Conferences and Reviews

Brain Tumors

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Recent advances in experimental tumor biology are being applied to critical clinical problems of primary brain tumors. The expression of peripheral benzodiazepine receptors, which are sparse in normal brain, is increased as much as 20-fold in brain tumors. Experimental studies show promise in using labeled ligands to these receptors to identify the outer margins of malignant brain tumors. Whereas positron emission tomography has improved the dynamic understanding of tumors, the labeled selective tumor receptors with positron emitters will enhance the ability to specifically diagnose and greatly aid in the pretreatment planning for tumors. Modulation of these receptors will also affect tumor growth and metabolism. Novel methods to deliver antitumor agents to the brain and new approaches using biologic response modifiers also hold promise to further improve the management of brain tumors.

(Black KL, Mazziotta JC, Becker DP: Brain tumors. West J Med 1991 Feb; 154:186-197)

Peripheral Benzodiazepine Receptors—Mechanisms in Brain Tumor Biology

KEITH L. BLACK, MD*: There are two classes of benzodiazepine receptors in mammalian tissues. One class of receptors (the "central" receptor) is located on neurons and is the site at which benzodiazepine ligands are thought to exert their antianxiety, anticonvulsant, and muscle relaxant effects.[1-3] These central binding sites are closely linked to γ-aminobutyric acid (GABA) receptors, modulate the GABA-regulated anion channel, and are located on the cell membrane.[2,4,5] The second class of benzodiazepine receptors (the "peripheral," nonneural receptor) is sparse in normal nervous tissue but prominent in many other tissues, such as kidney, heart, platelets, and lymphocytes.[6-8] High-affinity binding by peripheral benzodiazepine ligands to rodent glial tumor was shown in homogenate studies.[8-12] Based on these findings, it was recently suggested that peripheral benzodiazepine receptor ligands could be used specifically to image glial tumors in vivo and provide better definition of tumor borders and biologic character.[13,14] Second, but no less important, the dramatic increase in the expression of peripheral benzodiazepine receptors in brain tumors has recently prompted further investigation into a possible role of these receptors in brain tumor biology. Because the receptor was shown to localize on the outer membrane of mitochondria, considerable work has focused on the modulation of cell metabolism by the peripheral benzodiazepine receptor. Recent work has also suggested that selective peripheral benzodiazepine ligands may act as mitogenic agents and increase tumor cell proliferation and DNA synthesis.

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Brain Tumor Imaging

Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) techniques currently used to image tumors in the central nervous system rely on differences in tissue attenuation characteristics, a breakdown of the blood-brain barrier to contrast agents, mass effect, or changes in glucose or amino acid transport.[15] The limitations of these methods, most apparent in glial and other infiltrative tumors, are due to their failure to identify tumor cells that reside beyond the borders of the imaging abnormality.[16] An ability to image tumors with a ligand that binds specifically to tumor cells and readily crosses the intact blood-brain barrier might significantly improve tumor resolution in the brain and permit better identification of the outermost margin of tumor cells. Peripheral benzodiazepine receptor ligands seem to fulfill both criteria: they are not barred by the blood-brain barrier, and they have high specific binding to glial tumors.

The possibility that a peripheral benzodiazepine receptor ligand might be used specifically to image glial tumors was first suggested by the findings of Starosta-Rubinstein and associates.[13] Published findings from our laboratory were in agreement with this previous report that peripheral benzodiazepine ligands bind selectively to glial tumors in rats, with little binding to normal brain or necrotic tissue.[14] The intravenous administration of the selective peripheral benzodiazepine ligand, [^{3}H]PK 11195 (1-[2-chlorophenyl]-*N*-methyl-*N*-[1-methylpropyl]-3-isoquinoline carboxamide),

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
ED_{50} = median effective dose
MRI = magnetic resonance imaging
PET = positron emission tomography

or the mixed peripheral and central ligand, [^{3}H]flunitrazepam (after pretreatment with clonazepam to block central binding sites), showed binding densities of peripheral benzodiazepine receptors threefold to fivefold higher in experimental glial tumors compared with normal cortex. Peripheral binding could be displaced by the preadministration of excess PK 11195. Topographic correlation was excellent between areas of histologically verified tumor and high densities of peripheral benzodiazepine binding (Figure 1). It was further shown, however, that peripheral benzodiazepine binding was not exclusive to tumors of glial origin but that, in fact, substantial binding occurred in the experimental metastatic tumors. The nonexclusive binding of peripheral benzodiazepines to glial tumors was further supported by in vitro findings that peripheral ligands will bind to various tumors in humans (Table 1),[17] which suggests that they may have limited use as a marker to differentiate tumors. We did, however, find a significant correlation between high binding and the degree of malignancy in gliomas in humans (Table 2). In vitro studies also showed that the number of receptors (B_{max}) on C6 and Walker 256 tumors was increased rather than the affinity of the ligand for the receptor site (Table 3).[18]

Three-dimensional reconstructions were recently applied to autoradiographic images of peripheral benzodiazepine binding and compared with histologic images to confirm the spatial and structural accuracy of receptor mapping images in an experimental glial tumor. A close topographic correlation between histologic features and tumor binding was found. Similar techniques using positron-labeled peripheral benzodiazepine receptor ligands are now being applied in humans. Although current PET resolution is limited, small clusters of tumor cells may be located using these techniques. This could have important implications in identifying the surgical margins in subgroups of patients without diffuse spread of glial tumor cells where radical resections may prove beneficial. Based on the intensity of uptake, insight may be obtained into the biologic behavior of the tumor to help in preoperative planning and in determining prognosis.

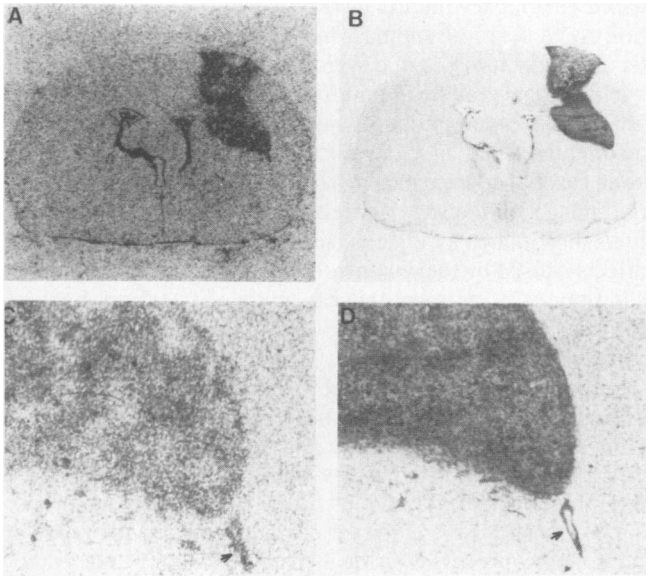

Figure 1.—A digitized autoradiogram **(A)** and thionin-stained section **(B)** show RG-2 tumor after the administration of [^{3}H]flunitrazepam with clonazepam. Binding to normal brain is slightly higher compared with [^{3}H]PK 11195 administration. In magnified comparisons of the same autoradiogram **(C)** and thionin-stained section **(D)**, tumor definition and correlation with histologic features remain high. A fingerlike projection of invading cells **(arrow)** seen on the magnified thionin-stained section **(D)** is also visualized on the magnified autoradiogram **(C; arrow)**.

Tumor Biology

The biologic role of peripheral benzodiazepine receptors in brain tumors is unclear. Unlike the central receptor, which is located on the cell membrane, the peripheral binding site is localized to the mitochondrial and nuclear subcellular fractions,[19,20] which implies a role for the receptor in oxidative metabolism and ion fluxes.

