48 Surgical Management of Low-Grade Gliomas

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CLASSIFICATION—PATHOLOGY

Astrocytomas, oligodendrogliomas, and mixed (oligoastrocytic) gliomas are low grade, that is, Grade I gliomas according to the classification of the World Health Organization (WHO). "The Yale Neuro-Oncology Tumor Data Bank reported an incidence of these oncotypes of 60%, 23.3%, and 16.7%, respectively, among all low-grade gliomas."[1]

Fibrillary, gemistocytic, protoplasmic, or mixed astrocytomas present different surgical problems according to whether they are solid or cystic. A solid astrocytoma has a hard or rubbery consistency, is sometimes cartilaginous, and is whitish in the fibrillary form; it is softer, gelatinous, and translucent in the gemistocytic and protoplasmic varieties. On the surface, the growth is either diffuse or apparently circumscribed. Under the surface, it usually has less consistency and tends to form either several small cysts or a single large one; a single large cyst is most often found in the fibrillary and gemistocytic varieties.[2] The pilocytic variety is rare among astrocytomas of the cerebral hemispheres and is found more often in the posterior fossa (cerebellum and brain stem), diencephalon, and anterior optic pathways. In most cases, cerebral pilocytic astrocytoma consists of a large unilocular cyst with a mural nodule; it differs from other forms of astrocytoma in biologic behavior and in a marked responsiveness to therapy.[3–5]

Oligodendroglioma is often very hard and gritty on section, because it contains palpable calcifications: it is grayish pink and has clear-cut limits on the surface (where it infiltrates the gyri, giving them a hypertrophied, "scalloped or garlanded" appearance) to become indistinct in depth, where small mucinous cysts may be found. Small nodules as hard as warts are found in the cortex and are detected by the surgeon on inspection or on palpation. When the tumor spreads through the leptomeninges, it forms large lumps that project beyond the surface like bluish red fungi. In such cases, the tumor may adhere to the dura mater and may be mistaken at first sight for a meningioma.[2]

Mixed oligoastrocytomas do not differ in gross appearance from true oligodendrogliomas and constitute a purely histologic variety. Tumors such as pleomorphic xanthoastrocytomas and gangliogliomas are low grade, usually resectable tumors with a very low incidence and will not be considered here.

Both oncotypes (astrocytoma and oligodendroglioma) occur preferentially in the frontal lobes, after which come the temporal, parietal, and occipital lobes, in this order. These diffusely infiltrative tumors do not respect boundaries, however, and most low-grade gliomas straddle the fissures to involve contiguous lobes.

There are no typical sites by oncotype, except perhaps the frontolateral region for oligodendroglioma. Both of these gliomas may be parasagittal, affecting the frontal and parietal lobes. Hard gliomas "of the edge," bordering on the sagittal fissure, develop along the medial gyri and may infiltrate the corpus callosum or spread contralaterally through the corpus callosum ("butterfly gliomas").

Whether these tumors emerge on the surface or are subcortical, they infiltrate the white substance diffusely and may spread in depth toward the ventricular system or basal nuclei. Gliomas arising from the diencephalon, which are distinguished by certain histologic and clinical features (occurrence of pilocytic astrocytomas, preference for youth) and which present peculiar biologic behavior and peculiar problems of treatment, are discussed in Chapter 61.

Any centrencephalic spread of a hemispheric glioma limits surgical resection, a point that is addressed in the section on Surgical Technique. Such spread occurs along the projection fibers (Fig. 48-1). Seeger[6] recognized two other possible routes of tumor spread: (1) along the associative fibers (intrahemispheric spread) and (2) along the commissural fibers (interhemispheric spread). An example of the latter is the contralateral spread via the corpus callosum, as already mentioned. An example of intrahemispheric spread is the subcortical migration of neoplastic cells via the short associative U-shaped fibers between two adjacent gyri.

However, tumor progression is a process of dislocation or infiltration of the surrounding neural tissue, and these two patterns of growth may explain the neurophysiologic data showing "in toto" displacement of eloquent areas but also the occasional presence of neural activity in the tumor core.[7]

The WHO classification criteria are purely histopathologic, and their limitations were highlighted in the 1980s and 1990s by the advances of immunohistochemistry, molecular biology, and neuroimaging. When classifying gliomas today, one must take account of specific markers of different cell types, parameters of cellular kinetics, and metabolic data relating to neoplastic tissue in vivo. Thus, tumor grading based solely on morphology is supplemented by neurodiagnostic grading (the presence or absence of contrast enhancement on computed tomograpy [CT] and magnetic resonance imaging [MRI]),[8] metabolic grading (increased glucose consumption on positron-emission tomography [PET]), and grading based on parameters of cellular molecular biology and kinetics.

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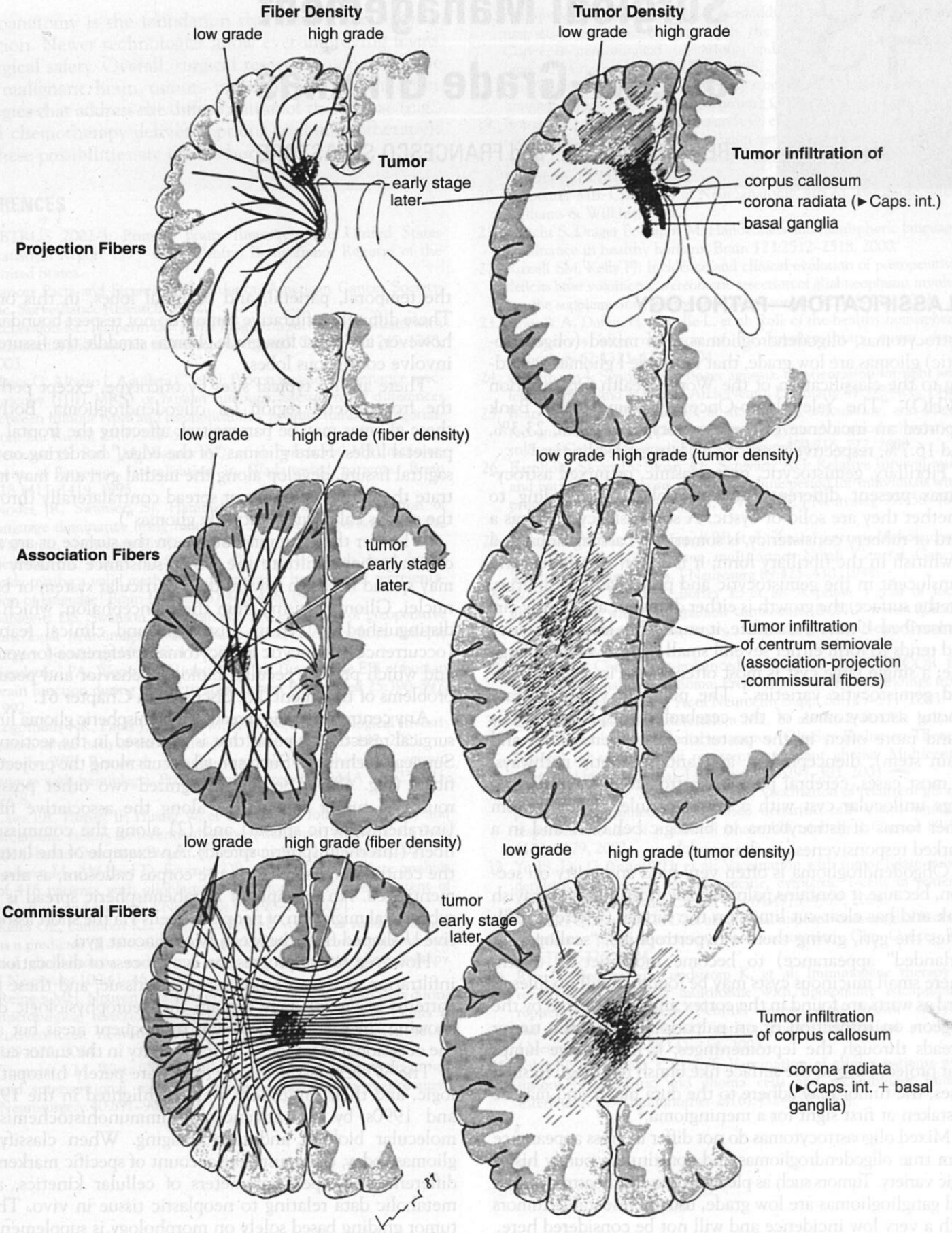

FIGURE 48-1 Patterns of tumor spread along the projection, association, and commissural fibers. (From Seeger W: Strategies of Microsurgery in Problematic Brain Areas. Vienna: Springer-Verlag, 1990, p 25.)

On the last point, histologically similar tumors may exhibit differing proliferative potential. Subgroups of low-grade astrocytomas exist that have different proportions of cells in the S phase of DNA synthesis, expressed by different values of the labeling index (LI). One subgroup with a low LI (<1%) is characterized by slow growth, and another with the same or higher LI is biologically more aggressive, which partially explains the very different clinical behavior often seen in histologically similar tumors.[9] The proliferative potential of a given tumor (expressed in the LI) correlates with necrosis and tissue hypervascularization rather than with the number of mitoses and cellular anomalies (or monstrosities).[10,11] This fact confirms the undue importance that was formerly attached to the mitotic count in gliomas as an index of growth rate. It is now known that mitoses may be lacking in a glioblastoma multiforme and may be present in a slow-growing oligodendroglioma.[12]

The PET tumor grading based on glucose consumption by area is also a better predictor of the long-term prognosis of gliomas than is histologic grading.[13]

The data on the biology of gliomas have been, in the last decade, increasing exponentially. These data will eventually form the basis of a new classification of the far from homogeneous group of low-grade gliomas.

Because low-grade gliomas do not constitute a homogeneous group, treatment clearly cannot be uniform in all cases, and the results are not easily comparable.

CLINICAL AND BIOLOGIC FEATURES OF LOW-GRADE GLIOMAS

Low-grade gliomas of the cerebral hemispheres occur less frequently than malignant gliomas (glioblastomas, primitive neuroectodermal tumors), affect a younger population, and have a better prognosis. Perhaps because these tumors occur less frequently and patients may remain well for a long time, few formal clinical trials have been mounted; therefore, the natural history of low-grade gliomas is less well known than is that of the high-grade varieties. In addition, the preoperative clinical history has changed substantially in recent years as a result of neuroimaging techniques, which have ensured much earlier diagnosis. In the pre-CT era, patients with low-grade hemispheric glioma often presented with headache, papilledema, and focal deficits, whereas today they undergo surgery after only a few episodes of convulsions and are absolutely normal neurologically. For example, in the series of Laws and co-workers,[14] consisting of patients treated between 1915 and 1975, 40% had papilledema at the time of presentation, almost half complained of headache, and 51% exhibited motor deficits. In the series of Gol,[15] composed of patients treated before 1960, 72% had a headache at the time of diagnosis, 59% papilledema, 56% hemiparesis, and 56% seizures. By contrast, in Piepmeier's series,[16] in which all the patients were diagnosed by CT, 5% initially had a headache 15%, motor weakness, and more than 90% seizure activity (the frequency of papilledema was not stated). In addition, in the series of Vertosick and associates,[17] 16% had headache, 8% papilledema, 16% motor deficits, and 92% seizures.

Epileptic activity in patients with low-grade cerebral gliomas is important not only clinically, because it is the earliest symptom, but also surgically. Electrocorticographic recordings in patients with a slow-growing glioma have revealed epileptogenic foci separate from the tumor.[18] This nontumoral cortex, though not marked by neuronal loss, nonetheless shows a change in neuronal subpopulations, that is, a reduction of neurons immunoreactive to γ-aminobutyric acid and to somatostatin,[19] which is an expression of local hyperexcitability. Hence, the seizures in these patients, which are often refractory to drugs, can be controlled only if the epileptogenic foci are removed along with the tumor. A patient with chronic epilepsy may thus have a glioma. Among 51 patients with epilepsy of 1 to 27 years' duration (mean duration of 11 years), Goldring and colleagues[20] found 40 gliomas, including 25 low-grade astrocytomas and 1 oligodendroglioma. In one patient with a 22-year history of epilepsy, they found a glioblastoma, evidently the outcome of secondary degeneration, as is discussed later. CT and, even better, MRI define the lesion, but these modalities have limitations: the lack of increase in lesion volume on serial CT scans does not exclude a tumor. The clinical features, warn Goldring and co-workers, may be very deceptive; a history typical of essential epilepsy does not exclude a tumor as the cause. For instance, generalized febrile convulsions in infancy followed by complex partial seizures—a history typical of temporal mesial sclerosis—was the history of some subjects with temporal glioma.

The biology (cellular kinetics and metabolism) of these nonsymptomatic tumors that have a long natural history (remaining silent or nonsymptomatic for years and then exploding dramatically) cannot be considered benign and certainly arouse scientific interest. Low-grade gliomas (astrocytomas, mixed gliomas, and ependymomas) have a lower percentage of cells in the S phase (LI = 2% to 6.7%) than do malignant gliomas (LI = 9.1% to 46.5%).[21] The growth fraction (GF) (i.e., the total number of cells involved in cellular proliferation as a proportion of the entire cell population of the tumor) is correspondingly low: GF = 0 to 4.5% in low-grade astrocytomas, and GF = 1.7% to 32.2% in glioblastomas.[22] Flow cytometry of nuclear DNA in well-differentiated gliomas shows that most of the cells have the same ploidy (as a rule, they are diploid), with little variation from one area of the tumor to another. Malignant gliomas, by contrast, display hyperploidy (up to octaploid cells) or aneuploidy, and the ploidy varies from one area of the tumor to another.[12] The disordered distribution of nuclear DNA evidently betrays the disordered reproduction of cells in malignant gliomas. As PET shows, low-grade gliomas are quantitatively comparable in blood flow, oxygen utilization, and glucose consumption to the adjacent normal brain tissue. Although no difference exists in blood flow between low-grade and high-grade gliomas,[23] glucose consumption is much higher in the latter.[24] PET also shows, through the uptake of [^{11}C]L-methionine, a much higher rate of protein synthesis in high- than in low-grade gliomas.[25]

A mature glioma takes much longer to grow than does a glioblastoma. Noninvasive estimates have been made on serial CT scans, but few data exist on mature gliomas. Tsuboi and associates[26] evaluated the doubling time in four Grade II astrocytomas and mixed gliomas at 937.3 ± 66.5 days and compared this with 48.1 ± 20.9 days on 11 glioblastomas. In mature gliomas, the production of daughter cells must be almost exactly equal to cell loss and inactivation. Hoshino[27] supplied a theoretical basis for this clinical intuition.

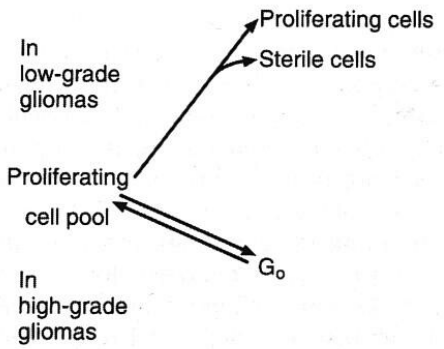

FIGURE 48-2 Cytodynamic of low-grade gliomas.

