Conferences and Reviews

Practical Guidelines for the Treatment of Malignant Gliomas

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The treatment of patients with malignant gliomas is palliative and encompasses surgery, radiotherapy, and chemotherapy. Outcome measures have demonstrated improvement in both survival and neurologic performance in patients undergoing complete or near-complete tumor resection. After surgery, involved-field radiotherapy (radiotherapy administered to the tumor and to the tissue in a 3-cm radius surrounding the tumor) has been shown to further improve survival rates when given in a total dose of 6000–6500 cGy. Survival is further improved by the coadministration of the chemoradiopotentiator hydroxycarbamide (hydroxyurea). The role of adjuvant or boost stereotactic radiotherapy is unclear, despite its frequent use. In addition, adjuvant chemotherapy has been shown to improve survival rates in approximately one-quarter of patients with glioblastoma multiforme and in the majority of patients with anaplastic astrocytoma. No a priori method exists, however, to predict which patient will benefit from adjuvant chemotherapy. As a consequence, all physiological young patients with good performance status or limited neurologic disability are treated with chemotherapy. The best results of adjuvant chemotherapy are achieved with a nitrosourea chemotherapy, either carmustine (BCNU) or a combination of procarbazine and lomustine (CCNU) and vincristine, known as PCV-3 therapy. Salvage chemotherapy is reserved for patients with tumor progression, some of whom benefit from a re-operation. Occasional patients with recurrent gliomas may be palliated by stereotactic radiotherapy.

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The incidence of primary brain tumors in the United States in adults is approximately 17,000 new cases per year.[1–5] This represents 2% of the estimated 800,000 new cases of cancer occurring in adults per year in the US. Primary brain malignancies in adults are an uncommon cancer with an incidence of 8 cases per 100,000 adults per year. In children, approximately 1,500 new cases of primary brain cancers are seen yearly,[6] which represents 25% of the 6,000 new cases of all pediatric cancer per year in the US. Brain cancer is the second most common childhood malignancy, with an incidence of 2 to 3 cases per 100,000 children per year.

Pathology

Of the estimated 17,000 primary brain tumors occurring annually in the US in adults, approximately 60% are gliomas.[1–5] Of these gliomas, 40% to 50% are glioblastoma multiforme, 30% to 35% are anaplastic astrocytomas, 15% to 20% are well-differentiated gliomas, and 2% to 4% are medulloblastoma. The types of gliomas by frequency of occurrence in adults are meningiomas (20%), pituitary adenomas (15%), and neurinomas or schwannomas (7%). In children, the most common intracranial neoplasms are astrocytomas (28%), medulloblastoma (25%), ependymomas (9%), craniopharyngiomas (9%), and glioblastoma multiforme (9%).[6]

Pathophysiology

Glial gliomas at diagnosis are best conceptualized as a multicompartmental inhomogeneous tumor volume. This is a result of variable oxygen tension, cell cycle kinetics, cellular heterogeneity, and capillary blood supply within the tumor. The average diameter of a glioma at diagnosis is 4 cm to 5 cm; average cell mass is 10^{12} cells. At diagnosis, a glioma has typically undergone 30 to 35 tumor cell doublings.

Aside from the rare occurrence of familial brain tumors, which constitute less than 1% of all patients

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ABBREVIATIONS USED IN TEXT

BCNU = carmustine
CCNU = lomustine
CT = computed tomography
MR = magnetic resonance
PCV-3 = procarbazine, CCNU, vincristine

with gliomas (for example, neurofibromatosis type I or II), the etiology of gliomas remains unknown.[1,2] Similar to other cancers, a multistep mutational process is assumed to occur, beginning in a previously normal glial cell or astrocyte from which gliomas appear to evolve. It is believed that 40% of glioblastoma multiforme evolve through such a multistep mutational process, giving rise to a primary glioblastoma. Glial tumors that evolve through this mutational process begin as a well-differentiated glioma, evolve to an anaplastic astrocytoma, and ultimately become glioblastoma multiforme. With each malignant stage, tumors progressively accumulate identifiable mutations. For example, chromosome 10 deletions are found in the majority of glioblastoma multiforme; in well-differentiated gliomas, mutations of the *P53* gene located on chromosome 17 are seen in the majority.[1,2] What initiates and promotes these mutational steps remains unknown. Sixty percent of glioblastoma multiforme appear to evolve *de novo* and are termed "secondary glioblastomas."