Studies of the effects of peripheral-type ligands have also reported an inhibition of the proliferation of thymoma cells,[21] the suppression of thymidine incorporation into the DNA of glial cells,[22] the blocking of mitogenesis in Swiss 3T3 cells, and the induction of differentiation in Friend erythroleuke-

TABLE 1.—*Specific Binding of [^{3}H]PK 11195 to Nonglial Human Brain Tumors**

Histologic Tumor Type	*Specific Binding, fmol/mg tissue*
Sarcoma	510.0
Meningioma	353.7 ± 93.6
Hemangiopericytoma	180.9
Primitive neuroectodermal tumor, n = 2	154.3
Craniopharyngioma	107.7
Normal	77.7 ± 28.4

*Values are expressed as the mean when n = 1. Standard deviation values are given when n ≥ 2.

TABLE 2.—*Specific Binding of [^{3}H]PK 11195 to Glial Tumors in Humans**

Histologic Tumor Type	*Specific Binding, fmol/mg tissue*
Normal, nonneoplastic	77.7 ± 28.4
Necrosis	74.8 ± 38.0
Infiltrated	219.8 ± 31.9
Low-grade glioma	267.3 ± 54.0
High-grade glioma	452.1 ± 46.5

*For statistical analysis (analysis of variance and unpaired Student's *t* test), regions of interest were defined as nonneoplastic (no neoplastic cells), necrotic (nonviable debris), infiltrated (tumor cells mixed with histologically appearing normal cells), low grade (glioma grades I and II), and high grade (glioma grades III and IV). The 3 necrotic sections were all from patients with high-grade gliomas. Infiltrated sections included patients from the high- and low-grade groups. Significant differences were found between nonneoplastic versus infiltrated ($P < .0005$), nonneoplastic versus low-grade ($P < .0005$), nonneoplastic versus high-grade ($P < .0005$), infiltrated versus high-grade ($P < .0005$), and low-grade versus high-grade ($P < .005$) tumors.

TABLE 3.—*Specific Binding of [^{3}H]PK 11195 to Rat Tumors**

Tissues	*K_d, nmol/liter*	*B_{max}, fmol/mg*
C6 glioma	2.09±0.74	1,089.3±232.2
RG-2 gliomas	2.29±0.30	1,027.3± 78.7
Walker	2.17±0.24	924.2±183.7
Normal cortex	2.04±0.49	62.1± 12.8

*Dissociation constant (K_d) and maximum benzodiazepine receptor (B_{max}) values for [^{3}H]PK 11195 in experimental tumors and normal rat brains are determined by Scatchard analysis. Values are expressed as the mean ± standard deviation of 3 independent experiments.

mia cells.[23] On the other hand, they enhance melanogenesis in melanoma cells[24] and enhance the specific induction of c-*fos* messenger RNA and protein by nerve growth factor more than 100-fold.[25] Diwan and co-workers reported the promotion of hepatocellular carcinogenesis in B6C3F1 mice by diazepam after initiation by *N*-nitrosodiethylamine.[26] These effects, however, were found at micromolar concentrations, whereas peripheral benzodiazepine receptors were saturated at concentrations in the nanomolar range.[9,21,27]

Because of the discrepancy between the dose of peripheral benzodiazepines needed to show growth control and their binding constants, we recently investigated the effects of peripheral benzodiazepines on cell proliferation of C6 glioma and on the mitogenesis of Swiss 3T3 cells in culture within the concentrations at which receptor binding occurs.[28] We found that PK 11195 increased the growth rate of C6 glioma cells by 20% to 30% in the nanomolar range in serum-free medium. Incorporating tritium-labeled thymidine into C6 glioma cells also increased their growth rate 22% and 25%, respectively, after treatment by the selective peripheral benzodiazepine ligands, PK 11195 and Ro 5-4864. When the effect of PK 11195 as a mitogenic agent was estimated by [^{3}H]thymidine incorporation using Swiss 3T3 cells, PK 11195 was found to increase DNA synthesis 170% over that of control at 10 nmol per liter. Higher concentrations of benzodiazepines inhibited DNA synthesis. Peripheral benzodiazepine binding sites, however, were shown to decrease in number after exposure to serum-free medium or to 10 nmol per liter of PK 11195.

It seems that peripheral benzodiazepine ligands have biphasic effects on cell proliferation. At concentrations in the nanomolar range, they stimulate [^{3}H]thymidine incorporation into DNA and increase cell proliferation in C6 glioma. They also show mitogenic activity in cell lines such as Swiss 3T3 cells. At micromolar concentrations, however, they inhibited DNA synthesis. Other authors, who have also suggested that peripheral benzodiazepines are involved in regulating cell proliferation,[21-25] have indicated an antiproliferative effect of benzodiazepines at the micromolar range. Pawlikowski and colleagues reported an antiproliferative action of peripheral-type benzodiazepines on human glioma at the micromolar range (1 to 100 μmol per liter).[22] A strong positive correlation between the binding affinity of benzodiazepines for the peripheral-type receptor and their antiproliferative activities was reported in mouse thymoma cells,[21] though there was no significant correlation between the activities of benzodiazepines and their reported degree of affinity.[6,23,24,29] In Wang's experiments there was an approximately 2,000-fold difference in dosage between receptor binding and biologic effects[21]; the median effective dose (ED_{50}) for Ro 5-4864 in inhibiting [^{3}H]thymidine incorporation into thymoma cells was 16.1 μmol per liter, whereas the intensity concentration where 50% of receptors were bound (IC_{50}) was 8.5 nmol per liter. An in vitro binding assay using autoradiography or cell homogenates showed that peripheral benzodiazepine binding should be saturated at 10 to 20 nmol per liter.[18,21] Clarke and Ryan used erythroleukemia cells in their study and concluded that differentiation was induced by the lipophilic properties of certain benzodiazepines.[23] To the contrary, the stimulation of cell growth of C6 cells and mitogenic activity of Swiss 3T3 cells were found in the nanomolar range, which corresponded to the binding affinities of the compounds for the peripheral benzodiazepine receptors. Ruff and associates also reported that the chemotaxis of human monocytes was enhanced with an ED_{50} of 10^{-13} mol per liter for Ro 5-4864, whereas a higher concentration ($>10^{-8}$ mol per liter) resulted in a reduced chemotactic response.[30] These findings also support our conclusion that peripheral benzodiazepines have a biphasic effect on cell proliferation.

Peripheral benzodiazepines, however, are not polypeptide growth factors like epidermal growth factor or platelet-derived growth factor that has been found to be active on glial cells. Also, because receptors for peripheral benzodiazepines are thought to localize on the mitochondrial outer membrane,[19,20] it will be worthwhile to investigate in future studies whether this receptor-ligand complex will significantly affect the mitochondrial DNA or whether the activated receptor transmits mitogenic signals to the nucleus.

Clinical Implications

Selective high-density binding by peripheral benzodiazepine ligands could be used clinically in several ways. First, these ligands are amenable to conjugation with potentially cytotoxic compounds. The localization of binding sites to nuclear and mitochondrial fractions could increase their therapeutic advantage compared with targets on the cell surface. The effect of the modulation of the peripheral receptor itself on tumor growth and differentiation also remains to be explored. Further, positron-labeled benzodiazepine ligands, such as carbon 11-labeled PK 11195, could potentially improve the definition of the outer border of tissues infiltrated with malignant tumor cells or indicate residual tumor after surgical therapy. These novel concepts are currently being investigated.