Determining the LI at necropsy in patients in whom it had been determined before operation, he found that, unlike immature gliomas, the well-differentiated varieties conserved the labeled cells for a long time. He, therefore, called this mode of cell proliferation of low-grade gliomas "conservative." In malignant gliomas, all the daughter cells proliferate, whereas in low-grade gliomas, one of two appears to retain the capacity for mitosis, whereas the other loses it. As a result, the proliferating pool grows moderately while sterile nonproliferating cells are continually being added to the cell population; therefore, the GF progressively slackens (Fig. 48-2).

However, the most worrying aspect of the biology of low-grade gliomas is the possibility alluded to earlier of malignant degeneration over time. In a study of 137 recurrent low-grade gliomas, Müller and co-workers[28] found that only 14% of Grade I astrocytomas had not changed grade by the time of the recurrence, whereas 55.5% had become Grade II, and 30.5% had become glioblastomas. Similarly, of 23 Grade I oligodendrogliomas, 15 (65.1%) had recurred as Grade II oligodendrogliomas and 2 (8.6%) as glioblastomas.[29] Laws and associates[14] found that at least half of the 79 low-grade astrocytomas in their series that recurred after treatment had advanced to Grade III or Grade IV. Zülch,[2] in a series of 104 supratentorial astrocytomas, found malignant degeneration in 23%. Rubinstein,[30] who studied 129 glioblastomas at necropsy, estimated that about 20% may have derived from the malignant degeneration of low-grade astrocytomas. Piepmeier found that over a median follow-up of 8 years, 50% of the astrocytomas and 10% of the oligodendrogliomas recurred as higher grade.[1] In the series of Wallner and co-workers,[31] 10 of the 29 patients with oligodendroglioma had a recurrence: at reoperation or at necropsy, only four had undergone no change, two had become glioblastomas, three had become Grade III mixed gliomas, and one had become a Grade II astrocytoma.

During the last 10 years, it has become evident that classification systems that are morphologically based are inadequate to describe either the biologic identity of these lesions or their biologic potential (malignant transformation).[32] The relevance of these features in the choice of therapeutic options and for determining a reliable prognosis has produced an overwhelming amount of studies on gliomas genetics and molecular biology, almost 75% of all the literature articles on the subject in recent years. A slow-growing tumor as the low-grade astrocytoma is expected to have a low proliferative activity. Many studies have identified as a measure of this activity the percentage of astrocytoma cells expressing the proliferation antigen Ki-67 MIB-1 (expressed during the entire cell cycle) and the proliferating nuclear antigen (PCNA) (only expressed during S_1 phase). For a low-grade glioma the MIB-1 Labeling Index should not exceed 4%.[33,34] MIB-1 expression reflects differences in biologic behavior, such as the rapid progression of a residual tumor or stable remaining tumor. MIB-1 LI is reported to be lower in "quiescent" tumors.[35]

However, it is a common experience that a variable percentage (50% to 85%) of low-grade gliomas undergo malignant transformation. The molecular neuropathologic basis of this process is the summation of significant genetic alterations.

These mutations concern two categories of genes: (1) oncosuppressors and (2) oncogenes. As a consequence, the former will lose function in two stages. At the beginning, a copy of the gene is lost through an inactivating mutation, often a deletion. This situation may establish a predisposition to tumor formation. A second genetic event, however, is necessary for the complete inactivation of a suppressor gene. For oncogenes, mutations have an activating effect, and only one could be enough to induce a neoplastic phenotype.[36]

Cytogenetic analysis identified several alterations in pilocytic astrocytomas, but none is specific. In only few cases, a modification of oncosuppressor gene p53 has been described. Through a comparative genome hybridization technique, detecting losses and gains of DNA copy number across the entire genome, a constantly increased copy number of 8q emerged as the most frequent change in low-grade gliomas.[37]

Conversely, in diffuse astrocytomas, the p53 mutation is more frequent and may represent an indicator of malignant transformation. In fact, astrocytomas with a significant gemistocytic fraction, typically carrying a p53 mutation, seem to progress more rapidly.[38] Protoplasmic astrocytomas have low MIB-1 indices, and p53 reactivity is observed in a few of these tumors.[39]

p53 genes regulate the G_1 phase of the cell cycle that activates p21, and its inactivation seems to play a relevant role in neoplastic progression, determining further genomic instability.[40] However, the function of p53 appears also to prevent DNA rupture, duplication errors, and anomalous regional genomic amplification, therefore deserving the appellative of DNA caretaker. In fact, the cell cycle is normally stopped by p53 to allow repair; if the latter is not possible, the cell undergoes apoptosis. Moreover, p53 is claimed to function as genomic gatekeeper (i.e., regulate the expression of many genes).[41] There is evidence that the loss of only one allele for p53 increases the risk of tumorigenesis, suggesting that a decreased genic dosage is sufficient to compromise the surveillance function.[42] The implications for therapy of these data are evident. For instance, adenoviral vectors may carry a normal p53 gene in mutated tumoral cell nuclei.[43]

The cell kinetics of a low-grade glioma should differ only slightly from normal adult astrocytes, and the inactivation of p53 is a consequence not only of mutation or allelic loss but also of "transcriptional silencing."[44] The overexpression of Mdm2, establishing a linkage to mutant or wild-type p53, inhibits transcription.[45]

The overexpression of *PDGFRB* (encoding for a growth factor) and the mutations of *TP53*, inactivating the p53,

have often been indicated as responsible for the proliferative stimulus, with the contemporary inhibition of apoptosis. *Bcl2* is a proto-oncogene that also blocks apoptosis.[46] Apoptosis is a sequence of morphologic and biochemical changes that lead to cell death. Tumorigenesis is the consequence not only of cell proliferation but also of the loss of the ability to undergo apoptosis. These events provide the necessary genomic instability for further phenotype changes, cell cycle deregulation, and the selection of malignant cell clones. Although in slow-growing gliomas the cell cycle is not deregulated, Grade II astrocytomas must have an imbalance between proliferative activity and apoptosis. Grade II astrocytomas have been divided in two groups with significantly different survival (1062 versus 1686 days), related to the value over or under 8% of the MIB-1 LI. The presence of well-differentiated astrocytes with a high MIB-1 LI suggests that cell cycle deregulation precedes further alterations with phenotypic transformation and that MIB-1 LI might be used as a prognostic indicator.[33]

There is still debate on the clonality of the resultant malignant tumors. The tumor originates from confluent clones of multiple transformed cells or from a single cell clone. Polymerase chain reaction assay studies through amplification of a high polymorphic microsatellite marker locus suggested that low-grade and malignant gliomas are usually monoclonal and that tumor cell migration represents the basis for extensively infiltrating tumors.[47] Different populations of cells with diverse genetic alterations may coexist in the same tumor, but this appears to be a transitional state, because the cell clone with the more efficient features of growth will rapidly prevail.

Loss of heterozygosity on chromosomes 19q and 1p are the most common reported alterations in oligodendrogliomas. The loss of a chromosome region carrying the residual copy of an oncosuppressor gene is revealed by a contiguous marker absence, using DNA amplification.[48]

Many factors that are intrinsic or extrinsic to the cell microenvironment keep under control the replication and differentiation of the neuroepithelial cell. Growth and trophic factors are small proteinic molecules identified in molecular biology studies that may represent potential pharmacologic agents to regulate neuroepithelial pathologic proliferation and differentiation. A peculiarity of this regulatory system is that the same factor may exert different and also opposite effects on neuroepithelial cells in different stages of differentiation or to neuroepithelial cells that belong to different parts of the nervous system.[49] This is probably the consequence of differences in number and type of growth factors receptors or of a fine modulatory intracellular process regarding transcription pathways of the signal generated after receptor–growth factor linkage. Therefore, tumors that are morphologically alike may differ substantially in their biologic behavior, as a result only of different receptor expression, thus disclosing further identification methods.

The transcriptional factors induce specific gene transcription, possibly modifying the cell phenotype. There are suggestions that activation of protein STAT 1 and STAT 2 by transcriptional factors allows differentiation toward an astrocytic phenotype of the neoplastic cells of the low-grade gliomas. Conversely, a differentiation to a high grade implies an inhibition of the pathway, determining lower levels of STAT proteins.[50] In view of future therapeutic application, this is evidence in favor of preservation of differentiation mechanisms also during oncogenesis.

Growth factors have been proved to determine the angiogenic potential of glioma cells, and angiogenesis has been used as a biologic marker for low-grade gliomas at risk of malignant transformation. Patients with more than seven microvessels counted on a 400-μm microscopic field of tumor tissue are reported to have a shorter survival time and a greater chance of tumor progression. Higher staining for vascular endothelial growth factor (VEGF) seems related to a worse prognosis.[51] Fibrillary astrocytomas, studied with determination of microvessel density and VEGF levels, appear not as a single pathologic entity but as a wide spectrum of tumors with differing tendencies toward malignant transformation. VEGF secretion may also represent the common pathway of microvascularization and progression to glioblastomas.[52] The p53 gene is thought to regulate VEGF and, consequently, tumor neovascularization.[53]

The recent progress in molecular neuropathology helped to discover anomalies of oncogenes and tumor suppressor genes, new sites for putative tumor suppressor genes (through microsatellite analysis), and peculiar molecular pathways for each tumor type. The presence of alterations in cell cycle regulatory genes of anaplastic gliomas may explain their amazing growth potential. Autocrine and paracrine growth factors and their respective protein receptors appear to contribute to glial and endothelial cell proliferation. The pattern of genetic alterations will help to further differentiate histopathologic entities into genetic distinct groups and to better define the mechanisms of angiogenesis. The common target is to establish a correlation between histopathologic, molecular, and clinical data.

NEURODIAGNOSTIC IMAGING

The "typical" imaging features for the diagnosis of a low-grade glioma in an adult patient were considered: CT scan hypodensity, without contrast enhancement; lack of contrast enhancement on a CT scan; hypointensity on short TR (repetition time) T1-weighted and hyperintensity on long TR T2-weighted MRI scans; no contrast enhancement on MRI.[54] Nevertheless, further experience has demonstrated the unreliability of these parameters also in high-standard radiodiagnostics. Forty-eight biopsies performed by Bernstein contradicted the radiologic diagnosis in 31.3% of cases, and a refutation of neuroimaging-based hypotheses followed the 20 bioptic procedures of Kondziolka in 50% of cases. Unrecognized pathologies included higher grade gliomas, oligodendrogliomas, mixed astrocytomas, and inflammatory lesions. However, the opinions of these authors are not convergent when the treatment of these patients has to be considered: histologic diagnostic confirmation with biopsy is imperative for Kondziolka, whereas Bernstein reserves biopsy for lesions that are very likely to be treated surgically. Bernstein recommends observation for others.[54,55]

Berger analyzed different MRI aspects of low-grade tumors while looking for a correlation with the histologic type. He concluded that no predictive value for histology exists in the presence of a cyst, the degree of mass effect, the cortical or subcortical location, the ratio of tumor volume T1-weighted versus T2-weighted, the diameter of the

tumor, the presence of hemorrhage, or vascular flow voids. Only T1 hypointensity seems to correlate well with the softness of a tumor at surgery. This could be explained by the loose structure of astrocytoma presenting with a microcystic mesh with some degree of mucinous degeneration. Less hypointense lesions express a firmer architecture as typically seen in oligodendrogliomas and mixed astrocytomas.[56]

Further steps in characterization of low-grade gliomas with a propensity to malignant transformation and in tumor boundary definition are represented by PET and high-resolution magic angle spinning proton (HRMAS 1H) magnetic resonance.

[^{11}C]Methionine PET has been reported to be useful to detect changes in the endothelium and blood-brain barrier related to malignant low-grade glioma transformation.[57,58] It proved to be better than fluorodeoxyglucose in delineating the borders of low-grade gliomas, but methionine uptake cannot differentiate anaplastic gliomas.[59]

Some researchers have claimed that a thallium-201 single photon emission CT (^{201}TI SPECT) scan can permit differential diagnosis between low-grade and high-grade gliomas.[60,61] Though less expensive than PET, it may give false-positive results in low-grade gliomas. It demonstrates high sensitivity for tumors with a bromodeoxyuridine LI equal or inferior to 5%.[62]

HRMAS 1H magnetic resonance spectroscopy produces well-resolved spectra of metabolites from an intact tissue specimen. The metabolic ratio presented the highest sensitivity in differentiating normal tissue from a tumor as well as in distinguishing between tumor groups. For instance, the resonance ratio of inositol to creatine may help to differentiate the tumor type.[63]

HRMAS 1H for choline showed that all progressive astrocytomas had elevated choline levels of more than 45%, whereas stable cases showed an elevation of less than 35%, no change, or even a decreased signal.[64–68]

1H nuclear magnetic resonance spectra of human brain tumor homogenates revealed a broad resonance at 5.3 to 5.4 ppm in glioblastomas and is not detectable in low-grade gliomas. This resonance has been identified as ceramide, a sphingosine–fatty acid combination portion of ganglioside (with an immunosuppressive activity), indicating an abundance of monounsaturated fatty acids. It is suggested a role for aberrant ganglioside and ceramide precursors in the grade of malignancy and invasiveness.[69]

There is evidence that no major difference exists between the PET investigation of glucose metabolism and the less expensive SPECT measurement of amino acid uptake(^{123}I-α-methyl tyrosine [^{123}IMT]).[70–72]

MANAGEMENT DECISIONS

With the advances in neurodiagnostics, the pathology that confronts the clinician today is different from what it was 20 years ago, and this development requires new and more demanding decisions. In the days of angiography, encephalography, and radionuclide scanning, low-grade cerebral gliomas reached the surgeon after years of history, when they had grown large, with mass effect and signs of hypertension. These gliomas sometimes already contained foci of dedifferentiation inside. Today, at the first convulsive seizures, CT and MRI reveal small, less malignant tumors in patients who are neurologically intact. When it is considered that this pathology arises in young individuals on the convexity of a cerebral hemisphere, frequently beside "eloquent" cortical and subcortical areas, the magnitude of the dilemma facing the surgeon becomes clear.[73]

Although oncologic surgery should generally be performed as early and as radically as possible, some contend that an operation should be postponed when serial scanning shows no change in the volume or structure of the lesion. Others argue that biopsy plus radiotherapy is just as effective as surgical resection. Yet others[17] question the use of radiotherapy because of its long-term detrimental effects, asserting that because these patients never die as a result of a progression of the low-grade tumor but instead of its malignant degeneration, a management strategy designed to prevent dedifferentiation would be just as effective as eradication of the original tumor. The point is highly controversial and must be examined from several perspectives (Table 48-1).

Surgery is questioned first because of the risk of postoperative deficits in a young, neurologically sound patient with a long life expectancy. This situation requires the utmost precision in the diagnosis of the anatomic limits of the tumor and the functional status of the most important adjacent nervous structures.

Second, early surgery has yet to be proved to improve survival. As is discussed later in the section on Results, one of the issues in long-term survival is a long preoperative history. The follow-up study of Laws and co-workers,[74] which is one of the most important studies in terms of numbers and time span, makes this point.

