

# Glioblastoma



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# Multiforme FROM BIOLOGY TO TREATMENT

**G**LIOMASTOMA IS THE MOST COMMON PRIMARY BRAIN TUMOR IN ADULTS. NEARLY 12,000 CASES ARE DIAGNOSED ANNUALLY IN THE UNITED STATES.<sup>3</sup> GLIOMASTOMA MULTIFORME (GBM) IS A MALIGNANT, RAPIDLY GROWING, PULPY OR CYSTIC TUMOR OF THE CEREBRUM OR THE SPINAL CORD.<sup>1</sup> IT IS ALSO CALLED ANAPLASTIC ASTROCYTOMA, GLIOMA MULTIFORME.<sup>2</sup>

GLIOMASTOMA IS BELIEVED TO ARISE FROM CELLS CALLED ASTROCYTES. GLIOMASTOMAS USUALLY PROGRESS AT THE SITE OF ORIGINAL GROWTH, BUT CAN TRAVEL TO OTHER PARTS OF THE BRAIN. THE LESION SPREADS WITH PSEUDO PROJECTIONS. IT IS COMPRISED OF A MIXTURE OF MONOCYTES, PYRIFORM CELLS, IMMATURE AND MATURE ASTROCYTES, AND NEURAL ECTODERMAL CELLS WITH FIBROUS OR PROTOPLASMIC PROCESSES.

In addition, glioblastomas, like other forms of brain tumors, can infiltrate normal brain tissue. This infiltration makes complete removal of glioblastomas virtually impossible, thereby necessitating other forms of therapy. Despite aggressive therapy, less than 5% of these patients are expected to live more than five years. Traditionally, treatment has consisted of maximal surgery followed by radiation therapy and chemotherapy. However, new advances in treatment have allowed for improvements in tumor control and in quality of life.

### Causes of the disease

GBM, the extreme expression of anaplasia among the glial neoplasms, accounts for 40% of all primary intracranial tumors.<sup>5</sup> Although no exact cause has been discovered for the disease, there are particular studies that have linked a cause with GBM. The charts of 100 patients with established diagnoses of GBM provided the data for a descriptive study of the patients' exposure to herbicides.<sup>9</sup> The study focused on place of residence and occupation prior to GBM diagnosis. Although the subjects reported residence in 33 of the 75 counties in Arkansas, more than one-third of the sample came from just three counties in which rice, cotton, or wood products are produced.

These industries were reported as the occupations of almost one-third the sample from which occupations involved a risk of herbicide expo-

sure. Radiation-induced gliomas are uncommon, with only 73 cases on record to date. The disease that most frequently occasioned radiation therapy has been lymphoblastic leukemia. A case of transmission of a GBM from the donor to a kidney transplant recipient in the absence of a previous ventriculosystemic shunt is described.<sup>3</sup>

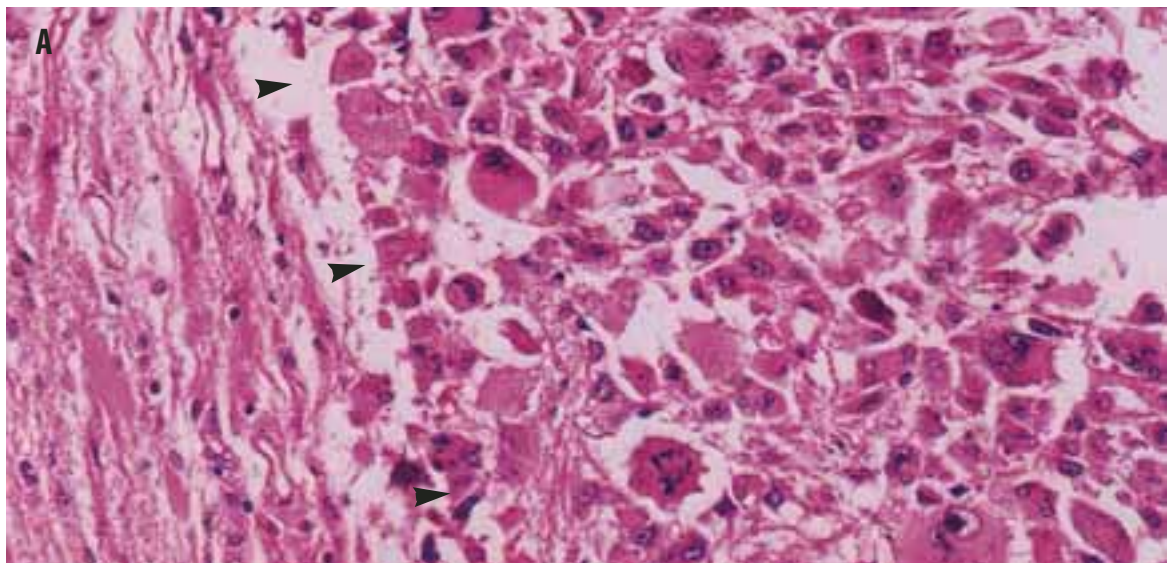
The recipient was a 48-year-old woman who developed a fever with no other associated symptoms 17 months post transplant. Physical examination revealed a large nonpulsatile mass on the upper pole of the donor kidney. Histopathological examination showed a highly cellular neoplasm with fusiform and globoid cells, a high grade of nuclear pleomorphism and mitosis, necrosis with pseudopalisading and vascular proliferation. Therefore, the risk of tumor transmission from donors with primary central nervous system tumors to kidney transplant recipients is real and should be considered when evaluating a graft mass in such patients.