Positron Emission Tomography in the Study of Cerebral Neoplasms

Approaches to Brain Tumor Imaging

JOHN C. MAZZIOTTA MD, PhD*: Although anatomically based imaging techniques have provided substantial information about cerebral gliomas, they can be inconclusive in detecting early tumors, in discriminating tumors from edema, the histologic grading of tumors, and in differentiating tumor recurrence from radiation necrosis.[31] Structural imaging techniques, such as x-ray computed tomography and magnetic resonance imaging, provide high-quality, high-resolution images of the site of cerebral neoplasms and the distortions they induce in adjacent cerebral structures by the mass effects caused by their own volume and attendant edema. In addition, by using agents such as iodinated contrast material in x-ray CT, alterations in the blood-brain barrier may also be detected by these techniques. Distinguishing actual sites of viable tumor from zones of necrosis or surrounding edema is difficult with such methods, however. Similarly difficult is clinically differentiating recurrent tumor from radiation necrosis in a patient who has new signs and symptoms that are referable to a site of previous tumor therapy.

Positron emission tomography measures a wide range of physiologic processes critical in understanding the pathophysiology of cerebral disorders.[32-35] These processes include the ability to examine cerebral physiology, biochemistry, hemodynamics, and pharmacokinetics in vivo in health and disease. Critical to the understanding of tumor growth and strategies to limit or block such growth is a knowledge of

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tumor metabolism, blood flow, protein synthesis, blood-brain barrier integrity, and the binding of specific compounds to receptors found on tumor cell surfaces. Each of these processes is important, but the study of the biochemical relations between the processes—that is, stoichiometry—may provide an even more sensitive indicator of tumor type, grade, and natural history.[4] In addition, the effect of the tumor on adjacent or distant tissue is important in understanding the constellation of signs and symptoms manifested by a patient at a given point in time. Thus, tumor edema may produce dysfunction in adjacent tissue either directly or by secondary ischemia. Simultaneously, functional deafferentation and deafferentation of pathways leading to and from the zone of tumor and edema may disrupt normal neuronal activity at far distant sites within and between the cerebral hemispheres and that affecting cerebrocerebellar neuronal connections.[34] Positron emission tomography can identify such local and distant functional disconnections.[34]

Because PET provides functional measures of neuronal activity and biochemistry, we can map normal sites of cerebral activity during behavior. Thus, patterns of cerebral metabolism and blood flow change when a subject is asked to do tasks that involve reading, listening, perceiving sensory stimuli, and movement.[32] By having patients with brain tumors perform such tasks, it is possible to identify whether critical neuronal networks, presumed to lie close to the site of a planned tumor resection, will be adversely affected by the surgical procedure, resulting in a major neurologic deficit for the patient.

Positron Emission Tomography

Positron emission tomography is an imaging technique that provides an accurate measurement of the concentrations of trace amounts of compounds labeled with positron-emitting isotopes introduced into the body either by inhalation or intravenous administration.[32] The imaging device produces cross-sectional and planar images of the distribution of the administered radiopharmaceutical agent. With the use of labeled compounds to trace physiologic processes, it is possible to use the local tissue concentrations, obtained from the PET images, to quantify these physiologic processes if the mathematic relation between the process and the concentration of the tracer in the tissue is understood. These mathematic relations are termed tracer kinetic models, and they are needed to understand the behavior of compounds in the body and to interpret the resultant data validly. This usually requires both a measurement of the time course of the concentration of the administered tracer in the blood and sequential images of the organ of interest using PET to determine the tissue tracer concentration. Once the model is validated, the procedure can be simplified and a single set of images can be taken at the end of a defined interval between administering the tracer and acquiring data.

Isotopes that emit positrons have several important qualities. Such isotopes include those of the natural elements of the body, such as nitrogen 13 (^{13}N; 10-minute half-life), carbon 11 (^{11}C; 20-minute half-life), and oxygen 15 (^{15}O; 2-minute half-life). Because these are isotopes of natural biologic elements, they can be incorporated into compounds that faithfully mimic the chemical behavior of the natural compound, thereby minimizing the perturbation of the biologic systems they are intended to trace. Because of the isotopes' short half-lifes, radiation doses to patients are low. A short half-life, however, produces several practical challenges. First, the radiochemical synthesis of the tracer compound must be rapid for there to be enough isotope left at the end of the synthesis for reasonable imaging in a patient. Second, the short half-life of a compound dictates that the isotopes and compounds, in general, must be made at the site of the PET imaging instrument.

TABLE 4.—*Positron Emission Tomography and the Management of Cerebral Gliomas*

Determines tumor grade, which aids in management decisions and guides prognosis
Determines effect of tumor on adjacent and remote cerebral tissues
Monitors progression, change in grade, and therapy effects
Helps in choice of optimal site for biopsy
Differentiates radiation necrosis from tumor recurrence

Isotopes used in PET studies are produced in charged-particle accelerators that include linear accelerators and cyclotrons. At present, the usual approach is to build compact cyclotrons that are used for medical applications, such as the production of positron-emitting isotopes. More than 500 compounds have been labeled with ^{15}O, ^{13}N, ^{11}C, and fluorine 18 (^{18}F) for use with PET.[35,36] These compounds range from simple labeled molecules such as water, carbon monoxide, and oxygen gas to carbohydrates, amino acids, fatty acids, neurotransmitter analogues and precursors, as well as receptor ligands.[35,36]

Positrons are emitted from unstable nuclei and travel a short distance in tissue before coming to rest. Once at rest they combine with nearby electrons, resulting in their mutual annihilation. The resultant energy of annihilation results in two photons emitted at an angle of 180 degrees to one another. These annihilation photons are detected by crystals in the PET camera and are converted into voltages by the system's electronics. Because of the 180-degree emission produced by positron annihilation, crystals on opposite sides of the patient are electronically linked (electronically collimated) to identify those events that take place in a given tomographic plane. This feature permits PET cameras to have uniform, high spatial resolution (state-of-the-art cameras have 6- to 7-mm resolution in all three dimensions).[37]

Thus, with the unique features of PET, including the use of isotopes of natural elements, valid tracer kinetic models, and the unique physical properties of positron decay, it is possible to quantify a wide range of physiologic, biochemical, and hemodynamic processes in the human body using this technique. When applied to the study of cerebral neoplasms, we can use these methods to measure tumor metabolism, blood flow, protein synthesis, blood-brain-barrier integrity, and the binding of specific ligands to membrane receptors. With this unique technique, we can collect previously unavailable data about cerebral neoplasms, which has proved useful in the management of patients with these disorders and in providing insights into the pathophysiology of the neoplastic process itself (Table 4). As these tumor properties are explored with PET, considerable studies have been done and several reviews have been reported.[38-49]

Glucose Metabolism

Tumors have an accelerated rate of glycolysis that can exist despite adequate oxygenation.[50-52] This property, once thought to be unique to tumors, is characteristic of increases

in intermediary metabolism seen with rapidly growing tissue of any type. Weber has shown a correspondence between the rate of tumor metabolism and the growth rate of individual malignant cells[51]; he has attributed this altered metabolism to changes in the concentrations of certain key rate-controlling enzymes in the metabolic pathway. The accelerated glycolytic pathway can be shown with PET studies of glucose metabolism using ^{18}F-labeled fluorodeoxyglucose.[53-55]

In studies of experimentally induced gliomas in animals[56] and human PET studies,[41,57-59] there was evidence of high glucose metabolism within the tumor itself. Hossmann and associates injected intracerebral glioma cells into rats to show that with tumor development, glucose use increased out of proportion to cerebral blood flow.[56] In addition, they found that blood flow decreases in the tissue immediately surrounding the tumor but not in the contralateral hemisphere.