Third, no proof exists that more generous resection correlates significantly with longer survival. A correlation of this kind, generally valid for any tumor, is argued by Salcman,[75] who cites Laws and associates.[14] However, although Laws and associates found a significantly higher 5-year survival rate among patients who had undergone total removal than among those who had undergone biopsy and subtotal removal or radical subtotal removal, statistical significance was not maintained at 15 years, total removal excluded. Furthermore, as these authors state, the most

TABLE 48-1 ▪ Surgery in Low-Grade Gliomas

Indications	Reasons That Surgery Is Questionable
Diagnosis and classification	Risk of postoperative deficits in a young, neurologically sound patient with a long life expectancy
Debulking the mass and alleviating symptoms	Early surgery has not been proved to lengthen survival
Reducing the proliferating cell pool	There is no significant correlation between the extent of surgical resection and the length of survival
Decreasing the number of cells inherently resistant to radiation therapy	
Preventing or reducing the risk of increase in malignancy	
Cytoreduction makes subsequent radiotherapy more effective	
Chemotherapy has proved ineffective in all cases	

favorable lesions tend to be treated more radically, and the least favorable (deep-seated, infiltrative, noncystic) more sparingly. Weir and Grace,[76] Piepmeier,[16] and Vertosick and colleagues[17] deny any significant correlation between the extent of surgical resection and the length of survival.

All these points, which tend to undermine the importance of surgery in low-grade cerebral gliomas, are counterbalanced by the following considerations, according to which surgery is indicated: (1) for diagnosis and classification, (2) for debulking the mass and relieving symptoms, (3) for reducing the proliferating cell pool, (4) for preventing or reducing the risk of degeneration, (5) for decreasing the number of cells inherently refractory to radiotherapy, (6) because cell reduction makes subsequent radiotherapy more effective, and (7) because chemotherapy has proved ineffective.

Each of these assertions calls for comment. First, surgery is valuable as a diagnostic check on a patch of low density on a CT scan and on one of low intensity in the T1 sequences and of increased intensity in the T2 sequences of MRI. A tumor must be differentiated from an infective or vascular lesion, and the borders of the tumor must be demarcated from the surrounding edema. The tumor must be typed not only histologically but also, if possible, for proliferative potential by immunochemistry (monoclonal antibodies to bromodeoxyuridine for the LI and antigen to Ki-67 for the GF). For these purposes, stereotactic surgery may be preferred to open surgery, a point that is discussed in Chapter 52. Surgical resection is needed for debulking the mass and palliating symptoms when a glioma is discovered at a late stage and has already grown large. In any case, surgical resection reduces the proliferating pool and delays the growth of the tumor. As Hoshino[27] pointed out, low-grade gliomas differ from more malignant gliomas in the lack of cellular traffic between the nonproliferating pool and the proliferating pool (see Fig. 48-2). In low-grade gliomas, the conservative mode of proliferation ensures the continual addition to the cell population of sterile, permanently nonproliferating cells (for which there is no return to the reproductive cycle). In glioblastoma, by contrast, frequent reciprocal traffic exists between nonproliferating and proliferating cells: its growth may be depressed by cell bunching; partial surgical resection may stimulate the cells in G_0 to return to the proliferating pool and thus end, paradoxically, by accelerating tumor growth. Nonetheless, surgical resection, however satisfactory, is always limited. As Sano[77] reminded us, 99% removal of a tumor corresponds with only a 2-log reduction of the number of cells that constitute a neoplastic population (10^7 to 10^8).

As we have seen, at the time of a recurrence, low-grade gliomas exhibit increased malignancy and resistance to treatment. Because it is not known which cells will be subject to dedifferentiation or what factors contribute to the process, the risk is presumably proportional to the number of neoplastic cells. Therefore, the most extensive cytoreduction possible should be advantageous. In addition, no one has ever suggested that surgical resection may favor dedifferentiation. On the evidence of Vertosick and associates,[17] two points emerge: (1) Patients who present dedifferentiation tended to be diagnosed at a younger age than did those who did not (mean of 33 vs. 43 years), and (2) those who received radiotherapy underwent dedifferentiation an average of 5.4 years later than did those who did not (3.7 years later). However, these data are preliminary and have not been statistically validated.

When does a low-grade glioma degenerate—that is, at what stage in its natural history? How can the change be detected in time? Clinical experience shows that dedifferentiation occurs several years after the initial symptoms of the tumor—on average 5 years after in the 12 cases of Francavilla and co-workers,[78] with a range of 1.5 to 10 years. PET with [^{18}F]-deoxyglucose is currently the most sensitive tool for detecting incipient malignant transformation, which manifests increased metabolism (increased glucose consumption), is focal (in agreement with the histologic data), and is similar to the hypermetabolic state observed in de novo malignant gliomas. One PET scan at one point in the natural history may not have predictive value, any more than does a histologic examination performed at that time. Serial PET scans are needed to identify variations in the biologic behavior of a tumor.

Apart from all the foregoing reasons, surgical resection is indicated in low-grade gliomas because no concrete alternative exists, given their biologic resistance to chemotherapy and scant sensitivity to radiotherapy. The cellular kinetics and metabolism of these oncotypes, which differ little from those of healthy nervous tissue, and the integrity of the blood-brain barrier prevent cytostatic agents from entering the tumor with a higher concentration gradient than that of the surrounding healthy tissue.[75] Radiotherapy is recommended in only a few cases, as is discussed later.

In conclusion, we can share in part the statements of Bernstein[79] regarding the presumed absence of negative prognostic indicators in a patient younger than 40 years of age, with epilepsy but without neurologic deficits, harboring a low-density intrinsic lesion, without enhancement and without mass effect. As mentioned, molecular markers may enhance the predictive accuracy. For a patient older than 40 years, with or without neurologic deficits, mass effect, or enhancement, we think that more aggressive treatment should be considered. For lobar lesions, we recommend the most radical surgery followed by radiotherapy; for deeper or "diffuse" lesions (particularly if located in "eloquent" areas), stereotactic biopsy and radiotherapy should be the treatment of choice.

PATIENT SELECTION AND CHOICE OF SURGICAL APPROACH

The conditions in favor of surgical treatment for slow-growing gliomas outweigh those in favor of waiting or abstaining both in number and in importance.

The surgical choice is between open resection and stereotactic surgery followed by other treatment (irradiation or interstitial radiotherapy). The criteria for the stereotactic option depend, according to Salcman,[80] on the characteristics of: (1) the tumor (centrally sited, poorly demarcated, extremely small, containing a large cyst or changing character), (2) the patient (either too ill for a craniotomy or neurologically intact), and (3) subsequent treatment (catheter-based, requires repeated sampling). "In essence, the same criteria employed in the selection of open versus closed techniques can be applied to low-grade tumors, but with more stringent emphasis on neurologic condition and radiographic definition."[75] In summary, in the case of

low-grade cerebral glioma, as for almost all other central nervous system diseases, surgical treatment must be tailored to the neurologic status and social needs of the patient, to the site and size of the lesion, to the ability of the surgeon, and to the facilities available to him or her. General directives can come only from randomized prospective studies conducted over a sufficiently long time by several institutions on series matched for pathology, patient selection, and management.

PREOPERATIVE EVALUATION

The brain is a singular organ in that many of its main functions are represented on its surface. Areas of the cortex both near and distant are connected subcortically by short and long associative fibers. A surgeon preparing to approach a subcortical hemispheric glioma traditionally has the problem of tumor projection to the surface in relation to the functionally most important cortex and its principal projections. Neuroimaging now solves this problem noninvasively. The rolandic fissure, which delineates the sensorimotor cortex, has always been the pole star of the topography of the cerebral cortex, something that Giacomini intuited in Turin in 1878.[81] That the rolandic fissure is the pole star does not, of course, apply to polar so much as to "central" sites: it is no accident that in the English-speaking world, the rolandic fissure is the central sulcus and the rolandic convolutions, the precentral and postcentral gyri. On the basis of careful studies on cadavers, Giacomini found a way of projecting the central sulcus onto the skull surface by means of an ingenious pair of cardboard compasses. The transverse line from ear to ear, intercepted at the vertex by the sagittal midline, is divided into segments, one on either side. When the vertical leg of the compasses is centered on the central point of one segment, the other leg, inclined at 30 degrees, identifies the sulcus (Fig. 48-3). Constant in site, unlikely to be displaced, especially in its medial portion, the pararolandic cortex is now detectable in the highest axial CT cuts (Fig. 48-4). Parasagittal MRI sections locate the central sulcus through the cingulate and marginal sulci. Less accurately, the lower half of the rolandic cortex is shown adjacent to the lateral sulcus: lateral sagittal MRI sections identify it with the perpendicular to the posterior roof of the insula (Fig. 48-5).[82] To identify the whole length of the central sulcus, 3-dimensional MRI is needed.[83] Imaged on the lateral surface of the hemisphere are also the inferior frontal gyrus and the superior temporal gyrus, which in the left hemisphere comprise Broca's area and the auditory area, respectively. Thus, a large part of the cortex, which is known traditionally as being "eloquent," is located via the rolandic area.

This precise anatomic definition supplied by neuroimaging may not be sufficient for planning and performing the operation for several reasons. First, the anatomic structures may be displaced or distorted, especially by slow-growing space-occupying lesions such as the ones that we are considering; therefore, the anatomic landmarks may be unreliable. The surgical damage feared by surgeons on the basis of the standard anatomic landmarks is, surprisingly and fortunately, not usually found in the postoperative course. Second, major centers and nervous pathways may or may not be infiltrated, damaged, or interrupted by the neoplastic process; the surgeon should know their functional status. Third, although the sensorimotor cortex is more constant in its anatomy, the cortex related to language and cognitive functions has a much more variable and complex organization, hence the need to see the functional data for the various cortical areas alongside

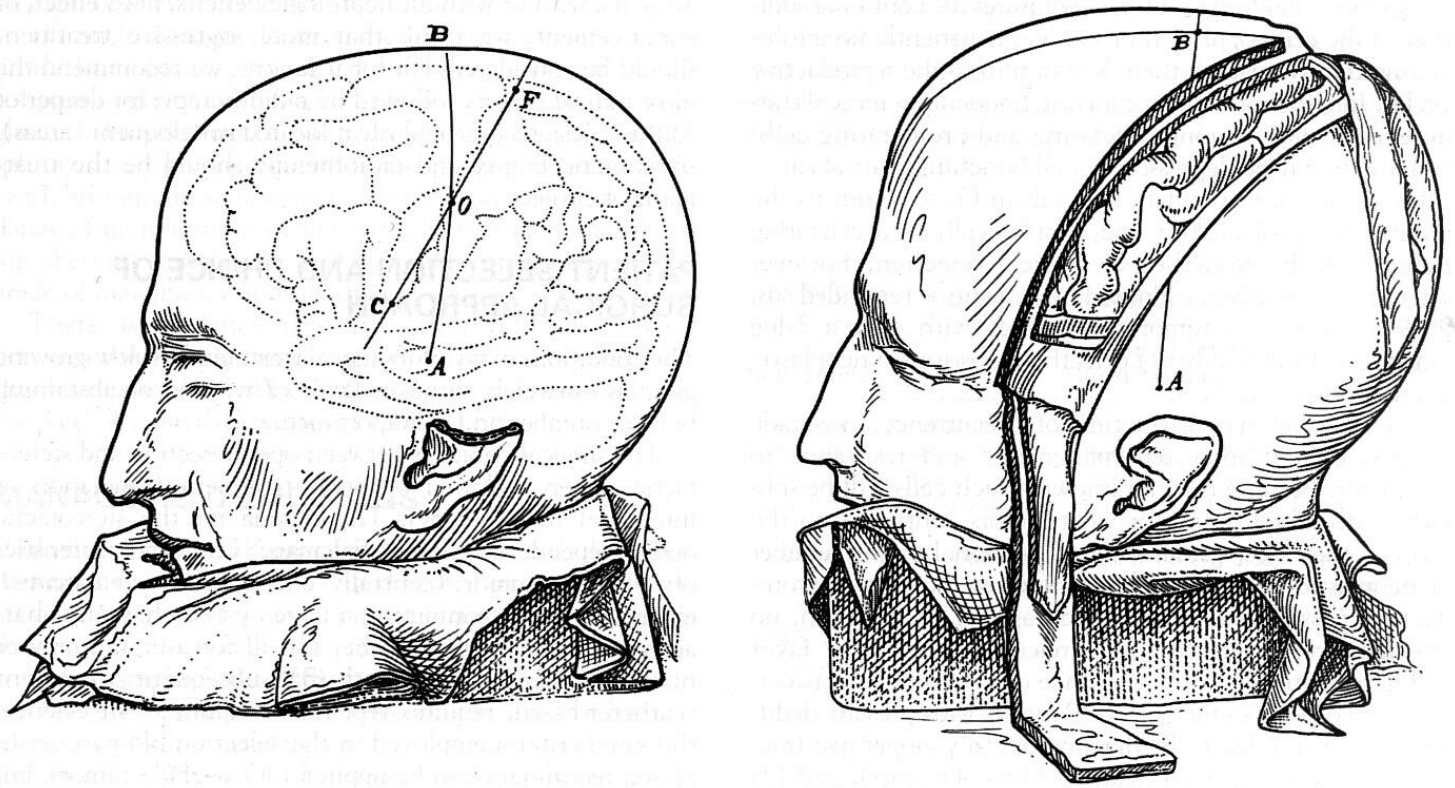

FIGURE 48-3 Goniometric identification of the central sulcus. (From Giacomini C: Guida allo studio delle circonvoluzioni cerebrali dell'uomo, 2nd ed. Torino: E Loescher, 1884.)

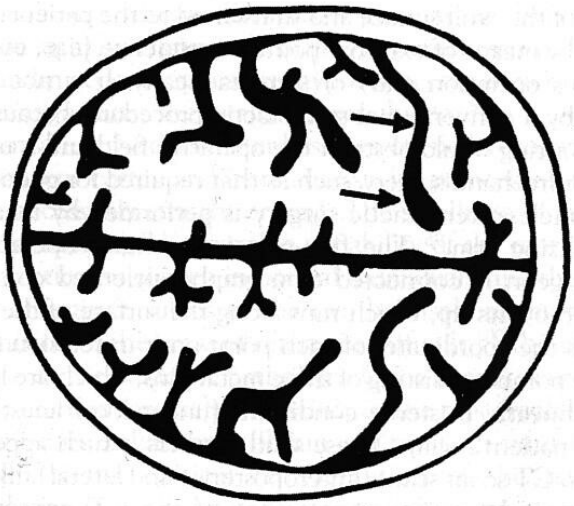

FIGURE 48-4 Tomographic aspect of the central sulcus.

or superimposed on the anatomic images. PET and single photon emission CT, which supply quantitative maps of physiologic, biochemical, and biophysical parameters but have poor spatial anatomic resolution, are superimposed on CT and MRI in the "computerized brain atlas."[84–87] The performance of various motor, verbal, and cognitive tasks or sensory stimulation is known to show a constant focal increase on PET, both in the glucose metabolism and in regional cerebral blood flow in certain areas of the cerebral cortex. For practical reasons, the regional blood flow has been investigated by use of $H_2{}^{15}O$. Once again, the rolandic cortex has proved to be the easiest to study, both on the motor side and on the sensory side: images are altered during either the performance of simple motor tasks involving a single limb or during sensory stimulation of it. Language, being a more complex function, still defies precise localization: numerous areas of the cortex and circuits are involved in the act of repeating words heard or of generating new ones; the nervous pathways activated in the production of new words and in getting used to them (repeating a list of names) are numerous. PET performed on volunteers and the speech map obtained by Ojemann and co-workers[88] by intraoperative stimulation (arrest or error in naming known objects presented) agree on the following: (1) extreme individual variation, (2) language cannot be located reliably on purely anatomic criteria, and (3) the traditional area of Broca needs to be revised.

