Malignant Brain Tumors—A Synopsis

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Brain cancers differ from other neoplasms due to the confines of the closed cranial vault, the comparatively small lethal tumor burden, and the failure of most common brain tumors to metastasize. In addition, different forms of brain cancer have different biologic, kinetic, metabolic and growth characteristics, making it difficult to discuss this field as a single entity.

An estimated 8,500 patients will die of brain cancer this year. The male/female ratio is 57:43 and the crude incidence rate, 4.5/100,000.¹ Tumors of the brain and central nervous system are the second most common cancer in children of both sexes under the age of 15 years, only surpassed in incidence by leukemia. The etiology of intracranial tumors is unknown and only a few cases of relatively rare forms, such as acoustic neurinoma and neurofibroma, appear to be hereditary. The incidence of cerebral metastases from a primary neoplasm elsewhere in the body is probably artifactually low, but will become a more significant problem as greater control of the primary disease begins to prolong life.

The most common brain cancer is the highly malignant glioblastoma multiforme, which accounts for one-quarter of reported cases.² (Table 1.) Malignant astrocytomas probably represent a less malignant form of this tumor. Ependymomas, oligodendrogliomas and medulloblastomas, found in less than two percent of patients, may well be a dif-

| Table 1. Incidence of Brain Tumors |
|-----------------------------------|
| Classifications         | Percent Incidence |
|-------------------------|-------------------|
| Glioblastoma Multiforme | 23.0              |
| Astrocytoma             | 13.0              |
| Ependymoma              | 1.8               |
| Malignant               |                   |
| Oligodendroglioma Glioma| 1.6               |
| Mixed & Other Gliomas   | 1.9               |
| Medulloblastoma         | 1.5               |
| Meningioma              | 16.0              |
| Pituitary Adenoma       | 8.2               |
| Neurilemoma             | 5.7               |
| Craniopharyngioma       | 2.8               |
| Sarcoma                 | 2.5               |
| Hemangioblastoma        | 2.7               |
| Pineal Tumor            | 1.1               |
| Metastatic              | 13.0              |
| Other                   | 6.0               |

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ferent biologic entity entirely. Because of their comparatively long survival rates, pleomorphic characteristics and rarity, these latter forms of brain cancer are difficult to study.

Meningiomas comprise approximately one-sixth of intracranial masses and are among those cancers which best respond to surgical extirpation. Tumors that cannot be completely resected surgically eventually recur and require reoperation. Recurrent meningiomas frequently undergo sarcomatous degeneration and take on more malignant and invasive appearances, thus demanding further aggressive therapy. Pituitary tumors (chromophobe and eosinophilic adenomas) and craniopharyngiomas present a combination of diagnostic, therapeutic and endocrinologic problems outside the scope of this review. Unless specifically noted, the term malignant glioma will be used to describe the group of neuroectodermal tumors that are the most lethal and, unfortunately, most common.

Patients with malignant gliomas have a median survival of less than six months; at the end of one year about 20 percent of patients are alive, and at the end of two years, less than 10 percent have survived. The survival curve is biphasic, with the second portion accounting for less than 10 percent of cases. Malignant glioma is a completely lethal disease.

The age distribution of brain tumors is similarly biphasic. Medulloblastoma, cerebellar astrocytoma and ependymoma, found mainly below the tentorium, have a childhood peak from ages five to nine. An adult peak between the ages of 40 to 60 years is seen predominantly in malignant gliomas and meningiomas, usually above the tentorium.

