John Gurbacs. *Intersection,* 1999. Oil, 41″ × 57″.

Progress in understanding the molecular biology and genetics of brain tumors in older patients has fostered treatments that are more effective or better tolerated.

Brain Tumors in the Older Person

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Background: *The incidence of brain tumors is increasing rapidly, particularly in the older population. Advances in molecular biology help to explain differences in biologic behavior and response to therapy of brain tumors in the elderly compared with younger patients. The number of elderly patients who desire and receive therapy for brain tumors and are included in clinical trials is increasing.*

Methods: *This article reviews the literature on the epidemiology, clinical aspects, and therapy of brain tumors, with emphasis on the older patient population.*

Results: *The increased incidence of brain tumors in the elderly is principally due to the increasing number of people who comprise the older population. Age and performance status are important independent prognostic indicators, together with tumor histology. Surgery, radiation therapy, and chemotherapy can benefit elderly patients with brain tumors with favorable histologies, tumor location, and good performance status. The response rates to available therapies are less favorable than in younger patients, and only a small number of elderly patients are enrolled in clinical studies addressing new treatment modalities.*

Conclusions: *Brain tumors in the elderly have specific characteristics that determine their biologic behavior and response to therapy. There is a need for clinical studies designed for treatment of brain tumors in older patients, and requirements for rehabilitation and support systems for the elderly need to be addressed.*

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Introduction

Brain tumors are primary or metastatic malignancies of the central nervous system with considerable morbidity and mortality. The overall incidence of brain tumors is increasing, with the highest increase noted in patients over 60 years of age. Until recently, these patients were managed with supportive care only and were not considered eligible for clinical trials. The attitude of the medical community toward offering treatments to elderly patients with malignancies is changing, and more elderly patients with brain tumors are

now treated aggressively.[1] Advances in understanding the molecular biology of brain tumors and the genetics of brain tumors in older patients have resulted in treatments that are more effective or at least better tolerated in this age group. The overall prognosis remains poor, however, and the search for more effective therapies is ongoing.

Epidemiology

Over the last 20 years, the overall incidence of cancer, including brain cancer, has increased by more than 10%, as reported in the National Cancer Institute statistics, with an average annual percentage change of approximately 1%.[2-6] Between 1973 and 1985, there has been a dramatic age-specific increase in the incidence of brain tumors.[2] The average annual percentage increases in primary brain tumor incidence for ages 75-79, 80-84, and 85 and older were 7%, 20.4%, and 23.4%, respectively.[5-8] Since 1970, the incidence of primary brain tumors in people over the age of 70 has increased sevenfold.[8] This trend continues in both the United States and the industrialized European countries.[9-16] This increase in incidence appears to be independent of diagnostic capabilities, although the introduction of computed tomography (CT) scans in 1973, followed by magnetic resonance imaging (MRI), allows for earlier and more accurate diagnosis.[17,18] Comparisons between age-related mortality rates suggest that increasing primary brain tumor mortality rates among the oldest age groups are directly proportional to the increasing population size of these age groups.[19-22] Malignant gliomas, particularly glioblastoma multiforme, are the most common primary brain tumors in the elderly.

The epidemiologic factors that have led to the increased incidence of brain tumors in all age groups are not well defined.[23-25] The incidence of some genetically transmitted diseases associated with brain tumors, such as neurofibromatosis and the familial cancer syndromes (eg, Li-Fraumeni), has not increased.[26,27] Also, there are no clearly established links between the occurrence of brain tumors and environmental factors such as pesticides, electromagnetic fields, and radiation exposure, except for higher risk for meningiomas in patients who had previously received radiation therapy (RT) to the head.[25,28] In some patients with a family history of malignancy, there are abnormalities of tumor suppressor genes and overexpression of oncogenes, which can be identified with molecular biology techniques.[26,27]

Age is a strong prognostic factor affecting survival.[29,30] An analysis based on Surveillance, Epidemiology, and End Results (SEER) data for 1973-1991 shows that for patients aged 65 and older, there was no apparent clinically significant improvement in survival rates for all tumor types compared with significantly improved survival rates for younger patients with anaplastic gliomas and medulloblastomas.[31,32] The 5-year survival rate for patients with glioblastoma multiforme is approximately 20% in patients less than 35 years of age, 10% in patients aged 35-54, and only 1% in patients 55 years of age and older.[1] Similar age-related trends are noted in patients with anaplastic astrocytomas (70%, 22%, and 15%, respectively) (Fig 1). The age-based survival data parallel the survival rates based on performance status, as measured by Karnofsky performance score (KPS). Approximately 50% of patients with malignant gliomas over the age of 55 are likely to have a KPS of less than 70 at diagnosis compared with only 20% in the younger patients group (Fig 2). The performance status is not the only determinant of survival in the elderly, but a low KPS influences the type of treatment these patients are offered.[30]

Diagnosis

The diagnosis of brain tumors is based on clinical presentation, imaging studies, and histology.[33,34] In the older population, intellectual decline over a short period of time, gait disturbances, and short-term memory deficits are clinical signs that may indicate the presence of a brain tumor and must be differentiated from "normal" aging signs.[35]

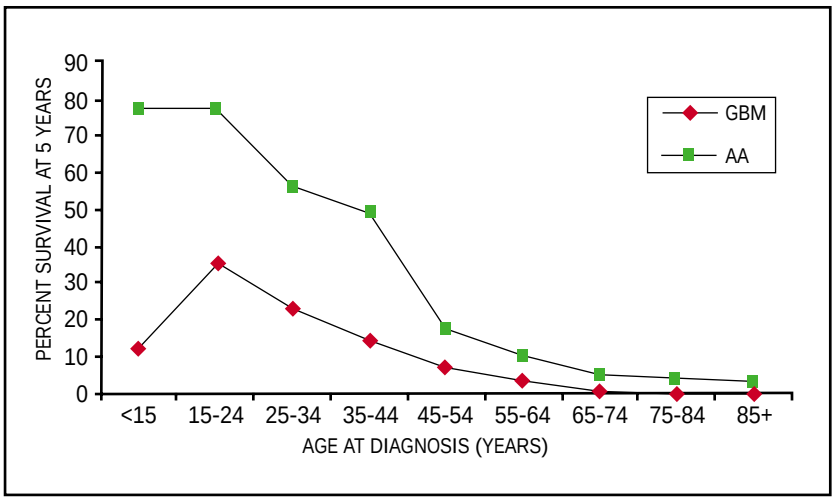

Fig 1. — Survival of patients with malignant gliomas at 5 years by age (1980-1985 surveys). GBM = glioblastoma multiforme, AA = anaplastic astrocytoma. From Flowers A. Brain tumors. In: Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology.* Amsterdam, The Netherlands: Harwood Academic; 1998:703-719. With permission from Gordon and Breach Publishers.