Studies by Di Chiro and colleagues at the National Institutes of Health have shown a remarkable correlation between the metabolic rate and histologic grade of gliomas.[41,57-65] The most consistent finding is the appearance of "hot spots" of hypermetabolism in virtually all grade III and IV gliomas (Figure 2).[41,57-59] Areas of hypermetabolism were only rarely seen in low-grade (I and II) tumors. On average, grade I and II gliomas had metabolic rates similar to that of normal white matter, whereas grade III and IV tumors have metabolic rates comparable with or in excess of normal grey matter (Figure 2).[41] In all cases, peak values for tumor metabolism were used. Similar results were obtained for the gliomas of the upper cervical spinal cord and brain stem.[59,65]

In a separate study by Tyler and co-workers, fluorodeoxyglucose and PET were used to determine tumor glucose metabolism versus tumor grade in 16 patients.[66] Although the highest metabolic rates found were among those patients with grade IV tumors, there were examples of high-grade tumors that apparently had low metabolic rates; all these patients were untreated at the time of tumor metabolism measurements. Tyler and associates analyzed their data in comparison to grey matter of the contralateral hemisphere,[66] whereas the group at the National Institutes of Health used white matter as their reference tissue.[41,58] Thus, there seem to be differences in the interpretation of results, owing in part to the fact that the latter study did not rely on visual inspection of "hot spots" but rather averaged the entire tumor volume and, in addition, studied patients who had been untreated at the time of imaging. Although there is not complete agreement, there generally seems to be an excellent correspondence between the metabolic rate and tumor grade.

The metabolic grading of glioma malignancy has prognostic importance.[67,68] In a study of 45 consecutive patients with proven high-grade gliomas (grades III and IV) studied at the National Institutes of Health, glucose metabolism was evaluated as a measure of prognosis.[67] All patients received radiation therapy before their entry into the study, 32 patients had received chemotherapy, and most patients (41/45) had contrast enhancement of their tumors on x-ray CT. Glucose use in the tumor was compared with that of the contralateral side. A ratio of 1.4:1 of tumor to nontumor was found to be the median level of glucose use, and patients were divided into two groups with regard to their survival (Figure 3).[69] Patients having tumors with high metabolism—ratios greater than 1.4—had a mean survival of 5 months; those with tumors having a ratio of less than 1.4 had a mean survival of 19 months. The histologic grade of tumors also correlated with survival, with the patients with grade III tumor surviving longer than those with grade IV. The PET findings, however, were superior to histologic variables in predicting ultimate prognosis. Thus, patients with metabolic tumor ratios greater than 1.4 had short survival times, regardless of their histologic grade.

Measurements of glucose metabolism by PET in cerebral neoplasms are useful in identifying the grade of tumor with respect to malignancy in the glioma series and in determining the prognosis for a patient. In addition, measurements of glucose metabolism support the concept put forth by Warburg nearly 60 years ago that accelerated glycolysis is a characteristic of tumors and is proportional to their degree of malignancy.[52]

Cerebral Blood Flow and Oxygen Use

Several investigators have examined the cerebral blood flow and oxygen use of cerebral neoplasms.[68-71] Despite the

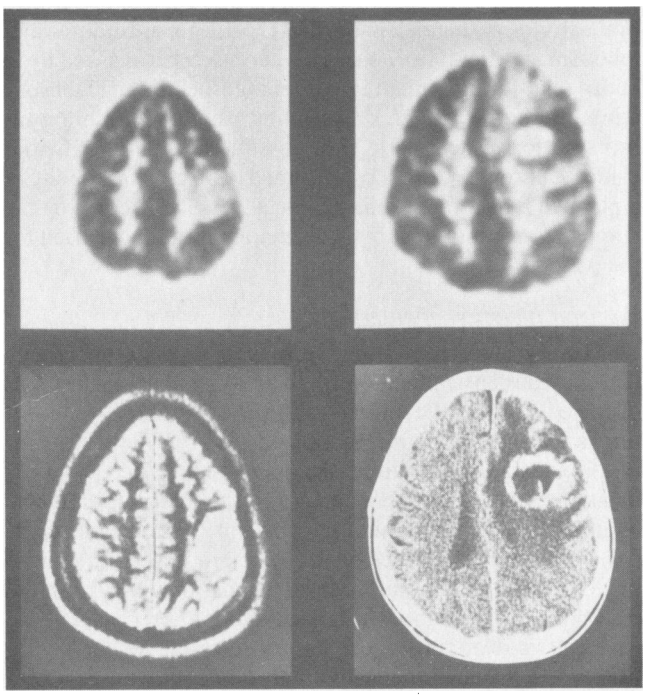

Figure 2.—High- and low-grade gliomas are differentiated with positron emission tomographic (PET) determinations of glucose metabolism. The upper row of images shows PET studies of glucose metabolism using [^{18}F]fluorodeoxyglucose (FDG), the bottom left is a magnetic resonance imaging (MRI) study, and the bottom right is an x-ray computed tomographic (CT) study after the administration of iodinated contrast material. The patient depicted in the left column has a low-grade (grade II) glioma of the frontoparietal cortex. Surrounding edema is obvious in the MRI scan. The glucose metabolism of this lesion is low and comparable with that of normal white matter. In contrast, the patient whose studies are depicted in the right column shows the appearance of a high-grade (grade IV) glioma in the frontal lobe. The x-ray CT study of this patient shows a central area of low attenuation surrounded by a low-density area that extends throughout the frontal and into the parietal lobe. The latter distribution is consistent with tumor-associated edema. The FDG-PET study of this patient shows a central area of low or absent metabolic activity consistent with tumor necrosis and a surrounding area of high metabolic activity comparable with that of the normal grey matter and consistent with a highly malignant glioma. Surrounding the hypermetabolic zone is a more general reduction in glucose metabolism in the adjacent frontal cortex, which may represent the effects of edema or pressure effects, or both, directly exerted by the tumor. Thus, while the site of these lesions, their attendant edema, and mass effects can be shown by x-ray CT or MRI, information about the histologic nature of tumors is, in addition, provided by measurements of glucose metabolism with PET.

fact that cerebral gliomas have an accelerated rate of the use of glucose, reflecting their high glycolytic rate, they have decreased oxygen use. These tumors shift away from oxidative metabolism (which supports the prediction of findings in animals) where fast-growing tumors have augmentation of the Embden-Meyerhof pathways despite adequate oxygen availability. These studies have included the measurements of local cerebral blood flow, oxygen use, and oxygen extraction fraction in cerebral gliomas and metastatic brain tumors using ^{15}O-labeled compounds and PET (Figure 4).[68-71] These results have been discussed by Beaney and associates with respect to cerebral and systemic tumors.[73,74] In addition, these authors found that surgical decompression of brain tumors reduces the abnormalities in blood flow and oxygen use, indicating a direct physiologic correlation with beneficial effects for this type of surgical treatment.

The stoichiometry of brain tumors indicates that they have enhanced glycolysis (increased glucose use), normal-to-mild reductions in cerebral blood flow but decreased cerebral oxygen use despite an adequate supply of oxygen in the arterial blood (low oxygen extraction fractions). These data are important in selecting the appropriate radiation or chemotherapeutic regimens for patients with tumors, particularly as they can be measured in individual patients to determine if their tumors are existing in oxygen-rich or oxygen-deprived environments. The use of PET to monitor the effects of therapeutic modalities while doing stoichiometric studies of the tumor can and should continue to play a significant role in the future understanding of the response of tumors to the maneuvers.