Nariai and colleagues[89] pointed out that a glioma may be located within a single gyrus without altering its external morphology. Alternatively, a tumor may cause swelling or distortion of the cortical surface of the gyrus. In the latter situation, 3-dimensional MRI may not warrant the identification of "eloquent" areas, and the functional mapping with PET [^{11}C]methionine seems to offer the necessary accuracy. Localization of speech, motor, and memory function is now achieved with good accuracy by functional MRI (fMRI), but it still represents only a surrogate guide to neurophysiologic intraoperative methods.[90,91]

ANESTHETIC CONSIDERATIONS AND AIDS TO SURGERY

Craniotomy for cerebral glioma is almost always performed with the patient under general anesthesia and with monitoring of various parameters (e.g., electrocardiographic reading, arterial pressure, central venous pressure, and blood gas analysis) and checking of the fluid balance. Black and Ronner[92] and Walsh and associates[93] have mapped the sensorimotor and language cortex in a few cooperative patients by use of electrical stimulation while the patients were under local anesthesia. Systemic anesthetic agents were used occasionally on completion of the mapping studies. Ebeling and colleagues[94] localized the motor cortex intraoperatively with patients under general anesthesia and with temporary decurarization. However, these are all isolated experiments. Somatosensory evoked potentials are more widely used for illustrating the rolandic cortex when tumors are adjacent to it. They require appropriate screening of the operating room to reduce artifacts. For cortical mapping, Berger and colleagues[95] operate on patients who are awake with mild fentanyl sedation, using a local anesthetic for the scalp. Alternatively, during bone flap removal, propofol provides a deep sedative effect that can be reversed in 10 minutes.

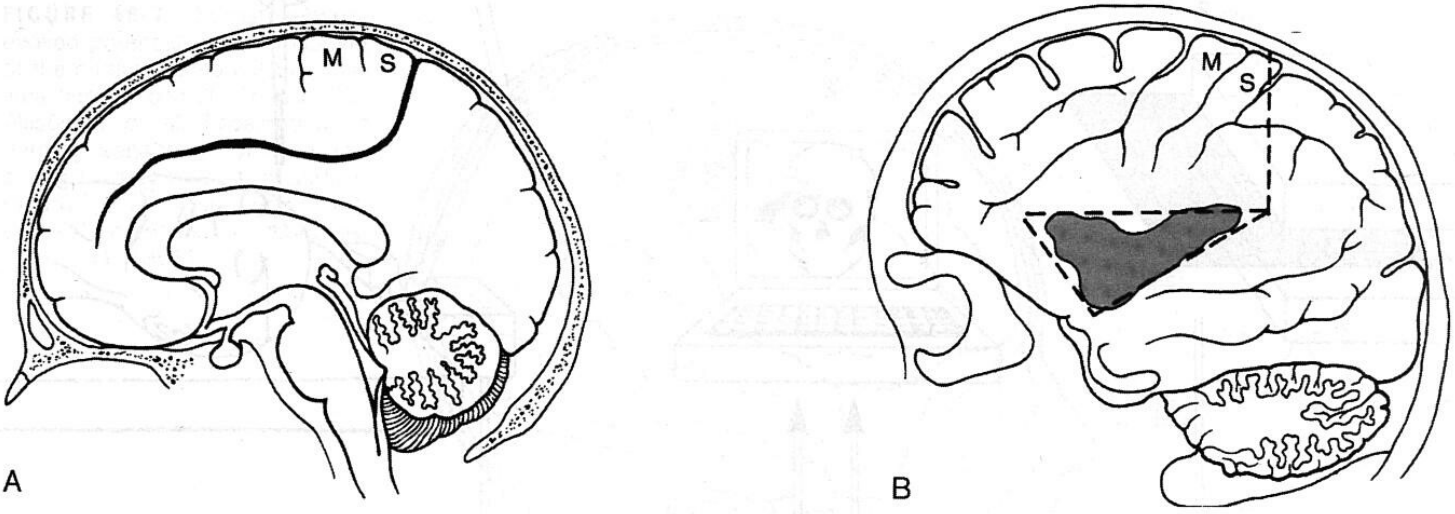

FIGURE 48-5 Geometric identification of central sulcus on magnetic resonance imaging. *A,* The parasagittal plane: the cingulate sulcus ends superiorly as the marginal sulcus (MS). *B,* The far lateral sagittal plane (*dashed line*).

Obviously, the operating microscope and microsurgical instruments, bipolar cautery, ultrasonic aspirators, and laser equipment are now part of routine neurosurgical practice. B-mode ultrasound with surface ultrasound probes is also useful in cases of subcortical glioma, as is explained later.

Last, the previous spatial incompatibility—recently resolved by "portable" CT and "in-built" MRI—between cumbersome neurodiagnostic machines and operating room demands, and also between stereotactic frames and freehand surgery, prompted few leading centers to develop sophisticated and complex equipment. The precision of stereotactic methods is often needed in the surgery for gliomas.

SURGICAL TECHNIQUE

Craniotomy

The importance of neuroimaging, especially with 3-dimensional MRI, in highlighting simultaneously the tumor and the layout of the cortex of the entire cerebral hemisphere concerned with its main sulci and gyri has already been discussed. The cerebral hemisphere can, furthermore, be sectioned according to various planes on the computer display to illustrate the relations between the tumor and the deep-seated structures (e.g., internal capsule, basal nuclei, and ventricular cavities). MR angiography relies on "angiographic" pulse sequences that potentiate the signal from the blood flow at the expense of that from the static tissues. Thus, the relations between the tumor and the cerebral vascular network are studied on the 3-dimensional model both on the surface of the hemisphere and in sections. The structural features of the tumor (e.g., cysts, calcifications, or necrosis) are also illustrated. As mentioned, functional data from eloquent structures may also be integrated by fMRI.

Knowing the volume and spatial disposition of the neoplastic mass in relation to the eloquent cortex and to no less eloquent deep structures can permit simulation of a test flap on the computer screen. This image is then projected onto the image of the skull surface and transferred to the patient's head either by means of external points of reference (e.g., eye, ear, previous operation scar) or stereotactically. It is not transferred by a conventional stereotactic procedure, because the frame or ring would obstruct the operative field and is unsuitable for freehand surgery, such as that required for gliomas.

Frameless stereotactic surgery is performed by means of a localizing arm.[96] The five-part jointed arm operated by the surgeon is connected to a graphic-oriented computer (Fig. 48-6). Its tip, which runs along the surface of the skull, records the coordinates of each point on it in relation to reference points consisting of three metal pins, which are lodged noncolinearly in sterile conditions (under local anesthesia) in the patient's scalp. These skull markers, which appear on the two CT scout scans (anteroposterior and lateral), likewise constitute the points of reference of the CT coordinates. Because the arm coordinates and CT coordinates are correlated in the same computer, after appropriate calibration the tip of the localizing arm that runs along the skull surface is shown on the CT scan by a cursor. The optimal approach to the underlying tumor, even if it is small, can easily be centered. The craniotomy is thus targeted and personalized. It may consist of a trephine hole 4 to 5 cm in diameter. The chosen approach need not be the most direct, but it must be the safest for the neurologic integrity of the patient.

Cortical Approach

In surgeries for subcortical lesions that do not emerge on the surface, the following procedure is used. After the dura mater is opened, the surgeon has to recognize the tumor, size up its spatial relations with the adjacent structures, and decide where to incise the cortex. B-mode ultrasound[97,98] now replaces manual palpation: it localizes the tumor in relation to the cortex, to the underlying ventricle, to the falx, to the tentorium, or to the bony base; it also characterizes the tumor structure (calcifications or secluded cysts), specifies its volume,[99] and demarcates its margins.

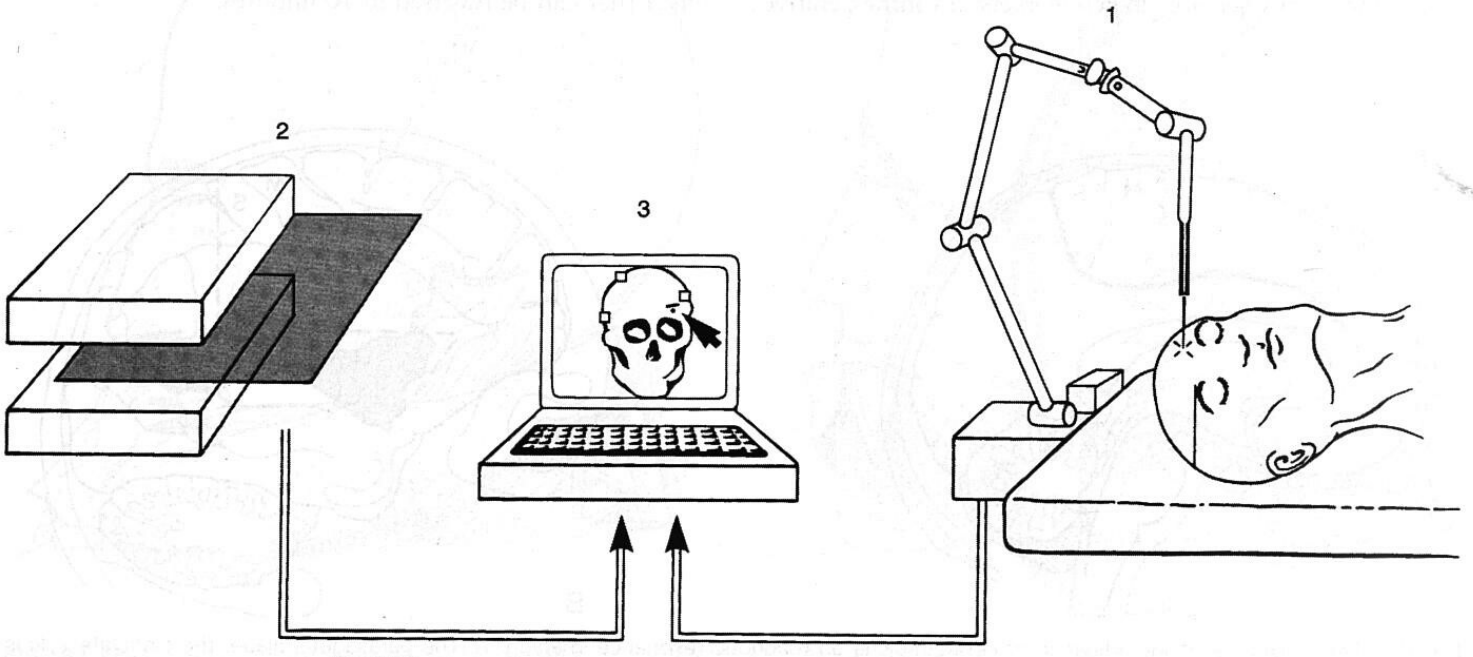

FIGURE 48-6 Frameless stereotactic surgery system. See text for details.

Although CT shows low-grade gliomas as hypodense, ultrasonography shows them as hyperechogenic.[98] The surrounding edema appears as hypoechogenic or very faintly echogenic against the healthy parenchyma.[99]

Even when the dura mater has been opened, recognition of the eloquent cortex and its relations with paracentral tumors is not necessarily straightforward. The smallness of the craniotomy opening, the extreme variability of the morphology of the cortical sulci even in normal individuals, and the asymmetry of a given sulcus in the two hemispheres may make recognition of the areas of reference difficult,[100] the more so because of the adjacent pathology. Once again, neurophysiologic methods are helpful, mainly in the topography of the rolandic cortex. Easiest to obtain and most constant (reproducible) is the cortical representation of the hand by somatosensory evoked potentials on stimulation of the contralateral median nerve. With the patient under general anesthesia, the topography of the hand is clear on both gyri separated by the central sulcus. The potentials are approximately mirrored in form on the two sides, the P_{20}–N_{30} waves being of greater amplitude in the precentral area and the N_{20}–P_{30} waves in the postcentral area (Fig. 48-7).[101] Focal somatosensory evoked potentials of great amplitude have also been obtained from the posterosuperior bank of the Sylvian fissure. Could this be a secondary somatosensory area?[102] Unfortunately, evoked potentials are not as helpful in identifying the visual and auditory cortex intraoperatively.

The cortex involved in the expression of language can only be demarcated by stimulation with the patient under local anesthesia. Electrostimulation of the cortex, pioneered by Bartholow[103] and Horsley[104] and later systematized by Penfield and Boldrey,[105] still has applications for delineation of speech areas,[88] as already discussed. Whatever the means used, the neurophysiologic and/or neuroradiologic identification of the eloquent cortex are an aid not only in the planning of an operation but also in its execution.[106,107] Because of possible displacement by the tumor, the surgeon is freer to be more aggressive than if he or she is working only from anatomic landmarks.

However, is there really a "silent" cortex? Brodmann's areas 1 through 7, 17 through 19, 27 through 28, and (in the dominant hemisphere) 40 through 45 are considered to be eloquent (Fig. 48-8). The problem with the remainder of the cortex is that it gives no elementary responses to stimulation; rather it is involved in complex mechanisms of neurophysiologic and neuropsychologic integration, and it does not give signals in laboratory animals that are easily applied to humans. Furthermore, although projection fibers (motor, special, or general sensory) underlie the eloquent cortex, short and long intrahemispheric associative fibers underlie the rest.

Desire to spare the lobar cortex and underlying fibers as far as possible has led to the proposal of the transsulcal surgical approach[108,109]: by using these natural corridors, the surgeon can go down 2 to 3 cm in pseudo depth without incising tissue, thus remaining outside the brain. Furthermore, because the sulci, especially the major ones, are full of fluid, their opening ensures decompressive depletion, hence the renewed interest in the anatomy of the cerebral sulci.[100,110] Several varieties of sulci are recognized: axial, limiting, opercular, and complete (Fig. 48-9). Their extreme variation from one individual to another and between hemispheres in a single individual is confirmed, and efforts are being made to define the numerous ways in which one sulcus continues with another (full, partial, or simulated communication). The depth of some sulci has been measured on several specimens: the superior frontal sulcus is 17 to 24 mm deep; the superior temporal, 15 to 25 mm; and the junction of the interparietal with the postcentral sulcus, 20 to 27 mm.[111] The course of the blood vessels in the sulci is not uniform: some descend to the bottom of the sulcus before penetrating the brain substance, whereas others only cross the sulcus to rise to the top of the adjacent gyrus.[69] In either case, they are easily dissected between the arachnoid trabeculations of the sulcus or retracted toward one or the other gyrus with a spatula. An advantage of a transsulcal over a transgyral incision is that the cortex is less thick at the bottom of a sulcus than at the summit of a gyrus. A disadvantage is that an incision at the bottom of a sulcus interrupts the subcortical associative U-shaped fibers that connect two neighboring gyri.