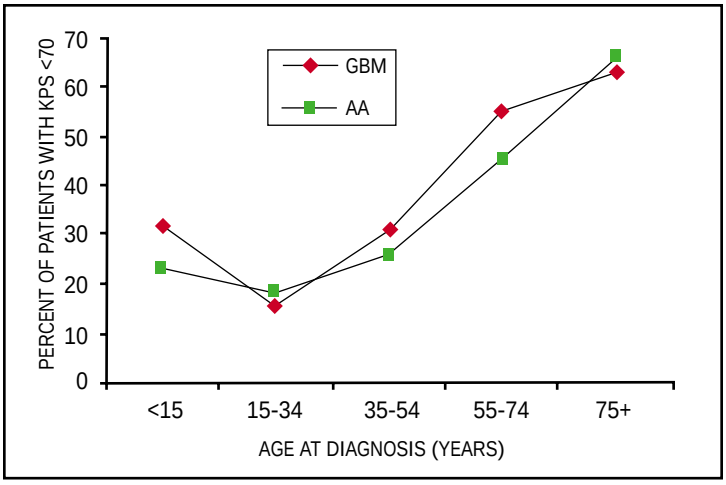

Fig 2. — Relationship of age and initial Karnofsky performance score <70 in patients with malignant gliomas (1980-1985 surveys). GBM = glioblastoma multiforme, AA = anaplastic astrocytoma. From Flowers A. Brain tumors. In: Balducci L, Lyman GH, Ershler WB, eds. *Comprehensive Geriatric Oncology.* Amsterdam, The Netherlands: Harwood Academic; 1998:703-719. With permission from Gordon and Breach Publishers.

Symptoms and Signs

The symptoms and signs are dependent on tumor location (Table 1). The majority of tumors in the elderly are in the cerebral hemispheres. Headaches and seizures are the most common symptoms at presentation. Headaches are localized and persistent, and they increase in severity as the tumor grows and exerts pressure. The seizures can be focal or generalized, and they may have localizing value. The presence of focal neurologic deficits helps to localize the lesion. The degree of neurologic compromise is an important factor in deciding the therapeutic approach. Tumors in the anterior frontal lobes, the anterior temporal lobes, or the base of the skull can grow to a large size with few or no symptoms or with nonspecific symptoms often ascribed to the aging process (eg, memory loss, personality changes, or some gait difficulties). More than 60% of malignant gliomas arise in the frontal and temporal lobes. The diagnosis of tumor can be suspected if the symptoms develop over a short period of time (ie, less than 6 months). Nonspecific cognitive and gait changes are also seen in patients with primary central nervous system lymphomas. Unilateral hearing loss, vertigo, and mild face weakness are symptoms caused by acoustic neuromas. Imaging studies help to differentiate these from vertebrobasilar insufficiency.

Radiologic Diagnosis

Neuroimaging studies are valuable tools in localizing the lesion(s) and may suggest the diagnosis and malignant character of a tumor.[36] Skull radiographs can reveal abnormalities of the sella turcica, suggesting a pituitary tumor or erosion of the bone as seen in patients with meningiomas, as well as calcifications in low-grade astrocytomas, oligodendrogliomas, or meningiomas. Cerebral angiograms help to distinguish tumors from vascular malformations or aneurysms, and

Table 1. — Symptoms and Signs of Brain Tumors

Tumor Location	Symptoms and Signs (Dominant Hemisphere)	Symptoms and Signs (Nondominant Hemisphere)
Frontal lobe	Personality changes, apathy, impaired planning, disinhibition or apathy, expressive aphasia, contralateral motor weakness, motor seizures	Personality changes (most marked with lesions in the right frontal lobe), motor weakness, motor seizures
Temporal lobe	Loss of verbal memory, short-term memory loss, fluent aphasia, complex partial seizures, contralateral homonymous superior quadrantanopia	Loss of visual spatial memory, complex partial seizures, contralateral homonymous superior quadrantanopia
Parietal lobe	Contralateral sensory deficit, aphasia syndromes, conduction aphasia, Gerstmann syndrome, alexia, agraphia, contralateral homonymous inferior quadrantanopia, sensory seizures	Contralateral sensory deficit, contralateral homonymous inferior quadrantanopia, contralateral hemibody neglect, visual neglect, constructional apraxia, dressing apraxia, sensory seizures
Occipital lobe	Contralateral homonymous hemianopia, alexia, prosopagnosia	Contralateral homonymous hemianopia
Posterior fossa	Headache due to obstructive hydrocephalus, focal findings depending on tumor location, vertigo, nystagmus, altered level of consciousness	

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they also define the blood supply of the tumor, thus assisting with the surgical management.

Contrast-enhanced CT and MRI scans of the brain are now the most utilized imaging modalities. MRI scan of the brain is becoming the imaging modality of choice for brain tumors. It allows visualization of the tumor in axial, coronal, and sagittal planes, thereby providing a three-dimensional view of the tumor and its relationship with the surrounding structures. MRI scans have greater tissue contrast resolution than CT scans and allow the visualization of not only very small lesions, but also lesions in the temporal tip, in the inferior frontal lobe or posterior fossa, and at the base of the skull. The paramagnetic substance gadolinium-diethylenetriamine pentaacetic acid helps to define the intracranial lesions, to differentiate neoplasms from other lesions, and to identify even subtle changes in the appearance of a tumor during treatment. MRI scans with gadolinium are also useful in diagnosing leptomeningeal metastases, which are seen with increased frequency as brain tumor patients survive longer. Positron emission tomography (PET) scans and single positron emission computed tomography (SPECT) scans are less useful at diagnosis, but they can help to distinguish tumor necrosis from radiation-induced necrosis in the follow-up of tumors after therapy.[37,38] MR spectroscopy is still a research tool; however, it has the potential to become a noninvasive diagnostic modality in differentiating low-grade from anaplastic gliomas.