Blood-Brain-Barrier Alterations

The initial PET studies of intracerebral neoplasms used gallium 68 (^{68}Ga)-labeled edetic acid to localize altered blood-brain-barrier sites.[75-78] These studies and others using rubidium 82 (^{82}Rb) resulted in discrete and precise localization of such tumors that correlated closely with iodinated contrast-enhanced x-ray CT images in the same patients.[79] Such studies have provided a quantitative model for calculating molecular diffusion rates in and near tumors.[78]

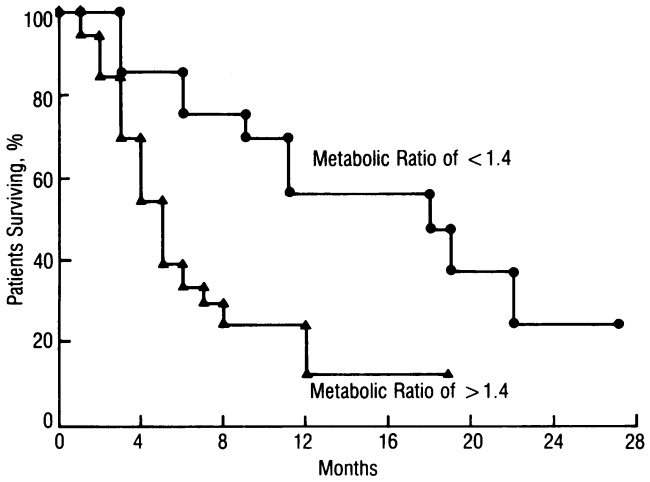

Figure 3.—Glucose metabolism is correlated with prognosis in patients with high-grade gliomas. The ratio of glucose metabolism in tumor relative to the contralateral brain tissue is termed the metabolic ratio. Patients having tumors with ratios greater than 1.4 had a mean survival of 5 months, whereas those with tumors having ratios of less than 1.4 had a mean survival of 19 months (from Patronas et al[67]; reproduced with permission).

Yen and associates used ^{82}Rb to examine patients with cerebral gliomas and intracranial metastases.[80] They showed the advantages of using this isotope, which are related to the increased mean residence time for rubidium relative to iodinated compounds, in addition to the rapid clearance of rubidium from the blood, which diminishes its recirculation. These authors concluded that ^{82}Rb imaging was more sensitive than contrast CT in detecting blood-brain-barrier alterations because of its higher distribution volume and smaller molecular size, making the penetration of minimal blood-brain-barrier defects possible.

Rubidium 82 has also been used to examine the effects of steroids and whole brain irradiation on blood-brain-barrier function.[81] It has been suggested that steroids decrease the permeability of tumor capillaries to small hydrophilic molecules, including some chemotherapeutic agents, and that steroid pretreatment prevents abrupt increases in tumor capillary permeability after cranial irradiation. Within 24 hours of administration, giving high doses of methotrexate results in alterations in the blood-brain barrier, as shown with the use of rubidium 82, and widespread depressions of glucose metabolism as determined with the use of fluorodeoxyglucose.[82] These alterations of cerebral glucose metabolism were associated with changes in neuropsychologic performance, which were identified in the absence of systemic methotrexate toxicity.[83]

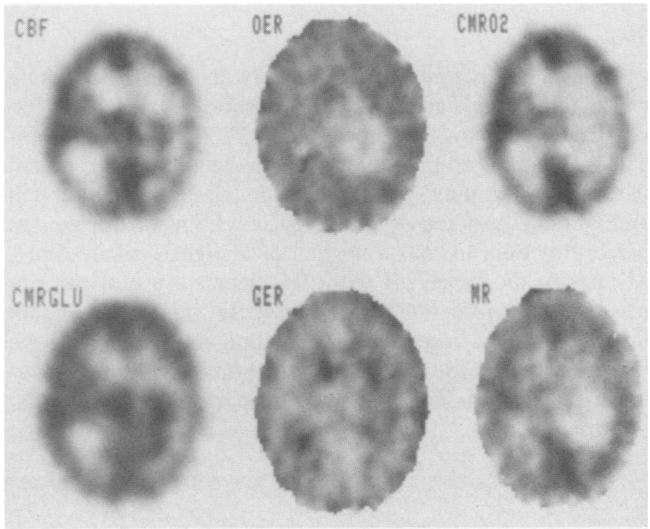

Figure 4.—Tumor stoichiometry was done in a patient with a high-grade cerebral glioma located in the depth of the right cerebral hemisphere. This patient was evaluated with positron emission tomography to determine cerebral blood flow (CBF), oxygen extraction ratio (OER), oxygen use ($CMRO_2$), glucose metabolism (CMRGLU), glucose extraction ratio (GER), and metabolic ratio (MR) of oxygen to glucose use. Blood flow is modestly but heterogeneously elevated in the tumor and suppressed in overlying cortical zones. Both oxygen use and extraction are severely reduced in the tumor itself, and the latter is moderately reduced in the overlying cortex. Glucose metabolism is increased in these lesions, as is typical of high-grade gliomas, but suppressed in overlying cortex, probably owing to edema and pressure effects. Glucose extraction is somewhat increased in the lesion, but the ratio of glucose to oxygen use is low. This latter finding is consistent with the finding of accelerated glycolysis in high-grade gliomas despite the adequate availability of oxygen, evidenced by the low extraction fraction of this lesion. Such a battery of studies in an individual patient permits the determination of the biochemical signature of lesions, such as cerebral gliomas, and the characterization of the biochemistry that underlies their growth and response to therapy. Combined studies such as these may prove critical in understanding the pathophysiology of tumor growth and may predict optimal approaches to their treatment (from Lammertsma et al[69,70]; reproduced with permission).

Amino Acid Incorporation

The initial use of [^{11}C]L-methionine with PET was reported in 1983 by Bergström and colleagues in a single patient with an anaplastic glioma.[83] Since then, amino acid uptake has been used by this group to identify, for biopsy placement, the site of low-grade gliomas that have minimal changes in blood-brain-barrier permeability or glucose use (Figure 5).[83] In addition, investigators at Johns Hopkins University have used [^{11}C]L-methionine and PET to evaluate brain tumors in children. These studies are done with methionine PET studies before and after a loading dose of a competing nonradioactive amino acid, such as L-phenylalanine, 100 mg per kg. The investigators noted a focal increase in the transport of methionine in all cases of pediatric astrocytomas and in one case of ependymoma.[84] Phenylalanine suppresses methionine uptake by the tumor, but the suppression is greater in surrounding tissue altered by radiation gliosis or edema. Thus, preloading with an amino acid that competes for the neutral amino acid carrier transport system results in a more specific and easily identifiable tumor site using labeled methionine.

^{11}C-Labeled L-leucine has also been used for estimates of protein synthesis in the human brain[85] and in cerebral tumors (Figure 6). Because protein synthesis is enhanced in rapidly growing tissue, PET measurements of this process may be a sensitive indicator of tumor cell growth and, hence, of prognosis and responsiveness to therapy.

