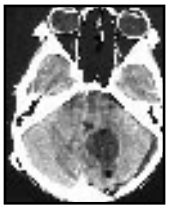


Figure 7. (far left) *Post-contrast MRI shows a large posterior fossa pilocytic astrocytoma with cyst within it. Note the brisk enhancement.*

Figure 8. (right) *Immediate post-operative CT scan demonstrating complete resection of the tumor and the opening of the fourth ventricle. Note the presence of air bubbles within the tumor's bed. CT and MRI show a tumor arising from within the vermis or cerebellar hemispheres. Typically there is a large cyst with a single enhancing mural nodule, although they can have multiple cysts or be completely solid. The solid component enhances briskly (Figures 5-8) of the solid part of the tumor.*

CME ACCREDITATION

The Central Illinois Neuroscience Foundation is accredited by the Illinois State Medical Society to sponsor continuing medical education for physicians.

CME CREDIT DESIGNATION

The Central Illinois Neuroscience Foundation designates this educational activity for a maximum of 1.0 hour in Category 1 Credit towards the AMA Physicians Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

TO RECEIVE CME CREDIT

To receive CME credit for this activity, please return a copy of this page via mail or fax with the requested information and completed answers by October 1, 2001 to: Central Illinois Neuroscience Foundation, 1015 South Mercer Avenue, Bloomington, IL 61701; Fax: (309) 663-2344. Your answers will be graded by the author and the corrected form will be returned with your CME certificate.

Continuing Medical Education Questions

1. Brain tumors are the second most common malignancy in children.
   ❑ True ❑ False
2. Low grade astrocytomas are most common among elderly people.
   ❑ True ❑ False
3. Low grade astrocytomas frequently present with seizures.
   ❑ True ❑ False
4. Low grade astrocytomas usually show no contrast enhancement of MRI and CT.
   ❑ True ❑ False
5. Low grade astrocytomas never change into a more malignant form.
   ❑ True ❑ False
6. Gross total resection of these tumors can improve survival and seizure control.
   ❑ True ❑ False
7. Stereotactic biopsy is a valid option for diffusely infiltrating tumors.
   ❑ True ❑ False
8. Radiation therapy plays a controversial role in the treatment of low grade astrocytomas
   ❑ True ❑ False
9. A five-year survival is rarely seen in low grade astrocytomas.
   q True q False
10. Pilocytic astrocytomas are most common in children and their surgical resection may lead to high chance of cure.
    ❑ True ❑ False

Spring 2001

Perspectives In Neuroscience

_____
Last Name

_____
First Name

_____
Address

_____
City/State/Zip

_____
Telephone ME Number

Actual Time Spent Completing this Activity _____

Test Responses

1)	T	F	6)	T	F
2)	T	F	7)	T	F
3)	T	F	8)	T	F
4)	T	F	9)	T	F
5)	T	F	10)	T	F

Educational Activity Assessment

1. Did this issue meet the stated learning objectives?
   ❑ Yes ❑ No
2. On a scale of 1 to 5, with 5 being the highest, how do you rank the quality of this educational activity?
   ❑ 5 ❑ 4 ❑ 3 ❑ 2 ❑ 1
3. Did you receive any evidence of bias for or against any commercial products? If yes, please explain.
   ❑ Yes ❑ No
4. On a scale of 1 to 5, with 5 being the highest, how do you rank the effectiveness of this activity, as it pertains to your practice?
   ❑ 5 ❑ 4 ❑ 3 ❑ 2 ❑ 1

Please state any topics that you would like to see discussed in future issues of **Perspectives in Neuroscience**

_____
_____
_____

BIBLIOGRAPHY

1. Albright AL, Pollack IF, Adelson PD, editors. Principles and Practice of Pediatric Neurosurgery. New York (NY): Thieme; 1999.
2. Greenberg MS. Handbook of Neurosurgery. 4th ed. Lakeland (FL): Greenberg Graphics, Inc.; 1997.
3. Burger PC, Scheithauer BW. Atlas of Tumor Pathology, Tumors of the Central Nervous System. Washington (DC): Armed Forces Institute of Pathology (Universities Associated for Research and Education in Pathology, Inc.); 1994.
4. Schmidek HH, editor. Schemidek & Sweet Operative Neurosurgical Techniques. Indications, Methods, and Results. 4th ed, Vol 1. Philadelphia (PA): WB Saunders Company, 2000.
5. Kaye AH, Laws, ER, editors. Brain Tumors. An Encyclopedic Approach. New York (NY): Churchill Livingstone, 1995.

COPYRIGHT PERMISSION

This Continuing Medical Education publication was sponsored and funded by the Central Illinois Neuroscience Foundation through grants and donations.

EDITOR: Ann R. Stroink, M.D., Director of CME
ASSISTANT EDITOR: Jennifer Johns
CME ADVISOR: Susan M. Farner, Ph.D.
GRAPHIC DESIGNER: Diane Uhls

central illinois NEUROSCIENCE FOUNDATION

1015 S. Mercer • Bloomington, IL 61701

Non-Profit Org.
U.S. Postage
PAID
Normal, Illinois
Permit No. 44