We work in the dark—
we do what we can—
we give what we have.
Our doubt is our passion,
and our passion is our task.
The rest is the madness of art.

Henry James

Someone once defined madness as doing the same thing over and over again, expecting a different result. Year after year we develop new technological methods (and new billing codes for these methods) that enable us to resect larger portions of a glioma more accurately. Despite these efforts, patients continue to die of recurrent disease. Over the past 40 years we have used the operating microscope, fluoroscine fluorescence, ultrasonic imaging, image-guided surgery, volumetric stereotaxy, intraoperative computerized tomography (CT)-guided surgery and, more recently, interventional magnetic resonance (MR) imaging. The paper by Studdbauer et al. in this issue represents yet another technological advance. None of these past technical improvements has made a significant difference in the survival of patients harboring these lesions (and I do not believe that this one has made a significant difference in the survival of patients).1

Dr. Bucy’s concept of glial tumors was and is identical to that held by many neurosurgeons: that glial tumors truly grow as a mass by local extension and that there is some, anywhere, a defined border at which the tumor ends and normal brain begins. This simple concept of a complex biology lends itself to a simplistic therapy: take it out! All we have to do is define the volume of a tumor and remove it. I must confess that at one time I actually believed this.

In the 1970s, I adapted some of Jean Talairach’s stereotactic resection techniques for epilepsy to the resection of gliomas. These procedures were based on the three-dimensional precise anatomical data set provided by CT scanning and MR imaging.3 In cases of glioblastoma multiforme (GBM) CT and MR imaging revealed a discrete contrast-enhancing mass surrounded by “edema.” The contrast-enhancing mass provided a convenient target for computer-assisted volumetric stereotactic resection. Postoperative imaging studies confirmed “gross-total resection” of these lesions. Did this high-tech, scientific, aggressive surgical approach followed by radiation and chemotherapy result in a cure? No, it did not. Tumors recurred in the margins of the “gross-total resection.” Patients died right on schedule (assuming that the pathological findings were correct). At best our procedures may have prolonged mean survival in patients with GBM from 37.5 to 50.5 weeks.2 Certainly, patients undergoing these radical resections lived longer than those who underwent biopsy alone. As a prognostic factor in malignant glioma, however, the extent of the surgical resection falls far behind factors over which a surgeon has no control: tumor grade, patient age, and Karnofsky Performance Scale score. In some studies, surgery does not even make it onto the radar screen of statistical significance.

In an attempt to understand what was happening in the region surrounding the contrast-enhancing mass, we performed CT and MR imaging-directed stereotactic serial biopsies in many patients harboring high- and low-grade gliomas. In these studies, we sampled not only the contrast-enhancing regions of the neoplasm, but also regions demonstrating hypodensity (“edema”) on CT scans, prolongation of the T1 signal on MR images and perilesional regions that appeared normal on MR imaging.6 Evaluation of these biopsies5 demonstrated isolated parenchyma. In fact, we confirmed in any MR imaging–defined abnormality as 7 cm (which was as far away as we sampled). In contrast, we demonstrated isolated tumor cells coexisting with intact normal brain parenchyma. In fact, we confirmed tumor cells in dead patients.

Undoubtedly, there is beauty found within the peritumoral region;6 however, it is not the tumor, but rather the extent of the invasion plus the extent of the resection that may be a significant cosmonomic hit—a “greater log-kill”—to the normal brain. The contrast enhancement plus the volume of T1 signal enhancement is resulting in a neurological deficit, and there is no assurance, even if the tumor will ultimately die of its disease.

All the previous discussion has been based on our experiences with stereotactic biopsies and stereotactic biopsies based on conventional CT and MR imaging. These procedures have been replaced in the healthy brain by modern imaging techniques in the determination of local tumor extension within solid tumors. New insights may be provided with appropriate surgical planning, including proton resonance and other paramagnetic compounds.

Proton MR spectroscopy is based on the magnetic properties of tissue. Proton MR spectroscopy provides detailed profile of tissue in the healthy brain and has been used for both normal and neoplastic components of normal and neoplastic tissue. Proton MR spectroscopy is based on the presence of various components of normal and abnormal tissues. Proton MR spectroscopy provides detailed profile of tissue in the healthy brain and has been used for both normal and neoplastic components of normal and neoplastic tissue.