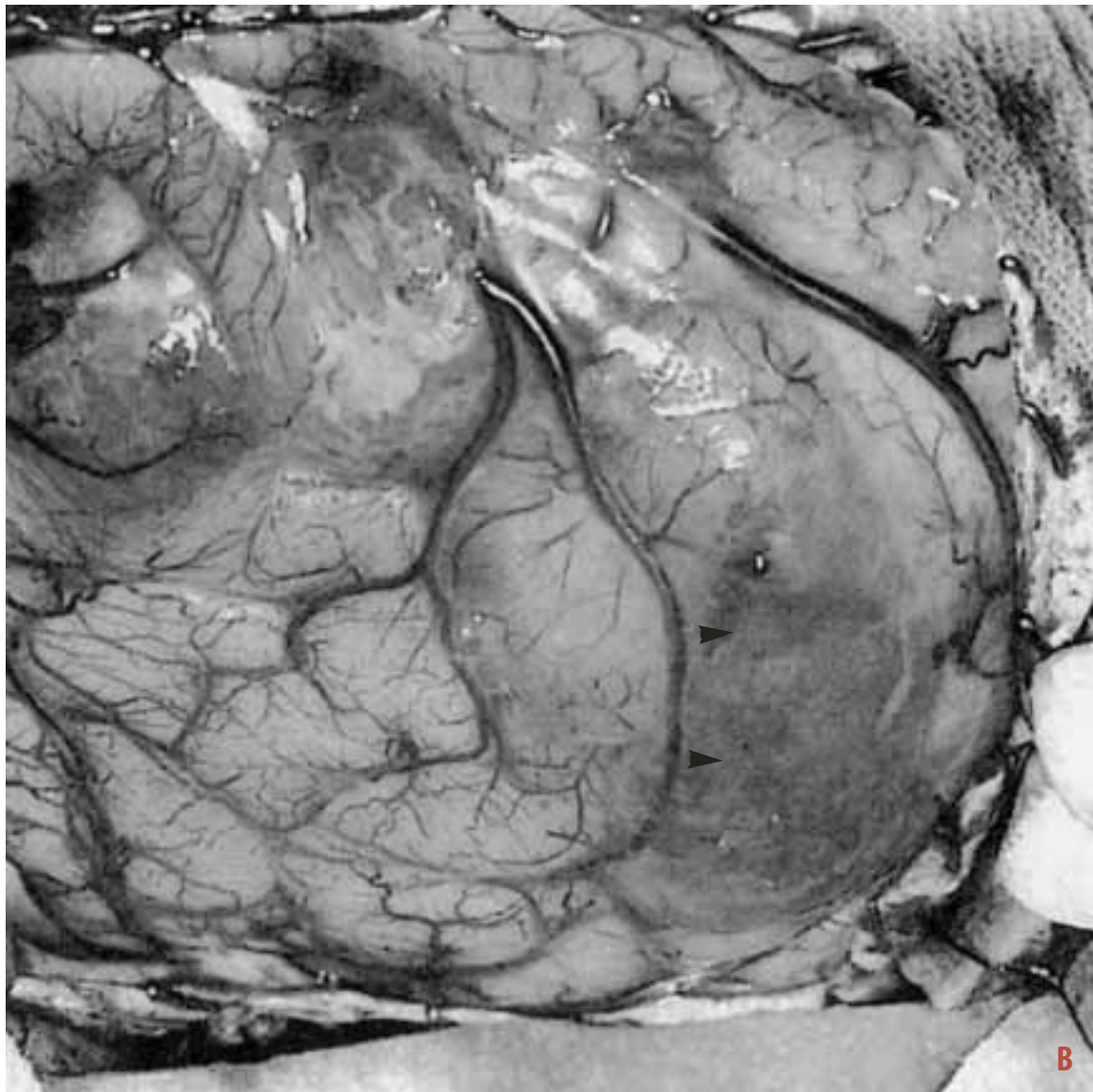
### Manifestations of the disease

Glioblastoma multiforme, beginning more often in the white matter, appears to be well demarcated because the surrounding brain is compressed, swollen, and edematous. The neoplasm is usually firmer than the adjacent tissue (Figure 1a-c). Its surface has a variegated gray, white, yellow (necrotic), and reddish brown (hemorrhagic) appearance. These colors are imported

## FIGURE 1

- ⊕ Micrograph demonstrating the border of the tumor, which consists of a rapid transition (following the arrows) from a solid, cellular zone of pleomorphic infiltrate to a compressed and edematous white matter.





**FIGURE 1**

ⓐ Intraoperative photograph showing the cortical involvement of glioblastoma. The tumor produces irregular thickening and discoloration of the gyri. (See arrows.) Many glioblastomas are not apparent on gross external examination.

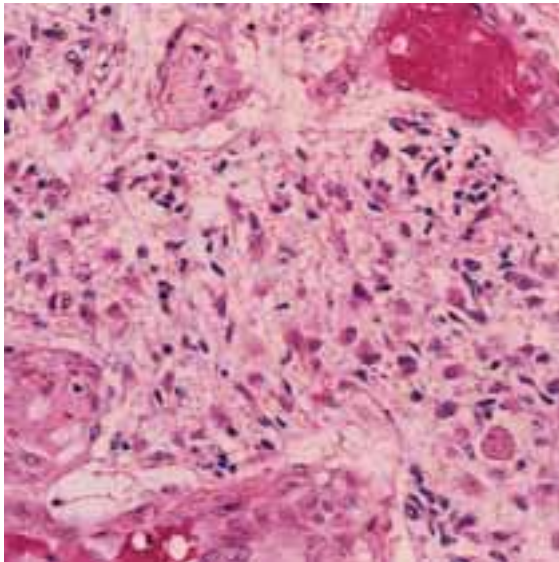