Pathologic Diagnosis

The pathologic examination of the tumor specimen on frozen section and fixated material defines the type of tumor and the histologic grade. Brain tumors can be primary or metastatic. Primary brain tumors are classified histologically based on the World Health

Table 2. — Grading of Malignant Gliomas

Grading System and Criteria	Grade I	Grade II	Grade III	Grade IV
Kernohan[39]				
• Cell anaplasia	None	Minimal	In half of cells	Extensive
• Cellularity	Mild	Mild	Increased	Marked
• Mitoses	None	None	Present	Numerous
• Vascular endothelial proliferation	None or minimal	None or minimal	More frequent	Marked
• Necrosis	None	None	Regional	Extensive
• Transition zone to normal brain	Broad	Broad	Narrow	May be sharply delineated
World Health Organization[41] • Based on cell type	Pilocytic astrocytoma	Astrocytoma (fibrillary, protoplasmic, gemistocytic, giant cell, combinations)	Anaplastic astrocytoma (astrocytoma with areas of anaplastic transformation)	Glioblastoma (anaplastic glial tumor with high cellularity and necrosis)
Daumas-Duport[40] • Nuclear abnormalities • Mitoses • Endothelial proliferation • Necrosis	None of the four criteria	One criterion	Two criteria	Three or four criteria
Ringertz[42]	Astrocytoma (tumor showing infiltrative growth pattern and mild to moderate hypercellularity; cytologic features resemble normal astrocytes with only mild nuclear abnormalities)	Anaplastic astrocytoma (cellular infiltrative astrocytic tumor containingastrocytes with moderate pleomorphism; mitoses and moderate vascular proliferation may be seen; no necrosis)		Glioblastoma multiforme (markedly pleomorphic astrocytic tumor with high cellularity, frequent mitoses, increased vascularity and necrosis)

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Organization classification. The most common primary brain tumors are gliomas, which are classified according to the cell type as astrocytic tumors, oligodendroglial tumors, or mixed gliomas. The grade of malignancy is based on the cellularity, presence of mitoses, vascular endothelial proliferation, and necrosis.[39] For an accurate grading, the pathologist needs to know if the patient received RT or chemotherapy prior to the surgical procedure. Tissue necrosis can be caused by RT and chemotherapy as well as by some malignant tumors, particularly glioblastoma multiforme.

Several classification schemes have been developed to grade malignant gliomas (Table 2).[39-42] The histologic features are important determinants of prognosis. Daumas-Duport et al[40] determined that the length of postoperative survival is inversely proportional to the number of histologic features of malignancy, such as nuclear atypia, mitoses, vascular endothelial proliferation, and necrosis found in the tumor.[43] From a practical standpoint, a three-tiered grading system is adequate for older patients since even low-anaplastic tumors (grade II) tend to behave more aggressively and need to be treated as anaplastic tumors rather than as low-grade tumors. Gliomas that occur before the age of 10 and after the age of 45 have a greater tendency to be undifferentiated and are associated with more aggressive behavior and shorter postoperative survival.[44] Oligodendrogliomas and mixed oligoastrocytomas carry a better prognosis.[45] Determination of tumor cell proliferation pattern, using mitotic index determination with bromodeoxyuridine (BUdR) or Ki-67 nuclear antigen or flow cytometry, is being investigated as a way to define prognosis.[46-50]

In recent years, research has focused on defining the genetic alterations and interactions among tumor-suppressor genes, oncogenes and their products, growth factors, and enzyme systems.[48,49] The goal of this research is to determine the mechanisms of oncogenesis, cell resistance, and repair mechanisms and to develop new treatment modalities based on the molecular biology data. The p53 tumor suppressor gene, found on chromosome 17p, is frequently altered in gliomas as it is in systemic cancers. Tumors with a high percentage of cells with mutated p53 gene grow rapidly and tend to recur faster and be more resistant to therapy. Overexpression of p53 occurs less often in patients over the age of 45.[51,52] Alterations on chromosome 17p are the most common seen in gliomas, even in low-grade gliomas. With a higher grade of malignancy, other chromosomal alterations are seen on chromosomes 9p, 19q, 4, 7, and 13. Alterations on chromosome 10 are seen in 50% of glioblastomas. The PTEN gene, located on 10q23, has been recently identified as a putative tumor suppressor gene.[53,54] Mutations in the PTEN gene have been found in high-grade adult gliomas and have a tendency to occur in older patients. The loss of chromosome 10 has been directly correlated with amplification of the epidermal growth factor receptor, which can be targeted for therapeutic interventions.[53,54] Ploidy studies indicate that for astrocytomas, survival is better for patients with aneuploid tumors than with euploid tumors. No such correlation was found for oligodendrogliomas.[49,52]

Meningiomas are more common in older patients (with a median age of 59) and have a female predominance. The 5-year survival rate is 92% for patients aged 45-74 and 70% for patients aged 75 and older.

Pituitary adenomas are also more common in the older population. In many cases, asymptomatic microadenomas are found on scans of the brain done for other reasons (eg, head trauma, headaches, or dizziness). Some patients present with galactorrhea or with the physical changes of acromegaly.

Acoustic neuromas are benign tumors also seen in older patients. They should be suspected in patients with unilateral hearing loss or vertigo that does not resolve with medical treatment. Depending on the age of the patient, the severity of symptoms, and the size of the tumor, management can be conservative (with symptomatic treatment and follow-up with serial scans) or more definitive (with surgery or stereotactic radiosurgery).

Differential Diagnosis

In older patients presenting with neurologic symptoms, the differential diagnosis is primarily with cerebrovascular disease. Neuroimaging studies can differentiate between tumor and stroke when the lesion does not respect a vascular distribution. They can also help to differentiate between hemorrhage due to hypertension and hemorrhage into a tumor. When the scan reveals enhancing lesions, the differential diagnosis is between primary and metastatic tumors. If the chest radiograph is normal, the most yielding procedure will be a biopsy of one of the lesions for tissue diagnosis. In this age group, infectious or vasculitic lesions are less common than in the younger patients.