Tumor pH

The pH of cerebral tumors has been determined using weak acids, such as ^{11}C-labeled carbon dioxide and ^{11}C-labeled dimethyloxazolidinedione.[86-89] These studies indicate that there is no reduction in pH in the microenvironment of tumors. Measurements of tumors in human subjects and in animal models indicate that the tissue within and adjacent to cerebral neoplasms has a normal or a slightly alkaline pH. Measuring the tissue pH with PET seems a useful concept because it may provide clinically relevant information about the regional acid-base state and metabolism, which may have therapeutic implications for the selection of chemotherapeutic agents and radiation therapy in patients with cerebral tumors.[88]

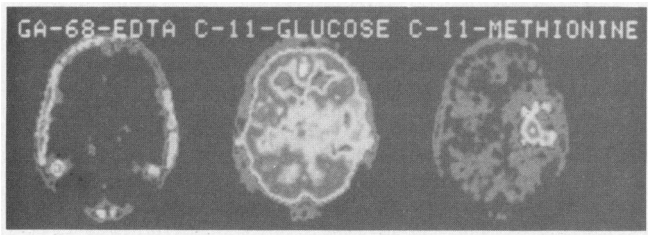

Figure 5.—The blood-brain-barrier integrity, glucose metabolism, and amino acid uptake are shown in a low-grade cerebral glioma. This patient has a low-grade glioma situated at the same site as that of the patient described in Figure 4, namely, deep in the right hemisphere. Blood-brain-barrier integrity is unaltered by this lesion, as evidenced by the absence of extravasation of gallium 68 edetic acid (EDTA), seen in the left image. Glucose metabolism is reduced by administering carbon 11-labeled glucose. Amino acid uptake of the tumor is high compared with surrounding brain, as shown by carbon 11-labeled L-methionine. Such studies indicate that the uptake of compounds such as amino acids may be useful in identifying the sites of viable tumor, particularly as a means of planning the optimal site of biopsy for such deep lesions in situations where contrast enhancement, as determined by positron emission tomography or x-ray computed tomography, is minimal and uninformative (from Bergstrom et al[85]; reproduced with permission).

Ligands

The properties of tumor receptors and the ability to measure these receptors with radioisotope-tagged ligands are areas of active research. This process can be simply extended to PET for determining the receptor properties of human tumors measured externally with a PET instrument. ^{11}C-Labeled ligands for peripheral benzodiazepine receptor complexes (for example, PK 11195), have already been developed and should be but one of several possible radiopharmaceutic approaches to understanding the cell-surface receptors of tumors systemically and in the brain.[13,90,91]

Similarly, dopamine receptors have been visualized in pituitary adenomas using PET and ^{11}C-labeled *N*-methylspiperone.[92] Patients were studied before and after haloperidol pretreatment to identify whether this compound would have significant blocking effects for dopamine receptors in pituitary adenomas. The tumor with the greatest uptake of the ligand and the greatest blocking effect from haloperidol pretreatment was in a patient with a hormonally active prolactinoma. Muhr and co-workers concluded that dopamine-receptor binding can be identified in pituitary tumors in vivo and that this technique can be useful in understanding not only the neuropharmacology of these tumors but also the varying response of prolactinomas to dopamine agonists.[92]

In addition to using PET to identify the tumor cell-surface receptors, it is also possible to examine chemotherapeutic

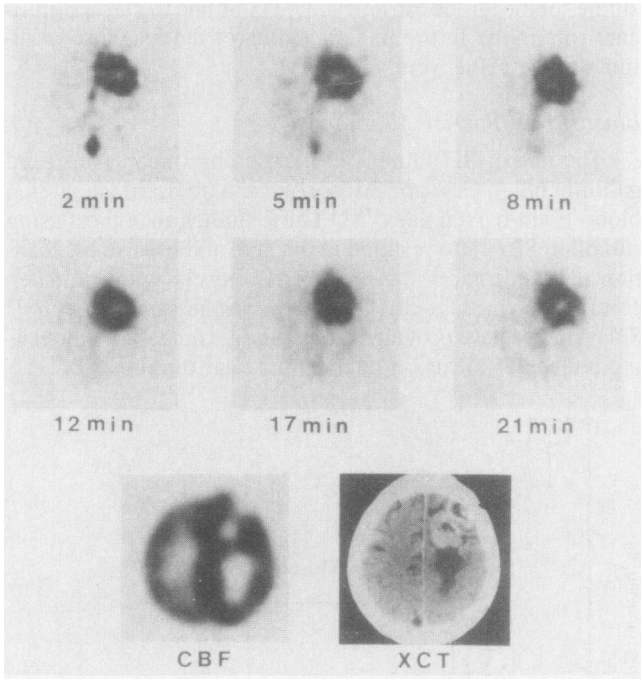

Figure 6.—Protein metabolism is shown in a high-grade (grade IV) cerebral glioma. The upper 6 images show the time course of uptake of [^{11}C]L-leucine in the brain of a patient with a right frontal grade IV glioma. The bottom images show cerebral blood flow (CBF) measured with positron emission tomography and iodinated contrast-enhanced x-ray computed tomography (XCT). The x-ray CT image shows two contrast-enhanced adjacent rings with central low attenuation characteristics. Posterior to these lesions is an area of low attenuation that extends into the white matter of the centrum semiovale. The cerebral blood flow study shows high flow in the areas of x-ray CT contrast enhancement with low or absent flow in the central zone. [^{11}C]Leucine uptake is higher in this lesion than in the normal adjacent brain. It shows a large ring pattern with a central zone of low uptake. Determinations of protein synthesis and amino acid uptake should parallel characteristics of tumor growth and may prove to be important variables for characterizing such growth in response to therapeutic interventions.

agents that have been labeled with positron-emitting isotopes. An example of this approach is typified by the use of ^{13}N-labeled cisplatin[93] or ^{11}C-labeled carmustine (1,3-bis-[2-chloroethyl]-1-nitrosourea; BCNU), a lipophilic alkylating agent.[94] Using [^{11}C]carmustine, Tyler and associates were able to directly compare the pharmacokinetics of intravenous versus superselective intra-arterial administration of the compound in patients with recurrent gliomas. Intra-arterial administration of the compound achieved concentrations that were, on the average, 50 times higher than those achieved with a comparable intravenous dose. The authors concluded that the degree of early metabolic trapping of carmustine in tumors correlated with their clinical response to this form of chemotherapy. Although the use of radiolabeled receptor ligands and labeled chemotherapeutic agents has yet to provide definitive information about the pathophysiology of cerebral neoplasms, these agents represent the tools available to neuro-oncologists for the study of these neoplastic processes. When these data are combined with the stoichiometric information derived from studies with blood flow, blood volume, metabolism, protein synthesis, and pH, they provide a broad set of biochemical and physiologic variables that characterize the natural history of tumors and their response to therapy.

Adjacent and Distant Effects of Tumors as Determined With Glucose Metabolism

All investigators who have examined tissue adjacent to cerebral neoplasms have noted reductions in glucose metabolism,[41,61,95] blood flow, and oxygen use.[73] With regard to glucose metabolism, 54 of 59 patients (92%) studied with PET had such reductions.[41,61,95] Overall metabolic rate reductions for glucose in peritumoral edema were 48% ± 15%. The metabolic rate reduction was proportional to the total volume of the tumor and its edema and to the magnitude of attenuation suppression measured by x-ray CT in edematous tissue. There was no correlation between the reduction in the metabolic rate in edematous tissue and tumor grade, tumor metabolic rate, tumor enhancement (with iodinated contrast on x-ray CT), the severity or duration of neurologic symptoms, the history of seizures, or the use of steroids or other anticonvulsant medications.