Neurologic Symptoms and Signs

Neurologic symptoms and signs affecting patients with glial neoplasms reflect the location of the tumor rather than the specific tumor histology. Symptoms may be either general (for example, associated with increased intracranial pressure) or focal (for example, hemiparesis). General symptoms include headaches, gastrointestinal upset with nausea or vomiting, personality changes, and slowing of cognitive function. Because the brain parenchyma does not have pain-sensitive structures, headache has been attributed to local swelling and distortion of pain-sensitive nerve endings associated with blood vessels primarily in the meninges.[7] Many tumors grow without headache as a prominent symptom; others lead rapidly to headache. Headaches can vary in severity and quality and frequently occur in the early morning hours or upon first awakening. Some patients complain of an uncomfortable feeling in the head rather than headache.

Gastrointestinal symptoms such as loss of appetite, nausea, and occasional vomiting occur in all patients but are more common in children and in patients harboring tumors in the infratentorial space (posterior fossa) as opposed to the supratentorial space. In general, these symptoms reflect raised intracranial pressure.

Changes in personality, mood, mental capacity, and concentration can be early indicators or may be the only abnormalities observed. In general, patients with brain tumors tend to sleep longer at night and nap during the day. These symptoms, while not unique to brain tumors, may easily be confused with depression or other psychologic problems.

Focal symptoms can be progressive or episodic. Episodic symptoms include seizures, which are an important harbinger of brain tumors. Although only 1% of patients presenting with seizures are diagnosed with a brain tumor, the association increases with increasing patient age. Seizures are a presenting symptom in approximately 20% of patients with supratentorial brain tumors. Rapidly growing malignant gliomas are likely to produce complex partial motor or sensory seizures, although generalized seizures are also common. In patients with slowly growing astrocytomas, such as gangliogliomas and oligodendrogliomas, partial seizures may antedate the clinical diagnosis by months or years. In a patient older than 40 years, incidence of focal seizures indicates a tumor as a possible cause unless proven otherwise. All patients presenting with focal seizures should undergo diagnostic contrast-enhanced magnetic resonance (MR) or computed tomography (CT) brain imaging. Additionally, all patients with symptomatic seizures should be maintained on anticonvulsant drugs, preferably as monotherapy.

The distribution of gliomas in the brain has a direct relationship to the mass of the involved brain region.[1,2] The most frequently occurring tumors by location are in decreasing order of frequency: frontal, parietal, temporal, and occipital lobes. The clinical pattern of tumor growth in the various brain regions is less stereotypic than that observed after stroke. Frontal lobe tumors may be asymptomatic or may produce slowing of contralateral hand movements, contralateral spastic hemiparesis, marked elevation in mood, or loss of initiative and dysphasia. Bifrontal disease is common, unfortunately, and can cause bilateral hemiparesis, spastic paraparesis, dementia, and severe impairment of the intellect, personality, and mood. Temporal lobe tumors may be clinically silent or may produce impairment of recent memory, homonomous quadrantanopsia, auditory hallucinations, and aggressive behavior. Involvement of the nondominant temporal lobe may lead to minor perceptual problems and spatial disorientation. Dominant temporal lobe involvement can lead to dysnomia, impaired memory, and aphasia. Parietal lobe tumors effect sensory and perceptual functions more than motor functions, although minor hemipareses frequently coexist. In addition, homonomous hemianopsia and visual inattention may occur with parietal lobe tumors. Occipital lobe tumors produce contralateral homonomous hemianopsia or visual distortions that take the form of nonformed visual hallucinations. Thalamic and basal ganglia tumors result in nonspecific headaches due to either hydrocephalus or raised intracranial pressure, usually contralateral sensory and motor abnormalities, and occasionally subcortical aphasias.

Treatment

Several considerations regarding brain tumor therapy are unique to glial neoplasms. The resident organ—the

brain—is, of course, vital to the patient. Approximately 15 different cell types can give rise to a primary brain tumor. The frequently obscure margins between tumor presence and a normal brain are best delineated by CT or MR brain imaging. The concept of "brain adjacent to tumor" (BAT) is also important: tumor infiltration frequently precedes tumor-related vascular changes seen on CT or MR imaging, resulting in an intact blood-brain barrier that limits drug access. Many classes of anticancer drugs are toxic to the central nervous system if the blood-brain barrier is extensively breached by either cerebrospinal fluid administration or by modification of the blood-brain barrier.