Treatment

The treatment of brain tumors is determined by the histologic type and the location in the cranial cavity, as well as the patient's performance status, neurologic status, age, and life expectancy as defined not only by the neurologic deficits, but also by coexisting med-

ical problems.[55-63] Benign tumors such as meningiomas, acoustic neuromas, or pituitary adenomas can be managed conservatively in older patients unless the symptoms warrant a more aggressive approach.[64] In the elderly, treatment of primary brain tumors raises particular challenges.

For gliomas, the conventional therapy involves surgery, RT, and chemotherapy.[55-63] However, new treatment modalities are being developed, as noted in Table 3. In the elderly, gliomas with a low-grade histology tend to have a more aggressive biologic behavior and need to be treated with RT and/or chemotherapy, as already mentioned.

Most primary brain tumors and metastatic tumors have surrounding vasogenic edema, which contributes to the neurologic symptoms. The edema is controlled with corticosteroids, diuretics or, in some cases, mannitol. The dosage of corticosteroids is based on the amount of edema and mass effect. In patients who undergo a wide resection of the tumor, corticosteroid use can be tapered off relatively quickly. Side effects with long-term corticosteroid use are gastric irritation, corticosteroid myopathy, Cushingoid appearance and, in some patients, osteoporosis, depression, or corticosteroid psychosis. For patients with diabetes who need to use corticosteroids, the blood glucose must be monitored carefully, and insulin therapy may be needed to control the hyperglycemia. In cases where corticosteroids are contraindicated (eg, those with an active peptic ulcer, heart failure, or uncontrolled diabetes), diuretics such as acetazolamide or furosemide can decrease the edema.

Surgery

Surgery is the first therapeutic intervention for brain tumors, with the goal of obtaining tissue for diagnosis and, whenever possible, debulking the tumor to relieve the pressure and bring about rapid clinical improvement.[64] In the elderly, surgery is considered to carry a higher risk of morbidity and mortality compared with younger patients.

When feasible, complete resection of the tumor has been shown to significantly increase the rate of survival by improving the patient's performance status and by providing cytoreduction, with a better chance of response to subsequent therapy. Outcome studies also have shown that patients who undergo resection have a better quality of life and are less likely to become depressed than patients who undergo only biopsy.[65-67] The survival advantage is particularly significant for anaplastic astrocytomas. The 5-year survival rates are 50% in patients with astrocytomas who had a total resection but only 20% in patients who had a biopsy only.[65] For patients with unresectable lesions or with associated significant medical problems, a stereotactic biopsy for tissue diagnosis is sufficient. The most important prognostic factor remains the extent of resection. The postoperative residual tumor volume (determined on enhanced CT or MRI scans) correlates inversely with survival.[68,69]

Table 3. — Treatment of Brain Tumors

Therapy	Methods
Surgery	Biopsy - open - stereotactic, frameless stereotactic Resection - craniotomy - computer-assisted, minimally invasive
Radiation therapy	External beam - conventional fractionation 1.8-2.0 Gy/day - hyperfractionation 1.2-1.6 Gy b.i.d., 1.0 Gy t.i.d. Radiosurgery - linear accelerator, gamma knife, particle beam, conformal Brachytherapy Boron neutron capture therapy Radiosensitizers
Chemotherapy	Routes of administration - intravenous - oral, intraarterial, blood-brain barrier modification - interstitial - intracavitary - intraventricular/intrathecal Drugs - alkylating agents - antimetabolites - polyamine inhibitors - topoisomerase inhibitors, vinca alkaloids Drug combinations
Immunotherapy	Interferons Monoclonal antibodies Immunoconjugates
Other agents	Retinoids Tamoxifen
Gene therapy	Herpes virus thymidine kinase/gancyclovir
Combined modalities	Chemoradiotherapy Chemotherapy and tamoxifen Retinoids and interferon Radioimmunotherapy

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Reoperation for recurrent or progressing tumors must be considered on a case-by-case basis, depending on the tumor type, expected survival, KPS, patient age, and plans for further therapy.[70,71] Age is a factor that can influence the outcome. In one study, survival after reoperation for recurrent gliomas was 57 weeks for patients younger than 40 years but only 36 weeks for older patients.[72] Other authors found a correlation between age and overall survival from diagnosis but no difference after reoperation.[66]

Perfected neurosurgical techniques such as computer-assisted minimal-access surgery have reduced the morbidity associated with open craniotomies and have shortened the length of hospital stay. These improvements have made such interventions safer and more acceptable for elderly patients with resectable tumors.[73]

Radiation Therapy

For malignant brain tumors, RT is considered to be the standard treatment.[74-79] For malignant gliomas, RT at doses of 50-60 Gy increases survival compared with surgery alone.[74] RT is also the treatment of choice for low-grade gliomas in elderly patients.[75] For malignant gliomas, RT is delivered to the area of tumor as visualized on CT or MRI scan plus an additional 3-cm margin.[76] New software allows three-dimensional RT planning. The total dose of radiation is delivered over a span of 30-33 days in daily fractions of 1.6-2.0 Gy. Age is again an important prognostic factor. In one study, the survival rate at 18 months was 64% in patients younger than age 40 but only 8% in patients older than age 60.[78,79] The performance status is an independent variable. The survival rate at 18 months for patients with an initial KPS of 70 or above is 34% compared with 13% for patients with a KPS score of 60 or below.[80]

The results of conventional fractionation RT have been disappointing in terms of providing a cure or at least long-term survival in patients with malignant gliomas. Reasons for failure are related to tumor cell resistance (particularly in hypoxic areas of the tumor), the presence of repair mechanisms, and the pattern of spread of these tumors along white matter tracts outside the radiation field.[81] Several different methods are under investigation to enhance radiosensitivity, provide protection to the normal brain tissue, and deliver higher doses of radiation to the tumor.

Investigational Radiation Therapy Methods

Hyperfractionation schedules allow the RT dose to be delivered in two or three daily treatments, while hypofractionation schedules use a once-weekly treatment. These modified RT schedules allow for either smaller doses administered at shorter time intervals so larger total doses can be used with less toxicity to the normal brain, or larger doses administered to reduce the morbidity related to RT.