Depending on the location of the tumor, symptomatology may either be highly localized, i.e. the ophthalmologic and endocrinologic manifestations of pituitary adenomas and craniopharyngiomas, or generalized, such as those indicative of increased intracranial pressure. Headache is the most common finding in malignant glioma, and is the presenting symptom in one-third of patients. (Table 2.) Approximately one-

| Symptoms                  | Percent Presenting Symptoms | Percent Symptoms At Any Time |
|---------------------------|-----------------------------|------------------------------|
| Headache                  | 33.0                        | 67.0                         |
| Seizures                  | 19.0                        | 36.0                         |
| Personality Change        | 12.0                        | 43.0                         |
| Motor Deficit             | 8.5                         | 44.0                         |
| Speech Deficit            | 5.8                         | 27.0                         |
| Visual (II, III, IV, VI)  | 4.5                         | 17.0                         |
| Sensory Deficit           | 4.0                         | 17.0                         |
fifth of patients present with seizures, while personality change is initially noted in 12 percent. Motor dysfunctions, such as ataxia or hemiplegia, are generally not the presenting symptoms; however, they often become apparent during the course of disease. No single symptom may be considered diagnostic of an intracranial tumor, but seizures are always highly suspicious.

The discovery of these symptoms clearly indicates the need for a detailed neurologic examination, starting with noninvasive techniques and proceeding to those that are more hazardous, but more definitive. (Table 3.) A combination of brain scan and electroencephalogram can pinpoint a lesion with more than 90 percent accuracy. (Figs. 1 and 2.) Arteriography is then required to determine more precisely the location and vascular pattern of the tumor. (Figs. 3 and 4.) Pneumoencephalography should be reserved only for unusual cases. Computerized axial tomography in the form of the EMI® scanner is just becoming available, and must still be compared to other diagnostic techniques.

Because of the enormous amounts of data which are stored and reduced to meaningful levels by computer, the CAT scan may become an immensely valuable diagnostic tool.

Definitive surgical resection offers patients the greatest chance for improved survival. It decompresses the already troubled brain, and in a brief period can reduce the tumor burden by one to two log fold, probably a greater reduction than any other single modality of treatment. In addition, definitive resection provides the time necessary to institute adjunctive therapy. Although surgery is associated with morbidity and mortality, current techniques have reduced this risk to a minimum.5

Radiotherapy combined with surgery is a common treatment for malignant gliomas. The most frequently used dose schedule is between 5,000 and 6,000 rads delivered at 1,000 rads a week during a five-day week.6 However, many radiotherapists have individualized approaches which they prefer. There have been too few controlled studies to indicate whether the same effect could

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**Table 3. Neurodiagnostic Tests and Their Relative Accuracy**

| Noninvasive | Percent Accuracy |
|-------------|------------------|
| Skull Film  | 39               |
| Echoencephalogram | 57          |
| Electroencephalogram | 77        |
| Brain Scan  | 85               |
| Computerized Axial Tomography | -        |
| Invasive    |                  |
| Arteriography | 83            |
| Pneumoencephalogram | 88         |

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be achieved with a lower dose, or whether higher doses might be even more effective. Irradiation of brain stem gliomas and medulloblastomas appears to have considerable clinical value; however, the cumulative effects of irradiation preclude repeated utilization and, hence, additional forms of therapy must be sought.

Chemotherapy in patients with brain cancer is a decade behind the sophisticated multimodality therapy currently employed for leukemia and Hodgkin's disease. However, this gap is rapidly closing. Virtually every agent available has been tried, but usually in debilitated patients or those with recurrent disease. Table 4 shows the collective response.
Fig. 3. Arteriogram, anterior-posterior projection, of the skull. Note displacement of the anterior cerebral arteries and abnormal vasculature indicative of the tumor.

Fig. 4. Left lateral arteriogram showing abnormal blood vessels associated with this tumor. The anterior cerebral artery appears to be stretched.

rate of patients with malignant glioma to single agent chemotherapy in Phase II studies. Significant responses appear to have occurred with many agents, but these "responses" and their duration must be clearly defined. Another parameter of response is length of survival, but it is a meaningless indicator when patients begin treatment at various stages of disease.

In a randomized study of 34 patients who received surgical resection and radiotherapy, the use of given 5-FU did not live significantly longer than those who did not receive the drug. Mithramycin was also evaluated in 96 patients with histopathologically proven malignant glioma, who had received standard therapy. Patients were randomized between mithramycin (25 mcg./kg./day IV, over eight hours for 21 days) and no mithramycin. The median survival was 23 weeks, without any differences between groups.