There are several variables that affect survival in patients with gliomas: the tumor histology and proliferative capacity; the patient's age and performance; the extent of surgery; and the doses of radiation therapy and chemotherapy.[1–6]

Glioma Classification

The classification of astrocytoma is confusing in that a number of systems are used. Kernohan introduced a system in 1949 that grades tumors from I to IV. Grade IV, often called glioblastoma multiforme, is the most malignant.[1,2] The World Health Organization in 1979 introduced a system of three grades (well-differentiated gliomas are Grade I, anaplastic astrocytomas are Grade II, and glioblastoma multiforme are Grade III) that is most often used today.[1,2] More recently, a group from the Mayo clinic introduced a classification schema whereby gliomas are divided into four grades;[1,2] the group presented convincing data supporting survival as a function of tumor grade. In general, median survival for well-differentiated gliomas is 4 to 5 years; for anaplastic astrocytoma, 3 years; and for glioblastoma multiforme, 1 year.

Proliferative Capacity

A variety of methods are available for estimating the proliferative capacity of tumors. Within the astrocytoma series, higher proliferation indices are seen with glioblastoma multiforme relative to well-differentiated gliomas.[1,2] Data show that within a glioma grade, tumors with higher proliferative capacity result in shorter survival.

Age

Age independently affects survival in patients with glial neoplasms.[1,2,6,8] The median survival rates of younger patients are longer than those of older patients with a similar tumor type. Laboratory studies show increased tumor cell cytotoxicity to either radiation or chemotherapy in tumors from younger patients and suggest that with increasing age, tumors acquire various resistance mechanisms, making them less responsive to therapy.

Surgery

The extent of surgery—biopsy versus subtotal versus total resection—has been shown in a number of studies to affect length of survival.[1,2,4,9] For example, data from the Japanese Brain Tumor Registry show an improvement in 5-year survival rates in patients with well-differentiated gliomas who undergo near- or gross-total resection compared with patients undergoing biopsy or partial resection.[10] Data from higher grade gliomas show that with gross total resection, a 2-year survival of 19% is achieved; a subtotal resection, however, has a 2-year survival of 0%.[11]

Objectives of surgery in a patient with a clinically and neuroradiographically probable malignant glioma are to establish a pathologic diagnosis; relieve mass effect on the surrounding brain, thereby improving patient symptoms and signs; and, if possible, perform a gross total resection.[1,2,11] Unfortunately, complete resection is accomplished in only 10% to 15% of patients with malignant gliomas, primarily because the tumor is located in eloquent regions of brain. The majority of patients thus have residual and measurable disease after definitive surgery.

Radiation Therapy

The Brain Tumor Study Group has looked at how radiation therapy as an independent variable affects survival in patients with malignant gliomas.[1,2,12–14] These studies on the dose-response relationship demonstrate that a radiation dose less than 4,500 cGy in Grade IV gliomas results in a median survival of approximately 13 weeks compared with a median survival of 42 weeks with a dose of 6,000 cGy. Moreover, the addition of radiation therapy and surgery is beneficial relative to surgical therapy only. This effect is seen for both Grade III and IV gliomas.

Radiotherapy is nearly always used in the treatment of malignant gliomas. The tumor is visualized by cranial contrast-enhanced MR or CT imaging before surgery and radiotherapy is administered to the tumor area and a 3-cm cuff surrounding the tumor. This "limited-field" method of radiotherapy is used on the majority of malignant gliomas (> 90%) because they recur at the site of the initial tumor, the junction of the initial tumor and the surrounding brain, or within 3 cm of the initial tumor edge. Because of this recurrence pattern, stereotactic radiotherapies have been used in both the initial treatment (adjuvant boost radiotherapy) and at the time of recurrence (salvage radiotherapy).[1,2]

Two categories of stereotactic radiotherapy are available: implantation of radioactive sources (interstitial brachytherapy) and external targeted radiotherapy administered either by the linear accelerator (linac radiosurgery) or by a focused array of radioactive cobalt sources (gamma knife).