ⓑ Anatomic specimen showing the left middle temporal gyrus enlarged by the tumor (at arrow). The left temporal lobe is swollen.

by multiple areas of recent and remote hemorrhage and necrosis. The microscopic appearance of these lesions is characterized by profuse numbers of pleomorphic and frequently bizarre cells (Figure 2). Among these are many cells with enlarged and irregular nuclei (Figure 3). Some cells can be identified by their processes as being of astrocytic origin (Figure 4). Other cells may be small with oval, hyperchromatic nuclei resembling the undifferentiated small cells of a bronchogenic carcinoma<sup>2</sup> (Figure 5). In other areas, there may be large cells with irregular large, vesicular nuclei and with an abundant eosinophilic cytoplasm suggesting an origin from gemistocytic astrocytes.<sup>2</sup> In many areas



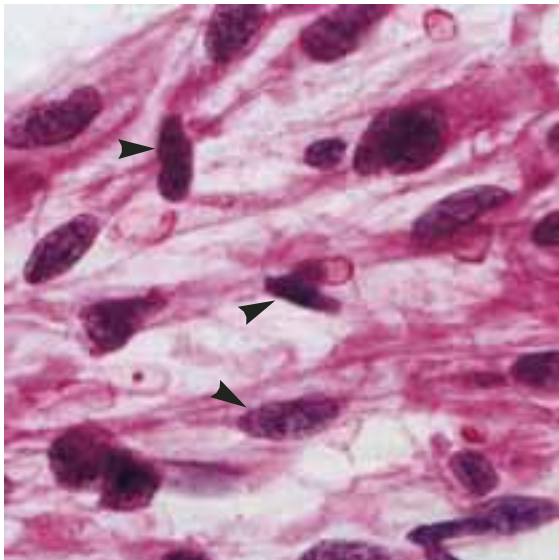
## FIGURE 2

Micrograph showing pleomorphism, increased cellularity, vascular hypertrophy and endothelial proliferation.