Hypofractionation schedules in which RT is delivered in weekly doses of 5.0-6.5 Gy over 6 weeks to a total dose of 36-39 Gy, together with administration of cisplatin or carboplatin as radiosensitizers, have been used for patients with a poor performance status (KPS of 60 or below). This approach was well tolerated and improved both performance status and survival in some of the patients.[82,83]

In accelerated fractionation schedules, the conventional dose of radiation is delivered in two or three daily fractions. The rationale is that shortened treatment time would improve the therapeutic ratio, with greater tumor control. Drugs such as carboplatin or BUdR are used as radiosensitizers. The toxicities in these studies are related to the myelosuppressive effect of the cytotoxic agents — skin rash with BUdR. These schedules are well tolerated, even by older patients. Accelerated fractionation has been used for hospitalized patients with poor performance status in order to shorten the duration of treatment.[84]

Hypoxic cell sensitizers such as misonidazole or lonidamine in combination with RT were promising in experimental studies. However, in randomized clinical trials, these agents showed no benefit in survival.

Halogenated pyrimidine analogues such as BUdR or iododeoxyuridine (IUdR) are incorporated into rapidly dividing cells and act as radiosensitizers. Phase II studies noted an increase in survival over conventional RT. Other studies have investigated the radiosensitizing effect of some chemotherapeutic agents including hydroxyurea, vincristine, and BCNU (carmustine). RSR13, an allosteric modifier of hemoglobin, is a novel radiosensitizer that binds covalently to hemoglobin and reduces oxygen-binding affinity, thus increasing oxygen release in the capillaries. RSR13 is now undergoing clinical trials. The difference in survival compared with conventional RT is not significant. Patients under the age of 60 seem to benefit most.[85]

Stereotactic radiosurgery is a noninvasive technique that allows delivery of high-dose single fractions of radiation to small, well-circumscribed tumors. The treatment is safe and effective, and because it is done in one single dose or a few fractionated doses in an outpatient setting, stereotactic radiosurgery is convenient for the patient and cost effective.[86,87] The morbidity associated with this approach is primarily related to increased peritumoral edema, which can be easily con-

trolled with corticosteroids. To date, no cognitive deficits have been described in patients who have received radiosurgery without conventional RT. For treatment of malignant gliomas, stereotactic radiosurgery is used as adjuvant therapy to external beam RT. Because of the infiltrative pattern of growth of these tumors, this technique cannot be used as the sole radiation modality.[88] Radiosurgery can also be administered in fractionated doses.[86]

Interstitial RT (brachytherapy) is a more invasive way of delivering high-dose radiation to a tumor while limiting the dose to the surrounding brain. A dose of 60 Gy or more can be delivered even after 60 Gy of external beam RT. Brachytherapy refers to treatment with radiation sources placed directly into the tumor mass or adjacent to tumors (eg, in the surgical cavity). The most commonly used isotopes for brachytherapy are ^{192}Ir and ^{125}I. Although more invasive than stereotactic radiosurgery and having greater morbidity, brachytherapy in malignant gliomas can be used for infiltrating or cavitary tumors and for tumors larger than 3 cm. Brachytherapy can be done as a boost to external beam RT or as salvage therapy at recurrence. It was shown to improve survival in patients with malignant gliomas.[89,90] Serious complications after brachytherapy are wound infections, cerebral edema, abscess into the tumor, hemorrhage, and radiation necrosis that requires surgical intervention. These complications make brachytherapy a less attractive treatment modality for elderly patients and for patients with poor performance status.

Radiation beams other than the usual photons and electrons are now under investigation. Beams of protons, neutrons, and π-mesons provide better dose localization on the tumor as well as radiobiological efficiency, while sparing the surrounding normal tissues. Radioimmunotherapy is another method to ensure dose localization, in which a monoclonal antibody coupled with a radionuclide is introduced into the tumor.[91] The monoclonal antibody is designed to bind to receptors expressed only by tumor and not by normal cells, thus sparing normal tissue.

Boron neutron capture therapy (BNCT) is a form of RT presently under investigation for treatment of malignant gliomas.[92] BNCT is mediated by short-range (less than 10 microns), high-energy particles resulting from neutron-induced disintegration of boron-10. There is preferential accumulation of boron-10 in conjunction with high thermal neutron flux at the tumor site. The bombardment of the boron nucleus with a slow neutron induces disintegration of boron, which yields ionizing radiation. Best results with BNCT were reported by Japanese investigators.[93] The studies do not specify differences, if any, in response based on tumor types, age, and performance status. The initial clinical trials have been marred by significant brain necrosis. The improved technologies have rekindled the interest in this treatment modality.[92]

Side Effects of Radiation Therapy

Regardless of the radiation modality used, RT may cause side effects that need to be discussed with patients and monitored. The reactions to RT are more significant when RT is administered to a large portion of the brain. The effects can be acute, early delayed, and late delayed.[94] Acute effects occur during treatment or shortly after completion of RT. Some patients experience headaches, probably related to edema, or a worsening of the neurologic deficits. Fatigue is another complaint and, depending on the tumor location, patients may experience nausea, sore throat, hearing loss, or blurred vision. These symptoms are transient and can be controlled with corticosteroids and reassurance. Early-delayed effects, which appear in the first 3 months after completion of RT, include somnolence, loss of appetite, and apathy. These effects are self-limiting and seem to be more severe in older patients. Late-delayed radiation injury occurs months or even years after completion of radiation. Patients experience short-term memory loss and cognitive decline.[94-99] CT or MRI scans reveal white matter changes bilaterally or may show focal radiation necrosis.[95] Areas of necrosis do enhance and can have surrounding edema, which is difficult to distinguish from recurrent tumor.[96] PET and SPECT scans can be helpful, showing metabolically hypoactive areas of radiation necrosis compared with the increased metabolic activity in tumor tissue.[37,38] The definitive differential diagnosis is done by biopsy.[97] The degree of cognitive impairment can be more severe in patients with tumors in the temporal lobes and in elderly patients with baseline mild dementia. In the latter patient population, the decision regarding RT must be based on tumor type and life expectancy. The degree of cognitive impairment can be quantitated using neuropsychometric evaluation prior to RT and at intervals of 6, 12, and 18 months.[97,99]

Chemotherapy

Chemotherapy is now established as accepted treatment for primary brain tumors.[100-102] The addition of chemotherapy to RT has been shown to prolong survival by another 6-18 months, depending on the grade of the tumor. Longer-term survivals have also been reported. While multiple clinical trials are investigating new drugs and drug combinations, only a small proportion of the overall population with brain tumors, and in particular patients over 65 years of age, are entered in clinical trials.