On superficial inspection, deciding which sulcus to approach is not always easy. The arachnoid must be incised at several points to distinguish first the deep from the shallow sulci and from a sulcus-like impression of an artery on the cortex (Fig. 48-10).[6] Rarely, minute blood vessels obstruct

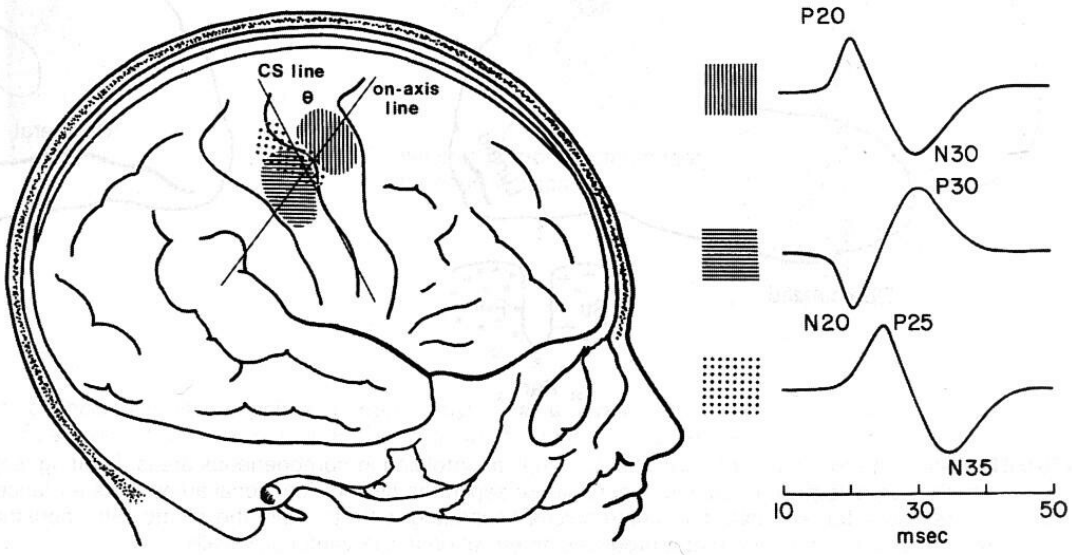

FIGURE 48-7 Somatosensory evoked potential–guided mapping of the cortical sensory (CS) motor area. (From Wood CC, Spencer DD, Allison T, et al: Localization of human sensory motor cortex during surgery by cortical surface recording of somatosensory evoked potentials. J Neurosurg 68:99–111, 1988.)

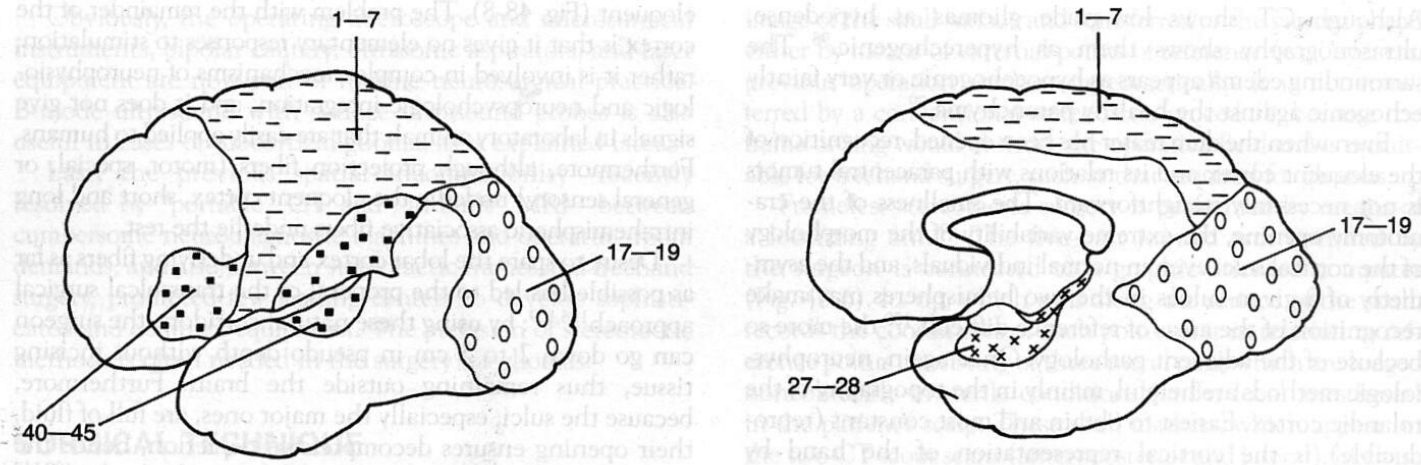

FIGURE 48-8 Schematic topography of eloquent cortical regions of the brain.

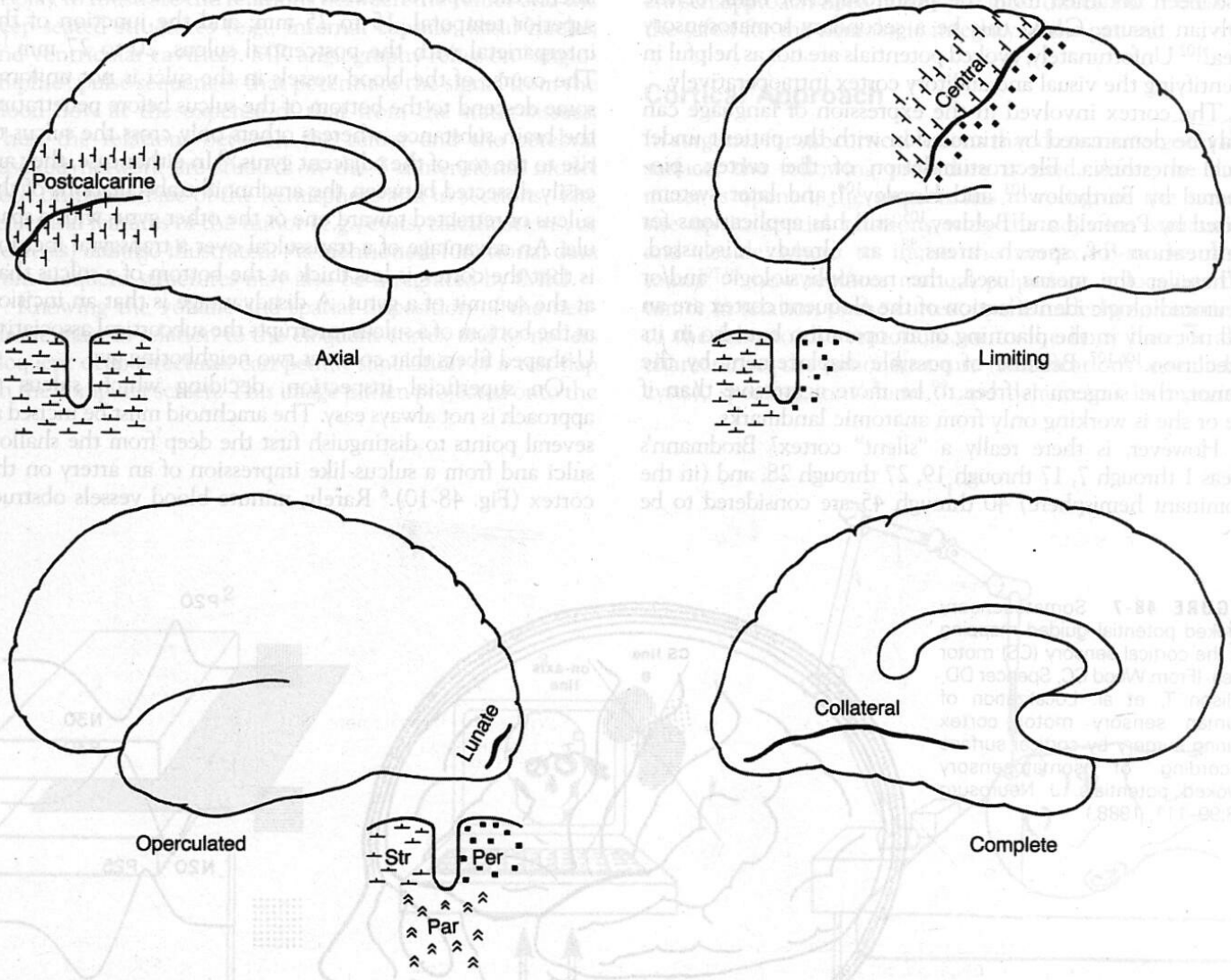

FIGURE 48-9 The four types of cortical sulci: Axial: an infolding in homogeneous areas. Limiting: separates the cortex into two areas different in both morphology and function. Operculated: separates distinct functional areas at its entrance, and often a third area of function is present in its floor—for example, the lunate sulcus separating with its walls the striate (Str), peristriate (Per), and parastriate (Par) areas. Complete: that which is so deep that it produces an elevation in the ventricular walls.

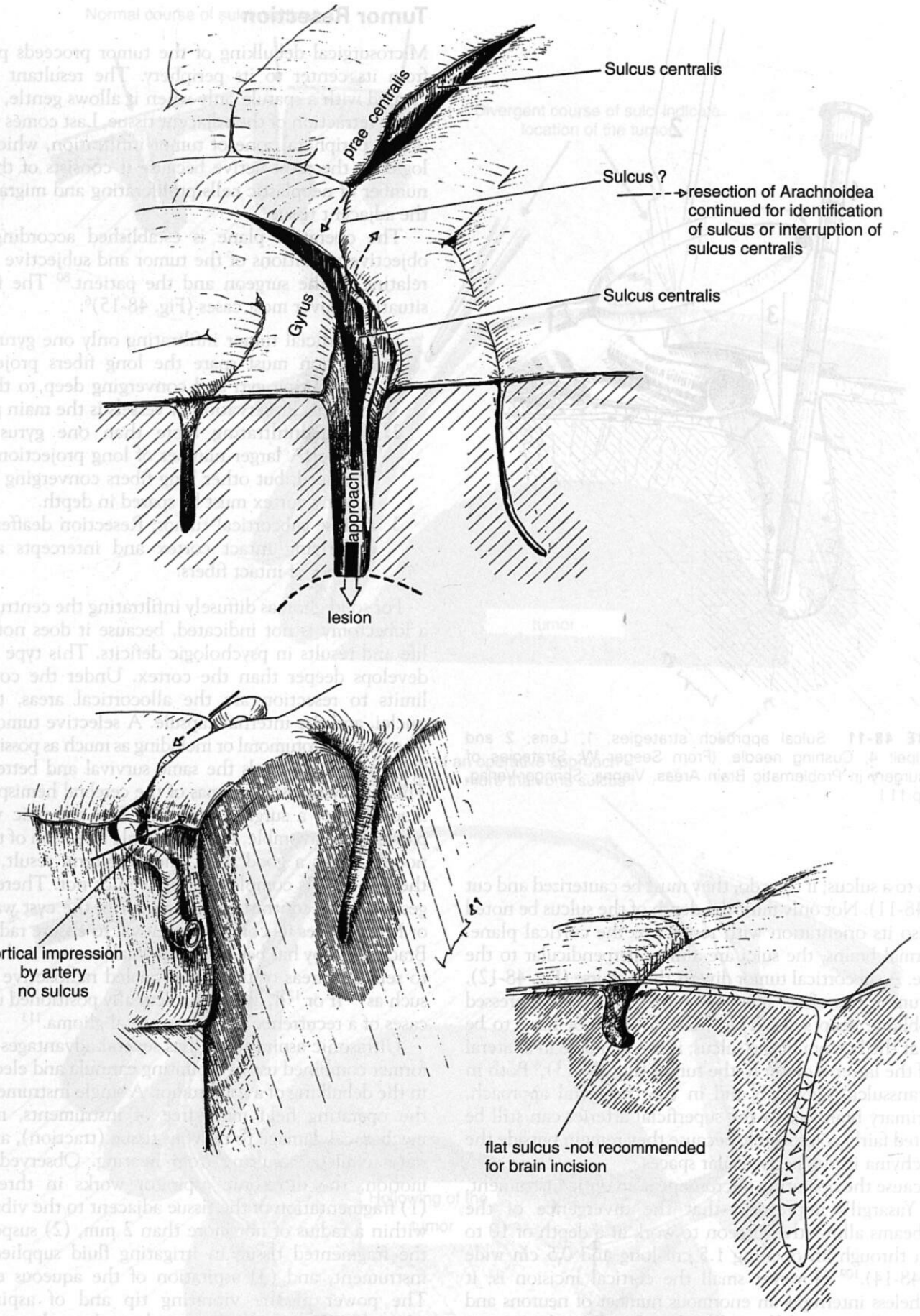

FIGURE 48-10 The arachnoid has to be incised at several points in order to distinguish the deep sulci from a sulcus-like impression of an artery on the cortex. (From Seeger W: Strategies of Microsurgery in Problematic Brain Areas. Vienna: Springer-Verlag, 1990, p 13.)

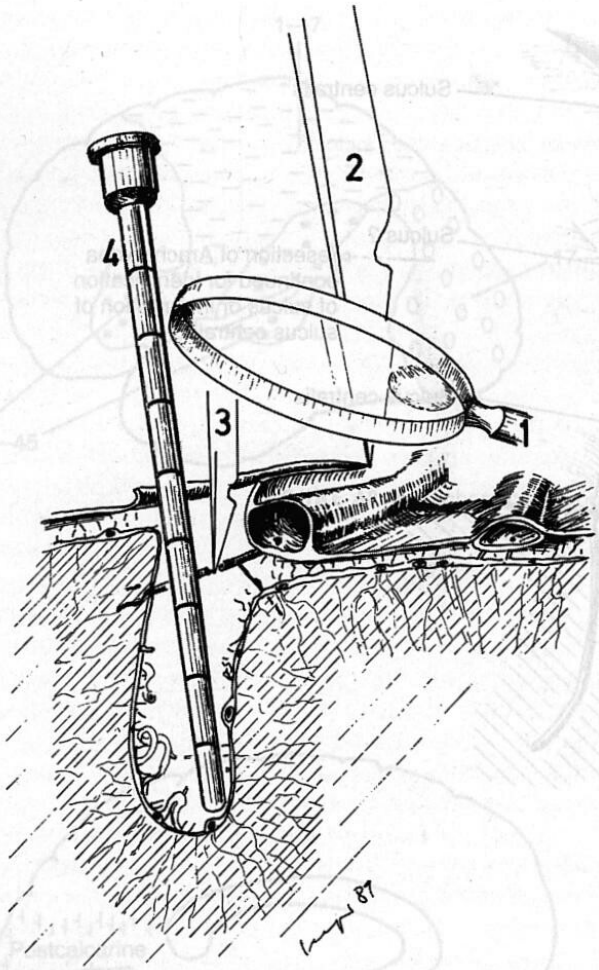

FIGURE 48-11 Sulcal approach strategies. 1, Lens; 2 and 3, scalpel; 4, Cushing needle. (From Seeger W: Strategies of Microsurgery in Problematic Brain Areas. Vienna: Springer-Verlag, 1990, p 11.)

access to a sulcus; if they do, they must be cauterized and cut (Fig. 48-11). Not only must the depth of the sulcus be noted but also its orientation with respect to the cortical plane. In normal brains, the sulci are almost perpendicular to the surface. A subcortical tumor diverts their course (Fig. 48-12). The tumor, therefore, must be sought via the compressed and oblique deep sulci. The incision does not have to be made at the bottom of the sulcus; it can be made in a lateral wall if the latter is closer to the tumor (Fig. 48-13).[6] Both in the transsulcal approach and in the transgyral approach, the primary branches of the superficial arteries can still be dissected fairly comfortably because they remain outside the parenchyma in the perivascular spaces.