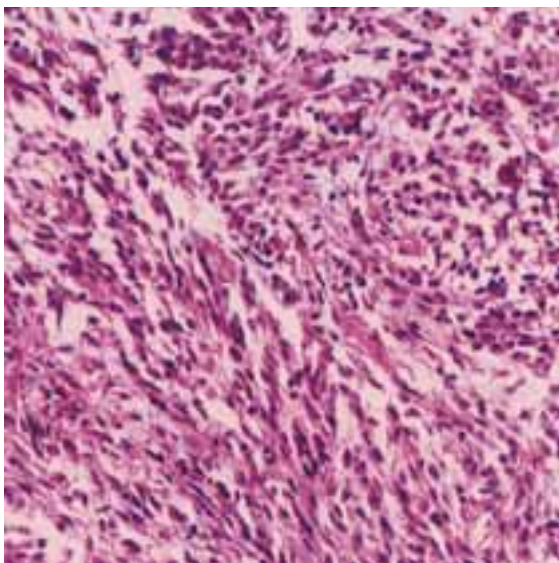
## FIGURE 3

Micrograph of characteristic features of glioblastoma. Note the elongated nuclei and bipolar processes shown by the arrows.



## FIGURE 4

Micrograph showing bipolar cells characteristic of fibrillary astrocytes with prominent processes.



within the neoplasm, one may find bizarre, multinucleated cells with abundant cytoplasm resembling strap cells of rhabdomyosarcomas.

Mitoses, often abnormal, are usually easily found either in clusters or spread fairly regularly throughout the neoplasm. In many regions within the neoplasm are large and small areas of necrosis, often with a garland of small cell nuclei at the periphery. Blood vessels are greatly increased in the number and usually show endothelial adventitial hypertrophy and hyperplasia<sup>7</sup> (Figure 6a-b). Occasionally, vessels with these changes are found well beyond the apparent microscopic limits of the neoplasm.

### Signs and symptoms of the disease

The patient who is diagnosed with glioblastoma multiforme has several signs and symptoms associated with the neoplasm.<sup>6</sup> In a general aspect, there is an increased intracranial pressure. The increase in ICP causes nausea, vomiting, headache, and papilledema. There are mental and behavioral changes associated with the disease. There are altered vital signs as follows: increased systolic pressure, widened pulse pressure, and respiratory changes. Speech and sensory disturbances are found with the disease. Children with GBM present with the above symptoms, plus the added symptoms of irritability and projectile vomiting.

On more of a locality aspect, a lesion on the midline of the brain would produce a headache, bifrontal or bioccipital, which is worse in the morning hours and manifests by coughing, straining, or sudden head movements. A growth in the temporal lobe would produce psychomotor seizures. Focal seizures are present in patients with a lesion in the central region of the brain. If the neoplasm is on the optic or oculomotor nerves, there are visual defects appreciated. Finally, a GBM lesion of the frontal lobe would cause abnormal reflexes and motor responses.

### Course of the disease

Characteristically, GMB infiltrates extensively, frequently crossing the corpus collosum and producing a bilateral lesion likened to a butter-

fly in its gross configuration (Figure 7a-b). Although any glioma may “dedifferentiated” to the level of GMB, in practice, the majority of these lesions manifest some evidence of astrocytic differentiation.<sup>4</sup>

GMB may occur at any age but it is most common in the adult years, with a peak incidence during the fifth and sixth decades. Glioblastoma may arise anywhere along the neuraxis, but it is most common in the cerebral hemispheres. In contrast, a predilection for the brain stem is apparent in those arising in childhood.

### Secondary diagnosis of the disease

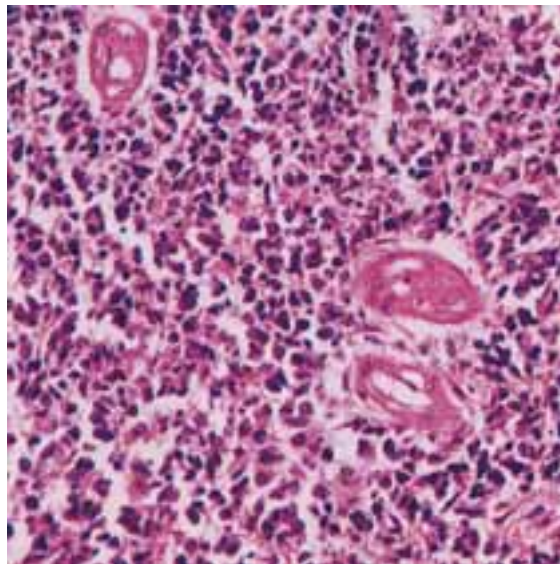
Diagnostic procedures for brain tumors include physical and neurological examinations, visual field and fundoscopic examination, CT scans and MRI, skull X-rays, technetium brain scans, electroencephalography, and cerebral angiography.