A wide range of destructive processes in the brain (for example, cerebral infarction) have been shown by PET to cause distant effects presumably due to the disconnection of afferent and efferent pathways traversing the site of tissue damage.[34] Cerebral neoplasms also show this phenomenon. Distant reductions in metabolism, typically linked with identical reductions in blood flow, have been measured for glucose and oxygen use.[41,64,69,95] In patients with deep cerebral gliomas, suppression of glucose metabolism in the overlying ipsilateral cortex has been identified.[41,64,66] The reverse situation is also true, and cases have been reported wherein cortical tumors have resulted in a suppression of metabolic rates in the ipsilateral thalamus of approximately 20%. When blood flow has been combined with metabolic measurements, it has been found that reductions of a similar degree in both variables occur in a coupled fashion.[69] This is good evidence that these distant effects are not a product of ischemia, but rather reflect functional disconnection of one structure from another.

Decreases in glucose metabolism for the cerebellar hemisphere contralateral to supratentorial gliomas have also been reported[29,34] and have a pattern similar to that seen in patients with cerebral infarctions. In 21 such patients with supratentorial tumors, 12 had contralateral suppression of cerebellar metabolism ranging in magnitude from 8% to 34%. All of these patients had either a tumor or tumor edema involving the sensorimotor frontoparietal cortex with or without thalamic involvement. In the nine patients without contralateral cerebellar metabolic suppression, the tumors were at sites other than those involving sensorimotor cortex. The degree of cerebellar metabolic abnormality was related to the size of the tumor, to the presence of hemiparesis, and possibly to the rapidity of growth of the tumor. The changes in cerebellar metabolism did not seem to correlate with the duration of symptoms. The interesting phenomenon of cross-cerebellar flow and metabolic suppression represents an example of the ability of PET functionally to show anatomic connections between the cerebral hemispheres and the posterior fossa. Similar results have been described in patients with other destructive lesions of the cerebral hemispheres as noted earlier.

Tumor Recurrence Versus Radiation Necrosis

Radiation necrosis can occur in patients receiving 50 to 60 grays (5,000 to 6,000 rads) of radiation to the brain. Neurologic signs and symptoms often occur months after therapy is completed. With the emergence of new or recurrent symptoms referable to the same site as before tumor therapy, it is virtually impossible for clinicians to differentiate between the two inciting processes. Both radiation necrosis and tumor recurrence are associated with mass effect, edema, and contrast enhancement using structural imaging modalities such as x-ray CT or MRI; these modalities have been of little help in differentiating the two disorders.

Because necrotic brain does not metabolize glucose, it has extraordinarily low metabolic rates and provides for relatively easy differentiation from recurrent high-grade tumor when measurements are made with fluorodeoxyglucose and PET (Figure 7). Recurrent high-grade tumors typically show glucose use with values similar to or in excess of normal grey matter. Irradiated but nonnecrotic brain tissue has severely reduced glucose metabolic rates. Patronas and co-workers described this phenomenon and accurately predicted biopsy or autopsy results in patients where this differential issue was of clinical importance.[63] Two patients had radiation necrosis, and three had recurrent tumors in this series.

In a separate and larger series by the same group, glucose metabolism was examined in 95 patients who were referred for the consideration of tumor recurrence versus radiation necrosis. Of these patients, 10 were accurately diagnosed as having radiation necrosis and 85 were accurately diagnosed as having recurrent tumor.[96] Similar results have been obtained in other laboratories.[97] One study of 34 patients had an overall accuracy of 84% in differentiating tumor recurrence from radiation necrosis. This last study, however, differs somewhat from the other protocols in that many of these patients had brachyradiation therapy rather than conventional external-beam therapy.[98]

The value of being able to determine noninvasively whether new signs and symptoms in a previously treated tumor patient represent recurrent tumor or radiation necrosis includes the obvious advantage of avoiding biopsy in every patient. Radiation necrosis can usually be managed medically with drugs to reduce edema. Evidence of recurrent

tumor and knowledge of its estimated histologic grade from PET can dictate the strategy for future therapy, including repeat surgical resection or guided biopsy when clinically indicated.

Functional Activation of the Brain for Surgical Planning

Increases in neuronal activity associated with behavioral tasks can be determined using PET by defining blood flow or glucose metabolism.[32] As noted earlier, the planning of surgical therapies for patients with brain tumors involves avoiding areas that are critical to the performance of key behavior tasks such as movement, audition, language, and vision (Figure 8). By combining structural images from MRI or x-ray CT with metabolic or blood flow activation studies and PET, it is possible to identify the relation between tumor sites and adjacent or surrounding areas of functional activity. For example, consider a patient with a low-grade glioma in the posterior frontal lobe close to, but not specifically invading, the motor cortex for the hand (Figure 2). On neurologic examination, the hand seems normal with only a minimal degree of clumsiness on complex testing. By measuring cerebral blood flow or glucose metabolism while the subject performs a behavioral task with the hand, it is possible to identify those cortical and subcortical structures that subserve the task in a given patient with cerebral tumor. Combining the distribution of the tumor identified from MRI, x-ray CT, or PET (the last using metabolism or tracers for cell-surface receptors such as those for peripheral benzodiazepine receptors), the three-dimensional spatial relation between the neuronal network subserving the motor task and the tumor can be simultaneously identified. With this information, it is possible to plan the extent of the operation, the site of the craniotomy, and the strategy for the resection. Such approaches should make surgical tumor treatment safer, resulting in lower morbidity as reflected by reduced neurologic deficits postoperatively.

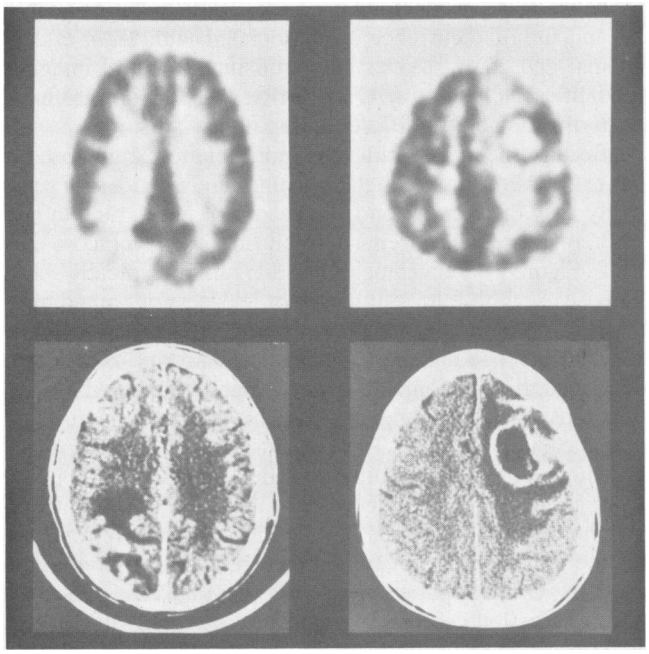

Figure 7.—The upper level of images is from positron emission tomographic studies of glucose metabolism using [^{18}F]fluorodeoxyglucose, whereas the bottom images are x-ray computed tomography (XCT) scans after iodinated contrast enhancement. The patient in the left column has radiation necrosis, and the patient on the right has a recurrent high-grade glioma. Both x-ray CT studies show contrast enhancement and surrounding low attenuation consistent with edema. A differential diagnosis based on x-ray CT alone, therefore, would not be possible, and such a decision would typically require a surgical biopsy. Glucose metabolism is low, or absent, in zones of radiation necrosis, as shown by the patient on the left. Recurrent tumor is evidenced by metabolism that equals or exceeds that of normal grey matter, as shown by the patient depicted in the right column. The patient on the right has a ring area of hypermetabolism surrounding a central zone of tumor necrosis. The reduction in glucose metabolism in the overlying frontal cortex is probably due to edema or pressure effects, or both.