Because the operating microscope is an optic instrument, it is Yasargil's impression that the divergence of the light beams allows the surgeon to work at a depth of 10 to 12 cm through an opening 1.5 cm long and 0.5 cm wide (Fig. 48-14).[109] However small the cortical incision is, it nonetheless interrupts an enormous number of neurons and their connections and fibers. A wedge of cortex with a section that is 1 mm^2 and 2.5 mm deep contains up to 60,000 neurons. Neuronal density varies, of course, from one area of the cortex to another, being greatest in the striate area and lowest, perhaps, in the precentral gyrus.

Tumor Resection

Microsurgical debulking of the tumor proceeds piecemeal from its center to its periphery. The resultant cavity is cleared with a spatula only when it allows gentle, nontraumatic retraction of the adjacent tissue. Last comes resection of the peripheral zone of tumor infiltration, which is biologically the most active because it consists of the largest number of neoplastic cells proliferating and migrating into the adjacent tissue.

The operative plane is established according to the objective conditions of the tumor and subjective variables relating to the surgeon and the patient.[80] The following situations cover most cases (Fig. 48-15)[6]:

1. Superficial tumor infiltrating only one gyrus: Tumor resection must spare the long fibers projecting to neighboring gyri and converging deep to the tumor margins. Preservation of vessels is the main problem.
2. Tumor infiltrating more than one gyrus on the surface: A larger number of long projection fibers is sacrificed, but other long fibers converging from the healthy cortex must be spared in depth.
3. Diffuse subcortical tumor: Resection deafferents the underlying intact cortex and intercepts a certain number of intact fibers.

For solid gliomas diffusely infiltrating the centrum ovale, a lobectomy is not indicated, because it does not prolong life and results in psychologic deficits. This type of tumor develops deeper than the cortex. Under the cortex, the limits to resection are the allocortical areas, the basal nuclei, and the internal capsule. A selective tumorectomy, whether centrotumoral or including as much as possible of the marginal zone, affords the same survival and better health. The rare cystic astrocytomas of the cerebral hemispheres are much less of a surgical problem. The pilocytic variety is particularly favorable, because simple resection of the mural nodule yields a good short and long-term result, whether the cyst wall is completely removed or not. There are suggestions that contrast enhancement of the cyst wall at CT or MR requires its complete removal to ensure radicality.[112] Brachytherapy has been used for small tumors and restricted to selected areas of the brain. Sealed radioactive isotopes, such as ^{192}Ir or ^{125}I, are stereotactically positioned usually in cases of a recurrence of a postsurgical glioma.[113]

Ultrasonic aspiration[114] has several advantages over the former combined use of aspirating cannula and electric loop in the debulking of a solid tumor. A single instrument leaves the operating field more free of instruments, minimizes mechanical damage to nervous tissue (traction), and eliminates damage resulting from heating. Observed in slow motion, the ultrasonic aspirator works in three stages: (1) fragmentation of the tissue adjacent to the vibrating tip within a radius of not more than 2 mm, (2) suspension of the fragmented tissue in irrigating fluid supplied by the instrument, and (3) aspiration of the aqueous emulsion. The power of the vibrating tip and of aspiration is adjustable. The speed of action depends on the consistency of the tissue to be removed. However, the lower the power of fragmentation, the less damage will occur to the vascular framework. Fragmentation is selective for a tissue with a large aqueous component and spares the vessel walls, which

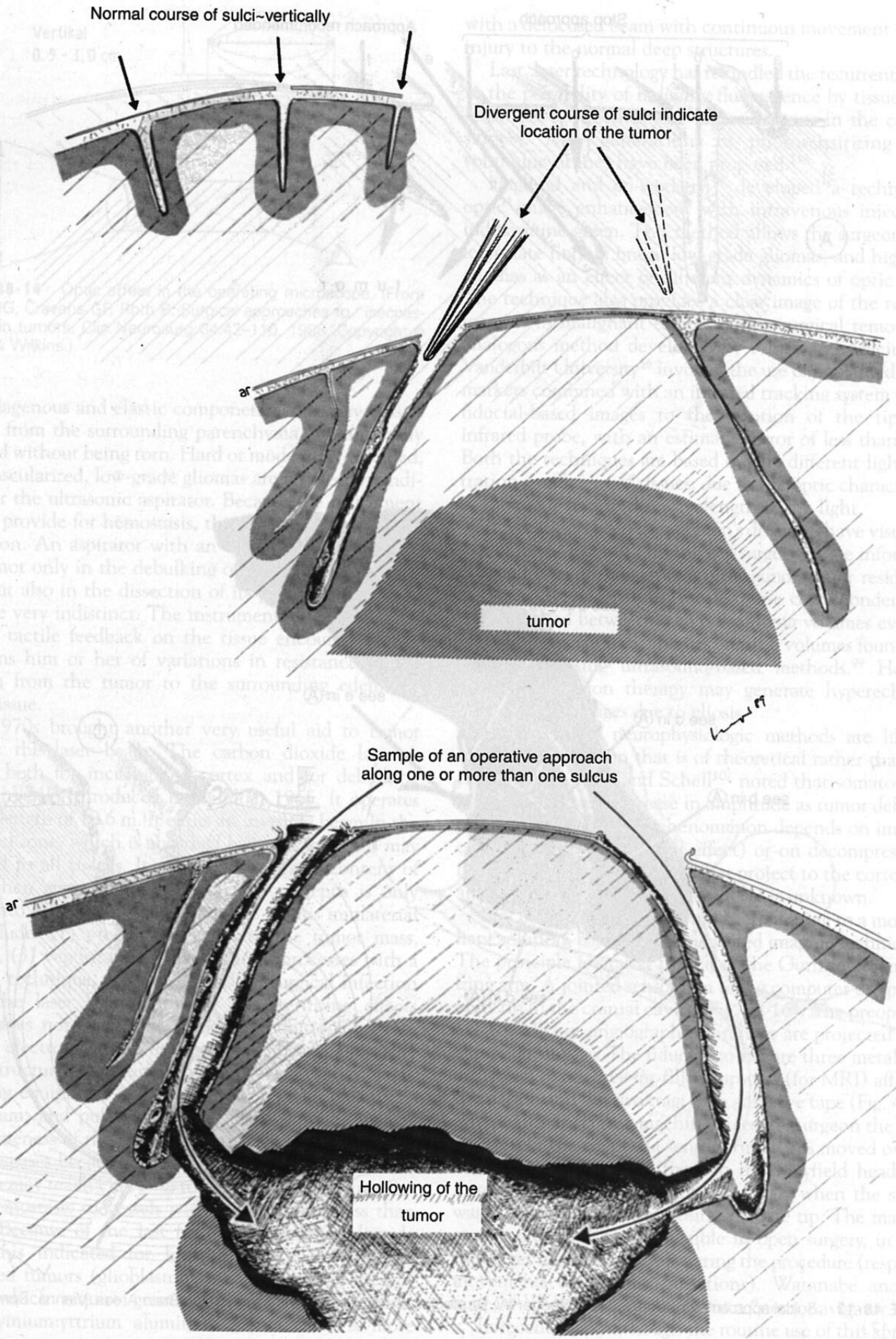

FIGURE 48-12 Tumoral distortion of the sulcal pattern of orientation. (From Seeger W: Strategies of Microsurgery in Problematic Brain Areas. Vienna: Springer-Verlag, 1990, p 15.)

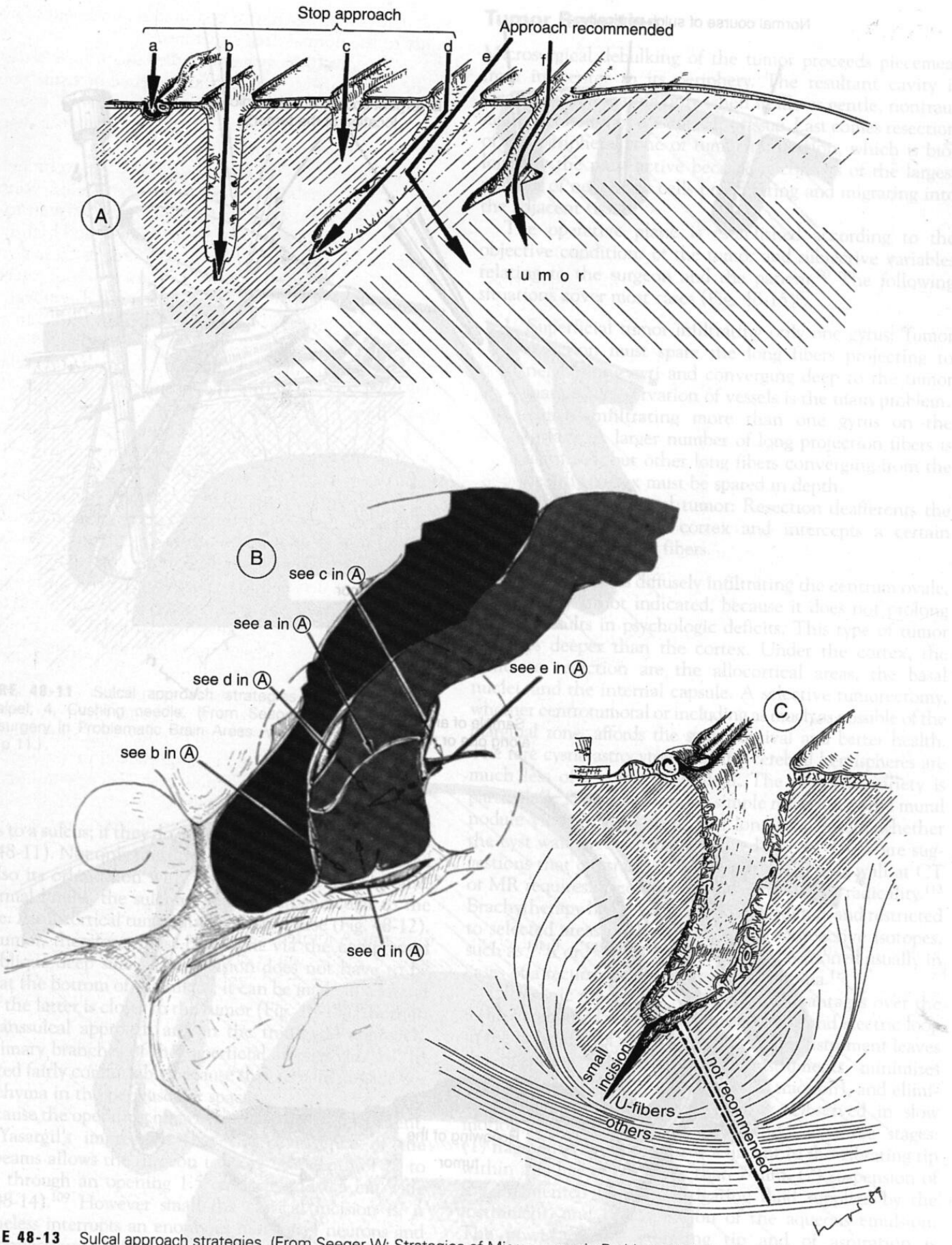

FIGURE 48-13 Sulcal approach strategies. (From Seeger W: Strategies of Microsurgery in Problematic Brain Areas. Vienna: Springer-Verlag, 1990, p 17.)

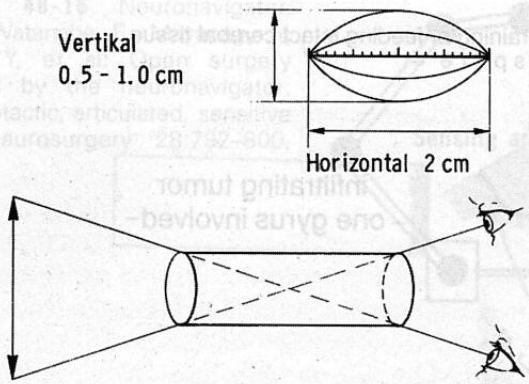

FIGURE 48-14 Optic effect in the operating microscope. (From Yasargil MG, Cravens GF, Roth P: Surgical approaches to "inaccessible" brain tumors. Clin Neurosurg 34:42–110, 1988. Copyright © Williams & Wilkins.)

have collagenous and elastic components. The tiny vessels are freed from the surrounding parenchyma and are easily cauterized without being torn. Hard or moderately calcified, poorly vascularized, low-grade gliomas are an elective indication for the ultrasonic aspirator. Because the instrument does not provide for hemostasis, this is handled by bipolar coagulation. An aspirator with an ultrasonic vibrating tip is useful not only in the debulking of the central mass of a glioma but also in the dissection of its peripheral margins, which are very indistinct. The instrument gives the operator some tactile feedback on the tissue encountered and thus warns him or her of variations in resistance in the transition from the tumor to the surrounding edema or healthy tissue.

The 1970s brought another very useful aid to tumor resection: the laser beam. The carbon dioxide laser is preferred both for incising the cortex and for debulking the tumor.[115–117] Introduced by Patel in 1965, it operates at a wavelength of 10.6 m. It emits an invisible beam in the far infrared zone, which is absorbed by water and thus may be applied to all tissues. It vaporizes the water content of tissues; when appropriate, the penetration depth is only 0.2 mm into soft tissue. The advantages of this immaterial knife include: (1) precise dissection of the tumor mass, (2) speed, (3) vaporization of deep tumor processes with a nontouch technique, and (4) less risk of surgical infection because the laser knife not only has sterilizing effects but also does not touch the tissues. In addition, because it has no electromagnetic field, it does not stimulate the nervous structures or interfere with the electrophysiologic monitoring equipment (e.g., electrocardiogram, electroencephalogram, and pulse rate). The disadvantages are the cumbersomeness of the equipment, the risk of explosion of anesthetic gases because of the high temperatures that the laser beam may reach (1700 °C to 1800 °C), and the restriction of hemostasis to vessels with a diameter of less than 0.5 mm. Because of the last feature, the carbon dioxide laser beamis indicated for low-grade gliomas. In more vascularized tumors (glioblastomas or angioblastic meningiomas), which require greater capacity for hemostasis, the neodymium:yttrium aluminum garnet laser is more suitable.

When a tumor is massive and superficial, it is best to use a focusing laser beam to shorten the vaporization time; in deep regions of the brain, the tumor should be vaporized with a defocused beam with continuous movement to avoid injury to the normal deep structures.

Last, laser technology has rekindled the recurrent interest in the possibility of inducing fluorescence by tissue photosensitizers to discover the tumor margins in the course of surgery. New generations of photosensitizing agents (phthalocyanine) have been proposed.[118]

Haglund and co-workers[119] developed a technique of optic image enhancement with intravenous injection of indocyanine green. This method allows the surgeon to differentiate normal brain, low-grade gliomas, and high-grade gliomas as an effect of different dynamics of optic signals. The technique also provides a clear image of the resection margins in malignant tumors during surgical removal. An analogous method developed by Allen and Maciunias at Vanderbilt University[56] involves the use of implanted fiducial markers combined with an infrared tracking system relating fiducial-based images to the position of the tip of an infrared probe, with an estimated error of less than 1 mm. Both the techniques are based on the different light penetration coefficient of tissues, due to the optic characteristics of the tissue and to the wavelength of the light.