Physical examination is used to assess motor and sensory function. Since the visual pathways travel through many areas of the cerebral lobes, detection of visual field defects can provide information about the location of the tumor. A fundoscopic examination is done to determine the presence of papilledema.

CT scans have become the screening procedure of choice for diagnosing and localizing brain tumors as well as other intracranial masses. MRI scans may be diagnostic when a CT scan does not detect a clinically suspected tumor (Figure 8). Skull X-rays are used to detect calcified areas within a neoplasm or erosion of skull structures due to tumors.

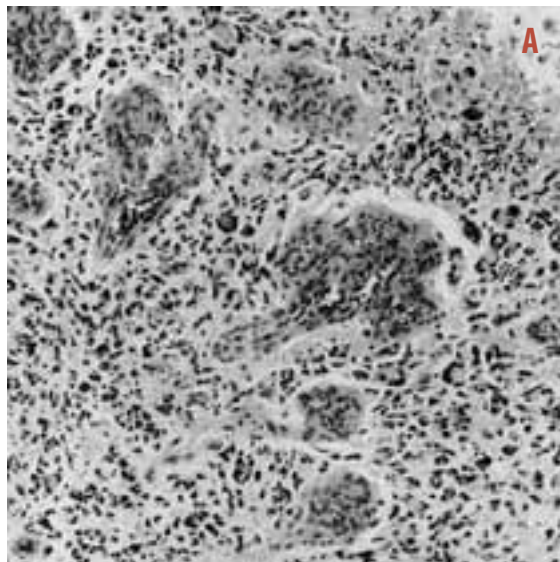
Brain tumors tend to disrupt the blood-brain barrier; as a result, the uptake of a radioactive isotope used in brain scans is increased within a tumor. About 70% of persons with a brain tumor have abnormal electroencephalograms; in some cases, the results of the test can be used to localize the tumor.<sup>4</sup> Cerebral angiography can be used to locate a tumor and visualize its vascular supply.

Scintigraphy using Indium-111-labeled anti-EGRf-425 has become useful in diagnosing GBM. In a study, 28 patients with intracranial neoplasms were injected with an average dose of 2.2 mCi of EGRf-425.<sup>9</sup> The immunoscintigra-



**FIGURE 5**

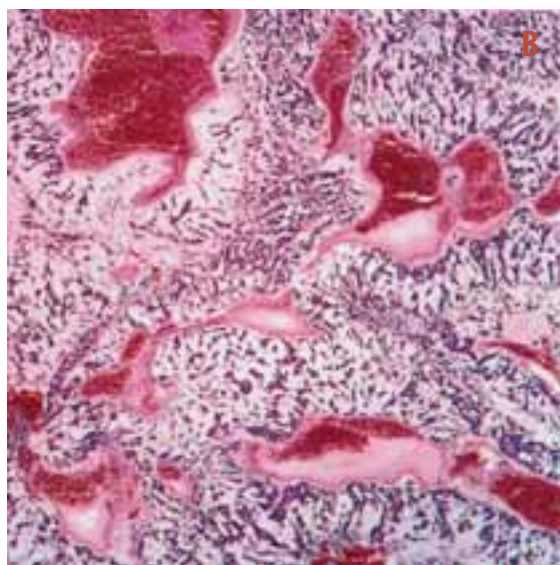
Micrograph showing the central zone of densely cellular small-cell glioblastoma with hyperchromatic nuclei and barely visible cytoplasm.



**FIGURE 6**

⊗ Micrograph showing bipolar cells characteristic of fibrillary astrocytes with prominent processes.

⊗ An unusual histologic pattern in glioblastoma is this gland-like configuration of the tumor cells in which there are large intercellular spaces.