Several factors determine chemotherapy failure. Brain tumors are heterogeneous, and glioma cells have been shown to express the multidrug resistance gene (MDR-1).[103] Repair enzymes such as glutathione-S-transferase and O^6-alkylguanine alkyl transferase counteract the cytotoxic effect of platinum compounds and nitrosoureas; some of the tumor cells are in the G_0 phase and are less susceptible to chemotherapy.[104,105] The DNA mismatch repair deficiency has been identified as an important mechanism conferring resistance to RT and methylating agents such as procarbazine and temozolomide.[105] The blood-brain barrier limits the brain tissue penetrance of drugs that are nonionized or are not liposoluble. The drugs should attain and maintain a cytocidal concentration in the tumor.[106-108] This is dependent on the physical and chemical properties of the drug and its pharmacokinetics. The half-life of the drug, intracellular binding, and capillary-to-cell diffusion are important factors. The dose, route of administration, and schedule of administration can influence the drug concentrations.

Several classes of drugs are used for the chemotherapy of brain tumors: alkylating agents, antimetabolites, natural compounds, urea analogs, methylhydrazine derivatives, and polyamine inhibitors.[102] Nitrosoureas are to date the most effective drugs for treatment of malignant gliomas.[109-117] The two most widely used nitrosoureas are 1,3bis-(2-chloroethyl)-1-nitrosourea (BCNU; carmustine), which is administered intravenously or intraarterially, and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU; lomustine), given orally. The clinical activity is similar for the two drugs, with 40% response rates. Resistance to BCNU is determined by the activity of the enzyme O^6-alkylguanyl alkyl transferase, which is not age dependent.[104] The dose-limiting toxicities are myelotoxicity and pulmonary fibrosis. Patients with chronic obstructive lung disease must be monitored closely during the treatment. Platinum compounds (cisplatin and carboplatin),[109,110] procarbazine,[111-115] and etoposide are also effective but do not offer a significant survival advantage over BCNU. Currently, chemotherapy with combined procarbazine, CCNU, and vincristine (PCV) is considered to be the most effective for low-grade or anaplastic oligodendrogliomas and for anaplastic astrocytomas.[113,114] Recent analysis, however, shows no clear survival advantage with PCV over BCNU.[115] In low-grade oligodendrogliomas, chemotherapy with PCV was shown to inhibit tumor growth and induce regression of the tumor on imaging studies.[116]

Temozolomide (Temodal), which has been recently approved by the Food and Drug Administration for the treatment of recurrent anaplastic gliomas, is still undergoing clinical trials in combination with RT and other chemotherapeutic agents. It is administered orally and is well tolerated with no significant myelotoxicity. It can be safely administered to elderly patients, and the efficacy does not appear to be age related.[117]

Chemotherapy is used traditionally after completion of RT as adjuvant treatment or at the time of tumor recurrence or progression.[118-120] Some chemotherapeutic agents (eg, BCNU, hydroxyurea, and vincristine) also have a radiosensitizing effect, and there are clinical trials using chemotherapy in conjunction with RT.[121] Recent reports suggest a benefit in using chemotherapy prior to RT, particularly in oligodendrogliomas.[122] Newer agents such as the topoisomerase I inhibitors topotecan and irinotecan (CPT-11) are also under investigation as preradiation chemotherapy for glioblastomas. Preradiation chemotherapy can be used for palliation in patients with low performance status.[122]

The most common side effect of chemotherapy is myelosuppression, which may require blood transfusions or the use of colony-stimulating factors. Myelosuppression from chemotherapy occurs earlier in the course of treatment in older patients. No significant nitrosourea-induced pulmonary toxicity was noted in patients over the age of 60, possibly because their survival rates are low, and pulmonary fibrosis occurs after several courses of treatment. Other common side effects of chemotherapy are nausea, fatigue, and loss of appetite. These side effects are mild, are usually self-limiting, and respond well to symptomatic treatment. Procarbazine can cause allergic reactions or, if dietary restrictions are not observed, can cause paroxysmal hypertension. Peripheral neuropathy is a common side effect of vincristine, cisplatin, and procarbazine. The symptoms are numbness in the hands and feet, constipation, and occasionally jaw pain or numbness. When the neuropathy affects the fine motor skills, the offending agent must be discontinued. Preexisting conditions such as diabetes, hypothyroidism, and vitamin B_{12} deficiency cause peripheral neuropathy. To avoid debilitating neuropathy, patients need to be evaluated neurologically before starting chemotherapy with these drugs. Patients treated with etoposide are at higher risk for second malignancies, mainly leukemias. In patients with malignant gliomas, long-term survival is low and does not allow enough time for a second malignancy to develop. These side effects are noted in all age groups.

Hormonal Therapy

Laboratory studies have shown that protein kinase C (PKC) is an important factor in promoting proliferation of malignant gliomas. Tamoxifen, an estrogen-receptor blocking agent commonly used in treating breast cancer, has been shown to inhibit proliferation of malignant

astrocytomas via nonestrogen-receptor-mediated PKC blockade. In clinical studies, the dose of tamoxifen shown to inhibit brain tumor growth is much higher than the dose used for breast cancer (40-100 mg b.i.d. vs 10 mg b.i.d.). The effect appears to be dose dependent and is cytostatic rather than cytotoxic. Still, in patients with good performance status, tamoxifen has been shown to increase survival. The antimitotic effect is not reversed by estrogen, indicating a nonestrogen-receptor-mediated mechanism of action. Tamoxifen does cross the blood-brain barrier[123,124] and is well tolerated, even at these high doses. Tamoxifen is now being studied in combination with BCNU as adjuvant therapy after RT. Because of its good safety profile and ease of administration, tamoxifen can be offered as an alternative treatment to elderly patients with malignant gliomas who had received RT and do not wish to take chemotherapy but would consider other forms of treatment. The incidence of thromboembolic complication from tamoxifen is higher in the brain tumor patients than in breast cancer patients, but these patients have an overall higher incidence of thromboembolism, even without tamoxifen.