The treatment of malignant gliomas remains a problem in that no contemporary treatments are curative;

most therapies are used to provide palliation (1 year in glioblastoma multiforme or 2 to 3 years in anaplastic astrocytoma) before tumor recurrence and tumor-related death. The role of adjuvant stereotactic radiotherapy is limited by its constraints—tumors need to be surgically accessible because there is a high probability of symptomatic radiation necrosis, and each radiotherapy method involves particular geometries. Radiosurgery is used for small-volume tumors, typically not exceeding 3 cm. By contrast, brachytherapy, regardless of the radioactive source, may treat tumors with maximum dimensions of 5 to 6 cm. Notwithstanding these differences, there is a paucity of data in the literature comparing outcomes of these stereotactic modalities.[1,2,12] With the proliferation of radiosurgery centers in the US, its noninvasive nature, and its lower cost compared with brachytherapy ($10,000 versus $40,000), radiosurgery is increasingly used in selected patients with malignant gliomas in both adjuvant and recurrent settings. The number of patients appropriate for these procedures, however, is comparatively small—less than one-quarter of all patients with malignant gliomas.

Another issue surrounding the use of stereotactic radiotherapy is its effectiveness compared with surgery and chemotherapy. Florell and colleagues argued that both selection and survival bias contaminate brachytherapy and, by extension, radiosurgery studies.[15] Patients treated with definitive surgery and postoperative salvage chemotherapy may have survival, time to tumor progression, and quality of life outcomes similar to those of patients treated with stereotactic radiotherapies, which suggests that these radiotherapies are not meaningfully better. Nevertheless, patient acceptability and lower cost make stereotactic radiotherapy attractive. Until more definitive results are obtained, stereotactic radiotherapy is likely to be commonly used as both adjunct boost and salvage therapy.

Chemotherapy

Different chemotherapy regimens for the treatment of patients with malignant gliomas are described in Table 1.[13,16–19] Chemotherapy may be used immediately after surgery and before radiotherapy, a method of administration termed "neo-adjuvant." Neo-adjuvant therapy, used primarily in the investigational treatment of pediatric brain tumors, has become the most common therapy in children under 3 years old.[6] Chemotherapy has also been used concurrently with radiation therapy to potentiate or sensitize the tumor to the effects of radiotherapy, which is termed "chemoradiosensitization" and, again, has primarily been used in an investigational setting.[1,2,16,17] After surgery and radiotherapy, chemotherapy can also be prescribed as adjuvant therapy. The results of numerous cooperative group studies favor the use of adjuvant chemotherapy for the treatment of malignant gliomas. Chemotherapy is often used for the treatment of recurrent malignant gliomas as salvage chemotherapy.[20–25] It is in the context of salvage chemotherapy that the majority of single-agent Phase I and Phase II chemotherapy studies of malignant gliomas have been performed.

In assessing the value of chemotherapy as an independent variable affecting survival, the University of California, San Francisco, Neuro-Oncology Service has tabulated their experience over many years.[16–18] Their data indicate that surgery followed by radiation therapy given in the treatment of glioblastoma multiforme results in a 1-year survival of 44%, a 3-year survival of 6%, and a 5-year survival of 0%. By comparison, surgery followed by radiation therapy followed by adjuvant chemotherapy using nitrosourea-based regimens for the treatment of glioblastoma multiforme results in a 46% 1-year survival, an 18% 3-year survival, and an 18% 5-year survival. Similarly, for highly anaplastic astrocytomas or Grade III gliomas, surgery followed by radiation therapy results in a 1-year survival of 60%, a 3-year survival of 20%, and a 5-year survival of 16%. With the addition of chemotherapy, 1-year survival increases to 80%, 3-year to 39%, and 5-year to 18%.