Clinical Strategies for Treating Malignant Brain Tumors

DONALD P. BECKER, MD*: The prognosis is poor for patients with primary malignant astrocytomas (Kernohan classification grades III and IV and World Health Organization classification anaplastic astrocytoma and glioblastoma) despite surgical excision and radiation or chemotherapy (or both). Malignant gliomas account for about half of the 9,000 new cases of primary brain tumors reported annually in the United States.[99] These infiltrative tumors progress rapidly. Resection followed by external-beam irradiation remains the standard treatment, yielding mean survival times of about 35 weeks from the time of the operation.[100,101] It is noteworthy that about 80% of patients have recurrence of the tumor within 2 cm of the initial tumor margin.[102] Some workers have therefore suggested that improved local control could lead to longer survival times.

The factors that have an important influence on patients'

*Professor of Surgery, Division of Neurosurgery, UCLA School of Medicine.

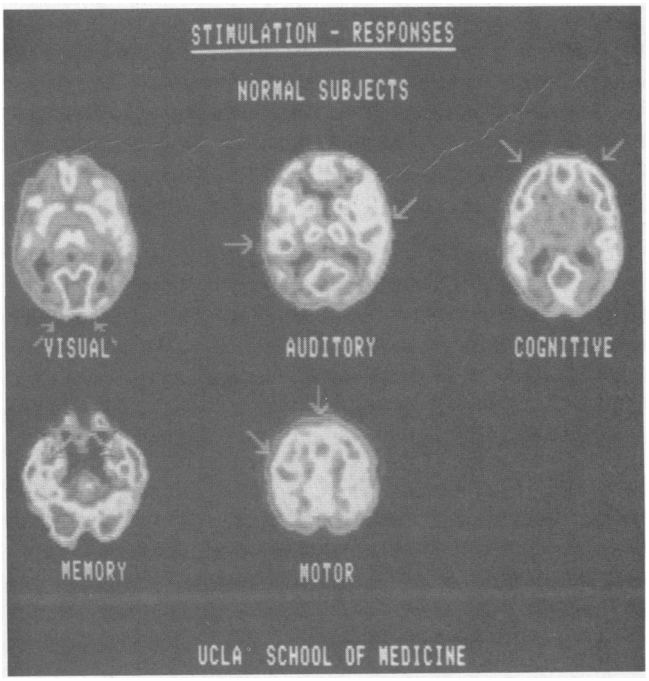

Figure 8.—Glucose metabolic responses are shown of normal subjects performing behavioral tasks. The arrows indicate areas of high metabolic rates indicative of increased neuronal activity. Normal patterns of metabolic responses to behavioral tasks can be used to map critical sites of functional neural networks in patients with cerebral tumors to avoid these areas during tumor resection, as in the two patients whose positron emission tomographic studies are shown in Figure 2. Both lesions are at or near the sensorimotor strip. Both of these patients have minimal signs of corticospinal tract dysfunction. A behavioral mapping study to examine displacement and position of the functional motor cortex (as seen in the "motor" image of this figure) would be useful in avoiding these critical areas during resection of the cerebral neoplasms (from Phelps and Mazziotta[32]).

survival with malignant gliomas include age, duration of symptoms, preirradiation performance state, tumor histology, accessibility to resection, extent of resection, radiotherapy, and a previous diagnosis of a low-grade glioma. Patients with gross total resections live longer than those with partial resection, and patients with any degree of resection live longer than those who undergo only a biopsy procedure. Also, patients with anaplastic gliomas in whom there was a history of low-grade glioma live considerably longer after the diagnosis of anaplastic glioma than do patients in whom anaplastic gliomas currently arose de novo. Some authors have reported a difference in survival of only 19 weeks in patients who have undergone biopsy to 76 weeks in patients with gross total resections. Age is a strong predictor of survival, with patients in the 18- to 44-year-old group having a median survival of 107 weeks in comparison with patients older than 65 years who have a median survival of only 23 weeks.

Recently thallium 201 (single photon emission CT) scans have been shown to correlate with tumor histology in patients with gliomas. A thallium index was developed based on the ratio of thallium 201 uptake in the tumor versus the nonneoplastic homologous area of brain. A thallium index of 1 represented no uptake. In these patients, an index of 1.5 or less showed a 90% or higher accuracy of predicting which patients will have low-grade gliomas versus an index of higher than 1.5, where the tissue specimen almost always showed a grade III or grade IV glioma. In our experience, the thallium scan is more accurate than the CT or MRI scan in predicting tissue histology because it does not rely merely on a breakdown of the blood-brain-barrier blood flow, but the thallium is recognized as a potassium analogue and is actively pumped into tumor cells by sodium-potassium-adenosine phosphatase.[103]

A slight increase in the number of long-term survivors is obtained by treatment with carmustine.[104] Its full potential, however, may be limited by the delivery of high doses to the tumor site while avoiding systemic toxicity. Various attempts to increase the concentrations of cytotoxic drugs in the brain have proved disappointing. Other forms of regional treatment, including interstitial irradiation, have had some success at local control. A novel approach has recently been developed to optimize local carmustine concentrations in the region of the tumor by what has been termed "interstitial chemotherapy." A biodegradable polymer, manufactured by Nova Pharmaceutical Corporation, Baltimore, Maryland, has been formulated into a solid wafer containing carmustine in the matrix. Encouraging results were obtained in a series of preclinical studies in rats, rabbits, and nonhuman primates to establish the biocompatibility, biodistribution, and efficacy of carmustine-containing polymer wafers when implanted intracerebrally.[105,106] Phase I clinical trials have recently been completed. In the first human study administering carmustine by interstitial chemotherapy using drug-loading polymer wafers, patients with malignant gliomas, for whom surgical therapy and radiation therapy or chemotherapy, or both, were ineffective, underwent a second surgical resection and the wafers were implanted into the margins of the surgical resection. The results of this study show that this may be a safe method for delivering chemotherapy into the brain. The wafers have the advantage that they can deliver extremely high concentrations of chemotherapy into the brain while avoiding the systemic side effects of the chemotherapeutic agent. In addition, there is prolonged exposure of the tumor cells to the chemotherapeutic compounds. Further, these wafers can be loaded with various antitumor modalities, so their full potential as a delivery tool for antitumor compounds to treat brain tumors is just beginning to be explored.

There has also been increasing interest in the impaired humoral and cellular immune function in patients with primary brain tumors. Recently there has been interest in the development of immune modifiers that stimulate the host immune system in patients with malignant brain tumors. Regimens using levamisole hydrochloride, poly IC, interferon, picibanial, or bacillus Calmette-Guérin vaccine have been attempted with limited success. A biologic response modifier, ImuVert (Cell Technology, Inc, Boulder, Colorado), prepared from the bacterium, *Serratia marcescens*, has recently been developed. ImuVert is known to stimulate the activity of human natural killer cells in vitro, using a standard chromium-release cytotoxicity test. In addition, it also causes the release of interleukin 2, interferon, and tumor necrosis factor and stimulates lymphocytic activated killer cells as well as antitumor macrophages. Because of the broad-based immune stimulation of ImuVert, clinical trials have recently begun testing its effects in patients with high-grade gliomas.

It is hoped that future treatment modalities may be able to convert this universally fatal disease to a chronic disease process that can be controlled. Controlling recurrence at the surgical margins and maintaining static growth of the tumors by stimulating patients' immune systems might lengthen survivals in these patients. Combinations of various therapies based on increasing knowledge of the biologic behavior of these tumors are currently being designed. A better definition of the surgical margins is critically needed, and a way to deliver antitumor compounds successfully across the blood-brain barrier specifically to tumor cells will improve dramatically the effectiveness of current therapeutic modalities.

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