Biologic Therapy

Biologic therapies with differentiating and immunomodulatory agents are presently under investigation as alternatives to the conventional forms of treatment.[125,126] They can be used alone or in combination with RT or chemotherapy. These agents are cytostatic rather than cytotoxic. The mechanisms of action are not yet completely elucidated.

Retinoids: The retinoids — 13-cis-retinoic acid (CRA) and all-trans-retinoic acid (TRA) — are natural and synthetic derivatives of vitamin A and have proven efficacy in some premalignant and malignant conditions.[127] In vitro studies demonstrated the differentiating and growth inhibitory effect of retinoic acid on glioma cells. The growth inhibition is related to a decrease in epidermal growth factor receptor-mediated phosphorylation activity. In clinical studies, CRA showed activity against malignant gliomas.[128,129] The side effects were relatively mild: dryness of the skin and mucosa and headache. In some patients, headaches appeared to be due to increased intracranial pressure (pseudotumor cerebri-type) and responded to treatment with diuretics and glycerol. Another complication of treatment with retinoids that is potentially fatal is pancreatitis, and the enzymes amylase and lipase must be monitored carefully during therapy. Both TRA and CRA are administered orally in doses of 60-120 mg/m^2 per day for 3 weeks, followed by 1 week of rest.

Immunomodulators: Interferons (IFNs) are naturally produced glycoproteins with antiviral, antiproliferative, and immunomodulatory properties.[130] Both IFN-α and IFN-β have demonstrated activity against malignant gliomas in vitro and in clinical trials.[130-133] IFN-α-2b modulates the activity of PKC by downregulating it.[130] There are reports of enhanced activity of IFN and other agents in combination against various tumors, as well as an antiangiogenic effect.[133-135]

Known side effects of IFN therapy are flu-like symptoms and hypotension. Some patients develop low back pain or arthralgia that at times can be severe enough to warrant discontinuing the treatment. This can make IFN less well tolerated by elderly patients with arthritis.

New Treatments for Malignant Gliomas

The management of brain tumors continues to bring new challenges for the treating physicians, and ongoing research is aimed at defining the biologic mechanisms of malignancy and developing new treatment modalities. Managed care policies and the need for cost containment make treatment decisions even more difficult, especially for elderly patients.

Modification of Conventional Therapies

While there has been significant progress in identifying the genes responsible for oncogenesis and drug resistance, finding effective treatments, particularly for malignant gliomas, has been less successful. Some studies combine conventional therapies with novel approaches, while others introduce new experimental treatments.

Factors that influence the efficacy of chemotherapeutic agents are the unique cytoarchitecture of the brain (with an effective blood-brain barrier), the infiltrative pattern of growth of some primary brain tumors, and the heterogeneity of tumor cells. New approaches to chemotherapy are directed at circumventing the blood-brain barrier, overcoming drug resistance mechanisms, and minimizing the systemic and neurotoxicity.

The blood-brain barrier can be circumvented by increasing the dose of the drug (with subsequent increased toxicity), by administering intraarterial chemotherapy with blood-brain barrier modification, or by using new delivery systems. Intratumoral administration has the advantage of allowing delivery of cytotoxic concentrations of drugs in the tumor bed, with no systemic toxicity. The disadvantages are related to diffusion problems and local toxicity (necrosis). RMP-7 is a bradykinin analog that opens the blood-brain barrier

selectively and increases penetration of chemotherapeutic agents into the brain.[136-137] Chemotherapy can be administered intratumorally via an Ommaya reservoir or through liposomes or biodegradable polymers. BCNU wafers (Gliadel) are now available commercially and can be placed into the tumor bed at the time of resection.[138]

Novel Therapies

Gene therapy refers to the introduction of new genetic material into cells to provide beneficial effect to the patient. The preferred method for gene transfer is through viral vectors, which have a high efficiency in infecting host cells by inserting their own genetic material into the host cell genome. Both retroviruses and adenoviruses are studied for use as vectors for gene therapy.[139,140]

The most publicized gene therapy clinical trial for brain tumors involves transfer of the herpes simplex virus thymidine kinase (HStk) gene into tumor cells, using retroviral vectors. HStk is an enzyme that phosphorylates the antiviral prodrug gancyclovir, which becomes virucidal and cytotoxic.[140] Few animal and clinical data are available regarding the efficacy of gene therapy for brain tumors, the long-term effects, and the safety of viral vectors.

Immunoconjugates are cytotoxic compounds that combine a ligand and a cytotoxic agent, which can be a radioisotope, a chemotherapeutic drug, or a toxin.[141] Clinical trials have been conducted on small numbers of patients with leptomeningeal carcinomatosis using immunoradiotherapy.[142] Current clinical trials are underway for treatment of malignant gliomas. Glioma cells express transferrin receptors, which are targeted with immunoconjugates using as ligands either monoclonal antibodies to transferrin receptors, or transferrin, conjugated with a toxin. The toxins are ribosomal inhibitors, either of plant (ricin) or bacterial (CRM-107) origin. The dose of toxin necessary for tumoricidal effect is smaller than predicted by the tumor volume, which indicates a bystander effect. The results of these trials are not yet available.[141,142]

Recent studies evaluate other biologic agents for treatment of malignant gliomas, targeting factors that intervene in cell replication or angiogenesis.

Malignant gliomas utilize mevalonate for synthesis of cholesterol and intermediates for cell replication. Lovastatin and phenylacetates inhibit the enzymes HMG-CoA reductase and MVA-PP decarboxylase and thus affect the mevalonate synthesis and utilization and induce cytostasis and apoptosis. Both lovastatin and phenylacetates are presently in clinical trials.[143,144]

Angiogenesis is an important feature in malignant gliomas. There are multiple angiogenesis factors that can be targeted specifically. Fumagillin, an antibiotic derived from the fungus *Aspergillus fumigatus Fresenius,* was noted to inhibit angiogenesis in vitro.[145] Endostatin and AGM-1470, synthetic analogs of fumagillin that are more potent and less toxic, are now in early clinical trials, and their efficacy is yet to be proven.[146] Thalidomide is an antiangiogenic drug that, in combination with carboplatin, has shown activity against anaplastic gliomas. Thalidomide is also now in clinical trials for meningiomas. Its mild side effects profile makes it an attractive drug for treatment of tumors in elderly patients.