Several fundamental points may be discerned from the above studies. First, no compelling data exists to support the use of neo-adjuvant treatment for malignant gliomas, with the exception of infantile gliomas.[6] Second, chemoradiosensitization with agents such as metronidazole, halogenated pyrimidines, and platinum compounds has not shown substantially improved outcome measures in patients with malignant gliomas.[1,2,17] The exception is the use of oral hydroxycarbamide ("hydroxyurea"). A series of studies by the Northern California Oncology Group/University of California, San Francisco, suggest that including hydroxycarbamide in a radiotherapy regimen improves median survival compared with radiotherapy alone in patients with malignant gliomas (Table 1).[16–18] And third, from extensive studies, the Brain Tumor Study Group concluded that nitrosoureas—particularly carmustine (BCNU) and lomustine (CCNU)—and high-dose oral procarbazine, are the most efficacious agents in the adjuvant treatment of malignant gliomas (Table 1).[16–19]

The Brain Tumor Study Group in addition conducted a randomized Phase III trial comparing intravenous to intra-arterial chemotherapy in the adjuvant treatment of malignant gliomas.[25] The study demonstrated no survival advantage when patients were treated by the intra-arterial route; in fact, the results suggest increased treatment-related morbidity in the intra-arterial treatment arm. Intra-arterial chemotherapy is not recommended for the treatment of malignant gliomas outside of investigational studies.[1,2,16–18,25]

The Northern California Oncology Group/University of California, San Francisco, and the M.D. Anderson Cancer Center have pursued trials using polyagent adjuvant chemotherapy in the treatment of patients with malignant gliomas.[16,18,20] These studies have convincingly shown that a combination of procarbazine, lomustine, and vincristine (PCV-3) is at least equivalent and perhaps superior to single-agent nitrosourea or BCNU when used as an adjuvant (Table 1). PCV-3's superiority is based on

TABLE 1.—*CHEMOTHERAPY REGIMENS FOR MALIGNANT GLIOMAS*

AGENT	*DOSE*	*ROUTE*	*SCHEDULE*	
Hydroxyurea[16]	300 mg/m^2	p.o	QID	Mon, Wed, & Fri. During RT
BCNU[16,17]	220 mg/m^2	I.V.	1x	Q 6–8 weeks
	80 mg/m^2	I.V.	QD x 3	Q 6–8 weeks
Procarbazine[23]	150 mg/m^2	p.o.	QD Days 1-28	Q 6–8 weeks
PCV-3[18]				
CCNU	110 mg/m^2	I.V.	Day 1	Q 6–8 weeks
Procarbazine	60 mg/m^2	p.o.	Days 8-21	Q 6–8 weeks
Vincristine	1.4 mg/m^2 (max. 2 mg)	I.V.	Days 8 & 29	Q 6–8 weeks
Cyclophosphamide and Vincristine[21]				
Cyclophosphamide	.75-1 gm/m^2	I.V.	Days 1 & 2	Q 3–4 weeks
Vincristine	1.0 mg/m^2	I.V.	Day 1	Q 3–4 weeks
Platinums[22]				
Carboplatin	400-450 mg/m^2	I.V.	Day 1	Q 4 weeks
	175 mg/m^2	I.V.	Day 1, 8, 15, 22	Q 6–8 weeks
Cisplatin	100 mg/m^2	I.V.	Days 1 & 8	Q 3–4 weeks
	35 mg/m^2	I.V.	Days 1-3	Q 3–4 weeks
TDPC - FUHU[20]				
6-Thioguanine	40 mg/m^2	p.o.	Day 1-3 Q6H x 12	Q 6–8 weeks
Procarbazine	50 mg/m^2	p.o.	Day 2 (start HR 60) Q6H x 4	Q 6–8 weeks
Dibromodulcitol	400 mg/m^2	p.o.	Day 2 (HR 60) x 1	Q 6–8 weeks
CCNU	110 mg/m^2	p.o.	Day 3 (HR 72) x 1	Q 6–8 weeks
5-Fluorouracil	1g/m^2/24HR	I.V.	Day 14 & 15	Q 6–8 weeks
Hydroxyurea	1g/m^2	p.o.	Day 15 (start HR 356) Q6H x 4	Q 6–8 weeks

Q: Every (QD: Once per day; Q6H: Every six hours; QID: Four times per day)
p.o.: Oral
RT: Radiotherapy; 1 x/x 1 = given once
x 3: Given three times; x 12 given twelve times; x 4:Given four times
HR # = Hour administered

median time to tumor progression and median survival in patients with anaplastic astrocytomas. The median survival of patients with glioblastoma multiforme, however, appears unaffected by PCV-3. But a subset of patients with this tumor type appear to benefit from either single- or polyagent adjuvant chemotherapy.