## FIGURE 7

- Ⓐ Gross photograph of a typical untreated case of glioblastoma. The classic “butterfly” configuration, is necrotic hemorrhagic mass.
- Ⓑ Coronal section of a pathology specimen showing massive involvement of the splenium of the corpus callosum by a glioblastoma with bilateral white matter extension.

phy findings were generally in agreement with the CT findings. The definite diagnosis was established by biopsy findings.

### Prognosis, survival rates, and treatments

The prognosis of patients with GBM is very poor. Although with recent advances in treatment of this neoplasm, the life expectancy of a patient with this disease without treatment is approximately 18 weeks. Radical surgery in conjunction with radical chemo and radiation therapy has increased the median survival rate to 62 to 72 weeks.

Surgery is part of the initial management of virtually all brain tumors. The development of microsurgical neuroanatomy, the operating

microscope, the fusion of imaging systems with resection techniques, advanced stereotactic and ultrasound technology, and intraoperative monitoring of evoked potentials have all served to improve the effectiveness of surgical resection. However, removal may be limited by the localization of the tumor and its invasiveness. Stereotactic surgery uses three-dimensional coordinates and CT and MRI to localize a brain lesion precisely.

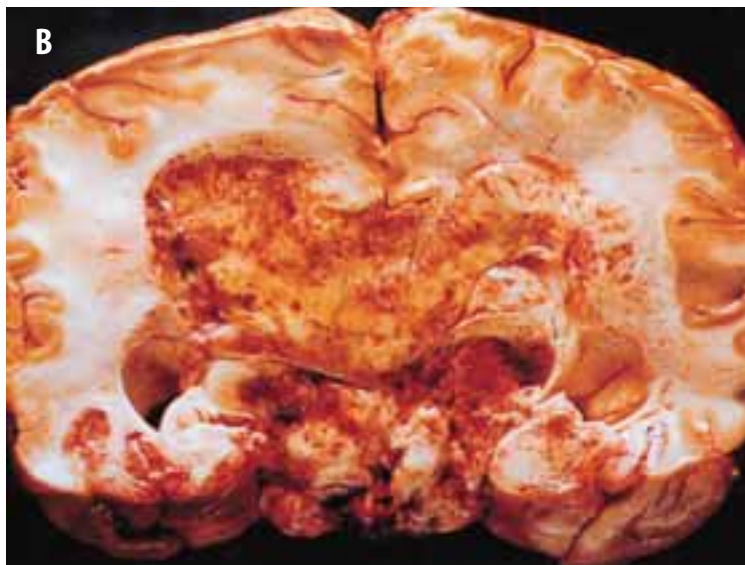
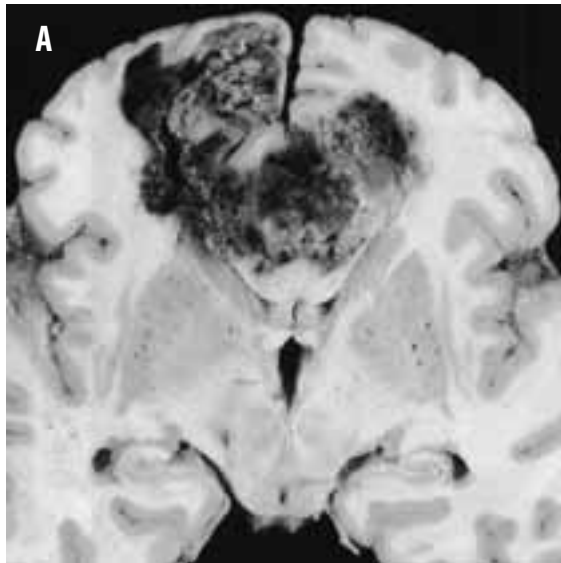
Ultrasound technology has been used for localizing and removing tumors. The ultrasonic aspirator, which combines a vibrating head with suction, permits atraumatic removal of tumors from cranial nerves and important cortical structures. Intraoperative monitoring of evoked potentials is a prudent adjunct to some types of surgery.

Most malignant brain tumors respond to external radiation. Radiation can increase longevity and, at times, can allay symptoms when tumors recur. The treatment dose depends on the tumor’s histologic type, radioresponsiveness and the anatomic site and level of tolerance of the surrounding tissue. Stereotactic radiosurgery, such as the Gamma Knife®, allows specific irradiation of the glioma. Narrow beams of radiation specifically target only the glioma. The normal brain is spared and does not receive significant exposure.