These novel therapies are still in the experimental phase. Larger studies and longer follow-up periods will be necessary to evaluate the safety and efficacy of these new therapies against brain tumors in all age groups as well as the differences, if any, in older patients.

Treatment of Primary Central Nervous System Lymphoma

In nonimmunocompromised patients, primary central nervous system lymphoma is a disease of the elderly. The management combines systemic and intrathecal chemotherapy with RT.[147] Clinical studies show that elderly patients tolerate intensive chemotherapy well. However, prognosis remains poor, with an average survival of only 1 year.

Treatment of Brain Metastases

The treatment modalities are similar for primary and metastatic brain tumors. For brain metastases, the choice of treatment is based also on the status of the systemic disease. When feasible, surgical resection will significantly improve the performance status and prolong survival.[148-150] Brain metastases are optimal lesions for radiosurgery. Chemotherapy can be considered for control of both brain and active systemic metastatic disease.[148]

Age-Related Issues

Diagnosis

Diagnosis of primary brain tumors in the elderly is more difficult and often delayed due to nonspecific symptoms that mimic the physical and cognitive changes seen in the normal aging process. If symptoms evolve over a relatively short period of time (less than 6 months), primary brain tumor or primary central nervous system lymphoma should be considered. An imag-

ing study, preferably an MRI scan of the brain, should be included in the diagnostic workup.

Treatment

There are no therapies designed specifically for treatment of brain tumors in the elderly, even though molecular biology studies indicate that there are specific age-related genetic alterations that determine both the clinical course and the tumor response to therapy. Furthermore, most clinical studies exclude patients over the age of 70. A recent analysis of enrollment in Southwest Oncology Group (SWOG) studies from 1993 to 1996 shows that although patients 65 years of age and older represent 44% of patients with brain tumors (Surveillance, Epidemiology, and End Results data), only 19% were enrolled in SWOG clinical trials.[151] This is due to several factors: stringent age and general health eligibility criteria, the misconception that elderly patients would not benefit from clinical trials, and the fact that there are no clinical trials designed for treatment of brain tumors in the elderly.

The decision to initiate treatment for a brain tumor in an elderly person should be based not only on age, but also on life-expectancy factors such as performance status, neurologic deficits, and coexistent chronic illnesses. These factors will determine the surgical risk in deciding for resection or biopsy as well as whether to consider radiosurgery or brachytherapy in addition to standard external beam RT. For elderly patients with malignant gliomas who have a poor long-term prognosis, conventional fractionation or hypofractionation RT provides palliation and can improve the quality of life over the short term.

Age is an important factor in determining the response of brain tumors to chemotherapy. Patients over the age of 60 have a lower response rate and shorter duration of response than patients 60 years of age or less.[152,153] Using tumor cells obtained from biopsy specimens, Rosenblum et al[153] demonstrated in vitro that the sensitivity of these cells to BCNU correlates strongly with the age of the patient. Tumor cells from patients 50 years of age or less were sensitive in 7 of 8 cases, but cells from only 1 of 8 patients over age 50 responded to BCNU. The reasons for this observed difference are not known. The outcomes for patients receiving chemotherapy are usually analyzed for the whole group. Only a few studies are evaluating age as a parameter of response. The differences in duration of response and survival are significant when comparing patients aged 50 and under with those over the age of 50.[152]

Many elderly patients have chronic illnesses that require medications; thus, special attention must be given to potential drug interactions of chemotherapeutic agents with antihypertensive and antidepressant drugs. Also, elderly patients have a decreased creatinine clearance that must be considered when calculating the dose of the chemotherapeutic drugs.

Quality-of-Life Issues

Brain tumors are debilitating diseases, affecting both the cognitive and physical abilities of the patient. Therapy must be aimed at improving the symptoms and the patient's performance status and minimizing the side effects of tumor treatments.[154] Even if the long-term prognosis is poor for patients with malignant gliomas, physical and occupational therapy will improve the patient's ability to perform activities of daily living. It is important that the necessary home equipment is available and that the family is actively involved in the rehabilitation process.[155,156] Most brain tumor patients develop reactive depression, which seems to be more severe in elderly patients and needs to be treated with medications. The choice of antidepressant depends on the patient's medical history (drugs with anticholinergic side effects must be avoided in patients with prostate hypertrophy or hypotension) and the chemotherapy regimen (tricyclic antidepressants and monoamine oxidase inhibitors should not be prescribed in patients taking procarbazine).

The nature of the tumor and the prognosis must be discussed with the patient and the family at the time of the diagnosis, in a manner that would neither discourage therapy nor raise false hope. Therapy can prolong survival with reasonably good quality of life. All the options should be discussed, and the patient should be allowed to make the choice.[157,158] The treating physicians need to involve the patient and family in management decisions, thus creating a support system for the patient.[159]

Practical Considerations

Brain tumors in elderly patients behave more aggressively and tend to be more resistant to available treatments. However, each case should be considered individually in deciding on therapy. The goals of therapy are to control the tumor growth and to improve the patient's neurologic status.[155] Age alone should not be the major determinant for therapeutic decisions. More aggressive therapy can benefit patients with good performance status, relatively small tumors that can be resected, and more favorable histologies. For patients with poor performance status, significant neurologic deficit that is not likely to improve with treatment, mul-

tifocal tumors, and debilitating medical problems, it is reasonable to limit the management to corticosteroids and supportive care or, if desired by the patient, to palliative RT.

Conclusions

Brain tumors continue to carry a poor prognosis despite aggressive multimodality therapy, and age has a negative influence on the prognosis. Currently, treatment is not curative, except for low-grade tumors such as meningiomas. New treatment modalities are being developed based on molecular biology data. At this time, the long-term efficacy of these new therapies is not known.

Elderly patients can benefit from therapy for brain tumors, and the treatment must be individualized. Recent advances in treating brain tumors with limited surgery, radiosurgery, and controlled toxicities have decreased the morbidity and improved the access and acceptance of elderly patients to brain tumor therapy. Clinical trials are needed that are designed specifically for the treatment of brain tumors in the elderly.

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