Combined modalities therapy has
been used for many neoplasms and is based on the assumption that synergistic and additive therapeutic potential can be achieved without increased toxicity through the administration of various agents which have different modes of action. BCNU (80 mg. /m²/day IV x three days every six to eight weeks) with and without radiotherapy (5,000-6,000 rads) was compared to the best conventional care in patients who had definitive surgical resection of neuropathologically diagnosed malignant glioma.³ Patients who received at least two doses of BCNU and 5,000 rads of radiotherapy had a median survival of 40.5 weeks, while those who received radiotherapy alone had a median survival of 37.5 weeks. Patients who had at least two courses of BCNU showed a median survival of 25 weeks, and those who received neither radiotherapy nor BCNU (but survived long enough to have received both if they had been prescribed) had a median survival of 17 weeks. It is significant to note that by 18 months, the great majority of patients who received only one mode of therapy had succumbed to their disease, while 25 percent of those who had received BCNU and radiotherapy were still alive.

A preliminary report of a randomized study of BCNU, vincristine and radiotherapy, compared to BCNU and vincristine alone, indicated no significant difference between the two treatment groups.¹⁰ Another preliminary Phase III study evaluating CCNU, with and without radiotherapy, has shown an increase in median survival time to progression of those who received both modes of therapy, but in the interim report there was no statistical difference in survival.¹¹ Phase II drug combination studies have evaluated BCNU and vincristine and found no superiority over BCNU alone.¹² Nor was the combination of CCNU, procarbazine and vincristine superior to either the nitrosourea or procarbazine alone. Current Phase III

| Chemotherapeutic Agent | Number of Patients | Percent Response |
|------------------------|--------------------|-----------------|
| Cyclophosphamide       | 21                 | –               |
| Mechlorethamine        | 23                 | –               |
| Thio-TEPA              | 21                 | 62              |
| Methotrexate           | 21                 | 33              |
| 5-FU                   | 32                 | –               |
| Mithramycin            | 45                 | 47              |
| Bleomycin              | 17                 | 88              |
| Vincristine            | 22                 | 32              |
| Vinblastine            | 46                 | 46              |
| BCNU                   | 69                 | 46              |
| CCNU                   | 63                 | 41              |
| Methyl CCNU            | 27                 | 22              |
| Procarbazine           | 21                 | 48              |
| Epipodophyllotoxin     | 14                 | 43              |
combined modalities studies are now evaluating the newest of the nitroso- 
soureas, methyl CCNU (220 mg./m² orally every six to eight weeks) with and 
without radiotherapy (6,000 rads), com-
pared to radiotherapy with and without 
BCNU (80 mg./m² IV for three days 
every six to eight weeks). Controlled 
Phase II studies are also attempting to 
specifically quantify the therapeutic ef-
ficacy of four single agents which might 
be of value in future Phase III combined 
modalities studies. These include pro-
carbazine, a lipid-soluble drug of tenta-
tive value; streptozotocin, a nitroso- 
urea analogue, and dibromodulcitol, both 
known to cross the blood-brain barrier; 
and Adriamycin, which has already 
shown a broad range of efficacy.

In summary, the treatment of malig-
nant gliomas has come more sharply into 
focus. Controlled and uncontrolled clinical 
trials are generating data which indicate 
that brain cancer may be subjected to 
the same vigorous analytic approach 
which has advanced the treatment of 
other cancers. The value of surgery 
alone compared to surgery plus radio-
therapy and/or chemotherapy is becom-
ing more defined. 5-Fluorouracil and 
mithramycin in conventional doses have 
been shown to be ineffective in the treat-
ment of this disease, while BCNU and 
radiotherapy are of modest, but signifi-
cant value. Further clinical trials are 
necessary to evaluate procarbazine, 
CCNU and methyl CCNU, as well as 
combined modalities therapy for ma-
lignant gliomas and other brain 
cancers.

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