Approach

The treatment of gliomas is predicated on accurate histological diagnosis (Figure 1). This can be achieved in essentially all tumors either by attempting gross total resection or by stereotactic biopsy using either CT or MR imaging. Malignant gliomas in adults are predominantly supratentorial and unifocal. Most generate considerable mass from both the tumor and the surrounding vasogenic edema. Steroids, usually dexamethasone, are used to mitigate these effects; dose adjustment is necessary to minimize steroid-related side effects. The standard approach to malignant supratentorial glioma in adults is to attempt a complete resection followed by irradiation therapy followed by nitrosourea-based adjuvant chemotherapy. Data support as complete a resection as possible; there is no change in surgical morbidity and an improvement in survival is realized.[26] The extent of surgical resection is best evaluated within 3 days of surgery by contrast-enhanced MR or CT imaging.[27] Contrast enhancement, within three days of surgery, accurately reflects a residual tumor. Brain tumor resection surgery has an overall operative mortality of 1% to 2%; 40% of patients remain normal or have minimal deficits after surgery, 30% manifest no postoperative

change relative to preoperative deficits, and 25% sustain an increased postoperative deficit.[26] In most, the deficit improves and patients regain ambulation and the ability to care for themselves.

Because a dose-response relationship exists with radiotherapy, brain tolerance doses of 6,000 cGy to 6,500 cGy are recommended.[12,14] Higher doses increase the incidence of radiation injury to the brain, including both radiation necrosis and vasculopathy. To minimize delayed-late radiation injury to a normal brain, which is manifested as progressive intellectual decline and a extra-pyramidal Parkinsonian-like syndrome, smaller volumes of the brain are generally irradiated.[12,14]

Chemotherapy as indicated above has a role in managing patients with malignant gliomas; no individual patient can be identified *a priori*, however, who will be responsive to chemotherapy (Figure 1).[16–19] Nonetheless, numerous studies have suggested that more than 25% of patients obtain a significant survival benefit with the inclusion of chemotherapy. Because the optimal chemotherapeutic regimen is not defined at present, patients should participate in investigational chemotherapeutic trials.[16–25] A multiagent regimen including procarbazine, CCNU, and vincristine (PCV-3) may be preferred to single-agent BCNU chemotherapy,[16,18] although numerous investigators still recommend single-agent BCNU adjuvant chemotherapy.

Stereotactic radiotherapy, either brachytherapy or stereotactic radiosurgery, may be used as adjuvant or salvage therapy.[1,2,12,14] Stereotactic radiotherapy must meet well-defined criteria: a definable target by CT or