The use of chemotherapy for brain tumors is somewhat limited by the blood-brain barrier. Chemotherapeutic agents can be administered intravenously, intra-arterially, intrathecally, or intraventricularly. Improved delivery of chemotherapeutic agents through the use of a biodegradable anhydrous wafer impregnated with the drug polifeprosan 20 with carmustine implanted into the tumor bed at the time of surgery shows promise. However, new classes of antitumor drugs targeting cell motility and angiogenesis (most notably thalidomide) are either in development or in clinical trials.<sup>10</sup>

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## About the author

Jeffrey J Cortese is a graduate of Baker College of Mount Clemens, Michigan, and has been certified since 1997. He works full time at Mount Clemens General Hospital, and part time at St. Joseph Mercy of Macomb Hospital. He is a member of AST's Neurosurgery Advisory Panel. Jeff was a speaker at AST's 33rd Annual National Conference in Las Vegas in May 2002.

## References

1. Galnze WD, Anderson LE, Anderson K. *Mosby's Medical Nursing, and Allied Health Dictionary*. 4th ed. St Louis, Mo: Mosby-Year Book, Inc; 1994: 675.
2. Rubin R, Farber JL. *Pathology*. Baltimore, Md: Lippincott-Raven Publishers; 1988: 1470.
3. Smith-Rocker JL, Garrett A, Hodged LC, Shue V. Prevalence of glioblastoma multiforme subjects with prior herbicide exposure. *Journal of Neuroscience Nursing*. October 1992; 24(5):260-4.
4. Salvati M, Artico M, Caruso R, Rocchi G, Orlando ER, Nucci. A report of radiation-induced gliomas. *Cancer*. January 1991;67(2): 392-7.
5. Val-Bernal F, Ruiz JC, Cotorruelo JG, Arias M. Glioblastoma multiforme of donor origin after renal transplantation: report of a case. *Human Pathology*. November 1993; 24(1): 1256-1259.
6. Baldonado AA, Stahl DA. *Cancer Nursing—A Holistic Multidisciplinary Approach*. 2nd ed. Garden City, NJ: Medical Examination Publishing Company, Inc; 1980:232-235.
7. Hensen DE, Albores-Saavedra J. *Pathology of Incipient Neoplasia*. 2nd ed. Philadelphia, Pa: WB Saunders; 1993; 530-531.
8. Porth CM. *Pathophysiology*. 4th ed. Baltimore, Md: Lippincott-Raven Publishers; 1994: 1187-9.
9. Mahley MS, Mettlin C, Natarajan N, Laws ER, Peace BB. National survey of patterns of care for brain-tumor patients. *J Neurosurg*. 1989;71:826-836.

Images courtesy of Bon Secours Hospital, Grosse Pointe, Michigan.



**FIGURE 8**

MRI appearance of glioblastoma as seen in the coronal, sagittal, and axial planes.



# Glioblastoma multiforme

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- What percentage does glioblastoma multiforme account for in all primary intracranial tumors?
  - 30%
  - 40%
  - 75%
  - 60%
- Which is characteristic of glioblastoma multiforme?
  - Arises from astrocyte cells
  - Grey, white, yellow, red, or brown appearance
  - Enlarged and irregular cell nuclei
  - All of the above
- Which of the following is NOT a symptom of increase intracranial pressure?
  - Nausea
  - Headache
  - Optic papilla
  - Papilledema
- A growth in the \_\_\_\_\_ of the brain would produce psychomotor seizures.
  - Temporal lobe
  - Cerebral lobe
  - Midline
  - Frontal lobe
- How long is the prognosis in a patient with untreated glioblastoma multiforme?
  - 12 weeks
  - 30 days
  - 1-2 years
  - 18 weeks
- Glioblastoma most commonly arises from white matter of the \_\_\_\_\_.
  - Cerebral hemispheres
  - Pons
  - Midbrain
  - Vermis
- In what age range does GBM most commonly occur?
  - Under 30 years old
  - 30-40 years old
  - 40-50 years old
  - 50-60 years old
- Which type of treatment is affected by the blood brain barrier?
  - Gamma Knife
  - Ultrasonic aspiration
  - Chemotherapy
  - Stereotactic surgery
- Polifeprosan 20 with carmustine is what type of drug?
  - Antibiotic
  - Diuretic
  - Chemotherapeutic
  - Steroid
- Approximately how many cases of glioblastoma multiforme are diagnosed annually?
  - 20,000
  - 5,000
  - 7,500
  - 12,000

## Glioblastoma multiforme

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