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appeared normal on imaging studies. We found that the actual extension of the tumor is indicated neither by CT nor MR imaging. Examination of tissue obtained by stereotactic serial biopsies of the peritumoral "edema," which surrounds the contrast-enhancing mass in these lesions, demonstrated isolated tumor cells coexisting with intact normal parenchyma. In fact, tumor cells could be found far from any MR imaging-defined abnormality, at least as far away as 7 cm (which was as far away as we sampled). In essence, we confirmed in live patients what Scherer had found in dead patients.

Undoubtedly, the greatest numbers of tumor cells can be found within the MR imaging-defined abnormality. Perhaps resection of this entire abnormality (the site of Gd-enhancement plus the volume of T1 prolongation) will provide a significant cosmetic hit—a "greater log-kill"—to the neoplasm. The number of tumor cells that can be removed is limited by "edema." Removing anything but the contrast-enhancing mass is removing functioning brain tissue, possibly resulting in a neurological deficit, and there is no assurance that the tumor will not recur anyway; we already know that isolated tumor cells lurk in regions beyond the MR imaging-defined abnormality. Certainly, there are rare exceptions to this, namely tumors that display imaging abnormalities confined to a frontal or temporal pole, which can be treated with a generous lobectomy. In my own experience, however, these cases are very rare and, although the patients do, in fact, live longer when treated in this manner, they ultimately die of their disease.

All the previous discussion has been based on our experiences with stereotactic volumetric resections and serial stereotactic biopsies based on conventional CT and MR imaging. These are based on epiphenomena: the concentration of unbound water in the diseased brain compared with that in the healthy brain and/or the existence of necrosis within solid tumor tissue defined by contrast enhancement. New insights into the biology of gliomas, however, may be provided by recent-generation MR imaging units with appropriate software capable of suppressing water proton resonance and observing the proton resonance of metabolic compounds in tissue.

Proton MR spectroscopy, the subject of the present paper, is based on the measured intensity of one or more metabolites. Proton MR spectroscopy supplies a biochemical profile of tissue contained in any defined voxel of the brain and has been used to characterize the biochemical components of normal and abnormal tissue. Typically brain neoplasms demonstrate increased levels of choline-containing compounds (Cho, associated with cell membrane and myelin turnover), decreased levels of N-acetylaspartate (NAA, an indicator of healthy neurons), and decreased levels of creatinine (Cr) and phosphocreatine which produce inorganic phosphates for the production of adenosine triphosphate. These levels reflect cell membrane turnover, neuronal loss, and a reduction in energy production. The pattern of high Cho and low NAA and Cr in comparison with normal levels differentiates abnormal from normal brain tissue and, more specifically, tumor within a specific voxel. This information has been useful for diagnostic purposes, such as differentiating gliosis or radiation necrosis from active tumor. Can it provide an actual description of where "tumor" ends and "normal" brain begins?

The technique would be very useful if a glial tumor characterized by solid tumor tissue and surrounding infiltrated parenchyma really had a clear border. We know that the contrast-enhancing mass in a malignant glioma comprises solid tumor tissue that contains no viable parenchyma. Tumor tissue usually has a clear histological border, which, in malignant gliomas, corresponds to volume defined by contrast enhancement (in low-grade gliomas this is usually not true). Tumor tissue can be removed without producing neurological deficit and that is not the problem. The problem I have with this paper is that the authors imply that there is also a defined border between infiltrated parenchyma and normal brain. Unfortunately, this border does not exist.

In discussions with patients, I like to compare tumor cell density with the density of people in and around major metropolitan areas. There are a lot of people per square mile in Manhattan, fewer in Westchester County, and still fewer in the farm lands of upstate New York. Similarly, the ratio of tumor cells to the normal cells of the infiltrated parenchyma does not suddenly fall to zero at some specific boundary. Tumor cell density usually decreases in a nonuniform manner. Where does the surgeon draw the line, so to speak?