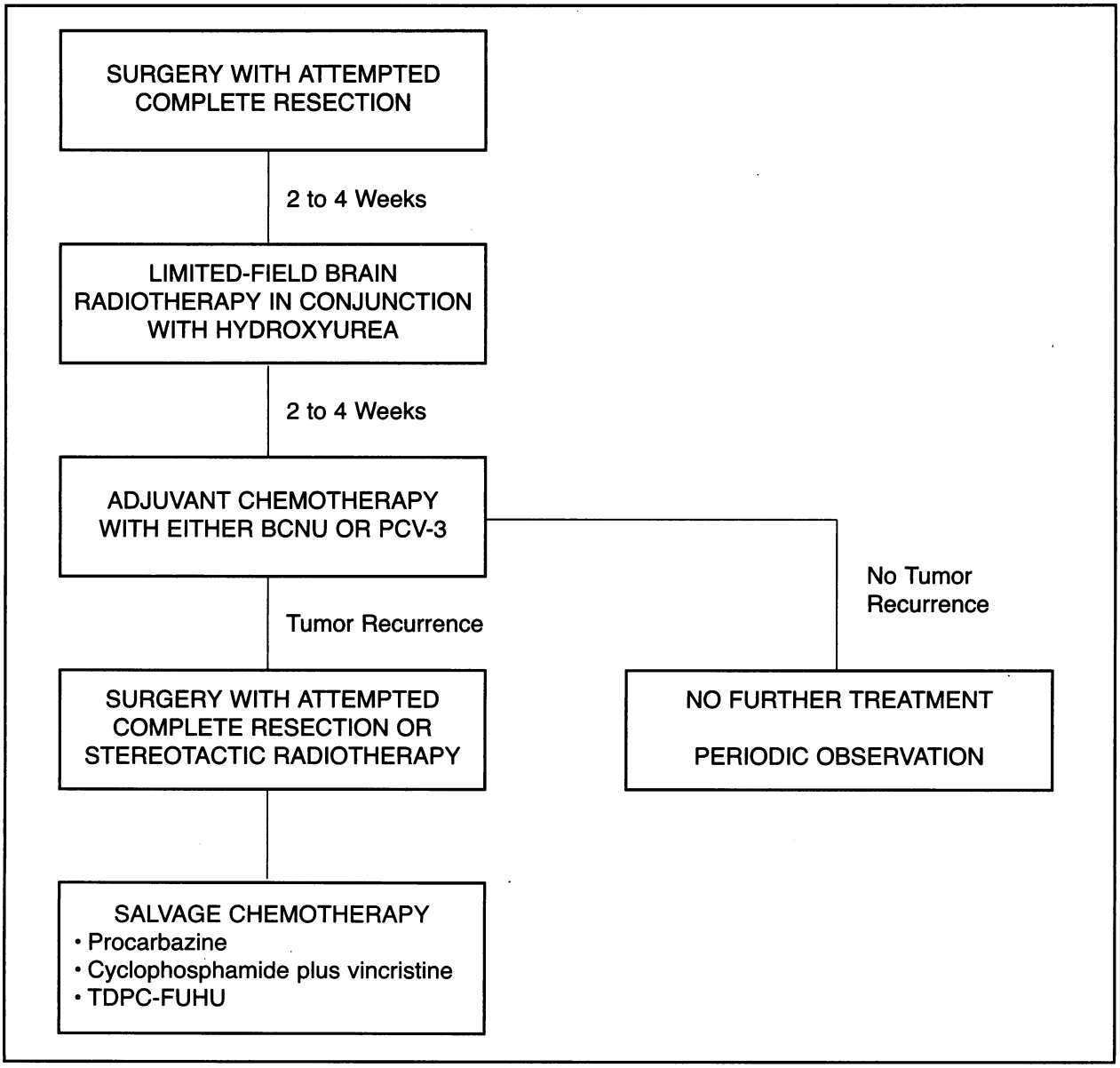

Figure 1.—Algorithm for the treatment of malignant gliomas.

brain imaging; unifocal legion; supratentorial location; absence of corpus callosum or deep nuclei involvement; surgically accessible location; noneloquent brain location; and no dimension of the tumor exceeding 5 to 6 cm for brachytherapy or 3 cm for stereotactic radiosurgery. These criteria mean that 10% to 15% of patients with high grade gliomas are eligible. Approximately 50% of patients treated with brachytherapy require reoperation for radiation necrosis with or without evidence of tumor recurrence. Evaluating radiation necrosis is difficult by conventional cranial MR or CT imaging. As such, the use of positron emission tomography (PET) or single photon emission computerized tomography (SPECT) has been used to differentiate between recurrent tumor and necrosis. The purported survival benefits seen in patients with Grade IV tumors treated adjuvantly with boost radiotherapy (either brachytherapy or stereotactic) may not be accurate—patient selection may account for much of this effect.[15]

In the majority of patients with recurrent gliomas, chemotherapy represents the only treatment available. Treatment intent in patients with recurrent malignant gliomas is palliative—long-term survivors, defined as those with a patient survival longer than than two years, are rare.

Clearly, new approaches to the treatment of malignant gliomas are necessary. Enrollment of patients into clinical trials, both at tumor diagnosis and after tumor recurrence, will generate new information regarding investigational therapies. A randomized trial is nearing completion that compares patients treated with or without adjuvant stereotactic radiosurgery; it hopefully will allow identification of patients who might benefit from this therapy. A variety of investigational chemotherapy protocols is available, such as the administration of Taxol during radiotherapy. Additionally, novel approaches such as the use of high-dose oral tamoxifen, anti-angiogenesis agents (for example, thalidomide) inhibitors of matrix metalloproteinases and gene therapies (for example, gene replacement with wild type *P53*) may offer improved therapies for patients with malignant gliomas.

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