It has always been the surgeon's dream to have visual control of his or her work during the surgery. Some information is supplied by intraoperative ultrasound: tumor residues are shown to be hyperechogenic. A close correspondence was demonstrated between low-grade glioma volumes evaluated with neuroimaging techniques and the volumes found intraoperatively using ultrasound-based methods.[99] However, previous radiation therapy may generate hyperechogenic false-positive images due to gliosis.

Intraoperative neurophysiologic methods are likely to make a contribution that is of theoretical rather than practical interest. King and Schell[102] noted that somatosensory evoked potentials increase in amplitude as tumor debulking proceeds. Whether the phenomenon depends on improved cerebral perfusion (general effect) or on decompression of fibers of the internal capsule that project to the cortex lying against the tumor mass (local effect) is unknown.

Since 1985, the problem has been moving to a more brilliant solution, based on sophisticated imaging techniques.[120] The principle is similar to that of the Guthrie-Adler localizing arm. A jointed sensor arm tells a computer the position of its tip in the cranial cavity (Fig. 48-16). The preoperative CT (or MRI or angiographic) findings are projected on the computer display. The fiducial points are three metal markers (for CT) or three fat-filled capsules (for MRI) affixed to the nasion and the two tragi with adhesive tape (Fig. 48-17). After calibration, the machine gives the surgeon the spatial position of the tip of the sensor arm as it is moved over the neuroimages. The arm, fixed to the Mayfield headrest, is introduced into the operative field only when the surgeon wants to know the exact position of the tip. The margin of error is around 2 mm, negligible in open surgery, in which the target inevitably moves during the procedure (respiratory movements or vascular pulsations). Watanabe and associates[120,121] called the instrument a "neuronavigator."

In recent years, although the routine use of this apparatus spread diffusely and many different models have been released by the industry, few reports appeared in the literature specifically addressing the surgical treatment of low-grade gliomas.

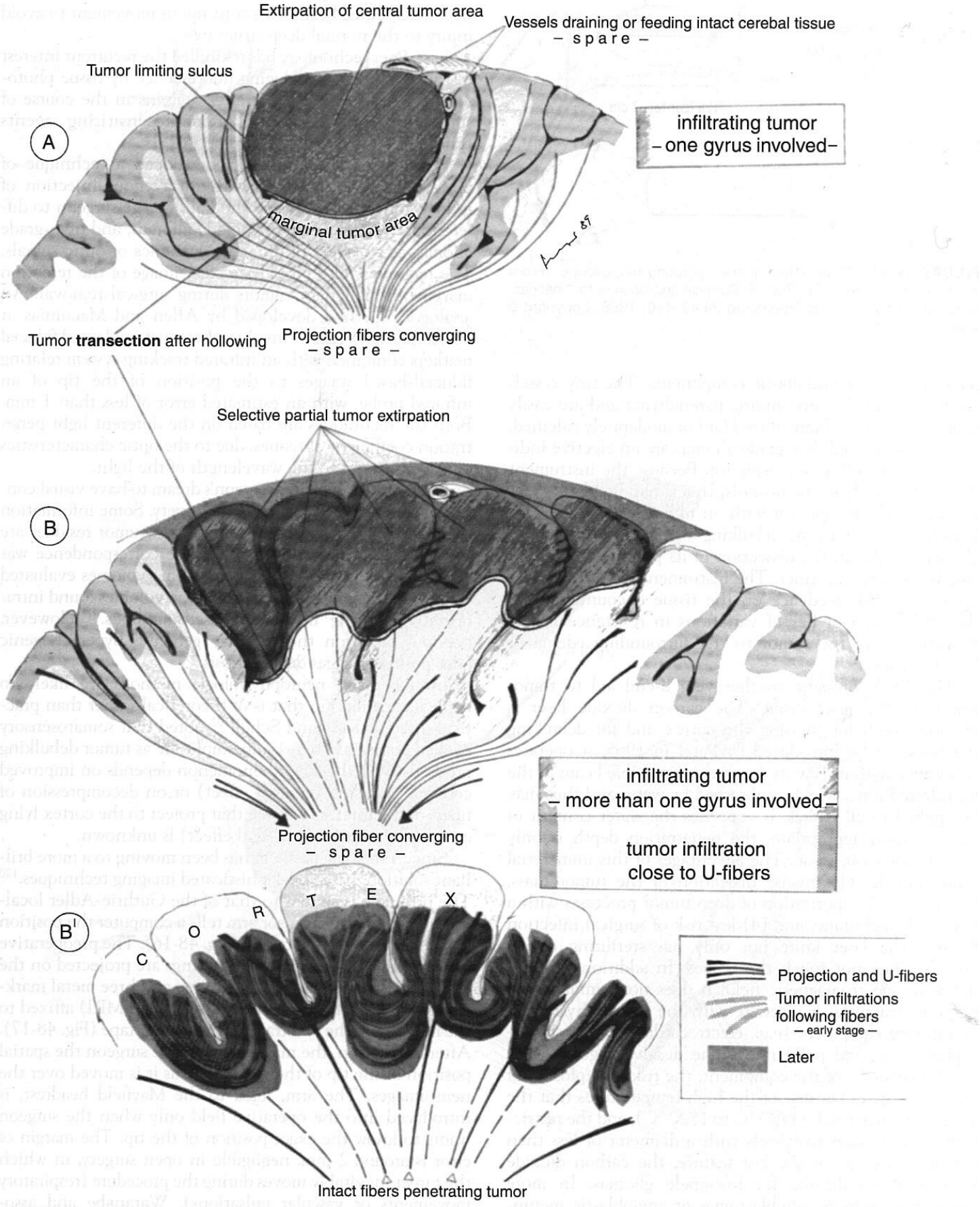

FIGURE 48-15 Different patterns of glioma infiltration. (From Seeger W: Strategies of Microsurgery in Problematic Brain Areas. Vienna: Springer-Verlag, 1990, p 21.)

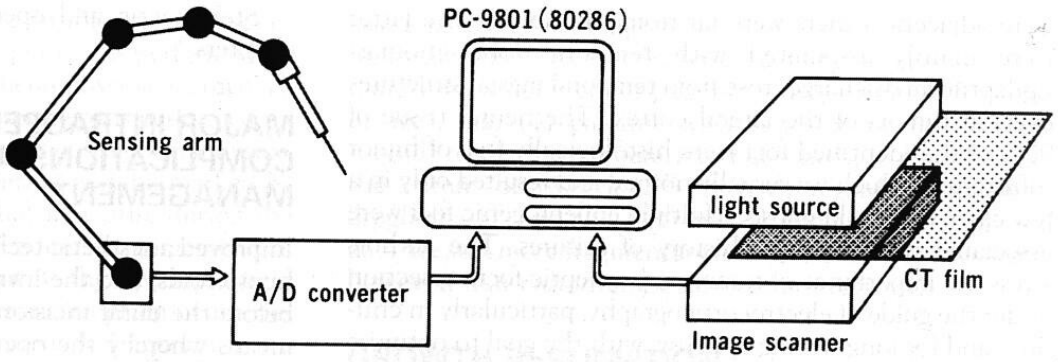

FIGURE 48-16 Neuronavigator. (From Watanabe E, Mayanagy Y, Kasugi Y, et al: Open surgery assisted by the neuronavigator: A stereotactic, articulated, sensitive arm. Neurosurgery 28:792–800, 1991.)

The spatial incompatibility between neurodiagnostic apparatus (CT, MRI, digital angiography) and the requirements of the operating room has been overcome by Kelly[122] by a complex organization centering on a heads-up display system, similar to that used on fighter aircraft, which projects the tumor sections obtained by the computer from CT or MRI data into the operating microscope. A detailed account is provided in Chapter 41. The introduction of portable CT and, moreover, high-field intraoperative MRI—the latter at this point available in a limited number of neurosurgical units—should provide more information about eloquent areas, allow adequate control over the surgical "work in progress," and consequently ensure better results. However, we are not as yet aware of reports detailing morbidity and recurrence figures in low-grade gliomas series using these intraoperative aids.[123–125]

Another method is that proposed by Hassenbusch and colleagues.[126] Craniotomy is performed under a stereotactic frame; when the dura mater has been opened, two or three stereomarkers are introduced at the tumor margins (the ones most difficult to distinguish or situated in the most critical areas) according to the coordinates supplied by CT or MRI (Fig. 48-18). They are "micropatties" (0.6 × 0.6 cm), each with a string tail or silicone sheeting microtubes, either of which are introduced through a microbiopsy forceps with the ends left emerging from the cortex. The stereotactic frame is then removed, and the surgeon proceeds to free-hand tumor resection. The advantage of this method is that the markers remain lodged at the edges of the tumor (in the brain adjacent to it) despite shifts in the tumor or in the cerebral hemispheres resulting from cyst drainage or tumor debulking.

Berger[56] also reports the use of ultrasonic guidance to introduce catheters at the tumor boundaries as a "fence" to mark the limit of surgical resection. The proposed method of ultrasonic neuronavigation includes a program to calculate the shift of intracranial content occurring with tumor progressive debulking and cerebrospinal fluid (CSF) removal, performing a continuous correction of the initial spatial parameters.

Associated Intractable Epilepsy

Often epileptic foci are associated to low-grade gliomas. Berger and co-workers[95] have registered intraoperatively this pathologic activity, establishing relevant correlations with the clinical status. Only in 6 of 45 patients studied did electrocorticography fail to demonstrate epileptic activity. Twenty-one patients harbored one epileptic focus, and 18 patients harbored at least two foci. Some of these foci

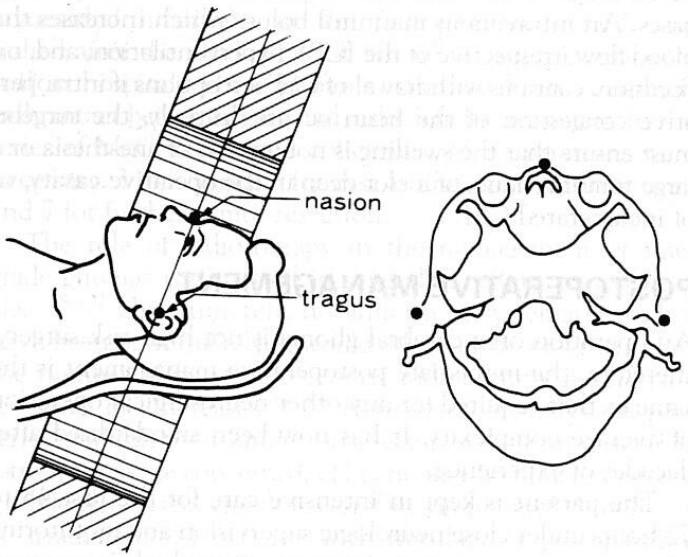

FIGURE 48-17 Artificial coordinates method(s): fiducial points. (From Watanabe E, Mayanagy Y, Kasugi Y, et al: Open surgery assisted by the neuronavigator: A stereotactic, articulated, sensitive arm. Neurosurgery 28:792–800, 1991.)

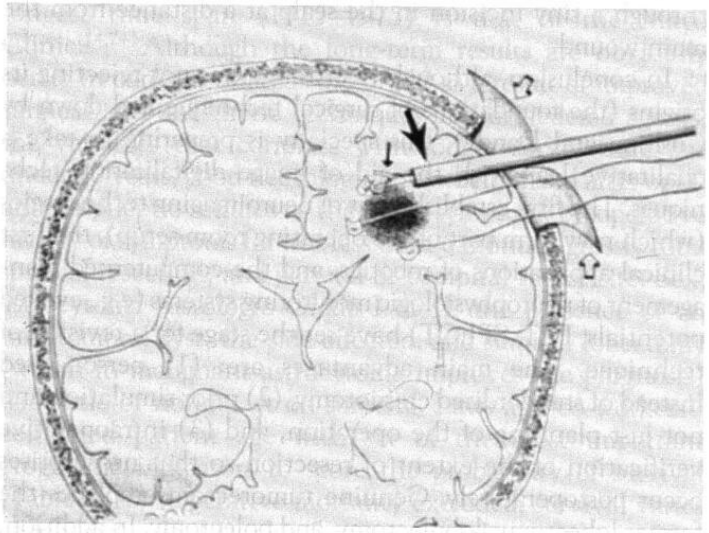

FIGURE 48-18 Artificial coordinates method(s): stereomarkers. (From Hassenbusch SJ, Anderson JS, Pillay PK: Brain tumor resection aided with markers placed using stereotaxis guided by magnetic resonance imaging and computed tomography. Neurosurgery 28:801–806, 1991.)

were adjacent; others were far from the tumor. The latter were mainly associated with temporal lobe gliomas. Epileptiform discharges rose from temporal mesial structures even in tumors of the lateral cortex. The neural tissue of 90% of the identified foci were histologically free of tumor infiltration, which was usually normal and resulted only in a few cases with mild gliosis. Multiple epileptogenic foci were associated with a longer history of seizures. The authors stress the importance of tumor and epileptic focus resection under the guide of electrocorticography, particularly in children and for long-lasting epilepsy, with the goal to optimize seizure control and allow possible interruption or reduction of drug therapy.

Hemostasis and Closure

Hemostasis is ensured in the usual way under the operating microscope by means of bipolar cautery, discontinuous irrigation with lukewarm isotonic saline solution, and dabbing of the walls with cottonoids. Even the smallest nontumoral vessels are spared. As little use as possible is made of foreign materials (e.g., fibrin sponge, oxidized cellulose net) for lining the cavity, which is then filled with physiologic saline.

An extended internal decompressive operation impinging on sound nervous tissue is now viewed with great circumspection, because any sacrifice of nervous tissue always involves neurologic or behavioral deficits, even if they are not detectable with the tests currently available. No such rule applies to the resection of epileptogenic cortical foci separate from the neoplastic mass, which is recommended by Ghatan and associates.[18]

Once the dural margins have been secured to the periosteum by interrupted sutures along the perimeter of the craniotomy, the dural flap is made watertight. The bone is replaced; because the craniotomy is small and its site is at the convexity, there is no point in removing the bone flap for decompression (the classic decompressive operation is to be performed at the base). If the surgeon desires, an epidural probe for prolonged intracranial pressure (ICP) recording is positioned by tunneling the cable beneath the scalp for a few centimeters and bringing it to the surface through a tiny incision in the scalp at a distance from the main wound.

In conclusion, although neurosurgery is not rejecting its origins (the foundations of surgical technique laid down by Cushing and Dandy), this specialty is preparing to take a qualitative leap with the aid of image digitalization techniques. The firm establishment of neuroimaging technologies (which now form part of the operating room setup), the first clinical applications of robotics, and the computerized management of neurophysiologic monitoring systems (e.g., evoked potentials, PET, SPECT) have set the stage for a revision of technique. The main advantages are: (1) personalized instead of standardized craniotomy, (2) prior simulation and not just planning of the operation, and (3) intraoperative verification of the extent of resection so that no surprises occur postoperatively. Genuine tumorectomy replaces the former lobectomy, lobulectomy, and polectomy. In addition, tumorectomy does not have to be total. The surgeon's aim is to remove the tumor, but he or she will later decide between grossly total resection and subtotal resection according to the requirements of the case.

Stereotactic and open biopsies are addressed in other chapters.