More work is needed to determine the histological concomitants of 'H-MR spectroscopy abnormalities in living patients harboring gliomas. Carefully performed stereotactic serial biopsy studies in which samples are obtained from 'H-MR spectroscopy-defined normal and abnormal regions of the brain are needed. These studies could very well use the cross-registration methods for surgical planning described by the authors of this paper. Nonetheless, I predict that these studies will reveal isolated tumor cells existing beyond the volume defined by the 'H-MR spectroscopy abnormalities. To be sure, the actual biology of these isolated cells is not really known; however, in tissue cultures and nude mouse models they demonstrate motility and growth, respectively.

All of this is a moot point; however, the tissue lying outside the contrast-enhancing mass, identified by abnormalities on 'H-MR spectroscopy (or T1 prolongation on MR imaging), is usually infiltrated functioning parenchyma. In most symptomatic patients, resection of infiltrated parenchyma identified by a prolonged T1 signal on MR imaging or on elevated level of Cho and reduced levels of NAA and Cr on 'H-MR spectroscopy includes important brain tissue and results in a postoperative neurological deficit. The incorporation of functional MR imaging for cortical motor, sensory, and speech localization, and techniques such as MR tractography will simply inform surgeons of what they cannot remove. Even with all of these methods, my prediction is that the glioma will almost always recur, within several months for high-grade gliomas and within a few years for low-grade gliomas, with variations induced by the predominant cell type of the lesion.

Nonetheless, we continue to update our surgical techniques using whatever new technology appears on the horizon. At present, surgery is the most efficient method for the reduction of tumor burden available. We must continue to develop new and less invasive methods to increase the efficacy, efficacy, and safety of our procedures. That is what we, as neurosurgeons, do. Nonetheless, glioma represents a
complex disease that must be understood and dealt with on a cellular level, if we are to see a significant improvement in survival or cure. In the meantime, we pursue the madness of our art.

References

RESPONSE: A Happy Sisyphus
La lutte elle-même vers les sommets suffit à remplir un coeur d’homme. Il faut imaginer Sisyphe heureux.
Albert Camus, Le Mythe de Sisyphe

We are very grateful for the thoughtful remarks made by our congenial colleague who has devoted so much effort to the treatment of gliomas and to computer-aided surgery. Dr. Kelly has written a brilliant essay about the apparently futile struggle of neurosurgeons against the biology of nature and, having read his sentiments, there is not much left to say. Why do we ceaselessly try to resect gliomas as radically as we can, knowing that we cannot cure our patients who eventually succumb to their disease? Do we not resemble a modern Sisyphus who again and again tries to fulfill his task while fully aware of his absurd situation? What makes us continue with our struggle to help patients with glioma? Dr. Kelly knows that we do many more absurd things such as using functional neuronavigation, tractography, and intraoperative MR imaging, to name a few techniques applied in glioma surgery. We do all this because we are humans who recognized our fate, but recognize sense within the absurdity of our situation. We believe that there is something good in what we do and that maybe we actually help our patients. We know that we cannot ultimately cure gliomas surgically because of all the important facts that Dr. Kelly has pointed out so masterfully. All we can do is navigate between Scylla and Charybdis. On the one hand is the temptation, of fered by new techniques of metabolic or molecular imaging, to resect greater amounts of tumor and, perhaps, too much functionally intact neuronal tissue. On the other hand we may choose safety and resect an insufficient amount of tumor. Either way we can never eliminate every migrating tumor cell, although the development of multimodal biological imaging is just beginning. All the same we will continue to perform surgery in our patients whenever appropriate—trying to remove the maximum tumor burden, trying to develop more and newer techniques to achieve this goal, trying to give our patients the best medical treatment available, and not losing heart because of the limitations that we face. Maybe it is as Albert Camus once wrote, “. . . the fight itself toward the summits suffices to fill a heart of man. One must imagine Sisyphus happy.”

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Abbreviations used in this paper:
DICOM = Digital Imaging and Communications in Medicine;
FOV = field of view; acquisition gradient-echo; SD = standard deviation; SE = spin-echo; 3D = three-dimensional.