MAJOR INTRAOPERATIVE COMPLICATIONS AND THEIR MANAGEMENT

Improved anesthetic technique, the prophylactic use of corticosteroids, and the intraoperative use of a mannitol bolus before the dural incision if the dura mater is tense are the means whereby the operative field is made fit for surgical manipulation. The surgeon takes great care not to damage veins and to prevent the leakage of blood into the CSF compartment (ventricles, cisterns, and sulci of the convexity). A spatula is used only if it does not traumatize the surrounding nervous tissue; scooping with retractors fixed to the Mayfield headrest is preferable to manual scooping, which is always discontinuous.

These conditions minimize the risk of intraoperative and postoperative complications. The intraoperative risks are lobar or hemispheric swelling, episodic or subcontinuous bleeding, and incarceration of CSF in the operative cavity or in a ventricular pole or, less likely, in a cistern. Swelling of the operative field may be the result of hyperemia (increased cerebral blood volume) or edema; either may be local or diffuse. Hydrostatic edema may be caused by congestion of a vessel that results from a rise in capillary and venous pressure after distention of the walls of resistance vessels. Hyperemia may be associated with normal, decreased, or increased blood flow.

Determination of the cerebral blood flow still presents technical problems and furnishes only an overall picture of the blood perfusion of each cerebral hemisphere. Particularly useful are regional blood flow data, which PET and SPECT can supply, but not in the course of an operation (except when high-field intraoperative MRI is available). Thus, we still do not know how the blood flow and cerebral metabolism are regulated in single areas of the brain adjacent to space-occupying lesions or after they have been evacuated surgically, nor do we know what the regional response will be to drugs or to variations in pressure of the respiratory gases. An intravenous mannitol bolus (which increases the blood flow irrespective of the ICP), hyperventilation, and, on occasion, cautious withdrawal of CSF are options if intraoperative congestion of the brain occurs. Initially, the surgeon must ensure that the swelling is not a result of anesthesia or a large tumor residue, of a clot deep in the operative cavity, or of incarcerated CSF.

POSTOPERATIVE MANAGEMENT

An operation on a cerebral glioma is not high-risk surgery; therefore, the immediate postoperative management is the same as that required for any other neurosurgical operation of average complexity. It has now been standardized after decades of experience.

The patient is kept in intensive care for the first 48 to 72 hours under close neurologic supervision and monitoring of autonomic parameters. Drainage, if applied, is removed after 24 hours. The ICP recording probe is removed on postoperative day 3. Antiedema osmotic treatment is discontinued on day 4, and corticosteroid therapy is titrated

down a few days later. Prophylactic antibiotics are discontinued between days 4 and 6. CT scanning is performed on day 7 of an uneventful course, and a neurophysiologic (evoked potentials) and neuropsychologic assessment is performed on day 10. Antiepileptic therapy or prophylaxis is given for years.

The immediate postoperative period may be marked by the same complications as those that may arise during the operation (e.g., brain swelling, bleeding, engorgement of CSF), as well as infarction adjacent to the operative field or distant from it, resulting from the interruption of arteries or veins. Neuroimaging and continuous ICP recording are diagnostic. To differentiate swelling resulting from congestion from that resulting from edema, CT scanning is essential after contrast injection. The hypodensity found in the standard images increases by a few Hounsfield units if the blood volume is increased, an increase that is too small, however, to be appreciable on the CT scan. Even minimal bleeding in the operative cavity, either subdural or extradural, shows up clearly on CT and MRI. Regarding ICP, whether a given cerebral perfusion pressure is sufficient in a particular individual to ensure perfusion to all parts of the brain is unknown. Particularly vulnerable are those areas adjacent to the operative focus, whose vascular autoregulation is presumably altered. It has been decided arbitrarily that an ICP of over 20 mm Hg must be corrected by hyperventilation and antiedema osmotic agents. These measures are adopted only in severe neurologic conditions, which are rarely found in patients with low-grade cerebral glioma. If infiltration of deep structures occurs, the surgeon will choose a biopsy rather than extensive resection. Indeed, if surgical series since the introduction of CT are evaluated, the following situation is illustrative. Of the 25 patients that Vertosick and associates[17] operated on between 1978 and 1988, 5 underwent debulking, 4 had an open biopsy, and 16 had stereotactic biopsy, with zero operative mortality and zero morbidity. Of Piepmeier's[16] 50 patients operated on between 1975 and 1985, 19 underwent total resection, 17 subtotal resection, and 14 biopsy, with only one postoperative death. In the series of McCormack and co-workers,[127] of 53 patients (10 gross total resections, 34 subtotal resections, and 9 biopsies) operated on between 1977 and 1988, only 1 died of myocardial infarction in the postoperative period, and 5 died after the 30-day period but while the patients were still in hospital. Three patients who had been neurologically intact before surgery had mild deficits thereafter. In the series of McCormack and colleagues, 15 reoperations were necessary: 3 for shunts, 3 for cyst aspiration, 2 for infection, and 7 for further tumor resection.

The role of radiotherapy in the management of low-grade gliomas is discussed in several excellent review articles.[128–132] Unfortunately, no uniform or systematic studies have been performed that would allow a firm judgment, but the number of patients receiving radiotherapy in the past few years has increased.[133,134] Retrospective analysis of past series, with all their limitations, seems to show that as far as astrocytomas are concerned, (1) patients who undergo surgery for pilocytic astrocytoma (even if incompletely) should not be irradiated; (2) patients with fibrillary or protoplasmic astrocytoma who have undergone gross total resection should not be irradiated but should be followed up closely with neuroimaging; (3) patients with these tumors who have undergone incomplete resection should receive conventional fractionated radiotherapy at doses of 4500 to 5500 cGy in a limited volume (dose to be reduced and commencement of radiotherapy deferred for patients younger than 2 to 3 years of age); and (4) patients with gemistocytic astrocytoma should receive postoperative radiotherapy regardless of the extent of resection.[135,136] With regard to oligodendrogliomas[137] and the rarer mixed gliomas, the published data are still more fragmentary and discordant. It does seem, however, that radiotherapy slows tumor regrowth.[133]

GROWTH RESUMPTION

It is more appropriate to speak of growth resumption long after treatment than of recurrence, because an infiltrating tumor is never completely eradicated. The literature supplies data on the rates of recurrence, on the length of the interval since operation, and on the histologic differences on the second appraisal (at surgery or at necropsy) compared with the first. Very few opinions on the treatment of a recurrence have been published. Among the series explicitly discussing this topic, one refers to a long period and the other to the CT era: Laws and colleagues[74] reported on 151 recurrences of Grade I and Grade II astrocytomas that were treated surgically between 1915 and 1976. Of the recurrences, 105 were treated surgically (alone or associated with other therapy), 36 nonsurgically, and 10 were not treated. The 12-month survival rates were 45.7%, 46.1%, and 47.6%, which is virtually the same for the three groups. McCormack and associates[127] reported on 24 recurrences among 41 patients who survived total or subtotal removal: 7 had a second operation, and 12 received chemotherapy. The mean survival of those who had a second operation was 12 months from the recurrence. The authors stated that neither reoperation nor chemotherapy prolonged postrecurrence survival. Such data increase the importance of the first management decision; at the time of recurrence, the tumors exhibit increased malignancy and resistance to treatment.

RESULTS

The largest series (461 cases) and the one covering the longest time span (1915–1975) is that of the Mayo Clinic.[14,74] Although the long-term results are obviously better in patients treated since 1950 as a result of improved surgical and anesthetic techniques and antiedema agents, the variables that correlate with longer survival are age under 20 years, good neurologic status before and after operation, epileptic seizures as the onset symptom, preoperative history of symptoms for not less than 6 months, grossly total surgical resection, and parietal or occipital tumor site. Sex, astrocytoma histologic Grade I or II, the presence of an intratumoral cyst, the side affected, and surgical lobectomy (which in malignant astrocytoma improves the prognosis) had little or no impact on survival. Laws and co-workers[14] combined patient age with six of the most important prognostic indicators to score the probability of survival (Table 48-2). Operative mortality excluded, survival varies widely (Fig. 48-19): the 5-year survival rate ranges from 69% to 35%. At 15 years, the rate is over 50% in low-risk patients, versus 16% for the mean. The effectiveness of postoperative radiotherapy could not be assessed per se but only in relation to other parameters. Its value is proved only

TABLE 48-2 ▪ Scoring System for Low-Grade Hemispheric Gliomas

Score = Age at Diagnosis × 0.072

+0	+1
Surgery after 1949	Surgery before 1949
No personality change	Personality change
Normal consciousness	Altered consciousness
Total resection	Partial resection
Site other than the frontal or temporal lobe	Frontal or temporal lobe
Mild postoperative neurologic deficit	Moderate-to-severe postoperative neurologic deficit

Scoring system based on the data by laws ER, Taylor WF, Clifton MB, Okazaki H: Neurological management of low-grade astrocytoma of the cerebral hemispheres. J Neurosurg 61:665–673, 1984.

in patients older than 40 years of age with high scores (i.e., with several risk factors). Patient age proved to be by far the most important factor in prognosis, more important than all the other clinical variables and forms of treatment combined, and this aspect is confirmed by the experience of many authors.[79,138,139] The reason for this result is unclear, but what is clear is a difference in biologic behavior of these oncotypes between the young and the adult host.

We dealt with the subject of different low-grade astrocytomas of the cerebral hemispheres as a whole, but we also mentioned that this pathologic entity includes three oncotypes: (1) the astrocytomas representing about 60%, (2) oligodendrogliomas approximately 23%, and (3) mixed oligoastrocytomas about 17%. Actually, the biologic and clinical features of these oncotypes are comparable if we consider the age at presentation, symptomatology, possibility of tumor progression to a higher grade, and absence of spinal diffusion or metastases. With respect to long-term survival, however, pure oligodendrogliomas emerge more favorably, pure astrocytoma appear worse, and mixed oligoastrocytomas display intermediate behavior.[140,141] The series of Shaw and colleagues[142] of the Mayo Clinic, which was drawn from a 20-year period, compares the survival of patients with pure and mixed oligodendrogliomas using

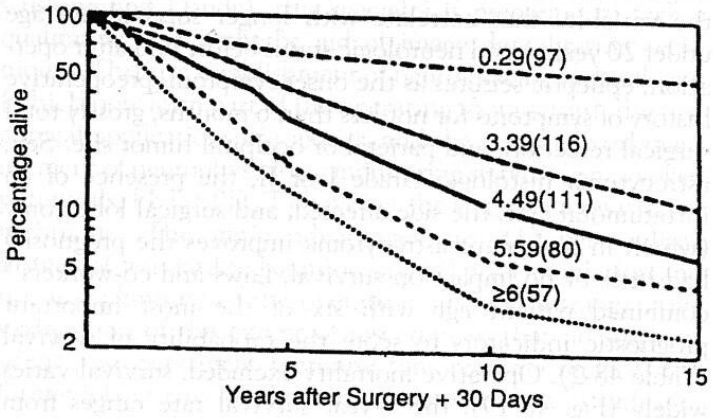

FIGURE 48-19 Score-based survival curves of patients with low-grade hemispheric glioma. See Table 48-2 for basis of scoring system. (From Laws ER, Taylor WF, Clifton MB, Okazaki H: Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. J Neurosurg 61:665-673, 1984.)

univariate and multivariate analysis and examining 14 prognostic indicators. The tumor grade emerged as the variable that was most significantly related to survival. Less significant was the extent of surgical resection. Younger age was also significantly related with a more favorable prognosis for both oncotypes so that, after gross total surgical resection, radiotherapy may not be required. Conversely, radiotherapy with doses of 5000 cGy is advocated in older patients and for partially resected tumors.

Reports confirm the importance of the length of clinical history among the clinical factors considered relevant for long-term prognosis. Tumors with a longer duration of symptoms and chronic epilepsy seem much less likely to progress toward malignancy over time.[143,144]

The routine use of CT since the time of the series by Laws and colleagues has added a new variable to be evaluated in the long-term prognosis of low-grade cerebral gliomas: the absence of contrast enhancement (i.e., the integrity of the blood-brain barrier) is associated with a better prognosis.[143]

The 1975 to 1985 experience of Yale University[16] shows that the only variables relevant to a better prognosis are age under 40 years and no contrast enhancement on the CT scan. The results of the 1977 to 1988 series at New York University[127] agree: multivariate regression analysis demonstrates that the most important prognosticators for improved survival are young age, absence of contrast enhancement of the original tumor on CT, and the performance status of the patient. The CT contrast enhancement of the original tumor is associated with a 6.8-fold increase in risk for a late recurrence. However, the prognostic significance of contrast enhancement is questioned by some authors,[1] whose further experience contradicts the results obtained in the series covering the decade 1975 to 1985. Bernstein[79] still ascribes some value to the presence of contrast enhancement as related to malignant progression, but Philippon and co-workers[145] deny these findings.

The value of aggressive surgical behavior has also been questioned.[144,146] The likelihood of malignant transformation has been demonstrated to be proportional to the preoperative tumor volume or to residual volume and the latter result inversely related to the time of recurrence.[147] On the other hand, Bernstein[79] emphasizes the unreliability of retrospective studies regarding tumors with different locations being treated differently: these limitations explain the dichotomy existing in the literature between supporters of aggressive surgery and supporters of "wait and see" behavior.

CONCLUSIONS

There has been a revival of scientific and clinical interest in low-grade gliomas, which were neglected for many years in the literature. Within this group of tumors, extraganglionic gliomas have attracted even less attention, and many surgical series group them together with those of the cerebellum, hypothalamus, brain stem, and anterior optic pathways. This grouping is inadvisable, because both histologically and biologically as well as from the diagnostic and therapeutic viewpoints, the latter gliomas are altogether different from those of the cerebral hemispheres.

One reason for this revival of interest is that in the neuroimaging age, the clinician is confronted with pathology

different from that seen 20 years ago. The clinician now sees a small lesion in a young, neurologically intact subject whose only complaint is a short history of epileptic seizures. The lesion is of the cerebral convexity, is diffusely infiltrative, and may have connections with the higher functions of the hemisphere: eloquent cortex, its projections, and associative fibers.

For tumors that are indolent for years, one may legitimately wonder whether aggressive treatment—surgery or radiotherapy—is appropriate in all cases and whether the potential benefits of treatment may not be counterbalanced by its risks and adverse effects.[73,148,149] Retrospective studies are of little help in shaping judgment, for the reasons given already (unselected series of tumors much larger than those that are treated now), to which must be added: nonuniformity of pathologic classification criteria, the question of sampling errors, nonuniformity in classifying preoperative neurologic status (Karnofsky's performance scale), nonuniformity of the extent of surgical resection or of a dose of radiotherapy, and the lack of a contemporary group of matched control subjects who did not receive treatment. The final and fundamental reason that retrospective studies are not helpful is the nonuniformity of biologic behavior of the tumor through time; it is subject to dedifferentiation in a high percentage of cases in the course of its natural history. We have no sure data on which to form a judgment regarding the optimal treatment for low-grade cerebral gliomas. These data can come only from prospective, randomized studies of large series. Meanwhile, surgery has both a diagnostic and a therapeutic role. Its diagnostic role may well diminish with advances in neuroimaging procedures, like PET and SPECT, and the chemical quantification in vivo of metabolites in selected regions of the brain, such as can be obtained with proton MR spectroscopy.[150] On the therapeutic front, surgery may well maintain its hold, unless valid alternatives are developed. Although surgery has so far been limited by the risks of damage that it induces, the progress of technology will reduce the risk of undesired side effects and allow surgery to be more aggressive and safer.

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